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Viewpoint

Precision Public Health and Structural Racism in the United States: Promoting Health Equity in the COVID-19 Pandemic Response

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Abstract

The COVID-19 pandemic has revealed deeply entrenched structural inequalities that resulted in an excess of mortality and morbidity in certain racial and ethnic groups in the United States. Therefore, this paper examines from the US perspective how structural racism and defective data collection on racial and ethnic minorities can negatively influence the development of precision public health (PPH) approaches to tackle the ongoing COVID-19 pandemic. Importantly, the effects of structural and data racism on the development of fair and inclusive data-driven components of PPH interventions are discussed, such as with the use of machine learning algorithms to predict public health risks. The objective of this viewpoint is thus to inform public health policymaking with regard to the development of ethically sound PPH interventions against COVID-19. Particular attention is given to components of structural racism (eg, hospital segregation, implicit and organizational bias, digital divide, and sociopolitical influences) that are likely to hinder such approaches from achieving their social justice and health equity goals.

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Structural Racism and Defective Data: Health Equity Threats for the Public Health Response Against COVID-19

Structural racism refers to “[a] system in which public policies, institutional practices, cultural representations, and other norms work in various, often reinforcing ways to perpetuate racial group inequity” [1]. Structural racism affects all social determinants of health. Its impact was accentuated and made more visible with the COVID-19 pandemic. Indeed, the US Centers for Disease Control and Prevention recognized the centrality of the social determinants of health in the disproportionate impact of the pandemic on racial and ethnic minority groups. In addition, they acknowledged the pervasive

contributing influences of (structural) racism across each one of these determinants [2]. Undeniably, since the start of the pandemic, a cornucopia of examples suggesting the impact of structural racism has surfaced [3]. This was particularly evident in countries from which statistics are presently available, such as the United States, showing devastating consequences for the health of racial and ethnic minorities [4]. For instance, as of November 2021 in the United States, the risk of dying from COVID-19 for non-White groups (except for the Asian non-Hispanic community) was about twice that of White people [5]. Such inequities can be partly explained by structural vulnerabilities influencing access to and quality of care offered to these racial/ethnic minority groups.

The structural vulnerabilities of some racial and ethnic minority groups to COVID-19 stem from political and social influences,

which were observed, for instance, to have a greater impact on their health than individual choices made [6]. These influences led to the normalization of discrimination, stereotyping, and prejudices, and ultimately impacted racial minorities' health and access to quality care [7]. Indeed, studies have demonstrated the existence of implicit racial/ethnic biases among health care professionals, and their presumed impact on the quality of care due to suboptimal patient-provider interactions with racial/ethnic minorities (see review [8]). For instance, emerging evidence based on billing data started indicating disparities in COVID-19 testing among racial and ethnic groups, with African Americans being less likely to be offered COVID-19 testing than Whites, even when presenting with similar symptoms such as fever and cough [9]. Aside from individual health care professionals, health care institutions and organizations can also harbor implicit biases regarding their approach toward minority groups. It was highlighted that testing centers for COVID-19 in the United States were predominantly located in wealthy and White neighborhoods, which further limits access to health care for people located in poor neighborhoods [10]. These implicit provider and institutional/organizational biases could be an additional source of structural health disparities for ethnic and racial groups during the COVID-19 pandemic [11]. Indeed, average threshold metrics for public health interventions (eg, those used as indicators for closing or opening schools/businesses) are biased if COVID-19 testing is carried out mostly in wealthy neighborhoods—where viral transmission rates are actually lower—and deprived neighborhoods (where residents are predominantly minorities) are insufficiently tested [12].

Additionally, public health recommendations for containing the spread of COVID-19 have been particularly difficult for racial and ethnic minority groups to implement, partly due to the downstream influences of structural racism [3,13]. As rightly noted by Krieger [14], racial and ethnic minority groups constitute a good percentage of low-wage workers, making them more vulnerable to the effects of the pandemic. They often live in crowded multigenerational houses (often a consequence of racial residential segregation and redlining policies—two historical examples of structural racism [15,16]), with neither the possibility of working remotely from the safety of their homes nor adequate access to COVID-19 testing and treatment (eg, because minorities are less likely to be insured) [3,17].

Other indicators of how structural elements determine health inequity for racial/ethnic minorities during the COVID-19 pandemic have been highlighted by some seroprevalence studies. For instance, a large-scale nationwide study carried out in the United States showed higher seropositivity rates (2- to 3-fold higher) for SARS-CoV-2 antibodies in dialysis patients residing in Hispanic and non-Hispanic Black neighborhoods in comparison to those residing in White (non-Hispanic) neighborhoods, and a 2-fold higher seropositivity for those living in poorer neighborhoods [18]. This study and others (eg, [19]) challenge the underlying assumption made elsewhere that “the risk of infection is homogeneous within the population” [19]. Such implicit assumptions are not only detrimental to the efforts made to contain the virus but they may also be a manifestation of structural racism itself. Indeed, one of the

defining characteristics of structural racism is its *invisibility* to the dominant racial/ethnic group [20]. The situation also highlights the need for more comprehensive data on the impact of the COVID-19 pandemic on racial and ethnic minorities, in particular for those living in disadvantaged neighborhoods.

In that regard, eminent public health researchers have raised the alarm regarding missing or incomplete data on racial/ethnic minorities [14,21]. Indeed, data on the impact of COVID-19 on racial and ethnic minorities were not systematically and uniformly collected across the United States [22]. This resulted in the skewing of our understanding of the deadly evolution of the virus within these communities, while hampering the ability to provide them with timely and adapted public health interventions and care [14,23]. Although US state and local public health departments were required—at latest by August 1, 2020—to report demographic data for COVID-19 cases, Krieger and colleagues [23] have shown that, despite the new reporting requirements, compliance was far from being achieved and much work still needs to be done in this regard.

In the COVID-19 era, the underreporting and inadequate reporting of racial and ethnic information create data gaps that hamper the proper functioning of public health institutions in initiating culturally appropriate measures to prevent the spread of the virus in these communities [24]. Given the fast pace at which the pandemic is evolving and the continuous need for updated public health responses, a paramount question is how these data gaps and structural racism could influence public health practice, in particular when innovative data-driven approaches are being considered as complementary to traditional public health interventions. In this paper, we thus reflect on how structural racism in the health care/public health domain and the defective collection of data on racial and ethnic minorities could undermine the health equity and social justice goals of precision public health (PPH) interventions.

Structural Racism and Defective Data: Potential Impact on PPH

To respond to this worrying public health situation while making use of existing and emerging data sources, Rasmussen and colleagues [25] argue for the need to implement PPH interventions as an additional tool to fight the pandemic. PPH means “the application and combination of new and existing technologies [...] to tailor preventive interventions for at-risk groups and improve the overall health of the population” [26]. Horton [27] is even more explicit in highlighting the importance of data in PPH and characterizes it as being “about using the best available data to target more effectively and efficiently interventions of all kinds to those most in need.” At least two distinct approaches to PPH exist. The first one is a reductionist version, where PPH focuses solely on the use of genetic information to tailor interventions to specific subgroups of the population (with the risk of neglecting foundational considerations of public health such as the impact of the social determinants of health). The second (wider and more encompassing) version does not limit itself to genetic information, but also considers other sources of data (eg, big data, granular population surveillance data, and data from mobile

apps) to guide public health practice [25,28]. Given the limits of focusing solely on genetic data to guide interventions (eg, risk of exacerbating existing health inequalities [29]), we find the second version of PPH more promising, as it uses a plethora of data sources [28], in particular if it will ally both high-risk strategies and population-based approaches to maximize the impact of public health interventions [30].

Although still in its infancy [31], PPH has already shown promise in the fight against COVID-19. For instance, at the start of the pandemic, pathogen genomics such as whole genome sequencing analysis, coupled with epidemiological data, was successfully used in the Netherlands to not only monitor the emergence of local or regional clusters of SARS-CoV-2, but also to help in understanding transmission patterns while guiding public health interventions in breaking the chain of transmission of SARS-CoV-2 [32]. Additionally, some innovative sources of digital data are also being used to reduce the transmission of SARS-CoV-2. The usefulness of participatory disease surveillance systems has already been demonstrated for the early detection of other transmissible diseases such as influenza-like illness [33]. In such systems, citizens can actively get involved in the public health response by directly reporting COVID-19-related symptoms via mobile apps or digital platforms [34]. Furthermore, the use of COVID-19 contact trackers, whereby cellphone tracking data are used to alert people who might have been in contact with an active case of COVID-19 [35], is another example of how PPH can be helpful in a pandemic context.

Given the disproportionate burden of the pandemic on racial/ethnic minorities, as previously argued, it would then be legitimate to consider them as part of those “most in need” [27] and thus principal supposed beneficiaries of PPH interventions during the COVID-19 pandemic. However, given the aforementioned issues related to structural racism and the skewed collection of data on minorities, it is important to consider the following two issues before the widespread deployment of PPH interventions in connection to COVID-19. First, one must reflect on how structural racism can influence the generation and use of data sets in public health practice (eg, data racism) [36]. Second, it is critical to explore how the use of certain data-driven technologies—which are becoming essential components of PPH—could lead to novel racial/ethnic discrimination in public health interventions for those “most in need” [27].

One set of technologies that has the capacity to both improve or worsen health inequities between ethnic and racial groups if employed in clinical care and PPH interventions is machine learning [37]. Machine learning can be defined as “a branch of artificial intelligence (AI) focused on building applications that learn from data and improve their accuracy over time without being programmed to do so” [38]. There are 3 main classifications of machine learning approaches, namely supervised, semisupervised, and unsupervised learning, depending on whether the machine learning algorithms are trained on labeled, semilabeled, or unlabeled data sets, respectively [39]. If such technologies are used in PPH, one of the important aspects to consider is the appropriateness of data sets used to train machine learning algorithms, in particular if

they are to be used in a population that is either underrepresented in the training data sets or has long been systemically disadvantaged and marginalized [40,41]. Indeed, individual and societal biases can be encoded in big data and other training data sets destined for public health practice and medical care [37,40]. This phenomenon is sometimes described as data racism, a term that refers to “the multiple systems and technologies - deployed in a range of fields - that either primarily target or disproportionately impact migrants and people of [color]” [36]. To better explain how data racism—combined with structural racism—could impact PPH interventions through machine learning techniques in the future, one can look at the unfortunate experiences emerging in the field of data-driven predictive policing [42].

PPH and predictive policing can be compared since they function according to analogous principles. Indeed, one of the foreseeable goals of PPH is to forecast disease outbreaks and identify hotspots or subgroups of the population for tailored interventions based on big data predictive analytics [43]. Similarly, predictive policing aims at forecasting the likelihood of a crime being committed in a specific location, to then prioritize focused police interventions in certain at-risk areas (eg, by having more frequent police patrols) or on people having some prespecified characteristics deemed relevant by the used software. Existing predictive policing software companies, such as PredPol, aspire to also be fair, since the “starting point is data: objective, agreed-upon facts that can be used to guide the discussion” [44,45]. PredPol claimed to provide fairer and more objective risk evaluation and predictions regarding crimes than subjective police assessment [44]. However, Richardson and colleagues [42] argue that, although PredPol took significant actions to reduce bias in their data sets when training their machine learning algorithms (eg, by excluding traffic citation data and data on drug-related crimes), such measures still do not capture the whole complexity and diversity of police interactions where bias can be introduced into the data. They also highlighted the methodological difficulties for vendors of such technologies to identify “these problematic practices and policies in real-time; therefore, any system that includes recent or live data may be subject to additional undocumented biases” [42]. Consequently, the alleged promise of being fair cannot always be kept, since data sets on which predictive policing is based often present relevant fallacies.

We can reasonably expect that PPH interventions might encounter an analogous set of problems, in particular considering the previously discussed COVID-19-related data crisis for racial and ethnic minority groups. Indeed, within the precincts of structural/data racism, machine learning algorithms will likely replicate some degree of discrimination unless appropriate measures are taken to address the situation [40]. Therefore, it is important for machine learning developers to have an adequate understanding of structural racism and its potential real-world ramifications through their software [46]. This could help ensure that the developed machine learning algorithms both advance public health utility and promote a fair distribution of resources along racial and ethnic lines, while minimizing the risks of worsening health inequities [46]. However, it is also important to note that addressing the technical flaws of machine learning

algorithms is catering only to the downstream consequences of structural racism and therefore this cannot be the silver bullet to reduce health inequities between racial and ethnic groups. To bridge the disparities between racial and ethnic groups will likely require changes at the societal, institutional, and individual levels, so that the upstream influences of structural racism are mitigated [47]. A few additional potential solutions that can help in tackling algorithmic biases have been discussed in a previous publication [40].

Aside from technological considerations, it is also paramount to tackle the low representation of racial/ethnic minorities (in particular those of African descent) in AI and machine learning communities. This can also be considered a consequence of structural racism in industrial and academic settings [48]. Racial and ethnic diversity in these communities could help safeguard against blatant and implicit discrimination toward minorities, even if these minority researchers could themselves be subsequently exposed to consequences from the power structures in place. Indeed, it is documented that some of the effects of structural racism in the workplace also involve microaggressions toward these minorities (eg, harassment, disrespect, racial slurs) by their White colleagues, which undermine their capacity to work, while operationalizing the corporate culture of maintaining racial hierarchy [20,49].

There are also other means by which structural racism could impact the generation of data for PPH during the COVID-19 pandemic. One of them is through the racial and ethnic digital divide, whereby minorities, as a consequence of their often-lower socioeconomic status, would be less likely to engage in PPH activities due to poorer internet access [50]. According to the Pew Research Center, in 2019, White individuals still have better access to the internet in comparison to other racial/ethnic groups (92% versus 86% in Hispanic individuals and 85% in African Americans) [51]. Therefore, public health surveillance systems relying on internet-collected data (eg, social media mining to guide interventions against COVID-19) may be particularly vulnerable to the underrepresentation of minority groups in the gathered data sets. The problem might also be that of overrepresentation of minorities in internet-collected data. For example, a recent study has found that—despite worse internet access—ethnic/racial minority groups are more likely to post COVID-19–related information on social media, possibly due to a “reversal of digital divides” or the fact that the pandemic has disproportionately impacted racial and ethnic minority groups, and that social media is often perceived as a coping strategy for stress and for obtaining community support [50]. Either way, the issue remains that proper public health surveillance should ensure the ethnic and racial representativeness of the collected data before initiating any public health intervention [50], or at least perform some sort of data adjustment to account for the selection bias.

Lastly, it cannot be ignored that structural racism could lead to more biased data sets for ethnic and racial minority groups because of the influence of sociopolitical factors on the functioning of public health institutions [52]. It is important to note that institutional (or structural) racism can influence the functioning of institutions in a number of ways (ie, at individual and organizational levels). For instance, institutions can either

become increasingly racialized and adopt racist motivations (eg, excluding or limiting employment of qualified minorities in decision-making positions, or employing a few of them only, as part of racial capitalism [53], to showcase that they are dedicated to diversity) or they can be burdened by other organizational structures that impede their achievements in terms of racial and health equity (eg, lack of resources and low care given to people of color) [52]. Indeed, it is well known that hospitals in marginalized neighborhoods (eg, those with a high percentage of people of color) are underfunded, understaffed, and sometimes filled with less skilled health care professionals, which then limit their ability to offer services and treatment comparable to those offered in other neighborhoods [15,54].

Therefore, such public health institutions could be hampered in generating high quality data on racial and ethnic minority groups due to (1) the limited resources dedicated to these groups, (2) the unrepresentative racial and ethnic composition of their decision-making teams and health care professionals, leading to viewing racial disparities from a “White framing,” (3) the lack of adequately trained professionals to fulfill these duties, and (4) hospital segregation—that is, the refusal of some of the most resourceful hospitals to treat racial/ethnic minority groups suffering from COVID-19 due to their lower socioeconomic conditions (eg, inferior health insurance plans, which is also a known consequence of structural racism) [40,54,55]. The unfortunate consequence could be that of contributing to the generation of biased data sets that do not reflect the lived reality of racial and ethnic minorities in facing COVID-19. Therefore, PPH interventions relying on these data sets would likely be limited in their effectiveness and health equity could never be achieved for all racial and ethnic groups, unless these different parameters are given due consideration.

Conclusions

In this article, we have highlighted the role of structural racism and the presence of defective data for racial and ethnic minorities as important factors to consider in designing ethically acceptable public health policies during and after the COVID-19 pandemic. Moreover, we have discussed PPH, an innovative approach to tackle public health issues such as COVID-19, which can however encounter several ethical challenges if the aforementioned issues of structural racism and defective data collection are not tackled. Our aim is not that of discouraging the use of PPH, which we consider as an important new element in the public health toolbox that deserves to be fully implemented to fight the COVID-19 pandemic; rather, we want to highlight a few issues that need to be considered by policy makers and scientists developing PPH measures to make sure that their efforts to improve public health do not ignore the danger posed by structural racism and defective data on minorities. In this regard, we join our voices to those cited in this article on the importance of having improved, harmonized, and nationwide data collection systems that are as free as possible from the influences of structural racism and inclusive of all racial and ethnic groups. Although insufficient on their own to promote health equity among racial and ethnic groups, these measures could be an important contribution to the effective and nondiscriminatory use of PPH approaches that are

inclusive of the racial and ethnic composition of the societies in which they are deployed. PPH approaches deserve to be better planned and their effectiveness critically assessed, and this will not be achieved unless their data and technological foundations are deep-rooted in health equity and social justice.

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Authors' Contributions

LDG was involved in the conceptualization of the manuscript, wrote the original draft and subsequently reviewed and edited the manuscript following other coauthors' suggestions and modifications made to the manuscript. AM was involved in the conceptualization of the manuscript, and in reviewing and editing of the original draft and subsequent versions. TW was involved in the conceptualization of the manuscript, supervised LDG during the writing of the original draft, and reviewed and edited the original draft and subsequent versions. BSE was involved in the conceptualization of the manuscript, and reviewed and edited the original draft and subsequent versions. BSE was also responsible for project administration and acquired funding from the Swiss National Science Foundation for this publication. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence

PPH: precision public health

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Viewpoint

Adaptation of an In-Person Internship to a Virtual Format for Public Health Undergraduates

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Abstract

The disruption of traditional, in-person learning due to the COVID-19 pandemic necessitated the rapid development and use of revised and novel learning opportunities using a variety of remote instructional methodologies. This viewpoint describes the process used by an undergraduate Public Health program to transition a traditional, in-person, semester-long, 480-hour internship to a virtual-only learning experience guided by the existing student learning outcomes. Working closely with public health professionals at existing internship agencies, alumni from the program, student interns, and program faculty developed a modified virtual internship composed of 6 components. The development of this modified virtual internship model was guided by previous research on the components of successful internships and the elements of high-impact learning practices.

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KEYWORDS

internship; remote learning; high-impact practice; COVID-19; public health education; learning outcomes; virtual learning; virtual internship; public health; health education; undergraduate education; virtual education

Introduction

The COVID-19 pandemic has brought unprecedented changes for college students. As SARS-CoV-2, the virus that causes COVID-19, is primarily spread through airborne transmission, institutions of higher education were noted as communities of concern, as dormitories have close living quarters, and classrooms are often set up in a way to allow collaboration rather than social distancing [1]. This concern was increased in densely populated areas where the pandemic was more prevalent. In March 2020, colleges began sending residential students home and making a shift to web-based learning, which brought about a sense of turmoil and loss for many. As COVID-19 persists, efforts to fully open campuses across the country have been hindered. The US Centers for Disease Control and Prevention suggested ways for institutions of higher education to reopen safely, which included staggered times in classrooms, limited gatherings, and proper use of face masks, noting that the safest option was offering virtual-only learning options, remote activities, and web-based events for students and faculty [2]. Research suggests that these changes evoke a

series of negative outcomes such as increased stress, anxiety, loneliness, academic burden [3,4]. In addition, closures and format pivots have led to lost opportunities for students, such as jobs and internships, as well as countless other challenges [5].

In response to the issues that arise due to what has been lost during the pandemic, many efforts have been made to retain high-quality and engaging learning experiences in a virtual format. In addition to coursework, other examples include experiences such as internships, which can better equip students for the workforce upon graduation. As many students have yet to gain this experience, the value of maintaining internship opportunities cannot be understated. More than half of graduating college students in the United States participated in at least 1 internship during their academic training [6]. Internship experiences are important, as research indicates that they can promote strong university-community partnerships [7]; they can improve interns' knowledge, research skills, and communication skills; and they can result in products that are useful to the internship site [8].

Purpose

The purpose of this viewpoint is to describe the process and experience of transitioning a traditional (in-person) internship to a virtual experience in the Public Health undergraduate program at a public university in New Jersey. The traditional internship is a 12-credit course where interns complete (1) an in-person, classroom-based, didactic experience; and (2) an in-person field placement.

Components of the Traditional Internship

Didactic Component

Prior to the semester in which the field placement occurs, students complete a 1-credit Introduction to Internship course. This in-person seminar-style course is designed to assist students in the development of the professional skills necessary for the successful completion of an internship in public health education. Topics of study include professional conduct, professional communication, resume development, interviewing skills, and job search strategies. Concurrent to the course, students work closely with the internship site coordinator to review the various types of public health education field placement settings and select their placement for the following semester. The internship site coordinator is a professional staff member who works in the academic department to coordinate and supervise the field placements.

During the 12-credit field placement semester, interns participate in classroom-based instruction necessary for the completion of a Capstone Project and faculty-led review for the certified health education specialist examination, administered by the National Commission for Health Education Credentialing, which interns take at the end of the semester. The Capstone Project provides interns the opportunity to demonstrate their understanding of public health education program planning and is the final assessment of their ability to develop a comprehensive health education program from conception through assessment, planning, implementation, and evaluation. While preparation for the certification exam does not demonstrate an intern's potential professional competence, it does provide both the

faculty member and the intern an important opportunity to gauge the intern's application and interpretation of knowledge.

Field Placement

The field placement is a supervised experience designed to allow interns to apply their newly acquired knowledge and skills in a professional work setting. The field placement occurs at an approved public health agency in the community where the intern works under the supervision of a public health professional, the internship site supervisor. Student learning outcomes center on the five following major themes: (1) exposure to the roles and responsibilities of an entry level public health educator in a public health agency; (2) examination of the ways in which theoretical concepts are applied to the realities of the field of public health education; (3) exploration of strategies for communicating and working with public health professionals; (4) self-reflection regarding career goals and lifelong learning; and (5) improvement of public speaking and audience management skills.

Interns spend approximately 28-30 hours per week at their field placement over the course of 15 weeks. During this time, interns work with their internship site supervisor, other partners at the agency, and stakeholders in the community to complete activities and projects that fall within the professional scope of practice for entry-level health education specialists. During this experience, 2 site visits are conducted by the internship site coordinator to review the intern's progress toward meeting the student learning outcomes of the field placement portion of the internship experience.

As the pandemic changed the nature of in-person instruction for institutions of higher education, an alternate structure for the internship needed to be developed. It was necessary that the new structure include robust activities and rich experiences that would substantively address the 5 student learning outcomes. The following is a description of the 6 components that were included in the virtual internship experience in the spring semester of 2021 to accommodate all students and provide what proved to be an experiential learning opportunity. A comparison of the components of traditional and virtual internships is displayed in [Table 1](#).

Table 1. Components of traditional and virtual internships.

Internships and components	Activities completed by intern
Traditional internship	
Didactic component (in-person)	<ul style="list-style-type: none"> • Capstone Project • Directed faculty-led preparation for credentialing exam
Field placement	<ul style="list-style-type: none"> • In-person placement project
Virtual internship	
Didactic component (web-based)	<ul style="list-style-type: none"> • Capstone Project • Directed faculty-led preparation for credentialing exam
Field placement	<ul style="list-style-type: none"> • Remote placement • Internship Site Project (new)
Professional development points (new)	<ul style="list-style-type: none"> • Minimum of 40 hours of professional development
Alumni mentorship program (new)	<ul style="list-style-type: none"> • Minimum of 8 mandatory mentorship sessions

Components of the Virtual Internship

Revised Didactic Component

The previously described faculty-led coursework was moved to a fully web-based format and maintained focus on the completion of the Capstone Project and preparation for the certification exam. Instruction for completing the Capstone Project was modified to suit the web-based learning environment. It included weekly content review using the University's web-based learning management platform, several required individual feedback sessions with the faculty member, and the frequent review of each intern's progress toward completion of the project. Web-based exam preparation consisted of faculty-supervised web-based study groups that met several times each week, weekly virtual practice exams, and faculty-recorded review sessions for each weekly exam.

Remote Field Placement

The Introduction to Internship course completed by students the semester prior to their field placement was moved to a web-based format and retained all the course content previously described. The main challenge during this semester was the identification of public health agencies that were willing and able to work with interns virtually. The internship site coordinator queried all existing internship site supervisors to determine if their agency had the ability to host an intern during the pandemic. As remote field placement sites were identified, it became apparent that many field placement sites would not have the capacity for a semester-long field placement, as was the case in pre-pandemic years. Therefore, the faculty decided to proceed with a shortened field placement experience that would be completed in 1 month, rather than the full semester. Furthermore, to increase the likelihood of meeting student learning outcomes and better manage the remote placements, fewer field placement sites were selected. Those that were selected agreed to take a different intern each month (1 each in February, March, and April). As a result, instead of having to recruit 60 unique field placements, only 20 were needed. This structure provided multiple benefits as the internship site

supervisors were able to develop a 4-week pattern of learning activities for the intern and then replicate that same pattern during the subsequent 2 months. Furthermore, this allowed the faculty to hand select those public health agencies who were best positioned to provide robust learning experiences in a truncated format. Finally, the new structure of the field placement assisted the internship site coordinator to quickly identify and rectify any emergent issues during an intern's field placement. This last point is particularly important because issues needed to be addressed quickly as the duration of the field placement was only 4 weeks.

Once field placement sites were identified, interns were assigned to a public health agency that aligned with their interests. Similar to what occurs during a traditional internship, during this virtual site rotation, interns met several times each week with agency staff and their internship site supervisor, completed assigned tasks, developed public health projects, learned about how the agency functions, attended work-related meetings, and engaged in other related learning activities. During the field placement, interns also worked on an Internship Site Project, a new addition to the virtual internship created to ensure that interns would have the opportunity to demonstrate the community-based health program planning principles that are central to the program's learning outcomes. The topic of this project was identified during the first 2 days of the field placement in consultation with the intern's site supervisor. The project was a collaboration between the intern and the agency and could be on any of the following topics: "Press release," "Strengths/Weaknesses/Opportunities/Threats analysis," "PowerPoint presentation," "Brochure," "Infographic," "Data analysis summary report," "Logic model," "Flyer," "Website development," and "Social-media posting."

Professional Development Points

Due to the shortened and web-based nature of the field placement, the faculty were concerned about the loss of opportunities for professional development, as the potential to attend professional meetings and conferences was limited during the pandemic. To highlight the need for public health educators

to remain updated on current public health information and developments and to emphasize the importance of lifelong learning, all interns engaged in professional development activities in the form of online trainings, webinars, and live virtual conferences. Interns earned “Professional Development Points” by participating in professional development opportunities selected from a faculty-created course catalog of free online opportunities offered by regional public health training centers, state and local health departments, and federal health agencies, such as the Centers for Disease Control and Prevention’s Train network.

When selecting professional development opportunities to include in the catalog, the faculty focused on choosing opportunities that reinforced issues around diversity, health equity, and social justice, as these topics are central to the program’s learning outcomes. Furthermore, opportunities for learning about topics that are not fully covered in the undergraduate curriculum (eg, maternal and child health, emergency preparedness, bioterrorism, and occupational health) were also included in the training catalog. The interns were required to complete a minimum of 40 hours of training, with 1 hour of training equivalent to 1 professional development point. As evidence of the completion of a professional development opportunity, the interns were required to complete a post-training evaluation to earn a Certification of Completion, which was then uploaded to their e-portfolio.

Alumni Mentorship Program

While the interns would be in contact with their internship site supervisor several times each week during their 4-week field placement, the faculty were concerned about the lack of periodic mentorship during the 2 months when the intern was not assigned to a field placement. To provide a consistent point of contact during the whole of the semester, each intern was assigned to a successful alumnus who served as their mentor. Alumni mentors were recruited by the program faculty the semester prior to field placement. All alumni mentors participated in an online training prior to the start of the field placements.

Over a 12-week period during the spring semester, the intern and the mentor met at least 8 times to review a predetermined set of discussion topics designed to help the intern gain a deeper understanding of what it is like to work in the public health field. Meetings with mentors were designed to help the intern better understand the transition from college to the professional public health work environment and identify the major issues that arise when working in the public health field. To facilitate these meetings, 8 discussion guides, which acted as a set of guiding questions that the intern should ask their mentor, were created. There was 1 discussion guide for each of the 8 required meetings. At the end of the semester, both the intern and the mentor provided written evaluations of this experience.

e-Portfolio

To provide a directed opportunity for self-reflection, career exploration, and preparation for the job search, all interns were required to compile an e-portfolio using the free web-based software system, WIX (Wix.com Inc). Training on how to

develop the e-portfolio was provided by a representative from WIX, and supervision of this component of the internship was provided by the internship site coordinator.

An e-portfolio serves several purposes. First, it is a digital compilation of student work upon which they can reflect on the tangible work they have produced. Second, it serves as a valuable means of assessment for faculty to comment on the strengths of the student’s work and areas for improvement. e-Portfolios can be accessed globally and are highly visible, a limitation of traditional portfolios. As they are easily accessible, e-portfolios can be shared with mentors, colleagues, and family members for review and comment [9]. Finally, e-portfolios can serve as a tool for students to compete for jobs after graduation. In their e-portfolio, the interns were required to include a resume, examples of prior classwork from preselected public health courses, the Internship Site Project, all earned professional development point certificates as proof of meeting the minimum number of required points, and the Capstone Project.

Discussion

Structuring the Virtual Internship

As the components of the virtual internship were being developed, careful attention was given to identifying what learning opportunities might be compromised in a virtual-only format and how program student learning outcomes would be met with revised and new activities. The shift of the fieldwork experience to the web-based environment called into question the quantity and quality of the interpersonal aspects that a traditional, in-person internship offers to student interns. The areas of primary concern were potentially lost opportunities to network, to be mentored by a professional within a physical work environment, and to demonstrate the skills and competencies necessary for entry-level health education practice.

The model that was developed for the remote internship experience considered these factors. The faculty wanted to offer experiences that, as best as possible, would mimic traditional work settings while at the same time offering alternate experiences for networking and mentoring; it also aimed to enable the intern to reflect on their skills and competencies and prepare for job search. As the importance of professional development and lifelong learning may be lost in the virtual context, it was critical that a professional development component be created for the virtual internship experience.

While developing the structure of the virtual internship, 2 frameworks were used to guide the selection of activities and experiences to ensure that the virtual internship would offer a high-quality experience that allowed interns to achieve the intended learning outcomes.

A “Pedagogy of Internships”

King and Sweitzer [10] describe 4 dimensions of learning and development that comprise a “pedagogy of internships.” These include professional, academic, personal, and civic dimensions. While each of these dimensions is readily apparent within and intentionally built into the traditional, in-person internship,

ensuring that each dimension was adequately addressed was a priority during the revision process.

The professional dimension of an internship allows for the exploration of career pathways, the application of skills in professional settings, and the opportunity to observe the patterns of work and behavior that occur in a potential work setting [10]. In the virtual internship model, this dimension is mainly addressed by the field placement experience and alumni mentorship program. The remote field placement exposes interns to the professional dimension directly through activities conducted by the agency to which the intern is assigned. Examples of these activities include virtual opportunities to interact with coworkers, attending online meetings, participating in the agency's programs, and receiving supervision from the internship site supervisor. Furthermore, the mentorship provided by the alumnus who works in the profession provides the opportunity to process the field placement experiences and explore career opportunities through a series of directed mentorship sessions.

The academic dimension of the internship focuses on the development of patterns of thinking that are consistent with the academic discipline, resulting in the intern's ability to think, in this case, like a health education specialist [10]. The academic dimension of the virtual internship is addressed by several components of the internship but is most clearly evidenced through the work that interns complete during the didactic component of the internship. Working closely with a faculty member, interns identify a topic for their Capstone Project and fully develop a public health education intervention from conception to completion. At the same time, the interns are involved in concentrated certification exam preparation, which serves to reinforce the concepts, frameworks, and skills necessary to think like a health education specialist. The interns are introduced to the importance of continuing education and lifelong learning through the professional development point requirement. Finally, the completion of the Internship Site Project during the field placement is yet another activity where the academic dimension of the internship is embedded.

The third dimension of an internship, the personal dimension, centers on the exploration of life skills beyond those necessary for professional practice. This includes the development of intellectual and emotional qualities such as flexibility, openness to differences, self-awareness, self-efficacy, and sound judgement [10]. The personal dimension is first addressed in the Introduction to Internship course. This experience exposes the student to many of the concepts related to working with others and effective communication. The virtual internship, through the field placement and mentorship components, supports interns in the continued exploration of these concepts. Topics of the mandatory mentorship sessions, for example, include goal setting, building rapport with coworkers, taking initiative, exploring conflict, and dealing with professional challenges. While the development of the e-portfolio provides interns an opportunity to document their academic achievements, it also allows interns to communicate other facets of their identity, such as hobbies, interests, personality characteristics, and life experiences.

The civic dimension addresses the ways in which professionals work with and serve society through their professional role [10]. This dimension was perhaps the area for which the faculty had the greatest concern when pivoting to the virtual format. The loss of three-quarters of the in-person time at the field placement called into question the quantity and quality of the interactions that interns would have with the individuals and populations served by the agency. As community engagement is a cornerstone of public health education practice, developing a mechanism for interns to engage in intentional ways with their constituents was critical. In the virtual internship, this was addressed through the completion of the Capstone Project and with the new requirement for the development of the Internship Site Project. The Capstone Project requires students to conduct a community needs assessment using multiple methods. Students engage in civic involvement through this process as they organize a program planning committee consisting of community members and involve the priority population in key informant interviews and focus groups. Observational research provides interns the opportunity to traverse the community as they complete windshield and walking surveys. As the pandemic limited the exposure to the community that interns typically have when completing these activities, the new Internship Site Project required that the intern work closely with their internship site supervisor to identify a discrete project that would directly involve the community in some way, while meeting some goal of the agency where the intern was placed. Examples of remote community involvement activities in which interns engaged include reviewing community needs assessment data with key stakeholders, involving community members in online planning meetings, creating digital health education materials with community input, health messaging via the field placement site's social media platforms, moderating web-based conferences, presenting data at virtual community coalition meetings, and working with community members to develop program evaluation instruments.

While moving toward the completion of the virtual internship model based on these 4 dimensions of learning and development, the faculty felt it was important to ensure that the new internship model remained a high-impact practice. Internships are routinely identified as being a high-impact practice. A high-impact educational practice is any teaching or learning experience that education research has shown to have a positive impact on students [11]. This analysis is relevant to those training health educators as well as public health agencies who will be hiring and working with these future professionals. Understanding what an intern may or may not have experienced during an internship can be helpful in determining future professional development needs.

Virtual Internship as a High-Impact Practice

A high-impact practice features 6 common elements. First, it requires work, where students are expected to engage in activities that require considerable time and effort. Next, it requires that students engage with others in an intentional way, including faculty, peers, supervisors, and coworkers. A high-impact practice also requires that students interact with and develop ways of working with individuals who are different from themselves. The provision of quality and frequent feedback

on performance in both formal and informal manners is another element of a high-impact practice. Students must also be provided with opportunities for the application of knowledge in new situations. Finally, a high-impact practice must provide students with the opportunity for self-reflection on their personal and professional development [12].

While each component of the virtual internship addresses most of the elements of a high-impact practice to some degree, it was important for the faculty to identify where they are addressed in a substantive and intentional manner. Table 2 provides a visual display of the components of the virtual internship that substantively addresses the 6 elements of a high-impact practice.

Table 2. Virtual internship as a high-impact practice.

	Capstone Project	CHES ^a exam preparation	Remote field placement	Professional development	Alumni mentorship	e-Portfolio
HIP ^b s are effortful	✓	✓	✓	✓	✓	✓
HIPs help students build substantive relationships	✓		✓		✓	
HIPs help students engage across differences	✓		✓	✓	✓	
HIPs provide students with rich feedback	✓	✓	✓		✓	
HIPs help students apply and test what they are learning in new situations	✓		✓			
HIPs provide opportunities for students to reflect on the people they are becoming			✓	✓	✓	✓

^aCHES: certified health education specialist.

^bHIP: high-impact practice.

Limitations

While conversion of a traditional internship to a virtual format described above maintained the key elements of a high-impact educational practice, there are some limitations to an exclusively online internship that deserve attention. First, revision of the traditional internship program into a virtual format was challenging as most elements of a virtual internship naturally rely on the use of remote technologies. Varied technologies were used in this virtual internship model, including campus-based learning management platforms, webinars, various presentation software, the opportunity to attend meetings and conferences online, working on team projects virtually, and meeting with mentors via social media platforms. Selection of specific technologies must consider issues such as accessibility, internet speed, as well as hardware and memory capacity. Alternate arrangements for students who do not have the necessary level of accessibility must be made available.

Furthermore, in a virtual internship experience, interns spend most of their time in front of a computer screen engaging in the various components of the program. As a result, the types of interpersonal interactions that naturally occur in an in-person environment are different in a virtual setting. This presents a particular challenge to educators when attempting to identify learning activities that closely replicate the work environment. Further research in this area is needed.

Moreover, as the intern is not able to engage with the community served by the field placement site in traditional ways, it is uncertain if the intern is fully able to understand the needs of the community. Therefore, a virtual internship must intentionally include opportunities for interaction with faculty, peers, mentors, and colleagues, as well as opportunities for deep engagement with community members so that interns develop a greater

understanding and empathy for the individuals in the community served by the field placement site.

Finally, as remote field placement sites were identified, it became apparent that a semester-long experience would not be possible, as most internship site supervisors indicated that they would not have the capacity for such a time-intensive field placement. This loss of contact hours is a limitation for which alternate activities needed to be identified. Mentorship opportunities and the emphasis on engagement in professional development opportunities were 2 ways in which the loss of contact hours was addressed in the virtual internship described in this viewpoint. The development of additional activities to address this loss of contact hours is warranted.

Suggestions for Further Study

There is no doubt that technology in educational settings will continue to play a major role in student learning. In recent decades, there has been accumulating evidence supporting the value of interventions delivered through digital technology, including but not limited to texting, telecommunications, and real time monitoring of symptoms and emotions [13-16]. Consequently, there is a need for individuals to learn and apply such technologies to help people make informed decisions about individual and community health [17-20]. The virtual internship, while prompted by necessity due to the COVID-19 pandemic, resulted in a wide range of benefits for students.

The benefits of a virtual internship include the ability for students to learn and practice skills related to communication with technology, the availability for interaction with supervisors with convenient timing and modalities, more frequent contacts at lower costs, and adapting to different (and potentially challenging) implementation contexts [21,22]. These benefits proved to be true in the development of the virtual internship described in this viewpoint.

In addition, the virtual internship experience enabled students to learn and practice new skills and for community members to benefit from education and outreach while helping to ensure the safety of students and the community, as well as reducing travel costs and increasing convenience. Finally, while the need for virtual learning opportunities were prompted by the COVID-19 pandemic, it seems almost certain that this need will likely persist, which increases availability and access to public health education for some populations who would otherwise suffer consequences from unanswered questions, and for students to become adept at skills that will be needed going forward [23].

Conclusion

The existing traditional undergraduate public health internship described in this viewpoint has undergone many modifications in its nearly 40-year history. However, no past revision was as extensive, necessary, or rapid as the transition to a virtual internship due to the COVID-19 pandemic. Guided by conceptual frameworks and the sincere desire on the part of the faculty to ensure that students received a robust learning experience, a virtual internship experience was developed that provided a well-organized and high-impact learning opportunity.

Conflicts of Interest

None declared.

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Viewpoint

Epidemiology, Secondary School Curricula, and Preparing the Next Generation for Global Citizenship

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Abstract

Because COVID-19 and other emerging infectious diseases are likely to play an increasingly important role in shaping American and global society in years to come, there is a need to prepare young people to make informed decisions in this changing global context. One way to do so is teaching and learning about basic principles of epidemiology in secondary schools. Improved understanding about the agent of infection, mechanisms of transmission, factors that increase or decrease susceptibility, place variation and environmental factors that facilitate or hinder transmission, reservoirs of infection (where the agent lives and multiplies), and when the disease is more or less likely to occur comprise the main facts about an infectious disease relevant to prevention and control. Improved understanding of these basic concepts could help future generations make informed decisions in a changing global context with emerging infectious diseases and a plethora of widely disseminated misinformation and disinformation. This viewpoint considers why learning about epidemiology in secondary school would benefit population health using COVID-19 as an illustration.

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KEYWORDS

COVID-19; epidemiology; secondary school; global citizenship; emerging infectious disease; public health; teaching; student; high school education; population health

Personal Choices in the Time of COVID-19

Controversies about personal choices and population health in the context of a global pandemic have been brought to the forefront as elected officials and citizens have taken sides regarding mandates for vaccination, mask use, and testing [1-5]. Concurrently, misinformation has been widely disseminated and has exacerbated public confusion as social media has changed the speed and reach of human communication [6-10]. COVID-19 and other emerging infectious diseases are likely to play an increasingly important role in shaping American and global society. This viewpoint considers why learning about epidemiology in secondary school would benefit population health using COVID-19 as an illustration.

As of the beginning of February 2022, there had been well over 5 million deaths worldwide from COVID-19 [11]. From the outset of the pandemic until the time of this writing (February 2022), the SARS-CoV-2 virus has disproportionately affected people based on age, race, and social determinants of health [12-15]. Additionally, COVID-19 has had universally negative global and domestic impact on education, the economy, physical and mental health, and family and community well-being [16-24]. COVID-19 is a global public health emergency [25].

As the novel coronavirus was spreading globally, another mass phenomenon was also occurring, namely, an *infodemic* [26,27]. Damage from misinformation (unintentionally incorrect or misleading information) and disinformation (intentionally incorrect or misleading information) is exacerbated by low levels of reading and health literacy, and a lack of understanding about disease transmission, prevention, and control [28-31]. It can be presumed that those who understand basic principles of

epidemiology have an advantage in interpreting the chaos unfolding around them, making more informed decisions about reducing exposure and susceptibility, and contributing to individual, family, and community health [32,33].

The US Centers for Disease Control and Prevention (CDC) defines epidemiology as the study of the distribution and determinants of disease in human populations and their subgroups [34]. There are person (ie, host) factors, place factors, and time factors that influence the distribution and determinants of diseases and other populationwide phenomena (eg, crime and violence or addiction). Epidemiology is distinct from medicine because, although they are both grounded in science, the former concentrates on individual treatment, while the latter focuses on populationwide prevention and treatment [35,36]. As such, epidemiology is the fundamental science driving public health decision-making [34].

Impetus for Change

Calls for including epidemiology in secondary school curricula are not new [37-42]. However, unlike any time in human history, COVID-19 revealed the challenge of educating the public as scientists scrambled to understand and create solutions in an environment where the people were routinely exposed to a plethora of misinformation and disinformation. There were several instances (eg, mask use and recommendations about the number of quarantine days required) when official government communications had to be revised or top governmental officials disagreed, which may have undermined public trust.

COVID-19 and other emerging infectious diseases are likely to play an increasingly important role in shaping American and global society in years to come. RNA viruses such as HIV, Chikungunya, and Dengue have been increasing over the last several decades [43-46]. This is also true for Lyme disease, which according to the CDC is affecting 20,000 to 30,000 people annually [47]. Coronaviruses in particular, of which there are hundreds, received attention from the severe acute respiratory syndrome (SARS) epidemic in Asia in 2003 [48] and Middle East respiratory syndrome (MERS) identification in the Arabian Peninsula in 2012 [49]. Mitigating the COVID-19 pandemic portends to change human interactions for the foreseeable future, and future generations need knowledge and health literacy skills to navigate inevitable epidemics in coming years.

There is strong justification for why learning about epidemiology in secondary schools is a sensible way to improve population health. First, to make informed decisions about reducing one's exposure and susceptibility to SARS-CoV-2 and its variants, young people need to comprehend the causes of the disease, modes of transmission, factors that affect susceptibility, and *what is and is not known given current scientific understanding*. Second, the study of epidemiology affords many opportunities to complement core curriculum such as history, language, science, and mathematics in an interesting and applicable way. Third, a lack of knowledge leads people to be more vulnerable to fake news, enables manipulative efforts of unscrupulous companies attempting to profit from a public health emergency, and can result in behaviors that compromise one's health and those around them. Fourth, greater

understanding about the science of epidemiology may help people distinguish differing points of view rooted in politics. We believe all adolescents should learn about the basic principles of epidemiology to be engaged citizens relevant to disease prevention and health promotion in general and with respect to emerging infectious diseases and COVID-19 in particular.

Basic Epidemiology of COVID-19

From the outset, we should be clear that our perspective on teaching about epidemiology is grounded in a health education lens. As such, the goal is focused on informed decision-making rather than particular behavior changes, with longer term aspirations related to quality of life and upward social mobility. There is a commitment to change by choice and to addressing the many social determinants of health that in too many cases constrain the ability to act on motivation. Another point to emphasize is that we focus on primary and secondary prevention because, despite historical investment in tertiary prevention (treatments after clinical disease has already occurred), primary and secondary prevention confer greater and more cost-effective benefits for population health.

Among the most basic facts when understanding any infectious disease is identifying the agent of infection, which for our purposes is SARS-CoV-2 and emerging variants [50]. There is also a need for basic understanding of mechanisms of transmission, which for COVID-19 include both direct and indirect possibilities. The mechanisms by which SARS-CoV-2 may be transmitted through direct contact would-be proximal contamination from someone coughing or sneezing directly on to another person while in close range [50]. During the early part of 2020, emphasis was placed on indirect transmission through fomites (ie, inanimate objects) [51], and less emphasis was placed on airborne aerosols and droplet transmission [50], though it became increasingly clear that the latter is responsible for the majority of propagated (person-to-person) transmission [50]. The implications here are for individuals to avoid densely populated and poorly ventilated indoor spaces, to social distance, and to use effective masks consistently and correctly when in poorly ventilated crowded spaces [50]. Another important basic fact is that humans infected with the disease are the major reservoir of infection [50]. It is also useful to understand the natural history of the disease, including the predisposing, presymptomatic, clinical, and convalescence stages. A centrally important fact is when an infected individual is most capable of transmitting the virus to a susceptible person, which in the case of SARS-CoV-2 can range from before symptoms appear to the ensuing days after. There are many important biological questions regarding how the virus is mutating and the extent to which variants are more pathogenic (contagious), virulent (proportion of severe and fatal cases), or resistant to vaccines [52].

Person Factors

A key aspect of descriptive epidemiology includes describing the characteristics of people that increase or decrease the likelihood of disease occurrence. Person (or host) factors are traditionally classified into biological, physical, and social

characteristics, but from a health education lens, behavioral, cognitive, and social/emotional characteristics are also important. The main biological factor related to COVID-19 is age, with older people at increased risk for more severe morbidity and mortality [53]. The main physical host factors are comorbidities (eg, cancer, chronic kidney disease, chronic lung diseases, certain neurological conditions, diabetes, and other diseases and treatments that may impede immune response) [54]. Social factors such as education and employment opportunities, income, and housing have a substantial effect on quality of life, longevity, and social mobility; this is exemplified in COVID-19 by the increased risk for people who have the lowest levels of income and education living in crowded, poorly ventilated spaces and having employment as essential workers [55-57]. According to the CDC, “the percent of Hispanic or Latino, non-Hispanic Black, and non-Hispanic American Indian or Alaska Native people who have died from COVID-19 is higher than the percent of these racial and ethnic groups among the total U.S. population” [58]. Person risk factors for COVID-19 of great interest are individual behaviors such as seeking and obtaining vaccination [51], social distancing [50], correct use of effective masks [50], and handwashing [50]. In turn, informed decision-making about these behaviors is influenced by cognitive factors such as awareness of controversial issues, up-to-date knowledge, and understanding that what is considered up-to-date has changed quickly in the COVID-19 pandemic. In turn, social/emotional factors such as fear, denial, disgust, and other feelings and emotions have been implicated in shaping individual choices as well [59-63].

Place Factors

Place is centrally important to almost all diseases and to population health. Epidemiologists use mapping to describe where disease is more or less common. Inter- and intra-national comparisons, urban/suburban/rural variations, and localities with highest and lowest rates of disease provide clues about causation and where to prioritize. Once observing place variations, for example, through mapping, epidemiologists explore how the biological, physical, and social environmental factors may influence disease distribution. What environmental characteristics foster versus destroy pathogenic agents? Many bacteria and viral agents of infection cannot survive in or are washed away by soap and water; optimal hand hygiene is one the best ways to prevent transmission of many pathogens, including SARS-CoV-2 [64]. Consideration of the physical environment might call students' attention to the importance of ventilation and how aerosols do or do not disperse within open air versus a crowded, poorly ventilated space [50]. As with most important population health issues, the social environment plays a dominant role in shaping morbidity and mortality outcomes. Social determinants have influenced risk of both infection and outcomes for COVID-19, with individuals with the lowest levels of income and education at highest risk [58]. Another example of how the social environment influences population health is investment in the scientific infrastructure that is needed to continue tracking and sequencing variants of SARS-CoV-2 [11]. In spring 2020, mapping showed that New York was the epicenter of COVID-19 in the United States.

The situation during March and April 2020 in New York City and New York State was dire and, sadly, was repeated in cities throughout the United States in the ensuing months, with health care systems becoming overwhelmed and the inability to manufacture and distribute personal protective equipment [65]. The pandemic has caused substantial negative effects on economies worldwide, especially those relying on population contact and movement (eg, transportation, tourism, food services, or event and entertainment) [16]. Politics and legislation provide many examples of contentious issues balancing the rights of individuals against harm to the community, and these issues play out in different ways in different states in the United States and globally. In places such as the United States where there is a large heterogeneous mix of cultural groups, challenges regarding what is and is not acceptable in terms of mask use, testing, containment, vaccination, and treatment seem inevitable.

Time Factors

Another element of descriptive epidemiology that warrants consideration is time factors, such as secular trends, seasonal variation, cyclical patterns, and short-term spikes, as well as when an infected individual is most likely to transmit disease to others. The tracking system built by Johns Hopkins University continues to show where COVID-19 rates are increasing, decreasing, or stable in different localities and how well prevention efforts are working to reduce disease incidence. For example, data plotting the occurrence of new cases, hospitalizations, and mortality can help people understand the risk level in their community and influence highly consequential policies such as closing schools and businesses. Recognition that SARS-CoV-2 is most pathogenic (able to infect others) on the day before and in the days following the onset of symptoms is essential knowledge for informing guidelines for testing, isolation, quarantine, and community mitigation.

Basic Metrics

Calculating primary metrics used in epidemiology such as incidence, prevalence, morbidity, and mortality rates only requires basic arithmetic. Likewise, understanding the ability of screening (testing) programs to distinguish people with and without the disease (sensitivity and specificity, respectively) can improve public understanding and decision-making. Another important health literacy skill is interpreting disease maps. These maps not only show where a disease is more or less common but also provide clues about the person and environmental factors that account for such variations. Herd immunity is another metric, which could be useful in helping individuals understand how and why their choices may cause harm to others.

Prevention and Community Mitigation

Addressing any infectious disease epidemic generally requires multiple strategies, including reducing susceptibility and environmental exposures, disease surveillance, and eradication. For COVID-19, reducing susceptibility through vaccination and reducing environmental exposure by interrupting transmission are the most efficacious for community mitigation. These, in turn, require behaviors that rely on individuals'

decisions. Early detection, containment, and treatment are also essential elements of a comprehensive approach.

Reducing susceptibility through vaccination has been one of the most stunning examples of public health breakthroughs in the last century, eradicating smallpox and substantially reducing many infectious diseases that took a large toll on human populations globally. Development, emergency use authorization, and distribution of vaccines to prevent COVID-19 are a remarkable example of scientific progress. At the same time, there has been an active and influential movement against vaccination, which has undermined uptake levels. Students have a right to know the benefits and risks of various vaccinations to help them make informed decisions on a personal level.

A second key strategy for prevention and control of infectious diseases in general and COVID-19 in particular involves reducing environmental exposure by interrupting transmission. This is mainly accomplished through isolation (separating sick people from others), quarantine (separating those exposed to see if they become sick), social distancing, correct use of effective masks when in close proximity of others, and avoiding or taking extra precautions when in poorly ventilated enclosed spaces.

Although reducing populationwide susceptibility and environmental exposures are most effective to prevent disease from occurring, early detection, containment, and treatment are also essential elements of an effective overall public health response. There are a range of testing and contact tracing programs, each with its limitations. Testing and contact tracing has enabled identification and containment of hot spots and is an integral part of a more comprehensive strategy. The efficacy of alternative treatment approaches continue to be implemented and evaluated.

Improved understanding about the agent of infection, mechanisms of transmission, characteristics of people that increase or decrease susceptibility, environmental factors that facilitate or hinder transmission, reservoirs of infection (where the agent lives and multiplies), and when the disease is more or less likely to occur comprise the main facts about an infectious disease that can help contribute to prevention and control. To the extent that secondary school students are well informed about these topics, they will be in a better position to make informed decisions and contribute to prevention and community mitigation.

Integrating Epidemiology into Secondary School Curriculum

The interdisciplinary orientation of epidemiology provides ample opportunities for practicing foundational skills in traditional academic subjects. Knowledge of the basic principles of epidemiology should be considered a cross-cutting topic that can help explain and reinforce academic skills across the curriculum. The following examples illustrate ways to integrate epidemiology into teaching and learning about history, language, science, and mathematics.

History

The origins of epidemiology have been traced back to Hippocrates' Humoral Theory of Disease around 400 BC as one of the first people to use rational versus supernatural thought to explain sickness and death. Galen of Pergamon expounded on Hippocrates theory in subsequent centuries along with Girolamo Fracastoro, Antonie van Leeuwenhoek, Ignaz Semmelweis, James Lind, Edward Jenner, John Snow, Louis Pasteur, and Robert Koch, among many others who contributed to the evolution of germ theory. More recent history tells of the remarkable discovery of antibiotics and vaccinations, which saved countless lives from historical scourges such as anthrax, bubonic plague, smallpox, cholera, measles, polio, and most recently COVID-19. There is an abundance of historical literature demonstrating how infectious diseases played a greater role in the outcome of war than military strategy [66,67]. Sadly, the role of how disease and famine continue to influence global populations provide examples of how studying peoples' culture and history influences individual, family, and community health. One reason why epidemiology provides a fruitful lens through which to view history is that one of the main premises of epidemiology is that understanding factors that affect populations (and population health) requires recognition of a wide range of possible influences, which is clearly applicable when trying to understand and interpret historical records.

Language

Not only does literature related to epidemiology provide opportunities for improving comprehension and vocabulary but it also provides examples of heroes throughout human history who devoted their lives to saving populations, how microbes have changed the course of war and geopolitical human history, and the extreme loss and human despair that disease has and continues to cause. Examples can be drawn from both fiction and nonfiction, for example, *Masque of the Red Death* (Edgar Allan Poe), *The End of October* (Henry Parsons), *Love in the Time of Cholera* (Gabriel García Márquez), *The Velveteen Rabbit* (Margery Williams), *The Plague* (Albert Camus), *The Ghost Map* (Steven Johnson), and short stories such as Stephen King's *Night Surf* or Boyle's *After the Plague*. Lepore's [68] article, *What Our Contagion Fables Are Really About*, reminds us that books can serve as a "salve and a consolation" especially in quarantine. Although the news and media throughout time covers the austere circumstances brought on by epidemics, Lepore [68] reminds us that "the existence of books, no matter how grim the tale, is itself a sign, evidence that humanity endures."

Science

The history of science is a phenomenal aspect of human evolution with respect to epidemiology. An example of a relevant narrative would be how humoral and miasma theories of disease fell by the wayside starting in the 1600s and culminating in greater acceptance of germ theory in the early 20th century. The concept of contagion and development of the microscope warrant study within a class on epidemiology, as would global epidemics throughout history such as the bubonic plague; cholera; smallpox; and more recently Zika, Ebola, MERS, and SARS, among other emerging infectious diseases

that originated as zoonoses (transmissions from animals to humans). The 20th century topics might cover development and widespread use of antibiotics and vaccines for various diseases. New frontiers in the 21st century, being driven, in part, by epigenetics, are being fueled by billions invested to improve understanding about the biological, physical, and social interactions between populations (their genomes and oral and gut microbiomes) and the environment, as well as how interactions between microbial and human populations and the environment, including climate change, are shaping emerging infectious diseases and human health. Basic understanding of scientific methods could help individuals distinguish more from less credible messages and communications.

Mathematics

At the heart of epidemiology is counting and making quantitative comparisons. In the 1600s John Graunt developed the Bills of Mortality in London, precursor to modern day vital statistics and global disease surveillance. These data are the basis for key aspects of domestic and global disease prevention and health promotion. Epidemiology can reinforce basic arithmetic skills by helping students learn how to calculate sensitivity, specificity, and predictive values of screening tests, and calculate relative and attributable risk and odds ratios. Basic understanding of public health metrics such as infant mortality, life expectancy, herd immunity, dependency ratios, crude, specific, and adjusted rates all provide opportunities for students to learn basic arithmetic skills while at the same time improving understanding about probability and risk, demography, and how risk and protective factors vary between population subgroups. One of the main proficiency areas in secondary school mathematics is quantitative comparisons, which is a key concept underlying descriptive epidemiology whereby disease rates of different subgroups are compared to generate hypotheses about possible causes.

Discussion

What to include in secondary school curriculum is a value laden decision. In most countries, secondary school curricular decisions are handled centrally. In the United States, the conceptualization and design of curricular scope and sequence is decentralized at state and local community levels. Decentralization can be advantageous because it can help adapt education to local social and cultural contexts, and move away from standardized accountability metrics that only measure narrowly defined abilities. At the same time, decentralization created challenges for ensuring that students learn content and skills to reduce their exposure and susceptibility during the COVID-19 public health emergency [69].

We believe that improved understanding about epidemiology in general and about COVID-19 in particular can help people make informed decisions. This includes basic epidemiological facts about COVID-19: caused by the SARS-CoV-2 virus and variants; primarily spreads through aerosol and droplet infections but can also be spread through a variety of direct and indirect mechanisms; virus mainly lives and multiplies in other people; virus cannot survive if exposed to soap and water; when

presymptomatic and symptomatic pathogenicity (ability to infect others) is highest; and perhaps most importantly, that individuals' decisions within an unequal and unfair set of constraints are the main determinants of becoming infected. What people know and are able to do plays a central role in risk reduction.

The emergence of SARS-CoV-2 and other infectious diseases result from human encroachment and destruction of the environment [70]. All indications sadly point to increased likelihood that zoonotic diseases will continue to evolve and infect humans. Now is an opportune time to rethink educational priorities to meet students' needs as global citizens.

Epidemiology uses science-based evidence of disease patterns. Augmenting curriculum in history, language, science, and mathematics can help students learn useful health literacy skills while developing mastery in the subject. Basic understanding about epidemiology and public health requires awareness of the many ethical issues encountered in public health policy, laws, and practice. Of value to any young person's education would be the ability to juxtapose individual freedoms versus public good, conflicting loyalties between funders and employers versus people served by programs, and the extent to which public health goals create agency and independence versus unsustainable dependency. Such education would align well with global citizenship.

Improved understanding about epidemiology is helpful for students because it will enable them to make more informed decisions during public health emergencies such as the COVID-19 pandemic and more generally for improving health literacy. Health literacy is predicated, in part, on searching for and evaluating the veracity of an increasingly growing amount of digital information. Distinguishing more from less credible information has become much more challenging in a context where digital communications instantly reach hundreds of millions of people and often contain misinformation and disinformation with respect to COVID-19 and a wide range of infectious diseases and other public health problems [71-76].

Epidemiology provides a useful framework and abundance of real-life examples for learning and practicing foundational skills related to history, language, science, and mathematics. In the current pandemic, students would benefit from improved understanding about how to calculate and reduce risks through practicing certain behaviors, and for more advanced students, simulations could be run illustrating the consequences for different proportions in a community behaving in different ways (eg, resulting in different levels of herd immunity).

The history of epidemiology shows how brilliant thinkers were able to view health problems from multiple perspectives, rebel against the dominant thought paradigm, and discover scientific truths that saved lives [77]. One of the most stunning public health findings in the last several decades is recognition that education is one of the most powerful predictors of well-being, social mobility, and longevity [78,79]. Now is an opportune time to reimagine education to help students make informed decisions in a rapidly changing global context.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention

MERS: Middle East respiratory syndrome

SARS: severe acute respiratory syndrome

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Review

Using Social Media to Understand Web-Based Social Factors Concerning Obesity: Systematic Review

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Abstract

Background: Evidence in the literature surrounding obesity suggests that social factors play a substantial role in the spread of obesity. Although social ties with a friend who is obese increase the probability of becoming obese, the role of social media in this dynamic remains underexplored in obesity research. Given the rapid proliferation of social media in recent years, individuals socialize through social media and share their health-related daily routines, including dieting and exercising. Thus, it is timely and imperative to review previous studies focused on social factors in social media and obesity.

Objective: This study aims to examine web-based social factors in relation to obesity research.

Methods: We conducted a systematic review. We searched PubMed, Association for Computing Machinery, and ScienceDirect for articles published by July 5, 2019. Web-based social factors that are related to obesity behaviors were studied and analyzed.

Results: In total, 1608 studies were identified from the selected databases. Of these 1608 studies, 50 (3.11%) studies met the eligibility criteria. In total, 10 types of web-based social factors were identified, and a socioecological model was adopted to explain their potential impact on an individual from varying levels of web-based social structure to social media users' connection to the real world.

Conclusions: We found 4 levels of interaction in social media. Gender was the only factor found at the individual level, and it affects user's web-based obesity-related behaviors. Social support was the predominant factor identified, which benefits users in their weight loss journey at the interpersonal level. Some factors, such as stigma were also found to be associated with a healthy web-based social environment. Understanding the effectiveness of these factors is essential to help users create and maintain a healthy lifestyle.

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KEYWORDS

obesity; web-based social factors; systematic review; social-ecological model

Introduction

Background

The obesity epidemic is a significant public health challenge in modern society. The growing prevalence of obesity and its implications in public health make it one of the most common, dangerous, and costly diseases globally [1]. One-third of the global population, over 2 billion people, are overweight or obese [2]. Obesity rates reached 39.8% among adults and 18.5%

among youth in the United States in 2016, a significant increase in these age groups since 1999 [3].

Obesity is recognized as a major risk factor for population health [4] because of its association with social stigma [5], chronic diseases [6], medical complications [7], reduced life expectancy [8], lower quality of life [9], and higher health costs for individuals [10] and the government [11]. The World Health Organization suggests that obesity is likely the cause of chronic diseases such as hypertension, type 2 diabetes, cardiovascular

diseases, and some cancers [12]. Women with obesity are more vulnerable to infertility, miscarriage, and other childbearing-related complications [7]. Obesity in childhood also increases the risk of other diseases and may even be carried through adolescence to adulthood [6]. Obesity also increases individual and fiscal expenditure. The annual medical cost of obesity in the United States was US \$147 billion in 2008, and the annual medical cost for an individual with obesity was estimated to be US \$1429 higher than that for individuals with a healthy weight [11]. Obesity may affect human development [8], suggesting that its prevalence could be detrimental to human life expectancy in the 21st century, reversing the increase in life expectancy seen in the 20th century. Global efforts are paramount in controlling the obesity pandemic.

Social Factors as Important Drivers of Obesity Pandemic

Recent developments in research have identified two main factors—exercise and diet [13,14]; however, there are other factors associated with obesity [15]. According to a study, a developed society is the leading cause of the current obesity pandemic in that it creates an obesogenic environment [16]. An obesogenic environment is defined as an environment where there is easy access to inexpensive and calorie-dense food, excessive food intake, insufficient physical activity, and inexpensive nonphysical entertainment [7,17]. An obesity epidemic with interconnected social factors could result in an obesity pandemic.

Social factors are defined as factors that affect an individual's lifestyle [18]. These influences have a significant effect on people's health-related behaviors [13,19]. Thus, social factors play an important role in the spread of obesity. For example, a study conducted by Christakis and Fowler [20] tracked a densely interconnected social network of 12,067 people for 32 years. It showed that a person's chances of becoming obese increases by 57% if he or she has a close relationship with someone who is obese. Furthermore, the self-perception of weight can also be influenced by peers. Previous research indicates that children and adolescents who are surrounded by many overweight peers might have inaccurate perceptions of their weight and underestimate it [21,22].

With the recent ubiquity of social technologies, these peer effects are expanding to the general public. A recent study on a large-scale social network showed that social influences also affect collective public health behaviors, such as habits associated with obesity and tobacco use [23]. Similarly, examining user interactions on social media has proven useful in understanding public attitudes and perceptions of health topics [24]. As a result, it is timely and imperative to understand web-based social factors in a web-based social environment to counteract the obesity epidemic.

Social Media for Understanding Obesity

Social network websites serve as web-based services that allow individuals to build social profiles, form connections with other users, and view other profiles in the system [25]. Popular social network websites such as Facebook, Twitter, and Reddit have attracted millions of users since they were first introduced in

2004, 2006, and 2005, respectively. A 2018 survey of US adults found that the social media landscape shows a long-standing trend of continuous use throughout the day and newly emerging narratives (eg, posts, tweets, and images) [26]. For example, 69% of US adults use at least one social media website; 74% of Facebook users and 46% of Twitter users access the website daily [27]. Internet integration may offer possibilities for accessing obesity-related information, including weight loss, obesity diagnosis, and weight management.

Social media platforms have the potential to change users' health behaviors. An increasing number of users' social interactions are publicly shared on the web, making social media a vital data source for studying public health, especially *lifestyle diseases* such as obesity [24]. Chang et al [28] systematically reviewed the use and impact of social media in web-based weight management and demonstrated that social media plays a role in retaining and engaging participants in weight management.

Review Aim

The primary aim of this review is to extend the knowledge on the influences of web-based social factors concerning obesity-related behavior to better inform future studies in examining interventions using social factors. This is the first study to systematically review the effects of web-based social factors on obesity-related behaviors in the web-based social media environment. Other related systematic reviews have examined obesity, social media use, and the effectiveness of social media in intervention studies for obesity prevention [29,30].

Methods

Data Sources and Search Strategy

We used three popular electronic databases—PubMed, Association for Computing Machinery (ACM), and ScienceDirect—in this review. PubMed is known as a comprehensive database in biomedical research [31]; the ACM database is maintained by the world's largest scientific and educational computing society [32]; and ScienceDirect provides access to an extensive database of scientific and medical research [33]. The search strategy in ACM and ScienceDirect was designed by combining the search terms social media and obesity. The full search string in ACM and ScienceDirect was *Social media AND obesity*. The MeSH (Medical Subject Heading) terms *social media* [34] and *obesity* were used in the PubMed search. The full search string in PubMed was *Social Media (MeSH) AND Obesity (MeSH)*. All searches were completed on July 5, 2019.

Study Selection and Screening

This study aims to review studies that used social media with elements of social factors for obesity research. To meet the review aim, we defined social media in this study as an internet-based platform allowing individual users to create and exchange content (eg, blogs, web-based discussion boards, and Twitter) based on a previous study by Kaplan and Haenlein [35].

All studies that met the inclusion criteria were included in this review. Inclusion criteria were defined as follows: (1) obesity was the primary study topic, (2) social media served as the main platform, (3) social interactions were incorporated, (4) the study was published in the peer-reviewed literature, and (5) the study was in the English language. To understand how web-based social factors can influence people in understanding or improving weight management outcomes, we either set organic or encouraged social interaction as an inclusion criterion. Other types of scholarly articles were excluded: comments, systematic reviews, conference reports, and letters. Moreover, design studies that only suggested the use of social media, such as a randomized controlled trial study design by Willis et al [36], were excluded.

On the basis of title and abstract, 2 independent reviewers first screened all articles. All articles were categorized into (1) included, if the paper met the inclusion criteria, (2) excluded, if this paper did not meet the inclusion criteria, and (3) needed full-text review, if the abstract could not provide enough information or was not available. A paper was then excluded at the screening stage if the 2 reviewers agreed to exclude it

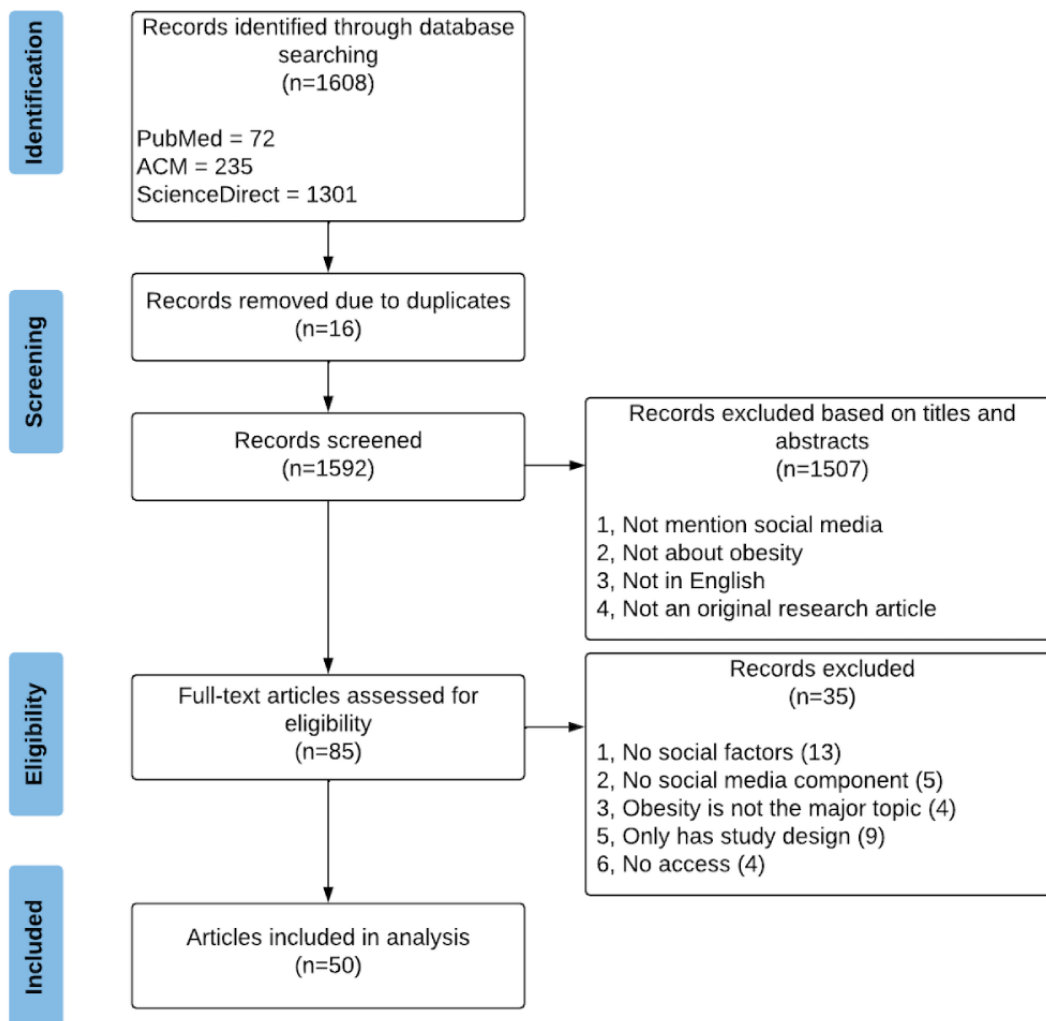
based on title and abstract. Except for the excluded articles, all articles were moved to the eligibility stage, which required 2 reviewers to perform a full-text review. At the eligibility stage, any disagreement was discussed to form a consensus. The third reviewer, a tiebreaker, was introduced if consensus could not be reached.

Results

Overview

In total, 1608 studies were identified from our selected databases and search strategy, of which 16 (1%) were duplicated (Figure 1). After removing the duplicates and assessing the title and abstract, 93.72% (1507/1608) of the articles were excluded, and 5.29% (85/1608) remained for full-text reading. A full-text examination excluded 2.18% (35/1608) of the articles. In total, 3.11% (50/1608) of the articles met our inclusion criteria and were included in this systematic review. We summarized the internet-based social factors and their corresponding effectiveness in the following section. Furthermore, we examined how different social media platforms were used in previous studies.

Figure 1. Study flow.



Web-Based Social Factors

Overview

Traditionally, obesity is linked to behavior at the individual level, such as overeating and lack of exercise. However, new studies have shed light on social factors that contribute to obesity-related behaviors. We investigated web-based social factors in this study. There is no universal definition of web-based social factors in the literature. Here, we defined web-based social factors as social factors that exist in web-based social environments and have the potential to affect users' behaviors. We focused on identifying web-based social factors and understanding their potential effect on users' obesity-related behaviors. We found 10 different web-based social factors used and mentioned in previous studies. The most common to the least common web-based social factors were social support and social ties, gender, geo-cultural factors, stigma, obesogenic environment, source credibility, school environments, social movements, policy, and social sharing behaviors. We will first discuss the most frequently mentioned social factors, social support and social ties.

Social Support and Social Ties

Social support is emotional comfort and material resources provided by peers connected in a social network. It is the most frequently mentioned factor in previous studies related to our study aim. Users of social media platforms can exchange social support. They view social media as a good place for finding and receiving social support and locating information platforms for those interested in changing their lifestyle and eating habits [37]. A previous study found that users who tried to use Twitter to record their weight loss journey reported receiving more social support from the internet-based environment than from their real families and friends [38].

In web-based communities, we identified two types of social support: informational support and emotional support. Informational support includes sharing resources and providing professional feedback through social networks [39-41]. Emotional support primarily comes from peers. Social culture and the concept of social media encourage users to be active with other users. In some intervention studies [40], program participants were instructed to discuss progress, issues, and goals with other participants using social media platforms. Through various platforms or programs, peer encouragement [42], peer support [43,44], and peer pressure [41] were identified.

Moreover, two platforms were found to be the major conduits for social support: blogs and Facebook. Savolainen [45] asserted that the main strength of web-based blogs is that they can provide emotionally supportive forums for sharing opinions. From a blogger's perspective, Leggatt-Cook and Chamberlain [43] learned that bloggers hope to create and build a community that will support them and their attempt to lose weight. Facebook's private groups have been widely used in intervention studies. These groups were created to share resources and serve as a platform for participants to communicate [40]. In a study by Waring et al [41], first-time mothers were often found to seek out other mothers' advice and support from Facebook

groups. Twitter is primarily used to collect public opinions, but it was also found to offer the opportunity to create a supportive network [39].

Social support is suggested to be very important for users who try to lose weight. Lack of support had a negative effect on weight loss. Pappa et al [44] found that the peer search for support was inversely associated with weight loss. Even in the anonymous platform Reddit, the authors observed an increasing number of users returning to the community, and greater weight loss was reported from users if they received support in the community [42]. The effectiveness of social support in weight loss has been reported to be positive. He et al [46] found that social support positively correlated with weight loss. Jane et al [37] also found that individuals had better health outcomes if supported by professionals. Chomutare et al [47] mentioned that their study found a positive correlation between web-based participation and weight loss by analyzing data on older women with obesity who were active in a web-based community. A study conducted on individuals with mental illness also found that weight loss was associated with perceived peer-group support because the participants felt compelled to pursue weight loss goals [48]. We also found a detracting study on the influence of social support on BMI reduction. An experiment on college students showed that students in the Facebook support group did not show a significant difference in BMI compared with the control group at the end of 24 months. However, the author reported that students in the intervention arm showed a significantly greater increase in the number of appropriate weight control strategies than those students who were not in the support group [49]. Similarly, a meta-analysis by Merchant et al [40] suggested that interventions that provide participants with professional support during their diets and physical activities are more effective than those that do not.

Social support is understood through social ties, the connections among peers. The social tie theory concludes that the probability of a person becoming obese increases if friends with obesity surround them [20]. A study by Phan et al [50] adopted the social tie theory in their experimental study, confirming that individuals tend to perform similar lifestyle behaviors as their friends from the internet-based environment. Social ties also affect received social support. Social support has a negative correlation with weak ties (ie, unfamiliar individuals) in the context of weight control. Chen et al [51] reported that participants found community competition and support from strong ties (eg, couples and parents) were motivating, whereas support from unfamiliar participants was demotivating.

Gender

We identified gender as a web-based social factor because we found 5 previous studies [39,41,52-54] indicating that women and men have different web-based social behaviors regarding obesity. Abbar et al [52] showed that women are often more willing to share information on the web, such as preparing low-calorie food, which was also supported by other related studies [55,56]. Women were more likely to share their family members' weight management experiences on social media. Only mothers of a childhood weight loss camp were willing to use social media to receive informational support and post their

children's progress [39]. In a Twitter-delivered weight loss program, Waring et al [41] found that a great proportion of women read each other's progress. These participants were reading other people's tweets more than posting their own progress. Women were critical when self-evaluating their weights. In a study by Kuebler et al [53], Yahoo! Answers data found that most women, when asked about their self-perspective on their weight, tended to overestimate. Web-based social norms show the characteristics of women and men that are socially constructed.

Geo-Cultural Factors

Users' health behaviors occur in a setting composed of web-based, social, and cultural environments. Geo-cultural factors explain how users' behaviors on the web are affected by their physical surroundings. Several studies have found that social media data can provide insight into the health conditions of US residents. A total of 3 studies by Gore et al [57], Culotta [58], and Abbar et al [52] used Twitter data to predict county-level health. Abbar et al [52] discovered that the calories of food mentioned in tweets correlated to the county's obesity rate. Gore et al [57] found that the tweets in areas with lower obesity rates had three features: (1) tweets had more positive sentiments, (2) more tweets mentioned fruits and vegetables, and (3) physical activities of any intensity were more frequently mentioned. Culotta [58] reported similar findings that negative emotions were found in tweets from areas with high obesity rates. Garimella [59] further validated the feasibility of using image data to track public health concerns. They found that user- and machine-generated image tags on Instagram could be used to forecast the county's obesity rate. By analyzing pictures on Instagram, Mejova et al [60] found that the number of fast-food restaurants in a county in the United States positively correlated with local obesity rates. They further revealed that locally owned restaurants with dietary and nutritional alternatives were more popular in areas with lower obesity rates. Another interesting finding from Weber and Mejova [61] showed that the percentage of profiles with a valid profile picture was higher in areas with a higher obesity rate. Another branch of the geo-cultural factor is involved in culture and religion. After a weight loss camp in Qatar, a study concluded that the religious month and cultural orientation were critical to the outcome, affecting users' web-based recording behavior [54]. These findings suggest that users' web-based obesity-related behaviors are related to location-specific environments.

Stigma

Stigmatization and associated discrimination—sometimes referred to as weight bias—affect the individual's mental and physical health and social behavior. Studies on Western culture highlight the stigmatization of individuals with obesity, showing that they are stigmatized and associated with laziness, low self-control, and moral laxity [55]. Social media is used to propagate social stigmatism, mainly in the form of fat-shaming, a practice of humiliating and criticizing overweight individuals on social media [62]. Mejova et al [62] found that up to 27.6% of non-URL tweets mentioning obesity were fat-shaming, with some self-hate messages. In a recent study by Karami et al [63],

Twitter users often coupled exercise-related terms with obesity. This could also indicate that individuals associate exercise and self-regulation (or lack of it) as the main cause and solution for obesity. Although the social stigmatism of obesity is widespread on the web, individuals have also pushed back social stigmatism using social media platforms. People expressed anger caused by the stigma of obesity on Twitter in a retaliatory manner to address widespread stigmatization against overweight and obese people [64].

Stigma has been found to undermine a user's mental health, but its effects on users' web-based interactions remain inconclusive. A person's mental health status revealed by social media data indicates that a user's mental health is affected by their social surroundings. A study by Kuebler et al [53] suggested that people with obesity residing in counties with higher levels of BMI have better physical and mental health than people with obesity living in regions with a low obesity rate. Another 2 studies investigated the impact of weight stigma by comparing web-based behavior between users with normal weight and users with obesity. May et al [65] did not find weight bias in their study because weight status had no effect on the rate of interactions and follow backs. However, a different study by Weber et al [61] found that users who were labeled as overweight had fewer followers and fewer directed tweets. Although stigmatization may not affect the user's web-based behavior, the widespread stigmatization on social media will diminish a user's mental health.

Obesogenic Environment

An obesogenic environment refers to an environment that promotes high-energy intake and sedentary behavior [66]. By analyzing the content users post on social media, we found that an obesogenic environment is one of the major causes of the obesity pandemic. A content analysis of frequent retweets about obesity by So et al [64] revealed that four major social determinants of obesity are discussed on Twitter: cheap and unhealthy food, school food systems, portion sizes, and dysfunctional food systems. Among these determinants, easy access to cheap, calorie-dense foods had the highest tweeting rates. This finding suggests that the web-based information environment is changed by the physical obesogenic environment by informing users' behaviors.

Source Credibility

Credible health information sources are persuasive [67]; however, some social media obesity-related information was found to be incomplete or inaccurate. A low-credibility source could exert a negative influence on users' obesity-related behaviors. The primary reason revealed by previous studies is that information from professionals is lacking. Web-based information from professionals about obesity proved to be more accurate than that from other users. Erdem and Sisik [68] analyzed the content of 300 YouTube clips on bariatric surgery, also known as weight loss surgery, and suggested that the content from professional accounts tends to be more accurate. In another study, Basch et al [69] analyzed the top 100 most widely viewed weight loss videos on YouTube and found only 1 professional video; consumer-created videos dominated the domain. Mejova [62] examined 1.5 million tweets mentioning

obesity and diabetes and found that only 23% of the content came from verified users (ie, Twitter accounts that are associated with a governmental or academic institution). Similarly, more individuals than organizations tweeted about childhood obesity [67].

Misinformation in content can also harm users. YouTube advertisements for rapid weight loss products and commercial videos focused too much on workouts instead of maintaining a balanced diet [69]. The top-cited domains relating to obesity and diabetes on Twitter are not affiliated with guidelines provided by governmental or academic institutions [24]. The discrepant information from user-generated content can lead to a drop in trust for these platforms. Messages presented in traditional social media platforms, such as blogs, were seen as a more reliable source than other newer social media platforms, such as Facebook [70]. Meitz et al [70] compared the source credibility perceptions among different platforms and found that messages on Facebook were perceived as significantly less relevant than messages presented in blogs. Together, these studies reinforce the importance of source credibility in conducting users' health behaviors.

School Environment

School, serving as a center of childhood development, has an influential role in a child's early behavioral development. Findings from social media content analysis suggest that the school environment is essential in affecting children's obesity-related behaviors. From one aspect, the school decides students' daily routines and food selection. So et al [64] argued against excess homework, and Harris et al [67] noted that most public schools do not regulate access to junk food. In addition, teachers' participation in combating childhood obesity is critical. In a preschool obesity prevention curriculum, parents showed a strong desire for more engagement from their classroom teachers [71]. Changing the school environment was the most common strategy to combat childhood obesity mentioned on Twitter. For example, a person tweeted, "Americans expect schools to lead in preventing childhood obesity" [67]. Users' attitudes toward school environments shape the internet-based discourse on childhood obesity.

Social Movements

Social movements are defined as organized efforts by a group of people to bring out or impede social or cultural changes [72]. Social media offers a new possibility of exploring social movements efficiently. In recent years, several distinct web-based trends regarding obesity have been found in social media: *body positivity*, *thinspiration*, *fitspiration*, and *HAES* (health at every size). The term *body positive* originally came from the 1960s feminist movement and resurfaced in the fat acceptance movement. A content analysis of *body-positive* images on Instagram showed that this movement seeks to challenge beauty standards while rejecting an inaccessible body image and promoting acceptance of all body types and appearances [55]. However, another prevailing trend called *thinspiration* surfaced with the intent of spreading thin body imagery and inspiring weight loss. Content analyses showed that body-positive images on Instagram drew a broad range of body sizes [55], whereas thinspiration images on Twitter tend

to depict ultrathin and scantily clad women [73]. Exposure to guilt-inducing and body-objectifying messages has been found to increase body dissatisfaction and negative mood. The study also showed that the more times individuals view thinspiration content, the higher the probability they will report eating disorder symptoms [69]. Subsequently, a new trend called *Fatspiration*, supporting fat acceptance, has become prominent in the mainstream [56] and was found on the web. Another trend, *HAES*, promoting wellness rather than weight loss, was also identified. However, discrimination against obesity has not yet been resolved. Fat stigmatization content within the *HAES* and *Fatspiration* tags were found in a content analysis of Instagram images [74]. Social media shapes the web-based information environment and helps us fully understand the context of social movements. Without understanding the full scope, there is a potential for a negative shift in social norms.

Policy

Governments have tried to combat obesity by establishing new policies. Three studies [67,75,76] used social media to study the public's attitude and reaction toward government policy. In 2016, the United Kingdom also published a plan to reduce England's rate of childhood obesity within the next 10 years, *Childhood obesity: a plan for action*. Most comments to the related web-based newspaper articles were considered negative in a study by Gregg et al [76]. Later, in 2017, Kang et al [75] collected relevant tweets to investigate the public's opinion on a new school meal policy. They found that 70% of tweets were neutral, although the number of negative tweets was still higher than that of positive tweets. Negative tweets expressed interest and concern about the policy and suspicion of the effectiveness of the campaign. Instead of worrying, some users also used social media to support the announcement and execution of policies. Harris et al [67] found *Bye Fitspiration Junk Food*, a US Department of Agriculture rule that requires healthier snacks for children and the adoption of the physical education classes as a core subject in schools, was a prominent movement in communication about childhood obesity on Twitter. Web-based information can shape an individual's attitude toward a certain policy. With social media, policy makers can better disseminate policies and raise public awareness.

Social Sharing Behaviors

We found 2 psychology theories related to web-based sharing behaviors in the literature: social sharing of emotions and cognitive dissonance theory. Social media makes it easier for users to share their opinions, and users' web-based obesity-related behaviors have been found to be guided by these theories. In 1995, Rime et al [77] proposed that emotion is a critical motivator in social sharing. The social sharing of emotions has shown that people have an innate need to tell others when they experience an emotionally impactful event [64]. According to So et al [64], a content analysis of frequent retweets about obesity on Twitter, the emotionally evocative tweets, specifically evoking amusement, were the most frequently retweeted. Another theory, cognitive dissonance theory, posits that we experience psychological discomfort when we encounter beliefs that are inconsistent with our own. As a result, people try to reduce this discomfort by exposing

themselves to information that helps them resolve cognitive conflicts. A study on Instagram pictures showed that people who reside in high-obesity areas are more willing to post food-related photos than the people in low obesity areas [60]. By understanding the underlying mechanisms of these phenomena, we can better manage obesity-related behaviors.

Study Year and Region

All the included studies were published between 2011 and 2019, and the number of each study by year is shown in Table 1. This number started to increase in 2014 (n=7) and reached a peak in 2017 (n=14). However, this is partly because our search was conducted in July 2019.

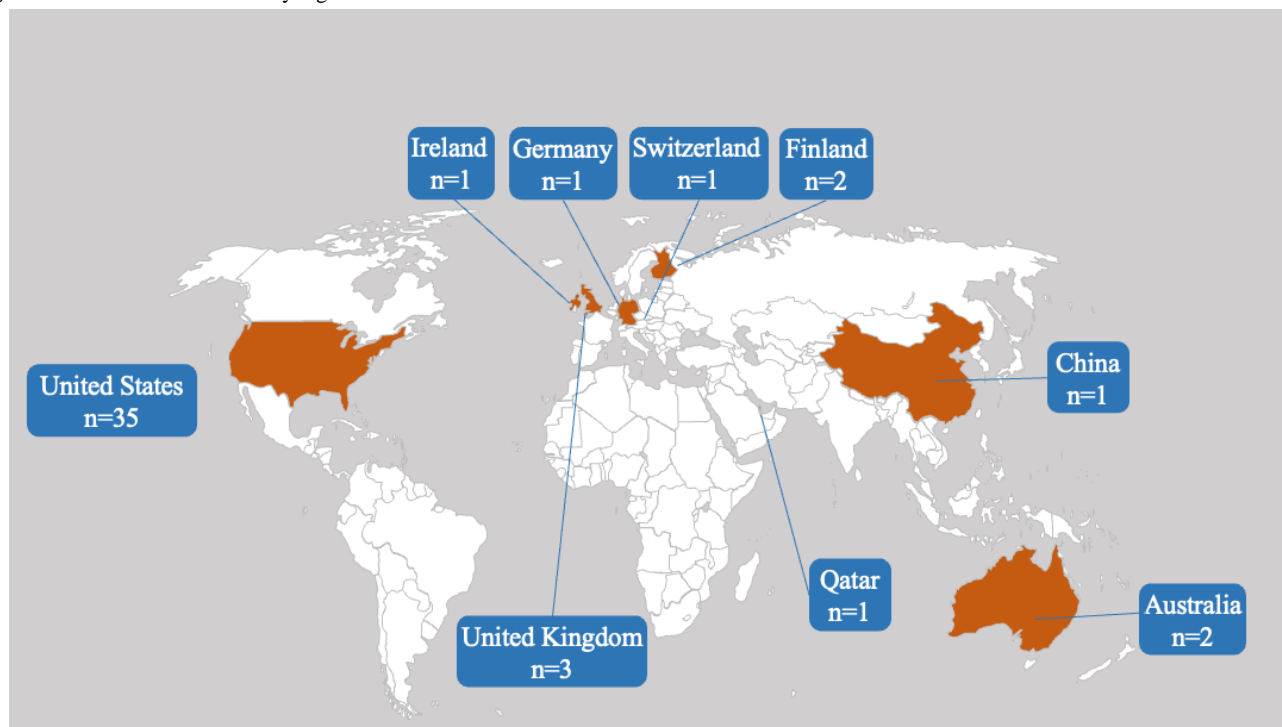
Table 1. Number of studies over year.

Year	Studies, n
2011	1
2012	1
2013	1
2014	7
2015	5
2016	12
2017	14
2018	8
2019	1

In total, 9 study regions were mentioned, with most of the studies coming from the United States (35/50, 70%). Except for China, Australia, and Qatar, all other regions were located in Europe. The number of studies conducted in other countries is shown in Figure 2. Several groups of users were studied; children, women of childbearing age (eg, pregnant women [78],

postpartum women [41], and mothers with newborns [79]), and adults with other relevant illnesses (eg, diabetes [51]) were the 3 leading types of user groups studied. Only the study by Aschbrenner et al [48] focused on adults with obesity and severe mental illness.

Figure 2. The distribution of study region.



Social Media Platforms and Their Roles

We identified 3 different roles that social media serves in each study. Inspired by a study by Leroux et al [80], three potential roles of social media in obesity-related studies were identified: data collection, intervention pathways, and ancillary resources.

Data collection is used to define when social media platforms were only used to collect the data used in the study. The intervention pathway defines social media use as a comprehensive channel in an intervention study. The role of social media includes delivering the message and serving as a

web-based communication platform for participants in weight management or loss interventions. We defined ancillary resources as the role when social media is used as an experimental platform. Data were also collected when serving as ancillary resources. The major difference between data collection and ancillary resources is the source of data. If the data were collected for the purpose of analyzing and understanding the data, we defined them as data collection; if the data were generated from the experiment, we defined them as ancillary resources. The type of study can be used to distinguish between intervention pathways and ancillary resources. Social media platforms only serve as an intervention pathway in an intervention study. These categories are mutually exclusive.

We also categorized social media platforms into six different types: microblogging, social networks, weblogs, photo or video sharing, web-based forums, and messaging. Facebook, the largest web-based social network, was the most frequently used (14/50, 28%). Facebook was used the most in intervention studies. Facebook was used as a message delivery channel, in which private groups were introduced as a smaller online support group for participants to share goal-related resources, individual signs of progress, and messages. Only 1 study collected data from Facebook by accessing public Facebook posts. [24]. Similar to Facebook, a Chinese social network platform, WeChat, was used in a study by He et al [46] as the intervention pathway. Twitter allows users to communicate with others from all over the world. Twitter, a microblogging platform, was used to collect data to understand public opinions (11/50, 22%). One study also used Twitter as an ancillary resource (1/50, 2%) to conduct their experiment. For example, May et al [65] created

4 Twitter accounts portraying women (2 obese and 2 normal or overweight) who were interested in weight loss and pretended to behave as regular users. Later, they examined the interaction with other users and mimicked users (eg, follow-back rate). Another study used Twitter as an intervention pathway to involve participants [39]. Few studies have investigated blogs (4/50, 8%), mainly because of the difficulty in extracting meaningful insights from large pieces of text.

Similarly, only 2 studies analyzed clips from YouTube because of the complexity of analyzing videos. Instagram, one of the most prominent photo-sharing platforms, was used in 7 studies. A total of 2 studies used Instagram as an intervention pathway in which participants were asked to upload their meals. In other studies, researchers analyzed public photos to understand public health [59], social movements [55,74], and social sharing behavior [60]. A small number of studies analyzed Twitter and Instagram data with extended data points. For example, researchers combined demographic and geolocation information to better predict the obesity rate of the regions [58]. Reddit has been used in several health-related studies [81]; however, we found only 2 studies using Reddit in our search. Another type of social media is a forum. We identified 3 studies that investigated Yahoo! Answers, a self-developed application (ie, HealthTogether), and another platform not specified in the literature. WhatsApp was chosen as the intervention pathway in 1 study as an alternative to the traditional SMS text messaging method. In this study, group-chat rooms were formed to deliver information and allow participants to communicate on the web. Table 2 presents in the information in a more comprehensive format. The amount of data used in the study and the major study participants are summarized in Table 3.

Table 2. A descriptive overview of social media platforms.

Type and platforms	Studies, n	Data collection, n	Intervention pathway, n	Ancillary resource, n
Microblog (n=14)				
Twitter	14	11	2	1
Social network (n=15)				
WeChat	1	0	1	0
Facebook	14	1	13	0
Weblog (n=4)				
Blogs	4	4	0	0
Photo or video sharing (n=11)				
Instagram	7	5	2	0
Pinterest	1	1	0	0
YouTube	3	3	0	0
Web-based forum (n=11)				
Reddit	2	2	0	0
Yahoo! Answers	1	1	0	0
Self-developed application	2	0	2	0
Unknown community	6	3	2	1
Messaging (n=1)				
WhatsApp	1	0	1	0

Table 3. Summary of individual studies.

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
Kang et al [75]	Twitter	United States	UNK ^a	14,317 related tweets	Policy	<ul style="list-style-type: none"> More negative tweets about the school meal policy have been detected. The main target negative opinions were campaign and food. 	Data collection
Fernandez-Luque et al [54]	WhatsApp; Instagram	Qatar	Children	UNK (intervention study)	Gender, geo-cultural factors	<ul style="list-style-type: none"> More active users tend to have better health outcomes. Females' engagement with social media is higher. Nutritional advice in weight loss campaigns must consider religious and cultural traditions. 	Intervention pathway
Lingetun et al [78]	Blogs	United States	Pregnant women with obesity or overweight	13 internet blogs	Gender	<ul style="list-style-type: none"> Three main themes of overweight pregnant women's blogs were identified: pregnancy as an excuse, perspectives on the pregnant body, and becoming a mother. 	Data collection
May et al [65]	Twitter	United States	Adults	UNK (experiment study)	Social support, gender, stigma	<ul style="list-style-type: none"> Investigated follow-back rates. The number of interactions and organic follows did not differ by weight status. Peers interacted more with each other than with professionals. Women need 5 weeks to build a web-based weight loss community on Twitter. 	Ancillary resource
Gore et al [57]	Twitter	United States	UNK	More than 25 million tweets	Geo-cultural factors	<ul style="list-style-type: none"> Geological areas with lower obesity rates (1) have happier tweets and (2) have more frequently discussed food, particularly fruits and vegetables, and physical activities. 	Data collection
So et al [64]	Twitter	United States	UNK	200,000 tweets	Social sharing, school environment, obesogenic environment, stigma	<ul style="list-style-type: none"> Tweets that are emotionally evocative or humorous and express individual-level concerns for obesity were more frequently retweeted than their counterparts. 	Data collection

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
Kent et al [24]	Facebook; Twitter	United States	UNK	291 Facebook posts; 1091 tweets	Obesogenic environment	<ul style="list-style-type: none"> This study aimed to understand the connection between obesity and cancer from Facebook and Twitter. They found that (1) most tweets focused on an associative or causal link between obesity and cancer, and (2) tweets contained more negative sentiment than Facebook posts. 	Data collection
Harris et al [67]	Twitter	United States	Children with obesity	1110 tweets	Source credibility, policy, school environment	<ul style="list-style-type: none"> This study investigated the communication about obesity on Twitter, and they found that (1) more tweets focused on individual behavior than on policy or environment, and (2) government or educational tweets attract more attention, but the number of these tweets is less. 	Data collection
Kuebler et al [53]	Yahoo! Answers	United States	Adults	3926 users' questions; 300 bullying questions	Gender, stigma, geo-cultural factors	<ul style="list-style-type: none"> Most women asking whether they were fat or obese were not fat or obese. Users with obesity were significantly more likely to ask for advice about bullying than thinner users. People with obesity who reside in counties with higher BMI may have better physical and mental health than people with obesity who live in counties with lower BMI. 	Data collection
Leggatt-Cook and Chamberla [43]	Blogs	United States	Adults	10 blogs	Social support	<ul style="list-style-type: none"> Weight loss bloggers typically write about daily success and failures, report calorie consumption, and exercise output, and post photographs of their changing bodies. 	Data collection
Mejova [62]	Twitter	United States	UNK	1.5 million tweets	Source credibility, stigma	<ul style="list-style-type: none"> Tweets afflicted with government or institution are likely to be retweeted more. The need to address the quality control of health information on social media is proposed. 	Data collection
Munk et al [15]	Instagram	United Kingdom	UNK	82,449 geo-tagged posts	Obesogenic environment	<ul style="list-style-type: none"> Sunday night is a good time to post on Instagram. There is no clear difference between thematic communities between high and low BMI areas. 	Data collection

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
Garimella et al [59]	Instagram	United States	UNK	200,000 images	Geo-cultural	<ul style="list-style-type: none"> Both user-provided and machine-generated image tags provide information that can be used to infer a county's health statistics. 	Data collection
Culotta [58]	Twitter	United States	UNK	1.4-M user profiles and 4.3 M tweets	Geo-cultural	<ul style="list-style-type: none"> Six of 27 health statistics show a significant correlation with the linguistic analysis of the Twitter activity in the top 100 most populous counties in the United States. Twitter information, together with demographic information, improves the model's performance. 	Data collection
Abbar et al [52]	Twitter	United States	UNK	892,000 tweets	Geo-cultural	<ul style="list-style-type: none"> The caloric values of the foods mentioned in the tweets were analyzed in relation to the state-wide obesity rate. 	Data collection
Weber and Mejo-va [61]	Twitter	United States	Overweight adults	1339 profile images	Geo-cultural, stigma	<ul style="list-style-type: none"> User profile pictures could be used to obtain the user's weight information. 	Data collection
Pappa et al [44]	Reddit	United States	UNK	Posts and comments of 107,886 unique users	Social support, gender	<ul style="list-style-type: none"> The 10 most-discussed semantic topics on posts in the LoseIt Reddit community were related to healthy food, clothing, calorie counting, workouts, looks, habits, support, and unhealthy food. 	Data collection
Loh et al [82]	Facebook; Instagram; Twitter	United States	Children	UNK (intervention study)	Social support	<ul style="list-style-type: none"> The study showed that social media and text messaging were innovative tools that should be included to increase the reach of multilevel community intervention. 	Intervention pathway
Ling et al [83]	Facebook	United States	Children	UNK (intervention study)	Social support	<ul style="list-style-type: none"> Participants in the survey mentioned that they enjoyed the Facebook platform because it provided new recipe and activity ideas and an opportunity to interact with other participants. 	Intervention pathway
He et al [46]	WeChat	China	Adults	UNK (intervention study)	Social support	<ul style="list-style-type: none"> An intervention based on WeChat platform was effective on weight loss only for males. Females show more activities on WeChat, but they lost less weight during the study. 	Intervention pathway
Erdem and Sisik [68]	YouTube	United States	Adults	175 videos	Source credibility		Data collection

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
						<ul style="list-style-type: none"> • There are no significant associations between the number of likes, dislikes, or views and usefulness score. • Videos uploaded by medical professionals typically contain more useful information. 	
Jane et al [37]	Facebook	Australia	Adults with obesity or overweight	UNK (intervention study)	Social support	<ul style="list-style-type: none"> • This study shows that participants do not rely on each other in the same way that they would typically rely on their offline social connections. • The Facebook group reported the greatest reductions in initial weight compared with the control group, which had no social media components. 	Intervention pathway
Fiks et al [79]	Facebook	United States	low-income mothers with a newborn	UNK (intervention study)	Social support	<ul style="list-style-type: none"> • Mothers of the intervention group were significantly less likely to pressure infants to finish food or give cereal in the bottle. 	Intervention pathway
Mejova et al [60]	Instagram	United States	UNK	20,848,190 posts	Obesogenic environment, social sharing	<ul style="list-style-type: none"> • There is a link between obesity and the density of fast-food restaurants. • Food sharing behavior is higher for high-obesity areas. 	Data collection
Cunha et al [42]	Reddit	United States	UNK	70,949 posts and 922,245 comments	Social support	<ul style="list-style-type: none"> • Users receiving feedback on their posts have a higher probability of returning to the community. • Returning users who received comments on their posts reported losing more weight. 	Data collection
Waring et al [39]	Twitter	United States	Women of childbearing age	UNK (intervention study)	Gender, social support	<ul style="list-style-type: none"> • Women of childbearing age are interested in a weight loss program that was delivered entirely via Twitter. 	Intervention pathway
Chomutare et al [47]	UNK	United States	Women with obesity	140 Women with obesity in an internet group	Gender, social support	<ul style="list-style-type: none"> • Women with high web-based participation levels lost more weight than do women with low participation levels. 	Data collection
West et al [84]	Facebook	United States	Adults	UNK (intervention study)	Social support	<ul style="list-style-type: none"> • Students maintained their weight, with no significant difference between weight gain prevention intervention group and control group over 9 weeks. 	Intervention pathway
	Facebook				Social support		

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
Aschbrenner et al [48]		United States	Adults with serious mental illness	UNK (intervention study)		<ul style="list-style-type: none"> This study shows that weight loss was significantly associated with perceived peer-group support. 	Intervention pathway
Merchant et al [40]	Facebook	United States	Adults	UNK (intervention study)	Social support	<ul style="list-style-type: none"> In a Facebook group that involved weight-loss controlled trial, the following were noted: (1) Polls are the most popular posts followed by photos. (2) Participants visibly engaged with posts less over time. Of participants, 3.4% reported passively engaging with the Facebook page. 	Intervention pathway
Chen et al [51]	HealthTogether	Switzerland	Adults	UNK (intervention study)	Social support	<ul style="list-style-type: none"> Collaborating with buddies to compete in achieving fitness goals in a group was reported as motivating for dyads with strong ties. 	Intervention pathway
Phan et al [50]	Web-based social network	United States	Adults	UNK (experiment study)	Obesogenic environment	<ul style="list-style-type: none"> By incorporating all the human behavior determinants and environmental events, the proposed novel deep learning model achieves more accurate results in predicting the future activity levels of users. 	Ancillary resource
Savolainen [45]	Blogs	Finland	UNK	50 blogs	Social support	<ul style="list-style-type: none"> Blogs provide an emotionally supportive forum that mainly serves to share opinions and information; they were seldom used for seeking information. 	Data collection
Church et al [85]	Facebook	UNK	Adults	UNK (intervention study)	Social support	<ul style="list-style-type: none"> Participants lose weight during the 6-week web-based clinical, emotional freedom techniques course and continue to lose weight in the following year, which indicates the long-term effects. 	Intervention pathway
Turner-McGrievy et al [86]	Facebook	United States	Vegan women with polycystic ovary syndrome	UNK (intervention study)	Social support	<ul style="list-style-type: none"> The study result suggests that engagement with social media may be effective for short-term weight loss among vegan women with PCOS^c. 	Intervention pathway
Lytle et al [49]	Social support website	United States	2-year college students	UNK (intervention study)	Social support, school environment		Intervention pathway

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
						<ul style="list-style-type: none"> The social networking encouraged intervention group, and the control group does not have a significant difference in BMI at the end of the 24-month intervention study. 	
Waring et al [41]	Facebook	United States	Postpartum women with overweight or obesity	UNK (intervention study)	Social support	<ul style="list-style-type: none"> Facebook-based intervention is feasible for overweight and postpartum women with obesity in weight loss. However, research is further needed to determine how to engage participants in social networks better. 	Intervention pathway
Basch et al [69]	YouTube	United States	UNK	98 weight loss videos	Source credibility	<ul style="list-style-type: none"> The number of videos about weight loss on YouTube from professionals is lacking. 	Data collection
Webb et al [74]	Instagram	United States	UNK	400 images	Social movement	<ul style="list-style-type: none"> Health at every size-tagged posts contain more physically active portrayals and weight stigma than do posts from fitspiration-tagged images. 	Data collection
Taiminen [87]	Facebook web-based forum	Finland	UNK	UNK (intervention study)	Social support	<ul style="list-style-type: none"> Active participants in the web-based community showed a more positive perception of achieving their goals, followed instructions more precisely, and perceived to receive more emotional support than participants who are not active in the web-based community. 	Intervention pathway
Hales et al [88]	Social POD ^b	United States	Overweight adults	UNK (intervention study)	Social support	<ul style="list-style-type: none"> The experiment group using a weight-loss mobile app lost significantly more weight than the comparison group. 	Intervention pathway
Meitz et al [70]	Facebook	Germany	Children	UNK (intervention study)	Source credibility	<ul style="list-style-type: none"> In a web-based media-embedded health campaign against childhood obesity, the following were noted: (1) participant's self-relevance varies based on different source credibility perceptions and (2) provocative messages in the campaign may result in negative persuasion effects. 	Intervention pathway
Ghaznavi and Taylor [73]	Twitter and Pinterest	UNK	UNK	300 images	Social movements		Data collection

Article	Platform	Region	Group	Data	Web-based social factors	Primary findings	Conceptual
						<ul style="list-style-type: none"> The study suggests thinspiration content promotes an objectified, sexual, extremely thin depiction of the thin ideal. Exposure to these contents has the potential harmful effects. 	
Appleton et al [89]	Web-based forums	Australia	UNK	34 discussion threads	Social support	<ul style="list-style-type: none"> Four major themes were detected in parents' web-based discussion forums about children obesity: seeking advice, sharing advice, social support, and making a judgment. 	Data collection
Karami et al [63]	Twitter	United States	UNK	4.5 million tweets	Social movement	<ul style="list-style-type: none"> Exercise and obesity, diabetes and obesity, diet, and obesity have a strong correlation with each other. The strongest correlation was found between exercise and obesity. 	Data collection
Swindle et al [71]	Facebook	United States	Parents	UNK (intervention study)	School environment	<ul style="list-style-type: none"> Facebook is a feasible platform to provide nutrition education and facilitate parent's engagement. 	Intervention pathway
De Brún et al [5]	Web-based message boards	Ireland	UNK	2872 obesity-relevant comments	Stigma	<ul style="list-style-type: none"> The study analyzed obesity-related comments from multi-topic web-based message boards and determined that obesity stigma is pervasive, and the discussion of the issue is highly acceptable. 	Data collection
Gregg et al [76]	Web-based forums	United Kingdom	UNK	1704 comments	Policy	<ul style="list-style-type: none"> The study analyzed associated comments to the United Kingdom government about childhood obesity strategy and determined the comments are largely negative. 	Data collection
Atanasova [90]	Blogs	United Kingdom	UNK	343 posts from 6 obesity blogs	Social support	<ul style="list-style-type: none"> The content of blogs highlighted the conclusion that there are no one-size-fits-all solutions to obesity that work for everyone. 	Data collection
Cohen et al [55]	Instagram	UNK	UNK	630 posts	Social movements	<ul style="list-style-type: none"> Body-positive posts depicted a broad range of body sizes and appearances. 	Data collection

^aUNK: unknown.

^bPOD: social pounds off digitally.

^cPCOS: polycystic ovary syndrome.

Discussion

Principal Findings

In this systematic review, we categorized and identified related the effects of web-based social factors on users' obesity-related behaviors and evaluated the role of social media. We adopted socioecological model to explain identified web-based social factors at different levels. Moreover, we discussed strategies for preventing obesity by using this socioecological model. We conclude the drawbacks found in the literature and provide suggestions for future studies.

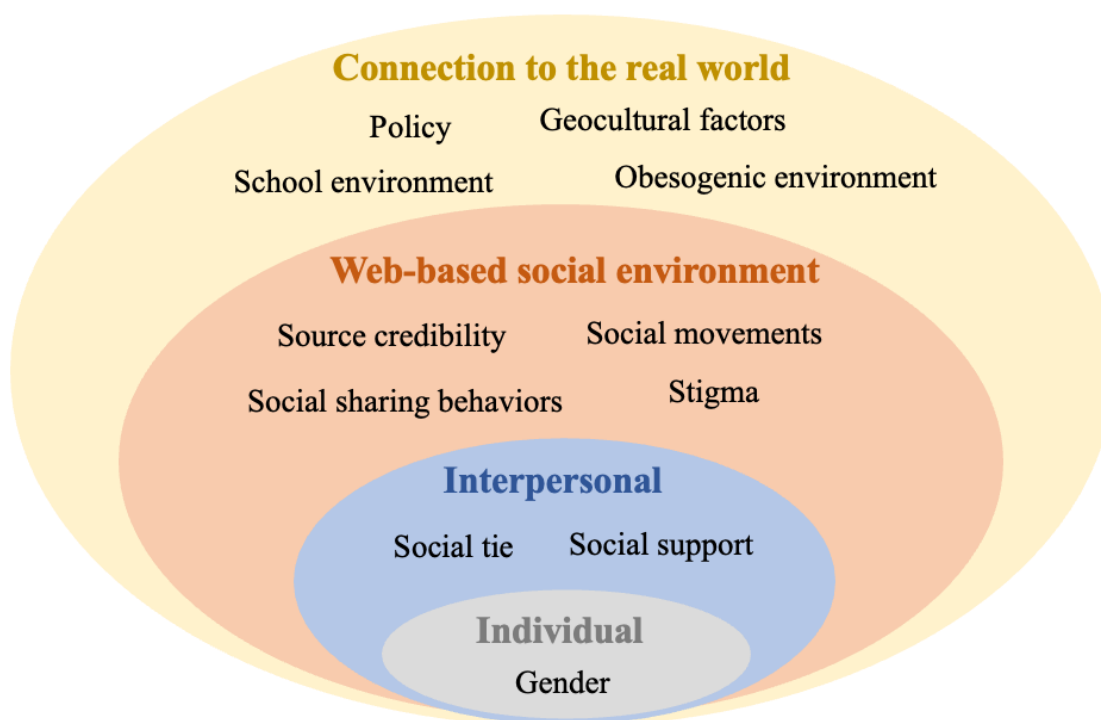
Socioecological Model

Socioecological models were developed to further the understanding of the dynamic interrelations among various personal and environmental factors [91]. Revised by Bronfenbrenner and Morris [92], the ecological theory of

Bronfenbrenner applies socioecological models to human development. The ecological framework identifies five environmental systems with which an individual interacts: microsystem, mesosystem, exosystem, macrosystem, and chronosystem [92]. Since its publication in 1979, the major statement of Bronfenbrenner on the theory of the ecology of human development has shown widespread influence on the way psychologists and others approach the study of human beings and their environments. This socioecological model is proposed to understand how web-based social factors affect behaviors and provide guidance for developing a successful program through web-based social environments.

We classified these web-based social factors into four levels based on their effects: individual, interpersonal, web-based social environment, and connection to the real world. The proposed socioecological model is shown in Figure 3.

Figure 3. Socioecological model.



We aimed to identify web-based social factors that can affect users' obesity-related behaviors. For the web-based environment, we use a 4-level socioecological model to better understand obesity and the effect of potential factors to help users combat obesity. This model considers the complex reciprocity between individual, interpersonal, web-based communities, social media platforms, and connections to the real world. This allowed us to understand the range of factors that potentially affect users' web-based behavior related to obesity. The overlapping rings in the model illustrate how factors at one level influence factors at another level. Besides helping clarify the effectiveness of these factors, the model also suggests that to intervene in a user's behavior, it is necessary to act across multiple levels of the model simultaneously.

The first level identifies the personal factors that affect a person's web-based behavior. The factor identified here was

gender. From a biological perspective, women's bodies are more vulnerable to obesity because women are more likely to store fat because of reproduction [93]. In the web-based environment, female users were more attentive to their shape and figure than were men and were more likely to search and share health information on the web through social media than were men.

The second level explores relationships that may increase or reduce the risk of obesity. People's close social connections or family members influences impact their behaviors and contribute to their habits. The factors we discovered at this level were social support and web-based social ties. Social support from social media websites has been suggested to be very effective in users' weight loss experiences, and web-based social ties have been proven to influence a person's lifestyle behaviors.

The third level examines the web-based social environment in which social relationships occur and the characteristics

associated with users' obesity-related behaviors. The factors that contribute to the web-based environment include source credibility, social movements, social sharing behaviors, and stigma. Social movements, stigma, and source credibility shape users' behaviors by changing the web-based environment. Exposure to content with obesity-associated stigma has been shown to have negative effects on users' mental health. Exposure to content from unreliable resources may harm users and further damage their trust in social media platforms. Moreover, exposure to social movements may negatively affect users' behavior. For example, exposure to content about *thinspiration* would increase a person's body dissatisfaction and negative mood. Social sharing behaviors change the web-based environment by directly changing users' sharing behavior. Users prefer sharing emotionally evocative content, especially when consistent with their beliefs.

The fourth level explores the broader societal factors that connect the virtual web-based environment to the real world. Factors at this level include policy, school environment, geo-cultural factors, and an obesogenic environment. The physical environment can inform a virtual web-based environment; for example, the number of fast-food restaurants and food calories mentioned in tweets correlated with the county's obesity rate. Users' unsatisfactory opinions of school environments and government policies are found through social media data.

Preventing Obesity

Reducing the obesity rate requires understanding the factors that influence obesity-related behaviors. This socioecological model helps practitioners develop effective prevention strategies.

Preventive strategies at the individual level promote attitudes, beliefs, and behaviors that combat obesity. The approach may include advocating for males to care more about their weight status and be aware of the importance of having a healthy lifestyle. Female opinion leaders could be encouraged to share healthier lifestyle tips to help women maintain a healthy lifestyle.

A prevention strategy at the interpersonal level may include designing family-focused weight loss programs and supporting users who want to combat obesity to join related web-based groups, share their weight loss or weight management experience on the web, and encourage other users.

Preventive strategies at the social environment level make a point of creating a healthier internet social environment; for example, improving the source credibility level by monitoring illegal advertisements and advocating professional organizations to post strategies combating obesity, coping with stigma issues by adopting state-of-the-art natural language processing technologies to remove stigmatized posts from social media, supervising the web-based environment by detecting major social movements that intersect with obesity, and building users' healthy life beliefs by encouraging positive social sharing on social media. Emotionally evocative posts are more easily accepted, depending on users' social sharing behaviors.

Preventive strategies related to the real-world level emphasize building a healthy societal environment and establishing a good

connection between the web-based environment and real society. Social policies from the government that lead a healthy lifestyle, a good school environment that provides children with a balanced diet, and an antiobesogenic environment can help maintain a healthy societal environment.

Data Variety

We observed some drawbacks in the included studies. The data variety needs to be expanded in future studies. First, the limitations of each social media platform should be considered. Although Twitter is one of the biggest web-based social network platforms, it may not serve as the best channel for collecting data and studying obesity-related topics. Twitter is a platform that makes data publicly available. Because of privacy and stigma concerns, some users may refuse to share confidential data on Twitter [82]. Comparing 3 major social media platforms (Facebook, Instagram, and Twitter) in a childhood obesity prevention intervention by Loh et al [82], Facebook—allowing more comprehensive communication and longer and more frequent posts than the other 2 social media platforms—was found to have the highest fidelity and engagement. In contrast, Twitter has the least engagement and fidelity [82].

Second, a large amount of image data is an emerging resource. We discovered that textual data were the leading type in previous studies, and a large amount of media-syncretic image data was dismissed. A study from Mejova et al [60] analyzed picture tags and images. Textual data, along with their associated features (eg, image, link, and user profile), could provide more insight. Third, the regions of the studies were too limited. The prevalence of obesity is also high in other areas of the world, such as Mexico [94]. Given the cultural differences, it is meaningful to understand the social elements of other areas. Another finding was that the data collected through experiments were not analyzed. Almost all intervention studies encouraged participants to interact with others on social media platforms; the efficacy of these social components did not receive adequate study. Only 2 studies performed quantitative analysis on user interaction behavior (eg, how many posts the user submits every day) [46,51] in an online support group. No qualitative analysis was employed on the textual data collected in the study, which could give us a clue as to how factors affect people's weight loss experience.

Finally, the data quantity in many studies was insufficient, considering the large number of people with obesity. For example, studies using blog data to perform qualitative analyses used just 10 [43] and 13 [78] blogs. Manually conducting a thematic analysis is indeed labor-intensive; however, with the development of deep learning, pretrained language models could be effectively employed to analyze large amounts of data.

Limitations

Our systematic review has some limitations. First, we only used three databases (PubMed, ACM, and ScienceDirect) in our study. If other databases, such as PsycINFO, Embase, and Scopus, were included in the study, we might have had additional and possibly different findings. Second, the MeSH term *social media* was created in 2012 [34]; thus, our study did not include studies published before 2012. This may have

skewed the results. Future studies should consider a broader search strategy for more comprehensive results. Third, many studies did not include a particular type of social factor and how those factors affected users; thus, the analysis of social factors was not sufficient. Finally, further discussion on the quality of study design, types of bias, and other limitations of the investigated studies can bolster our findings.

Conclusions

We provided a comprehensive review of social media in relation to understanding obesity and isolating web-based social factors,

including platforms, data, and study results. We proposed a 4-level socioecological model to explain the dynamic interrelationships among users' obesity-related behaviors, personal characteristics, users' interpersonal connections, web-based social environments, and the real world. Understanding the potential role of these factors will benefit us in several aspects: understanding users' web-based social behaviors concerning obesity, calibrating web-based social factors for weight management intervention studies, and disseminating educational information to the public.

Conflicts of Interest

None declared.

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Abbreviations

ACM: Association for Computing Machinery

HAES: health at every size

MeSH: Medical Subject Heading

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Review

Use of HIV Recency Assays for HIV Incidence Estimation and Other Surveillance Use Cases: Systematic Review

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Abstract

Background: HIV assays designed to detect recent infection, also known as “recency assays,” are often used to estimate HIV incidence in a specific country, region, or subpopulation, alone or as part of recent infection testing algorithms (RITAs). Recently, many countries and organizations have become interested in using recency assays within case surveillance systems and routine HIV testing services to measure other indicators beyond incidence, generally referred to as “non-incidence surveillance use cases.”

Objective: This review aims to identify published evidence that can be used to validate methodological approaches to recency-based incidence estimation and non-incidence use cases. The evidence identified through this review will be used in the forthcoming technical guidance by the World Health Organization (WHO) and United Nations Programme on HIV/AIDS (UNAIDS) on the use of HIV recency assays for identification of epidemic trends, whether for HIV incidence estimation or non-incidence indicators of recency.

Methods: To identify the best methodological and field implementation practices for the use of recency assays to estimate HIV incidence and trends in recent infections for specific populations or geographic areas, we conducted a systematic review of the literature to (1) understand the use of recency testing for surveillance in programmatic and laboratory settings, (2) review methodologies for implementing recency testing for both incidence estimation and non-incidence use cases, and (3) assess the field performance characteristics of commercially available recency assays.

Results: Among the 167 documents included in the final review, 91 (54.5%) focused on assay or algorithm performance or methodological descriptions, with high-quality evidence of accurate age- and sex-disaggregated HIV incidence estimation at national or regional levels in general population settings, but not at finer geographic levels for prevention prioritization. The remaining 76 (45.5%) described the field use of incidence assays including field-derived incidence (n=45), non-incidence (n=25), and both incidence and non-incidence use cases (n=6). The field use of incidence assays included integrating RITAs into routine surveillance and assisting with molecular genetic analyses, but evidence was generally weaker or only reported on what was done, without validation data or findings related to effectiveness of using non-incidence indicators calculated through the use of recency assays as a proxy for HIV incidence.

Conclusions: HIV recency assays have been widely validated for estimating HIV incidence in age- and sex-specific populations at national and subnational regional levels; however, there is a lack of evidence validating the accuracy and effectiveness of using

recency assays to identify epidemic trends in non-incidence surveillance use cases. More research is needed to validate the use of recency assays within HIV testing services, to ensure findings can be accurately interpreted to guide prioritization of public health programming.

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KEYWORDS

HIV; recency; incidence; surveillance; recent infection

Introduction

There are many reasons to identify recently acquired HIV infections on a population level, including to (1) better understand current transmission of HIV in a country, region, or population subgroup; (2) evaluate whether specific prevention interventions are having the desired impact; and (3) focus limited resources for prevention or treatment services on groups of people or geographic locations with the greatest potential benefit (eg, reducing risk for onward transmission) [1]. HIV assays designed to detect recent infection, also known as “recency assays,” can be used to gain an understanding of these epidemic dynamics.

Recency assays discriminate recent from longstanding infection in an individual using 1 or more biomarkers, typically using an understanding of the typical patterns of immune response maturation following initial infection [2]. Individual recency assay results can be used in a cross-sectional survey to estimate incidence by building on the common epidemiological equation $P = I \times D$ (ie, prevalence = incidence \times duration of infection) [3]. However, the accuracy of the incidence estimate is dependent on accurate knowledge of the performance characteristics of the recency assay or algorithm, specifically mean duration of recent infection (MDRI; ie, the average time after infection that individuals are classified as recently infected) and false recent rate (FRR; the proportion of long-infected individuals misclassified as recently infected), and the precision of the estimate is sensitive to these same parameters [4].

To date, no recency assay has fully met the target product profile for HIV incidence estimation as set out by the Foundation for Innovative Diagnostics (FIND) and the World Health Organization (WHO) in 2016 [5]. Numerous factors have been identified that adversely affect recency assay performance and lead to substantial misclassification of longstanding infections as recent (ie, raise the FRR). Factors that can affect assay performance include natural variability in individual immune responses (in particular, elite control of HIV or natural viral suppression), variability in biomarker progression for different HIV-1 subtypes, the types of specimens collected and storage methods, advanced HIV disease, and treatment with antiretroviral therapy (ART) or use of pre-exposure prophylaxis (PrEP) [6-9]. The effect of ART on increasing the FRR of recency assays appears to be more pronounced when a person receives treatment very early after initial infection [10,11], which is complicated by rapid improvements in treatment coverage worldwide, as well as uptake of PrEP. Other factors that may impact assay performance but are not yet well-characterized include sex, pregnancy status, and the presence of comorbidities [12-14].

Since the release in 2011 of technical guidance on the use of recency assays to estimate population-level HIV incidence from the WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) [1], the field has changed substantially, motivating release of interim guidance at various times [12,15-18]. Numerous examples in the peer-reviewed literature now highlight the necessity of adjustments at a local level to improve the accuracy of incidence estimates derived using recency assays within population-based surveys [13,19-28]. Beyond that primary application, however, many countries and organizations have become increasingly interested in using recency assays within HIV case surveillance systems and routine HIV testing services to measure indicators other than incidence, such as the identification of epidemiologically linked clusters of recent infections, geographic hotspots, or subpopulations with relatively high, ongoing, or emerging transmission, to inform prioritization of HIV prevention, testing, and partner notification or contact tracing interventions. These types of epidemic monitoring and evaluation strategies are generally referred to as “non-incidence surveillance use cases” for recency assays [29]. However, the nonrandom nature by which people are included in these types of surveillance systems and programs requires special attention to characterize and, ideally, mitigate the effect of selection biases on the accuracy of these non-incidence estimates.

To our knowledge, no previous systematic review has been completed of literature related to the use of HIV recency assays for surveillance purposes. We endeavored to identify published evidence that could be used to validate methodological approaches to HIV incidence estimation and other measures of recency of HIV infection using recency assays. Findings from this systematic review were designed to inform a revised technical guidance on the use of HIV recency assays for identification of epidemic trends, whether for HIV incidence estimation or for other non-incidence indicators of recency, to be released by the WHO and UNAIDS in 2022. This guidance is intended to help raise global awareness of benefits and pitfalls of the use of these assays for surveillance purposes, and set clear standards for their appropriate use.

Objectives

Our systematic review had 3 primary objectives:

1. Understand the use of recency testing in surveillance and programmatic and laboratory settings (to provide incidence estimates or for non-incidence surveillance use cases);
2. Review methodologies for implementing recency testing in population surveys, case surveillance systems, and routine monitoring and evaluation activities; and

3. Highlight use cases that have employed a recency assay or recent infection testing algorithm (RITA) within specific populations, with special attention to variations in assays, settings, and methods of analysis for calculating HIV incidence estimates or employing recency assays for non-incidence surveillance use cases. Within this category, one of our specific goals was to identify evidence that not only presents results of “proportion testing recent” or similar, but also reviews the methodological choice to use a simple proportion of recency or assess “factors associated with testing recent” as a proxy for HIV incidence or other indicators of ongoing HIV transmission within case surveillance systems.

Methods

Eligibility Criteria for the Systematic Review

The systematic review included 2 sets of searches, each with a different strategy. Strategy 1 involved looking for articles about recency assay performance in laboratory and field survey settings. To be eligible for inclusion in the review, articles

needed to describe some aspect of performance of recency assays/methodologies (eg, MDRI, FRR, accuracy, number tested, and proportion recently infected; or correlation, R, percent agreement, or kappa related to another standard assay) *and* needed to address validation of method. As we were not looking to perform a meta-analysis of assay performance (ie, MDRI or FRR in various study populations) but rather review the evidence regarding validity of various methodologies for the use of these assays for surveillance purposes, simply reporting the use of a recency assay with a specific MDRI and FRR was insufficient for inclusion. Rather, to be included articles needed to compare findings with those of another standard assay, or describe in detail the methodological choices made and rationale for doing so. They also needed to use commercially available assays/methodologies used to determine recency of infection (Table 1), as the primary motivation for the review was to inform the WHO/UNAIDS technical guidance that would only cover assays that could be purchased and implemented by countries according to package inserts. Articles reviewing the use of a laboratory-developed (home-grown) assay that was not commercially available were excluded from the review.

Table 1. List of commercially available recency assays at the time of the review.

Product name (manufacturer)	Assay type
Asanté HIV-1 Rapid Recency Assay (Sedia Biosciences)	Rapid, point of care
HIV Swift Recent Infection Assay (Maxim Biomedical)	Rapid, point of care
Sedia HIV-1 Limiting Antigen Avidity (LAg-Avidity) EIA (Sedia Biosciences)	Laboratory based
Maxim HIV-1 LAg-Avidity EIA Kit (Maxim Biomedical)	Laboratory based
Genetics Systems HIV-1/HIV-2 Plus O EIA (Bio-Rad, avidity protocol)	Laboratory based
ARCHITECT HIV Ag/Ab Combo (Abbott, avidity protocol or unmodified protocol)	Laboratory based
VITROS Anti-HIV 1+2 (Ortho Diagnostics, avidity protocol)	Laboratory based
Geenius HIV-1/2 Confirmatory (Bio-Rad, modified protocol)	Laboratory based
INNO-LIA HIV I/II Score (Fujirebio, Inc.)	Laboratory based
Sedia BED HIV-1 Incidence EIA (Sedia Biosciences)	Laboratory based

Strategy 2 involved looking for articles about surveillance and programmatic utilization of recency testing. To be eligible for inclusion, articles needed to describe some aspect of population-level utility (identification of “hotspots,” clusters, case surveillance, or incidence estimation), using commercially available recency assays/methodologies (eg, RITAs, adapted assay protocols) to determine recency of HIV infection. Studies could present either qualitative or quantitative data and could be descriptive studies lacking a comparator, as long as studies clearly presented outcomes specific to HIV recency testing.

Search Strategy

The literature search for the systematic review was conducted in PubMed and Web of Science, and included literature published in any language and in any indexed journal including preprint servers without peer review, from January 1, 2010, to November 11, 2021, by searching title, abstract, and MeSH terms/author keywords.

For the Strategy 1 search, search terms included HIV, recency assay, incidence assay, test for recent infection (TRI), recent infection testing algorithm (RITA), multiassay algorithm, performance, false recent rate/ratio (FRR), proportion false recent, and mean duration of recent infection (MDRI). For the Strategy 2 search, search terms included recent infection/acute infection, recent infection testing algorithm, multiassay algorithm, incidence estimates, case surveillance, hotspot identification, hotspot mapping, cluster detection, procedures and protocols, and HIV. See [Multimedia Appendix 1](#) for search sets and terms and [Multimedia Appendix 2](#) for the detailed search code.

Given that much of the research output in the field of HIV recency assay utilization is published in formal reports or presented in conference abstracts, we extended the search beyond traditional literature databases to include “gray literature,” that is, literature that is not formally published in peer-reviewed journals or books. We conducted a search of the gray literature through internet search engines and through

websites of major international funders, subject matter conferences, and organizations involved with HIV surveillance (Multimedia Appendix 3) employing the following search terms across sites: “surveillance,” “recency testing,” “case surveillance,” “incidence estimation,” “hotspot,” and “HIV”.

We used a step-wise approach during the screening and reviewing process. After search and duplicate removal, SF screened titles and abstracts to identify papers potentially related to the focus areas and eligibility criteria. After screening was complete, full text of remaining articles was then independently reviewed by DF and SS to determine if the study met eligibility criteria; SF served as a tiebreaker for any articles for which the 2 preliminary screeners were not in agreement about inclusion. Once the full-text review was complete, SF hand-searched the references of all included articles for additional, potentially

eligible articles. DF and SS then reviewed these articles and determined eligibility according to the process outlined above.

Prior to conducting our search, we developed a formal protocol and circulated it among stakeholders at the WHO and UNAIDS for approval; we have made the protocol available in unmodified form as Multimedia Appendix 4 to this article.

Assessment of Evidence Strength

The literature included in the systematic review was rated by strength of published evidence using a 23-point rubric that we designed custom for this purpose (Figure 1). For each piece of evidence, 3 team members (SF, DF, and SS) independently rated the strength of evidence through a Microsoft Excel-based scoring rubric designed to implement the grading structure detailed in Figure 1. If there was disagreement between 2 of the team members, the third performed an assessment using the rubric and served as a tiebreaker.

Figure 1. Rubric used to evaluate strength of evidence for each item reviewed. A score ranging from 1–5 was assigned to each item based on the 5 criteria in this rubric. Items with a score of 1 for source of information or detail in which methodology is described (see cells 1A and 1B with hatched shading) were automatically categorized as “weak evidence”, regardless of other criteria scores. Similarly, items with a score of 2 for detail in which methodology is described (see cell 2B with hatched shading) were automatically categorized as “moderately weak evidence” regardless of other criteria scores. Each item was then assigned an overall strength of evidence rating based on the sum of the criteria scores.

Criteria	Rubric scores and definitions				
	1	2	3	4	5
A. Source of information	Unpublished, not publicly available	Presentation, poster, conference abstract, or publication in a journal that is not peer reviewed	Formal published report, publicly available	Peer-reviewed publication in reputable journal	Peer-reviewed publication in reputable journal, with at least one citation
B. Detail in which methodology is described	No description, or description of using “standard methods” not specified	Citation of published methods/guidance used	General description of statistical methods	Detailed description of statistical methods, falling short of meeting STARD guidelines ^a	Detailed description of statistical methods, meeting STARD guidelines ^a where applicable
C. Scope and scale of program		Single-facility program	Program for a single/small set of regions, or focus on key populations	Large national survey or surveillance program	
D. Presence of protocol	No protocol for use of assays in surveillance use cases	Informal protocol for use of assays in surveillance use cases	Formal protocol for use of assays in surveillance use cases, but unpublished	Public, published formal protocol for use of assays in surveillance use cases	
E. Rigor of laboratory protocols	No specified quality assurance (QA) procedures or lab tech training	Informal QA procedures or initial but not ongoing training	Presence of local, formal QA and protocols, with minimal lab tech training	Presence of local, formal QA system and protocols for ongoing lab tech training	Use of international or national QA systems and robust lab tech training

^aStandards for Accuracy in Reporting Diagnostic studies (STARD) guidelines [111]



Overall strength of evidence based on total item score (total score range: 4-23)

Weak	Moderately Weak	Moderately Strong	Strong	Very Strong
4-5	6-10	11-16	17-21	22-23

Results

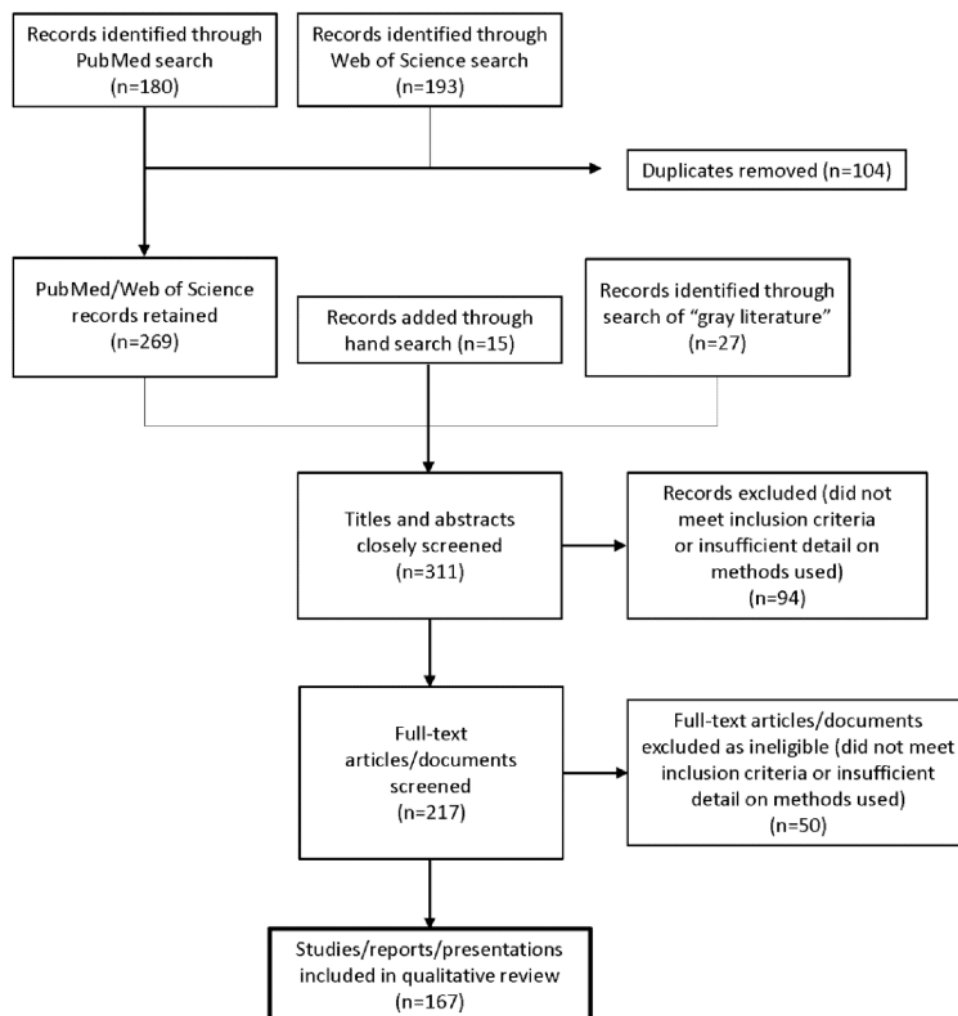
Overview

The search was conducted on November 11, 2021, and resulted in 180 records identified via MEDLINE (PubMed) and 193 records identified via Web of Science. Of these, 104 were duplicates, which were removed. An additional 27 records were identified through an internet search of gray literature and 15 records were identified through a hand search of the references in previously identified records.

Literature Screening Steps

After deduplication, the remaining 311 documents from the search were initially scanned by SF for eligibility. This initial “quick screen” excluded 94 articles that very clearly did not meet inclusion criteria for the review, or did not contain sufficient detail on methods to have utility in the review. The remaining 217 documents were then subjected to a full-text review, which was conducted independently by both DF and SS. After excluding 50 full-text articles that did not meet our predefined inclusion criteria, a total of 167 studies, reports, or presentations were retained across both focus areas (Figure 2) and were graded for strength of evidence.

Figure 2. Flowchart of search process and results.



Characteristics of Included Studies

Among the 167 pieces of evidence that were identified through the systematic review and that met the inclusion criteria, 91 (54.5%) [3,7-14,18,20-28,30-100] focused on assay performance, algorithm performance, or methodological descriptions of incidence estimation. The quality of evidence was “very-strong” (58/91), “strong” (21/91), “moderately strong” (9/91), and “weak” (3/91) in these 91 articles. The remaining 76 (45.5%) pieces of evidence described field-derived incidence and non-incidence use cases or both. Of these, 45 (59%) described use for incidence estimation, 25 (33%)

described non-incidence use cases, and 6 (8%) described both incidence and non-incidence use cases.

Among the 51 articles describing the use of recency assays for estimation of HIV incidence, 16 (31%) [101-116] described *national surveillance* in the form of population-based surveys (including 10 from the US-supported Population-based HIV Impact Assessment (PHIA) surveys). Another 12 (24%) [117-128] were also population-based surveys with a representative sampling strategy, but had a community-level (subnational) focus. Most evidence related to national or subnational incidence surveillance was judged to be “very strong” (10/28), “strong” (6/28), or “moderately strong” (8/28),

with more details of strength ratings found in [Multimedia Appendix 5](#). These population-based incidence use cases are also sometimes known as *impact assessment* use cases, because they are intended for repeat implementation to assess changes in incidence over time as a result of HIV prevention or care interventions. There were 3 more studies that also used recency assays to estimate incidence for intervention impact assessment, but in the more narrow context of blood donor policy implementation [129] or behavioral randomized controlled trials [130,131]. The remaining 20 articles [132-151] described calculation of incidence among *key* or *sentinel populations*, including those accessing routine HIV testing or blood donation programs. Key or sentinel population surveillance involves testing within populations that are either of specific interest because they are at higher risk for infection (key) or considered to be representative of a larger population (sentinel). Sentinel and key population surveillance may be facility based or community based. For example, needle and syringe distribution programs are a good point of contact with people who inject drugs, sexual health clinics may provide access to men who have sex with men and sex workers, and antenatal clinics are used to sample pregnant women. All evidence in this category was of “very strong” (5/20) or “strong” (15/20) quality ([Multimedia Appendix 5](#)).

Among the 31 articles describing non-incidence use cases, 24 used recency testing to assess risk factors predicting recent infection [126-128,149,150,152-170] for purposes of *targeted prevention planning*. A total of 6 used recency testing as part of cluster identification or analysis (including 5 that also used recency assays for determining risk factors associated with recency) [153,154,161,162,167,171], 2 used recency testing for geographic comparisons or hotspot mapping [172,173], and 5 used it for other purposes, including examining recency trends in the same population over time [166] and evaluating patterns of drug resistance [151,174-176]. One report was exploring feasibility and utility of incorporating recency testing into HIV programs, and simply reported recency proportions found through the project [151]. The quality of evidence was “very strong” (10/31) or “strong” (12/31), with the remainder (9/31, 29%) providing evidence that was “moderately weak” or “weak.”

[Multimedia Appendices 5](#) and [6](#) provide details on each of the 167 pieces of evidence included in this review, including the strength rating and topic of focus for each item.

Use of Recency Assays for HIV Incidence Estimation

There were 51 documents included in this review that provided methods and findings related to the field use of recency assays for HIV incidence estimation. As detailed above, 32 studies in this review used recency assays to estimate incidence for surveillance of subnational regions or key or sentinel populations; however, these strategies have also been used extensively at a national level. In 2015 the UNAIDS and WHO released guidelines on monitoring the impact of the HIV epidemic using population-based surveys, including using recency assays for estimation of incidence [177]. Since then, 16 population-based surveys with published results have utilized this approach for national surveillance, the majority (n=11)

[102-111,116] of which were part of the global PHIA [178] (including 1 that published an analysis using PHIA data, but was not an official PHIA report) [116]. These surveys involve cross-sectional, household-based, nationally representative sampling of adults and adolescents aged 15 years and older, with some surveys also including children aged 0-14 years. All PHIA countries were located in sub-Saharan Africa, except Haiti (which did not contribute evidence to this review) [179]. PHIA participants receive home-based HIV testing and counseling. Those who are HIV positive undergo a laboratory-based RITA. During the first 3 PHIA surveys in Malawi, Zimbabwe, and Lesotho, the RITA included the Sedia HIV-1 Limiting Antigen (LAg) Avidity assay in combination with viral load. The subsequent 7 surveys added antiretroviral detection to the LAg and viral load tests as an enhanced measure to distinguish recent from long-term infections. Incidence estimates were obtained from the RITA result in accordance with an established cross-sectional incidence estimator [4] and performance characteristics were consistently specified as MDRI = 130 days (95% CI 118-142), time cut-off = 1.0 year, and residual proportion false recent = 0.0%, with no uncertainty incorporated into the FRR parameter. No adjustment for subtype-related variation in MDRI was made, except in the case of Uganda, where an MDRI of 153 days was used due to Uganda’s subtype A and D-dominated epidemic [102]. Survey weights were utilized for all estimates to account for the complex sampling design. The sample size of PHIA surveys is designed to provide subnational-level (eg, provinces, regions) estimates of viral load suppression among people living with HIV aged 15-49 years with a 95% CI of $\pm 10\%$ or less, which typically yields reasonably precise estimates of national-level HIV incidence among people aged 15-49 years. As a result, these surveys were able to generate HIV incidence estimates disaggregated by sex and high-level region, but not estimates that could be used to target HIV prevention or care to specific districts or key populations.

In addition to the 10 PHIA studies, another 8 studies [113,117,119,134,137,140,145,147] used similar methods to calculate incidence—a published MDRI without local adaptation, and an assumed FRR of 0—and 6 used a published MDRI without reference to FRR (presumably also assuming no false recent results from the RITA) [112,118,126,130,131,136]. In each of these cases, the authors noted that by including viral load or other factors in the RITA designed to reduce FRR, further FRR adjustment was considered unnecessary. The other 27 studies used a variety of other approaches to address MDRI and FRR. Only 3 studies locally adapted both the MDRI and the FRR as part of the analysis [125,129,151]. One study locally adapted the MDRI by weighting for local subtype distribution but assumed 0 FRR [133], and 7 studies used a published MDRI but locally estimated the FRR based on internal data [114,120,121,123,132,138,143]. One study used an FRR of 0 for the main analysis, and compared incidence results with those generated assuming an FRR of 0.39% in a sensitivity analysis [124]. Two studies used a published MDRI and a published FRR (ie, from another study’s published findings of the assay’s FRR) that was different from 0 [116,148]. The remaining 13 studies estimated incidence using alternate estimators not

incorporating MDRI or FRR, both with adjustments of assay performance made for the local context [128,135,139,142,149] and no local assay-based adjustments [101,115,122,127,141,144,146,150].

Non-incidence Surveillance Use Cases of HIV Recency Assays

One of our objectives in the review was to identify evidence that not only presents results of “proportion testing recent” or similar, but also reviews the methodological choice to use a simple proportion of recency or assess “factors associated with testing recent” as a proxy for HIV incidence or another indicator of ongoing HIV transmission within case surveillance systems. Although there were 31 documents identified across the 11-year review period that were reporting on the use of recency assays for non-incidence use cases, all of those papers reported their estimates of non-incidence recency indicators (such as “proportion recent”) without attention to whether these indicators were valid proxies of ongoing HIV transmission. As many as 19 of these studies used a recency assay as part of a RITA (along with at least one other recency assay, viral load, CD4, or similar) to help reduce misclassification rates [126,127,151-156,159,163,165,167,168,170,172-176]. Three studies adjusted their recency calculations in some other way (eg, incorporating sensitivity or specificity of the assay into estimates) [149,158,180] and the remaining 9 used the assay results according to a prespecified cut-off with no further adjustment [150,157,160-162,164,166,169,171]. Recency proportions were typically presented as [number recent]/[number tested with recency assays] × 100%, with no articles reporting original results that discussed a strategic choice of denominator to improve validity. While 10 articles compared methods for addressing misclassification or referred to the challenges of assay misclassification as a remaining limitation in their analysis, most did not include this consideration in their report [127,148,151,153,155,161,163,166,168,169].

Evidence Documenting Assay Performance, Algorithm Performance, or Incidence Estimation Methodologies

Of the 91 studies devoted to assays, algorithms, or methods of incidence estimation, 59 evaluated the performance of 1 or more assays. Among these, 46 (78%) evaluated avidity assays (eg, Maxim HIV-1 LAg-Avidity EIA), 23 (39%) evaluated BED assays (eg, Sedia BED HIV-1 Incidence EIA), 4 (7%) evaluated rapid assays (Asanté HIV-1 Rapid Recency Assay, or Maxim Swift HIV Recent Infection Assay), and 3 (5%) evaluated comparative antigen reactivity assays (eg, Geenius HIV-1/2 Confirmatory–modified protocol). These studies reported various aspects of assay performance, including FRR (38/59), MDRI (31/59), sensitivity and specificity (10/59), and correlation of results between different assays (12/59). In addition, 20 of the studies explored a range of assay cut-off thresholds, to identify a cut-off that would achieve optimal FRR and MDRI results. Details of which studies are in which categories can be found in [Multimedia Appendix 6](#).

While 16 of the 59 studies utilized standard sample panels from the Consortium for the Evaluation and Performance of HIV Incidence Assays (CEPHIA) or other sources, the majority evaluated assays against patients from 1 or more geographic

regions, including Africa (20/59), North America (13/59, 12 from the United States), western Europe (11/59), east Asia (8/59), the Caribbean (3/59, Trinidad), eastern Europe (1/59, Estonia), and south Asia (1/59, Iran; [Multimedia Appendix 6](#)). Importantly, these studies found that key performance parameters, such as FRR, MDRI, optical density, or avidity index, were impacted by a wide range of patient characteristics, including ART treatment status (18/59); HIV viral load levels (16/59); HIV subtype (10/59); elite controllers or slow progressors (8/59); low CD4 count, advanced infection, or AIDS (6/59); sex (4/59); risk factors such as male sex, injection drug use, or sex work (2/59); postpartum status (1/59); and sample type (plasma vs dried blood spot, 1/59).

In addition to the studies examining assay performance, another 19 of the 91 examined the performance of algorithms that included 1 or more recency assays ([Multimedia Appendix 6](#)). Among these, 11/19 (58%) evaluated algorithm FRR, 9/19 (47%) evaluated MDRI or other window parameters, and 9/19 (47%) evaluated algorithm impact on incidence estimates. The studies evaluated algorithm performance among patients from a variety of regions, including Africa (12/19), North America (6/19, 5 United States and 1 Mexico), South America (1/19, Brazil), western Europe (1/19), and east Asia (1/19). Among these studies, algorithm performance was found to be impacted by patients’ ART status (4/19), HIV viral load (3/19), CD4 count or advanced infection (3/19), and HIV subtype (2/19).

While most of these studies examined only 1 or a handful of algorithms, those by Laeyendecker et al [75,76], Kassanje et al [54], Konikoff et al [24], and Brookmeyer et al [41] explored the performance of hundreds to thousands of potential algorithm configurations, involving numerous combinations of cut-off values across several assays applied to a common set of samples, to identify optimal algorithms for the specific assays used.

Finally, 13 of the 91 studies addressed various aspects of methodologies for estimating incidence using recency assays. While these studies represented a diverse assemblage, they fell broadly into several categories. A total of 5 presented statistical methodologies for managing uncertainties in the window periods of recency assays [12,33,40,67,70]; 3 provided a comparison of the results of assay-based estimates of HIV incidence with estimates using other incidence methods such as longitudinal surveys, acute infection (RNA positive/antibody negative) staging within cohorts, and dynamic models such as UNAIDS Estimation Projection Package (EPP)/Spectrum and Thembisa [39,43,57]; 2 studies presented novel statistical methods for estimating HIV incidence from the use of recency assays in cross-sectional surveys [31,48]. Bao et al [46] adapted the UNAIDS EPP to incorporate data from incidence assays, to narrow the uncertainty intervals of estimated incidence. The 2015 meeting report from the WHO Working Group on HIV Incidence Assays reviewed various early efforts to estimate incidence through HIV case surveillance using recency assays [18]. Finally, Welte et al [3] proposed a set of optimal characteristics for recency assays as a potential guide for the future development of new assays for estimating incidence.

Discussion

Principal Findings

Despite the widespread use of HIV recency assays for both HIV incidence estimation and non-incidence surveillance use cases, evidence on validated and accurate uses of recency assays for non-incidence surveillance remains weak. Based on the evidence identified through this review, there is a clear rationale for the use of recency assays for population-level HIV incidence estimation, and convincing evidence regarding best practices for this use.

In the meantime, while already in wide use, use of recency assays for non-incidence use cases remains questionable. Godin and colleagues [181] recently presented results of a simulation analysis to compare the accuracy of various HIV recency indicators as a proxy for incidence, using different denominators for the proportions calculated. (As they did not report any original recency testing results, this paper was not eligible for inclusion in this review.) In this comparison, the authors found that recency indicators calculated as the [number of recent results]/[number of HIV-positive tests]—as is commonly used among the studies contained in this review—was not, in fact, a satisfactory proxy for HIV incidence, and in some cases even resulted in identifying temporal trends in an opposite direction from the incidence trend. Godin et al [181] suggested that estimating the proportion recent as the [number of recent results]/[number of people at risk for HIV acquisition] was more indicative of incidence trends; however, this method of calculating recency in non-incidence use cases was not reported by any of the studies or programs found in our review.

There were 24 analyses included in this review that assessed predictors or correlates of recent infection. Implied in these analyses is an assumption that subgroups with significantly greater odds of recent infection are currently experiencing *more* HIV transmission than other subgroups, and that the disparity could be intervened upon by targeting public health prevention efforts to these subgroups. Our analysis, which identified scant evidence validating this methodological assumption, highlights the wasteful expenditures in the public health response to HIV. Misidentification of clusters, hotspots, and other imprecisely defined proxy indicators of incidence through recency testing may result in misdirected or poorly designed prevention plans and missed opportunities for targeting limited resources. Simple calculation of a “proportion recent” in an HIV testing setting may be difficult to interpret, and is affected by both the denominator used (ie, new HIV diagnoses versus people at risk for HIV) and changes in testing coverage and frequency of diagnostic testing in the population. An unexpectedly high or rising proportion of new diagnoses being classified as recent infections may indicate either (1) ongoing transmission or (2) that the testing program is capturing more recent infections because most older infections have already been diagnosed.

More evidence about the appropriate interpretation and use of these types of indicators is necessary.

More reports of countries or studies using HIV recency assays for identification and mapping of geographic hotspots will likely emerge as a result of the US President’s Emergency Plan for AIDS Relief (PEPFAR) “TRACE” initiative (Tracking with Recency Assays to Control the Epidemic) in the near future. Beginning in fiscal year 2019, PEPFAR funded 16 countries (El Salvador, Eswatini, Ethiopia, Guatemala, Kenya, Lesotho, Malawi, Namibia, Nicaragua, Panama, Rwanda, Tanzania, Uganda, Vietnam, Zambia, and Zimbabwe) who are nearing the 90-90-90 targets to introduce the TRACE initiative [182]. Through TRACE, a lateral flow rapid recency assay is conducted as a supplementary test in routine HIV testing services or within HIV case surveillance—combined with viral load results where possible—to detect recent infection among people newly diagnosed with HIV in all (or most) facility- and community-based testing sites in a country to drive prevention and care planning. Hopefully findings from these efforts will be forthcoming in the literature, along with further evidence validating the use of recency assays for this purpose.

Limitations

There are several limitations to our systematic review. First, given our search strategy many of the articles included in this review involved findings relevant to the performance of specific commercially available recency assays. However, some of those assays (eg, the Sedia BED HIV-1 Incidence EIA) are technically available but no longer in wide use, due to inferior performance for HIV incidence estimation compared with other available assays. Further, some assays included in this review are not available in all countries globally. Second, as with all systematic reviews, our review was time limited. Therefore, it is possible that some relevant literature that has been recently published or that was missed by our choice of search terms in the prespecified protocol is not included in this review.

Conclusions

Surveillance strategies to accurately estimate HIV incidence or detect patterns of recent transmission are critical to global efforts to end the HIV epidemic. However, these calculations are only useful if they are timely and accurate, with potential biases clearly defined. Calculations that are considerably higher or lower than reality may result in incorrect interpretations of the data, and misalignment of resources as a result. This review found ample evidence to guide the use of recency assays in population-based surveys to accurately estimate HIV incidence. However, more research is needed to validate their use within HIV testing services and to explore best practices for calculating HIV recency indicators other than incidence to ensure that findings from recency testing can be accurately interpreted to guide prioritization of public health programming.

Conflicts of Interest

SNF and EG have received consulting income and research support from Sedia Biosciences Corporation, Gilead Sciences, and through the CDC-funded TRACE program, as a subcontract from the University of California, San Francisco.

Multimedia Appendix 1

Search sets and terms used for title, abstract, and MeSH terms/author keyword searches.

[\[DOCX File, 14 KB - publichealth_v8i3e34410_app1.docx\]](#)

Multimedia Appendix 2

Search code.

[\[DOCX File, 14 KB - publichealth_v8i3e34410_app2.docx\]](#)

Multimedia Appendix 3

Websites searched for eligible grey literature during the review.

[\[DOCX File, 14 KB - publichealth_v8i3e34410_app3.docx\]](#)

Multimedia Appendix 4

Assessing the utility of HIV recency assays for surveillance purposes: systematic review protocol.

[\[DOCX File, 157 KB - publichealth_v8i3e34410_app4.docx\]](#)

Multimedia Appendix 5

Sources identified during a systematic review of the literature (as described in the 'Methods' section) are organized below. Sources are ordered by (1) literature type (peer-reviewed vs gray), then (2) strength of evidence (highest to lowest), and then (3) last name of the first author (alphabetical).

[\[DOCX File, 121 KB - publichealth_v8i3e34410_app5.docx\]](#)

Multimedia Appendix 6

Evidence included in this review, including the strength rating and topic of focus for each item.

[\[XLSX File \(Microsoft Excel File\), 27 KB - publichealth_v8i3e34410_app6.xlsx\]](#)

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Abbreviations

ART: antiretroviral therapy

CEPHIA: Consortium for the Evaluation and Performance of HIV Incidence Assays

EPP: Estimation Projection Package

FIND: Foundation for Innovative Diagnostics

FRR: false recent rate

LAg: limiting antigen

MDRI: mean duration of recent infection

PHIA: Population-based HIV Impact Assessment

RITA: recent infection testing algorithm

TRI: test for recent infection

UNAIDS: United Nations Programme on HIV/AIDS

WHO: World Health Organization

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Original Paper

Evaluating the Increased Burden of Cardiorespiratory Illness Visits to Adult Emergency Departments During Flu and Bronchiolitis Outbreaks in the Pediatric Population: Retrospective Multicentric Time Series Analysis

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Abstract

Background: Cardiorespiratory decompensation (CRD) visits have a profound effect on adult emergency departments (EDs). Respiratory pathogens like respiratory syncytial virus (RSV) and influenza virus are common reasons for increased activity in pediatric EDs and are associated with CRD in the adult population. Given the seasonal aspects of such challenging pathology, it would be advantageous to predict their variations.

Objective: The goal of this study was to evaluate the increased burden of CRD in adult EDs during flu and bronchiolitis outbreaks in the pediatric population.

Methods: An ecological study was conducted, based on admissions to the adult ED of the Centre Hospitalier Universitaire (CHU) of Grenoble and Saint Etienne from June 29, 2015 to March 22, 2020. The outbreak periods for bronchiolitis and flu in the pediatric population were defined with a decision-making support tool, PREDAFLU, used in the pediatric ED. A Kruskal-Wallis variance analysis and a Spearman monotone dependency were performed in order to study the relationship between the number of adult ED admissions for the International Classification of Diseases (ICD)-10 codes related to cardiorespiratory diagnoses and the presence of an epidemic outbreak as defined with PREDAFLU.

Results: The increase in visits to the adult ED for CRD and the bronchiolitis and flu outbreaks had a similar distribution pattern (CHU Saint Etienne: $\chi^2_3=102.7$, $P<.001$; CHU Grenoble: $\chi^2_3=126.67$, $P<.001$) and were quite dependent in both hospital settings (CHU Saint Etienne: Spearman $\rho=0.64$; CHU Grenoble: Spearman $\rho=0.71$). The increase in ED occupancy for these pathologies was also significantly related to the pediatric respiratory infection outbreaks. These 2 criteria gave an idea of the increased workload in the ED due to CRD during the bronchiolitis and flu outbreaks in the pediatric population.

Conclusions: This study established that CRD visits and bed occupancy for adult EDs were significantly increased during bronchiolitis and pediatric influenza outbreaks. Therefore, a prediction tool for these outbreaks such as PREDAFLU can be used to provide early warnings of increased activity in adult EDs for CRD visits.

KEYWORDS

respiratory infections; emergency departments; flu outbreak; bronchiolitis outbreak; cardiorespiratory illness; time series analysis; influenza; bronchiolitis; outbreak; pediatrics

Introduction

Respiratory infections have a strong impact on the number of visits in pediatric emergency departments (EDs) during the epidemic periods of flu and bronchiolitis [1]. Seasonal respiratory pathogen activity is also linked to increased use of health care services across patients of all ages [2,3]. In the pediatric population, a diagnosis of a respiratory infection is easy to make. The broad use of rapid flu tests in the pediatric ED allows an easy and precise diagnosis of flu infections. The symptoms of bronchiolitis are well identified and lead to an easy diagnosis. In the adult population, increased activity in the adult ED during respiratory pathogen activity is related to an excess of respiratory complaints [4] but also with more diverse causes, mostly due to patient comorbidities [5].

In the pediatric ED, influenza activity and respiratory syncytial virus (RSV) circulation are the main cause of seasonal overload. The PREDAFLU application was developed for the Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne in order to anticipate the overload of activity due to respiratory infections in the pediatric population. This application allows a real-time analysis of pediatric emergency admissions in order to provide an early warning of increased activity related to influenza and bronchiolitis [6,7]. This surveillance helps determine the level and trend of respiratory infections. When an outbreak of respiratory infection is identified, this information is used to trigger additional resources in the hospital: physicians, nurses, beds. This knowledge allows pediatric EDs to be more agile and better prepared for the additional load. For the adult population, the increase in activity, morbidity, and mortality due to respiratory infections represents a significant burden for health services [8-10]. Although an accurate tool such as PREDAFLU is available in pediatrics, it is a challenge for the adult population [11,12].

This challenge is indeed illustrated in [Multimedia Appendix 1](#). Taking all the pathogen codes associated with respiratory infections, the daily patient flow is displayed. It is very clear on this figure that the number of patients evolves in a quasiperiodic way on the one hand but with several periodicities and an extremely important variability. We also notice that infections are diagnosed during the summer months, which has no correlation with a viral presence of influenza or RSV and does not cause any noticeable congestion in the EDs. In order to have the same conditions of preventive detection as the conditions of exercise in the PREDAFLU tool, we used the set of early detectors in PREDAFLU on the adult patient flow. As we could expect, the detectors detected the start of an epidemic in the months of June, July, or December. Even if we suppress the June or July alarm, the detection obtained is much later than the detection proposed by the pediatric patient analysis. This indicates the difficulty of giving an early, daily, and reliable alarm for the increase in adults.

Given that the pathogens, RSV and influenza virus, are common for both populations, using PREDAFLU as an early detector of increased activity for both the pediatric and adult populations would add value for the ED.

The primary objective of this study was to determine if the increase in CRD admissions to the adult ED during respiratory infection outbreaks in the pediatric ED, as defined by the decision-making tool PREDAFLU, was a significant parameter. The underlying idea was to provide an early warning of adult ED overload due to CRD by using pediatric data. The pediatric data were extracted by using an easy and already readily available tool.

We also aimed to determine if the occupancy of the ED, percentage of occupancy for CRD diagnosis compared with total occupancy, mean length of ED stay, and ratio of admissions for CRD visits in the adult ED could be discriminating parameters with respect to respiratory infection outbreaks.

Methods

Ethics Consideration

This study does not involve intervention on humans, but is an analysis of "emergency room summaries" carried out in accordance with the decrees governing clinical research in France, in particular with regard to the information to be provided to individuals. However, our study started before 2018, the date of promulgation of the decrees, and therefore is not subject to this law [5]. In view of these elements, we have no ethical elements to report according to the French authorities.

The Advisory Committee on Data Processing regarding research in the Field of Health (Comité Consultatif sur le Traitement de l'Information en matière de recherche dans le domaine de la Santé [CCTIRS] Number: 16-660) and the Commission Nationale de l'Informatique et des libertés ([CNIL] Number: DR-2017-394) authorized the collection and the processing of data for this project.

Study Design

This was an ecological study design based on a retrospective review of data related to admissions to the adult ED. The data processed were raw epidemiologic descriptive data.

CHU Grenoble is located in the heart of Grenoble, a city of about 450,000 inhabitants. In 2019, the adult ED had 59,546 admissions, and the pediatric ED had 33,000 admissions. CHU Saint Etienne is located in an agglomeration of 400,000 inhabitants, and its adult and pediatric EDs registered 53,081 and 35,000 admissions, respectively, in 2019.

Patients were managed similarly within the 2 ED hospital facilities. A triage nurse would start with an evaluation of the patient in order to guide them to the most appropriate emergency area. The care would start in the ED, and then, depending on

the clinical state and type of care or investigations required, the patient would be sent home, be transferred to a short stay unit (SSU; Unité d'Hospitalisation de Courte Durée), or be admitted to a medical ward within the hospital. The length of stay in the SSU was different depending on the hospital and the local setting. The decision to direct a patient to the SSU or a standard hospital service was affected by multiple factors including the pathology severity, need for specialized care management, or availability of downstream beds. When a patient was admitted to the SSU, they could either be sent back home after appropriate

care or be transferred to another service in the hospital depending on bed availability and type of care required. We can therefore infer that, although the 2 hospitals had similar care pathways, the length of stay in the different services (ED or SSU) could be quite different.

Records for the patient visits to EDs in CHU Saint Etienne and Grenoble (France) from June 29, 2015 to March 22, 2020 were extracted from the Résumés de Passages aux Urgences database (Table 1).

Table 1. Population and emergency department (ED) visits from July 2015 to March 2020.

Visit characteristics	During respiratory infection outbreak period	Outside a respiratory outbreak period	All periods
Total ED visits: CHU^a Grenoble			
Number of visits	96,870	159,999	256,869
Mean age (years)	51.54	50.95	51.18
Men, n (%)	51,922 (53.60)	87,055 (54.41)	138,992 (54.11)
Total ED visits: CHU Saint Etienne			
Number of visits	106,866	139,544	247,410
Mean age (years)	47.87	47.29	47.55
Men, n (%)	57,088 (53.42)	75,284 (53.95)	132,909 (53.72)
ED visits with cardiorespiratory diagnoses: CHU Grenoble			
Number of visits	6213	6148	12,361
Mean age (years)	73.35	75.86	74.9
Men, n (%)	3284 (52.86)	3460 (56.28)	6744 (54.56)
ED visits with cardiorespiratory diagnoses: CHU Saint Etienne			
Number of visits	6507	6030	12,537
Mean age (years)	74.34	74.64	74.5
Men, n (%)	4837 (52.25)	3338 (55.36)	6785 (54.12)

^aCHU: Centre Hospitalier Universitaire.

Study Protocol

Population

All the admissions to the EDs of CHU Saint Etienne and Grenoble from June 29, 2015 to March 22, 2020 were included in the study. Both hospitals had independent but identical information systems. The 2 hospitals used the International Classification of Diseases (ICD)-10 standard for the classification and standardization of diagnoses. Given the high number of diagnostic codes available, the way a diagnosis was coded in the system could vary from one hospital or one physician to another. Thus, in order to insure the most exhaustive selection among the admissions while obtaining comparable data between the 2 hospitals, we identified all the ICD-10 codes that could be used in cases of CRD diagnosis (Multimedia Appendix 2). This selection was made with the assistance of emergency specialists accustomed to the use of

the system, with the objective of having an exhaustive list of diagnostic codes.

The data related to adult ED admissions for CRD diagnosis were thus aggregated by week for the period studied. Admission data linked to ICD-10 codes for CRD were also compared with the data based on all admissions to the ED, regardless of ICD-10 diagnosis.

With regard to the adult population, there was no seasonal increase in activity in terms of weekly number of ED visits in CHU Saint Etienne or Grenoble (Figure 1). Nevertheless, during respiratory pathogen activity, the ED experienced increased workload that could be identified on a time series graph of the occupancy for all ICD-10 diagnoses (Figure 2). In January 2016, the number of visits to the ED of CHU Grenoble nearly doubled compared with 2015. This was due to the merger of 2 EDs in Grenoble. The drop in the number of ED visits or occupancy seen in March 2020 was due to the COVID-19 outbreak.

Figure 1. Time series of emergency department (ED) visits for all diagnoses at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne.

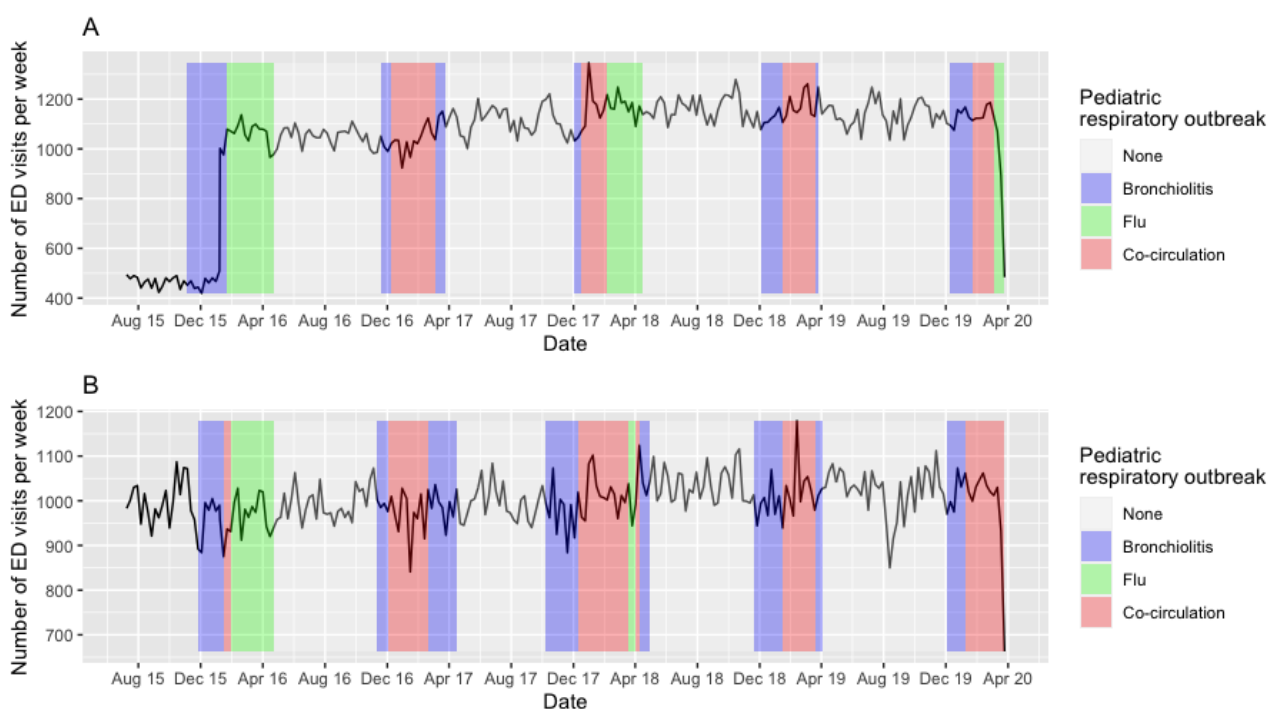
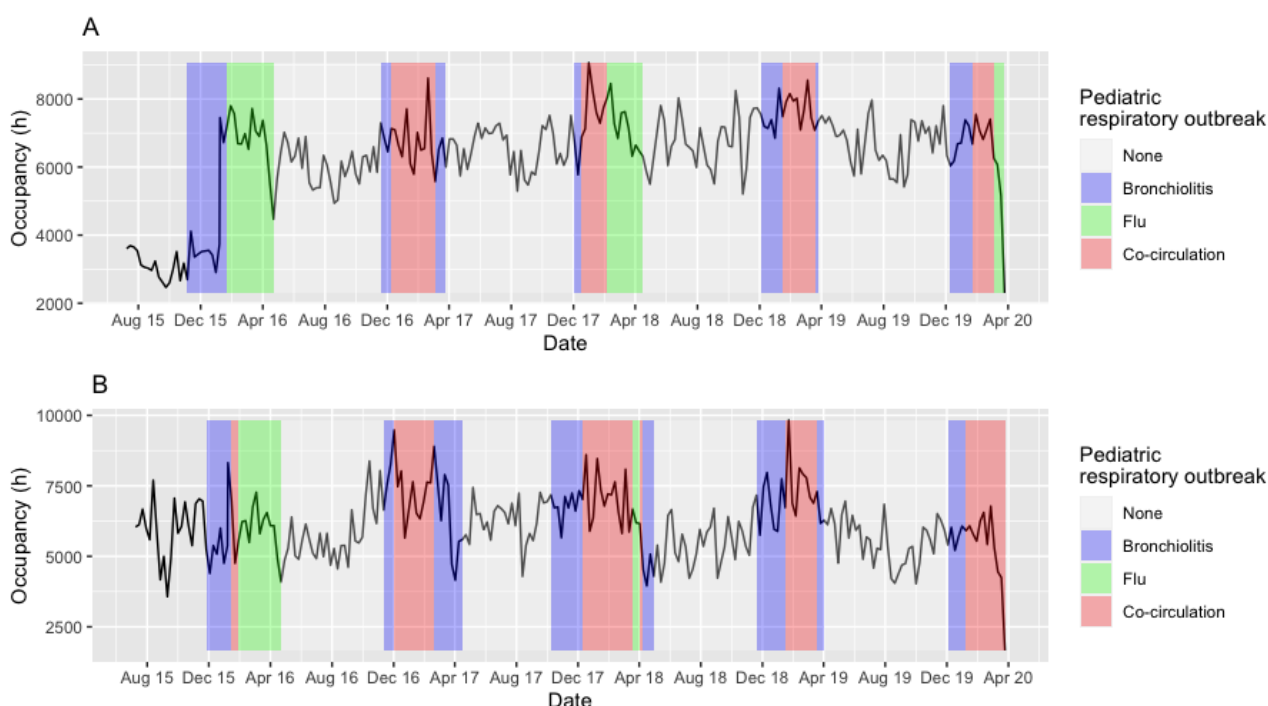


Figure 2. Time series of emergency department (ED) occupancy for all diagnoses at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne.



Respiratory Virus–Related Infection Outbreaks in Pediatric EDs

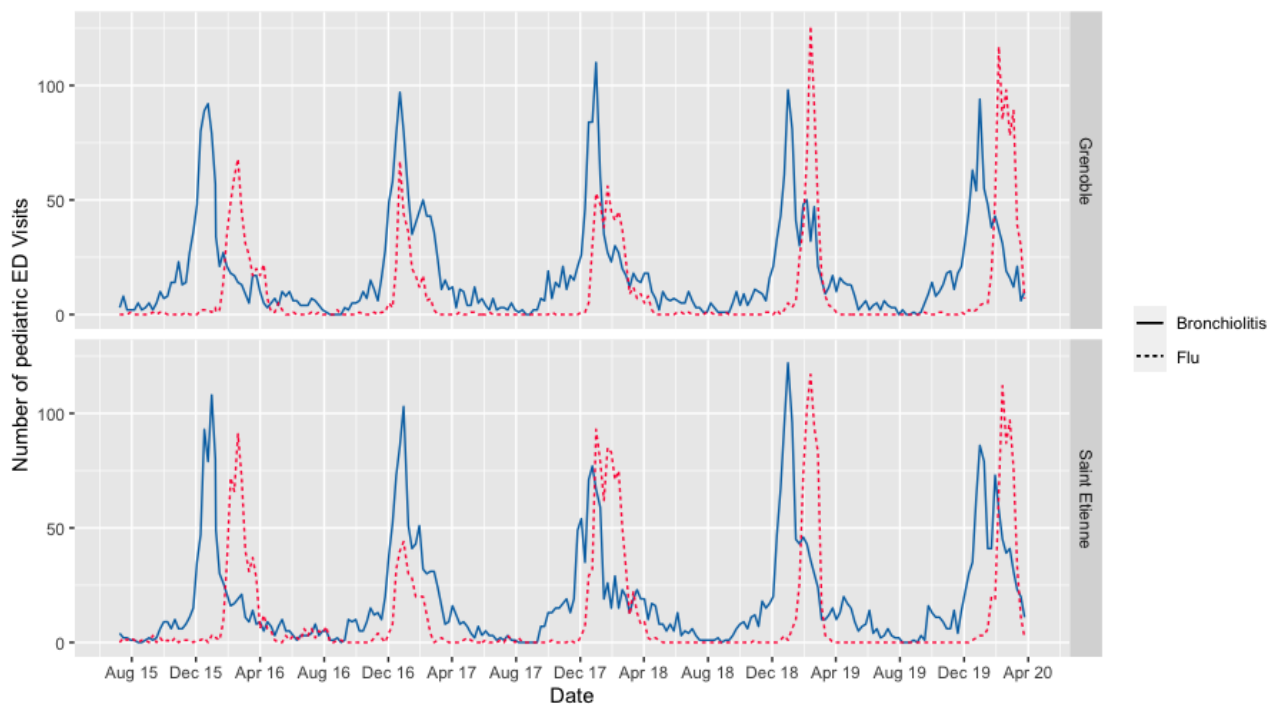
The web application PREDAFLU is a web-based decision-making support tool used in pediatric EDs to provide real-time activity monitoring of epidemic episodes of flu and bronchiolitis. The definition of an outbreak period is set in PREDAFLU [6,7] with 50%, 80%, and 100% confidence levels. We decided to define an outbreak period when a 50% confidence

was proposed. A flu outbreak was defined as 3 consecutive days of positive tests. A bronchiolitis outbreak was defined as a sudden increase in the number of admissions for this diagnosis, compared with usual trends. Therefore, PREDAFLU allowed a precise definition of the timeframe of epidemic periods between July 2015 and March 2020 (Multimedia Appendix 3). Since the web application took into account the data based on pediatric ED admissions in both CHU Saint Etienne and Grenoble (Figure 3) to define the onset of outbreaks, the dates

of outbreaks may vary from one hospital to the other. The advantage of PREDAFLU is that it provides a real-time definition of the periods, whereas the true epidemic periods can

only be determined retrospectively. As a consequence, the defined PREDAFLU periods were not true epidemic periods and were larger than the true epidemic periods.

Figure 3. Time series of bronchiolitis and flu outbreaks in the pediatric emergency department (ED) at Centre Hospitalier Universitaire (CHU) Grenoble and CHU Saint Etienne.



Statistical Analysis

All analysis was performed on a weekly basis (Monday to Sunday) based on the date of ED attendance. The number of the week was calculated using the ISO 8601 standard. For each week, each hospital center, and all ICD-10 codes, several elements were calculated: the number of ED admissions, ED occupancy, mean length of stay in the ED, percentage of bed occupancy, and percentage of total ED visits.

The nonparametric Kruskal-Wallis variance analysis test was used to determine the differences among the number of ED visits for the identified ICD-10 codes depending on the presence of bronchiolitis or flu outbreaks in the pediatric population. The Spearman correlation test was used to analyze the dependency between the number of adult ED admissions with a diagnosis of CRD and the weekly categorization during or outside epidemic outbreak. The Dunnett test was used to perform a pairwise comparison of the number of ED admissions during each outbreak period (bronchiolitis, flu, or cocirculation) with the number of ED admissions outside the outbreak period. Then, box-whisker plots detailed the results with the median and the 95% CI for each outbreak. Further analysis of variance was conducted to determine if the presence of respiratory infection outbreaks had an impact on other criteria of the health care pathway. The analysis was carried out on the total ED occupancy, percentage of total occupancy, mean duration in the ED, and percentage of total ED visits for the identified ICD-10

diagnostic code. The analysis on these secondary criteria was performed with the same statistical method as for the main criteria.

All analyses were performed using R v3.6.4 (The R Foundation for Statistical Computing).

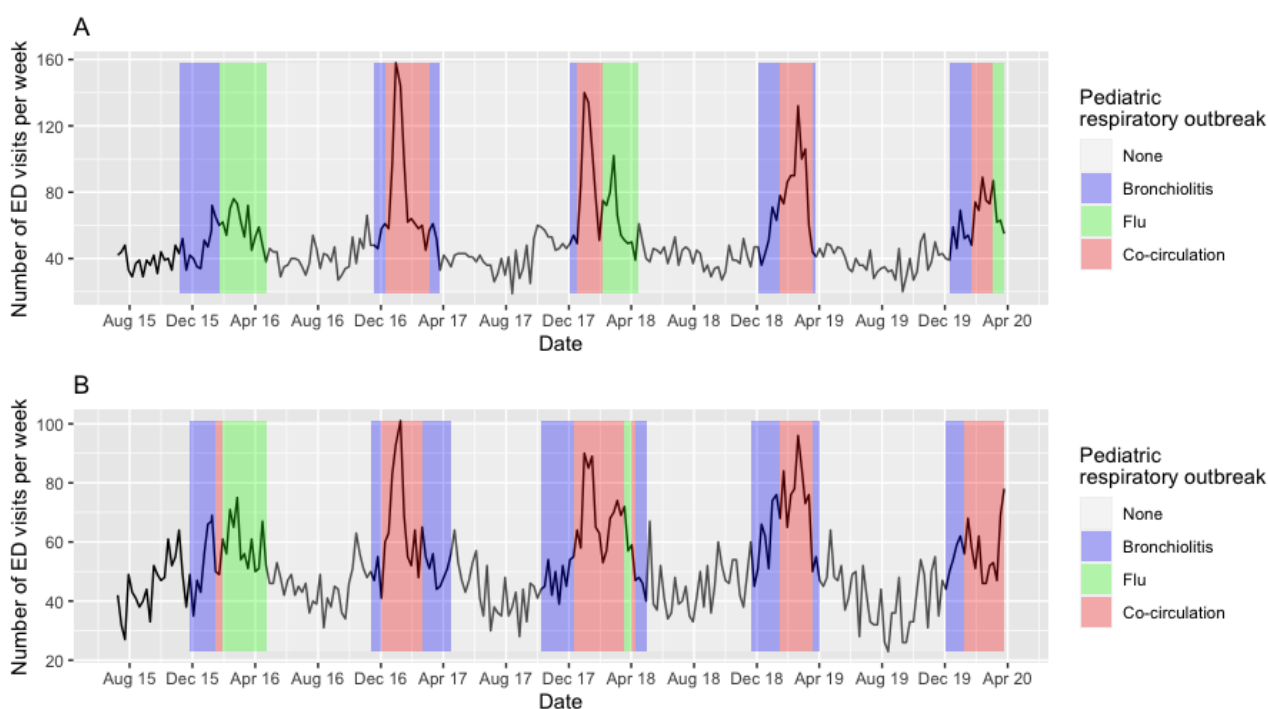
Results

Statistical analyses were performed on all the CRD admissions to the adult ED of CHU Saint Etienne and Grenoble from June 29, 2015 to March 22, 2020. The variation of these data, aggregated by weeks, was then analyzed regarding the virus circulation period in the pediatric population.

CRD ED Visits: Descriptive Analysis of the Time Series

For all the identified ICD-10 diagnostic codes, the pattern of the number of weekly visits to the adult ED increased during the outbreak periods of flu and bronchiolitis in the pediatric population for the 5 years studied and in a similar manner at CHU Saint Etienne and CHU Grenoble (Figure 4). During the winter of 2015-2016, the period of cocirculation of bronchiolitis and flu was very short compared with the other years. The peak of the ED visits was lower than the other winters in which the cocirculation period is much more important. For the winters of 2016-2017, 2017-2018, 2018-2019, and 2019-2020, the peak of weekly visits was similar in magnitude and occurred mainly during the cocirculation period.

Figure 4. Time series of emergency department (ED) visits for a cardiorespiratory decompensation diagnosis at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne.



Variance Analysis of the Number of ED Visits Related With Respiratory Infection Outbreaks in the Pediatric Population

The analysis of the data for CHU Saint Etienne showed that the median number of ED visits during the outbreak period was 56 (95% CI 54-61) compared with 44 (95% CI 42-46) outside the outbreak periods (ie, a median increase of 12 ED visits per week for CRD pathologies). The difference between these 2 groups, based on the Kruskal-Wallis test, was significant ($\chi^2_3=102.7$, $P<.001$). The Spearman test showed a moderate positive monotone dependency between the number of ED visits for CRD and the presence of an outbreak as defined by PREDAFLU ($\rho=0.67$; $P<.001$).

The analysis of the data for CHU Grenoble showed that the median number of ED visits during the outbreak period was 60 (95% CI 55-63) compared with 40 (95% CI 38-42) outside the outbreak periods (ie, a median increase of 20 ED visits per week for CRD pathologies). The difference between these 2 groups, based on the Kruskal-Wallis test, was significant ($\chi^2_3=126.67$, $P<.001$). The Spearman test showed a moderate positive correlation between the number of ED visits for CRD and the presence of an outbreak as defined by PREDAFLU ($\rho=0.71$; $P<.001$).

In addition to the analysis of the link between number of ED visits for CRD and respiratory infection outbreaks in the pediatric population, distinct and separate peaks were observed when breaking down the outbreak periods per respiratory infection type outbreak. We identified 4 different periods. The

first period involved no respiratory illness diagnoses in the pediatric ED. The second period corresponded to a bronchiolitis outbreak. The third one was a flu outbreak. And finally, the fourth period was during outbreaks of both bronchiolitis and flu.

The analysis of the data for CHU Saint Etienne showed that the median numbers of ED visits were 51 (95% CI 48-55) during the bronchiolitis outbreak, 59 (95% CI 51-71) during the flu outbreak, and 64 (95% CI 58-69) for flu and bronchiolitis (Figure 5).

The analysis of the data for CHU Grenoble showed that the median numbers of ED visits were 51 (95% CI 46-54) during the bronchiolitis outbreak, 62 (95% CI 53-72) during the flu outbreak, and 76 (95% CI 62-90) for flu and bronchiolitis.

The Dunnett test was used to perform a multiple comparison of the number of ED visits during each outbreak period. The chosen reference for the Dunnett test was the period with no respiratory illness. The Dunnett test was significant for all comparisons (all, $P<.001$). It also highlighted the largest difference for the outbreak period with both bronchiolitis and flu. The results were similar for CHU Saint Etienne and CHU Grenoble (Table 2).

The number of CRD visits to the adult ED of CHU Saint Etienne and Grenoble was a discriminating parameter for populations determined by the nonepidemic and epidemic periods. As a result, the increase in median visits significantly corresponded with the epidemic period defined by PREDAFLU. This increase was also significant for the outbreak of flu alone or bronchiolitis alone but to a lesser extent.

Figure 5. Box-whisker plots of the number of emergency department (ED) visits at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne. CRD: cardiorespiratory decompensation.

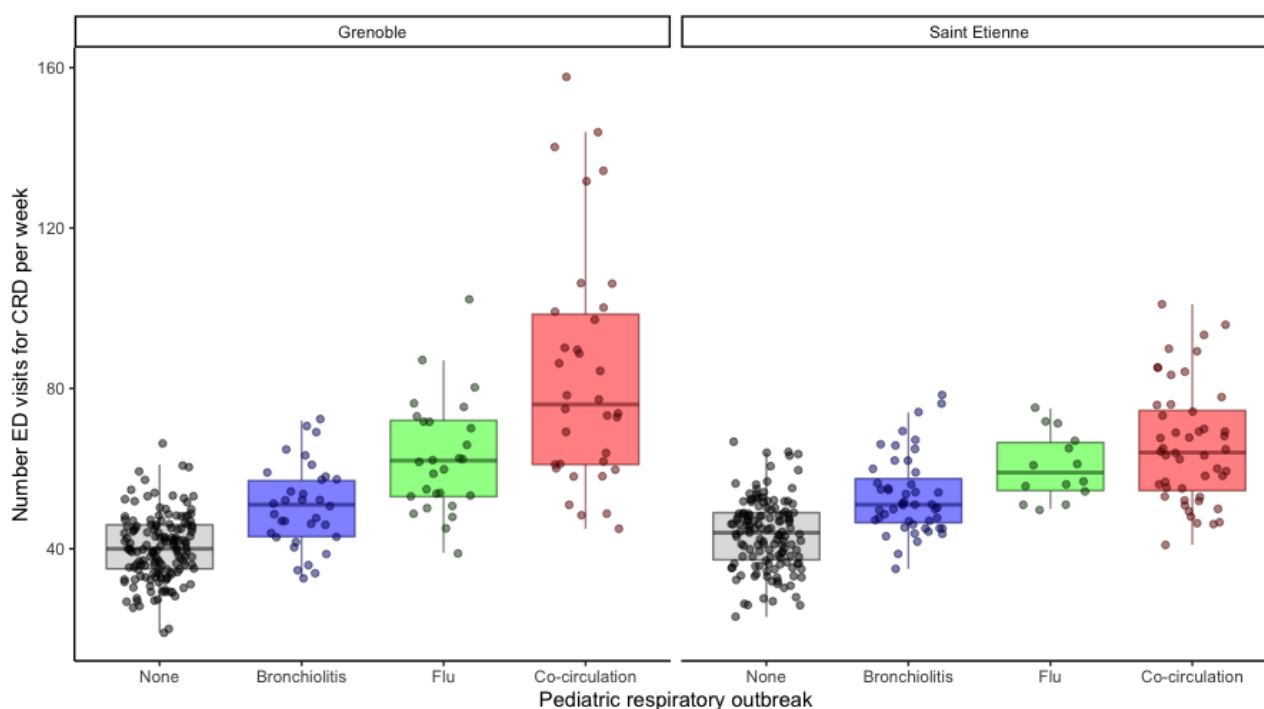


Table 2. Dunnett test for multiple comparisons of the number of emergency department (ED) visits for cardiorespiratory decompensation at Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne.

Reason for ED visit	Estimated number of visits	SE	<i>t</i> value	<i>P</i> value
CHU Grenoble				
Bronchiolitis: none	+10.430	2.689	3.878	<.001
Flu: none	+22.490	2.925	7.689	<.001
Cocirculation: none	+43.676	2.657	16.440	<.001
CHU Saint Etienne				
Bronchiolitis: none	+9.524	1.745	5.459	<.001
Flu: none	+16.790	2.897	5.795	<.001
Cocirculation: none	+22.040	1.731	12.733	<.001

Results for Secondary Criteria

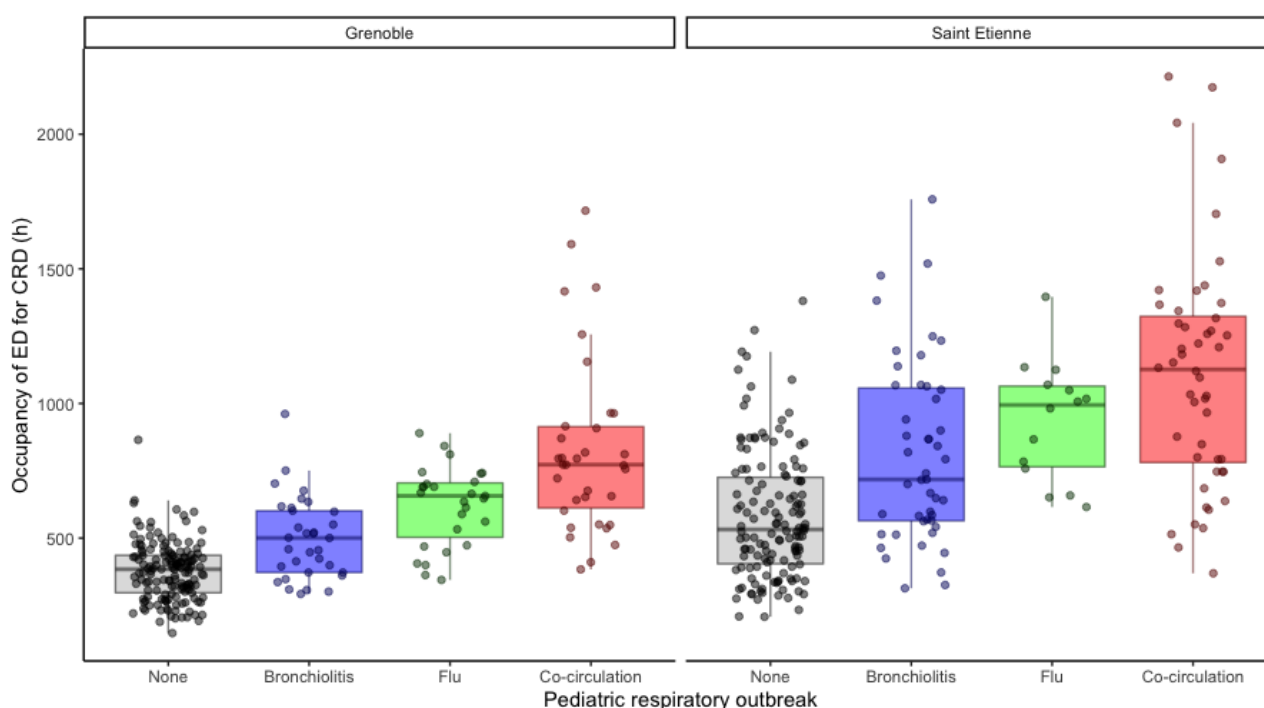
Analysis by Total Occupancy in the ED for a CRD Diagnosis

The total occupancy in the ED for CRD was defined by the total time spent in the ED for all CRD visits during a given week. The difference between the outbreak periods, based on the Kruskal-Wallis test, was significant for CHU Saint-Etienne ($\chi^2_3=75.071$, $P<.001$) as well as for CHU Grenoble ($\chi^2_3=107.12$, $P<.001$). The Spearman test showed no real monotone dependency between the occupancy per hour for CRD diagnosis

and the presence of an outbreak as defined by PREDAFU (CHU Saint Etienne: $\rho=0.55$, $P<.001$; CHU Grenoble: $\rho=0.65$, $P<.001$). The monotone dependency was weaker when considering the occupancy compared with the total number of ED visits. The Dunnett tests were significant for all outbreak periods (Table 3). The box-whisker plot for the ED occupancy showed an increase of 69% between the median occupancy outside an outbreak and during an outbreak for CHU Saint Etienne and 63% for CHU Grenoble (Figure 6). The largest increase was during the cocirculation of flu and bronchiolitis (112% for CHU Saint-Etienne; 101% for CHU Grenoble).

Table 3. Dunnett test for multiple comparisons of emergency department (ED) occupancy for cardiorespiratory decompensation at Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne.

Reason for ED visit	Estimated occupancy	SE	<i>t</i> value	<i>P</i> value
CHU Grenoble				
Bronchiolitis: none	+121.43	31.73	3.827	<.001
Flu: none	+242.47	34.50	7.027	<.001
Cocirculation: none	+451.89	31.34	14.419	<.001
CHU Saint Etienne				
Bronchiolitis: none	+229.11	51.38	4.459	<.001
Flu: none	+355.26	85.34	4.163	<.001
Cocirculation: none	+529.17	50.98	10.379	<.001

Figure 6. Box-whisker plots of emergency department (ED) occupancy at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne. CRD: cardiorespiratory decompensation.

Analysis by Percentage of Total Occupancy

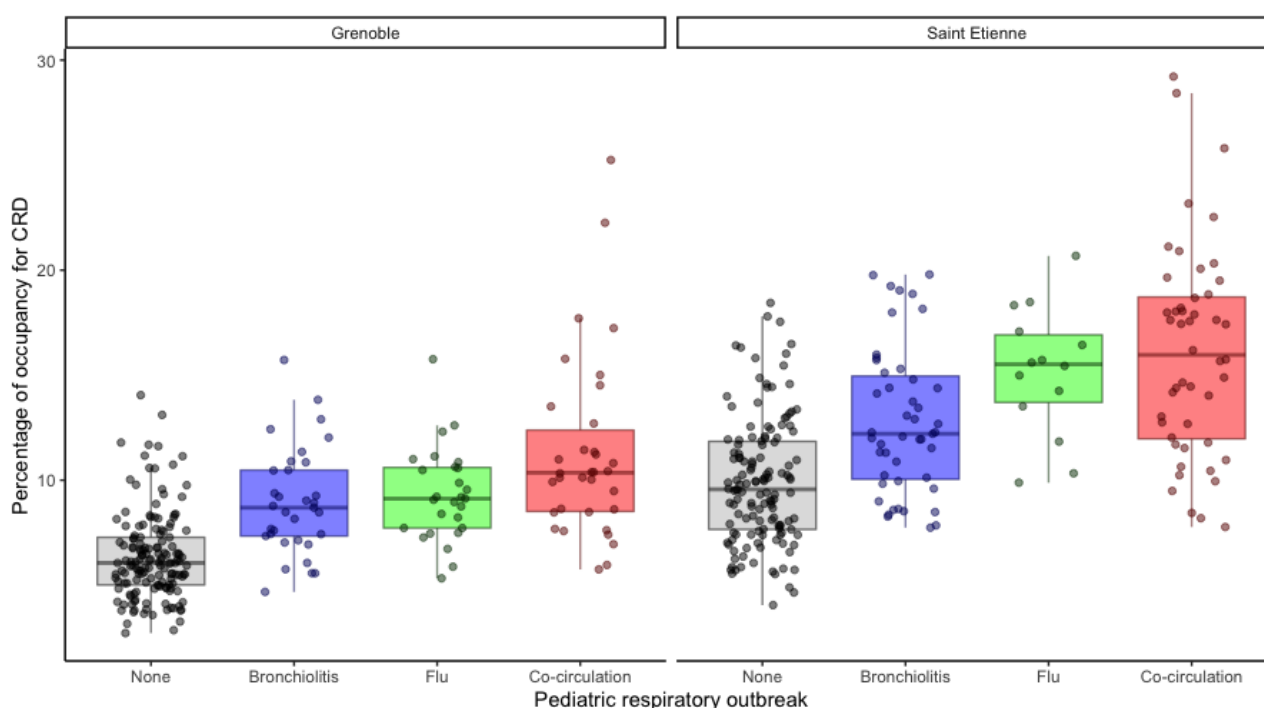
The percentage of total occupancy was defined by the ratio of total occupancy for CRD to the total occupancy for all diagnoses. The difference between the outbreak periods, based on the Kruskal-Wallis test, was significant for CHU Saint-Etienne ($\chi^2_3=77.211$, $P<.001$) as well as for CHU Grenoble ($\chi^2_3=88.165$, $P<.001$). The Spearman test still showed no real monotone dependency between the percentage of occupancy for a CRD diagnosis and the presence of an outbreak as defined by PREDAFLU (CHU Saint Etienne: $\rho=0.56$, $P<.001$; CHU Grenoble: $\rho=0.60$, $P<.001$). The monotone dependency was weaker when considering the occupancy compared with

the total number of ED visits. The Dunnett tests were significant for all outbreak periods (Table 4). The box-whisker plot for the percentage of ED occupancy showed an increase of 49% in the percentage of occupancy between the period with no outbreak and with an outbreak for CHU Saint Etienne (Figure 7). The increase was 52% for CHU Grenoble. The largest increase was during the cocirculation of flu and bronchiolitis (67% for CHU Saint-Etienne; 62% for CHU Grenoble).

This result meant the number of ED visits for CRD was more important during an outbreak period, and the workload increase for CRD, measured by the occupancy, was more important during the outbreak relative to the other pathologies.

Table 4. Dunnett test for multiple comparisons of the percentage of emergency department (ED) occupancy for cardiorespiratory decompensation at Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne.

Reason for ED visit	Estimated percentage	SE	<i>t</i> value	<i>P</i> value
CHU Grenoble				
Bronchiolitis: none	+2.59	0.4928	5.256	<.001
Flu: none	+2.94	0.5360	5.487	<.001
Cocirculation: none	+4.93	0.4868	10.130	<.001
CHU Saint Etienne				
Bronchiolitis: none	+2.87	0.6019	4.771	<.001
Flu: none	+5.27	0.9996	5.270	<.001
Cocirculation: none	+6.17	0.5972	10.324	<.001

Figure 7. Box-whisker plots of the percentage of emergency department (ED) occupancy for cardiorespiratory decompensation (CRD) at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne.

Analysis by Average Duration in the ED for a CRD Diagnosis

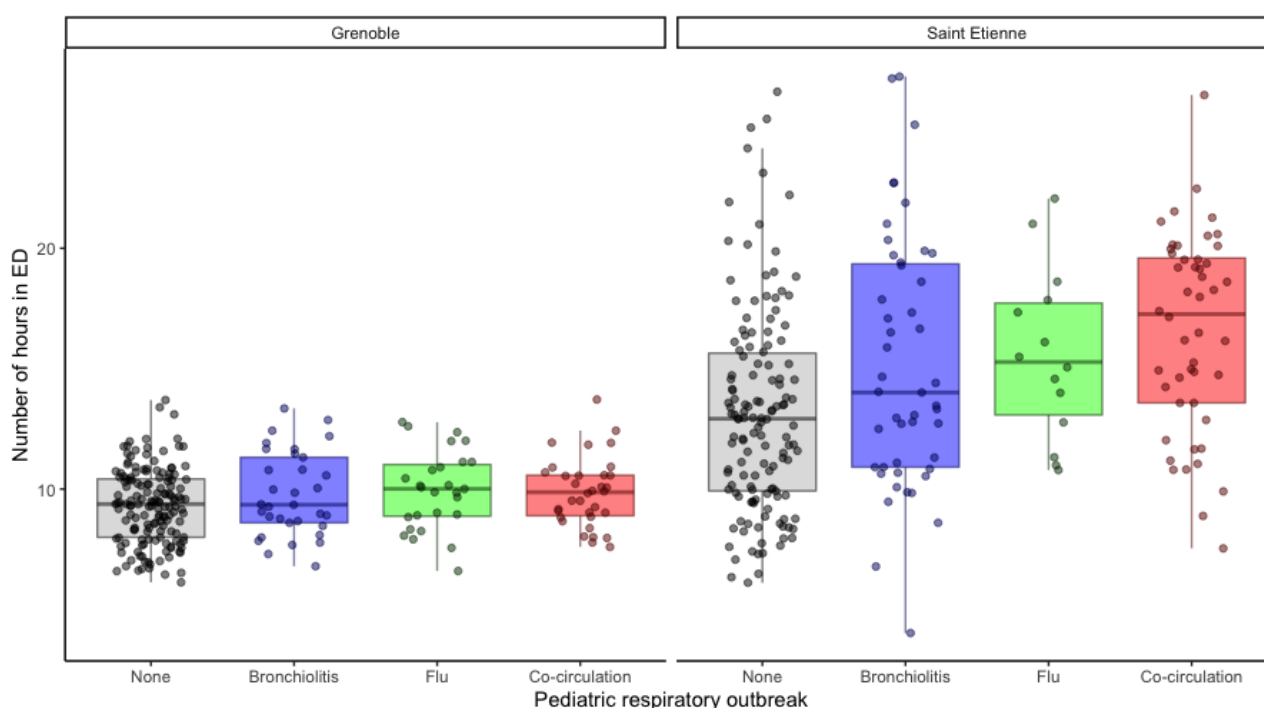
The difference between the outbreak periods, based on the Kruskal-Wallis test, was significant for CHU Saint-Etienne ($\chi^2_3=25.495$, $P<.001$) but was not significant for CHU Grenoble ($\chi^2_3=5.8927$, $P=.12$). The Spearman test showed a very weak positive dependency between the mean duration in the ED for a CRD diagnosis and the presence of an outbreak as defined by PREDAFLU (CHU Saint Etienne: $\rho=0.32$, $P<.001$; CHU Grenoble: $\rho=0.15$, $P=.02$). Thus, there was no monotone

dependency with the mean duration in the ED for a CRD diagnosis. The Dunnett test was not significant during the flu outbreak at CHU Saint-Etienne and was not significant for all outbreaks at CHU Grenoble (Table 5). Moreover, the box-whisker plot showed a maximum mean increase in the duration in the ED of 4.3 hours at CHU Saint-Etienne and less than 1 hour at CHU Grenoble (Figure 8). This difference was too small to have clinical value.

This result meant the mean duration in ED for CRD diagnosis was independent from the presence or absence of a flu or bronchiolitis outbreak in the pediatric population as defined by PREDAFLU.

Table 5. Dunnett test for multiple comparisons of the number of hours in the emergency department (ED) for cardiorespiratory decompensation at Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne.

Reason for ED visit	Estimated percentage	SE	<i>t</i> value	<i>P</i> value
CHU Grenoble				
Bronchiolitis: none	+0.46	0.3012	1.535	0.33
Flu: none	+0.62	0.3276	1.901	0.16
Cocirculation: none	+0.55	0.2976	1.836	0.19
CHU Saint Etienne				
Bronchiolitis: none	+1.98	0.7421	2.669	0.02
Flu: none	+2.39	1.2325	1.943	0.15
Cocirculation: none	+3.37	0.7363	4.583	<.001

Figure 8. Box-whisker plots of the number of hours in the emergency department (ED) occupancy for cardiorespiratory decompensation (CRD) at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne.

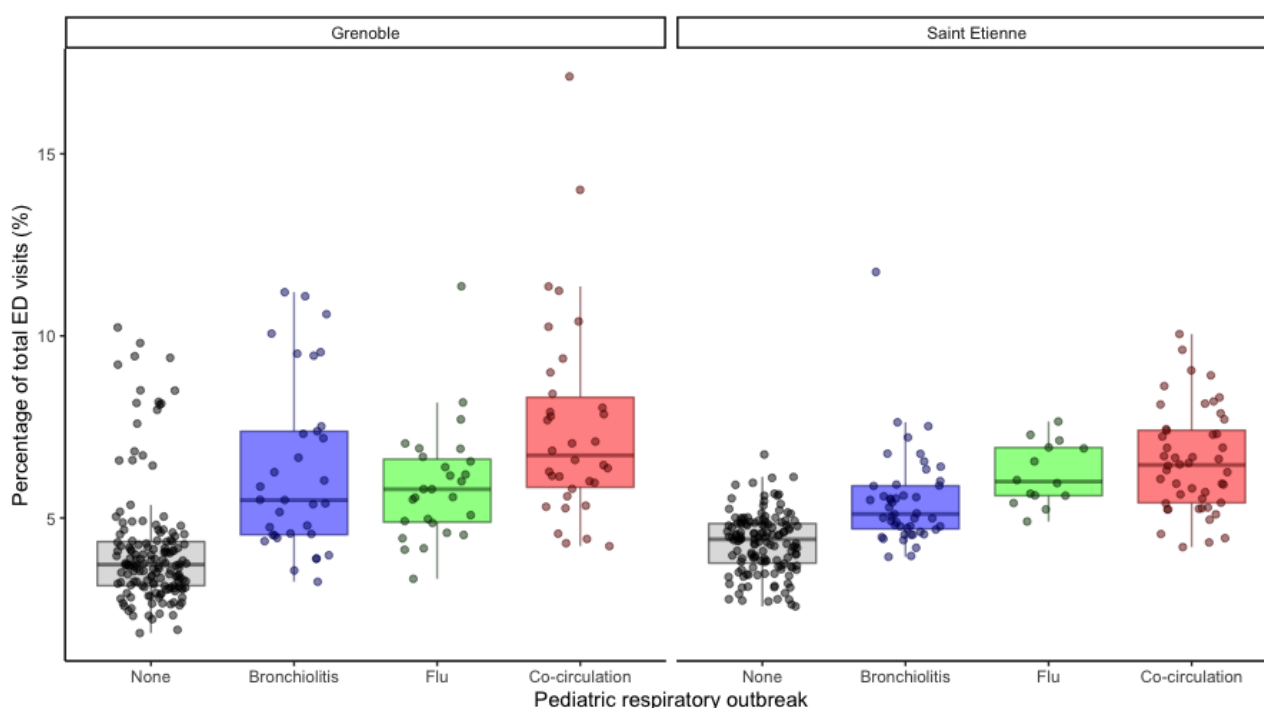
Analysis by Percentage of Total ED Visits for CRD

The percentage of total ED visits for CRD was defined as the ratio of the weekly number of ED visits for CRD to the total number of ED visits for all diagnoses. The difference between the outbreak periods, based on the Kruskal-Wallis test, was significant for CHU Saint-Etienne ($\chi^2_3=114.5$, $P<.001$) as well as for CHU Grenoble ($\chi^2_3=93.415$, $P<.001$). The Spearman test showed a moderate positive dependency between the percentage

of total ED visits for a CRD diagnosis and the presence of an outbreak as defined by PREDAFLU (CHU Saint Etienne: $\rho=0.68$; $P<.001$; CHU Grenoble: $\rho=0.61$, $P<.001$). This was a more significant value. The Dunnett tests were significant for all outbreak periods (Table 6). For this criterion, as for the other, the box-whisker plot for Saint Etienne and Grenoble (Figure 9) showed the largest increase during the cocirculation of flu and bronchiolitis compared with the other outbreak periods (46% for CHU Saint-Etienne; 80% for CHU Grenoble).

Table 6. Dunnett test for multiple comparisons of the percentage of total emergency department (ED) visits for cardiorespiratory decompensation at Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne.

Reason for ED visit	Estimated percentage	SE	<i>t</i> value	<i>P</i> value
CHU Grenoble				
Bronchiolitis: none	+2.16	0.3744	5.773	<.001
Flu: none	+1.77	0.4072	4.342	<.001
Cocirculation: none	+3.40	0.3699	9.203	<.001
CHU Saint Etienne				
Bronchiolitis: none	+1.15	0.1784	6.438	<.001
Flu: none	+1.89	0.2964	6.376	<.001
Cocirculation: none	+2.25	0.1770	12.681	<.001

Figure 9. Box-whisker plots of the percentage of total emergency department (ED) visits for cardiorespiratory decompensation (CRD) at (A) Centre Hospitalier Universitaire (CHU) Grenoble and (B) CHU Saint Etienne.

Discussion

Main Findings

The pediatric data concerning the virus circulation were clearly an important variable capable of discriminating between the variations in adult ED visits for CRD. Furthermore, the increase in visits corresponds to an outbreak period. This result was demonstrated for CHU Saint Etienne as much as for CHU Grenoble. The number of ED visits for a CRD diagnosis increased by 27.3% in CHU Saint Etienne and by 50% in CHU Grenoble during a pediatric respiratory infection outbreak. When the data regarding the types of respiratory infections were analyzed, the highest peak was observed during the period of time in which flu and bronchiolitis coexisted. This confirmed the link of an epidemic outbreak to the number of adult ED visits, which was similar for both hospital settings.

The monotone dependency between the number of ED visits for CRD and the presence of a pediatric outbreak as defined by PREDAFLU was moderate but may still be considered as significant. Indeed, the outbreak periods defined by PREDAFLU are based on a real-time analysis of the trends in the pediatric ED for bronchiolitis and flu, with confidence periods of 50%, 80%, and 100% [6,7]. This means the periods defined by PREDAFLU were necessarily larger than epidemic periods classically defined through laboratory-confirmed tests. The moderate dependency found during this study would probably be stronger with a more precise definition of the epidemic periods.

The total ED occupancy for CRD was also a variable capable of significantly discriminating between the populations. During outbreaks of flu or bronchiolitis, we observed an increase in the CRD occupancy by 69.1% in CHU Saint Etienne and by 62.9% in CHU Grenoble. This factor was related to the increased occupancy rate in the ED. The percentage of ED visits for CRD

compared with the total number of visits is another variable or parameter of importance, significantly showing the visit evolution during a pediatric respiratory infection outbreak (increase of 28.4% for CHU Saint Etienne and 63.6% for CHU Grenoble).

Finally, the increase in the mean length of stay in the ED was not statically significant nor had clinical significance. Indeed, the increase in the median duration of a stay in the ED for a CRD diagnosis was too small to have a clinical impact on the organization.

This demonstrates that the number of visits for CRD pathologies is more important during outbreak periods relative to the total number of visits, and these visits were also more time-consuming. The combination of these factors highlighted the reason why the increased burden for CRD illness visits has such a strong impact on the adult ED during a pediatric respiratory infection outbreak.

Strengths and Weaknesses of the Study

The emergency activity related to CRD is not subject to intense seasonal variations. Furthermore, there is no statistical method nor virological rapid tests that allows a precise follow up of such pathologies in the adult ED or can predict increased activity in this setting. This study illustrated the existing relationship between pathologies specific to adult emergency settings and those specific to pediatric emergency settings. One of this study's main strengths lies in the demonstration of the usefulness of a simple and predictive tool for the pediatric emergency setting like PREDAFLU for an adult setting. This tool has been successfully used for several years in CHU Grenoble and Saint Etienne and allows, through data analysis coming from the pediatric emergency setting, prediction of the start of bronchiolitis and flu outbreaks, with daily updates. PREDAFLU is a simple and reliable tool that could be used to anticipate increased adult ED activity related to CRD.

One weakness of this study concerns the number of hospitals included. Only CHU Grenoble and Saint Etienne took part in the study. They are 2 hospitals of similar sizes and are relatively close geographically. This could constitute a population selection bias.

Comparison With Prior Work

A key feature of the PREDAFLU surveillance tool is the ability to provide an early warning of respiratory infection outbreaks. This tool is based on syndromic surveillance and on a rapid flu test. The results presented here show that increased ED attendances for CRD may occur during an outbreak of flu or bronchiolitis.

Previous studies have shown the impact of RSV and flu on a higher risk of heart failure [13-16], chronic obstructive pulmonary disease, pneumonia, bronchitis, or other respiratory tract infections [17,18]. Several studies have identified clear predictable patterns driven primarily by viral circulations of respiratory diseases and heart failure within an elderly population [19,20]. Other studies focused on trying to identify leading indicators for the outbreak [21,22], to predict epidemic size by undertaking virologic surveillance [23,24], or to monitor

the epidemic periods by performing syndrome surveillance [25-27]. But in all cases, the main challenge is to build a prediction model to forecast an increase in the workload in the ED. Several studies have developed artificial neural network solutions based on environmental, weather, or pollutant data to provide an early detection of peak activities in the ED for respiratory symptoms [28,29]. Other studies used admission information during ED triage to build a prediction model for hospital admission [30]. A review of forecasting applications in health science outlined the challenges in forecasting, including the necessity for a clear definition of health data, the difficulty in forecasting extreme health events, and the necessity to cross-validate the health forecasting models [31]. Other, more general, work has attempted to predict the number of cases presenting to EDs each day. The results are currently rather disappointing. In a fairly focused area, our work contributes to improving the concepts of models that can be used more widely [32].

Our study is unique in that we investigated and showed the benefit of an easy-to-use and reliable forecasting tool for respiratory infections outbreaks in the pediatric ED to anticipate an increase in the activity related to CRD in the adult ED.

Implications for Clinicians or Managers

The rationale for this work is that epidemics of RSV in the pediatric population may be related to epidemics of CRD in older adults in EDs. This hypothesis assumes that older adults in decompensation are infected with RSV. This has been confirmed in the recent literature, which clearly shows that this virus is found in these clinical situations [33,34] and that it is responsible for a non-negligible fraction of cases [35] on the one hand. On the other hand, this hypothesis implies that RSV circulates in an epidemic mode and that its circulation, when it exists, is massive. This is precisely how RSV epidemics in children are described [36]. Our hypothesis is that RSV, whose circulation increases considerably during bronchiolitis epidemics, is transmitted by children to the elderly and that the circulation of pediatric RSV therefore makes it possible to predict the occurrence of CRD in elderly adults in the ED with better performance than the analysis of adult data alone.

The findings of this study could be useful to emergency physicians and heads of EDs. There could be organizational implications in the use of pediatric emergency indicators related to bronchiolitis and flu outbreaks in order to forecast increased activity due to CRD in the adult population.

The impact of admission for CRD in the adult population has strong implications in the workload of ED and other medicine departments in hospital settings. It usually concerns older populations with significant comorbidities. Furthermore, such pathologies frequently lead to a long hospitalization and require important care organization. The ability to have an indicator to follow (number of CRD visits as shown in this work) such pathologies would allow a much more efficient and effective organization of ED.

A potentially heavy patient overload could indeed be managed in a more flexible way by adapting the ED situation, such as an increase in the number of physicians and nurse shifts or the

opening of additional community medicine beds. Hospitals could also communicate more efficiently with medicine departments directly concerned by the increase in such patients (internal, cardiovascular, infectious, or geriatric medicine services). These services would thus be able to forecast sufficient numbers of downstream beds and lighten the burden in emergency services during these difficult periods. The first to benefit from such an organizational shift would be the patients who would then be managed sooner with adequate service.

Future Work

Admissions to the adult ED used in this study corresponded to previously defined ICD-10 diagnosis, as related to an extended CRD definition. A study of the diagnosis codes used in different hospital settings could lead to the identification of common standard codes that would be more concise and specific.

Furthermore, a study including other seasonal pathologies with virological results from hospital laboratories could possibly help to highlight other relationships between pediatric and adult emergency settings.

Finally, this study would benefit from the inclusion of other hospital settings in different regions of various population size and characteristics, in urban and rural areas. That would allow a validation of this study's findings on a larger scale and help define a more precise threshold for increased activity in the ED. Bronchiolitis and flu outbreaks can vary in length and intensity; these variations may also be correlated with CRD admissions.

Conclusion

The analysis of the data concerning ED admissions for CRD in the adult population does not allow for anticipation of the increase in admissions for these diagnoses. This study demonstrated that it is possible to extend the usage of a surveillance tool like PREDAFLU, used to forecast outbreaks of bronchiolitis and flu in the pediatric population, to provide an early warning for an increase in ED visits for CRD in the adult population. This easy-to-use tool can be used to anticipate an overload in ED for these pathologies and to adapt organizational processes.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Time series of cardiorespiratory decompensation (CRD) admission in the adult emergency department (ED) at Centre Hospitalier Universitaire (CHU) Grenoble and Saint Etienne.

[PNG File , 263 KB - [publichealth_v8i3e25532_app1.png](#)]

Multimedia Appendix 2

Cardiorespiratory selection codes from the ICD-10 Version 2019.

[DOCX File , 14 KB - [publichealth_v8i3e25532_app2.docx](#)]

Multimedia Appendix 3

Bronchiolitis outbreak periods.

[DOCX File , 16 KB - [publichealth_v8i3e25532_app3.docx](#)]

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Abbreviations

CHU: Centre Hospitalier Universitaire
CRD: cardiorespiratory decompensation
ED: emergency department
ICD: International Classification of Diseases
RSV: respiratory syncytial virus
SSU: short stay unit

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Original Paper

Identifying COVID-19 Outbreaks From Contact-Tracing Interview Forms for Public Health Departments: Development of a Natural Language Processing Pipeline

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Abstract

Background: In Wisconsin, COVID-19 case interview forms contain free-text fields that need to be mined to identify potential outbreaks for targeted policy making. We developed an automated pipeline to ingest the free text into a pretrained neural language model to identify businesses and facilities as outbreaks.

Objective: We aimed to examine the precision and recall of our natural language processing pipeline against existing outbreaks and potentially new clusters.

Methods: Data on cases of COVID-19 were extracted from the Wisconsin Electronic Disease Surveillance System (WEDSS) for Dane County between July 1, 2020, and June 30, 2021. Features from the case interview forms were fed into a Bidirectional Encoder Representations from Transformers (BERT) model that was fine-tuned for named entity recognition (NER). We also developed a novel location-mapping tool to provide addresses for relevant NER. Precision and recall were measured against manually verified outbreaks and valid addresses in WEDSS.

Results: There were 46,798 cases of COVID-19, with 4,183,273 total BERT tokens and 15,051 unique tokens. The recall and precision of the NER tool were 0.67 (95% CI 0.66-0.68) and 0.55 (95% CI 0.54-0.57), respectively. For the location-mapping tool, the recall and precision were 0.93 (95% CI 0.92-0.95) and 0.93 (95% CI 0.92-0.95), respectively. Across monthly intervals, the NER tool identified more potential clusters than were verified in WEDSS.

Conclusions: We developed a novel pipeline of tools that identified existing outbreaks and novel clusters with associated addresses. Our pipeline ingests data from a statewide database and may be deployed to assist local health departments for targeted interventions.

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KEYWORDS

natural language processing; public health informatics; named entity recognition; contact tracing; COVID-19; outbreaks; neural language model; disease surveillance; digital health; electronic surveillance; public health; digital surveillance tool

Introduction

As of December 1, 2021, the state of Wisconsin (WI) confirmed 884,701 cases of SARS-CoV-2 (COVID-19) [1]. At the county level, health departments use the free-text fields from COVID-19 initial case interview (contact-tracing) forms to identify potential businesses and facilities where transmission of the virus occurred and when individuals were infectious. During surges, public health workers encounter a high caseload and are overwhelmed with an abundance of free-text information in the interview forms. Current methods to mine the free-text fields are manual and a keyword-based approach, without rapid and systematic methods for finding cluster hotspots for targeted interventions (ie, guide risk communication, policy to limit capacity in certain businesses, compliance in enforcing orders at facilities and businesses). Methods in natural language processing (NLP) and machine learning have augmented workflows for COVID-19 care in other settings that are strained for resources and staffing [2-4], and may prove to be useful for health departments and their COVID-19 data teams that interact with the contact tracers and surveillance systems.

Named entity recognition (NER) is an NLP task to classify words according to a class, for example, identifying a token as a person, organization, or location. Current systems have leveraged the strength of pretrained neural language models [5] trained on a large corpus of data to achieve accuracy scores above 90% for NER tasks. Many of these systems are publicly available and have been fine-tuned to be run “out of the box” for applications, but there remains a paucity in the literature demonstrating its benefits in public health for outbreak surveillance work. Prior work in health care has demonstrated success in using pretrained neural language models for biomedical and clinical entity normalization [6] and building computable disease phenotypes [7]. The opportunities for public health providers and policy makers to leverage methods in NLP for data analytics is growing and becoming more accessible for nontechnical departments [8].

We aimed to develop an NLP pipeline that uses a pretrained NER neural language model applied to contact-tracing interview forms recorded in the Wisconsin Electronic Disease Surveillance System (WEDSS) to identify potential outbreaks during the COVID-19 pandemic. Further, we sought to design a novel location-mapping tool to identify the most likely address for a given named entity from our NER tool. The objective of our study was to measure the precision and recall for both the NER tool and the location-mapping tool in our NLP pipeline for identifying new clusters and existing outbreaks. Our pipeline may serve as a benchmark in public health informatics to assist contact-tracing efforts for targeted policies during COVID-19 and other pandemics, and provide scaled automation for state and local health department staff.

Methods

Data Source

WEDSS is a secure web-based system designed to facilitate reporting, investigation, and surveillance of communicable diseases, which includes data on COVID-19 since January 2020. WEDSS encompasses all of Wisconsin, but this study was a collaboration with Public Health Madison & Dane County (PHMDC), which serves the second-largest county in Wisconsin by population. Both structured and unstructured fields were extracted from WEDSS for our analyses, including the text fields from the county-level data containing relevant contact-tracing fields from the case interview forms. The case interview forms contained the followings sections: (1) symptoms; (2) laboratory and clinical information; (3) medical conditions; (4) COVID-19 risks, including travel; (5) residential and occupation settings; (6) potential sources of illness; (7) isolation and quarantine measures; (8) facility intervention; (9) contact-tracing details; and (10) investigation notes. The text fields included addresses for businesses, facilities, and schools where the exposed individual may have entered or worked. The investigation note field was the longest text field with a median token count of 127 (IQR 67-233) and frequently included dates and names of places visited by the individual during their exposure period. For the pipeline development, 26 structured and unstructured text fields from WEDSS data extracts were concatenated into 1 document as input into our language model. There was 1 document per case, and model runs were at the case level. Postprocessing of the named entities included the removal of frequently occurring named entities (ie, “Wisconsin,” “GMT”) identified from 12 months of posttesting case interview forms and removal of duplicate named entities.

Confirmed cases were individuals with a positive molecular or polymerase chain reaction (PCR) test result detecting SARS-CoV-2 RNA, filtered by the date of the test result. In alignment with the Centers for Disease Control and Prevention (CDC) case definition [9], individuals who tested positive were counted each time they had a new COVID-19 infection (defined as a positive test 90 days or more after their previous COVID-19 infection). Therefore, people may have been counted more than once, but this occurred in less than 1% of cases. Probable cases were cases not positive by a confirmatory laboratory test method (ie, PCR or molecular test) but met 1 of the following: (1) test positive using an antigen test method, (2) have symptoms of COVID-19 and a known exposure to COVID-19 (ie, being a close contact of someone who was diagnosed with COVID-19), or (3) have COVID-19 or SARS-CoV-2 listed on the death certificate.

There is no standard definition for a “cluster” or “outbreak” (the terms are interchangeable), and the CDC states the definition for outbreaks is relative to the local context [10]. Therefore, we followed the PHMDC definition for a cluster, which is 2 or more cases associated with the same location,

group, or event around the same time [11], which we examined across 7-day intervals. Henceforth, we use the term “cluster” for a cluster identified from our NER tool and “outbreak” as the cluster that is identified and validated by the PHMDC COVID-19 data team following standard operating procedures and recorded in WEDSS.

The NER Tool

We used a pretrained cased Bidirectional Encoder Representations from Transformers (BERT) base model [12], which was fine-tuned on the data set from the Conference on Computational Natural Language Learning (CoNLL)-2003 NER shared task [13]. This English data set remains 1 of the largest corpora in the public domain for NER, with 1393 Reuters news stories with a total of 35,089 annotated labels (5648 in the test set) across the categories of location, organization, person, and miscellaneous. The pretrained BERT model implemented in the Python Transformers library is maintained on the HuggingFace model repository [14-16]. The model reported an F_1 score of 91.3, with a recall of 91.9 and a precision of 90.7, on the CoNLL-2003 test data set. At the time of this publication, the model represented the state of the art in NER [15]. We used the “out of the box” model and did not attempt to further fine-tune the models or adjust hyperparameters.

The text fields from WEDSS were preprocessed to remove nonmeaningful entities, such as contact tracers’ names. Postprocessing of the named entities included the removal of frequently occurring terms (ie, “Wisconsin,” “GMT”), the removal of duplicate named entities within 1 document, the removal of subword tokens that are occasionally tagged by the model, and the removal of patterns that were not informative. A WordPiece tokenizer was used to build groups of up to 512 tokens from each document, which were then fed into the model. For all case IDs from the extracted WEDSS data that had the same named entity reported, the average predicted probability

was provided as the score for the likelihood of identifying it as a person, organization, location, or miscellaneous.

Entities found by the NER pipeline that were associated with an outbreak already discovered by contract tracers were identified through fuzzy matching. Known outbreak names and entities from the NER tool that shared an incident ID were also matched via the token sort ratio (each string to compare is tokenized and sorted alphabetically, and then similarity is calculated as $\text{similarity} = [2 \times \text{number of matching characters} / \text{total number of characters}] \times 100$). Entities and outbreaks with a token sort ratio of 70 or more were deemed to be matches.

The Location-Mapping Tool

During the development of our NER pipeline, we noted many named entities containing common business names that may have multiple locations within a county, such as “McDonald’s” or “Walmart.” Therefore, we developed a location-mapping tool into the pipeline using the Google Places Application Program Interface (API) to determine probable matches for locations that were near 1 or more case IDs within a cluster (Figure 1). The Google Places API requires searches to be within a circular zone with a maximum radius of 30 km. A sample search is shown in Figure 2. Multiple successive searches were permitted, although each search will increase API costs, and saturating a large search area with API calls would neither be optimal nor efficient. The commute distances for over two-thirds of the businesses in 36 major metropolitan areas in Wisconsin were between 0 and 24 miles [17], so 1 assumption of the mapping algorithm was that the named entity would be within commuting distance from the individual’s home residence. Therefore, the individual’s latitude/longitude coordinates for each case ID in the cluster were extracted from WEDSS, and a k-means unsupervised approach was applied to identify the centroid coordinates from Google Places for the cluster of case IDs for a particular named entity.

Figure 1. Process map for NER tool and location-mapping tool. ETL: extract, transform, and load; NER: named entity recognition.

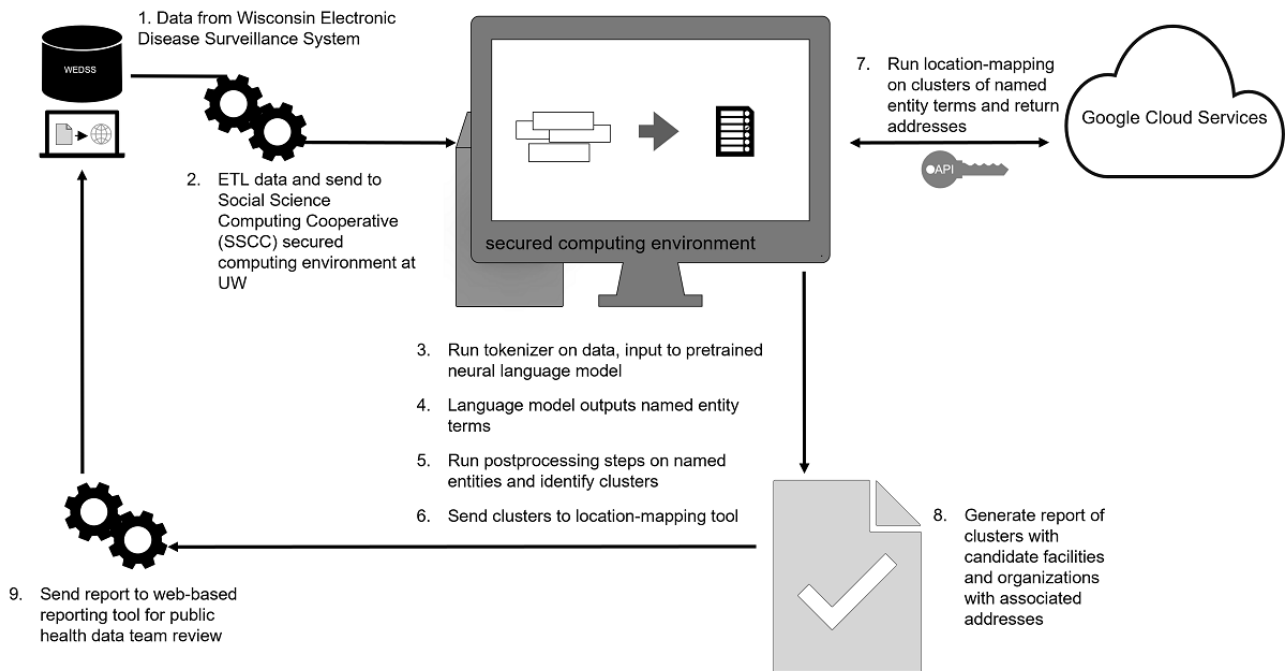
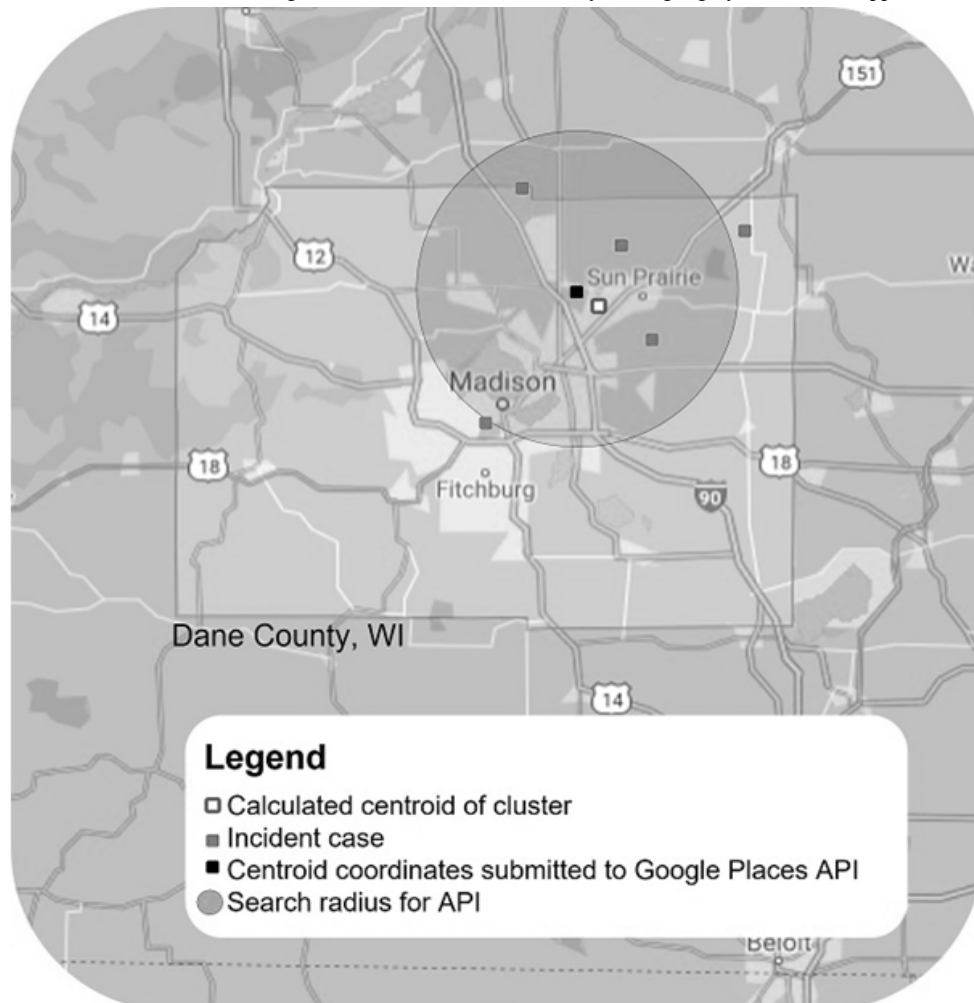


Figure 2. Location-mapping example for a cluster of COVID-19 clusters in Dane County as of October 2021. The grey dots show incident cases for a possible or known cluster/outbreak. The white dot shows the calculated centroid point of this cluster. The black dot shows the obfuscated centroid latitude/longitude point that is submitted to the Google Places API, which is shown by the larger gray circle. API: Application Program Interface.



The location mapper provided the most likely address for the named entity. If an exact match could not be made, then the top 3 results were filtered using fuzzy string matching. In either case, a predicted probability for each business address match was provided, and these results were then merged into a final report to provide an address associated with a named entity for use in contact tracing. Named entities that mapped to city names across the states of Wisconsin, Minnesota, Iowa, Michigan, and Illinois were filtered out because they were not specific enough to determine a precise location.

To comply with the Google Places API terms of service, we extracted the organizations and location names from the fields of all COVID-19-related forms in the WEDSS data to create an internal database of named entities for mapping between our NER tool and the Google Places API results. Therefore, no Google data were cached. The search algorithm only used the Google Places API to perform a search for named entities that matched our internal database of named entities. The full process map for the pipeline and reporting system is displayed in [Figure 1](#).

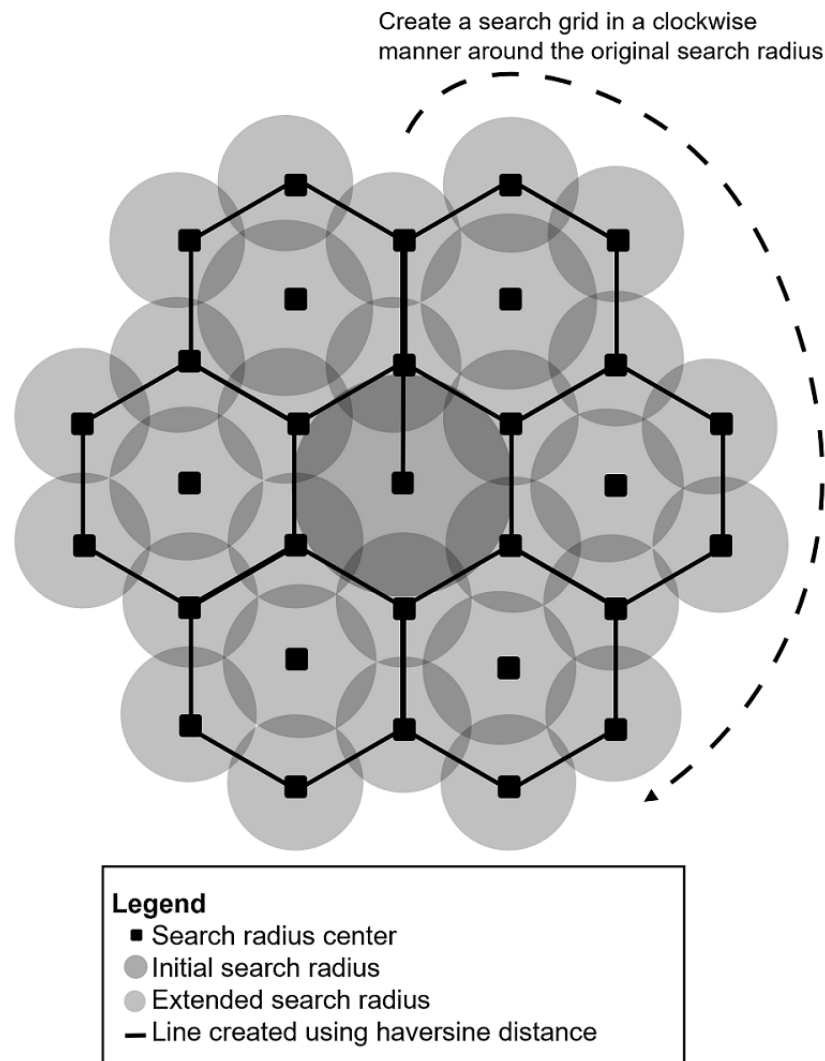
The process map begins with the WEDSS data source and proceeds with an extract, transform, and load (ETL) procedure onto an on-premise Health Insurance Portability and Accountability Act (HIPAA)-secure computing environment at the University of Wisconsin (UW). The relevant fields from the case report interview forms go through feature engineering and the WordPiece tokenizer for the pretrained neural language model to classify named entities as business names and facilities.

Only named entities that meet the criteria for a cluster with >2 incident IDs are sent to the location-mapping tool. The location-mapping tool identifies the centroid longitude/latitude of the cluster with a random shift for deidentification purposes. Next, the Google Places API is executed for the shifted centroid location, and proximity results of business and facility names are run against the named entities from the NER tool. An extended search radius is processed if no addresses are returned on the initial run. The top 3 results are shown from a fuzzy-matching schema with priority scores and shared in a report that is sent back to a web-based reporting system at the Wisconsin Department of Health Services (DHS). Any health department employee may view the report through the web-based reporting system.

The Extended Location Algorithm

Some named entities that were submitted to the location-mapping tool were outside the 30 km search radius, but they may still be relevant for identifying novel clusters. For the named entities outside the search radius, we developed an extended search algorithm that covered a larger search radius and located business or organization names that would map to a given named entity not found within the initial 30 km search radius. The algorithm created and utilized a grid of interlocking equilateral triangles. The search grid first extended outward from the original latitude/longitude centroid point and then rotated in a clockwise manner around this centroid point, creating interlocking triangles ([Figure 3](#)). Each vertex of each triangle in the grid would become a new latitude/longitude starting point for an API call.

Figure 3. Framework for the extended location-mapping algorithm. If a named entity is not found within the initial search radius, additional search radii are created extending outward from the original search by creating a series of interlocking equilateral triangles, where each vertex of the triangle is a new API starting search point. The extended search stops when at least 1 match is found or the maximum distance is reached. API: Application Program Interface.



The curvature of the earth would mean that this grid would not follow straight lines, so we used an implementation of the haversine formula to create polygons with curved shapes in our grid [18]. Creating polygons by drawing outward would necessarily mean that the end of each rotation of the grid may not be the start of the rotation, so we set the search radii of each API call to overlap to ensure total coverage from the searches, and to account for this distance error between the starting point and ending point of the rotation. The extended searching stopped when either of the following occurred: (1) at least 1 search result was found by the API call, or (2) the grid reached a maximal range of 250 km from the original centroid latitude/longitude point.

Evaluation of the NER Tool in the NLP Pipeline

All confirmed and probable individual cases in Dane County between July 1, 2020, and June 30, 2021, served as the retrospective validation data set. The NER tool was evaluated against confirmed outbreak facility/business names or valid business addresses linked to cases that were recorded in the WEDSS database. The named entities produced from the NER

tool that met the criteria for a cluster (>2 instances of the named entity) within a 1-week period and matched a confirmed outbreak in WEDSS were labeled as true positives (TPs). In addition, named entities with >2 instances within a 1-week period that had a valid business address in WEDSS were also included in the TP group and represented novel clusters. The rationale to include both confirmed and unconfirmed outbreaks (potentially novel clusters) into the TP group was because they met the PHMDC definition for a cluster and contained a valid address that warranted an investigation (unverified outbreak) or avoided a redundant investigation (verified outbreak). Named entities that were produced from the NER tool without an address match in WEDSS were labeled as false positives (FPs). False negatives (FNs) were defined as confirmed outbreaks in the WEDSS data set that did not have a corresponding named entity from the NER tool. Evaluation metrics were report as precision = $[TP/(TP + FP)]$ and recall = $[TP/(TP + FN)]$. These metrics are also known as positive predictive value and sensitivity, respectively. Evaluation of the NER tool was performed across a study period of 12 months. The precision and recall across the 12 months were reported to provide the

largest sample size for reporting metrics. Monthly metrics were also reported to represent seasonal variation and various public health policies that affected case rates and prevalence, which would also affect precision [19].

Evaluation of the Location-Mapping Tool in the NLP Pipeline

For the location-mapping algorithm, a separate set of precision and recall measures were reported. TPs were defined as a business address in our internal database of addresses from WEDDS that mapped to a Google Places API address for a named entity produced by the NER tool. An FP was a Google Places API address that did not map to the WEDSS database of addresses. An FN was defined as a named entity from the NER tool that mapped to our internal database of business names but returned no Google Places API address when a plausible API result could be found. Due to limitations on cost and computational resources, validation for the location-mapping

algorithm was only performed for 1 month (October 2020). For both NER and location mapping validation, precision and recall measures were generated with bootstrapped 95% CIs.

Report Generation for the COVID-19 Data Team at the Health Department

The goal of the pipeline was to generate a summary report from the contact-tracing forms collected in WEDSS across any time interval and identify potential clusters. A sample report is shown in Table 1 as a weekly report. Each cluster in the report also included the associated case IDs to guide the COVID-19 data team and the predicted probability for that cluster. Known outbreaks that were already identified by the COVID-19 data team or were under investigation were also extracted from WEDSS and included in the report to prevent redundancy in targeted policy efforts. The most likely address for each named entity was also provided from the location-mapping tool, along with a predicted probability.

Table 1. Example summary report for contact tracers for the county health department^a.

Named entity ^b	Type	Frequency ^c	Predicted probability 1 ^d	Case IDs ^e	Outbreak entity ^f	Address ^g	Predicted probability 2 ^h
Sun Prairie	Place	12	0.67	12345, 12346	Sun Prairie	— ⁱ	100.0
Local retailer	Organization	7	0.54	12347, 12349, 22221	Retailer 001	Keys and Things, 21 Science Dr., Madison, WI	95.2
Big-box store	Organization	3	0.45	13347, 18349, 22221	Boxstore 08	Circuited City, 1561 Rocky Rd., Verona, WI	87.1
Fast-food place	Organization	2	0.71	17247, 18149, 29121	—	Burger Time 1234 State St., Madison, WI	88.2

^aThe example is based on fictitious data and not sourced from the original Wisconsin Electronic Disease Surveillance System (WEDSS) data due to privacy restrictions.

^bNamed entity: result from the named entity recognition (NER) pipeline. Named entities only qualified as cluster outbreaks if they had >2 case IDs associated with them.

^cFrequency: unique mentions of NER across available case IDs from the reporting period.

^dPredicted probability 1: average predicted probability from the classifier for the type of named entity.

^eCase IDs: unique case IDs for lookup by the contact tracer.

^fOutbreak entity: known outbreak exposures.

^gAddress: matched named entity using the longitude/latitude for the address from k-means clustering from Google Places Application Program Interface (API).

^hPredicted probability 2: predicted probability from the location-mapping tool.

ⁱNo result from the NER or location-mapping tool.

The Institutional Review Board at the UW approved this study, and a data use agreement was established between the Wisconsin DHS and the UW. No data were shared outside the approved UW research environment and its approved users without explicit permissions by the UW and the DHS. The pipeline is currently available in the State of Wisconsin's public health reporting system, and the source code is open source and publicly available [20].

Results

Characteristics of COVID-19 Cases and Noncases

Of the 46,902 confirmed and probable cases, only 1595 (3.40%) were probable cases and the remainder were confirmed cases of COVID-19. In Dane County, non-Hispanic Whites accounted for 30,423 (64.87%) of the confirmed and probable cases, and the median age was 30 years (IQR 20-47); see Table 2. The most frequently reported occupation was student, but the missingness of the occupation variable in our WEDSS extract was high at over 75%. Additional demographics for the WEDSS

data set are shown in Table 2. The 7-day moving average for cases and noncases in Dane County are shown in Figure 4 with delineation of the mask mandate policies between January 2020

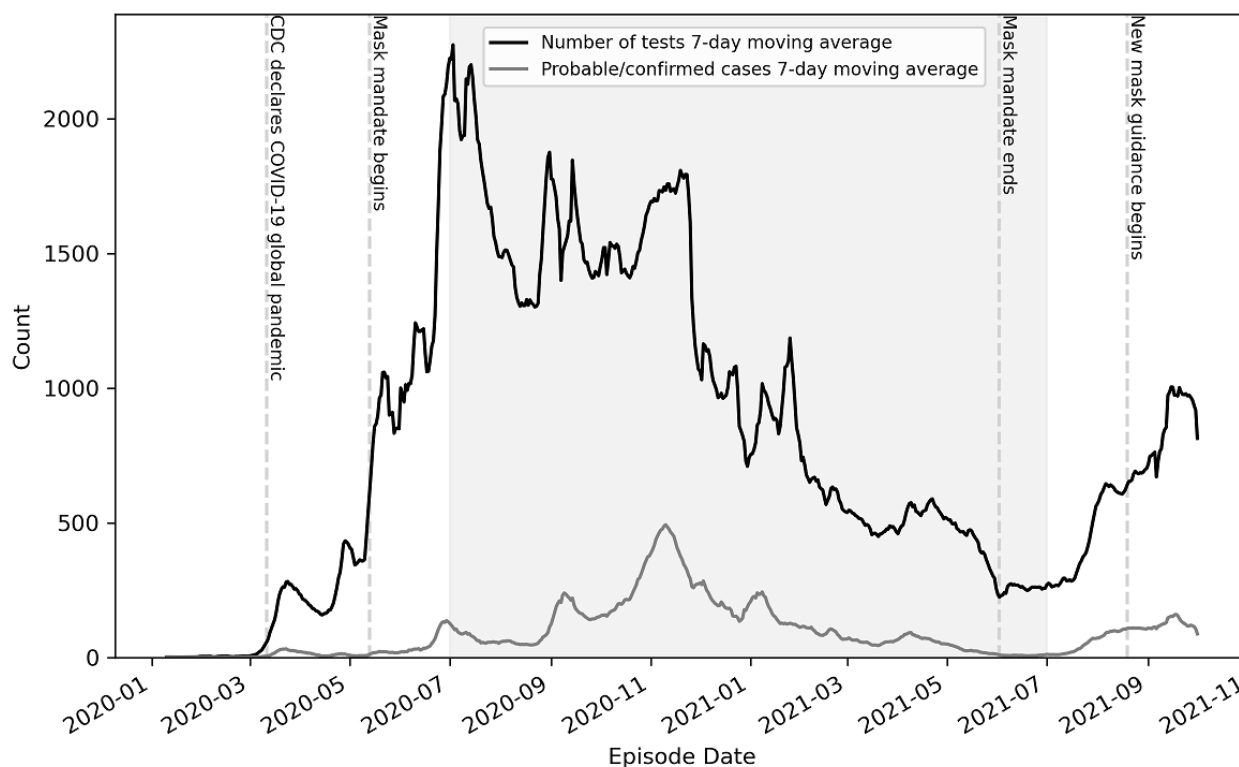
and September 2021. The gray-shaded region represents the 12-month validation period in which we analyzed the NER tool for this study.

Table 2. Characteristics of COVID-19 cases and noncases in Dane County, Wisconsin, between July 1, 2020, and June 30, 2021.

Individual characteristics	Negative cases (N=323,424)	Probable/confirmed cases (N=46,902)	Total (N=370,326)
Age (years), median (IQR)	32 (20-51)	30 (20-47)	31 (20-51)
Sex, n (%)			
Male	152,852 (47.26)	23,506 (50.12)	176,358 (47.62)
Female	165,482 (51.17)	23,314 (49.71)	188,796 (50.98)
Unknown	5090 (1.57)	82 (0.17)	5172 (1.40)
Race/ethnicity, n (%)			
Non-Hispanic White	199,629 (61.72)	30,423 (64.87)	230,052 (62.12)
Non-Hispanic Black	14,302 (4.42)	3266 (6.96)	17,568 (4.74)
Hispanic	23,878 (7.38)	6662 (14.20)	30,540 (8.25)
Other	85,615 (26.47)	6551 (13.97)	92,166 (24.89)
Occupation, n (%)^a			
Not recorded	311,809 (96.41)	37,083 (79.06)	348,892 (94.21)
Nonuniversity student	3099 (0.96)	2391 (5.10)	5490 (1.48)
University student	1161 (0.36)	903 (1.93)	2064 (0.56)
Retired	573 (0.18)	468 (1.00)	1041 (0.28)
Unemployed	502 (0.16)	429 (0.91)	931 (0.25)
Other	6280 (1.94)	5628 (12.00)	11,908 (3.22)
City, n (%)			
Madison	159,983 (49.47)	23,949 (51.06)	183,932 (49.67)
Sun Prairie	22,667 (7.01)	3722 (7.94)	26,389 (7.13)
Fitchburg	16,104 (4.98)	2983 (6.36)	19,087 (5.15)
Middleton	15,991 (4.94)	1838 (3.92)	17,829 (4.81)
Verona	15,224 (4.71)	1745 (3.72)	16,969 (4.58)
Other	93,455 (28.90)	12,665 (27.00)	106,120 (28.66)

^aMultiple responses were possible.

Figure 4. Trend over time of COVID-19 cases and noncases in Dane County, Wisconsin, between January 1, 2020, and October 31, 2021. Data are retrieved from the WEDSS. Line graphs of categories are aggregated by day and averaged in a moving 7-day window between January 2020 and October 2021. The CDC declared COVID 19 a global pandemic on March 11, 2020. The Public Health Madison and Dane County Initial mask mandate (Order 1) went into effect on May 13, 2020, and was updated and modified until June 2, 2021. Mandate 2 (Face-Covering Emergency Order) went into effect on August 19, 2021. The vertical dashed lines are demarcations for health policy changes. The gray-shaded area represents the validation period for our pipeline analysis. CDC: Centers for Disease Control and Prevention; WEDSS: Wisconsin Electronic Disease Surveillance System.



The validation data set comprised 4,183,273 total BERT tokens and 15,051 unique BERT tokens across the free-text fields in the contact interview forms. The longest field was “InvestigationNotes” with a median token count of 126.5 (IQR 67.0-232.5).

Across 12 months of validation, the recall was 0.67 (95% CI 0.66-0.68) and precision was 0.55 (95% CI 0.54-0.57). Of note, the precision and recall scores were variable from month to month as COVID-19 surges waxed and waned. The best performance was during surge months with a high volume of cases. Between October 2020 and January 2021, when caseloads ranged between 3300 and 7100, respectively, the recall was between 0.69 and 0.72, respectively. However, during months with fewer cases, such as between May 2021 and June 2021

(caseloads ranged between 149 and 410), the recall dropped down to 0.33 and 0.29, respectively. A similar trend was observed for precision, with a peak at 0.64 and a trough at 0.30 (Table 3). Across all months, the NER tool identified more potential outbreaks than were confirmed in WEDSS.

During the 1-month location-mapping tool validation period (October 2020), the F_1 score was 0.93, with a recall of 0.93 (95% CI 0.92-0.95) and a precision of 0.93 (95% CI 0.92-0.95). There were 355 named entities that did not return a result for the Dane County search radius, but the extended location algorithm matched addresses in 202 (56.9%) of those named entities to our internal database of named entities for potentially novel clusters.

Table 3. Results from the NER^a tool by month for Dane County, Wisconsin, between July 1, 2020, and June 30, 2021.

Month	Cases, N	Confirmed outbreaks, n (%)	Total outbreaks identified by Automated Public Outbreak Localization through Lexical Operations (APOL-LO), n (%)	Precision (95% CI)	Recall (95% CI)	F ₁ score
July 2020	508	137 (27.0)	251 (49.4)	0.51 (0.40-0.62)	0.28 (0.23-0.34)	0.37
August 2020	783	133 (17.0)	350 (44.7)	0.34 (0.25-0.44)	0.23 (0.17-0.29)	0.27
September 2020	2693	256 (9.5)	889 (33.0)	0.51 (0.46-0.56)	0.56 (0.51-0.59)	0.53
October 2020	4619	459 (9.9)	1267 (27.4)	0.64 (0.60-0.67)	0.69 (0.67-0.71)	0.66
November 2020	7129	564 (7.9)	1906 (26.7)	0.62 (0.59-0.65)	0.70 (0.68-0.72)	0.66
December 2020	3772	308 (8.2)	1078 (28.6)	0.58 (0.54-0.62)	0.70 (0.67-0.73)	0.64
January 2021	3361	241 (7.2)	1062 (31.6)	0.53 (0.49-0.58)	0.72 (0.69-0.75)	0.61
February 2021	2339	157 (6.7)	899 (38.4)	0.42 (0.36-0.47)	0.56 (0.51-0.61)	0.48
March 2021	1513	134 (8.9)	647 (42.8)	0.37 (0.31-0.43)	0.52 (0.46-0.57)	0.43
April 2021	1460	161 (11.0)	639 (43.8)	0.46 (0.39-0.53)	0.50 (0.45-0.55)	0.48
May 2021	410	81 (19.8)	233 (56.8)	0.41 (0.28-0.52)	0.33 (0.23-0.4)	0.36
June 2021	149	21 (14.1)	88 (59.1)	0.30 (0.12-0.52)	0.29 (0.11-0.44)	0.30

^aNER: named entity recognition.

Discussion

Principal Findings

We developed a novel pipeline of tools that are able to extract large amounts of surveillance data and summarize a report to highlight existing and potential outbreaks and their associated addresses. The summary report was designed in weekly intervals and by county to identify outbreaks in a systematic approach for any region in the state of Wisconsin. We demonstrated the performance of our pipeline by focusing in Madison & Dane County, and we showed our pipeline performs best during high-case-volume periods when automated methods for contact-tracing efforts may be most needed. In addition, our pipeline has the potential to identify novel cluster outbreaks not identified by traditional methods. Ultimately, our tool may overcome existing limitations for data teams that need to build keywords and manually scan free-text reports for potential locations of outbreaks.

Tools leveraging methods in artificial intelligence have emerged for public health applications during the COVID-19 pandemic [21-23], and utilizing NLP for targeted policy efforts from contact-tracing data continues to be an area of interest as more tools are developed or become available [24,25]. Others have shown the benefit of pretrained neural language models for COVID-19 surveillance using nontraditional and unconventional public health data sources, such as Twitter feeds [26]. Informatics tools using more conventional methods have been developed using known contact details with a public health agency [25,27]; however, the study did not identify potential or novel outbreaks. We demonstrated the utility of an “out of the box” pretrained neural language model for NER to automatically scan the contact interview forms of COVID-19 cases and provide contact tracers with a simplified and organized

summary report of existing and potential outbreak clusters. Our pipeline of tools follows the CDC guidelines for implementation and use of digital tools to augment traditional contact-tracing efforts [24]. As traditional approaches continue at the PHMDC and the state of Wisconsin to investigate and report positive cases into their surveillance system, our tool may help focus and guide data teams to clusters during high-volume caseloads. We also shared a novel location-mapping technology that uses the raw data from the state’s surveillance system and provides addresses to further reduce mining efforts from the larger databases.

The motivation for this work began with the COVID-19 data team at the PHMDC contacting the data science team at the UW to assist in methods to overcome the difficulties in mining the many free-text fields in the contact interview forms. Like other states and counties in the region, Dane County surged during the fall and winter months and our tool showed recall rates above 70% during these periods. Although the precision values were lower due to FPs, reviewing the FPs in our summary reports may still be less burdensome to data teams than manually scanning the free-text fields or building customized rule-based, keyword algorithms of individual reports. The more important determinant was reducing FNs of potentially missed outbreaks by having an acceptable recall. The accuracy of our tool dropped during months with caseloads below several hundreds, but we anticipate the tool may be less utilized during these periods because staff have more time to identify and investigate outbreaks through existing standard operating procedures. Currently, a version of the report has been incorporated into a statewide reporting system for beta testing and application across any county in the state of Wisconsin (Figure 1). First, the data from WEDSS are fed into the NLP pipeline via an ETL process in an on-premise, HIPAA-secure computing environment at the UW. The results are developed as a flat file output and returned

to the state's Department of Health Services Office of Health Informatics in a second ETL process into a statewide reporting system for access by end users at county health departments via a web interface. Our next steps are to examine acceptance by our PHMDC health department data team with pilot validation testing and to monitor for adoption, similar to what others have described [28]. We have integrated our pipeline to work in the existing statewide reporting system for counties.

Although the private sector with companies such as Google has led the field in geomapping technologies, we leveraged their location software to support our unique location-mapping tool. We remained compliant with license agreements by first building our own internal database of all potential business names and organizations derived from our WEDSS database. This allowed us to perform API calls and identify any matches without storing any of Google's data and violating any license agreements to use the tool. We noted some of the NER places were chain restaurants and stores, so using unsupervised methods to identify a centroid longitude/latitude within a cluster allowed us to predict the most likely location of the business identified from the NER tool. Our precision and recall scores for this part of the system were high and potentially reduced the time needed by staff to identify exact addresses. Contact-tracing interview forms are collected at the county-level across the state of Wisconsin and recorded into the central WEDSS database, so we expect our tool may be scaled statewide to capture more rural regions or cover commute distances that span multiple counties.

Limitations

Several limitations occurred in our work. First, we ran the NER tool as an "out of the box" solution without any further tuning. The training data set for fine-tuning a BERT-base-NER model came from a specific span of time and may not generalize well

to our domain. However, due to time and resource constraints, we could not invest in building an internally annotated data set for fine-tuning. We expect model performance may continue to improve with domain adaptation, but we opted to develop our pipeline with the current general-purpose state-of-the-art tool. Second, we assumed the radius around the centroid of home addresses for clusters captured all relevant locations from our location-mapping tool. This does not account for individuals traveling from out of state or further distances from home. We did attempt to mitigate this issue with our extended mapping algorithm that had a radius of 250 km. Lastly, our tool was flexible for processing contact interview forms spanning different time intervals, but the delays in transfer of ETL data from the state of Wisconsin reporting system to PHMDC policy makers prevented a real-time alert system for the tool. Our current system can refresh every 24-48 hours from the time case report forms are entered into WEDSS, which remains useful to data analysts who are backlogged on reviewing cases during heavy-load periods. Our data use agreement prevented the real-time, on-site application of the pipeline by PHMDC staff, but this remains a future direction in data access and software development for our tool. Lastly, future work will incorporate results on the potentially new clusters to verify their relevance for investigation and confirm an outbreak. Prospective evaluation of the tool was not possible, given existing staff demands from the pandemic.

Conclusion

Our automated pipeline ingests data from a statewide database, and it may be deployed across counties to assist other health departments in Wisconsin in targeted policies during outbreaks. The tool is open source and an interoperable resource that may be used by neighboring states as well. Further, our pipeline may also be applied for other communicable disease and surveillance efforts that requires analysis of free-text data.

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Conflicts of Interest

MMC has a patent pending (ARCD P0535US.P2) for risk stratification algorithms for hospitalized patients and has received research support from EarlySense (Tel Aviv, Israel). The remaining authors have no conflicts of interest.

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Abbreviations

API: Application Program Interface
BERT: Bidirectional Encoder Representations from Transformers
CDC: Centers for Disease Control and Prevention
CoNLL: Conference on Computational Natural Language Learning
DHS: Department of Health Services
ETL: extract, transform, and load
NER: named entity recognition
NLP: natural language processing
PHMDC: Public Health Madison & Dane County
FN: false negative
FP: false positive
TP: true positive
UW: University of Wisconsin
WEDSS: Wisconsin Electronic Disease Surveillance System

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Original Paper

Analysis of Demographic Characteristics of Users of a Free Tobacco Cessation Smartphone App: Observational Study

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Abstract

Background: Tobacco use continues to be the leading preventable cause of death, disease, and disability in the United States. Since 2000, Washington state has offered free tobacco “quitline” services to help its residents stop using tobacco. In 2015, the state began offering free access to a tobacco cessation smartphone app to absorb excess quitline demand. Since most publicly funded tobacco cessation programs are designed to provide access to populations disproportionately impacted by tobacco use, it is important to consider who these public health interventions reach.

Objective: The aim of this study is to understand who used a free cessation app and the extent to which users represented populations disproportionately impacted by tobacco use.

Methods: This is an observational study of 1280 adult Washington state residents who registered for and activated the cessation app. Demographic data were collected as part of the sign-up process, examined using standard descriptive measures, and assessed against state-level surveillance data for representativeness.

Results: Participants were primarily non-Hispanic White (978/1218, 80.3%), identified as female (780/1236, 63.1%), were between ages 25-54 years (903/1186, 76.1%), had at least some college education (836/1222, 68.4%), and reported a household income under US \$50,000 (742/1055, 70.3%). Fewer respondents were from rural counties (359/1220, 29.4%); identified as lesbian, gay, bisexual, pansexual, queer, questioning, or asexual (LGBQA; 153/1222, 12.5%); were uninsured (147/1206, 12.2%); or were currently pregnant, planning pregnancy, or breastfeeding (42/624, 6.7%). However, relative to available state data for tobacco users, there was high representation of women, 35- to 54-year-olds, college graduates, and LGBQA individuals, as well as individuals with low household income, poor mental health, Medicaid insurance, and those residing in rural counties.

Conclusions: A diverse population of tobacco users will use a free cessation app, including some demographic groups disproportionately impacted by tobacco use. With high reach and high efficacy, it is possible to address health disparities associated with tobacco use and dependence treatment among certain underserved and at-risk groups.

(*JMIR Public Health Surveill* 2022;8(3):e32499) doi:[10.2196/32499](https://doi.org/10.2196/32499)

KEYWORDS

mobile applications; mHealth; eHealth; smartphone app; tobacco; smoking cessation; public health; smoking; application

Introduction

Smoking and secondhand smoke exposure in the United States lead to approximately 480,000 deaths each year [1], and tobacco

use continues to be the leading preventable cause of death, disease, and disability [2]. It is widely accepted that there is no safe level of cigarette smoking [3] and that smoking cessation has benefits at any age [2,4].

Among US adults in 2019, cigarette smoking (14%) was the most common form of tobacco use, followed by electronic cigarettes (e-cigarettes; 4.5%), cigars (3.6%), smokeless tobacco (2.4%), and pipes (1%) [5]. In Washington state (WA), nearly 1 in 5 (17.4%) [6], or 1 million, adults use one or more of these tobacco products [7]. In WA, as in the US, adults who use tobacco are disproportionately male; lesbian, gay, bisexual, pansexual, queer, questioning, or asexual (LGBQA); have low educational attainment; have low household income; have poor mental health; and live in rural areas [5,6].

Over the last several decades, the rate of smoking has declined largely due to tobacco control policies such as tobacco taxes, smoke-free workplaces and spaces, public awareness campaigns, and the availability of effective cessation treatments [8]. Cessation options have been available direct-to-consumer and through employers, health insurance plans, and publicly sponsored programs. One such state-sponsored program is tobacco “quitlines,” for which there is a large body of supporting evidence [9]. Quitlines, which typically offer free phone counseling, web-based resources, and cessation medications [10], represent a cost-effective, population-based approach for reducing tobacco-related disease and death [8], and are available in all states and, increasingly, internationally [11].

In 2000, the WA Department of Health (DOH) started one of the first state quitlines in the United States [12] and continues to offer free evidence-based cessation resources to residents. Following the loss of state quitline funding, the DOH began offering free access to a smartphone app in 2015 to absorb excess quitline demand and reach a broader audience with cessation services. In this paper, we describe the demographic characteristics of adults who activated a tobacco cessation app, and compare these demographics to those of the broader WA adult tobacco user population to understand the extent to which populations disproportionately impacted by tobacco use have used the app.

Methods

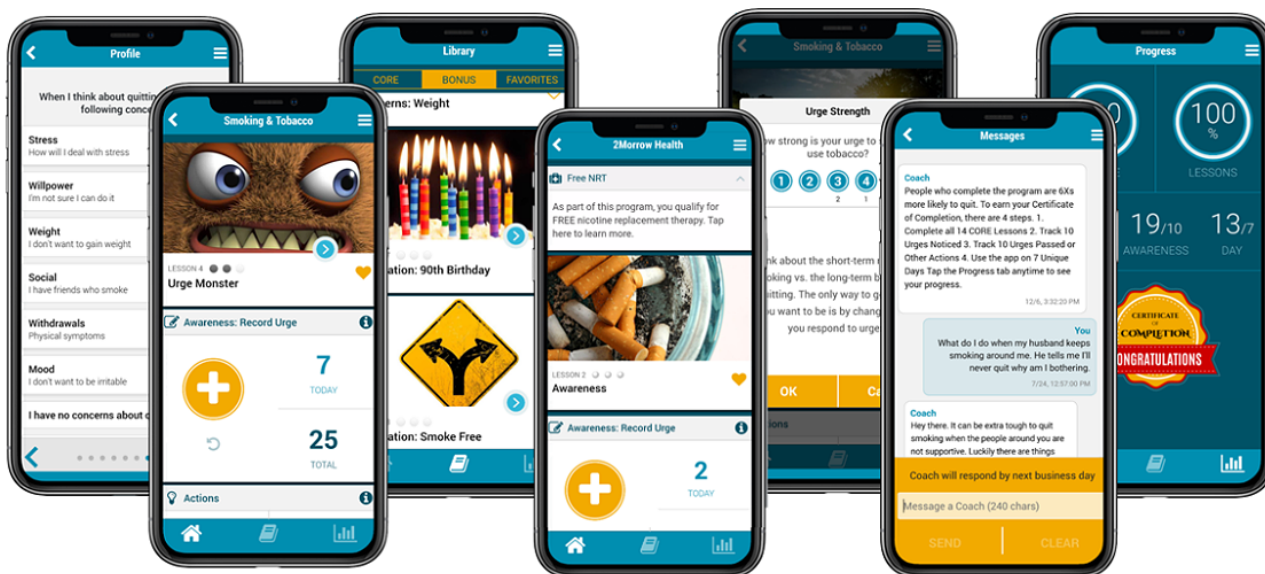
Background and Ethical Approval

The present study is a real-world observational study based on data from 1280 WA residents who registered for and activated the 2Morrow Health Smoking & Tobacco app (2Morrow Inc) between October 1, 2018, when the DOH last updated its sign-up process and questions, through December 31, 2020. Demographic data were collected as part of the sign-up process (described below), examined using standard descriptive measures, and compared to the overall WA tobacco user population. The Washington State Institutional Review Board determined that this study did not constitute human subject research and was deemed exempt from the associated ethical requirements (2021-044).

App Description

The 2Morrow Health Smoking & Tobacco app (Figure 1) is a self-guided smartphone app designed to teach tobacco users how to manage unhelpful thoughts, urges, and cravings caused by nicotine addiction. The app was originally developed and tested by researchers at the Fred Hutchinson Cancer Research Center in Seattle, WA, and brought to market by 2Morrow Inc through an exclusive licensing arrangement. The app is evidence-informed, grounded in acceptance and commitment therapy principles, and scientifically tested [13-15]. The app is designed to help all tobacco users, regardless of tobacco type(s) used. The app includes lessons and content on how to plan to quit and how to deal with cravings; it also includes tools for setting a quit date, developing a quit plan, and tracking when a participant lets urges pass. Furthermore, the app includes algorithm-based messages and notifications, such as helpful tips and reminders, and provides users the ability to text with trained coaches within the app. Information is provided about cessation medications and how to use them as part of the quitting process. Participants who successfully complete the core content and meet certain program milestones are issued a certificate of completion; however, all participants have continued access to all resources for up to one year.

Figure 1. 2Morrow Health Smoking & Tobacco app. NRT: nicotine replacement therapy.

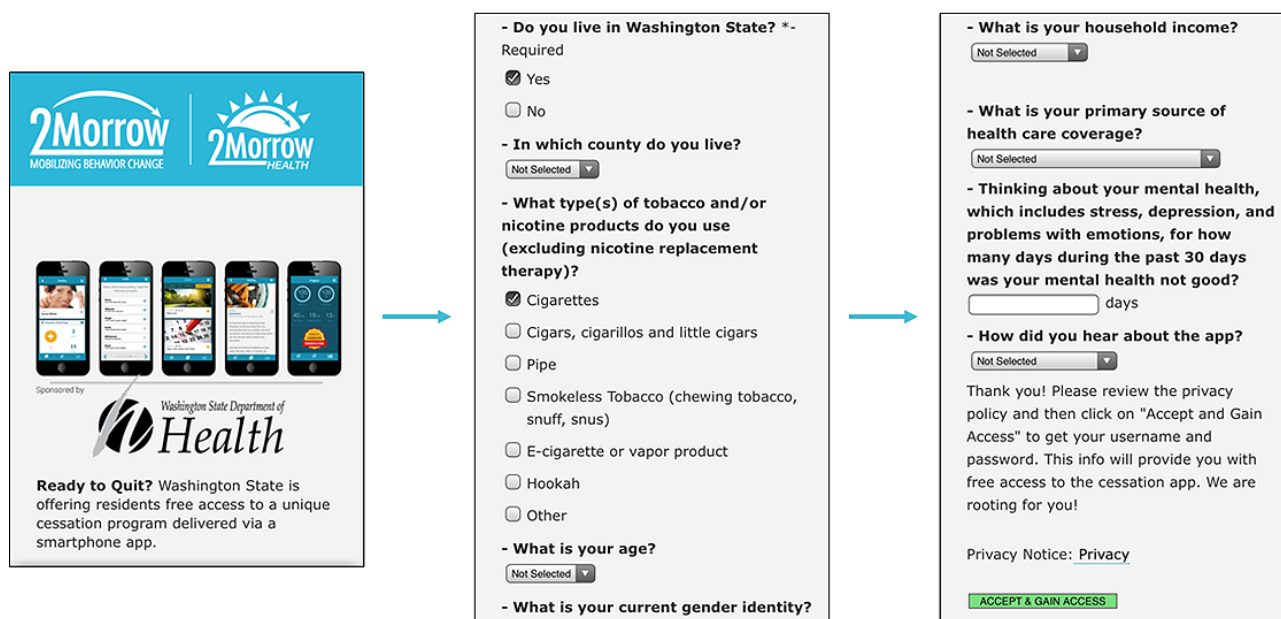


Sign-up Process

Promotional efforts varied throughout the 27 months for which sign-up data were examined, but generally relied upon the DOH website and business card-sized promotional materials distributed to the public through DOH tobacco prevention contractors. All promotional messaging directed prospective users to the DOH website using a short URL. This webpage linked them to the sign-up survey hosted on the 2Morrow website (Figure 2). For web browsers with the default language set to Spanish, the sign-up questions were automatically translated into Spanish. After completing the sign-up survey,

participants were directed to review and accept the privacy policy to obtain a username and password, which would provide them with free access to the cessation app. Participants were informed of how their data might be used; the 2Morrow privacy policy read “We use de-identified information...to improve our programs and measure their impact and effectiveness to Users, and to conduct surveys and continue our research to improve our Services, which may result in published reports or articles.” Once participants signed up, 2Morrow provided them with a unique username and password combination that granted them free access to the app for 12 months upon download and activation.

Figure 2. Excerpts from app sign-up page.



Data Collection and Measures

Demographic data were collected during sign-up. In addition to a question that requires prospective users to confirm that they live in WA, the sign-up survey includes as many as 16 optional demographic questions. Demographic data collected includes the following: age group, sex and gender, sexual orientation, race and ethnicity, education level, county, household income level, source of health care coverage (if any), mental health status, and type(s) of tobacco used. Prospective users who indicated a female sex assignment at birth were also asked if they are currently pregnant, planning pregnancy within the next 3 months, and/or breastfeeding.

Many questions were based on those used in the state's Behavioral Risk Factor Surveillance System (BRFSS) surveys [6], so that the DOH could assess user representativeness of the broader WA adult tobacco user population. The BRFSS is an annual population-based, random-digit dial telephone survey of noninstitutionalized adults aged 18 years or older, and results are weighted to a variety of population characteristics. These questions, and others developed with input from state tobacco prevention community partners, were asked so that the DOH

could also estimate its reach within certain populations. In 2020, the BRFSS combined landline and cell phone response rate was 47.4%. In the BRFSS, being a tobacco user is defined as being a current cigarette smoker, e-cigarette user, or smokeless tobacco user. Current cigarette smokers are respondents who report having smoked 100 or more cigarettes (or five packs) in their life and who report currently smoking every day or some days. Respondents who report currently using e-cigarettes or smokeless tobacco every day or some days are categorized as current e-cigarette and smokeless tobacco users, respectively. Use of multiple tobacco products is defined as currently using two or more tobacco products. More products were assessed during app intake than were assessed on the BRFSS, so there are two versions of multiple use among app users presented in [Table 1](#); one version is the rate of using two or more of any of the available tobacco products assessed on the app, and the other only considers cigarettes, e-cigarettes, and smokeless tobacco for the sake of comparability to the BRFSS multiple tobacco product use rate.

Counties with a population of less than 100 persons per square mile and counties smaller than 225 square miles were categorized as rural [16].

Table 1. Characteristics of October 2018 to December 2020 tobacco cessation app users and 2020 Washington state (WA) tobacco users.

Characteristic	App users, N=1280		WA tobacco users		P value
	Value, n (%)	95% CI	Value (%) ^a	95% CI	
Gender					
Female	780 (63.1)	60.3-65.8	42.4	39.5-45.4	<.001
Male	441 (35.7)	33-38.4	57.4	54.4-60.3	<.001
Nonbinary/other	15 (1.2)	0.7-2	N/A ^{b, c}	N/A	N/A
Not reported ^d	44	N/A	N/A	N/A	N/A
Age in years					
18-24	77 (6.5)	5.2-8	11.1	9.2-13.2	<.001
25-34	256 (21.6)	19.3-24	22.8	20.2-25.6	.50
35-44	349 (29.4)	26.8-32.1	19.7	17.4-22.2	<.001
45-54	298 (25.1)	22.7-27.7	16.8	14.8-18.9	<.001
55-64	173 (14.6)	12.6-16.7	16.9	14.9-19	.12
65 and up	33 (2.8)	1.9-3.9	12.7	10.9-14.6	<.001
Not reported	94	N/A	N/A	N/A	N/A
Educational attainment					
Less than high school	77 (6.3)	5-7.8	12.4	10.3-14.8	<.001
High school graduate or GED ^e	309 (25.3)	22.9-27.8	32.2	29.4-35	<.001
Some college	485 (39.7)	36.9-42.5	40.7	37.8-43.7	.62
College graduate	351 (28.7)	26.2-31.4	14.8	13-16.6	<.001
Not reported	58	N/A	N/A	N/A	N/A
Household income in US \$					
Less than 15,000	270 (25.6)	23-28.3	10.2	8.6-12.1	<.001
15,000-24,999	189 (17.9)	15.6-20.4	17.6	15.3-20.1	.86
25,000-34,999	154 (14.6)	12.5-16.9	11.6	9.6-13.9	.05
35,000-49,999	129 (12.2)	10.3-14.4	14.8	12.7-17.1	.09
50,000-74,999	139 (13.2)	11.2-15.4	15.5	13.2-18	.14
75,000 or more	174 (16.5)	14.3-18.9	30.3	27.4-33.3	<.001
Not reported	225	N/A	N/A		
Ethnicity and race					
Hispanic (all races)	78 (6.4)	5.1-7.9	7.2	5.7-9	.43
American Indian/Alaska Native (NH ^f)	21 (1.7)	1.1-2.6	3.3	2.3-4.5	.02
Asian (NH)	35 (2.9)	2-4	5.4	3.7-7.4	.02
Black (NH)	35 (2.9)	2-4	5.3	3.9-7	.01
Multiracial (NH)	60 (4.9)	3.8-6.3	3.2	2.4-4.2	.02
Native Hawaiian/Pacific Islander (NH)	11 (0.9)	0.5-1.6	1.3	0.7-2.1	.37
White (NH)	978 (80.3)	77.9-82.5	73.7	70.8-76.4	<.001
Not reported	62	N/A	N/A	N/A	N/A
Sexual orientation					
Heterosexual	1069 (87.5)	85.5-89.3	90.8	89-92.5	.01
LGBQA ^g	153 (12.5)	10.7-14.5	9.2	7.5-11	.01
Not reported	58	N/A	N/A	N/A	N/A

Characteristic	App users, N=1280		WA tobacco users		P value
	Value, n (%)	95% CI	Value (%) ^a	95% CI	
Mental health (MH)					
Less than 14 days of poor MH in the past month	715 (64.4)	61.5-67.2	74.4	71.6-77	<.001
14 or more days of poor MH in the past month	395 (35.6)	32.8-38.5	25.6	23-28.4	<.001
Not reported	170	N/A	N/A	N/A	N/A
Pregnancy status^h					
Currently pregnant, planning pregnancy, or breastfeeding	42 (6.7)	4.9-9	N/A	N/A	N/A
Not currently pregnant, planning pregnancy, or breastfeeding	582 (93.3)	91-95.1	N/A	N/A	N/A
Not reported	169	N/A	N/A	N/A	N/A
Health insurance					
Employer or union health plan	412 (34.2)	31.5-36.9	41.6	38.6-44.7	<.001
Individual or family health plan	86 (7.1)	5.7-8.7	6.2	4.8-7.9	.41
Medicaid	356 (29.5)	27-32.2	18.8	16.5-21.3	<.001
Medicare	140 (11.6)	9.9-13.6	15	13-17.1	.01
None (uninsured)	147 (12.2)	10.4-14.2	12.5	10.5-14.8	.82
Other	31 (2.6)	1.8-3.6	2.6	1.8-3.5	>.99
TRICARE, Veteran's Affairs, or military	34 (2.8)	2-3.9	3.3	2.2-4.7	.58
Not reported	74	N/A	N/A	N/A	N/A
WA geography					
Nonrural counties	861 (70.6)	67.9-73.1	75.1	72.7-77.3	.01
Rural counties	359 (29.4)	26.9-32.1	24.9	22.7-27.3	.01
Not reported	60	N/A	N/A	N/A	N/A
Products usedⁱ					
Cigarettes	1133 (90.9)	89.1-92.4	70.3	67.5-73	<.001
E-cigarette ^j or vapor product	172 (13.8)	11.9-15.8	31.3	28.5-34.2	<.001
Smokeless tobacco	64 (5.1)	4-6.5	16.0	13.9-18.2	<.001
Multiple (2 or more of cigarettes, e-cigarettes, and smokeless tobacco)	155 (12.4)	10.6-14.4	15.6	13.4-18	.03
Multiple (2 or more of any product)	202 (16.2)	14.2-18.4	N/A	N/A	N/A
Cigars, cigarillos, and little cigars	74 (5.9)	4.7-7.4	N/A	N/A	N/A
Pipe	20 (1.6)	1-2.5	N/A	N/A	N/A
Other	32 (2.6)	1.8-3.6	N/A	N/A	N/A

Characteristic	App users, N=1280		WA tobacco users		P value
	Value, n (%)	95% CI	Value (%) ^a	95% CI	
None selected/not reported	33	N/A	N/A	N/A	N/A

^aData in this column are from Washington state's Behavioral Risk Factor Surveillance System (BRFSS) surveys. Absolute values are not provided.

^bN/A: Not available.

^cA nonbinary response option for this category was not provided by the BRFSS surveys.

^dAll percentages are calculated based on the number of participants who reported data for each category.

^eGED: General Educational Development.

^fNH: non-Hispanic.

^gLGBQA: lesbian, gay, bisexual, pansexual, queer, questioning, or asexual.

^hThis question was only asked of the 793 participants who reported a female sex assignment at birth (not displayed).

ⁱParticipants were asked which type(s) of tobacco and/or nicotine products they use, and they could select multiple options; hookah tobacco is not displayed due to low response frequency.

^je-cigarette: electronic cigarette.

Analysis

App data examined included individuals who signed up for the app between October 1, 2018, and December 31, 2020, and met program eligibility (verified living in WA). The analysis excluded individuals who did not activate the app by January 28, 2021, (n=1177), and 11 additional individuals who reported being less than 18 years old.

R software, version 4.0.4 (R Foundation for Statistical Computing) was used for data analysis, the R tidyverse package was used to generate frequencies and proportions for all variables, and exact confidence intervals for binomial proportions were estimated using the epitools package.

The WA 2020 BRFSS was used to generate prevalence estimates representative of the WA adult population of tobacco users. The total BRFSS sample size was 12,902. The R survey package was used to calculate weighted prevalence estimates and asymmetric 95% confidence intervals of demographic and risk factor distributions among current tobacco users. To compare BRFSS and app proportions, z-scores for two-sample means and two-sided *P* values were calculated and considered significant when $P < .01$, an approach consistent with the US Centers for Disease Control and Prevention (CDC) recommendations for assessing health disparities [17]. BRFSS estimates are not reported if the relative standard error exceeds 30%.

For both app user and BRFSS percentages, missing data were excluded from the analysis. Frequencies of missing values for optional demographic questions asked of app users at sign-up are presented as "Not reported" in Table 1.

Results

The analysis included 1280 participants. Participants were primarily non-Hispanic White, identified as female, were between ages 25-54 years, had at least some college education, and reported a household income under US \$50,000 (Table 1). Fewer respondents were from rural counties, identified as LGBQA, were uninsured, or were currently pregnant, planning pregnancy, or breastfeeding. Of the different types of tobacco and nicotine products participants were asked if they currently

use, cigarettes were by far the most commonly reported, followed by e-cigarettes, cigars, and smokeless tobacco. Missing data ranged from a low of 2.6% (33/1280; types of tobacco and nicotine products used) to a high of 21.3% (169/793; pregnancy status among women).

Compared to BRFSS estimates of WA tobacco users, app users were significantly more likely to be female, age 35-54 years, non-Hispanic White or multiracial, LGBQA; they were also more likely to report poor mental health and live in a rural county (Table 1). College graduates, individuals reporting a household income of less than US \$15,000 per year, and individuals with Medicaid insurance were also overrepresented (Table 1). Finally, tobacco users who report using e-cigarettes and/or smokeless tobacco products were far less likely to use the app than BRFSS estimates might suggest (Table 1).

Discussion

Principal Results

Overall, this study shows that a mobile tobacco cessation app reached a diverse population, including relatively large proportions of some groups disproportionately impacted by tobacco use; there was high representation of LGBQA individuals as well as individuals with low household income, on Medicaid insurance, with poor mental health, and residing in rural counties.

Research shows that 68% of smokers are interested in quitting [18] and that over 55% attempt to quit each year [18,19]. However, despite the existence of treatment options, less than one-third of smokers use these when trying to quit, and most use pharmacological support rather than behavioral support [18]. Furthermore, younger adults and certain ethnic and racial groups are less likely to seek help or use treatment [20]. Although there is a growing body of evidence evaluating [21,22] and testing the effectiveness of cessation apps [13-15,23,24], there is little known about who these apps can reach and benefit when offered, for free, to an entire population. Since most publicly funded tobacco cessation programs are designed to provide access to underserved communities and groups disproportionately impacted by tobacco use, both effectiveness

and reach are important considerations for these public health interventions. This paper adds to this literature.

Lack of access to smartphone technology can serve as an obstacle to digital or app-based treatments. This is of concern for low-income populations who are less likely to own smartphones [25] and programs attempting to reach these underserved tobacco users. However, many of those who activated the app in our study also reported low incomes. These findings suggest that a mobile app for smoking cessation may be of relatively high interest among low-income populations.

Digital health cessation studies have shown that younger tobacco users are more likely to use web-based programs [26] as well as other digital programs, such as texting and mobile apps, than their older counterparts [27], who are more likely to call quitlines [28,29]. Our study demonstrates how states can complement their population-level cessation strategy with an app to reach and engage tobacco users in the quitting process relatively early in life. This is important because people who can quit smoking by age 40 gain 3 additional years of life expectancy compared to those who quit after age 50 [4].

This study benefited from large sample sizes, which allowed for the detection of frequent significant differences between the app user group and the BRFSS tobacco user population. In addition to individuals with low household income and 35-54-year-olds, the BRFSS comparisons revealed that LGBQA individuals, college graduates, those with poor mental health, those on Medicaid insurance, and those who reside in rural counties all activated the app in greater proportions than otherwise expected among the state's population of tobacco users. As in comparable digital health cessation interventions and state quitline studies, there were also disproportionately high rates of use among tobacco users who identify as female and/or non-Hispanic White [27-29].

Of note, 1 in 15 women who used the app were pregnant, breastfeeding, or planning pregnancy, which inspired the DOH and 2Morrow to codevelop a tailored module of the app for this high-risk population [30], for whom other digital cessation interventions have demonstrated promise [31].

Offering a free cessation app may help state funders and other program sponsors reach these and potentially other priority populations who are known to have disproportionately high rates of tobacco use and tobacco-related disease. By offering

cessation programs through different modalities, a telephonic quitline and a mobile app, the DOH can achieve broader demographic reach.

Limitations

The generalizability of these results may be limited by a few factors. First, participants were not required to complete the demographic survey items to download and use the mobile app, which resulted in some missing data that could affect the interpretation of findings. Second, it is possible that participants could have registered and activated the app more than once across the study period, so some counts may be inflated. Third, the app was only promoted to WA residents, so the results may not generalize to other states or national populations. The DOH did not have any significant paid promotions for the app, which limits the conclusions about who might use the app, when robustly and continuously promoted. Additionally, 12 months into the app user data collection period for this study, the DOH and 2Morrow launched a vaping cessation program [32], the sign-up page for which was linked to the same webpage as the tobacco cessation app. Developed for teenagers and young adults who use e-cigarettes, this simultaneous offering may have reduced the number of app users who reported using e-cigarettes or vapor products in this study. Finally, both BRFSS and the app collected self-reported information which may be subject to systematic misclassification due to various reporting biases, such as social desirability or recall bias.

Conclusions

The results from this study indicate that a diverse population of tobacco users, varying in terms of race, ethnicity, mental health status, sexual orientation, and other demographic characteristics, will use a free cessation app. Individuals who used the app in this study largely represent the demographic groups most at risk for cigarette smoking and associated premature disease and death. This may have implications for health equity. Understanding who uses cessation apps is important for developers and funders alike; this information can be used to address gaps in use, such as by developing marketing and outreach strategies or examining new product features that may be needed to appeal to different users. The extent to which users engage with the app should be explored and continuously improved upon to maximize effectiveness and, therefore, public health impact.

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Conflicts of Interest

SMZ is a paid consultant working for 2Morrow, Inc.

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Abbreviations

BRFSS: Behavioral Risk Factor Surveillance System

CDC: US Centers for Disease Control and Prevention

DOH: Washington State Department of Health

e-cigarettes: electronic cigarettes

GED: General Educational Development

HHS: US Department of Health and Human Services

LGBQA: lesbian, gay, bisexual, pansexual, queer, questioning, or asexual

NH: non-Hispanic

WA: Washington state

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Original Paper

Perception of the Food and Drug Administration Electronic Cigarette Flavor Enforcement Policy on Twitter: Observational Study

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Abstract

Background: On January 2, 2020, the US Food and Drug Administration (FDA) released the electronic cigarette (e-cigarette) flavor enforcement policy to prohibit the sale of all flavored cartridge-based e-cigarettes, except for menthol and tobacco flavors.

Objective: This research aimed to examine the public perception of this FDA flavor enforcement policy and its impact on the public perception of e-cigarettes on Twitter.

Methods: A total of 2,341,660 e-cigarette-related tweets and 190,490 FDA flavor enforcement policy-related tweets in the United States were collected from Twitter before (between June 13 and August 22, 2019) and after (between January 2 and March 30, 2020) the announcement of the FDA flavor enforcement policy. Sentiment analysis was conducted to detect the changes in the public perceptions of the policy and e-cigarettes on Twitter. Topic modeling was used for finding frequently discussed topics about e-cigarettes.

Results: The proportion of negative sentiment tweets about e-cigarettes significantly increased after the announcement of the FDA flavor enforcement policy compared with before the announcement of the policy. In contrast, the overall sentiment toward the FDA flavor enforcement policy became less negative. The FDA flavor enforcement policy was the most popular topic associated with e-cigarettes after the announcement of the FDA flavor enforcement policy. Twitter users who discussed about e-cigarettes started to talk about other alternative ways of getting e-cigarettes after the FDA flavor enforcement policy.

Conclusions: Twitter users' perceptions of e-cigarettes became more negative after the announcement of the FDA flavor enforcement policy.

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KEYWORDS

electronic cigarette; FDA flavor enforcement policy; Twitter; Food and Drug Administration; enforcement; policy; e-cigarettes; e-cigarette flavor; tobacco flavors; prohibit; sale

Introduction

Background

An electronic cigarette, also known as an e-cigarette or e-cig, is a battery-powered product that typically delivers nicotine in the form of an aerosol [1]. E-cigarette liquid normally contains

propylene glycol/vegetable glycerin and flavorings, sometimes contains other additives, such as sweeteners and cannabidiol oil, and frequently contains nicotine [2]. The popularity of e-cigarettes has rapidly increased in recent years, especially among teenagers. According to the 2019 National Youth Tobacco Survey (NYTS), from 2018 to 2019, the proportion of high school current (past 30 days) e-cigarette users increased

from 20.8% to 27.5%, and the proportion of middle school current (past 30 days) e-cigarette users increased from 4.9% to 10.5% [3]. Because of the appealing device appearance and various flavor choices, e-cigarettes are more attractive to teenagers and young adults [2].

The e-cigarette flavor choices in the market have rapidly increased in recent years. One study showed that there were more than 460 brands and 7700 unique e-cigarette flavors as of January 2014 [4]. During 2014, the number of e-cigarette brands increased by 10.5 per month, and there were 242 new flavors added each month on average [4]. However, after various federal and state regulations on flavored e-cigarettes, the number of e-cigarette brands and flavors possibly shrank. Among all available e-cigarette flavors, fruit and sweet flavors have been the most popular ones over time [5]. However, the health impact of flavored e-cigarettes is always a major public concern. One study showed that e-cigarette flavorings could lead to endothelial dysfunction, which may increase cardiovascular disease risks [6]. Regardless of the nicotine concentration, e-cigarettes with cinnamon and menthol flavors are more harmful than those with other flavors [6]. Another study showed that both diacetyl and 2,3-pentanedione were associated with changes in gene expression, which impaired both the production and function of the cilia [7]. In addition, our several recent studies found a significant association of e-cigarette use with self-reported wheezing and chronic obstructive pulmonary disease, as well as self-reported difficulty concentrating, remembering, or making decisions in both youth and adults [8-12]. Several studies showed evidence of the effectiveness of e-cigarettes in smoking cessation and reduction with no harm in users up to 2 years, which could potentially benefit current cigarette smokers [13-17]. However, e-cigarettes have no health benefits for youth and adults who have never used any tobacco products before [3,11,18-29].

In order to prevent youth access to flavored e-cigarettes, in November 2018, the Food and Drug Administration (FDA) announced several policies to protect youth, including restricting the sale of flavored e-cigarettes to physical and online stores, with customer age restriction and verification [30]. On January 2, 2020, the FDA announced the flavor enforcement policy that restricted the sale of unauthorized flavored e-cigarette products due to the current epidemic of e-cigarette use among youth [31]. This policy restricted cartridge-based flavored e-cigarette products other than tobacco and menthol flavors, and any e-cigarette product that was targeted to teenagers and young adults. The FDA flavor enforcement policy was implemented on February 6, 2020.

Objective

To examine the impact of the FDA flavor enforcement policy, we proposed to investigate how the FDA flavor enforcement policy affects the public perception of e-cigarettes and, subsequently, the potential changes in e-cigarette user behavior using Twitter data. Twitter had around 48.35 million active users in the United States in 2019 [32]. Based on the Twitter demographics in 2020, 32% of Twitter users are in the age range of 13 to 17 years, and 38% of Twitter users are in the age range of 18 to 29 years [33]. Similar to the demographics of e-cigarette

users, the majority of Twitter users are teenagers and young adults. There are over 5 million youth currently using e-cigarettes. Around 27.5% of high-school students and 10.5% of middle-school students reported using e-cigarettes in 2019 [34]. Twitter data include user information, such as geolocation, which allows us to identify Twitter users from the United States. Twitter has been used in a previous study to examine public reactions to the FDA rule regulating e-cigarettes [35]. Thus, Twitter was chosen as the data source of this research.

In this study, we compared the changes in sentiment toward the FDA flavor enforcement policy and e-cigarettes before and after the FDA flavor enforcement policy. In addition, we tried to examine if there was an intention for potential behavior changes in e-cigarette use with the FDA flavor enforcement policy. The findings of this study provide important insights about the potential effects of the FDA flavor enforcement policy, which could be useful for further policy decision making about the regulation of flavored e-cigarettes to protect public health.

Methods

Data Collection From Twitter

E-cigarette-related tweets were downloaded through a Twitter streaming application programming interface (API) using keyword searching based on a list of e-cigarette-related keywords, including “e-cig,” “e-cigs,” “ecig,” “ecigs,” “electroniccigarette,” “ecigarette,” “ecigarettes,” “vape,” “vapers,” “vaping,” “vapes,” “e-liquid,” “ejuice,” “eliquid,” “e-juice,” “vapercon,” “vapeon,” “vapefam,” “vapenation,” and “juul” [5,36,37]. Twitter data were collected during 3 time periods, from June 13, 2019, to August 22, 2019 (before the announcement of the FDA flavor enforcement policy), from January 2, 2020, to February 5, 2020 (between the announcement and the implementation of the FDA flavor enforcement policy), and from February 6, 2020, to March 30, 2020 (after the implementation of the FDA flavor enforcement policy). Tweets from September to December 2019 were not included in this study because during this period many different policies on flavored e-cigarettes were either announced or implemented in different states, such as Michigan, New York, Rhode Island, Oregon, Montana, Washington, New Jersey, and Massachusetts. As a result, a total of 3,874,047 e-cigarette-related tweets were collected after removing retweets.

In order to investigate Twitter users' perceptions of e-cigarettes within the United States only, another layer of geographic filtering was applied to users' geolocations. US geolocation keywords that contained both the full names and abbreviations of 50 states in the United States, such as “California,” “Illinois,” and “Florida,” as well as big cities, such as “Los Angeles,” “Chicago,” and “Miami,” were used for filtering. As a result, 2,341,660 e-cigarette-related tweets within the United States were obtained, with 644,686 tweets before the announcement of the FDA flavor enforcement policy, 702,488 tweets between the announcement and implementation of the FDA flavor enforcement policy, and 994,486 tweets after the implementation of the FDA flavor enforcement policy.

Lastly, a third layer of filtering was applied to obtain tweets related to the FDA flavor enforcement policy. The filtering keywords included “FDA ban,” “flavor ban,” “ban,” and any combination of “FDA,” “flavor,” and “ban.” A total of 190,490 FDA flavor enforcement policy–related tweets were collected, with 29,120 tweets before the announcement of the FDA flavor enforcement policy, 89,539 tweets between the announcement and the implementation of the FDA flavor enforcement policy, and 71,831 tweets after the implementation of the FDA flavor enforcement policy. The complete data collection and filtering process is showed in a flowchart in [Multimedia Appendix 1](#).

Sentiment Analysis

VADER (Valence Aware Dictionary and Sentiment Reasoner) was used as the sentiment analyzer to analyze Twitter users’ thoughts and perceptions of e-cigarettes, and analyze Twitter users’ thoughts and perceptions of the FDA flavor enforcement policy [38]. VADER used a combination of quantitative and qualitative methods by constructing and validating lexical features, which are specifically for microblog-like contexts, as well as combining these lexical features with embodying grammatical and syntactical conventions for expressing and emphasizing sentiment intensity [38]. The overall performance score of VADER sentiment analysis on social media text is the highest compared with the other 8 methods [38]. Every tweet will obtain a sentiment score, ranging from -1.00 to $+1.00$. According to the suggested threshold for determining positive, neutral, and negative posts, negative posts were defined as tweets with sentiment scores in the range of -1.00 to -0.05 , neutral posts were defined as tweets with sentiment scores in the range of -0.05 to $+0.05$, and positive posts were defined as tweets with sentiment scores in the range of $+0.05$ to $+1.00$ [38]. In order to compare the sentiment results between different time periods, the number of tweets in each time period with positive, neutral, and negative sentiments was further normalized by the total number of tweets in each time period. In addition, the proportions of positive, neutral, and negative tweets between different time periods were tested by a 2-proportion Z test in order to determine the significances of sentiment proportion differences between different periods. The *P* values were calculated with 2-sided testing, and the significant level was set at 5%.

Topic Modeling

Topic modeling, specifically latent Dirichlet allocation (LDA) modeling, was used to determine the popular topics among e-cigarette–related tweets. LDA is a generative text model for analyzing and clustering words and terms in the given document and generating topics with keywords and their corresponding weights, which indicated the possibility of appearance in the document [39].

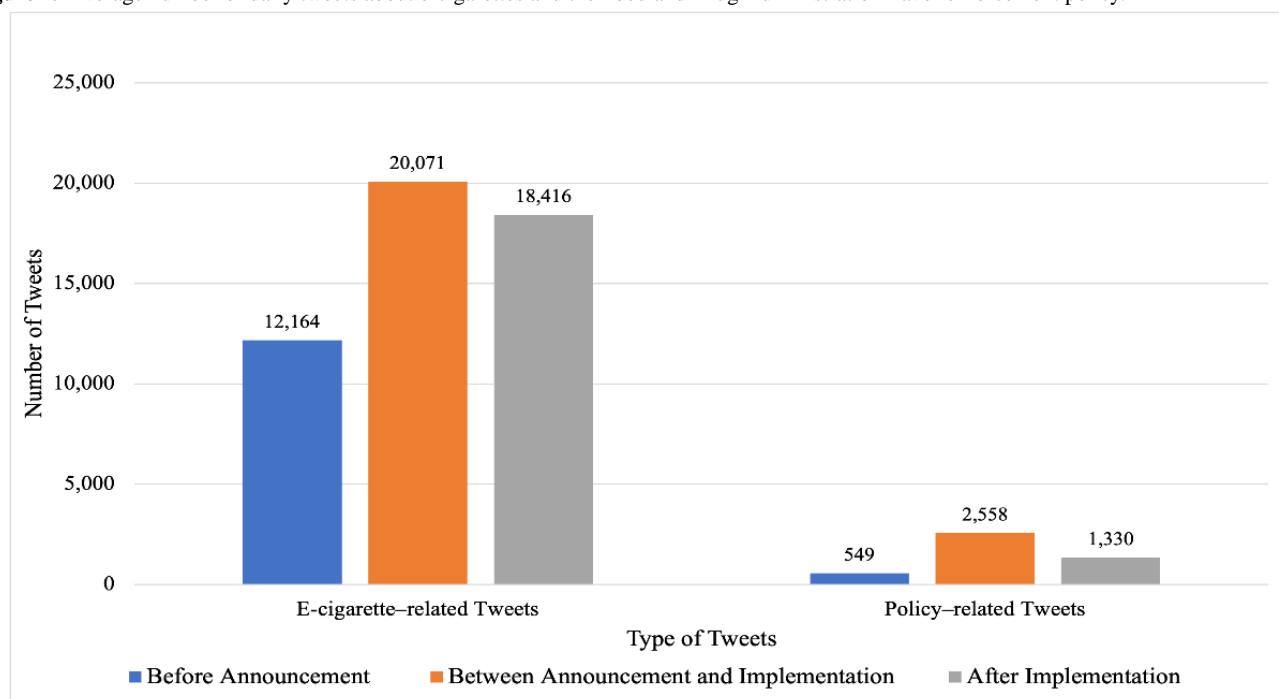
According to a research survey published in 2018, the LDA method is one of the most powerful and popular methods used for topic modeling of social network data for knowledge discovery and behavior analysis [40]. A recent paper published in 2020 compared several topic modeling methods for social data analysis and found that the LDA method extracted more meaningful topics than many other topic modeling methods compared [41]. Twitter is one of the most popular social networks that could be used to explore the topics discussed on e-cigarettes and the FDA flavor enforcement policy through LDA modeling.

We applied topic modeling to the e-cigarette tweets in the 3 time periods. First, in order to ensure consistency in the process of the training model, all characters were in lower case, and all words were in the same tense by using the spaCy lemmatization function. In addition, stop words, such as personal pronouns and prepositions, were removed by using Natural Language ToolKit (NLTK) packages. Furthermore, in order to get precise and meaningful results, frequent bigrams (eg, flavor ban) and trigrams (eg, food drug administration) were identified by using the Gensim package, which were considered as a single term rather than separated words during model training. The number of topics was chosen from 3 to 10, and the optimal number of topics was determined by the coherence score of each LDA model result. Lastly, the keywords of the fitted LDA topic model and the percentage distribution of each topic were obtained using the pyLDAvis package.

Results

Number of Tweets Related to E-Cigarettes and the FDA Flavor Enforcement Policy

To examine the impact of the FDA flavor enforcement policy on the discussion about e-cigarettes on Twitter, the total amount of tweets was normalized by the number of days before and after the FDA flavor enforcement policy. As shown in [Figure 1](#), the daily average tweets about e-cigarettes and the FDA flavor enforcement policy after the announcement and implementation of the FDA flavor enforcement policy were much higher than that before the announcement of this policy, for example, 12,164 daily e-cigarette–related tweets before the announcement versus 20,071 daily tweets between the announcement and implementation of the FDA flavor enforcement policy. The daily average amount of related tweets after the implementation of the FDA flavor enforcement policy was slightly lower than that between the announcement and implementation of this policy, for example, 18,416 daily tweets versus 20,071 tweets related to e-cigarettes.

Figure 1. Average number of daily tweets about e-cigarettes and the Food and Drug Administration flavor enforcement policy.

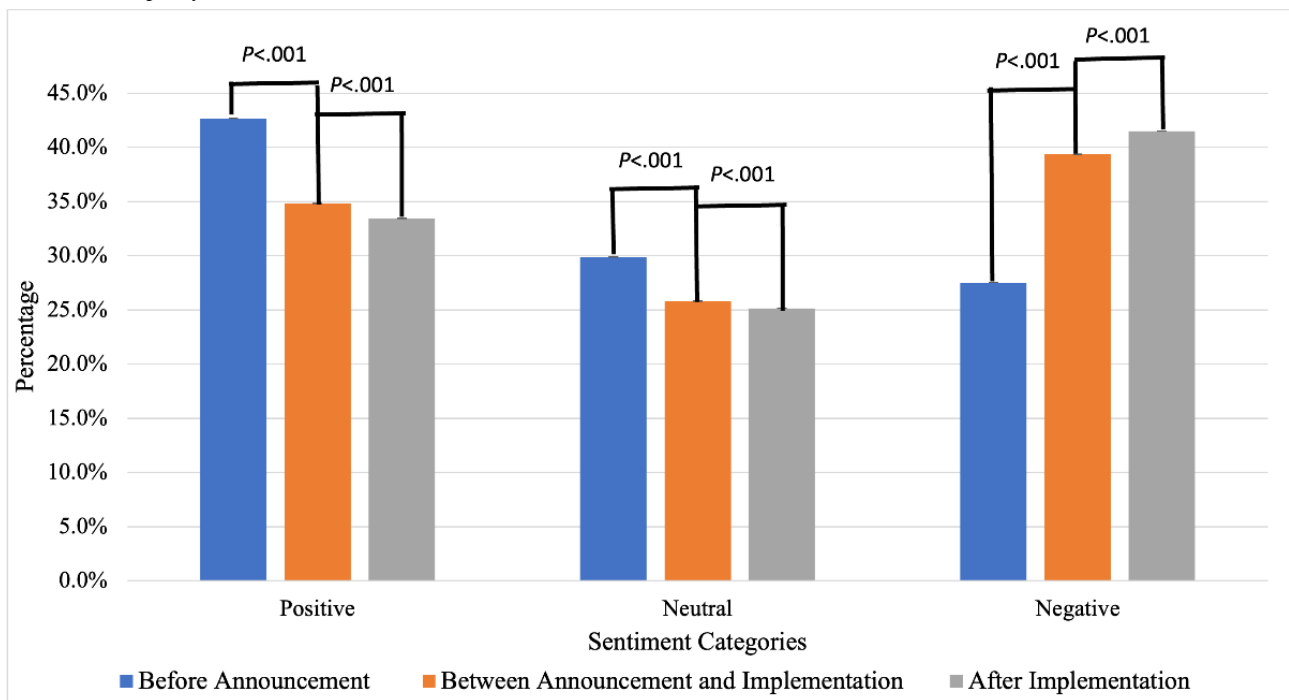
Public Perception of E-Cigarettes and the FDA Flavor Enforcement Policy on Twitter

In order to investigate the perceptions of Twitter users toward e-cigarettes and the FDA flavor enforcement policy, sentiment analysis was conducted, and the proportions of tweets with positive, neutral, and negative sentiments were calculated before and after the FDA flavor enforcement policy. For the better understanding of the sentiment results, [Multimedia Appendix 2](#) included examples for positive, neutral, and negative sentiment tweets from 3 different time periods.

As shown in [Figure 2](#), the proportion of tweets with positive sentiment toward e-cigarettes decreased significantly ($P < .001$) with the announcement and implementation of the FDA flavor

enforcement policy compared to that before the announcement of the FDA flavor enforcement policy, from 42.6% (95% CI 42.5%-42.8%) to 34.8% (95% CI 34.7%-34.9%) and 33.4% (95% CI 33.3%-33.5%). In contrast, the proportion of tweets with negative sentiment toward e-cigarettes significantly increased ($P < .001$) from 27.5% (95% CI 27.4%-27.6%) to 39.4% (95% CI 39.2%-39.5%) and 41.5% (95% CI 41.4%-41.6%). The overall average sentiment score of e-cigarette tweets was positive (0.071) before the announcement of the FDA flavor enforcement policy. In contrast, the overall average sentiment score toward e-cigarettes became negative after the announcement of the FDA flavor enforcement policy, with -0.016 between the announcement and implementation, and -0.024 after the implementation of the FDA flavor enforcement policy.

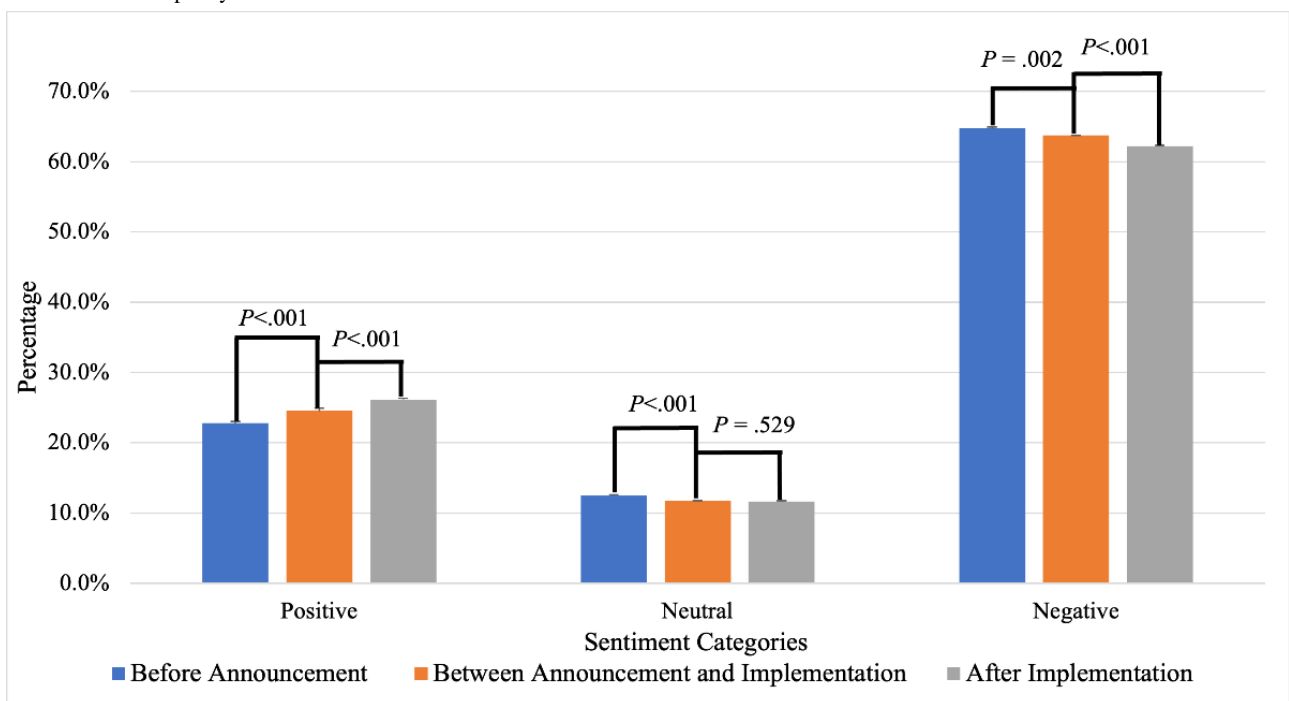
Figure 2. Changes in the public perception of e-cigarettes on Twitter with the announcement and implementation of the Food and Drug Administration flavor enforcement policy.



Different from the changes in sentiment toward e-cigarettes, for the FDA flavor enforcement policy-related tweets, the proportion of tweets with positive sentiment increased significantly ($P < .001$) from 22.8% (95% CI 22.3%-23.2%) to 24.5% (95% CI 24.0%-25.0%) and 26.2% (95% CI 25.6%-26.7%), while the proportion of tweets with negative sentiment decreased significantly ($P = .002$ and $P < .001$) with the announcement and implementation of the FDA flavor

enforcement policy from 64.8% (95% CI 64.2%-65.3%) to 63.7% (95% CI 63.2%-64.3%) and 62.2% (95% CI 61.7%-62.8%) (Figure 3). For the FDA flavor enforcement policy-related tweets, the overall sentiments were always negative. The average sentiment score was -0.249 before the announcement, -0.246 between the announcement and implementation, and -0.226 after the implementation.

Figure 3. Changes in the public perception of the Food and Drug Administration flavor enforcement policy on Twitter with the announcement and implementation of the policy.



Topics Related to E-Cigarettes

The LDA topic modeling was applied to e-cigarette-related tweets in order to determine any change in the e-cigarette-related topics discussed by the Twitter users over

time. An optimal number of topics was selected by the highest coherence score. Across the 3 time periods, the topics discussing *stop vaping* with the keywords “stop” and “quit” were prevalent (Table 1).

Table 1. Top topics related to e-cigarettes before and after the Food and Drug Administration flavor enforcement policy.

Time frame and topic	Tokens, n (%)	Keywords
Before the announcement (n=644,686)		
Stop vaping and smoking to protect health	201,142 (31.20)	vape, vaping, lung, smoke, get, go, people, stop, cancer, health
New e-cigarette flavor use among friends	158,593 (24.60)	vape, new, ude, level, link, case, dear_ncan, space_nasking, use, friend
Single Juul pod equals a pack of cigarettes	153,435 (23.80)	juul, hit, be, pod, say, still, stare, go, iterally, single
Vaping leads to nicotine addiction for those who unlikely smoke	131,516 (20.40)	smoking, cigarette, generation, whole, create, first, start, addiction, unlikely, statistically
Between the announcement and implementation (n=702,488)		
Ban on flavored tobacco products due to lung disease	231,119 (32.90)	vaping, vape, cigarette, smoking, product, flavor, ban, quit, lung, people
Ways to buy vaping products	174,920 (24.90)	vape, would, buy, get, think, shop, go, need, take, look
Time to stop vaping and smoking	167,192 (23.80)	smoke, time, vape, juul, stop, early, good, hit, read, drink
Epidemic of teenager vaping	129,258 (18.40)	vape, kid, school, new, vapefam, high, top, epidemic, give, vaper
After the implementation (n=994,486)		
Vaping and smoking have risks to get COVID-19	354,037 (35.60)	vape, vaping, smoking, smoke, want, could, know, risk, covid, people
Buy Juul products through shipping	225,748 (22.70)	vape, juul, get, shop, keep, still, flavor, product, sure, ship
Intention to stop vaping	210,831 (21.20)	take, vape, stop, late, note, dah, photo, see, guy, friend
Vaping and corona virus can cause respiratory disease	202,875 (20.40)	go, lung, vape, virus, people, young, bro, respiratory, disease, affect

Before the announcement of the FDA flavor enforcement policy, the e-cigarette-related topics included “Stop vaping and smoking to protect health,” “New e-cigarette flavor use among friends,” etc. After the announcement of the FDA flavor enforcement policy, the topic about “Flavor ban” became popular. At the same time, discussions about “Ways to buy vaping products” or “Buy products through shipping” were getting popular. In addition, after the implementation of the FDA flavor enforcement policy (after February 6, 2020), there were increasing discussions about COVID-19 and e-cigarettes with the appearance of “covid” and “virus” keywords in the topics.

Discussion

Principal Findings

To ameliorate the high prevalence of e-cigarette use in the United States, especially among teenagers and young adults, the FDA announced and implemented an enforcement policy on flavored e-cigarettes in 2020. In this study, we investigated the changes in perceptions of e-cigarettes and the FDA flavor enforcement policy before and after the announcement and implementation of this policy using Twitter data. In addition, frequent topics discussed together with e-cigarettes by Twitter users were examined.

The proportion of tweets with positive sentiment toward e-cigarettes decreased while the proportion of tweets with negative sentiment increased after the announcement of the FDA flavor enforcement policy compared with before the announcement of the policy. These results suggested that the perceptions of US Twitter users toward e-cigarettes were significantly affected by the announcement and implementation of the FDA flavor enforcement policy. The Twitter users’ perceptions of e-cigarettes in general became more negative with the announcement and implementation of the FDA flavor enforcement policy. Different from e-cigarette-related tweets, tweets about the FDA flavor enforcement policy had opposite trends. The proportion of tweets with positive sentiment increased while the proportion with negative sentiment decreased with the announcement and implementation of the FDA flavor enforcement policy.

Comparison With Prior Work

Several topics that were frequently discussed with e-cigarettes were common during the 3 time periods, such as health concerns (lung cancer and respiratory disease) and quit vaping, which might be partially due to the occurrence of e-cigarette or vaping product use-associated lung injury in 2019 [42]. After the announcement of the FDA flavor enforcement policy, Twitter users had more discussions about the flavor ban, which was

consistent with the increase in the number of tweets about the policy. We showed that the daily average number of policy-related tweets after the announcement of this policy was high. Furthermore, after the announcement of the FDA flavor enforcement policy, topics about alternative ways to get flavored e-cigarettes became one of the most significant themes discussed on Twitter.

To prevent the epidemic of e-cigarette use, the FDA announced several tobacco regulation policies. For example, in April 2014, the FDA released proposed regulation on selling and distributing tobacco products and enhancing the requirement for warning notices on the products [43]. One study conducted an online survey to investigate current smokers' awareness and perceptions of potential e-cigarette regulation and various policies in the United States [44]. The survey results showed that 83.5% of respondents agreed e-cigarettes should be regulated by the FDA. Although the majority of Twitter users expressed negative emotions in their discussions about the FDA flavor enforcement policy, our study showed that the proportion of Twitter users who expressed positive emotions in their discussions about the FDA flavor enforcement policy slightly increased after the announcement and implementation of the FDA flavor enforcement policy. This might indicate that there were more people supporting the e-cigarette regulation policy and realizing the harm of e-cigarette products after the announcement and implementation of the FDA flavor enforcement policy. Another study was conducted to investigate key conversation trends and patterns over time on Twitter during 2013-2014 [45]. The results showed that "policy and government" was the second most common theme among e-cigarette-related tweets, which indicated that people were willing to discuss and share opinions about e-cigarette policy on Twitter.

With the FDA flavor enforcement policy, the public perception of e-cigarettes became more negative. Furthermore, with the announcement of the FDA flavor enforcement policy, e-cigarette users started to discuss about what they would do, for example, quit vaping or find an alternative. These results suggest that the FDA policy had some significant effects on the use of flavored e-cigarettes, which might potentially change user behavior. A recent survey study examined the effectiveness of the FDA warning label on e-cigarette-related products among college students, and the results showed that the warning label proposed by the FDA was more effective than that created by companies, which reduced more college students' intentions to use e-cigarettes with the FDA warning notices [46].

During the process of exploring e-cigarette-related conversations on Twitter, we identified topics about the ongoing COVID-19 pandemic and vaping at the beginning of 2020, which was consistent with another social media study on Twitter about COVID-19 and vaping [47]. People had questions on the potential risks of vapers for COVID-19 infection, and whether vaping, linked to lung inflammation, could make individuals more susceptible to COVID-19 infection [47]. However, currently, there is limited evidence about the association between vaping and COVID-19 infection, which needs further investigation.

Limitations

In this study, Twitter data were used to investigate the changes in the public perception of the FDA flavor enforcement policy. User demographic information, including gender, age, and ethnicity, were not directly available from the Twitter public API, which might limit our further study on the public perceptions of the FDA flavor enforcement policy and e-cigarettes in different demographic groups. Twitter users do not represent the general population, and Twitter users who tagged their geolocation may or may not represent all Twitter users, which might introduce some bias in this study. Moreover, social bots (agents that communicate more or less autonomously on social media) were not identified and removed from the final data, which might bias the results. In this study, we had different numbers of days of Twitter data before and after the FDA flavor enforcement policy to avoid a possible effect of the New York State law on banning all flavored vaper products that was announced on April 3, 2020, and implemented on May 18, 2020, which might cause comparison bias in the results [48]. In addition, people's actions toward the FDA flavor enforcement policy, such as quit vaping, switch back to smoking, and switch to other flavored e-cigarette products, were not investigated in this study, which will be our future research directions. However, our study did show that e-cigarette users were inclined to find an alternative way to get e-cigarette products.

Conclusion

Our study showed that the announcement and implementation of the FDA flavor enforcement policy might have influenced Twitter users' perceptions of e-cigarettes. The findings of this study provide valuable insights into public responses to the FDA flavor enforcement policy, which can be used as an important guideline for future FDA policies on further regulating flavored e-cigarettes.

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Authors' Contributions

XL, ZX, and DL conceived and designed the study. XL analyzed the data. XL wrote the manuscript. XL, LS, ZX, and DL assisted with interpretation of analyses and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Flowchart of the data collection and filtering process.

[[PNG File , 93 KB - publichealth_v8i3e25697_app1.png](#)]

Multimedia Appendix 2

Tweet examples in positive, neutral, and negative sentiment categories.

[[DOCX File , 19 KB - publichealth_v8i3e25697_app2.docx](#)]

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Abbreviations

- API:** application programming interface
FDA: Food and Drug Administration
LDA: latent Dirichlet allocation
VADER: Valence Aware Dictionary and Sentiment Reasoner

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Original Paper

United States Influenza Search Patterns Since the Emergence of COVID-19: Infodemiology Study

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Abstract

Background: The emergence and media coverage of COVID-19 may have affected influenza search patterns, possibly affecting influenza surveillance results using Google Trends.

Objective: We aimed to investigate if the emergence of COVID-19 was associated with modifications in influenza search patterns in the United States.

Methods: We retrieved US Google Trends data (relative number of searches for specified terms) for the topics influenza, Coronavirus disease 2019, and symptoms shared between influenza and COVID-19. We calculated the correlations between influenza and COVID-19 search data for a 1-year period after the first COVID-19 diagnosis in the United States (January 21, 2020 to January 20, 2021). We constructed a seasonal autoregressive integrated moving average model and compared predicted search volumes, using the 4 previous years, with Google Trends relative search volume data. We built a similar model for shared symptoms data. We also assessed correlations for the past 5 years between Google Trends influenza data, US Centers for Diseases Control and Prevention influenza-like illness data, and influenza media coverage data.

Results: We observed a nonsignificant weak correlation ($\rho = -0.171$; $P = 0.23$) between COVID-19 and influenza Google Trends data. Influenza search volumes for 2020-2021 distinctly deviated from values predicted by seasonal autoregressive integrated moving average models—for 6 weeks within the first 13 weeks after the first COVID-19 infection was confirmed in the United States, the observed volume of searches was higher than the upper bound of 95% confidence intervals for predicted values. Similar results were observed for shared symptoms with influenza and COVID-19 data. The correlation between Google Trends influenza data and CDC influenza-like-illness data decreased after the emergence of COVID-19 (2020-2021: $\rho = 0.643$; 2019-2020: $\rho = 0.902$), while the correlation between Google Trends influenza data and influenza media coverage volume remained stable (2020-2021: $\rho = 0.746$; 2019-2020: $\rho = 0.707$).

Conclusions: Relevant differences were observed between predicted and observed influenza Google Trends data the year after the onset of the COVID-19 pandemic in the United States. Such differences are possibly due to media coverage, suggesting limitations to the use of Google Trends as a flu surveillance tool.

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KEYWORDS

COVID-19; influenza; surveillance; media coverage; Google Trends; infodemiology; monitoring; trend; United States; information-seeking; online health information

Introduction

Google Trends is a tool that retrieves the relative amount of Google searches for specified terms based on location and a user-chosen timeframe [1]. Google Trends provides relative search volume data (on a scale of 0-100), consisting of the number of searches for specific terms relative to the total number of searches in the chosen timeframe [1]. Research based on Google Trends data is largely situated within the field of infodemiology, which is the practice of analyzing information in an electronic medium (particularly the internet) to improve public health and policy [2]. Information on the volume of web searches is a relatively new alternative to information gathered from traditional surveys, and several studies [3] have been conducted using search volume data since the first, which monitored the severe acute respiratory syndrome epidemic that occurred in 2002. The use of internet search data from Google Trends as a complement to traditional survey data is appealing, among other reasons, because data are provided on a real-time basis and web searches are performed anonymously, allowing for a greater range of data on sensitive topics [4-7].

Google Trends data have been used to monitor both chronic and acute diseases. Search volume data related to the common cold were found to be correlated with asthma incidence and to forecast asthma hospitalizations [8,9]. Additionally, Fang and colleagues [10] found that an increase in searches related to chronic obstructive pulmonary disease from 2007 to 2020 was correlated with several estimates of chronic obstructive pulmonary disease morbidity. For acute conditions, particularly infectious diseases, Seifter et al [11] noticed that Google searches on the keywords “Lyme disease, tick bite, [and] cough” reflected geographic locations and times of year that Lyme disease infections typically peak. Carneiro and Mylonakis [12] found that Google Trends search patterns for West Nile virus, respiratory syncytial virus, and avian influenza were correlated with those of seasonal or cyclical viral outbreaks. Yuan et al [13] found that searches on fever, gastroenteritis, and watery diarrhea were correlated with Google Trends norovirus data; some of these searches were also correlated with actual norovirus cases from New York, California, and the United States as a whole.

Several studies [14-17] have been conducted to assess internet search patterns on COVID-19 symptoms, individual protection equipment or measures, and vaccines, among others (although these were solely assessed the first months of the pandemic, when media coverage interest on the COVID-19 pandemic was particularly high [17]).

One of the most frequently assessed infectious diseases using Google Trends is influenza, which has been studied with mixed results. Cho et al [18] found there was a strong correlation between Korea Centers for Disease Control and Prevention (KCDC) influenza-like illness data and Google Trends data for 2007-2012 flu seasons [18]. Zhang et al [19] expanded upon the utility of Google Trends data by constructing an influenza outbreak predictor that was capable of successfully predicting influenza outbreaks. Similarly, Samaras et al [20] found a strong, statistically significant correlation between Google search data

and influenza-like illness rates in Greece and in Italy, and using autoregressive integrated moving average models, they successfully predicted influenza peaks 4 weeks prior to their occurrence. On the other hand, although Ginsberg et al [4] found Google queries could be used to estimate influenza-like illness accurately in all 9 public health regions of the United States, they also noted potential artificial surges in influenza-related search volume after unusual media coverage that affected the ability of Google Trends data to be used in direct forecasting.

There also exists a substantial body of literature that examines the use of Google Flu Trends, which is an algorithm designed for the sole purpose of predicting influenza outbreaks [21,22]. Deployed in November 2008, Google Flu Trends used Google search data to estimate the intensity of an influenza epidemic and to predict US Centers for Disease Control and Prevention (CDC) data on the number of patient visits due to influenza-like illness. Its algorithm is based on the top 45 searches that had the highest correlation with US CDC influenza-like illness data (extracted from 50 billion of the most-searched Google terms) between 2003 and 2007; however, the 45 terms were never explicitly released, which means there is a lack of replicability. Furthermore, Google Flu Trends did not predict the 2009 influenza A–H1N1 pandemic [21,22] and overestimated the prevalence of flu cases for 100 out of 108 weeks starting in August 2011 [22]. The underestimation of the first 2009 wave of H1N1 in the United States was partially attributed [23] to the public’s general lack of knowledge regarding H1N1 (in contrast with the second wave, from 2009-2010, which reflected actual flu patterns). Google Flu Trends was unsuccessful in its attempts to monitor and predict the course of influenza outbreaks solely based on internet search data, which serves as a warning of the volatility of internet search data and its potential to not reflect true disease case data.

Success in monitoring or predicting outbreaks using Google Trends data depends on the keywords used. In Google Trends data collection, selecting the proper keywords is “key for valid results [6].” Kang et al [24] found that based on the specific keyword used (“influenza a,” “fever,” “cold,” or “cough”), the correlation between Google Trends and influenza surveillance data (from 56 sentinel clinics of the official Guangdong CDC from 2008 to 2011) would change—for all 4 years, “fever” was significantly correlated with Guangdong CDC data; however, “H1N1” was not significantly correlated with any year’s data. Ultimately, Kang et al [24] suggest that analysts should be cautious when there is high media coverage for a particular influenza season or strain, because of the potential bias in internet search patterns.

Similarly, however, the emergence of COVID-19 could have also distorted Google Trends influenza search patterns. Both COVID-19 and influenza are respiratory diseases and share several common symptoms (such as fever, cough, and sore throat [25]) alongside seasonality [26]. An analogous scenario was demonstrated [27], identifying that searches for asthma and chronic obstructive pulmonary disease peaked in March 2020, and the increase in asthma searches was attributed to the potential shared respiratory effects of COVID-19 and asthma and to the large media coverage on COVID-19.

The severity of the COVID-19 pandemic has led to a heightened sense of risk and constant media coverage, which has caused individuals to search the internet for more information on COVID-19. Because surges in COVID-19 searches could affect Google Trends flu search patterns, altering Google Trends' capacity to be used as a supplemental surveillance tool, we aimed to assess and quantify the extent to which the emergence of COVID-19 was associated with fluctuations in Google Trends influenza search patterns in the United States.

Methods

Study Design

We collected Google Trends data for influenza, COVID-19, and their shared symptoms using the framework by Mavragani and Ochoa [6]. We (1) determined the correlation between influenza searches and COVID-19 searches during the first year of the COVID-19 pandemic in the United States (January 21, 2020 to January 20, 2021), (2) developed a time series model based on data from previous years to predict flu search data which we compared with observed data in order to detect irregularities in influenza search patterns since the emergence of COVID-19; (3) developed a time series models based on data from previous years to predict shared symptoms data which we compared with observed data to detect irregularities in shared symptoms search patterns since the emergence of COVID-19; and (4) determined the correlations between search data and data from other sources for the past 5 years (including US CDC surveillance data and influenza media coverage volume) in order to detect any changes since the emergence of COVID-19.

Data Collection

Keyword Selection

Although in past Google Trends flu research [18,20,24], specific keywords have been used, we employed search topics, which are a group of terms that share the same concept across languages. Topics cover an array of variations, typos, and related searches, precluding the need to enter a set of individual terms, while maintaining the consistency of search queries across all timeframes. We extracted Google Trends data using the topics "Coronavirus disease 2019" and "Influenza", and queried cough + fever + "sore throat" + "difficulty breathing" for assessing the shared symptoms between COVID-19 and influenza; specific categories and subcategories within Google Trends were not selected for any keyword searches.

Region and Period Selection

We retrieved Google Trends data for the United States at a national level. In addition, we extracted data for the 4 most populous states (California, Texas, Florida, and New York) to assess regional variations in the strength of correlations and predictions. We extracted data from January 21, 2016 to January 20, 2021, corresponding to a period of 5 complete years. Each full year was defined as starting on January 21, because the US CDC confirmed the first COVID-19 infection in the United States on January 21, 2020. This allowed us to analyze a full year after the first COVID-19 case and streamline the collection of past years' data. For simplicity, we will refer to each period

set using the years (ie, for data extracted from January 21, 2016 to January 20, 2017, we will simply state 2016-2017).

Other Data Sources

The US CDC monitors the cyclical progression of influenza by tracking weekly cases of influenza-like illness (defined as a fever, cough, or sore throat without known cause other than the flu) [25]. We retrieved these data from January 21, 2016 to January 20, 2021, for the United States data and for California, Texas, and New York (no data were available for Florida) from the CDC's FluView Interactive App [28]. Since the FluView shows data from week 40 of one year to week 39 of the next, we spliced together the influenza-like illness data from different flu seasons.

We accessed an open-source platform (Media Cloud) to retrieve the percentage of media stories concerning influenza. We extracted US data from January 21, 2016 to January 20, 2021 using the query "flu OR influenza." Data from each of the 4 most populous states were also retrieved. Weekly averages were calculated based on daily data.

Data Analysis

Data analysis was performed using SPSS (version 25; IBM Corp) and R (version 4.0.4) software. P values $< .05$ were considered statistically significant.

Spearman correlation coefficients were calculated for the entire year and quarterly periods (13 weeks) of the year to assess the relationship between COVID-19 and influenza data from Google Trends.

We then assessed how predicted Google Trends flu data differed from actual data since the emergence of COVID-19 to detect eventual irregularities in flu search patterns. To do that, we extracted Google Trends flu data from 2016-2021 and, based on data from 2016-2020. We built seasonal autoregressive integrated moving average (SARIMA) models [27]. An identical process was performed to compare forecasted and observed Google Trends data for shared symptoms relative search volume.

SARIMA models were used to forecast 2020-2021 data based on past data provided and accounting for seasonal patterns. The models were defined by $(p,d,q)(P',D,Q)s$, with p corresponding to the order of autoregression, d corresponding to the degree of difference, q corresponding to the order of the moving average part, P' corresponding to the seasonal order of autoregression, D corresponding to the degree of difference following seasonal integration, Q corresponding to the seasonal moving average, and s corresponding to the length of the seasonal period. We set $s=52$ weeks (since there are approximately 52 weeks in a year), and we selected d and D so that the 2016-2020 time series appeared stationary (ie, with a constant variance and no extreme fluctuations or overall increasing or decreasing behavior); p and P' were selected based on partial autocorrelation function plots, and q and Q were selected based on autocorrelation function plots. SARIMA models were selected based on the results of the Ljung-Box test and on the Akaike information criteria of tested models.

To compare predicted and observed relative search volumes, we calculated the Spearman correlation coefficients for

2020-2021 and for each quarter. We calculated the mean absolute difference and percent difference between observed and predicted Google Trends data and determined the number of weeks for which the observed data exceeded predicted confidence intervals.

We calculated the Spearman correlation coefficients between Google Trends data for influenza and US CDC influenza-like illness data and between Google Trends data for influenza and Media Cloud influenza media coverage data from 2016 to 2021. To assess whether CDC influenza-like illness and media coverage data differed substantially in 2020-2021 compared to those from previous years, we built SARIMA models and determined the number of weeks for which the observed data

exceeded predicted confidence intervals ([Multimedia Appendix 1](#)).

Results

Google Trends COVID-19 and Influenza Data

We observed nonsignificant weak correlations between influenza and COVID-19 Google Trends data for the United States at the national level ($\rho=-0.171$; $P=.23$) and for each state (California: $\rho=-0.179$; $P=.20$; Florida: $\rho=-0.173$; $P=.22$; New York: $\rho=-0.161$; $P=.26$; Texas: $\rho=-0.188$; $P=.18$) ([Figure 1](#)). Similarly, quarterly correlations were nonsignificant ([Table 1](#)) and mostly weak ([Figure 2](#)).

Figure 1. Influenza and COVID-19 topic relative search volumes from January 21, 2020 to January 20, 2021.

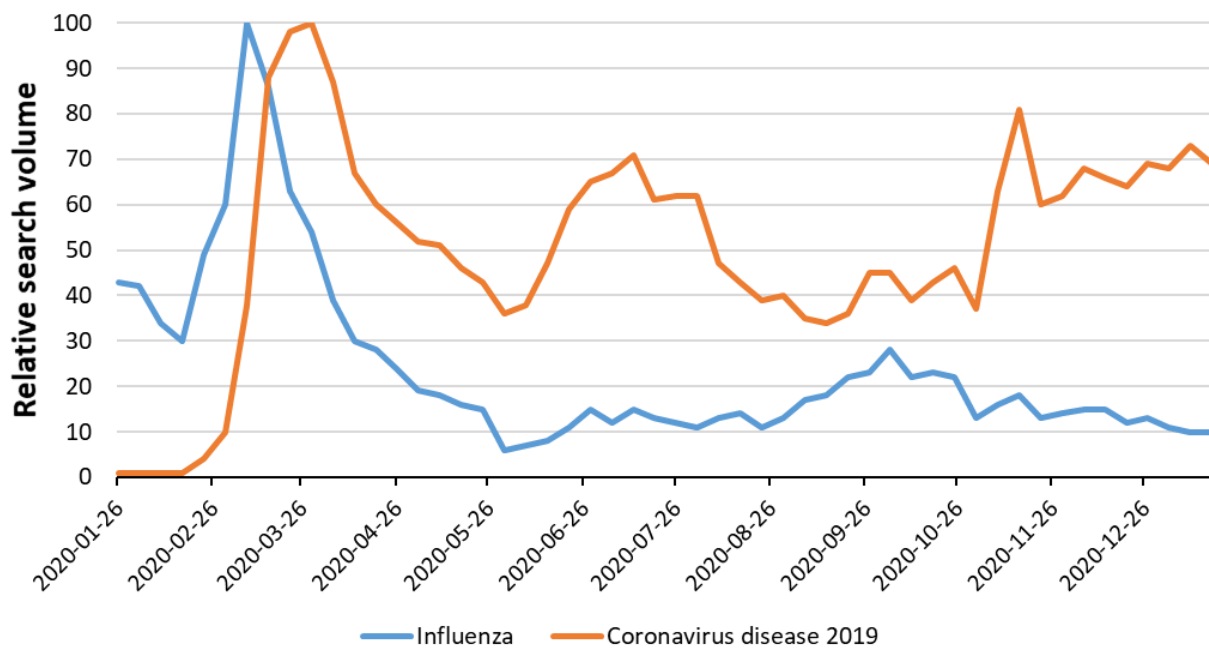
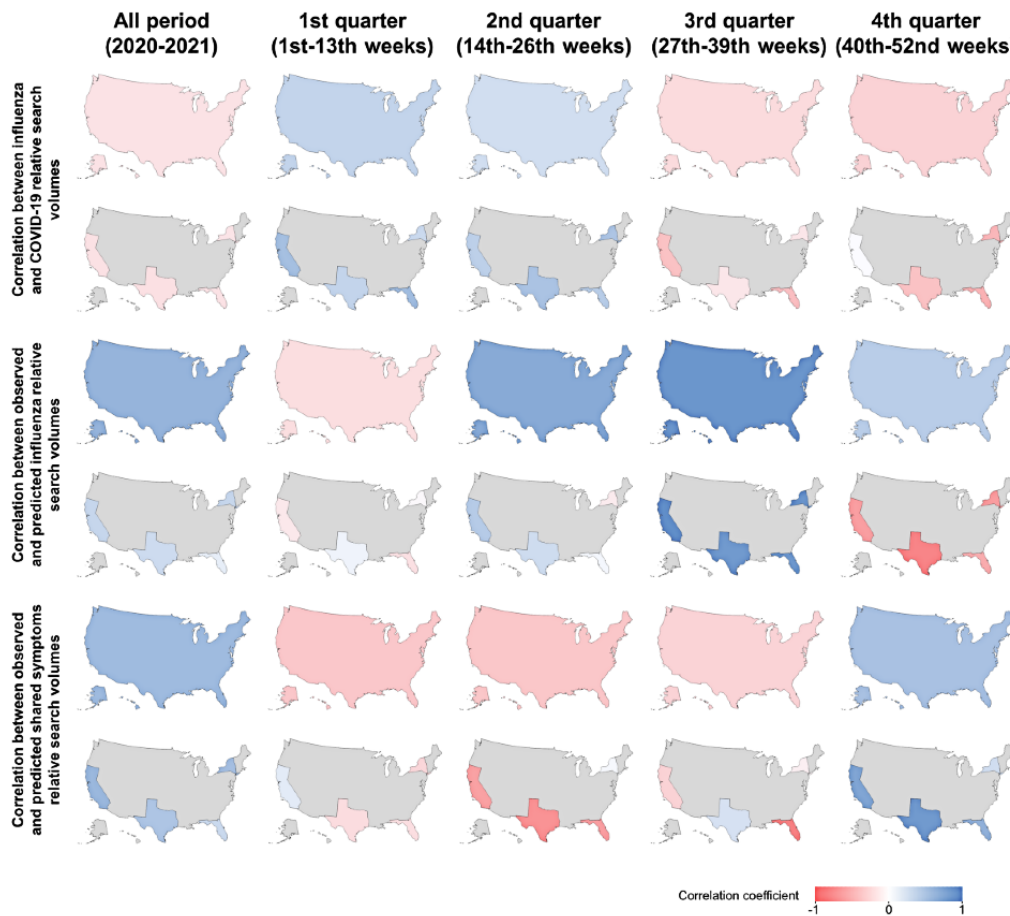


Table 1. Correlation between influenza and COVID-19 relative search volumes.

Region and period ^a	ρ	<i>P</i> value
United States of America		
Entire period	-0.171	.23
1st quarter	0.358	.23
2nd quarter	0.271	.37
3rd quarter	-0.224	.46
4th quarter	-0.281	.35
California		
Entire period	-0.179	.20
1st quarter	0.498	.08
2nd quarter	0.391	.19
3rd quarter	-0.392	.19
4th quarter	0.012	.97
Florida		
Entire period	-0.173	.22
1st quarter	0.531	.06
2nd quarter	0.409	.16
3rd quarter	-0.405	.17
4th quarter	-0.482	.10
New York		
Entire period	-0.161	.26
1st quarter	0.311	.30
2nd quarter	0.487	.09
3rd quarter	-0.146	.63
4th quarter	-0.465	.11
Texas		
Entire period	-0.188	.18
1st quarter	0.354	.24
2nd quarter	0.503	.08
3rd quarter	-0.144	.64
4th quarter	-0.392	.18

^aEntire period: January 21, 2020 to January 20, 2021; 1st quarter: January 26, 2020 to April 19, 2020; 2nd quarter: April 26, 2020 to July 19, 2020; 3rd quarter: July 26, 2020 to October 18, 2020; 4th quarter: October 25, 2020 to January 17, 2021.

Figure 2. Correlation heatmaps (national and statewide) for (A) influenza and COVID-19 relative search volumes, (B) observed and predicted influenza relative search volumes, and (C) observed and predicted shared symptoms relative search volumes.



Predicted Versus Observed Google Trends Influenza Data

At the national level, observed influenza relative search volume fell outside predicted confidence intervals for 6 out of 52 weeks (11.5%) (Figure 3), all of which occurred during the first quarter. The average difference between observed and predicted relative search volume values was 12.9 units (mean percent difference 48.4%). For the entire period, the correlation between observed

and predicted relative search volume, $\rho=0.632$ ($P<.001$) (Figure 2); however, for the first quarter, the correlation (which included the 6 weeks for which observed Google Trends values went beyond the confidence interval for predicted values) reported value was strikingly different and not significant ($\rho=-0.204$; $P=.28$) (Table 2).

For California, Florida, and Texas, all weeks in which observed influenza relative search volumes fell outside predicted confidence intervals occurred during the first quarter.

Figure 3. Predicted and observed influenza relative search volume (RSV) values from January 21, 2020 to January 20, 2021. The red line shows the observed relative search values for influenza, the blue line represents the predicted values for influenza searches, and the shaded blue area represents the confidence intervals for predicted values.

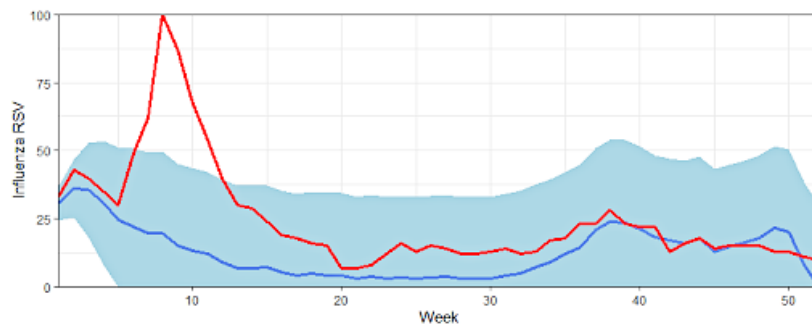


Table 2. Correlation between predicted and observed influenza relative search volumes.

Region and period ^a	ρ	<i>P</i> value	Weeks outside predicted CIs, n (% ^b)
United States of America			
Entire period	0.632	<.001	6 (11.5)
1st quarter	-0.204	.28	6 (46.2)
2nd quarter	0.720	.02	0 (0)
3rd quarter	0.899	<.001	0 (0)
4th quarter	0.417	.002	0 (0)
California			
Entire period	0.338	.01	7 (13.5)
1st quarter	-0.132	.67	7 (53.8)
2nd quarter	0.436	.14	0 (0)
3rd quarter	0.946	<.001	0 (0)
4th quarter	-0.626	.02	0 (0)
Florida			
Entire period	0.130	.36	10 (19.2)
1st quarter	-0.184	.55	10 (76.9)
2nd quarter	0.050	.87	0 (0)
3rd quarter	0.806	<.001	0 (0)
4th quarter	-0.514	.07	0 (0)
New York			
Entire period	0.338	.01	21 (40.4)
1st quarter	-0.022	.94	10 (76.9)
2nd quarter	-0.114	.71	4 (30.8)
3rd quarter	0.866	<.001	2 (15.4)
4th quarter	-0.634	.02	5 (38.5)
Texas			
Entire period	0.292	.04	5 (9.6)
1st quarter	0.082	.79	5 (38.5)
2nd quarter	0.288	.34	0 (0)
3rd quarter	0.861	<.001	0 (0)
4th quarter	-0.804	<.001	0 (0)

^aEntire period: January 21, 2020 to January 20, 2021; 1st quarter: January 26, 2020 to April 19, 2020; 2nd quarter: April 26, 2020 to July 19, 2020; 3rd quarter: July 26, 2020 to October 18, 2020; 4th quarter: October 25, 2020 to January 17, 2021.

^bFor the entire period, out of 52 weeks. For a quarter, out of 13 weeks.

Predicted Versus Observed Google Trends Data on Shared Symptoms

At the national level, observed relative search volume data for shared symptoms fell outside predicted confidence intervals (Figure 4) for the same 6 weeks as those of influenza relative search volume data. The average difference in relative search volume between the actual and predicted data was 8.7 units

(mean percent difference 20.2%). The correlation for the entire period was significant ($\rho=0.578$; $P<.001$) (Table 3). For individual states, a more diverse pattern was observed when comparing observed versus predicted shared symptoms relative search volume data (e.g., in California, there were only 4 weeks outside predicted intervals – all occurring during the first quarter -, while in New York, there were 18 weeks outside predicted intervals, occurring in all quarters) (Figure 2).

Figure 4. Predicted and actually observed relative search volume (RSV) values on symptoms common to both influenza and COVID-19 from January 21, 2020 to January 20, 2021. The red line shows the observed relative search values, the blue line represents the predicted relative search values, and the shaded blue area represents the confidence intervals for predicted values.

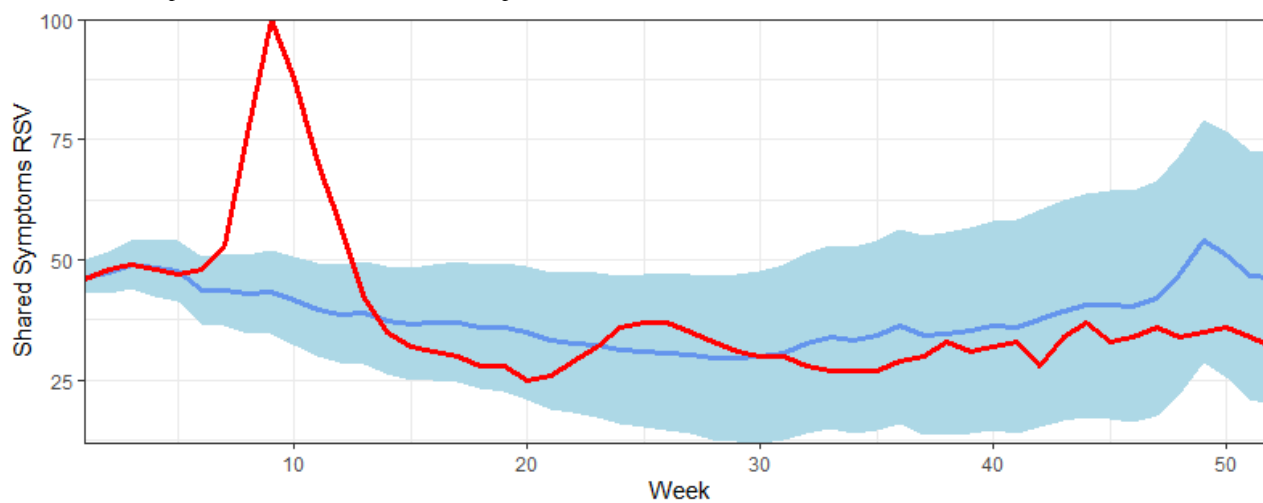


Table 3. Correlations between predicted and actually observed shared symptoms (between influenza and COVID-19) relative search volumes.

Region and period ^a	ρ	<i>P</i> value	Weeks outside predicted CIs, n (% ^b)
United States of America			
Entire period	0.578	<.001	6 (11.5)
1st quarter	-0.354	.24	6 (46.2)
2nd quarter	-0.359	.23	0 (0)
3rd quarter	-0.273	.37	0 (0)
4th quarter	0.518	.07	0 (0)
California			
Entire period	0.603	<.001	4 (7.7)
1st quarter	0.155	.61	4 (30.8)
2nd quarter	-0.610	.03	0 (0)
3rd quarter	-0.281	.35	0 (0)
4th quarter	0.759	.003	0 (0)
Florida			
Entire period	0.303	.03	9 (17.3)
1st quarter	-0.200	.52	8 (61.5)
2nd quarter	-0.599	.03	0 (0)
3rd quarter	-0.768	.002	0 (0)
4th quarter	0.615	.03	1 (7.7)
New York			
Entire period	0.537	<.001	18 (34.6)
1st quarter	-0.254	.40	7 (53.8)
2nd quarter	0.041	.89	3 (23.1)
3rd quarter	-0.083	.79	1 (7.7)
4th quarter	0.274	.36	7 (53.8)
Texas			
Entire period	0.484	<.001	21 (40.4)
1st quarter	-0.214	.48	6 (46.2)
2nd quarter	-0.711	.006	5 (38.5)
3rd quarter	0.237	.44	0 (0)
4th quarter	0.864	<.001	10 (76.9)

^aEntire period: January 21, 2020 to January 20, 2021; 1st quarter: January 26, 2020 to April 19, 2020; 2nd quarter: April 26, 2020 to July 19, 2020; 3rd quarter: July 26, 2020 to October 18, 2020; 4th quarter: October 25, 2020 to January 17, 2021.

^bFor the entire period, out of 52 weeks. For a quarter, out of 13 weeks.

Correlations Between Google Trends and Other Data Sources

For each of the 4 previous years, strong positive correlations were observed in the United States for CDC influenza-like illness data and Google Trends relative search volume data (Figure 5) and for CDC influenza-like illness data and media coverage; correlations for 2020-2021 were weaker than those of the previous years. Similarly, for 2020-2021, correlations between CDC influenza-like illness data and media coverage for influenza in each state, except New York, were weaker than for those of the previous years. Correlations between Google

Trends influenza and influenza media coverage tended to be as strong in 2020-2021 as in the previous years (Table 4).

For CDC influenza-like illness data, there was a strong correlation between observed and predicted data ($\rho=0.701$; $P<.001$). Despite this finding, on average, observed values tended to be lower than forecasted values but were still within forecasted confidence intervals when considering the entire 2020-2021 period. For influenza media coverage, the correlation between observed and predicted values was low ($\rho=-0.063$; $P=.66$), with observed data falling outside predicted confidence intervals for 14 weeks, mostly during the first quarter.

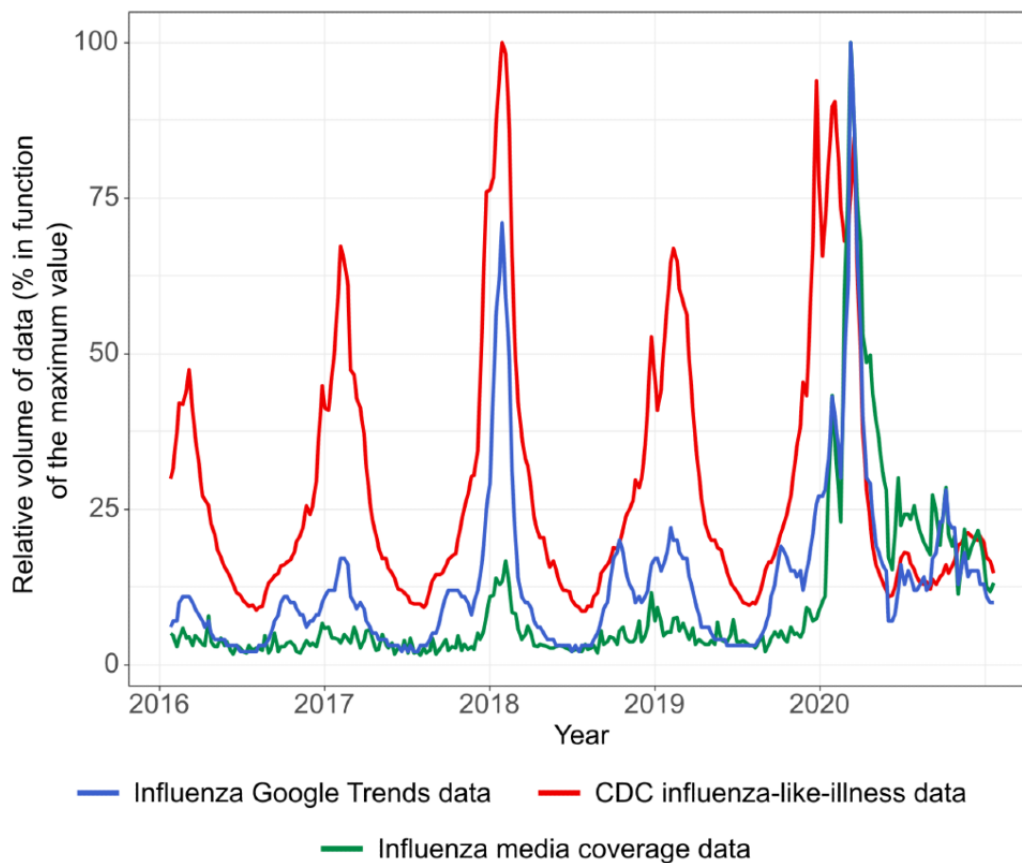
Figure 5. Relative volume of data for influenza Google Trends data, CDC influenza-like illness data, and influenza media coverage data.

Table 4. Correlations between Google Trends relative search volume, US Centers for Disease Control and Prevention influenza-like illness case report, and media coverage data.

Region and period ^a	Relative search volume and case reports		Relative search volume and media coverage		Relative case reports and media coverage	
	ρ	<i>P</i> value	ρ	<i>P</i> value	ρ	<i>P</i> value
United States of America						
2016-2017	0.753	<.001	0.483	<.001	0.643	<.001
2017-2018	0.869	<.001	0.607	<.001	0.689	<.001
2018-2019	0.846	<.001	0.878	<.001	0.864	<.001
2019-2020	0.902	<.001	0.707	<.001	0.720	<.001
2020-2021	0.643	<.001	0.746	<.001	0.440	.001
California						
2016-2017	0.739	<.001	0.483	<.001	0.586	<.001
2017-2018	0.817	<.001	0.648	<.001	0.740	<.001
2018-2019	0.733	<.001	0.805	<.001	0.700	<.001
2019-2020	0.744	<.001	0.604	<.001	0.668	<.001
2020-2021	0.408	.002	0.706	<.001	0.093	.51
Florida						
2016-2017	— ^b	—	0.195	.17	—	—
2017-2018	—	—	0.571	<.001	—	—
2018-2019	—	—	0.733	<.001	—	—
2019-2020	—	—	0.521	<.001	—	—
2020-2021	—	—	0.694	<.001	—	—
New York						
2016-2017	0.837	<.001	0.511	<.001	0.518	<.001
2017-2018	0.766	<.001	0.668	<.001	0.484	<.001
2018-2019	0.867	<.001	0.815	<.001	0.726	<.001
2019-2020	0.826	<.001	0.684	<.001	0.654	<.001
2020-2021	0.685	<.001	0.825	<.001	0.533	<.001
Texas						
2016-2017	0.671	<.001	0.379	.006	0.464	<.001
2017-2018	0.882	<.001	0.519	<.001	0.531	<.001
2018-2019	0.868	<.001	0.546	<.001	0.519	<.001
2019-2020	0.919	<.001	0.495	<.001	0.543	<.001
2020-2021	0.449	<.001	0.707	<.001	0.184	.19

^aEach period is defined as starting in January 21 and ending in January 20 of the subsequent year.

^bThere were no influenza-like illness data for Florida.

Discussion

Principal Results

In this study, we noted atypical Google Trends influenza search patterns in the year after the emergence of COVID-19 compared to expected patterns, which could limit the accuracy when using Google Trends as an influenza surveillance tool. This claim is supported by (1) disparities between the predicted and observed influenza relative search volume data, (2) a lack of significant

correlations in the first quarter between forecasted and observed relative search volume for influenza data, and (3) weak correlations between CDC influenza-like illness and Google Trends influenza data.

For the United States as a whole, in 6 out of 52 weeks, influenza relative search volumes exceed predicted confidence intervals. Similar results were observed in each assessed state. Importantly, weeks when observed values exceeded predicted ranges for the United States (and most weeks for individual

states) were within the first quarter, which was also when correlations between actual and predicted Google Trends influenza data were weaker than 2016-2020 correlations. Interestingly, this was also the quarter in which influenza media coverage was at its highest.

The strength of the correlations between CDC influenza-like illness and Google Trends influenza data decreased in 2020-2021 compared with those of previous years. The same, however, did not occur for the correlations between influenza media coverage and Google Trends influenza data, which remained strong, even given the increase in influenza media coverage in the first quarter of 2020-2021. These findings support the connection between Google Trends searches and media coverage on influenza, which have remained closely associated throughout the pandemic.

We did not observe a strong positive correlation between Google Trends data for COVID-19 and influenza from January 21, 2020 to January 20, 2021 in states or the country as a whole. While our study does not establish a direct correlation or causal link between the 2 diseases, the timing of the search peak of influenza and of shared symptoms (Figures 3 and 4) supports the hypothesis that high interest in COVID-19, its symptoms, and main differential diagnoses (including the flu) during the first quarter may have prompted higher volumes of news discussing influenza, which likely affected the search patterns for the flu (similar search peaks have been observed for other respiratory diseases, such as asthma and chronic obstructive pulmonary disease, possibly for the same reasons [27]). During this quarter (from January 19 to April 12), the first diagnosis of COVID-19 (on January 21) and a declaration of a public health emergency (February 3) occurred in the United States [29]. In fact, peaks in relative search volumes for influenza (in the week of March 8, 2020) and COVID-19 (in the week of March 29) occurred in quick succession (Figure 1). Furthermore, during the week that influenza relative search volume peaked, the World Health Organization declared COVID-19 a pandemic (on March 11) and the United States declared a national emergency (on March 13) [29].

Comparison With Prior Work

Our study highlights that flu searches can reflect not only the epidemiology of influenza but also be influenced by external factors, specifically media-garnering developments such as the COVID-19 pandemic, which provides evidence to counter claims that Google Trends can be used single handedly to predict influenza outbreaks accurately [19,20]. When we compared forecasted and observed flu search volume data, 6 weeks of forecasts were inaccurate, which included the week in which flu relative search volume peaked, because the peak in relative search volume for influenza and spikes in search interest were neither reflected in CDC influenza-like illness case report data nor predicted by the SARIMA model. Such spikes are often the least predictable due to rapid media propagation, highlighting possible limitations of predictive models in accounting for sudden surges in searches. Previous studies [24] had already warned of the possibility that high-media events inflate influenza searches and distort flu search patterns. We investigated COVID-19 and noticed closely timed relative search volume

peaks for influenza and COVID-19, with some unpredicted observed influenza relative search volume activity in the same timeframe that COVID-19 relative search volume and media presence rose [24].

Previous works have also assessed the influence of media coverage on internet search activity [17,27,30]. This influence does not include solely infectious diseases. For example, Cervellin et al [23] found that searches for the keyword “autism” surged consistently in May, potentially due to World Autism Day in April, but were likely not in accordance with real epidemiological data. In our study, Google Trends influenza data, similar to those for asthma and chronic obstructive pulmonary disease [27], peaked in March 2020, in the same week that the United States declared a national emergency.

Importantly, other than for 2020-2021, Google Trends and CDC influenza-like illness data displayed strong correlations, in accordance with the findings of a previous study [18], which showed strong correlations between national influenza surveillance data and Google Trends influenza data in Korea for the 2007-2012 flu seasons. Although our results suggest that Google Trends cannot be used as a sole tool to predict influenza outbreaks, they do not preclude the use of Google Trends as a tool for predicting the present and the very near future that is complementary to traditional surveillance systems, which has been previously discussed [31,32]. Using Google Trends data in combination with past influenza data may help decreasing the error of flu surveillance and hospitalizations predictions in the United States in comparison with using only past surveillance or hospitalization data [33,34]. The application of data correction methods to Google Trends may be particularly useful in improving the accuracy of predictions [32,35].

We were also able to quantify media coverage on influenza. While previous Google Trends influenza-like illness and influenza research assessed correlations between Google Trends data and official surveillance data with yearly intervals of data [18,24], when appropriate, we also used quarterly data. There were relevant across-quarter differences both in terms of correlations between observed and predicted data and in the number of weeks that the observed data went beyond predicted intervals. Using smaller intervals of time addresses seasonality and significant events. In fact, the first quarter of 2020-2021 included many of the first declarations of COVID-19 and emergency declarations, while in the third quarter, influenza searches returned to a relatively predictable pattern. This may have been, in part, because of the summer season in the Northern Hemisphere, which is a period of low activity for both seasonal coronaviruses and influenza [30].

Limitations

This study has some limitations. First, the specific keywords that Google uses for defining the influenza and COVID-19 disease topics are not directly stated, but using topic searches was preferable to using search terms because topics encompass a wide range of relevant keywords.

For shared symptoms, we were not able to use topics because there was no topic encompassing all symptoms, and queries had to be built with combinations of keywords. The choice of

keywords can decisively influence results [24]. In our study, there were more potentially relevant terms than those we included, but many of these symptoms tended to be broad, thus, to minimize the effect of broad search terms, we limited the number of terms in our search query. Even with this concession, at both the nation and state level, there were noticeable variations in observed and predicted shared symptoms relative search volume, which limited drawing conclusions based on shared symptoms data.

Another limitation is the fact that Google Trends presents searches in relative volume instead of as an absolute number of searches. The latter would facilitate comparisons between influenza and COVID-19 queries and reveal more information about the absolute search interest in each disease. Additionally, because Google Trends is based on Google search engine data, older individuals, individuals with less education, individuals with low income, and individuals in rural areas or isolated from technology may be underrepresented in internet searches [2].

The weaker correlation between CDC influenza-like illness and Google Trends influenza data for 2020-2021 may, not only be explained by changes in search patterns for influenza, but also, by a decrease in actual case numbers for influenza after the emergence of COVID-19 (eg, from the widespread adoption of individual protective measures) [36], which may also hamper the reliability of using Google Trends in influenza surveillance. However, in the first quarter of 2020-2021, when we detected the greatest differences in Google Trends influenza patterns, there was no observable decline in CDC influenza-like illness data compared with that expected based on previous years' data.

Finally, we only used data from a single country; conclusions may not be generalizable to other countries; however, we conducted an exploratory analysis, applying the same methodology to other countries with English as one of the official languages (such as Canada, United Kingdom, Ireland, Australia, and New Zealand) and displaying high-quality relative search volume data, which demonstrated consistent findings for correlations between predicted and observed Google Trends influenza data, with more disparate results observed for shared symptoms (Multimedia Appendices 2 and 3). Despite the focus on the United States, the methodology framework of our study can be extended to other countries with developed national

influenza surveillance systems and reliable access to the internet, which would provide a new understanding of national-scale variations in influenza search patterns since the onset of COVID-19.

This study also has important strengths. We were able to compare observed data and predicted data by using time series forecasting methods for influenza data and shared symptoms data. We did not build models simultaneously incorporating Google Trends and CDC influenza-like illness data, as suggested by some [37], because our aim was, not to nowcast influenza-like illness rates, but rather, to assess correlations and differences between observed and predicted values). In addition, we assessed correlations between Google Trends influenza and CDC influenza-like illness data for a 5-year period, finding evidence that there may be ramifications from the emergence of COVID-19 on US disease surveillance.

In future studies, as the COVID-19 pandemic in the United States (and all states) constantly evolves due to new variants and waves of infections, research into Google Trends influenza searches after January 2021 would help to continually assess the shifts in Google Trends searches and the reliability of Google Trends. Each subnational territory's Google Trends influenza and COVID-19 relative search volume data could yield a more comprehensive picture of regional search patterns.

Conclusions

Influenza search patterns deviated from those of previous years once COVID-19 gained media presence, even when accounting for the seasonality of influenza searches, and 2020-2021 yielded the weakest correlations between CDC and Google Trends flu data over a 5-year period—both findings suggest that the accuracy of Google Trends as a supplementary influenza surveillance tool in periods of highly mediatized respiratory infections breakouts should be carefully assessed. Furthermore, although we cannot posit that COVID-19 search interest directly influences Google Trends flu data, we found that media coverage likely factored into the noticeably irregular influenza search patterns, and we caution against solely relying on Google Trends data for influenza surveillance, because media influence may cause Google Trends searches to diverge from normal patterns.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Seasonal autoregressive integrated moving average (SARIMA) models for forecasting influenza and shared symptoms relative search volume data for 2020-2021.

[DOCX File, 14 KB - [publichealth_v8i3e32364_app1.docx](#)]

Multimedia Appendix 2

Correlation between influenza and COVID-19 in majority native English-speaking countries other than the United States of America.

[[DOCX File , 15 KB - publichealth_v8i3e32364_app2.docx](#)]

Multimedia Appendix 3

Correlations between predicted and observed (1) influenza relative search values and (2) shared influenza and COVID-19 symptoms relative search values in majority native English-speaking countries other than the United States.

[[DOCX File , 18 KB - publichealth_v8i3e32364_app3.docx](#)]

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Abbreviations

- CDC:** US Centers for Disease Control and Prevention
KCDC: Korea Centers for Disease Control and Prevention
SARIMA: seasonal autoregressive integrated moving average

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Original Paper

Geosocial Networking Smartphone App Use and High-Risk Sexual Behaviors Among Men Who Have Sex With Men Attending University in China: Cross-sectional Study

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Abstract

Background: Gay apps are smartphone-based geosocial networking apps where many men who have sex with men (MSM) socialize and seek sex partners. Existing studies showed that gay app use is associated with greater odds of high-risk sexual behaviors and potentially more HIV infections. However, little is known about this behavior among young MSM.

Objective: We conducted this study to understand gay app use and its influencing factors among MSM attending university in China.

Methods: From January to March 2019, participants were recruited from 4 regions with large populations of college students in China: Chongqing, Guangdong, Shandong, and Tianjin. The eligibility criteria were MSM aged 16 years or older, self-identified as a university student, and being HIV negative. A self-administered online structured questionnaire was used to collect data on sociodemographic information, sexual behaviors, gay app use, substance use, and HIV testing history. We performed multivariable log-binomial regression to assess correlates of seeking sex partners via gay apps.

Results: A total of 447 MSM attending university with an average age of 20.4 (SD 1.5) years were recruited. Almost all participants (439/447, 98.2%) reported gay app use at some point in their life, and 240/439 (53.7%) reported ever seeking sex partners via gay apps. Blued (428/439, 97.5%) was the most popular gay app. Higher proportions of sexual risk behaviors (including seeking sex partners via apps [$P<.001$], engaging in group sex [$P<.001$], having multiple sex partners [$P<.001$], unawareness of sex partners' HIV status [$P<.001$], and using recreational drugs during sex [$P<.02$]) were positively associated with the increase in the frequency of gay app use. In multivariable analysis, participants who used gay apps to seek sex partners might be more likely to have multiple sex partners in the past 3 months (adjusted prevalence ratio [APR] 1.53, 95% CI 1.33-1.76; $P<.001$), engage in group sex in the past 3 months (APR 1.55, 95% CI 1.35-1.78; $P<.001$), and have sex partners with unknown or positive HIV status (APR 1.72, 95% CI 1.46-2.01; $P<.001$).

Conclusions: Seeking sex partners via gay apps may associate with the increased high-risk sexual behaviors among MSM attending university. The causality between seeking sex partners via gay apps and increased high-risk sexual behaviors should be further investigated so as to inform potential policies for HIV prevention.

Trial Registration: Chinese Clinical Trial Registry ChiCTR1900020645; <http://www.chictr.org.cn/showprojen.aspx?proj=34741>

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KEYWORDS

gay app; men who have sex with men; student; China; smartphone; mobile phone

Introduction

Gay apps are smartphone-based geosocial networking apps where men who have sex with men (MSM) socialize. In recent years, gay apps have gained increasing popularity in the MSM community. Grindr has more than 3 million daily users in nearly 200 countries [1,2]. Blued is the first gay app originating from China and has more than 40 million registered users worldwide [3]. Gay apps have become the main platform for seeking sex partners and romantic relationships among MSM [4,5] thanks to the geo-positioning function, which facilitates MSM to socialize with nearby partners [5,6].

The widespread use of gay apps brings about challenges to HIV prevention in MSM. Existing studies showed that gay app users reported more sex partners than nongay app users [7,8]. Gay app users had more frequent sexual behaviors and were more likely to engage in unprotected sex with partners met via gay apps [8,9]. Moreover, MSM who have used gay apps for over 1 year were more likely to drink alcohol, use illicit drugs, and abuse substances, making them more vulnerable to HIV [10]. However, some studies found gay apps might be conducive to HIV control, as gay apps could be used to disseminate HIV knowledge [11] and promote HIV testing [12].

MSM attending university in China have become a key population of HIV/AIDS transmission [13,14]. The number of annual newly diagnosed HIV cases among students is over 3000 since 2017, which is mostly attributable to homosexual behavior among men [15]. High-risk behaviors such as condomless sex, group sex, and drug use during anal intercourse are prevalent among MSM attending university, and these behaviors may render this population more vulnerable to HIV [16]. Compared with nonstudent MSM, it is more difficult to approach and investigate this young group. This is largely because most of them only recently realized their sexual orientation and are not ready to disclose their sexuality. They are also concerned about stigma from peers if they disclose their sexuality [17]. Their discrete status is a barrier to timely access to HIV prevention and care services.

Previous studies have found that MSM using gay apps tend to be younger and better educated [1], raising concerns about potential effects of gay app use on MSM attending university. However, literature on gay app use in MSM attending university is scarce and the following aspects are not well understood: (1) the characteristics of MSM attending university who use gay apps. (2) Does the use of gay apps facilitate risky sex behaviors, thus leading to an increased risk of HIV infection? (3) Can gay apps be utilized to promote sexual health among this young

population? Therefore, this study aims to understand (1) the relationship between frequency of gay app use and engagement in sexual risk behaviors, (2) the relationship between seeking sex partners via gay apps and engagement in sexual risk behaviors.

Methods

Participants

From January to April 2019, the study was conducted in 4 regions with large populations of college students in China, including Chongqing in southwest China, Guangdong in south China, Shandong in east China, and Tianjin in north China. Individuals were eligible for participation if they were male; aged 16 years or older; university student (technical diploma and undergraduate students); MSM (having sexual behaviors including mutual masturbation, oral sex, or anal sex with male partners); HIV negative or unknown; and willing to provide informed consent. Each participant received free HIV testing services and 50 Chinese Yuan (~US \$7.9) as compensation after enrollment. All data were stored anonymously in encrypted storage space, and personally identifiable information was stored separately from other behavioral and test result data.

Ethical Approval

The study has been approved by the Ethics Review Board of Sun Yat-sen University (SYSU-SPH2018044) and registered with the Chinese Clinical Trial Registry (Registration number: ChiCTR1900020645).

Procedure and Measurements

For sampling and recruitment, the methodology has previously been published elsewhere [18]. Briefly, recruitment of participants was promoted both online and offline. For online recruitment, study advertising campaigns were placed on the social network. For offline recruitment, the study advertisement was distributed to the collaboration of community-based organizations (CBOs), health clinics, and student associations. After reading study advertisements online or offline, participants could make an appointment to join the study at a preferred CBO. After scanning the QR code on a smartphone, participants finished the online questionnaire at the CBO site. A self-administrated online structured questionnaire was used to collect each participant's sociodemographic information (including age, ethnicity, educational status, involvement in class leadership, academic performance, student loans, sexual orientation, and gender of sex partner in lifetime), sexual behaviors (including the age at first anal intercourse, commercial sex in lifetime, forced sex in lifetime, group sex in the past 3

months, number of sex partners in the past 3 months, condomless sex in the past 3 months, and HIV serostatus of sex partners in the past 3 months), gay app use, recreational drug use, and HIV testing. Gay app use was assessed by the question, "Have you ever used any gay app?", and subsequent questions about specific gay app use behaviors, including preference, duration, frequency, and purpose. We also assessed seeking sex partners via gay apps by the question "During the past 3 months, have you ever used gay apps to seek sex partners?", and subsequent questions including the number of sex partners, group sex, condomless sex, and HIV serostatus of sex partners. Recreational drug use was assessed by asking "Have you ever used any of the below-listed recreational drugs during sex? Popper (alkyl nitrites), ecstasy, crystal methamphetamine, and ketamine." The HIV testing was conducted with rapid HIV testing (Alere Determine HIV-1/2; Alere Medical Co., Ltd.) at the location of CBOs; those who tested positive were referred to the local Centers for Disease Control and Prevention (CDC) for confirmation testing and subsequent treatment services [19]. HIV infections in this study were confirmed results.

Statistical Analysis

We used mean and SD to describe continuous variables, and proportions to describe categorical variables. Chi-square test for trend was used to test the linear trend in the proportion of

engaging in sexual risk behaviors with the increase in the frequency of app use. Univariable log-binomial regressions were performed to assess correlates (sociodemographic variables, sexual behaviors) of seeking sex partners via gay apps. Multivariable log-binomial regressions were conducted to use *seeking sex partners via the gay apps* as the independent variable and *sexual behavior in past 3 months* (including group sex, number of sex partners, condomless sex, and HIV status of sex partners) as the dependent variable. Each variable of sexual behaviors was examined independently in separate regression models, adjusted for sociodemographic variables. Variables with $P < .05$ were retained in the final model. Results were presented with an adjusted prevalence ratio (APR) and 95% CI. All data were analyzed using R (version 3.6.1; R Foundation).

Results

Participants

A total of 447 MSM attending university with an average age of 20.4 (SD 1.5) years were recruited in the study (Table 1). The majority of participants self-identified as gay (382/447, 85.5%). Most participants were undergraduate (355/447, 79.4%) students and self-reported academic performance above the average (354/447, 79.2%).

Table 1. Characteristics and gay app use among men who have sex with men attending university in China (N=447)

Variables	Values, n (%)
Age (years)	
≤20	236 (52.8)
≥21	211 (47.2)
Education	
Undergraduate	355 (79.4)
Junior college	92 (20.6)
Academic performance	
Below average	93 (20.8)
Average and above	354 (79.2)
Sexual orientation	
Homosexual	382 (85.5)
Bisexual	44 (9.8)
Other	21 (4.7)
Gay apps used^a	
Blued	428 (97.5)
Aloha	226 (51.5)
Jack'd	38 (8.7)
Grindr	37 (8.4)
Others	33 (7.5)
The most frequently used apps (past 3 months; n=439)	
Blued	318 (72.4)
Aloha	84 (19.1)
Others	37 (8.4)
Number of gay apps used (n=439)	
1	393 (89.5)
≥2	46 (10.5)
Length of gay app use (months; n=439)	
≤5	55 (12.5)
6-12	30 (6.8)
≥13	354 (80.6)
Frequency of gay app use (past 3 months; n=439)	
Monthly	125 (28.5)
Weekly	173 (39.4)
Daily	141 (32.1)
Time (hours) spent on gay app per day (past 3 months; n=439)	
≤0.5	362 (82.5)
1	38 (8.7)
≥2	39 (8.9)
Purpose of gay app use (past 3 months; n=439)^a	
Relationships	199 (45.3)
Following others' updates	185 (42.1)

Variables	Values, n (%)
Making friends	171 (39.0)
Hooking up with sex partners	161 (36.7)
Chatting	119 (27.1)
Watching live streaming	56 (12.8)
Type of sexual behavior with sex partners known via gay apps (past 3 months; n=240)^a	
Anal sex	197 (82.1)
Oral sex	164 (68.3)
Masturbation	97 (40.4)
HIV status of last sex partners known via gay apps (past 3 months; n=240)	
Negative	93 (38.8)
Positive	6 (2.5)
Unknown	141 (58.8)

^aMultiple choice.

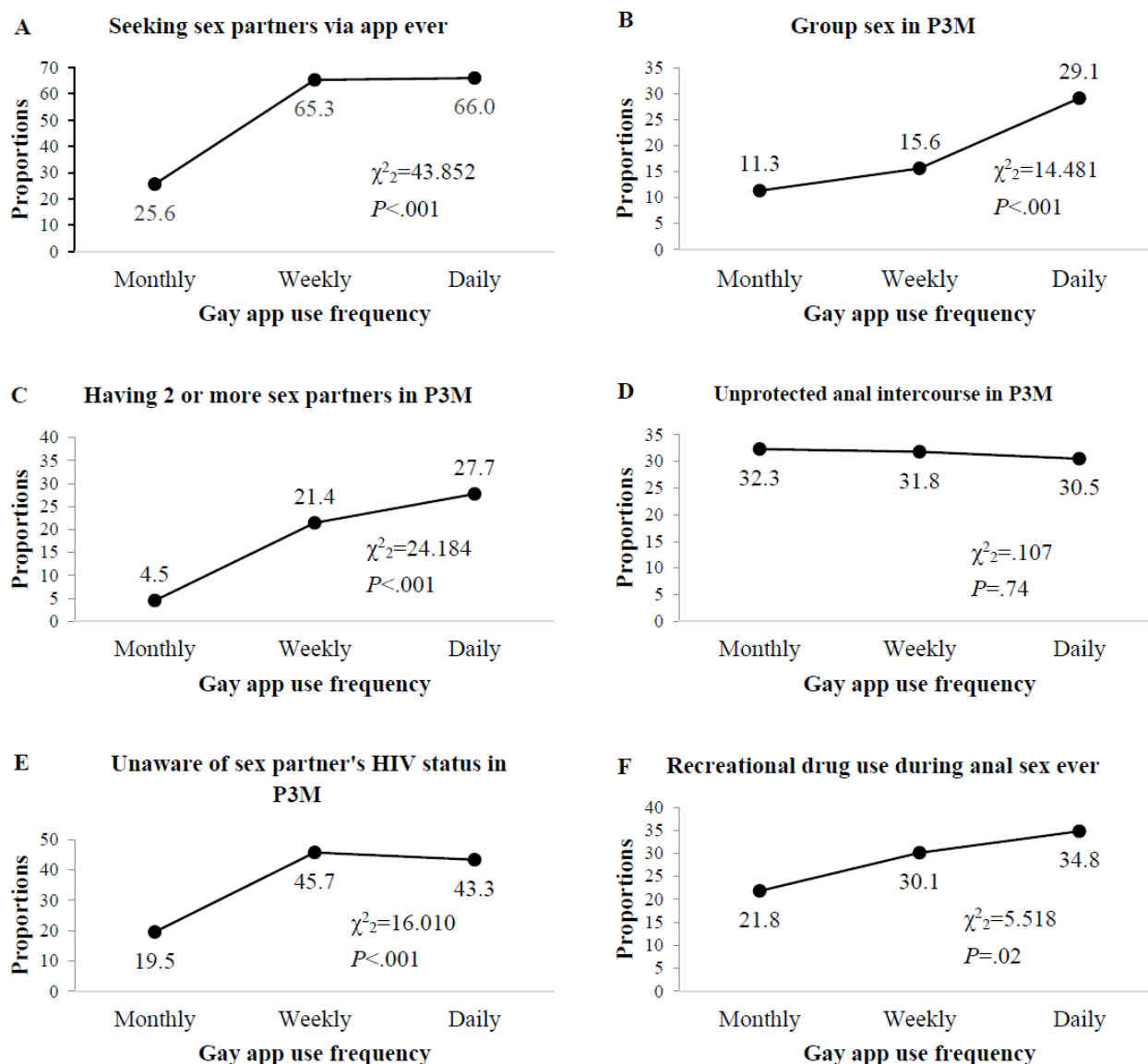
Gay App Use

Among MSM attending university enrolled in the study, 439/447 (98.2%) reported ever using gay apps (Table 1). The most popular gay apps were Blued (428/439, 97.5%) and Aloha (226/439, 51.5%); likewise, the most frequently used gay apps in the past 3 months were also Blued (318/439, 72.4%) and Aloha (84/439, 19.1%). Most participants reported using only 1 type of app (393/439, 89.5%), over 12 months of usage time (354/439, 80.6%), and using less than 1 hour per day (362/439, 82.5%). The top 3 purposes for using gay apps were looking for a romantic relationship (199/439, 45.3%), following others' updates (185/439, 42.1%), and making friends (171/439, 39.0%). The majority of participants (197/240, 82.1%) reported engaging

in anal sex with sex partners met via apps and over half (141/240, 58.8%) did not know the HIV status of last sex partner.

The frequencies of gay app use were months (125/439, 28.5%), weeks (173/439, 39.4%), and days (141/439, 32.1%) in the past 3 months among MSM attending university (Table 1). Chi-square test for trend showed that higher proportions of sexual behaviors, including seeking sex partners via apps ($P<.001$), engaging in group sex ($P<.001$), having multiple sex partners ($P<.001$), unknown sex partners' HIV status ($P<.001$), and using recreational drugs during sex ($P<.02$), were positively associated with the increase in the frequency of gay app use (Figure 1).

Figure 1. Behavioral changes over increasing frequency of gay app use among MSM attending university: (A) seeking sex partners with gay apps use frequency; (B) group sex with gay apps use frequency in past 3 months; (C) having two or more sex partners with gay apps use frequency in past 3 months; (D) unprotected anal intercourse with gay apps use frequency in past 3 months; (E) unaware of sex partners' HIV status with gay apps use frequency in past 3 months; (F) recreational drug use during anal sex ever. P3M: Past 3 months.



Seeking Sex Partner via Gay Apps

Table 2 shows the characteristics of seeking sex partners via gay apps among MSM attending university. As many as 240 reported using gay apps to seek sex partners. In multivariable analysis, participants who used gay apps to seek sex partners

were more likely to have multiple sex partners in the past 3 months (APR 1.53, 95% CI 1.33-1.76, $P<.001$), engage in group sex in the past 3 months (APR 1.55, 95% CI 1.35-1.78, $P<.001$), and have sex partners with unknown or positive HIV status (APR 1.72, 95% CI 1.46-2.01, $P<.001$).

Table 2. Correlates of seeking sex partner via gay apps among men who have sex with men attending university in China for past 3 months.

Variables	N	Seeking sex partner via gay apps		
		n (%)	Univariate prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)
Age (years)				
≤20	236	122 (51.7)	1	
≥21	211	118 (55.9)	1.08 (0.91-1.29)	
Education				
Undergraduate	355	193 (54.4)	1	
Junior college	92	47 (51.1)	0.94 (0.75-1.17)	
Academic performance				
Below average	93	48 (51.6)	1	
Average and above	354	192 (54.2)	0.95 (0.77-1.18)	
Sexual orientation				
Other	21	10 (47.6)	1	
Bisexual	44	23 (52.3)	1.21 (0.43-3.41)	
Homosexual	382	207 (54.2)	1.30 (0.54-3.14)	
Gender of sex partner				
Only male	423	231 (54.6)	1	
Both male and female	13	6 (46.2)	1.18 (0.65-2.14)	
Age at first anal intercourse (years)				
≤17	113	65 (57.5)	1	
≥18	323	172 (53.3)	1.08 (0.90-1.30)	
Commercial sex (lifetime)				
No	420	220 (52.4)	1	
Yes	27	20 (74.1)	1.84 (0.96-3.50)	
Forced sex (lifetime)				
No	418	231 (55.3)	1	
Yes	18	9 (50.0)	0.92 (0.57-1.47)	
Group sex (past 3 months)				
No	364	170 (46.7)	1	1
Yes	83	70 (84.3)	3.40 (2.05-5.66)	1.55 (1.35-1.78)
Number of sex partners (past 3 months)				
≤2	365	166 (45.5)	1	1
≥3	82	74 (90.2)	5.59 (2.87-10.87)	1.53 (1.33-1.76)
Condomless sex (past 3 months)				
No	306	144 (47.1)	1	1
Yes	141	96 (68.1)	1.24 (0.98-1.57)	0.98 (0.84-1.14)
HIV status of sex partners (past 3 months)				
Negative	281	111 (39.5)	1	1
Positive or unknown	166	129 (77.7)	1.97 (1.67-2.32)	1.72 (1.46-2.01)
Recreational drug use^a during sex				
No	317	154 (48.6)	1	

Variables	N	Seeking sex partner via gay apps		
		n (%)	Univariate prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)
Yes	130	86 (66.2)	1.52 (1.17-1.98)	
HIV testing				
No	49	25 (51.0)	1	
Yes	398	215 (54.0)	1.07 (0.79-1.45)	
HIV infection				
Negative	437	234 (53.5)	1	
Positive	10	6 (60.0)	1.16 (0.54-2.50)	

^aRecreational drug includes popper (alkyl nitrites), ecstasy, crystal methamphetamine, and ketamine.

Discussion

Principal Findings

To our knowledge, this is the first study to characterize gay app use among MSM attending university in China. We found that almost all MSM attending university used gay apps, and those who used gay apps to seek sexual partners were likely to be more engaging in high-risk sexual behaviors, including multiple sexual partners, group sex, commercial sex, and recreational drug use during sex.

We found a high prevalence (439/447, 98.2%) of gay app use among MSM attending university, which was much higher than that in nonstudent MSM (ranging from 40% [20] to 60% [21,22]). Previous studies have shown the differences in age distribution for app use among MSM, with younger age groups using them more frequently [21,23]. The mean age of participants in our study was 20 (SD 1.5) years, indicating that MSM attending university were a younger subgroup of MSM. Therefore, they are more likely to use gay apps compared with nonstudent MSM.

The popularity of gay app use among MSM attending universities was accompanied by some high-risk behaviors. Our study found that high-risk behaviors, including engaging in group sex in the past 3 months, having 2 or more sex partners in the past 3 months, failing to know sex partners' HIV status in the past 3 months, and using recreational drugs during sex, increased with the frequency of gay app use. Previous studies have indicated that men using gay apps could facilitate sexually risky behaviors [7,22,24]. Moreover, MSM attending university who used gay apps to seek sex partners were more likely to have multiple sex partners, engage in group sex and commercial sex, and use recreational drugs. This is consistent with previous studies among nonstudent MSM in China that found gay app users had more sex partners and more group sex compared with those who did not use apps to seek sex partners [20,22,25]. Notably, high-risk behaviors, including multiple sex partners, group sex, and commercial sex, could increase the risk of infection with HIV or other sexually transmitted infections. Therefore, additional interventions are needed to address the sexual risk behaviors associated with seeking sex partners via apps.

Literally all MSM attending university have used gay apps at some point, which points to the potential feasibility of using

gay app-based platforms to engage them in HIV prevention and care programs. Barriers, such as stigma, discrimination, and disclosure of sexuality, prevent young MSM from seeking traditional venue-based HIV prevention services. Because social networking apps are very popular among young people [26,27], there may be opportunities to facilitate HIV prevention efforts via these apps. Some app-based HIV interventions achieved desirable results. For example, since an HIV testing campaign using app push messages to promote HIV testing has been launched on Blued in 2015, over 15,000 MSM have tested for HIV, of whom over 2000 self-identified as university students. The number of those who tested for HIV increased substantially from 836 in 2013 before the campaign to 7315 in 2017 after the campaign [12]. Given that gay apps can instantly reach millions of targeted individuals, app-based interventions include information on HIV self-testing, pre-exposure prophylaxis, post-exposure prophylaxis, and HIV treatment as prevention, and thus may benefit a broad group in the MSM community.

We found Blued and Aloha were the most popular gay apps among MSM attending university, and the majority of those reported using only 1 app (393/439, 89.5%). There were 43 brands of gay apps in China in 2018 [28], and among nonstudent MSM 65.9% used only 1 app, and 23.2% used 2 apps [21]. Currently, there are regional differences in gay app use. While English language-based gay apps such as Grindr and Jack'd have subscribers from many countries, the gay app market in China is dominated by local apps such as Blued and Aloha. Those differences in gay app choices may be attributed to linguistic and cultural differences among MSM. Blued and Aloha are also platforms for HIV care services.

Limitations

There were limitations. First, there may be a selection bias in the study population. Participants were recruited mainly through online advertisements and enrolled offline for HIV testing at CBO site, which may exclude student MSM who hide their sexual orientation and were not willing to attend on-site testing at CBO. This deeply hidden population may be frequent users of gay apps, and the lack of such a population among participants may limit the generalizability of the study. Second, the study results may be affected by social desirability reporting bias because sensitive private information was based on self-reporting by participants. Third, the design of the

cross-sectional study prevents making causal inferences between using an app to seek sex partners and risk behaviors.

Conclusions

Our study suggests high gay app use among MSM attending university and using apps to seek sex partners may be associated

with increased high-risk sexual behaviors. The causality between seeking sex partners via gay apps and increased high-risk sexual behaviors should be further investigated so as to inform potential policies for HIV prevention.

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Authors' Contributions

This study was conceived and designed by HZ and SF in consultation with the other authors. SF and PL were responsible for field study, data compilation, and data analysis. All authors have contributed to the interpretation of data and study findings. SF, PL, and YH drafted the manuscript with all authors critically reviewing the paper.

Conflicts of Interest

None declared.

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Abbreviations

- APR:** adjusted prevalence ratio
CBO: community-based organization
CDC: Centers for Disease Control and Prevention
MSM: men who have sex with men

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Original Paper

Development and Evaluation of Short-Form Measures of the HIV/AIDS Knowledge Assessment Tool Among Sexual and Gender Minorities in Brazil: Cross-sectional Study

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Abstract

Background: In theoretical models of health behavior, knowledge about disease transmission and self-protective behaviors are conceptualized as important drivers of behavior change. Several studies conducted in Brazil point to an unfortunate convergence of sexual and gender minority (SGM) populations with low levels of HIV knowledge and younger age, lower education, engagement in higher-risk sexual behavior, and never having tested for HIV. Measures to assess level of HIV knowledge have been previously published, including the 12-item HIV/AIDS Knowledge Assessment (HIV-KA) tool. However, measure length can be a barrier to assessment.

Objective: We started from the 12-item HIV-KA tool and developed candidate short forms using statistical procedures, evaluated their psychometric properties, and tested the equivalency of their associations with other measures of HIV knowledge compared to the 12-item version.

Methods: A convenience sample of SGM was recruited during September 2020 to complete an online survey through advertisements on two social networking apps (Grindr and Hornet). The survey instrument included items on sociodemographic information, prior HIV testing and HIV test results, preexposure prophylaxis (PrEP) and antiretroviral treatment use, sexual behavior, and 3 HIV knowledge measures: the HIV-KA, World Health Organization Knowledge About HIV Transmission Prevention Indicator, and the Brief HIV Knowledge Questionnaire. We used exploratory factor analysis and confirmatory factor analysis (CFA) to assess the factor structure of the of the HIV-KA. We used optimal test assembly (OTA) methods to develop candidate short forms of the HIV-KA and evaluated them based on prespecified reliability, concurrent validity, and statistically equivalent convergent validity criteria.

Results: Among 2552 SGM individuals from Brazil, mean age was 35.1 years, 98.2% (2507/2552) cisgender men and 1.8% (45/2552) transgender/nonbinary, 56.5% (1441/2552) White, and 31.0% (792/2552) self-reported HIV positive. CFA indicated

a 1-factor structure for the 12-item HIV-KA. Concurrent validity correlations were high for all short forms with 6 items, but only versions with 9 items were as reliable as the full-length form and demonstrated equivalency for convergent validity correlations. Suggesting post hoc convergent validity, HIV knowledge scores using the 9- and 10-item short forms were higher for participants who perceived the Undetectable Equals Untransmittable (U=U) slogan as completely accurate versus not accurate. Suggesting post hoc concurrent validity, participants of younger age, of Black, Pardo or indigenous race, and reporting lower education and lower income scored lower on HIV knowledge. Participants who never tested for HIV scored lower than those who tested negative or positive, while those currently using PrEP scored higher than those reporting past or never use.

Conclusions: OTA methods were used to shorten the 12-item HIV-KA to 9-item and 10-item versions while maintaining comparable reliability and validity among a large sample of Brazilian SGM. However, these short forms did not shorten sufficiently to justify deviation from the full measure.

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KEYWORDS

HIV; knowledge; sexual and gender minorities; Brazil; preexposure prophylaxis

Introduction

Mirroring the dynamics of the HIV epidemic in Latin America, North America, and Western Europe, the Brazilian HIV epidemic is concentrated in key populations, such as gay, bisexual, and other men who have sex with men (MSM) [1,2] and transgender women [3]. In Brazil, the causes for this epidemiological profile are inherently multidimensional, involving vulnerability, risk, stigma, and discrimination, as well as behavioral, political, and programmatic issues [4,5]. Policies focusing on HIV prevention have incorporated HIV educational strategies as a main component as theoretical models of health behavior suggest that knowledge influences behavior [6]. More generally, knowledge about disease transmission and self-protective behaviors are conceptualized as important drivers of behavior change, thus influencing multiple decision-making models in the field of sexually transmitted infections, especially HIV [7].

Although mixed results exist on the direct link between knowledge and engagement in risky sexual behavior, a study conducted among men in Cape Town, South Africa, where HIV knowledge was low, showed that HIV testing combined with greater HIV knowledge led to reduced engagement in risky sexual behaviors [8]. Several studies conducted in Brazil point to an unfortunate convergence of sexual and gender minority (SGM) status with low level of HIV knowledge and younger age, lower education, engagement in higher-risk sexual behavior, and never having tested for HIV [9-12]. These findings highlight the vulnerabilities related to the social and cultural construction of the Brazilian HIV epidemic and the social inequalities. Moreover, these results indicate the important role that governmental and other stakeholder actions can have in improving indicators related to HIV knowledge.

Several measures to assess level of HIV knowledge have been published. A widely used measure is the World Health Organization Knowledge about HIV Transmission Prevention Indicator (WHO-KI), a 5-item measure proposed in a United Nations General Assembly Special Session that assesses knowledge of essential facts about transmission including correctly identifying ways of preventing sexual transmission of HIV and rejection of major misconceptions about HIV transmission [13]. Another measure is the Brief HIV Knowledge

Questionnaire (HIV-KQ), a short version (18 items) of the 45-item HIV Knowledge Questionnaire, which has shown to be internally consistent, stable, and appropriate for individuals with low education. However, it may be considered somewhat outdated as it does not address new paradigms of HIV prevention and treatment, such as treatment as prevention [14] and pre- and postexposure prophylaxis [15]. In 2019, Guimarães et al [11] developed the HIV/AIDS Knowledge Assessment tool (HIV-KA), a 12-item measure in Brazilian Portuguese which includes items that address treatment as prevention and pre- and postexposure prophylaxis. The measure was applied in a large sample of gay, bisexual, and other MSM (n=4716) from 12 Brazilian cities, and results were analyzed using item response theory. Corroborating prior studies, individuals of higher socioeconomic status had a higher level of HIV knowledge.

The study of an individual's sexual practices and its possible determinants, including HIV transmission knowledge, requires the concomitant measurement of multiple behaviors (eg, sexual behaviors, substance use) and knowledge-based and psychological constructs (eg, knowledge about transmission, perceptions of risk) which yield long study instruments. Importantly, we have observed that young, less-educated SGM who are most vulnerable to HIV acquisition are less likely to complete surveys [16]. Hence, shortening HIV knowledge instruments could help increase completion rate or allow for additional measures to be included in a given survey. Optimal test assembly (OTA) is a branch-and-bound, mixed-integer programming procedure that relies on estimates obtained from an item response theory model to select an optimal subset of items that best satisfy objective, reproducible, and prespecified constraints [17]. OTA was originally used in high-stakes large-scale educational assessments, but its use has been expanded to the creation of shortened forms of patient-reported outcomes [18-23]. This procedure has been shown to successfully produce replicable and reproducible shortened forms of minimal length [24].

This is a cross-sectional study of users of social networking apps for gay, bisexual, and other cisgender MSM and transgender and nonbinary or gender nonconforming individuals in Brazil. Our objective was to assess the psychometric properties of the HIV-KA among SGM and develop short forms

of the tool using statistical procedures. To reach these objectives, we started with the 12-item HIV-KA from Guimarães et al [11] and developed candidate short forms, evaluated their psychometric properties, and tested the equivalency of their associations with other measures of HIV knowledge compared to the 12-item version. Using objective decision rules and two different convergent validity measures, we assessed two shortened forms, one per validity measure. Last, we used post hoc convergent validity to assess the properties of the two shortened forms.

Methods

Participants and Procedures

A convenience sample of SGM was recruited during September 2020 to complete an online survey through advertisements on two social networking apps (Grindr and Hornet). Grindr is a location-based social networking and online dating app launched in 2009 that has since become the largest and most popular gay mobile app in the world. Hornet, another location-based social networking and online dating platform, was launched in 2011 and is available as an app and on the web. For Grindr, advertisement banners were randomly displayed to users for 2 weeks. Hornet users received 1 inbox message with a link to the survey. Participants needed to provide electronic informed consent before initiating the survey. No compensation was provided, and no personally identifiable information was collected except for IP address. Participant eligibility included age 18 years and older and residency in Brazil. Exclusion criteria were self-identifying as a cisgender woman and an incorrect response to any of 3 attention questions that were included throughout the survey instrument at approximately every 15 items [25]. A full version of the survey instrument is provided in [Multimedia Appendix 1](#).

Ethics Approval

This study was approved by the National Institute of Infectious Diseases Programa Inova at the Oswaldo Cruz Foundation (FIOCRUZ) institutional review board (#CAAE 01777918.0.0000.5262) in accordance with all applicable regulations.

Survey Instrument

The survey was programmed on Alchemer survey software. The survey was in Portuguese and contained 55 questions, with certain questions conditionally presented using branching logic. Survey links remained active for 1 month. Respondents were able to change and review answers. Four authors systematically checked the usability and technical functionality of the electronic questionnaire on different platforms and operating systems before starting the survey.

The survey instrument was divided into 3 sections. Section 1 included items on sociodemographic information (age, gender, sexual orientation, race/skin color, education, family monthly income, and state of residence). Section 2 included items referring to prior HIV testing and HIV test results. HIV-negative and unknown-status participants were questioned about preexposure prophylaxis (PrEP) use (current, never, or past), and those who were not currently using PrEP responded to 2

questions about sexual behavior during the previous 6 months (condomless anal sex and condomless receptive anal sex). HIV-positive participants were questioned about use of antiretroviral treatment (ART), and if in use, adherence (prior 7 days) was measured using the 3-item WebAd-Q instrument [26]. Section 3 included items of 3 HIV knowledge measures: HIV-KA [11], HIV-KQ [7], and WHO-KI [13]. These 3 measures use the same response format, which includes the options “true,” “false,” and “I don’t know.” The total score of each instrument was calculated by summing across all items that the participant answered correctly (“I don’t know” was coded as an incorrect response). Higher scores reflect greater knowledge. We also included a question about perceived accuracy of the Undetectable Equals Untransmittable (U=U) slogan [27-29]. Individuals were able to provide an email address if they wished to receive the correct answers to HIV knowledge questions 1 month after the study was terminated.

Measures

HIV-KA [11] is a 12-item measure previously used to assess knowledge among 4176 MSM in 12 Brazilian cities with a respondent-driven sampling methodology used for recruitment. The tool was evaluated using item response theory with difficulty and discrimination parameters estimated by marginal maximum likelihood and the knowledge score (θ) estimated by the expected a posteriori method based on Bayesian statistical principles.

HIV-KQ [7] is an 18-item measure evaluated for its psychometric properties among low-income US adults ($n=1019$). Results indicated strong levels of internal consistency and test-retest stability. For this study, we excluded 3 items: one was considered not relevant to the Brazilian context (“A natural skin condom works better against HIV than does a latex condom”), and 2 were deemed less relevant for SGM populations (“A woman cannot get HIV if she has sex during her period” and “There is a female condom that can help decrease a woman’s chance of getting HIV”).

WHO-KI [13] is a 5-item measure developed to assess progress in building knowledge of essential facts about HIV transmission among key populations. It is endorsed by the WHO and recommended as a tool to monitor key populations’ knowledge.

We assessed whether respondents correctly perceived the accuracy of the prevention benefits of U=U through the question “With regard to HIV-positive individuals transmitting HIV through sexual contact, how accurate do you believe the slogan Undetectable=Untransmissible is?” as used in previous studies [27-29]. Response options were based on a Likert-type scale from 1 (completely inaccurate) to 4 (completely accurate) plus a fifth option (I don’t know what “undetectable” means).

Statistical Analysis

Descriptive statistics of the study population are provided. We randomly split the study population in half and assessed the factor structure of all items of the HIV-KA together as a single measure with exploratory factor analysis (EFA) in the first half followed by confirmatory factor analysis (CFA) in the second half. EFA was used to identify the number of factors and assess item factor loadings. EFA was performed using robust weighted

least squares estimator given the categorical nature of the survey items, chi-square test statistic, and geomin oblique rotation [30]. A Cattell scree test on the sedimentation graph was examined. The number of factors was chosen based on the scree plot (eigenvalues), model adequacy, and overall interpretability. CFA used a weighted least squares estimator with a diagonal weight matrix, robust standard errors, and a mean- and variance-adjusted chi-square statistic with delta parameterization [31]. To assess model fit, the chi-square test, Tucker-Lewis Index (TLI) [32], comparative fit index (CFI) [33], root mean square error of approximation (RMSEA) [34], and standardized root mean residual (SRMR) [33] were used. Since the chi-square test is highly sensitive to sample size, it can lead to the rejection of well-fitting models [35]. Therefore, the TLI, CFI, and RMSEA fit indices were emphasized. Good fitting models may be indicated by a TLI and CFI ≥ 0.95 , RMSEA ≤ 0.06 , and SRMR < 0.08 [36].

Then, with the whole sample, a generalized partial credit item response theory model (GPCM) [37] was fit to all 12 items of the HIV-KA. The GPCM estimates 2 types of parameters for each item: a threshold parameter, which measures the level of knowledge at which people are more likely to answer the question correctly than incorrectly, and a discrimination parameter, which measures the strength of the association between that item and the underlying construct (HIV knowledge). From these item-level parameters, item information functions were estimated for each item and summed pointwise to obtain the test information function (TIF). The TIF measures the total amount of Fisher information in each item and is inversely related to the standard error of measurement of the underlying construct—that is, greater precision in the measurement of the underlying construct [38].

We used methods described by Harel et al [24]. Briefly, OTA systematically explores the space of all possible shortened versions of a fixed length to optimize the height of the TIF, thus minimizing the standard error of measurement of the underlying construct [24,39,40]. Here, for each possible length of shortened form (3 to 11), the OTA procedure created a candidate shortened version of the HIV-KA. Forms of length 1 and 2 were not generated because a minimum of 3 items are needed for the single-factor model to be identifiable [41]. Based on previously established guidelines [24], the OTA procedure was anchored at 5 points across the spectrum of the underlying construct (−5, −3, −1, 1, 3), jointly maximizing the shortened form's TIF at these points [17].

Each of the candidate short forms and the full-length form were scored using two procedures to obtain estimates of each participant's level of HIV knowledge. First, the summed scores across all items included in the form were calculated by adding item scores for each item included in the form. Second, factor scores, which estimate a level of a latent construct, were estimated from the GPCM for each participant for each form through an application of Bayes theorem. Both summed scores and factor scores were used due to the reliance on the former in research and the improved measurement properties of the latter [42,43].

Resulting from the OTA procedure are candidate shortened forms, each with the applicable optimal items. Removal of items implies a reduced amount of test information as compared to the full-length form. The selection of the final form was based on 5 criteria: reliability, concurrent validity based on summed scores, concurrent validity based on factor scores, convergent validity based on summed scores, and convergent validity based on factor scores. Applying these 5 criteria concurrently ensured that the final selected shortened version maintained desirable measurement properties across these categories.

Accordingly, we first generated the candidate shortened forms and assessed each form's reliability against the full-length form using a Cronbach alpha coefficient [44]. The shortened version was required to maintain at least 95% of the value of Cronbach alpha for the full-length form. Second, we estimated concurrent validity for both summed and factor scores by calculating a Pearson correlation coefficient between the scores on each candidate shortened version and the scores on the full-length form. For both the summed and factor scores, these correlations were required to be at least 0.90, ensuring that the shortened version demonstrated high concurrent validity.

Next, for convergent validity, we used two different criteria based on 2 HIV knowledge measures (HIV-KQ and WHO-KI, [Multimedia Appendix 2](#), Figure S1), and, in so doing, created 2 potential shortened forms—one validated against the HIV-KQ and the other validated against the WHO-KI. We assessed convergent validity through the correlation between participant scores on short forms and the 2 HIV knowledge measures. The candidate short forms were required to demonstrate statistical equivalence with the convergent validity of the full-length of each measure through an application of equivalence testing. Equivalence testing assesses whether the difference between 2 correlations is within a prespecified range, in this case set at .05 [45]. To assess statistical significance, we applied the Benjamini-Hochberg correction procedure for each of the hypothesis tests used (candidate shortened versions \times 2 scoring procedures) [46].

Finally, post hoc convergent and concurrent validity of the shortened forms were evaluated. We calculated the mean scores and 95% confidence intervals when using the 2 candidate shortened forms according to the participant's response to the perceived accuracy of the U=U slogan (dichotomized into completely accurate vs partially accurate, inaccurate, completely inaccurate, or "I don't know what undetectable means"). Additionally, we calculated mean scores with 95% confidence intervals of the candidate shortened forms according to select variables. As observed in a prior study [11], we hypothesized that the scores of the shortened forms would be associated with age, race, education, and income. We also hypothesized that participants reporting access to HIV prevention services, measured by prior HIV testing [47] and PrEP use, would score higher in the shortened forms of the HIV-KA.

All analyses were conducted in R software (version 4.0.2, R Foundation for Statistical Computing) [48]. The GPCM was fit using the ltm package [49], and the OTA analysis was conducted using the lpSolveApi package [50].

Results

Descriptive Statistics of the Study Population

Of 3368 participants who initiated the survey, 2552 answered all items of the 3 HIV knowledge measures of interest and were included in analyses ([Multimedia Appendix 2](#), Figure S2 and Table S1). Mean age of study participants was 35.1 years, with the overwhelming majority being cisgender men self-identified as gay or bisexual. Most participants self-reported as White,

had a college education or higher, and were earning more than US \$400 per month. Most (1510/2552, 59.2%) reported prior HIV testing and a negative HIV status; 31.0% (792/2552) self-reported as HIV positive. The vast majority (785/792, 99.1%) of HIV-positive participants had initiated ART, and, among these, most (472/785, 60.1%) were ART-adherent. Most (1534/1760, 87.2%) of HIV-negative or unknown participants were not currently using PrEP and reported condomless anal sex in prior 6 months ([Table 1](#)).

Table 1. Descriptive characteristics of participants included in the cross-sectional study among sexual and gender minorities, September 2020, Brazil.

	Value
Age (years), mean (SD)	35.1 (9.8)
Age (years), median (IQR)	33 (28-41)
18-24	322 (12.6)
25-34	1069 (41.9)
35-44	722 (28.3)
45-54	311 (12.2)
55+	125 (5.0)
Gender, n (%)	
Cisgender man	2507 (98.2)
Transgender/nonbinary	45 (1.8)
Sexual orientation, n (%)	
Gay	2196 (86.1)
Bisexual	302 (11.8)
Hetero/pansexual/other	54 (2.1)
Race/skin color	
White	1441 (56.5)
Pardo	745 (29.2)
Black	297 (11.6)
Asian	28 (1.1)
Indigenous	18 (0.7)
Not declared	23 (0.9)
Education, n (%)	
Middle school	100 (3.9)
High school	671 (26.5)
College+	1765 (69.6)
Family monthly income (US \$), n (%)	
Low ($\leq 2 \times$ minimum wage or ≤ 400)	752 (29.5)
Middle ($> 2-6 \times$ minimum wage or 401-1200)	1138 (44.6)
High ($> 6 \times$ minimum wage or > 1200)	662 (25.9)
Region, n (%)	
South/Southeast	2121 (83.1)
North/Northeast/Central-West	431 (16.9)
Recruitment, n (%)	
Grindr	1753 (68.7)
Hornet	737 (28.9)
Other	62 (2.4)
HIV test, n (%)	
Never tested	250 (9.8)
Negative	1510 (59.2)
Positive	792 (31.0)
ART^a self-report adherence (n=785, initiated ART), n (%)	
Yes	472 (60.1)

	Value
No	313 (39.9)
PrEP^b use (n=1760, HIV negative or never tested), n (%)	
Never	1412 (80.2)
Current	226 (12.8)
Past	122 (6.9)
Condomless anal sex (n=1760, HIV negative or never tested), n (%)	
Yes	717 (40.7)
No	1043 (59.3)
Measures of HIV knowledge, mean (SD)	
HIV-KA ^c	10.99 (1.46)
HIV-KQ ^d	13.07 (1.85)
WHO-KI ^e	4.76 (0.58)
Perceived U=U ^f slogan as completely accurate, n (%)	1600 (62.7)

^aART: antiretroviral therapy.

^bPrEP: preexposure prophylaxis.

^cHIV-KA: HIV/AIDS Knowledge Assessment tool.

^dHIV-KQ: Brief HIV Knowledge Questionnaire.

^eWHO-KI: World Health Organization Knowledge about HIV Prevention Indicator.

^fU=U: Undetectable=Untransmittable.

Factor Structure

The EFA of the 12-item HIV-KA (EFA sample; n=1276) yielded 1 eigenvalue of factor greater than 1 (Factor 1 eigenvalue 2.04). Based on examination of the scree plot, we judged that a 1-factor solution provided the most interpretable model. Results from the CFA (CFA sample; n=1276) indicated that a 1-factor structure showed reasonably good fit: $\chi^2_{66}=1352.1$, $P<.001$; CFI=0.94; TLI=0.93; RMSEA=0.03; SRMR=0.11. The item loadings ranged from 0.18 (item 8) to 0.75 (item 5).

Item Response Theory Model and OTA

The GPCM was fit on the 12 items of the HIV-KA. Item content with the discrimination parameters estimated from the GPCM are provided in Table S2 of [Multimedia Appendix 2](#). The 3 items with the highest amount of discriminative ability and, therefore, the most influential on the TIF were items 2, 4, and 5. The items with the least amount of discriminative ability and, therefore, the least influential on the TIF were items 8, 9, and 11. Individual item information functions generated from the estimates of the GPCM and the test information function for the full-length form and the 2 short forms are provided in Figures S3 and S4, respectively, of [Multimedia Appendix 2](#).

Selection of the Final Shortened Version

Short forms with at least 8 items had Cronbach $\alpha=.59$ or higher, suggesting a moderate level of reliability compared with

full-length (for which Cronbach $\alpha=.64$, [Table 2](#)). Short forms with the applicable items resulting from the OTA procedure are shown in Table S3 of [Multimedia Appendix 2](#). Concurrent validity correlations were high for all short forms with 6 items or more based on factor score correlations ([Table 2](#)). For convergent validity, all versions with at least 9 items demonstrated statistically significant equivalency for the correlations between the summed and factor scores with the HIV-KA ([Table 3](#)). The 9-item shortened form was the shortest candidate version to fulfill our requirements when validating against the HIV-KQ for the equivalency analysis, while the 10-items shortened form was the shortest candidate when validating against the WHO-KI.

The selected short forms include, for example, the items addressing PrEP (item 1: “There are medications for HIV-negative people to take before having sex with other people to prevent HIV infection”), treatment as prevention (item 2: “An HIV-infected person who is taking HIV/AIDS medications has a lower risk of transmitting the virus to another person”), and postexposure prophylaxis (item 4: “There are medications for HIV/AIDS to be used after a situation of risk of infection [ie, unprotected sex, sexual violence]”; [Table 3](#)). The 3 items that were consistently dropped from the selected short versions were item 8 (“When having intercourse with only one faithful partner, not infected with HIV, the risk of contracting the virus is lower”), item 9 (“There is a cure for HIV”), and item 10 (“A healthy-looking person may be infected with the HIV virus”).

Table 2. Psychometric properties of the short forms of the HIV/AIDS Knowledge Assessment tool in the cross-sectional study among sexual and gender minorities, September 2020, Brazil.

Short form	Cronbach alpha	Correlation of summed scores with full form scores (95% CI)	Correlation of factor scores with full form score (95% CI)
3 items	.25	0.740 (0.722-0.758)	0.704 (0.684-0.723)
4 items	.42	0.798 (0.784-0.812)	0.803 (0.788-0.816)
5 items	.52	0.856 (0.846-0.866)	0.883 (0.874-0.891)
6 items	.56	0.889 (0.881-0.897)	0.918 (0.912-0.924)
7 items	.56	0.897 (0.889-0.904)	0.922 (0.916-0.928)
8 items	.59	0.919 (0.912-0.924)	0.941 (0.936-0.945)
9 items	.62	0.949 (0.945-0.953)	0.971 (0.968-0.973)
10 items	.63	0.962 (0.959-0.965)	0.980 (0.978-0.981)
11 items	.65	0.980 (0.978-0.981)	0.995 (0.995-0.996)
12 items	.64	1 (1-1)	1 (1-1)

Table 3. Convergent validity and equivalency analysis results for the HIV/AIDS Knowledge Assessment tool in comparison to the Brief HIV Knowledge Questionnaire and the World Health Organization Knowledge about HIV Prevention Indicator in the cross-sectional study among sexual and gender minorities, September 2020, Brazil.

Short form	Summed scores	Factor scores	Equivalency analysis corrected <i>P</i> values	
			Summed scores	Factor scores
Correlations with HIV-KQ^a				
3 items	0.390 (0.357-0.423)	0.425 (0.392-0.456)	>.99	>.99
4 items	0.431 (0.399-0.462)	0.404 (0.371-0.436)	>.99	>.99
5 items	0.456 (0.425-0.486)	0.420 (0.388-0.451)	>.99	>.99
6 items	0.507 (0.478-0.536)	0.470 (0.439-0.500)	>.99	.83
7 items	0.511 (0.481-0.539)	0.474 (0.444-0.504)	.93	.53
8 items	0.526 (0.498-0.554)	0.496 (0.466-0.525)	.02	<.001
9 items	0.525 (0.496-0.553)	0.486 (0.455-0.515)	.01	<.001
10 items	0.536 (0.508-0.564)	0.495 (0.465-0.524)	<.001	<.001
11 items	0.566 (0.539-0.592)	0.520 (0.491-0.548)	<.001	<.001
12 items	0.561 (0.534-0.587)	0.521 (0.492-0.548)	<.001	<.001
Correlations with WHO-KI^b				
3 items	0.396 (0.363-0.428)	0.418 (0.385-0.449)	>.99	>.99
4 items	0.430 (0.398-0.461)	0.395 (0.362-0.428)	>.99	>.99
5 items	0.416 (0.383-0.447)	0.369 (0.335-0.402)	>.99	>.99
6 items	0.457 (0.426-0.487)	0.415 (0.383-0.447)	>.99	>.99
7 items	0.472 (0.441-0.502)	0.426 (0.393-0.457)	>.99	>.99
8 items	0.566 (0.539-0.591)	0.508 (0.478-0.536)	<.001	<.001
9 items	0.538 (0.510-0.565)	0.476 (0.445-0.505)	.46	<.001
10 items	0.549 (0.521-0.575)	0.483 (0.453-0.512)	.002	<.001
11 items	0.561 (0.533-0.587)	0.496 (0.466-0.525)	.001	<.001
12 items	0.584 (0.558-0.609)	0.509 (0.480-0.537)	.001	<.001

^aHIV-KQ: Brief HIV Knowledge Questionnaire.

^bWHO-KI: World Health Organization Knowledge about HIV Prevention Indicator.

Post Hoc Convergent and Construct Validity of the Shortened Forms

HIV knowledge scores using both the 9-item and 10-item short forms were higher among participants who perceived the U=U slogan as completely accurate versus not accurate (Table 4). Participants of younger age, of Black, Pardo, or indigenous race,

and reporting lower education and lower income scored lower on HIV knowledge. Participants who never tested for HIV scored lower than those who tested negative or positive, while those currently using PrEP scored higher than those reporting past or never use. Last, knowledge scores were very similar for those reporting condomless receptive anal sex or not as well as among those reporting as ART-adherent or not.

Table 4. Post hoc convergent and construct validities of the short forms of the HIV/AIDS Knowledge Assessment tool scales according to study variables in the cross-sectional study among sexual and gender minorities, September 2020, Brazil.

	9-item mean (95% CI)	10-item mean (95% CI)
Convergent validity		
Perceived U=U^a slogan as completely accurate		
Yes	8.49 (8.44-8.54)	9.46 (9.41-9.51)
No	7.86 (7.77-7.96)	8.83 (8.73-8.92)
Construct validity		
Age (years)		
18-24	7.80 (7.63-7.97)	8.73 (8.54-8.91)
25-34	8.30 (8.23-8.37)	9.26 (9.19-9.34)
35-44	8.30 (8.22-8.39)	9.28 (9.20-9.37)
45-54	8.20 (8.07-8.33)	9.17 (9.04-9.31)
55+	7.94 (7.72-8.16)	8.92 (8.70-9.15)
Race/skin color		
White or Asian	8.30 (8.24-8.35)	9.27 (9.21-9.33)
Black, Pardo, or indigenous	8.08 (8.00-8.16)	9.03 (8.95-9.12)
Education		
Middle school	7.16 (6.76-7.56)	8.02 (7.59-8.45)
High school	7.89 (7.79-7.99)	8.85 (8.74-8.95)
College+	8.40 (8.35-8.45)	9.38 (9.33-9.43)
Family monthly income		
Low	7.85 (7.74-7.96)	8.79 (8.68-8.91)
Middle	8.31 (8.25-8.38)	9.28 (9.22-9.35)
High	8.43 (8.36-8.50)	9.41 (9.34-9.48)
HIV test		
Never tested	7.29 (7.07-7.52)	8.20 (7.96-8.44)
Negative	8.19 (8.13-8.25)	9.16 (9.10-9.23)
Positive	8.53 (8.46-8.59)	9.49 (9.43-9.56)
PrEP^b use		
Never	7.98 (7.91-8.06)	8.94 (8.87-9.02)
Current	8.49 (8.38-8.60)	9.47 (9.36-9.58)
Past	8.20 (7.95-8.46)	9.16 (8.89-9.44)
Condomless receptive anal sex		
Yes	8.09 (7.99-8.19)	9.05 (8.95-9.16)
No	8.05 (7.96-8.13)	9.01 (8.93-9.09)
ART^c adherence		
Yes	8.58 (8.50-8.65)	9.54 (9.46-9.62)
No	8.47 (8.36-8.57)	9.44 (9.34-9.55)

^aU=U: Undetectable=Untransmittable.

^bPrEP: preexposure prophylaxis.

^cART: antiretroviral therapy.

Discussion

Principal Findings

In this study, we used a novel OTA method to generate valid short-form measures of the HIV-KA. The OTA procedure generated 9-item and 10-item shortened forms that satisfied our prespecified criteria in terms of reliability, concurrent validity, and convergent validity. These versions maintained high reliability and high concurrent validity with the full-length form, as well as statistically equivalent convergent validity correlations with HIV-KQ and WHO-KI. Our results indicate that 9-item and 10-item HIV-KA versions could be used among Brazilian SGM to assess HIV knowledge. Nonetheless, unless the number of items is a critical issue for a particular study, we argue that the shortened forms were not short enough (only shortened by 2 to 3 items) to justify recommendation as these would not be directly comparable to existing studies that have used the full-length version.

The OTA method is a replicable method that maintains performance standards based on objective criteria and, as such, selected short forms can be said to fulfill prespecified reliability and concurrent and convergent validity. The reliability of the shortened forms was of the same magnitude as the full-length form while showing high concurrent validity with the full-length form. Statistically equivalent convergent validity correlations using 2 HIV knowledge measures (HIV-KQ and WHO-KI) were also shown for both summed and factor scores.

The selected short forms included the items addressing recent paradigms of HIV prevention and treatment, such as preexposure prophylaxis, treatment as prevention, and postexposure prophylaxis. The 3 items removed from the short forms showed the lowest discriminative ability, indicating that they were less useful in the construction of the HIV knowledge score. Notwithstanding, semantic aspects of the items may have impacted the results. Particularly, for item 8, the item with the lowest discriminative ability, the wording may have caused confusion. Item 8 states that the risk of infection is lower when it would have been more appropriate to say that the risk is null (“When having intercourse with only one faithful partner, not infected with HIV, the risk of contracting the virus is lower”). Moreover, the use of the word lower suggests that it is lower than some other situation that the item does not specify. For example, compared to complete sexual abstinence, the risk may be higher, although it is lower compared to other sexual behaviors.

Our results also indicate post hoc convergent validity for the shortened forms using the 1-item measure on the perceived accuracy of U=U, a slogan launched in 2016 by the Prevention Access Campaign to translate scientific evidence into a community message that highlights how people living with HIV on antiretroviral treatment with suppressed viral load cannot transmit HIV to their sexual partners [51]. The scientific evidence supporting U=U has accumulated over the past decade and is contingent on the body of knowledge showing effectiveness of treatment as prevention, in which the use of ART among people living with HIV reduces HIV transmission yielding public health as well as personal health benefits [14].

The observed convergent validity thus reinforces the value of the proposed shortened forms to measure HIV knowledge among SGM. Of note, mean HIV knowledge score was high considering all 3 measures, and the proportion of individuals perceiving U=U as accurate was higher than observed in a 2019 survey conducted among Brazilian gay, bisexual, and other MSM [29]. This may indicate that perceived accuracy of the U=U slogan actually increased among SGM from Brazil over time, an important positive finding as understanding the accuracy of U=U empowers those living with HIV, improving treatment adherence, and decreasing HIV-related stigma [52]. Additionally, it may also enhance scale-up of PrEP, which is available at no cost through the Brazilian public health system. However, there are significant sociodemographic differences between the sample populations, with the current sample having more participants from the South/Southeast of Brazil and with higher education and income. As such, these differences may also play a role explaining the increased perceived accuracy of U=U.

Although only slightly shorter than the original 12-item HIV-KA measure, the 9-item or 10-item shortened forms may be preferred as they reduce participant burden, which is particularly important for participants who may have difficulty completing self-reported questionnaires. As observed in this study (Multimedia Appendix 2, Table S1) and in previous online surveys conducted by our group among SGM, those aged 18 to 24 years reporting lower income and lower education who had never been tested for HIV were more likely to not complete the survey [16]. Future studies should assess whether using the 9-item or 10-item shortened forms ultimately reach SGM populations that are more sociodemographically diverse. The number of HIV cases among young gay, bisexual, and other MSM continues to rise in Brazil [53] and, although scarce, age-dependent HIV incidence rate estimates also show that younger gay, bisexual, and other MSM are the most vulnerable [54]. In this regard, the unbiased representation of gay, bisexual, and other MSM on surveys addressing HIV transmission knowledge and sexual behavior is paramount to improve and aid development of prevention campaigns to these groups. Furthermore, beyond objective knowledge, we echo the recent call for promoting prevention literacy, whereby knowledge of the multiple prevention modalities is promoted to allow individuals to make the decisions that are optimal for their health while also promoting community advocacy and mobilization [55]. Shorter questionnaires with accessible and appealing language constructed with community participation may increase completion rate, and, consequently, the value of the collected information particularly as applicable to vulnerable groups.

Ad hoc construct validity of the HIV-KA shortened forms showed that those of younger age, non-White race, reporting lower education and lower income scored lower on HIV knowledge. A study from Brazil on 4129 MSM recruited by respondent-driven sampling in 12 Brazilian cities in 2016 observed that not only was the prevalence of unprotected receptive anal intercourse higher among younger participants, they scored lower on HIV knowledge and were less likely to have been tested for HIV in the past, despite having more years of schooling [47]. This lower HIV knowledge may be a

contributing factor to higher vulnerability to HIV infection. Indeed, multiple studies using different measures of HIV-related knowledge have shown a link between testing and knowledge with a gradient of increased knowledge as you move from the categories of never tested to HIV-negative and HIV-positive [28,29,56]. One hypothesis for this finding is that exposure to the health care setting and counseling during testing may increase HIV-specific knowledge. This rationale could also possibly explain why PrEP users who routinely have to access health services to refill their prescriptions also scored higher. That said, it is impossible to determine temporality and it may well be that those who are more knowledgeable about HIV are also more likely to get tested or use PrEP. We observed no correlation between HIV knowledge scores and report of condomless receptive anal sex, a finding also reported previously [56]. Future studies could explore motivations for engagement in high-risk sexual behavior and perhaps how HIV knowledge could help inform safer sexual practices.

Limitations

There are several study limitations that must be considered. This study used cross-sectional data, and therefore the sensitivity to change and test-retest reliability of the HIV-KA short forms could not be assessed. All collected data were self-reported by participants and may be subject to measurement errors that can arise in the collection, recall, or recording of information. Participants were recruited from a convenience online sample and may not reflect other SGM populations in Brazil. As for any study design, online samples have strengths that should be acknowledged which include the reaching geographically diverse populations as well as individuals from remote regions and those completely disconnected from HIV prevention services [57]. The challenges include the need for testing of survey instrument on a variety of hardware devices and software platforms, for effective means of advertising to diverse

populations and to maintain participant anonymity, among others [57]. Our participants were mostly cisgender, and additional studies should include a greater representation of transgender and nonbinary individuals. Additionally, the survey was advertised as about HIV knowledge and this may have influenced participant selection, possibly overrepresenting those already living with HIV. The OTA procedure is sensitive to the investigator-defined choice of decision criteria in the selection of the final shortened version. These decision criteria, when applied in future studies, must be carefully considered by researchers. Furthermore, the OTA method treats the 12 items of the HIV-KA as if they represented a full item bank of possible items. It is possible that if other items were considered than a different set of items would have been selected into the final short form. Lastly, this analysis should be replicated in other samples of SGM populations, as well as other populations, to increase the generalizability and to confirm that the selected short forms are optimal for other populations.

Conclusion

In conclusion, this study showed how OTA methods might be used to shorten the 12-item HIV-KA to 9-item and 10-item versions while maintaining comparable reliability and validity among a large sample of Brazilian SGM. While OTA was primarily used for the development of high-stakes educational testing, it has now been used, as well, to successfully shorten patient-reported outcome measures in several patient populations. This study is the first, to our knowledge, to use OTA to shorten a knowledge assessment tool. Although the shortened forms in this study did not represent substantial reductions in items, OTA represents an important methodology as we attempt to maximize the information we collect in the least burdensome way possible, which can be supported by reducing the number of items in surveys.

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Authors' Contributions

RCF, TST, and PML conceived of the study and designed the surveys. DRBB was responsible for study implementation, advertisement, and procedures. RCF, PML, and DH analyzed the data. MDGBC and BDT were responsible for data analysis guidance and interpretation of findings. RCF, TST, PML, and DH wrote the first draft. All authors reviewed and critically revised the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Questionnaire.

[[DOCX File, 19 KB - publichealth_v8i3e30676_app1.docx](#)]

Multimedia Appendix 2

Supplemental materials.

[[DOCX File , 237 KB - publichealth_v8i3e30676_app2.docx](#)]

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Abbreviations

ART: antiretroviral treatment

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CFA: confirmatory factor analysis

CFI: comparative fit index

EFA: exploratory factor analysis

FIOCRUZ: Programa Inova at the Oswaldo Cruz Foundation

GPCM: generalized partial credit item response theory model

HIV-KA: HIV/AIDS Knowledge Assessment tool

HIV-KQ: Brief HIV Knowledge Questionnaire

MSM: men who have sex with men

OTA: optimal test assembly

PrEP: preexposure prophylaxis

RMSEA: root mean square error of approximation

SGM: sexual and gender minority

SRMR: standardized root mean residual

TIF: test information function

TLI: Tucker-Lewis Index

U=U: Undetectable=Untransmittable

WHO-KI: World Health Organization Knowledge About HIV Transmission Prevention Indicator

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Original Paper

The Disease and Economic Burdens of Esophageal Cancer in China from 2013 to 2030: Dynamic Cohort Modeling Study

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Abstract

Background: Esophageal cancer (EC) is the sixth leading cause of tumor-related deaths worldwide. Estimates of the EC burden are necessary and could offer evidence-based suggestions for local cancer control.

Objective: The aim of this study was to predict the disease burden of EC in China through the estimation of disability-adjusted life years (DALYs) and direct medical expenditure by sex from 2013 to 2030.

Methods: A dynamic cohort Markov model was developed to simulate EC prevalence, DALYs, and direct medical expenditure by sex. Input data were collected from the China Statistical Yearbooks, Statistical Report of China Children's Development, World Population Prospects 2019, and published papers. The JoinPoint Regression Program was used to calculate the average annual percentage change (AAPC) of DALY rates, whereas the average annual growth rate (AAGR) was applied to analyze the changing direct medical expenditure trend over time.

Results: From 2013 to 2030, the predicted EC prevalence is projected to increase from 61.0 to 64.5 per 100,000 people, with annual EC cases increasing by 11.5% (from 835,600 to 931,800). The DALYs will increase by 21.3% (from 30,034,000 to 36,444,000), and the years of life lost (YLL) will account for over 90% of the DALYs. The DALY rates per 100,000 people will increase from 219.2 to 252.3; however, there was a difference between sexes, with an increase from 302.9 to 384.3 in males and a decline from 131.2 to 115.9 in females. The AAPC was 0.8% (95% CI 0.8% to 0.9%), 1.4% (95% CI 1.3% to 1.5%), and -0.7% (95% CI -0.8% to -0.7%) for both sexes, males, and females, respectively. The direct medical expenditure will increase by 128.7% (from US \$33.4 to US \$76.4 billion), with an AAGR of 5.0%. The direct medical expenditure is 2-3 times higher in males than in females.

Conclusions: EC still causes severe disease and economic burdens. YLL are responsible for the majority of DALYs, which highlights an urgent need to establish a beneficial policy to reduce the EC burden.

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KEYWORDS

esophageal cancer; disease burden; disability-adjusted life year; economic burden

Introduction

Esophageal cancer (EC) is a serious malignant tumor that originates from the esophageal epithelium. According to 2020

Global Cancer Statistics, EC is the sixth leading cause of death and the seventh most common cancer worldwide [1]. The incidence of EC has a considerable disparity in geographical distribution, with the highest EC burden in East Asia, and China

had the highest number of new EC cases and deaths in 2017 [2,3]. In China, EC ranked as the fourth leading cause of death and the fifth most common cancer in 2012 [4]. There were an estimated 286,700 new cases and 210,900 deaths in 2012, with incidence and mortality rates of $21.2/10^5$ and $15.2/10^5$, respectively [5,6]. Although EC incidence and mortality have decreased, EC still causes a huge burden on society, families, and individuals, with new cases and deaths increasing by 52.3% and 40.0%, respectively, from 1990 to 2017 in China [1]. More specifically, in China, over 90% of EC patients are diagnosed with invasive cancer, 20% of them have already developed distant metastasis, and the overall 5-year survival rate is approximately 18.4% [6,7].

In China, morbidity and mortality due to EC have been well-documented; however, its prevalence, premature death rate, and disability rate, and their estimates in the next decades, have not yet been investigated in detail. Moreover, over the past decades, fewer data have been available on the estimation of direct medical expenditure caused by EC [8,9]. The existing studies mostly focus on the average direct medical expenditure per patient, the average per hospital visit, or the average daily expenditure per patient [10]. However, little is known about the total direct medical expenditure and its development trends due to EC. "Health China 2030" released the key healthy indicators that life expectancy will increase by 3 years and reach 79 years by 2030, the premature death rate caused by major chronic diseases will decline by 30%, and the proportion of personal health expenditure among the total health expenditure will decline by 25% [11]. All of these factors put forward an even greater need for the prevention and control of chronic diseases.

In this study, we estimated the EC prevalence, premature death rate, and disability rate, as well as the disability-adjusted life years (DALYs) rate and direct medical expenditure from 2013 to 2030 by sex. We provide the average annual percentage change (AAPC) of DALY rates and the average annual growth rates (AAGR) of direct medical expenditure. We hope that our study will offer policymakers evidence-based suggestions for the precise prevention and control of EC, and help to reduce the societal and economic burdens of EC in China.

Methods

Data Source

We chose the year 2012 as the baseline year. The birth rate, all-cause mortality, sex ratio, and standard life expectancy at birth from 2012 to 2019 were collected from the China Statistical Yearbook released by the Bureau of Statistics of China [12]. Infant mortality from 2012 to 2019 was drawn from the Statistical Report of China Children's Development (2011-2020) [13]. All cohort data for subsequent years were drawn from the World Population Prospects 2019 released by the United Nations Population Division [14]. The birth rate and infant mortality for boys and girls were calculated for both sexes combined according to the sex ratio at birth. All-cause mortality for males and females was computed by the mortality of both sexes combined with the sex ratio of the total population and the risk ratio of all-cause mortality in males compared to females

obtained from the Tabulation on the 2010 Population Census of the People's Republic of China [15].

We used an age-specific population and all-cause mortality, age-specific EC incidence, mortality in 2012, and EC fatalities to estimate the EC prevalence in 2012, average age of onset, and duration of EC through the DisMod model [16]. Age-specific population and all-cause mortality were estimated using the data collected from the 2010 Population Census of the People's Republic of China. EC incidence and mortality were collected from published data [6,17], whereas the fatality was estimated based on survival data [6]. Additionally, the AAPC of EC incidence and mortality were used to simulate the subsequent yearly incidence and mortality of EC [6,17].

Measures

Calculation of DALYs

DALYs are a time-based measure of the overall burden of disease, representing the sum of the years of life lost (YLL) due to premature mortality and years lived with a disability (YLD) due to disease. One DALY represents a loss of the equivalent of 1 year of full health [18]. The calculations are as follows [19]:

$$DALY=YLL+YLD$$

$$YLL=KCe^{\gamma\alpha}/(\gamma+\beta)^2 \{e^{-(\gamma+\beta)(L+\alpha)} [-(\gamma+\beta)(L+\alpha)-1] - e^{-(\gamma+\beta)\alpha} [-(\gamma+\beta)\alpha-1]\} + 1-K/\gamma(1-e^{-\gamma L})^4$$

$$YLD=DKCe^{\gamma\alpha'} \{e^{-(\gamma+\beta)(L'+\alpha')} [-(\gamma+\beta)(L'+\alpha')-1] - e^{-(\gamma+\beta)\alpha'} [-(\gamma+\beta)\alpha'-1]\} + D(1-D)/\gamma(1-e^{-\gamma L'})^4$$

where K is the age-weighting modulation factor, C is a necessary constant to adjust for unequal age weights, γ is the standard discount rate, β is the standard age weight, L is the standard expectation of life at age α , α is the age at death, D is the disability weight, α' is the age of onset of the disability, and L' is the duration of the disability. The key parameters were set as follows: $K=1$, $C=0.1658$, $\gamma=0.03$, and $\beta=.04$. L is the difference between the standard life expectancy at birth and the average age at death due to EC, α is defined as the sum of the average age at onset and the duration of EC, and D was estimated using values addressed in the Disability Weights for the Global Burden of Disease (GBD) 2013 study and clinical stage data for China. According to the GBD report, the disability weights of EC diagnosis/therapy and control (stage I-II), cancer with preterminal metastasis (stage III), and the terminal phase (IV) are 0.288, 0.451, and 0.540, respectively [20]. EC clinical stage data were collected from a 10-year multicenter retrospective survey, and the proportions of stage I-II, stage III, and stage IV disease were 45.5%, 33.8%, and 20.7%, respectively [7]. Consequently, the weighted average disability weight was 0.395. Additionally, EC prevalence was used to calculate the YLD.

Direct Medical Expenditure Per Patient

Direct medical expenditure represents the total direct medical expenditure that occurs in the hospital. The annual average direct medical expenditure per patient was estimated using the following formula: $C_{2012} \times (1+AAGR)^{N+1}$, where C_{2012} is the annual average direct medical expenditure per patient in 2012 that was collected from the China Health Statistics Yearbook

2013 and AAGR was estimated using the average annual direct medical expenditure per patient from 2010 to 2017 that was released by the China Health Statistics Yearbook 2010-2017 (see Table S1 in [Multimedia Appendix 1](#)) [21]. The AAGR is simply calculated by the annual percentage growth divided by the number of years using the following formula:

$$\text{AAGR} = \sum [V_{\text{ending}}/V_{\text{beginning}} - 1] \times 100\% / N - 1,$$

where V_{ending} represents the future value, $V_{\text{beginning}}$ represents the present value, and N represents the number of years. Additionally, the AAGR was converted to US \$ using purchasing power parities of 3.506 in 2017 [22].

Statistical Analysis

Cohort Markov Model

We constructed a dynamic cohort Markov model with five states, including newborn, health, EC, EC-specific death, and other deaths. We assumed EC-specific death as the nonabsorbing state. Figure S1 in [Multimedia Appendix 1](#) displays the model, with arrows representing the transition of the cohort population between states that was determined by the predefined transition probabilities. A cycle of 1 year was chosen.

The transition from newborn to health was estimated using the following formula: $T_{\text{newtohealth}} = R_{\text{b}} \times \text{Count_alive} \times (1 - M_{\text{Inf}})$, where $T_{\text{newtohealth}}$ represents the annual number of people transferred from the state of newborn to the health state, R_{b} is the annual birth rate, Count_alive is the number of people still alive at the end of the last simulation cycle summed by the number of people in the health state and EC state, and M_{Inf} is the annual infant death probability. The number of people transferred from the state of newborn to the state of other death is equal to $1 - T_{\text{newtohealth}}$. We used the EC annual incidence probability to determine the number of people transferred from the health state to the EC state. The annual death probability for health was defined as the non-EC annual death probability, which was calculated by the difference between all-cause death probability and EC-related death probability. The annual death probability of the EC state was composed of two parts: the annual EC fatality probability and the non-EC death probability.

Additionally, we examined the AAPC of DALY rates, including the 95% CIs, as well as the AAGR of direct medical expenditure. TreeAge Pro 2019 was used to estimate DALYs and direct medical expenditure, and JoinPoint Regression Program software (version 4.7.0.0) was used to calculate the AAPC of DALY rates and the 95% CIs [23,24]. Other analyses were performed using Stata 14.0.

Sensitivity Analysis

One-way sensitivity analyses were performed to estimate the extent to which the model's calculations were affected by the uncertainty of the input data. Sensitivity analyses were confined to the birth rate and all-cause mortality for both sexes, the sex ratio of the total population, the AAPC for EC incidence and mortality, the 5-year survival rate, and the AAGR of the direct medical expenditure. The ranges of the birth rate, all-cause mortality, and sex ratio of the total population were derived from World Population Prospects 2019. The ranges of the AAPC for EC incidence and mortality and the 5-year survival rate were the 95% CIs collected from published papers. The range of the AAGR for direct medical expenditure was assumed to be simply a "plausible" range, which varied by $\pm 10\%$ of the base case value.

Validation

We performed the internal validation by comparing the input EC incidence with the simulated EC incidence by the model. The goodness of fit was computed by plotting the model predictions versus the inputs and fitting a linear curve without an intercept. The squared linear correlation coefficient (R^2) simulated by linear regression was used to examine the goodness of fit of the model.

Results

Internal Validation

The simulated EC incidence by the model closely matched the input data (Figure S2 in [Multimedia Appendix 1](#)). The regression line slope was 1.01 and the R^2 was 0.99, which demonstrated good consistency between the two estimates.

Predicted EC Prevalence and the Number of People With EC

From 2013 to 2030, the prevalence of EC will increase from 61.00 to 64.5 per 100,000 and peak at 67.9 per 100,000 in 2020. In males, there was a dramatic increase predicted for EC incidence, from 82.0 to 96.4 per 100,000, whereas the incidence is predicted to first increase and then decrease in females, resulting in an overall decrease from 38.9 to 31.6 per 100,000. The total EC cases will increase by 11.5% (from 835,600 to 931,800), and will peak at 961,500 in 2021. The EC cases in males will increase by 22.9% (from 575,500 to 707,500), whereas in females, it will first increase and then decrease, with an overall decrease of 13.8% (from 260,100 to 224,3000). [Table 1](#) summarizes the details.

Table 1. Predicted prevalence of esophageal cancer and the number of people diagnosed with esophageal cancer from 2013 to 2030 in China, by sex.

Year	Males		Females		Total	
	Prevalence (per 100,000)	Cases, n	Prevalence (per 100,000)	Cases, n	Prevalence (per 100,000)	Cases, n
2013	82.0	575,500	38.9	260,100	61.0	835,600
2014	86.1	607,600	40.4	270,900	63.8	878,500
2015	89.0	631,100	41.1	277,000	65.6	908,100
2016	91.1	648,600	41.3	279,900	66.8	928,500
2017	92.4	661,900	41.1	280,500	67.4	942,300
2018	93.4	672,300	40.7	279,400	67.7	951,600
2019	94.3	680,600	40.2	277,100	67.9	957,700
2020	94.9	687,100	39.6	273,800	67.9	961,000
2021	95.3	691,800	38.9	269,800	67.7	961,500
2022	95.6	695,500	38.1	265,300	67.5	960,700
2023	95.8	698,500	37.3	260,500	67.2	959,000
2024	95.9	701,100	36.5	255,600	66.8	956,600
2025	96.0	703,400	35.6	250,500	66.4	953,900
2026	96.1	704,700	34.8	245,300	66.0	950,000
2027	96.2	705,700	34.0	240,000	65.7	945,700
2028	96.3	706,500	33.2	234,700	65.3	941,200
2029	96.4	707,100	32.4	229,500	64.9	936,500
2030	96.4	707,500	31.6	224,300	64.5	931,800

DALYs, the DALY Rate, and the AAPC

Figure 1 presents the DALYs due to EC by sex in China between 2013 and 2030. From 2013 to 2030, the total DALYs for both sexes will increase by 21.3% (from 30,034,000 to 36,444,000). DALYs will increase by 32.6% in males (from 21,266,000 to 28,209,000); in contrast, they will decrease overall by 6.1% in females (from 876,800 to 823,500). Significantly, YLL contributed to over 90% of the DALYs for both sexes. Figure 2 displays the DALY rates per 100,000 people by year and sex.

The results of the Joinpoint regression analysis address the statistical significance of the AAPC in DALY rates. From 2013 to 2030, the overall DALY rates per 100,000 will increase from 219.2 to 252.3, and will peak at 262.1 in 2021. The AAPC will be 0.8% (95% CI 0.8%-0.9%). In males, there was an obvious increase from 302.9 to 384.3, with 1.4% (95% CI 1.3%-1.5%) of the AAPC. However, an overall significant downward trend was shown in females (from 131.2 to 115.9), which peaked at 147.4 in 2017. The AAPC will be -0.7% (95% CI -0.8% to -0.7%).

Figure 1. The predicted disability-adjusted life years (DALYs) of esophageal cancer by sex from 2013 to 2030. YLL: years of life lost; YLD: years lived with a disability; AGR: annual growth rate.

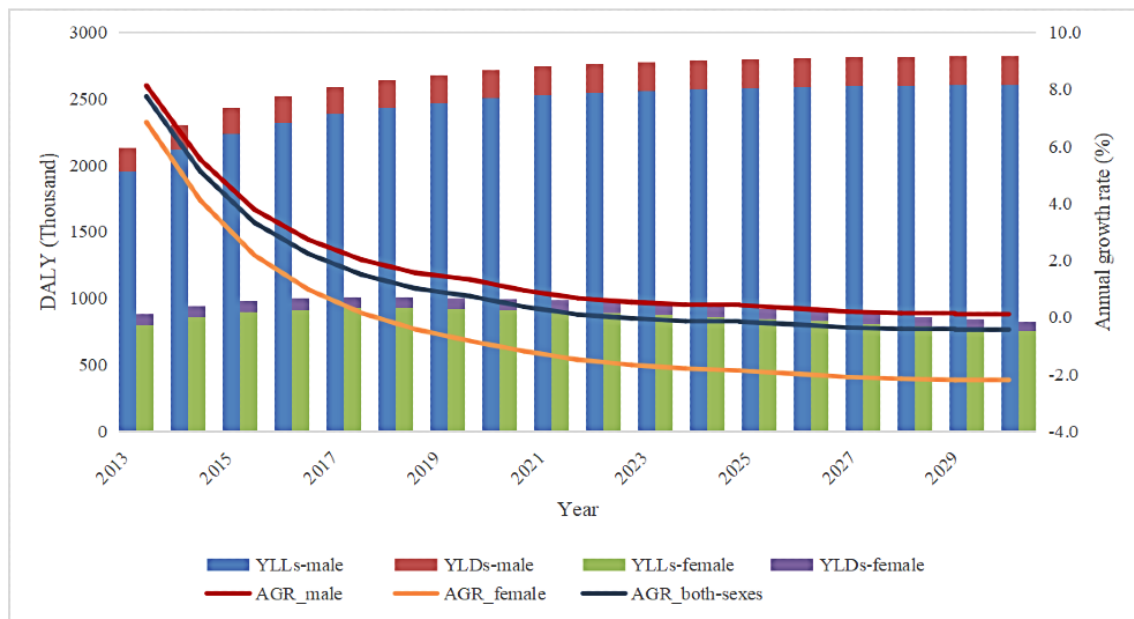
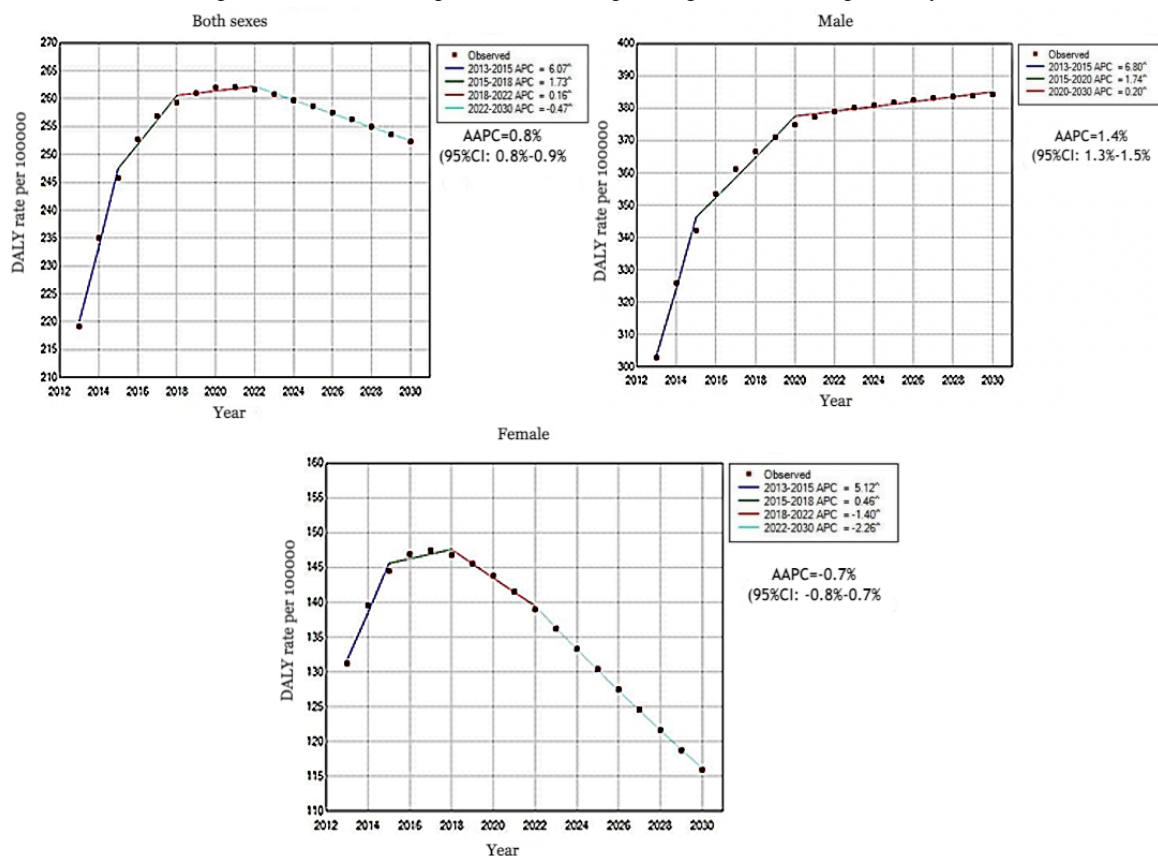


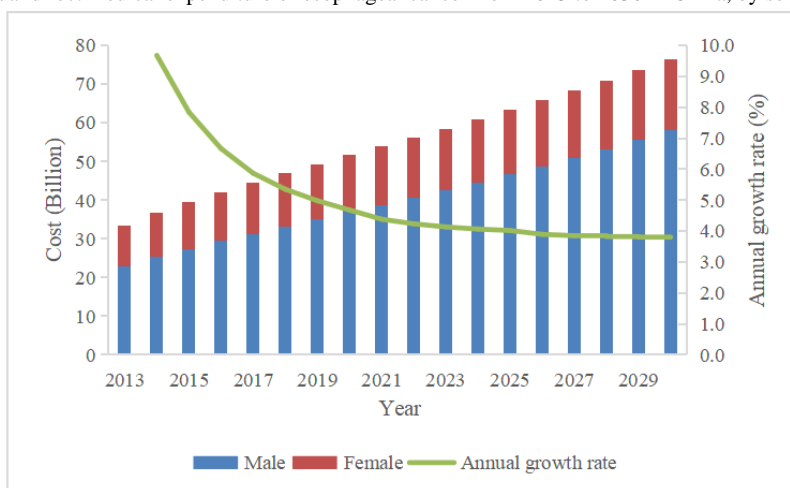
Figure 2. The predicted changing trend of disability-adjusted life years (DALYs) due to esophageal cancer from 2013 to 2030 in China, by sex. In all 3 graphs, the Annual Percent Change (APC) and the Average Annual Percentage Change (AAPC) are significantly different from zero at $\alpha=.05$ level.



Projected Annual Direct Medical Expenditure

The predicted annual direct medical expenditure for both sexes will increase significantly (Figure 3). From 2013 to 2030, the total annual direct medical expenditure will increase by 128.7% (from US \$33.4 billion to US \$76.4 billion). The AAGR will

be 5.0%, and the annual growth rate will decline from 9.7% to 3.8%. Male patients will have 2.2-3.2 times higher direct medical expenditure than female patients, which will increase by 152.2% and 76.9% (from US \$23.0 billion to US \$58.0 billion and from US \$10.4 billion to US \$18.4 billion) in males and females, respectively.

Figure 3. Estimated total annual direct medical expenditure of esophageal cancer from 2013 to 2030 in China, by sex.

Sensitivity Analysis

The results of the sensitivity analysis indicated that changes in the AAGR of direct medical expenditure, 5-year survival rate, and AAPC of EC incidence have a substantial impact on the direct medical expenditure of EC, whereas the disability weight,

5-year survival rate, AAPC of EC incidence, risk ratio of all-cause mortality, and birth rate have an obvious impact on the DALYs. Table 2 and Table 3 summarize the changes in the cumulative direct medical expenditure and DALYs due to EC according to the variations in key input data considered in the sensitivity analyses for males and females, respectively.

Table 2. Changes in the estimated cumulative direct medical expenditure (DME) and disability-adjusted life years (DALYs) of esophageal cancer in males in China according to the key parameters considered in the sensitivity analyses.

Parameter	Changes in estimated DME, billions (%)			Changes in estimated DALYs, thousands (%)		
	2030	2025	2020	2030	2025	2020
Baseline value	741.7	475.2	261.9	49957.5	35889.7	22037.9
AAGR^a of DME						
0.0475 instead of 0.0432	33.1 (4.5)	14.8 (3.1)	4.9 (1.7)	NC ^b	NC	NC
0.0388 instead of 0.0432	-32.2 (-4.3)	-14.7 (-3.1)	-4.9 (-1.9)	NC	NC	NC
5-year survival rate						
0.208 instead of 0.199	12.3 (1.7)	7.2 (1.5)	3.3 (1.3)	-130.8 (-0.3)	-139.3 (-0.4)	-135.9 (-0.6)
0.190 instead of 0.199	-12.4 (-1.7)	-7.3 (-1.5)	-3.4 (-1.3)	131.0 (0.3)	139.9 (0.4)	137.5 (0.6)
Risk ratio of all-cause mortality						
1.47 instead of 1.33	-2.7 (-0.4)	-1.2 (-0.3)	-0.4 (-0.2)	-146.0 (-0.3)	-71.5 (-0.2)	-24.4 (-0.1)
1.20 instead of 1.33	2.8 (0.4)	1.2 (0.3)	0.4 (0.2)	153.2 (0.3)	74.9 (0.2)	25.5 (0.1)
Birth rate						
High estimates ^c	2.6 (0.4)	0.3 (0.1)	NC	107.2 (0.2)	12.14 (0.0)	NC
Low estimates ^c	-2.6 (-0.4)	-0.3 (-0.1)	NC	-107.6 (-0.2)	-12.2 (0.0)	NC
Sex ratio of the total population						
High estimates ^d	-0.1 (0.0)	-0.01 (0.0)	NC	-5 (0.0)	-0.5 (0.0)	NC
Low estimates ^d	0.1 (0.0)	NC	NC	5.0 (0.0)	0.6 (0.0)	NC
Risk ratio of infant mortality						
1.04 instead of 0.95	NC	NC	NC	-1.2 (0.0)	0.7 (0.0)	-0.2 (0.0)
0.85 instead of 0.94	NC	NC	NC	1.5 (0.0)	-0.6 (0.0)	0.2 (0.0)
Disability weight						
0.435 instead of 0.395	NC	NC	NC	393.2 (0.8)	284.0 (0.8)	176.1 (0.8)
0.356 instead of 0.395	NC	NC	NC	-393.2 (-0.8)	-284.0 (-0.8)	-176.1 (-0.8)
All-cause mortality						
High estimates ^e	NC	NC	NC	NC	NC	NC
Low estimates ^e	NC	NC	NC	NC	NC	NC

^aAAGR: average annual growth rate.

^bNC: no changes in estimated costs or DALYs.

^cSee Table S2 in [Multimedia Appendix 1](#).

^dSee Table S3 in [Multimedia Appendix 1](#).

^eSee Table S4 in [Multimedia Appendix 1](#).

Table 3. Changes in the estimated cumulative costs and disability-adjusted life years (DALYs) of esophageal cancer (EC) in females in China according to the key parameters considered in the sensitivity analyses.

Parameter	Changes in estimated cost, billions(%)			Changes in estimated DALYs, thousands (%)		
	2030	2025	2020	2030	2025	2020
Baseline value	279.5	191.1	111.7	17687.7	13382.4	8628.1
AAGR^a of DME^b						
0.0475 instead of 0.0432	11.8 (4.2)	5.8 (3.0)	2.0 (1.8)	NC ^c	NC	NC
0.0388 instead of 0.0432	-11.4 (-4.1)	-5.7 (-3.0)	-2.0 (-1.8)	NC	NC	NC
AAPC^d of EC incidence						
-0.016 instead of -0.025	18.3 (6.5)	7.7 (4.0)	2.1 (1.9)	873.3 (5.0)	402.4 (3.0)	109.1 (1.3)
-0.035 instead of -0.025	-18.4 (-6.6)	-8.0 (-4.2)	-2.2 (-2.0)	-891.9 (-5.0)	-422.9 (-3.2)	-117.9 (-1.4)
AAPC of EC mortality						
-0.011 instead of -0.027	NC	NC	NC	0.9 (0.0)	0.4 (0.0)	0.1 (0.0)
-0.042 instead of -0.027	NC	NC	NC	-0.8 (0.0)	-0.3 (0.0)	-0.1 (0.0)
5-year survival rate						
0.208 instead of 0.199	6.9 (2.5)	4.2 (2.2)	2.0 (1.8)	-57.9 (-0.3)	-71.8 (-0.5)	-77.5 (-0.9)
0.190 instead of 0.199	-6.4 (-2.3)	-4.0 (-2.1)	-1.9 (-1.7)	53.3 (0.3)	66.6 (0.5)	72.9 (0.8)
Risk ratio of all-cause mortality						
1.47 instead of 1.33	1.0 (0.4)	0.8 (0.2)	0.2 (0.2)	51.2 (0.3)	27.0 (0.2)	10.0 (0.1)
1.20 instead of 1.33	-1.1 (-0.4)	-0.5 (-0.3)	-0.2 (-0.2)	-53.3 (-0.3)	-28.1 (-0.2)	-10.3 (-0.1)
Birth rate						
High estimates ^e	0.7 (0.3)	0.1 (0.1)	NC	27.0 (0.2)	3.2 (0.0)	NC
Low estimates ^e	-0.7 (-0.3)	-0.1 (-0.1)	NC	-27.2 (-0.2)	-3.2 (0.0)	NC
Sex ratio of the total population						
High estimates ^f	NC	NC	NC	-1.2 (-0.0)	-0.1 (0.0)	NC
Low estimates ^f	NC	NC	NC	1.2 (0.0)	0.1 (0.0)	NC
Risk ratio of infant mortality						
1.04 instead of 0.95	NC	NC	NC	0.4 (0.0)	0.19 (0.0)	0.1 (0.0)
0.85 instead of 0.94	NC	NC	NC	-0.5 (0.0)	-0.2 (0.0)	-0.1 (0.0)
Disability weight						
0.435 instead of 0.395	NC	NC	NC	147.6 (0.8)	112.3 (0.9)	73.3 (0.9)
0.356 instead of 0.395	NC	NC	NC	-147.6 (-0.8)	-112.3 (-0.8)	-73.3 (-0.9)
All-cause mortality						
High estimates ^e	NC	NC	NC	NC	NC	NC
Low estimates ^e	NC	NC	NC	NC	NC	NC

^aAAGR: average annual growth rate.^bDME: direct medical expenditure.^cNC: no changes in estimated costs or DALYs.^dAAPC: average annual percentage change.^eSee Table S2 in [Multimedia Appendix 1](#).^fSee Table S3 in [Multimedia Appendix 1](#).

Discussion

Principal Findings

To the best of our knowledge, this is the first modeling study on the national disease burden of EC in China. According to our estimates, the disease and economic burdens due to EC will increase substantially over the next few decades. From 2013 to 2030, the EC prevalence will increase by 11.5% (from 835,600 to 931,800); the total DALYs will increase by 21.3% (from 30,034,000 to 36,444,000); the DALY rates per 100,000 people will increase from 219.2 to 252.3, with an AAPC of 0.8%; and the direct medical expenditure will increase by 128.7% (from US \$33.4 billion to US \$76.4 billion), with an AAGR of 5%. Additionally, we found large variations in burdens between sexes: the prevalence and direct medical expenditure was 2.2-3.2 times higher and DALYs were 2.4-3.4 times higher in males than in females.

China ranks close to the top in terms of the highest number of EC incident cases, deaths, and DALYs worldwide [2]. The DALY rates per 100,000 in 2017 were twice as high as those in the rest of the world (222.6 vs 119.9) [2]. This is largely because of the higher aging population, low social demographic index, and high-risk lifestyles related to EC in China. Our estimated DALY rates in 2017 were slightly higher than the estimates provided by the GBD 2017 Esophageal Cancer Collaborators (256.9 vs 222.6). This discrepancy is probably due to the different sources of the data used for calculating the DALYs. Almost all of the DALYs were attributed to YLL due to premature death, which is quite consistent with previous studies [19,25,26]. Additionally, the burden from EC in China has geographic disparities, and high-risk areas cause an almost 4-times higher burden than that estimated at the national level (810.0 vs 219.2 per 100,000) [19].

Despite previous studies indicating a decrease in the incidence and mortality of EC over the past decades, this study suggests a continuous increase in the prevalence of EC, DALYs, and direct medical expenditure. This is driven primarily by the increasing absolute number of EC cases. Additionally, the sensitivity analysis demonstrated that the incidence of EC, 5-year survival rate, and disability weight have a considerable impact on DALYs. Collectively, these findings suggest the significance of reducing the incidence of EC, premature death, and personal direct medical expenditure, and improving the 5-year survival rate and disease health-related quality of life.

Consequently, policymakers should adopt comprehensive effective strategies to reduce the burden caused by EC, possibly focusing on the consciousness of cancer prevention, early detection, early diagnosis, and early treatment, as well as the demand for and access to cancer prevention and treatment knowledge. First, screening should be highly recommended since it is the major strategy for primary and secondary disease prevention, and could detect the disease in the early stage to treat it effectively [27]. Additionally, considering the cost-effectiveness and the large disparities according to age, sex, and other higher-risk behaviors, a finer delineation of strategies should be specified for individuals at different risk levels [28,29]. Second, improving health literacy, including

personal health literacy and organizational health literacy, is positively related to awareness of cancer risk and knowledge, health behavior and screening, early cancer symptom recognition, cancer screening behavior, health service resource utilization, treatment compliance, and quality of life [30]. Moreover, educational interventions using social media should be suggested to promote self-management and strengthen health literacy [31,32]. Furthermore, clinical treatment and terminal care should be strengthened to improve the quality of life and 5-year survival rate.

China has suffered a high catastrophic health expenditure (CHE). The total out-of-pocket payment expenses accounted for approximately 30% of the total health expenditure, increasing by 120.6% between 2010 and 2019 [33]. The average incidence of CHE in recent decades was 23.3% (95% CI 21.1%-25.6%) [34], whereas it was 60.1% in cancer patients [27,35]. The overall incidence of CHE in EC patients was 69.2%, followed by colon cancer, breast cancer, and liver cancer [27]. Specifically, CHE is closely linked with health insurance, which reached 73.6% and 100% in patients under the new rural cooperative medical scheme and in patients without coverage by health insurance, respectively [27]. Although the predicted annual growth rate of direct medical expenditure due to EC will decline and the proportion of direct medical expenditure among total health expenditure will decrease from 0.47% to 0.36% between 2013 and 2017, the estimated absolute direct medical expenditure will still increase over the next decades [33]. Thus, EC remains a severe economic burden. Moreover, esophageal squamous cell carcinoma (ESCC) is the dominant histological subtype of EC in China, and studies have shown a strong inverse relationship between ESCC and socioeconomic status [2,36,37]. Financial capability largely determines the treatment and health service utilization for cancer patients in China. The current insurance schemes are insufficient to address these disparities [38]. All of these findings imply that more integrated strategies are needed, including improving a household's economic level, expanding the breadth of insurance coverage, reinforcing prepayment hospital insurance methods, and strengthening the public assistance system. Additionally, the scope of national drug centralized volume-based procurement should be expanded, since it has substantial importance in reducing medical costs and the expenditure of medical insurance funds, saving procurement funds, and reducing the patients' burdens due to use of the drug [39,40].

Limitations

Some limitations should be noted when interpreting our results. First, it is difficult to examine the external validation of our model since there are no comparable published data. However, our model has good face and internal validity because it was developed based on the structure of the DisMod II model, which presents the dynamic development of EC very well, and goodness-of-fit analyses showed the internal validity. Second, our model underestimates the total economic burden of EC, since the indirect and hidden costs were not simulated. Third, the input data were estimated based on past data values, which cannot provide accurate evaluations. However, the sensitivity analysis presented the changes caused by the uncertainty of the

inputs. Moreover, the goodness-of-fit analysis showed the good internal validity of the model.

Conclusion

EC still causes serious disease and economic burdens in China, and DALYs and direct medical expenditures will continue to increase over the next decades. Male patients have a higher burden than female patients. YLL account for the majority of DALYs. Comprehensive strategies should be implemented for

the improvement of EC prevention and control, including screening, improving health literacy, improving a household's economic level, expanding the breadth of insurance coverage, reinforcing prepayment hospital insurance methods, strengthening the public assistance system, and expanding the scope of national drug centralized volume-based procurement. In addition, clinical treatment and terminal care should be strengthened to improve quality of life.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Supplementary data (Figures S1-S2, Tables S1-S11).

[DOCX File, 230 KB - [publichealth_v8i3e33191_app1.docx](#)]

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Abbreviations

AAGR: average annual growth rate
AAPC: average annual percentage change
CHE: catastrophic health expenditure
DALY: disability-adjusted life year
EC: esophageal cancer
ESCC: esophageal squamous cell carcinoma
GBD: Global Burden of Disease
YLD: years of life lost due to disability
YLL: years of life lost due to premature mortality

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Corrigenda and Addenda

Correction: Identifying COVID-19 Outbreaks From Contact-Tracing Interview Forms for Public Health Departments: Development of a Natural Language Processing Pipeline

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In “Identifying COVID-19 Outbreaks From Contact-Tracing Interview Forms for Public Health Departments: Development of a Natural Language Processing Pipeline” (*JMIR Public Health Surveill* 2022;8(3):e36119), the authors noted a few errors.

In the originally published paper, the following two sentences appeared under the “Results” section:

Of the 46,798 confirmed and probable cases, only 1588 (3.39%) were probable cases and the remainder were confirmed cases of COVID-19. In Dane County, non-Hispanic Whites accounted for 30,358 (64.87%) of the confirmed and probable cases, and the median age was 30 years (IQR 20-47).

These sentences have been corrected to:

Of the 46,902 confirmed and probable cases, only 1595 (3.40%) were probable cases and the remainder were confirmed cases of COVID-19. In Dane County, non-Hispanic Whites accounted for 30,423 (64.87%) of the confirmed and probable cases, and the median age was 30 years (IQR 20-47).

In the corrected version of the paper, [Table 2](#) has been updated and can be viewed below. The originally published [Table 2](#) is in [Multimedia Appendix 1](#).

Table 2. Characteristics of COVID-19 cases and noncases in Dane County, Wisconsin, between July 1, 2020, and June 30, 2021.

Individual characteristics	Negative cases (N=323,424)	Probable/confirmed cases (N=46,902)	Total (N=370,326)
Age (years), median (IQR)	32 (20-51)	30 (20-47)	31 (20-51)
Sex, n (%)			
Male	152,852 (47.26)	23,506 (50.12)	176,358 (47.62)
Female	165,482 (51.17)	23,314 (49.71)	188,796 (50.98)
Unknown	5090 (1.57)	82 (0.17)	5172 (1.40)
Race/ethnicity, n (%)			
Non-Hispanic White	199,629 (61.72)	30,423 (64.87)	230,052 (62.12)
Non-Hispanic Black	14,302 (4.42)	3266 (6.96)	17,568 (4.74)
Hispanic	23,878 (7.38)	6662 (14.20)	30,540 (8.25)
Other	85,615 (26.47)	6551 (13.97)	92,166 (24.89)
Occupation, n (%)^a			
Not recorded	311,809 (96.41)	37,083 (79.06)	348,892 (94.21)
Nonuniversity student	3099 (0.96)	2391 (5.10)	5490 (1.48)
University student	1161 (0.36)	903 (1.93)	2064 (0.56)
Retired	573 (0.18)	468 (1.00)	1041 (0.28)
Unemployed	502 (0.16)	429 (0.91)	931 (0.25)
Other	6280 (1.94)	5628 (12.00)	11,908 (3.22)
City, n (%)			
Madison	159,983 (49.47)	23,949 (51.06)	183,932 (49.67)
Sun Prairie	22,667 (7.01)	3722 (7.94)	26,389 (7.13)
Fitchburg	16,104 (4.98)	2983 (6.36)	19,087 (5.15)
Middleton	15,991 (4.94)	1838 (3.92)	17,829 (4.81)
Verona	15,224 (4.71)	1745 (3.72)	16,969 (4.58)
Other	93,455 (28.90)	12,665 (27.00)	106,120 (28.66)

^aMultiple responses were possible.

The correction will appear in the online version of the paper on the JMIR Publications website on March 24, 2022, together with the publication of this correction notice. Because this was

made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Multimedia Appendix 1

Originally published Table 2.

[[DOCX File, 15 KB - publichealth_v8i3e37893_app1.docx](#)]

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Original Paper

Tracking Demographic Movements and Immunization Status to Improve Children's Access to Immunization: Field-Based Randomized Controlled Trial

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Abstract

Background: Countries' Expanded Program on Immunization (EPI) contribute to the reduction of mortality and morbidity, but access to these vaccines remains limited in most low-income countries.

Objective: We aim to assess whether involving community volunteers (CVs) to track children's vaccination status and demographic movements and using recorded data to plan catch-up immunization sessions can improve children's vaccination timeliness, completeness, and coverage.

Methods: This was a field-based randomized controlled trial and communities of the Fouban health district in West Cameroon were allocated to intervention or control groups. In the intervention group, a CV per community was trained to visit households monthly for a year to assess and record in a register, details of EPI-targeted children, their demographic movements and immunization status. The scanned recorded pages were sent to the health center immunization team through WhatsApp and used to organize monthly community catch-up immunization sessions. In the control group, EPI vaccination sessions were routinely conducted. Surveys were conducted at 6 and 12 months from the beginning of the intervention in both study groups to assess and compare immunization timeliness, coverage, and completeness.

Results: Overall, 30 buildings per cluster were surveyed at midline and endline. Of the 633 and 729 visited households in the intervention group at midline and endline, 630 (99.5%) and 718 (98.4%), respectively, consented to participate. In the control group, 507 and 651 households were visited and 505 (99.6%) and 636 (97.7%), respectively, consented to participate. At 12 months intervention, the month one timeliness of bacille Calmette–Guerin (BCG) vaccine did not increase in the intervention group compared with the control group for the age groups 0-11 months (adjusted odds ratio [aOR] 1.1, 95% CI 0.7-1.8) and 0-59 months (aOR 1.1, 95% CI 0.9-1.4), and significantly increased for the first-year BCG vaccine administration for the age group 0-23 months (aOR 1.5, 95% CI 1.1-2.2). The coverage of diphtheria-pertussis-tetanus and hepatitis B+Hemophilus influenzae type B (DPT-Hi +Hb) dose 3 (aOR 2.0, 95% CI 1.5-2.7) and of DPT-Hi+Hb dose 1 (aOR 1.8, 95% CI 1.4-2.4) vaccines increased significantly in the intervention group compared with the control group in the age groups 12-59 months and 12-23 months,

respectively. Specific (DPT-Hi+Hb dose 1 to DPT-Hi+Hb dose 3: aOR 1.9, 95% CI 1.4-2.6) and general (BCG to measles: aOR 1.5, 95% CI 1.1-2.1) vaccine completeness increased significantly in the intervention group compared with the control group.

Conclusions: Findings support that involving CVs to track children's vaccination status and demographic movements and using recorded data to plan catch-up immunization sessions improve children's vaccination timeliness, completeness, and coverage. This strategy should be adopted to improve access to vaccination for EPI target populations and the consistency verified in other contexts.

Trial Registration: Pan African Clinical Trials Registry PACTR201808527428720; <https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3548>

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KEYWORDS

immunization status; coverage; completeness; timeliness; EPI vaccines; children under five; Fouban; Cameroon; mobile phone

Introduction

Background

The Expanded Program on Immunization (EPI) has successfully contributed to reducing infant morbidity and mortality worldwide. In many contexts, the EPI's performance in terms of coverage, completeness, and timeliness remains low and associated with outbreaks of vaccine-preventable diseases [1-3]. In Cameroon, 11 vaccines are planned to be administered to children aged 0-11 months under the EPI [4]. These vaccines are routinely offered at health facilities on a scheduled day on a weekly basis or on a monthly basis in communities with limited geographic access to the vaccination health facilities. Because of limited resources at health facilities (human, financial, vaccine supply and cold chain infrastructure, transportation, and power supply) on the one hand and false perceptions of vaccination, poor information and knowledge of caregivers, and demographic movements of the population on the other hand, many children fail to receive their planned vaccine doses or be vaccinated on time or complete their vaccination schedule as required by the national EPI [1,5].

The 2018 Demographic Health Survey conducted at the household level reported 86.7%, 71.5%, and 65.3% vaccination coverage for bacille Calmette-Guerin (BCG), diphtheria-pertussis-tetanus and hepatitis B+Hemophilus influenzae type B3 (DPT-Hi+HB3), and first-dose measles-rubella vaccines, respectively, among children aged 12-23 months, with a zero-dose proportion of 9.7% [6]. These performances are far below the objectives of the EPI in Cameroon [7]. Many other studies and reports have highlighted heterogeneous immunization coverage rates in Cameroon and a high dropout rate in children's vaccination cascade. Low vaccination coverage as well as poor timeliness and completeness rates have been reported to be associated with a high incidence of EPI vaccine-preventable diseases [8,9]. Poor maternal socioeconomic status, failing to remember the vaccination schedule, limited access to health care services, below par population health care-seeking behaviors, false perceptions of vaccination, misestimating the targeted population, migrations, and demographic movements are the most cited factors contributing to the low immunization coverage and incomplete vaccination schedule among children [10].

Strategies have been tested in many countries to reduce missed opportunities of vaccination and improve access to vaccines. The strategies frequently reported to have shown some positive impact include providing information on immunization to parents and community members, distributing memory cards specifically designed to help remember immunization schedules, offering vaccines through proximity vaccination sessions with or without incentives, identifying unvaccinated children during home visits and referrals to health facilities, and integration of immunization services within other services [11,12].

Rationale

During previous EPI supervision activities, we observed that many children and pregnant women miss out on vaccinations during scheduled periods because of short- or long-term travel. In the national immunization guidelines, no procedure has been planned to catch up and reduce the time gaps between the recommended vaccination dates and the dates of vaccine administration. In approximately one-third of the 191 currently functional health districts, most deliveries occur in communities and newborns are not brought into contact with health facilities and thus not considered when planning outreach vaccination sessions. Similarly, periodic trips of caregivers with children as well as immigrants and emigrants are not taken into account when planning or monitoring health facility or outreach immunization sessions. Nomads move constantly from one village to another and are not targeted by immunization sessions. In some cases, nomads' children receive several doses of the same vaccine at any time on their travels, but none is recorded. This often leads to delaying vaccinating or not vaccinating approximately 30% to 70% of the EPI target population depending on the health district. We assume that a periodic and systematic tracking of children who missed either the timing or ≥ 1 doses of immunization because of the demographic movement of the parents or limited geographic access to immunization sites and organizing adequate catch-up immunization sessions could significantly improve these children's immunization coverage, timeliness, and completeness. The aim of this project is to test whether using community volunteers (CVs) to record vaccination status and demographic movements of children at the household level and using the recorded data to plan immunization sessions and catch-up sessions for children missing out on vaccination can improve EPI vaccination timeliness, completeness, and coverage.

Methods

Trial Ethical Approval and Registration

The protocol was evaluated and approved by the Cameroon National Ethics Committee for Human Health Research (2018/07/1058/CE/CNERSH/SP), authorized by the Cameroon Ministry of Public Health (631-19-18), and registered with the Pan African Clinical Trials Registry (PACTR201808527428720) on August 22, 2020. Before participation in this study, all heads of households were informed about the survey, and their consent was required before any data were collected in the household. Any data that could reveal the identity of participants were coded and access limited to study members.

Trial Design

This was a cluster randomized controlled trial in which communities of the targeted health district were randomly assigned to either the intervention group or the control group. In the intervention group, CVs were trained to visit households monthly to record children's immunization status and demographic movements in a community register. The recorded pages of the register were scanned and sent to the health facility in charge of vaccination for the planning of outreach vaccination

sessions in the communities in need. For the control group, EPI vaccination was organized as per routine, meaning on a weekly basis at health facilities or on a monthly basis for outreach activities in communities with limited access to vaccination sites. Community-based surveys were conducted among the intervention and control groups 6 and 12 months after the beginning of the intervention to assess and compare vaccination coverage, timeliness, and completeness rates.

Study Site and Period

The field phase of this study was conducted from mid-2018 to the third quarter of 2019 in the Fouban health district, West Region, Cameroon. This district is inhabited by seminomadic people who move periodically each year with part of, or all, their household and cattle in search of pasture or for farming activities. From weekly reports of the Epidemiological Surveillance Unit of the Department for the Control of Disease, Epidemics, and Pandemics, Cameroon Ministry of Public Health, it was found that Fouban is one of the health districts that has been affected by at least one outbreak of an EPI vaccine-preventable disease during each of the 5 previous years. Figures 1, 2, and 3 present the clusters involved in the baseline, midline, and endline surveys, respectively.

Figure 1. Map of the Fouban health district: clusters involved in the baseline survey.

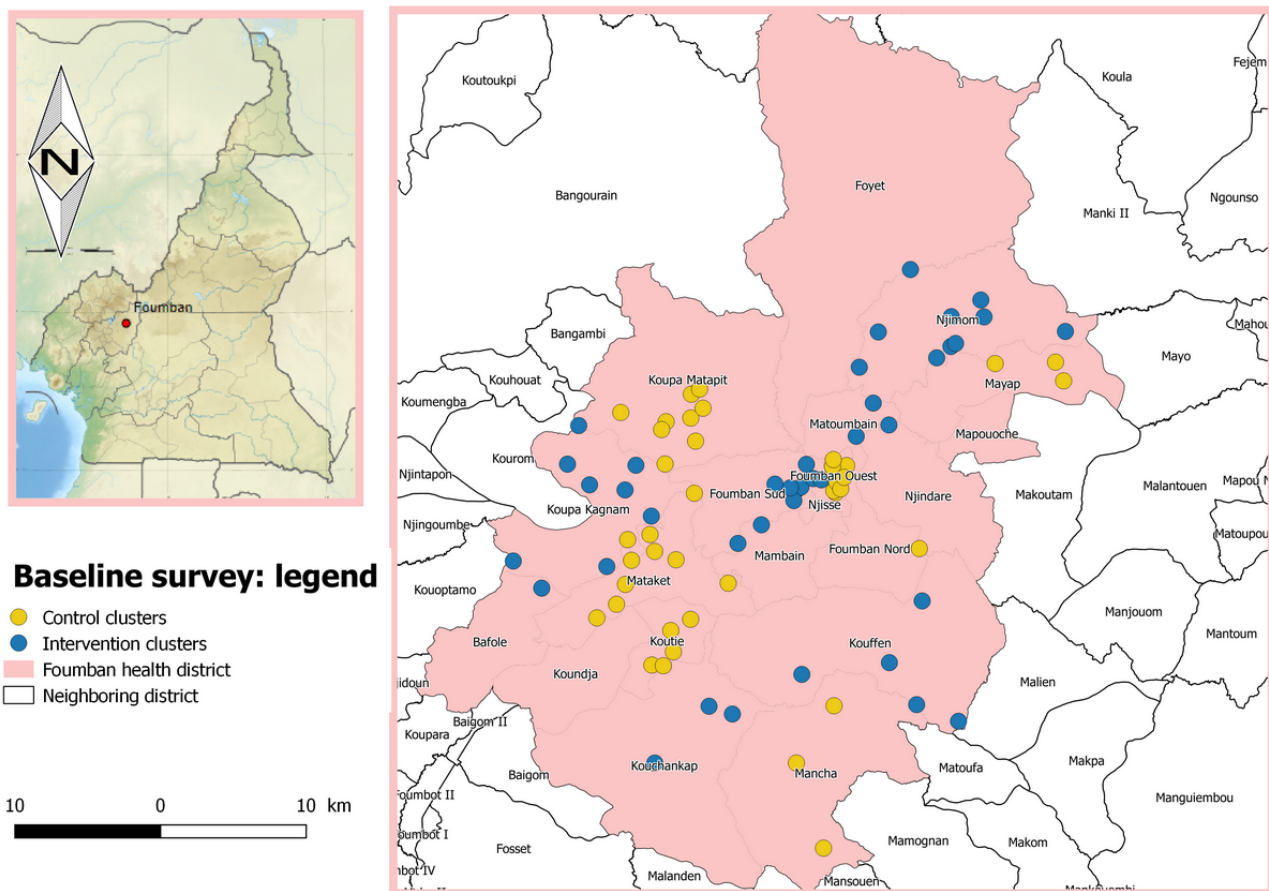


Figure 2. Map of the Fouban health district: clusters of the midline survey.

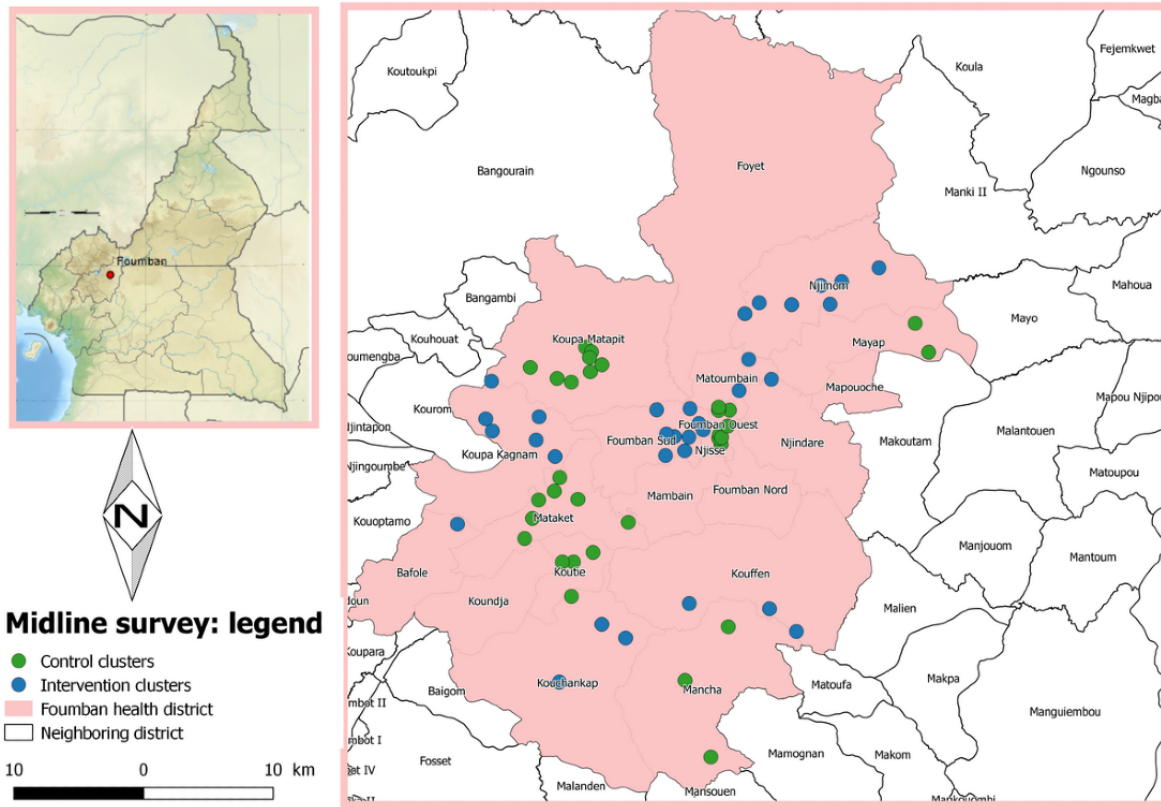
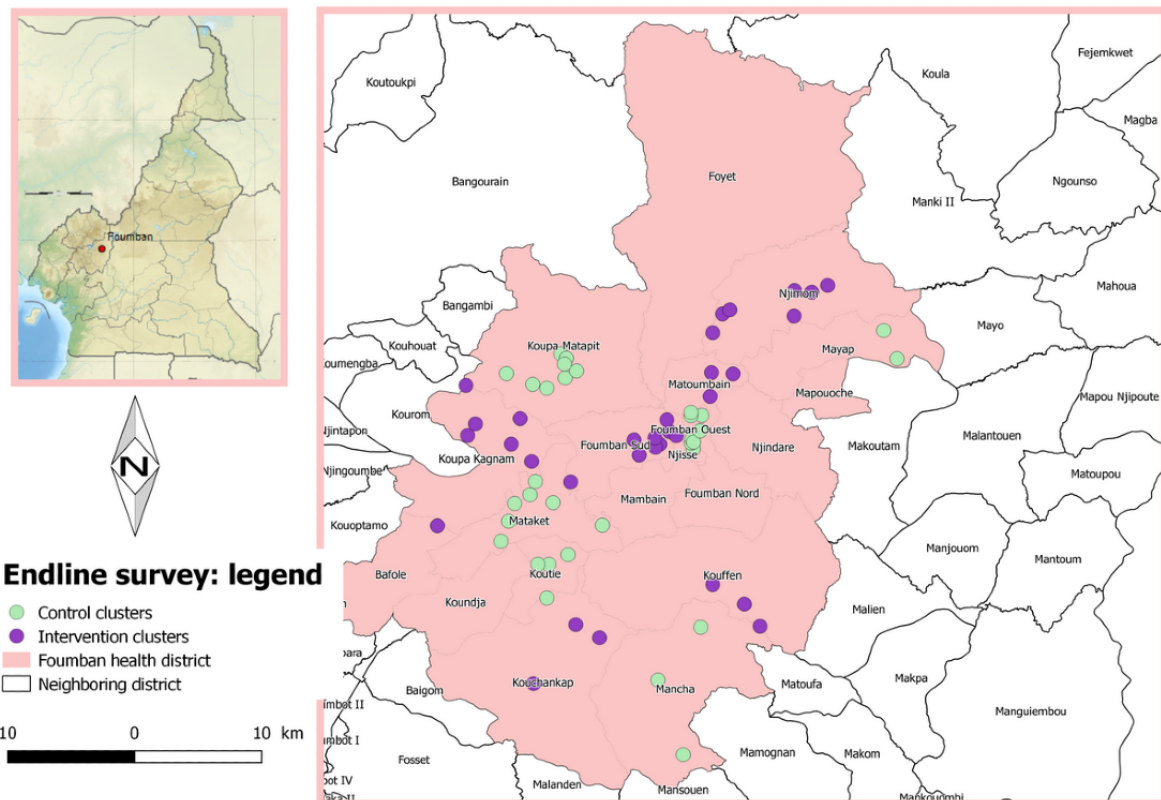


Figure 3. Map of the Fouban health district: clusters involved in the endline survey.



Sampling and Randomization of Clusters

In this study, we considered a *community* to be the smallest geographic area (quarter) with a traditional leader (commonly called head of quarter) gathering 100-300 households in rural areas or 200-500 households in urban areas. The list of communities was obtained from the heads of health areas. Communities with limited access to a vaccination health facility and either having a poor vaccination performance (administrative DPT-Hi+HB3 vaccination coverage 70% in the routine EPI target population) or having recorded a confirmed case of an EPI vaccine-preventable disease in the previous year (2017) were included. Communities with limited seasonal accessibility limiting the monitoring of the intervention during some period of the implementation of the intervention were excluded.

Selected communities were stratified according to their setting (urban or rural), the importance of yearly population movements, the distance to the vaccination health facility, and the occurrence of EPI vaccine-preventable diseases in the previous year. In each stratum, communities were ranked in alphabetic order from A to Z and in blocks of 2. All combinations of blocks were listed and a single-digit number assigned to each combination. Numbers were generated from Table XXXIII of Yates and Fisher [13] as follows: an arbitrary point was chosen in the table and numbers read in a single-digit row by row across the page. Each number read and corresponding to a pair of communities dictated the distribution of these communities by study group. Each community was divided into subunits of up to 200 buildings called clusters using the Google Maps app installed on a smartphone. From previous experience, this is the number of buildings that can be visited in a week by a CV to implement planned activities. One of these clusters per village was randomly chosen per community and targeted to receive the study intervention.

Participants

All children aged 0-59 months living in households of the selected clusters were eligible. This included the age group targeted by the Cameroon national EPI for routine immunization (0-11 months) and the catch-up vaccination group program (12-59 months) [4]. Children arriving in a household to stay for less than a month were excluded, and those leaving or planning to stay out of the household for more than a month were also excluded. Those leaving the household for less than a month were included. Parents of children leaving the household to stay away for more than a month were followed up on telephone, when possible, to sensitize them to the necessity of completing the child's vaccination program.

Intervention

In each community, a CV was proposed by the head nurse of the competent health center and trained to visit households of the cluster monthly and record in a register all children aged 0-59 months and their demographic movements for the previous and next months and assess their immunization status from the vaccination card or by using a tracking grid if the child did not have a vaccination card. The CVs were from, and inhabitants of, the targeted communities and able to read at least one official

language as well as speak the local language. They were persons usually employed by the health system for community interventions (eg, vaccination campaigns). The recorded information page was scanned each month after the visit of all targeted households of a CV's community and sent through WhatsApp to the immunization team of the competent health center. The information was used by the vaccination team that has received standardized training on reading and using WhatsApp images to plan and implement monthly community immunization sessions. This community vaccination session was conducted with the collaboration of the CVs who choose an accessible vaccination site in the community and inform parents with children needing vaccinations about the session. The activities of vaccination teams and CVs were supervised monthly.

Control

In the control group, immunization sessions were conducted as per routine. This meant the organization of weekly vaccination sessions by the vaccination team at health facilities and, when possible, monthly vaccination sessions in communities lacking geographic access to the vaccination facilities.

Outcomes Assessment

Data to assess effects of the intervention were collected using baseline, midline, and endline surveys. The baseline survey was conducted before the intervention, the midline survey was conducted 6 months after the beginning of the intervention, and the endline survey was conducted at the end of the implementation period. Each survey lasted for a week. The baseline survey also provided data on population characteristics and children's access to EPI vaccination before the intervention. Each cluster was mapped using the *My position* function of the Google Earth smartphone app and divided into subclusters of approximately 30 buildings, assuming that each cluster had at least 20 children aged 0-59 months (as determined from a pretest conducted in the area). One subcluster was randomly selected per cluster and all its households visited for data collection. Data were collected by trained and supervised surveyors using immunization cards, the community immunization register, and questionnaires administered to parents of children. The primary data collected included the immunization status and time regarding the administration of the BCG, polio zero, DPT-Hi+HB1, DPT-Hi+HB2, and DPT-Hi+HB3 vaccines, as well as sociodemographic characteristics. The sampling and implementation processes of the baseline, midline, and endline surveys were similar but independent. The surveys were conducted by independent survey teams different from the team in charge of implementation of the intervention under investigation.

The primary outcome was the documented children's immunization timeliness, defined as the proportion of children aged <5 years with documented BCG vaccine administration in the first month of life.

The secondary outcomes included the following:

- Documented general EPI-vaccine completeness of children aged 12-59 months, defined as the proportion of children who started the vaccination schedule with the BCG vaccine

and completed it by receiving the measles–rubella vaccine, as documented in the immunization card.

- Documented specific immunization completeness of children aged 12-59 months, defined as the proportion of children who received the DPT-Hi+HB1 vaccine and completed pentavalent vaccination doses by receiving the DPT-Hi+HB3 vaccine, as documented in the immunization card.
- Overall children's immunization timeliness, defined as the proportion of children completing all their EPI-recommended vaccines within the first year of life, as documented in the immunization card or not documented but tracked from the caregiver's memory.
- Overall children's immunization completeness, defined as the proportion of children who started the vaccination schedule with the BCG vaccine and completed it by receiving the measles–rubella vaccine, as documented in the immunization card or not documented but tracked from the caregiver's memory.
- Documented children's immunization coverage, defined as the proportion of children who received the DPT-Hi+HB3 vaccine, as documented in the immunization card.
- Overall children's immunization coverage, defined as the proportion of children who received the DPT-Hi+HB3 vaccine, as documented in the immunization card or tracked from the caregiver's memory.
- Documented recruitment rate, defined as the proportion of children starting the vaccination schedule with the BCG vaccine, as documented in the immunization card.
- Overall recruitment rate, defined as the proportion of children starting the vaccination schedule with the BCG vaccine, as documented in the immunization card or tracked from the caregiver's memory.

The effects of the intervention were assessed by comparing completeness, timeliness, and coverage rates estimated from the intervention and control groups.

Sample Size Estimate

Using Stata software (version 16.0 IC; StataCorp LLC), we estimated that the minimum number of children required to test the intervention was 20 children aged <5 years per cluster in at least 23 clusters of the control group and at least 20 clusters in the intervention group. The estimate assumes between-cluster coefficients of variation of 0.38 and 0.19 in the control and intervention groups, respectively (estimated from baseline surveys in clusters assigned to each group), to reach 20 children aged <5 years per cluster in each group, α of .05, and 90% power to detect a 10% 2-sided variation of the BCG vaccination timeliness (defined as the proportion of children aged <5 years with documented BCG vaccine administration in the first month of life). The estimate was guided by the method of estimating cluster randomized controlled trials proposed by Batistatou et al [14]. We adjusted the sample size to 32 clusters of at least 20 children per cluster per study group, assuming that 10% of the targeted children would be unreachable (nonresponse and absence during the survey week) and to ensure sufficient power to prevent cluster variation in the estimated outcomes.

Data Analysis

The effect of the intervention was assessed by estimating per study group, and comparing, the following: (1) yearly immunization timeliness rates for the BCG vaccine (proportion of children aged 0-59 months with evidence of vaccination in the first month of life) and the measles–rubella vaccine (proportion of children aged 12-23 months with evidence of vaccination when aged 9-11 months); (2) the coverage of the BCG vaccine (proportion of children aged 0-59 months who were vaccinated) and the DPT-Hi+HB1, DPT-Hi+HB3, and measles–rubella vaccines (proportion of children aged 12-59 months who were vaccinated); and (3) the specific completeness (proportion of children who completed the DPT-Hi+HB1 and DPT-Hi+HB3 vaccines) and general completeness (proportion of children who completed the BCG and measles–rubella vaccines) when aged 12-59 months. Odds ratios for children being vaccinated, being vaccinated on time, and completing vaccination were estimated and adjusted for the child's place of birth, guardians' level of education, type of population (seminomadic or sedentary), profession, walking time to the vaccination site, and religion and controlled for variability of the child's age using logistic regression random effect. Data were collected using Open Data Kit–designed forms on smartphones, verified in the field, and submitted to a secure server. Data were monitored and cleaned in Microsoft Excel 2013 and analyzed using Stata software (version 16.0 IC).

Survey Procedures

GPS coordinates were collected at the limits of each selected cluster to map the area and retrieve the map on Google Earth. With the help of CVs, each cluster was divided into multiple subclusters of approximately 30 buildings each. One subcluster was randomly selected, and all the inhabited households of the buildings in this subcluster were visited. All heads of households were informed by the survey team about the project, and only households of those consenting were enrolled. In these households, immunization status data of all children aged 0-59 months were collected from the caregiver and from their immunization cards, along with information on any demographic movement in the previous 6 months. Closed households were visited up to 3 times on 3 different days before being classified as closed. The study team arranged appointments with heads of households and the children's guardian if they were busy on the first day of the visit. Heads of households and guardians who could not be met after 3 appointments on 3 different days were considered nonrespondents. Children with caregivers refusing to respond to the questionnaires as well as children normally living in the household but absent during the data collection period were excluded.

The study questionnaires were pretested and developed into electronic forms by the data management team. Skip patterns as well as required and formatted fields were used to ensure data accuracy and completeness. Data were collected by trained surveyor teams with smartphones using the Open Data Kit Collect app. Each team of 3 surveyors was trained on the study procedures and supervised daily for participant sampling, informed consent, and data collection processes. A protected web server was deployed by the data management team to

compile the survey data. During the survey, completed forms were uploaded to the server daily by the supervisor after reviewing and correcting discrepancies. The data management team ensured daily data cleaning; shared reports with field supervisors; and monitored corrections, updates, and backups. These procedures were the same for both study groups for the baseline, midline, and endline surveys.

Ethical Consideration

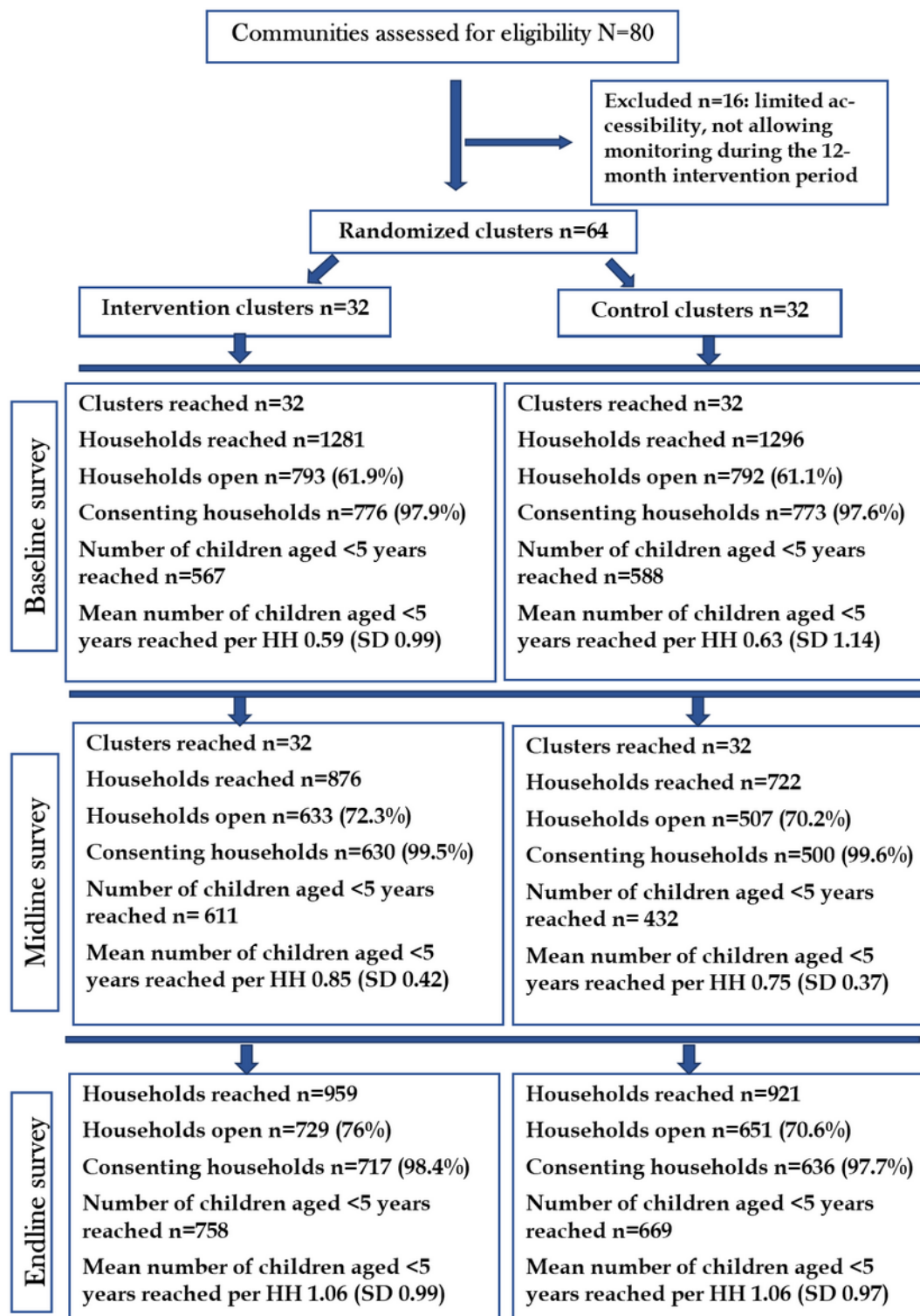
The aim of this study is to test an intervention expected to improve timely access of children to EPI vaccines in areas where children have limited access to vaccination. It involved interacting with communities, heads of households, and caregivers to collect data on children's vaccination status and demographic movements and organizing vaccination catch-up sessions. All local health, administrative, and traditional authorities with jurisdiction over the targeted study areas were visited and informed about the study and their permission obtained before the implementation of this study. All caregivers were fully informed about the study and provided consent for their participation and that of their children before being included in the study. Surveillance of adverse events was conducted routinely by the health facilities in charge. Data collected in registers for the monitoring of children's vaccination status were shared between the CVs and the health facility vaccination team, but data extracted from these registers for the

study purpose were anonymous and stored in a secure database with access limited to members of the study team. The results and recommendations of the study were presented to representatives of targeted communities, CVs, local and ministerial health authorities, and funders.

Results

Participants and Participant Flow

Clusters from 80 communities in Fouban health district were selected and assessed for eligibility. Of the 80 clusters, 16 (20%) were excluded because they were not accessible enough to facilitate the monitoring of activities all through the year and 64 (80%) were included. Of these 64 clusters, 32 (50%) each were randomly assigned to the intervention and control groups. The mean numbers of buildings, households, and children aged 0-5 years per cluster for both study groups were 161.0 (SD 49.9; 95% CI 149.9-172.1), 119.2 (SD 36.9; 95% CI 109.3-129.0), and 89.7 (SD 36.1; 95% CI 81.7-99.2), respectively. [Figure 4](#) shows the CONSORT (Consolidated Standards of Reporting Trials) flowchart presenting the distribution of visited and consenting households and mean number of children aged <5 years in subclusters selected from the clusters assigned to the intervention and control groups during the midline and endline surveys conducted to assess the effects of the intervention.

Figure 4. CONSORT (Consolidated Standards of Reporting Trials) flowchart of the study. HH: household.

Baseline Characteristics of Study Arms

Baseline characteristics of communities with access to a vaccinating health facility, household and children's guardians are presented in [Table 1](#). In each of these communities, clusters

with a mean of 160.1 (SD 52.5; 95% CI 143.3-176.9) buildings were assigned to the intervention group and clusters with a mean of 161.4 (SD 47.7; 95% CI 146.6-177.2) buildings were assigned to the control group.

Table 1. Baseline characteristics of households (HHs) and children's guardians in the control and intervention study groups.

Variable	Control		Intervention		Chi-square (<i>df</i>)	<i>P</i> value
	Total	Value, n (%)	Total	Value, n (%)		
HHs						
HHs with approachable road accessible all year round	1295	1290 (99.6)	1281	1280 (99.9)	1.5 (2)	.22
Walking time from HH to health center <1 hour	1295	817 (63.1)	1281	584 (45.6)	79.5 (2)	<.001
HHs hosting seminomadic populations	1092	584 (18.6)	1012	269 (26.6)	12.2 (2)	<.001
Farming as main source of income in the HH	776	231 (29.8)	773	233 (30.1)	0 (2)	.87
HHs with uncemented floor	776	320 (41.2)	773	297 (38.4)	1.3 (2)	.26
Characteristics of children's guardians						
Woman as child's guardian	588	556 (94.9)	567	531 (93.7)	0.8 (2)	.36
Adolescent as child's guardian ^a	583	46 (7.9)	563	43 (7.6)	0 (2)	.87
Noneducated guardians	588	58 (6.3)	567	100 (17.6)	14.8 (2)	<.001
Muslim guardians	588	503 (85.5)	567	504 (88.9)	2.9 (2)	.09
Unemployed guardians	588	358 (60.9)	567	341 (60.1)	0.1 (2)	.91

^aOf the 1155 respondents, 1146 (99.22%) answered the question about the age of the child's guardian.

Baseline Characteristics of Clusters, Households, and Participants in Both Study Groups

Of the 32 clusters in each study group, 8 (33%) were urban clusters and 24 (67%) were rural clusters. Of the 32 clusters in each study group, the control group had 5 (16%) with mainly seminomadic populations, whereas the intervention group had 3 (9%; Table 1). The difference between the groups was not significant (Fisher exact test=0.708; dof=2).

Baseline Documented Vaccination Coverage per Study Arm

The distribution of baseline vaccination coverage per study arm is presented in Table 2. Vaccination coverage regarding the BCG vaccine, which is the first vaccine administered, the DPT-Hi+HB1-3 vaccines, which are the main indicators of EPI performance, and the measles-rubella vaccine was not different at baseline between the study groups.

Table 2. Baseline documented (with vaccination card) vaccination coverage in the clusters allocated to the control and intervention groups.

Vaccine	Vaccination coverage in clusters				Chi-square (<i>df</i>)	<i>P</i> value
	Control		Intervention			
	Total	Value, n (%)	Total	Value, n (%)		
BCG ^a coverage among children aged 0-59 months	588	169 (28.7)	567	183 (32.3)	2.8 (2)	.25
BCG vaccination within the first months of life among children aged <5 years	588	148 (25.2)	567	158 (27.9)	1.2 (2)	.29
BCG vaccination within the first months of life among children aged 0-11 months	144	60 (41.7)	140	66 (47.1)	0.9 (2)	.35
BCG vaccination within the first 12 months of life among children aged <5 years	588	165 (28)	567	175 (30.9)	1.1 (2)	.29
BCG vaccination within the first 12 months of life among children aged 0-23 months	270	104 (38.5)	254	105 (42.1)	0.7 (2)	.40
Pentavalent 1 coverage among children aged 12-59 months	427	104 (24.4)	444	96 (21.6)	0.9 (2)	.34
Pentavalent 3 coverage among children aged 12-59 months	427	82 (19.2)	444	85 (19.1)	0 (2)	.98
Pentavalent 3 coverage among children aged 12-23 months	114	27 (23.7)	126	31 (24.6)	0 (2)	.87
MR ^b coverage among children aged 12-59 months	427	68 (15.9)	444	58 (13.1)	1.4 (2)	.23
MR vaccination within the first 9-11 months of life among children aged 12-59 months	427	55 (12.9)	444	49 (11)	0.7 (2)	.40
Specific completeness (DPT-Hi+HB1-3 ^c)	427	80 (18.7)	444	85 (19.1)	0(2)	.88
General completeness (BCG-MR)	427	58 (10.7)	444	58 (13.1)	1.4 (2)	.23

^aBCG: bacille Calmette–Guerin.

^bMR: measles–rubella.

^cDPT-Hi+HB: diphtheria-pertussis-tetanus and hepatitis B+Hemophilus influenzae type B.

Flow per Study Arm of Some Characteristics During the Study Period

The distribution per study arm of the characteristics presented in [Table 3](#) did not differ at baseline, but there were statistical differences regarding some attributes such as the mean number

of households visited at least once by a CV during the previous 6 months, mean number of births in the previous 6 months at midline, proportion of open households, mean age of children, number of households visited at least once by a CV during the previous 6 months, and availability of the vaccination card among children aged <5 years at the endline.

Table 3. Evolution of some study arm characteristics from baseline to midline and endline surveys.

Characteristics	Baseline survey					Midline survey					Endline survey				
	Intervention	Control	Chi-square (df)	t test (df)	P value	Intervention	Control	Chi-square (df)	t test (df)	P value	Intervention	Control	Chi-square (df)	t test (df)	P value
Proportion of open HHs ^a , n/N (%)	793/1281 (61.9)	792/1296 (61.1)	0.2 (2)	— ^b	.69	633/876 (72.3)	507/722 (70.2)	0.8 (2)	—	.37	729/959 (76)	651/921 (70.6)	6.8 (2)	—	<.001
Proportion of open HHs consenting to participate, n/N (%)	776/793 (97.9)	773/792 (97.6)	0.5 (2)	—	.50	630/633 (99.5)	500/507 (99.6)	2.7 (2)	—	.10	717/729 (98.4)	636/651 (97.7)	0.8 (2)	—	.38
Number of children aged <5 years reached per HH, mean (SD)	0.59 (0.99)	0.63 (1.14)	—	0.93 (2)	.35	0.85 (0.42)	0.75 (0.37)	—	1.67 (2)	.09	1.060 (0.99)	1.057 (0.97)	—	0.054 (2)	.96
Age of children aged <5 years (in months), mean (SD)	26.01 (16.76)	26.16 (16.26)	—	0.18 (2)	.86	24.51 (16.7)	25.55 (16.08)	—	1.003 (2)	.31	27.33 (20.12)	30.0 (20.62)	—	2.48 (2)	.01
Proportion of girls among children, n/N (%)	283/567 (49.9)	307/588 (52.2)	0.3 (2)	—	.60	287/611 (47)	225/432 (52.1)	2.6 (2)	—	.10	371/758 (48.9)	342/669 (51.1)	—	0.312 (2)	.74
Number of HHs visited at least once by a CV ^c during the previous 6 months, mean (SD)	0.11 (0.48)	0.09 (0.44)	—	0.46 (2)	.65	5.96 (3.64)	2.57 (2.05)	—	18.57 (2)	<.001	5.30 (4.54)	1.77 (1.87)	—	18.19 (2)	<.001
Number of births in the previous 6 months, mean (SD)	0.071 (0.32)	0.074 (0.28)	—	0.19 (2)	.84	0.14 (0.37)	0.10 (0.33)	—	1.965 (2)	.05	0.17 (0.40)	0.165 (0.41)	—	0.275 (2)	.78
Number of deaths among children aged <5 years in the previous 6 months, mean (SD)	0.008 (0.10)	0.009 (0.09)	—	0.22 (2)	.82	0.014 (0.13)	0.006 (0.08)	—	1.245 (2)	.21	0.025 (0.19)	0.026 (0.18)	—	0.170 (2)	.87

Characteristics	Baseline survey					Midline survey					Endline survey				
	Intervention	Control	Chi-square (df)	t test (df)	P value	Intervention	Control	Chi-square (df)	t test (df)	P value	Intervention	Control	Chi-square (df)	t test (df)	P value
Number of children aged <5 years who left the HH for at least a month during the previous 6 months, mean (SD)	0.061 (50.35)	0.057 (0.32)	—	0.34 (2)	.83	0.16 (0.71)	0.18 (0.70)	—	0.441 (2)	.65	0.154 (0.59)	0.202 (0.63)	—	1.414 (2)	.16
Number of children aged <5 years who arrived in the HH in the previous 6 months to stay for at least a month, mean (SD)	0.10 (0.48)	0.11 (0.51)	—	0.61 (2)	.54	0.114 (0.19)	0.0701 (0.38)	—	1.65 (2)	.09	0.093 (0.61)	0.091 (0.37)	—	0.082 (2)	.93
Availability of vaccination card among children aged <5 years, n/N (%)	187/567 (33)	173/588 (29.4)	1.8 (2)	—	.18	293/611 (48)	180/432 (41.7)	4.0 (2)	—	.05	643/758 (84.8)	502/669 (75)	—	21.5 (2)	<.001

^aHH: household.

^bNot available.

^cCV: community volunteer.

Estimated Outcomes of the Intervention for the Evaluation Periods

At midline, the timeliness (proportion of children with BCG vaccination in the first month of life) did not vary, whereas DPT-Hi+HB1 and measles–rubella vaccination coverage in the age group 12-59 months increased significantly in the intervention group compared with the control group. Specific and general vaccine completeness were not different between

the control and intervention groups. At endline, the timeliness (proportion of children with BCG vaccination in the first month of life) did not vary, whereas the coverage of all vaccines, apart from the BCG vaccine, in the age group 0-59 months increased significantly as did the specific and general vaccine completeness in the intervention group compared with the control group. [Table 4](#) presents the coverage of vaccines with respect to age groups at midline and endline.

Table 4. Outcomes of the intervention at midline and endline.

Vaccine dose	Age group (in months)	Outcomes of midline survey						Outcomes of endline survey					
		Coverage: intervention group		Coverage: control group		aOR ^a (95% CI)	P value	Coverage: intervention group		Coverage: control group		aOR (95% CI)	P value
		Total	Value, n (%)	Total	Value, n (%)			Total	Value, n (%)	Total	Value, n (%)		
D ^b : BCG ^c coverage	0-59	611	382 (62.5)	432	256 (59.3)	0.9 (0.7-1.2)	.34	758	303 (40)	669	231 (34.5)	1.3 (1.0-1.7)	.08
D: BCG vaccination in the first month of life	0-59	611	186 (30.4)	432	153 (35.4)	0.8 (0.5-1.3)	.34	758	264 (34.8)	669	215 (32.1)	1.1 (0.9-1.4)	.50
D: BCG vaccination in the first month of life	0-11	167	73 (43.7)	105	64 (61)	0.9 (0.5-1.9)	.84	219	105 (48)	169	78 (46.1)	1.1 (0.7-1.8)	.69
D: BCG vaccination in the first year of life	0-23	252	107 (42.1)	270	104 (38.5)	1.6 (0.7-3.4)	.51	352	200 (56.8)	276	135 (48.9)	1.5 (1.1-2.2)	.02
D: DPT-Hi+HB1 ^d coverage	12-59	444	176 (39.7)	327	103 (31.5)	1.5 (1.0-2.0)	.02	539	230 (42.7)	500	143 (28.6)	1.8 (1.4-2.4)	<.001
D: DPT-Hi+HB3 coverage	12-59	444	149 (33.6)	327	92 (28.1)	1.3 (1.0-1.8)	.10	539	205 (38)	500	117 (23.4)	2.0 (1.5-2.7)	<.001
D: DPT-Hi+HB3 coverage	12-23	134	57 (42.5)	99	42 (42.3)	1.1 (0.8-1.5)	.64	133	73 (54.9)	107	44 (41.1)	1.7 (1.0-3.0)	.04
D: Measles-rubella coverage	12-59	444	143 (32.2)	327	74 (22.6)	1.7 (1.2-2.2)	.02	539	214 (39.7)	500	100 (20)	2.6 (1.9-3.5)	<.001
D: Measles-rubella coverage	12-23	134	49 (36.6)	99	31 (31.3)	1.3 (0.7-2.3)	.37	133	73 (54.9)	107	37 (34.6)	2.3 (1.3-3.9)	.003
Specific completeness	12-59	444	143 (32.2)	327	89 (27.2)	1.3 (0.9-1.8)	.11	539	196 (36.4)	500	114 (22.8)	1.9 (1.4-2.6)	<.001
General completeness	12-59	444	106 (23.9)	327	73 (22.3)	1.3 (0.8-1.5)	.49	539	145 (26.9)	500	96 (19.2)	1.5 (1.1-2.1)	<.001

^aaOR: adjusted odds ratio.

^bD: documented.

^cBCG: bacille Calmette-Guerin.

^dDPT-Hi+HB: diphtheria-pertussis-tetanus and hepatitis B+Hemophilus influenzae type B.

Discussion

Principal Findings

This study assessed the effect of monthly household visits and tracking of vaccination status and demographic movements of children aged <5 years for the planning of community-based catch-up immunization sessions on immunization coverage, timeliness, and completeness. To the best of our knowledge, this is an innovative approach that has not yet been tested. One year after the implementation of the intervention, the timeliness

of BCG vaccine administration in the first month of life increased in the intervention group compared with the control group for the age groups 0-11 months and 0-59 months, but the increase was not significant, whereas the increase was significant for the first-year BCG vaccine administration for the age group 0-23 months. The BCG vaccine immunization coverage for the age group 0-59 months increased in the intervention group but not significantly compared with the control group, whereas the increase was significant for the DPT-Hi+HB3 and measles-rubella vaccines for the age groups 12-59 months and 12-23 months. Specific (DPT-Hi+HB1 and DPT-Hi+HB3) and

general (BCG–measles–rubella) vaccine completeness increased significantly in the intervention group compared with the control group.

The immunization schedule of the EPI vaccines in a given country is based on local epidemiology and maturity of children's immune systems [15,16]. In Cameroon, the EPI vaccination calendar is drawn from the document of EPI norms and standard operating procedures [4]. Despite the fact that this calendar is posted at almost all health facilities in the country, very few children receive the EPI vaccines during the recommended period [1]. From the baseline status in which there was no difference in the BCG vaccination timeliness in the intervention group compared with the control group, the BCG vaccine administration in the first year of life improved significantly in the intervention group compared with the control group 1 year after the implementation of the tested intervention. In contrast, the rate for the BCG vaccine administration in the first month of life increased in the intervention group compared with the control group, although the increase was not statistically significant, in the age groups 0–11 months and 0–59 months. The effect of the intervention evaluated in this study has not been evaluated in a previous study to the best of our knowledge. Interventions such as reminders were tested in other settings and were found to not significantly increase the coverage and timeliness of some EPI vaccines [17,18]. The fact that the intervention did not significantly improve the timeliness of BCG vaccine administration at 1 month for the age group 0–59 months was probably because of some reasons such as the following: a large proportion of the evaluated age group had passed the age of eligibility to receive the BCG vaccine given that the Cameroon EPI does not allow catch-up doses of BCG vaccines for children aged ≥ 1 year [4]. In addition, frequent BCG vaccine stockouts were recorded by vaccination teams, health facilities, and the health district resulting from problems in the supply system and vaccine wastage. To prevent vaccination wastage, most vaccination teams had decided not to open the BCG vial when fewer than 15 children in need were present at a vaccination session. Several appointments were given to reach the minimum number of children before opening the BCG vial, and this delayed the vaccination schedule. Other reasons could have explained the low timeliness rate in the control and intervention groups, but the fact that characteristics were randomized in the 2 study groups could reduce the effect of some of these determinants [19]. Contamination of the control area by the intervention was noted and probably contributed to reducing the difference in the effect of the intervention on vaccine timeliness, and this is supported by the increasing number of visits by CVs to households in the control group from the baseline to midline and endline surveys. The fact that the first-year BCG vaccination coverage in the age group 0–23 months (those who spent part of their first year of life in the project intervention period) was significantly higher in the intervention group than in the control group supports that despite multiple appointments caused by the fear of high vaccine wastage and other obstacles, the intervention was associated with a longer time to induce a significant increase of vaccine timeliness in the intervention group compared with the control group. The effect of the intervention can be considered the only explanation for the higher BCG vaccine coverage in the first

year of life in the intervention group as expected, and the identified confounders were used for adjustment when computing the analysis comparing the first-year BCG vaccine timeliness rates in both study groups. These results indicate that even with multiple appointments given by vaccination teams to reduce BCG vaccine wastage and with other barriers preventing a proportion of children from being vaccinated in time, new strategies are needed to significantly improve children's access to the BCG vaccination in their first month of life; for example, a study could examine whether reducing the number of vaccine doses per BCG vial may be more effective in reducing vaccine wastage, as well as reducing the number of appointments that need to be made, which delays childhood immunization. Another study could examine the contribution of synchronization of BCG vaccination sessions by different vaccination teams in a given district and the mutualization of BCG vials to reduce vaccine wastage and delays. Given that the intervention significantly improved children's access to BCG vaccination before the end of their first year of life, we believe that it can be recommended in similar contexts as this study and evaluated in other contexts with the hope of using it to improve children's timely access to BCG vaccination in other contexts in need.

Vaccination coverage determines herd immunity for each targeted disease. The initial situation that existed before the intervention tested in this study could be described as one of low vaccination coverage among children for most EPI vaccines offered [1,6]. The results of the midline and endline surveys conducted 6 months and 12 months, respectively, after the beginning of the intervention show progress, with a significant increase in vaccination coverage in the intervention group for the DPT-Hi+HB3 and measles–rubella vaccines for the age groups 12–23 months and 12–59 months. The fact that there was no significant difference regarding BCG and measles–rubella vaccination coverage between the 2 groups before the intervention, that the assigning of clusters to the intervention and control groups was randomized, and that confounders were adjusted for when comparing vaccination coverage in both study groups support that the intervention contributed to the higher DPT-Hi+HB3 and measles–rubella vaccination coverage in the intervention group. Several studies have pointed out parental and guardian forgetfulness, ignorance, refusal of vaccination, limited geographic access of children to vaccination health facilities, and lack of updated data on vaccine targets because of population movements as factors that limit children's access to vaccination and contribute to low EPI-vaccine coverage in children [20–22]. The intervention tested in this study proposes periodic household visits to track the immunization status of children and their demographic movements, the organization of community-based immunization catch-up sessions to vaccinate those who need to be vaccinated, and communication with parents and caregivers to convince them to bring these children to the organized vaccination sessions. The intervention thus makes it possible to determine the number of EPI-targeted children living in each community each month, identify those needing each of the EPI vaccinations, use this information to communicate with parents and vaccination teams, and organize immunization sessions at locations and on dates chosen by the community and thus more accessible to the children's guardians.

This is expected to increase immunization coverage, given that it helps to anticipate the main determinants limiting children's access to EPI vaccines. A given number of interventions targeting health care providers, caregivers, parents or guardians, and communities and testing several strategies such as reaching out (by SMS text messages or telephone calls), home visits, and training have shown varying degrees of effectiveness in improving immunization coverage [12,23,24]. The particularity of the intervention tested in this study is that it combines several approaches tested in previous studies and innovates by involving CVs in the assessment of immunization status and using 2 immunization coverage–monitoring registers, one of which is used by the community to update children's immunization status, with the updated pages scanned and sent using WhatsApp to the health facility to update the health facility–based register for planning of immunization sessions. The intervention also involves collaboration among households, CVs, and vaccination teams to organize catch-up vaccination sessions. These innovations help to promote the sustainability of our intervention because it is locally organized at a lower cost, it is accepted by the different actors involved in vaccination campaigns, and is therefore expected to be easily scalable across contexts. We recommend that this intervention should be considered an alternative strategy for health systems that plan to address the issue of low EPI vaccination coverage.

The EPI aims to give each cohort of children a package of a certain number of doses of vaccines in their childhood. This package enables each of these cohorts to be protected against vaccine-preventable childhood infectious diseases. A number of studies indicate that vaccine completeness remains quite insufficient for several cohorts of children born in Africa, including in Cameroon [1,5]. As noted with regard to the timeliness and coverage of some key vaccines probably attributable to the intervention tested in this study, the specific (DPT-Hi+HB1 and DPT-Hi+HB3) and general (BCG–measles–rubella) vaccine completeness increased significantly in the intervention group of this study. In addition to the reasons presented in the previous paragraph supporting children's access to vaccination, the intervention contributed to improving the timeliness because it included repeated household visits to monitor the progress of children's vaccination status and ensured that they received all doses of the recommended vaccines. This adds to the already discussed benefit of this intervention, which is its ability to act as a tool to monitor single and subsequent vaccine doses recommended by the EPI.

Limitations

Some limitations were associated with the methodology and implementation of this project. The availability of some vaccines was not assured throughout the project period. This was beyond the control of the study team because supplying vaccines for a routine EPI initiative is the responsibility of the health system and thus was not part of the intervention. The unavailability of vaccines was very heterogeneous in terms of duration, geographic area, and reason but was more frequent and more extensive in terms of duration and geographic area for the BCG vaccine. The reason was the high wastage rate resulting from the high number of doses in the vial compared with the number

of children expected to be vaccinated and the obligation to apply the open vial policy. The fact that this was the case for both the intervention and control groups likely contributed to reducing the magnitude of difference in the outcomes between the 2 study groups.

A number of constraints overlapped with the implementation of the project and could contribute to reducing the difference in effect between the intervention group and the control group. Because of the lack of human resources, the health workers in charge of vaccination were unable to attend a certain number of vaccination sessions planned as part of the intervention in the community. The absence of cold chain infrastructure at some health facilities and the periodic unavailability of electricity due to interruptions in electricity supply contributed to reducing the access of the targeted population to the intervention. In addition, the study area has benefited from half-a-dozen campaigns offering a number of interventions to the community and using the vaccination teams and CVs involved in this project, thus contributing to reducing the promptness and coverage of the activities planned in the evaluated intervention through work overlap. Furthermore, the movement of children with their parents or caregivers for agricultural and animal husbandry activities probably contributed to reducing the access of the targeted population to the intervention. Contamination of the control area by the intervention was noted. Both zones (where the study clusters are located) are in charge of routine EPI initiatives, and the heads of the health centers in these zones meet monthly to present and discuss their vaccine performances. During the evaluation surveys, we noted an increase in household visits by volunteers in the control group to implement the project intervention. The evaluation of the effect of the intervention focused on the documented immunization status of children in the households. A child's immunization record is the best source of data to certify the child's immunization status, but the retention of immunization records by caregivers was not certain and could contribute to underestimating immunization coverage in the intervention and control groups.

These limitations on vaccine availability, cold chains, human resources, contamination, and nonretention of immunization records are part of the context in which the intervention was tested. The fact that the effect of the intervention remains significant for several outcomes in the intervention group suggests that the intervention may improve vaccine timeliness, coverage, and completeness despite these constraints. These results also mean that by ensuring the minimum availability of human resources, cold chain infrastructure, and vaccines, a greater benefit from the intervention can be expected.

Conclusions

We can conclude from this study that training CVs and organizing and supervising them to ensure monthly household visits to assess the immunization status of children and communicate it to vaccination teams to organize catch-up vaccination sessions increases the timeliness, coverage, and completeness of routine EPI-vaccine administration in the target population. This was illustrated in this study by an increase, although not significant, of first-month BCG vaccine administration timeliness for the age groups 0-11 months and

0-59 months in the intervention group, as well as a significant increase of first-year BCG vaccine administration timeliness for the age group 0-23 months in the intervention group. The coverage of DPT-Hi+HB3 and measles-rubella vaccines for the age groups 12-23 months and 12-59 months as well as the specific (DPT-Hi+HB1 and DPT-Hi+HB3) and general (BCG-measles-rubella) vaccine completeness also illustrated this. In health districts with similar contexts to the one where the intervention was tested, the tested intervention should be proposed to the health system to improve children's access to EPI vaccines. The efficiency of this intervention should be evaluated in other contexts. For the evaluation and

implementation of the intervention, we recommend ensuring the minimum prerequisites for the implementation of the intervention activities, such as the availability of human resources to ensure, when necessary, the immunization activities; the availability of vaccines and cold chain infrastructure; the involvement of a motivated and trained team of supervisors; logistic support for the immunization teams; and the coverage of the shortfall in terms of work by the teams involved when other activities are ongoing. The benefit of this strategy compared with that of the immunization campaign with regard to improving access to immunization and prevention of vaccine-preventable diseases should be assessed.

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Authors' Contributions

JA designed the project and drafted the manuscript. JA and MYN developed and ensured the development of the protocol and supervised its implementation. JA, FFKD, APG, and MYN developed the data collection tools and monitored data collection. KHTN, MYN, APG, EG, LA, FFKD, MT, CN, MDT, and BK revised the protocol and the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

CONSORT Checklist (V 1.6.1).

[PDF File (Adobe PDF File), 66 KB - [publichealth_v8i3e32213_app1.pdf](#)]

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Abbreviations

BCG: bacille Calmette–Guerin

CONSORT: Consolidated Standards of Reporting Trials

CV: community volunteer

DPT-Hi+HB: diphtheria-pertussis-tetanus and hepatitis B+Hemophilus influenzae type B

EPI: Expanded Program on Immunization

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Original Paper

A Bayesian Network to Predict the Risk of Post Influenza Vaccination Guillain-Barré Syndrome: Development and Validation Study

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Abstract

Background: Identifying the key factors of Guillain-Barré syndrome (GBS) and predicting its occurrence are vital for improving the prognosis of patients with GBS. However, there are scarcely any publications on a forewarning model of GBS. A Bayesian network (BN) model, which is known to be an accurate, interpretable, and interaction-sensitive graph model in many similar domains, is worth trying in GBS risk prediction.

Objective: The aim of this study is to determine the most significant factors of GBS and further develop and validate a BN model for predicting GBS risk.

Methods: Large-scale influenza vaccine postmarketing surveillance data, including 79,165 US (obtained from the Vaccine Adverse Event Reporting System between 1990 and 2017) and 12,495 European (obtained from the EudraVigilance system between 2003 and 2016) adverse events (AEs) reports, were extracted for model development and validation. GBS, age, gender, and the top 50 prevalent AEs were included for initial BN construction using the R package *bnlearn*.

Results: Age, gender, and 10 AEs were identified as the most significant factors of GBS. The posttest probability of GBS suggested that male vaccinees aged 50-64 years and without erythema should be on the alert or be warned by clinicians about an increased risk of GBS, especially when they also experience symptoms of asthenia, hypesthesia, muscular weakness, or paresthesia. The established BN model achieved an area under the receiver operating characteristic curve of 0.866 (95% CI 0.865-0.867), sensitivity of 0.752 (95% CI 0.749-0.756), specificity of 0.882 (95% CI 0.879-0.885), and accuracy of 0.882 (95% CI 0.879-0.884) for predicting GBS risk during the internal validation and obtained values of 0.829, 0.673, 0.854, and 0.843 for area under the receiver operating characteristic curve, sensitivity, specificity, and accuracy, respectively, during the external validation.

Conclusions: The findings of this study illustrated that a BN model can effectively identify the most significant factors of GBS, improve understanding of the complex interactions among different postvaccination symptoms through its graphical representation, and accurately predict the risk of GBS. The established BN model could further assist clinical decision-making by providing an estimated risk of GBS for a specific vaccinee or be developed into an open-access platform for vaccinees' self-monitoring.

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KEYWORDS

adverse events; Bayesian network; Guillain-Barré syndrome; risk prediction; trivalent influenza vaccine

Introduction

Background

Influenza vaccine is currently the most effective intervention to prevent millions of influenza-related visits to the physician each year [1]. Although the benefits of getting vaccinated far outweigh its risks, influenza vaccine is occasionally associated with adverse events (AEs), and as with most of medicine, there is a very rare chance of an influenza vaccine causing a severe reaction [1]. Guillain-Barré syndrome (GBS) is the most common and most severe acute paralytic neuropathy [2] that develops in susceptible individuals after infection and, in rare cases, after immunization (including influenza vaccination) [3]. The estimated incidence of GBS among the general population ranges from 0.8 to 1.9 cases per 100,000 person-years [4]. Although some epidemiological studies suggested that there may be a very small increased risk of GBS after influenza vaccination [5,6], causality remains controversial [3,7,8] and is out of the scope of this study. The identification of GBS is largely based on clinical patterns [2], and meticulous monitoring, supportive care, and the early start of specific treatment are necessary for patients with GBS [9]. Therefore, determining the key factors of GBS and predicting its occurrence are vital for improving the prognosis of these patients.

The Vaccine Adverse Event Reporting System (VAERS), managed by the Centers for Disease Control and Prevention and the US Food and Drug Administration, is a nationwide passive surveillance program to detect possible safety problems for US-licensed vaccines [10]. VAERS accepts reports of postvaccination AEs from 1990 to the present and collects information such as vaccinees' age, gender, the experienced AEs, and the recovery status. A primary objective of VAERS is to monitor fluctuations in known AEs that might indicate a potential safety problem with a vaccine [10]. GBS is one such concern and is the targeted AE of this study. Previous studies of GBS onset based on VAERS data reported that GBS generally occurs 2 weeks after influenza vaccination, which is later than that of most other influenza vaccine-related AEs [11,12]. Besides, some clinical features (eg, muscular weakness, pain, and autonomic dysfunction) that can be used to identify GBS [13] are also recorded as separate AEs in VAERS. Thus, performing a deep data mining of VAERS and identifying the most informative GBS-related AEs is significant and valuable work. The identified AEs first help in forming a future study hypothesis for etiological research of GBS and then can further be used to develop risk-prediction models that enable early warning.

Existing efforts focus on the measurement and prediction of clinical course and outcome of GBS, and good prognostic models have been developed [14-17]. However, as far as we know, there is no publication on a forewarning model of GBS, except for our previous work [18], which constructed a multivariate logistic regression model using GBS-related AEs in VAERS to predict risk of GBS. Nevertheless, conventional

linear models (eg, multiple linear regression model and logistic regression model) may be biased in dealing with collinearity and complex interactions when analyzing multiple predictors. In addition, it is difficult to succinctly present or explain the subtle patterns behind a particular prediction with general machine learning methods (eg, artificial neural network and support vector machine).

Bayesian Network Model

A Bayesian network (BN) is an emerging type of probabilistic graph model for predicting risk of outcomes of interest [19]. As a well-established type of probabilistic classifier, a BN model has the advantages of identifying interactions among variables that are often neglected by conventional statistical models and outputting an intuitive conditional probability table (CPT) for decision-making. In addition, the Markov blanket (MB) theory gives BN models the capacity for identifying the most significant factors contributing to the outcome. BN models have been applied for predicting risk of AEs in, among many others, radiotherapy [20] and hemodialysis [21] and have previously been shown to perform well at predicting the risk of other diseases using electronic health records [22-24]. However, whether a BN model can identify the most significant factors of GBS and integrate them to predict GBS remains to be determined.

Because of the rarity of many postvaccination AEs, especially for GBS, many longitudinal studies or cohort studies are underpowered in identifying risk factors for early detection. The large amount of data accumulated since 1990 in VAERS provides an opportunity for such studies: among influenza vaccine-related VAERS reports, trivalent influenza vaccine (FLU3)-related VAERS reports compose a major portion. The purpose of our investigation is to identify the most significant factors of GBS using FLU3-related VAERS reports, generate a novel risk prediction model, and estimate the probability of GBS occurrence. This study was reported following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement [25] ([Multimedia Appendix 1](#)). For a specific vaccinee who has certain AEs, the estimated risk from the risk prediction models could help to measure the risk of GBS and allow for timely diagnosis and treatment. We believe our work is complementary to other investigations and could ultimately lead to useful insights for clinical decision-making.

Methods

Data Processing

The VAERS database had received more than 400,000 vaccine-associated AE reports by the end of 2018. Each report had been manually annotated at the preferred-term level in the Medical Dictionary for Regulatory Activities by domain experts. We extracted all the FLU3-related VAERS reports between 1990 and 2017. The reports were excluded if they met either of the following criteria: (1) missing age values or age <0.5 years

and (2) unknown gender status. We finally included 79,165 completed reports and 2978 unique AE symptoms, including GBS.

Ethics Approval and Consent to Participate

Ethics approval and consent to participate are not applicable to this study because the VAERS database we used is publicly available [26]. The EudraVigilance vaccine AE data were requested from the European Medicines Agency.

Learning a BN

A BN B can be defined as a pair [27]:

$$B(G, \Theta), G = (V, E)$$

Here, $G = (V, E)$ is a directed acyclic graph that encodes the structure of the BN, in which each node X_i in V corresponds to a domain variable (discrete or continuous) and E consists of a set of directed arcs (or edges) that connect pairs of nodes. As in a genealogical chart, a parent node points to a child node with a directed arc, and an arc between 2 variables indicates a relationship of direct dependence. Furthermore, the Markov property states that any node X is conditionally independent of any other nodes, given its MB, and the MB of a node includes its parents, its children, and the children's other parents (spouses). Θ is a set of parameters that quantify the graph edges by specifying the conditional probability distributions; in the discrete case, they are denoted as CPTs. The joint probability distribution P factorized as a product of multiple conditional probability distributions also denotes the dependency or independency structure of the directed acyclic graph:



Here, $Pa(X_i)$ represents the parent nodes of X_i .

Accordingly, the process of learning a BN can be separated into two steps: BN structure learning and BN parameter learning. Many state-of-the-art BN structure learning algorithms have been proposed to determine the topology of a BN from data, and maximum likelihood estimation (MLE) and Bayesian parameter estimation are two popular methods for parameter learning. In addition, prior knowledge of the structure or parameters can also be integrated into the BN learning process.

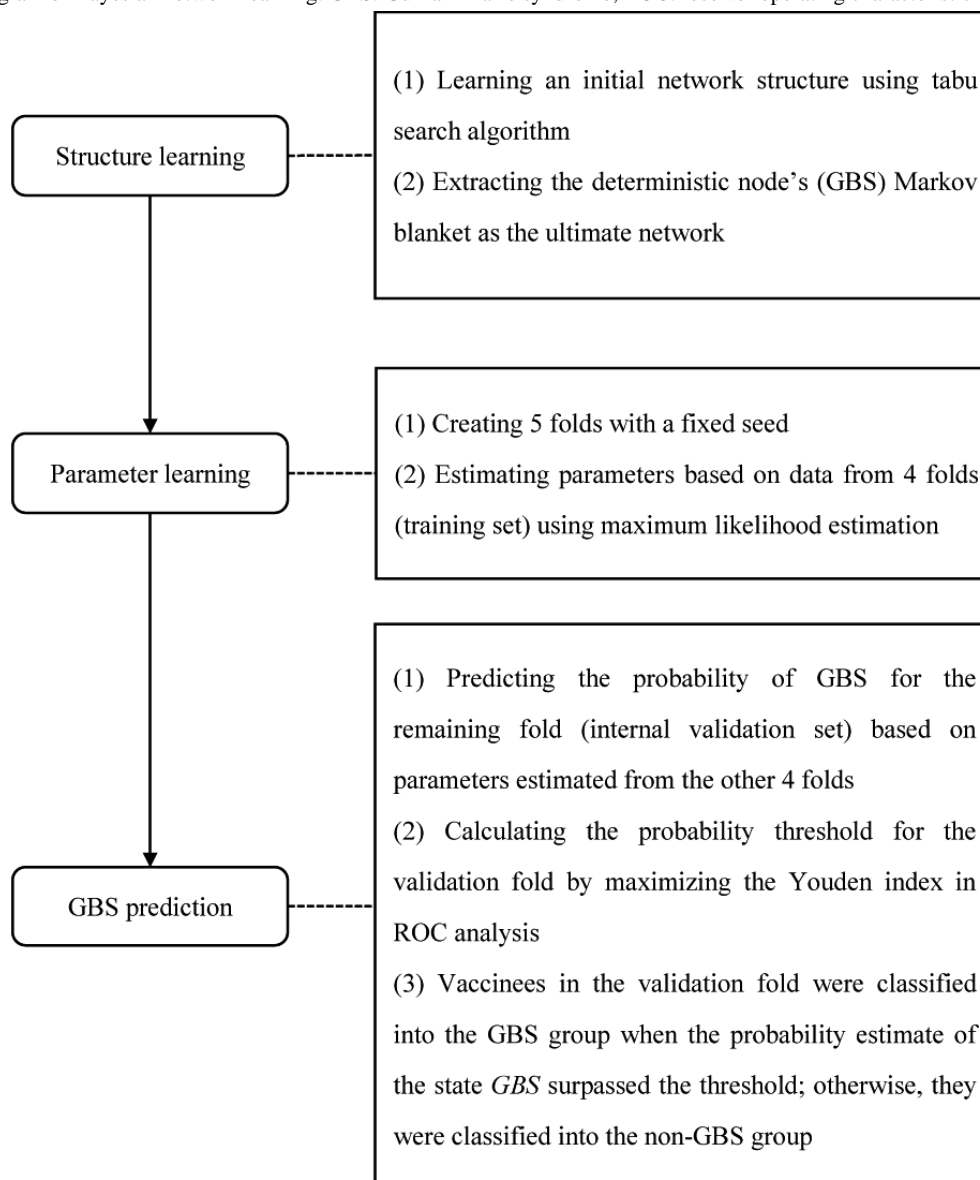
Statistical Analysis

Age was discretized into four groups: 0.5-17, 18-49, 50-64, and ≥ 65 years. All AEs were binary variables, with status *true* or *false* indicating whether the AE occurred or did not occur, respectively. We sorted all the AEs by their prevalence in the US data and selected the top 50 for further analysis (we also performed the analysis with the top 100 AEs to compare different networks). The prevalence of the top 50 AEs was compared between the GBS group and the non-GBS group using the Pearson chi-square test. To avoid inflating type I error caused

by multiple comparisons, a 2-sided P value $<.001$ (Bonferroni correction) was used to indicate a statistically significant difference.

GBS was set as the deterministic node, and all 53 variables (GBS, age, gender, and the top 50 AEs) were included in construction of the initial network. The flow diagram of BN learning is shown in Figure 1. Tabu search is a higher-level heuristic procedure that maintains the advantage of score-based structure learning algorithms and escapes the trap of local optimality [28]. For the first step, we obtained an initial network structure using the tabu search algorithm, with setting as a blacklist of arcs (no other variable can point to age or gender) and a whitelist of arcs (both age and gender point to GBS) based on prior knowledge [2]. Generally, we should consult domain experts to adjust those illogical arcs in the initial network to obtain a more reasonable structure. However, many variables were included in the initial network; therefore, we chose to extract the MB of GBS as the ultimate network from the perspective of model complexity and the Markov property. The strength of the conditional-dependence relationships among nodes was measured by Bayesian information criterion score gain or loss that would be caused by each arc's removal. For the second step, we performed 5-fold cross-validation 100 times, learned parameters using MLE based on 4 folds (ie, training folds), and obtained CPTs quantifying the probability of each state of a node based on all possible combinations of its parent nodes' values. In a discrete BN such as the one used in this study, parameters learned by MLE are approximately equal to the frequency of specific value of a node in the training data when fixing its parent nodes' values. Finally, we predicted the probability of GBS for the remaining fold (ie, validation fold) based on parameters estimated from training folds and calculated the probability threshold for the validation fold by maximizing the Youden index in the receiver operating characteristic curve analysis. Vaccinees in the validation fold were classified into the GBS group when the probability estimates of the state *GBS* surpassed the threshold; otherwise, they were classified into the non-GBS group.

Area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and predictive accuracy were used to assess the performance of the established BN. Here, sensitivity implies the ability of a model to identify a patient as a positive result, specificity implies the ability of a model to identify a nonpatient as a negative result, AUC is a comprehensive index that integrates a model's sensitivity and specificity, and accuracy implies the ability of a model to correctly identify both patient and nonpatient. The results of internal validation folds were averaged to obtain the ultimate indices, and their 95% CIs were calculated using the approximate normal distribution method. R (version 4.0.0; The R Foundation for Statistical Computing) packages, including *bnlearn*, *pROC*, *gmodels*, and *caret*, were used for the statistical analyses.

Figure 1. Flow diagram of Bayesian network learning. GBS: Guillain-Barré syndrome; ROC: receiver operating characteristic curve.

External Validation

The performance of the BN established from the US data was validated using the European EudraVigilance data. The European data were obtained from the European Medicines Agency in 2016 and included AE reports following influenza vaccines from 2003 to 2016. We filtered out records with missing age values or unknown gender status, as well as those reported outside the European Union area, and finally a total of 12,495 completed records were extracted. It is worth mentioning that the European data covered not only FLU3 but also other influenza vaccines such as quadrivalent influenza vaccine and monovalent influenza vaccine (H1N1 influenza vaccine) because of data access limitation and the formulation of FLU3 in Europe is different from that in the United States.

The same set of variables as in the US data (GBS, age, gender, and the top 50 AEs) were extracted from the European data, and age was also discretized into 4 groups as stated in the *Statistical Analysis* section. During the external validation procedure in the European data, we applied the BN structure

and its parameters learned from all the US data to predict the probability of GBS in European vaccinees and categorized them into two classes (GBS and non-GBS) as we did in the internal validation folds. The same performance metrics were applied.

Results

Descriptive Analysis

On the basis of the VAERS and EudraVigilance data, the cumulative probability of GBS was 1.26% within 28 years following the US FLU3 vaccine and 1.71% within 14 years following all the European flu vaccines (Table 1). For the US population, the median age of the GBS group was higher than that of the non-GBS group (median 57, IQR 42-68 years vs median 50, IQR 29-66 years), and this trend was similar and more obvious in the European population (median 60, IQR 49.25-72.00 years vs median 46, IQR 22.00-64.00 years). For the GBS reporters in both the United States and Europe, the percentage of 4 age groups increased gradually and this disease

was slightly more frequent in men than in women, both of which were consistent with previous studies [2].

Among the top 50 AEs, 33 (66%) presented significant association with GBS in the US data, whereas only 9 (18%) presented significant association with GBS in the European data (Table 2). Of the AEs significantly associated with GBS, only 15% (5/33; asthenia, fatigue, paresthesia, hypesthesia, and

muscular weakness) showed a positive association in the US data, whereas 100% (9/9) of the significant AEs (pain, pain in extremity, asthenia, fatigue, paresthesia, hypesthesia, tremor, musculoskeletal pain, and muscular weakness) showed positive association in the European data, with these 9 AEs including the aforementioned 5 AEs. As for the total prevalence of the top 50 AEs, only 12 (24%) had no significant difference between the United States and Europe.

Table 1. Demographic characteristics of 79,165 US (Vaccine Adverse Event Reporting System, trivalent influenza vaccine [FLU3], 1990-2017) reports and 12,495 European reports (EudraVigilance, all flu vaccines, 2003-2016).

Characteristics	GBS ^a	Non-GBS	Total
US FLU3 vaccine reports, 1990-2017 (N=79,165)			
Number of reports, n (%)	996 (1.26)	78,169 (98.74)	79,165 (100)
Age (years), median (IQR)	57 (42-68)	50 (29-66)	50 (29-66)
0.5-17	57 (5.72)	13,199 (16.89)	13,256 (16.74)
18-49	276 (27.71)	25,146 (32.17)	25,422 (32.11)
50-64	326 (32.73)	17,147 (21.94)	17,473 (22.07)
≥65	337 (33.84)	22,677 (29.01)	23,014 (29.07)
Men, n (%)	505 (50.70)	23,327 (29.84)	23,832 (30.10)
European flu vaccine reports, 2003-2016 (N=12,495)			
Number of reports, n (%)	214 (1.71)	12,281 (98.29)	12,495 (100)
Age (years), median (IQR)	60 (49.25-72)	46 (22-64)	46 (22-65)
0.5-17	6 (2.80)	2691 (21.91)	2697 (21.58)
18-49	48 (22.43)	3987 (32.46)	4035 (32.29)
50-64	74 (34.58)	2548 (20.75)	2622 (20.98)
≥65	86 (40.19)	3055 (24.88)	3141 (25.14)
Men, n (%)	125 (58.41)	4949 (40.30)	5074 (40.61)

^aGBS: Guillain-Barré syndrome.

Table 2. Top 50 prevalent adverse events screened from the US data, and comparisons between the US and European data.

Adverse events	US FLU3 ^a reports, 1990-2017				European flu vaccine reports, 2003-2016				US vs Europe, <i>P</i> value, total
	Total (%)	GBS ^b (%)	Non-GBS (%)	<i>P</i> value	Total (%)	GBS (%)	Non-GBS (%)	<i>P</i> value	
Pyrexia	138.85	58.23	139.88	<.001	140.86	79.44	141.93	.01	.55
Injection-site erythema	126.36	2.01	127.94	<.001	15.53	0	15.80	.06	<.001
Pain	125.40	113.45	125.55	.25	29.77	112.15	28.34	<.001	<.001
Injection-site pain	119.16	7.03	120.58	<.001	30.97	4.67	31.43	.03	<.001
Erythema	89.69	3.01	90.79	<.001	23.37	4.67	23.70	.07	<.001
Pain in extremity	86.79	73.29	86.97	.13	46.74	177.57	44.46	<.001	<.001
Injection-site swelling	86.07	3.01	87.13	<.001	12.48	0	12.70	.10	<.001
Headache	77.52	61.24	77.73	.05	103.16	88.79	103.41	.49	<.001
Pruritus	71.33	2.01	72.22	<.001	23.53	18.69	23.61	.64	<.001
Chills	68.46	22.09	69.06	<.001	37.21	32.71	37.29	.73	<.001
Dizziness	63.45	32.13	63.85	<.001	60.02	65.42	59.93	.74	.14
Nausea	62.70	25.10	63.18	<.001	55.14	23.36	55.70	.04	.001
Urticaria	60.75	2.01	61.49	<.001	27.85	0	28.34	.01	<.001
Rash	59.50	10.04	60.13	<.001	26.57	9.35	26.87	.11	<.001
Injection-site warmth	55.91	< 0.01	56.62	<.001	4.08	0	4.15	.34	<.001
Dyspnea	50.67	57.23	50.58	.34	47.94	70.09	47.55	.13	.19
Myalgia	49.52	49.20	49.52	.96	66.43	56.07	66.61	.54	<.001
Vomiting	45.60	26.10	45.85	.003	42.26	37.38	42.34	.72	.09
Asthenia	44.78	296.18	41.58	<.001	39.62	121.50	38.19	<.001	.01
Fatigue	37.96	59.24	37.69	<.001	72.91	135.51	71.82	<.001	<.001
Paresthesia	37.57	332.33	33.81	<.001	43.06	345.79	37.78	<.001	.003
Cough	37.16	32.13	37.23	.40	38.02	23.36	38.27	.26	.64
Edema, peripheral	35.20	9.04	35.54	<.001	5.52	4.67	5.54	.87	<.001
Malaise	32.22	27.11	32.29	.36	55.62	56.07	55.61	.98	<.001
Skin, warm	31.34	1.00	31.73	<.001	1.92	0	1.95	.52	<.001
Hypesthesia	31.31	289.16	28.03	<.001	26.65	285.05	22.15	<.001	.005
Swelling	30.76	3.01	31.11	<.001	5.28	0	5.37	.28	<.001
Arthralgia	28.59	19.08	28.71	.07	39.06	37.38	39.08	.90	<.001
Injection-site edema	28.09	1.00	28.44	<.001	2.40	0	2.44	.47	<.001
Injection-site hypersensitivity	26.38	2.01	26.69	<.001	0.24	0	0.24	.82	<.001
Diarrhea	24.30	24.10	24.31	.97	27.29	42.06	27.03	.18	.05
Hyperhidrosis	23.08	7.03	23.28	<.001	18.65	9.35	18.81	.31	.002
Tremor	21.82	14.06	21.91	.09	9.68	32.71	9.28	<.001	<.001
Injection-site pruritus	21.26	< 0.01	21.53	<.001	3.60	0	3.66	.38	<.001
Injected-limb mobility decreased	20.78	2.01	21.02	<.001	2.96	0	3.01	.42	<.001
Feeling hot	19.88	< 0.01	20.14	<.001	10.40	9.35	10.42	.88	<.001
Injection-site reaction	19.39	1.00	19.62	<.001	8.48	0	8.63	.17	<.001
Musculoskeletal pain	18.91	12.05	19.00	.11	11.20	46.73	10.59	<.001	<.001
Injection-site induration	18.86	< 0.01	19.10	<.001	4.16	0	4.23	.34	<.001

Adverse events	US FLU3 ^a reports, 1990-2017				European flu vaccine reports, 2003-2016				US vs Europe, <i>P</i> value, total
	Total (‰)	GBS ^b (‰)	Non-GBS (‰)	<i>P</i> value	Total (‰)	GBS (‰)	Non-GBS (‰)	<i>P</i> value	
Cellulitis	18.63	1.00	18.86	<.001	2.16	0	2.20	.49	<.001
Muscular weakness	17.75	230.92	15.03	<.001	25.13	266.36	20.93	<.001	<.001
Vasodilatation	17.61	2.01	17.81	<.001	0.32	0	0.33	.79	<.001
Neck pain	17.51	16.06	17.53	.73	7.20	4.67	7.25	.66	<.001
Mobility decreased	16.32	24.10	16.22	.05	3.92	14.02	3.75	.02	<.001
Immediate postinjection reaction	16.28	3.01	16.45	<.001	0	0	0	— ^c	—
Chest pain	16.21	18.07	16.18	.64	13.93	14.02	13.92	.99	.06
Rash, erythematous	15.61	2.01	15.79	<.001	4.88	0	4.97	.30	<.001
Injection-site rash	15.45	1.00	15.63	<.001	1.36	0	1.38	.59	<.001
Syncope	15.42	8.03	15.52	.06	29.21	4.67	29.64	.03	<.001
Tenderness	15.40	3.01	15.56	.001	1.20	4.67	1.14	.14	<.001

^aFLU3: trivalent influenza vaccine.

^bGBS: Guillain-Barré syndrome.

^cNot available.

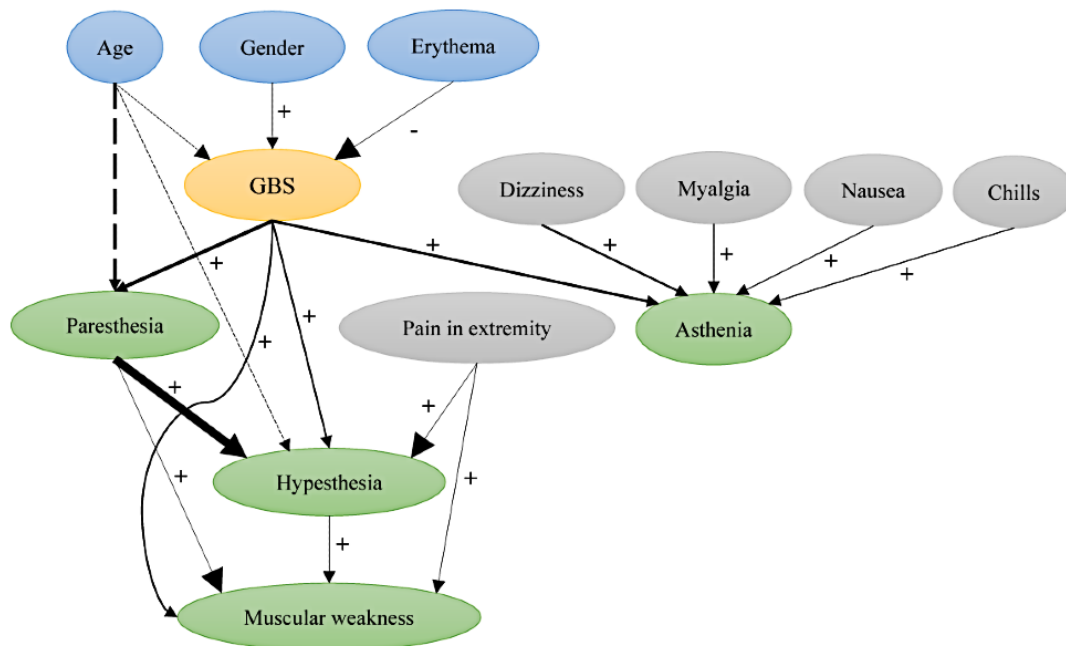
The Established BN

The MB of the GBS, that is, the ultimate network structure (Figure 2), contained three parent nodes (age, gender, and erythema), four child nodes (asthenia, hypesthesia, muscular weakness, and paresthesia), and five spouse nodes (chills, dizziness, myalgia, nausea, and pain in extremity), and they were the most significant factors of GBS. Among these, age also played a spouse node role when it coacted with GBS in influencing the occurrence of paresthesia and hypesthesia. Besides, paresthesia was also a spouse node that interacted with GBS to influence hypesthesia and muscular weakness, and hypesthesia also acted as a spouse of GBS in influencing muscular weakness. As an arc pointing from a parent node to a child node indicates a chronological order, we may learn from the MB that age, gender, and erythema acted on the occurrence of GBS; subsequently, GBS interacted with the spouse nodes

and further evolved into symptoms of asthenia, hypesthesia, muscular weakness, and paresthesia. The remaining AEs (40/50, 80%) were conditionally independent of GBS through the nodes in the MB and were pruned to retain a more compact network.

The arc thickness in Figure 2 is proportional to the strength of the conditional-dependence relationship; it serves to show that the conditional-dependence relationship between paresthesia and hypesthesia was the strongest, followed by that between GBS and paresthesia, between age and paresthesia, and between GBS and asthenia (detailed strength values can be found in Table S1 in Multimedia Appendix 2). Furthermore, we found that most of the parent nodes had a positive correlation with their child nodes in our network, except for the negative correlation between erythema and GBS, and the risk of GBS, paresthesia, and hypesthesia first increased and then decreased with increasing age.

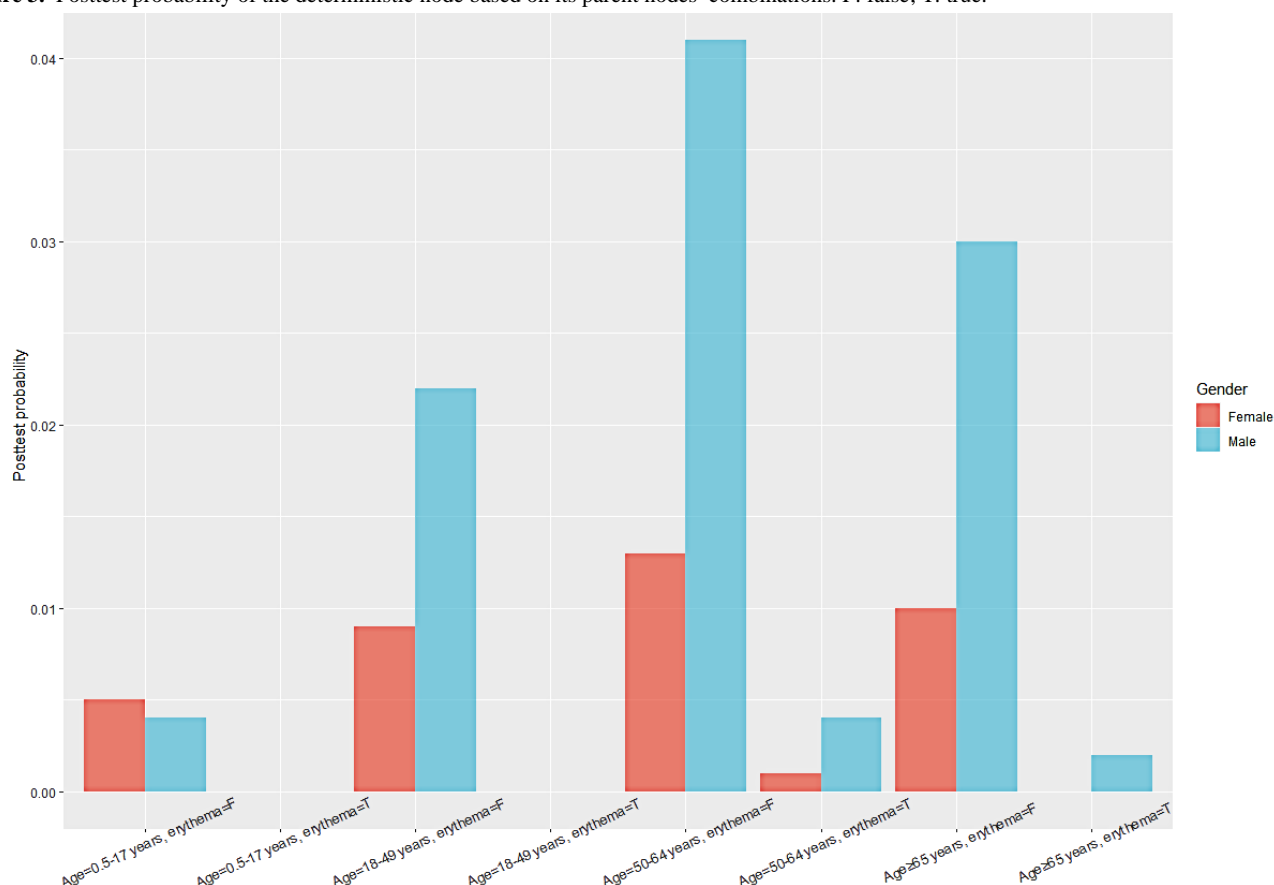
Figure 2. Structure of the established Bayesian network. Labeled ovals represent nodes; arrows (arcs) represent conditional-dependence relationships. The oval in yellow represents the deterministic node, ovals in blue represent the deterministic node's parent nodes, ovals in green represent the child nodes, and ovals in gray represent the spouse nodes. Arc thickness is proportional to the strength of the conditional-dependence relationship. Minus (-) or plus (+) sign indicates either negative or positive association, respectively, between the nodes; arcs in dashed lines indicate a U-shaped association between 2 nodes. GBS: Guillain-Barré syndrome.



Posttest Probability of the Deterministic Node

The posttest probability of GBS based on the status of its 3 parent nodes is shown in Figure 3. It suggested that male vaccinees aged 50-64 years and without erythema had the highest probability of acquiring GBS, followed by vaccinees aged ≥65 years or those aged 18-49 years, with the other 2 features remaining unchanged. Female vaccinees aged 50-64

years and without erythema also tended to experience GBS, but male vaccinees in the same situation had almost triple the risk. In contrast, vaccinees with different other combinations of the aforementioned 3 parent nodes showed a reduced probability of acquiring GBS. Vaccinees who experienced the AE of erythema were estimated to have almost no chance of acquiring GBS.

Figure 3. Posttest probability of the deterministic node based on its parent nodes' combinations. F: false; T: true.

Performance of the BN

The constructed BN model performed desirably at predicting GBS, with an AUC of 0.866 (95% CI 0.865-0.867), sensitivity of 0.752 (95% CI 0.749-0.756), specificity of 0.882 (95% CI 0.879-0.885), and accuracy of 0.882 (95% CI 0.879-0.884) at a probability threshold of 0.014 (95% CI 0.0136-0.0143) for the internal validation. The best performance of the BN during cross-validation reached an AUC of 0.906. As for the external validation in the European data, the established BN obtained values of 0.829, 0.673, 0.854, and 0.843 for AUC, sensitivity, specificity, and accuracy, respectively.

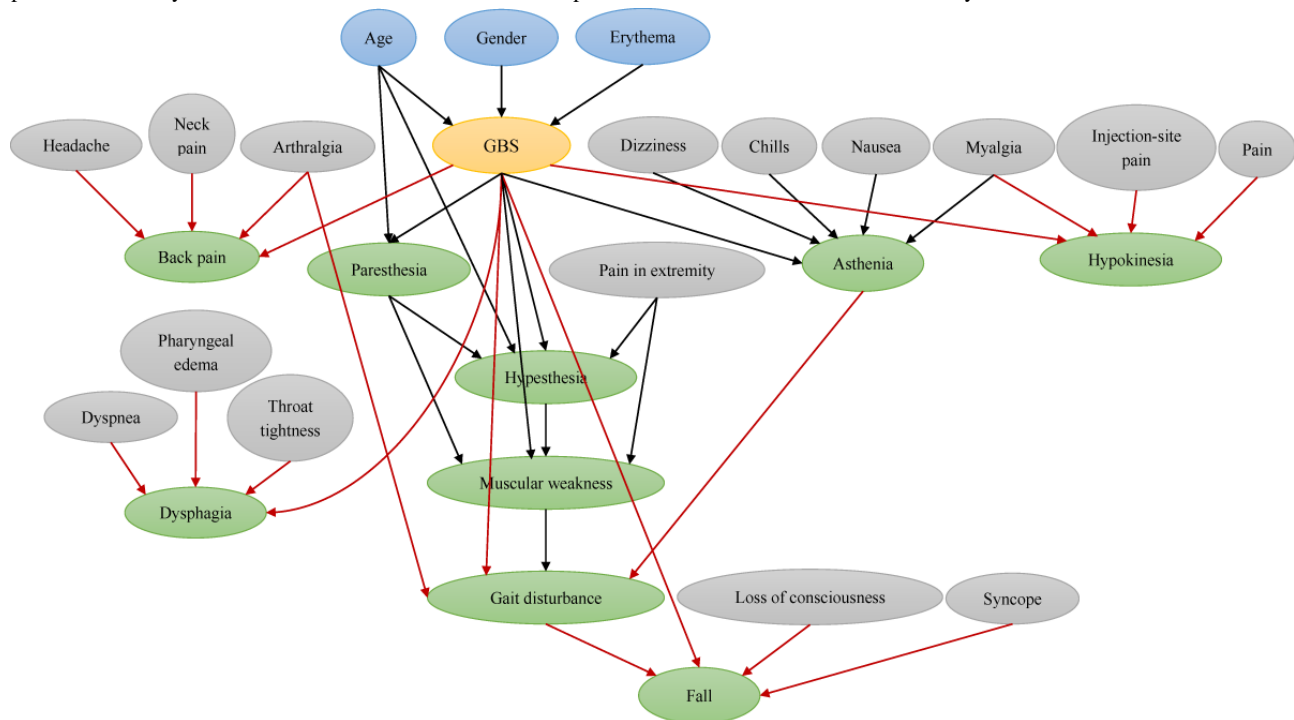
BN Development and Validation With the Top 100 AEs

The BN structure learned from the top 100 AEs (Figure 4) contained the structure learned from the top 50 AEs. Compared

with the BN structure learned from the top 50 AEs, there were 5 more child nodes (back pain, dysphagia, fall, gait disturbance, and hypokinesia) and 10 more spouse nodes (headache, neck pain, arthralgia, injection-site pain, pain, dyspnea, pharyngeal edema, throat tightness, loss of consciousness, and syncope) in the new structure.

The new BN model had a slightly improved performance compared with the previous one, obtaining an AUC of 0.883 (95% CI 0.881-0.884), sensitivity of 0.787 (95% CI 0.784-0.790), specificity of 0.891 (95% CI 0.889-0.893), and accuracy of 0.890 (95% CI 0.888-0.892) at a probability threshold of 0.012 (95% CI 0.0115-0.0122) for the internal validation and achieving values of 0.832, 0.664, 0.915, and 0.911 for AUC, sensitivity, specificity, and accuracy, respectively, in the external validation.

Figure 4. The Bayesian network structure established from the top 100 adverse events. Labeled ovals represent nodes; arrows (arcs) represent conditional-dependence relationships. The oval in yellow represents the deterministic node, ovals in blue represent the deterministic node's parent nodes, ovals in green represent the child nodes, and ovals in gray represent the spouse nodes. Arcs in red indicate the added arcs in the new structure compared with the Bayesian network structure learned from the top 50 adverse events. GBS: Guillain-Barré syndrome.



Discussion

Principal Findings

BN models are highly attractive because of their ability to describe complex probabilistic interactions among variables and to determine a unique joint probability distribution over multiple variables for probabilistic inference. In this study, we identified the 10 most informative GBS-related AEs from the MB of GBS; constructed the joint probability distribution based on age, gender, and these 10 AEs to predict the likelihood of GBS; and achieved a desirable performance.

In accordance with previous studies [2,13], the established BN structure also suggested sensory signs of asthenia, hypesthesia, muscular weakness, and paresthesia as clinical features of GBS. Besides, it recommended that age, gender, and erythema should also be taken into account for identifying GBS in clinical practice. Although many epidemiological studies have reported increased age and male gender as risk factors for GBS [29-32], none took these two demographic characteristics as a basis for identification of GBS occurrence. Our efforts may promote the advancement of precision medicine in GBS identification. Furthermore, the symptom of erythema, which is an observable and not easily overlooked body sign, provides more explicit information than sensory signs for vaccinees or clinicians to evaluate GBS risk. Moreover, additional symptoms of chills, dizziness, myalgia, nausea, and pain in extremity should also raise doubt about an increased risk of GBS; these symptoms have been presented in many case reports [33-35] but have not been used for GBS identification. In addition, our BN structure presented complex interactions among variables visually, which helped in understanding trigger mechanisms of occurrence of

different postvaccination symptoms, although their causality still warrant further verification.

Although all the variables contained in the network structure were used to predict GBS, we also calculated a simplified posttest probability of GBS using only information regarding three GBS parent nodes (age, gender, and erythema) and obtained some interesting results. A highly cited meta-analysis integrated 16 original GBS-related studies and obtained a generalized estimate of incidence; the age-specific estimates showed that GBS incidence increased by 20% for every 10-year increase in age [4]. However, we found that the risk of GBS first increased and then decreased with increasing age, based on VAERS data, peaking in the age group of 50-64 years and declining in the age group of ≥ 65 years. In fact, several articles reported a similar U-shaped relationship between age and GBS [29-32,36,37], whereas the random-effects negative binomial regression model the researchers used did not detect this fluctuation [4]. In line with previous studies [29-32], our study also found that men had a higher risk of GBS than women. As for the negative correlation we found between erythema and GBS, we searched medical archives extensively and a study pointed out that intermittent erythema in GBS was quite rare and should be recognized as a rare manifestation of GBS [33]. To sum up, our findings suggested that male vaccinees aged 50-64 years and without erythema should be on the alert or be warned by clinicians about an increased risk of GBS, especially when they also experience symptoms of asthenia, hypesthesia, muscular weakness, or paresthesia.

To our knowledge, this BN model is the second attempt to use VAERS data for GBS risk prediction after our previous logistic regression model [18]. This model performed well at predicting

GBS both in internal cross-validation and external validation, with AUC reaching 0.866 and 0.829, respectively, which was superior to the performance of the logistic regression model (0.775 and 0.769, respectively). This superiority originated from the different GBS-related AEs we screened through MB and the complex interactions considered in the BN model. In the external validation, although the established BN model had a barely satisfactory performance with a sensitivity of 0.673, it performed well in specificity (0.854), which is an important index because a higher value is an indication of a model with fewer misdiagnoses. The accuracy in the external validation (0.843) also corroborated that the established BN model is worth trying in medical practice. In addition, the minor differences in performance between the top 50 AEs-based networks and top 100 AEs-based networks illustrated that the BN structure learned from the top 50 AEs had already included the most informative GBS-related AEs. As clinical practice prefers a more compact model, albeit with slightly less predictive power, we primarily reported the BN model learned from the top 50 AEs.

The established BN model not only provides a promising tool for clinicians to assist in decision-making, but it can also be incorporated into a web platform, making it convenient for people who want to monitor their own risk of GBS based on mild symptoms. Furthermore, few input symptoms are needed by the BN model, making it more easily acceptable to the general population, which may facilitate this monitoring behavior. Given the natural progression of GBS, it may evolve to respiratory arrest and death, but the prognosis improves considerably with accurate diagnosis and prompt treatment.

However, there are several limitations to consider. First, both VAERS and the EudraVigilance system are spontaneous reporting systems and accept reports submitted without validation; therefore, reporting biases are inevitable. For example, Medical Dictionary for Regulatory Activities preferred

terms annotated by domain experts in VAERS may overlap and reporting may be stimulated by possible publicity. Second, because many AEs are sparse in the annual data, we chose to use data across all years in constructing the BN model. This approach neglected the influence of different formulations of influenza vaccines in different years possibly related to GBS risk. Third, the cohort we analyzed was restricted to the VAERS FLU3 and EudraVigilance influenza vaccines; thus, the BN model should be interpreted and applied with caution and this novel risk prediction model needs to be further studied, validated, and evaluated by prospective studies. Fourth, there may be potential overfitting problems driven by the MLE method; nonetheless, the good performance during the external validation indicated that overfitting issues were controlled well in this study. Finally, BN modelling requires the assumption of the Markov property; thus, some dependence relationships may not be revealed yet in the ultimate network. An interesting future direction is to *quantify* the marginal dependency between the occurrence of GBS and each of the 10 identified AEs that are deemed to be predictive of GBS, using bivariate generalized linear mixed effects models or the transformation-free Sarmanov family [38,39].

Conclusions

In conclusion, this study developed and externally validated a BN model for GBS risk prediction based on large-scale US and European influenza vaccine postmarketing cohort data. The findings illustrated that a BN model can effectively identify the most significant factors of GBS, improve understanding of the complex interactions among different postvaccination symptoms through its graphical representation, and accurately predict the risk of GBS both in internal and external validation. The established BN model could further assist clinical decision-making by providing an estimated risk of GBS for a specific vaccinee or be developed into an open-access platform for vaccinees' self-monitoring.

Acknowledgments

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Authors' Contributions

Y Hao was responsible for the concept and design of the study. Y Huang and YJ acquired, analyzed, and interpreted the data. Y Huang drafted the manuscript. All authors critically revised the manuscript for important intellectual content. Y Huang was responsible for statistical analysis, and Y Hao was responsible for supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) checklist. [[DOCX File, 50 KB](#) - [publichealth_v8i3e25658_app1.docx](#)]

Multimedia Appendix 2

The strength of the conditional-dependence relationships between nodes.

[DOCX File , 13 KB - [publichealth_v8i3e25658_app2.docx](#)]

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Abbreviations

- AE:** adverse event
- AUC:** area under the receiver operating characteristic curve
- BN:** Bayesian network
- CPT:** conditional probability table
- FLU3:** trivalent influenza vaccine
- GBS:** Guillain-Barré syndrome
- MB:** Markov blanket
- MLE:** maximum likelihood estimation
- VAERS:** Vaccine Adverse Event Reporting System

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Original Paper

Adverse Events of Interest Following Influenza Vaccination in the First Season of Adjuvanted Trivalent Immunization: Retrospective Cohort Study

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Abstract

Background: Vaccination is the most effective form of prevention of seasonal influenza; the United Kingdom has a national influenza vaccination program to cover targeted population groups. Influenza vaccines are known to be associated with some common minor adverse events of interest (AEIs), but it is not known if the adjuvanted trivalent influenza vaccine (aTIV), first offered in the 2018/2019 season, would be associated with more AEIs than other types of vaccines.

Objective: We aim to compare the incidence of AEIs associated with different types of seasonal influenza vaccines offered in the 2018/2019 season.

Methods: We carried out a retrospective cohort study using computerized medical record data from the Royal College of General Practitioners Research and Surveillance Centre sentinel network database. We extracted data on vaccine exposure and consultations for European Medicines Agency–specified AEIs for the 2018/2019 influenza season. We used a self-controlled case series design; computed relative incidence (RI) of AEIs following vaccination; and compared the incidence of AEIs associated with aTIV, the quadrivalent influenza vaccine, and the live attenuated influenza vaccine. We also compared the incidence of AEIs for vaccinations that took place in a practice with those that took place elsewhere.

Results: A total of 1,024,160 individuals received a seasonal influenza vaccine, of which 165,723 individuals reported a total of 283,355 compatible symptoms in the 2018/2019 season. Most AEIs occurred within 7 days following vaccination, with a seasonal effect observed. Using aTIV as the reference group, the quadrivalent influenza vaccine was associated with a higher incidence of AEIs (RI 1.46, 95% CI 1.41-1.52), whereas the live attenuated influenza vaccine was associated with a lower incidence of AEIs (RI 0.79, 95% CI 0.73-0.83). No effect of vaccination setting on the incidence of AEIs was observed.

Conclusions: Routine sentinel network data offer an opportunity to make comparisons between safety profiles of different vaccines. Evidence that supports the safety of newer types of vaccines may be reassuring for patients and could help improve uptake in the future.

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KEYWORDS

influenza; influenza vaccines; adverse events of interest; computerized medical record systems; sentinel surveillance

Introduction

Seasonal epidemics of influenza lead to an estimated 3 to 5 million cases of severe illness and about 290,000 to 650,000 respiratory deaths annually worldwide, and vaccination is the most effective form of influenza prevention [1]. The United Kingdom has a long-standing national influenza vaccination program for targeted population groups, and different types of vaccines are recommended for these groups to achieve optimal immunogenicity and effectiveness. In the 2018/2019 season, following updated guidance from the Joint Committee on Vaccination and Immunisation, the adjuvanted trivalent influenza vaccine (aTIV) was recommended for adults 65 years and older, the quadrivalent influenza vaccine (QIV) for adults aged 18 years to younger than 65 years in clinical at-risk groups, and the quadrivalent live attenuated influenza vaccine (LAIV) for children.

Seasonal influenza vaccines are known to be associated with a range of adverse events of interest (AEIs), including minor ones like fever, malaise, and injection site soreness, and more serious AEIs such as anaphylaxis have been documented [2]. Study findings show an association between seasonal flu vaccination and Guillain-Barré syndrome in some years [3], while oculo-respiratory syndrome is rarely reported [4]. Since 2016, the European Medicines Agency (EMA) required all vaccine manufacturers to conduct annual postmarketing enhanced safety surveillance studies. As 2018/2019 is the first influenza season following the licensure of aTIV in the United Kingdom, it is yet unknown whether this particular type of vaccine is associated with a higher incidence of AEIs compared to other types of vaccines.

We conducted this study to calculate the relative incidence (RI) of AEIs following seasonal influenza vaccination; compare the incidence of AEIs between aTIV, QIV, and LAIV; and explore whether the settings in which the vaccination took place had an effect on AEIs.

Methods

Study Design and Data Sources

We used a retrospective cohort design involving computerized medical record data from the Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) sentinel network. The RCGP RSC is a nationally representative primary care sentinel network with over 50 years of history in influenza and respiratory disease surveillance [5]. At the time of this study, the RCGP RSC network contained more than 8 million patient records from 336 member general practices across England. Clinical encounters of patients visiting their general practitioners (GPs) for adverse events are recorded into a GP electronic medical record system using 5-byte Read or Clinical Terms Version 3 codes.

We extracted data from all patients who had received a seasonal influenza vaccine between September 1, 2018, and April 30, 2019. We excluded patients older than 100 years, those who attended practices involved in EMA enhanced surveillance programs [6-8], and those who received monovalent pandemic

influenza vaccines. Patients were followed up retrospectively for occurrence of a list of AEIs prespecified by the EMA, and those who presented with compatible symptoms were included in this study [9].

Variables

We extracted the following data: age, sex, self-reported ethnicity, index of multiple deprivation (IMD), vaccination date, vaccine manufacturer, vaccine valency (number of viral strains included), route of administration, date of any AEI, type of AEI, and dates of registration and deregistration at the practice.

Determination of Vaccine Type and Vaccination Setting

First, we used prescription data (where available) and clinical event data to assign drug name, manufacturer, valency, and route of administration. Second, for the records without prescription data, batch numbers were collated for each drug name to assign manufacturer, valency, and administration route. For records with both prescription and clinical data available, conflicting data were excluded from the analysis. We coded vaccinations where we had sufficient information to identify the vaccination as having taken place within a practice.

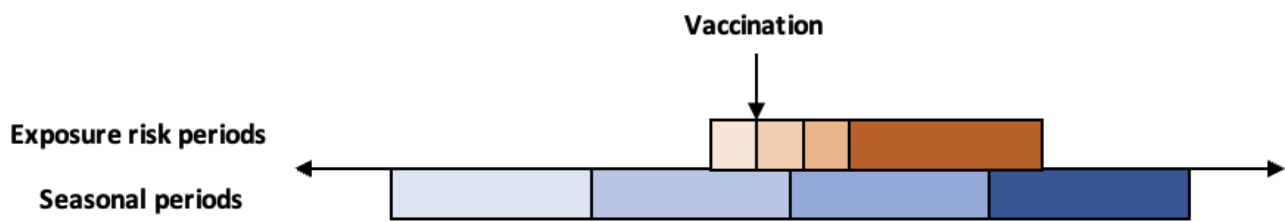
Statistical Analyses

We used a self-controlled case series approach [10,11], a method typically used to investigate adverse events following administration of medications or vaccinations. It is a case-only method for investigating the association between a time-varying exposure and an outcome event, in which any time-invariant confounding is automatically controlled for as each patient acts as their own control.

We computed descriptive statistics to provide an overview of the demographic characteristics of the study sample.

We conducted three separate models to address the three aforementioned study aims. The observation period used in all models was from September 1, 2018, to April 30, 2019. Where an individual registered with the practice after September 1, 2018, or deregistered with the practice before April 30, 2019, their observation period was defined as the number of days they remained registered. In model 1, we defined the exposure risk periods relative to the day of vaccination (day 0) as days -7 to -1, days 0 to 6, days 7 to 13, and days 14 to 45, and defined seasonal periods within the observation period as days 0 to 29, days 30 to 59, days 60 to 89, days 90 to 119, days 120 to 149, days 150 to 179, days 180 to 209, and days 210 to 241 from the beginning of the influenza season (see Figure 1 for an illustration). The time outside of the defined exposure risk periods is used as the control for each individual patient. Where an individual received the vaccination very early or very late in the season, parts of the exposure risk periods that fell outside of our defined observation period were not included. We calculated the RI of AEIs following vaccination for the different exposure periods and for the different seasonal periods. In models 2 and 3, we focused on the first 7 days post vaccination as the exposure risk period and modeled potential modification effects of vaccine type and vaccination settings by including an interaction term in the model [12].

Figure 1. Simplified illustration of SCCS model for a hypothetical individual showing four risk periods (days -7 to -1 , days 0 to 6 , days 7 to 13 , and days 14 to 45 , where day 0 is day of vaccination), and four of eight 30-day periods in the influenza season.



All statistical analysis was performed using R 3.4.4 (R Foundation for Statistical Computing) [13] with the packages tidyverse version 1.2.1 [14], SCCS version 1.1 [15], lubridate [16], and tableone [17]. Graphical output was generated using the packages ggplot2 [18] and ggthemes version 3.5.0 [19].

Ethical Considerations

All potentially identifiable data were pseudonymized as close to the source as possible and not made available to researchers; data were not extracted for patients who opted out of data sharing. All data are stored and processed at the RCGP RSC secure data and analytics hub, the University of Surrey. According to the Health Research Authority and Medical Research Council Regulatory Support Centre's online decision tool, this study falls under the category of service evaluation and does not require further ethical review. This study was approved by RCGP.

Results

Study Participants

A total of 1,024,160 unique individuals who received seasonal influenza vaccinations were identified, of which 165,723 individuals presented with symptoms compatible with vaccine-related AEs. Baseline demographic characteristics of the study participants are presented in Table 1. The median age of the cohort was 66 years, with slightly more women than men, and the majority of the study participants were of White ethnicity. The age-sex profile showed a peak between the ages of 2 and 9 years, and a marked increase in uptake from the age of 65 years (Figure 2). The IMD distribution, however, showed a slight overrepresentation of patients from less deprived neighborhoods (see Table 1).

Figure 2. Age-sex profile for seasonal influenza vaccine recipients in the United Kingdom's Royal College of General Practitioners Research and Surveillance Centre network who reported adverse events of interest between September 1, 2018, and April 30, 2019 ($n=165,723$). F: female; M: male.

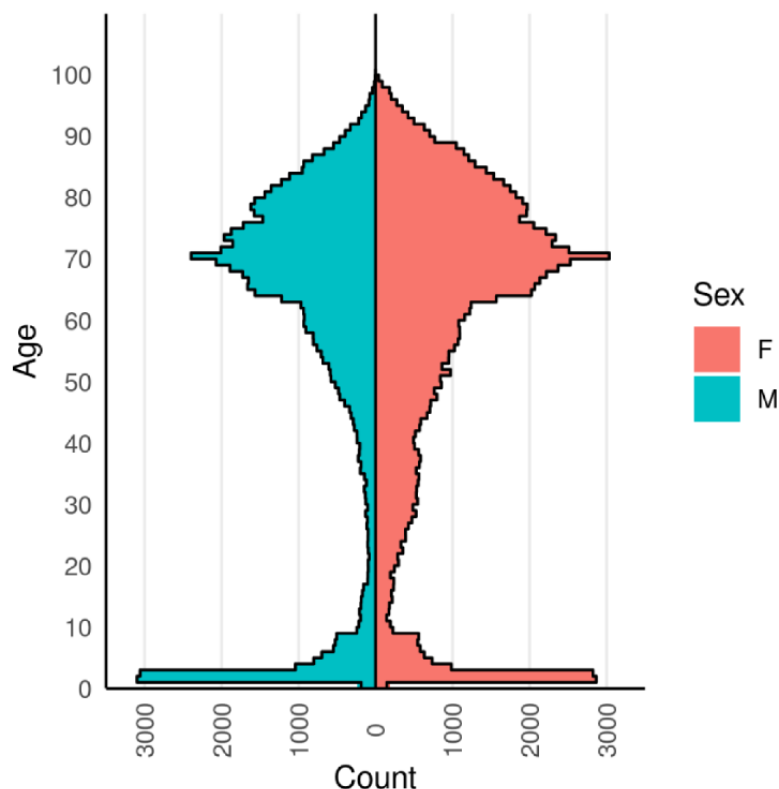


Table 1. Demographic characteristics of seasonal influenza vaccine recipients in the United Kingdom's Royal College of General Practitioner Research and Surveillance Centre network who reported adverse events of interest between September 1, 2018, and April 30, 2019, (n=165,723) by type of vaccine.

	aTIV ^a (n=92,336)	QIV ^b (n=51,616)	LAIV ^c (n=21,771)
Age (years), mean (SD)	76.27 (8.2)	47.58 (14.8)	4.86 (4.0)
Sex, n (%)			
Female	52,598 (57.0)	32,702 (63.4)	10,596 (48.7)
Male	39,738 (43.0)	18,914 (36.6)	11,175 (51.3)
Ethnicity, n (%)			
White	71,358 (77.3)	36,206 (70.1)	11,677 (53.6)
Asian	3104 (3.4)	4849 (9.4)	1595 (7.3)
Black	869 (0.9)	1774 (3.4)	493 (2.3)
Mixed	224 (0.2)	548 (1.1)	525 (2.4)
Other	313 (0.3)	620 (1.2)	220 (1.0)
Missing data	16,468 (17.8)	7619 (14.8)	7261 (33.4)
Index of multiple deprivation quintile, n (%)			
1 (most deprived)	11,143 (12.1)	11,665 (22.6)	3690 (16.9)
2	12,816 (13.9)	9534 (18.5)	3609 (16.6)
3	18,685 (20.2)	9428 (18.3)	3923 (18.0)
4	22,894 (24.8)	10,207 (19.8)	4712 (21.6)
5 (least deprived)	25,369 (27.5)	9726 (18.8)	5339 (24.5)
Missing data	1429 (1.5)	1056 (2.0)	498 (2.3)
BMI, mean (SD)	28.06 (5.9)	30.52 (7.8)	18.64 (5.2)
Smoking status, n (%)			
Nonsmoker	47,068 (51.0)	27,406 (53.1)	2991 (13.7)
Ex-smoker	36,032 (39.0)	12,614 (24.4)	36 (0.2)
Active smoker	8414 (9.1)	10,011 (19.4)	111 (0.5)
Missing data	822 (0.9)	1585 (3.1)	18,633 (85.6)
Alcohol consumption level, n (%)			
Nondrinker	8558 (9.3)	5544 (10.7)	164 (0.8)
Safe	9172 (9.9)	4982 (9.7)	41 (0.2)
Hazardous	14,649 (15.9)	6307 (12.2)	40 (0.2)
Alcoholism	1463 (1.6)	1654 (3.2)	1 (0.0)
Missing data	58,494 (63.3)	33,129 (64.2)	21,525 (98.9)

^aaTIV: adjuvanted trivalent influenza vaccine.

^bQIV: quadrivalent influenza vaccine.

^cLAIV: live attenuated influenza vaccine.

Vaccine Type

We were able to identify the vaccine administered in 77.8% (797,285/1,024,160) of the records. The main types of vaccines used in 2018/2019 included aTIV, QIV, and LAIV. A small number of trivalent vaccines (TIVs) were also identified (n=1526); as they were not recommended in the national influenza vaccination program, we excluded them from the analyses.

Adverse Event of Interest

The incidence rates of AEs for which patients sought consultation in the 7 days post vaccination are listed in [Table 2](#), grouped by category of surveillance condition. We observed AEs in every EMA category, from the most common ones of cough, myalgia, rash, and headache to the more severe ones such as Guillain-Barré syndrome (n=4) and anaphylaxis (n=6).

Table 2. Number of adverse events of interest reported following seasonal influenza vaccination in the United Kingdom's Royal College of General Practitioners Research and Surveillance Centre between September 1, 2018, and April 30, 2019, by type of vaccine.

	aTIV ^a (total doses n=454,567)				QIV ^b (total doses n=238,654)				LAIV ^c (total doses n=102,538)			
	Total events in season, n	Events within 7 days of vaccination, n	7-day cumulative incidence (events per 100,000 doses)	Events within 7 days/total events in season	Total events in season, n	Events within 7 days of vaccination, n	7-day cumulative incidence (events per 100,000 doses)	Events within 7 days/total events in season	Total events in season, n	Events within 7 days of vaccination, n	7-day cumulative incidence (events per 100,000 doses)	Events within 7 days/total events in season
Fever/pyrexia												
Fever (unspecified)	2413	75	16.50	0.03	1959	83	34.78	0.04	3107	87	84.85	0.03
Mild fever ($\leq 38.5^{\circ}\text{C}$)	6150	133	29.26	0.02	3493	90	37.71	0.03	5248	140	136.53	0.03
Moderate fever ($38.6\text{--}39.5^{\circ}\text{C}$)	563	13	2.86	0.02	344	13	5.45	0.04	1352	23	22.43	0.02
High fever ($>39.5^{\circ}\text{C}$)	67	0	0	0	28	1	0.42	0.04	220	1	0.98	0.00
Gastrointestinal												
Decreased appetite	1284	71	15.62	0.06	487	36	15.08	0.07	359	14	13.65	0.04
Diarrhea	9388	350	77.00	0.04	3631	185	77.52	0.05	1262	32	31.21	0.03
Nausea	2365	110	24.20	0.05	1170	82	34.36	0.07	166	14	13.65	0.08
Vomiting	2323	61	13.42	0.03	1571	69	28.91	0.04	1264	39	38.03	0.03
General nonspecific symptoms												
Drowsiness	331	10	2.20	0.03	70	4	1.68	0.06	17	0	0	0
Fatigue	5406	290	63.80	0.05	3449	290	121.51	0.08	297	11	10.73	0.04
Headache	7169	356	78.32	0.05	8883	617	258.53	0.07	919	34	33.16	0.04
Irritability	58	9	1.98	0.16	81	4	1.68	0.05	17	1	0.98	0.06
Malaise	4451	144	31.68	0.03	1596	65	27.24	0.04	367	11	10.73	0.03
Local symptoms (ie, local erythema)	49	5	1.10	0.10	29	10	4.19	0.34	6	0	0	0
Musculoskeletal												
Arthropathy	515	28	6.16	0.05	321	23	9.64	0.07	3	0	0	0
Muscle aches/myalgia	35,421	1911	420.40	0.05	17,836	1381	578.66	0.08	951	32	31.21	0.03
Neurological												
Bell palsy	217	9	1.98	0.04	193	9	3.77	0.05	12	0	0	0
Guillain-Barré syndrome	26	3	0.66	0.12	4	0	0	0	1	0	0	0
Peripheral tremor	1379	79	17.38	0.06	385	27	11.31	0.07	22	2	1.95	0.09
Seizure/febrile convulsions	784	33	7.26	0.04	693	21	8.80	0.03	263	9	8.78	0.03
Rash	13,351	671	147.61	0.05	5888	445	186.46	0.08	3920	145	141.41	0.04
Respiratory/miscellaneous												
Conjunctivitis	5140	269	59.18	0.05	1892	111	46.51	0.06	1709	57	55.59	0.03
Coryza	610	27	5.94	0.04	491	30	12.57	0.06	347	20	19.50	0.06
Cough	42,829	1882	414.02	0.04	21,251	1500	628.52	0.07	8408	348	339.39	0.04
Epistaxis	3142	114	25.08	0.04	790	52	21.79	0.07	586	26	25.36	0.04
Hoarseness	1168	49	10.78	0.04	619	37	15.50	0.06	37	0	0	0
Influenza-like illness	1283	64	14.08	0.05	1347	54	22.63	0.04	205	9	8.78	0.04

	aTIV ^a (total doses n=454,567)				QIV ^b (total doses n=238,654)				LAIV ^c (total doses n=102,538)			
	Total events in season, n	Events within 7 days of vaccination, n	7-day cumulative incidence (events per 100,000 doses)	Events within 7 days/total events in season	Total events in season, n	Events within 7 days of vaccination, n	7-day cumulative incidence (events per 100,000 doses)	Events within 7 days/total events in season	Total events in season, n	Events within 7 days of vaccination, n	7-day cumulative incidence (events per 100,000 doses)	Events within 7 days/total events in season
Nasal congestion	3041	149	32.78	0.05	1727	119	49.86	0.07	465	19	18.53	0.04
Oropharyngeal pain	3488	144	31.68	0.04	3926	177	74.17	0.05	1915	58	56.56	0.03
Rhinorrhoea	654	29	6.38	0.04	301	25	10.48	0.08	243	6	5.85	0.02
Wheezing	2873	191	42.02	0.07	2633	370	155.04	0.14	2302	119	116.05	0.05
Sensitivity/anaphylaxis												
Anaphylactic reactions	32	0	0	0	69	4	1.68	0.06	15	0	0	0
Facial edema	280	8	1.76	0.03	187	8	3.35	0.04	20	0	0	0
Hypersensitivity reactions	750	48	10.56	0.06	697	68	28.49	0.10	289	14	13.65	0.05

^aaTIV: adjuvanted trivalent influenza vaccine.

^bQIV: quadrivalent influenza vaccine.

^cLAIV: live attenuated influenza vaccine.

Timing of AEs

We observed a slight reduction in the incidence of AEs in the 7 days prior to vaccination (RI 0.91, 95% CI 0.89-0.94). The 7 days following vaccination showed an elevated incidence (RI 1.88, 95% CI 1.84-1.91). The period of day 8 to 14 was not associated with a significant increase in incidence, and the period of day 15 to 45 only showed a marginally increased incidence (RI 1.01, 95% CI 1.00-1.03; [Table 3](#)).

We also observed a seasonal pattern of AEs, with increasing incidence as the influenza season progresses, reaching a peak around February, and then the incidence declines until the end of the season. The exception to this pattern is the 30-day period that encompasses the end-of-year holidays, which showed a lower incidence compared to the preceding and succeeding 30-day periods ([Table 3](#)).

Table 3. Model 1: relative incidence of adverse events of interest in the exposure risk and seasonal periods, as reported by seasonal influenza vaccine recipients in the United Kingdom's Royal College of General Practitioners Research and Surveillance Centre network between September 1, 2018, and April 30, 2019.

	Relative incidence (95% CI)	P value
Exposure risk period		
Days -7 to -1	0.91 (0.89-0.94)	<.001
Days 0 to 6	1.88 (1.84-1.91)	<.001
Days 7 to 13	1.01 (0.99-1.04)	.28
Days 14 to 45	1.01 (1.00-1.03)	.03
Time from start of influenza season (reference: days 0 to 29)		
Days 30 to 59	1.11 (1.09-1.13)	<.001
Days 60 to 89	1.15 (1.14-1.17)	<.001
Days 90 to 119	1.07 (1.06-1.09)	<.001
Days 120 to 149	1.29 (1.27-1.31)	<.001
Days 150 to 179	1.33 (1.31-1.35)	<.001
Days 180 to 209	1.26 (1.24-1.28)	<.001
Days 210 to 241	1.08 (1.06-1.10)	<.001

Vaccine Type and Vaccination Setting

To compare the incidence of AEIs associated with the different types of vaccines, we incorporated an interaction term in the model. The results showed that relative to aTIV, QIV was associated with more AEIs (RI 1.46, 95% CI 1.41-1.52), whereas LAIV was associated with fewer AEIs (RI 0.78, 95% CI 0.73-0.83; Table 4).

Similarly, we added an interaction term to the model to explore whether vaccination setting had an impact on rates of AEIs. There appeared to be no significant difference in rates of AEIs whether or not the vaccination took place within a practice (RI 0.97, 95% CI 0.66-1.43; Table 5).

Table 4. Model 2: relative incidence of adverse events of interest, as reported by seasonal influenza vaccine recipients in the United Kingdom's Royal College of General Practitioners Research and Surveillance Centre network between September 1, 2018, and April 30, 2019, and modification effects of vaccine type.

	Relative incidence (95% CI)	P value
Exposure risk period		
Days 0 to 6	1.61 (1.57-1.65)	<.001
Time from start of influenza season (reference: days 0 to 29)		
Days 30 to 59	1.11 (1.09-1.12)	<.001
Days 60 to 89	1.16 (1.15-1.18)	<.001
Days 90 to 119	1.08 (1.07-1.10)	<.001
Days 120 to 149	1.30 (1.28-1.32)	<.001
Days 150 to 179	1.34 (1.32-1.36)	<.001
Days 180 to 209	1.27 (1.25-1.29)	<.001
Days 210 to 241	1.09 (1.07-1.10)	<.001
Vaccine type (reference: adjuvanted trivalent influenza vaccine)		
Quadrivalent influenza vaccine	1.46 (1.41-1.52)	<.001
Live attenuated influenza vaccine	0.78 (0.73-0.83)	<.001

Table 5. Model 3: relative incidence of adverse events of interest, as reported by seasonal influenza vaccine recipients in the United Kingdom's Royal College of General Practitioners Research and Surveillance Centre network between September 1, 2018, and April 30, 2019, and interaction term for vaccination setting.

	Relative incidence (95% CI)	P value
Exposure risk period		
Days 0 to 6	1.85 (1.25-2.73)	.002
Time from start of influenza season (reference: days 0 to 29)		
Days 30 to 59	1.11 (1.09-1.13)	<.001
Days 60 to 89	1.16 (1.14-1.18)	<.001
Days 90 to 119	1.08 (1.06-1.10)	<.001
Days 120 to 149	1.30 (1.28-1.32)	<.001
Days 150 to 179	1.34 (1.32-1.36)	<.001
Days 180 to 209	1.27 (1.25-1.29)	<.001
Days 210 to 241	1.09 (1.07-1.10)	<.001
Vaccination setting (reference: not in practice)		
In practice	0.97 (0.66-1.43)	.88

Discussion

Key Findings

In this study, we examined the incidence of AEIs following seasonal influenza vaccination, and the moderation effects of vaccination type and setting. We demonstrated that AEIs most

occurred within 7 days post vaccination, although a small increase in incidence was also detected between days 15 and 45. Similar to observations from earlier influenza seasons, we also found a small "healthy vaccinee" effect in the 7 days leading up to vaccination, possibly due to patients who felt unwell deferring vaccination [20]. The seasonal pattern we

observed was expected, as many of the AEs are more common in winter.

Vaccination type had a significant effect on the incidence of AEs in the 7 days post vaccination; we found that LAIV was associated with the lowest incidence, followed by aTIV and QIV. The incidence of AEs following immunization with LAIV was 22% lower than that with aTIV, which in turn had a 46% lower incidence of AEs than QIV. Data from earlier influenza seasons also showed a similar pattern where LAIV was associated with lower incidence of AEs compared to QIV [20]. The finding that aTIV was associated with lower rates of AEs than QIV was unexpected, as previous clinical trials and postlicensure studies have either reported higher reactogenicity with aTIV compared to TIV or similar safety profiles between the two [21-23].

Vaccination setting did not influence the incidence of AEs; receiving the influenza vaccine outside of a practice was not associated with higher rates of AEs. In the United Kingdom, most of these vaccinations not administered in a practice would have taken place in a pharmacy. In recent years, several countries have introduced pharmacy-based influenza vaccination services to enhance vaccination coverage. Their convenience and accessibility are thought to address some of the factors that contribute to vaccine hesitancy. Previous studies have reported that patient experiences are generally positive [24] and that vaccine delivery was safe [25]. Our findings are in accordance with prior research that influenza vaccines administered outside of a practice are safe, and leveraging this to enhance vaccination coverage may be particularly important in a pandemic, and commissioning other providers in addition to pharmacists may be an option to consider. The only downside of pharmacist vaccination is that there is no electronic transmission of administration into GP computerized medical record systems [26].

Strengths and Limitations

The RCGP RSC is a nationally representative sentinel network, and practices receive feedback about data quality, so only data that meet a quality threshold are included in our report. However, it is important to acknowledge that the data used in this study is based on GP consultations, and patients are unlikely to seek medical attention for commonly expected or minor AEs but tend to self-manage instead, or they may have directly attended the hospital for more severe AEs. Furthermore, we were unable to identify brand-specific information for a proportion of the vaccinations; most often this is where vaccines are not administered in general practice [26]. Given that different types of vaccines were offered to different age groups in the 2018/2019 season, it is possible that the differences in rates of AEs that we observed reflect differences in reactogenicity.

Further Research

To date, most vaccines have had egg-based manufacturing, but in the 2019/2020 season cell-based manufactured vaccines were introduced [27]. A similar comparison of AEs should be conducted to compare cell-based with egg-based QIV. Additionally, the sentinel system has had to adapt for the COVID-19 pandemic [28,29]; this has resulted in the expansion of the network size and the strengthening of its infrastructure [30]. The United Kingdom has ordered over 90 million COVID-19 vaccine doses [31], and the sentinel system could be used to monitor AEs associated with its administration.

Conclusions

The incidence of AEs varied between different types of vaccines and can be compared using routine sentinel network data. Here, we report that aTIV are associated with fewer AEs than QIV, but more AEs than LAIV. Rates of AEs were similar whether a vaccine took place in or outside of a practice. These findings should be reassuring for patients, address some of the factors that contribute to vaccine hesitancy, and may help improve vaccination coverage in future influenza seasons.

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Authors' Contributions

SdL conceived the concept for the study. OA, MJ, and SdL participated in the study design. RSMT with input from MJ generated key code and conducted the analysis. JS performed data extraction. RSMT, OA, and SdL contributed to manuscript preparation. All authors contributed to manuscript revision.

Conflicts of Interest

SdL is the Director of the Royal College of General Practitioners Research and Surveillance Centre; has received funding through his University for studies from Eli Lilly, AstraZeneca, Sanofi, GSK, Seqirus, and Takeda; and has been a member of advisory boards for influenza for Seqirus and Sanofi.

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Abbreviations

AEI: adverse event of interest
aTIV: adjuvanted trivalent influenza vaccine
EMA: European Medicines Agency
GP: general practitioner
IMD: index of multiple deprivation
LAIV: live attenuated influenza vaccine
QIV: quadrivalent influenza vaccine
RCGP: Royal College of General Practitioners
RI: relative incidence
RSC: Research and Surveillance Centre
TIV: trivalent vaccine

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Original Paper

The Transition of Social Isolation and Related Psychological Factors in 2 Mild Lockdown Periods During the COVID-19 Pandemic in Japan: Longitudinal Survey Study

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Abstract

Background: Lockdowns and stay-at-home orders announced internationally for COVID-19 have led to physical and social distancing, with reports of many individuals experiencing social isolation (SI) and loneliness. Although the emergency declaration in Japan was declared as a “mild” lockdown requested by the government without penalties for violations, the lockdown measures, including SI, had several influences on people’s lives and mental health as in other countries. Furthermore, Japan declared a state of emergency multiple times; thus, it is necessary to examine the influence of the transition of SI caused by repeated emergency declarations and the deterioration of mental health associated with these changes.

Objective: This study longitudinally investigated the transition of SI and its related factors during the mild lockdown under 2 declared states of emergency in Japan and analyzed psychosocial characteristics by extracting clusters where people with specific transition patterns of SI predominated.

Methods: We collected data on 7893 inhabitants (3694 [46.8%] women, 49.6 [SD 13.7] years old) living in the 7 prefectures where the initial emergency declaration was applied. The investigations took place online in the final phase of the first and second states of emergency: phase 1 (between May 11 and 12, 2020) and phase 2 (between February 24 and 28, 2021). Nonparametric Bayesian coclustering was used to visualize the exhaustive interaction structure between the transition pattern of SI and the psychosocial variables.

Results: There were no improvements in social networks and loneliness between the 2 phases, although psychological distress significantly improved and depression slightly decreased. Overall, 3868 (49%) of the 7893 participants remained socially isolated through phases 1 and 2, and 947 (12%) were socially isolated in phase 2, even though they were not socially isolated in phase 1. More participants experienced persistent SI in unmarried, childless, and low-household-income groups. The persistent-SI group had fewer cohabitants than other transition pattern groups. The nonparametric Bayesian coclustering results showed that most clusters, including participants without SI throughout phases 1 and 2, had healthy behaviors, more interactions, good relationships, and less loneliness and psychological stress. Furthermore, the cluster in which relationships deteriorated in phase 1 recovered in phase 2. Comparatively, the clusters with SI throughout phases 1 and 2 were divided into clusters with increased loneliness and psychological stress; clusters were close to participants’ average scores in this study. The clusters with increased loneliness and psychological stress were notable for deteriorating relationships and less online interaction.

Conclusions: This study revealed the actual state of transition of SI and related psychological, social, and behavioral factors under repeated declarations of a state of emergency. These results should help construct intervention methods that fit individual characteristics of people in SI during a pandemic.

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KEYWORDS

coronavirus disease 2019; mild lockdown; social isolation; longitudinal survey; public health; surveillance; epidemiology; COVID-19; pandemic; lockdown; psychological behavior; social factors; mental health

Introduction

COVID-19 has rapidly spread worldwide since its outbreak in December 2019 [1]. To deter the spread of COVID-19, many countries have imposed a lockdown with restrictions on outings, service closures, etc. Although lockdowns are expected to prevent the spread of infection, they also cause psychological distress and economic damage [2-4].

Lockdowns and stay-at-home orders announced internationally for COVID-19 have led to physical and social distancing, with reports of many individuals experiencing social isolation (SI) [1,5,6]. Previous research in the elderly reported that individuals who were socially isolated before the pandemic were particularly vulnerable to the negative psychological impacts of the COVID-19 lockdown [6]. However, greater social support during the pandemic was reported to be inversely associated with thoughts of suicide and self-harm [7]. In addition, elevated loneliness during stay-at-home orders is strongly associated with more severe depression and suicidal ideation [8,9]. Thus, SI and the resulting loneliness under stay-at-home orders for COVID-19 are a critical public health concern.

The impact of the “mild” lockdown [10] following the declaration of a state of emergency in Japan has attracted attention. On April 7, 2020, the Japanese government declared a state of emergency due to the COVID-19 outbreak in 7 prefectures [11]. The state of emergency expanded nationwide on April 16, 2020, and was lifted in a phased manner starting on May 14, 2020. In the middle of the third wave of COVID-19, the Japanese government again declared a state of emergency in 4 prefectures on January 8, 2021, and 7 more on January 14. The second state of emergency was lifted in stages starting in March, except for 1 prefecture, where the state was lifted on February 7. Although many countries were in lockdown with penalties for violations, a distinguishing feature of the Japanese policy for COVID-19 was the government requesting that people refrain from going out, except for emergencies, and temporarily close certain businesses, with no penalties imposed for violations. As the emergency declaration in Japan was a “request” by the government, it did not prohibit people from going out or meeting other people. However, Japan’s mild lockdown influenced people’s lives in many ways, as in other countries, such as lifestyle changes due to teleworking or online classes held in many schools and economic damage due to decreased income or job loss.

Additionally, this lockdown significantly transformed activity in Japan; for example, the number of monthly train users in April 2020 and February 2021 prominently decreased by 45.5%

compared to the previous year [12,13]. Our previous research reported severe SI, loneliness, and psychological distress during the first mild lockdown in Japan [5,10,14,15]. Furthermore, our previous study reported that people experienced extreme SI in the first state of emergency. Again, being male, being middle aged, and having a lower income predicted SI. In contrast, being a student was inversely associated with SI [5].

However, just as many countries have repeatedly declared lockdowns, Japan has also repeatedly declared emergencies, as mentioned earlier. Therefore, it is necessary to examine the influence of the transition (ie, worsening, improving, or maintaining) of SI caused by the prolonged pandemic and emergency declarations and the relationship between the transition pattern and the deterioration of mental health associated with the prolonged pandemic [16]. By examining these findings, we might clarify whether SI in the pandemic is a persistent problem rather than a temporary one and whether people who did not show SI problems in the early stages of the pandemic will later reveal such issues. In addition, clarifying the psychosocial characteristics of people who manifest different transition patterns of SI can provide information to consider what kind of help is needed based on individuals’ characteristics.

Therefore, the purpose of this study was to longitudinally investigate the transition of SI from the beginning of the pandemic to the end of a specified period, and its related factors by surveying during the mild lockdown under 2 declared states of emergency in Japan. We also analyzed psychosocial characteristics by extracting clusters where people with specific transition patterns of SI (development or maintenance of a state of SI in particular) predominated.

Methods

Participants and Data Collection

The survey was conducted online between May 11 and 12, 2020 (phase 1) and between February 24 and 28, 2021 (phase 2), the final phase of the state of emergency. In phase 1, we conducted an online survey of inhabitants living in the 7 prefectures where the emergency declaration measures were first applied (Tokyo, Kanagawa, Osaka, Saitama, Chiba, Hyogo, and Fukuoka) in order to detect precisely the impact of the mild lockdown. We conducted a follow-up survey on the same participants in phase 2. We recruited participants according to the following inclusion criteria: (1) inhabitants living in the 7 prefectures mentioned earlier and (2) age \geq 20 years. The exclusion criteria were as follows: (1) age $<$ 18 years, (2) high school students, and (3) living outside the seven prefectures. We determined that the target sample in phase 1 was 11,000 because of the possibility

of dropouts from the follow-up survey and the large sample size required for nonparametric Bayesian coclustering with many variables. These prefectures were assumed to be susceptible to a mild lockdown due to their large populations and the large number of COVID-19 cases reported in these areas. In phase 1, the number of people in each prefecture was determined based on the ratio of the number of people living in Tokyo ($n=2783$, 24.6%), Kanagawa ($n=1863$, 16.4%), Osaka ($n=1794$, 15.8%), Saitama ($n=1484$, 13.1%), Chiba ($n=1263$, 11.1%), Hyogo ($n=1119$, 9.9%), and Fukuoka ($n=1027$, 9.1%).

The participants of this study were recruited through Macromill, Inc (Tokyo, Japan), a global marketing research company. This company has access to more than 1,300,000 registered members with diverse characteristics regarding sex and age of all prefectures in Japan. This online survey system automatically eliminated duplicate answers from a single respondent. Approximately 80,000 registered people who lived in the target areas were recruited by email, and data were collected on an online platform. (The target sample in phase 1 was $n=11,000$.) Participants completed the online survey after receiving a link to it. All participants voluntarily responded to the survey anonymously and provided informed consent online before completing the survey. Participants received a clear explanation of the survey procedure and could interrupt or terminate the survey at any time without requiring a reason. The questionnaire format, excluding the default items provided by Macromill, Inc (sex, age, occupation, annual household income, marital status, and presence of children) did not allow participants to proceed to the next page if there were items they had not answered. All the participants received Macromill points for their participation, which constitute an original point service of Macromill, Inc, and the participants can exchange these points for prizes or cash.

This study was approved by the Research Ethics Committee at the Graduate School of Social and Industrial Science and Technology, Tokushima University (acceptance no. 212). The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

The data for this study were partly extracted from a database containing data used in our previous paper [16]. The extracted data were secondarily reanalyzed with different dependent and independent variables compared to those in the studies mentioned earlier.

Measurements

Sociodemographic Data

We collected participants' sociodemographic information, including age, sex, employment status (employed, homemaker, student, unemployed, or other), marital status, and annual household income (<JPY 2.0 million, JPY 2.0–3.9 million, JPY 4.0–5.9 million, JPY 6.0–7.9 million, \geq JPY 8.0 million, or unknown; a currency exchange rate of JPY 1=US \$0.0086 is applicable). The details of the survey items are available on an open data platform (Open Science Framework). In addition, information was collected on whether the individual or a family member was a health care worker, was currently being treated for a mental condition or severe physical disease, and had a history of treatment for a mental disorder or severe physical

illness. This information was used to compare the impact on the group assumed to be vulnerable to the lockdown effects in previous studies [17–20]. Although this information was collected in phase 1, the number of cohabitants was included in the survey in phase 2. Therefore, we needed to confirm whether the number of cohabitants could affect the SI scores of our participants, as the response option for the SI scale in this study was the number of people in their social network.

Social Isolation

Since the emergency declaration, we measured social networks using the Japanese version of the abbreviated Lubben Social Network Scale (LSNS-6, [21]). The LSNS-6 is a shortened version of the Lubben Social Network Scale [22] that includes items on the network size of relatives or friends who provide emotional and instrumental support. The LSNS-6 consists of 3 items related to the family network and 3 related to the friendship network.

The number of people in the network was calculated using a 6-point scale (0=none; 1=1 person; 2=2 people, 3=3 or 4 people; 4=5–8 people; and 5=9 or more people) for each item [23]. The total score ranged from 0 to 30 points, with higher scores indicating a larger social network and <12 points indicating SI. An LSNS-6 score of <12 points varied strongly related to sociodemographic and socioeconomic factors [24], while the score predicted depression and the development of poor physical capability [25]. The Cronbach α coefficient of the LSNS-6 for our data in phase 1 was .859.

Loneliness

We measured loneliness using the Japanese version of the University of California, Los Angeles (UCLA) Loneliness Scale, Version 3 (UCLA-LS3, [26]). The UCLA-LS3 consists of 10 items, each rated from 1 (never) to 4 (always) [27]. The total scores ranged from 10 to 40, with higher scores indicating higher levels of loneliness. The Cronbach α coefficient of the UCLA-LS3 for our data in phase 1 was .868. Loneliness and SI are conceptually distinct, with SI generally defined in terms of the objective availability of social contacts and the frequency of contact with social network members. In contrast, loneliness refers to the perception that personal and social needs are not being met [28,29]. Moreover, SI has been reported to relate to loneliness and is often a risk factor [30].

Psychological Distress

Psychological distress was measured using the Japanese version of the Kessler Psychological Distress Scale-6 (K6, [31]), a nonspecific psychological stress scale, and a 6-item screening instrument measuring distress over the past 30 days. Each question was rated on a scale of 0 (never) to 4 (always), with total scores ranging from 0 to 24. Owing to its brevity and high accuracy, the K6 is considered an ideal scale for screening for mental disorders in population-based health surveys as it is brief and highly accurate [31–33]. The Cronbach α coefficient of K6 for our data in phase 1 was .913.

We also used the Japanese version of the Patient Health Questionnaire-9 (PHQ-9, [34]) to collect basic information about the participants' mental health; the PHQ-9 consists of 9

questions. Participants reported depressive symptoms during the past 4 weeks, with a score of 0 (none) to 3 (nearly every day) [35]. The Cronbach α coefficient of PHQ-9 for our data in phase 1 was .910.

Lifestyle, Coping Behavior, and Stressors Related to the Mild Lockdown

With extensive references to the literature on the COVID-19 pandemic [17,19,20,36,37], we developed 8 lifestyle and coping behavior items and 7 stressors were assumed to be associated with the mild lockdown (refer to [15,38] and [Multimedia Appendix 1](#)). We asked participants to rate the frequency of implementation and experience of these items from the start of the mild lockdown to the time of the survey on a scale of 1 (not at all) to 7 (extremely). Item details are described in our published papers [15,38]. This study treated these Likert scale values as interval scales for convenience, and parametric tests were performed on them.

Statistical Analysis

The LSNS-6 scores of phases 1 and 2 were classified into 2 groups based on the cut-off point (12 points): with and without SI. The participants were further divided into the following 4 groups: those with no SI in both phases 1 and 2 (no-SI group), those with SI in phase 1 but not in phase 2 (improved-SI group), those with no SI in phase 1 but SI in phase 2 (worsened-SI group), and those with SI in phases 1 and 2 (persistent-SI group). The chi-square test and the *t* test were applied to compare sociodemographic characteristics and psychological indexes (LSNS-6, UCLA-LS3, K6, and PHQ-9) between individuals who participated only in phase 1 and individuals who participated in phases 1 and 2. The chi-square test compared sociodemographic data between the 4 groups. Additionally, repeated 2-way ANOVA was conducted to compare psychological indexes and mild-lockdown items for COVID-19 between the SI groups and between phases. Nonparametric Bayesian coclustering [39] visualized the exhaustive interaction structure between the transition pattern of SI and psychosocial variables exceeding the lower limit of the small effect size when comparing the 4 SI groups. These variables were not strongly correlated with others (ie, $r < 0.7$). We selected the variable that had a more prominent group difference. Overall, 15,000 iterations based on the Bayesian optimization principle were

performed to calculate the log marginal likelihood, which indicates the goodness of fit of the model. The log marginal probabilities were computed among the models, and the model with the highest log marginal likelihood was adopted. We converted the continuous variables to *z* values and assigned values between -3 and 3 to each isolation group according to the *z* value range: -3 for the no-SI group, -1 for the improved-SI group, 1 for the worsened-SI group, and 3 for the persistent-SI group. For all tests, significance was set at $\alpha = .05$, 2-tailed. Statistical analyses were performed using SPSS Statistics version 25.0 (IBM Corp, NY, USA), MATLAB R2017a (Mathworks, Inc., Natick, MA, USA), and RStudio version 1.1.442.

Results

Descriptive Results

Table 1 shows the sociodemographic characteristics in our data. In phase 1, a total of 11,333 individuals participated, and we conducted a follow-up survey on them in phase 2. A total of 7893 individuals participated in phases 1 and 2 (3694 [46.8%] women, mean age 49.6 [SD 13.7] years, range 18-89 years), and thus, 3440 (30.35%) of 11,333 individuals who participated in phase 1 did not respond in phase 2. In addition, significantly more females than males participated only in phase 1. Individuals who participated only in phase 1 had significantly higher LSNS-6, K6, and PHQ-9 scores and substantially lower ages and UCLA-LS3 scores than individuals who participated both in phases 1 and 2 ([Multimedia Appendix 2](#)).

Regarding the number of people ($N=7893$) in each group classified based on the cut-off point of the LSNS-6, the no-SI group had 2296 (29.1%), the improved-SI group had 765 (9.7%), the worsened-SI group had 964 (12.2%), and the persistent-SI group had 3868 (49.0%) people (**Table 1**). The number of cohabitants in each SI group was 2.4 (SD 1.4) in the no-SI group, 2.2 (SD 1.4) in the improved-SI group, 2.2 (SD 1.3) in the worsened-SI group, and 1.8 (SD 1.2) in the persistent-SI group. There was a significant difference in the number of cohabitants between SI groups ($F_3=106.79$, $P < .001$, $\eta^2=0.039$). Multiple comparisons showed that the persistent-SI group had significantly fewer cohabitants than other SI groups. The worsened-SI group had considerably fewer cohabitants than the no-SI group (all $P < .001$).

Table 1. Comparison of sociodemographic characteristics by transition pattern of SI^a.

Sociodemographic indexes at time 1	Total, n (%)	LSNS ^b group				Group difference		
		No SI, n (%)	Improved SI, n (%)	Worsened SI, n (%)	Persistent SI, n (%)	χ^2 (df)	P value	Cramer V ^c
Overall	7893 (100%)	2296 (29.1)	765 (9.7)	964 (12.2)	3868 (49.0)	N/A ^d	N/A	N/A
Sex						71.62 (3)	<.001	0.095
Male	4201 (53.2)	1061 (25.3) [-] ^e	427 (10.2)	503 (12.0)	2210 (52.6) [+] ^f	N/A	N/A	N/A
Female	3692 (46.8)	1235 (33.5) [+]	338 (9.2)	461 (12.5)	1658 (44.9) [-]	N/A	N/A	N/A
Age (years)						99.92 (6)	<.001	0.080
18-39	1926 (24.4)	620 (32.2) [+]	189 (9.8)	260 (13.5) [+]	857 (44.5) [-]	N/A	N/A	N/A
40-64	4714 (59.7)	1213 (25.7) [-]	437 (9.3)	563 (11.9)	2501 (53.1) [+]	N/A	N/A	N/A
≥65	1253 (15.9)	463 (37.0) [+]	139 (11.1)	141 (11.3)	510 (40.7) [-]	N/A	N/A	N/A
Occupation						113.53 (12)	<.001	0.069
Employed	5384 (68.2)	1501 (27.9) [-]	521 (9.7)	700 (13.0) [+]	2662 (49.4)	N/A	N/A	N/A
Homemaker	1236 (15.7)	470 (38.0) [+]	125 (10.1)	133 (10.8)	508 (41.1) [-]	N/A	N/A	N/A
Student	111 (1.4)	53 (47.7) [+]	11 (9.9)	14 (12.6)	33 (29.7) [-]	N/A	N/A	N/A
Unemployed	901 (11.4)	207 (23.0) [-]	83 (9.2)	90 (10.0) [-]	521 (57.8) [+]	N/A	N/A	N/A
Other	261 (3.3)	65 (24.9)	25 (9.6)	27 (10.3)	144 (55.2) [+]	N/A	N/A	N/A
Marital status						241.29 (3)	<.001	0.175
Married	5174 (65.6)	1727 (33.4) [+]	546 (10.6) [+]	689 (13.3) [+]	2212 (42.8) [-]	N/A	N/A	N/A
Unmarried	2719 (34.4)	569 (20.9) [-]	219 (8.1) [-]	275 (10.1) [-]	1656 (60.9) [+]	N/A	N/A	N/A
Children						313.05 (3)	<.001	0.199
Yes	4477 (56.7)	1575 (35.2) [+]	490 (10.9) [+]	599 (13.4) [+]	1813 (40.5) [-]	N/A	N/A	N/A
No	3416 (43.3)	721 (21.1) [-]	275 (8.1) [-]	365 (10.7) [-]	2055 (60.2) [+]	N/A	N/A	N/A
Annual household income (JPY)^g						262.84 (12)	<.001	0.120
<2.0 million	438 (5.5)	57 (13.0) [-]	23 (5.3) [-]	30 (6.8) [-]	328 (74.9) [+]	N/A	N/A	N/A
2.0-3.9 million	1421 (18.0)	319 (22.4) [-]	127 (8.9)	166 (11.7)	809 (56.9) [+]	N/A	N/A	N/A
4.0-5.9 million	1562 (19.8)	431 (27.6)	146 (9.3)	198 (12.7)	787 (50.4)	N/A	N/A	N/A
6.0-7.9 million	1078 (13.7)	326 (30.2)	118 (10.9)	145 (13.5)	489 (45.4) [-]	N/A	N/A	N/A
≥8.0 million	1613 (20.4)	627 (38.9) [+]	177 (11.0) [+]	196 (12.2)	613 (38.0) [-]	N/A	N/A	N/A
Health care worker (self)						7.58 (3)	.06	0.031
Yes	407 (5.2)	133 (32.7)	40 (9.8)	60 (14.7)	174 (42.8) [-]	N/A	N/A	N/A
No	7486 (94.8)	2163 (28.9)	725 (9.7)	904 (12.1)	3694 (49.3) [+]	N/A	N/A	N/A
Health care worker (family)						38.26 (3)	<.001	0.070
Yes	625 (7.9)	243 (38.9) [+]	61 (9.8)	81 (13.0)	240 (38.4) [-]	N/A	N/A	N/A
No	7268 (92.1)	2053 (28.2) [-]	704 (9.7)	883 (12.1)	3628 (49.9) [+]	N/A	N/A	N/A
Treatment of current severe physical diseases						3.93 (3)	.27	0.022
Yes	378 (4.8)	95 (25.1)	39 (10.3)	43 (11.4)	201 (53.2)	N/A	N/A	N/A
No	7515 (95.2)	2201 (29.3)	726 (9.7)	921 (12.3)	3667 (48.8)	N/A	N/A	N/A
Treatment of previous severe physical diseases						1.32 (3)	.72	0.013
Yes	659 (8.3)	183 (27.8)	62 (9.4)	77 (11.7)	337 (51.1)	N/A	N/A	N/A
No	7234 (91.7)	2113 (29.2)	703 (9.7)	887 (12.3)	3531 (48.8)	N/A	N/A	N/A
Treatment of current psychological problems						54.65 (3)	<.001	0.083

Sociodemographic indexes at time 1	Total, n (%)	LSNS ^b group				Group difference		
		No SI, n (%)	Improved SI, n (%)	Worsened SI, n (%)	Persistent SI, n (%)	χ^2 (df)	P value	Cramer V ^c
Yes	431 (5.5)	63 (14.6) [-]	41 (9.5)	50 (11.6)	277 (64.3) [+]	N/A	N/A	N/A
No	7462 (94.5)	2233 (29.9) [+]	724 (9.7)	914 (12.2)	3591 (48.1) [-]	N/A	N/A	N/A
Treatment of previous psychological problems						61.71 (3)	<.001	0.088
Yes	875 (11.1)	167 (19.1) [-]	89 (10.2)	92 (10.5)	527 (60.2) [+]	N/A	N/A	N/A
No	7018 (88.9)	2129 (30.3) [+]	676 (9.6)	872 (12.4)	3341 (47.6) [-]	N/A	N/A	N/A

^aSI: social isolation.

^bLSNS: Lubben Social Network Scale.

^cCramer V: 0.100, small; 0.300, medium; 0.600, large.

^dN/A: not applicable.

^e[-]: adjusted residuals ≤ -1.96 .

^f[+]: adjusted residuals ≥ 1.96 .

^gIn our data set, although 982 (12.4%) of 7893 participants did not provide any data regarding annual household income, there were no missing data for the other variables. The table does not include the "Unknown" classification of yearly household income (799/7893, 10.1%).

Transition of Social Isolation and Sociodemographic Characteristics

Table 1 shows the differences in sociodemographic characteristics based on the transition pattern of SI. There were significant differences between the 4 groups of SI in all sociodemographic characteristics except for "Health worker (self)" and "Treatment of current/previous severe physical diseases" (ie, $P < .05$). Results of the chi-square test that exceeded the lower limit of "small effect size" (ie, Cramer $V > 0.100$) indicated unmarried or childless people were more prevalent in the persistent-SI group. In contrast, married people and individuals with children were more commonplace in other SI groups. Additionally, individuals in lower-annual-household-income groups (<JPY 200 million or between JPY 2.0 and 3.9 million) were more prevalent in the persistent-SI group. Individuals in higher-annual-household-income groups (\geq JPY 8.0 million) were more prevalent in the no-SI and improved-SI groups.

Transition of Social Isolation and Psychological or COVID-19 Related Variables

Tables 2-4 display the differences and interactions between phases and the transition of SI in psychological or COVID-19-related variables. Regarding interactions between phases and groups, the results were significant on the LSNS-6, UCLA-LS3, K6, and items about lifestyle and stress management during the mild lockdown ("Deterioration of

relationship with familiar people," "Difficulties owing to the lack of daily necessities," and "Difficulties in work or schoolwork"). In contrast, the results only on the LSNS-6 exceeded the lower limit of "small effect size" (ie, generalized η^2 [η_G^2] > 0.010). The simple main effect test in the LSNS-6 indicated a significant difference between each group in phases 1 and 2 and between phases in all groups.

Group classification had significant effects on all variables except COVID-19-related anxiety. At the same time, the results exceeded the lower limit of "small effect size" on the LSNS-6, UCLA-LS3, K6, PHQ-9, and lifestyle and stress management items during the mild lockdown and the "Deterioration of relationship with familiar people" item. The multiple comparison test indicated significant differences between all groups, excluding the improved-SI group and the worsened-SI group, on the LSNS-6, UCLA-LS3, K6, PHQ-9, and lifestyle and stress management items during the mild lockdown. Regarding "Deterioration of relationships with familiar people," a significant difference between the no-SI group and other groups was evident.

Regarding the effect of phase, results were significant for all variables except for "Healthy sleep habits." In contrast, results exceeded the lower limit of "small effect size" on the K6 as well as items on "Online interaction with familiar people," "COVID-19-related anxiety," "Difficulties owing to the lack of daily necessities," and "Difficulties in work and schoolwork."

Table 2. Differences and interactions between phases^a and transition of SI^b on different scales.

Phase	Mean score (SD)				Effect of phase			Effect of group			Interaction		
	No SI	Improved SI	Worsened SI	Persistent SI	<i>F</i> (<i>df</i>)	<i>P</i> value	η_G^{2c}	<i>F</i> (<i>df</i>)	<i>P</i> value	η_G^2	<i>F</i> (<i>df</i>)	<i>P</i> value	η_G^2
LSNS-6^d													
1	16.84 (3.71)	7.89 (2.77)	14.58 (2.73)	5.50 (3.31)	15.18 (1, 7889)	<.001	0.000	8071.80 (3, 7889)	<.001	0.640	2046.36 (3, 7889)	<.001	0.066
2	16.46 (3.55)	14.56 (2.83)	7.81 (2.93)	5.21 (3.28)	N/A ^e	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
UCLA-LS3^f													
1	19.56 (4.67)	23.07 (4.61)	22.26 (4.55)	26.41 (5.20)	10.51 (1, 7889)	.001	0.000	1096.28 (3, 7889)	<.001	0.259	38.59 (3, 7889)	<.001	0.002
2	19.87 (4.86)	22.13 (4.76)	23.38 (4.59)	26.62 (5.33)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
K6^g													
1	3.99 (4.38)	5.23 (5.37)	4.96 (4.88)	6.12 (5.77)	536.70 (1, 7889)	<.001	0.013	103.10 (3, 7889)	<.001	0.030	2.64 (3, 7889)	.048	0.000
2	2.63 (4.01)	3.37 (4.87)	3.68 (4.82)	4.71 (5.63)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
PHQ-9^h													
1	3.05 (4.06)	4.41 (5.39)	4.19 (5.05)	5.53 (5.93)	168.90 (1, 7889)	<.001	0.004	126.46 (3, 7889)	<.001	0.038	2.32 (3, 7889)	.073	0.000
2	2.4 (3.89)	3.27 (5.19)	3.49 (4.88)	4.77 (6.07)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

^aPhase 1: between May 11 and 12, 2020, in the final phase of the first state of emergency; phase 2: between February 24 and 28, 2021, in the final phase of the second state of emergency.

^bSI: social isolation.

^c η_G^2 : 0.010, small; 0.060, medium; 0.140, large.

^dLSNS-6: Lubben Social Network Scale (shortened version).

^eN/A: not applicable.

^fUCLA-LS3: University of California, Los Angeles (UCLA) Loneliness Scale, Version 3.

^gK6: Kessler Psychological Distress Scale-6.

^hPHQ-9: Patient Health Questionnaire-9.

Table 3. Differences and interactions between phases^a and transition of SI^b with regard to lifestyle and coping behavior during the mild lockdown.

Phase	Mean score (SD)				Effect of phase			Effect of group			Interaction		
	No SI	Improved SI	Worsened SI	Persistent SI	<i>F</i> (<i>df</i>)	<i>P</i> value	η^2 ^c	<i>F</i> (<i>df</i>)	<i>P</i> value	η^2	<i>F</i> (<i>df</i>)	<i>P</i> value	η^2
Exercise													
1	4.70 (1.64)	4.19 (1.74)	4.29 (1.73)	3.73 (1.84)	231.42 (1, 7889)	<.001	0.007	172.62 (3, 7889)	<.001	0.047	9.25 (3, 7889)	<.001	0.001
2	4.27 (1.85)	4.04 (1.80)	3.69 (1.87)	3.37 (1.92)	N/A ^d	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Healthy eating habits													
1	4.85 (1.37)	4.29 (1.50)	4.50 (1.39)	4.02 (1.58)	59.83 (1, 7889)	<.001	0.002	174.34 (3, 7889)	<.001	0.049	11.40 (3, 7889)	<.001	0.001
2	4.64 (1.48)	4.38 (1.62)	4.18 (1.58)	3.84 (1.67)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Healthy sleep habits													
1	5.11 (1.61)	4.57 (1.74)	4.93 (1.62)	4.48 (1.80)	0.36 (1, 7889)	.55	0.000	95.49 (3, 7889)	<.001	0.025	9.59 (3, 7889)	<.001	0.001
2	5.15 (1.62)	4.81 (1.65)	4.71 (1.73)	4.48 (1.83)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Favorite activity													
1	4.47 (1.51)	3.96 (1.63)	4.18 (1.53)	3.68 (1.68)	165.71 (1, 7889)	<.001	0.006	140.84 (3, 7889)	<.001	0.037	14.76 (3, 7889)	<.001	0.002
2	4.09 (1.64)	3.95 (1.65)	3.64 (1.64)	3.38 (1.70)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Offline interaction with familiar people													
1	4.10 (1.82)	3.54 (1.76)	3.82 (1.77)	3.12 (1.78)	80.24 (1, 7889)	<.001	0.003	248.96 (3, 7889)	<.001	0.057	8.41 (3, 7889)	<.001	0.001
2	3.85 (1.77)	3.54 (1.74)	3.30 (1.72)	2.84 (1.73)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Online interaction with familiar people													
1	3.82 (2.01)	3.15 (1.85)	3.53 (1.92)	2.54 (1.73)	383.57 (1, 7889)	<.001	0.015	294.38 (3, 7889)	<.001	0.070	25.13 (3, 7889)	<.001	0.003
2	3.10 (1.89)	2.84 (1.76)	2.72 (1.77)	2.18 (1.56)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Preventive behaviors of COVID-19													
1	5.92 (1.38)	5.41 (1.68)	5.65 (1.47)	5.25 (1.82)	8.39 (1, 7889)	.004	0.000	93.90 (3, 7889)	<.001	0.024	14.08 (3, 7889)	<.001	0.002
2	5.83 (1.39)	5.51 (1.62)	5.30 (1.74)	5.29 (1.79)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Optimism													
1	4.65 (1.34)	3.94 (1.47)	4.25 (1.42)	3.57 (1.53)	65.02 (1, 7889)	<.001	0.002	336.67 (3, 7889)	<.001	0.081	18.09 (3, 7889)	<.001	0.002
2	4.76 (1.41)	4.41 (1.51)	4.18 (1.46)	3.79 (1.55)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

^aPhase 1: between May 11 and 12, 2020, in the final phase of the first state of emergency; phase 2: between February 24 and 28, 2021, in the final phase of the second state of emergency.

^bSI: social isolation.

^c η^2 : 0.010, small; 0.060, medium; 0.140, large.

^dN/A: not applicable.

Table 4. Differences and interactions between phases^a and transition of SI^b with regard to stressors related to the mild lockdown.

Phase	Mean score (SD)				Effect of phase			Effect of group			Interaction		
	No SI	Improved SI	Worsened SI	Persistent SI	<i>F</i> (<i>df</i>)	<i>P</i> value	η^2 G ² ^c	<i>F</i> (<i>df</i>)	<i>P</i> value	η^2 G ²	<i>F</i> (<i>df</i>)	<i>P</i> value	η^2 G ²
Deterioration of household economy													
1	3.55 (1.77)	3.70 (1.71)	3.78 (1.77)	3.81 (1.77)	119.88 (1, 7889)	<.001	0.004	16.53 (3, 7889)	<.001	0.005	0.31 (3, 7889)	.82	0.000
2	3.27 (1.73)	3.41 (1.65)	3.49 (1.69)	3.56 (1.76)	N/A ^d	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Deterioration of relationship with familiar people													
1	2.09 (1.42)	2.51 (1.53)	2.33 (1.44)	2.53 (1.55)	63.22 (1, 7889)	<.001	0.003	41.39 (3, 7889)	<.001	0.011	8.68 (3, 7889)	<.001	0.001
2	2.34 (1.53)	2.60 (1.52)	2.67 (1.55)	2.61 (1.57)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Frustration													
1	3.04 (1.69)	3.27 (1.73)	3.27 (1.66)	3.35 (1.76)	7.52 (1, 7889)	.01	0.000	20.07 (3, 7889)	<.001	0.006	2.56 (3, 7889)	.05	0.000
2	2.98 (1.70)	3.11 (1.67)	3.32 (1.72)	3.24 (1.74)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
COVID-19-related anxiety													
1	4.04 (1.66)	3.97 (1.66)	4.07 (1.64)	3.98 (1.71)	418.68 (1, 7889)	<.001	0.015	0.65 (3, 7889)	.58	0.000	1.46 (3, 7889)	.22	0.000
2	3.48 (1.68)	3.54 (1.63)	3.54 (1.65)	3.49 (1.71)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
COVID-19-related sleeplessness													
1	2.33 (1.49)	2.55 (1.54)	2.57 (1.56)	2.50 (1.52)	4.57 (1, 7889)	.03	0.000	10.07 (3, 7889)	<.001	0.003	0.95 (3, 7889)	.42	0.000
2	2.31 (1.46)	2.52 (1.56)	2.51 (1.51)	2.42 (1.48)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Difficulties owing to the lack of daily necessities													
1	3.45 (1.79)	3.48 (1.79)	3.61 (1.84)	3.65 (1.84)	1037.98 (1, 7889)	<.001	0.046	5.91 (3, 7889)	<.001	0.001	4.41 (3, 7889)	.004	0.000
2	2.53 (1.59)	2.70 (1.62)	2.69 (1.57)	2.61 (1.58)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Difficulties in work or schoolwork													
1	3.64 (2.01)	3.65 (1.94)	3.79 (1.95)	3.56 (1.97)	746.47 (1, 7889)	<.001	0.028	4.43 (3, 7889)	.004	0.001	2.93 (3, 7889)	.03	0.000
2	2.77 (1.74)	2.97 (1.78)	2.97 (1.75)	2.83 (1.75)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

^aPhase 1: between May 11 and 12, 2020, in the final phase of the first state of emergency; phase 2: between February 24 and 28, 2021, in the final phase of the second state of emergency.

^bSI: social isolation.

^c η^2 G²: 0.010, small; 0.060, medium; 0.140, large.

^dN/A: not applicable.

Comprehensive Interaction Structure between Transition Pattern of Social Isolation and the Psychosocial Variables

The results of nonparametric Bayesian coclustering are shown in Figure 1 and Table 5. Clusters with more than 50% of the data in a particular group and adjusted residuals greater than

1.96 are clusters A, B, D, E, G, K, L, and N (Table 5, see values in italics). Of these clusters, we describe next clusters in which each variable had a notable feature (refer to red boxes in Figure 1). Multimedia Appendix 3 is a supplementary document displaying a visualization of differences in scores among the clusters.

For cluster A (720/1309 [55.0%] no-SI group in Table 5), healthy behaviors and attitudes, more online and offline interactions, decreased deterioration of relationships (especially in phase 1), and lower UCLA-LS3 and K-6 scores were maintained throughout phases 1 and 2 (see red box in Figure 1, cluster A).

For cluster B (661/1215 [54.4%] persistent-SI group in Table 5), the deterioration of relationships in phase 1 improved in phase 2. In contrast, online interactions, common in phase 1, decreased in phase 2 (see red box 1 in Figure 1, cluster B). The high UCLA-LS3 and K-6 scores were not higher than the average score throughout phases 1 and 2 (see red box 2 in Figure 1, cluster B).

Cluster D (725/947 [76.6%] persistent-SI group in Table 5) experienced deterioration of relationships, low online interactions (see red box 3 in Figure 1, cluster D), and high UCLA-LS3 and K-6 scores throughout phases 1 and 2 (see red box 4 in Figure 1, cluster D).

Cluster E (534/847 [63.0%] persistent-SI group in Table 5) experienced less deterioration of relationships and fewer online interactions throughout phases 1 and 2. Their scores on the

UCLA-LS3 and K-6 were close to the mean scores of all participants (see red box in Figure 1, cluster E).

Cluster K (106/193 [54.9%] no-SI group in Table 5) maintained lower UCLA-LS3 and K-6 scores and high levels of online and offline interactions throughout phases 1 and 2 (see red box in Figure 1, cluster K).

Cluster L (100/171 [58.5%] no-SI group in Table 5) showed healthy behaviors and attitudes and high levels of online and offline interactions throughout phases 1 and 2. These characteristics were prominent, especially in cluster L. However, they maintained lower UCLA-LS3 and K-6 scores and deteriorated relationships, common in phase 1, and improved in phase 2 (see red box in Figure 1, cluster L).

Cluster N (110/138 [79.7%] persistent-SI group in Table 5) maintained fewer healthy behaviors and attitudes, fewer online and offline interactions, deterioration of relationships, and higher UCLA-LS3 and K-6 scores throughout phases 1 and 2 (see red box in Figure 1, cluster N).

In addition, we did not extract clusters for many improved-SI or worsened-SI groups.

Figure 1. Comprehensive interaction structure of psychosocial variables associated with transition pattern of SI. The red boxes indicate variables with notable features in each cluster. K6: Kessler Psychological Distress Scale-6; P1: phase 1; P2: phase 2; SI: social isolation; UCLA-LS3: University of California, Los Angeles (UCLA) Loneliness Scale, Version 3.

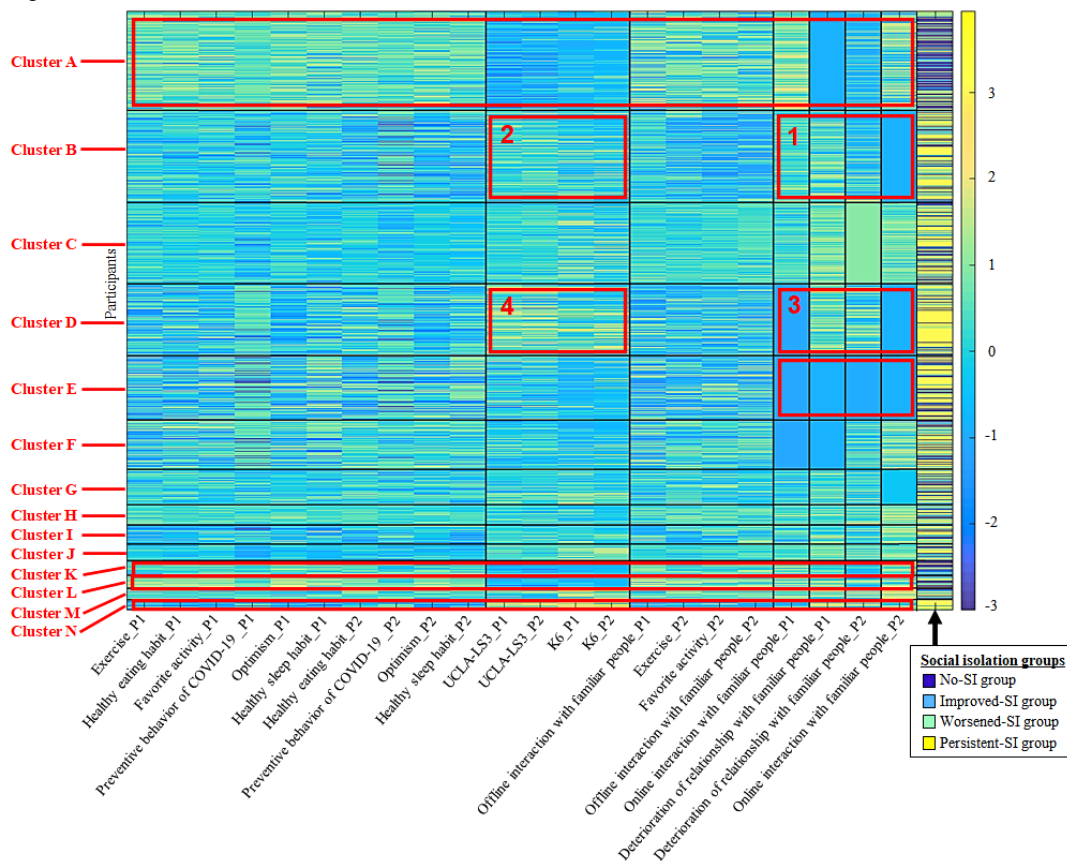


Table 5. Number and percentage of each cluster in each SI^a group.

Results ^b	Cluster													
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Total, N	1309	1215	1070	947	847	650	466	266	251	219	193	171	151	138
No SI														
n (%)	720 (55.0)	282 (23.2)	272 (25.4)	96 (10.1)	175 (20.7)	192 (29.5)	93 (20.0)	96 (36.1)	61 (24.3)	46 (21.0)	106 (54.9)	100 (58.5)	54 (35.8)	3 (2.2)
Adjusted residuals	22.6	-4.9	-2.8	-13.7	-5.7	0.3	-4.5	2.6	-1.7	-2.7	8.0	8.6	1.8	-7.0
Improved SI														
n (%)	118 (9.0)	108 (8.9)	124 (11.6)	67 (7.1)	62 (7.3)	61 (9.4)	47 (10.1)	37 (13.9)	28 (11.2)	32 (14.6)	20 (10.4)	19 (11.1)	26 (17.2)	16 (11.6)
Adjusted residuals	-0.9	-1.0	2.3	-2.9	-2.5	-0.3	0.3	2.4	0.8	2.5	0.3	0.6	3.2	0.8
Worsened SI														
n (%)	195 (14.9)	164 (13.5)	138 (12.9)	59 (6.2)	76 (9.0)	74 (11.4)	76 (16.3)	31 (11.7)	35 (13.9)	26 (11.9)	28 (14.5)	29 (17.0)	24 (15.9)	9 (6.5)
Adjusted residuals	3.2	1.5	0.7	-6.0	-3.0	-0.7	2.8	-0.3	0.9	-0.2	1.0	1.9	1.4	-2.1
Persistent SI														
n (%)	276 (21.1)	661 (54.4)	536 (50.1)	725 (76.6)	534 (63.0)	323 (49.7)	250 (53.6)	102 (38.3)	127 (50.6)	115 (52.5)	39 (20.2)	23 (13.5)	47 (31.1)	110 (79.7)
Adjusted residuals	-22.1	4.1	0.8	18.1	8.7	0.4	2.1	-3.5	0.5	1.1	-8.1	-9.4	-4.4	7.3

^aSI: social isolation.

^bClusters A, B, D, E, G, K, L, and N had >50% of data in a particular group and adjusted residuals >1.96 (italicized values).

Discussion

Principal Findings

There were no improvements in social networks (the LSNS-6 score) and loneliness between the 2 emergency declarations, although psychological distress significantly improved and depression slightly decreased. This result may be because the same number of people in the group who had no SI problems (LSNS-6 score ≤ 12) in phase 1 but became socially isolated (LSNS-6 score < 12) in phase 2 and vice versa were included in the target population of this study. These groups were smaller than the group whose SI status remained unchanged. However, we confirmed that the LSNS-6 score and the UCLA-LS3 score observed at each time point tended to be lower and higher, respectively, than in previous studies conducted during the nonpandemic period; the mean score of the LSNS-6 was 16.2 points and that of UCLA-LS3 was 17.5 points [21,26]. Regarding the presence of SI in the 2 periods under the declaration of the state of emergency, 3868 (49%) of the 7893 participants remained socially isolated through both periods, and 947 (12%) were socially isolated at the time of the second declaration, even though they were not socially isolated at the time of the first declaration. Approximately 4815 (61%) of the 7893 participants became socially isolated at the time of the second declaration. At the same time, as a change in the psychological scale described earlier, there were significant decreases in online interactions with familiar people, COVID-19-related anxiety, difficulties owing to the lack of daily necessities, and difficulties in work or schoolwork. Although various COVID-19-related life problems improved

and online connections decreased, which may correspond to the lack of improvement only in SI and loneliness. The comparisons by transition patterns of SI in these variables showed that individuals with persistent SI had severe loneliness, psychological distress, and depression; a worsened lifestyle and stress management during the mild lockdown; and deteriorated relationships with familiar people. Still, there were no significant differences between the improved- and worsened-SI groups. Additionally, there were no prominent interactions between transition patterns of SI and phases. Although various indicators changed across the participants, and various problems related to persistent SI were observed, no characteristics of time series changes in psychosocial variables in a specific transition pattern of SI were found.

Comparing the demographic data by transition patterns of SI, there were more unmarried or people without children with persistent SI. The persistent-SI group had fewer cohabitants than other transition pattern groups. This result is not surprising, since marital status and family structure are difficult to change. However, this result indicates that the number of people in the persistent-SI group is low, but also that there are few people with whom they can talk about their problems or whom they can ask for help. Therefore, this suggests that the mental health of people with these demographic characteristics should be of concern. In addition, more people in the low-income group had persistent SI, while more people in the high-income group had no SI or improved SI. At the time of the first emergency declaration [15], our previous results reported that low household income is associated with SI. Furthermore, this study indicated that among individuals who were socially isolated

during the first emergency declaration, those with high incomes experienced less SI during the second declaration. However, this was not seen in many people with low incomes.

In the nonparametric Bayesian coclustering, the primary focus concerned clusters in which a particular transition pattern of SI predominated. Most of the clusters with participants without SI throughout phases 1 and 2 had healthy behaviors, more interactions, good relationships, and lower levels of loneliness and psychological stress. Furthermore, the clusters in which relationships deteriorated in phase 1 recovered in phase 2. Comparatively, the clusters with SI throughout phases 1 and 2 were further divided into clusters with increased loneliness and psychological stress and clusters close to the participants' average scores in this study. Among these clusters, clusters with increased loneliness and psychological stress were notable for deteriorating relationships and fewer online interactions. These results suggest that even if the transition pattern of SI is similar, mental health and lifestyles may differ; therefore, it may not be appropriate to apply universal interventions to people in a state of continuous SI. However, we did not detect any clusters in which only participants with a particular transition pattern of SI were accounted for, and clusters with many improved-SI or worsened-SI groups were not extracted. Therefore, the transition pattern of SI may not have contributed much to the clustering of participants in this study; thus, these results should be interpreted with caution.

As this study and other previous studies have shown, SI during the COVID-19 pandemic has been severe; therefore, it should be urgently addressed to protect people's mental health. However, research on intervening in SI or loneliness during the pandemic has not been sufficiently conducted [40]. This study showed various possible factors that contribute to SI, and the causal relationship between SI and these factors may not be uniform. Thus, intervention methods will differ depending on each person's SI experience background. This study demonstrates the necessity of careful assessment of the psychological, social, and behavioral characteristics associated with SI to evaluate the mechanisms of SI in each individual and intervene appropriately. Therefore, this study's results will be beneficial for developing intervention methods that fit the characteristics of individuals for those who are socially isolated during a pandemic.

Limitations

This study had several limitations. First, we did not assess the quality of relationships with relatives and friends. Even if the

network size is small, mental health may be good if the quality of the relationships is sufficient. Second, we did not exclude people who did not stay in a mild lockdown for any reason (eg, work) and people affected by COVID-19, and we could not adjust for their effect on the results of the study. In the future, it would be useful to investigate whether the participants were in an environment affected by the mild lockdown or COVID-19. Third, we collected the data for this study through an online survey and could not conduct random sampling. Thus, we cannot guarantee the sample's representativeness, which could not be matched to the proportions of each age group and gender group in each region. Additionally, populations registered with online survey companies may be more willing to participate in surveys than nonregistered populations. They may have social networks to obtain information about such survey cooperation. There may be more people with severe SI in the nonenrolled population who could have different characteristics and need additional support from the findings of this study. Fourth, the significant differences between people who responded in phases 1 and 2 and people who responded only in phase 1 were indicated in some sociodemographic characteristics and psychological variables. Fifth, items on the treatment of psychological problems and physical diseases asked only about their presence or absence, and the definition of these problems was left to the participants. These differences may have caused a selection bias. Therefore, it was up to the participants to decide whether psychosomatic disorders, for example, were included in either category.

Conclusion

We longitudinally investigated the transition of SI and its related factors by surveying during the mild lockdown under Japan's 2 declared states of emergency. When the second declaration occurred, more than half of the population was socially isolated. Moreover, many people became socially isolated between the first and second declarations, particularly low-income, unmarried, or childless individuals. Among individuals with persistent SI, there were 2 groups: those whose mental health was deteriorating and those whose mental health was not deteriorating, with the former having more problems with relationships and interactions. This study's results emphasized variables that should be evaluated explicitly in interventions for SI during a pandemic and may help develop more effective intervention methods tailored to each person's characteristics.

Acknowledgments

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N Sugaya, TY, CU, and N Suzuki conceived, designed, and performed the study; contributed to and wrote the paper; and approved the final manuscript. N Sugaya analyzed the data.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Items about lifestyle, coping behavior, and stressors related to mild lockdown.

[[DOCX File , 16 KB - publichealth_v8i3e32694_app1.docx](#)]

Multimedia Appendix 2

Comparisons of sex ratio, age, and psychological indexes between individuals who participated both in phase 1 and 2 and individuals who participated only in phase 1.

[[DOCX File , 14 KB - publichealth_v8i3e32694_app2.docx](#)]

Multimedia Appendix 3

Characteristics of psychosocial variables in each cluster.

[[DOCX File , 297 KB - publichealth_v8i3e32694_app3.docx](#)]

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Abbreviations

K6: Kessler Psychological Distress Scale-6

LSNS-6: Lubben Social Network Scale (shortened version)

PHQ-9: Patient Health Questionnaire-9

SI: social isolation

UCLA-LS3: University of California, Los Angeles (UCLA) Loneliness Scale, Version 3

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Original Paper

Official Websites Providing Information on COVID-19 Vaccination: Readability and Content Analysis

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Abstract

Background: Online information on COVID-19 vaccination may influence people's perception and willingness to be vaccinated. Official websites of vaccination programs have not been systematically assessed before.

Objective: This study aims to assess and compare the readability and content quality of web-based information on COVID-19 vaccination posted on official/governmental websites. Furthermore, the relationship between evaluated website parameters and country vaccination rates were calculated.

Methods: By referring to an open data set hosted at Our World in Data, the 58 countries/regions with the highest total vaccination count as of July 8, 2021, were identified. Together with the websites from the World Health Organization and European Union, a total of 60 vaccination campaign websites were targeted. The "frequently asked questions" or "questions and answers" section of the websites were evaluated in terms of readability (Flesch Reading Ease score and Flesch-Kincaid Grade Level), quality (Health On the Net Foundation code [HONcode] certification and Quality Evaluation Scoring Tool), and content stating vaccination duration of protection and potential side effects.

Results: In terms of readability, the Flesch Reading Ease score of the vaccination frequently asked questions websites ranged between 11.2 and 69.5, with a mean of 40.9 (SD 13.2). Meanwhile, the Flesch-Kincaid Grade Level ranged between 6.5 and 17.6, with a mean of 12.1 (SD 2.8). In terms of quality, only 2 websites were HONcode certified, and the Quality Evaluation Scoring Tool score of the websites ranged between 7 and 20, with a mean of 15.3 (SD 3.1). Half of the websites (25/50) did not present a publication date or date of the last update. Regarding the duration of protection offered by the vaccines, 46% (23/50) of the websites stated that they do not know, and another 40% (20/50) did not address it. Five side effects of the vaccinations were most frequently mentioned, namely, fever/chill (41/50, 82%), various injection site discomfort events (eg, swelling, redness, or pain; 39/50, 78%), headache (36/50, 72%), fatigue (33/50, 66%), and muscle/joint pain (31/50, 62%).

Conclusions: In general, the content quality of most of the evaluated websites was good, but HONcode certification should be considered, content should be written in a more readable manner, and a publication date or date of the last update should be presented.

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KEYWORDS

COVID-19; coronavirus; SARS-CoV-2; vaccine; readability; content quality; online health information; side effect; public health; medicine; quality; perception

Introduction

The COVID-19 pandemic has affected the global population since the end of 2019 and has no signs of resolution as of late 2021. Its fatality rate varied by population and viral strains, with earliest rates reported to be 2.3% in China and 7.2% in Italy [1]. A recent meta-analysis computed an overall infection fatality rate of 0.68% [2]. The COVID-19 morbidity has incurred substantial economic burden, and a study examining the matter estimated that the mean direct medical costs (cost incurred by patient care in the hospital; eg, bed service, consultation, nursing, imaging, medicine, and laboratory) were US \$3755 and indirect costs (including income loss due to premature death and productivity loss due to hospitalization and during recovery) were US \$11,634 per person [3]. Another study reported that patients with COVID-19 stayed in the hospital for 5 days on average, and the incurred median hospital costs were US \$12,046 [4]. In short, the COVID-19 pandemic has caused a heavy burden on society and public health on a global scale. Being a powerful tool to counteract infection, currently available vaccines against COVID-19 may substantially aid mitigation of this pandemic.

Meanwhile, vaccination against COVID-19 became possible at the end of 2020. In general, vaccination is able to provide both health benefits for people, as well as to save medical care costs; reduce productivity loss; improve outcomes in unvaccinated community members (eg, through herd effects); and maintain economic, social, and political stability [5]. Vaccination may by some people even be perceived as a social contract that considers social welfare and moral obligation beyond self-interest, as a recent study found that the more compliant individuals regarding vaccination showed less generosity toward those who were not vaccinated [6].

On this background, vaccine hesitancy poses an issue for maximizing the population that could be vaccinated. It was found that one-third of the United Kingdom's and Ireland's population display COVID-19 vaccine hesitancy or even resistance [7]. Concerns about side effects and vaccine efficacy were two main reasons for not getting the COVID-19 vaccine [8]. Misinformation might worsen this situation, and in this regard, the provision of official COVID-19-related information in a comprehensible way could prevent people from seeking information or misinformation from nontrustworthy websites [9]. For example, YouTube has boosted the search rankings of provaccine videos, but viewers directed to antivaccine videos were likely to be exposed to additional links to antivaccine videos [10]. Therefore, governmental or official websites should serve as authoritative sources of COVID-19-related information.

Readability and quality metrics of these websites are important, as the internet may eliminate barriers in the access to health information and hence eliminate misinformation for the public if the presented materials are of good quality and can be easily comprehended by the majority of the population [11]. Difficulty reading vaccine information may influence attitudes toward acceptance of or hesitancy to take vaccinations [12]. Previously, it was found that campaign websites could boost vaccine coverage [13]. The exact reasons were unclear, and it could have two implications. First, it could be that better websites would lead to higher vaccine coverage. Second, it could also be that places with lower vaccine coverage would put more effort to optimize their websites to promote/increase vaccine coverage. Regardless, it would be relevant to evaluate the relationship between website metrics and vaccination data.

This study aims to assess the readability and content quality of official COVID-19 vaccination campaign websites worldwide to reveal if their contents were easily understandable and mentioned the side effects and duration of vaccine protection, which are important factors in determining the support for getting vaccinated [14].

Methods

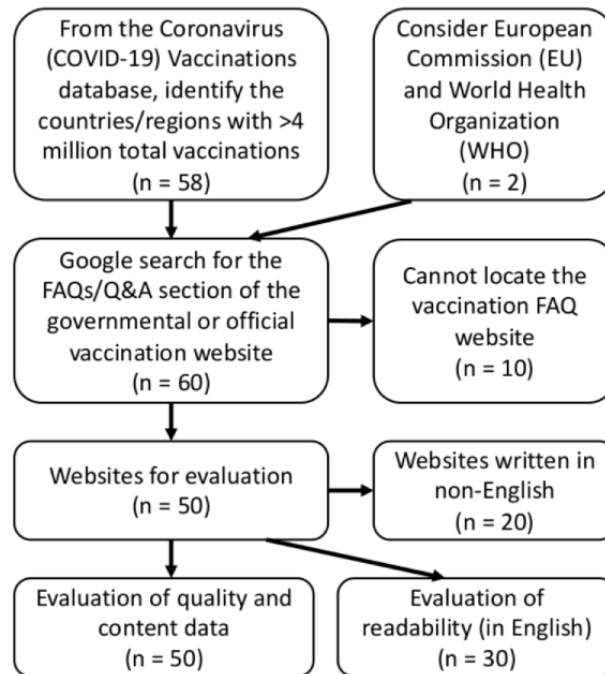
Data Source and Search Strategy

The open and actively updated data set named Coronavirus (COVID-19) Vaccinations [15], hosted by the Our World in Data database, was accessed on July 8, 2021. There were 58 countries/regions with their total vaccination count exceeding 4 million doses. For these 58 countries/regions the total vaccination count and vaccination dose per 100 people were noted. The governmental or official vaccination website was searched via Google with the phrases “official,” “COVID,” and “vaccine.” After entering these three terms, the first 10 result pages were examined to identify the relevant official vaccination website. The “frequently asked questions” (FAQs) or “questions and answers” (Q&As) section was identified and analyzed. This particular section was selected assuming that this would be the page where citizens sought for official information in the first place. Together with the websites of the World Health Organization (WHO) and European Union, we attempted to collect information from a total of 60 websites. As many European countries are in the European Union, the public living in Europe may look for information not only from their own country's website but also from the EU website. Similarly, the WHO is the global health authority, and many people may look for information from its website as well. Therefore, websites from the WHO and European Union were included in this study. If there were multiple websites for one country (eg, vaccination

websites from different governmental departments), then the one with FAQs targeting the public was selected. If such a section was not available from any of the websites, then the country would be coded as “cannot locate the vaccination FAQ

website” (n=10; see Figure 1). The total vaccination count and vaccination dose per 100 people would be assessed with the website metrics to reveal if a better prepared website would relate to better vaccination coverage.

Figure 1. Flowchart of the selection of governmental or official COVID-19 vaccination websites for evaluation. FAQ: frequently asked question; Q&A: question and answer.



The website identification was performed by four authors (AWKY, EK, EDP, and AGA). The data extraction was performed by AWKY and double-checked by AGA. Disagreements in these procedures were solved by discussion and consensus reached between AWKY and AGA.

Readability Assessment

For readability assessment (limited to websites with English versions only), the first 5 answers from the FAQs or Q&As page were transferred to Office Word software (Microsoft Corporation). The first 5 answers were used for evaluation, as online health information seekers rarely go beyond the first page of a search [16], and we reasoned that 5 FAQs would occupy a similar page space. The Flesch Reading Ease score and Flesch-Kincaid Grade Level statistic [17] were computed automatically by its built-in Spelling and Grammar function. A higher Flesch Reading Ease score indicates the text is more readable: reading difficulty is considered very easy if the score approaches 100, whereas the score range of 60 to 70 is considered standard [18,19]. In contrast, the value for the Flesch-Kincaid Grade Level indicates the grade level required for a reader to understand the text [17]. The American Medical Association and National Institutes of Health recommended that patient information materials should be written in the third to seventh grade level [20,21]. In the United States, the third grade means the third school year after kindergarten (third year of primary school) when students are aged around 8 to 9 years. Similarly, seventh grade means the seventh school year after kindergarten when students are aged around 12 to 13 years. The readability of websites without the English version were not evaluated, but they were still evaluated for the subsequent

analyses (quality assessment and listing of protection duration and side effects) following Google Translation to English.

Quality Assessment

Content quality was first assessed by the Health On the Net Foundation code (HONcode) certification status (ie, whether a website bore the HONcode badge). The Health on the Net Foundation is affiliated with the United Nations and issues the HONcode for health care websites that filed an application and met the required standard [22]. A dedicated web browser toolbar can be installed [23] to identify the certification status of a website, as used by previous researchers [24]. Having a HONcode certification is good, as it indicates the website reaches a standard of offering quality health information.

As this HONcode only gave a binarized certification status (certified or not) to the websites, we also used the Quality Evaluation Scoring Tool (QUEST) to evaluate the FAQ sections in seven aspects, namely, authorship, attribution to sources/references, type of study attributed to, conflict of interest, currency of presented information, complementarity of the patient-doctor relationship (support or no support of the relationship), and tone [25]. Readers can refer to the second figure by Robillard et al [25], published with open-access, for the complete description of the coding and scoring of QUEST. There is no cutoff score for QUEST, but the original research team reported that a score ≤ 11 indicated the worst scores from a survey of 290 online articles [26].

Listing of Protection Duration and Side Effects

We recorded the number of Q&As from each website. The stated protection duration and the side effects of vaccinations listed on the websites were also recorded.

Data Collection

It was not possible to collect all data within a single day. Data were collected since the day of the database search (July 8, 2021). On the last day of data collection (September 29, 2021), the publication dates and dates of the last update from all websites were collected to ensure a fairer evaluation of recency.

Statistical Analysis

The Pearson correlation test was conducted to evaluate if the two readability metrics, QUEST score, and number of Q&As were correlated with the total vaccination count and vaccination dose per 100 people. Data from the WHO and European Union

were not included in the correlation test or regional counts. Statistical tests were performed with SPSS (version 26.0; IBM Corp). Results were deemed significant if $P < .05$.

Results

Overall Data Collection Situation

The 60 investigated vaccination FAQs websites are listed in [Table 1](#). By the United Nations geoscheme, 22 of the 58 selected countries/regions were in Asia, 22 in Europe, 4 in North America, 7 in South America, 2 in Africa, and 1 in Oceania. There were 10 countries for which we could not locate a vaccination FAQs website. There were 20 countries that provided non-English websites only. Therefore, quality and content data were available from 50 websites, whereas readability data were available from 30 websites.

Table 1. The 60 investigated governmental or official COVID-19 vaccination websites as accessed on July 8, 2021 (listed in descending order of total vaccination count).

Country/region	Total vaccination count (million), n	Vaccination dose per 100 people, n	Official vaccination FAQs ^a website
China	1340.0	93.3	[27]
India	358.1	26.0	[28]
United States	331.7	99.2	[29]
Brazil	110.1	51.8	[30]
Germany	79.7	95.2	[31]
United Kingdom	79.5	117.2	[32]
France	57.2	84.6	[33]
Turkey	55.8	66.2	[34]
Italy	54.7	90.5	[35]
Japan	52.6	41.6	[36]
Mexico	48.5	37.6	[37]
Indonesia	48.5	17.7	[38]
Spain	45.2	96.8	[39]
Russia	45.1	30.9	[40]
Canada	40.7	107.8	[41]
Poland	30.7	81.2	[42]
Chile	23.6	123.2	[43]
Argentina	23.3	51.6	[44]
South Korea	19.9	38.8	[45]
Morocco	19.5	52.8	[46]
Colombia	19.4	38.2	Cannot locate the vaccination FAQs website
Saudi Arabia	19.1	54.8	[47]
Pakistan	18.2	8.3	[48]
Netherlands	16.9	98.6	[49]
United Arab Emirates	15.7	159.0	[50]
Philippines	12.2	11.1	[51]
Belgium	11.7	100.7	[52]
Thailand	11.6	16.7	[53]
Israel	10.9	125.7	[54]
Bangladesh	10.1	6.1	[55]
Malaysia	10.0	31.0	[56]
Hungary	9.8	101.9	Cannot locate the vaccination FAQs website
Portugal	9.5	93.0	[57]
Romania	9.1	47.1	[58]
Greece	9.0	86.0	[59]
Sweden	8.8	87.3	[60]
Czechia	8.7	81.2	[61]
Australia	8.6	33.6	[62]
Dominican Republic	8.4	77.4	Cannot locate the vaccination FAQs website
Peru	8.3	25.3	[63]
Austria	8.3	92.6	[64]

Country/region	Total vaccination count (million), n	Vaccination dose per 100 people, n	Official vaccination FAQs ^a website
Cambodia	8.1	48.7	Cannot locate the vaccination FAQs website
Switzerland	7.7	89.1	[65]
Cuba	6.8	59.7	Cannot locate the vaccination FAQs website
Kazakhstan	6.1	32.7	[66]
Singapore	5.9	101.4	[67]
Iran	5.7	6.8	Cannot locate the vaccination FAQs website
Denmark	5.6	97.4	[68]
Serbia	5.3	78.2	Cannot locate the vaccination FAQs website
Ecuador	4.8	27.2	Cannot locate the vaccination FAQs website
Finland	4.6	82.8	[69]
Egypt	4.5	4.4	Cannot locate the vaccination FAQs website
Sri Lanka	4.5	21.2	Cannot locate the vaccination FAQs website
Ireland	4.5	90.9	[70]
Norway	4.4	81.4	[71]
Uruguay	4.2	121.3	[72]
Jordan	4.2	41.0	[73]
Hong Kong	4.1	55.3	[74]
World Health Organization	N/A ^b	N/A	[75]
European Commission	N/A	N/A	[76]

^aFAQ: frequently asked question.

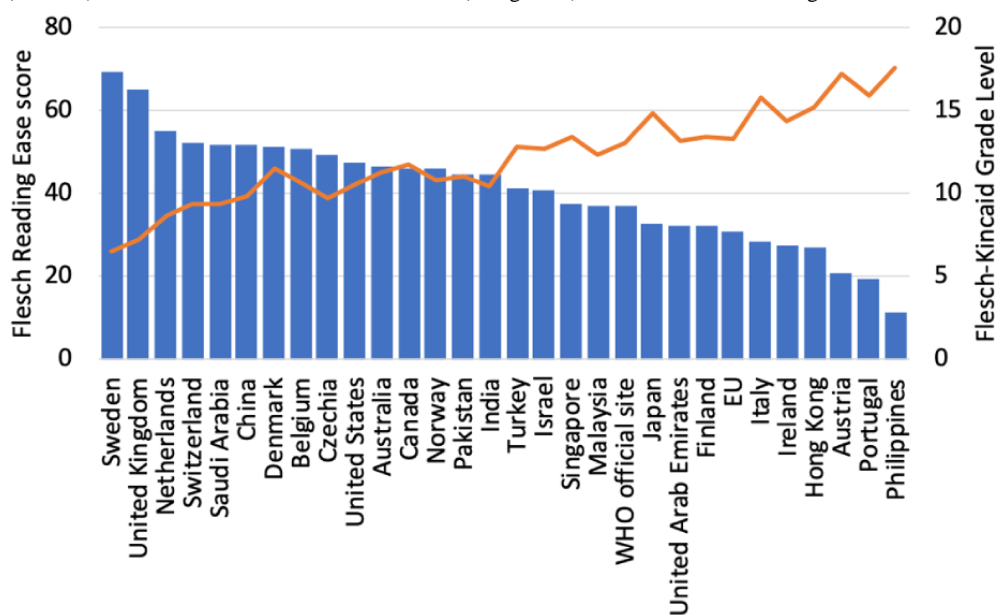
^bN/A: not applicable.

Readability Assessment

The Flesch Reading Ease score of the vaccination FAQs websites ranged between 11.2 and 69.5, with a mean of 40.9

(SD 13.2). The websites of Sweden and the United Kingdom had a score above the threshold of 60 (Figure 2). In particular, the most difficult website was from the Philippines, with a score of 11.2.

Figure 2. Readability assessment of the governmental or official COVID-19 vaccination websites. The recommended standards are >60 for Flesch Reading Ease score (blue bar) and <7 for Flesch-Kincaid Grade Level (orange line). WHO: World Health Organization.



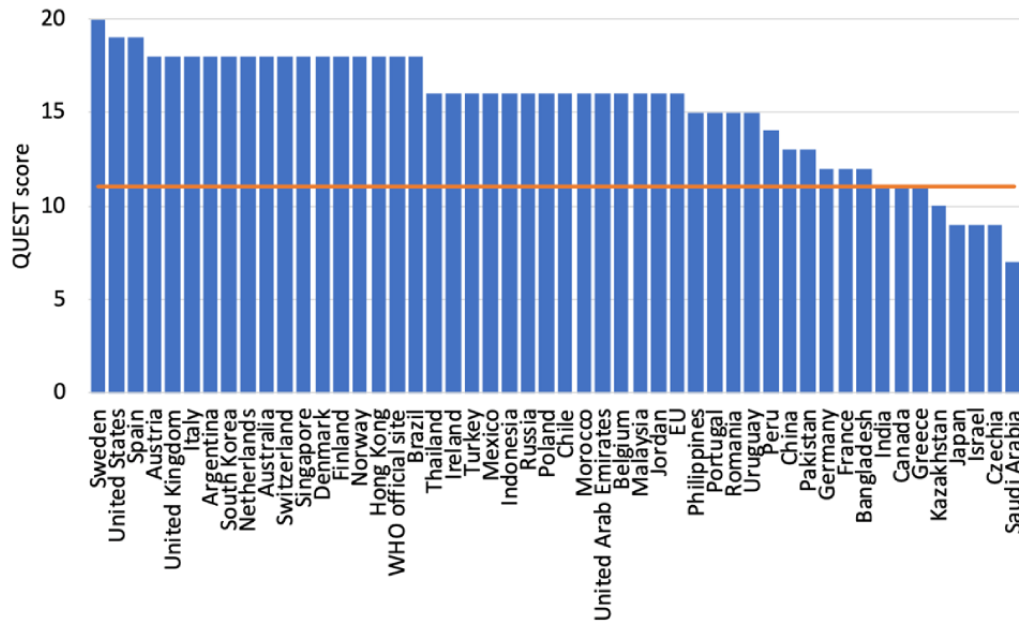
Meanwhile, the Flesch-Kincaid Grade Level of the websites ranged between 6.5 to 17.6, with a mean of 12.1 (SD 2.8). Only the website of Sweden was within the targeted range (Flesch-Kincaid Grade Level 6.5; [Figure 2](#)).

Quality Assessment

Only the websites from Switzerland and the WHO were HONcode certified. The QUEST score of the analyzed websites ranged between 7 and 20, with a mean of 15.3 (SD 3.1). Only 5 websites did not reach the recommended score of 11 ([Figure](#)

3). A detailed breakdown of the score revealed that only Sweden and Canada explicitly mentioned the authorship. None of the websites listed references to identifiable scientific studies. Besides, half of the websites (25/50) did not present a publication date or date of the last update. For the 25 websites that listed a date of the last update, all of them were updated in the year 2021 (n=12 in September, n=2 in August, n=3 in July, n=2 in June, n=3 in April, n=2 in February, and n=1 in January). Four of them also listed a publication date, ranging from October 23, 2020, to April 7, 2021.

Figure 3. Quality assessment of the governmental or official COVID-19 vaccination websites. The recommended level of the QUEST score is ≥11 (orange line). QUEST: Quality Evaluation Scoring Tool; WHO: World Health Organization.

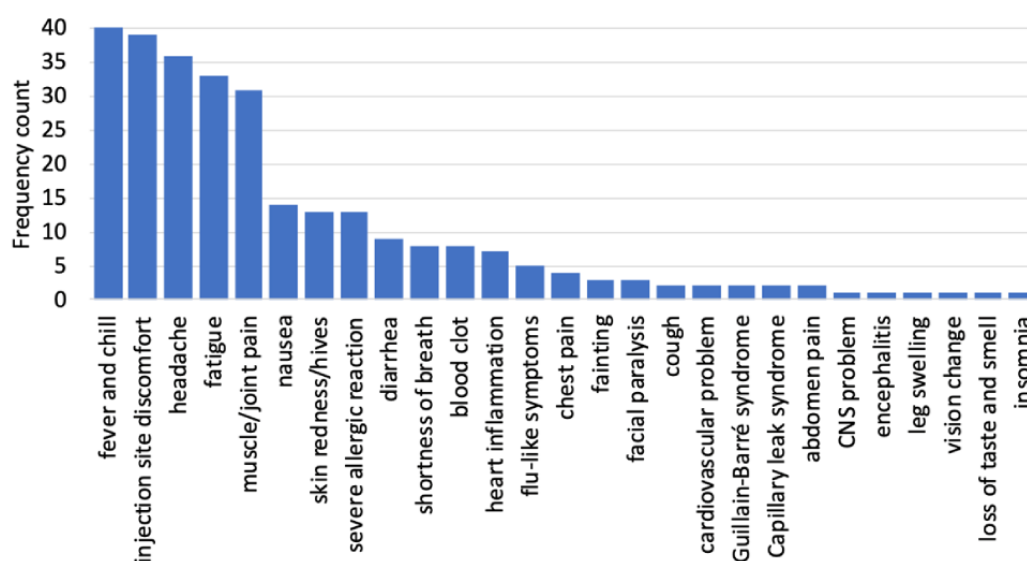


Listing of Protection Duration and Side Effects

The number of Q&As listed in the websites ranged from 6 to 150, with a mean of 36.5 (SD 35.1). Regarding the duration of protection offered by the vaccines, 46% (23/50) of the websites stated that they do not know, and another 40% (n=20) did not address this aspect. The remaining websites stated that the vaccine could provide protection for at least 6 months (n=2), 6

to 8 months (n=1), at least 9 months (n=1), at least 9 to 12 months (n=1), and at least 12 months (n=2). Five side effects were most frequently mentioned, namely, fever/chill (n=41, 82%), various injection site discomfort events (eg, swelling, redness, or pain; n=39, 78%), headache (n=36, 72%), fatigue (n=33, 66%), and muscle/joint pain (n=31, 62%). Other side effects were mentioned much less frequently (<28%). [Figure 4](#) lists the frequency counts of mentioned side effects.

Figure 4. List of side effects caused by vaccination as mentioned by the governmental or official COVID-19 vaccination websites. CNS: central nervous system.



No Relationship Between Vaccination and Website Metrics

Pearson correlation tests revealed that the Flesch Reading Ease score, Flesch-Kincaid Grade Level, QUEST score, and number of Q&As had no significant relationship with total vaccination count ($P=.35$, $.29$, $.47$, and $.23$, respectively) and vaccination dose per 100 people ($P=.30$, $.44$, $.33$, and $.59$, respectively).

Discussion

Principal Findings

As information on COVID-19 vaccination might influence vaccination progress, we set out to assess governmental websites providing information on COVID-19 vaccination in 60 countries/regions and organizations, and finally identified and analyzed 50 websites that promote COVID-19 vaccination programs.

Readability remained an issue for most of the analyzed websites. Even though we analyzed the FAQs section of the websites, which are supposed to be reader friendly, all but 1 failed to meet the recommendation by the American Medical Association and National Institutes of Health of being easily understood by a seventh grader or below [20,21], and only 2 met the recommendation of a Flesch Reading Ease score of 60 to 70 [18,19]. One of the potential reasons could be that the information disseminated in these vaccination campaign websites must be accurate and explanatory to minimize any risks of legal consequences. Hence, the choice of words would be careful and explanatory clauses added to lengthen the sentences. For example, the Philippines website was as difficult to read as a standard auto insurance policy (see Flesch [77] for more examples). It listed a simple question “are there enough vaccines for filipinos” with an answer composed of 2 long sentences with many polysyllabic words:

The prioritization framework for COVID-19 vaccination based on the WHO Strategic Advisory Group of Experts (SAGE) on Immunization, together

with the recommendations of independent bodies of experts including the Interim National Immunization Technical Advisory Group (iNITAG) and the Technical Advisory Group (TAG), was formulated due to the limited global supply of COVID-19 vaccine products. With the guidance of this principle, the Philippine National Deployment and Vaccination Plan formulated strategies and contingencies to ensure the equitable distribution of vaccine products for all Filipinos.

Certainly, readability and content quality are two different aspects valued by online health information seekers. HONcode certification was reported as an indicator correlated to the content accuracy of online health information [78]. In this context, it is interesting to observe that the surveyed vaccination websites did not present certifications. Since the Health On the Net Foundation is affiliated with the United Nations and its certification is globally recognized, more efforts should be made to get certified, especially as these vaccination websites are accessed by many people on a daily and global basis. However, most of them actually had a QUEST score of ≥ 11 , meaning that their content quality was good. The most frequently listed side effects in the websites were consistent to the ones most frequently reported by people receiving the COVID-19 vaccines [79,80]. This consistency is beneficial, as information seekers will feel that the website is trustworthy and provides accurate descriptions of what to be expected if they want to be vaccinated. Although none of the websites listed references to identifiable scientific studies, it could be argued that the FAQs websites were primarily intended for provision of the most important and updated information; references might not be highly sought after by the information seekers in this scenario.

The majority of the websites either did not mention the duration of protection or stated that they did not know how long vaccination could protect citizens. Despite this particular missing (or unknown) piece of information, these 48 countries/regions still had the highest total vaccination counts. To get vaccinated may be influenced by many different considerations, wherefore

readability, quality, and content of the vaccination websites were not the only potential influencing factors. Higher frequency of exposure to positive information about COVID-19 vaccination was associated with a higher intention to be vaccinated [81]. Meanwhile, public health authorities should also monitor social media continuously to identify newly developed antivaccine arguments and provide updated information to clear the doubts and debunk the myths [82]. These aspects should be carefully considered by the authorities as they update/improve the campaign websites. This survey found that only a small proportion of the websites were last updated in September 2021. It suggested that the rest of these websites should be updated more frequently to provide up-to-date information.

Initially, it was a bit surprising to find that there was no relationship between vaccination counts and website metrics. However, it could be explained by the fact that people could access vaccine information via many sources such as newspapers, magazines, YouTube, and Facebook. A previous study [83] revealed that the commonest reasons for agreeing to be vaccinated included “to protect themselves and others” (29%), “belief in vaccination and science” (16%), and “to help stop the virus spread” (15%), which could be intuitive and might not be affected by vaccination website readability.

This study found that only 2 of the 50 surveyed websites were HONcode certified. This was consistent to a recent survey on online misinformation about COVID-19, for which the certification rate was reported to be 1.8% (2/110) [84]. It was similarly reported that it was difficult to comprehend the privacy policies of COVID-19 contact tracing apps, with their reading level between 7th and 14th grade [85]. Considered together, the take-home message for the authoritative bodies and policy makers is to further improve the COVID-19 vaccination campaign items (eg, websites or apps) by making them more comprehensible and more trustworthy with certification.

This study surveyed the FAQs section of official vaccination websites. However, people may seek online information from other sources such as online discussion forums, news outlets, and blogs. Readability and content quality of such sources was outside the scope of this study and might provide an interesting topic for further research. Furthermore, some official vaccination websites did not have FAQs sections, and thus, no data were extracted. Meanwhile, the initial decision to target 60 websites/countries was relatively arbitrary. Therefore, readers should be aware that not all websites across all countries were included. For the non-English language websites, content were only analyzed after translation to English via Google Translate. Therefore, readability could not be assessed. Even for the websites that presented English materials, some biases or issues may still exist. In particular, because English could be a primary language for some countries but not the others or even for certain populations within a country instead of the entire population, bias might be introduced. Hence, the content could be written as a primary version, a translated version, or even provided by automated website translation beyond our notice. Instead of choosing the desired language by clicking a button, a country might provide FAQs sections in other languages at completely different websites not evaluated in this study. In addition, the potential reuse of content from EU/WHO websites by country websites was not assessed. Readers should be aware of these issues during the interpretation of the readability assessment results.

Conclusions

The following points could be concluded: the content quality was good, HONcode certification should be considered, content should be written in a more readable manner, and web pages should be updated more frequently to keep the information up to date. In short, COVID-19 vaccination FAQs websites basically provide good quality information, but more efforts should be paid to make them more readable and updated.

Conflicts of Interest

None declared.

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Abbreviations

- FAQ:** frequently asked question
- HONcode:** Health On the Net Foundation code
- QUEST:** Quality Evaluation Scoring Tool
- Q&A:** question and answer
- WHO:** World Health Organization

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Original Paper

Subphenotyping of Mexican Patients With COVID-19 at Preadmission To Anticipate Severity Stratification: Age-Sex Unbiased Meta-Clustering Technique

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Abstract

Background: The COVID-19 pandemic has led to an unprecedented global health care challenge for both medical institutions and researchers. Recognizing different COVID-19 subphenotypes—the division of populations of patients into more meaningful subgroups driven by clinical features—and their severity characterization may assist clinicians during the clinical course, the vaccination process, research efforts, the surveillance system, and the allocation of limited resources.

Objective: We aimed to discover age-sex unbiased COVID-19 patient subphenotypes based on easily available phenotypical data before admission, such as pre-existing comorbidities, lifestyle habits, and demographic features, to study the potential early severity stratification capabilities of the discovered subgroups through characterizing their severity patterns, including prognostic, intensive care unit (ICU), and morbimortality outcomes.

Methods: We used the Mexican Government COVID-19 open data, including 778,692 SARS-CoV-2 population-based patient-level data as of September 2020. We applied a meta-clustering technique that consists of a 2-stage clustering approach combining dimensionality reduction (ie, principal components analysis and multiple correspondence analysis) and hierarchical clustering using the Ward minimum variance method with Euclidean squared distance.

Results: In the independent age-sex clustering analyses, 56 clusters supported 11 clinically distinguishable meta-clusters (MCs). MCs 1-3 showed high recovery rates (90.27%-95.22%), including healthy patients of all ages, children with comorbidities and priority in receiving medical resources (ie, higher rates of hospitalization, intubation, and ICU admission) compared with other adult subgroups that have similar conditions, and young obese smokers. MCs 4-5 showed moderate recovery rates (81.30%-82.81%), including patients with hypertension or diabetes of all ages and obese patients with pneumonia, hypertension, and diabetes. MCs 6-11 showed low recovery rates (53.96%-66.94%), including immunosuppressed patients with high comorbidity rates, patients with chronic kidney disease with a poor survival length and probability of recovery, older smokers with chronic obstructive pulmonary disease, older adults with severe diabetes and hypertension, and the oldest obese smokers with chronic obstructive pulmonary disease and mild cardiovascular disease. Group outcomes conformed to the recent literature on dedicated age-sex groups. Mexican states and several types of clinical institutions showed relevant heterogeneity regarding severity, potentially linked to socioeconomic or health inequalities.

Conclusions: The proposed 2-stage cluster analysis methodology produced a discriminative characterization of the sample and explainability over age and sex. These results can potentially help in understanding the clinical patient and their stratification for

automated early triage before further tests and laboratory results are available and even in locations where additional tests are not available or to help decide resource allocation among vulnerable subgroups such as to prioritize vaccination or treatments.

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KEYWORDS

COVID-19; subphenotypes; clustering; characterization; observational; epidemiology; Mexico

Introduction

In mid-January 2020, Mexico reported the first cases of COVID-19. In early March 2020, disease caused by SARS-CoV-2 was declared by the World Health Organization (WHO) as a pandemic [1]. As of August 13, 2020, a total of 20,439,814 confirmed cases of COVID-19 had been reported to the WHO, and 744,385 lives had been lost [2].

The COVID-19 pandemic has led to an unprecedented global health care challenge for both medical institutions and researchers. They have been making a huge effort to describe specific COVID-19 risk factor associations and severity outcomes, and personalized therapeutic options for COVID-19 patients are yet under investigation [3-5]. Recognizing different COVID-19 subphenotypes—the division of populations of patients into more meaningful subgroups driven by clinical features [6,7]—and their severity characterization may assist clinicians during the clinical course, research efforts, and the surveillance system. However, the availability of information to investigate such subphenotypes and consequent decision-making often varies both according to the stage at which patients are in the COVID-19 clinical workflow (eg, before admission, at admission, or during hospitalization) and according to hospital access possibilities (eg, hospitalized versus ambulatory patients), especially in locations where hospitalization is difficult. In addition, the patient age and sex entail a potential correlation between subgroup characterization and their severity characterization, which requires prudent usage in machine learning (ML) models.

Several studies have suggested potential COVID-19 subphenotypes, mainly within specific comorbidities such as pulmonary diseases or diabetes [8,9] or related to distinct genetic variants [10]. However, the Mexican population has its own particularity due to a high prevalence of comorbidities, like hypertension, diabetes—a leading cause of death in 2020 [11]—and obesity, which is leading the population to having undesirable risks for severe COVID-19 outcomes, higher than many other high-income countries [12]. Since distinct target populations often present with heterogeneous clinical characterization and severity outcomes, it remains crucial to gain a transparent understanding regarding the characterization of COVID-19 subphenotypes in Mexican patients to help anticipate individuals' prognostic outcomes if one gets infected and evaluate subphenotypic severity presentations.

Unsupervised ML is well-known for its usefulness in finding patterns in data [13,14]. We describe the results of an unsupervised ML meta-clustering approach to identify potential subphenotypes of COVID-19 patients in Mexico based on previously existing comorbidities, habits, and demographic

features (ie, age and sex). Stratification on sex and age groups was included for 3 primary reasons: (1) to reduce potential ML models' biases in best representing the majority (eg, young adults) but not underrepresenting other groups (eg, children and older adults) [15]; (2) to reduce potential confounding factors from age and sex, which are highly correlated with comorbidities, habits, and mortality (ie, age-sex clusters may help reveal more well-detailed patterns and phenotypical descriptions); and (3) to reduce interpretation biases (eg, if one healthy cluster presents a mortality rate of 98.5% but includes patients from all ages, this specific mortality rate may vary across 2 patients from the same cluster whose age differ significantly [eg, children versus adults]). See section 1 of [Multimedia Appendix 1](#) for further details. In addition, we assessed the clusters' source variability, namely the variability by Mexican states and types of clinical institutions (TCIs), to discern what types of clusters are prone to be in certain Mexican states or TCIs.

By using a population-based cohort of more than 700,000 patient-level cases, this is probably the largest cluster analysis about coronavirus patient-level cases to date. Other studies proposed unsupervised ML methods for aggregated population data [16], computed tomography image analyses [17,18], molecular-level clustering [19], or coronavirus-related scientific texts [20]. To date, several studies have provided results from unsupervised ML on patient-level epidemiological data [21-28]. To our knowledge, however, no characterized age-sex subphenotypes nor population-based studies with solely phenotypical information available at preadmission to aid automated risk stratification have been conducted, and neither characterized the Mexican population, which is generally more vulnerable due to its particularity of a high prevalence of comorbidities.

Performing accurate triage upon admission, especially in ambulatory settings, is often challenging, significantly depending on the patient information available to the physicians. This work, therefore, aimed to characterize age-sex unbiased COVID-19 subphenotypes that may potentially establish target groups for triage systems to assist clinicians in efficiently allocating limited resources and prioritize vaccination among subgroups who are more vulnerable when they get infected during the pandemic. As these subphenotypes are based on easily available data, such as previous disease and lifestyle habits, rather than COVID-19-related symptoms (eg, fever and nausea), vital signs, or biomarkers that are not often available in the first days of COVID-19 infection or difficult to obtain due to limited resources, our work therefore could support early triage prior to further tests and laboratory results and even provide guidance in areas where such tests are not available.

Methods

Data Collection and Processing

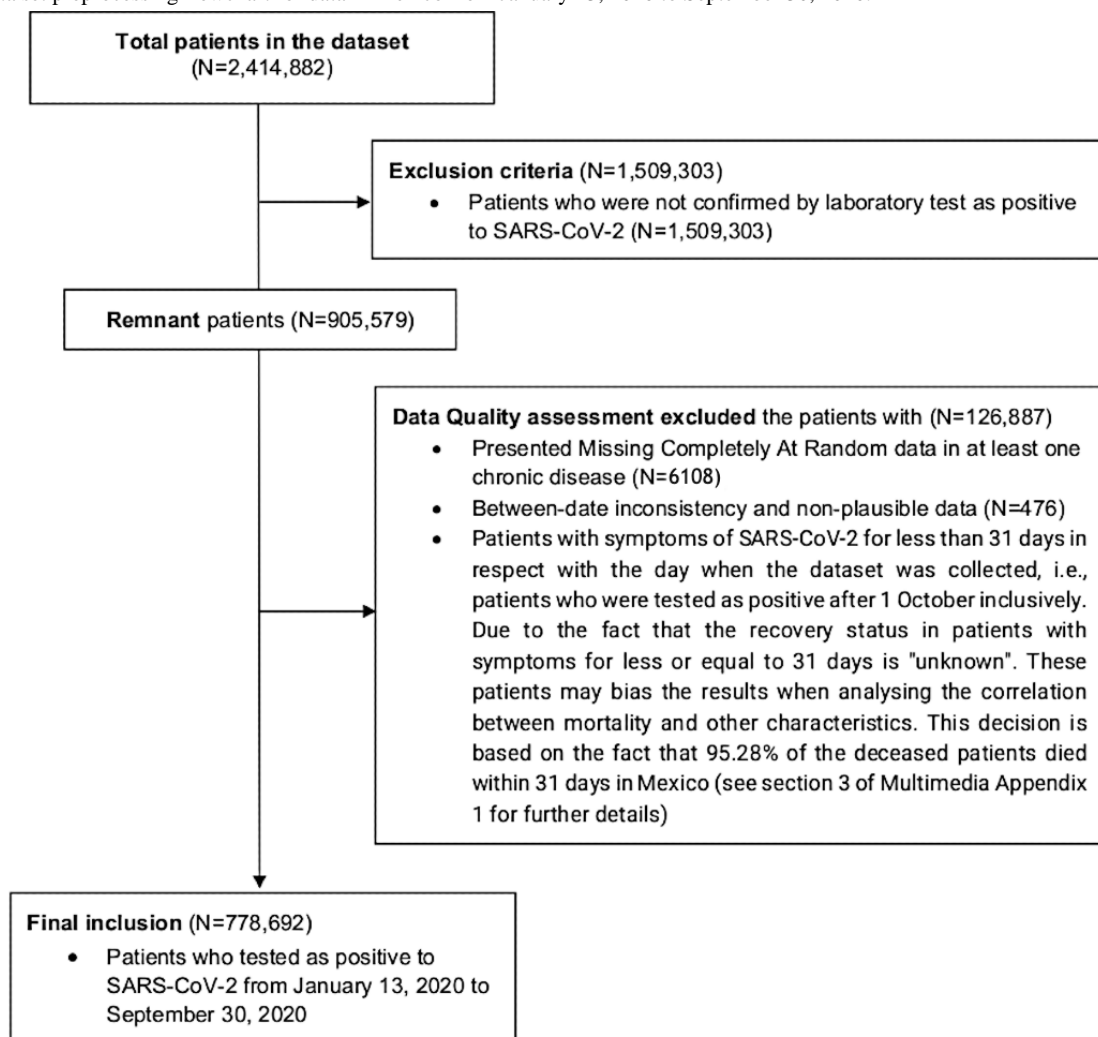
We used the data set collected by the General Epidemiology Directorate of the Mexican Ministry of Health, which is an open-source data set comprised of daily updated data from suspected COVID-19 cases (in public and private hospitals from all over the country), of which the positive cases were confirmed by laboratory tests for SARS-CoV-2 [29]. The data set is anonymized, open-access, and published by the Mexican government. The use of data followed the MX terms of free use of the Open Data of the Mexican Government [30]. As of November 2, 2020, the data set was comprised of a total of 2,414,882 cases, including patient-level demographic, comorbidity, habit, and prognosis data, for both positive and nonpositive cases. Noteworthy, the official website does not explicitly mention the source (each public and private health institution) for some of the information. Consulting with different health professionals, we concluded that it is more likely that every lab-confirmed patient with COVID-19 took a questionnaire in which the patients initially self-reported their

comorbidities, and only those who were hospitalized were given a battery of tests to detect or confirm the highest-risk comorbidities, such as diabetes and hypertension.

We performed a series of data quality assessments such as detecting missing data and outliers, between-date inconsistency, erroneous data, and nonplausible data, and we also assessed potential temporal biases using temporal variability statistical methods [31]; no significant temporal changes were found (section 2 of [Multimedia Appendix 1](#)). However, we found that 95.28% of patients lost their lives within 31 days after the infection, which led us to remove the patients with symptom onset less than 31 days prior to the moment the data set was collected (ie, patients who showed symptoms after September 30, 2020) since these patients' survival status in the future was still "unknown" (section 3 of [Multimedia Appendix 1](#)). Thus, patients infected after September 30, 2020, were excluded.

[Figure 1](#) describes the study inclusion and exclusion criteria and the data quality assessment process outcomes in a CONSORT-like flowchart. The final sample included 778,692 positive cases.

Figure 1. Data set preprocessing flowchart for data in Mexico from January 13, 2020 to September 30, 2020.



Study Measures

We derived 6 outcome variables related with the prospective patient's severity. The first was the patient outcome (deceased or not) from the date of death record. The second was the number of days from symptom onset to hospital admission. Third, we categorized 2 variables describing the overall survival at 15 days and 30 days after symptom onset. Lastly, we categorized 2 variables that also described the overall survival

at 15 days and 30 days after symptom onset but only for the deceased patients.

[Table 1](#) shows the list of studied variables. Sections 4 to 6 in [Multimedia Appendix 1](#) describe additional information on the original data set, baseline characteristics of the COVID-19 patients alongside descriptive statistics in age-sex groups of the study sample, and association between pregnancy and outcomes.

Table 1. List of variables contained in the data set for the study cases; they were originally coded in Spanish and translated into English by the authors for this work. Section 4 in [Multimedia Appendix 1](#) provides the description of the original data set.

Variable	Description	Type (value/format)
Sex	Sex of the person (defined in the metadata published by the Mexican government)	Discrete (Male, Female)
Age	Age in years at the time of the admission	Numerical integer
Pregnant	Presence of pregnancy	Discrete (Yes, No)
Obesity	Presence of obesity	Discrete (Yes, No)
Smoke	Presence of smoking habit	Discrete (Yes, No)
Pneumonia	Presence of pneumonia	Discrete (Yes, No)
Diabetes	Presence of diabetes	Discrete (Yes, No)
COPD ^a	Presence of chronic obstructive pulmonary disease	Discrete (Yes, No)
Asthma	Presence of asthma	Discrete (Yes, No)
INMUSUPR ^b	Presence of immunosuppression	Discrete (Yes, No)
Hypertension	Presence of hypertension	Discrete (Yes, No)
CKD ^c	Presence of chronic kidney disease	Discrete (Yes, No)
Cardiovascular	Presence of cardiovascular	Discrete (Yes, No)
Other disease	Presence of other diseases	Discrete (Yes, No)
Hospitalized	Whether a patient was hospitalized or ambulant	Discrete (Yes, No)
Intubated	Whether a patient was intubated	Discrete (Yes, No)
ICU ^d	Whether a patient had been in an intensive care unit	Discrete (Yes, No)
Other case contact	Whether a patient was detected to have contact with other coronavirus cases	Discrete (Yes, No)
Result_lab	Coronavirus test result	Discrete (Positive SARS-CoV-2, Non-Positive SARS-CoV-2, Pending, Inadequate result, Not Applied)
Admission_date	The date when a patient attended the care unit (not necessarily hospitalized)	Date (dd/mm/yyyy)
Symptoms_date	The date of symptom onset	Date (dd/mm/yyyy)
Death_date	The date of death	Date (dd/mm/yyyy)
Entity_um	The state where a patient received attention from a medical unit	Discrete
TCI ^e	The type of institution in the National Health System that provided medical care	Discrete ^f
Outcome ^g	Death result of the patient (we used this to calculate mortality and recovery rate)	Discrete (Deceased, Non-Deceased)
Survival>15days ^g	Whether a patient survived more than 15 days from symptoms onset	Discrete (Yes, No)
Survival>30days ^g	Whether a patient survived more than 30 days from symptoms onset	Discrete (Yes, No)
Survival>15days_deceased ^g	Whether a deceased patient survived more than 15 days from symptom onset	Discrete (Yes, No)
Survival>30days_deceased ^g	Whether a deceased patient survived more than 30 days from symptom onset	Discrete (Yes, No)
From Symptom to Hospital days ^g	The days that it took between symptom onset and hospitalization	Numerical integer

^aCOPD: chronic obstructive pulmonary disease.

^bINMUSUPR, immunosuppression.

^cCKD: chronic kidney disease.

^dICU, intensive care unit.

^eTCI: type of clinical institution.

^fIMSS (Mexican Institute of Social Security), SSA (Secretariat of Health), ISSSTE (Institute for Social Security and Services for State Workers), PRIVATE, PEMEX (Mexican Petroleum Institution), STATE, SEMAR (Secretariat of the Navy), SEDENA (Secretariat of the National Defense), IMSS-BIENESTAR, UNIVERSITARY, MUNICIPAL, RED CROSS, DIF (National System for Integral Family Development).

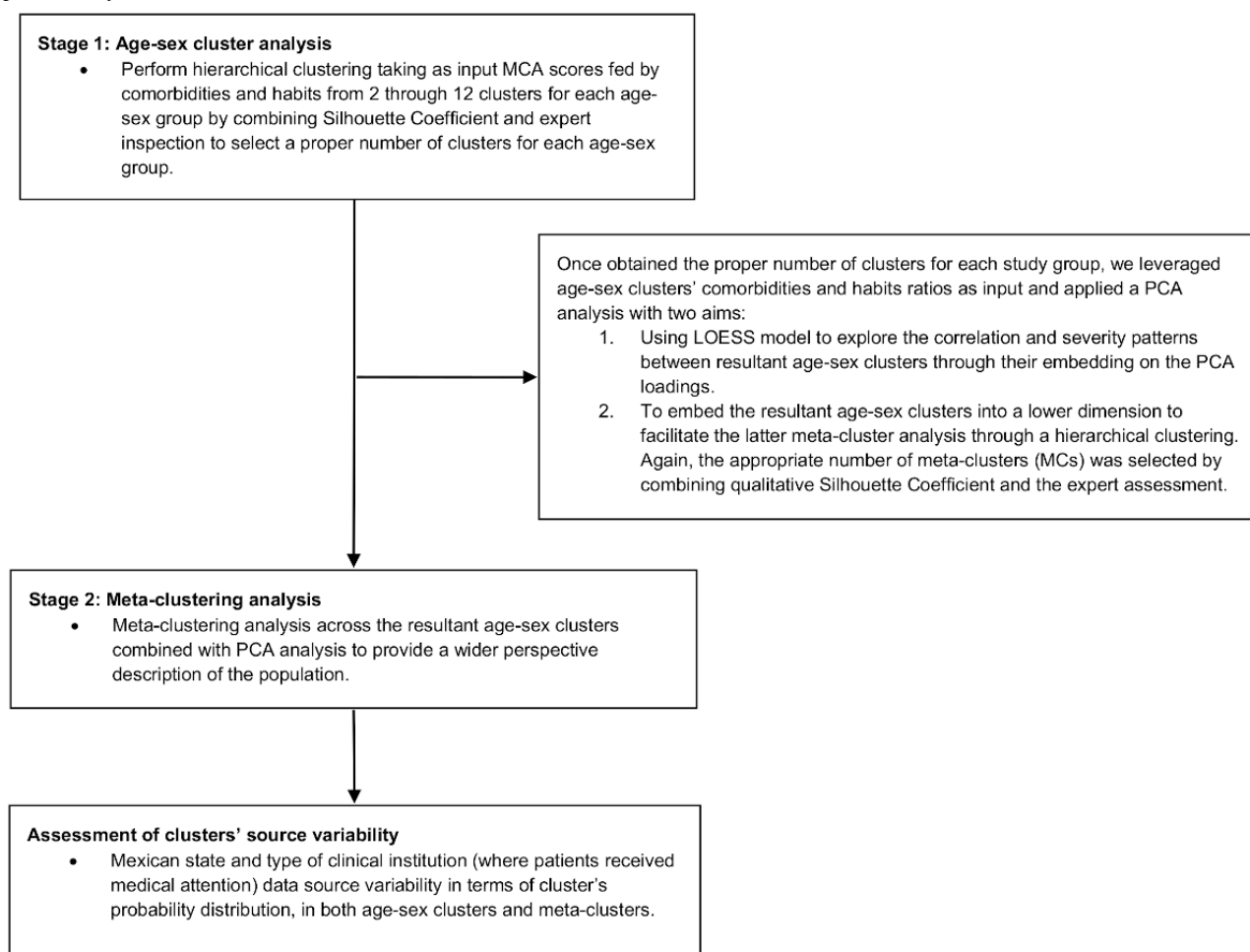
[§]Variables that were created by combining or transforming other variables in the original data set.

Meta-Clustering Methodology

We applied a 2-stage subgroup discovery approach (Figure 2 summarizes the full methodology). In both stages, we used the Ward minimum variance method with Euclidean squared distance [32] to perform hierarchical clustering fed by a dimensionality reduction algorithm—principal component analysis (PCA) or multiple correspondence analysis (MCA) [33,34]—that took as input 11 variables including 9 comorbidities—pneumonia, diabetes, chronic obstructive pulmonary disease (COPD), asthma, immunosuppression,

hypertension, chronic kidney disease (CKD), cardiovascular disease, and other diseases—alongside 2 unhealthy habits, namely obesity and smoking. In order to select the most representative PCA and MCA components to feed the hierarchical clustering, we considered values with an eigenvalue higher than the average. Dimensionality reduction is known to help in the process of clustering by compressing information into a smaller number of variables, making unsupervised learning less prone to overfitting [35], as well as to facilitate further visual analytics to prevent the potential ML black-box issue [36].

Figure 2. Research methodology flowchart. LOESS: locally estimated scatterplot smoothing; MCA: multiple correspondence analysis; PCA: principal component analysis.



In the first stage, we used the entire data set—778,692 patients—since unsupervised ML does not require splitting the data into training and test data [13,14]. We applied individually hierarchical clustering analyses, taking as the input the MCA scores fed by comorbidities and habits for the stratified groups according to sex and age (<18, 18-49, 50-64, and >64 years) to reduce potential biases and confounding factors, since age and sex are highly correlated with comorbidities, habits, and mortality. Then, we applied PCA and a locally estimated scatterplot smoothing (LOESS) model [37] to the resultant age-sex clusters' features to visually explain their correlations and severity relationships. We created a cluster heat map to help understand the characteristics of each age-sex cluster.

In the second stage, in a population description providing a wider perspective, we performed a hierarchical clustering again fed by PCA scores obtained via the resultant age-sex clusters, taking as input their comorbidities and habits ratios. Then, we quantified the features of the resultant meta-clusters (MCs) via a table and summarized these quantified features into a qualitative table to help interpret the main features of the resultant MCs.

For each subgroup analysis, we implemented cluster analyses from 2 through 12 clusters. The proper number of subgroups was obtained by combining a quantitative approach using the silhouette coefficient [38]—which measures the tightness and

separation of the objects within clusters, reflecting how similar an object is to its own cluster compared with other clusters—and a qualitative cluster analysis audited by the authors of this work, including medical, health informatics, and ML experts from Spain and Mexico. We first selected the group of clusters that showed relatively better silhouette coefficient values, then adjusted the number for the most reasonable and clinically distinguishable groups regarding clinical phenotypes. This process was supported by the pipelines and exploratory tool we developed in previous work [39,40].

Finally, we performed a source variability assessment [41] using heat maps to analyze the severity tendency among different data sources based on the clusters' probability distributions between Mexican states and several TCIs where patients received medical attention.

Data processing and analyses were performed using RStudio (version 3.6) and Python (version 3.8). Temporal and source variability—data quality analyses—were performed using the `EHRtemporalVariability` [31] and `EHRsourceVariability` [41-43] packages. Further information about the methods and codes that support the findings of this study are available in section 7 of [Multimedia Appendix 1](#).

Results

Age-Sex Cluster Analysis

After evaluating the stratified clustering results, we selected the following number of clusters (k) for each specific age-sex group: <18-Male: $k=5$; <18-Female: $k=4$; 18-49-Male: $k=7$; 18-49-Female: $k=7$; 50-64-Male: $k=9$; 50-64-Female: $k=8$; >64-Male: $k=8$; >64-Female: $k=8$. This resulted in 56 age-sex clusters in total. Section 8 of [Multimedia Appendix 1](#) provides the number of individuals for each age-sex cluster. The second-stage meta-clustering analysis uncovered 11 clinically distinguishable MCs among the 56 age-sex clusters.

[Figure 3](#) describes the relationships among different comorbidities and habits in the original 56 age-sex clusters

through the first 2 principal components ([Figure 3A](#)). It also provides the correspondence to their assigned MCs ([Figure 3B](#)) and their LOESS delineations for distinct severity outcomes ([Figure 3C](#), [Figure 3D](#), [Figure 3E](#), [Figure 3F](#), [Figure 3G](#), and [Figure 3H](#)).

The PCA uncovered noticeable patterns and characterizations among the clusters representing different ages in both sexes. Young adults are prone to asthma and habitual smoking, whereas older adults are prone to many comorbidities such as hypertension, diabetes, obesity, COPD, pneumonia, and CKD. The results also show that obesity and habitual smoking—both positively correlated—are strongly separated from immunosuppression and other diseases, which are both positively correlated.

The LOESS models showed that children had fewer days between symptom onset and hospitalization and higher rates of intensive care unit (ICU) admission, intubation, and hospitalization than adults with similar conditions ([Figure 3D](#), [Figure 3E](#), [Figure 3G](#), and [Figure 3H](#)). In contrast, MC3 (a young obese cluster with moderate asthma and smoking rates) behaved inversely.

Inspecting the relationship between the PCA and LOESS models showed that CKD was significantly associated with a shorter survival length among deceased patients and an increase in intubation rates ([Figure 3E](#), [Figure 3D](#)). Mortality constantly increased from children to older adults, but the most severe zones were those for pneumonia, CKD, and COPD ([Figure 3C](#)), independent of the age groups.

[Figure 4](#) describes and quantifies the features of the 56 age-sex clusters and relates them to their MCs. [Figure 4](#) reinforces that children had a faster time from symptom onset to hospitalization and were prone to ICU admission despite presenting with a similar clinical condition as adults (eg, cluster <18M3 versus 50-64F5). Regarding sex discrepancies, female patients showed a better recovery rate (RR) despite presenting with similar clinical conditions as male patients (eg, >64M1 versus >64F1).

Figure 3. Principal component analysis (PCA) of the 56 age-sex clusters, meta-clustering results, and locally estimated scatterplot smoothing (LOESS)–based delineations for 7 severity ranges: (A) PCA from 56 age-sex stratified clusters; (B) scatterplot of the 11 meta-clusters (MCs) defined from the 56 clusters; (C) LOESS scatterplot for mortality; (D) LOESS scatterplot for intensive care unit (ICU) admission; (E) LOESS scatterplot for intubation; (F) LOESS scatterplot for survival at 15 days among deceased patients; (G) LOESS scatterplot for hospitalization; and (H) LOESS scatterplot for days from symptom onset to hospitalization. All the scatter plots share coordinates. Each subgroup is denoted using the following abbreviation: [AgeGroup][Sex][ClusterID].

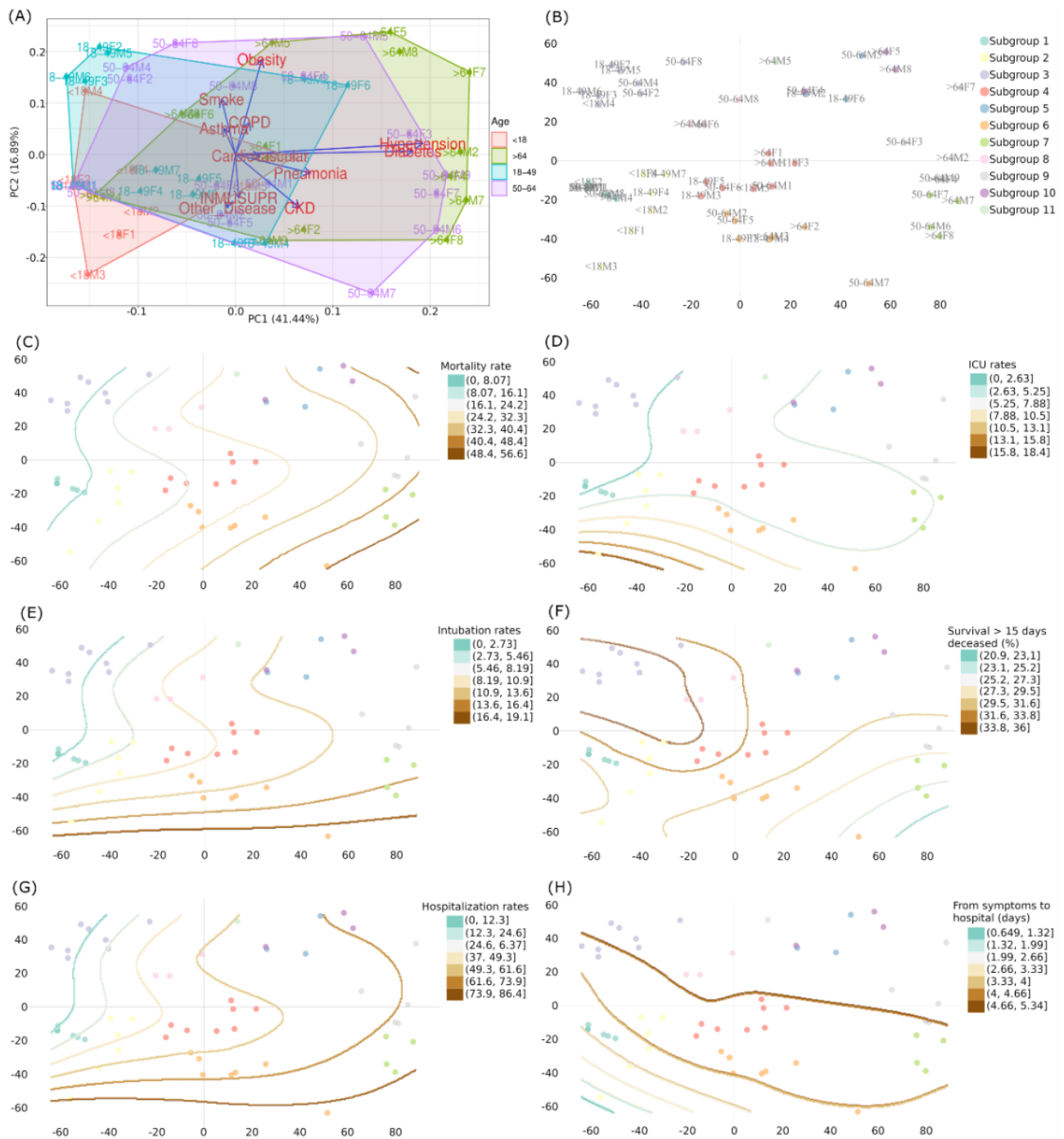
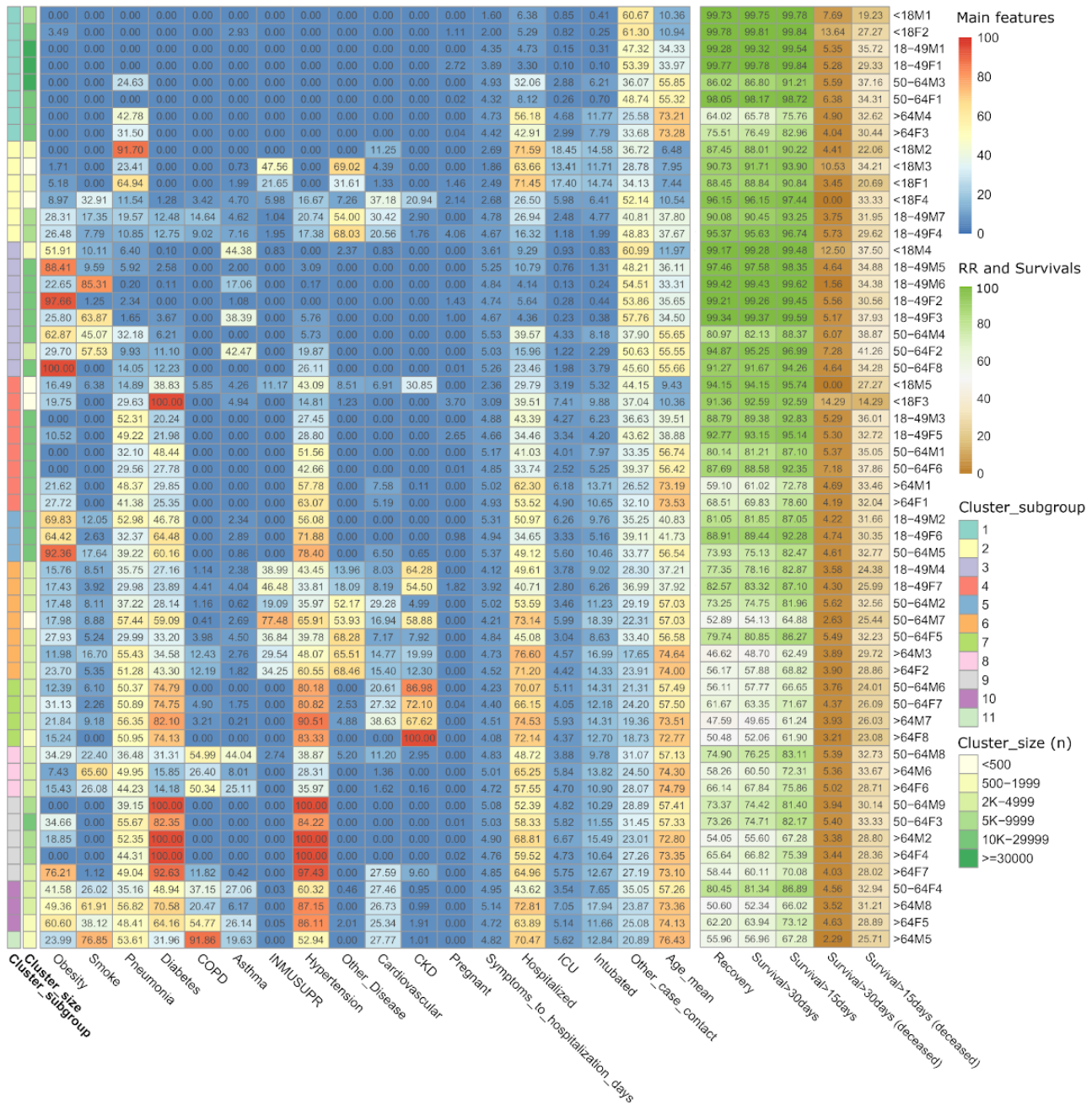


Figure 4. Heat map showing the quantified characteristics among 56 age-sex-specific clusters of the 11 meta-clusters (MCs) of data collected in Mexico between January 13, 2020 and September 30, 2020.; the size of each cluster (n) was categorized into 6 ranges. CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; RR: recovery rate.



Meta-Clustering Analysis

Table 2 represents the quantified features of the 11 resultant MCs. Figure 5 summarizes the main features of the 11 resultant MCs. Variable values were categorized according to clinical meaningful thresholds proposed by the authors as defined in the table legend. Next, we describe the clinically distinguishable main epidemiological findings for each MC.

MC1 included the 2 healthiest clusters per each age-sex group, with a very high RR (90%). Most deceased patients in MC1 with pneumonia were older patients (Figure 4). MC2 included

children and young individuals (mean age 18 years) with healthy habits and little incidence of relevant diseases (13% immunosuppression, 17% cardiovascular disease, 4% CKD), albeit the RR was very high (91%). In addition, MC2 had the highest ICU admission rate (9%), driven by 3 child clusters whose ICU rates varied from 13.41% to 18.45%. MC3 included young adults (mean age 40 years) with significant obesity and smoking as well as a low incidence of other diseases and very high RR (95%). Despite the similarly high RRs in MC1 to MC3, MC1 and MC3 showed a low incidence of pneumonia, while one-third of the patients in MC2 had pneumonia.

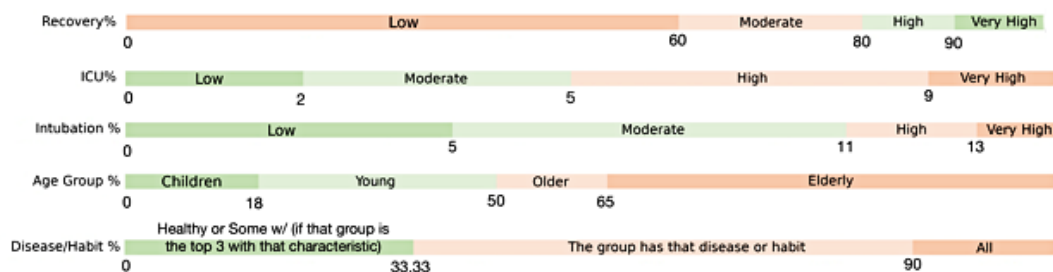
Table 2. Distribution of age, features, and comorbidities with the quantitative description of demographic features, treatment, and epidemiological characteristics among the 11 meta-clusters (MCs) based on the arithmetic mean presuming that each age-sex cluster is representative of its population; thus, the size (n) of each age-sex cluster was ignored.

Characteristics	MC1	MC2	MC3	MC4	MC5	MC6	MC7	MC8	MC9	MC10	MC11
Age-sex clusters (total n=56), n	8	6	8	8	3	7	4	3	5	3	1
Patients in the MC (total n=778,892), n	407,005	13,826	11,3537	11,1950	42280	21642	9239	9687	40557	7777	1192
Demographics											
Age (years), mean	43.4	18	39.8	44.8	46.4	56.3	65.3	68.7	66.8	68.2	76.4
Female sex, %	50	50	50	50	33.33	42.86	50	33.33	60	66.67	0
Age range (years), %											
<18	25	66.67	12.5	25	0	0	0	0	0	0	0
18-49	25	33.33	50	25	66.67	28.57	0	0	0	0	0
50-64	25	0	37.5	25	33.33	42.86	50	33.33	40	33.33	0
>64	25	0	0	25	0	28.57	50	66.67	60	66.67	100
Pregnancy (yes), %	0.49	1.28	0.3	0.8	0.33	0.26	0.01	0	0.01	0	0
Habits, %											
Obesity	0.44	11.78	59.88	12.01	75.54	18.89	20.15	19.05	25.94	50.51	23.99
Smoker	0	9.67	34.09	0.8	10.77	8.1	4.38	38.03	0.22	42.02	76.85
Comorbidities, %											
Diabetes	0	4.42	4.5	39.06	57.14	35.62	76.44	20.45	95	61.23	31.96
COPD ^a	0	4.51	0	0.73	0	5.1	2.03	43.91	2.36	37.46	91.86
Asthma	0.37	3.2	18.17	1.15	2.03	2.69	0.49	25.72	0.08	19.79	19.63
INMUSUPR ^b	0	13.03	0.1	1.4	0	40.38	0	0.91	0	0.03	0
Hypertension	0	9.13	7.59	41.15	68.79	46.79	83.71	34.38	96.33	77.86	52.94
Other disease	0	38.32	0.3	1.22	0	48.63	1.85	1.73	0	0.82	0
Cardiovascular	0	17.52	0.1	2.46	2.17	14.25	21.64	4.73	5.52	26.51	27.77
CKD ^c	0	4.27	0	3.87	0.22	31.84	81.67	1.04	1.92	1.28	1.01
Treatment, %											
Hospitalized	19.87	46.08	14.15	42.22	44.91	58.56	70.72	57.17	60.8	60.11	70.47
ICU ^d	1.59	9.82	1.23	4.48	5.06	4.01	4.87	4.81	5.56	5.24	5.62
Intubated	3.44	9.03	2.18	7.9	8.46	12.12	13.38	11.5	12.13	12.42	12.84
Pneumonia, %	12.36	37	9.08	37.18	41.52	42.44	52.14	43.55	48.1	46.8	53.61
Recovery, %	90.27	91.37	95.22	82.81	81.3	66.94	53.96	66.43	64.95	64.42	55.96
Survival >15 days, %	93.46	93.73	97.01	88.39	87.27	76.34	65.37	77.1	75.26	75.34	67.28
Survival >30 days, %	90.74	91.8	95.5	83.74	82.14	68.26	55.71	68.2	66.33	65.88	56.96
Survival >15 days (deceased), %	30.76	28.64	36.21	31.09	31.59	28.46	24.8	31.7	29.73	31.01	25.71
Survival >30 days (deceased), %	6.61	4.64	5.93	5.79	4.52	4.2	3.82	5.26	4.04	4.24	2.29
Time from symptom onset to hospitalization (days), mean	3.78	3.2	4.87	4.37	5.21	4.48	4.3	4.85	4.92	4.94	4.82
Other case contact, %	45.84	40.23	51.18	36.6	36.04	27.39	20.9	27.88	27.56	28	20.89

^aCOPD: chronic obstructive pulmonary disease.^bINMUSUPR: immunosuppression.^cCKD: chronic kidney disease.^dICU: intensive care unit.

Figure 5. Main features of the 11 resultant meta-clusters, sorted by recovery, in addition to the thresholds for the different severity outcomes and input variable categories; based on data collected in Mexico between January 13, 2020 and September 30, 2020. COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; INMUSUPR: immunosuppression.

Meta-cluster ID	Recovery	ICU	Intubation	Age group	Habit	Comorbidity	Pneumonia
1	Very high	Low	Low	All	Healthy	Healthy	No
2	Very high	Very high	Moderate	Children & Young	Healthy	Some w/ INMUSUPR, cardiovascular or other disease.	Yes
3	Very high	Low	Low	Young adults	Obesity Smoke	Some w/ asthma	No
4	High	Moderate	Moderate	All	Healthy	Diabetes Hypertension	Yes
5	High	High	Moderate	Young adults	Obesity	Diabetes Hypertension	Yes
6	Moderate	Moderate	High	Older adults	Healthy	Diabetes Hypertension INMUSUPR Other disease Some w/ CKD	Yes
8	Moderate	Moderate	High	Elderly	Smoke	Hypertension COPD Some w/ diabetes or asthma	Yes
9	Moderate	High	High	Older adults & Elderly	Healthy	All Diabetes All Hypertension	Yes
10	Moderate	High	High	Elderly	Obesity Smoke	COPD Hypertension Diabetes Some w/ asthma or cardiovascular.	Yes
7	Low	Moderate	Very High	Older adults & Elderly	Healthy	Diabetes Hypertension CKD Other disease Some w/ cardiovascular.	Yes
11	Low	High	High	Elderly	Smoke	Hypertension All COPD Some w/ diabetes, asthma or cardiovascular.	Yes



MC4 included individuals of all ages with healthy habits, but, unlike MC1, most patients in MC4 had hypertension (41%) or diabetes (39%), but not both simultaneously. MC5 included young adults with obesity (75%), diabetes (57%), or hypertension (69%). Despite this dissimilarity, MC4 and MC5 still had similarly high RRs, of approximately 80%. From MC4 onwards, all MCs had a 40% to 50% incidence of pneumonia,

as provided on the case report, which does not exclude the possibility that some patients developed pneumonia days after. Noteworthy, in MC4 to MC11, more than 70% of the deceased patients were diagnosed with pneumonia.

The RRs from MC6 and MC8-MC10 were similar (64%-67%). MC6 included older adults with no obesity nor smoking but with a high prevalence of diseases including diabetes,

hypertension, immunosuppression, or others. MC8 included older adults who habitually smoked, plus hypertension (34%) or COPD (44%), both smoking-related diseases. Similarly, MC10 included older adults with obesity (50%) or habitual smoking (42%), who also had COPD (37%) but with a much higher incidence of diabetes (61%) and hypertension (78%). MC9 included older adults with both diabetes (95%) and hypertension (96%).

MC7 and MC11 had the lowest RRs (54% and 56%, respectively). MC7 included older adults with common diseases (diabetes, hypertension, and cardiovascular disease) plus CKD (81%). CKD stands out as the differential factor between similar MCs with low RRs, such as MC6 or MC9. MC11 was similar to MC8 and MC10; the key differences were the higher prevalence of smoking (78%, which doubles the former) and COPD (almost all patients, 91%) and a mean age 8 years older (76 years versus 68 years). In addition, MCs that included older obese patients who habitually smoked (MC8, MC10, and MC11) had significantly higher COPD and cardiovascular disease incidences, associations that did not occur with the young smokers (MC3).

Assessment of Clusters' Source Variability

Regarding state variability, half of the Mexican states were prone to higher probabilities of healthy clusters with better RRs, lower hospitalization rates, lower ICU rates, and lower intubation rates among each age-sex group (Figure 6A; eg,

18F2, 18M1, 18-49F1, 18-49M1, 50-64F1) and MCs (Figure 6B), whereas another one-half behaved inversely. Hidalgo, Baja California, and Morelos represented the healthiest groups, in contrast to Oaxaca, Coahuila de Zaragoza, and Durango, which represented the less healthy. Surprisingly, Mexico City showed a significantly higher probability of having healthier clusters than the State of Mexico, albeit the populations of their main urban areas are close, and both have similar resources and economic development levels.

Regarding variability in the TCIs (Figure 7A, Figure 7B), the Secretariat of Health (SSA), the National System for Integral Family Development (DIF), private institutions, and the Red Cross were more likely to have healthier, young patients. This pattern occurred inversely in other TCIs, especially the Mexican Petroleum Institution, for which the probabilities of severe clusters were generally higher. The clinical institutions of the armed forces (Secretariat of the Navy [SEMAR], Secretariat of the National Defense [SEDENA]) were mostly healthy, intuitively with a higher probability of male patients. Noteworthy, among the 3 primary TCIs in Mexico, the public health system (SSA) had more mild comorbidities and relatively higher probabilities of having healthy clusters among each age-sex group, mostly in MC1 (57%) and MC3 (16%), whereas in the 2 main social security systems (Mexican Institute of Social Security [IMSS], Institute for Social Security and Services for State Workers [ISSSTE]), the situation was just the opposite.

Figure 6. Heat maps of the probability distribution of the (A) 56 age-sex specific clusters and (B) 11 meta-clusters (MCs) for each Mexican state where patients received treatment or medical attention, using data collected in Mexico between January 13, 2020 and September 30, 2020. Rows represent the clusters, and columns represent the states and are arranged according to a hierarchical clustering of their values. We compared the clusters' distribution within each age range to circumvent any correlation or association with comorbidities and habits.

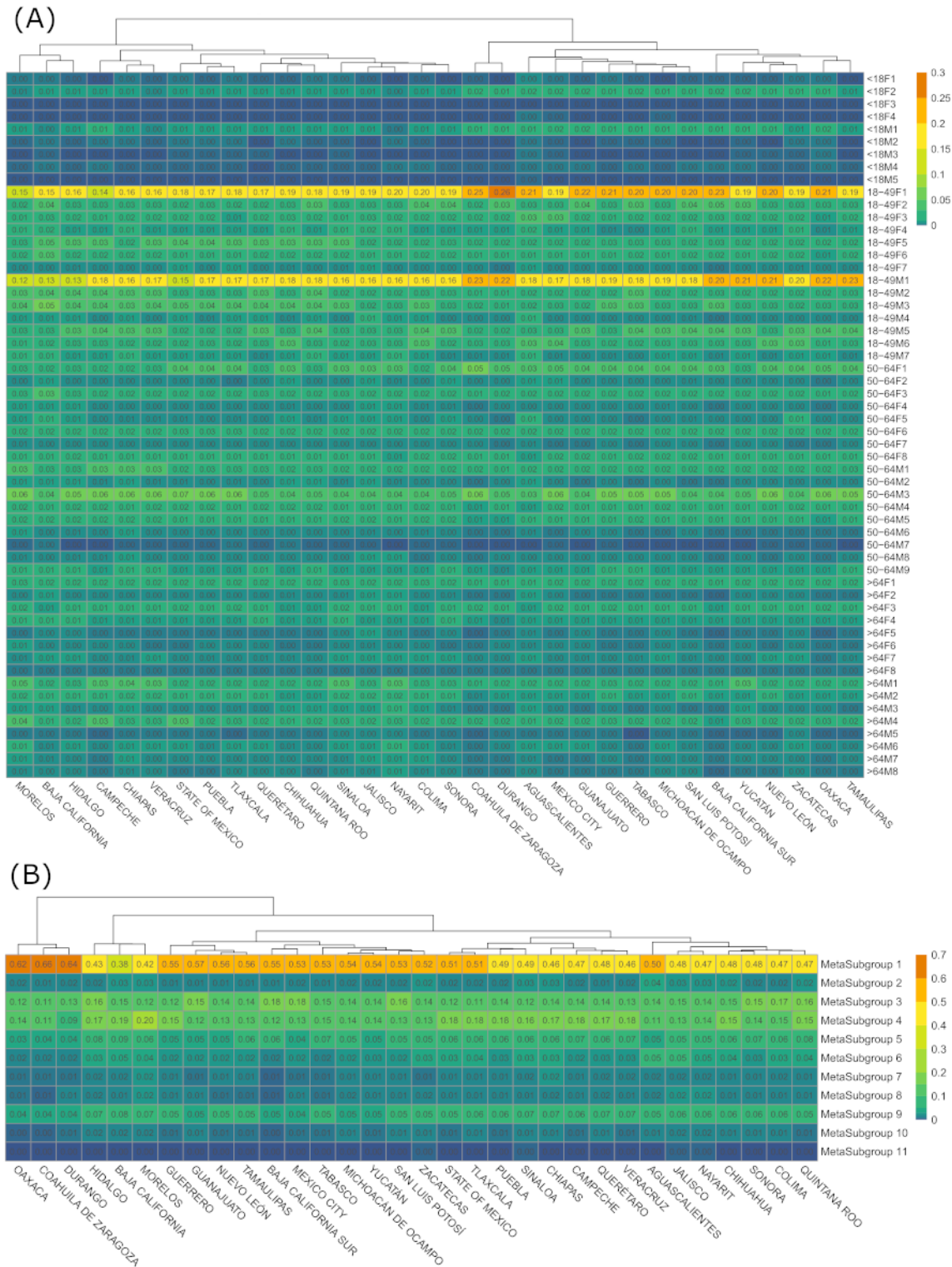
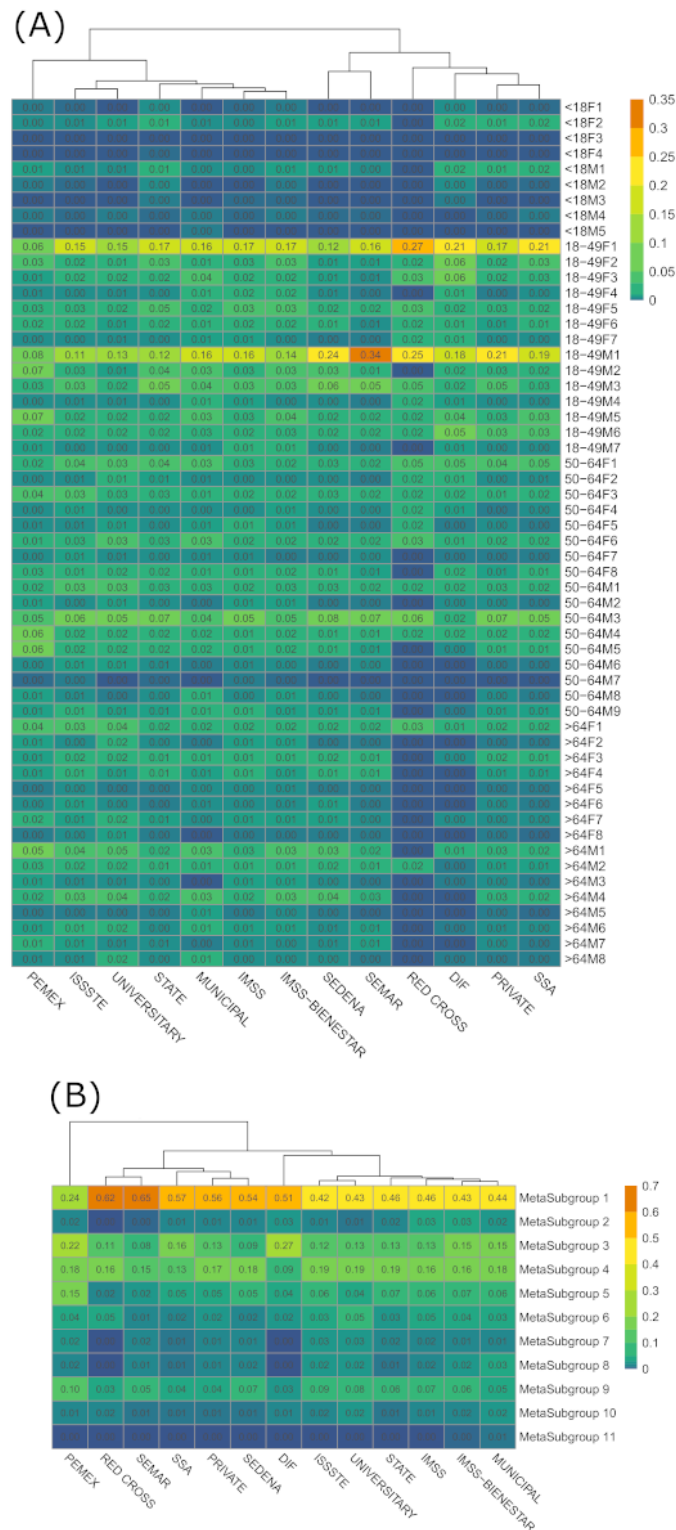


Figure 7. Heat maps of the probability distribution of the (A) 56 age-sex specific clusters and (B) 11 MCs for each type of clinical institution (TCI), using data collected in Mexico between January 13, 2020 and September 30, 2020. Rows represent the clusters, and columns represent the TCIs and are arranged according to a hierarchical clustering of their values. We compared the clusters' distribution within each age range to circumvent any correlation or association with comorbidities and habits. DIF: National System for Integral Family Development; IMSS: Mexican Institute of Social Security; ISSSTE: Institute for Social Security and Services for State Workers; PEMEX: Mexican Petroleum Institution; SEDENA: Secretariat of the National Defense; SEMAR: Secretariat of the Navy; SSA: Secretariat of Health.



Discussion

Meta-Clustering

Main Findings

Previous literature has reported isolated risk factors and their association with severe progression of several diseases. However, the use of such information to improve clinical decision-making is potentially limited. In this work, no single clinical variable nor lifestyle habit was enough to characterize the COVID-19 subphenotypes, a typical phenomenon when the data set has many categorical variables. This reflects the reality of clinical practice: Patients do not usually fall into subgroups of “all good” or “all bad” outcomes, and neither of the patient outcomes can be concluded by a single variable. However, when considering the variables together, our study uncovered 11 clinically distinguishable MCs among 56 plausible age-sex clusters; these MC-defined subphenotypes alongside age-sex stratification may represent different disease mechanisms and outcomes.

Each of the 11 MCs shows clinical consistency: Their group outcomes can be potentially predicted from the proposed input variables, according to the literature published to date. From an outcome perspective, a dividing line can be clearly drawn between MCs 1-5 and MCs 6-11. Although the former had high RRs, the latter had low RRs. Several factors can explain these findings, mainly age, habits, and comorbidities. Since all MCs were 30%–60% women within their input age-sex clusters, the association between sex and mortality is hard to see based only on MCs. However, the age-sex cluster analysis showed clearly better outcomes in female patients despite presenting with similar conditions as male patients. Therefore, considering both age-sex clusters and MCs is essential for better characterization that reveals more relevant detailed information in COVID-19 subphenotypes.

Hereinafter, we discuss our results in accordance with both MCs and age-sex clusters and relate them with supporting literature to discuss the clusters' clinical consistency through the associated risk factors, including age, habits, and comorbidities, as well as on the clusters' sources. Finally, we present recommendations based on this study and discuss possible limitations.

Age

The 2 groups with very high RRs were MC2 and MC3, which included children and young adults. Age may play a protective role against the disease for 2 reasons. First, as proven by MC3 versus all single-aged groups (MCs 6-11), the incidence of pneumonia was lower in young healthy groups; hence, a good RR could be attributable to mild disease caused by SARS-CoV-2. Second, as shown by the good RRs in MC2 (children with severe disease), response to treatment is probably also better at younger ages.

In addition, children (MC2) were prioritized for medical attention compared with adults with similar clinical conditions in Mexico. After discussion with Mexican clinicians, one explanation seems to be that, at an early age, decompensation

or deterioration caused by a pulmonary disease is faster in children than in adults and has a higher risk of death. In adults, there is often some time margin to evaluate the evolution of the patient's condition before intubation or ICU admission, but the same is not true for children. Furthermore, if, in addition to the presence of pneumonia, the groups are defined by conditions such as CKD and cardiovascular issues, a child who already has those issues could be perceived as having a much higher risk or being more vulnerable than an older person. These results are supported by recent literature; for example, a study with a small cohort from Madrid [44] found 10% of 41 children with COVID-19 required ICU admission. Another study [45] showed that severe COVID-19 can also happen in small children and adolescents, in which risk factors for ICU admission included age younger than 1 month, male sex, signs of lower respiratory tract infection, and presence of a pre-existing medical condition.

Regarding the association between older age and outcomes, MCs 6-11 were exclusively composed of older adults with poor outcomes. However, overall survival cannot be explained only by age but also the presence of comorbidities and habits: Although MC11 had the highest mortality and mean age, MC7 had a similar RR with a mean age approximately 10 years younger, similar to the groups with better RRs. Besides, as widely described in the literature [46], older chronological age is not necessarily linked to higher mortality, but physiological age can be. MC1 and MC4 support this fact, since, despite containing the same number of groups of each age, they had similar RRs to the RRs of groups composed only of young adults with little incidence of previous disease (MC2, MC3) and groups composed of young adults with some frequently occurring diseases, such as diabetes and hypertension (MC5).

Of note, the clustering for the individual age-sex groups with an age >64 years revealed that centenarians (individuals of over 100 years old) repeatedly fell in the age-sex clusters with better outcomes. This fact conforms with the well-studied good health and low frailty scores [47] of this subpopulation.

Habits

The roles of obesity and smoking as risk factors for severe disease are complex, since they are both associated with the development of many conditions (eg, COPD [48] or cardiovascular disease [49]). In our study, the influence of obesity seems to be clear, by comparing MC4 and MC5; although both had diabetes, hypertension, and moderate RRs, they were differentiated by the fact that MC4 included patients of all ages without obesity and MC5 had mostly young adults with obesity. This seems to suggest that obese young adults may behave as “older,” implying higher mortality [46,50]. However, we found just the opposite in young individuals without pre-existing comorbidities: MC1 and MC3 had similar RRs, even though MC3 had a significant number of obese patients or smokers.

These findings suggest the role of habits cannot be considered alone but always with age, comorbidities, and duration of unhealthy habits. Our results found that smoking is a risk factor for severe COPD and cardiovascular disease, primarily in older patients (MC8, MC10, and MC11). Therefore, it is reasonable that the longer that one is a smoker, the greater the incidence

of severe disease. In young patients, however, the evidence of smoking's negative influence is not so straightforward. Some reviews have presented current smoking as a protective factor versus former smoking, while it is clearly a risk factor versus never smoking [51]. Our results showed that groups with young smokers have RRs that are not inferior to age-matched nonsmoking groups, as proven by the RR of MC3 versus that of MC2.

Regarding obesity, its influence is not so clear in older groups since all had a high ratio of certain comorbidities. Still, in young obese patients without a comorbidity (18-49M5 and 18-49F2), obesity seems unrelated to mortality.

Comorbidities

Diabetes and hypertension had the highest prevalences among the recorded comorbidities. Their prevalences seem to explain the decrease in RRs from MC1 and MC3 to MC4 and MC5, all of which are young adult groups. In older MCs (6-11), the results are harder to evaluate independently since both diseases were present in nearly every group, not specifically characterizing any cluster except MC9 (older patients with both diseases simultaneously alongside a low RR). These findings are in accordance with the current literature that has reported both diabetes and hypertension are independent risk factors for severe disease [46,52,53].

Immunosuppressed patients fell mostly within MC6 (older adults with diabetes, hypertension, immunosuppression, and other diseases). Of note, immunosuppressed patients were not in the clusters with the lowest RRs. This conforms with some reports that described that immunosuppression has not been confirmed as a relevant factor for disease severity, except for in patients with cancer [54,55]. MC6 also had few patients with CKD, a factor that has been studied as a key factor for disease progression [56,57], and it may be a cause for the immunosuppression in this group (odds ratio 9.65, 95% CI 9.05-10.28) according to the prevalence of immunosuppression in patients with CKD versus those without CKD.

MC7 was characterized by a high prevalence of CKD and other diseases. In this group, the RR was roughly 10% lower than in other severe subgroups. We found that CKD was highly associated with mortality and a shorter survival length. This accords with a report that revealed CKD was the factor that best explained mortality [58], implying patients with CKD could be vulnerable.

MC8 was similar to MC10 and MC11 to some extent since they all had patients with COPD. Most patients with COPD are older with comorbidities with poor outcomes, which conforms to several reviews that reported patients with COPD have an increased risk of severe pneumonia and poor outcomes when they develop COVID-19 [59,60].

Cardiovascular disease was homogeneously distributed among the groups, particularly in MC7, MC10, and MC11. Nowadays, cardiovascular disease may be a double-edged factor, since it is a proven risk factor for COVID-19 severity, but some of the treatments used, such as ACE inhibitors, have also proved to be protective against severe infections from SARS-CoV-2 [61,62].

Assessment of Clusters' Source Variability: State and Types of the Clinical Institution

Reliable subphenotype characterization that reflects the geographical and health care settings from which they are ascertained is crucial [63]. To date, variability in severity between Mexican states and TCIs is rarely reported [64-66] nor is variability assessed independently from age and sex. As an example, one state (eg, Morelos) may show higher severity if it includes more older and male patients, but when we compare age-sex groups, the results showed no difference in the probability of higher severity within age-sex groups of the same age range.

The interstate and TCI variability we found may be influenced by many factors such as the number and type (urban/rural) of population, sociocultural context, health care policy, quantity of medical institutions, availability of resources, and virus transmission level. Some states are more industrialized and have more economical resources (eg, Mexico City, Jalisco, the State of Mexico) than others (eg, Oaxaca, Chiapas, Guerrero). The differences found between Mexico City and the State of Mexico regarding the distribution of healthy clusters are hard to explain due to their proximity and similarities in the type of population and availability of medical resources.

One possible explanation for the differences in severity between social security institutions (IMSS and ISSSTE) and local public hospitals (SSA) is that SSA are administrated by the local states and the resources among states often differ. This phenomenon could influence these institutions' quality and resources to attend their populations. Another supportive explanation is that, when an SSA receives severe patients and has insufficient medical resources, these patients can be transferred to the IMSS COVID-19 facilities. Consequently, this may saturate IMSS and deplete the limited resources due to an increasing number of patients, making the distribution of resources harder. These results conform with those of previous studies showing that the risk of death for an average patient attending IMSS and ISSSTE is twice the national average and 3 times higher relative to that of private clinical institutions [64]. In addition, the variability may also be explained by differences in COVID-19 testing strategies, rather than actual differences in the epidemiology of the underlying disease or population in these areas.

Recommendations

Although a young age predisposes a patient to mild disease, we suggest that a key factor to explain the dividing line between "high," "moderate," and "low" RRs across all ages is using age in combination with habits and comorbidities. In addition, the relationship between the patient's age and duration of unhealthy habits may help establish more useful prognoses and correlations.

Regarding the comorbidities that are associated with increased risk, our findings suggest that diabetes and hypertension are independent risks for severe disease and are associated with lower RRs. Patients with CKD could be more vulnerable in terms of mortality and survival length and are prone to immunosuppression. Patients with COPD are more likely to have an increased risk of severe pneumonia and poor outcomes.

The complex association between severity and patients' sources (states or TCIs) implies a crucial socioeconomic and health care resource-level inequality. Thus, we suggest that future research should consider both state and TCI combined with MCs and age-sex subgroups (eg, using the proposed meta-clustering approach), leading to better subphenotype characterization.

As part of a surveillance system, these findings could help anticipate patients with potential poorer outcomes and help decision-making regarding vaccination priority or resource allocation. This can be important to make use of additional patient information (habits, comorbidities, sources) as well as age, in contrast to certain recommendations or policies for vaccinations based primarily on older age, profession, or social status, such as in Spain or the United States [67,68]. In fact, in some cases, such recommendations or policies might be imprecise (eg, as shown previously, higher chronological age is not necessarily linked with higher mortality; centenarians tend to have a greater probability of a good outcome, and children with complex clinical pre-existing conditions may have worse outcomes than healthy older people).

Limitations

As a possible limitation, we excluded patients who showed symptoms less than 31 days prior (ie, who were confirmed after September 30) to avoid a possible effect on the analysis of survival outcomes, which impeded us from using the most recent data that could have had changed epidemiological characteristics. In addition, the analyzed data set is public and open source, published by the Mexican government, but there is no clear statement about the source of some of the information reported by each public and private health institution and captured by the data system. The fact that more complete or accurate data might be available for those patients with more severe illness might result in differential misclassification reinforcing the clustering of factors with higher severity in some cases. In addition, requiring the patients to have laboratory-confirmed infection could result in individuals with more severe disease or acknowledged comorbidities—or other risk factors for severe outcomes—to be included in the study; however, this allowed us to focus on determining subphenotypes

within this more severe population. Furthermore, the data set did not include additional relevant information about the patients who were discharged, readmitted, or vaccinated and did not include the duration of comorbidities and unhealthy habits. Further studies with population-based data regarding subphenotype characterization among discharged patients who underwent posthospitalization surveillance or were readmitted as well as the vaccinated population are highly needed.

Conclusions

The analysis of COVID-19 subphenotypes from the proposed 2-stage cluster analysis produced a discriminative characterization and explainability over just age and sex. The resultant 11 MCs provided the bases for a deep understanding of the epidemiological and subphenotypic characterization of COVID-19 patients based on pre-existing comorbidities, habits, demographic characteristics, patient provenance, and TCIs, as well as identified the correlations between these characteristics and possible clinical outcomes of each patient-specific profile. These unbiased subphenotypes may help establish target groups for automated stratification or triage systems to support clinicians with early triage prior to further tests and laboratory results, especially in those areas where such tests are not available; prioritize vaccination among the general population; and provide the bases for planning personalized therapies or treatments.

The proposed age-sex stratification and meta-clustering technique have the potential to help design a novel data-driven model for the stratification of COVID-19 patients. In addition, the results shed light on robust conclusions about associations and causality between the subphenotypic presentation and clinical outcomes. Future studies can explore the treatment and vaccination implications, to provide guidance on clinical triage and customize therapy, and also develop clinically robust subphenotype classification methodologies combined with the proposed 2-stage cluster analysis. As the concern for efficient triage and personalized treatment increases, we facilitate further replicability of the study and generalization to data from other countries by making our experiment's codes available.

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Authors' Contributions

LZ, CS, JMGG, and JAC designed the research. LZ, NR, CS, JMGG, JAC, and JMM conducted the research. LZ and CS processed and analyzed the data and performed the statistical analysis. All authors assessed the clinical consistency of the cluster analyses. LZ, NR, and CS drafted the manuscript. All authors revised the manuscript critically and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental Materials.

[[DOCX File , 863 KB - publichealth_v8i3e30032_app1.docx](#)]

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Abbreviations

CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease
DIF: National System for Integral Family Development
ICU: intensive care unit
IMSS: Mexican Institute of Social Security
ISSSTE: Institute for Social Security and Services for State Workers
LOESS: locally estimated scatterplot smoothing
MC: meta-cluster
MCA: multiple correspondence analysis
ML: machine learning
PCA: principal component analysis
RR: recovery rate
SEDENA: Secretariat of the National Defense
SEMAR: Secretariat of the Navy
SSA: Secretariat of Health
TIC: type of clinical institution
WHO: World Health Organization

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Original Paper

Risk Factors of COVID-19 Critical Outcomes in the Eastern Mediterranean Region: Multicountry Retrospective Study

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Abstract

Background: The establishment of empirical evidence in the Eastern Mediterranean Region necessitates the implementation of wide-scale studies to describe the demographic, clinical features, and severity profile of patients with COVID-19.

Objective: This study aims to assess the patterns of COVID-19 severity and mortality in seven countries, and to determine the risk factors of COVID-19 severity and mortality.

Methods: This multicountry study was based on a retrospective review of medical records of hospitalized patients confirmed to have COVID-19. This study includes data from Iraq, Pakistan, Sudan, Somalia, Morocco, Egypt, and Yemen. All demographic and clinical data were extracted from hospital records (paper files) by trained data collectors.

Results: A total of 4141 patients were included in this study from seven countries. Comorbidities were reported by nearly half of the patients, with hypertension (n=1021, 24.7%) and diabetes (n=939, 22.7%) being the most common. Older age, diabetes mellitus, hypertension, and heart diseases were significantly associated with COVID-19 severity and mortality. Ever smoking and renal diseases were significantly associated with severity but not mortality, while male gender, respiratory diseases, and malignancy were significantly associated with mortality but not severity.

Conclusions: The study confirms the role of comorbidities and demographic features on the severity and mortality of COVID-19. Understanding the contributing factors ensures attentive care and informs clinical management of patients with poorer prognoses in the early stages of diseases.

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KEYWORDS

critical outcomes; COVID-19; severity; mortality; outcome; risk factor; retrospective; implementation; demographic; pattern; trend; risk

Introduction

On December 31, 2019, cases of pneumonia of unknown etiology were reported from Wuhan City, Hubei Province of China [1]. Later, SARS-CoV-2 was identified as a causative agent, and the disease was named COVID-19. The World Health Organization (WHO) declared SARS-CoV-2 to be a global pandemic on March 11, 2020 [1,2]. Globally, 200,840,180 cases of COVID-19 were confirmed and 4,265,903 deaths were reported as of August 6, 2021. In the Eastern Mediterranean Region (EMR), a total of 12,949,856 cases and 240,395 deaths were reported as of August 6, 2021 [3]. The recent forecasting by Institute for Health Metrics and Evaluation has projected COVID-19-related deaths in North Africa and the Middle East to reach up to 327,956 deaths by December 2021 [4].

As many of the countries in the region are experiencing war and political instability, cases and deaths are underreported because of inadequate testing facilities, weak health system response, and inadequate vital registration and documentation [5]. The high hospital admissions and poor surge capacity of critical care were experienced as one of the key health facility challenges that would undermine the response to the COVID-19 pandemic [5]. Difficulties in the estimation of COVID-19 hospital admission rates were highlighted early during the pandemic, as it depends on community testing and admission criteria, which varies between countries. Studies from China, Europe, and the United States have indicated rates of admission to intensive care ranging from 5% to 32%, respectively [6-9].

A recent report showed that Iran has accumulated the highest number of cumulative deaths (n=85,694, case-fatality rate [CFR] 2.6%), followed by Pakistan (n=22,582, CFR 2.3%) and Iraq (n=17,515, CFR 1.2%) [10]. Whereas, Yemen reported the highest CFR (19.7%) followed by Sudan (7.5%). The lowest CFR was reported from Qatar (0.2%) [10]. The difference in the population profile and health system capacity between countries might result in variation in epidemiological characteristics and clinical outcomes. It is worth noting that the Middle East region has a high prevalence of diabetes and cardiovascular diseases (CVDs) that may contribute to heighten

the severity of the disease resulting in high mortality and lifelong disability [11-13].

Severe cases of COVID-19 are more likely to deteriorate to conditions that necessitate vital and timely care [6,7]. Epidemiological studies in China, Canada, the United States, and the United Kingdom have identified risk factors associated with severe cases of COVID-19 that require hospital admission [6-9]. Old age, chronic comorbidities, and male sex have consistently been cited as risk factors associated with COVID-19 severity and increased mortality [14-16]. Other risk factors including chronic obstructive pulmonary disease (COPD) and smoking were reported in other studies [17].

Despite the fact that there is limited evidence on the severity of COVID-19 across the EMR, recent studies from Iraq were consistent with global evidence that old age, male gender, and pre-existing comorbidities were associated with increased mortality among hospitalized patients with COVID-19 [18,19].

The establishment of empirical evidence in the EMR necessitates the implementation of wide-scale studies to describe the demographics, clinical features, and severity profiles of patients with COVID-19. Assessing the risk factors of the severe form of COVID-19 is essential to develop appropriate risk reduction strategies and to plan resources for health care as the pandemic unfolds. Furthermore, it will inform clinical management by predicting clinical outcomes and prognostic markers to facilitate the development of a care pathway for COVID-19 critical care. Thus, this study aims to assess the patterns of COVID-19 severity and mortality in seven countries, and to determine the risk factors of COVID-19 severity and mortality.

Methods

Study Design and Data Sources

This multicountry study was based on a retrospective review of medical records of hospitalized patients confirmed to have COVID-19. This study included data from Iraq, Pakistan, Sudan, Somalia, Morocco, Egypt, and Yemen. All data were extracted from hospital records (paper files) by trained data collectors who used a standardized Kobo collect form for data entry. In

all participating countries, the data collected were for patients admitted to hospitals by October 2020.

In Iraq, data were collected for patients with COVID-19 who were admitted during the period between June 1 and 30, 2020, to any one of the six selected hospitals in Baghdad and one hospital in Babylon. The seven hospitals were selected out of the 10 hospitals that received patients with COVID-19 in Baghdad and Babylon because of the presence of Field Epidemiology Training Program residents who collected the data. In Sudan, the study was limited to Khartoum and Gazira states, as they were the high spots for COVID-19 in the country. The data were collected from the two main secondary isolation centers and two primary isolation centers (all hospital records of patients with a confirmed diagnosis between March 2020 and October 2020 were included). In Morocco, data were collected from the Cheikh Zaid International University Hospital of Rabat City, which was dedicated to the hospitalization of patients with COVID-19. In Egypt, data from El-Agoza Hospital in Giza governorate (a high-risk governorate) were collected between May and June 2020. El-Agoza Hospital was designated for the screening and isolation of patients with COVID-19. In Yemen, data were collected on patients with COVID-19 who were admitted to three main isolation hospitals in Sana'a City. In Pakistan, data were collected from two hospitals in Rawalpindi (Benazir Bhutto Hospital and Holy Family Hospital) and two other hospitals in Islamabad (Pakistan Institute of Medical Sciences and Pakistan Air force Hospital) of cases admitted between February and August. All four hospitals were COVID-19 treatment centers. In Somalia, data of patients admitted between March and August to De-Martino Hospital (the only COVID-19 treatment center in Mogadishu) were collected.

Data Abstraction Form

A standardized data collection tool for all countries was developed and converted to the Kobo Toolbox form. The form consisted of four sections. The first section included patients' baseline and demographic characteristics (age, gender, smoking history, health care worker [HCW] or not, travel history, and history of contact with patients with confirmed COVID-19). The second section included variables related to clinical history and presentation severity, signs and symptoms, and comorbidities. The third section included severity classification. Section four included outcomes (fully recovered, discharged improved, palliative discharge/disable, and death).

Variable Definitions

WHO guidelines were used to define the history of contact (exposure during the 2 days before and the 14 days after the

onset of symptoms) and travel history (history of travel 14 days before symptom onset) [20]. The severity of the disease was classified into mild (upper respiratory disease), moderate (pneumonia but no need for oxygen), severe (pneumonia and need oxygen), and critical (needs intensive care unit admission) [21]. Clinical outcomes were defined as follows: fully recovered (negative polymerase chain reaction [PCR] test before discharge or full resolution of symptoms as noted by the attending physician), discharged improved (no PCR was done before discharge but the patient was discharged based on improvement in the clinical picture), palliative discharge/disable (discharged with long-term disability due to COVID-19), and death. During the analysis, we grouped the first three categories under "survivors" and compared them to the fourth category "death." Critical outcomes included death, palliative discharge, or disability.

Ethical Considerations

Ethical approval was obtained from the institutional review boards in selected countries, and hospital permissions were sought to access patients' records. Data were coded to maintain confidentiality. All data files were encrypted and saved in a secure database with limited access to the study team.

Data Management and Analysis

Data were entered and managed using the Kobo Toolbox (a tool developed by the Harvard Humanitarian Initiative to be used for field data collection in challenging environments) and then exported to SPSS version 23 (IBM Corp) for analysis. Data were described using percentages and counts. The differences between percentages were tested using the chi-square test. Two separate multiple logistic regression analyses were conducted to determine factors associated with COVID-19 severity and mortality. The final logistic regression models included significant variables only. A *P* value less than .05 was considered statistically significant.

Results

Demographic and Relevant Characteristics

A total of 4141 patients were included in this study from seven countries, of which Iraq and Pakistan composed almost 60% of the sample followed by Sudan ($n=1011$, 24.4%). Almost 38% ($n=1571$) of patients aged 40-59 years, and male patients constituted 63.8% ($n=2641$) of the sample. About 14.6% of patients were ever smokers. Almost 4% were HCWs. A history of contact with a patient with COVID-19 was indicated by 40.8% ($n=1690$) of patients. [Table 1](#) shows the demographic and relevant characteristics of patients.

Table 1. Demographic and relevant background characteristics of patients with COVID-19 (N=4141).

Variables	Patients, n (%)
Country	
Iraq	1438 (34.7)
Pakistan	1199 (29.0)
Sudan	1011 (24.4)
Somalia	230 (5.6)
Morocco	123 (3.0)
Egypt	71 (1.7)
Yemen	69 (1.7)
Age (years)	
<40	1193 (28.8)
40-59	1571 (37.9)
≥60	1377 (33.3)
Sex	
Male	2641 (63.8)
Female	1500 (36.2)
Profession	
Non-health care workers	3994 (96.5)
Health care workers	147 (3.5)
History of contact with patient with COVID-19 (yes)	1690 (40.8)
Smoking	
Never	3537 (85.4)
Ever	604 (14.6)

Comorbidities and Clinical Manifestations

The most common symptoms on admission were fever (n=3198, 77.2%), followed by cough (n=3009, 72.7%) and shortness of breath (n=2224, 53.7%). Other common clusters encompassing musculoskeletal symptoms (myalgia or arthralgia, or backache or fatigue) were reported by 37.6% (n=1557) of patients. A

cluster of enteric symptoms was less common in this study (n=398, 9.6%). Comorbidities were reported by nearly half of patients, with hypertension being the most common comorbidity (n=1021, 24.7%), followed by diabetes (n=939, 22.7%). Multiple comorbidities were also reported in almost half of the patients (n=2153, 52%; [Table 2](#)).

Table 2. Distribution of study participants by clinical manifestations and comorbidities (N=4141).

Variables	Patients, n (%)
Comorbidities	
No comorbidity	2408 (48.2)
Hypertension	1021 (24.7)
Diabetes mellitus	939 (22.7)
Heart diseases	303 (7.3)
Renal disease	140 (3.4)
Asthma	111 (2.7)
Respiratory diseases (COPD ^a and other respiratory diseases)	61 (1.5)
Malignancy	62 (1.5)
Immune compromising conditions	45 (1.1)
Liver disease	22 (0.5)
Symptoms	
Asymptomatic	124 (3.0)
Fever	3198 (77.2)
Cough	3009 (72.7)
Shortness of breath	2224 (53.7)
Musculoskeletal manifestations	1557 (37.6)
Sore throat	683 (16.5)
Headache	664 (16.0)
Loss of taste or smell	474 (11.4)
Chest pain	458 (11.1)
Gastrointestinal or gastroenteric symptoms (nausea/vomiting/diarrhea/abdominal pain)	364 (8.8)
Sputum production	156 (3.8)
Nasal congestion	118 (2.8)
Conjunctival congestion	37 (0.9)
Hemoptysis	36 (0.9)
Other symptoms	134 (3.2)

^aCOPD: chronic obstructive pulmonary disease.

Factors Associated With COVID- 19 Severity and Mortality

Of all patients, 27.6% (n=1143) had mild disease, 22.7% (n=940) had moderate disease, 28.9% (n=1197) had severe disease, and 20.7% (n=857) had critical disease. The bivariate analysis had shown that increased age, non-health professions,

ever smoking, and comorbidity history, particularly hypertension, diabetes mellitus, heart diseases, and respiratory diseases, were significantly associated with severe or critical COVID-19. Whereas mortality was consistently associated with the aforementioned factors in addition to the male sex, cerebrovascular disease, and malignancy (Table 3).

Table 3. Bivariate analysis of factors associated with COVID-19 severity and mortality.

Variable	Severity			Mortality		
	Mild-moderate, n (%)	Severe-critical, n (%)	<i>P</i> value	Survivors, n (%)	Deaths, n (%)	<i>P</i> value
Sex			.45			.005
Male	1318 (49.9)	1323 (50.1)		2132 (80.7)	509 (19.3)	
Female	767 (51.1)	733 (48.9)		1263 (84.2)	237 (15.8)	
Age (years)			<.001			<.001
<40	849 (71.2)	344 (28.8)		1115 (93.5)	78 (6.5)	
40-59	779 (49.6)	792 (50.4)		1334 (84.9)	237 (15.1)	
≥60	457 (33.2)	920 (66.8)		946 (68.7)	431 (31.3)	
Working in health care setting			<.001			<.001
Non-health care workers	1965 (49.2)	2029 (50.8)		3254 (81.5)	740 (18.5)	
Health care workers	120 (81.6)	27 (18.4)		141 (95.9)	6 (4.1)	
Positive history of contact with patient with COVID-19	1116 (66.0)	574 (34.0)	<.001	1456 (86.2)	234 (13.8)	<.001
Smoking			<.001			.29
Ever	228 (37.7)	376 (62.3)		486 (80.5)	118 (19.5)	
Never	1857 (52.5)	1680 (47.5)		2909 (82.2)	628 (17.8)	
Comorbidities			<.001			<.001
Hypertension	353 (34.6)	668 (65.4)	<.001	714 (69.9)	307 (30.1)	<.001
Diabetes mellitus	319 (34.0)	620 (66.0)	<.001	650 (69.2)	289 (30.8)	<.001
Heart diseases	91 (30.0)	212 (70.0)	<.001	190 (62.7)	113 (37.3)	<.001
Renal disease	25 (17.9)	115 (82.1)	<.001	108 (77.1)	32 (22.9)	.13
Asthma	50 (45.0)	61 (55.0)	.26	91 (82.0)	20 (18.0)	>.99
Respiratory diseases	21 (34.4)	40 (65.6)	.01	38 (62.3)	23 (37.7)	<.001
Malignancy	21 (33.9)	41 (66.1)	.009	43 (69.4)	19 (30.6)	.009
Immunocompromising conditions	12 (26.7)	33 (73.3)	.001	39 (86.7)	6 (13.3)	.41
Liver disease	8 (36.4)	14 (63.6)	.19	16 (72.7)	6 (27.3)	.26
Tuberculosis	19 (33.9)	37 (66.1)	.01	42 (75.0)	14 (25.0)	.17
Cerebrovascular disease	8 (42.1)	11 (57.9)	.47	12 (63.2)	7 (36.8)	.03

The multiple logistic regression indicated that increased age and smoking were significantly associated with severity ($P<.001$). Patients older than 60 years were three times more likely to develop a severe or critical form of COVID-19 compared to patients younger than 40 years. Patients with smoking history were 10 times more likely to develop severe or critical disease course compared to nonsmokers (odds ratio [OR] 9.7, 95% CI 5.1-18.5; $P<.001$). Not having a history of

contact with patients with COVID-19 (OR 2.8, 95% CI 2.4-3.2; $P<.001$) and being non-HCWs (OR 2, 95% CI 1.2-3.1; $P=.004$) were also significantly associated with developing a severe form of COVID-19. Of comorbidities, renal diseases (OR 3.3, 95% CI 2.1-5.2; $P<.001$), heart diseases (OR 1.7, 95% CI 1.3-2.2; $P<.001$), diabetes (OR 1.4, 95% CI 1.2-1.7; $P<.001$), and hypertension (OR 1.2, 95% CI 1-1.5; $P=.03$) were associated with increased odds of severe disease (Table 4).

Table 4. Multiple logistic regression of factors associated with COVID-19 severity and mortality.

Covariates	Factors associated with COVID-19 severity		Factors associated with COVID-19 mortality	
Sex (female vs male)	— ^b	N/A ^c	0.8 (0.7-1)	.02
Age (years)				
<40 (reference)	N/A	N/A	N/A	N/A
40-59	2 (1.7-2.4)	<.001	1.9 (1.5-2.5)	<.001
≥60	3.1 (2.6-3.8)	<.001	4 (3.1-5.3)	<.001
Profession				
Health care workers (reference)	N/A	N/A	N/A	N/A
Non-health care workers	2 (1.2-3.1)	.004	2.4 (1.5-6)	.04
History of contact with patient with COVID-19 (no vs yes)	2.8 (2.4-3.2)	<.001	1.4 (1.2-1.7)	<.001
Diabetes mellitus (yes vs no)	1.4 (1.2-1.7)	<.001	1.6 (1.3-1.9)	<.001
Hypertension (yes vs no)	1.2 (1-1.5)	.03	1.3 (1.1-1.6)	.003
Heart diseases (yes vs no)	1.7 (1.3-2.2)	<.001	1.8 (1.4-2.3)	<.001
Renal disease (yes vs no)	3.3 (2.1-5.2)	<.001	—	N/A
Respiratory diseases (yes vs no)	—	N/A	2.1 (1.2-3.7)	.009
Malignancy (yes vs no)	—	N/A	1.8 (1-3.3)	.04
Symptomatic (yes vs no)	—	N/A	4.5 (1.6-12.6)	.004
Smoking (ever vs never)	9.7 (5.1-18.5)	<.001	—	N/A

^aOR: odds ratio.

^bNot entered in the model because the variable was not statistically significant.

^cN/A: not applicable.

Increasing age was a strong predictor of mortality in hospitals, as the older age group (>60 years) was associated with an increased odds of death by almost four times compared to the younger age category (OR 4, 95% CI 3.1-5.3; $P<.001$). The history of contact with patients with COVID-19s and being a non-HCW had higher odds of mortality. Female sex was associated with lower odds of mortality (OR 0.8, 95% CI 0.7-1.0; $P=.02$). Comorbidities associated with high odds of mortality included respiratory diseases (OR 2.1, 95% CI 1.2-3.7; $P=.009$), heart diseases (OR 1.8, 95% CI 1.4-2.3; $P<.001$), malignancy (OR 1.8, 95% CI 1.0-3.3; $P=.04$), and diabetes mellitus (OR 1.6, 95% CI 1.3-1.9; $P<.001$). Renal diseases and smoking history had no significant association with mortality (Table 4).

Discussion

Principal Results

The data of a cohort of patients with COVID-19 hospitalized in seven different countries were collected and analyzed. The proportion of hospitalized patients with severe or critical illness in this study (49.6%) is remarkably higher than what is being reported from other parts of the world on hospitalized patients with COVID-19 [22-25]. To our knowledge, only one study from Wuhan reported a severity profile as high as 49.1% [26]. However, given that the study was conducted among hospitalized patients rather than in the community, these proportions are not a true representative of the COVID-19

severity spectrum in this region. At the beginning of the pandemic, the health care facilities used to admit patients with COVID-19 of different severity for the sake of isolation and treatment of those patients. Later, with the increase in the number of patients, the health care facilities in most of these countries started to reserve the already limited hospital beds to treat the more severe cases, which in turn shifted the majority of mild/moderate cases to be treated at home.

We found older age, diabetes mellitus, hypertension, and heart diseases to be associated with both severity and mortality. Furthermore, ever smoking and renal diseases were associated with severity but not mortality, while male gender, respiratory diseases (COPD or other respiratory diseases), and malignancy were associated with mortality but not severity. The latter category is of special importance, given the fact that these patients might die even if they do not experience severe or critical illness. The majority of these findings are consistent with previous studies on COVID-19 severity or mortality [27-31].

What Is Already Known on This Topic

Unraveling the pathophysiology of COVID-19 is still a work in progress. Nevertheless, the role of angiotensin-converting enzyme 2 (ACE2) receptors is widely recognized as a key player in the disease process. ACE2 is a metallopeptidase that is expressed in various human organs [32] and is thought to be the cell entry point for SARS-CoV-2 [33]. Among others, it has been found on cell membranes of the nasal epithelium, alveolar

epithelial cells of the lungs, the small intestine enterocytes, vascular endothelial cells, and cardiovascular system cells [32-35]. It is believed that negative regulation of the renin-angiotensin system (RAS) is a main function of ACE2. RAS has been linked to lung injury [36,37], which has led to concluding that ACE2 has a protective effect on the lungs [38,39] and that its pre-existing deficiency might lead to a more severe or even fatal COVID-19 [40].

Older patients, males, and patients with type 2 diabetes mellitus were frequently found to have severe or fatal COVID-19 in epidemiological studies. Interestingly, they were also found to have lower ACE2 expression, which might help explain why they are disproportionately affected by poor COVID-19 outcomes [41-43]. Furthermore, age (the earliest and most widely recognized predictor of COVID-19 severity and mortality) showed the strongest correlation with low ACE2 expression [41].

In addition to ACE2 downregulation, other biological and nonbiological factors might help explain some of our findings. For example, differences in the biological and molecular level in older patients (as compared to younger ones) might have their contribution to the disease course [44]. In particular, two cardinal features of the aging immune system are probably the culprits: immune senescence (a general decline in the overall performance of the immune system, innate and acquired) and inflamm-aging (a systemwide persistent proinflammatory status) [44-46]. However, some have argued that age-associated comorbidities, rather than age itself, are the major factor behind these findings [47]. However, in this paper, we found that age is an independent risk factor on top of the comorbidities from the multiple logistic regression (Table 4).

Diabetes mellitus is another risk factor where the dysregulated immune response is thought to play a role in a patient's susceptibility to critical COVID-19 outcomes. Similar to aging, patients with diabetes are in a state of low-grade chronic inflammation [48]. Furthermore, diabetes is associated with reduced activity of natural killer cells and impaired cell-mediated adaptive immunity (chemotaxis, phagocytosis, cytokine secretion, and T-cell abnormalities) [48].

The fact that an overactive RAS is a key aspect of the pathogenesis of CVD (heart diseases and hypertension) [49,50] might explain the association between CVD and fatal COVID-19. An already existing abnormal cytokine profile in patients with these comorbidities can be part of the explanation as well [51-53]. Knowing that cytokine storm is frequently linked to severe and fatal COVID-19 strengthens the biological plausibility of this explanation [8,54].

Similar to CVD, some renal diseases are characterized by an overactive RAS [55] and linked to dysregulated cytokine function and proinflammatory status [56,57]. Although patients with renal diseases were more likely to have severe illness in our study, we found no association with mortality. This is inconsistent with previous reports [58,59], which might be explained by differences in renal disease definitions and severity levels of the studied patients. These same reasons might explain why, unlike other studies [60], we found no association between liver disease and critical COVID-19 outcomes.

The defective local physiological function of the respiratory system in patients with COPD and other respiratory diseases could explain their predisposition to worse COVID-19 outcomes. Conversely, asthma was not associated with COVID-19 severity or mortality. The evidence in the literature on asthma has been inconclusive [61].

Comparison With Prior Work

Despite the fact that smoking is probably underestimated in our study due to associated stigma, particularly among women, we were able to find an association with severity. However, this same underestimation might be the reason why, unlike previous reports [17], we could not find an association with mortality. Another reason is the fact that in our study, due to small cell size, we combined former and current smokers under the same category, while in other studies, mortality was found to be associated with current rather than former smokers [17].

Unexpectedly, we also found not working in a health care setting and not having a history of contact with a known COVID-19 case to be associated with both severity and mortality. These findings should be interpreted with caution though; patients with a known COVID-19 contact history might be better informed and more likely to seek help early and thus less likely to have critical outcomes.

There is also the possibility that the history of contact is underreported mainly for two reasons. First, the stigma around the disease may prevent many people from telling everyone around them; thus, many people may not realize that they had been in contact with a patient with COVID-19.

Second, the societies in the EMR are among the most social in the world and being friendly to strangers is the social norm. In Iraq, for example, religious mass gatherings where strangers often socialize without observing social distancing is a frequent occurrence. There is a decent possibility that some of the patients in this study might, unknowingly, had come in contact with presymptomatic or mild COVID-19 cases during one of these events.

Similar to our study, a meta-analysis by the American Journal of Emergency Medicine [62] found that HCWs were less likely to have severe or critical disease, or to die of COVID-19. The proposed explanation by the authors seems to hold for our study as well: that HCWs tend to come from a younger age demographic and have fewer comorbidities [62,63]. Further analysis of the characteristics of HCWs in our study revealed that only 4.8% of them were 60 years or older, while the majority (89/147, 60.5%) were younger than 40 years, and 34.7% (51/147) were aged between 40 and 59 years. Additionally, only 4.1% (6/147) had comorbidities.

What This Study Adds

Almost a year has passed since the COVID-19 pandemic started, and still the best intervention we have to fight it with is nonpharmaceutical measures. There is no definite treatment to date, and although good news on effective vaccines is emerging, it might take a few years until enough of the population has access to a vaccine. That is why, in the hospital setting, it is still imperative to identify which patients are at higher risk of

developing severe disease or dying of COVID-19. Although many studies reported on this worldwide, to our best knowledge, this is the first large multicenter study coming out of the EMR.

Limitations

This study has its limitations. First, the study was conducted in a hospital setting, which limits our ability to generalize our findings to the general population. Second, given that in many hospitals in the selected countries hospital admissions were reserved for the most severe cases, our study might be biased toward more severe outcomes. Finally, some variables might

be underreported due to the inability of the HCWs in the overwhelmed facilities to collect all data for all patients.

Conclusions

This study reports on risk factors of COVID-19 severity and mortality in the seven countries. In a hospital setting, health care providers should be more attentive to older patients, men, smokers, and patients with certain comorbidities (diabetes, hypertension, heart diseases, COPD, malignancy, and renal diseases), as they were shown to be more likely to have severe or fatal COVID-19 in our study.

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Conflicts of Interest

None declared.

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Abbreviations

ACE2: angiotensin-converting enzyme 2
CFR: case-fatality rate
COPD: chronic obstructive pulmonary disease
CVD: cardiovascular disease
EMR: Eastern Mediterranean Region
HCW: health care worker
OR: odds ratio
PCR: polymerase chain reaction
RAS: renin-angiotensin system
WHO: World Health Organization

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