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Viewpoint

Making the COVID-19 Pandemic a Driver for Digital Health: Brazilian Strategies

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Abstract

The COVID-19 outbreak exposed several problems faced by health systems worldwide, especially concerning the safe and rapid generation and sharing of health data. However, this pandemic scenario has also facilitated the rapid implementation and monitoring of technologies in the health field. In view of the occurrence of the public emergency caused by SARS-CoV-2 in Brazil, the Department of Informatics of the Brazilian Unified Health System created a contingency plan. In this paper, we aim to report the digital health strategies applied in Brazil and the first results obtained during the fight against COVID-19. Conecte SUS, a platform created to store all the health data of an individual throughout their life, is the center point of the Brazilian digital strategy. Access to the platform can be obtained through an app by the patient and the health professionals involved in the case. Health data sharing became possible due to the creation of the National Health Data Network (*Rede Nacional de Dados em Saúde*, RNDS). A mobile app was developed to guide citizens regarding the need to go to a health facility and to assist in disseminating official news about the virus. The mobile app can also alert the user if they have had contact with an infected person. The official numbers of cases and available hospital beds are updated and published daily on a website containing interactive graphs. These data are obtained due to creating a web-based notification system that uses the RNDS to share information about the cases. Preclinical care through telemedicine has become essential to prevent overload in health facilities. The exchange of experiences between medical teams from large centers and small hospitals was made possible using telehealth. Brazil took a giant step toward digital health adoption, creating and implementing important initiatives; however, these initiatives do not yet cover the entire health system. It is expected that the sharing of health data that are maintained and authorized by the patient will become a reality in the near future. The intention is to obtain better clinical outcomes, cost reduction, and faster and better services in the public health network.

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KEYWORDS

COVID-19; digital technology; Brazil; public health; medical informatics; digital health; strategy; outbreak; system; data; health data; implementation; monitoring

Introduction

The year 2020 was marked by the outbreak of COVID-19, the disease caused by the highly contagious virus SARS-CoV-2, which created many challenges for the scientific community and health services worldwide. COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, forcing public health authorities in all countries to adopt measures focusing on surveillance, rapid case identification, interruption of community transmission, and strong public communication to contain the spread of the virus, mitigate its impact on human health, and attempt to prevent the collapse of health systems [1]. In this context, effective, integrated, and safe recording, management, and follow-up of patients' clinical data at the different levels of a health system are fundamental to better address the situation imposed by the COVID-19 pandemic [2,3]. However, health care systems are composed of multiple agents and services, which cannot always share patients’ clinical data adequately and at the necessary speed to address the pandemic scenario.

The COVID-19 pandemic has several peculiar characteristics that set it apart from other pandemics previously faced by the world, such as the number of infected individuals, the high transmissibility levels, the broad spectrum of symptoms, and the rapid evolution of patients to severe conditions [4]. In addition, the COVID-19 pandemic is occurring in an era of massive technological advancement, when digital health solutions have been extensively discussed but have not yet been widely deployed and accepted [5]. Considering this adverse scenario, at the same time that the COVID-19 pandemic has exposed the deficiencies of health care systems worldwide, it is providing an opportunity to develop and test innovative solutions extremely quickly to strengthen public health measures [6]. In this context, in this paper, we aim to share the Brazilian digital health initiatives that were implemented to mitigate the damage caused by COVID-19. These initiatives were created by a special committee linked to the information technology (IT) department of the Brazilian Unified Health System, which is considered to be one of the most extensive public health systems in the world.

The Brazilian Health System

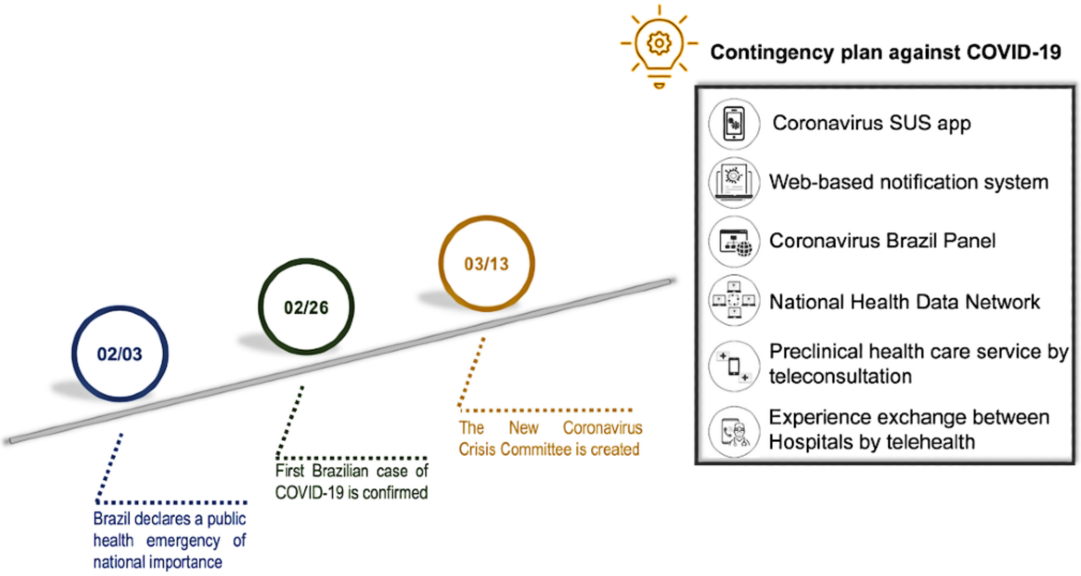
On February 3, 2020, Brazil declared a public health emergency of national importance. The first case of COVID-19 in Brazil was confirmed in São Paulo on February 26 [7], two months after China notified the WHO about the emergence of a series of cases of pneumonia of unknown cause [8]. As of May 22, 2021, Brazil had an accumulated record of 16,047,439 cases and 448,208 deaths, with the number of cases increasing every day [9].

The dynamic and high-risk scenario for the population caused by the new coronavirus required forceful responses from the entire health system, especially from the Unified Health System (*Sistema Único de Saúde*, SUS). SUS is the Brazilian public health system; it was created in 1988, inspired by the United Kingdom's National Health Service. To date, Brazil is considered to be the only country with a population of more than 200 million people to have a universal health care system, and approximately 75% of the population uses SUS exclusively. SUS coordinates national actions and orchestrates the efforts of states, municipalities, and even supplementary health; it is maintained by public power, with supplementary participation of private initiatives [10].

Although the use of information and communications technology (ICT) in the health area was guaranteed in Brazil by Organic Law No 8080 in 1990, due to the lack of investments and ethical and bureaucratic issues, the insertion of technology and data sharing has not yet become a reality for health services. Based on the National eHealth Strategy Toolkit published by the WHO in 2012, the Brazilian digital health strategy was approved in 2017 and defined the digital health strategy as a fundamental SUS dimension. The program that “materializes” the Brazilian eHealth strategy is Conecte SUS, which is based on two structuring projects: the National Health Data Network (*Rede Nacional de Dados em Saúde*, RNDS) and the Program to Support Computerization and Qualification of Primary Health Care Data (*Programa de Apoio à Informatização e Qualificação dos Dados da Atenção Primária à Saúde*, Informatiza APS). The RNDS aims to promote the exchange of information between the different services of the Health Care Network, allowing transition and continuity of care in the public and private sectors. Informatiza APS aims to support the computerization of health units and the qualification of primary health care data across the country [11].

Conecte SUS is a standardized, modern, and interoperable platform of services, information, and connectivity that is, in itself, transformative for health. This platform predicts the integration of citizens’ health information in an extensive data network organized by the Ministry of Health (RNDS); this platform will bring benefits both to citizens—who will have access to their trajectory in SUS—and to health professionals and managers, who will have a set of information that will improve the continuity of care and decision-making [11]. Conecte SUS was structured as a pilot project. In November 2019, this project started in one Brazilian state to validate the conducted planning and refine the proposal to expand the program throughout Brazil. However, on March 2020, plans designed within the Brazilian strategy for digital health faced the COVID-19 pandemic. On March 13, 2020, the SUS IT department (DATASUS) established the New Coronavirus Crisis Committee, which is responsible for evaluating new health management technologies and prioritizing the care and prevention guidelines of the Ministry of Health itself. The main strategies and actions adopted by DATASUS to assist the Ministry of Health were published as a contingency plan. The contingency plan proposed a series of strategies for a quick and efficient response to the virus through direct communication with the population and with public and private health systems. Thus, through the contingency plan, Brazilian strategies for digital health transformation, such as Conecte SUS and the RNDS, were redirected to address the virus. Moreover, the contingency plan developed some specific strategies for the pandemic moment: the creation of an app related to the virus (Coronavirus SUS app), the restructuring of a compulsory web-based notification system, a web-based panel of official disease data, and the use of telemedicine for patient care (Figure 1). All these strategies will be explained in the next section.

Figure 1. The digital health strategies deployed in Brazil in response to COVID-19. SUS: Sistema Único de Saúde (Unified Health System).



Contingency Plan

Addressing the COVID-19 pandemic requires information at different levels, from the registration of notifications, deaths, and results of performed tests to the provision of services aimed at prevention and care. Among these services are self-assessment, teleconsultation, active search for patients, and advanced applications for identifying trends and vulnerable populations. To encompass all these demands, Conecte SUS systematizes a health care and data ecosystem for COVID-19. This ecosystem comprises specific layers for information security, interoperability between systems, notification processes and health surveillance, mobile apps, and access channels, as detailed below.

The RNDS is a federated interoperability layer. Several digital health applications, notably electronic health records (EHRs), hospital and laboratory management systems, portals, and mobile apps (for citizens, health professionals, and managers), exchange information through a service bus. The RNDS had recently been tested as a pilot project in a Brazilian state when the COVID-19 pandemic arrived in Brazil. As health emergency care priorities were modified, the RNDS had to quickly assume the COVID-19 national data repository position, acting on reception and integration of case notifications and results of laboratory tests as well as distribution and sharing of data and epidemiological information. The data about the epidemiologic situation of COVID-19 in Brazil were published in the Coronavirus Brazil Panel, the official communication vehicle. The Ministry of Health provides daily updates of the number of confirmed cases of COVID-19, the number of deaths, and the lethality rate of the virus based on data provided by the state health departments of the 27 Brazilian federative units. The website presents data related to the country, separate data for each state, and cases per epidemiological week as well as an epidemic curve. This communication platform contains georeferenced records of all COVID-19 cases registered in the country. The platform provides an interactive, graphic view of the cases [12].

In its first phase, the RNDS allowed the sharing of COVID-19 laboratory test results performed anywhere in the country through services developed according to the HL7 Fast Healthcare Interoperability (FHIR) standards and Logical Observation Identifiers Names and Codes terminology. Currently, the RNDS is also integrated with the web-based notification system, allowing interoperability between the reported cases and the results of laboratory tests. In this context, for cases registered in the network, the test results are received automatically, and tests performed on individuals who have not yet been informed generate a notification. Interoperability allows digital automation of the process, which was previously conducted manually by epidemiological surveillance teams and clinical laboratories. By the end of April 2021, more than 14 million results of COVID-19 tests were sent to the RNDS by 153 laboratories [13].

Additionally, the Conecte SUS Portal is being made available, where citizens, health professionals, and managers will be able to access information in the RNDS with the primary purpose of improving health care and allowing continuity of care. In March 2021, the Conecte SUS app was endowed with new features to facilitate the vaccination process in the country: the Digital Vaccination Card and the National Vaccination Certificate for anyone who is immunized against COVID-19. In this context, for all citizens to access their information, states and municipalities must send information from the Administrated Immunobiological Registry to the RNDS. Up to April 2021, more than 39 million vaccine registrations were sent to the RNDS, and the Conecte SUS mobile app was downloaded more than 11 million times [13].

COVID-19 case control in Brazil started on March 20, 2021, when the Ministry of Health declared the community transmission stage of COVID-19 and determined mandatory immediate notification (within 24 hours) of all suspected cases—including cases of influenza and severe acute respiratory syndrome (SARS)—for public and private services [14]. There are two types of notification systems: one for mild influenza, mainly used by basic health units, called e-SUS Notifica, and another, used to record hospitalized SARS cases and deaths, called Sistema de Informação de Vigilância Epidemiológica da Gripe (SIVEP-Gripe).

The notification system, e-SUS Notifica, was exclusively improved to update COVID-19 and receive daily data from each basic health unit in the whole country and private health care units. Consolidated accounts are created, and the numbers of individuals with suspected infection, individuals with confirmed disease, and deaths are automatically obtained. This total number is updated every day at 7 PM on the Ministry of Health website if everything proceeds as expected. In practice, the system is fed from a consolidated number. Every day, workers assigned to each function update their unit's data and summarize the numbers that form the consolidated report released by the Ministry. These workers, who are often physicians or a nurses, reconcile assistance with notification. This notification process is already part of the work routine in health services and is governed by Ordinance 204/2016, which lists the diseases and conditions of compulsory notification. The factor that has changed from the previous daily process to that of the COVID-19 pandemic is the time of notification. As the pandemic is a public health event that has national and international importance, agility in treating the disease has exponential significance.

In addition to the notification, all patient information must be recorded in citizens' medical records, preferably in an electronic version (EHR), to enable longitudinal and coordination of care as well as eventual epidemiological investigation and the subsequent formulation of policies and strategies for prevention. The registration must be performed directly by the professional who addressed the case and not simply by surveillance; moreover, confirmed cases should not be the only cases entered into the system. The judgment to define a suspected case must be clinical-epidemiological and performed by a health care professional. Upon laboratory confirmation, and through the interoperability allowed by the RNDS, the laboratory result is automatically inserted in the notification form.

To make the population aware of the disease caused by the new coronavirus and to assist in the dissemination of information for prevention and guidance, the Ministry of Health launched the Coronavirus-SUS app, which has the following features: list of the symptoms of COVID-19, advice on how to prevent the disease, actions to take in case of suspected infection, a map indicating nearby health units, and official Ministry of Health news focused on COVID-19. The app allows the user to assess their health status concerning COVID-19, performs automatic notifications based on health data entered by the user, and offers guidelines and recommendations for the user.

If necessary, the app directs the user to a teleconsultation or face-to-face clinical care. The latest update to the app provided contact tracing functionality, which generates a warning if the user has physically approached someone who tested positive for SARS-CoV-2 in the previous 14 days. The system depends on the voluntary collaboration of people who tested positive. Still, before generating the alert, this information is confirmed by cross-checking between the person's examination and the integrated records of the surveillance platform (e-SUS Notifica) and the RNDS. The cell phones of the people who had contact (either acquaintances or strangers on the street) anonymously exchange keys via Bluetooth through the app. These keys are stored, and if, in the future, the owners of the keys test positive, all other users with whom they had contact will be notified. The app's home page has a red button with the question "Are you feeling bad?" that brings up a list of questions to aid a self-diagnosis of COVID-19 infection. The app was made available in 10 countries, including North Korea, Panama, China, and Argentina, and it has already been downloaded by more than 10 million users [15].

One of the strategies developed by the Primary Health Care Secretary, in partnership with DATASUS, was the system of Preclinical Health Care–TeleSUS. In the call center/teleconsultation model, through four service channels (the Coronavirus SUS app, WhatsApp, Dial 136, and the Virtual Assistant on the Ministry of Health Portal), citizens can be evaluated, be notified, and receive a medical certificate, if necessary. The channels assist the patients through the ChatBot Service, Audible Recognition Unit Service, Preclinical Service, and remote monitoring. The TeleSUS initiative aims to promote home isolation of the potentially contaminated population or members of risk groups (those who do not show signs of severe disease), avoiding overcrowding in primary health care units. One of the structuring solutions of this system is a robot that makes telephone calls to citizens over 60 years of age to offer guidance, provide systematic follow-up, and, if necessary, refer them to a teleconsultation or face-to-face service. With the integration with the RNDS and e-SUS Notifica, the Preclinical Care System allows professionals to generate notifications related to the pandemic, access test results from public and private laboratories, and consult the patient's clinical history through the Conecte SUS platform [16].

Another resource developed by the Ministry of Health, in partnership with the Institutional Development Support Program of the Unified Health System (*Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde*, PROADI-SUS), offers, through the Tele-UTI Project COVID-19 Brazil, a daily routine/horizontal visit service using telemedicine resources, through which the multidisciplinary teams of large centers advise teams at smaller hospitals by teleconference. A hotline is also available for health professionals to assist in handling severe cases and discussing safety protocols every day from 7 AM to 7 PM.

Challenges and Opportunities

The whole context of health data sharing becomes even stronger amid a pandemic, which requires daily updates of epidemiological data for control and decision-making by governments and health systems. The COVID-19 pandemic has demonstrated the importance and usefulness of digital health strategies and has allowed the insertion of these solutions into health care systems in the long term. However, it is essential to understand that digital health adoption is only in the early stages, not only in Brazil but worldwide [17]. Policy makers are first dealing with the considerable challenge of adapting technology to their domestic health frameworks. Furthermore, each country must consider the diversity and necessity of their population to increase the acceptability of digital technologies in health.

The need for urgency in decision-making implied by the COVID-19 outbreak required Brazil to take an important step toward digital health implementation. However, there is still a long way to go to fully implement digital solutions in the health area. One of the significant challenges for eHealth in Brazil is the computerization of primary care units. To enable the RNDS to share health data, health systems must have access to the internet and use the EHR. To achieve this, one of the pillars of the Conecte SUS program is Informatiza APS. The objective of Informatiza APS is to qualify health data and computerize all family health and primary health care teams in the country. Through the Informatiza APS project, between October 2019 and January 2021, the number of computerized units increased from 55% to 67% [13]. Additionally, over 44% of computerized units use EHR systems that are different from that created by the Ministry of Health (the Electronic Citizen Medical Record), generating losses in terms of data interoperability and integration between the different levels of the health system [11]. The main challenge raised by municipal managers for the advancement of computerization is the scarcity of infrastructure and trained teams to implement the EHR and guarantee data submission through the RNDS. Additional difficulties have been mentioned, such as power fluctuation (peaks and lack), internet connection (speed oscillation and lack of provider), public insecurity in units (theft of equipment), insufficiency of equipment, and lack of a deployment team [11].

Direct digitization at the point of data collection and automated reporting is not a reality worldwide. When we examine the COVID-19 cases and deaths reported in the United States, for example, the numbers drop substantially every Sunday and Monday, with case numbers rebounding later in the week. This fluctuation occurs because most countries still collect data through paper reporting and forms [18]. The use of web-based notifications directly at the point of care integrated with the RNDS allowed the Brazilian government to track COVID-19 more effectively. However, delays still occur in correct notification because some health units are not computerized and provide the notification manually.

In the current state of emergency, the Brazilian federal government enacted Law No 13989 of April 15, 2020, authorizing the use of telemedicine during the COVID-19 pandemic and allowing physicians to care for their patients virtually. In less than four months, TeleSUS made 7.4 million calls. Worldwide, telehealth will provide citizens with access to adequate and qualified information, and it represents an important alternative to avoid contagion and facilitate social distancing [19,20]. Telemedicine still faces barriers to its expansion due to the gaps and inequalities in access to ICT by health facilities and citizens; however, it can be used to care for patients who do not have COVID-19 [21]. Clinical trials have demonstrated that teleconsultations resulted in high satisfaction among health care providers and patients, independent of disease progression, with lower costs than traditional visits [22].

For the digital transformation to occur, several points must be discussed, among them the guarantee of equity and universality of access (premises of SUS) and ways to engage the population, health professionals, and managers. This is because individuals who do not have the necessary knowledge to use the technologies cannot benefit them [23]. Especially in a continental country such as Brazil, which has very marked social differences among its population, it is necessary to think about public policies for the insertion of technology in health that do not reinforce social inequality and do not result in worse outcomes for the most vulnerable population. Crawford and Serhal (2021) [24] proposed a Digital Health Equity Framework to consider the health equity factors. They point out that together with person-centered care, digital health equity should be incorporated into health provider training and should be supported at the individual, institutional, and social levels.

The development and use of apps in the health care field is a reality, and the number of mobile apps created has been increasing. These apps have been implemented for training, information sharing, risk assessment, self-management of symptoms, contact tracing, home monitoring, and decision making. They are considered valuable tools for citizens, health professionals, and decision-makers in facing critical challenges imposed by the pandemic. In a general manner, apps can help reduce the burden on hospitals, provide access to credible information, track the symptoms and mental health of individuals, and discover new predictors [25]. However, the security and privacy of the shared data still need to be improved. An analysis of 50 mobile apps developed worldwide during the COVID-19 pandemic indicated that only 16 of them guaranteed that users' data would be anonymous, encrypted, and secured, and also would be transmitted on the web and reported only in an aggregated format. These apps continuously collect and process sensitive personally identifiable information, such as health information, location, and direct identifiers. The fear of having their data used in the wrong way could decrease users' adherence to this type of app [26]. The project Conecte SUS implies the circulation of patient data between mobile apps and digital platforms. As the digital health applications are executed in a heterogeneous and decentralized environment, blockchain technology was adopted at the RNDS because it presents itself as the most robust solution to security issues, naturally addressing security, performance, access, and scalability issues. Recent studies have shown the advantages of using blockchain technology to register health data [27-29]. The technology guarantees information security and allows a distributed location, maintaining the local access of each health provider to their data and sharing through an interconnected blockchain network between participating organizations [28,30].

To ensure that data will be collected and used safely and transparently, the Brazilian government sentenced the General Data Protection Law (*Lei Geral de Proteção de Dados Pessoais*, LGPD) on August 16, 2020. The main objective is to make digital health an innovative path capable of promoting the service's improvement to the population and the transition and continuity of care through safe and transparent access to the clinical history of the user. The LGPD defines people as the exclusive owners of their data and determines the health data as sensitive data. The use of personal health data by third parties will not be allowed. However, disclosing certain information for the benefit of the community or public health reasons is permitted, without prejudice to the patient's intimacy and privacy, through anonymity. Individual health data can only be accessed by health professionals involved in the case (through the Conecte SUS portal) and with the prior consent of the data owner, who must be informed both about the use and who made that use and its purpose.

After the end of the implementation phase, only with COVID-19 data, the RNDS will resume its initial strategy, prioritizing establishments that already use the Electronic Citizen Medical Record system and establishments that use the Management Application for University Hospitals. The Electronic Citizen Medical Record is the service that allows the collection of health records. It is available free of charge to municipal governments for the management of primary health care. The new version of this service and the RNDS are at an advanced stage in the 10 municipalities chosen for this initial phase [31].

The adoption of EHRs has provided consolidated technology for storing patient clinical data [32]. This concept has more recently evolved into the idea of the personal electronic health record (PHR). The main difference between a traditional RES and a PHR is that the latter allows interaction with patients through access to clinical data [33]. It is expected that Conecte SUS will be the central point of access to procedures performed in the future. The tool should function as a PHR and allow citizens to monitor their health situation, enable health professionals to access their patients' tests and clinical history to continue care, and allow managers to monitor health indicators.

A long road has been taken to facilitate the exchange of health information between different primary care establishments in Brazil. Strategies that are part of the digital health revolution in Brazil were redirected to mitigate the damage caused by SARS-CoV-2. Still, these strategies must resume their purposes when the situation becomes stable. The ethical use of health data through an information platform that has high availability, but is safe and accessible at the same time, will undoubtedly allow greater participation by society. The emergence of new services, research, and innovation will benefit the population and Brazil.

Conclusion

Brazil has been working to digitally transform the health sector since the Brazilian digital health strategy launch in 2017. The COVID-19 pandemic accelerated this transformation and has created enormous challenges for decision makers. The pandemic is a national test of acceptance and of the ability of Brazilian citizens to use and engage with digitizing health and communications services. It is still too early to assess Brazil's experience in implementing digital solutions for the entire population; there is a long way to go before achieving digital health implementation due to technological issues and territorial, financial, and ethical issues. The approaches of IT and health professionals are also fundamental because the digital health revolution will only occur if clinicians embrace this challenge. More research is needed to explore and analyze the pitfalls, make the right decisions, and define the challenges of this digital experience for the unified health system, private institutions, and employees and consumers.

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Authors' Contributions

BD wrote the first draft of the paper. JNS and CAC revised the subsequent drafts critically for important intellectual content. All coauthors approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work and for ensuring its integrity and accuracy.

Conflicts of Interest

None declared.

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Abbreviations

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior
EHR: electronic health record
FHIR: Fast Healthcare Interoperability
ICT: information and communications technology
Informatiza APS: Programa de Apoio à Informatização e Qualificação dos Dados da Atenção Primária à Saúde (Program to Support Computerization and Qualification of Primary Health Care Data)
IT: information technology
LGPD: Lei Geral de Proteção de Dados Pessoais (General Data Protection Law)
PHR: personal electronic health record
PROADI-SUS: Programa de Apoio ao Desenvolvimento Institucional do Sistema Único de Saúde (Institutional Development Support Program of the Unified Health System)
RNDS: Rede Nacional de Dados em Saúde (National Health Data Network)
SARS: severe acute respiratory syndrome
SIVEP-Gripe: Sistema de Informação de Vigilância Epidemiológica da Gripe
SUS: Sistema Único de Saúde (Unified Health System)
WHO: World Health Organization

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Original Paper

Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE): Overview, Components, and Public Health Applications

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Abstract

Background: The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) is a secure web-based tool that enables health care practitioners to monitor health indicators of public health importance for the detection and tracking of disease outbreaks, consequences of severe weather, and other events of concern. The ESSENCE concept began in an internally funded project at the Johns Hopkins University Applied Physics Laboratory, advanced with funding from the State of Maryland, and broadened in 1999 as a collaboration with the Walter Reed Army Institute for Research. Versions of the system have been further developed by Johns Hopkins University Applied Physics Laboratory in multiple military and civilian programs for the timely detection and tracking of health threats.

Objective: This study aims to describe the components and development of a biosurveillance system increasingly coordinating all-hazards health surveillance and infectious disease monitoring among large and small health departments, to list the key features and lessons learned in the growth of this system, and to describe the range of initiatives and accomplishments of local epidemiologists using it.

Methods: The features of ESSENCE include spatial and temporal statistical alerting, custom querying, user-defined alert notifications, geographical mapping, remote data capture, and event communications. To expedite visualization, configurable and interactive modes of data stratification and filtering, graphical and tabular customization, user preference management, and sharing features allow users to query data and view geographic representations, time series and data details pages, and reports. These features allow ESSENCE users to gather and organize the resulting wealth of information into a coherent view of population health status and communicate findings among users.

Results: The resulting broad utility, applicability, and adaptability of this system led to the adoption of ESSENCE by the Centers for Disease Control and Prevention, numerous state and local health departments, and the Department of Defense, both nationally and globally. The open-source version of Suite for Automated Global Electronic bioSurveillance is available for global, resource-limited settings. Resourceful users of the US National Syndromic Surveillance Program ESSENCE have applied it to the surveillance of infectious diseases, severe weather and natural disaster events, mass gatherings, chronic diseases and mental health, and injury and substance abuse.

Conclusions: With emerging high-consequence communicable diseases and other health conditions, the continued user requirement–driven enhancements of ESSENCE demonstrate an adaptable disease surveillance capability focused on the everyday needs of public health. The challenge of a live system for widely distributed users with multiple different data sources and high throughput requirements has driven a novel, evolving architecture design.

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KEYWORDS

health surveillance; outbreak detection; population health

Introduction

Background

In recent decades, public health disease surveillance relied on laboratory confirmation and passive participation. Often, the lack of automated detection and reporting resulted in time delays that impeded prompt mitigation activities. Public health institutions thus began using enhanced surveillance techniques with the potential for timely epidemic detection and tracking. These techniques have been incorporated in electronic and increasingly internet-based health surveillance systems for everyday use by health monitors. Intensive efforts to establish health surveillance systems occurred at multiple institutions and government agencies in the late 1990s. As a result, a substantial collection of review papers, system-specific evaluations, and evaluation criteria have emerged [1-4].

The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) system originated as a collaboration between two such projects. A project of Dr Michael Lewis, then a medical resident under Dr Julie Pavlin at the Walter Reed Army Institute for Research (WRAIR), applied US military clinic visit data for outbreak detection in a project called *ESSENCE* [5]. Concurrently, for the same purpose, Johns Hopkins University Applied Physics Laboratory (JHU/APL) combined civilian data from hospital emergency departments (EDs), physician office visits, over-the-counter (OTC) sales, and school absenteeism records, first with internal funding, then for the State of Maryland [6]. The two groups joined forces in anticipation of possible bioterrorist activity at the turn of the century as January 1, 2000, approached, and this collaboration, along with similar efforts at other institutions, led to further funded development in the multicenter Bio-Event Advanced Leading Indicator Recognition Technology (BioALIRT) program of 2001-2003 for the Defense Advanced Research Project Agency [7]. In leading one of four BioALIRT research teams, the JHU/APL and WRAIR groups further matured the ESSENCE system concept.

Following the terror attacks of September 11, 2001, ESSENCE was expanded in Maryland, increasingly operationalized in state and local civilian health monitoring agencies and implemented in all global US military treatment facilities. Since then, fueled by a succession of initiatives driven by both bioterrorism and natural public health concerns, versions of ESSENCE have been implemented in the Department of Defense (DoD), the Veterans Administration (VA), the Centers for Disease Control and Prevention (CDC), and state and regional public health agencies across the United States and, through collaborative DoD efforts, internationally. Following the widespread use of ESSENCE and enhancements at JHU/APL to meet users' evolving needs, the CDC National Syndromic Surveillance Program (NSSP) adopted ESSENCE in 2014 as the standard analytic surveillance and visualization engine on the BioSense Platform for state and local public health monitors [8,9]. Nearly 6000 health care facilities covering 49 states and the District of Columbia contribute ED data to the BioSense Platform daily [10]. The user benefits of ESSENCE have long surpassed the *Early Notification* part of its acronym to include aspects of situational awareness, such as tracking and characterization of known health events, assessing the burden of all-hazard threats such as severe weather, environmental hazards, and substance abuse, and rumor control to enable improved public health response. In 2021, there are approximately 3800 ESSENCE users, including approximately 3000 recent frequent users. These users are spread among ESSENCE installations in 23 states and local jurisdictions, the DoD system, the NSSP system serving most US states, and several instances in private organizations.

A timeline detailing the historical development of ESSENCE is presented in Multimedia Appendix 1.

Objectives

This study aims to describe how the architecture, analytics, visualizations, and user collaboration tools in ESSENCE have empowered public health at local and regional levels despite resources that are often scarce compared with those of other government institutions, with discussion of the lessons learned over the past 20 years and the continuing challenges of emerging population health threats. Through the main text and supplementary files on the technical details, this paper will describe the various ways by which ESSENCE enables user institutions to meet the standards set for public health surveillance systems [11], from engaging stakeholders to providing technical justification to sharing lessons learned. In the context of this paper, the *Methods* section refers to the data architecture, analytic methods, and visualizations provided by ESSENCE, and the *Results* section refers to the surveillance capabilities that have thus been realized by system users.

Methods

This section describes the general functionality and main components of ESSENCE, including data types and management, analytic methods, and visualizations. The details of these components are provided in Multimedia Appendices 1-4.

System Overview

ESSENCE is a health surveillance system that uses advanced analytics and visualizations to expose anomalies in both traditional and nontraditional public health data, with the goal of enabling public health to find and monitor outbreaks of health events and make decisions. ESSENCE users access a secure web-based tool to conduct disease surveillance for the purpose of timely detection, situational awareness, and descriptive epidemiologic analysis of baseline disease patterns and outbreaks. For an effective public health response, public health authorities must have the ability to identify the infected population so that further spread can be contained. Leveraging the near real-time availability of an increasing number of data sources, ESSENCE analytical and alerting capabilities provide an opportunity for public health users to capture the early stages of an outbreak and track its progress. ESSENCE enables the integration of electronic data from both clinical and nonclinical sources to enhance situational awareness. For most users, the primary clinical data source is hospital ED chief complaint records. In addition, based on availability, public health agencies incorporate other data types, such as OTC medication sales, poison control call center data, prescription drug data, reportable disease data, vital statistics mortality data, and school absentee data. Once raw data reach ESSENCE, the analysis, visualization, and communication features of ESSENCE allow the end user to gather and organize the resulting wealth of information into a coherent view of population health status and to communicate findings among other users and stakeholders.

As a result of ongoing user feedback daily and event-based disease surveillance needs, ESSENCE features include spatial and temporal statistical alerting, custom querying, user-defined alert notifications, geographical mapping, remote data capture, and event communications.

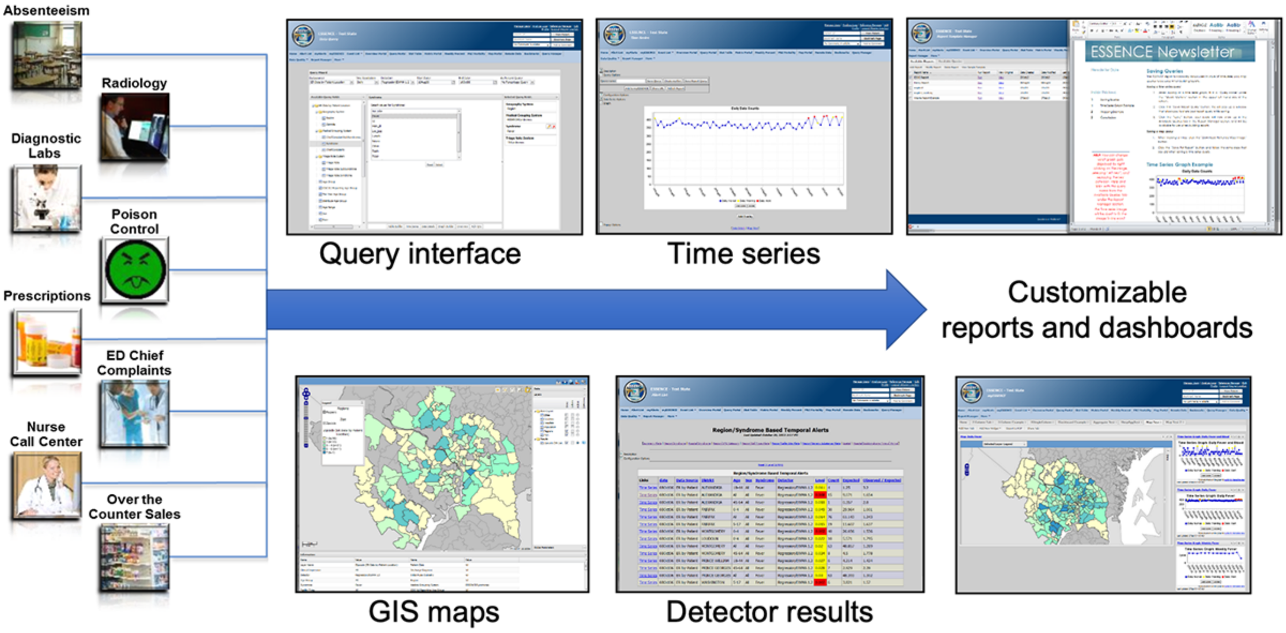
ESSENCE provides three main functions:

1. Data ingestion or preprocessing: traditional and nontraditional data sources are electronically received by ESSENCE, and many are mapped to syndrome groupings.

   During the ingestion process, data are cleansed (eg, duplicate records removed and invalid characters removed), updated (eg, existing records information is updated with new information), and categorized (eg, syndrome and subsyndrome categories assigned to records).
2. Alerting: multiple temporal and spatial alerting algorithms are applied to each data set to develop a list of alerts or flags for further investigation by public health officials. In addition to algorithms developed by JHU/APL and the WRAIR, ESSENCE can incorporate algorithms required by the jurisdiction where the system is deployed.
3. Analysis and visualization: ESSENCE data and alerts can be analyzed and visualized in multiple ways in the system, both spatially and temporally.

These component functions are illustrated schematically in Figure 1. They are introduced in the following sections, with an additional file for each to provide details.

Figure 1. Schematic overview of Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) features showing a sampling of users' data types, analysis modes, and screen interfaces. ED: emergency department; GIS: geographic information system.



Data Types and Syndrome or Feature Selection

The types of data analyzed in ESSENCE are the prerogative and responsibility of the jurisdiction, although JHU/APL provides the capability for basic types. The ESSENCE system is data agnostic—the only requirement for a monitored data type is the inclusion of a data field. The data time resolution is also unrestricted. Data frequencies in ESSENCE range from seconds to years, although daily data are the most common. All but a few users monitor hospital ED data. Most ESSENCE user jurisdictions face the burden of acquiring their data sources, gaining approval for their routine intended use, and extracting features for monitoring. The level of effort varies greatly depending on the data source. Various users also monitor or have monitored the records of the data sources listed below. Sources known to be currently or formerly tracked among users' ESSENCE systems for routine prospective monitoring include OTC remedy sales, physician office visits, laboratory test orders and results, school absenteeism and health office or nurse records, reportable disease cases, poison center call records, Assistant Secretary for Preparedness and Response Disaster Medical Assistance Teams data for disaster response [12], cardiovascular and other chronic diseases from inpatient encounters, livestock and companion animal health encounters, human vitals measurements, death records, emergency medical services and 911 calls, and climate and air quality data.

Users have also incorporated or adapted data from other surveillance systems, such as the National Poison Data System [13]. Although not all these sources have proven useful for routine surveillance, users have used the system to investigate their utility and to seek the best data usage.

In separate studies or projects, individual user jurisdictions or their research partners have also used ESSENCE to analyze records of radiology impressions; genomic sequencing data; zoo animal health; environmental sensor outputs; sales of specific products, such as thermometers, orange juice, and tissues; social media posts and searches; and fantasy sports data. Multiple content formats used in ESSENCE include Health Level-7 (HL-7) formats for hospital data and National Emergency Medical Services Information System (NEMSIS) formats for emergency medical services data. File formats include delimited or tabbed or fixed-width American Standard Code for Information Interchange (ASCII) text, XML, and JavaScript Object Notation (JSON).

Each data source has its own challenges for user jurisdictions to obtain sustained electronic access from data providers and any requisite government approval. When a data stream of any of these sources is acquired for routine monitoring, an immediate question is how to use the streaming data to track the health outcomes of interest. An often-applied procedure is to track the counts of subcategories of the data expected to correspond to these outcomes. These subcategories are commonly called *syndromes*, generalizing the medical definition of this term, denoting disease-related collections of signs and symptoms. Thus, in the surveillance context, a *syndrome* may refer to grouped hospital visits associated with a fixed collection of symptoms, laboratory tests ordered for certain conditions, web searches containing sets of terms, billing records covering any of a class of remedies, or other subgroups depending on the data source. Syndrome formation is a critical step that may use only a fraction of all streaming data and may produce few or many groups to track. The number and composition of syndromes depend on the richness of the data, the number of outcomes of interest, and the resources of the monitoring institution for investigation and response.

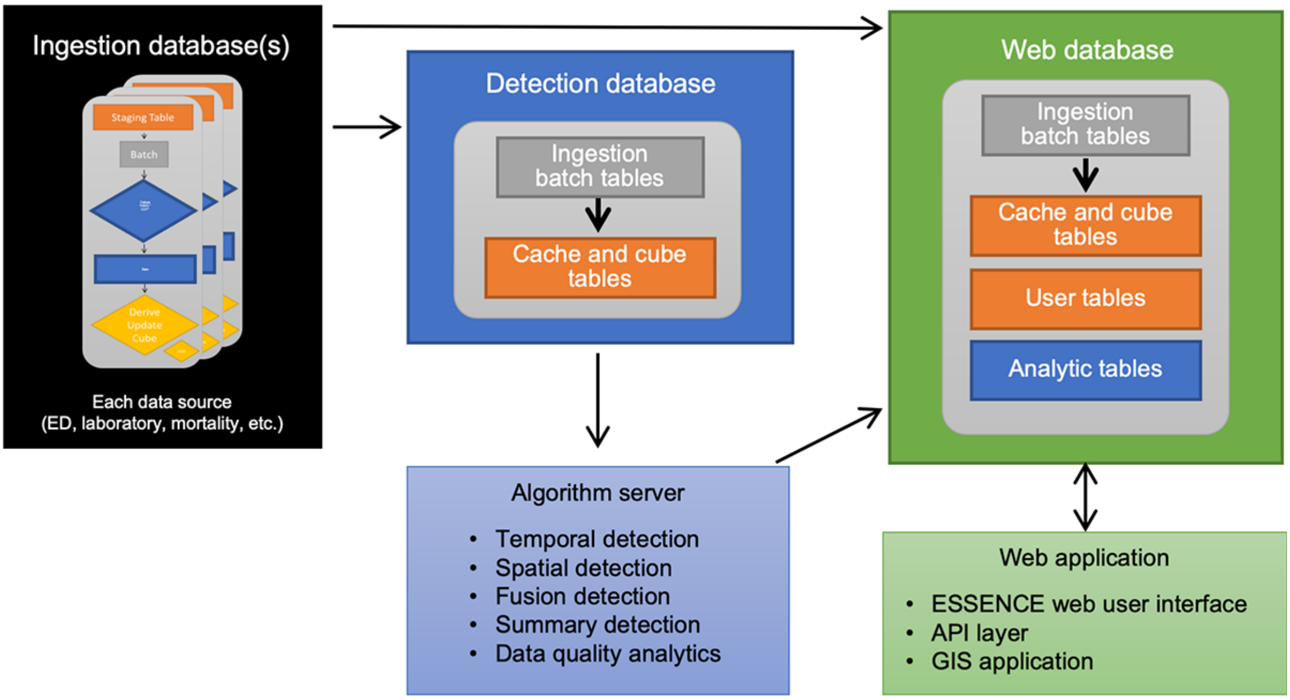
Syndromes and subsyndromes used in ESSENCE vary depending on the available clinical grouping systems and the needs of the user site. Early versions of ESSENCE formed syndrome groups using diagnosis codes, which have disadvantages of late assignment and emphasis on billing practice in many medical systems. Examples include respiratory and gastrointestinal subsyndromes, such as asthma. Categorization soon switched to the use of free-text chief complaint or reason-for-visit data fields. For this categorization, the JHU/APL ESSENCE team developed the Chief Complaint Processor (CCP), a versatile, stand-alone program for weighted keyword-based classification by free-text fields. The CCP is highly configurable, with tables including sets of syndromes and subsyndromes with classification rules allowing complex logic, positive and negative weighting of component terms, abbreviation and spelling rules, and a list of unmodifiable terms. For example, CCP puts a record with a chief complaint of *nausea* or *vomiting* in the gastrointestinal category. The CCP creates a ChiefComplaintsParsed field for the use of classification rules after treatment of abbreviations, some misspellings, and other cleanup [14]. These classifications have enabled additional natural language processing and machine learning initiatives by both ESSENCE developers and users, and findings from these initiatives are shared among users with each emerging health threat [15-17].

As with diagnosis code-based processing, syndrome groups are tabulated, plotted, and monitored each day with statistical alerting algorithms for early potential outbreak indications.

Architecture, Security, Preprocessing, and Quality Management

The software architecture used for ESSENCE is a 3-tier web application with a presentation layer as a user front end, a business layer for the application of algorithms, and a back end for databases. All automated data transfers occur over secure virtual private networks. Multiple, data-dependent preprocessing steps include deduplication procedures, formation of syndrome fields, calculation of distances, and derivation of additional fields and flags based on jurisdictional business rules and logic. The flow diagram is shown in Figure 2. Multimedia Appendix 2 describes these features in detail.

Figure 2. Flow diagram illustrating typical Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) data flow with databases and tables, generalized to account for diversity among user needs and server configurations. API: application program interface; ED: emergency department; GIS: geographic information system.



Alerting Methods Using Statistics and Artificial Intelligence

The following principles were derived from ESSENCE users to guide method selection and to clarify the interpretation of results.

General considerations include:

- These methods are not intended to identify outbreaks positively without supporting evidence. Their purpose is to direct the attention of limited monitoring staff with increasingly complex data streams to data features that merit further investigation. They have also been useful for corroborating clinical suspicions, rumor control, tracking of known or suspected outbreaks, monitoring of special events and health effects of severe weather, and other locally important aspects of situational awareness. Successful users value these methods more for the latter purposes and do not base public health responses solely on algorithm alerts.
- These algorithms are one-sided tests that monitor only unusually high counts, not low ones. Low counts could result from a critical outbreak situation that prevents data reporting, but there are many more common reasons for low counts (such as unscheduled closings or system problems), so the algorithms do not test for abnormally low counts.
- In addition to the data- and disease-specific considerations below, the algorithm selection was also driven by system considerations. Users need to monitor many types of data rapidly. External covariates, such as climate data or clinic schedules, may not be available for prompt analysis. Many methods in the literature, armed with retrospective data of a certain type, depend on the analysis of substantial history. Day-to-day users, often with only a small fraction of time available for monitoring, will not wait for several minutes for each query. Building separate algorithms for each user data stream is impractical, especially because sufficient data history is unavailable for many standard time series and all ad hoc series; therefore, ESSENCE methods have been adapted from the literature and engineered for appropriate matching to the data and timely results.
- If the time series monitored by algorithms represent many combinations of clinical groupings, age groups, and geographic regions, excessive alerting may occur simply because of the number of tests applied. The summary alert method was implemented to limit excessive alerting. This method is based on the control of the false discovery rate, that is, the expected ratio of false alerts to the total alert count, and its statistical implementation in ESSENCE is detailed in Multimedia Appendix 3. Aside from analytic methods to control alerting, default alert lists should be limited to results from the time series of interest to the user, either by system design or by the user's active specification. For example, one method of reducing the default alert list is to restrict algorithms to all-age time series groupings. Depending on the scope of the user's responsibility, the alert list may also be restricted according to both epidemiological interest and the resources available for investigation. For example, a monitor of a national-level system with algorithms applied to many facilities may be interested only in alerts with at least 5 to 10 cases. In circumstances of heightened concern, these restrictions can be relaxed, or the user can use ESSENCE advanced querying methods to apply algorithms to age groups and/or subsyndromes.

Individual alerting algorithms implemented in ESSENCE are listed and described in Multimedia Appendix 3.

Visualization

Both standard and user-customizable visualizations are available in ESSENCE, many shaped in response to user ideas and requests. Highly configurable and interactive modes of data stratification and filtering, graphical and tabular customization, user preference management, and sharing features allow users to query data and view geographic representations, time series and data details pages, and reports. Figure 2 shows examples of the standard plots and maps. Multimedia Appendix 4 (Figures S1-S4) summarizes key features with explanations and screenshots of novel visualizations developed for ESSENCE to fulfill requests of the user community.

Results

Overview of Findings

The results in this section represent a broad range of ESSENCE applications, especially those not previously published in the peer-reviewed literature, which demonstrate how ESSENCE monitors health threats at national, state, and local jurisdictions. Rather than giving the results of one analytic method applied to a particular data set, we show the results of the data architecture, analytics, and visualizations described in the previous section for public health objectives achieved by users. The following sections demonstrate the system simplicity, flexibility, and acceptability, key attributes from published system evaluation guidelines [18]. The examples in these sections were chosen to show the breadth and depth of the application to meet these criteria. For the other attributes, each ESSENCE user has local surveillance objectives and constraints that impose the requirements of performance metrics, such as sensitivity, positive predictive value, and timeliness. Algorithms described in the analytic details supplement were developed to maximize the local sensitivity or positive predictive value tradeoff and other practical metrics.

In addition to the versions used and shared by the US surveillance community, the applications below refer to the open-source Suite for Automated Global Electronic bioSurveillance (SAGES) toolkit that ESSENCE developers have provided for non-US health monitors, including OpenESSENCE and ESSENCE Desktop editions [19,20]. On the basis of the features and functionality of ESSENCE, tools within SAGES were developed specifically for use in low- and middle-income countries with limited resources but do not include some of the more recent analytics and visualization tools requested by users across the NSSP.

Infectious Disease Applications

Early applications of ESSENCE focused on the detection of infectious disease outbreaks, with much attention paid to influenza-like illness because it is a prodrome for multiple naturally occurring diseases and for many potentially weaponized for bioterrorism [21,22]. Civilian [23], military [22], and VA [24] ESSENCE users monitored for outbreaks of seasonal and nonseasonal outbreaks of febrile respiratory infections, gastrointestinal infections caused by contaminated food or water, and rarer infections.

Surveillance systems were particularly helpful in tracking the pandemic of the novel H1N1 influenza in 2009 [24]. The pandemic was important as an interregional use of surveillance systems to track a common threat. For example, the National Capital Region Disease Surveillance Network, comprising ESSENCE users at health departments in the District of Columbia and parts of the states of Maryland and Virginia, shares population-level disease incidence information to promote interjurisdictional surveillance. In 2009, this network allowed National Capital Region public health practitioners to track the course of the pandemic from the spring through the fall, comparing the overall and age-specific burden of illness to national and neighboring state trends. A broader collaboration between ESSENCE and non-ESSENCE system users adopted a standardized definition of influenza-like illness to enable uniform local tracking of the pandemic across the United States [25].

Users have applied ESSENCE to form and share queries for indications of other infectious diseases using text from chief complaints, discharge diagnosis, and triage notes when available. Infectious threats tracked in published examples include general waterborne diseases [26], tuberculosis [17], rabies [27], and Middle East Respiratory Syndrome [15]. In recent years, concerns over mosquito-borne diseases have generated new queries by multiple users and occasionally uncovered important cases [16].

The health department of Maricopa County, Arizona, presented an example of the benefits of surveillance systems in June 2018. The department had added an ESSENCE query for signs of Rocky Mountain spotted fever, which is not endemic to that county, because of concerns that cases transferred from endemic areas might be missed. A child’s patient record was signaled by the query, and the department contacted the hospital. This contact led to the reversal of a medication decision that might have been fatal to the child [28].

Such monitoring activities have repeatedly uncovered unreported cases of diseases for which reporting is mandatory [29]. These findings illustrate the importance of redundancy with systems such as ESSENCE to avoid missing important cases, even when traditional reporting mandates exist.

At the submission of this manuscript, the intense collaboration of ESSENCE users is focused on tracking the COVID-19 pandemic. General queries on COVID-like illness and specific ones involving pneumonia and specific symptom sets are being refined and shared [30].

Applications for Tracking Burden of Severe Weather and Natural Disaster Events

Health departments have used ESSENCE for preparedness, health burden assessment, and response to severe storms and other natural disasters. The state of Oregon conducted a successful program to mitigate the effects of wildfires [31]. This program featured customized ESSENCE queries with other coordinated efforts among state and local health departments and preparedness teams. Among several states that use

ESSENCE to monitor the effects of hurricanes, the Tennessee Health Department devised queries to determine the volume and clustering of patients in local hospitals because of storms in other states [32]. Effective monitoring of some events requires a combination of multiple data sources. Following a prolonged storm-related power outage, the health department of Seattle-King County, Washington, combined data from the ESSENCE ED data with ambulance calls and public utility data to monitor for cases and clusters of carbon monoxide poisoning and food poisoning [33]. More recently, the Florida Health Department monitored carbon monoxide poisoning after Hurricane Irma in 2017 [34]. Institutions using ESSENCE are increasingly incorporating environmental and other data sources in their systems for richer situational awareness of disaster-related health threats [35,36].

Applications for Mass Gathering Surveillance

Scheduled mass gathering events such as political conventions and major athletic competitions concern population health monitors because (1) such events are bioterrorism opportunities to harm many victims and gain media attention, (2) infections through contaminated food or water could spread rapidly through the expanded population, (3) those visiting for several days could import infections or take them back to their own cities, and (4) a surge of patients could overwhelm local care provider resources. Adequate preparedness and response require coordination across jurisdictional boundaries, but privacy laws often restrict patient-level data sharing. ESSENCE syndrome definitions and queries have been customized for many such events. In 2007, Marion County, Indiana, and Cook County, Illinois, were home counties for the competing teams in Super Bowl XLI, and the game was hosted in Miami-Dade, Florida. The health departments of these geographically distant counties were ESSENCE users, and customization of their systems for the days surrounding the event helped coordinate surveillance despite only 2 weeks' notice after the teams were determined [37].

A partnership between the Florida Department of Health and the US HHS Office of the Assistant Secretary for Preparedness and Response to improve the response of Disaster Medical Assistance Teams produced a new ESSENCE module that was deployed for health monitoring of the 2012 Republican National Convention in Tampa [36]. State and county health departments used ESSENCE for coordinated monitoring of crowds at the US Olympic Trials in July 2016 [38]. In January 2017, the Washington DC Department of Health used ESSENCE queries along with other data sources for health surveillance at the 58th US presidential inauguration [39].

For monitoring of events outside the United States, JHU/APL developed the SAGES system, the open-source version of ESSENCE designed for global resource-limited settings, in 2014 to monitor the 8th Micronesian Games held in Federated States of Micronesia, Pohnpei, and the 3rd International Conference on Small Island Developing States in Apia, Samoa [40].

Applications for Chronic Disease and Mental Health Surveillance

The use of ESSENCE to monitor risk factors and incidence of chronic disease and mental health disorders has proliferated since a DoD ESSENCE study using clinic and prescription data to monitor behavioral health in 2004 [41]. The Boulder County, Colorado Health Department recently implemented and tested multiple queries to monitor mental health [42].

Addressing ESSENCE utility for chronic diseases in general, the Cook County Illinois health department applied machine learning methods to assess the utility of ESSENCE ED data for monitoring cardiovascular disease, acute myocardial infarction, acute coronary syndrome, stable angina, stroke, diabetes, hypertension, asthma, and chronic obstructive pulmonary disease. From correlational validation testing based on 8 full years of chief complaint text and electronic medical record data, they concluded that ESSENCE data are suitable for monitoring all these conditions except stable angina and hypertension "at local, state, or national levels" [43]. The Nebraska State Health Department has used ESSENCE to monitor for cardiovascular disease for several years, and the Florida State Department similarly monitors acute myocardial infarction incidence [44].

Applications for Injury and Substance Abuse Surveillance

An unexpected but arguably the most helpful benefit of ESSENCE to health department users is to facilitate communication and collaboration among agency divisions. An important example in the context of the ongoing opioid overdose crisis has been the strengthening of connections between syndromic surveillance specialists and groups specializing in injury prevention, behavioral health, and drug abuse. Adaptations of ESSENCE included queries for both prescription and illicit drug types and overdose cluster detection to help inform public health response tactics, such as needle exchange and naloxone distribution.

Multiple health departments have applied ESSENCE to gain awareness of the locations and subpopulations at risk of injuries from falls [45]. The Boston Public Health Commission in Massachusetts used it to monitor for hearing loss, acute depression, and explosion-related injuries in the aftermath of the 2013 Boston Marathon bombing and subsequent manhunt. The St Louis Missouri Health Department established ESSENCE queries for injuries indicative of bomb-making activities [46].

Monitoring for substance abuse is common among ESSENCE users. The Tri-County Health Department in Colorado uses its system to investigate the adverse effects of marijuana use [47]. The Florida State Department queries for ED visits resulting from synthetic marijuana [48] and for novel street drugs, such as Flakka, as they become known public health problems [49]. Recently, the opioid crisis has stimulated intense collaboration, including shared syndrome definitions and analytic case-finding tools among geographically scattered institutions using ESSENCE [50-52].

The ongoing adaptation of ESSENCE to meet the needs of the understaffed public health practice community has provided a means to share methods and information, although data are often not shareable. The common analytic platform has enabled an evolving user ecosystem of multiple working groups, and the US CDC currently hosts the NSSP Community of Practice, with subgroups including Syndrome Definition, Data Quality, and Technical Committees [53]. The Syndrome Definitions committee promotes the analysis of common queries among geographically scattered user sites and the US CDC [54], thus improving communication between local and national health monitors. Epidemiologists, system designers, and other stakeholders may find and share resources on committee websites and through the NSSP Knowledge Repository [30]. A primary example is the opioid overdose crisis, a noninfectious threat. In addition to analytics and visualizations to support the activities related to this crisis, developers and users have worked together to acquire additional data sources, such as emergency medical incidents, poison center calls, and death records, to determine the benefit of fusing information varying in specificity and timeliness into a common surveillance picture to better inform awareness and interventions.

Regarding data standards that are essential among the many NSSP stakeholders, Multimedia Appendix 2 refers to the reference tables and business logic to convert data field entries into categorical values from standard sources such as the Public Health Information Network Vocabulary Access and Distribution System and from evolving standards developed by NSSP Data Sharing and Syndrome Definitions workgroups.

Discussion

Principal Findings

In the *Results* section, the multiple applications of ESSENCE installations by health departments at various levels and the surveillance community initiatives enabled and expedited by the system illustrate the combined effect of the technical components described in the *Methods* section and developed over 20 years, driven by the major influence of public health users. The following sections describe the lessons learned, key innovations, and user-driven enhancements.

Lessons Learned

Several principles have driven the success of ESSENCE since its origins in the late 1990s.

Versatility

Users have valued the configurability and adaptability of ESSENCE. Default categorization of complex data into syndromic groupings has always been valuable to users who are inexperienced or who do not have the time to formulate or validate their own categories for monitoring. Conversely, health departments with greater analysis capacity have long demanded surveillance systems that allow them to create their own categories to track, and ESSENCE customization with query-building features using both diagnosis codes and free text has grown along with the sophistication and broadening needs of health department users. Precomputed, canned analysis products are not found in ESSENCE. However, versatility presents challenges to database design and to the selection and adaptation of statistical analysis tools. Surveillance data evolve with institutional information systems and formats, coding practices, and epidemiological concerns. Typically, users cannot wait for several minutes for data retrieval and time-consuming model runs. Alerting algorithms applied prospectively to detect disparate events in a wide variety of data types cannot match the detection performance of models developed retrospectively using historical data sets labeled with target events for a particular syndrome. The ESSENCE algorithm baselines do not span years, not only for storage and computational reasons but also because for many users' desired data types, stable data or any data are available only within the past year. Hence, ESSENCE alerting algorithms, adapted from published applications of models and control charts in health care settings [55-57], use rolling baselines of weeks rather than years.

Facilitating Communication

Multiple ESSENCE users have remarked that one of the system's main benefits has been to facilitate communication with other divisions within a health department, with external local and federal agencies, and with care facilities that provide data and can benefit from the broader geographic perspective that a surveillance system enables. Hence, substantial ESSENCE development has occurred in response to user requests for custom analysis comparisons, visualizations, and report formats, allowing overburdened users to concentrate on the task of routine health monitoring. In situations where data sharing is precluded by county or state regulations, ESSENCE communication tools have enabled information sharing. The sharing and query-building tools in the visualization section have been increasingly used to enhance collaboration among NSSP subcommittees as well as individual users.

Multiple Analysis Modes

The applicability of individual analysis modes, such as univariate and multivariate time series monitoring, spatiotemporal cluster detection, and single case identification all depend on the nature and quality of available data. For example, the spatial scan statistic implemented in ESSENCE can avoid issues of jurisdictional boundaries, but only if data location fields are present and reliably represented in the data. In many data sources, the limitation of location fields to zip codes or postal codes restricts the geographic precision of clusters of interest. Health monitors generally require multiple methods to analyze population health data. A notable example is that ESSENCE users in multiple health departments have discovered unreported cases of reportable disease that traditional sentinel surveillance is mandated to communicate to public health. The various analysis modes of ESSENCE provide affordable and sometimes beneficial redundancy and safety net functionality.

The following list summarizes these lessons for developers of other systems:

- Accommodation for a variety of processing systems and data types, flow, and format.
- Features facilitating shareable ad hoc queries and reports to investigate novel concerns.
- A suite of analytic tools allowing multiple looks at available data, tools that provide prompt feedback and do not require years of data history.

- Provision of default views as well as tools to modify and arrange them as desired while avoiding canned or precomputed visualizations.
- Integrated collaboration features and user events to foster direct community involvement in system evolution.

Innovation

The development of ESSENCE has produced novel features in areas of complex, disparate data management, analytical methods, and the enhancement of user reporting and collaboration, interrelated efforts to empower health monitors. The data management advances include architecture and data transfer capabilities to meet the needs of institutions with varying resources. Analytics advances require data quality examination methods and alerting algorithms appropriate for diverse data time series that meet rapid response needs and do not require more than a few months of data history. User experience enhancements include customizable visualization and reporting features that provide unique time- and resource-saving capabilities.

User-Driven Enhancements

Recent ESSENCE projects have produced a variety of user capability enhancements. For sharing information within and across jurisdictions, web-based features allow users to share what they are doing within ESSENCE with peers and to see what others are querying and find interesting. Text analysis and visualizations facilitate the creation of ad hoc local free-text queries. These features provide correlation, trend, and association analytics to help the user determine what terms or phrases should or should not be included in queries.

Back-end tools and checks with visualizations allow the user to closely monitor the local ESSENCE system for data issues and irregularities. These administrative capabilities help managers and users maintain day-to-day system availability and improve the visibility of issues that may develop over time.

Recently added visualizations and cohort clustering analytic tools for longitudinal assessment allow users to determine categories of patients who use health care systems that provide data to ESSENCE. These tools can show patient-level usage trends to inform the allocation of health care resources in a community.

Conclusions

Installations of ESSENCE have provided systems capable of meeting public health surveillance requirements at multiple levels of purview and jurisdiction. The data architecture runs on modular configurations of a variable number of servers, with the number contingent on the data volume, number of active users, and frequency of required analysis operations; hence, the ESSENCE data architecture accommodates the acquisition and transfer processes of small and very large health departments. Essential to the growth of ESSENCE has been the capability provided to the user community to drive system development to meet its evolving needs. Users are provided with multiple syndrome and subsyndrome categories but are not limited by them or by canned or precomputed visualizations. Tools are provided to build simple or arbitrarily complex queries and dashboards for routine monitoring. The rich set of analytic methods includes alerting algorithms and other tracking tools applicable to sparse or rich data streams, with adjustment for only the most common data issues. These tools require historical baseline data of at most a few months, both accommodating limited historical data and providing fast turnaround for understaffed public health monitors. Although these algorithms cannot be tuned to particular syndromic categories or health events as in retrospective studies, they are designed for a range of common data types and behaviors. Current data missingness and lateness indicators are also provided to help users assess the reliability of the visualizations and statistics that they view. Finally, ESSENCE provides a growing suite of communications capabilities for customizable reporting, sharing, and convenient download for additional analytics. These combined features have streamlined onboarding, promoted methods and information sharing among the public health community, and enabled the diverse, all-hazards applications described earlier.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) history highlights.
[DOC File , 36 KB - publichealth_v7i6e26303_app1.doc]

Multimedia Appendix 2
The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) data architecture, security, and preprocessing.

[DOC File , 85 KB - publichealth_v7i6e26303_app2.doc]

Multimedia Appendix 3
Principles and details of The Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE) alerting algorithms.
[DOC File , 257 KB - publichealth_v7i6e26303_app3.doc]

Multimedia Appendix 4
Visualization tools in the Electronic Surveillance System for the Early Notification of Community-Based Epidemics (ESSENCE).
[DOC File , 714 KB - publichealth_v7i6e26303_app4.doc]

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Abbreviations

CCP: Chief Complaint Processor
CDC: Centers for Disease Control and Prevention
DoD: Department of Defense
ED: emergency department
ESSENCE: Electronic Surveillance System for the Early Notification of Community-Based Epidemics
JHU/APL: Johns Hopkins University Applied Physics Laboratory
NSSP: National Syndromic Surveillance Program
OTC: over-the-counter
SAGES: Suite for Automated Global Electronic bioSurveillance
VA: Veterans Administration
WRAIR: Walter Reed Army Institute for Research

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Original Paper

Development of the Czech Childhood Cancer Information System: Data Analysis and Interactive Visualization

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Abstract

Background: The knowledge of cancer burden in the population, its time trends, and the possibility of international comparison is an important starting point for cancer programs. A reliable interactive tool describing cancer epidemiology in children and adolescents has been nonexistent in the Czech Republic until recently.

Objective: The goal of this study is to develop a new web portal entitled the Czech Childhood Cancer Information System (CCCIS), which would provide information on childhood cancer epidemiology in the Czech Republic.

Methods: Data on childhood cancers have been obtained from the Czech National Cancer Registry. These data were validated using the clinical database of childhood cancer patients and subsequently combined with data from the National Register of Hospitalised Patients and with data from death certificates. These validated data were then used to determine the incidence and survival rates of childhood cancer patients aged 0 to 19 years who were diagnosed in the period 1994 to 2016 (N=9435). Data from death certificates were used to monitor long-term mortality trends. The technical solution is based on the robust PHP development Symfony framework, with the PostgreSQL system used to accommodate the data basis.

Results: The web portal has been available for anyone since November 2019, providing basic information for experts (ie, analyses and publications) on individual diagnostic groups of childhood cancers. It involves an interactive tool for analytical reporting, which provides information on the following basic topics in the form of graphs or tables: incidence, mortality, and overall survival. Feedback was obtained and the accuracy of outputs published on the CCCIS portal was verified using the following methods: the validation of the theoretical background and the user testing.

Conclusions: We developed software capable of processing data from multiple sources, which is freely available to all users and makes it possible to carry out automated analyses even for users without mathematical background; a simple selection of a topic to be analyzed is required from the user.

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KEYWORDS

cancer epidemiology; children; data visualization; software development

Introduction

Childhood and adolescent cancers (or *childhood cancers* for short) are classified among rare diseases as their incidence rates are orders of magnitude lower than cancer incidence rates in adults. About 400 new cases of childhood cancers are diagnosed in the Czech Republic each year. Although childhood cancers are rare in terms of absolute numbers, they are the second leading cause of death among children (after injuries).

The web portal SVOD (System for Visualisation of Oncology Data) [1] provides representative epidemiological data on cancer in the Czech Republic. However, it is not entirely convenient for childhood cancers. The main issue is a different classification system of childhood cancers, which takes into consideration differences between childhood and adult cancers; unlike the classification system of adult cancers, which is based on the site of the primary tumor, the classification system of childhood cancers is primarily based on morphology.

For this reason, the Institute of Health Information and Statistics of the Czech Republic (IHIS CR), together with the Institute of Biostatistics and Analyses at the Faculty of Medicine of the Masaryk University (IBA FM MU), the Department of Paediatric Oncology at the University Hospital Brno, and the Department of Paediatric Haematology and Oncology at the University Hospital in Motol, decided to develop a new web portal entitled the Czech Childhood Cancer Information System [2] (CCCIS), which would provide information on childhood cancer epidemiology in the Czech Republic.

The primary objective of the CCCIS portal is to provide comprehensible overviews of epidemiological data on the incidence of childhood cancers in the Czech Republic and mortality and survival data related to cancers in childhood and adolescents. The CCCIS portal also aims to provide relevant information on childhood cancer in the Czech Republic to the international community; this is the reason why the portal is available not only in the Czech language but also in English. The authors of this paper asked the following exploratory questions, which are answered in the Discussion section: how can detailed analytical views—covering incidence, mortality, and survival—be methodically and technically designed and subsequently implemented; is it possible to determine epidemiological trends of selected cancer diagnoses, based on available representative data; and what are the current survival rates in childhood cancer patients in the Czech Republic?

Methods

Data Sources

Data on childhood cancers, which are used on the portal, have been obtained from the Czech National Cancer Registry (CNCR), which is administered by IHIS CR [3]. These data were validated using the clinical database of childhood cancer patients [4] and subsequently combined with data from the National Register of Hospitalised Patients [5] and with data from death certificates [6]. These validated data were then used to determine incidence and survival rates of childhood cancer patients aged 0 to 19 years who were diagnosed in the period 1994 to 2016. Data from death certificates were used to monitor long-term mortality trends. Demographic data on the population of interest were obtained from outputs of the Czech Statistical Office [7]. International data sources were used as well: incidence data from the International Incidence of Childhood Cancer [8], mortality data from the European Cancer Information System [9], and survival data from the international comparative study CONCORD-3 [10].

Classification

Cancers were classified into 12 main groups, according to the International Classification of Childhood Cancer, 3rd Edition (ICCC-3) [11]. All diagnostic groups (I-XII) with behavior 3 (primary malignant tumors) plus diagnoses from groups III (central nervous system [CNS] and miscellaneous intracranial and intraspinal neoplasms) and Xa (intracranial and intraspinal germ cell tumors) with behavior 0/1 (benign neoplasms or those of uncertain or unknown behavior) were considered to be malignant tumors. As regards mortality data, the most common causes of childhood cancer deaths according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10) [12] are shown, namely, the following list of diagnoses: all malignant neoplasms (C00-C97); malignant neoplasms of bone and articular cartilage (C40-C41); malignant neoplasms of connective and soft tissue (C47, C49); malignant neoplasms of brain, spinal cord, and other parts of the CNS (C70-C72); non-Hodgkin lymphoma (C82-C86); and leukemias (C91-C95).

Analysis of Epidemiological Data

In terms of statistical analyses, the web portal CCCIS focuses on three epidemiological indicators: incidence, mortality, and survival. Incidence is the number of new cases diagnosed in a given period in a given population. The CCCIS portal makes it possible to express the incidence in several different ways. First, absolute numbers show the overall burden of the population with a given disease. Second, crude incidence is the number of new cases arising per 1 million children in a given population. If the population of interest only comprises persons in a given age interval (eg, 10-14 years), we are talking about an age-specific incidence. Third, the age-standardized incidence is the theoretical incidence rate that a given population would have if it had a standard age structure. The portal makes it possible to calculate the European age-standardized incidence rate (ASR-E) [13] and the world age-standardized incidence rate (ASR-W) [14]. Mortality is the number of deaths from a given diagnosis (the so-called cause-specific mortality) occurring in a given period in a given population. As is the case with incidence rates, mortality on the CCCIS portal can also be expressed in absolute numbers, rates per 1 million children, age-specific rates, and age-standardized rates to European or world standard population. Overall survival rates were used to evaluate the patients' survival, corresponding to the overall monitored survival, regardless of the cause of death. The overall 1-, 2-, 3-, 4-, and 5-year survival was calculated using the life tables method with 1-year intervals, where death from any cause was the event of interest.

Design and Development

CCCIS is a web portal equipped with an online data browser, which has been developed using the modern and practice-proven Symfony PHP framework in version 3.4 [15]. Using this framework for systematic design, development, and implementation of web applications significantly accelerates individual stages and generally facilitates the applications' administration and extensibility. It is therefore possible to react relatively quickly to users' needs and requirements to adapt current functionalities or to add new functionalities. The Twig template engine has been used to create page templates, and the Doctrine Object Relational Mapper has been used to map the objects—both had been released together with the Symfony framework. The data repository has been built on an open-source object-oriented system, PostgreSQL, which is currently routinely used to organize more complex data structures [16]. The main advantages of PostgreSQL include the support of the developer community, the possibility of advanced performance optimization, and a high quality of technical documentation, making it possible to administer the entire database system and the individual databases without problems.

The import itself into the database is performed by automatic scripts, which upload the new database contents. Maintaining the uniformity of the data model and data purity and quality (thoroughly validated by analysts and developers) are essential requirements for a successful import. The dependence on third-party libraries is dealt with by Yarn (front end) and Composer (back end). A large proportion of the portal has been designed to be responsive (ie, displayed content is automatically adjusted depending on the user's device—desktop, tablet, mobile phone). However, responsiveness is not complete in several parts containing the data browser; the mobile version is not fully supported in this instance because the user interface is far too complex (graphics, filters, analysis settings). The responsive front end has been developed using the Zurb Foundation framework and the jQuery library. The webpack tool has been used to compile the final package of styles and Javascript functions. The interactive data browser requires a special functionality, which is provided by extension components of Javascript libraries; in particular, d3.js, NVD3, and Datatables have been used for interactive data visualizations. We had already applied a similar approach to the development of web applications in the past, namely, in interactive data browsers focused on several issues in Czech health care [17-20].

Data and Application Security

One of the basic requirements of this project was to secure the entire application, including the data layer. The application has been designed to resist potential third-party attacks and to respond flexibly. The communication between the client and the server takes place in a secure way via the HTTPS protocol. This encrypted transmission is nowadays used as standard, and it is common practice to secure the flow of data in this way. The application itself, built on the Symfony framework, has other security mechanisms that are built into it. Respecting standard implementation approaches ensures that exposure to basic attacks such as cross-site scripting, cross-site request forgery, or various types of injection, especially SQL injection, is avoided.

Server-side protection is provided mainly by a network firewall. Another effective way to detect possible third-party attacks is to set up well-configured resource and traffic monitoring, log errors and accesses from the external internet environment, and alert the administrator to nonstandard events.

Protection of the data itself is another necessary requirement to be met. The underlying data, which are used by the portal for rendering visualizations, are cleaned of all personal and sensitive information on patients and their hospital stays. Therefore, it is impossible to directly connect the records to a specific patient. The data are securely stored in a database that is accessible only from predefined locations (these are always part of an internal network) and to a limited set of users whose permissions are restricted to certain data operations. The data are always sent to the client side in an aggregated form, as required for the final visualization. It is important to perform the aggregation operation before sending so that the data cannot be broken down into individual rows at the client side. At the same time, with potentially small numbers of records, the result of the analysis is not sent, and the user is notified of this fact. Thus, the identification of a specific person is effectively prevented.

Validation and User Testing

Feedback was obtained and the accuracy of outputs published on the CCCIS portal was verified using the following methods, which are generally suitable to identify potential shortcomings not only in terms of contents but also in terms of design of the user interface and control elements.

The *validation of theoretical background*, which describes the basic terms, the methodology of cancer classification, and static analytical reports, was performed internally (ie, in cooperation with the analytical team and a group of senior doctors who are specialists in childhood cancers and have many years of experience with the methodology of childhood cancer classification). At the same time, all three sections of the interactive data browser were thoroughly checked; complex analytical views of incidence, mortality, and survival rates according to user settings were extensively tested.

User testing involved simple instructions to go through individual sections of the portal and to provide subjective feedback as regards the overall visual style, control elements, and user-friendliness.

The outputs from both assessments were extensively discussed by the team of authors, and selected suggestions, which fit in with the overall concept of the portal, were subsequently implemented.

Results

Basic Description of the CCCIS Portal

The web portal CCCIS [2] is a stand-alone online presentation, which has been freely available on the internet since November 2019, without the necessity of user authentication. The portal is allowed to be indexed and therefore to be found by standard search engines. Users can access the published contents via a web browser, and all communication takes place via the HTTPS protocol (ie, in a secured and encrypted manner). The CCCIS portal is divided into several sections:

- The *Introduction* section provides basic information about the portal objectives and contents. Participating institutions and the team of authors are introduced. This section also describes the source of data that have been used for statistics and for interactive data views. News related to childhood cancers in the Czech Republic are also involved.
- The *Methodology* section describes how childhood cancers are classified according to the international classification system.
- The *Statistics* section contains an overview of information and descriptive attributes on provided views of the data set. The section is divided into incidence, mortality, and survival. Static analyses are also available for download; however, this feature is only available in the Czech language.
- The *Interactive data views* section provides graphical outputs, which make it possible for users to go through available data sets in an interactive manner. All data sets are regularly updated, based on data from the CNCR and data from a clinical database. Like the Statistics section, the Interactive data views section is divided into incidence, mortality, and survival subsections. This section of the portal is described in more detail in the next section of this paper.
- The *Publications* section provides a list of articles published in research journals and a list of conference papers.

Introduction of the CCCIS Browser

The interactive browser is the principal component of the portal, containing predefined analytical tools that make it possible for the user to look into epidemiological data from different points of view, both in graphical and tabular representation. From the user's viewpoint, this is how the interactive browser is used:

- Selection of the main module (incidence, mortality, survival)
- Selection of analysis type
- Selection of the analyzed group of patients, setting the analysis outputs

Selection of the main module is the first step to begin with any analysis. The principal epidemiological analyses, the so-called modules, cover the following topics: incidence, mortality, and survival. After selecting the main module, the user needs to select the required type of analysis, which means analysis by year of diagnosis, by sex, by cancer type, by age and cancer type combined (this option is only available in the incidence and mortality modules), or by international comparison. Individual types of analyses can be selected in the upper part of the screen. After selecting the required analysis type, an analytical window is displayed, showing the results with basic settings. These settings can be further adjusted on two levels.

Options for the Analyzed Group of Patients

Options for the analyzed group of patients can be selected using the following filters:

- Diagnosis (or cancer type): selection of diagnosis by ICCC-3 (in the incidence and survival modules) or by ICD-10 (in the mortality module)
- Sex: the entire population of children, boys only, or girls only
- Age: selection of age categories 0 to 19 years, 0 to 14 years, <1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, or 15 to 19 years (in the incidence and mortality modules), or 0 to 19 years, 0 to 14 years, or 15 to 19 years (in the survival module)
- Period/years: a scrollbar can be used in the incidence and mortality modules to select individual years or a span of years (currently between 1994 and 2016); as for the survival module, only the predefined periods 1999 to 2004, 2005 to 2010, and 2011 to 2016 can be selected

These filters can be combined, and a detailed view of selected topics can be obtained in this way. Unsuitable or illogical variables in the context of the selected analysis are inactive (gray). The *reset filters* button can be used to restore the original analysis settings.

Detailed Settings of the Analysis Output

Depending on the selected analysis, the software offers a suitable computational method such as absolute numbers; annual numbers; percentages; rate per 1 million children; ASR-E; ASR-W; and 1-, 2-, 3-, 4-, or 5-year overall survival rate. The toggle switch *Group years?* in the Incidence and Mortality modules makes it possible to visualize data for individual years (the *off* position) or for years grouped together (the *on* position). In the *International comparison* analysis, this toggle switch is always in the *on* position, making it possible to compare data from the Czech Republic with data from other European countries.

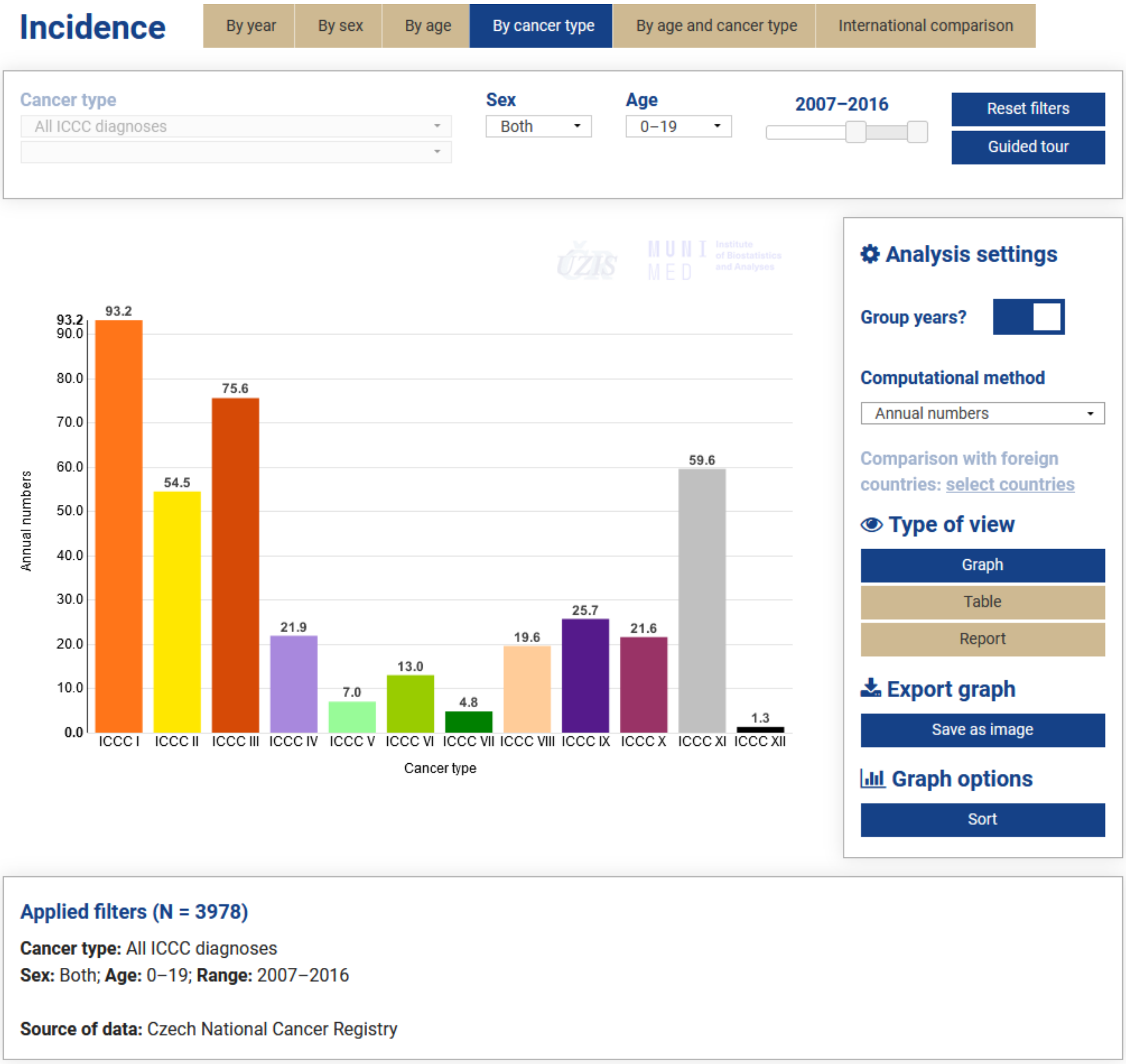
The primary output of the interactive tool is a graph displayed in the center of the working window, including the description of applied filters and the data source. Apart from this graphical output, results can also be displayed in the form of a data table. Graphical outputs can be downloaded as images, whereas tabular outputs can be copied, printed, or downloaded as *.csv or *.xlsx files. Short reports describing the main epidemiological indicators have been written to provide basic overviews of selected diagnoses.

As an illustration, Figure 1 shows the Incidence module, namely, the analysis by cancer type, with the toggle switch *Group years?* being in the *on* position, *annual numbers* selected as the computational method, the time filter set to the period 2007 to 2016, and the graph sorted in descending order. We can see that leukemias (ICCC I) are the most common childhood cancers (ie, those diagnosed in patients aged 0 to 19 years), followed by CNS tumors (ICCC III), other malignant epithelial neoplasms, and malignant melanomas (ICCC XI) and lymphomas (ICCC II).

For illustrative purposes, the Survival module is described (see Figure 2), namely, the analysis by age, with *Leukemias* selected as the cancer type and 1-, 2-, 3-, 4-, and 5-year survival selected as the computational method. We can see that survival rates in the period from 2011 to 2016 differ significantly: patients aged

15 to 19 years have markedly lower 5-year overall survival rates than younger patients.

Figure 1. Czech Childhood Cancer Information System Interactive data views, incidence by cancer type. ICCC: International Classification of Childhood Cancer.



Incidence

Cancer type All ICCC diagnoses

Sex Both

Age 0–19

2007–2016

Group years?

Computational method Annual numbers

Comparison with foreign countries: select countries

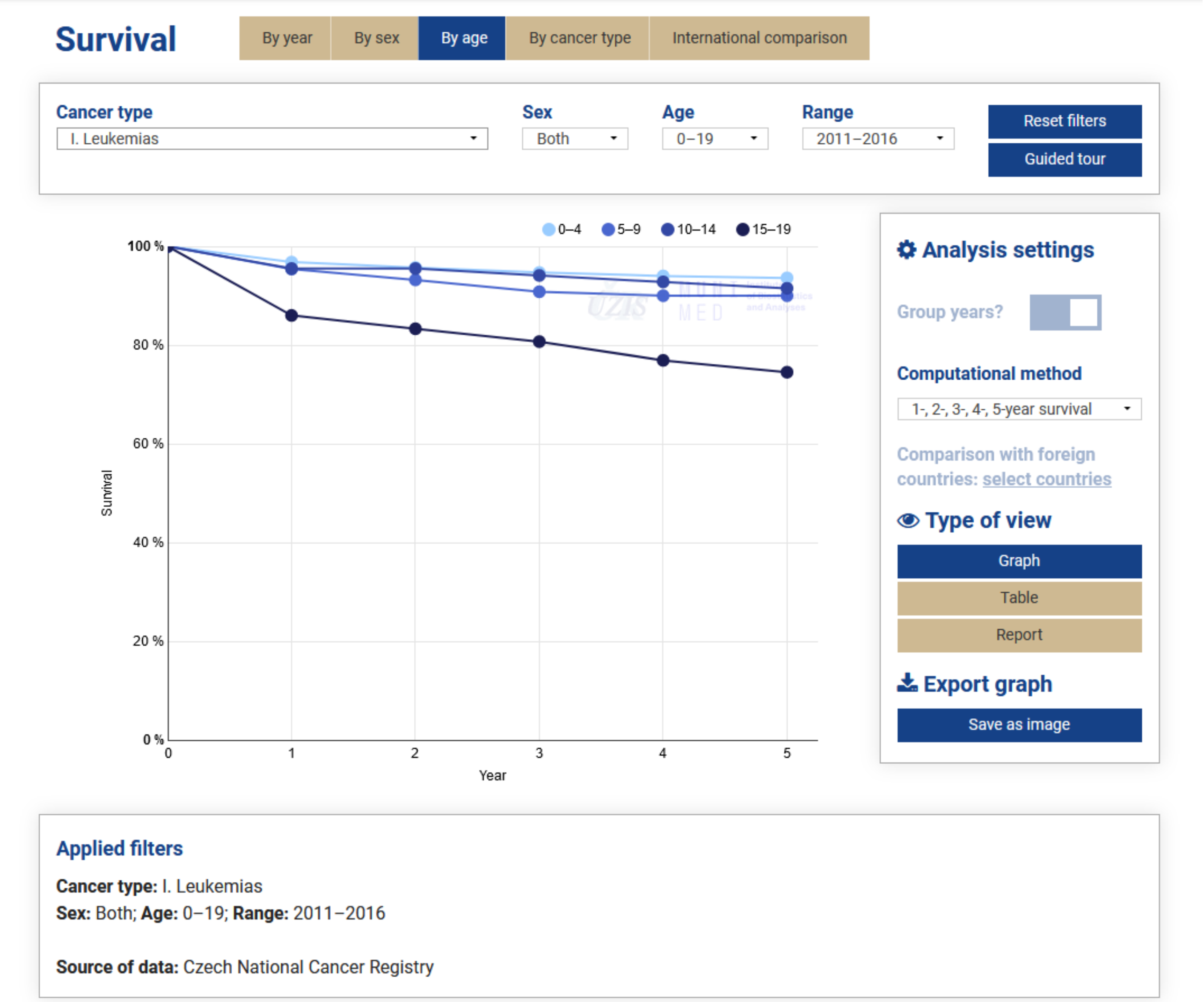
Applied filters (N = 3978)

Cancer type: All ICCC diagnoses

Sex: Both; **Age:** 0–19; **Range:** 2007–2016

Source of data: Czech National Cancer Registry

Figure 2. Czech Childhood Cancer Information System Interactive data views, survival by age.



Cancer type: I. Leukemias

Sex: Both

Age: 0–19

Range: 2011–2016

Computational method: 1-, 2-, 3-, 4-, 5-year survival

Comparison with foreign countries: select countries

Applied filters

Cancer type: I. Leukemias

Sex: Both; **Age:** 0–19; **Range:** 2011–2016

Source of data: Czech National Cancer Registry

Benefit for Users

The software is capable of processing data from multiple sources, is freely available to all users, and makes it possible to carry out automated analyses even for users without mathematical background; a simple selection of a topic to be analyzed is required from the user. This online available software tool makes it therefore possible for anyone to display long-term trends of childhood cancer incidence, mortality, and survival, and to compare data from the Czech Republic to those from abroad. All analytical outputs are displayed in both graphical and tabular outputs. The aggregation of data over time periods is another indisputable advantage of the interactive browser.

Evaluation of the CCCIS Portal

The validation of the static contents was carried out as an internal review of static texts and analytical reports. The comments were of rather formal character, aiming to unify the published information from the linguistic and visual points of view. The CCCIS portal was also assessed by experts, namely, by two senior doctors dealing with childhood cancer patients on a daily basis, who were asked to follow a given scenario using the CCCIS portal (full description of this scenario including feedback is available at [21]).

Discussion

Principal Results

The main findings of this study are summarized in the following discussion in the form of answers to three exploratory questions, which were asked in the Introduction section.

How can detailed analytical views—covering incidence, mortality, and survival—be methodically and technically designed and subsequently implemented? The basic methodical concept of the CCCIS portal lies in the division of the presented contents into three parts (theoretical background, interactive data views, analytical reports), which make up a compact set of information comprehensible to experts in the field and health care professionals. Clear and appropriate definitions of basic terms, together with the description of the International Classification of Childhood Cancer, explain relevant issues to users. The interactive browser represents a unique dynamic tool that makes is possible to set different views of available data sets, including the type of view (graph, table, report) and subsequent download. Analytical reports provide a summary overview of childhood cancer epidemiology in the Czech Republic and detailed reports for individual ICCC groups. The technical solution itself is based on the robust PHP development Symfony framework, with the PostgreSQL system used to accommodate the data basis.

Is it possible to determine epidemiological trends of selected cancer diagnoses based on available representative data? The interactive browse makes epidemiological data available through predefined analytical tools. Users can look into epidemiological indicators—incidence, mortality, and survival of selected cancer diagnosis—by selecting the main module (incidence, mortality, or survival), followed by the selection of the required type of analysis (by year of diagnosis, sex, age, cancer type, age and cancer type combined, and international comparison), and the selection of the patient group to be involved in the analysis. Absolute numbers; annual numbers; rates per 1 million children; age-standardized rates to European or world standard population; and the overall 1-, 2-, 3-, 4-, and 5-year survival can be displayed, depending on the selected analysis.

What are the current survival rates in childhood cancer patients in the Czech Republic? The overall 1-, 2-, 3-, 4-, and 5-year survival rates for 12 main ICCC groups can be obtained using the main *Survival* module of the interactive browser, after selecting the type of analysis and possibly by being more specific about the group of patients to be involved in the analysis. The highest 5-year survival in the period 2011 to 2016 was observed in retinoblastoma (ICCC V), and in other malignant epithelial neoplasms and malignant melanomas (ICCC XI). By contrast, the lowest 5-year survival rates were observed in soft tissue and other extraosseous sarcomas (ICCC IX) and in hepatic tumors (ICCC VII).

Future Visions

The CCCIS portal will be further developed within the joint workplace of the IHIS CR and IBA FM MU. Comments and suggestions provided by users themselves will play an important role in this process. Specific questions will be formulated in cooperation with the expert society, probably requiring additional analytical outputs.

Comparison With Other Works

Publicly available portals describing childhood cancer epidemiology in other European countries, namely, in Ireland [22], Switzerland [23], and the United Kingdom [24], have become our motivation. The Irish web portal provides an interactive analytical reporting for incidence; the Swiss and the UK websites are static but provide information not only on incidence but also on mortality and survival of childhood cancer patients. The new CCCIS portal combines the approaches previously mentioned and thus enables interactive analytical reporting of incidence, mortality, and survival.

Conclusions

The CCCIS portal is the result of a long-term cooperation of a state organization directly coming under the Ministry of Health of the Czech Republic and selected specialized workplaces in the academic sphere. Doctors, representatives of a department administering the National Health Information System, data analysts, systems analysts, graphic designers, and developers have worked together to create a platform that makes accessible valuable and interesting views of available data in a user-friendly form. The web portal is available for anyone at [2], providing basic information for experts (ie, analyses and publications) on individual diagnostic groups of childhood cancers. It involves an interactive tool for analytical reporting, which provides information on the following basic topics in the form of graphs or tables: incidence, mortality, and overall survival.

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Conflicts of Interest

None declared.

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Abbreviations

ASR-E: European age-standardized incidence rate
ASR-W: world age-standardized incidence rate
CCCIS: Czech Childhood Cancer Information System
CNCR: Czech National Cancer Registry
CNS: central nervous system
IBA FM MU: Institute of Biostatistics and Analyses at the Faculty of Medicine of the Masaryk University
ICCC-3: International Classification of Childhood Cancer, 3rd Edition
ICD-10: International Statistical Classification of Diseases, Tenth Revision
IHIS CR: Institute of Health Information and Statistics of the Czech Republic
SVOD: System for Visualisation of Oncology Data

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Original Paper

Public Discussion of Anthrax on Twitter: Using Machine Learning to Identify Relevant Topics and Events

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Abstract

Background: Social media allows researchers to study opinions and reactions to events in real time. One area needing more study is anthrax-related events. A computational framework that utilizes machine learning techniques was created to collect tweets discussing anthrax, further categorize them as relevant by the month of data collection, and detect discussions on anthrax-related events.

Objective: The objective of this study was to detect discussions on anthrax-related events and to determine the relevance of the tweets and topics of discussion over 12 months of data collection.

Methods: This is an infoveillance study, using tweets in English containing the keyword “Anthrax” and “*Bacillus anthracis*”, collected from September 25, 2017, through August 15, 2018. Machine learning techniques were used to determine what people were tweeting about anthrax. Data over time was plotted to determine whether an event was detected (a 3-fold spike in tweets). A machine learning classifier was created to categorize tweets by relevance to anthrax. Relevant tweets by month were examined using a topic modeling approach to determine the topics of discussion over time and how these events influence that discussion.

Results: Over the 12 months of data collection, a total of 204,008 tweets were collected. Logistic regression analysis revealed the best performance for relevance (precision=0.81; recall=0.81; F_1-score=0.80). In total, 26 topics were associated with anthrax-related events, tweets that were highly retweeted, natural outbreaks, and news stories.

Conclusions: This study shows that tweets related to anthrax can be collected and analyzed over time to determine what people are discussing and to detect key anthrax-related events. Future studies are required to focus only on opinion tweets, use the methodology to study other terrorism events, or to monitor for terrorism threats.

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KEYWORDS

anthrax; big data; internet; infodemiology; infoveillance; social listening; digital health; biological weapon; terrorism; Federal Bureau of Investigation; machine learning; public health threat; Twitter

Introduction

Background

Terrorism can be traced back to almost 2000 years ago when the Sicarii-Zealots, a Jewish resistance group, used assassins to stab Roman legionnaires or Jewish collaborators, use poison, or kidnap Temple Guard staff for ransom [1]. Terrorism can take many forms, and while each government agency has their own definition of terrorism, all agencies concur that the purpose is to instigate widespread fear in the target population [2-4].

The fear resulting from terrorism typically causes more damage to our economy and social fabric than the act of terror itself. Examples include an upsurge in hate crimes following the September 11, 2001, attacks on the World Trade Center (New York City, New York) and the fear of opening mailboxes after the anthrax attacks of 2001 [5,6]. Hence, in addition to neutralizing terror attacks before they occur, efforts to combat terrorism are also focused on minimizing negative social after-effects of attacks that do occur. To this end, it is imperative to identify and address fears and misconceptions to mitigate the additional damage.

Some terrorists utilize chemical, biological, radiological, and nuclear weapons or explosives (CBRNe) to instill fear. The anthrax attacks of 2001 are an example of bioterrorism where a biological weapon (anthrax) was used in the United States. The anthrax attacks are the only example of the use of a CBRNe agent in the United States. Nonetheless, there have been several anthrax hoaxes where people have received packages or envelopes with powder that is not anthrax. Considering the continued hoaxes and concern over an impending anthrax attack, it is important to continue to monitor for anthrax-related events.

Social media has facilitated studies on opinions and reactions to anthrax-related events in real time, thus eliminating the time lag and response bias associated with traditional survey methods. Infodemiology is the study of determinants and distribution of information on the internet, allowing data to be collected and analyzed in real time [7]. Infodemiology has enabled studies on public behavior and opinions during the COVID-19 pandemic [8,9], conspiracy theories [10], and public behavior and opinions during the Zika pandemic [11,12]. Anthrax, or *Bacillus anthracis*, is a gram-positive, rod-shaped, spore-forming, facultative anaerobic, aerobic, nonmotile bacterium [13]. Human anthrax infection occurs through three routes: gastrointestinal, cutaneous, and inhalation (pulmonary) [14]. Cutaneous anthrax is the most common but least dangerous form of infection, gastrointestinal anthrax has rarely been reported in the United States, and inhalation anthrax is considered the deadliest form. Irrespective of the route of infection, anthrax responds well to antibiotics when treated before the onset of symptoms [15-17]. Weapons-grade anthrax has been treated to reduce clumping, has a low electrostatic charge, a uniform particle size, and a high spore concentration [14]. An aerosol release of *B. anthracis* would be invisible and odorless, with the potential to travel several kilometers before dissipating [18]. This combination of a high infection rate, high virulence, and ease of spread makes anthrax an ideal bioweapon.

Related Studies

Nordin et al [19], performed a computer simulation of uniform exposure to an anthrax release in the air intakes in the Mall of America (Bloomington, Minnesota). The completeness and timeliness of detecting the attack depended on the infection rate. The study by Nordin et al [19] improves upon detection using traditional methods and may allow natural outbreaks to be detected faster.

Mandl et al [20] suggested a 4-stage detection procedure for measuring outbreak detection using semisynthetic data sets. In the first stage, data were grouped by syndrome. In the modeling stage, historic data were used to understand temporal and spatial patient distributions. This was followed by the detection stage where predictions based on the model were compared to observed data. In the last stage, the health department determined if the outbreak was worth investigating on the basis of the large deviations observed in stage 3 [20].

The simulated anthrax epidemic injection model developed by Buckeridge et al [21] also consisted of four components: agent dispersion, infection, disease and behavior, and data sources. The models developed by Buckeridge et al [21] and Mandl et al [20] may also improve methods of detecting natural outbreaks and terrorism through their comparison with background noise. This study not only compared peak-to-background noise but also used real-time rather than historic data.

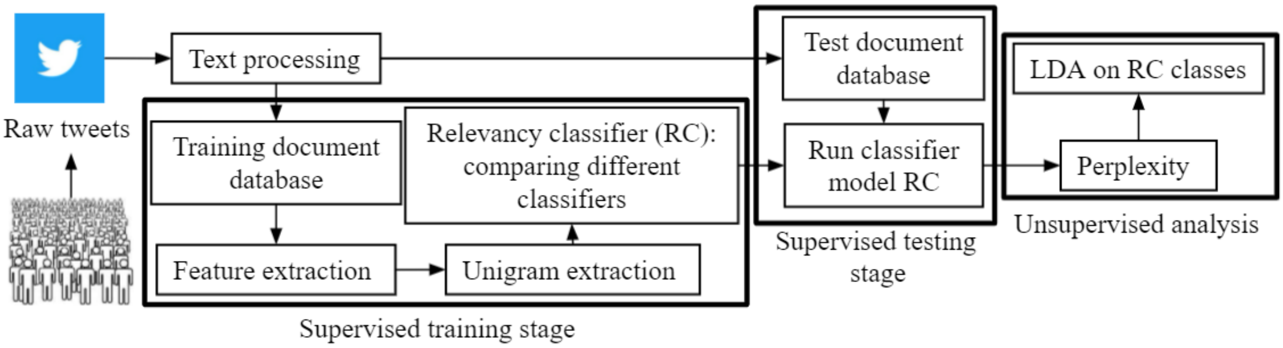
Kulldorf et al [22] used 3 different data sets to generate a null model, where each person in New York City is equally likely to contract anthrax, and 35 alternative models where 1 or more zip codes were assigned an increased risk on day 31, 32, or 33 post exposure. Kulldorf et al [22] reported that the statistical power was higher when more days had elapsed since the onset of the outbreak. Kulldorf et al [22] took a week to detect an event using simulated data.

The aforementioned studies are based on historic or simulated data and demonstrate how computers can improve event detection speed and precision compared to traditional survey methods. Furthermore, they explain how using naturally occurring events highlights the usefulness of their methods, but analysis using actual event data is needed. Real-time data encompassing 20 events that occurred will be used in this study. The aforementioned studies were also focused on detecting events from among physician visits, whereas event detection and the analysis of public opinions on the events were the focus of this study.

Aims of the Study

We aimed to carry out an exploratory analysis focused on developing a framework for detecting discussions on anthrax-related events on Twitter and topic modeling over several months. Using the methods shown in Figure 1, the following research questions were addressed: Event detection (R1): were discussions on anthrax-related events detected on Twitter? What events led to these discussions? Classification performance analysis (R2): what was the classification performance in detecting the tweets relevant to anthrax-related events? Topical analysis (R3): what were the main discussion topics during each month of data collection over a year-long period (September 25, 2017, to August 15, 2018)?

Figure 1. Methods for a hierarchical supervised classification technique. Large black boxes indicate where supervised machine learning algorithms were trained, supervised machine learning algorithms were tested, and where unsupervised machine learning algorithms were used. LDA: Latent Dirichlet allocation.



Methods

Methods Overview

A combination of natural language processing and machine learning techniques was used in this study to detect anthrax-related events and determine how tweets on anthrax change over time. Specifically, a classifier system was built for finding relevant tweets on anthrax and then categorizing them by month (Figure 1).

A primary concern of researchers using social media data is whether the data are public or private [23]. Tweets collected by using hashtags are generally considered public data since users are broadcasting their opinions to other users discussing the same topic [23]. For ethical reasons, tweets were not collected from specific accounts or through direct messages, the data were deindividualized, and usernames were removed from all collected tweets; therefore, all data collected were public data.

Tweets containing the keyword “Anthrax” and “*Bacillus anthracis*” in English were collected from September 25, 2017, through August 15, 2018, using the Twitter application programming interface (API) using real-time endpoints (Spyder Python 3.6). Tweets were collected in accordance with Twitter’s application programming interface documentation; hence, the tweets collected in this study constitute a subset as opposed to all tweets containing the keywords used. Data collected included text from 204,008 tweets as well as the date and time when the tweet was posted. These 204,0008 tweets included retweets and consisted of a random sample of all tweets containing 1 or both keywords.

Event Detection (Addressing R1)

The number of tweets over time was plotted to detect anthrax-related events. If a 3-fold spike in tweets occurred within a 24-hour period, it was considered an event. A 3-fold spike was chosen because it allowed all spikes corresponding to anthrax-related topics to be detected but did not eliminate any important topics. Time of detection was determined as the time between an event occurring and when the first tweet regarding the event was detected. For all the events, the exact time of the event could not be determined; hence, the time when the first news article was posted or the time when a weblink reference in a tweet was posted was used instead. All times were converted to EST for delay calculations. Tweets about the Mueller investigation were a topic of discussion throughout data collection. At the time of the spikes, several tweets were highly retweeted along with other individual comments about the proceedings, which made it difficult to determine what caused the spikes in tweets. Therefore, the first highly retweeted tweet was used to determine the start of the spike and to obtain the article, weblink reference, or tweet that led to the spike.

Classification Performance (Addressing R2)

A CBRNe expert and 2 data analysts trained by the expert annotated 5000 random unique tweets as “relevant” (scored as 1) or “not-relevant” (scored as 0) to create a gold standard data set. Cronbach α was used to evaluate interrater reliability between annotators using StataIC (version 15, Stata Corp).

If the tweet was about *B. anthracis*, it was considered relevant. For example, the tweet “RT: Remind me again, why did DC invade Iraq? Yellow cake and Nuclear weapons? Anthrax and Bio weapons? 9/11 Saudis?” was annotated as “relevant” since it mentions anthrax as one of the possible reasons why the United States invaded Iraq, whereas the tweet “Anthrax - In The End Official” was annotated as “not-relevant” because it refers to a song by the metal band “Anthrax.” The relevant tweets were then further categorized by the month and day when they were tweeted.

Before data analysis, the tweets had to be preprocessed by removing weblinks, hashtags, at-mentions, retweet indicators, and non-ASCII (American Standard Code for Information Interchange) characters. Data were further normalized by removing punctuation, numbers, uppercase letters, and white spaces. Terms such as single letters, stop words, and the search terms “anthrax” and “*Bacillus anthracis*,” which do not convey any additional meaning about the topics, were removed. Features included parts of speech (adjectives, singular nouns, past-tense verbs, past-participle verbs, verbs, determiners, prepositions, personal pronouns, plural nouns, singular proper nouns, predeterminers, and adverbs), the top 20 unigrams, and the top 20 bigrams. Feature codings were used to train the classifiers. All features were coded on the basis of the presence (scored as 1) or absence (scored as 0) of them in the tweet. The algorithms were then trained using the presence or absence codings for all features. All features were used for each machine learning algorithm.

Supervised machine learning algorithms including logistic regression, naïve Bayes classifier, support vector machine, and random forest were used for classifying relevance and events. These supervised methods rely on labeled data (tweets) to “learn” the nature of the tweets toward correctly classifying them. Tweets were categorized as relevant or not and then further divided by month.

The performance of each supervised algorithm was evaluated using 10-fold cross-validation, which serves to partition the data into 10 disjoint sets with equal samples from all classes [24]. The algorithm then trains on 10-1 of the sets and tests on the single hold-out set, repeating until all sets have been used for training 10-1 times and testing once. The performance of the machine learning algorithms was tested using a holdout of 500+1000 additional random tweets. Precision, recall, and F_1-scores were calculated to test the performance on the holdout of 500+1000 additional tweets.

Topical Analysis (Addressing R3)

Topic modeling using an unsupervised machine learning analysis was used to determine the most common topics of discussion during each month of data collection. Latent Dirichlet allocation (LDA) was chosen for topic modeling. LDA is an unsupervised machine learning technique that identifies the most common topics in tweets by clustering words with similar meanings [25]. In LDA, each document is represented by a mixture of topics, and each topic is represented by a mixture of words. In this study, topic modeling was used to determine the underlying topics for each month of data collection.

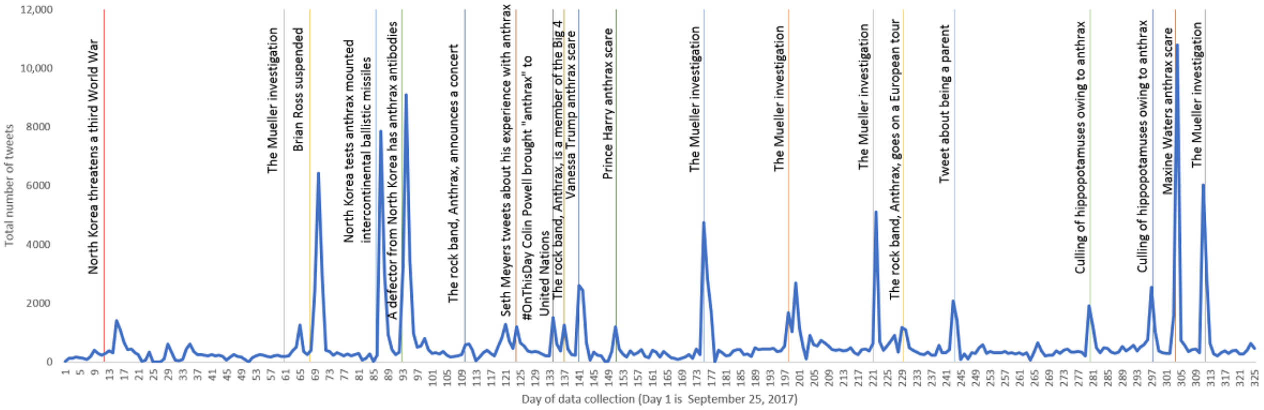
To determine the number of topics to include in the LDA analysis, the perplexity measure was chosen. Perplexity was used to evaluate the LDA results by testing the number of topic models from 2 to 100 for each month. The point at which the perplexity measure leveled off was used to indicate the optimal number of topics.

Results

Event Detection (Addressing R1)

In total, 20 events were detected over the course of data collection (Figure 2), of which 6 concerned current anthrax-related events, 3 were about North Korea having access to anthrax, 3 were about anthrax scares, and 5 were related to the former director of the US Federal Bureau of Investigation (FBI) Robert Mueller, who oversaw the FBI during the anthrax attacks and was in charge of investigating the collusion with Russia during data collection. One was a news report about reporter Brian Ross being suspended owing to an erroneous report. Reporter Brian Ross was a topic of discussion because he also erroneously reported that Iraq and Saddam Hussein were responsible for the anthrax attacks, even though he was told that his story was inaccurate [26]. One event commemorated the anniversary of Colin Powell having brought a vial of “anthrax” to the United Nations, claiming that it is from Iraq. Culling of hippopotamuses owing to anthrax infection led to 2 events. Two were tweets that were highly retweeted: 1 from Seth Meyers about working at Saturday Night Live when they received the letter related to anthrax and another about using anthrax on the parents of bullies. Three events were announcements related to the band Anthrax, which were of no interest in this study and were removed by the relevance classifier.

Figure 2. Line graph showing the number of tweets collected during each day of data collection (September 25, 2017, to August 15, 2018). Vertical lines indicate when news was first published about one of the detected anthrax-related discussions.



The exact time of an event occurring could not be determined for all the detected events. Therefore, the time of report was based on when the original tweet was posted or when the weblink to the corresponding article or video in the tweet was posted (Table 1). Times between the original tweet and the start of the retweets was within minutes, as seen with the tweet from Seth Meyers, the tweet about being a parent, 2 tweets about the Mueller investigation, and a tweet announcing the band Anthrax is a member of the Big 4. Most tweets based on a new article started within a few hours of the article being posted. The longest time between an article and a tweet about the article concerned an article in The Federalist about former FBI Director Robert Mueller and a one about him “botching” investigations throughout his career.

Table 1. Time of the news report or the first tweet concerning a detected discussion, time of the first tweet discussing the news article or the first retweet, and the time between the event and its detection.

Event	Time of report	Time of detection	Time between report and detection
North Korea threatens a third World War	October 6, 2017, at 1:29 PM	October 6, 2017, at 5:35 PM	4 hours 6 minutes
The Mueller investigation	November 24, 2017, at 3 AM	November 25, 2017, at 5:02 PM	~1 day 15 hours
Brian Ross suspended	December 1, 2017 (clock time unknown)	December 1, 2017, at 4:14 PM	<24 hours
North Korea tests anthrax-mounted intercontinental ballistic missiles	December 19, 2017, at 7:32 PM	December 20, 2017, at 12:32 AM	5 hours
North Korean defector has anthrax antibodies	December 26, 2017, at 9:51 AM	December 26, 2017, at 2:53 PM	5 hours 2 minutes
Anthrax band announces a concert	January 11, 2018, at 3:47 AM	January 12, 2018, at 3:03 PM	~12 hours
Seth Meyers tweets about an anthrax experience	January 26, 2018, at 3:27 AM	January 26, 2018, at 3:28 AM	1 minute
#OnThisDay Collin Powell brought "anthrax" to the United Nations	February 5, 2018, at 9:46 AM	February 5, 2018, at 9:57 AM	11 minutes
Anthrax band is a member of the Big 4	February 8, 2018, at 2:40 AM	February 8, 2018, at 2:41 AM	1 minute
Vanessa Trump anthrax scare	February 12, 2018, at 10 AM	February 12, 2018, at 6:14 PM	~8 hours
Prince Harry anthrax scare	February 22, 2018, at 5:59 AM	February 22, 2018, at 10:58 AM	4 hours 59 minutes
The Mueller investigation	March 18, 2018, at 2:20 AM	March 18, 2018, at 2:20 AM	<1 minute
The Mueller investigation	February 8, 2018 (clock time unknown)	April 10, 2018, at 4:36 AM	~2 months
The Mueller investigation	May 3, 2018, at 9:59 PM	May 4, 2018, at 1:59 AM	4 hours
Anthrax band's European tour	May 11, 2018, at 4 AM	May 11, 2018, at 8 AM	4 hours
Tweet about being a parent	May 25, 2018, at 11:34 AM	May 25, 2018, at 3:34 PM	4 hours
Culling of hippopotamuses owing to anthrax	July 1, 2018, at 9 AM	July 1, 2018, at 12:59 PM	3 hours 59 minutes
Culling of hippopotamuses owing to anthrax	July 18, 2018, at 3:09 AM	July 18, 2018, at 7:09 AM	4 hours
Maxine Waters anthrax scare	July 24, 2018, at 3:22 PM	July 24, 2018, 10:26 PM	7 hours 4 minutes
The Mueller investigation	August 1, 2018, 1:47 PM	August 1, 2018, at 1:47 PM	<1 minute

Classification Performance (Addressing R2)

Initially, 204,008 tweets were collected. After preprocessing, 201,152 tweets remained. A random subset of 5000 unique tweets was manually labeled as "relevant" or "not-relevant" to *B. anthracis*. The distribution of relevant versus not-relevant tweets in the gold standard was uneven, with more relevant (n=3239 of 5000, 64.78%) than not-relevant tweets (n=1761 of 5000, 35.22%). The distribution of all relevant (n=165,844 of 201,152, 82.45%) vs not-relevant tweets (n=35,308 of 201,152, 17.55%) was also uneven, but with a larger proportion of relevant tweets. The difference in the ratio between the gold standard and final count is due to the gold standard including unique tweets, while several relevant tweets were retweeted numerous times in the actual data set.

The interrater reliability for relevancy was 0.87 (76% agreement) between raters. This indicates adequately high agreement [27]. Accordingly, a machine learning algorithm needed to be trained on the basis of the gold standard data set.

The performance metrics for the 4 machine learning algorithms on the gold standard are shown in Table 2. All algorithms had acceptable levels of performance (F_1-score=0.72-0.80; precision=0.75-0.81; recall=0.75-0.81) with logistic regression analysis revealing an optimal performance with regard to precision (0.81), recall (0.81), and the F_1-score (0.80).

Table 2. Precision, recall, and F_1-score for the relevance machine learning algorithms with optimal performance on logistic regression analysis.

Machine learning algorithm	F_1-score	Precision	Recall
Support vector machine	0.72	0.75	0.75
Random forest	0.78	0.78	0.79
Naïve Bayes classifier	0.79	0.79	0.79
Logistic regression	0.80	0.81	0.81

A confusion matrix was created by comparing the annotated data from the CBRNe expert to the sum of the predictions of each of the holdout sets (n=10). Most tweets were classified correctly through logistic regression analysis (true-positive=1116; true-negative=2931; false-positive=645; false-negative=308) compared to the support vector machine (true-positive=2993; true-negative=737; false-positive=1024; false-negative=246), random forest (true-positive=2802; true-negative=1120; false-positive=641; false-negative=437), and naïve Bayes classifier (true-positive=2566; true-negative=1361; false-positive=400; false-negative=637). The majority of misclassification was the algorithm classifying not-relevant tweets as relevant for logistic regression analysis (false-positive=645), the support vector machine (false-positive=1024), and random forest (false-positive=641), whereas the majority of misclassification was false-negative for the naïve Bayes classifier (false-negative=637).

An additional 500+1000 random, unique tweets not included in the gold standard were coded by the CBRNe expert and the logistic regression algorithm trained with the gold standard. Precision, recall, and the F_1-score were determined between the expert's and logistic regression's codings and found to be adequately high (500: precision=0.65, recall=0.83, and F_1-score=0.73; 1000: precision=0.58, recall=0.95, and F_1-score=0.72). The substantial agreement indicates that the gold standard was a suitable representation of the entire corpus. The relevant tweets were further examined to determine how discussions on anthrax change over time and how anthrax-related events influence that discussion.

Topical Analysis (Addressing R3)

Event-Related Topical Analysis

Of the 25 topics, 16 were related to the events detected (6 were about the Mueller investigation, 2 were about threats from North Korea, 3 were about an anthrax scare, and 2 were about culling of hippopotamuses, Seth Meyers, and being a parent) (Table 3). The topic of the Mueller investigation was discussed throughout 2018 and included tweets discussing perceived past failings of Former FBI Director Robert Mueller.

Threats from North Korea was a topic in September or October and December and concerned fear regarding North Korea threatening a third World War and reports a defector from North Korea who tested positive for anthrax antibodies.

During data collection, 3 anthrax scares were reported. The first 2 occur in February with regard to Prince Harry and 2 weeks later, with regard to Donald Trump Jr. The third scare occurred in July with regard to Representative Maxine Waters. These were called scares because all 3 letters or packages contained a powder, which was not anthrax.

The topic of culling of hippopotamuses includes tweets about culling of hippopotamuses in Namibia in September or October and Zambia in May owing to anthrax outbreaks in herds of hippopotamuses.

The last 2 events that were topics of discussion were Seth Meyers and being a parent. Seth Meyers was a highly retweeted tweet in February from Seth Meyers, which described his experience of working at Saturday Night Live when the anthrax attack occurred at the National Broadcasting Company. Being a parent was a tweet from a user who indicated why he/she was afraid to become a parent because he/she might transmit anthrax to the parents of bullies.

Table 3. Results of topic modeling for each month of data collection (September 25, 2017 to August 15, 2018) (N=26 topics).

Month	Topic
September and October	- (#1) Threats from North Korea - (#2) Responsible - (#3) Culling of hippopotamuses
November	- (#1) Vaccine - (#2) Angela Merkel
December	- (#1) Threats from North Korea - (#2) India
January	- (#1) Seth Meyers - (#2) The Mueller investigation
February	- (#1) New York Post - (#2) Anthrax scare - (#3) Anthrax scare - (#4) Korean War
March	- (#1) The Mueller investigation - (#2) Travis Air Force Base
April	- (#1) Abortion - (#2) The Mueller investigation
May	- (#1) The Mueller investigation - (#2) Culling of hippopotamuses - (#3) Being a parent
June	- (#1) Cattle - (#2) The Mueller investigation - (#3) Abortion
July	- (#1) Anthrax scare - (#2) The Mueller investigation
August	- (#1) The Mueller investigation

Non–Event-Related Topical Analysis

The remaining 10 topics were not detected events (2 about abortion, the New York Post, the Travis Air Force Base, India, cattle, Angela Merkel, responsible, vaccine, and the Korean War) (Table 3). “Abortion,” “New York Post,” and “Travis Air Force Base” concern scares. “India” and “cattle” both discuss natural anthrax outbreaks. “Angela Merkel” and “responsible” were both highly retweeted tweets. “Vaccine” and the “Korean War” both refer to controversies related to anthrax in the United States.

The 2 times “abortion” was a topic both discuss what it is like to work at an abortion clinic with the constant threats including an anthrax scare. “The New York Post” details a person’s experience working at the New York Post when they received a scare. “The Travis Air Force Base” discusses a suspicious package at the base and includes mentions of other events.

The topic “India” was the result of a research study in India, which reported that anthrax remains in the soil for 50-60 years. The topic “cattle” discusses a natural outbreak of anthrax in a herd of cattle in South Dakota.

“Angela Merkel” was a highly retweeted post that compared Angela Merkel to anthrax. Regarding “responsible,” a user jokingly asked how to tell someone they were responsible for anthrax attacks.

“Vaccine” concerns the controversial anthrax vaccine. “Korean War” concerned the use of biological weapons by the United States during the Korean War. Both are controversial topics with “vaccine” being a topic of discussion throughout data collection.

Discussion

Event Detection (Addressing R1)

Of the 26 topics discovered over the 12 months of data collection, 12 were related to current anthrax events (3 about anthrax scares, 2 about threats from North Korea, and 7 about the Mueller investigation) (Multimedia Appendix 1). Seven topics were tweets that were highly retweeted (“responsible,” “Seth Meyers,” “New York Post,” “being a parent,” and “abortion”). Natural outbreaks were highlighted by 2 topics (“culling of hippopotamuses” and “cattle”). Two topics stemmed from responses to news articles (“Angela Merkel” and “India”).

The topic "vaccine" stemmed from people who discussed the controversy regarding the armed forces requiring troops to be vaccinated against anthrax.

Classification Performance (Addressing R2)

The majority of tweets concerned anthrax-related events. This class imbalance was in the random sample of labeled tweets and the total corpus, which shows that the gold standard was an accurate representation of the data. The relevance classifier performed well, with logistic regression analysis revealing an optimal performance. Error analysis revealed that the logistic regression classifier performs well with new data and was adequately generalizable to handle a large data set.

Topical Analysis (Addressing R3)

Event-Related Topical Analysis

Although we were screening topics related to bioterrorism, natural outbreaks also trended as topics of discussion. The outbreaks discussed in this study resulted in a cull—selective killing of infected animals to prevent further disease spread—to prevent the spread of anthrax among hippopotamuses and cattle. While culls do not relate to terrorism, they can be controversial, which is why they emerged as topics [28]. While outrage and controversy were expressed in relation to both culls and attacks, tweets about culls are not useful for studying public reactions to bioterrorism-related anthrax events.

The topics "Seth Meyers," "abortion," and "New York Post" indicate that on anniversary dates or when similar events occur, people discussed the past use of weaponized anthrax or anthrax-related scares. One example was a discussion on the use of bioweapons by the United States during the Korean War. These topics also show that people tweet about their experiences with a past event when a similar event is occurring. All 3 tweets discussed how terrified they were and show that they are still affected, almost 2 decades later. Owing to discussions on past events during current ones, it will be important for government agencies to create a classifier to separate out tweets that discuss past events from those that discuss emerging events. However, these tweets will still need to be studied to inform how people might react to current events.

Non–Event-Related Topical Analysis

The topics "responsible," "being a parent," "Angela Merkel," "vaccine," and "India" show examples of what people discuss when an anthrax-related event is not occurring. When anthrax-related events are not occurring, people would still discuss new research findings, as demonstrated with the topic "India," which included tweets that shared a news story wherein researchers found anthrax remains in the soil for 60 years. The emergence of "India" as a topic shows that people at risk of infection pay attention to news that might affect them.

Sometimes, joke tweets become viral, such as the one related to "responsible" joking about telling someone that they were responsible for the anthrax attacks, or another tweet about mailing anthrax to the parents of children who bullied their child. The people making these jokes do not understand the seriousness of anthrax or consider their risk to be nonexistent.

The topic "Angela Merkel" resulted from an article in a German newspaper where members of the Christian Democratic Union of Germany wanted Angela Merkel to resign because they disagree with her policies, and a person commented comparing Angela Merkel to anthrax. Tweets such as this one comparing someone to anthrax implies that the tweeter considers this person harmful, similar to calling someone "toxic." These tweets likely do not indicate a threat but do indicate a large dislike or distrust of the person or group. Tweets wishing someone had anthrax or comparing someone to anthrax will remain topics for discussion when events are not occurring because of people expressing how much they dislike someone or how much they do not want to do something.

Tweets concerning the anthrax vaccine will be another topic of constant discussion owing to the controversy about its side effects. A majority (86%) of people who received the anthrax vaccine reported side effects, which led to some people to argue that the vaccine should be halted until one with fewer side effects is developed [29]. However, the Pentagon disagreed and stated that the current vaccine is the most reliable and safest way to protect service members. The dispute over the vaccine resulted in a constant stream of tweets throughout the year. Previous studies on vaccine sentiments can serve as a guide for the Pentagon to understand why people are so adversative to the vaccine, in order to address this fear [30-34].

Usefulness of The Methods

Events were detected within 1-4 hours of the event, which was an improvement over previous studies [19-22]. While machine learning techniques were used specifically for detecting anthrax-related events, they are much more widely applicable; machine learning techniques could detect other terrorism-related events, answer other questions, or be used on other social media platforms. The usefulness of the methods is currently being demonstrated with the FBI's search for the insurgents who invaded the Capitol building. The culprits could be identified by collecting and analyzing tweets containing the hashtags #stormthecapitol and #patriotparty and limiting tweets to those in English, which contain images or videos.

Limitations

There are some limitations related to our data set and to using social media. These limitations include language constraints, the use of LDA, and bot accounts. These are standard limitations associated with infodemiology studies [35-39].

Demographics

The use of data from Twitter has an inherent sampling bias. Future studies could utilize other social media platforms to account for this bias. The search application programming interface only collects 1% of tweets from people with public profiles.

Language Constraint

Our data were restricted to tweets in English, which limits the generalizability of our findings. Limiting tweets to those in English limited the ability to study topics such as "culling of hippopotamuses" and "India," the former having originated in Namibia and Zambia, and the latter in India. Future studies could address this limitation through the analysis of tweets in the prominent language spoken where the event occurred. Slang may have also affected our results. Anthrax is slang for smoking marijuana. Tweets using anthrax as slang were labeled as not-relevant, but some may have been misclassified. We may have also missed tweets discussing anthrax without using our keywords.

LDA

LDA has had some problems in the past with the number of revealed topics being greater than the number of true topics [40]. This was addressed by using perplexity and by combining topics covering the same tweet or topics that had ≥4 of the same most frequently used words. Before performing LDA, tweets were segregated into separate documents where each document included only tweets about that topic. All relevant tweets were separated by month before the LDA was performed on the tweets within that respective month.

Tweets By Bots

People who want to spread their message to as many people as possible program bots to spam their messages on social media platforms. If this is a concern for future studies based on these data, we would recommend checking each account to ensure that it is not a bot by using previously developed code or removing all duplicate and retweeted tweets to prevent bots from influencing such studies. In this study, tweets about the anthrax vaccine and Gulf War Syndrome, and about Matt Dehart, a hacker arrested by the FBI, who claimed that he was arrested and tortured to keep secrets, may have been from bot accounts [41]. Since this study aimed to provide a descriptive analysis of what people discuss about anthrax, and how these discussions relate to bioterrorism events, there was no need to attempt to identify bot accounts.

Interpretation of Peak Height

There is no guideline on what specific peak height indicates an event. A 3-fold spike was chosen because it allowed for the detection of all spikes related to anthrax events, without detecting spikes due to random noise. Future studies can start with this 3-fold spike but may need to adjust it on the basis of their results.

Future Prospects

Future studies could further classify relevant tweets as discussing an event or not. This would help with misclassification being skewed towards false-positive findings and allow for a more detailed analysis of discussions about certain events.

To maximally harness this framework, future studies can utilize more social media platforms to eliminate the demographic bias, sample social media posts in all languages, which are related to a CBRNe event, and to identify and exclude bot accounts to determine what the general public thinks about an event. Other studies should focus on opinion tweets and exclude news stories, use these methods to analyze an actual anthrax attack, and study misconceptions or misinformation about anthrax. In this study, news posts were highly retweeted and skewed topics toward reports rather than people's opinions. A study should also focus on social media platforms that people with extremist opinions use, to prevent incidents such as invasion of the Capitol.

Conclusion

This was the first study to successfully create an automated tweet classification tool to analyze topics of discussion regarding anthrax related-events in real time. Through citizen sensing, detection time has decreased from 2 weeks to a few hours, advancing the field's methodological capabilities for analyzing public discussions on CBRNe events. Our methods have been demonstrated to be effective and trustworthy for detecting discussions on anthrax-related events and classifying tweets as relevant or not-relevant. FBI analysts will be able to immediately detect CBRNe events using the framework of this study.

This study is important because it decreased detection time from a week to a few minutes to hours and developed a reliable and trustworthy framework that can be used for any CBRNe-related event. This will allow experts to address fear and misconceptions in real time, mitigating the additional damage that occurred after the anthrax attacks. Monitoring social media may also help rescuers locate people who may have left the scene before they could be decontaminated or properly treated. These methods could also help identify people involved in a terrorism incident if they take photographs or carry out a livestream, similar to what happened at the Capitol building.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Topics, keywords, and example tweets for each topic of discussion over the twelve months of data collection.
[DOCX File , 36 KB - publichealth_v7i6e27976_app1.docx]

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Abbreviations

CBRNe: chemical, biological, radiological, and nuclear weapons or explosives
FBI: Federal Bureau of Investigation
LDA: latent Dirichlet allocation

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Original Paper

Factors Influencing Clinicians' Willingness to Prescribe Pre-exposure Prophylaxis for Persons at High Risk of HIV in China: Cross-sectional Online Survey Study

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is an effective HIV prevention measure. Clinicians play a crucial role in PrEP implementation, and their knowledge, attitudes, and career experience may affect their willingness to prescribe PrEP. However, little is known about the attitudes and willingness of clinicians to prescribe PrEP in countries without PrEP-specific guidelines.

Objective: We aimed to determine the factors associated with clinicians being willing to prescribe PrEP in China.

Methods: Between May and June 2019, we conducted an online cross-sectional survey of clinicians in 31 provinces across the six administrative regions in China on the WeChat smartphone app platform. Multivariable logistic regression was used to determine factors associated with willingness to prescribe PrEP.

Results: Overall, 777 HIV clinicians completed the survey. Most of the respondents had heard of PrEP (563/777, 72.5%), 31.9% (248/777) thought that PrEP was extremely effective for reducing the risk of HIV infection, and 47.2% (367/777) thought that it was necessary to provide PrEP to high-risk groups. After adjusting for age, gender, ethnicity, and educational background of the clinicians, the following factors significantly increased the odds of the clinicians being willing to prescribe PrEP: having worked for more than 10 years, compared to 5 years or less (adjusted odds ratio [aOR] 2.82, 95% CI 1.96-4.05); having treated more than 100 patients living with HIV per month, compared to 50 patients or fewer (aOR 4.16, 95% CI 2.85-6.08); and having heard of PrEP (aOR 7.32, 95% CI 4.88-10.97). Clinicians were less likely to be willing to prescribe PrEP if they were concerned about poor adherence to PrEP (aOR 0.66, 95% CI 0.50-0.88), the lack of PrEP clinical guidelines (aOR 0.47, 95% CI 0.32-0.70), and the lack of drug indications for PrEP (aOR 0.49, 95% CI 0.32-0.76).

Conclusions: About half of all clinicians surveyed were willing to prescribe PrEP, but most surveyed had a low understanding of PrEP. Lack of PrEP clinical guidelines, lack of drug indications, and less than 11 years of work experience were the main barriers to the surveyed clinicians' willingness to prescribe PrEP. Development of PrEP clinical guidelines and drug indications, as well as increasing the availability of PrEP training, could help improve understanding of PrEP among clinicians and, thus, increase the number willing to prescribe PrEP.

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KEYWORDS

WeChat; pre-exposure prophylaxis; clinicians; willingness to prescribe; HIV prevention; China

Introduction

Pre-exposure prophylaxis (PrEP) is a highly effective preventative strategy for HIV; through a combination of HIV approaches recommended by the World Health Organization (WHO), PrEP can reduce HIV transmission [1]. PrEP strategies involve key HIV-negative populations who take antiretroviral medications and attend routine visits with an HIV clinician in order to prevent HIV transmission. Recent clinical trials among men who have sex with men (MSM) have shown that daily oral PrEP and on-demand PrEP can prevent 86% and 96% of HIV infections, respectively [2]. Tenofovir disoproxil fumarate/emtricitabine (TDF/FTC; brand name Truvada) has been approved by the WHO for PrEP use among adults and adolescents at risk of HIV [3,4]. About 40 countries around the world have incorporated PrEP into their health systems, 10 of which have carried out nationwide programs [2]. The other 30, including China, are implementing pilot projects exploring the acceptability, effectiveness, and cost of PrEP [2,5]. At present, only a few countries have provided support on implementing this new strategy through country-specific guidelines for clinicians [3,6].

Before prescribing PrEP, physicians must assess the HIV risk of the patient, their likely adherence, and any potential side effects in order to ensure effective use of PrEP [7-10]. PrEP is most effective at reducing HIV risk when targeted toward high-risk populations [6]. Assessing likely adherence is crucial, as patients with low adherence to PrEP did not have a reduction in HIV risk [11]. In addition, as some high-risk populations have anxiety and depression [12], any potential side effects of PrEP must be assessed by the clinician prior to prescribing PrEP. Thus, any support in making these judgments before prescribing is needed.

One potential method to support clinicians in prescribing PrEP is through providing clinical guidelines to standardize HIV risk assessment. In countries where national PrEP clinical guidelines have been issued, physicians weigh PrEP-related knowledge, attitudes, and experiences when making their decision to prescribe PrEP [13,14]. Some developed countries (eg, the United States, the United Kingdom, and Canada) have examined the attitudes and intentions to prescribe PrEP among clinicians through investigations [15-22]. However, in low- and middle-income countries that do not have national PrEP clinical guidelines, clinicians' knowledge and willingness to prescribe PrEP has not previously been well-reported.

Despite the high burden caused by the HIV epidemic, China has been slower to implement PrEP compared to other developed countries [2], and few studies have evaluated PrEP use in China. The National Health Commission in China has stated that the country needs to promote PrEP implementation by carrying out nationwide pilot work. The Chinese Center for Disease Control and Prevention has established pilot projects in seven provinces, running from October 2008 to November 2019, to study the feasibility of using PrEP in key populations [23]. In addition, China Medical University carried out real-world research of PrEP use among MSM in Shenyang, Beijing, Chongqing, and Shenzhen starting in December 2018; this research concluded in December 2020 [24]. In addition to these real-world studies on PrEP implementation, several studies have also shown that Chinese MSM are very willing to use PrEP [25,26]. However, the current proportion of PrEP prescriptions in key populations in China is less than 1%, much lower than that in other developed countries (9.5% in the United States and 2.5% in Australia) [27]. Clinicians may be reluctant to prescribe PrEP because of limited understanding, thus leading to this low percentage of prescriptions among key groups in China.

To evaluate PrEP-related attitudes among Chinese clinicians, we conducted a nationwide online survey investigating PrEP-related awareness and attitudes, experience with PrEP, and potential perceived barriers to being willing to prescribe PrEP.

Methods

Respondents and Procedures

Between May and June 2019, we conducted a nationwide anonymous online survey among Chinese HIV clinicians in 31 provinces across six administrative regions. The questionnaire was designed based on current literature of HIV prevention using PrEP in China and with the support of subject matter experts. Clinicians with clinical medical qualifications were eligible for the study if they were currently working in a position at an infectious disease or general hospital that included treating patients living with HIV. We reached out to HIV clinicians through the two largest professional work groups in China on WeChat, the most popular social media app in China: the *National clinicians group focusing on HIV/AIDS* and the *National physician platform for the communication of difficult HIV/AIDS cases*. The administrators of these two WeChat groups confirmed the clinical identities and specialties of their members, and removed any members with nonclinical identifications. Thus, 937 HIV clinicians were eligible for this survey (Multimedia Appendix 1). After conducting a pilot study with 50 eligible participants by convenience sampling, which was included in the final results, we evaluated the accuracy and reliability of the questionnaire and modified the survey accordingly. To recruit participants from the remaining eligible clinicians, we posted a brief description of the survey, including the purpose and significance, and links to the questionnaire. The inclusion criteria for this survey were as follows: (1) 18 years of age or older, (2) practicing in an HIV-related medical institution, and (3) treated at least one person living with HIV over the past year. Based on the open ID of WeChat, each individual was allowed to access the online survey only once and the answers could be reviewed or changed before submission. We confirmed the identity of participants through collected self-reported information about medical background and relevant experience. After submission of the completed questionnaire, we provided a subsidy of 30 Yuan (US $4.50) to participants to compensate for the time they spent completing the survey (ie, about 6 to 10 minutes). We used self-reported contact information only to deliver the subsidy. Ethical approval was obtained from the Institutional Review Board of the First Affiliated Hospital of China Medical University ([2019]2015-138-9). In our analysis, we followed the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guidelines (Multimedia Appendix 2).

Measures

After providing online informed consent, clinicians completed a voluntary anonymous survey. The questionnaire asked about sociodemographic characteristics; medical background; PrEP-related knowledge, attitudes, and experience; and barriers to prescribing PrEP (Multimedia Appendix 3).

The primary outcome of this study was the percentage of clinicians willing to prescribe PrEP to key populations based on their response—*yes* or *no*—to the following question: "Do you think it is necessary for clinicians to provide PrEP to HIV high-risk populations to reduce HIV infections?" The questionnaire also asked about the location, administrative level, and type of hospital where they practiced; their academic title; length of their career; and the average number of patients living with HIV treated in the past month. We then assessed PrEP-related knowledge: whether participants had ever heard of PrEP, their understanding of PrEP, how effective they thought PrEP was for reducing the risk of HIV infections, and whether clinical guidelines for PrEP were available in China. We also asked how often they recommend PrEP to MSM, heterosexual males, heterosexual females, and serodiscordant couples. Respondents were also asked how often they saw high-risk groups actively seeking a PrEP prescription in the past 6 months and potential barriers to them prescribing PrEP.

Statistical Analysis

Continuous variables were categorized for analysis. Age was grouped into five categories (25, 26-39, 40-49, 50-59, and 60 years), length of career was grouped into three categories (5, 6-10, and 11 years), and average number of patients living with HIV treated per month was also grouped into three categories (50, 51-100, and 101 patients). We described the distribution of the variables by presenting the frequency and percentage. We then conducted univariable and multivariable logistic regression to determine predictors of clinicians being willing to prescribe PrEP and presented crude odds ratios (ORs) and adjusted ORs (aORs) with the corresponding 95% CIs. If there were no clinicians in a specific cell in a comparison, 0.5 was added to all cells to compute the OR [28]. Significant predictors in the univariable analysis were included in the multivariable logistic regression. We adjusted for age, gender, ethnicity, and educational background of the clinician in the multivariable model. All statistical analyses were performed with SPSS, version 25.0 (IBM Corp). A two-tailed P value of less than .05 was considered statistically significant.

Results

Demographic and Medical Background Characteristics

A total of 777 eligible clinicians completed the survey, which represented a response rate of 82.9% (777/937) (Multimedia Appendix 1). Among these 777 survey responses, 50 (6.4%) were from the pilot survey. The median age of the participants was 42 years (IQR 36-48), around half were female (417/777, 53.7%), the most common ethnicity was Han (712/777, 91.6%), and most had a bachelor's degree or above (743/777, 95.6%). The highest proportion of participants were from South Central China (201/777, 25.9%). The distribution of HIV clinicians surveyed at the province level and economic level is included in Multimedia Appendix 4. Approximately half of the participants worked in infectious disease hospitals (394/777, 50.7%), and 54.2% (421/777) were deputy chief physicians or chief physicians. Slightly more than half (432/777, 55.6%) had worked for more than 5 years, and 59.3% (461/777) treated an average of 50 or fewer patients living with HIV per month (Table 1).

Table 1. Demographic and medical background characteristics of clinicians.

Characteristic	Value (N=777), n (%)
Demographic characteristic	
Age (years)	
≤25	3 (0.4)
26-39	302 (38.9)
40-49	331 (42.6)
50-59	131 (16.9)
≥60	10 (1.3)
Ethnicity	
Han	712 (91.6)
Non-Han	65 (8.4)
Gender	
Male	360 (46.3)
Female	417 (53.7)
Administrative region of China[a]	
South Central	201 (25.9)
Southwest	199 (25.6)
Northeast	164 (21.1)
East	116 (14.9)
North	71 (9.1)
Northwest	26 (3.3)
Education level	
Technical secondary school	5 (0.6)
Junior college	29 (3.7)
Bachelor’s degree or above	743 (95.6)
Medical background and experience	
Type of hospital	
General	383 (49.3)
Infectious disease	394 (50.7)
Academic title	
General physician	82 (10.6)
Attending doctor	274 (35.3)
Deputy chief physician	221 (28.4)
Chief physician	200 (25.7)
Specialization	
HIV	649 (83.5)
General infectious diseases	128 (16.5)
Length of career (years)	
≤5	345 (44.4)
6-10	184 (23.7)
≥11	248 (31.9)
Average number of patients living with HIV treated per month	
≤50	461 (59.3)

Characteristic	Value (N=777), n (%)
51-100	128 (16.5)
≥101	188 (24.2)

[a]The 31 provinces were located across six administrative regions.

Self-Rated Knowledge, Attitudes, and Experience Associated With PrEP and Barriers to Prescribing

In this study, 72.5% (563/777) of the clinicians reported that they had heard of PrEP; however, only 30.8% (239/777) had an excellent or good understanding of PrEP, and 31.9% (248/777) thought that PrEP was extremely effective for reducing the risk of HIV infection. Most clinicians (635/777, 81.7%) considered that PrEP clinical guidelines were not available in China. About half (367/777, 47.2%) believed that it was necessary for clinicians to provide PrEP to HIV high-risk populations to reduce HIV infections and were, thus, defined as willing to prescribe PrEP. Clinicians were more likely to mostly recommend PrEP to serodiscordant couples (439/777, 56.5%), followed by MSM (309/777, 39.8%). Few clinicians (201/777, 25.9%) often or occasionally saw high-risk populations actively seeking PrEP prescriptions. Among the clinicians surveyed, concerns about prescribing PrEP included the following: side effects of treatment (484/777, 62.3%), promoting the occurrence of high-risk sexual behaviors (476/777, 61.3%), and poor adherence to PrEP (383/777, 49.3%) (Table 2).

Figure 1 depicts the six administrative regions of China; the percentages of clinicians from these regions who self-reported an excellent or good understanding of PrEP, who found that PrEP was necessary for high-risk groups, and who treated 50 or fewer patients living with HIV per month are shown in Table 3.

Table 2. Self-rated knowledge, attitudes, experience, and barriers associated with pre-exposure prophylaxis (PrEP).

Variable	Value (N=777), n (%)
Self-rated knowledge	
Heard of PrEP	
Yes	563 (72.5)
No	214 (27.5)
Understanding of PrEP	
Excellent	86 (11.1)
Good	153 (19.7)
Low	538 (69.2)
Effectiveness of PrEP on reducing the risk of HIV infection	
Extremely effective	248 (31.9)
Possibly effective	106 (13.6)
Not sure	419 (53.9)
Ineffective	4 (0.5)
PrEP clinical guidelines are available in China	
Yes	142 (18.3)
No	635 (81.7)
Attitudes towards PrEP	
Providing PrEP to high-risk groups	
Necessary	367 (47.2)
Not necessary	410 (52.8)
Recommend PrEP prescription to men who have sex with men	
Mostly	309 (39.8)
Frequently	254 (32.7)
Seldom	55 (7.1)
Never	159 (20.5)
Recommend PrEP prescription to heterosexual males	
Mostly	59 (7.6)
Frequently	309 (39.8)
Seldom	154 (19.8)
Never	255 (32.8)
Recommend PrEP prescription to heterosexual females	
Mostly	58 (7.5)
Frequently	352 (45.3)
Seldom	153 (19.7)
Never	214 (27.5)
Recommend PrEP prescription to serodiscordant couples	
Mostly	439 (56.5)
Frequently	197 (25.4)
Seldom	58 (7.5)
Never	83 (10.7)
Experience related to PrEP	
See high-risk groups actively seeking PrEP prescriptions	

Variable	Value (N=777), n (%)
Often	50 (6.4)
Occasionally	151 (19.4)
Seldom	213 (27.4)
Never	363 (46.7)
Perceived barriers to prescribing PrEP	
Concerned about promoting the occurrence of high-risk sexual behaviors	
Yes	476 (61.3)
No	301 (38.7)
Concerned about increasing the risk of other sexually transmitted diseases	
Yes	120 (15.4)
No	657 (84.6)
Concerned about poor adherence to PrEP	
Yes	383 (49.3)
No	394 (50.7)
Concerned about drug resistance	
Yes	271 (34.9)
No	506 (65.1)
Concerned about side effects of PrEP	
Yes	484 (62.3)
No	293 (37.7)
Concerned about the cost of PrEP	
Yes	462 (59.5)
No	315 (40.5)
Concerned about reduction of resources for patients living with HIV	
Yes	123 (15.8)
No	654 (84.2)
Concerned about lack of PrEP clinical guidelines	
Yes	140 (18.0)
No	637 (82.0)
Concerned about lack of drug indications	
Yes	108 (13.9)
No	669 (86.1)

Figure 1. The six administrative regions of China.

Table 3. Pre-exposure prophylaxis (PrEP)–related knowledge, attitudes, and medical experience of clinicians in six administrative regions of China.

Variable and regions of China	Value, n (%)
Self-reported an excellent or good understanding of PrEP	
South Central (n=201)	63 (31.3)
Southwest (n=199)	58 (29.1)
Northeast (n=164)	49 (29.9)
East (n=116)	39 (33.6)
North (n=71)	21 (29.6)
Northwest (n=26)	9 (34.6)
PrEP was necessary for high-risk groups	
South Central (n=201)	95 (47.3)
Southwest (n=199)	90 (45.2)
Northeast (n=164)	87 (53.0)
East (n=116)	54 (46.6)
North (n=71)	26 (36.6)
Northwest (n=26)	15 (57.7)
Treated 50 or fewer patients living with HIV per month	
South Central (n=201)	135 (67.2)
Southwest (n=199)	108 (54.3)
Northeast (n=164)	90 (54.9)
East (n=116)	69 (59.5)
North (n=71)	40 (56.3)
Northwest (n=26)	19 (73.1)

Predictors of Clinicians Being Willing to Prescribe PrEP

Table 4 presents the crude ORs of potential factors that could affect clinicians' willingness to prescribe PrEP. All significant factors in the crude analysis were analyzed using multivariable logistic regression (Figure 2). After adjusting for age, gender, ethnicity, and educational background, the following clinicians were more likely to be willing to prescribe PrEP: those who had been working for more than 10 years, compared to 5 years or fewer (aOR 2.82, 95% CI 1.96-4.05); those who heard of PrEP (aOR 7.32, 95% CI 4.88-10.97); and those who often had high-risk populations actively requesting PrEP prescriptions, compared to never requesting (aOR 79.35, 95% CI 18.78-335.31).

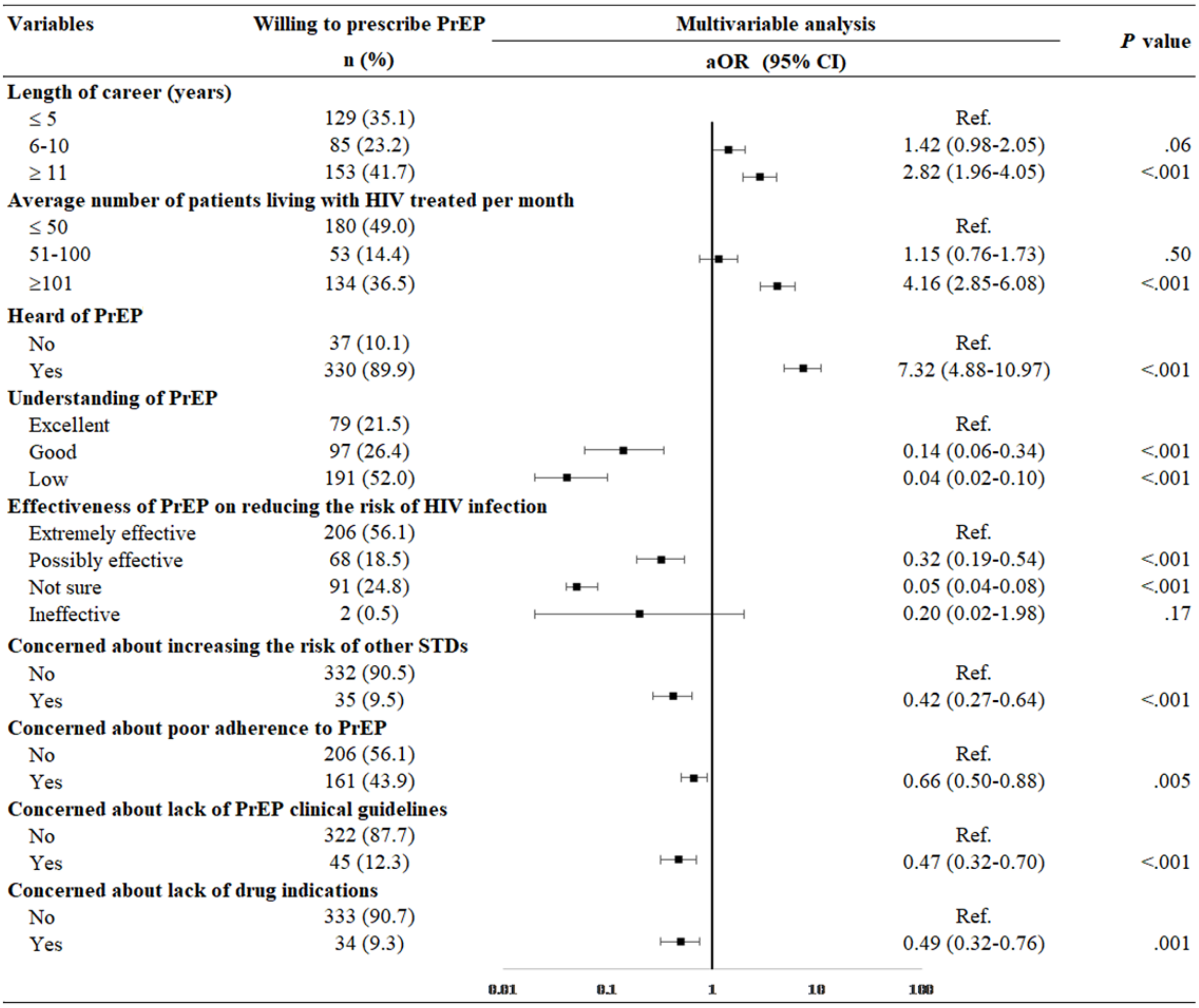
Clinicians who had a low understanding of PrEP, compared to an excellent understanding (aOR 0.04, 95% CI 0.02-0.10), or were not sure about the effectiveness of PrEP on reducing the risk of HIV infection, compared to self-reporting PrEP as extremely effective (aOR 0.05, 95% CI 0.04-0.08), were less likely to be willing to prescribe PrEP. In addition, clinicians who were concerned about the lack of PrEP clinical guidelines (aOR 0.47, 95% CI 0.32-0.70) or the lack of drug indications (aOR 0.49, 95% CI 0.32-0.76) were less likely to be willing to prescribe PrEP.

Table 4. Univariable logistic regression of predictors of clinicians being willing to prescribe pre-exposure prophylaxis (PrEP) (N=777).

Variable	Willing to prescribe PrEP		Odds ratio (95% CI)	*P* value
	Yes (n=367), n (%)	No (n=410), n (%)		
Age (years)				
26-39	146 (39.8)	156 (38.0)	Reference	
≤25	0 (0)	3 (0.7)	0.15 (0.01-2.98)	.22
40-49	141 (38.4)	190 (46.3)	0.79 (0.58-1.09)	.15
50-59	76 (20.7)	55 (13.4)	1.48 (0.98-2.23)	.07
≥60	4 (1.1)	6 (1.5)	0.71 (0.20-2.58)	.61
Ethnicity				
Han	337 (91.8)	375 (91.5)	Reference	
Non-Han	30 (8.2)	35 (8.5)	0.96 (0.57-1.59)	.86
Administrative region of China				
Northeast	77 (21.0)	87 (21.2)	Reference	
South Central	106 (28.9)	95 (23.2)	1.26 (0.83-1.91)	.27
Southwest	89 (24.3)	110 (26.8)	0.91 (0.60-1.38)	.67
East	54 (14.7)	62 (15.1)	0.98 (0.61-1.59)	.95
North	26 (7.1)	45 (11.0)	0.65 (0.37-1.16)	.14
Northwest	15 (4.1)	11 (2.7)	1.54 (0.67-3.56)	.31
Type of hospital				
General	170 (46.3)	213 (52.0)	Reference	
Infectious disease	197 (53.7)	197 (48.0)	1.25 (0.95-1.66)	.12
Academic title				
General physician	37 (10.1)	45 (11.0)	Reference	
Attending doctor	142 (38.7)	132 (32.2)	1.31 (0.80-2.15)	.29
Deputy chief physician	95 (25.9)	126 (30.7)	0.92 (0.55-1.53)	.74
Chief physician	93 (25.3)	107 (26.1)	1.06 (0.63-1.77)	.83
Length of career (years)				
≤5	129 (35.1)	216 (52.7)	Reference	
6-10	85 (23.2)	99 (24.1)	1.44 (1.00-2.07)	.05
≥11	153 (41.7)	95 (23.2)	2.70 (1.93-3.78)	<.001
Average number of patients living with HIV treated per month				
≤50	180 (49.0)	281 (68.5)	Reference	
51-100	53 (14.4)	75 (18.3)	1.10 (0.74-1.64)	.63
≥101	134 (36.5)	54 (13.2)	3.87 (2.68-5.59)	<.001
Heard of PrEP				
No	37 (10.1)	177 (43.2)	Reference	
Yes	330 (89.9)	233 (56.8)	6.78 (4.58-10.03)	<.001
U nderstanding of PrEP				
Excellent	79 (21.5)	7 (1.7)	Reference	
Good	97 (26.4)	56 (13.7)	0.15 (0.07-0.36)	<.001
Low	191 (52.0)	347 (84.6)	0.05 (0.02-0.11)	<.001
Effectiveness of PrEP on reducing the risk of HIV infection				
Extremely effective	206 (56.1)	42 (10.2)	Reference	

Variable	Willing to prescribe PrEP		Odds ratio (95% CI)	*P* value
	Yes (n=367), n (%)	No (n=410), n (%)		
Possibly effective	68 (18.5)	38 (9.3)	0.37 (0.22-0.61)	<.001
Not sure	91 (24.8)	328 (80.0)	0.06 (0.04-0.09)	<.001
Ineffective	2 (0.5)	2 (0.5)	0.20 (0.03-1.49)	.12
See high-risk groups actively seeking PrEP prescriptions				
Never	88 (24.0)	275 (67.1)	Reference	
Seldom	111 (30.2)	102 (24.9)	3.40 (2.37-4.88)	<.001
Occasionally	120 (32.7)	31 (7.6)	12.10 (7.62-19.20)	<.001
Often	48 (13.1)	2 (0.5)	75.00 (17.86-314.88)	<.001
Concerned about promoting the occurrence of high-risk sexual behaviors				
No	152 (41.4)	149 (36.3)	Reference	
Yes	215 (58.6)	261 (63.7)	0.81 (0.61-1.08)	.15
Concerned about increasing the risk of other sexually transmitted diseases				
No	332 (90.5)	325 (79.3)	Reference	
Yes	35 (9.5)	85 (20.7)	0.40 (0.26-0.62)	<.001
Concerned about poor adherence to PrEP				
No	206 (56.1)	188 (45.9)	Reference	
Yes	161 (43.9)	222 (54.1)	0.66 (0.50-0.88)	.004
Concerned about side effects of PrEP				
No	143 (39.0)	150 (36.6)	Reference	
Yes	224 (61.0)	260 (63.4)	0.90 (0.68-1.21)	.50
Concerned about lack of PrEP clinical guidelines				
No	322 (87.7)	315 (76.8)	Reference	
Yes	45 (12.3)	95 (23.2)	0.46 (0.32-0.68)	<.001
Concerned about lack of drug indications				
No	333 (90.7)	336 (82.0)	Reference	
Yes	34 (9.3)	74 (18.0)	0.46 (0.30-0.72)	.001

Figure 2. Predictors of clinicians being willing to prescribe pre-exposure prophylaxis (PrEP) (N=777). aOR: adjusted odds ratio; Ref.: reference; STD: sexually transmitted disease.



Variables	Willing to prescribe PrEP n (%)	Multivariable analysis aOR (95% CI)	*P* value
Length of career (years)			
≤ 5	129 (35.1)	Ref.	
6-10	85 (23.2)	1.42 (0.98-2.05)	.06
≥ 11	153 (41.7)	2.82 (1.96-4.05)	<.001
Average number of patients living with HIV treated per month			
≤ 50	180 (49.0)	Ref.	
51-100	53 (14.4)	1.15 (0.76-1.73)	.50
≥101	134 (36.5)	4.16 (2.85-6.08)	<.001
Heard of PrEP			
No	37 (10.1)	Ref.	
Yes	330 (89.9)	7.32 (4.88-10.97)	<.001
Understanding of PrEP			
Excellent	79 (21.5)	Ref.	
Good	97 (26.4)	0.14 (0.06-0.34)	<.001
Low	191 (52.0)	0.04 (0.02-0.10)	<.001
Effectiveness of PrEP on reducing the risk of HIV infection			
Extremely effective	206 (56.1)	Ref.	
Possibly effective	68 (18.5)	0.32 (0.19-0.54)	<.001
Not sure	91 (24.8)	0.05 (0.04-0.08)	<.001
Ineffective	2 (0.5)	0.20 (0.02-1.98)	.17
Concerned about increasing the risk of other STDs			
No	332 (90.5)	Ref.	
Yes	35 (9.5)	0.42 (0.27-0.64)	<.001
Concerned about poor adherence to PrEP			
No	206 (56.1)	Ref.	
Yes	161 (43.9)	0.66 (0.50-0.88)	.005
Concerned about lack of PrEP clinical guidelines			
No	322 (87.7)	Ref.	
Yes	45 (12.3)	0.47 (0.32-0.70)	<.001
Concerned about lack of drug indications			
No	333 (90.7)	Ref.	
Yes	34 (9.3)	0.49 (0.32-0.76)	.001

Discussion

Principal Findings

This is the first cross-sectional survey to assess the knowledge, attitudes, and experience of HIV clinicians regarding PrEP in China. While the proportion of clinicians surveyed who had heard of PrEP was only slightly less compared to the proportion in other developed countries, understanding of PrEP was much lower in China. Of those surveyed, 72.5% (563/777) had heard of PrEP, which was slightly lower than the percentage in the United States (75% to 96%) [15-18] or in the United Kingdom (77%) [19]. Only 30.8% of clinicians (239/777) rated their knowledge of PrEP as good or excellent in our study, which was much lower than previously reported in the United Kingdom (80%) [19] and Canada (83.6%) [20]. We also found that 47.2% (367/777) of the clinicians were willing to provide PrEP to high-risk groups. In comparison, the pooled prevalence of clinicians who were willing to prescribe PrEP in a meta-analysis was 66% in the United States [21], and the proportion found in Canada was 45.4% [20]. As there are no PrEP guidelines in China, standardized education and guidance on PrEP is limited, leading to low awareness on PrEP. In addition, as Chinese clinicians have a shorter period of professional training and the education levels of clinicians are relatively lower in remote areas, they may be younger and less experienced when beginning their clinical work compared with experienced clinicians in western countries such as the United States [18,22]. This shorter training period and the lower education levels may limit their PrEP-related knowledge and ability to prescribe PrEP to key populations; thus, this group of clinicians in China should be given priority for training. While this survey also found that about half of Chinese clinicians were willing to prescribe PrEP, their knowledge of PrEP was low compared to other developed countries.

We found that over half of clinicians (53%) surveyed had seen high-risk groups actively seeking PrEP prescriptions, which is higher than the percentage in the United States (43%) [13]. Although Chinese MSM have a limited understanding of PrEP [26,29,30], they are willing to actively seek PrEP prescriptions, with a proportion of 75% in the relevant studies [2,25,31], while the proportion is about 60% in the United States [32].

Our study also identified the factors that promote or hinder the clinician in being willing to prescribe PrEP. Clinicians in infectious disease hospitals with longer work experience were more likely to be willing to prescribe PrEP for high-risk groups compared to those earlier in their careers. Previous studies have found that clinicians who attended more clinical training sessions were more likely to be willing to prescribe PrEP [15,16,33]. Thus, these clinicians with the longer careers could have been more likely to prescribe PrEP because they had more targeted clinical training and more extensive clinical experience over time. To increase the willingness to prescribe PrEP among those with less work experience, junior clinicians from general hospitals should specifically undergo PrEP-related training.

Concerns about the lack of PrEP clinical guidelines and drug indications were two independent barriers to clinicians' willingness to prescribe PrEP. Clinicians surveyed who were concerned about the lack of PrEP clinical guidelines had about half the odds of being willing to prescribe PrEP compared to those who were not concerned. Thus, development and implementation of PrEP guidelines could substantially increase the number of clinicians who are willing to prescribe PrEP and support the national implementation of PrEP [15,34]. The current Chinese guidelines, published in 2018, for diagnosis and treatment of HIV and AIDS only includes the definition of PrEP [35] and does not include any information on PrEP-related inclusion criteria, laboratory testing, PrEP regimens and adherence, or potential side effects. In addition, clinicians who were concerned about lack of PrEP indications were significantly less likely to be willing to prescribe PrEP compared to those who were not concerned. At the time this study was conducted, PrEP was not approved in China for HIV prevention. Thus, clinicians could be held liable for any possible side effects of PrEP, decreasing the number willing to prescribe PrEP. This potential problem was addressed in August 2020 when the National Medical Products Administration of China approved the use of Truvada for HIV prevention. Removing this barrier should lead to more clinicians who are willing to prescribe PrEP.

The results of this survey can support the future implementation of PrEP in China. First, by determining that concerns about lack of PrEP guidelines and drug indications leads to lower likelihood of being willing to prescribe PrEP, our study suggests that China must implement and promote national PrEP guidelines. While these guidelines are currently under development, it is imperative that they are published and distributed as soon as possible [23]. Second, our finding that less experienced clinicians were less likely to prescribe PrEP, combined with previous findings that PrEP-specific training led to clinicians being more willing to prescribe PrEP, suggest that junior clinicians should attend PrEP-specific training sessions [36].

Strengths and Limitations

This study was the first survey about PrEP-related knowledge, attitudes, and experience and barriers to prescribing PrEP among Chinese clinicians. By determining barriers in prescribing PrEP that must be addressed, our work will help promote PrEP implementation in China. We also conducted an online survey and obtained responses from all 31 provinces, while previous studies have conducted surveys only in a limited geographic area.

However, our study was limited by the small sample size compared to the total number of HIV clinicians in China, and the clinicians eligible for this study were not randomly sampled from all HIV clinicians in China. We also had few participants from certain provinces; in particular, provinces in the northwest where the proportion of clinicians who self-identified ethnically as Han was low. Therefore, our results are not representative of all HIV clinicians in China. Second, because this study was cross-sectional, we could not evaluate any causal relationship between potential factors and the clinicians' willingness to prescribe PrEP. Third, as this survey was based on self-reported knowledge and attitudes toward PrEP, their subjective answers could be impacted by response bias. Fourth, while the ratio of HIV clinicians from infectious disease hospitals and from general hospitals is generally 2:1 in China, in our study, the ratio was about 1:1. This lower representation of HIV clinicians from infectious disease hospitals could lead to selection bias and make our results less representative of HIV clinicians working in infectious disease hospitals. Lastly, as HIV prevention regulations vary substantially between different countries, we cannot extrapolate our China-specific results to other countries.

Conclusions

This survey found that a high proportion of Chinese clinicians had heard of PrEP, but many had limited understanding and incorrect knowledge of PrEP. The current lack of national clinical guidelines and drug indications for PrEP may lead to clinicians being less willing to prescribe PrEP. To address these barriers, the government must publish and promote national PrEP guidelines and clinicians with limited work experience should undergo PrEP-specific training to increase and promote use of PrEP among high-risk groups and reduce the risk of HIV infections.

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Authors' Contributions

HS, JX, and HD conceived and designed the study. HD collected and cleaned the data. JX and SC analyzed the data and interpreted the results. JX, HW, WT, XH, YJ, WG, SC, ZY, and SL wrote, revised, and interpreted the study results of the manuscript. HD and SC contributed equally as first authors. JX and HS contributed equally as corresponding authors. All authors have read and approved the final manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant recruitment for the survey.
[DOCX File , 248 KB - publichealth_v7i6e24235_app1.docx]

Multimedia Appendix 2
CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist.
[DOCX File , 27 KB - publichealth_v7i6e24235_app2.docx]

Multimedia Appendix 3
English version of the study questionnaire.
[DOCX File , 28 KB - publichealth_v7i6e24235_app3.docx]

Multimedia Appendix 4
The distribution of HIV clinicians at the province level and economic level.
[DOCX File , 228 KB - publichealth_v7i6e24235_app4.docx]

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Abbreviations

aOR: adjusted odds ratio
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
MSM: men who have sex with men
OR: odds ratio
PrEP: pre-exposure prophylaxis
TDF/FTC: tenofovir disoproxil fumarate/emtricitabine
WHO: World Health Organization

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Review

The Use of Social Media in Detecting Drug Safety–Related New Black Box Warnings, Labeling Changes, or Withdrawals: Scoping Review

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Abstract

Background: Social media has become a new source for obtaining real-world data on adverse drug reactions. Many studies have investigated the use of social media to detect early signals of adverse drug reactions. However, the trustworthiness of signals derived from social media is questionable. To confirm this, a confirmatory study with a positive control (eg, new black box warnings, labeling changes, or withdrawals) is required.

Objective: This study aimed to evaluate the use of social media in detecting new black box warnings, labeling changes, or withdrawals in advance.

Methods: This scoping review adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist. A researcher searched PubMed and EMBASE in January 2021. Original studies analyzing black box warnings, labeling changes, or withdrawals from social media were selected, and the results of the studies were summarized.

Results: A total of 14 studies were included in this scoping review. Most studies (8/14, 57.1%%) collected data from a single source, and 10 (71.4%) used specialized health care social networks and forums. The analytical methods used in these studies varied considerably. Three studies (21.4%) manually annotated posts, while 5 (35.7%) adopted machine learning algorithms. Nine studies (64.2%) concluded that social media could detect signals 3 months to 9 years before action from regulatory authorities. Most of these studies (8/9, 88.9%) were conducted on specialized health care social networks and forums. On the contrary, 5 (35.7%) studies yielded modest or negative results. Of these, 2 (40%) used generic social networking sites, 2 (40%) used specialized health care networks and forums, and 1 (20%) used both generic social networking sites and specialized health care social networks and forums. The most recently published study recommends not using social media for pharmacovigilance. Several challenges remain in using social media for pharmacovigilance regarding coverage, data quality, and analytic processing.

Conclusions: Social media, along with conventional pharmacovigilance measures, can be used to detect signals associated with new black box warnings, labeling changes, or withdrawals. Several challenges remain; however, social media will be useful for signal detection of frequently mentioned drugs in specialized health care social networks and forums. Further studies are required to advance natural language processing and mine real-world data on social media.

(JMIR Public Health Surveill 2021;7(6):e30137) doi:10.2196/30137

KEYWORDS

adverse event; black box warning; detect; pharmacovigilance; real-world data; review; safety; social media; withdrawal of approval

Introduction

Clinical trials are a primary measure of the efficacy and safety of drugs before they are marketed. However, the limited number of subjects and study period makes it difficult to detect rare adverse drug reactions (ADRs) [1]. For example, 10,000 subjects are required to detect a very rare ADR (with a frequency of <1 in 10,000 individuals). More subjects are needed to obtain significant results. Furthermore, the controlled environment of clinical trials does not fully reflect the effects of different ages, comorbidities, and drug-drug interactions on ADRs in the real world. Hence, it is important to investigate the real-world data (RWD) of marketed drugs for mining ADR signals. Pharmacovigilance is defined as the science of detecting, assessing, understanding, and preventing drug-related adverse effects or problems [2]. Postmarketing surveillance studies and mining of spontaneous adverse event reporting systems are the 2 principal methods of pharmacovigilance.

In recent years, social media has become an essential part of everyday life. Social media platforms (eg, Facebook, Twitter, and patient forums) are where people share experiences and opinions. Patients use social media to increase their health knowledge and exchange advice and information [3]. Social media has become a new source of RWD on ADRs. Researchers expect social media to identify signals that conventional pharmacovigilance methods (eg, postmarketing surveillance studies and spontaneous adverse event reporting systems) have not identified or to identify signals earlier than conventional methods. In addition, social media can be monitored in real time, and adverse events caused by off-label use, unknown in clinical trials, can be detected.

Many studies have investigated the detection of early ADR signals on social media. Tricco et al [4] conducted a scoping review, which included 77 pharmacovigilance studies that used social media, from 2001 to 2016. Another review by Pappa and Stergioulas [5] qualitatively analyzed 100 pharmacovigilance studies that used social media, from 2007 to 2018. Both these reviews summarized the social media platforms used in research and data analysis methods, and the advantages and challenges of pharmacovigilance using social media. Compared to conventional pharmacovigilance methods, pharmacovigilance studies using social media are still in their infancy [4,5]. However, social media has the potential to complement existing pharmacovigilance systems [6].

The reliability of signals derived from social media is questionable [7]. Positive controls are essential for ensuring signal accuracy and verifying the usefulness of social media for mining previously unknown ADRs. Considering the purpose of pharmacovigilance, new black box warnings, labeling changes, and withdrawals are appropriate as positive controls, rather than well-known ADRs already on the drug label. Patients usually post mild and common ADRs (eg, pain or fatigue) on social media platforms; hence, testing whether mining social media data can detect significant ADRs (appearing as new black box warnings, labeling changes, or withdrawals) is necessary [8].

This scoping review aimed to determine how well social media helps detect new black box warnings, labeling changes, or withdrawals in advance.

Methods

Search Strategy

This study followed a preplanned protocol and adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist [9]. Two biomedical databases, PubMed and EMBASE, were searched to identify relevant literature. Search terms (Multimedia Appendix 1) consisted of 15 popular social networks worldwide and sites mentioned in previous scoping reviews [4,10]. There were no restrictions on publication language and publication year. The search was conducted on January 7, 2021. We searched the reference lists of relevant literature (eg, recent reviews and selected articles in this scoping review) for inclusion. Additional Google Scholar searches have been made to include grey literature. EndNote X9 (Clarivate Analytics) was used to manage the literature.

Study Selection

Two authors independently evaluated the eligibility of the studies. Articles were included if they focused on the analysis of drug safety–related new black box warnings, labeling changes, or withdrawals from social media data. Studies were excluded if they did not study new black box warnings, labeling changes, or drug withdrawals, did not use social media data (eg, data of the US Food and Drug Administration [FDA] Adverse Event Reporting System [FAERS]), or were not original articles (eg, reviews, protocols, and conference abstracts). If the same data were assessed using the same analytic method, an article that could encompass other studies was selected.

Owing to the nature of computer science research, conference proceedings that contained data were included as an exception. Unlike most other academic disciplines, computer science often considers conference proceedings as a last-resort means of reporting research findings [11]. Conference proceedings are typically between 4000 and 7000 words in length, similar to journal articles, which allows sufficient details of the study to be reported [11].

Study selection proceeded in 2 stages. First, titles and abstracts were screened for eligibility. Second, full texts were reviewed to finalize the articles for analysis. Any discrepancy between the 2 authors was resolved through discussion.

Data Extraction

Data were extracted by an author and recorded in a preprepared data extraction table. The extracted data were reviewed by other authors, and the data extraction form was continuously modified. The extracted data included article characteristics (eg, author and publication year), target social media platforms, study drugs, analytical methods, main results, and limitations mentioned by the authors.

Results Synthesis

The study results were aggregated or summarized during qualitative synthesis. Additionally, descriptive statistical analysis was conducted for the frequency and proportion of the social media platforms and analytical methods used in the studies. Social media platforms were categorized in accordance with the classification of Pappa and Stergioulas [5]: generic social networking sites (SNS) and specialized health care social networks and forums. Generic SNS include Facebook and Twitter, and specialized health care social networks and forums include generic health-centered SNS (eg, PatientsLikeMe, DailyStrength, MedHelp, and WebMD), medicine-focused sharing platforms (eg, Ask a Patient and Medications.com), and disease-specific web-based health forums.

Results

Characteristics of Selected Studies

Figure 1 shows the study selection process. We identified 75 articles from PubMed and 169 from EMBASE. Google Scholar and bibliographic searches yielded 87 and 15 studies, respectively. Through the deduplication and 2-step selection process, 14 studies were finally included in this scoping review [12-25]. Table 1 provides the details of the included studies and the social media sources used in each study.

Figure 1. Flowchart of the protocol of the scoping review.

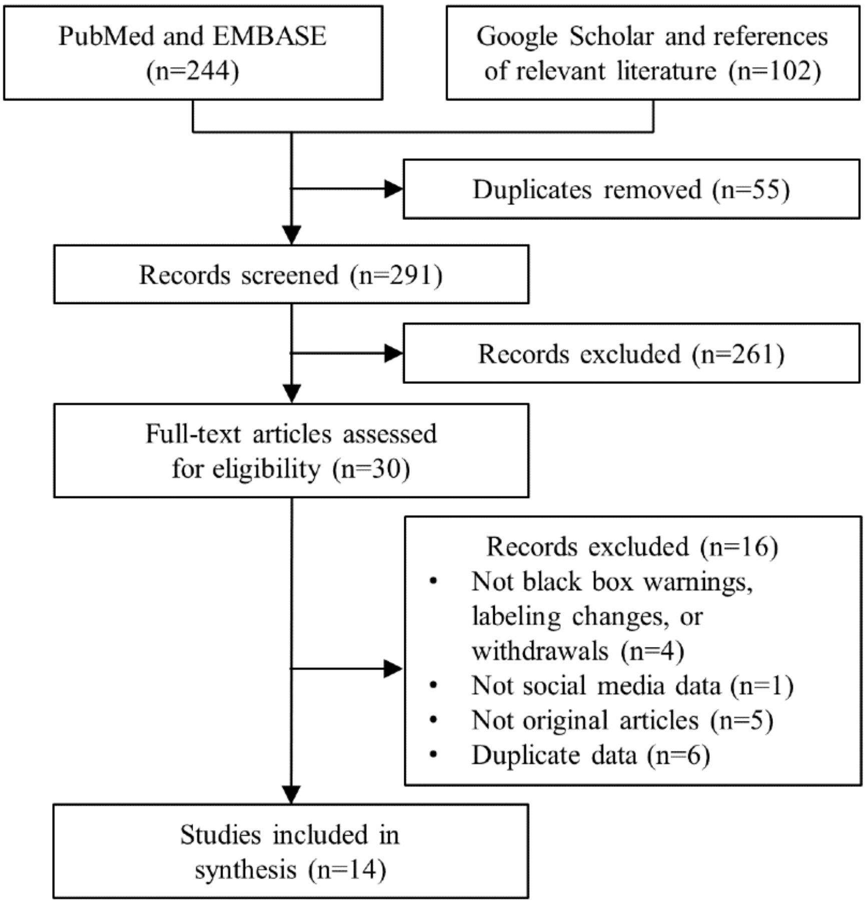


Table 1. Characteristics of social media sources.

Number	Author (year)	Social media platforms	Duration	Study drugs	Number of posts
1	Caster et al (2018) [12]	Twitter, Facebook, and 407 patient forums	March 2012-March 2015	75 drugs (Harpaz et al [26] reference set and WEB-RADR reference set)	6,279,424 posts from Twitter and Facebook (690,492 posts with an indicator score threshold of 0.4); 42,721 posts from 407 patient forums using with an indicator score threshold of 0.7
2	Pierce et al (2017) [13]	Facebook and Twitter	March 2009-October 2014	10 drugs	935,246 posts (704,283 nonspam posts)
3	Duh et al (2016) [14]	Ask a Patient	2001-2014	Sibutramine and atorvastatin	270 posts on sibutramine and 998 posts on atorvastatin
4[a]	Yang et al (2015) [15]	MedHelp	1997-2011	20 drugs with >500 threads for each	16,344 posts (8053 posts on 10 drugs that were on alert or had a revised label)
5[a]	Yang et al (2015) [16]	MedHelp	1997-2011	20 drugs with >500 threads for each	16,344 posts
6	Feldman et al (2015) [17]	MedHelp, exchanges.webmd.com, HealthBoards, and ehealthforum.com	1999-2013	Cholesterol-lowering drugs and antidepressants	41,086 posts for cholesterol-lowering drugs and 273,990 for antidepressants
7	Coloma et al (2015) [18]	Facebook, Google+, and Twitter	Until September 2014	Rosiglitazone	2537 posts related to rosiglitazone and cardiovascular events
8	Patki et al (2014) [19]	DailyStrength	—[b]	20 normal and 18 black box drugs[c]	20,486 posts (normal: 10,399, black box: 7327, withdrawn: 2760)
9	Abou Tamm et al (2014) [20]	Three French websites (Doctissimo, Atoute.org, and Vivelesrondes)	—	Benfluorex	220 initial posts and 660 secondary posts
10	Adjeroh et al (2014) [21]	Twitter and general web search queries	2008-2012	46 drugs that had a Food and Drug Administration alert	2 million posts on Twitter
11	Wu et al (2013) [22]	Online discussions using forum search engines such as Google Discussion Search	2000-2011	4 drugs	178,871 posts
12	Liu et al (2013) [23]	Diabetes patient forum	February 2009-November 2012	Antidiabetic drugs	185,874 posts
13	Chee et al (2011) [24]	Yahoo Groups	—	Not prespecified	Not mentioned[d]
14	Chee et al (2009) [25]	Yahoo Groups	—	Natalizumab, rofecoxib, and celecoxib	20,000 posts on natalizumab and 867,659 posts on rofecoxib and celecoxib

[a] Same data but different analytical methods were used.

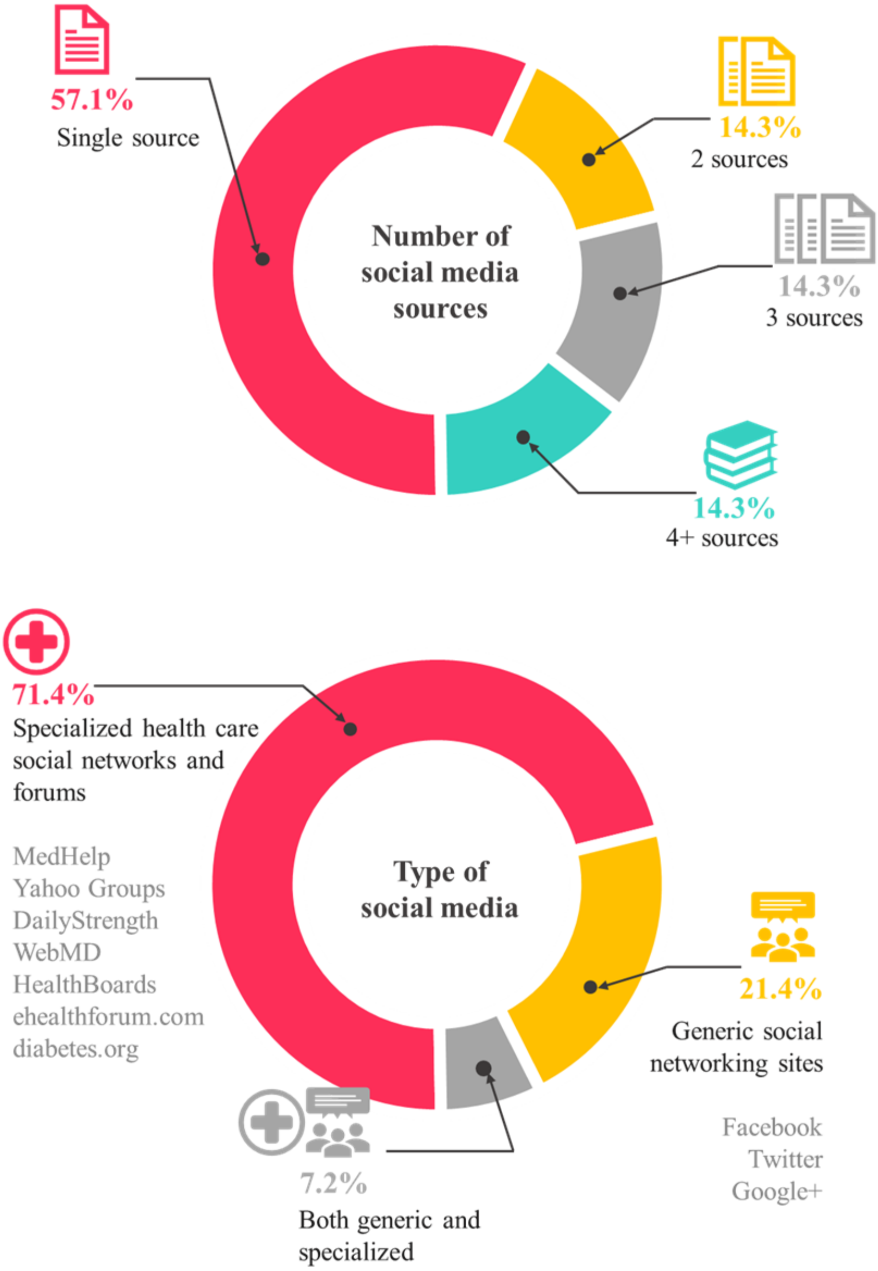
[b] —: data not available.

[c] The number of drugs withdrawn was not mentioned.

[d] There is a total of 12,519,807 messages in 27,290 public Health & Wellness Yahoo! groups.

Figure 2 shows the number and type of social media sources. Most studies (n=8 of 14, 57.1%) collected data from a single source. Meanwhile, Caster et al [12] collected posts from Twitter, Facebook, and 407 patient forums. Specialized health care social networks and forums were used in 10 (71.4%) studies, and 3 (21.4%) studies used generic SNS. MedHelp (n=4 of 14, 28.6%), Twitter (n=4 of 14, 28.6%), Facebook (n=3 of 14, 21.4%), and Google (n=3 of 14, 21.4%) were frequently used sites.

Figure 2. Number and type of social media sources.

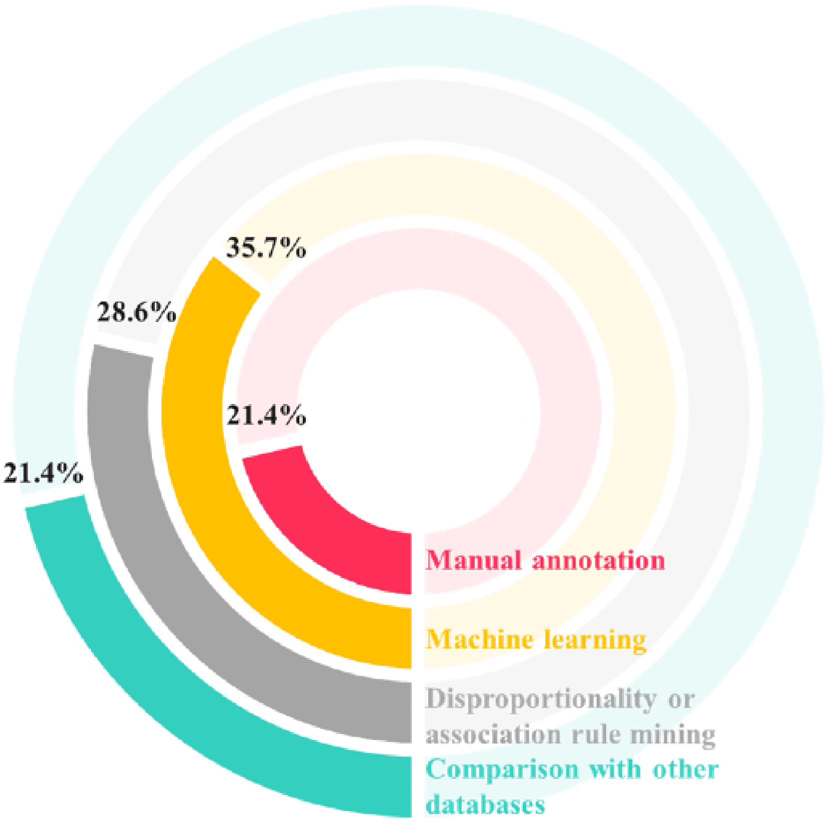


The number of posts collected varied from hundreds to tens of millions according to the type of sources and study drugs (Table 1). Studies using generic SNS platforms collected a relatively large number of posts compared to those using specialized health care social networks and forums. However, the large volume of posts collected on generic SNS are noisy and difficult to process [5]. For example, Pierce et al [13] sampled 935,246 posts that named 10 selected drugs from Facebook and Twitter over 5.5 years. Among them, 98,252 posts resembled adverse events (Proto-AEs), and only 6 posts described certain, probable, and possible cases of interest [13]. Yang et al [15] collected 8053 posts that named 10 drugs over 4 years on MedHelp.

Methods Used for Detecting New Black Box Warnings, Labeling Changes, or Withdrawals

The analytical methods used in the studies varied considerably. Figure 3 indicates the analytical methods used in each study (Multimedia Appendix 1). Three (21.4%) studies conducted by Duh et al [14], Coloma et al [18], and Abou Taam et al [20] manually annotated posts for the presence or absence of selected adverse events. After manual annotation, a time-series analysis or frequency analysis was conducted. This analysis was possible because the number of posts used in these 3 studies ranged from hundreds to thousands. However, this analytical method is difficult to implement with a higher number of posts.

Figure 3. Analytical methods in the studies included in this scoping review.



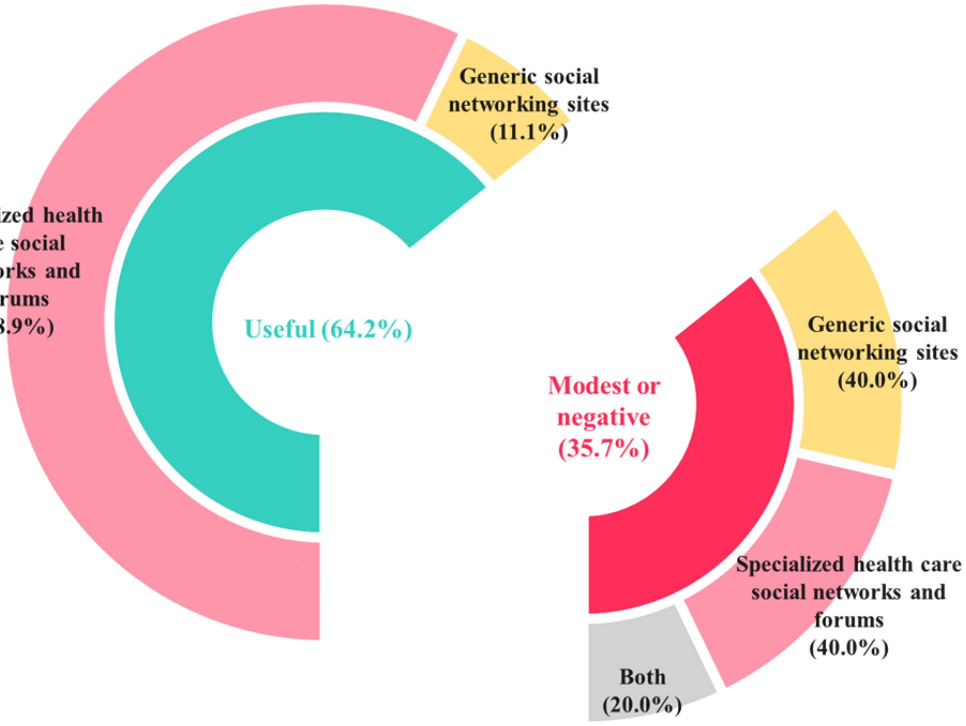
Five (35.7%) studies adopted machine learning algorithms for detecting ADRs from social media. Feldman et al [17] utilized an unsupervised relation extraction for mining drug-ADR relations. Patki et al [19] used machine learning algorithms for the binary classification of social media posts as ADR or non-ADR. Liu et al [23] used a kernel-based learning method to extract adverse events in patient forums and then used semisupervised learning algorithms to classify report sources into patients' experiences or not. Chee et al [24] used machine learning algorithms to classify drugs as watchlist and nonwatchlist drugs. Pierce et al [13] used automated classifiers that identified Proto-AEs and then manually reviewed the cases and assessed causality.

Caster et al [12] conducted a disproportionality analysis to detect signals and compared the area under the receiver operating characteristic curve with a World Health Organization global pharmacovigilance database (VigiBase database). Yang et al [15], Yang et al [16], and Feldman et al [17] computed a lift measure for association rule mining to evaluate the likelihood of a particular drug-ADR relationship. Other methods include a tensor-based technique [16], discriminative classification and generative modeling [22], sentiment analysis [25], and peak-labeling signal fusion [21].

Detection Performance

Nine (64.2%) studies reported that social media monitoring allowed for the detection of black box warnings, labeling changes, or withdrawals 3 months to 9 years in advance [14-17,20-24]. Most (88.9%) of these studies were conducted on specialized health care social networks and forums (Figure 4). One post that mentioned the occurrence of benfluorex (Mediator)-cardiac valvulopathy in a woman was posted in a patient forum 7 months before withdrawal [20]. Chee et al [24] identified 4 drugs (hydromorphone [proprietary name: Palladone], cerivastatin [Baycol], trovafloxacin [Trovan], and rofecoxib [Vioxx]) that were withdrawn by analyzing Yahoo Groups. Furthermore, posts related to sibutramine, which was not a watchlist drug at the time of the study but was later withdrawn owing to the risk of cardiac arrest and stroke, were observed more than a year ago [24]. Sibutramine was the fifth-highest-risk drug in the study [24]. In Duh et al's [14] study on sibutramine, social media mentions of sibutramine-related cardiac issues helped predict those in FAERS 11 months later. In a study by Adjeroh et al [21], 30 of 46 (65.2%) drugs were detectable prior to FDA alert. Depending on the drug, adverse events could be detected 3 months (fluvastatin [Lescol]) to 35 months (codeine and atorvastatin [Lipitor]) before the FDA alert [21]. Wu et al [22] reported that the discussion frequency of arrhythmia due to propoxyphene/acetaminophen (Darvocet obviously exceeded the threshold since 2006, 4 years before the drug's recall. Adverse events of 3 other drugs, namely simvastatin (Zocor) drospirenone/ethinyl estradiol (Yaz and Yasmin), were also detected 4-6 years prior to FDA action [22]. Yang et al [15] and Yang et al [16] analyzed the same data by association rule mining and the tensor-based technique. Association rule mining detected 6 of 14 ADRs, which included fluoxetine (Prozac)–induced suicidal thoughts (1 year in advance), methylphenidate (Concerta)–induced blurred vision (2 years in advance), fluoxetine (Prozac)–induced depression (5 years in advance), fluvoxamine (Luvox)–induced suicidal thoughts (5 years in advance), simvastatin–induced kidney disease (6 years in advance), and lansoprazole-induced diarrhea (13 years in advance) [15]. The tensor-based technique allowed more ADRs (11 of 14) to be detected 1-7 years earlier than association rule mining [16]. Feldman et al [17] reported that unsupervised relation extraction from web-based forums identified statin-induced cognitive impairment (labeling changes in 2012) as early as 9 years prior to the FDA label change. In the same study, Feldman et al [17] identified a significant relationship between bupropion (Wellbutrin) and agitation 7 years before FDA action. AZDrugMiner, developed by Liu et al [23], could detect rosiglitazone (Avandia)–induced myocardial infarction (18% of adverse events) and cardiac disorder (13% of adverse events) at high frequency from patient forums.

Figure 4. Perspectives on pharmacovigilance using social media and sources of social media.



Five (35.7%) studies reported modest or negative results. Of these, 2 (40%) used generic SNS, and 1 (20%) used generic SNS and specialized health care social networks and forums (Figure 4). Caster et al [12] reported that signal detection in social media performed poorly and was not recommended. The area under the receiver operating characteristic curve of social media varied between 0.47 and 0.53 for the reference sets, while that of VigiBase ranged between 0.64 and 0.69 [12]. On Twitter and Facebook, only 16% and 6% of positive controls were detected before their index dates in the WEB-RADR and Harpaz references, respectively [12]. In a study by Pierce et al [13], proto-AEs were observed for only 2 of 10 drugs studied. Dronedarone-induced vasculitis reported by the FDA in April 2012 was indicated on social media in December 2010. However, as FAERS received its first report in July 2010, social media was 5 months late [13]. Only 1 positive signal was identified on social media before FAERS. The correlation between Banana Boat sunscreen and skin burns was observed on social media on June 2, 2012, and the FAERS first report appeared 17 days later [13]. Coloma et al [18] reported that the number of posts on rosiglitazone-induced cardiovascular events tended to increase with regulatory action. However, only 10 of 2537 posts described personal experiences of rosiglitazone-induced cardiovascular events. Patki et al [19] classified posts with or without ADR and classified the drugs as black box or normal drugs on the basis of the number of ADR-related posts. The classifier for black box drugs revealed a modest F-score of 0.6 [19]. Levofloxacin (Levaquin) and baclofen were misclassified as normal drugs because the number of posts was small, and the posts mainly referred to usefulness and not ADRs [19].

Challenges

Table 2 categorizes the study limitations. There are currently several challenges associated with the use of social media for pharmacovigilance in terms of social media coverage, data quality, and analytic processing.

Table 2. Challenges associated with the use of social media for pharmacovigilance.

Challenges	References
Coverage	
Limited social media coverage (generalizability to other data sources)	[12-14,18]
Lack of user population representation	[18]
Not a balanced coverage of all drugs and medical conditions	[14,18,24]
Limited coverage period	[12,14]
Data quality	
Use of colloquial language: misspellings or use of nonmedical terms and slang	[13,15,16]
Data duplication (double-counting)	[13,14]
Lack of medical and demographic information	[14]
Lack of causality information	[25]
Nonvalidated or incomplete data or misinformation	[14]
Low signal-to-noise ratio	[12,14,18,19,25]
Processing	
Curation burden due to data volume	[13]
Word-level analysis or does not reach semantic or discourse levels	[15,18,22-24]

Different types of social media platforms have different user characteristics and types of data. Since studies have been conducted on limited social media platforms, analytical methods that were applicable to one platform may not be suitable on another platform. Typically, younger individuals use social media; therefore, adverse events that occur mainly in older people or those associated with drugs used for geriatric diseases can be underestimated. Data obtained from patient forums tend to be biased toward specific patients or drugs.

The low signal-to-noise ratio of the data makes the preprocess and analytical process burdensome. Social media, of course, is noisier than databases that collect only adverse drug events. In particular, the number of posts on generic social networking sites that are unrelated to adverse events is much higher than that of specialized health care social networks and forums.

There are extensive social media data to classify manually, but an understanding of natural language has not yet reached human levels. Nonetheless, many studies analyzed whether drug and adverse event–related terms are in the same sentence or post.

Discussion

Principal Findings

As interest in the use of social media in pharmacovigilance has increased, there have been steadily review papers on pharmacovigilance using social media. Most of the reviews focused on the data sources or analytical methods used in individual studies. Positive controls have allowed us to assess whether social media can detect significant unknown signals. A recent review [27] summarized studies that determined whether signals can be detected through social media before the actions of regulatory authorities. In this scoping review, we reviewed 14 studies on the application of social media in detecting new black box warnings, labeling changes, or withdrawals. Some studies in our review are not included in other previous reviews such as the one by Caster et al, who expressed a negative opinion. Our scoping review has the advantage of being the most state-of-the-art review that analyzed detection performance (eg, time interval between signals detected on social media and regulatory authority action).

Most studies have reported that meaningful signals could be detected before regulatory authorities take action. Signals were identified 3 months to 9 years in advance on social media, depending on social media sources and drug-ADR pairs. Most studies that have reported the usefulness of social media have used specialized health care social networks and forums. These sources have more patient experiences while fewer unrelated posts, which have helped overcome the disadvantages of low signal-to-noise ratios. Therefore, specialized health care social networks and forums are suitable sources for pharmacovigilance using social media. Furthermore, drugs such as benfluorex, sibutramine, drospirenone/ethinyl estradiol, methylphenidate, and fluoxetine, which may interest social media users, have yielded favorable outcomes.

A recent study by Caster et al [12], which used a large number of social media platforms, revealed a poor performance. Study drugs were not actively included on social media in their study. The detection performance of social media varies depending on the study drug, and social media–based pharmacovigilance will be useful for restrictive drugs. Thus, an approach to select drugs to monitor adverse events with social media will need to be developed. Differences in reference sets and statistical analysis also explain why Caster et al's findings differed from those of other studies. The study used the WEB-RADR reference (independent of regulatory action) as well as the Harpaz reference (based on FDA labeling changes). Disproportionality analysis, which is commonly used for signal detection in spontaneous adverse event–reporting systems, was used instead of other methods tailored to the analysis of social media. The results of a pilot study conducted in 2018 are in line with those of the study by Caster et al [12]. Studies have reported 6 proto-AEs on Twitter and patient forums that meet the criteria for disproportionality [7]. Five of 6 selected adverse events were observed a median of 252 (range 144-367) days later on social media [7]. Negative views in recent studies have made the application of social media hesitant. We eagerly anticipate the results of the Adverse Drug Reactions from Patient Reports in Social Media study, which is currently underway in France [28].

Several challenges are associated with the use of social media for pharmacovigilance. Studies have reported a coverage problem, which makes their findings difficult to generalize. Therefore, pharmacovigilance cannot be entirely dependent on social media, but rather social media can be used to supplement existing pharmacovigilance measures. The challenges of low signal-to-noise ratios and word-level analysis might be resolved by enhancing natural language processing (NLP) and machine learning algorithms. While there have been recent rapid advances, computers still cannot fully understand human language at a semantic or discourse level. NLP techniques will need further improvements to meaningfully analyze the vast amount of RWD in social media.

Limitations

This study has several limitations. First, while there was no restriction on the language of the papers retrieved from PubMed and EMBASE and references to related papers were searched, there may still be studies that we missed. Second, social media platforms that were widely used or derived from previous reviews were used as search terms. Therefore, we may have possibly missed information on minor social media platforms. Lastly, this is a rapidly developing field. Although we updated our search before submission, new studies may be published as of this publication. In particular, the Adverse Drug Reactions from Patient Reports in Social Media study is ongoing; hence, our results will need to be updated.

Conclusions

Social media, along with conventional pharmacovigilance measures, can be used to detect signals associated with new black box warnings, labeling changes, or withdrawals. Several challenges remain; however, social media will be useful for signal detection for frequently mentioned drugs in specialized health care social networks and forums. Further studies are required to advance NLP and mine RWD on social media.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary Tables. Table 1: Search terms. Table 2: Analytical methods.
[DOCX File , 22 KB - publichealth_v7i6e30137_app1.docx]

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Abbreviations

ADR: adverse drug reaction
FAERS: FDA Adverse Event Reporting System
FDA: Food and Drug Administration
NLP: natural language processing
Proto-AEs: posts that resembled adverse events
RWD: real-world data
SNS: social networking site

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Original Paper

Incorporating Unstructured Patient Narratives and Health Insurance Claims Data in Pharmacovigilance: Natural Language Processing Analysis of Patient-Generated Texts About Systemic Lupus Erythematosus

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Abstract

Background: Gaining insights that cannot be obtained from health care databases from patients has become an important topic in pharmacovigilance.

Objective: Our objective was to demonstrate a use case, in which patient-generated data were incorporated in pharmacovigilance, to understand the epidemiology and burden of illness in Japanese patients with systemic lupus erythematosus.

Methods: We used data on systemic lupus erythematosus, an autoimmune disease that substantially impairs quality of life, from 2 independent data sets. To understand the disease's epidemiology, we analyzed a Japanese health insurance claims database. To understand the disease's burden, we analyzed text data collected from Japanese disease blogs (tōbyōki) written by patients with systemic lupus erythematosus. Natural language processing was applied to these texts to identify frequent patient-level complaints, and term frequency–inverse document frequency was used to explore patient burden during treatment. We explored health-related quality of life based on patient descriptions.

Results: We analyzed data from 4694 and 635 patients with systemic lupus erythematosus in the health insurance claims database and tōbyōki blogs, respectively. Based on health insurance claims data, the prevalence of systemic lupus erythematosus is 107.70 per 100,000 persons. Tōbyōki text data analysis showed that pain-related words (eg, pain, severe pain, arthralgia) became more important after starting treatment. We also found an increase in patients' references to mobility and self-care over time, which indicated increased attention to physical disability due to disease progression.

Conclusions: A classical medical database represents only a part of a patient's entire treatment experience, and analysis using solely such a database cannot represent patient-level symptoms or patient concerns about treatments. This study showed that analysis of tōbyōki blogs can provide added information on patient-level details, advancing patient-centric pharmacovigilance.

(JMIR Public Health Surveill 2021;7(6):e29238) doi:10.2196/29238

KEYWORDS

social media; adverse drug reaction; pharmacovigilance; text mining; systemic lupus erythematosus; natural language processing; NLP; lupus; chronic disease; narrative; insurance; data; epidemiology; burden; Japan; patient-generated

Introduction

Pharmacovigilance, monitoring drugs during their product lifecycle to detect, assess, understand, and prevent adverse effects or other problems [1], is facing a challenge in refining its systems and regulations to accommodate increasing data volume and advancing data analysis techniques. A recent report suggests that it is necessary to broaden the scope of pharmacovigilance to enhance patient care and safety [2]. Since modern pharmacovigilance activities rely heavily on clinicians and upon the pharmaceutical industry, information on disease burden and psychology at the patient level is often difficult to capture from health care databases [3], though these patient data are essential for understanding disease.

To expand the scope of pharmacovigilance to patients' viewpoints, it is necessary to include data sources that can be used to analyze patient situations. Several studies [4-6] have explored the use of web-based resources such as Twitter in pharmacovigilance to include patients' viewpoints. Similarly, in Japan, we previously examined Japanese-language disease blogs (*tōbyōki*) as a resource for patient-generated data from the internet to augment pharmacovigilance [7]. In these blogs, we found that patients share information about adverse events, drugs, and distress due to adverse events. Such information can improve our understanding of disease epidemiology, treatment status, and burden by providing details that cannot be captured by existing health care data sources.

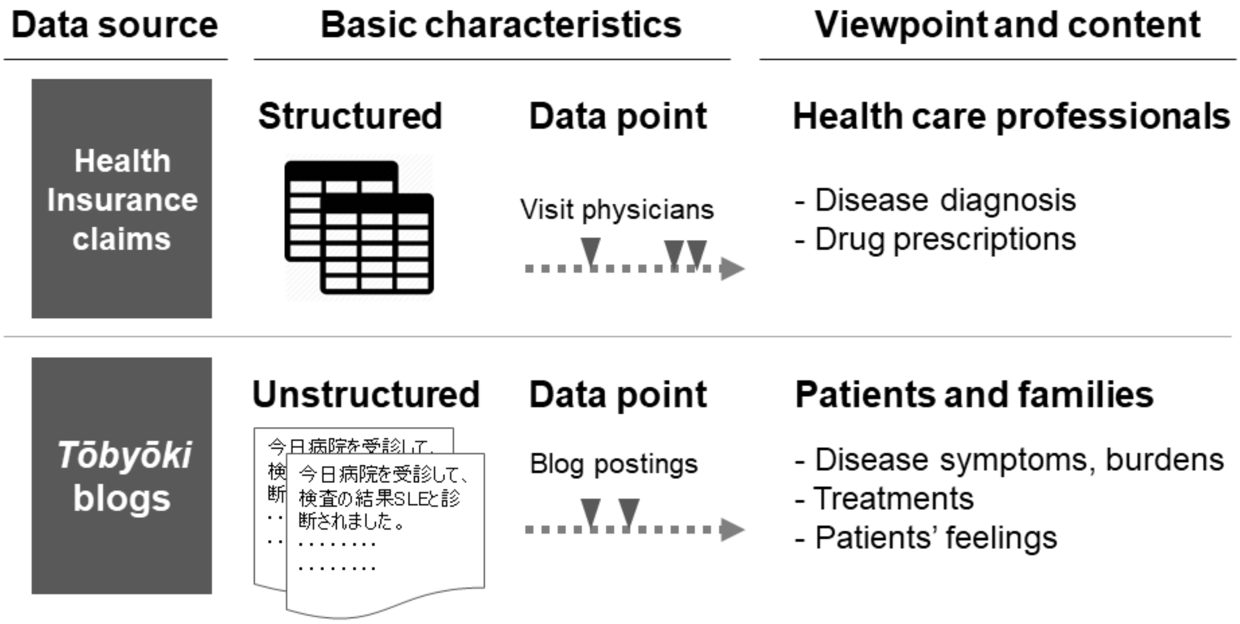
Although several studies [4,8] have reported the utility of patient-derived data from the web for pharmacovigilance, concern over the effect of irrelevant data (ie, noise) has led some researchers to recommend that these data alone should not be used to derive pharmacovigilance statistics [9]. Using data from additional sources is one way to minimize this effect. We believe that this methodology is important to achieve patient-centric pharmacovigilance, particularly in areas where disease management requires an understanding of both epidemiology and burden from patients' perspectives.

Systemic lupus erythematosus is a complex, autoimmune disease; information from multiple sources should be considered in disease management. In Japan, limited epidemiological information on systemic lupus erythematosus is available [10]. Systemic lupus erythematosus has been reported to impair quality of life [11], and patients with systemic lupus erythematosus have suggested that the most important topics to consider in disease management are strengthening well-being and minimizing disease burden [12]. The objective of this study was to examine the value of the combined analysis of patient-derived text data and health care professional–derived data, in conjunction with natural language processing techniques, in implementing patient-centric pharmacovigilance for systemic lupus erythematosus.

Methods

To understand epidemiology, treatments, and disease burden in patients with systemic lupus erythematosus, we analyzed 2 independent data sets: health insurance claims data and *tōbyōki* blog data. Each data set has its own advantages, therefore, using both provides greater insight on the epidemiology and burden of the disease (Figure 1). In this study, it was necessary to use each database according to its strengths; therefore, the analyses and results are presented separately for each point of focus.

Figure 1. For each data source used in this study—health insurance claims data or tōbyōki blogs—basic characteristics such as data structures, data points, and contents are shown.



Ethics Statement

The study protocol was reviewed and approved by the Research Institute of Healthcare Data Science (RI2018008). The board waived informed consent because the data sources do not contain identifying information.

Data Sources

Health Insurance Claims Data

We analyzed a Japanese health insurance claims database (JMDC Inc), which contains data from more than 3 million individuals enrolled in the database as of 2015. Patient data from January 1, 2015 to December 31, 2016 were extracted. International Classification of Diseases tenth revision [13] (ICD-10) codes were used to identify data from patients with systemic lupus erythematosus (ICD-10 code: M32); those with at least 2 claims with code M32, each in a different month, were extracted [10].

Tōbyōki Blog Data

As reported previously [7], we used a database of anonymous, publicly available *tōbyōki* blogs maintained by Initiative Inc. *Tōbyōki* is translated as *a diary-like account of a struggle with disease*. Each *tōbyōki* blog was manually checked to judge whether it was a *tōbyōki* blog or an irrelevant blog. *Tōbyōki* blogs were then manually tagged by disease (systemic lupus erythematosus or lupus nephritis) based on the blog's title or introduction page. *Tōbyōki* blogs written in Japanese by patients with systemic lupus erythematosus or lupus nephritis between January 1, 2010 and February 7, 2018 were included in this study. To protect patient anonymity [14], all analysis results were output as summarized data and not individual-level data.

Prevalence and Incidence of Systemic Lupus Erythematosus

Health Insurance Claims Data

Using the health insurance claims data, we identified patients with prevalent systemic lupus erythematosus, defined as systemic lupus erythematosus diagnosed between January 1, 2015 and December 31, 2016, and calculated the overall prevalence (with 95% CI), as well as by age and by gender. We also estimated the incidence (with 95% CI) by calculating the number of patients with incident systemic lupus erythematosus, defined as an initial diagnosis between January 1, 2015 and December 31, 2016 (no systemic lupus erythematosus diagnosis in the preceding 12 months) divided by the total population during both years.

Systemic Lupus Erythematosus Treatments

Health Insurance Claims Data

Data from patients with systemic lupus erythematosus was used to identify medications during patients' follow-up periods. Medications were coded according to the Anatomical Therapeutic Chemical classification system [15] or procedure codes, and data were summarized descriptively.

Tōbyōki Blog Data

Unstructured text written by patients was deconstructed into words using morphological analysis. Drug names mentioned in blogs were analyzed and summarized descriptively.

Patient Complaints of Disease-Specific Symptoms

Health Insurance Claims Data

Symptom outcomes cannot be obtained from health insurance claims data.

Tōbyōki Blog Data

We explored patients' skin abnormality and photosensitivity symptoms, which are characteristics of systemic lupus erythematosus [11]. Symptom terms were identified by corpus-based morphological analysis and summarized descriptively. We also performed word co-occurrence network analysis, as described previously [7], to map the occurrence of words in conjunction with specific known symptoms of systemic lupus erythematosus.

Pain and Health-Related Quality of Life

Tōbyōki Blog Data

We assumed that *tōbyōki* blogs would contain descriptions of patients' experiences and burdens during systemic lupus erythematosus treatment, which are difficult to assess using existing health care databases. To uncover such information from patients' narratives, we applied natural language processing techniques. First, because we assumed that the first mention of a drug was the closest to the time the drug was prescribed, we identified those that contained mentions of typical drug therapies for systemic lupus erythematosus by searching the content of each blog. Then, we identified blogs that included any information from both before and after mentioning therapy for systemic lupus erythematosus by manually reviewing the blog contents to explore longitudinal changes and patient characteristics.

The number of pain-related words used in relation to systemic lupus erythematosus treatments was analyzed; term frequency–inverse document frequency (TF-IDF) analysis was conducted, which assigns a weight to each term based on the frequency of its occurrence in the document, to highlight the word characteristics for each text; a higher score may indicate that the term x is important for the document y.

where $TF_{x,y}$ represents the frequency of term x in document y, df_x represents the number of documents containing term x, and N represents the total number of documents.

We also sought to explore information on health-related quality of life from the unstructured patient narratives using the EQ-5D-5L questionnaire (EuroQol Group), which is a widely used validated instrument, consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), for assessing health-related outcomes in both the general population and patients [16]. Based on the Japanese version of the EQ-5D-5L questionnaire [17], each dimension's questionnaire items were manually reviewed to identify terms for that dimension. For instance, in the mobility dimension, for the statement "I have no problems in walking about," we identified the terms "mobility" and "walking." We (authors TO, ST, YM, MM, HK, and SW) independently identified related words, and discrepancies in the results were resolved by discussion.

Data Analysis Tools

SAS software (version 9.4; SAS Institute) was used for data analysis. To process the unstructured text, we performed morphological analysis using MeCab [18], an open-source Japanese segmentation tool. Morphological analysis is commonly conducted to delimit words in text in which words are not separated by spaces, which is a characteristic of the Japanese language. R statistical software (version 3.6.2; The R Foundation) was used for text mining and data visualization.

Results

Study Population Characteristics

We analyzed health insurance claims data from 4694 patients with systemic lupus erythematosus and *tōbyōki* blog data from 671 patients with systemic lupus erythematosus. Health insurance claims data showed that systemic lupus erythematosus was more prevalent in females than in males (Table 1). More *tōbyōki* blog entries were written by females (634/671 patients, 94.5%) than by males (36/671 patients, 5.4%). The age distribution of patients represented in *tōbyōki* blogs was younger than that of patients represented by the health insurance claims data.

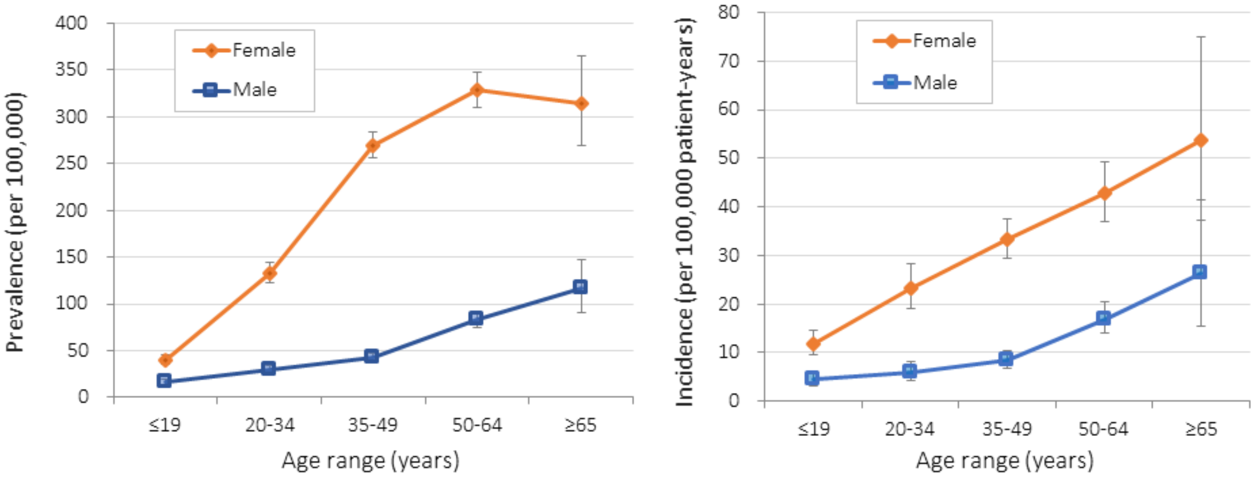
Table 1. Patient characteristics.

Age category	Health insurance claims data			*Tōbyōki* blog data			
	Total, n (%)	Male, n (%)	Female, n (%)	Total, n (%)	Male, n (%)	Female, n (%)	Unknown, n (%)
All	4694 (100)	994 (100)	3700 (100)	671 (100)	36 (100)	634 (100)	1 (100)
≤19 years old	275 (5.9)	86 (8.7)	189 (5.1)	125 (18.6)	5 (13.9)	120 (18.9)	0 (0.0)
20-34 years old	449 (9.6)	123 (12.4)	326 (8.8)	233 (34.7)	15 (41.7)	218 (34.4)	0 (0.0)
35-49 years old	2175 (46.3)	337 (33.9)	1838 (49.7)	71 (10.6)	6 (16.7)	65 (10.3)	0 (0.0)
50-64 years old	1557 (33.2)	379 (38.1)	1178 (31.8)	5 (0.7)	0 (0.0)	5 (0.8)	0 (0.0)
≥65 years old	238 (5.1)	69 (6.9)	169 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	237 (35.3)	10 (27.8)	226 (35.6)	1 (100)

Prevalence and Incidence of Systemic Lupus Erythematosus

Using health insurance claims data, we found that the overall prevalence of systemic lupus erythematosus was 107.70 per 100,000 persons and was 4.4 times higher for females than that for males; females had a higher prevalence than males in all age groups (Figure 2). Similarly, the overall incidence of systemic lupus erythematosus was 16.86 per 100,000 person-years, and the incidences for all age ranges were higher for females than those for males.

Figure 2. (A) Prevalence and (B) incidence of systemic lupus erythematosus for each age range, stratified by sex. Error bars represent 95% confidence intervals.



Systemic Lupus Erythematosus Treatments

Based on health insurance claims data, immunosuppressants, such as oral corticosteroids, and disease-modifying antirheumatic drugs were drugs frequently prescribed to patients with systemic lupus erythematosus (Table 2). Similarly, steroids, disease-modifying antirheumatic drugs, immunosuppressants, and therapeutic agents for osteoporosis were identified most frequently as drugs that patients mentioned (at least once) in *tōbyōki* blog data.

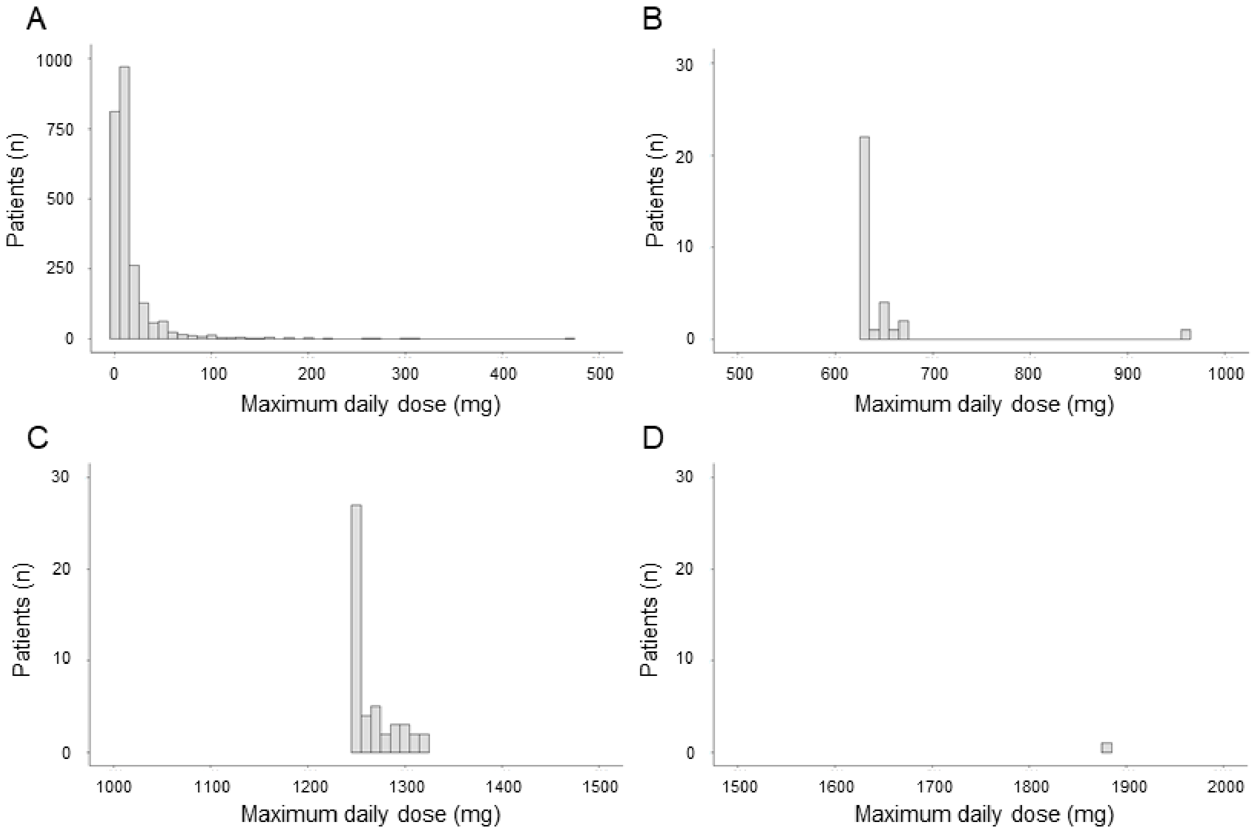
Table 2. Systemic lupus erythematosus drug treatments.

Drug treatments	Patients, n (%)
Health insurance claims data (EphMRA ATC[a] classification of drug [code])	
All patients	4694 (100)
Oral corticosteroids, plain [H02A2]	2529 (53.9)
Proton pump inhibitors [A02B2]	1622 (34.6)
Antirheumatics, nonsteroidal plain [M01A1]	1432 (30.5)
All other antiulcerants [A02B9]	1333 (28.4)
Other immunosuppressants [L04X-]	1266 (27.0)
Bisphosphonates for osteoporosis and related disorders [M05B3]	1224 (26.1)
Vitamin D [A11C2]	1129 (24.1)
Nonnarcotics and antipyretics [N02B-]	1089 (23.2)
Topical antirheumatics and analgesics [M02A-]	1083 (23.1)
Systemic antihistamines [R06A-]	1023 (21.8)
Plain topical corticosteroids [D07A-]	891 (19.0)
Statins (HMG-CoA reductase inhibitors) [C10A1]	771 (16.4)
H2 antagonists [A02B1]	745 (15.9)
Expectorants [R05C-]	738 (15.7)
Angiotensin-II antagonists, plain [C09C-]	731 (15.6)
***Tōbyōki* blog data (generic name of drug)**	
All patients	671 (100)
Steroid	499 (74.4)
Prednisolone	470 (70.0)
Loxoprofen sodium hydrate	220 (32.8)
Tacrolimus hydrate	190 (28.3)
Alendronate sodium hydrate	114 (17.0)
Aspirin	109 (16.2)
Acetaminophen	104 (15.5)
Lidocaine, Adrenaline bitartrate	101 (15.1)
Cyclophosphamide hydrate	99 (14.8)
Azathioprine	93 (13.9)
Alfacalcidol	89 (13.3)
Aztreonam	88 (13.1)
Calcium L-aspartate hydrate	83 (12.4)
Cyclophosphamide hydrate	82 (12.2)
Mycophenolate mofetil	80 (11.9)

[a] Anatomical Therapeutic Chemical classification.

For the steroids that, based on both data sets, were frequently used as treatments, we analyzed dose information using health insurance claims data (Figure 3). Among 2604 patients with systemic lupus erythematosus who had at least 1 prescription record for any steroid, 634 patients (24.3%) were prescribed 20 mg or more a day prednisone equivalent, 1844 patients (70.8%) were prescribed less than 20 mg, and 125 patients (4.8%) were prescribed an unidentified dose. The distribution of steroid dosages exhibited 3 peaks: the first, at 0.5-100 mg/day, seemed to represent maintenance therapy and the second and third peaks, at 625-675 mg/day and 1250-1325 mg/day, respectively, seemed to represent steroid pulse therapy.

Figure 3. Distribution of the maximum daily dose of steroids: (A) 0-500 mg, (B) 500-1000 mg, (C) 1000-1500 mg, and (D) 1500-2000 mg.



Patient Complaints of Disease-Specific Symptoms

Patient-level complaints that are not necessarily recognized as disease names cannot be derived from health insurance claims data. Symptoms that commonly present with systemic lupus erythematosus, such as “pain” and “feeling tired,” and some disease-specific symptoms, such as “moon face” and “arthralgia,” appeared frequently in blog text (Table 3). “Anxiety” and “stress,” which are neuropsychiatric symptoms associated with systemic lupus erythematosus, also frequently appeared. In addition, some terms representing conditions in patients’ lives, such as “pregnancy” (276/671, 47%) and “miscarriage” (69/671, 10%), appeared.

Table 3. Symptoms of systemic lupus erythematosus identified from tōbyōki blog data.

Symptoms mentioned in *Tōbyōki* blog data[a]	Patients, n (%)
All patients	671 (100)
Pain	508 (75.7)
Symptom	504 (75.1)
Anxiety	498 (74.2)
Adverse drug reaction	495 (73.8)
Stress	467 (69.6)
Aggravation	430 (64.1)
Appetite	416 (62.0)
Headache	389 (58.0)
Shock symptom	386 (57.5)
Feeling tired	382 (56.9)
Recovery	354 (52.8)
Feeling itchy	326 (48.6)
Cough	322 (48.0)
Inflammation	297 (44.3)
Feeling abnormal	296 (44.1)
Swelling	296 (44.1)
Nausea	296 (44.1)
Moon face	295 (44.0)
Arthralgia	292 (43.5)
Slight fever	292 (43.5)

[a] Number of patients who described each symptom at least once in their tōbyōki blog.

We also conducted word co-occurrence network analysis to understand the characteristics of photosensitivity and erythema, which are 2 symptoms that are specific to systemic lupus erythematosus. In the word co-occurrence network analysis for photosensitivity (Figure 4), "photosensitivity" and "sunlight," which were prespecified as central terms, were included in subgraph02 and subgraph04, respectively. Comorbid diseases and symptoms such as "Raynaud's phenomenon," "symptom," "deterioration," "headache" and "stressed" were observed. Other subgraphs did not connect directly; they included terms primarily related to "sunlight," such as "sun protection goods" (subgraph01: "parasol," "long sleeve," "hat," etc), "sun protection and symptoms" (subgraph03: "itching," "rash," "sunglasses," "hoodie," etc), "sun protection (location)" (subgraph05: "shadow," "location," etc), and "positive feeling" (subgraph06: "feeling," "good," "best," "cloudy," "indoor," etc). The co-occurrence network of "erythema" (Figure 5) showed some symptoms as subgraphs. We classified subgraph themes as (1) skin and its color; (2) photosensitivity and its prevention; (3) symptoms of erythema; (4) cheeks; (5) degree and location of skin symptoms; (6) general symptoms of systemic lupus erythematosus; (7) itching; (8) appearance of hand, foot, and skin; (9) face and mouth symptoms; (10) other symptoms (moon face, fever, etc); and (11) timing of skin symptoms.

Figure 4. Network of words co-occurring with photosensitivity in tōbyōki blogs of patients with systemic lupus erythematosus. Because the original language of the blogs is Japanese, English translations are shown.

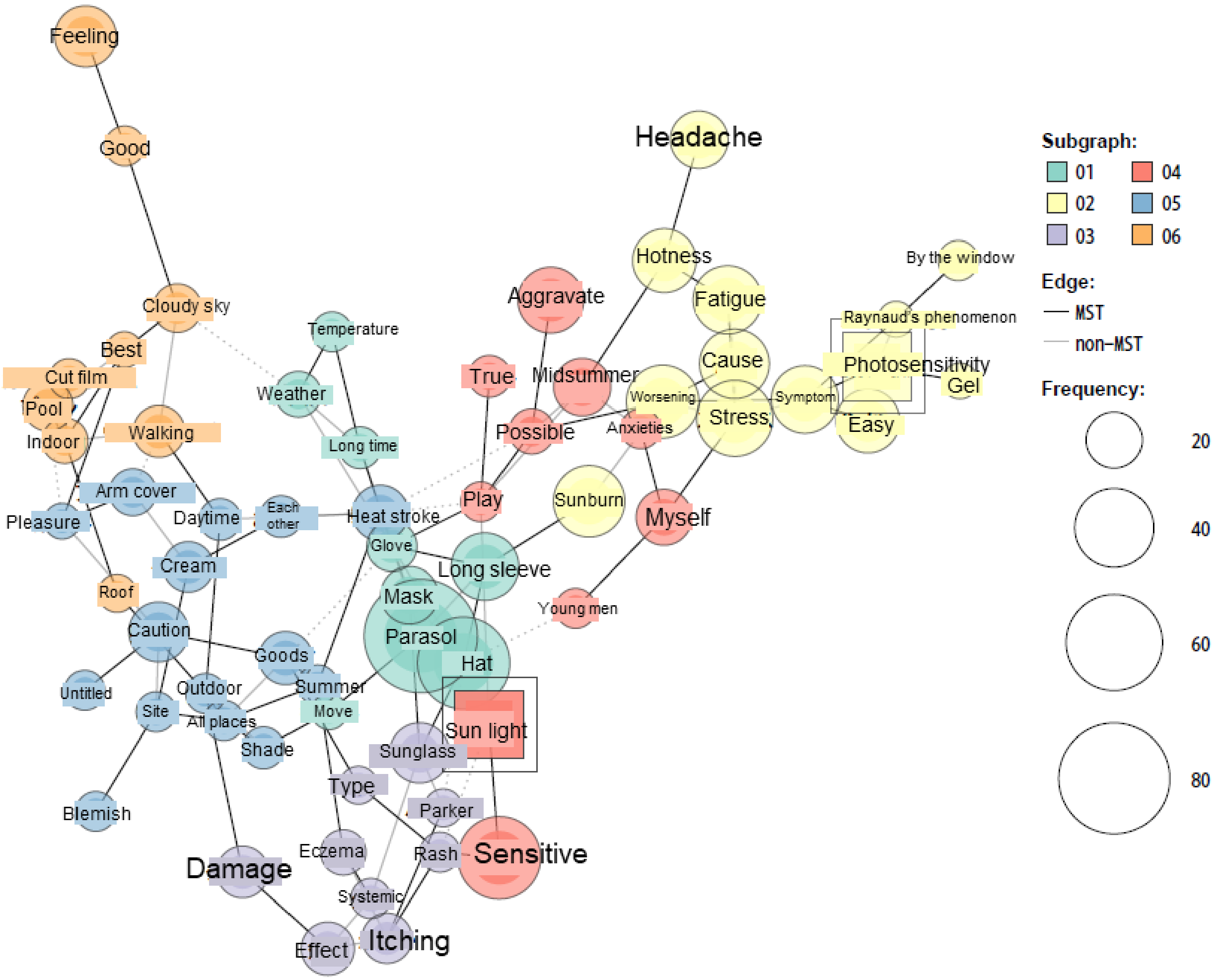
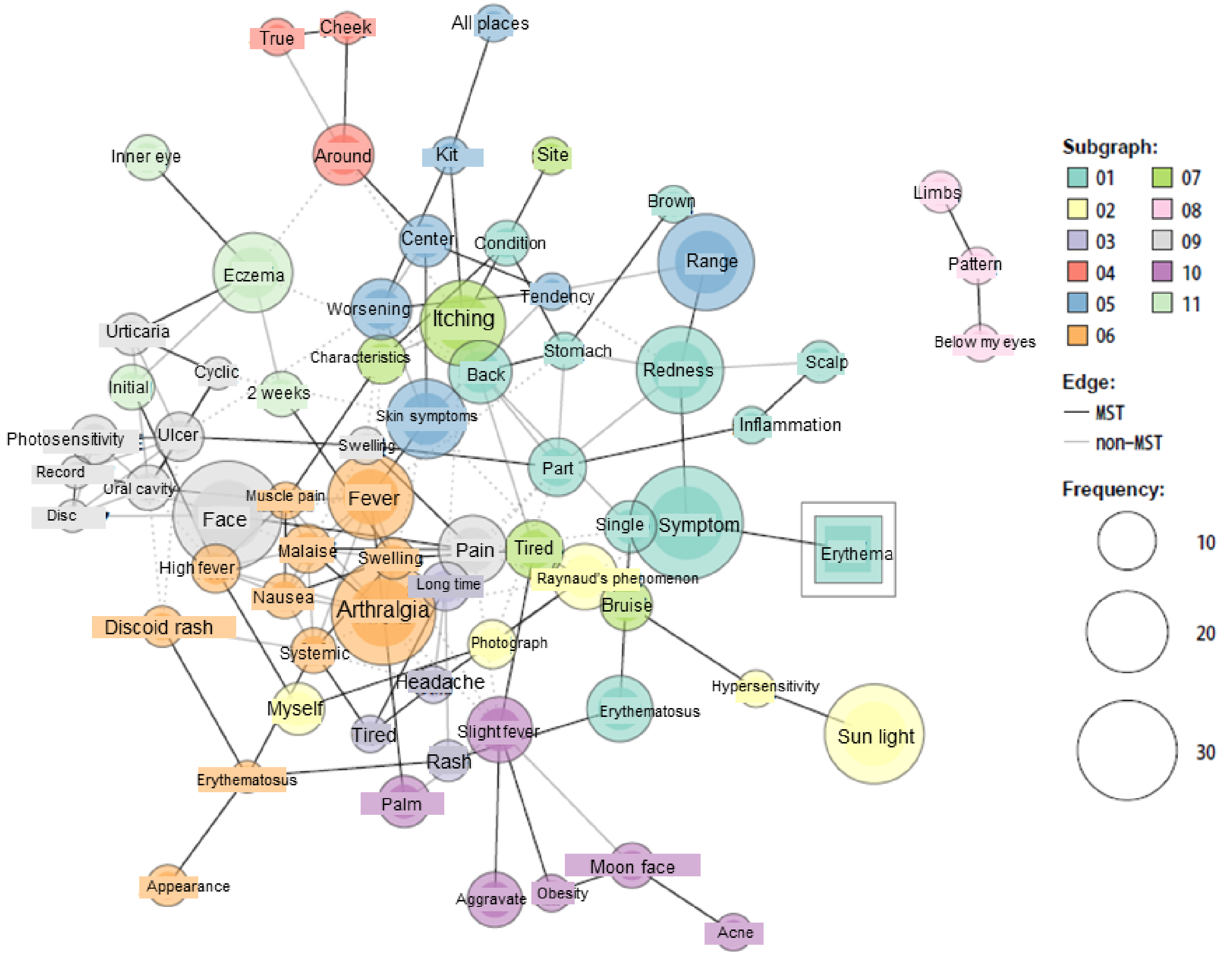


Figure 5. Network of words co-occurring with erythema in tōbyōki blogs of patients with systemic lupus erythematosus. Because the original language of the blogs is Japanese, English translations are shown.

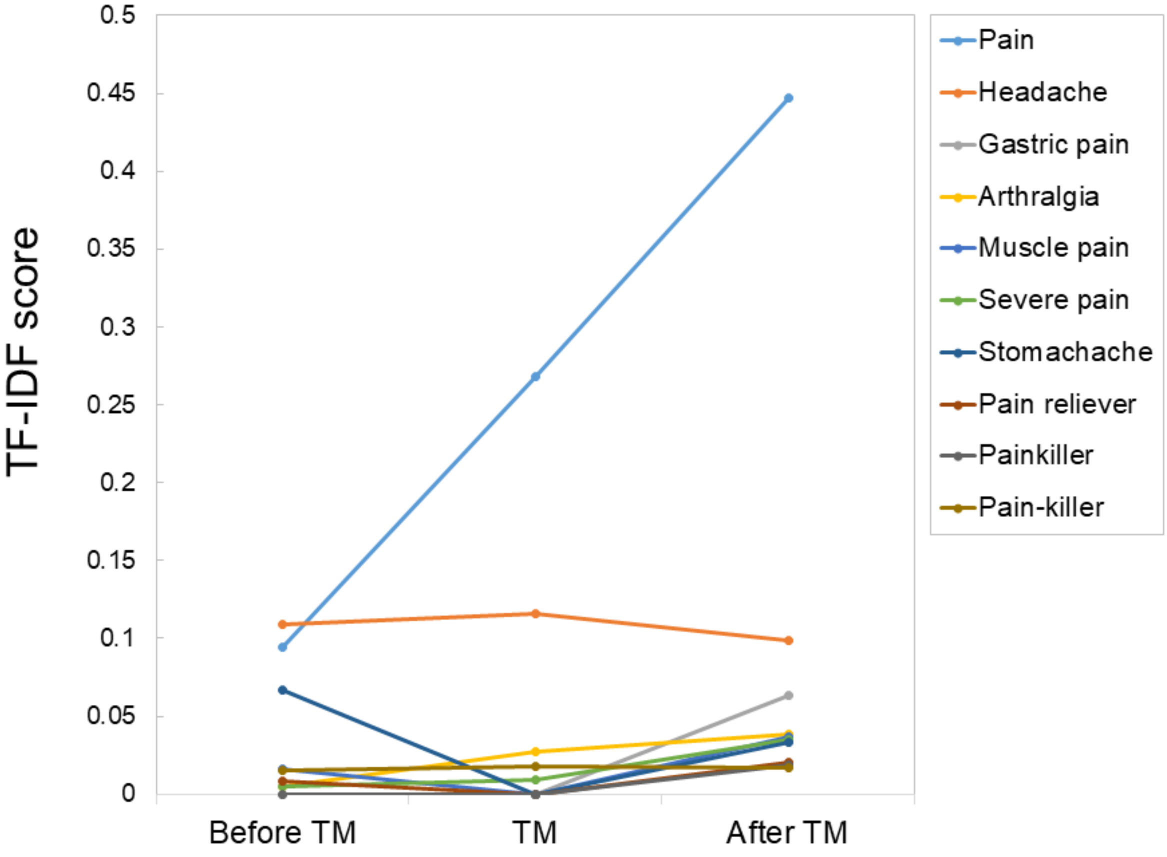


Analysis of Pain and Elements in Health-Related Quality of Life

Among 671 *tōbyōki* blogs regarding systemic lupus erythematosus, 41 were identified as including information both before and after therapy was mentioned for systemic lupus erythematosus. Entries from the 41 blogs were divided into 3 periods: those from before mentioning therapy (number of pages identified: 10,064) those that were the first mention of therapy (number of pages identified: 515), and those from after mentioning therapy (number of pages identified: 109,977). TF-IDF analysis was conducted to examine changes in the number of pain-related words during the 3 periods.

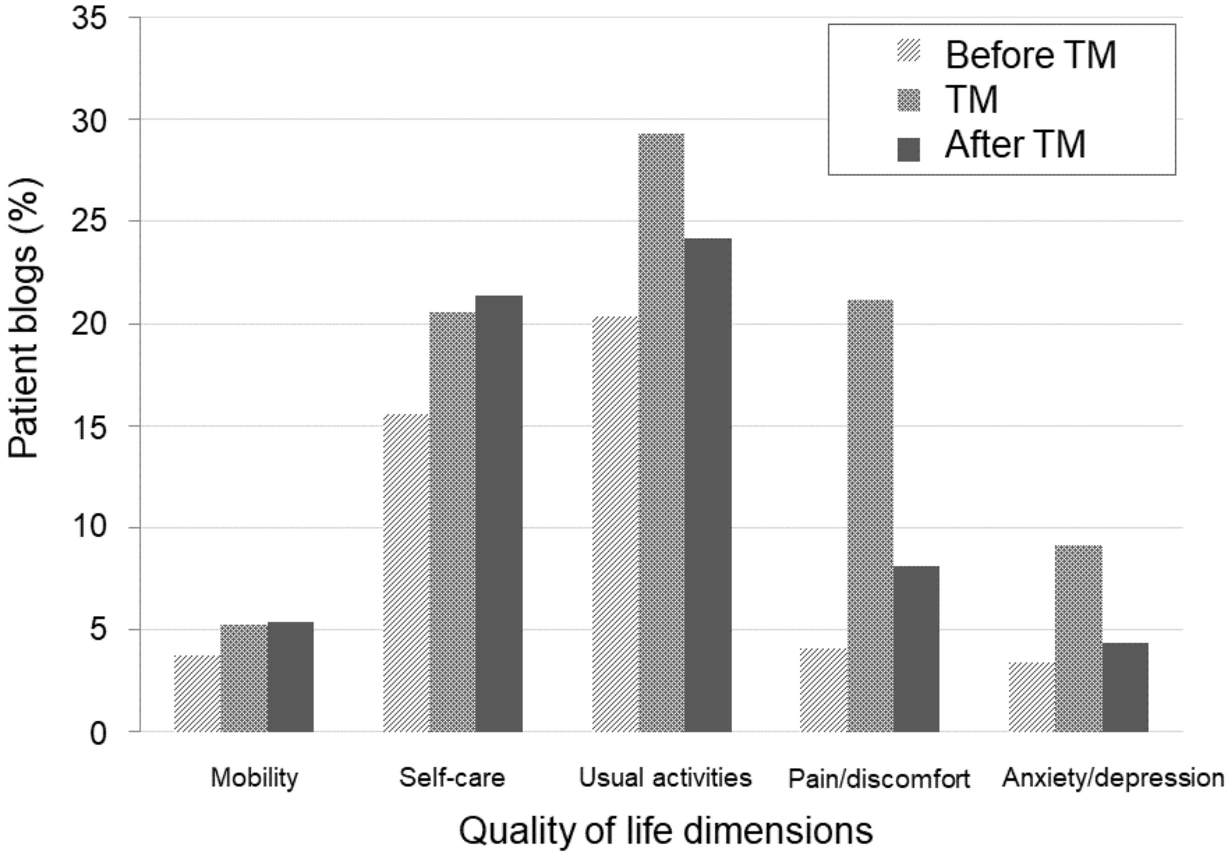
Pain-related words had higher TF-IDF values after therapy had been mentioned than those before therapy was mentioned (Figure 6). Symptoms with a large increase in TF-IDF (ratio >4) after therapy had been mentioned were pain, gastric pain, arthralgia, and severe pain; however, the TF-IDF for stomachache was less after therapy had been mentioned than that before (ratio ≤0.5).

Figure 6. Changes in the importance of pain-related words before and after mentioning treatments. TF-IDF: term frequency–inverse document frequency; TM: therapy mentioned.



We examined the distribution of health-related quality of life words in the *tōbyōki* blogs (Figure 7). For all 5 dimensions, the frequency of words was higher when therapy was first mentioned or after therapy had been mentioned than that in the pretreatment period. For usual activities, pain/discomfort, and anxiety/depression words, the frequency of each term was highest when therapy was first mentioned, followed by the after therapy had been mentioned period and before therapy was mentioned. For mobility and self-care words, frequency increased from before therapy was mentioned period, when therapy was first mentioned, to after therapy was mentioned. Pain was most frequently mentioned when therapy was first mentioned (5.2 times more than before treatment was mentioned). Usual activities words were frequently mentioned in all 3 periods.

Figure 7. Health-related quality of life estimated from pre-specified keywords mentioned in tōbyōki blogs, corresponding to the 5 dimensions of the EuroQOL 5D-5L questionnaire. TM: therapy mentioned.



Discussion

Principal Results

In this study, analysis of *tōbyōki* blog and health insurance claims data facilitated comprehensive understanding of disease epidemiology, treatment, and patient burden. Although health care data sources such as health insurance claims data derived from health care professionals have played a central role in pharmacovigilance, these data do not include information about subjective symptoms or burden. Analyzing patient-written data sources using natural language processing techniques may be an efficient approach for gaining a more detailed understanding of patient burden for disease management.

The overall prevalence (Figure 2) of systemic lupus erythematosus was 107.70 per 100,000 persons and was 4.4 times higher among females, which are similar trends to those reported in the United States [19]. Systemic lupus erythematosus patients in Japan who have written *tōbyōki* blogs tended to be young. More patients represented by *tōbyōki* blogs were between 20 and 34 years old, whereas more patients represented by health insurance claims data were between 35 and 49 years old, suggesting that younger patients with systemic lupus erythematosus are more likely to write *tōbyōki* blogs than older patients. Given these differences in age distribution, *tōbyōki* blog data would be better suited for use in understanding disease burden in younger patients with systemic lupus erythematosus.

In both health insurance claims data and *tōbyōki* blog data, we found similar drug treatment trends (Table 2). Steroids appeared most frequently. Given that steroids are the standard treatment for systemic lupus erythematosus and that patients with systemic lupus erythematosus have a high burden of disease caused by adverse reactions to steroid treatment [20], the high frequency of steroid mentions in the blogs could reflect patients' high attention to such treatment. A recent report suggests that immunosuppressive treatments for systemic lupus erythematosus remain poorly tolerated in some subsets of patients [21]; this high frequency of immunosuppressant mentions may also partly reflect patients' worries about this type of treatment. Health insurance claims data cannot reflect the actual feelings of patients about their treatments. We revealed that the descriptions of a drug in *tōbyōki* blogs may be used to detect and evaluate burden, such as the patient's attention and anxiety about the drug, which medical doctors and pharmaceutical companies do not always understand.

Although information on how the symptoms of the primary disease change (improve or deteriorate) with treatment and adverse events is vital in pharmacovigilance, it is impossible to obtain patient-level symptom information from health insurance claims data alone. In the clinical course of systemic lupus erythematosus, anorexia, general malaise, skin symptoms, and swelling of the face are known to occur [11]. Through the analysis of *tōbyōki* blogs, the sites where characteristic symptoms occurred could be estimated for example, "appetite," "feeling tired," "feeling itchy," and "moon face" were identified, which were not obtained from health insurance claims data (Table 3). In addition, several terms related to physical appearance were also found, suggesting that patients may feel burdened by the negative effects of skin symptoms on their appearance (Figure 5). Thus, text data (patients' blogs) enabled us to clarify patient-level symptoms and understand effects of treatments.

TF-IDF analysis showed that pain-related words became more important after the start of treatment than they were before the start of treatment (Figure 6). Headache and stomachache had lower scores after treatment than before treatment. This may suggest that some complaints voiced in daily life may be mentioned less frequently after treatment and may become less important than the primary disease. Since the TF-IDF score for gastric pain increased after treatment, it is likely that gastric pain may be an adverse event associated with treatment, since gastric pain would be mentioned similarly before treatment and during treatment if gastric pain was an effect of the primary disease.

In health-related quality of life data from *tōbyōki* blogs (Figure 7), since one of the main symptoms of systemic lupus erythematosus is pain, the frequency of pain-related expressions was high at the start of treatment. It is possible that pain was described as a motive for treatment, especially when first mentioning the treatment. The frequency of references to pain decreased after the start of treatment; it is possible that even as pain symptoms continued, patients gradually become accustomed to the pain, leading to a decrease in the frequency of blog mentions. Another possibility is that even if the pain continued, the descriptions used to convey the emotional feeling caused by the pain may change to another expression that was not captured in the analysis. The most frequently mentioned health-related quality of life dimension at any treatment point was usual activities, suggesting that patients are concerned about the influence of disease symptoms on these activities. The continuous increase in mobility and self-care descriptions may reflect increased attention to physical disability due to disease progression. Mentions of usual activities decreased after treatment compared to those during treatment, but the decrease (18% decrease) was less than that observed for pain (62% decrease) and anxiety/depression (53% decrease). This may also suggest that physical freedom decreases as the disease progresses. Health-related quality of life analysis would be difficult to perform using health care data alone. Our study indicated that health-related quality of life information could be inferred for the patient population based on the text information in *tōbyōki* blogs.

Comparison With Prior Work

As a strength of this study, we applied several unique approaches to obtain effective insights from *tōbyōki* blogs. Although patient-level complaints can be expected in disease blogs, it is often difficult to quantitatively evaluate such information; therefore, qualitative evaluations such as word clouds and co-occurrence network diagrams are generally used. The unique approach taken in this study assumed that the first mention of a drug was the closest to the time the drug was prescribed. This assumption allowed comparisons between text data characteristics before and after a drug was mentioned. In pharmacovigilance, this approach could become an effective way to explore patient burden before and after treatment. Health-related quality of life is usually assessed through questionnaires administered when recruiting patients; however, this approach can be time-consuming and costly. In this study, we showed that *tōbyōki* blog data can contain health-related quality of life information and that it might be possible to identify elements related to health-related quality of life using text-mining approaches. Only a few studies have reported efforts to extract health-related quality of life information from unstructured patient-derived texts such as forums [22] or tweets [23]. A text-mining approach to patients' unstructured data might also benefit the identification of psychological symptoms, which is difficult to measure using health care databases.

Limitations

This study has several limitations. First, because *tōbyōki* blogs are written by only a segment of the patient population, generalization of the findings requires caution. For instance, older adults might be underrepresented in internet sources [24]. Second, as a patient's condition becomes more severe, they may find it more difficult to continue writing their *tōbyōki* blog. This bias should be considered when interpreting the results. Third, text-mining analytics used in this study did not take into account dependency, syntax, and context in sentences. Thus, we did not distinguish between "pain has occurred" and "pain has disappeared," and both would have been treated as a mention of pain. In future studies, analysis can be improved by using more advanced natural language processing techniques that can make this distinction. Last, we only used a single questionnaire (EQ-5D-5L) as an exploratory component of the analysis. Other disease-specific instruments for patients with systemic lupus erythematosus, such as PROMIS [25] or LupusQoL [26], should be investigated in future studies.

Conclusions

A classical medical database represents only a part of a patient's entire treatment experience, and analysis using solely such a database cannot represent patient-level symptoms or patient concerns about treatments. This study showed that web-based text data from patients could add detailed patient-level information, which can be used to advance patient-centric pharmacovigilance.

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Authors' Contributions

All authors contributed to the conception and study design. Data analysis and interpretation were performed by SM, TO, ST, YM, MM, and HK. SM drafted the initial manuscript, with support from TO, ST, MM, and HK. All authors contributed to revising the manuscript and approved the final version.

Conflicts of Interest

All authors are employees of Chugai Pharmaceutical Co Ltd, which provided support in the form of salaries for all authors but did not have any additional role in study design, data analysis, manuscript preparation, or the decision to publish the manuscript.

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Abbreviations

TF-IDF: term frequency–inverse document frequency

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Original Paper

The Association Between Short-term Exposure to Ambient Air Pollution and Patient-Level Home Blood Pressure Among Patients With Chronic Cardiovascular Diseases in a Web-Based Synchronous Telehealth Care Program: Retrospective Study

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Abstract

Background: The association between short-term exposure to ambient air pollution and blood pressure has been inconsistent, as reported in the literature.

Objective: This study aimed to investigate the relationship between short-term ambient air pollution exposure and patient-level home blood pressure (HBP).

Methods: Patients with chronic cardiovascular diseases from a telehealth care program at a university-affiliated hospital were enrolled as the study population. HBP was measured by patients or their caregivers. Hourly meteorological data (including temperature, relative humidity, wind speed, and rainfall) and ambient air pollution monitoring data (including CO, NO_2, particulate matter with a diameter of <10 µm, particulate matter with a diameter of <2.5 µm, and SO_2) during the same time period were obtained from the Central Weather Bureau and the Environmental Protection Administration in Taiwan, respectively. A stepwise multivariate repeated generalized estimating equation model was used to assess the significant factors for predicting systolic and diastolic blood pressure (SBP and DBP).

Results: A total of 253 patients and 110,715 HBP measurements were evaluated in this study. On multivariate analysis, demographic, clinical, meteorological factors, and air pollutants significantly affected the HBP (both SBP and DBP). All 5 air pollutants evaluated in this study showed a significant, nonlinear association with both home SBP and DBP. Compared with demographic and clinical factors, environmental factors (meteorological factors and air pollutants) played a minor yet significant role in the regulation of HBP.

Conclusions: Short-term exposure to ambient air pollution significantly affects HBP in patients with chronic cardiovascular disease.

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KEYWORDS

ambient air pollution; blood pressure; cardiovascular disease; chronic disease; climate; home blood pressure; particulate matter; pollution; remote monitoring; telehealth care; telemonitoring; weather

Introduction

Air pollution is a great hazard to public health [1-5]. Previous studies have shown that long-term exposure to ambient air pollution increases respiratory morbidity and cardiopulmonary disease–related mortality [6,7], while short-term exposure increases cardiovascular disease–related mortality and nonfatal events [8]. The most prominent air pollutants that potentially affect human health include nitrogen oxides (NOx, including NO_2 and NO), CO, O_3, SO_2, particulate matter with a diameter of <10 µm (PM_{10}), and particulate matter with a diameter of <2.5 µm ($PM_{2.5}$). Hypertension is among the most prominent risk factors contributing to cardiovascular diseases, and the potential detrimental effect of air pollution on blood pressure (BP) is considered one of the mechanisms underlying the exacerbation in cardiovascular outcomes. However, the association between short-term or long-term exposure to ambient air pollution and BP has been inconsistent in previous studies, and most of these studies were epidemiological [9-12]. In this retrospective study, we aimed to evaluate the effect of short-term exposure to ambient air pollution on patient-level home blood pressure (HBP).

Methods

Patient Population

We retrospectively enrolled patients with chronic cardiovascular diseases (CVDs) who participated in telehealth care at National Taiwan University Hospital (NTUH), Taipei, Taiwan, between January 2009 and December 2013 as the study population. We excluded patients who did not reside in Taipei City during the study period. Informed consent was obtained from all participants. The study was approved by the institutional review board of NTUH. Chronic CVDs included coronary artery disease, prior myocardial infarction, heart failure, peripheral artery disease, prior stroke, and hypertension.

Telehealth Care Program

In this study, we used a fourth-generation telehealth program developed by Anker et al [13]. The program was designed specifically to offer home care for chronic CVDs. We had previously described the details of this program [14-18]. Briefly, single-lead electrocardiography, BP, heart rate, and oxygen saturation were measured at home, daily and on demand, and the data were instantaneously transmitted to the NTUH Telehealth Center. Case managers would call patients or their caregivers daily and on demand to evaluate patient conditions and provide instructions as needed. There was a call center, and full-time case managers and in-charge cardiologists were available 24 hours a day, 7 days a week. Medical decisions were discussed with patients' primary care physicians in the case of any major acute event.

Data Collection

Demographic, clinical (diagnosis of specific diseases), and medication data were obtained from the electronic database of NTUH. All biometric data were measured at home and automatically transmitted to the NTUH server. Biometric data were meant to be measured at least twice daily, ideally after waking up and before sleeping, but each patient or caregiver could have his/her own habit to select a time point and interval within a day to measure biometric parameters. We used the AViTA BPM65ZB sphygmomanometer (AViTA Corp), which is an electronic digital upper arm BP monitor. Hourly meteorological data (including temperature, relative humidity, and wind speed) of Taipei City during the study period were obtained from the Central Weather Bureau, Taiwan. Hourly ambient air pollution monitoring data (including CO, NO_2, PM_{10}, $PM_{2.5}$, and SO_2) during the same study period were obtained from the Environmental Protection Administration, Taiwan.

Statistical Analysis

Statistical analysis was performed using the R software (version 3.4.2, The R Foundation for Statistical Computing). In statistical testing, a 2-sided *P* value of ≤.05, was considered significant. The distribution properties of continuous variables are expressed as mean (SD) and median (IQR) values, and categorical variables are presented as frequencies and percentages. The differences in the distributions of continuous variables between male and female subjects were examined using the Wilcoxon rank-sum test. Differences in the distributions of categorical variables were compared using the Fisher exact test. Multivariate analysis was conducted by fitting multiple linear regression models to estimate the adjusted effects of age, sex, comorbidities (including hypertension, diabetes mellitus, cancers, atrial fibrillation, heart failure, prior myocardial infarction, coronary artery disease, prior stroke, and peripheral artery disease), heart rate, antihypertensive agents, seasons, meteorological factors, air pollutants, and other predictors of home systolic and diastolic blood pressure (SBP and DBP).

Since the use of antihypertensive agents, values of meteorological factors, and concentrations of air pollutants varied over time, we defined and included the following three groups of time-dependent covariates in our linear regression analyses:

1. Antihypertensive agents: among the 6 most common classes of antihypertensive drugs, we considered the classes of antihypertensive medications and the number of classes of antihypertensive medications used on the day of BP measurement.
2. Meteorological factors: these included hourly averaged outdoor temperature, relative humidity, and wind speed within the hour of BP measurement.
3. Air pollutants: we determined hourly inverse-distance weighted mean concentrations of 5 air pollutants (CO, NO_2, PM_{10}, $PM_{2.5}$, and SO_2) and the amount of rainfall within the hour of BP measurement, where the distances were calculated from each patient's home location to the 6 air quality monitoring stations in Taipei City, based on the corresponding latitudes and longitudes. Instant and cumulated air pollutant concentrations at hours 0, 3, 6, 12, and 18 and days 1, 2, 3, 4, 5, 6, and 7 were included in the multivariate analysis to evaluate the possible lag effect of each pollutant.

Simple and multiple generalized additive models (GAMs) were fitted to assess the nonlinear effects of continuous covariates and identify appropriate cut-off points for discretizing continuous covariates, if necessary, during stepwise variable selection. Further details on statistical analysis are provided in Multimedia Appendix 1.

Results

Patient Population and Demographics

A total of 253 patients with CVD who participated in the NTUH Telehealth Care Program from January 2009 to December 2013 were enrolled in this study. A total of 110,715 HBP measurements were carried out accordingly for these patients. The details of this patient population, including the per-patient and per-measurement demographics and clinical characteristics, have already been reported previously [18]. The data distributions of the air pollutant concentrations are summarized in Table 1. The mean temperature, humidity, and wind speed had been reported previously [18]. The mean concentration of NO_2, PM_{10}, $PM_{2.5}$, CO, and SO_2 were 23.67 (SD 6.80) ppb, 46.83 (SD 21.03) µg/m^3, 27.96 (SD 10.77) µg/m^3, 0.74 (SD 0.25) ppm, and 3.05 (SD 1.19) ppb, respectively. The air quality standards recommended by the World Health Organization for these pollutants, during the study period, were based on the 2005 version of the update [19].

Table 1. Data distribution of air pollutants from among 110,715 observations obtained by 253 patients included in this study.

Air pollutant	Mean (SD)	Minimum	Maximum	Median
NO_2 (ppb)	23.67 (6.80)	4.43	63.01	23.19
PM_{10}[a] (µg/m^3)	46.83 (21.03)	11.64	842.87	42.60
$PM_{2.5}$[b] (µg/m^3)	27.96 (10.77)	8.16	140.39	26.07
CO (ppm)	0.74 (0.25)	0.14	2.74	0.70
SO_2 (ppb)	3.05 (1.19)	0.58	14.85	2.79

[a] PM_{10}: particulate matter with a diameter of <10 µm.

[b] $PM_{2.5}$: particulate matter with a diameter of <2.5 µm.

Multivariate Analysis

Multivariate analysis was conducted by fitting multiple linear regression models to estimate the adjusted effects of demographic, clinical, and meteorological factors and air pollutants on home SBP and DBP measurements. The use of antihypertensive agents, values of meteorological factors, and concentrations of air pollutants were all defined and computed as time-dependent covariates. Multivariate analysis of the predictors for SBP and DBP on fitting 1 multiple linear regression model with the stepwise variable selection procedure is shown in Tables 2-7. With regard to SBP and DBP, the significant demographic and clinical characteristics are listed in Tables 2 and 5, meteorological factors in Tables 3 and 6, and air pollutants in Tables 4 and 7, respectively. The hourly averaged temperature had a linear negative effect on both SBP and DBP, while the other meteorological factors had significant nonlinear correlations with home SBP and DBP, as reported previously [18]. The exact statistical data for these meteorological factors were not identical to those reported previously, since this multivariate analysis was performed by using a new model that also included air pollutants. Similarly, CO, NO_2, SO_2, $PM_{2.5}$, and PM_{10} concentrations were significantly correlated with home SBP and DBP, and the effects were considered nonlinear. The cut-off points for discretizing the continuous covariates with nonlinear effects on the mean values of SBP and DBP (mmHg) were determined objectively, using the corresponding GAM plots during stepwise variable selection. The GAM plots representing the relationships between SBP and different environmental factors are shown in Figure 1-5. The bar plots of regression coefficient estimates for home SBP and DBP are shown in Multimedia Appendix 2. The green, blue, and red bars represent the demographic and clinical factors, meteorological parameters, and air pollution parameters, respectively. Of note, although the demographic, clinical, meteorological, and air pollution parameters significantly affected home SBP and DBP, it seemed that the “traditional” factors (demographic and clinical) had a more prominent effect on HBP than the environmental factors.

The multiple linear regression model for SBP (n=110,715; R^2=0.1286) indicates that the Pearson correlation coefficient between the observed value of SBP and the model-predicted value of SBP was $0.1286^{½}$=0.3586, and that for DBP (n=110,715; R^2=0.2219) indicates that the Pearson correlation coefficient between the observed value of DBP and the model-predicted value of DBP was $0.2219^{½}$=0.4711.

Table 2. Multivariate analysis of the predictors for systolic blood pressure by fitting 1 multiple linear regression model with stepwise variable selection: demographic and clinical characteristics.

Covariate	Parameter estimate	SE	*t* value	Pr>|*t*|
Intercept	125.0560	0.8216	152.2027	<.001
Male	–0.5184	0.1133	–4.5771	<.001
AF[a]	0.5663	0.1370	4.1323	<.001
Coronary artery disease without myocardial infarction	3.0135	0.1086	27.7503	<.001
Coronary artery disease with myocardial infarction	–0.5264	0.1708	–3.0820	.002
Cancer	3.0896	0.1402	22.0379	<.001
Chronic heart failure	–4.0580	0.1228	–33.0523	<.001
CVA[b]	1.1025	0.1336	8.2507	<.001
PAOD[c]	–1.7202	0.1855	–9.2744	<.001
ARB[d] × AB[e]	4.1642	0.4037	10.3161	<.001
ARB × BB[f]	1.8479	0.2601	7.1044	<.001
ARB × CCB[g]	–3.2486	0.2218	–14.6451	<.001
BB	–0.7201	0.1743	–4.1310	<.001
CCB × AB	–8.0115	0.3885	–20.6223	<.001
CCB × ACEI[h]	–8.3039	1.2350	–6.7237	<.001
CCB × BB	–3.9889	0.2950	–13.5204	<.001
CCB × Diuretics	1.0011	0.2187	4.5766	<.001
Diuretics × AB	7.1806	0.2805	25.6013	<.001
Diuretics × ACEI	1.5441	0.4555	3.3902	.001
Diuretics × BB	2.0257	0.2549	7.9458	<.001

[a] AF: atrial fibrillation.

[b] CVA: cardiovascular accident.

[c] PAOD: peripheral arterial occlusion disease.

[d] ARB: angiotensin receptor blocker.

[e] AB: alpha blocker.

[f] BB: beta blocker.

[g] CCB: calcium channel blocker.

[h] ACEI: angiotensin-converting enzyme inhibitor.

Table 3. Multivariate analysis of the predictors for systolic blood pressure by fitting 1 multiple linear regression model with stepwise variable selection: meteorological factors.

Covariate	Parameter estimate	SE	*t* value	Pr > |*t*|
Temperature	–0.6352	0.0127	–49.9892	<.001
DM[a] × temperature	0.1882	0.0045	41.4358	<.001
HTN[b] × temperature	0.2101	0.0047	44.5223	<.001
ARB[c] × temperature	0.1528	0.0057	26.6504	<.001
CCB[d] × temperature	0.0520	0.0078	6.6818	<.001
Diuretics × temperature	–0.0217	0.0059	–3.6496	<.001
0.557 < Wind speed 12 hours ago ≤ 3.73	0.3100	0.1008	3.0752	.002
1.976 < Wind speed on day 0 ≤ 4.43	0.5216	0.1099	4.7471	<.001
1.983 < Wind speed 1 day ago ≤ 3.895	0.2267	0.1044	2.1707	.03
1.793 < Wind speed 2 days ago ≤ 3.634	0.3138	0.0990	3.1702	.002
1.587 < Wind speed 4 days ago ≤ 3.923	0.2128	0.0995	2.1380	.03
1.855 < Wind speed 6 days ago ≤ 3.575	0.3155	0.0979	3.2221	.001
Relative humidity ≤ 65.774 or > 84.596	0.5365	0.1000	5.3641	<.001
Relative humidity 6 hours ago ≤ 72.967 or > 92.905	0.4753	0.1096	4.3364	<.001
Relative humidity 12 hours ago ≤ 56.324 or > 78.989	0.3813	0.1178	3.2365	.001
Relative humidity 24 hours ago > 76.11	0.4278	0.1209	3.5391	<.001
Relative humidity 2 days ago ≤ 67.752 or > 82.532	0.3446	0.1003	3.4362	.001
Relative humidity 4 days ago ≤ 65.366 or > 82.318	0.4172	0.1044	3.9960	<.001
Relative humidity 6 days ago ≤ 58.849 or > 81.108	0.5261	0.1331	3.9527	<.001
Log rainfall	–0.2074	0.0593	–3.4984	.001
Log cumulated rainfall in the past 4 days	–0.2981	0.0684	–4.3564	<.001
Log rainfall 6 days ago < –0.106	0.6989	0.1652	4.2296	<.001

[a] DM: diabetes mellitus.

[b] HTN: hypertension.

[c] ARB: angiotensin receptor blocker.

[d] CCB: calcium channel blocker.

Table 4. Multivariate analysis of the predictors for systolic blood pressure by fitting 1 multiple linear regression model with stepwise variable selection: air pollutants.

Covariate	Parameter estimate	SE	*t* value	Pr>|*t*|
Log CO concentration 3 hours ago	–0.6620	0.1186	–5.5800	<.001
Log cumulated CO concentration in the past 5 days	1.1985	0.2965	4.0422	<.001
Log NO_2 concentration	0.4520	0.1493	3.0276	.003
2.571 < Log NO_2 concentration 3 hours ago ≤ 3.654	0.3311	0.1113	2.9752	.003
Log NO_2 concentration 6 hours ago	0.7517	0.1154	6.5136	<.001
2.188 < Log NO_2 concentration 18 hours ago ≤ 3.185	0.4333	0.0986	4.3971	<.001
3.062 < Log NO_2 concentration 3 days ago ≤ 3.497	0.4392	0.1026	4.2810	<.001
3.063 < Log NO_2 concentration 4 days ago ≤ 3.483	0.3689	0.1027	3.5929	<.001
2.567 < Log NO_2 concentration 5 days ago ≤ 3.507	0.4131	0.1435	2.8781	.004
3.059 < Log NO_2 concentration 6 days ago ≤ 3.494	0.4837	0.1037	4.6650	<.001
3.043 < Log NO_2 concentration 7 days ago ≤ 3.468	0.3438	0.1004	3.4256	.001
Log $PM_{2.5}$[a] concentration 3 hours ago < 2.284	1.1068	0.3245	3.4105	.001
Log $PM_{2.5}$ concentration 4 days ago ≤ 3.243 or > 4.378	0.5000	0.1031	4.8481	<.001
Log $PM_{2.5}$ concentration 6 days ago ≤ 3.034 or > 3.826	0.3055	0.1076	2.8383	.005
2.848 < Log PM_{10}[b] concentration 18 hours ago ≤ 3.828	0.4819	0.1032	4.6690	<.001
Log SO_2 concentration 3 hours ago < –0.271	3.5314	1.0028	3.5216	<.001
Log SO_2 concentration 24 hours ago > 1.561	0.4552	0.1372	3.3164	.001
Log SO_2 concentration 5 days ago > 1.316	0.2970	0.1187	2.5025	.01

[a] $PM_{2.5}$: particulate matter with a diameter of <2.5 µm.

[b] PM_{10}: particulate matter with a diameter of <10 µm.

Table 5. Multivariate analysis of the predictors for diastolic blood pressure by fitting 1 multiple linear regression model with stepwise variable selection: demographic and clinical characteristics.

Covariate	Parameter estimate	SE	*t* value	Pr>|*t*|
Intercept	65.7236	0.7686	85.5088	<.001
Male	–1.2416	0.0793	–15.6608	<.001
Age < 72.424 years	8.5878	0.0783	109.6523	<.001
AF[a]	–0.8389	0.0916	–9.1609	<.001
Coronary artery disease with myocardial infarction	–0.3166	0.1088	–2.9105	.004
Cancer	0.4197	0.0942	4.4572	<.001
CHF[b]	–0.8912	0.0806	–11.0540	<.001
CVA[c]	3.2332	0.0896	36.0651	<.001
PAOD[d]	1.8971	0.1279	14.8373	<.001
ARB[e] × AB[f]	6.8305	0.2722	25.0906	<.001
ARB × BB[g]	5.6929	0.1636	34.7953	<.001
ARB × CCB[h]	–3.3888	0.1369	–24.7458	<.001
ARB × diuretics	–3.4067	0.1401	–24.3191	<.001
CCB × ACEI[i]	–10.7720	0.8297	–12.9827	<.001
CCB × BB	–0.4592	0.1868	–2.4583	.01
CCB × diuretics	2.2884	0.1298	17.6274	<.001
Diuretics × AB	–3.4526	0.2494	–13.8457	<.001
Diuretics × ACEI	2.5617	0.3943	6.4973	<.001
Diuretics × BB	–1.7401	0.1616	–10.7675	<.001

[a] AF: atrial fibrillation.

[b] CHF: congestive heart failure.

[c] CVA: cerebrovascular accident.

[d] PAOD: peripheral occlusive arterial disease.

[e] ARB: angiotensin receptor blocker.

[f] AB: alpha blocker.

[g] BB: beta blocker.

[h] CCB: calcium channel blocker.

[i] ACEI: angiotensin converting enzyme inhibitor.

Table 6. Multivariate analysis of the predictors for diastolic blood pressure by fitting 1 multiple linear regression model with stepwise variable selection: meteorological factors.

Covariate	Parameter estimate	SE	*t* value	Pr>|*t*|
Temperature	–0.1608	0.0130	–12.3600	<.001
Temperature 12 hours ago	–0.1058	0.0135	–7.8265	<.001
Temperature 18 hours ago ≤ 16.992 or > 28.649	0.5042	0.0714	7.0590	<.001
Temperature 7 days ago	0.0753	0.0124	6.0722	<.001
DM[a] × temperature	0.0694	0.0030	22.9718	<.001
HTN[b] × temperature	0.0857	0.0032	26.9498	<.001
AB[c] × temperature	–0.1161	0.0083	–13.9588	<.001
ACEI[d] × temperature	–0.0323	0.0096	–3.3598	.001
ARB[e] × temperature	0.0623	0.0046	13.5546	<.001
Diuretics × temperature	–0.0177	0.0045	–3.9649	<.001
Wind speed	0.1122	0.0250	4.4919	<.001
Wind speed 18 hours ago	0.0612	0.0230	2.6618	.008
Wind speed 3 days ago	0.1358	0.0318	4.2695	<.001
Wind speed 5 days ago > 3.734	0.3835	0.0892	4.3014	<.001
Wind speed 7 days ago > 4.56	0.7900	0.1750	4.5145	<.001
Relative humidity 6 hours ago ≤ 67.108 or > 91.436	0.3259	0.0719	4.5359	<.001
Relative humidity 12 hours ago ≤ 57.1 or > 78.822	0.2567	0.0836	3.0700	.002
Relative humidity 18 hours ≤ 34.851 or >77.249	0.2478	0.0983	2.5216	.01
Relative humidity 24 hours ago ≤ 47.631 or >77.286	0.2813	0.0893	3.1501	.002
Relative humidity 2 days ago ≤ 64.191 or > 81.286	0.2489	0.0728	3.4188	.001
Relative humidity 4 days ago ≤ 64.291 or > 81.392	0.3521	0.0729	4.8281	<.001
Relative humidity 5 days ago ≤ 54.611 or > 76.3	0.3089	0.0852	3.6268	<.001
Relative humidity 6 days ago ≤ 54.383 or > 79.265	0.5044	0.0985	5.1202	<.001
Relative humidity 7 days ago ≤ 58.455 or >76.46	0.5243	0.0856	6.1239	<.001
Log rainfall > –2.252	0.3004	0.0824	3.6452	<.001
Log rainfall 3 hours ago ≤ –0.372 or > 0.817	0.4580	0.1538	2.9783	.003
–2.251 < Log rainfall 6 hours ago ≤ 0.379	0.3796	0.0856	4.4340	<.001
–2.246 < Log rainfall 12 hours ago ≤ 0.177	0.3282	0.0874	3.7542	<.001
–2.228 < Log rainfall 18 hours ago ≤ 3.202	0.1674	0.0846	1.9797	.05
–2.165 < Log rainfall 2 days ago ≤ 0.145	0.4425	0.0681	6.4961	<.001
–2.168 < Log rainfall 4 days ago ≤ 0.068	0.3491	0.0682	5.1162	<.001
–2.153 < Log rainfall 5 days ago ≤ 0.026	0.3042	0.0691	4.4003	<.001
–2.193 < Log rainfall 7 days ago ≤ –0.266	0.5065	0.0666	7.6091	<.001
–2.044 < Log cumulated rainfall in the past 6 days ≤ –0.735	0.5517	0.0691	7.9805	<.001
Log cumulated rainfall in the past 7 days	–0.5756	0.0538	10.7067	<.001

[a] DM: diabetes mellitus.

[b] HTN: hypertension.

[c] AB: alpha blocker.

[d] ACEI: angiotensin converting enzyme inhibitor.

Table 7. Multivariate analysis of the predictors for diastolic blood pressure by fitting 1 multiple linear regression model with stepwise variable selection: air pollutants.

Covariate	Parameter estimate	SE	*t* value	Pr>|*t*|
Log CO concentration	0.3966	0.0970	4.0907	<.001
Log CO concentration 12 hours ago	–0.9318	0.0759	–12.2815	<.001
–0.41 < Log CO concentration 24 hours ago ≤ 0.527	0.4100	0.0713	5.7517	<.001
Log CO concentration 2 days ago ≤ –0.426 or > 0.366	0.2789	0.0743	3.7546	<.001
Log cumulated CO concentration in the past 5 days > 0.034	1.0558	0.2096	5.0366	<.001
Log cumulated CO concentration in the past 7 days > 0.006	0.7773	0.2050	3.7921	<.001
Log NO_2 concentration 6 hours ago	0.1645	0.0763	2.1566	.03
2.226 < Log NO_2 concentration 18 hours ago ≤ 3.209	0.3400	0.0689	4.9383	<.001
Log cumulated NO_2 cconcentration in the past 1 day > 3.163	0.1880	0.0887	2.1203	.03
Log NO_2 concentration 2 days ago < 2.695	0.6081	0.1352	4.4984	<.001
3.1 < Log NO_2 concentration 3 days ago ≤ 3.6	0.2480	0.0727	3.4093	.007
Log NO_2 concentration 7 days ago	–0.9739	0.1572	–6.1965	<.001
Log $PM_{2.5}$[a] concentration 1 day ago ≥ 2.734	0.6872	0.1397	4.9188	<.001
Log $PM_{2.5}$ concentration 2 days ago > 3.547	0.2638	0.0871	3.0294	.003
Log $PM_{2.5}$ concentration 3 days ago ≥ 2.598	0.4660	0.1869	2.4936	.01
Log $PM_{2.5}$ concentration 6 days ago > 3.559	0.2502	0.0827	3.0256	.003
Log PM_{10}[b] concentration 1 day ago	–0.5895	0.1264	–4.6622	<.001
0.926 < Log SO_2 concentration ≤ 2.325	0.2053	0.0768	2.6736	.008
0.77 < Log SO_2 concentration 3 hours ago ≤ 1.902	0.1994	0.0718	2.7766	.006
0.73 < Log SO_2 concentration 18 hours ago ≤ 1.819	0.2264	0.0683	3.3144	.001
1.062 < Log SO_2 concentration 24 hours ago ≤ 2.926	0.2025	0.0726	2.7908	.005
0.772 < Log SO_2 concentration 5 days ago ≤ 1.558	0.2316	0.0696	3.3270	.001
0.946 < Log SO_2 concentration 6 days ago ≤ 1.604	0.2500	0.0682	3.6660	<.001
Log SO_2 concentration 7 days ago	0.5296	0.1162	4.5578	<.001

[a] $PM_{2.5}$: particulate matter with a diameter of <2.5 µm.

[b] PM_{10}: particulate matter with a diameter of <10 µm.

Figure 1. Generalized additive model (GAM) plot showing the relationship between systolic blood pressure and CO exposure.

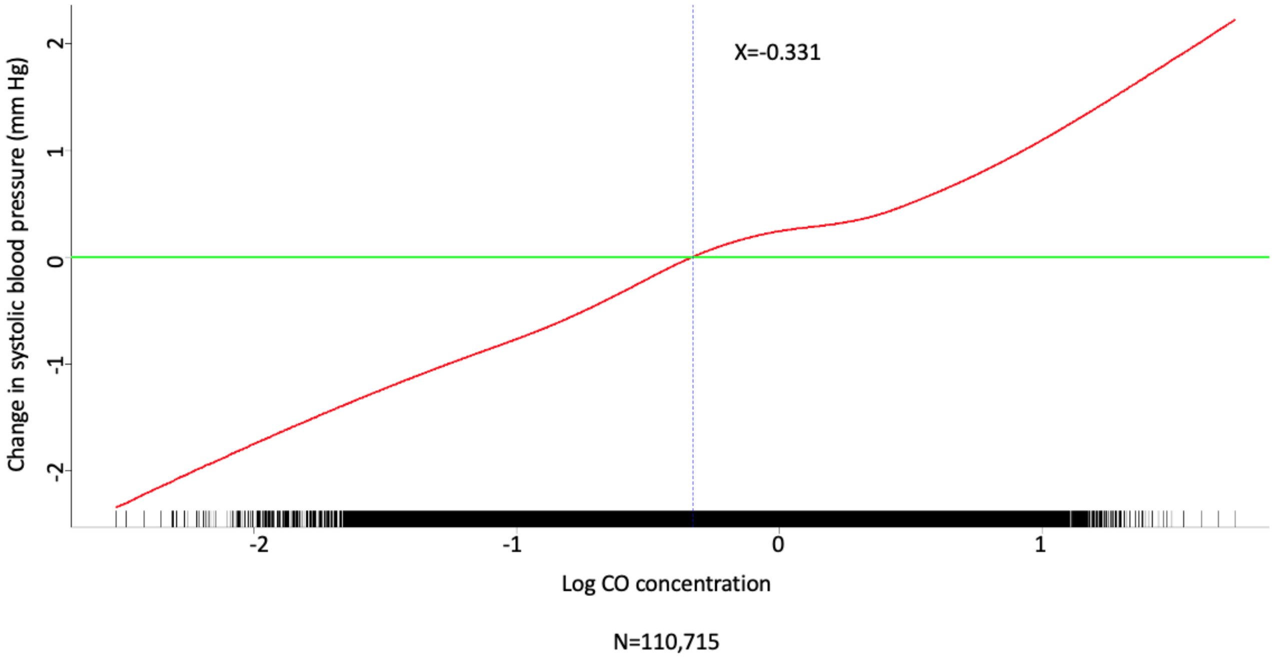


Figure 2. Generalized additive model (GAM) plot showing the relationship between systolic blood pressure and SO_2 exposure.

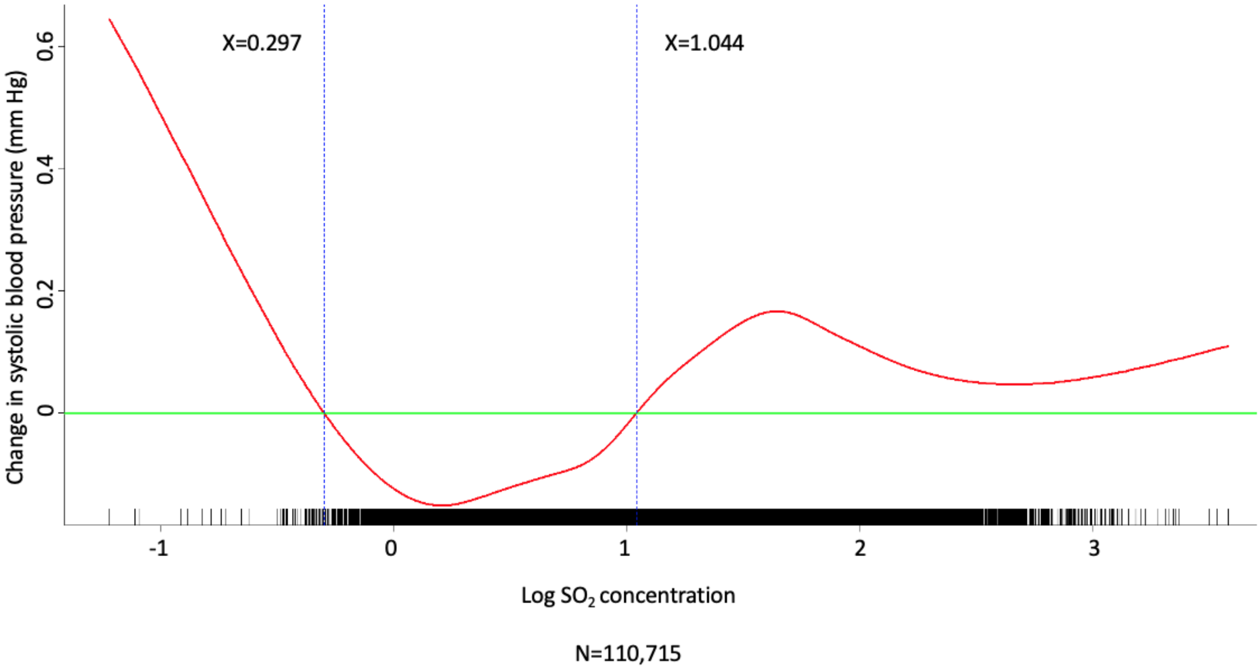


Figure 3. Generalized additive model (GAM) plot showing the relationship between systolic blood pressure and NO_2 exposure.

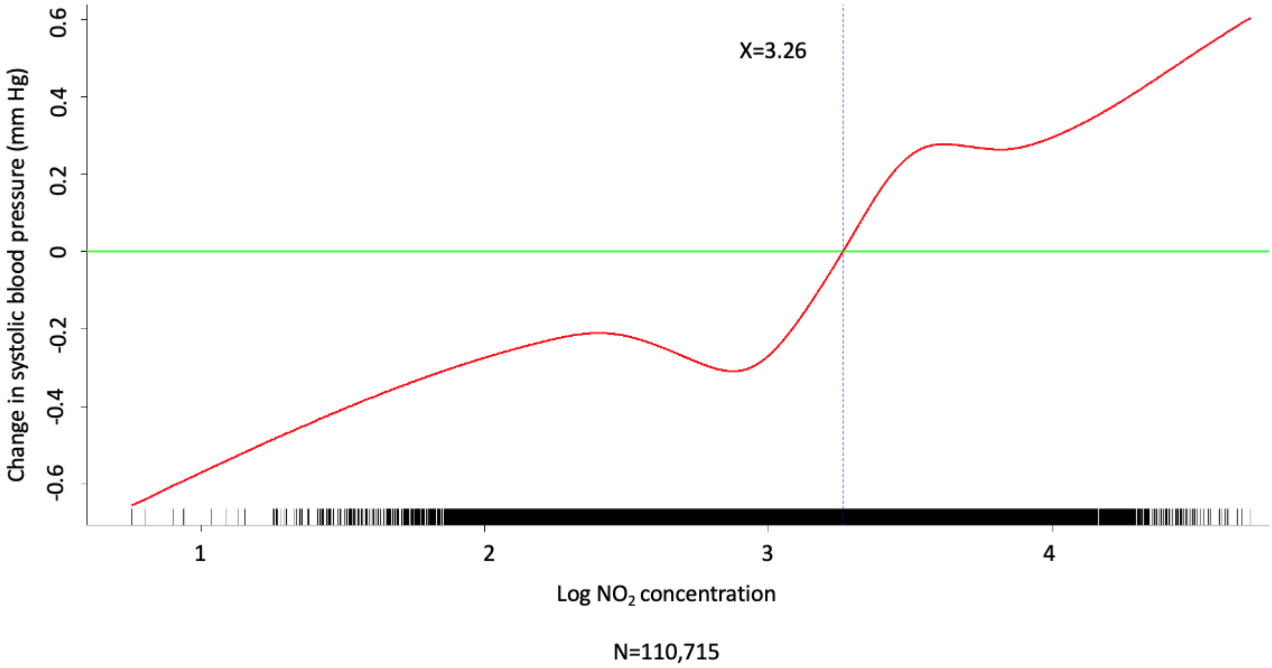


Figure 4. Generalized additive model (GAM) plot showing the relationship between systolic blood pressure and PM_{10} exposure. PM_{10}: particulate matter with a diameter of <10 μm.

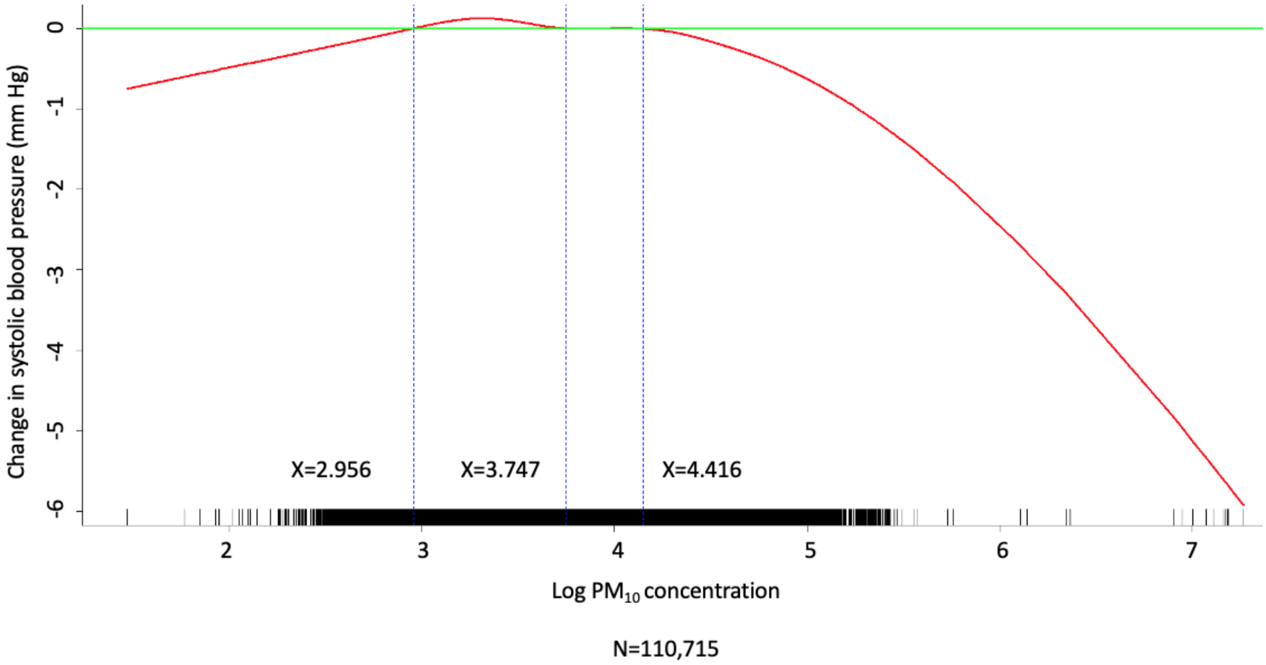
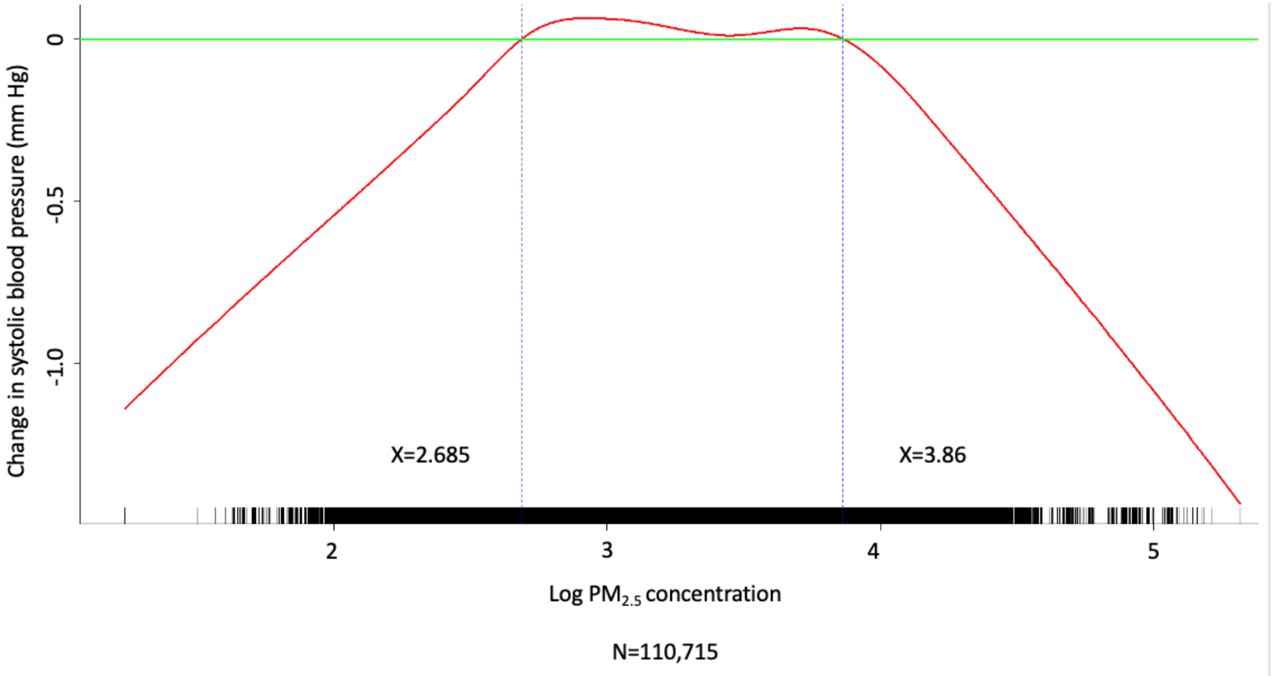


Figure 5. Generalized additive model (GAM) plot showing the relationship between systolic blood pressure and $PM_{2.5}$ exposure. $PM_{2.5}$: particulate matter with a diameter of <2.5 µm.



Discussion

Principal Findings

Human health is significantly correlated with genomic and environmental factors. Wild [20] defined the "exposome" in 2005 as a concept that "encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards." Among these factors in the exposome, air pollution poses a major threat to human health. Exposure to ambient air pollution, either over the short or long term, increases cardiovascular mortality accordingly [6,8]. The detrimental effect of air pollution on BP is considered one of the mechanisms leading to this outcome. However, the association between short-term or long-term exposure to ambient air pollution and BP is inconsistent in the literature. Among the routinely monitored air pollutants, $PM_{2.5}$ is considered one of the most dangerous agents influencing human health. Brook et al [8] adequately described the association between particulate matter air pollution and CVD, suggesting that exposure to ambient $PM_{2.5}$ would potentially increase BP. A few mechanisms explaining why $PM_{2.5}$ increases BP have been reported before: (1) altering the autonomic nervous system to favor a sympathetic tone [21], (2) increasing oxidative stress through endogenous proinflammatory mediators or vasculo-active molecules [22,23], (3) directly influencing the vascular endothelium [24,25], and (4) inducing abnormal DNA methylation [26,27]. Many studies have investigated the association between exposure to ambient $PM_{2.5}$ and BP, which has been reported before, but the effect was inconsistent. To date, 4 meta-analyses have addressed this issue. Liang et al [9] reported positive associations among $PM_{2.5}$, SBP, and DBP. Zhang et al [10] reported that a high SBP is significantly associated with the exposure to $PM_{2.5}$, while a high DBP is only associated with the exposure to PM_{10}, but not $PM_{2.5}$. Cai et al [11] reported that short-term exposure to SO_2, $PM_{2.5}$, and PM_{10} was significantly associated with an increased risk of hypertension. The association between BP and air pollutants other than PM has not been investigated in detail. In a recent meta-analysis by Yang et al [12], short-term exposure to ambient air pollution was significantly associated with hypertension (PM_{10}, $PM_{2.5}$, SO_2, and NO_2), SBP ($PM_{2.5}$ and SO_2), and DBP (PM_{10}, $PM_{2.5}$, SO_2, and NO_2). However, these meta-analyses were mainly performed on the basis of epidemiological studies. To our knowledge, our study is the first to investigate the relationships among demographic, clinical, meteorological factors, air pollutants, and HBP at the patient level.

There are some notable findings in this study. First, at the patient level, ambient air pollution was significantly associated with HBP, both SBP and DBP, and the culprit pollutants included all of the 5 pollutants (PM_{10}, $PM_{2.5}$, SO_2, NO_2, and CO) that were included in this study. The association between HBP and ambient air pollution was surprisingly nonlinear, given that most previous studies used a linear model to evaluate the effect of ambient air pollution on BP and hypertension. Yang et al [12] suspected that the relationship between ambient air pollution and BP was nonlinear, and this may be the reason why even meta-analyses that have been well performed could not adequately explain the association between ambient air pollution and BP because most previous studies mistakenly used a linear model. One of the strengths of this study was that we considered HBP rather than office BP measurements, which was the case in most of the previous studies. HBP is now considered a more important predictor than office BP for future coronary and cerebral events [28]. All ambient air pollutants investigated in this study significantly affected HBP, while in prior meta-analyses, only some of the ambient air pollutants were significantly associated with hypertension, SBP, and DBP. This could explain why ambient air pollution poses a great hazard to human health. Data regarding medication in this study are also important. No study thus far has investigated whether antihypertensive agents play a role in the association between ambient air pollution and BP. Our prior study [18] showed that short-term exposure to low ambient temperature significantly increases HBP, and that this effect could be modified by antihypertensive agents. In this study, the potential confounding effect of medications was also considered, but ambient air pollutants still showed significant associations with HBP. Limited by the statistical model, the exact effect of each class of antihypertensive agents on the relationship between ambient air pollution and HBP could not be fully elucidated. Of note, although there were significant associations between environmental factors and HBP, demographic and clinical factors seemed to play an even more important role in HBP, as shown in Multimedia Appendix 2. Nonetheless, since hypertension has such a marked impact on human health, a holistic approach for BP control, including adequate modification of environmental exposure (both meteorological factors and ambient air pollutants), should be adopted. The importance of air pollution control cannot be overemphasized.

Limitations

This study has a few limitations. First, this was a retrospective registry with a relatively small number of patients. Second, the study population comprised patients with chronic CVD with great adherence and health insights as they opted to participate in a telehealth care program. Thus, whether the study results can be extrapolated to other patient populations should be carefully considered. Third, individual ambient air pollutant concentrations were calculated using a spatial model that might not reflect true personal exposure. Jiang et al [29] reported that even people who were geographically close could have distinct personalized exposomes. Without precise assessment of personal environmental exposure, further evaluation of the associations between the environment and human health seems futile. Jiang et al [29] reported that novel wearable devices that are capable of assessing both biotic and abiotic exposure may be used to solve this problem. As shown in our previous study [18] and in this study, meteorological factors (including temperature, relative humidity, and wind speed) and ambient air pollutants (NO_2, PM_{10}, $PM_{2.5}$, CO, and SO_2) had significant effects on human health at the patient level and should be considered in future studies on abiotic exposure among exposomes. Fourth, the possible interactions among air pollutants, including synergistic effects and collinearity, were not addressed in this study. Fifth, this study reports a nonlinear relationship between BP and ambient air pollutants, but further evaluation of the dose-effect curve was limited by the current statistical methods. Similarly, the interactions between ambient air pollution and other environmental factors, such as meteorological factors, were not addressed in this study. Multiscale entropy is a novel nonlinear method that has been applied to predict outcomes in a few clinical settings, including trauma [30], after cardiac arrest on mechanical circulatory support [31], acute stroke [32], and autonomic imbalance after myocardial infarction [33]. Further studies may also apply this method to evaluate the effect of ambient air pollution on BP. Sixth, this study only investigated the effect of short-term exposure to ambient air pollution; the effect of long-term exposure remains unknown. Seventh, ozone is an important air pollutant associated with an elevated BP [34-38]. However, during the study period (2009-2013), ozone was not routinely monitored by the Environmental Protection Administration in Taiwan; hence, it was not feasible to evaluate the relationship between ozone and HBP in the current study. Finally, the lag effect of each air pollutant on BP was not precisely determined in this study because of the complexity of the statistical analysis.

Conclusions

Short-term exposure to ambient air pollution significantly affects both home SBP and DBP in patients with chronic CVD, and the relationship between ambient air pollution and HBP is nonlinear.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
More Statistical Details.
[DOCX File , 17 KB - publichealth_v7i6e26605_app1.docx]

Multimedia Appendix 2
Additional figure and figure legends.
[DOCX File , 395 KB - publichealth_v7i6e26605_app2.docx]

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Abbreviations

BP: blood pressure
CVD: cardiovascular disease
DBP: diastolic blood pressure
GAM: generalized additive models
HBP: home blood pressure
NTUH: National Taiwan University Hospital
PM_{10}: particulate matter with a diameter of <10 µm
$PM_{2.5}$: particulate matter with a diameter of <2.5 µm

SBP: systolic blood pressure

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Corrigenda and Addenda

Correction: Community Mitigation of COVID-19 and Portrayal of Testing on TikTok: Descriptive Study

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Related Article:

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In “Community Mitigation of COVID-19 and Portrayal of Testing on TikTok: Descriptive Study” (JMIR Public Health Surveill 2021;7(6):e29528), one error was noted.

Due to a system error, the name of one author, Hao Tang, was replaced with the name of another author on the paper, Alessia Pellicane. In the originally published paper, the order of authors was listed as follows:

> *Corey H Basch, Jan Mohlman, Joseph Fera, Alessia Pellicane, Alessia Pellicane, Charles E Basch*

This has been corrected to:

> *Corey H Basch, Jan Mohlman, Joseph Fera, Hao Tang, Alessia Pellicane, Charles E Basch*

In the originally published paper, the ORCID of author Hao Tang was incorrectly published as follows:

> *0000-0002-8220-6584*

This has been corrected to:

> *0000-0003-3002-1374*

The correction will appear in the online version of the paper on the JMIR Publications website on June 29, 2021, 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.

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Corrigenda and Addenda

Correction: Convalescent Plasma for the Prevention and Treatment of COVID-19: A Systematic Review and Quantitative Analysis

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In “Convalescent Plasma for the Prevention and Treatment of COVID-19: A Systematic Review and Quantitative Analysis” (JMIR Public Health Surveill 2021;7(4):e25500), some symbols (<, >, and ~) were missing in 13 places in the paper due to an XML conversion error. The following corrections have been made:

- In Table 1, row “Pseudovirus capture assay...,” column “Summary,” the passage “(neutralizing antibody titers 1:16 to 1:1024)” has been corrected to “(neutralizing antibody titers <1:16 to >1:1024)”.
- In Table 2, row “Al Helali et al…,” column “Outcomes/main findings,” the passage “few days after CP transfusion and negative PCR[b] test for COVID-19 in 48 h” has been corrected to “few days after CP transfusion and negative PCR[b] test for COVID-19 in <48 h”.
- In Table 2, row “Jiang et al…,” column “Details of CP,” the passage “Collected by apheresis from a donor who had recovered from SARS-CoV-2 infection for 14 days, with an ELISA[e] antibody titer 1:1000” has been corrected to “Collected by apheresis from a donor who had recovered from SARS-CoV-2 infection for >14 days, with an ELISA[e] antibody titer >1:1000.”
- In Table 2, row “Kong et al…,” column “Outcomes/main findings,” the passage “Patient’s viral load decreased significantly, by a factor of 18” has been corrected to “Patient’s viral load decreased significantly, by a factor of ~18.”
- In Table 2, row “Fung et al…,” column “Details of CP,” the passage “without a PCR test; ELISA anti–SARS-CoV-2 spike protein IgG titer 1:400” has been corrected to “without a PCR test; ELISA anti–SARS-CoV-2 spike protein IgG titer >1:400.”
- In Table 2, row “Joyner et al…,” column “Interventions and comparisons,” the passage “All patients were treated with at least one unit (200 mL) of CP with the option to administer” has been corrected to “All patients were treated with at least one unit (~200 mL) of CP with the option to administer.”
- In Table 2, row “Rahman et al…,” column “Outcomes/main findings,” the passage “…1 still hospitalized, and 3 patients died 3 months after the CP transfusion.” has been corrected to “...1 still hospitalized, and 3 patients died ~3 months after the CP transfusion.”
- In Table 2, row “Shen et al…,” column “Details of CP,” thee passage “Obtained from 5 patients who recovered from COVID-19; anti–SARS-CoV-2 IgG titer 1:1000 as determined by ELISA and a neutralization titer 40” has been corrected to “Obtained from 5 patients who recovered from COVID-19; anti–SARS-CoV-2 IgG titer >1:1000 as determined by ELISA and a neutralization titer >40.”
- In Table 2, row “Wei et al…,” column “Interventions and comparisons,” the passage “One or two 200-mL doses of CP were administered 8 weeks after symptom onset” has been corrected to “One or two 200-mL doses of CP were administered >8 weeks after symptom onset.”

- In Table 2, row “Abolghasemi et al…,” column “Details of CP,” the passage “ELISA antibody titer cutoff index 1.1” has been corrected to “ELISA antibody titer cutoff index >1.1.”

The correction will appear in the online version of the paper on the JMIR Publications website on June 30, 2021, 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.

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Original Paper

Using Machine Learning to Compare Provaccine and Antivaccine Discourse Among the Public on Social Media: Algorithm Development Study

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Abstract

Background: Despite numerous counteracting efforts, antivaccine content linked to delays and refusals to vaccinate has grown persistently on social media, while only a few provaccine campaigns have succeeded in engaging with or persuading the public to accept immunization. Many prior studies have associated the diversity of topics discussed by antivaccine advocates with the public's higher engagement with such content. Nonetheless, a comprehensive comparison of discursive topics in pro- and antivaccine content in the engagement-persuasion spectrum remains unexplored.

Objective: We aimed to compare discursive topics chosen by pro- and antivaccine advocates in their attempts to influence the public to accept or reject immunization in the engagement-persuasion spectrum. Our overall objective was pursued through three specific aims as follows: (1) we classified vaccine-related tweets into provaccine, antivaccine, and neutral categories; (2) we extracted and visualized discursive topics from these tweets to explain disparities in engagement between pro- and antivaccine content; and (3) we identified how those topics frame vaccines using Entman's four framing dimensions.

Methods: We adopted a multimethod approach to analyze discursive topics in the vaccine debate on public social media sites. Our approach combined (1) large-scale balanced data collection from a public social media site (ie, 39,962 tweets from Twitter); (2) the development of a supervised classification algorithm for categorizing tweets into provaccine, antivaccine, and neutral groups; (3) the application of an unsupervised clustering algorithm for identifying prominent topics discussed on both sides; and (4) a multistep qualitative content analysis for identifying the prominent discursive topics and how vaccines are framed in these topics. In so doing, we alleviated methodological challenges that have hindered previous analyses of pro- and antivaccine discursive topics.

Results: Our results indicated that antivaccine topics have greater intertopic distinctiveness (ie, the degree to which discursive topics are distinct from one another) than their provaccine counterparts (t_{122}=2.30, P=.02). In addition, while antivaccine advocates use all four message frames known to make narratives persuasive and influential, provaccine advocates have neglected having a clear problem statement.

Conclusions: Based on our results, we attribute higher engagement among antivaccine advocates to the distinctiveness of the topics they discuss, and we ascribe the influence of the vaccine debate on uptake rates to the comprehensiveness of the message frames. These results show the urgency of developing clear problem statements for provaccine content to counteract the negative impact of antivaccine content on uptake rates.

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KEYWORDS

antivaccination movement; Twitter messaging; public health informatics; supervised machine learning algorithm; unsupervised machine learning algorithm; qualitative content analysis; data visualization; infodemiology; infodemic; health misinformation; infoveillance; social listening

Introduction

Background and Specific Aims

Vaccine-critical social media content has been suggested as a major obstacle to immunizing the public against vaccine-preventable diseases [1-4]. According to a 2019 survey on internet use in the United States, 79% of adults are on social media [5], and a separate health-focused survey conducted in 2019 found that 75% of adults read medical information on social media [6]. Over a 5-year period from 2012 to 2017, the percentage of people seeking medical advice online increased from 8% to 31.5% [7]. Simultaneously, the spread of antivaccine content has accelerated on social media [8], fostering groundless fears about immunization [9].

Exposure to antivaccine content on social media has been associated with delays in and refusal of vaccination [3]. While the development of tailored messages (eg, text messages) has increased immunization rates [10], public provaccine campaigns via social media have yielded limited success, as shown in several systematic reviews of interventions for various vaccines [4,11-19]. Given that there is a methodological barrier to assessing the impact of public campaigns on regional immunization rates, the current literature has not yet fully explicated how the antivaccine movement continues to engage and persuade the public to deny immunization despite provaccine advocates' counteracting efforts. Therefore, there is a need to compare pro- and antivaccine advocates in terms of the discursive topics they deploy on social media to engage and persuade audiences to accept or deny immunization.

This study comparatively analyzed pro/antivaccine content on social media on the spectrum of engagement persuasion devised based on digital marketing [20-23] and social influence literature [24]. Literature on digital media marketing suggests that the effectiveness of a campaign should be evaluated on a broader spectrum from engagement to persuasion because engaging audiences with content that competes against numerous other sources of content for their attention is a precursor to persuasion [20,21]. Simultaneously, literature on social influence within a large public network (eg, social media) states that public engagement is a foundation upon which one can exert influence on the audience's attitudes and behaviors [24]. Based on this literature on digital marketing and social influence on a digital network, we define the engagement-persuasion spectrum as *a wide range of discursive strategies devised to influence an audience's attitudes and behaviors about a target matter on social media*. This spectrum starts with engaging the audience with the content and concludes with persuading the audience to accept the claims included in the content.

As a way of fostering engagement, a greater diversity of discursive topics has been suggested [20]. Antivaccine advocates employ more diverse topics than their provaccine counterparts, and previous researchers have claimed that this results in higher engagement [25-28]. However, the diversity of topics (ie, the number of topics discussed) is not sufficient to harness public engagement [20]. Social media campaigns ought to ensure that the topics discussed are distinct from one another, thus attracting a wider range of individuals with diverse interests, and that discourse surrounding a topic is internally consistent and coherent so they make sense to the public [20]. We herein call the former *intertopic distinctiveness* and the latter *intratopic consistency*.

Persuasion should follow engagement, which in this case is the effort by pro- and antivaccine advocates to encourage the public to accept or deny immunization. Framing vaccines in communications with individuals (eg, parents) has been suggested as a viable option for this purpose [29,30]. However, how the pro- and antivaccine messages fit into Entman's four dimensions [31] is less known. Entman's message frames are persuasive techniques used in propaganda in which a speaker tries to predispose the audience to a one-sided view of an issue while downplaying other perspectives. Indeed, antivaccine advocates disproportionately emphasize safety concerns while downplaying the preventive benefits of vaccines. When used consistently, Entman's frames can induce behavioral and attitudinal changes among audiences [31]. Therefore, identifying how Entman's four frames are used in pro- and antivaccine content will enable us to gauge how persuasive is each side.

The overall objective of this study was to compare the discursive topics pro- and antivaccine advocates deploy to influence the public to accept or deny immunization on the engagement-persuasion spectrum. Our overall objective was pursued using three specific aims as follows: (1) we classified tweets into provaccine, antivaccine, and neutral categories; (2) we extracted and visualized the intertopic distinctiveness and intratopic consistency of the discursive topics among the pro- and antivaccine tweets classified in (1); and (3) we identified how those topics frame vaccines along Entman's four framing dimensions. Our rationale for the first specific aim was that an automatic pro- or antivaccine classification is necessary for analyzing discursive topics on each side due to the sheer volume of vaccine-related content created and circulated on social media on a daily basis. Our justification for the second specific aim was that we need an autonomous method that considers the numerous linguistic features included in pro- and antivaccine tweets and extracts topics from both sides without human bias. The achievement of these first two aims explains higher engagement among antivaccine advocates than their provaccine counterparts. Our rationale for the third specific aim was that an analysis of the pro- and antivaccine topics along Entman's four dimensions would allow us to better understand how antivaccine advocates succeed in persuading the public to reject immunization as compared to their provaccine counterparts.

In achieving these aims, we make several contributions to methodological advances. First, we collected a large coverage of both pro- and antivaccine social media posts that fairly represent both parties [32]. Second, we developed a machine learning (ML)-based automatic classifier of pro- and antivaccine posts and unsupervised clustering for extracting discursive topics. This set of ML algorithms will aid future researchers in assessing the effectiveness of public health campaigns on social media and hence facilitate the successful development of future interventions. Lastly, we conducted a multistep content analysis that combines interpretive (inductive) with objective (deductive) coding to identify the topics within the dimensions of Entman's four message frames. In so doing, we alleviated methodological challenges that have hindered an analysis of pro- and antivaccine discursive topics from a broader engagement-persuasion perspective.

Prior Studies on Pro- and Antivaccine Advocates on Social Media

Antivaccine advocates on social media have shown more notable engagement patterns than their provaccine counterparts. On Instagram and Facebook, interaction tends to be higher with antivaccine content than with provaccine content [33,34]. Antivaccine articles are shared more widely than provaccine articles [28]. Although the number of provaccine tweets exceeds the number of antivaccine tweets, the proportion of antivaccine users on Twitter is rising, having nearly doubled from 8.1% to 16% between 2015 and 2018 [35]. Moreover, those who have been exposed to antivaccine content on Twitter and Facebook [34,36] are more likely to disseminate similar antivaccine content. Parents exposed to antivaccine content on Facebook were 1.6 times more likely to consider vaccines to be unsafe [37]. Antivaccine communities are more integrated with users who are undecided about vaccines compared to provaccine users, who remain on the periphery [26].

This higher user engagement has been attributed to a higher diversity of topics included in antivaccine rhetoric compared with provaccine content. Strong themes have emerged among antivaccine communities, and they tend to cover a more expansive and generalizable range of content than provaccine communities [26]. This expansive range of topics is conducive to defining a broad "in group" based on shared values as follows: distrust of the government and pharmaceutical companies, health and safety awareness, the use of natural health and wellness strategies [25-28], emphasis on religion and morality [25,27], and advocacy for individual liberties [25,27]. Antivaccine communities also tend to share news reports and personal narratives among themselves, elevating the visibility and pertinence of select issues across communities on social media [4,28]. Memon et al [38] conducted a network and linguistic analysis of vaccine-related tweets and found that antivaccine communities use more specific, dramatized, and personalized linguistic features, have higher network density, and demonstrate higher echo-chamberness than do provaccine advocates. Furini and Menegoni [39], Faasse et al [40], and Okuhara et al [41] defined the characteristics of topics used by pro- and antivaccine groups such as the tendency for antivaccine sites to focus on vaccine side effects and for provaccine sites to focus on vaccine primary effects.

These seminal works, however, have not yet fully explicated the intertopic distinctiveness or intratopic consistency of discursive topics discussed by pro- and antivaccine advocates, even though these factors are known to foster user engagement [20,42]. In addition, few prior studies have applied Entman's message framing to explain how antivaccine advocates portray vaccines as harmful rather than beneficial [39-41]. Our suggested comparison between pro- and antivaccine content using the engagement-persuasion spectrum therefore helps explain both why and how antivaccine communities demonstrate higher engagement and affect uptake rates despite opposition from provaccine advocates.

Hypotheses Development on the Engagement-Persuasion Spectrum

Recent studies on social media marketing posit that a variety of content should be created to actively engage customers in a dialogue with the speaker [20]. This marketing perspective is relevant because pro- and antivaccine advocates compete to keep the audience engaged in their content with the ultimate goal of persuading the public for or against vaccines [26].

Although a diversity of topics in social media content is linked to increased user engagement, simply counting the number of topics discussed is not sufficient [20,42]. Instead, one ought to consider intertopic distinctiveness, which aids in serving a wider array of individuals with various interests [20]. For instance, if provaccine advocates discuss various issues only in the realm of contagious diseases (eg, herd immunity), individuals who believe they have strong immunity (eg, young people) may not engage with such content. The COVID-19 pandemic has made clear the importance of intertopic distinctiveness. Communicating the harms of the viral infection was not enough to encourage some people in their 20s and 30s to comply with the measures of state lockdowns or social distancing in the United States. It is therefore important to develop various distinct topics to attract individuals with different interests (eg, herd immunity, fitness, and lifestyle). Next, intratopic consistency helps the audience make sense of the content, thereby facilitating the achievement of communication goals [20]. Especially in the uncontrolled space of social media, establishing consistency of messaging keeps the audience engaged [20]. Creating a coherent and consistent image of a reference object (in this case, vaccines) by coordinating and connecting messages, arguments, and statements is an integral part of social media communication [20]. Accordingly, we assessed whether antivaccine topics indeed have higher intertopic distinctiveness and intratopic consistency than provaccine topics.

Our next step was to measure the persuasiveness of messages. Prior studies have suggested that message frames are a viable option in terms of counteracting ever decreasing immunization rates. For instance, McGlone et al [29] have studied the possibilities for provaccine framing by health care sources to communicate with parents through text messages. Shoup et al [30] incorporated message framing into social media by observing and categorizing mothers' conversations on a moderated platform created specifically for patients of Colorado's health system.

Despite such prior pioneering attempts, these studies have not yet adopted Entman's four message frames [43-45]. Entman's message framing refers to the strategic and deliberate selection of content for messages with the purpose of attaching positive or negative meaning to an initially neutral topic [31,44]. Frames can illuminate or downplay specific aspects of an issue so that recipients of the message will begin to view the issue from the speaker's perspective [31]. Antivaccine advocates emphasize injuries and conspiracies surrounding vaccines so as to convince viewers to consider vaccines unsafe, while provaccine advocates underscore the preventive benefits of vaccines and portray them as public health assets [46]. Entman [31] asserts that speakers frame an issue through (1) defining it, (2) interpreting its cause, (3) morally evaluating it, and (4) recommending a remedy to it. Parties that consistently use these four message frames have a greater influence on the majority of receiving audiences [31], and this influence induces attitudinal and behavioral changes [24]. Therefore, we employed Entman's four message frames to analyze whether and how antivaccine advocates employ these four frames more comprehensively than provaccine advocates.

Methods

Overview

We adopted a multimethod approach to analyze discursive topics in large-scale vaccine debates on public social media sites. Our approach combined (1) large-scale balanced data collection from a public social media site (ie, Twitter), (2) the development of a supervised classification algorithm for categorizing tweets, (3) the application of an unsupervised clustering algorithm for identifying prominent topics discussed on both sides, and (4) multistep qualitative content analysis for identifying the prominent discursive topics and how vaccines are framed in these topics.

Step 1: Data Collection

Before and throughout our data collection, we identified, refined, and verified the keywords used to reach a large coverage of pro- and antivaccine tweets during our data collection period. Prior to embarking on the data collection, we studied previous academic and popular literature to identify relevant keywords and performed weekly tests by retrieving tweets using the search terms to ensure that they remained relevant. In particular, from previous academic literature [25] and popular press articles about the vaccine debate (from the *Washington Post*, the *New York Times*, and *Time* magazine from January 1, 2016, to September 1, 2019), we initially identified a list of 81 keywords related to the vaccine debate on Twitter.

Using these keywords, we then collected data every day in October 2019 and checked to determine how many tweets were retrieved on a weekly basis per keyword. From these weekly analyses, we eliminated 29 keywords for which the median weekly count of tweets retrieved was zero, because the absence of tweets retrieved by these keywords for an entire week indicated that these keywords were no longer relevant. Finally, using the remaining 52 keywords, we collected tweets every day in November 2019.

During our data collection in November 2019, we investigated whether any new topics or trending hashtags related to vaccines that had not been included in our set of keywords had emerged. To do so, we referred to the list of the top 50 trending topics on Twitter, which has been used by prior researchers (eg, Zubiaga et al [47]) to identify popular topics that trigger wider conversations on Twitter. Following Zubiaga et al [47], we checked the top 50 trending topics and hashtags for each day in November 2019, but no new vaccine-related topics emerged. Because Twitter was the source of our data collection, the absence of emerging vaccine-related hashtags in the Twitter top 50 trending topics during our data collection period suggests that our data collection is comprehensive, up to date, and relevant. A list of the 52 keywords is provided in Multimedia Appendix 1.

Our use of 52 keywords could have led to repeated collection of the same tweets if we had not carefully tracked and eliminated them. For instance, two of our keywords, *vaccine* and *sb276*, could retrieve a tweet such as "End Vaccine Tyranny now! End SB276" twice. To avoid redundancy in our data collection, we gathered the unique tweet IDs (tweet_ids) for each post. We kept track of all tweet_ids that we encountered each time we retrieved tweets using a keyword. In the case of collecting a retweet, which also contained the original tweet, we checked the original tweet to see if its tweet_id matched one that we had already collected. If it did not, we added the unique tweet_id to our list and saved the text of the tweet to a file. If the tweet_id was in our list, it was determined to be redundant and was not collected. The total number of tweets collected was 39,962 (11,103 provaccine, 8169 antivaccine, and 20,691 neutral tweets)

Step 2: Automatic Tweet Classification Algorithm

Next, we annotated tweets to construct our training set. Our initial annotation involved two members of the research team working simultaneously to ensure the correctness of annotations. The two coauthors communicated throughout the annotation process to resolve any disagreements and ambiguities in the annotations and to prevent any errors.

To improve generalizability and alleviate the researchers' bias in our annotations, we also employed an independent annotator who was not aware of the study's hypotheses to label a sample of our tweets. This independent coder was thoroughly trained by a member of the author team. Upon completion of the training, the coder was given 300 tweets to label as pro- or antivaccine. The set was an equal split between 150 pro- and 150 antivaccine tweets that had previously been annotated by the authors. We chose 300 tweets based on Durivage's convention for adequate sample sizes to validate the annotations [48] within a 5%-10% margin of error, assuming a 95% CI. The interrater reliability, measured with the Cohen kappa agreement statistic [49], was 0.83, indicating the highest range of Cohen kappa agreement between the two sets of labels. Our final annotated data set contained 5611 labeled tweets, consisting of the following classes: antivaccine (n=1550), provaccine (n=1639), and neutral (n=2422). The "neutral" class refers to the set of tweets that were neutral to vaccines or unrelated to vaccines even though we had collected tweets using vaccine-related keywords as described in *Step 1: Data Collection*.

The annotated tweets were then used to train a classifier for labeling the vaccination stance of the tweets. For reproducibility purposes, the Jupyter notebook containing our Python code and the results of its execution run can be obtained online [50,51]. First, each of these annotated tweets was preprocessed to generate its feature vector representation. Specifically, we applied NLTK's TweetTokenizer function to segment each tweet into a set of individual tokens (eg, terms, hashtags, and mentions). Terms corresponding to stop words were automatically removed using NLTK's stop word list augmented with our own list of stop words [51]. A feature vector was then constructed for each tweet by applying the CountVectorizer function from Python's Scikit-Learn library. This function takes as input a tweet message and returns a vector of frequencies for each unigram, bigram, hashtag, or mention that appears in the tweet. After preprocessing, each tweet was represented by a feature vector of length 15,948.

Once the feature vector for each tweet was constructed, we used Scikit-Learn's KFold split function to partition the data into 10 disjoint folds so that we could apply 10-fold cross-validation to train and evaluate our classifier. To do so, we iteratively chose nine of the 10 folds to be our training set while leaving the remaining fold out as test data. Using Scikit-Learn's l1-regularized logistic regression classifier (with its default hyperparameter value as a regularizer), we trained a model on the training set and applied it to the withheld test data. This process was repeated until each fold was used exactly once as the test data. As the class distribution was potentially imbalanced, we also applied the oversampling technique on the training set to ensure that the induced model was not biased toward accurately predicting the larger class only. This was accomplished by resampling the training examples from the smaller classes (ie, pro- and antivaccine) until every class had an equal proportion in the training data. The logistic regression classifier was then trained on the balanced training data, and its induced model was then applied to the withheld test fold.

Logistic regression is a binary classifier for estimating the conditional probability that an input feature x belongs to class y using the following equation:

where $\sigma(z)$ is known as the logistic function, and $\{\mathbf{w}, w_0\}$ are the model coefficients. The coefficients were estimated during training using the maximum likelihood estimation approach. This approach can be described as follows. Let $\{(\mathbf{x}1, y1), (\mathbf{x}2, y2), \ldots, (\mathbf{x}_N, y_N)\}$ denote the training set of N labeled tweets. The logistic regression classifier was trained to minimize the following l1-regularized negative log-likelihood function:

The l1-regularization penalty was used to prevent the model from overfitting the training data. We applied the default hyperparameter value (C=1) from Scikit-Learn's implementation of logistic regression as our regularization penalty. Although it is possible to obtain better results with more careful hyperparameter tuning, the default option was found to be sufficient to produce high accuracy. This is because the number of training examples was sufficiently large to ensure that the test accuracy was quite stable. For example, the test accuracy values varied only slightly between 87% and 91%, as λ varied by two orders of magnitude from 0.1 to 50.

Furthermore, because there were three types of classification labels (provaccine, antivaccine, and neutral), the classifier used the strategy of one versus all to train three binary models to predict each class. Specifically, each binary model was trained to distinguish the tweets of one label (eg, provaccine) from the other two categories. In the prediction step, the classifier applied all three models to each given tweet and assigned it to the class label with the highest aggregated confidence score.

We evaluated the performance of the logistic regression classifier using stratified 10-fold cross-validation. The classifier showed high overall classification accuracy of around 90.1%, which is the percentage of all labeled tweets predicted correctly by the classification models. The detailed classification results for the three categories are shown in the confusion matrix in Table 1.

In addition, we report the precision, recall, and F-measure of the classifier for each tweet class in Table 2.

The results shown in Table 1 can also be aggregated to analyze the classifier's performance in terms of distinguishing between tweets that are either pro- or antivaccine and those that belong to the neutral class. The confusion matrix for the two categories is given in Table 3, with an accuracy of around 96.2%.

The precision, recall, and F-measure of the two categories are shown in Table 4.

Table 1. Confusion matrix for the three classes of tweets.

Actual class	Predicted class		
	Antivaccine	Provaccine	Neutral
Antivaccine	1344	166	40
Provaccine	175	1364	100
Neutral	25	48	2349

Table 2. Precision, recall, and F-measure for the three classes of tweets.

Class	Precision	Recall	F-measure
Antivaccine	87.0%	86.7%	86.9%
Provaccine	86.4%	83.2%	84.8%
Neutral	94.4%	97.0%	95.7%

Table 3. Confusion matrix for the binary classification of tweets.

Actual class	Predicted class	
	Provaccine or antivaccine	Neutral
Provaccine or antivaccine	3049	140
Neutral	73	2349

Table 4. Precision, recall, and F-measure for the binary classification.

Class	Precision	Recall	F-measure
Provaccine or antivaccine	97.7%	95.6%	96.6%
Neutral	94.4%	97.0%	95.7%

Note that if we had explicitly trained a logistic regression classifier to distinguish between the two categories (provaccine or antivaccine vs neutral) instead of simply aggregating the results from Table 1, we would have obtained a similar test accuracy of around 96.1%.

Finally, we retrained the l1-regularized logistic regression classifier on the entire 5611 labeled tweets and applied them to the Twitter data we collected for November 2019. The final distribution of the classified tweets was as follows: provaccine, 11,103; antivaccine, 8168; and neutral, 20,691.

Step 3: Topic Analysis Using K-Means Clustering

Identification of Discursive Topics on Each Side of the Vaccine Debate

Next, we extracted the topical clusters of the pro- and antivaccine tweets that had been downloaded and classified as described above. Specifically, we used the K-means algorithm in the Scikit-Learn Python package [52]. We chose K-means clustering because unlike other algorithms, it has high stability when employing a large amount of data with many dimensions [53]. Clusters derived from the K-means clustering algorithm contain common words mentioned at a similar frequency rate. Thus, each cluster shows a group of words that appear together frequently, comprising a topic of emerging tweets.

To determine the number of clusters (k) in both data sets, we measured their silhouette coefficients. The silhouette coefficient is a measure of cluster cohesion that considers the within-group and between-group distances between the members of each cluster. If the silhouette coefficient is 1, then the members in the same cluster are closer to each other than to those belonging to other clusters. If it is −1, then the components of the clusters are completely misclassified. If it is 0, then the clusters are not well separated because their within-group and between-group distances are close to each other [54].

In Figure 1A and B, we plotted the average silhouette coefficients for k=0 to k=30 in our data. For provaccine tweets, the silhouette score was the highest at k=23 (silhouette=0.0166). Thus, we used k=23 as the number of clusters (topics) for provaccine tweets. Among antivaccine tweets, k=24 had the highest silhouette score (0.0123).

Using these k values for the analysis, we identified the prominent clusters of both pro- and antivaccine tweets as those having at least 5% of the total tweets in the data set. For the provaccine tweets, this included clusters with a count higher than 472. For the antivaccine tweets, this included clusters with a count higher than 396. There were four prominent provaccine clusters and four prominent antivaccine clusters. Figure 2 shows the counts for each of these prominent clusters.

Prior to proceeding to the subsequent analyses, we noticed that the top 50 words in three clusters on each side consisted entirely of Twitter handles. These were provaccine clusters 3, 16, and 18 and antivaccine clusters 3, 5, and 7. This suggests that these clusters entail closed-loop tweets and responses to those tweets rather than open dialogues among the public. Consider a long thread of tweet exchanges between two people, @JohnDoe and @JaneDoe, as an example. These clusters represent closed-loop conversations between individual accounts rather than discussion topics among a large group of vaccine advocates, and hence, they are not included in the subsequent analyses.

Figure 1. Determining the optimal cluster size (k) for (A) provaccine and (B) antivaccine tweets.

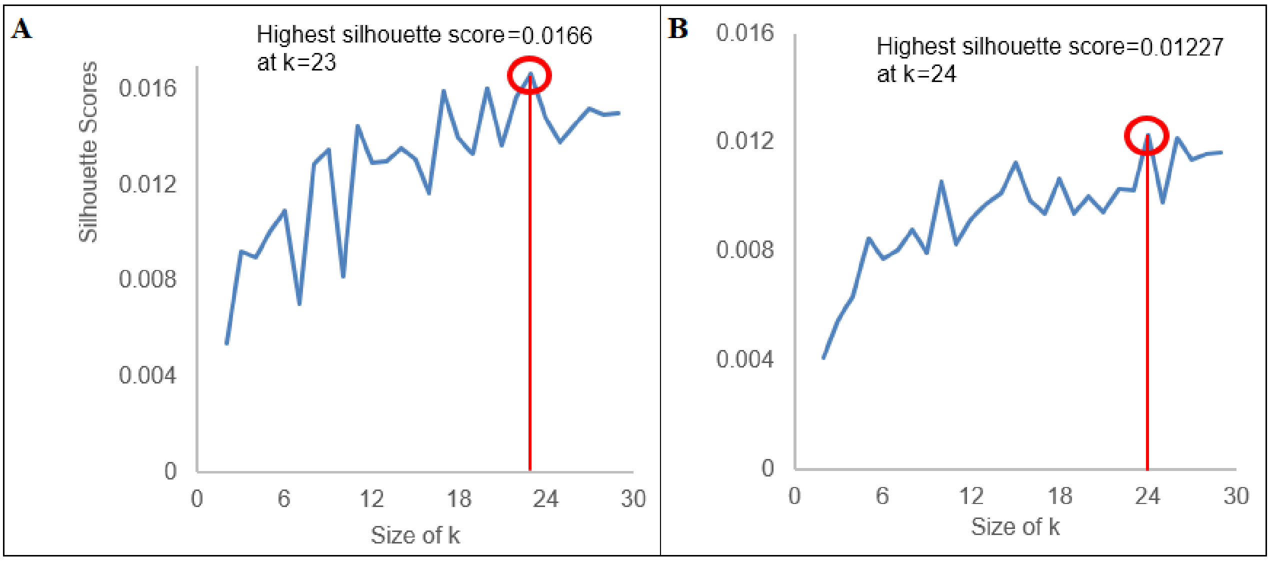
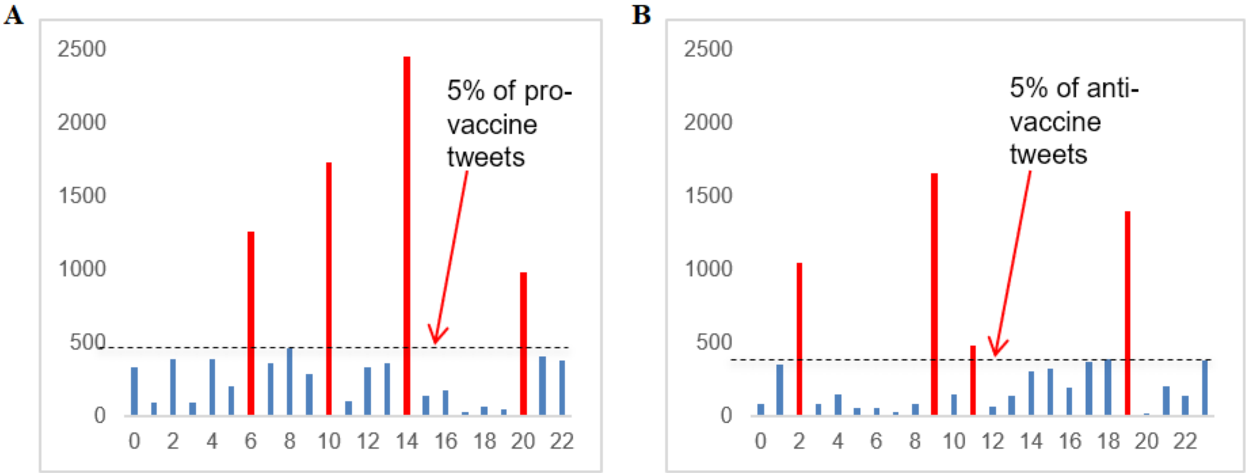


Figure 2. Provaccine (A) and antivaccine (B) cluster counts. In A, clusters 6, 10, 14, and 20 each hold over 5% of the tweets in the data set. In B, clusters 2, 9, 11, and 19 each hold over 5% of the tweets in the data set.



Intertopic Distinctiveness and Intratopic Consistency

Among the selected clusters, we examined the intertopic distinctiveness and intratopic consistency. The former is depicted as the distance between circles, and the latter is depicted in terms of the radius of each circle. The distance between clusters refers to the intertopic distinctiveness. A larger distance indicates distinct topics in the connected pair of clusters, while a smaller distance represents indistinct topics. The distance was calculated as follows:

where *x* and *y* refer to data points (tweets) in the clusters X and Y, and *x′* and *y′* refer to the centers of clusters X and Y. A distance score of less than 1 means there is significant overlap between the connected pair of clusters, and a score of 1 or greater indicates that the clusters are distinct.

The radii of the circles of clusters measure the intratopic consistency. A larger circle is associated with more inconsistent tweets in the cluster, and a smaller circle is associated with more consistent tweets in the cluster. The radius of each circle was calculated as follows:

where *x* refers to tweets as data points in the cluster X. The inconsistency (*x*, *x′*) is the separation between the data points *x* and *x′*, where *x′* is the center of the current cluster X. |X| is the total number of elements in cluster X.

Step 4: Qualitative Content Analysis

In addition to calculating intertopic distinctiveness and intratopic consistency, we applied a two-phased qualitative content analysis to the predominant clusters to identify the message frames used by the pro- or antivaccine clusters. In Figure 2, we selected four predominant provaccine clusters and four predominant antivaccine clusters, each of which have over 5% of the total collected tweets. Our two-phased content analysis consists of first identifying the main topics that appear in each of the predominant clusters and then identifying the frames used in each of the identified topics. This multistep coding was conducted because Entman [31] asserted that message frames should be identified from the topics, not from individual messages such as tweets. In the first phase, we extracted the main discursive topics for each prominent cluster, and in the second phase, we identified the framing used for each topic. Specifically, in the first phase, we exploited the advantages of inductive coding, whereby new concepts emerging in the clusters were identified [55]. In the second phase, we developed a detailed coding scheme to match our clusters to Entman's (1993) framework [55,56]. Our coding scheme included explicit definitions, examples, and procedures for each category, noting "exactly under what circumstances a passage can be coded with a category" [57]. The coding scheme is presented in Multimedia Appendix 2. Additionally, we employed a second independent coder who had no knowledge of the hypotheses. The interrater reliability with Cohen kappa agreement statistic was 0.83, indicating the highest range of Cohen kappa agreement between the coder and the authors' categorization [49].

Results

Results From K-Means Clustering: Visualization and Significance Testing of Intertopic Distinctiveness and Intratopic Consistency

From Figure 1, we took 20 provaccine clusters and 21 antivaccine clusters, excluding three on each side that were comprised of Twitter handles only, as described in the previous section *Identification of Discursive Topics on Each Side of the Vaccine Debate*. Additionally, as noted earlier in the same section, we took four prominent clusters (clusters with over 5% of the total tweets) from each of the pro- and antivaccine sides as shown in Figure 2. Then, we plotted the prominent clusters in relation to the rest of the clusters within the respective side of the vaccine debate to visualize intertopic distinctiveness and intratopic consistency, as shown in Figures 3 and 4. Specifically, we positioned the prominent clusters in the center of each chart and related them to the rest of the clusters on their respective sides.

Figure 3. Distance between prominent provaccine clusters and the rest of the clusters.

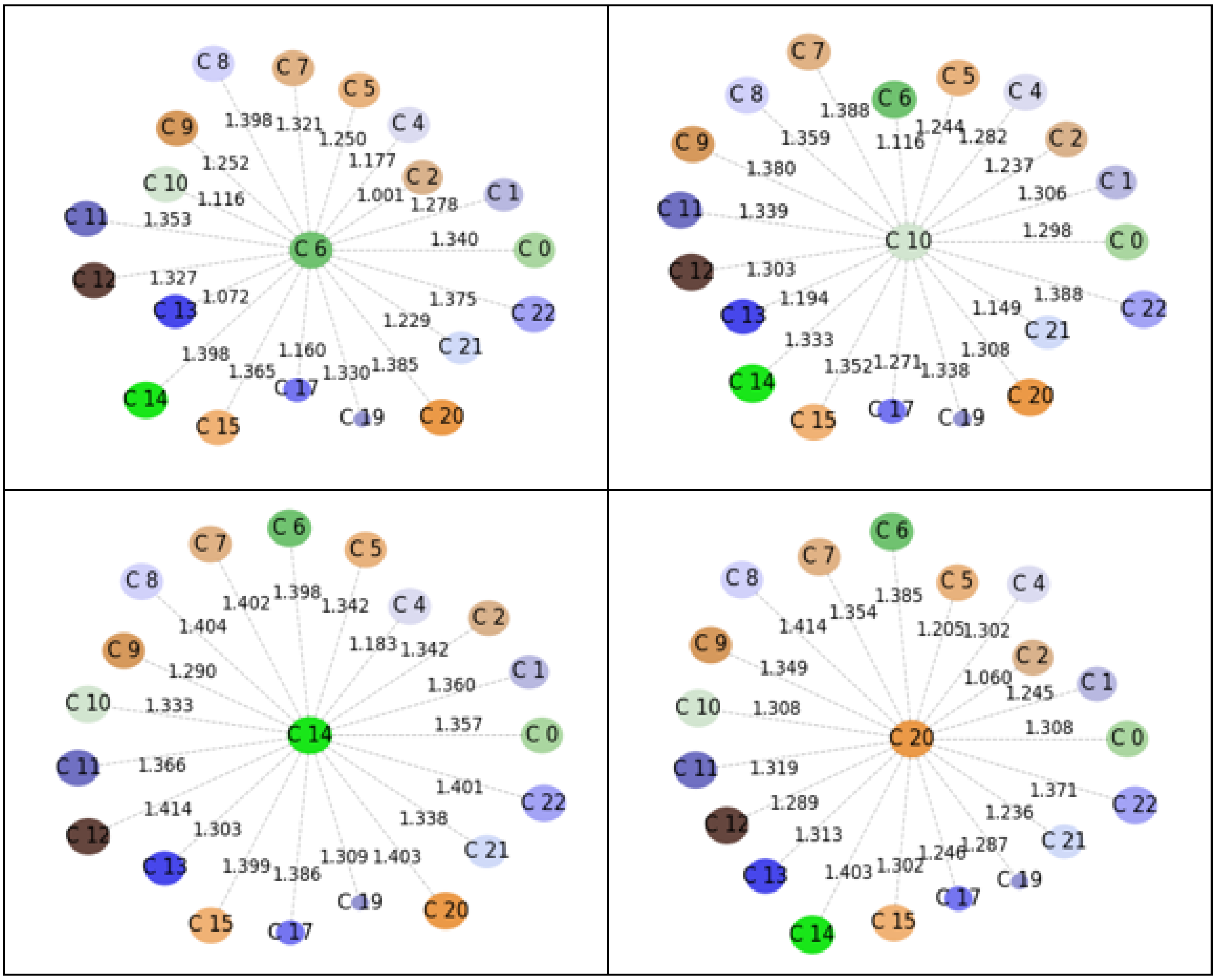
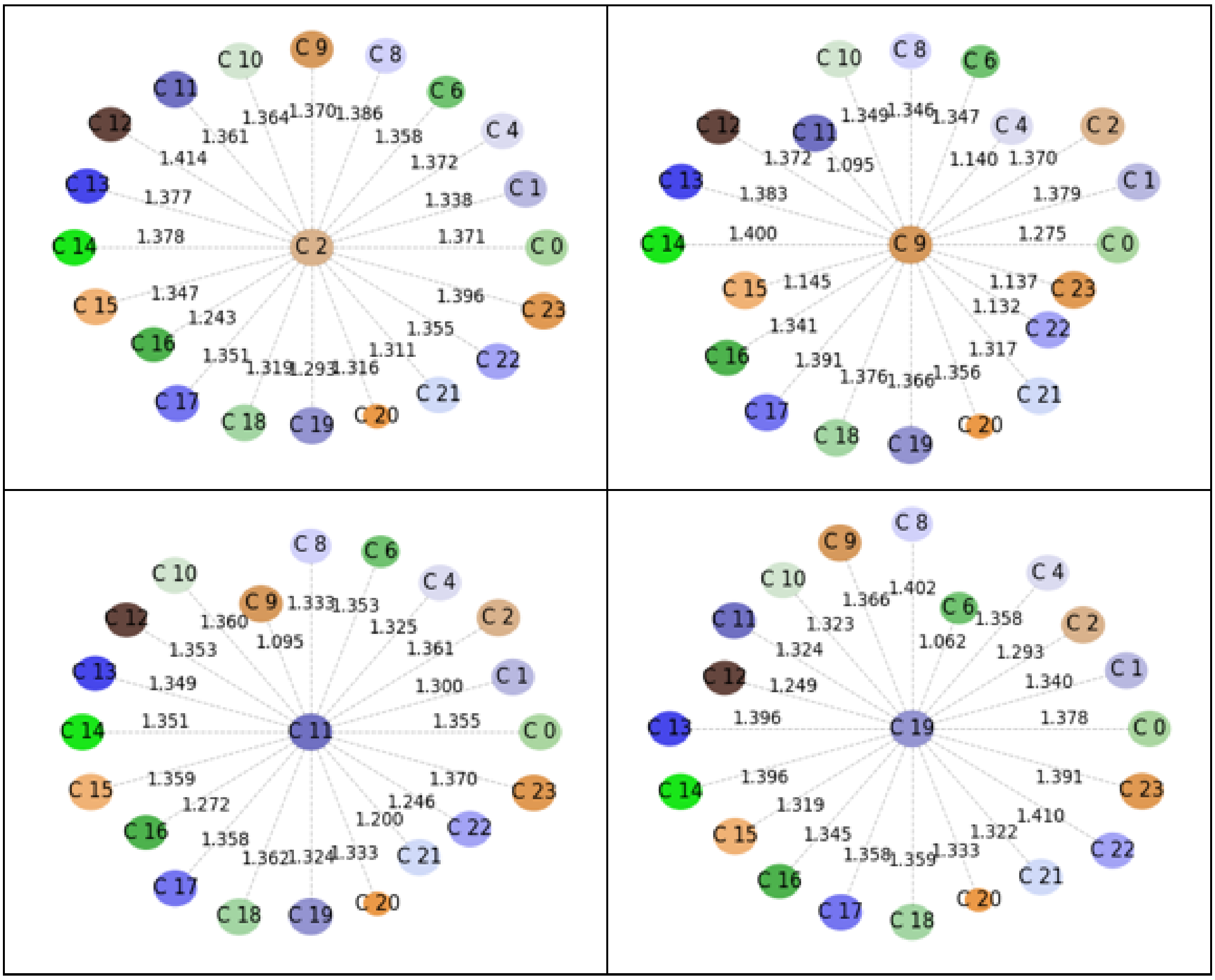


Figure 4. Distance between prominent antivaccine clusters and the rest of the clusters.



Figures 3 and 4 show that the provaccine clusters were less distinct among themselves than were the antivaccine clusters. We hereafter label the provaccine clusters as Pro-C[cluster number] and the antivaccine clusters as Anti-C[cluster number]. The shortest distance was found between Pro-C6 and Pro-C2, and the distance score was 1.001. The shortest distance found on the antivaccine side was 1.095 between Anti-C11 and Anti-C9. In addition, the mean distance between the prominent provaccine clusters (clusters 6, 10, 14, and 20) and the rest of the clusters was 1.30 (SD 0.09). The mean distance between the prominent antivaccine clusters (clusters 2, 9, 11, and 19) and the rest of the clusters was 1.33 (SD 0.07). Our t test result showed that there was a significant difference in the distances between the pro- and antivaccine clusters (t_{122}=2.30, P=.02 [two-tailed]).

Next, we compared the radii difference between the pro- and antivaccine clusters as a measure of intratopic consistency. As noted above, a smaller radius is associated with more consistent tweets within a cluster. The provaccine cluster radius mean was 0.91 (SD 0.14), and the antivaccine cluster radius mean was 0.95 (SD 0.08). We conducted a one-tailed t test given a prior study suggesting the higher density and echo-chamberness of antivaccine advocates [38]. There was no significant difference between the radii of the provaccine and antivaccine clusters at the significance level of .05 (t_{40}=0.99, P=.33 [two-tailed]).

Results From the Qualitative Content Analysis: Message Frames Used by Pro/Antivaccine Advocates

Tables 5 and 6 show the results of our two-phased content analysis. Our inductive coding results revealed two findings that had received less attention in the literature. First, provaccine advocates engaged in attacking antivaccine advocates (Pro-C14), and this topic had the most tweets (2450/11,103, 22.1%; over one-fifth of provaccine tweets). It is well known that antivaccine advocates attack government policies and pharmaceutical companies for being profit driven; however, it is less known that provaccine advocates also engage in condemning antivaccine advocates, except for the following two studies. A thematic analysis of the Australian provaccine movement identified hostility among provaccine advocates toward those who do not share their views [58]; however, this study was limited to the Australian context only. A qualitative interview with antivaccine mothers and women showed that antivaccine advocates believed that they were being stigmatized [9], but this study did not show how provaccine advocates' hostility was manifested in tweets. Our result showed not only that provaccine advocates criticize antivaccine advocates, but also that this criticism is the most prominent message conveyed by provaccine advocates on Twitter. This result provides a significant implication. Condemning antivaccine advocates can backfire and can only aggravate their mistrust of medical professionals and make their movement resilient [59]. Second, antivaccine advocates suggest a larger conspiracy theory beyond the connections between pharmaceutical industries and the government, including insurance policies, prescription drugs, and opioids (Anti-C9).

Table 5. Message frames used in prominent provaccine clusters.

Cluster	Count	Examples	Phase 1 inductive coding: Common topics found in each cluster	Phase 2 deductive coding: Entman's four message frames
Pro-C6	1256 tweets	*At least 115 countries have HPV vaccine in their normal routine vaccination. The vaccine prevents against HPV which causes cervical cancer. #SABCNews*	Vaccine efficacy (preventive benefits)	(4) Suggest efficacy of vaccines as remedies
Pro-C10	1732 tweets	*Reasons why I get my flu shot: -not a fan of the flu -my mom is immunocompromised from cancer -some people are allergic and can't get the vaccine -other people are immunocompromised -I trust science and scientists.*	Vaccine saves the vulnerable and the immunocompromised	(3) Moral judgment of the vaccines as creating herd immunity (social good)
Pro-C14	2450 tweets	*Dear antivaxxers… I'm busting my ass in grad school working on fungal vaccine development bc I wanted a creative way to poison the masses? I woulda just started a cult if that was my goal... xo A pissed off scientist.*	Criticizing antivaccine advocates	(2) Identify antivaccine advocates as the ones who cause the problem
Pro-C20	984 tweets	*Hey pls get vaccinated because i know at least three people at my school who aren't vaccinated simply because they don't want to and not because of any legitimate reason.*	Encouraging vaccine mandates for school children	(4) Suggest mandated vaccines as remedies

Table 6. Message frames used in prominent antivaccine clusters.

Cluster	Count	Examples	Phase 1 inductive coding: Common topics found in each cluster	Phase 2 deductive coding: Entman's four message frames
Anti-C2	1044 tweets	• *If education is the ticket to success #vaccines are the perfect tool to widen the class gap. While vaccine-free rich kids make the most of learning opportunities vaccines doom others to peonage by lowering their IQ and making it tough to function let alone excel in school.*	• Advocating exemption for mandatory school immunization	(4) Suggest vaccine exemptions as remedies
Anti-C9	1654 tweets	• *The CDC FDA and NIH excel at their core mission of spreading chronic ailments through tainted vaccines to generate huge profits for Big Pharma and Big Medicine.* • *@DemocratFed @FloBo2018 Big Pharma is immune from lawsuit spends more $$$ on lobbyists than any other industry and the CDC has been caught covering up data from studies. Only mind controlled slaves would support vaccine mandates. Are you a slave?*	• Corrupted connection between pharmaceutical companies and the government (especially Democrats) • Overarching conspiracy theory connecting prescription drugs, insurance, and opioids	(3) Moral judgment about the health care system as profit driven
Anti-C11	479 tweets	• *So Pharma is in a rush to wipe out the control group to reach 100% vaccination rates before people wake up. Anyone who supports these mandatory vaccine bills (A2371A in NY SB 276 in CA etc.) is engaged in racketeering crimes against humanity. There will be trials.*	• Schemes of pharmaceutical companies and injuries to children	(2) Identify pharmaceutical companies as causing the problems
Anti-C19	1397 tweets	• *The #vaccine is safe Doc insists the virus is contagious and dangerous. Mom says she must check. She later learns the vaccine carries the risk of twisting the bowel requiring surgery. The momentary rush of pleasing a doctor isn't worth a lifetime of suffering for your baby.*	• Vaccine injuries and safety concerns	(1) Define the problems as unsafe vaccines that cause injuries

Our deductive coding results indicated that provaccine themes can be classified into three of Entman's message frames, but one category, "defining the problem based on a cultural value," was missing. In other words, provaccine advocates do not clearly define the current problem, thereby failing to communicate the urgency of the matter to the public. Instead, they identify antivaccine advocates as the cause of the problem (Entman's frame #2, Pro-C14) and make moral judgments, for example, that vaccines are needed to create herd immunity (Entman's frame #3, Pro-C5). They also suggest vaccine efficacy and school mandates as remedies to the problem (Entman's frame #4, Pro-C6 and Pro-C20).

In contrast, antivaccine advocates clearly define the current problem, namely the connection between pharmaceutical companies and policy makers (especially Democrats) (Entman's frame #1, Anti-C9). They also identify pharmaceutical companies as causing the problem (Entman's frame #2, Anti-C11), seek to increase exemptions to mandated vaccines for public school entry (Entman's frame #3, Anti-C2), and make moral judgments about vaccination policies as causing injuries and endangering children's safety (Entman's frame #4, Anti-C19).

These findings suggest that provaccine advocates do not use message frames as comprehensively as antivaccine advocates do in terms of Entman's four frames. In particular, while provaccine advocates identify the cause of the problem, make moral judgments, and suggest remedies for the problem, they do not clearly state what this problem is. In contrast, antivaccine advocates provide a compelling statement of the current problem (vaccine injuries) in addition to using Entman's three other frames.

Discussion

Summary of the Findings

In this study, we aimed to comparatively analyze discursive topics in pro- and antivaccine content on the engagement-persuasion spectrum. Our overall objective was pursued with three specific aims as follows: (1) the development of an ML algorithm for automatic classification of pro- and antivaccine tweets, (2) the proposal of an unsupervised ML algorithm for topic analysis (ie, intertopic distinctiveness and intratopic consistency), and (3) the identification of frames used in these topics along Entman's four dimensions. Our results indicated that antivaccine advocates have significantly higher intertopic distinctiveness than provaccine advocates, but there was no difference between the two groups in terms of intratopic consistency. Our results also indicated that antivaccine advocate messages employ all four major frames that are known to be persuasive, while provaccine advocate messages fail to define the problem.

The first result on the higher intertopic distinctiveness explains the higher engagement among antivaccine communities on social media than that of provaccine advocates, as reported in the current literature [26]. Audiences' higher engagement in a topic is the first step to inducing behavioral changes favorable to the topic [60]. The higher intertopic distinctiveness of the antivaccine advocates' topics helps explain how engaging the antivaccine content is, keeping the antivaccine movement resilient and even thriving despite numerous efforts to counteract their messages. The first finding and its implications therefore help us fulfill our first specific aim. The second result suggested a reason why large-scale public provaccine campaigns on social media have rarely been associated with increasing vaccine uptake. Provaccine advocates do not clearly define the current problem; instead, they focus on criticizing and morally judging antivaccine advocates, as well as suggesting remedies. The absence of a clear problem statement limits their capacity to communicate the urgency of the matter at hand. This second result thus fulfills our second specific aim. We must note that no significant difference in intratopic consistency was discerned between pro- and antivaccine content, in contrast to our expectation. We attribute this nonsignificant result to the use of dramatized linguistic features [38] and the frequent references to personal anecdotes and news articles by antivaccine advocates [4,28]. Such varied linguistic features and stories employed by antivaccine advocates could explain why we did not find their topics more consistent than those of their provaccine counterparts. We discuss this point further in the subsequent section *Limitations of the Study and Suggestions for Future Research*.

Contributions to Knowledge Advancement and Methodology Development

This study contributes to both methodology development and knowledge advancement. First, we developed an ML algorithm that automatically classifies tweets into three classes as follows: provaccine, antivaccine, and neutral. This algorithm has a high accuracy rate (over 90%), which is among the highest for existing algorithms developed for vaccine debates on social media [61,62]. Further, unlike previous work that adopted a one- or two-category classification [34,46], our inclusion of the third category (ie, neutral) screened out irrelevant and neutral tweets with an accuracy rate of 96.2%, allowing us to focus on pro- and antivaccine content only. This algorithm will benefit future researchers who wish to build a public database for social media vaccine debates.

Second, we proposed a way to operationalize and visualize the topics of vaccine debates using K-means clustering. Specifically, our visualization methods can be used to depict intertopic distinctiveness (ie, the distinctiveness of each topic in relation to other topics) and intratopic consistency (ie, the consistency of the themes discussed in each topic). Although the wide variety of topics among antivaccine advocate communities has been noted in earlier studies [25-28], their intertopic distinctiveness and intratopic consistency have not been noted. This study is the first to show that antivaccine topics are distinct from one another, which potentially makes the antivaccine content more engaging to a wider range of individuals with idiosyncratic interests. Future researchers and public health officials may employ these new visualization tools in their efforts to assess the effectiveness of any large-scale health communication campaign.

Third, we devised a two-phased qualitative content analysis whereby we first extracted the prominent topics of each cluster and then identified the message frame employed in that topic following the widely accepted procedure for qualitative content analysis [57]. We also developed a detailed coding scheme and employed an independent coder to ensure the reliability and objectivity of our coding [57]. These coding sheets can benefit future researchers who aim to analyze the topics of the vaccine debate in-depth and develop interventions for disseminating provaccine messages [26].

These methodological advances enabled us to contribute to knowledge advancement in the social media vaccine debate. Many prior studies have examined different patterns of engagement and the diversity of topics between pro- and antivaccine advocates on social media [26,38-41,63-65]. However, comparisons from the broader engagement-persuasion spectrum remain unexplored. In particular, the intertopic distinctiveness and intratopic consistency among the two sides have not yet been compared, even though they are measures of social media users' engagement with a topic. In addition, Entman's message framing has not been applied to vaccine debates on social media, although message framing is one of the fastest growing topics in interpersonal vaccine communication [46]. The integrated analyses in this study help identify reasons for the findings reported in prior studies, specifically why antivaccine communities demonstrate higher engagement [39-41,63,64], density, and echo-chamberness [26,38] and how antivaccine advocates successfully dissuade the public from immunization despite opposition from their provaccine counterparts.

Limitations of the Study and Suggestions for Future Research

The advantages of our study come with several limitations. First, we collected tweets only in November 2019, during which survivorship bias and semantic shifts could have occurred in the vaccine debate on Twitter. To mitigate potential issues with survivorship bias, we selected November, which is during the peak season for antivaccine posts on Twitter [62], to properly represent the antivaccine movement on Twitter. To mitigate likely issues with semantic shifts, we comprehensively chose keywords that were relevant to the vaccine debate prior to embarking upon the data collection and verified that we covered the most current keywords throughout the data collection period.

Our data collection from only Twitter is the second limitation. However, Twitter is one of the most commonly adopted data collection sites for vaccine debates due to its advantage as a public microblogging site where anyone in the public can join in the vaccine debate [62]. Other social media sites, such as Facebook, can be an option but have stricter privacy settings that prohibit researchers from downloading users' posts. However, we acknowledge that an analysis of more diverse social media may reveal differences unique to each platform.

Third, we analyzed only textual tweets, although social media vaccine debates often employ visual components in their posts [66]. As more social media become visual rather than textual, it will become important to understand how these images deliver a message, and it may be that these topics are different from the ones conveyed in text [66]. These limitations can be overcome by future researchers who expand their data collection for a longer period of time from multiple social media platforms and who develop multimodal algorithms to analyze both text and images.

Fourth, we made an assumption that pro/antivaccine advocates attempt to persuade the public to accept or deny immunization, not each other. As the intended audience for tweets is unclear on social media, this assumption is a potential limitation of this study. However, prior studies have shown that pro/antivaccine advocates are less likely to try to persuade each other due to confirmation and selection biases [26,34]. Rather, pro/antivaccine advocates are more likely to persuade undecided individuals in the general public given the larger presence of undecided individuals (74 million out of 100 million Facebook users) compared to pro/antivaccine advocates on a social media platform [26] and given the main purpose of using Twitter being reaching and persuading a larger audience [67].

Finally, our *t* test result did not show a significant difference between pro- and antivaccine content in terms of intratopic consistency. We attribute this nonsignificant result to antivaccine advocates' use of various linguistic features [38] and frequent references to secondary sources [28], which may have interfered with our assessment of the intratopic consistency of antivaccine content. One explanation for such nonsignificant results would be that the varied messages seen in antivaccine content make the audience allocate more cognitive capacity to make sense of messages than they would with identical messages, thus making the content more engaging [42]. The current literature on social media marketing has not yet reconciled the conflicting findings between the effectiveness of consistent messages and varied messages for engagement. A comparison between the two may be an opportunity for future researchers.

Conclusion

Although digital networks have brought several important benefits to public health [10], they have facilitated the propagation of vaccine misinformation. We proposed ML algorithms for automatically classifying a large number of vaccine-related tweets into three classes (provaccine, antivaccine, and neutral), used K-means clustering to quantify and visualize the characteristics of each side of the vaccine debate, and used a two-phased qualitative content analysis to compare both sides of vaccine activism from an integrated communication perspective. Our results indicate that antivaccine content has higher intertopic distinctiveness and frames vaccines along Entman's four dimensions. These results provide an explanation for the higher engagement among antivaccine advocates and emphasize the urgency of developing a clear problem statement for provaccine content to counteract decreasing immunization rates.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Keywords used for downloading tweets.
[DOCX File , 27 KB - publichealth_v7i6e23105_app1.docx]

Multimedia Appendix 2
Qualitative coding scheme.
[DOCX File , 25 KB - publichealth_v7i6e23105_app2.docx]

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Abbreviations

ML: machine learning

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Original Paper

YouTube Videos Related to the Fukushima Nuclear Disaster: Content Analysis

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Abstract

Background: YouTube (Alphabet Incorporated) has become the most popular video-sharing platform in the world. The Fukushima Daiichi Nuclear Power Plant (FDNPP) disaster resulted in public anxiety toward nuclear power and radiation worldwide. YouTube is an important source of information about the FDNPP disaster for the world.

Objective: This study's objectives were to examine the characteristics of YouTube videos related to the FDNPP disaster, analyze the content and comments of videos with a quantitative method, and determine which features contribute to making a video popular with audiences. This study is the first to examine FDNPP disaster–related videos on YouTube.

Methods: We searched for the term “Fukushima nuclear disaster” on YouTube on November 2, 2019. The first 60 eligible videos in the relevance, upload date, view count, and rating categories were recorded. Videos that were irrelevant, were non-English, had inappropriate words, were machine synthesized, and were <3 minutes long were excluded. In total, 111 videos met the inclusion criteria. Parameters of the videos, including the number of subscribers, length, the number of days since the video was uploaded, region, video popularity (views, views/day, likes, likes/day, dislikes, dislikes/day, comments, comments/day), the tone of the videos, the top ten comments, affiliation, whether Japanese people participated in the video, whether the video recorder visited Fukushima, whether the video contained theoretical knowledge, and whether the video contained information about the recent situation in Fukushima, were recorded. By using criteria for content and technical design, two evaluators scored videos and grouped them into the useful (score: 11-14), slightly useful (score: 6-10), and useless (score: 0-5) video categories.

Results: Of the 111 videos, 43 (38.7%) videos were useful, 43 (38.7%) were slightly useful, and 25 (22.5%) were useless. Useful videos had good visual and aural effects, provided vivid information on the Fukushima disaster, and had a mean score of 12 (SD 0.9). Useful videos had more views per day (*P*<.001), likes per day (*P*<.001), and comments per day (*P*=.02) than useless and slightly useful videos. The popularity of videos had a significant correlation with clear sounds (likes/day: *P*=.001; comments/day: *P*=.02), vivid information (likes/day: *P*<.001; comments/day: *P*=.007), understanding content (likes/day: *P*=.001; comments/day: *P*=.04). There was no significant difference in likes per day (*P*=.72) and comments per day (*P*=.11) between negative and neutral- and mixed-tone videos. Videos about the recent situation in Fukushima had more likes and comments per day. Video recorders who personally visited Fukushima Prefecture had more subscribers and received more views and likes.

Conclusions: The possible features that made videos popular to the public included video quality, videos made in Fukushima, and information on the recent situation in Fukushima. During risk communication on new forms of media, health institutes should increase publicity and be more approachable to resonate with international audiences.

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KEYWORDS

YouTube; Fukushima nuclear disaster; social media; risk communication; disaster; video platform; radiation; public safety; nuclear disaster

Introduction

The Great East Japan Earthquake (magnitude 9.0) and subsequent tsunami on March 11, 2011, caused an accident at the Fukushima Daiichi Nuclear Power Plant (FDNPP). The FDNPP (location: 37° 25′ North, 141° 02' East) is located approximately 200 km northeast of Tokyo. This disaster released massive amounts of radioactive material into the environment [1] and resulted in public anxiety toward nuclear power and radiation worldwide [2,3]. Fukushima City will host 6 softball games and 1 baseball game for the Tokyo Olympic games [4], and food from Fukushima Prefecture will be served. Almost 9 years after the nuclear disaster, environmental and food safety issues are again drawing worldwide attention [5,6].

Social media can be defined as interactive communication media that have been fused into human lives worldwide [7,8]. YouTube (Alphabet Incorporated) has become the most popular video-sharing platform worldwide and is the second most visited website, with 2 billion monthly users [9,10]. Younger generations in particular are being raised in a time of social media and are learning to acquire information from these media. Previous studies have shown that YouTube can create a platform for and play a positive or negative role in risk communication [7].

Anxiety toward nuclear power is an important social issue. The public lacks knowledge about radiological issues and distrusts information provided by authorities [11]. They need multiple sources of information after the nuclear disaster. Therefore, cooperation among authorities, stakeholders, specialists, international organizations, traditional media, social media, and other networks is required for effective risk communication [12,13]. YouTube is thought to be an important source of information about the FDNPP disaster for the world. However, some studies in the medical and education fields have reported concerns about misleading information in YouTube videos [14-16]. Even information from commentators on large media platforms were full of hyperbole about the Fukushima nuclear disaster [17]. The massive amounts of information on social media that were posted after the disaster have also resulted in distrust toward authorities [18]. Sugimoto et al [19] found that rumors about disaster information from mass media were related to high fear of radiation.

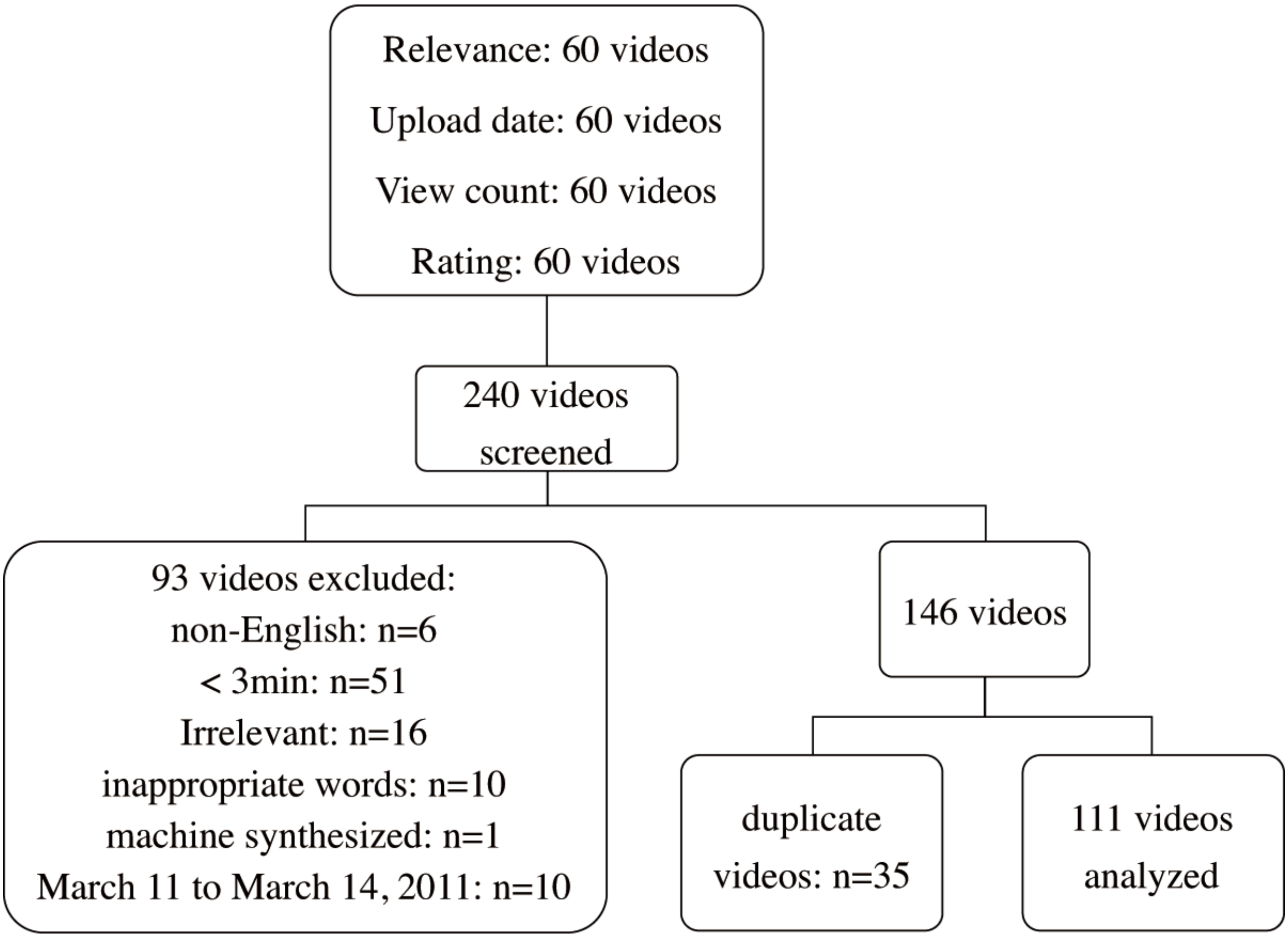
This study aimed to examine the characteristics of YouTube videos related to the FDNPP disaster, analyze the content and comments of videos with a quantitative method, and determine which features contribute to making a video popular with audiences.

Methods

Selection of Videos

On November 2, 2019, videos were identified by using the search term “Fukushima nuclear disaster” on YouTube via the Google Chrome browser. YouTube sorts videos into the following four filter categories: relevance, upload date, view count, and rating. The first 60 eligible videos in each category were recorded (Figure 1). Videos that were irrelevant, were non-English, had inappropriate words, were machine synthesized, and were less than 3 minutes long were excluded. Videos that were less than 3 minutes long were found to be repeated summaries of news or reports of the nuclear accident. Therefore, these were excluded. Furthermore, videos released from March 11 to March 14, 2011, were excluded because they were mainly news that were reported during the emergency period of the disaster. In total, 146 videos met our inclusion criteria. After excluding 35 duplicate videos, 111 videos were analyzed.

Figure 1. Flowchart showing the systematic video search and selection processes.



Collected Data

Characteristics of the videos, including the number of subscribers, length, the number of days since the video was uploaded, video popularity (views, views/day, likes, likes/day, dislikes, dislikes/day, comments, and comments/day), region, and affiliation (nonprofit organization or university, news source, for-profit company or organization, and private individual or layperson), were recorded (Table 1).

Table 1. Descriptive characteristics of videos.

Characteristics (N=111)	Value, mean (SD)	Value, median (range [minimum to maximum]; IQR)
Length (minutes)	23 (28)	12 (3-176; 31)
Number of days video was posted after the FDNPP[a] disaster (March 14, 2011, to November 2, 2019)	1173 (1080)	898 (3-3154; 2047)
Number of authorship subscribers	1,522,000 (5,317,000)	15,000 (0-42,900,000; 851,000)
Total number of views	261,367 (619,315)	4826 (20-4,918,238; 241,671)
Number of views/day	632 (2388)	19 (0.04-16,34; 344)
Number of likes	2474 (5483)	53 (2-39,000; 2743)
Number of likes/day	27 (169)	0.4 (0-1625; 4)
Number of dislikes	298 (946)	298 (1-66,000; 173)
Number of dislikes/day	0.7 (2)	0.03 (0-15; 0.3)
Number of comments	533 (1042)	20 (0-6253; 766)
Number of comments/day	3 (15)	0.1 (0-135; 1)

[a] FDNPP: Fukushima Daiichi Nuclear Power Plant.

We divided videos into the following five types based on format parameters: news and interviews, formal presentations, informal presentations, educational videos, documentaries. The following parameters of videos were also recorded: whether Japanese people effectively participated in the video, whether the video recorder personally visited Fukushima, whether the video contained theoretical knowledge of radiation, and whether the video contained information about the recent situation in Fukushima (after January 2017).

The tone of the videos was coded as neutral and mixed or negative by two independent evaluators. No videos were coded as having a positive tone. Neutral and mixed videos were those that reported news or recorded the situation in Fukushima and interviews without personal comments and judgment. Negative videos presented conspiracy theories about Japan and described serious health risks to people in the world. The top 10 comments of each video were collected and divided into the following six categories by two independent evaluators: (1) conspiracy theories (eg, "Japan is not honest"); (2) serious health risks (eg, "Be careful with radioactivity. Especially avoid Fukushima foods"); (3) positive comments on the video (eg, "Great video. All the necessary details and easy to understand. I would like news reports to be like this, not the very superficial coverage that is usually available to the public"); (4) negative comments on the video (eg, "Is he going to actually talk about Fukushima or just himself?"); (5) negative comments on official agencies (eg, "The backup generators are built under the reactor. If they are outside it would have been avoided"); and (6) other (eg, "What a disaster").

Evaluation Tool

Based on previous studies on educational and medical videos [14,15,20-22], we modified our evaluation tool to identify useful, popular science videos about the Fukushima nuclear disaster. Useful, popular science videos provided scientifically correct and understandable knowledge, and its contents were acceptable to the public. The major criteria comprised the following: (1) content about radiation and the Fukushima disaster are scientifically correct; (2) the video is balanced and unbiased; (3) sounds are clear, and the background is free from noise; (4) images are clear; and (5) the video vividly captures the event and is engaging. The minor criteria comprised the following: (1) the video covers the topic identified; (2) the video is designed at the general audience level; (3) the creator or the organization providing the video is mentioned; and (4) information about the recent situation in Fukushima is provided.

Each item in the major criteria has two scores and in the minor criteria has one score [21]. Videos were categorized as useless (score: 0-5), slightly useful (score: 6-10), and useful (score: 11-14). Useful videos were well made and provided scientifically correct and unbiased information about the Fukushima disaster. Two independent evaluators who were knowledgeable about radiation protection and the Fukushima nuclear power plant accident scored each video. If the two evaluators' scores differed, reviewers discussed the videos in a meeting and reached an agreement.

Statistical Analysis

Data were expressed as medians, minimums, and maximums. Normality was checked by using the Kolmogorov-Smirnov test. Since the variables were not normally distributed, nonparametric statistical tests were used. A Spearman correlation analysis was conducted to determine if video popularity correlated with the key parameters and scores. The Kruskal-Wallis test and Mann-Whitney U test were used to compare continuous variables. Statistical analysis was performed by using SPSS 21.0 (IBM Corporation). The significance level was set to $P<.05$.

Results

Characteristics of Videos

The descriptive information of 111 videos is summarized in Table 1. In total, 39 videos had a closed comment section or had no comments. Based on the posting dates, 11, 7, 13, 8, 3, 8, 12, 8, and 11 videos were uploaded on 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, and 2019, respectively. The median duration of the videos was 12.1 minutes. Videos were posted from March 2011 to November 2019. The median number of views per day was 4826, and the number of views widely ranged from 20 to almost 5 million. Of the 111 videos examined, 109 (98.2%) had more likes than dislikes. The median number of comments per day was 0.12 (range 0-134.7).

The format of the videos, authorship type, and the nationality of video uploaders are shown in Multimedia Appendix 1. Of the 111 videos, 43 (38.7%), 41 (36.9%), 11 (9.9%), 9 (8.1%) and 6 (5.4%) videos were news and interviews, informal presentations, documentaries, formal presentations, and educational videos, respectively. No significant differences in video popularity (likes/day and comments/day) were found among the five video formats (likes/day: P=.17; comments/day: P=.38).

Private individuals and laypersons posted 40/111 (36%) of the videos, news sources posted 32/111 (29%) of the videos, nonprofit organizations or universities posted 19/111 (17%) of the videos, and for-profit companies or organizations posted 17/111 (15%) of the videos. News sources and for-profit companies or organizations had more subscribers than nonprofit organizations or universities and private individuals and laypersons. In addition to news sources, organizations and individuals uploaded different types of videos, including on-the-spot interviews, press conferences, news about the accident, wastewater treatment, explanations of the principles and processes of the nuclear accident, and personal opinions. However, only videos made by for-profit companies or organizations received more views per day than those made by nonprofit organizations or universities (P=.01) and laypersons (P=.03). Videos uploaded by private individuals and laypersons (P=.02), for-profit companies or organizations (P=.004), and news sources (P=.02) received more likes/day than nonprofit organizations or universities.

Of the 111 video uploaders, 45 (40.5%) uploaders were from the United States and only 14 (13%) uploaders were from Japan. Video posters from the United States received more subscribers, views per day, likes per day, and comments per day than those from Japan. Videos from other countries received more views per day (P=.01) and likes per day (P=.04) than those from Japan. In total, 60% (24/40), 21% (9/43), 18% (3/17), and 16% (3/19) of videos with a negative tone were uploaded by private individuals and laypersons, news sources, for-profit companies or organizations, and nonprofit organizations or universities, respectively.

Useful Popular Science Videos About the Fukushima Nuclear Disaster

Of the 111 videos, 43 (38.7%) videos were useful, 43 (38.7%) were slightly useful, and 25 (22.5%) were useless (Table 2). The mean content score of the videos was 8.4 (SD 3.8). No significant difference was found between the content scores provided by the two evaluators (*P*=.99). Useful videos had good visual and aural effects, provided vivid information on the Fukushima disaster, and had a mean score of 12 (SD 0.9). The correlations between the total video scores and the number of subscribers, views per day, and likes per day were significant (*P*<.001). Useful videos had more views per day (*P*<.001), likes per day (*P*<.001), and comments per day (*P*=.02) than useless and slightly useful videos.

Table 2. Detailed characteristics of videos based on usefulness.

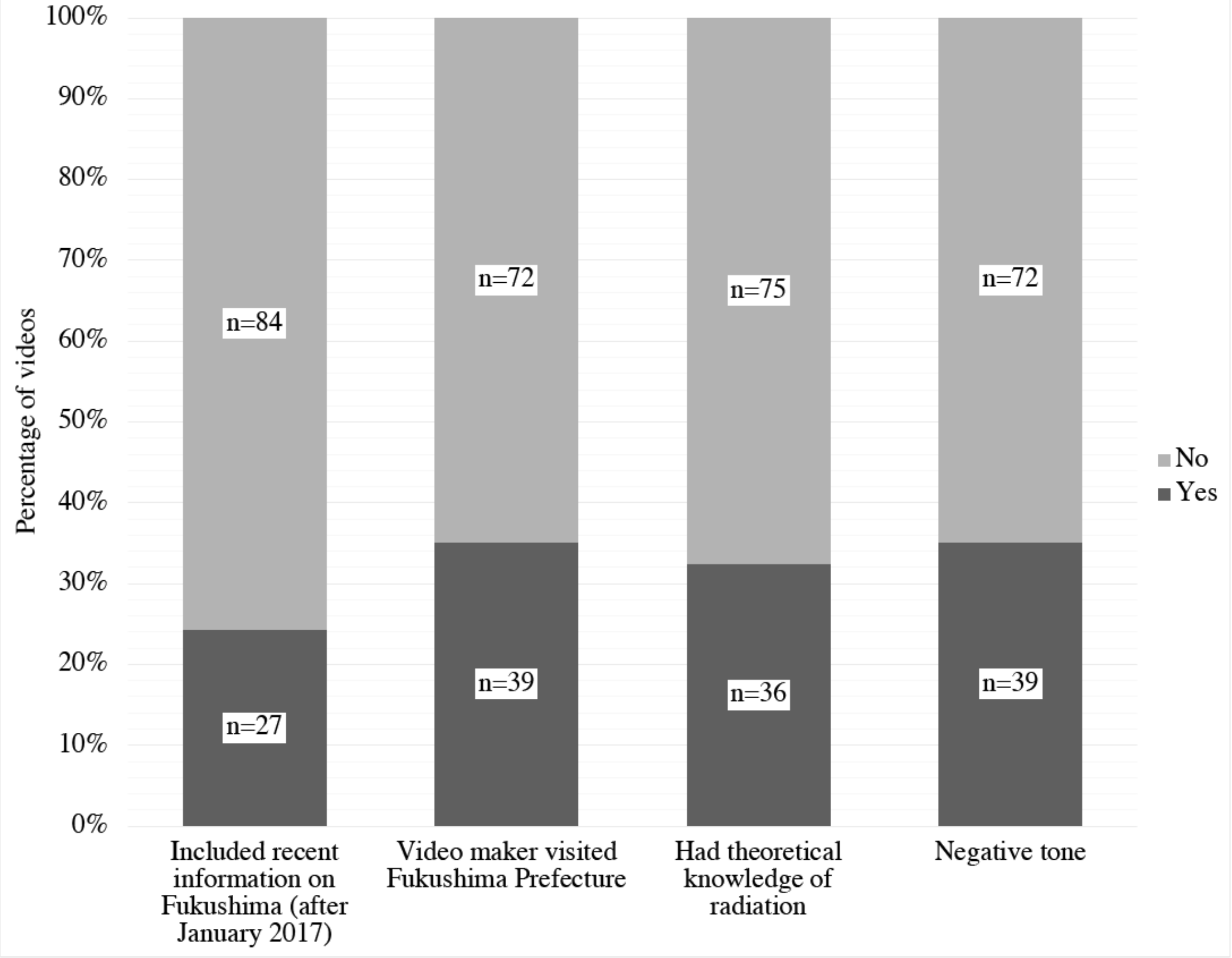
Characteristic	Useless (n=25), mean (SD; median; IQR)	Slightly useful (n=43), mean (SD; median; IQR)	Useful (n=43), mean (SD; median; IQR)	*P* value
Number of subscribers	1247 (6136; 1; 18)	921 (2412; 3; 50)	2282 (6759; 313; 1439)	<.001
Number of views/day	56 (161; 0.7; 47)	253 (599; 3; 298)	1345 (3700; 244; 603)	<.001
Number of likes/day	2 (5; 0.03; 1)	4 (8; 0.03; 4)	70 (282; 3; 6)	<.001
Number of dislikes/day	0.3 (0.6; 0.07; 0.5)	1 (2; 0.1; 1)	1.2 (3; 0.2; 0.6)	.37
Number of comments/day	0.5 (0.8; 0.1; 0.9)	1.4 (2.4; 0.4; 3)	8 (26; 0.6; 1)	.02

The popularity of videos had a significant correlation with clear sounds (likes/day: *P*=.001; comments/day: *P*=.02), vivid information (likes/day: *P*<.001; comments/day: *P*=.007), and understanding content (likes/day: *P*=.001; comments/day: *P*=.04).

Key Parameters

We defined 4 key parameters after reviewing the videos (Figure 2). Videos about the recent situation in Fukushima had more likes per day (*P*=.01) and comments per day (*P*=.04). Video posters who made videos in Fukushima had more subscribers (*P*<.001), views per day (*P*=.003), and likes per day (*P*=.01). Videos with theoretical knowledge of radiation had more subscribers (*P*=.04) and dislikes per day (*P*=.02). There was no significant difference in likes per day (*P*=.72) and comments per day (*P*=.11) between negative and neutral- and mixed-tone videos.

Figure 2. Distribution of the four key characteristics of videos.



Comment Content Analysis

Of the 588 comments extracted from videos, 292 (49.7%) comments were negative and included conspiracy theories and criticisms of official agencies and the Japanese government. For example:

> *Their government said they would use rice from Fukushima for Olympic.* [711 likes]
>
> *Japan is lying to its people and neighbors. They lie that their radioactive food is safe.* [659 likes]

Positive comments on videos comprised 73 (12.4%) of comments. For example:

> *The older employees should be considered a hero. I believe nuclear plant workers who saved or slowed a devastating reaction should be internationally recognized as a hero.* [5 likes]

Discussion

Principal Findings

In this study, videos had a high number of views, likes, dislikes, and comments, indicating that viewers seek FDNPP-related information on YouTube. Private individuals and laypersons uploaded the greatest number of videos that provided information about personal experiences in Fukushima Prefecture, summaries of news, personal opinions, and their perspectives on the nuclear accident. Japanese health-related institutions' videos comprised 12.6% (14/111) of FDNPP accident videos; this shows that these institutions did not pay sufficient attention to the YouTube platform in terms of the distribution of information overseas. It should be noted that no private individual and layperson uploaders were from Japan in this study. One of the reasons for this may be that only English videos were collected. Experts and the government should encourage people living in Fukushima Prefecture to engage with YouTube and show their real lives to the world.

Useful videos that had good quality and provided reliable radiation knowledge received more views, likes, and comments. The uploaders of these videos had more subscribers. The evaluation tool in this study was scientifically correct, balanced, and unbiased, but for the public, scientifically correct information and video tone were not statistically important elements of video popularity. This indicated the possibility of a large amount of misleading information being accessible to the public. A previous study also reported that governmental organizations' health information videos had limited impact [23]. The public has shown less interest in scientific educational videos and more in personal experiences [24]. The possible features that made videos popular to the public included the following: (1) the quality images and visuals, (2) sounds without background noises, (3) vivid and engaging content (4) understandable information, (5) videos made in Fukushima (personal experiences), (6) information on the recent situation in Fukushima, and (7) more subscribers.

In our sample of videos, educational and documentary videos that held a neutral position accounted for 15.3% (17/111) of the videos. Compared to the number of medical videos, there were fewer educational videos about nuclear accidents on YouTube [16]. One reason for this may be the cost and complexity of producing documentaries and educational videos. However, our analysis showed that various types of videos did not differ in popularity. Public health agencies may consider making simple videos, such as sightseeing and fieldwork recordings, to convey real-life situations in Fukushima Prefecture. The form of videos and the content they cover is not as important to the public as they are to experts. Instead of using complex scientific language, videos can use plain language to reach a wider audience in social media [18].

The most commonly watched videos were uploaded by for-profit companies or organizations, while the lowest number of likes per day was found on videos from nonprofit organizations or universities. The primary purpose of some videos was to attract viewers; thus, it is not surprising that the majority of video content was misinformation and conspiracy theories. Some studies have also reported on misleading health information on social media [23,25]. After the Fukushima nuclear accident, 80% of the total number of tweets on Twitter were created by 2% of influential accounts [26]. However, YouTube users can find varied videos when they conduct searches with keywords. Due to the difficulty of regulating YouTube videos and the platform's popularity, misleading videos may result in false impressions of the FDNPP disaster.

Our results show that half of the comments (292/588, 49.7%) were negative while the negative-tone videos comprised only 35.1% (39/111) of the total number of examined videos. For example, following a documentary uploaded by National Geographic, 1 comment said:

> *Fukushima was dangerous, is dangerous and will be dangerous.*

We believe that videos that portrayed personal experiences elicited more engagement, as evidenced by the high number of views and likes and by the fact that videos describing the recent situation in Fukushima had more likes and comments.

Limitations

This study has several limitations. First, only 1 search term—"Fukushima nuclear disaster"—was used, which might have resulted in videos on the study topic being missed. Second, we only analyzed videos in English and recorded publicly available metrics. In a follow-up study, it will be necessary to analyze Japanese videos of the Fukushima nuclear accident. Second, ours is a cross-sectional study that was conducted in November 2019; more videos have been made available since then. Last, although we used an evaluation tool, the subjectivity of judgment existed in this study. Conducting further research on content analysis of YouTube and improving the evaluation tools of popular science videos are necessary.

Conclusions

This study is the first to examine the Fukushima nuclear disaster–related information specifically found on YouTube. A large amount of information on the Fukushima nuclear disaster is available on YouTube. In this cross-sectional study, 38.7% (43/111) of YouTube videos provided useful information about the Fukushima nuclear disaster. However, for the public, scientifically correct information and video tone were not statistically essential elements in video popularity. The possible features that made videos popular to the public included good technical design, understandable content, personal experiences, and publishers' popularity. During risk communication on new forms of media, health institutes should increase publicity and try to be more approachable to resonate with international audiences.

Authors' Contributions

L Cui designed the study. L Chu and L Cui made the observations, analyzed the data, and wrote this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Format of videos, authorship type and uploader nationality.
[DOCX File , 16 KB - publichealth_v7i6e26481_app1.docx]

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Abbreviations

FDNPP: Fukushima Daiichi Nuclear Power Plant

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Original Paper

Risk Assessment of Importation and Local Transmission of COVID-19 in South Korea: Statistical Modeling Approach

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Abstract

Background: Despite recent achievements in vaccines, antiviral drugs, and medical infrastructure, the emergence of COVID-19 has posed a serious threat to humans worldwide. Most countries are well connected on a global scale, making it nearly impossible to implement perfect and prompt mitigation strategies for infectious disease outbreaks. In particular, due to the explosive growth of international travel, the complex network of human mobility enabled the rapid spread of COVID-19 globally.

Objective: South Korea was one of the earliest countries to be affected by COVID-19. In the absence of vaccines and treatments, South Korea has implemented and maintained stringent interventions, such as large-scale epidemiological investigations, rapid diagnosis, social distancing, and prompt clinical classification of severely ill patients with appropriate medical measures. In particular, South Korea has implemented effective airport screenings and quarantine measures. In this study, we aimed to assess the country-specific importation risk of COVID-19 and investigate its impact on the local transmission of COVID-19.

Methods: The country-specific importation risk of COVID-19 in South Korea was assessed. We investigated the relationships between country-specific imported cases, passenger numbers, and the severity of country-specific COVID-19 prevalence from January to October 2020. We assessed the country-specific risk by incorporating country-specific information. A renewal mathematical model was employed, considering both imported and local cases of COVID-19 in South Korea. Furthermore, we estimated the basic and effective reproduction numbers.

Results: The risk of importation from China was highest between January and February 2020, while that from North America (the United States and Canada) was high from April to October 2020. The R_0 was estimated at 1.87 (95% CI 1.47-2.34), using the rate of $\alpha=0.07$ for secondary transmission caused by imported cases. The R_t was estimated in South Korea and in both Seoul and Gyeonggi.

Conclusions: A statistical model accounting for imported and locally transmitted cases was employed to estimate R_0 and R_t. Our results indicated that the prompt implementation of airport screening measures (contact tracing with case isolation and quarantine) successfully reduced local transmission caused by imported cases despite passengers arriving from high-risk countries throughout the year. Moreover, various mitigation interventions, including social distancing and travel restrictions within South Korea, have been effectively implemented to reduce the spread of local cases in South Korea.

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KEYWORDS

COVID-19; transmission dynamics; South Korea; international travels; imported and local transmission; basic reproduction number; effective reproduction number; mitigation intervention strategies; risk; assessment; transmission; mitigation; strategy; travel; mobility; spread; intervention; diagnosis; monitoring; testing

Introduction

The COVID-19 outbreak has affected people worldwide. A novel virus named SARS-CoV-2 was identified as the pathogen responsible for the outbreak of COVID-19 [1]. The common symptoms of COVID-19 include fever, dry cough, fatigue, chills, headache, and sore throat. Furthermore, severe symptoms of COVID-19, including high fever, severe cough, and shortness of breath, are often indicative of pneumonia [2]. The first case of COVID-19 was reported in Wuhan, China, in early December 2019. On March 11, 2020, the World Health Organization (WHO) declared the outbreak a global pandemic [3]. As of October 31, 2020, a total of 45,551,965 confirmed cases and more than 1,189,306 deaths were reported in 214 countries worldwide. The world has experienced a couple of epidemics caused by coronaviruses from the same family as SARS-CoV-2, such as severe acute respiratory syndrome (SARS) caused by SARS-CoV in 2003 and Middle East respiratory syndrome (MERS) caused by MERS-CoV in 2012, which had a large impact similar to that of the currently ongoing COVID-19 pandemic. However, the impact of COVID-19 is different in many aspects and has been more devastating than that of the other two outbreaks [4-6]. Due to the substantial growth of international travel, the complex network of human mobility has allowed pathogens to spread globally within a short time scale. In particular, the recent new COVID-19 variants have motivated the implementation of strengthened border control and lockdowns worldwide [7].

In this regard, most researchers have confirmed that COVID-19 was exported via air travel from mainland China. Researchers have developed many mathematical, statistical, and computational models to analyze air traffic data and estimate the consequent effects. Many researchers have investigated COVID-19 transmission dynamics in various ways. They have analyzed the characteristics of pathogen transmission cases in various experiments using elaborate computational models; their findings have enlightened us on how COVID-19 may affect us in the future. International air travel volume has been significantly related to the spread of COVID-19 worldwide. A network-driven model of global spread employed air traffic data to demonstrate and compare the impacts of the H1N1 epidemic in 2009 and the SARS epidemic in 2003 [8]. Furthermore, the risk of MERS-CoV exportation worldwide was evaluated by incorporating seasonal air traffic flows and the time-varying incidence of cases in Middle Eastern countries [9].

Various studies have investigated the global spread of COVID-19 during the early stages of the pandemic. One study examined how COVID-19 was imported into Europe by analyzing air traffic data [10]. Another study investigated the risk of transmission of COVID-19 through flights from four major cities in China (Wuhan, Beijing, Shanghai, and Guangzhou) to the passengers’ destination countries [11]. The study identified a risk index of COVID-19 transmission based on the number of travelers to destination countries, weighted by the number of confirmed cases in the departed city as reported by the WHO. The importation risk of COVID-19 cases by air travel from infected areas in China was assessed [12]. The risk before and after the travel ban in Hubei province was compared. Travel restrictions and border control measures have been enforced in China and other countries to limit the spread of the disease [13]. The results of a previous study showed that the daily risk of exporting a minimum of one COVID-19 case from mainland China via international travel exceeded 95% on January 13, 2020 [13].

Furthermore, the risk of imported COVID-19 cases was investigated in China by measuring a risk index from inbound international flights in previous studies [14,15]. These studies evaluated policy implications based on the index to adjust international air travel restrictions dynamically. Another study analyzed imported cases of COVID-19 in Taiwan in terms of characteristics, infection source, symptom presentation, and route of identification of imported cases [16]. The study confirmed that the strict enforcement of countermeasures was effective in preventing community transmission. The risks of both importation and exportation of COVID-19 have been investigated in a previous study [17]. The study evaluated the risk of importation and exportation of COVID-19 in all airports of 73 countries during the early stages of the pandemic until March 3, 2020.

The complex network of human mobility has been identified as an essential factor responsible for the rapid spread of COVID-19 globally. Due to the special situation between South Korea and North Korea, international flights are the most common way to enter South Korea. In particular, due to a large number of international travelers from China, South Korea was one of the earliest countries to experience a COVID-19 outbreak. In the absence of vaccines and treatments, South Korea implemented and maintained stringent interventions such as large-scale epidemiological investigations, rapid diagnosis, case isolation, contact tracing, quarantine, and social distancing. Despite the overall dramatic decrease in international flights, there is still a constant inflow of flights from high-risk countries. Therefore, the risk of COVID-19 in South Korea must be assessed.

In this study, we investigated the impact of international travel on the local transmission dynamics of COVID-19 in South Korea. First, we identified the relationship between the number of international travelers and country-specific confirmed cases of COVID-19. We computed the country-specific importation risk of COVID-19, accounting for the number of travelers entering South Korea, the number of confirmed cases in the originating countries, and the population of the originating countries. Second, statistical modeling was employed to capture the impact of secondary transmission caused by both imported and local cases of COVID-19 and determine the basic reproduction number (R_0) and the effective reproduction number (R_t). Finally, we assessed the impact of imported cases on local transmission of COVID-19.

Methods

Epidemiological Data

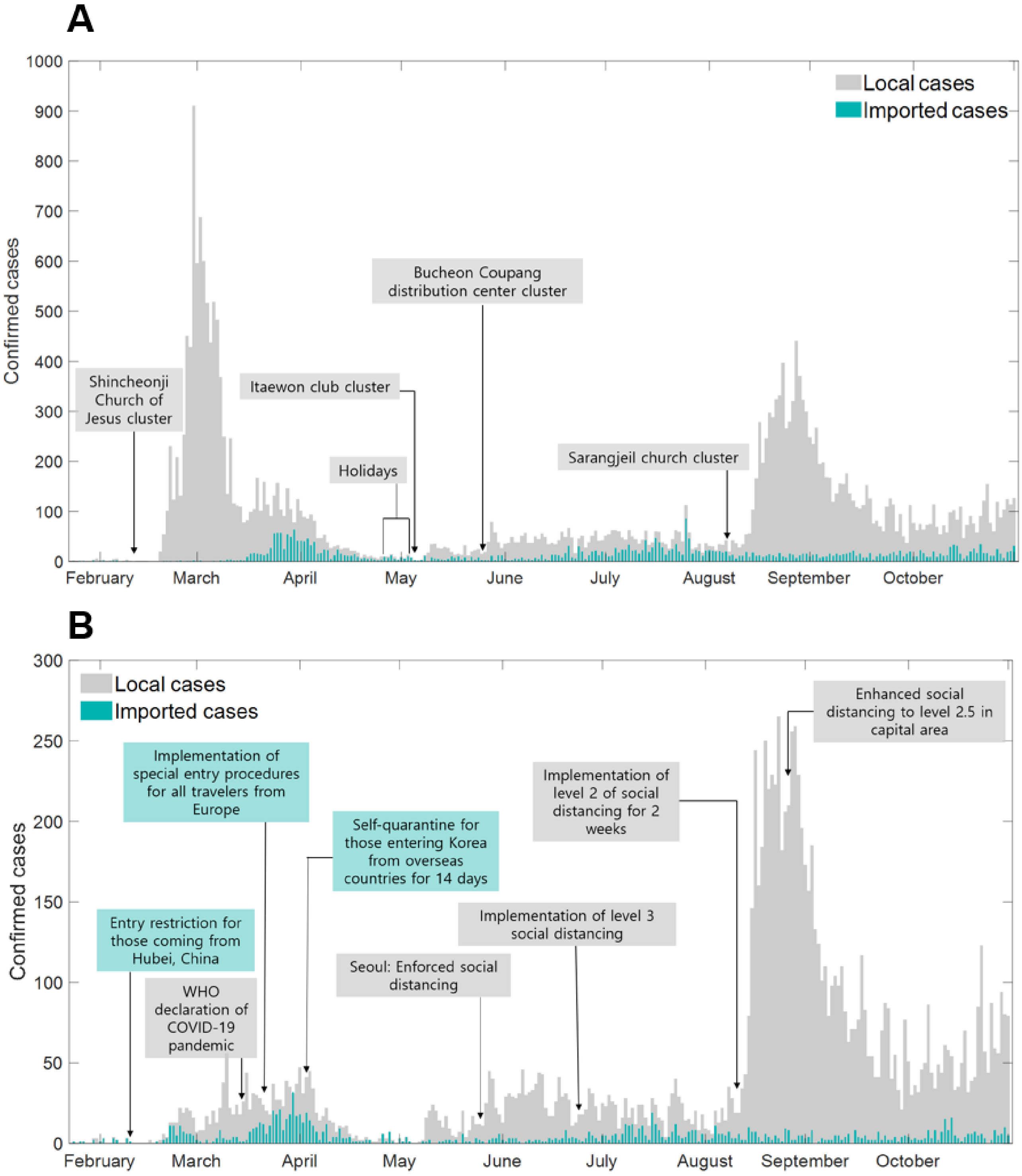
We analyzed country-specific epidemiological data on COVID-19 cases and international travel volume in South Korea from January to October 2020. First, data on the number of confirmed COVID-19 cases in South Korea were extracted from the Korea Disease Control and Prevention Agency (publicly available data) [18]. The epidemiological data included the dates of confirmation, dates of symptom onset, and transmission classification (local transmission/imported cases) [19]. Second, data on the monthly number of passengers entering South Korea in 2019-2020 were gathered from Incheon International Airport (publicly available data) [20]. Third, data on the number of confirmed cases of COVID-19 from the countries of origin were collected from the WHO situation report [21] and countries' populations were obtained from [22]. The country-specific data are presented in Table S1 and Figures S1-S5 in Multimedia Appendix 1.

Epidemiological Characteristics of COVID-19 Transmission Dynamics in South Korea

We have presented the epidemic curves of local and imported cases in South Korea in Figure 1A and in Seoul and Gyeonggi in Figure 1B. Most COVID-19 cases occurred in March 2020 (due to the explosive outbreaks in Daegu and Gyeongbuk), and the number of cases in Seoul and Gyeonggi increased steadily from May 2020, leading to a larger outbreak in September 2020. Figure 1B shows the epidemic curve in Seoul and Gyeonggi along with the timeline of screening and quarantine interventions (green box) and social distancing interventions (gray box). The list of selected interventions is presented in Table S2 in Multimedia Appendix 1. The COVID-19 transmission dynamics in South Korea showed spatial heterogeneity. There were two major hotspots. First, the early outbreak was primarily in the Daegu and Gyeongbuk areas from February to April 2020 due to the Shincheonji Church–related clusters, as shown in Figure 1A and reported previously [23,24]. Second, the late outbreak was primarily in the Seoul and Gyeonggi areas in September and November 2020, as it was triggered by the Sarangjeil Church–related gathering on August 15, 2020, as shown in Figure 1A.

The timeline of the administrative measures implemented in South Korea is shown in Figure 1B and Table S2 in Multimedia Appendix 1. The Korean government, Seoul, and Gyeonggi implemented administrative countermeasures in response to the COVID-19 outbreak, including guidelines for entry restrictions followed by the 2-week self-quarantine guidelines from a different period combined with social distancing interventions.

Figure 1. Epidemic curve of imported cases and local cases in South Korea. (A) Daily number of imported and local cases of COVID-19 in South Korea. (B) Daily number of imported and local cases in Seoul and Gyeonggi. Gray bars and green bars represent local cases and imported cases, respectively. WHO: World Health Organization.



Risk of Importation of COVID-19

We aimed to calculate the country-specific importation risk of COVID-19 based on the number of international travelers, confirmed cases in the originating countries, and the population of the originating countries. The countries were grouped as Europe (the United Kingdom, Germany, and France); China and Asia except China; and North America (the United States and Canada). Country-specific importation risk is defined as a function of three factors: population, the number of confirmed cases of COVID-19, and passengers entering South Korea [25,26]. The risk of importation from a given country in a given month was derived as follows:

where t is the month from January 2020 to October 2020 (t=1,2,…,10) and c is a group of countries (c={China, Asia [except China], Europe, North America}). $I_{c,t}$ stands for the monthly confirmed cases of COVID-19 in a month t and an originating country c. The population-adjusted density of infectious travelers was obtained by $I_{c,t}$ dividing its population pop_c of country c. $T_{c,t}$ represents the number of passengers traveling from country c in a month t. The normalized risk for country c in month t was as follows:

where $Max(\text{Risk}_{c,t})$ indicates the maximum of the $\text{Risk}_{c,t}$ for month t and country c. Moreover, we obtained a correlation between the monthly number of passengers and cases of COVID-19. We calculated the monthly Pearson correlation coefficients between the number of passengers and the number of COVID-19 cases corresponding to different countries including Japan, Vietnam, the Philippines, the United States, China, Thailand, Taiwan, Malaysia, Singapore, Germany, France, Canada, and the United Kingdom. The Pearson correlation coefficients are higher than 0.7 from April 2020, indicating that the number of passengers had a linear relationship with the number of COVID-19 cases in 2020. Overall, this implied that prompt country-specific surveillance should be implemented for a more cautious screening process that may be applied to passengers from higher-risk countries. The high correlation was due to two major countries—China was the highest risk country in the early stages of the pandemic, while the United States was the highest risk country in the later stages of the pandemic.

Estimation of Reproduction Numbers

In this section, a renewal equation was employed to estimate the R_0. The R_0 is defined as the average number of susceptible individuals infected by a single primary case. Previous studies on COVID-19 estimated the R_0 to be 2-3 [26-28]. In this study, we have categorized the total cases into locally transmitted (local cases) and imported cases. The total incidence of COVID-19 at time t, denoted by $i(t)$, is the sum of local cases ($i_L(t)$) and imported cases ($i_o(t)$)—that is, $i(t)=i_o(t)+i_L(t)$. The renewal equation for the transmission dynamics of COVID-19 is defined as follows [29,30]:

where $f\tau$ is the probability distribution of the serial interval in τ, and α is the relative contribution of the imported cases to secondary disease transmission ($0\leq\alpha\leq1$) [27,31]. A serial interval is the time interval from illness onset in a primary case (infector) to that in a second case (infectee) [28]. The serial interval was assumed according to the gamma distribution with a mean of 4.8 days (SD 2.3 days) [31,32]. The likelihood function, assuming that the daily counts follow a Poisson distribution, is defined as the following:

where t_n is the final time. We estimated the R_0 using the early confirmed cases from January 10 to February 25, 2020, using equations 3 and 4. Here, α is the relative contribution of imported cases to secondary disease transmission [27,31]. In Seoul and Gyeonggi, there were secondary confirmed cases of importation until April 2020, and there were very few secondary confirmed cases due to stringent interventions such as screening and the self-quarantine policy from April to June 2020. In total, 48 secondary cases related to imported cases were reported until June 2020, and the parameter α was calculated based on the total confirmed cases by April and June 2020. As of April 2020, the value of α was 7.57%, which was reduced to 3.63% in June 2020.

The R_0 is relevant only in a largely susceptible population. Therefore, we also introduced the time-dependent reproduction number R_t, calculated as the ratio of the number of new locally infected cases at time t and all infected individuals at time t. The details of the R_t computation can be found elsewhere [30,33]. The effective reproduction number was estimated on sliding windows of width W days, which was assumed to be a constant value over the time window (W-day average of R_t).

If W=1, the R_t is derived as follows:

Ethical Considerations

The data are presented in Table S1 in Multimedia Appendix 1. The data sets were fully anonymized and did not include any personally identifiable information. Thus, ethical approval was not required for the analysis.

Results

Overview

Relation between the number of passengers and imported cases was explored and the normalized country-specific risk was obtained. Among four groups of countries, China had a high risk of importation until February 2020. Afterward, North America showed a high risk of importation. The number of imported cases in Korea had a high correlation with the normalized risk, and the Spearman correlation coefficient was 0.82. The R_0 was estimated at 1.87 (95% CI 1.47-2.34) with the rate of α=0.07 in Seoul and Gyeonggi. R_0 was varied according to α to be between 1.83 and 3.94 in South Korea. The R_t in South Korea and in Seoul and Gyeonggi were shown and interpreted along with the control interventions.

Imported and Local Cases of COVID-19 in South Korea

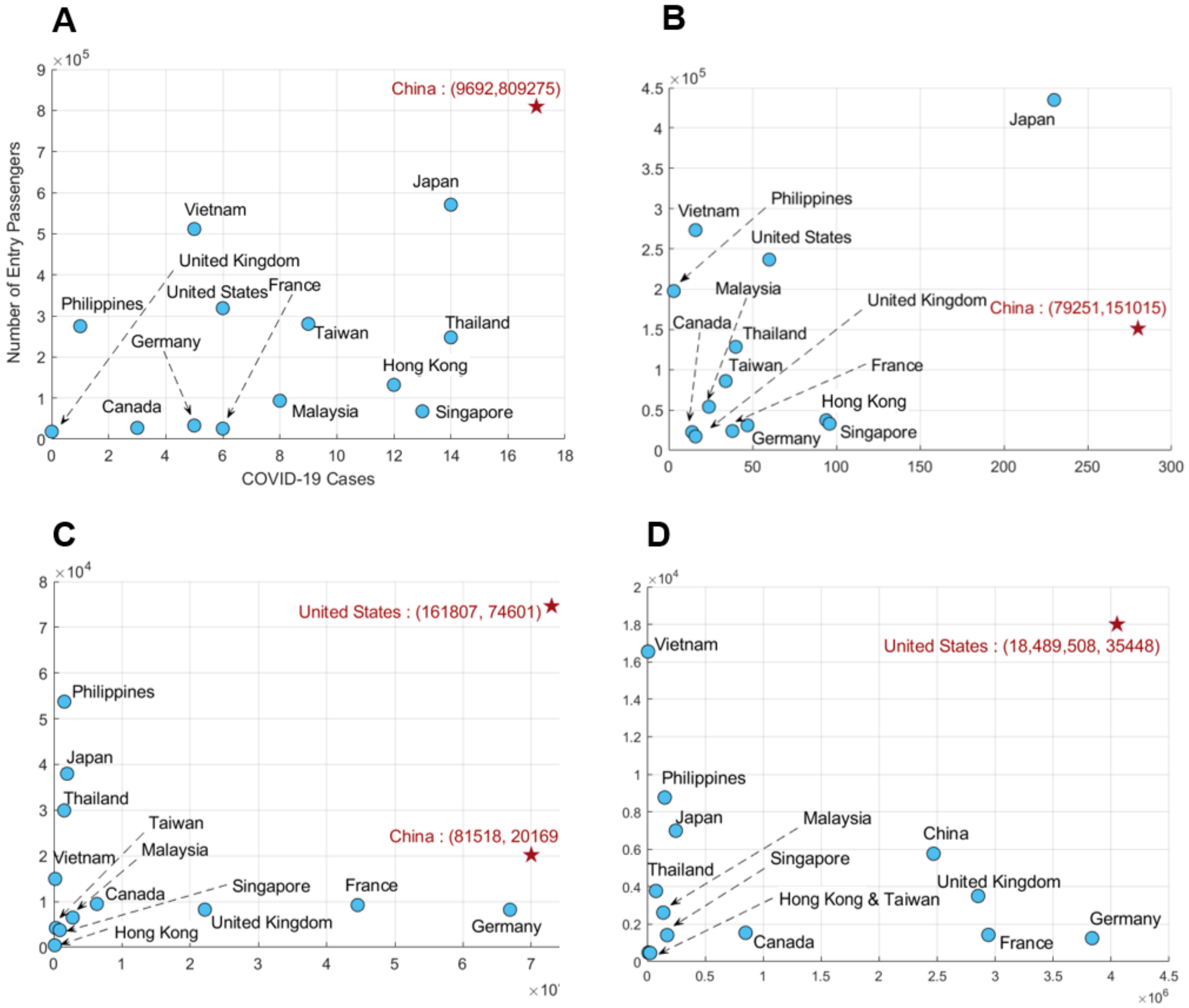
Figure S1 in Multimedia Appendix 1 illustrates a summary of the epidemiological data on COVID-19 cases in South Korea. The top panels of Figure S1A in Multimedia Appendix 1 show the overall characteristics of the confirmed cases from February to October 2020. The leftmost panel shows the ratio of COVID-19 cases by region: 43% in the Seoul and Gyeonggi areas, 33% in the Daegu and Gyeongbuk areas, and 24% in the rest of South Korea. The second panel shows the ratio of imported cases (14%) to local cases (86%). The third panel shows the number of confirmed cases in Seoul and Gyeonggi and the ratio of imported cases (10%) to local cases (90%). The rightmost panel shows that 31% of imported cases were reported in Seoul and Gyeonggi. Seoul and Gyeonggi are the regions with the most inflow of foreigners in South Korea as they have major international airports (ie, Incheon International Airport and Gimpo International Airport).

Figure S1B in Multimedia Appendix 1 shows the monthly proportion of imported cases from five continents and the total proportion of imported cases (top left panel). A list of country-specific imported cases is given in Table S1 in Multimedia Appendix 1. The number of imported cases from China was large during January and April 2020, while that from North America and Europe increased until April 2020. However, the number of imported cases from Asia increased rapidly from May to October 2020; Asia (50.6%), North America (28.1%), and Europe (17.8%) accounted for most of the cumulative imported cases.

Relation Between the Number of Passengers and Imported Cases of COVID-19

The importation risk implies that a country with more COVID-19 cases and more travelers entering South Korea has a higher risk of importation. Figure 2 shows the relationship between the number of passengers entering South Korea in 2020 and the monthly confirmed cases of COVID-19 between January and April in 2020. After February 2020, the number of Chinese passengers rapidly decreased due to the emerging outbreak of COVID-19 in China, as shown in Figures 2A and 2B. The number of confirmed cases and the number of passengers entering South Korea from the United States increased from March to October 2020, as shown in Figure S2 in Multimedia Appendix 1. This indicated that the number of passengers was dramatically reduced since the COVID-19 pandemic began, owing to travel bans and restrictions (see Table S2 in Multimedia Appendix 1). Next, the number of international travelers who arrived in South Korea in 2020 was compared with that in 2019 (Figure S3 in Multimedia Appendix 1). The number of country-specific confirmed cases and passengers per month from the top 13 countries from January to October 2020 are shown in Figures S4 and S5 in Multimedia Appendix 1, respectively. The number of cases in China was reduced dramatically from March 2020 (Figure S4A in Multimedia Appendix 1), while the number of cases in the United States, the United Kingdom, France, Germany, Canada, and Malaysia continued to increase until October 2020 (Figures S4H-M in Multimedia Appendix 1). However, the number of passengers was greatly reduced, regardless of country, as shown in Figure S5 in Multimedia Appendix 1.

Figure 2. Relationship between the monthly number of passengers entering South Korea and COVID-19 cases at originating countries in (A) January, (B) February, (C) March, and (D) April 2020. The red stars represent particularly large numbers of COVID-19 cases (China and the United States).



Importation Risk of COVID-19

We presented the risk of country-specific importation in Figure 3 and Table 1. Between January and February 2020, the risk of importation from China was the highest among the countries studied, while that from North America (the United States and Canada) showed a significantly high risk of importation from April to October 2020. The number of imported cases was highly correlated with the normalized risk (the Spearman correlation coefficient and Kendall correlation coefficient were 0.82 and 0.64, respectively).

Figure 3. The country-specific risk of case importation from the top 13 countries to South Korea from January to October 2020.

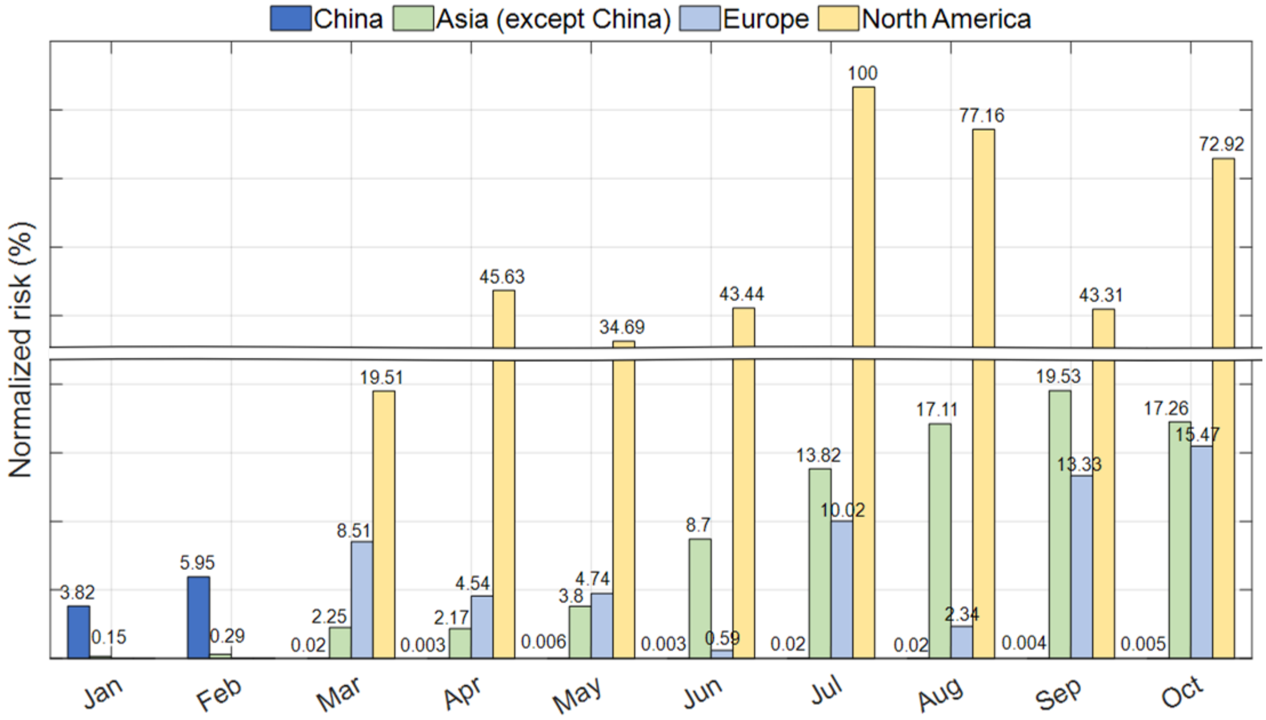


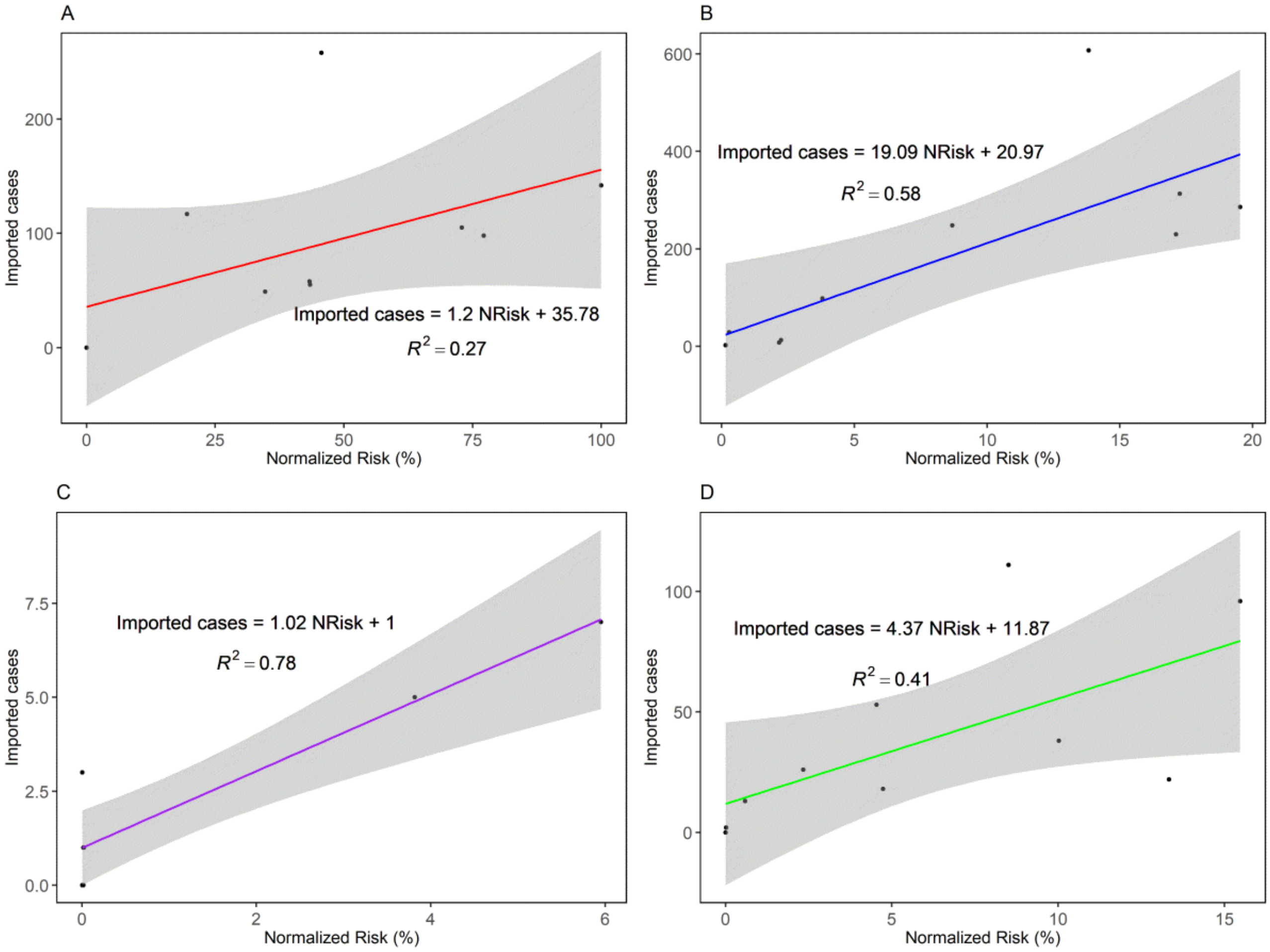
Table 1. Normalized risk of importation in South Korea by country using data on population, number of COVID-19 cases, and number of passengers from January to October in 2020.

Country/region (population) and month	COVID-19 cases, n	Passengers, n	Normalized risk of importation, %
Europe (214,921,407)			
January	11	77,183	0.002
February	115	72,133	0.02
March	141,116	25,656	8.51
April	453,720	6182	4.54
May	584,312	3450	4.74
June	634,734	4963	0.59
July	684,781	6224	10.02
August	833,071	6701	2.34
September	1,233,958	4595	13.33
October	2,715,743	4441	15.47
Asia, except China (3,032,800,000)			
January	168	5,535,607	0.15
February	1254	1,397,128	0.29
March	70,717	190,649	2.25
April	224,609	57,968	2.17
May	558,836	40,838	3.8
June	1,105,224	47,219	8.7
July	1,786,777	46,420	13.82
August	2,709,219	37,908	17.11
September	3,410,902	34,362	19.53
October	3,009,642	34,419	17.26
China (1,399,620,000)			
January	9701	1,089,779	3.82
February	79,285	236,911	5.95
March	81,824	24,381	0.02
April	83,287	6242	0.003
May	85,012	9479	0.006
June	85,674	11,120	0.003
July	88,423	15,323	0.02
August	90,839	19,579	0.02
September	91,480	18,690	0.004
October	92,402	16,193	0.005
North America (365,968,433)			
January	9	346,090	0.004
February	74	259,247	0.02
March	168,124	84,074	19.51
April	1,061,615	36,987	45.63
May	1,805,819	33,757	34.69
June	2,640,886	37,676	43.44
July	4,504,036	38,869	100

Country/region (population) and month	COVID-19 cases, n	Passengers, n	Normalized risk of importation, %
August	5,982,879	37,783	77.16
September	7,110,608	27,809	43.31
October	8,989,268	28,109	72.92

Figure 4 showed the results of regression analysis between the country-specific risk and the number of imported cases according to the four different countries/regions. The estimated values using the regression analysis are summarized in Table S3 in Multimedia Appendix 1. All countries had a positive relationship between imported cases and the risk of importation because the estimates of the slopes were positive. The linear regression models were well fitted, especially for China (R^2=0.78). Asia (except China) was the most affected region with respect to the risk of importation. It is clear that imported cases entering from Asia (except China) can increase much more if the risk importation of Asia (except China) is elevated.

Figure 4. Regression analysis between the imported cases in South Korea from (A) North America, (B) Asia (except China), (C) China, and (D) Europe, and normalized risk (%). The dots indicate the number of imported cases in South Korea and solid lines represent the fitted linear regression. NRisk: normalized risk.



Reproduction Number

We varied α from 0 to 1 and estimated the R_0 for the early COVID-19 outbreak in Seoul and Gyeonggi based on COVID-19 confirmed cases from January 10 to February 25, 2020, while the R_0 in South Korea was based on COVID-19 confirmed cases from February 1 to February 19 (Table 2). Figure 5 shows the comparison between the COVID-19 data and estimated cases (Figure 5A) and cumulative local cases (Figure 5B). The corrected Akaike information criterion was calculated at 159.08 and the Bayesian information criterion was 160.84. Table 2 illustrates the estimation of R_0 with varying α. The estimated R_0 was 1.87 (95% CI 1.47-2.34) with α=0.07 and 1.49 (95% CI 1.17-1.87) with α=1.0. This indicated that the value of R_0 decreased with increasing α since there was no secondary infection from imported cases (α=1).

Figure 5. Comparison between estimated cases and observed cases of COVID-19 in Seoul and Gyeonggi using R_0 when α=0.07. (A) Daily local cases in Seoul and Gyeonggi. (B) Cumulative local cases in Seoul and Gyeonggi. The red bar shows the estimated cases, while the blue bar shows the observed COVID-19 cases in the Seoul and Gyeonggi regions.

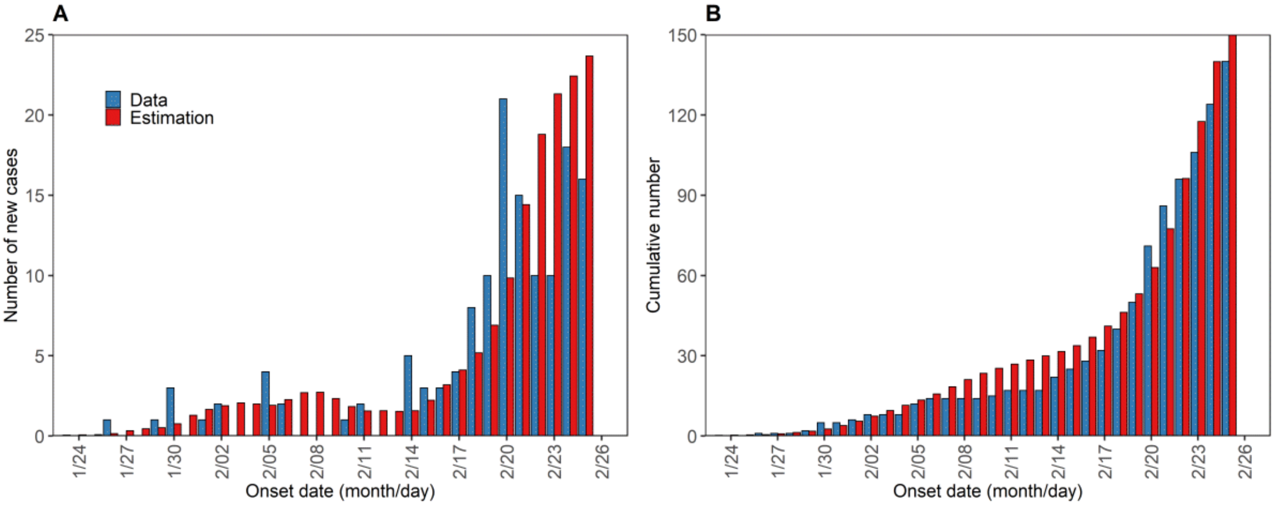


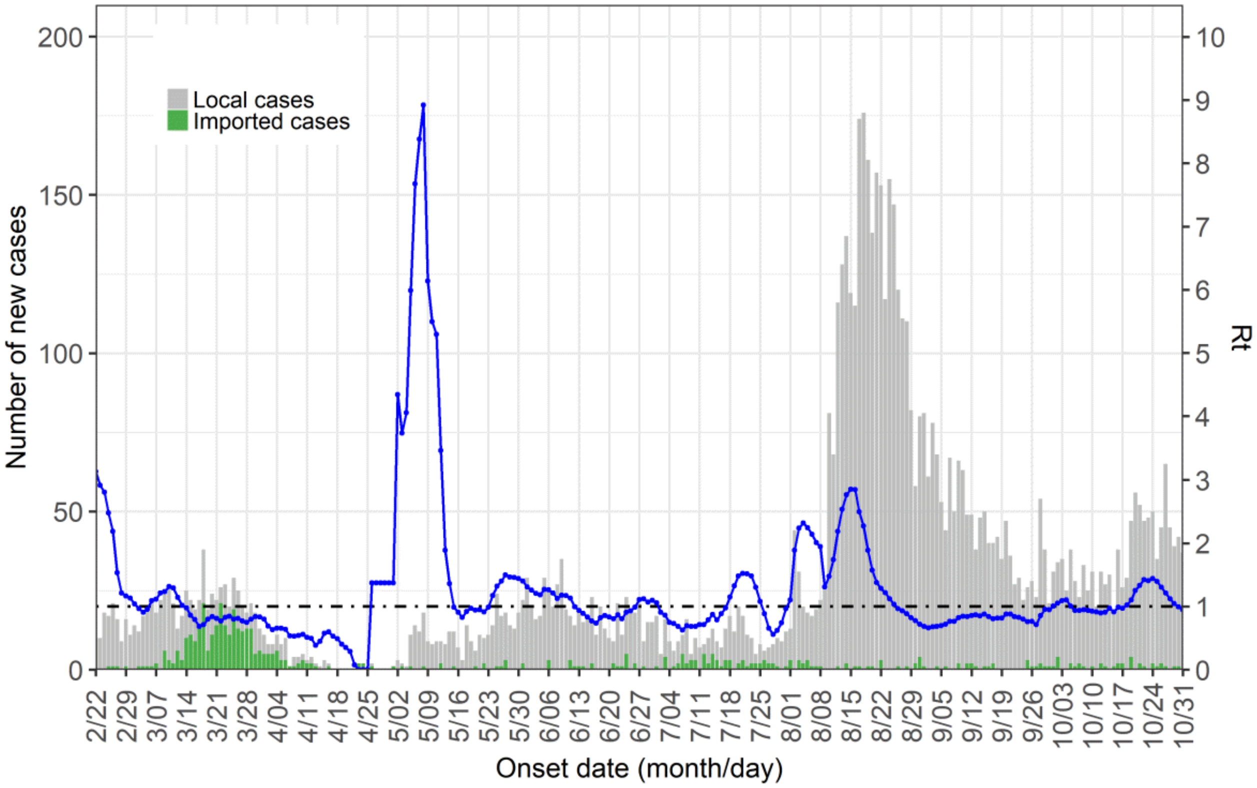
Table 2. Estimation of R_0 by α.

α value	R_0 of Korea (95% CI)[a]	R_0 of Seoul and Gyeonggi (95% CI)[a]
0.00	3.94 (2.18-6.04)	1.89 (1.49-2.38)
0.07	3.76 (2.11-5.75)	1.87 (1.47-2.34)
0.10	3.63 (2.05-5.58)	1.85 (1.46-2.33)
0.30	2.98 (1.71-4.66)	1.76 (1.38-2.21)
0.50	2.53 (1.47-4.00)	1.67 (1.31-2.10)
0.70	2.19 (1.28-3.50)	1.59 (1.25-2.00)
1.00	1.83 (1.08-2.94)	1.49 (1.17-1.87)

[a] 95% CI was calculated from profile likelihood [34].

The R_t was calculated for α=0.07 and the daily epidemic curves of imported (green) and local (gray) cases and the R_t values (blue curve) in the Seoul and Gyeonggi regions are shown in Figure 6. On March 11, 2020, when the WHO declared a pandemic situation, the R_t value fell below 1. At the beginning of the holiday season in early May 2020, the value again increased rapidly. In addition, there was a large outbreak in August and September 2020 due to a public gathering from all over South Korea on August 15, 2020. We conducted the sensitivity analysis for R_t according to the different time windows and α values (Figures S6A and S6B in Multimedia Appendix 1). Additionally, the R_t in South Korea from April to October 2020 is shown in Figures S6C and S6D in Multimedia Appendix 1.

Figure 6. Local and imported cases and R_t in Seoul and Gyeonggi. The daily epidemic curves of imported (green) and local (gray) cases are shown. The blue curve shows the value of R_t when α=0.07 and the black horizontal line denotes R_t=1.



Discussion

Principal Findings

In this study, we analyzed country-specific epidemiological data and data on passengers entering South Korea from January to October 2020. First, the correlation between the number of passengers and COVID-19 cases by country was calculated. A country with more confirmed cases showed a higher risk of importation. Second, the country-specific risk was highly correlated with the number of imported cases by country (Spearman correlation coefficient=0.82); China had the highest importation risk of COVID-19 in the early stages of the pandemic (January and February 2020), while North America (United States and Canada) showed the high importation risk from April to October 2020. Third, for the early stages of the COVID-19 pandemic, the R_0 was estimated at 1.87 (95% CI 1.47-2.34), which was similar to the R_0 of COVID-19 of approximately 2-3 in Wuhan, China [28,35,36]. Finally, we estimated the R_t by employing the renewal equation, accounting for the effects of control interventions.

Mainland China and South Korea experienced a steep rise in the number of COVID-19 confirmed cases in the early stages of the COVID-19 pandemic [3,32]. It appears that the two governments' respective reactions to the novel virus resulted in a successful reduction in infection rates; however, the cost burden that the two countries had to bear was quite different. China implemented a lockdown in Hubei province and strict border control measures against higher-risk countries [37,38]. In China, active measures driven by the central government to retard the progress of epidemic diseases appear to be effective in impeding the spread of COVID-19; however, Chinese people had to pay burdensome costs during the initial outbreak of COVID-19 [39]. South Korea used strict social distancing measures and self-quarantine without restricting borders. However, South Korea expanded the volume of testing and promptly traced the contacts of confirmed cases [32,40].

There were potential risk factors that could have led to a larger outbreak of COVID-19 in South Korea. First, negative serial intervals indicated presymptomatic transmissions, highlighting the potential risk of transmission from asymptomatic cases. In South Korea, 12.7% of serial intervals were negative (199 pairs among 1567 symptomatic pairs), which could lead to large outbreaks as secondary transmission before the appearance of symptoms cannot be prevented [40,41]. Second, the R_0 was estimated at 1.49 in Seoul and Gyeonggi, indicating that an epidemic might be possible. Third, the number of imported cases increased substantially from April 2020, although passenger volume has been rapidly decreasing due to the increase in COVID-19 cases. However, a large outbreak of COVID-19 caused by imported cases did not occur because of the policy of testing passengers arriving from other countries and isolating them for a minimum of 2 weeks; this policy was implemented on April 1, 2020, and reduced the risk of the spread of COVID-19.

This study has several limitations. First, this study relied on confirmed cases in South Korea. However, there were a substantial number of asymptomatic infections as 12.5% of serial intervals were negative [41], which represents presymptomatic transmission [32,40]. Thus, we did not consider secondary transmission caused by imported and local cases. Second, we analyzed the impact of imported cases on the local transmission of COVID-19 and found that the impact of imported cases had decreased since the strict implementation of airport screening and quarantine measures from April 2020 [24,42] (Table S2 in Multimedia Appendix 1). Therefore, the potential risk of infection from imported cases was regarded as a less important factor. However, the reason for the small outbreaks resulting from imported cases was due to strengthened screening inspection and self-quarantine measures for those entering South Korea, which were implemented on April 1, 2020. This means that secondary transmission by imported cases can play a critical role in COVID-19 transmission. Finally, the risk was estimated by month as monthly passenger volume data were available. If daily data were given, the risk by country could be computed daily or weekly. However, we observed a significantly different risk of importation of COVID-19 from overseas countries.

Despite these limitations, we investigated the risk of importation of COVID-19 using country-specific epidemiological data and passenger volume. By combining social distancing, screening, and self-quarantine for all travelers entering South Korea, the mitigation of COVID-19 transmission caused by imported cases in South Korea was highly successful. These efforts—accompanied by identification of the source of infection and strengthened quarantine measures for travelers from overseas countries—should be continued. Therefore, it is urgent to assess the risk of importation and maintain an effective surveillance system for COVID-19 in South Korea.

Strict control interventions were implemented to prevent the spread of COVID-19 in South Korea since the first case was confirmed in the country on January 20, 2020. The COVID-19 outbreak in South Korea has been successfully suppressed without strict lockdowns. First, the Korean government has constructed a rapid testing and diagnosis system [40,43]. Previous studies have shown that most cases have been confirmed within a week of illness onset [24,43]. Moreover, drive-through screening centers were initiated on February 23, 2020, in Daegu, South Korea [44]. This system contributed to the rapid diagnosis and further testing of suspected cases. The entire drive-through testing procedure takes about 10 minutes, and it is helpful for diagnosing infections early in cases with mild symptoms or asymptomatic cases. Second, the widespread epidemiological investigation of contact tracing was conducted in infected as well as suspected cases [40]. Social distancing strategies and mask wearing have been recommended since February 2020. Social distancing has been found to mitigate the spread of COVID-19 cases [40,45,46]. Third, the Korean government introduced a “special entry procedure,” which was applied to all passengers from mainland China from February 4, 2020, to control imported cases. Subsequently, all passengers from overseas countries were quarantined for 14 days after April 1, 2020. Combined control interventions, including social distancing efforts, appear to have succeeded in preventing the spread of COVID-19 in South Korea.

Since the severity of COVID-19 outbreaks and health policies differ across countries, a country-specific surveillance system would be more efficient than a uniform screening and surveillance policy for every country. Another notable feature of South Korean border control is that the number of international travel hubs is limited, and passenger traffic can be effectively monitored. This, in turn, helps in diagnosing and tracing imported cases without imposing a strict lockdown. It is important to estimate the country-specific risk of importation by identifying high-risk countries to prevent recurrent outbreaks due to importation of cases. It would be helpful to access a finer level of information to estimate the effective reproduction number as the risk indicator of importation and local transmission. Therefore, our framework can also be applied to countries that have similar immigration policies. Furthermore, a risk assessment of imported cases between neighboring countries that do not implement border control (eg, the Schengen zone or Central America-4 Free Mobility Agreement) might be challenging.

Conclusions

Data on international passengers entering South Korea, the severity of the COVID-19 outbreak in originating countries, and country-specific imported cases were analyzed to compute the risk of importation of COVID-19 into South Korea. China was a high-risk country for importation in the early stages of the pandemic until March 2020, while the United States and Canada showed a high risk of importation after April 2020. Moreover, statistical model accounting was employed to estimate the R_0 and R_t using epidemiological data on imported and locally transmitted cases. Our results highlighted that rapid diagnosis and prompt implementation of case isolation and quarantine were effective in preventing secondary infections caused by imported cases through the continuous inflow of passengers traveling from high-risk countries. Therefore, multiple mitigation interventions (social distancing, a rapid diagnosis system, and movement restriction) should be implemented to reduce the spread of local and imported cases in South Korea.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary data.
[DOCX File , 1004 KB - publichealth_v7i6e26784_app1.docx]

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Abbreviations

MERS: Middle East respiratory syndrome
SARS: severe acute respiratory syndrome
WHO: World Health Organization

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Original Paper

Impact of Public Health and Social Measures on the COVID-19 Pandemic in the United States and Other Countries: Descriptive Analysis

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Abstract

Background: The United States of America has the highest global number of COVID-19 cases and deaths, which may be due in part to delays and inconsistencies in implementing public health and social measures (PHSMs).

Objective: In this descriptive analysis, we analyzed the epidemiological evidence for the impact of PHSMs on COVID-19 transmission in the United States and compared these data to those for 10 other countries of varying income levels, population sizes, and geographies.

Methods: We compared PHSM implementation timing and stringency against COVID-19 daily case counts in the United States and against those in Canada, China, Ethiopia, Japan, Kazakhstan, New Zealand, Singapore, South Korea, Vietnam, and Zimbabwe from January 1 to November 25, 2020. We descriptively analyzed the impact of border closures, contact tracing, household confinement, mandated face masks, quarantine and isolation, school closures, limited gatherings, and states of emergency on COVID-19 case counts. We also compared the relationship between global socioeconomic indicators and national pandemic trajectories across the 11 countries. PHSMs and case count data were derived from various surveillance systems, including the Health Intervention Tracking for COVID-19 database, the World Health Organization PHSM database, and the European Centre for Disease Prevention and Control.

Results: Implementing a specific package of 4 PHSMs (quarantine and isolation, school closures, household confinement, and the limiting of social gatherings) early and stringently was observed to coincide with lower case counts and transmission durations in Vietnam, Zimbabwe, New Zealand, South Korea, Ethiopia, and Kazakhstan. In contrast, the United States implemented few PHSMs stringently or early and did not use this successful package. Across the 11 countries, national income positively correlated (r=0.624) with cumulative COVID-19 incidence.

Conclusions: Our findings suggest that early implementation, consistent execution, adequate duration, and high adherence to PHSMs represent key factors of reducing the spread of COVID-19. Although national income may be related to COVID-19 progression, a country’s wealth appears to be less important in controlling the pandemic and more important in taking rapid, centralized, and consistent public health action.

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KEYWORDS

surveillance; COVID-19; public health; health policy; global health; policy; epidemiology; descriptive epidemiology

Introduction

By the end of the first year of the pandemic, the United States had the highest global, cumulative COVID-19 case and death counts [1]. Additional challenges, such as newly emergent lineages of SARS-CoV-2 with increased transmission potential and issues in COVID-19 vaccine distribution and administration, have increased the burden on public health systems worldwide [2]. The implementation of public health and social measures (PHSMs) such as stay-at-home orders, limited gatherings, and the closure of nonessential workplaces is a crucial method for preventing and mitigating the spread of COVID-19. In spring of 2020, the Health Intervention Tracking for COVID-19 (HIT-COVID) database was developed to catalogue the global implementation and relaxation of COVID-19–related PHSMs [3]. Many other PHSM surveillance systems also collect data that can be used to inform pandemic responses [4-6]. These PHSMs have been shown to be effective, both individually and in combination, against COVID-19 globally. For example, a recent study found that from January to May 2020, limiting gatherings, closing businesses, closing schools and universities, and implementing stay-at-home orders were individually effective at reducing the time-varying reproduction number (R_t) of SARS-CoV-2 [7]. An earlier study found that in combination, limited gathering sizes, business closures, educational institution closures, and stay-at-home orders reduced COVID-19 transmission from January to May 2020 in 11 European countries [8]. The implementation of PHSMs is a key marker of how public health systems address the COVID-19 pandemic. Poor COVID-19 outcomes in the United States of America have been attributed to a failure to consistently, quickly, and effectively implement PHSMs [9]. We sought to analyze the epidemiological evidence for the impact of PHSMs on COVID-19 transmission in the United States and compare these data to those for 10 other countries—places that provide sources of learning to the United States.

Methods

We analyzed the timing and stringency of PHSMs that were implemented from January 1 to November 25, 2020, compared them against time series for daily case counts of COVID-19, and compared the United States to Canada, China, Ethiopia, Japan, Kazakhstan, New Zealand, Singapore, South Korea, Vietnam, and Zimbabwe.

These 10 countries were chosen for comparison with the United States based on their varying income levels and geographies and were selected as comparators for the US COVID-19 response, which was reported in a previously published, high-profile commentary on global PHSM effectiveness [9]. Canada was chosen for its comparatively lower death rate; China was chosen for being the first country affected by COVID-19 and having a large population; Japan was chosen for its older population; New Zealand was chosen for being geographically isolated; Singapore and South Korea were chosen for their geographic proximity to China; Vietnam was chosen for being a lower-middle–income country; and Ethiopia, Kazakhstan, and Zimbabwe were chosen for having less medical infrastructure and manufacturing capacity.

For ease of analysis, we focused on the following eight categories of PHSMs: border closures, contact tracing, household confinement, mandated face masks, quarantine and isolation, school closures, limited gatherings, and a state of emergency. These categories of PHSMs were chosen based on a brief literature review, data availability in the HIT-COVID database, and an exploratory data analysis. The stringency of PHSM implementation was classified in the HIT-COVID surveillance database as strongly implemented, partially implemented, or not implemented based on the specific details of each PHSM. After being abstracted from government or news websites, data on PHSM timing and stringency in the HIT-COVID database undergo internal auditing by both the person who entered the data and the database management team [3]. PHSM and case count data were derived from the HIT-COVID database, the World Health Organization PHSM global database, and the European Centre for Disease Prevention and Control [5,10]. For each country, the date and stringency of PHSM implementation were plotted against the number of daily national COVID-19 cases from January 1 to November 25, 2020. Additionally, we compared the 11 countries' cumulative incidence rates to 40 variables that described national measures of social, demographic, economic, and health system characteristics [11-14]. The analysis was performed by using the HIT-COVID R package version 4.0.3 [15]. All data used in this analysis were publicly available, and this study did not constitute human subjects research; therefore, ethical review was not required.

Results

According to the HIT-COVID database, from January 1 to November 25, 2020, 11,999 PHSMs were implemented in 148 countries. Of these PHSMs, 5,695 fell into the eight categories that were defined for analysis in this study. School closure was the most common measure (1592/5695, 27.95%), followed by border closures (1481/5695, 25.98%), quarantine and isolation (705/5695, 12.39%), limited gatherings (629/5695, 11.06%), household confinement (573/5695, 10.05%), face mask mandates (272/5695, 4.78%), a state of emergency (269/5695, 4.73%), and contact tracing (174/5695, 3.04%).

We compared the cross-country timing and stringency of PHSMs to COVID-19 epidemic curves, as shown in Figures 1 and 2. The results show that implementing a specific package of PHSMs—quarantine and isolation, school closures, household confinement, and limited social gatherings—earlier and more stringently coincided with limited case counts and transmission durations in Ethiopia, Kazakhstan, New Zealand, South Korea, Vietnam, and Zimbabwe. Further, these countries' case counts and transmission durations were lower than those of the United States. Singapore and South Korea implemented similar PHSMs, including less stringent household confinement, but both countries substantially lowered the epidemic curve further than the United States. China implemented fewer PHSMs for shorter durations via more targeted subnational implementation. Japan implemented strong quarantine and isolation measures along with early school closures but did not maintain the same level of stringency as that of the package of 4 PHSMs. Canada initially implemented strict PHSMs but did not maintain this level of stringency across the country. Canada is now facing a resurgent epidemic and has a relatively high cumulative COVID-19 incidence rate, though it is still much lower than that of the United States.

In contrast, the United States did not implement the package of 4 PHSMs that were shown to be effective in the 6 countries mentioned above. The United States implemented few PHSMs fully or early during the pandemic. Although the US government implemented some PHSMs early in the pandemic, these PHSMs were only partially implemented; they were not strongly implemented like the PHSMs of most of the other countries in this analysis.

Border closures, state-of-emergency declarations, and mandated mask wearing did not show strong temporal overlap with epidemic growth across the 11 countries, though some of these PHSMs may have been important in individual countries (eg, border closures in New Zealand). The adherence to mask wearing seemed to vary widely across countries.

The 11 countries differed significantly in terms of many demographic, economic, social, and health system characteristics. These differences may contribute to their varying success. After comparing the countries' cumulative COVID-19 incidence rates with national measures of social, demographic, economic, and health systems factors, we found only 1 positive correlation (r=0.624; r^2=0.389) between national income (measured as gross national income per capita in US dollars) and cumulative COVID-19 incidence (Figure 3). Lower-income countries performed better than higher-income countries; the three countries with the lowest incomes had the lowest incidence rates, and the two countries with the highest incomes had the highest incidence rates.

Figure 1. COVID-19 epidemic curves and public health and social measure timelines for China, Canada, Ethiopia, Japan, New Zealand, and South Korea (January 1 to November 25, 2020).

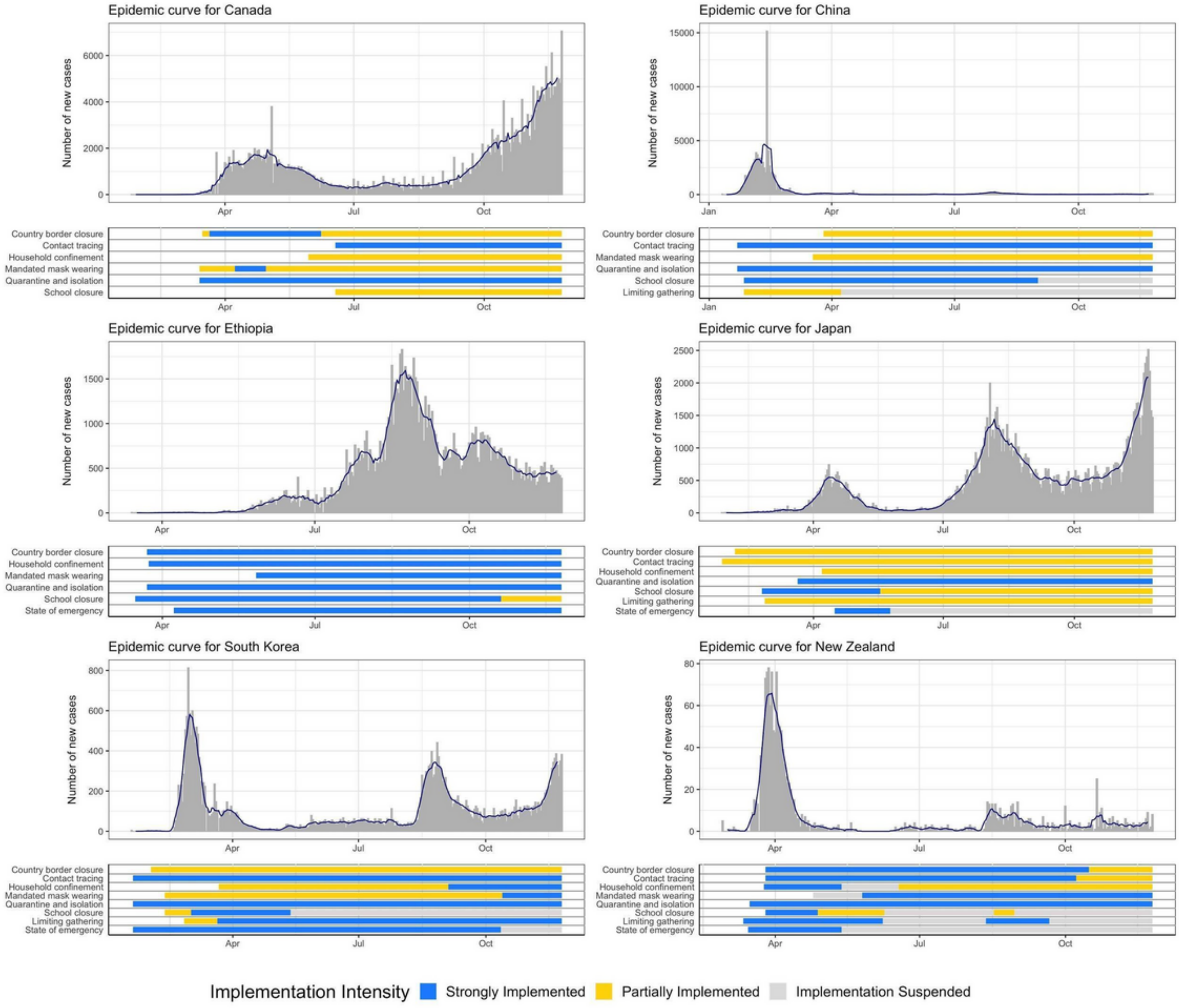


Figure 2. COVID-19 epidemic curves and public health and social measure timelines for Kazakhstan, Singapore, the United States, Vietnam, and Zimbabwe (January 1 to November 25, 2020).

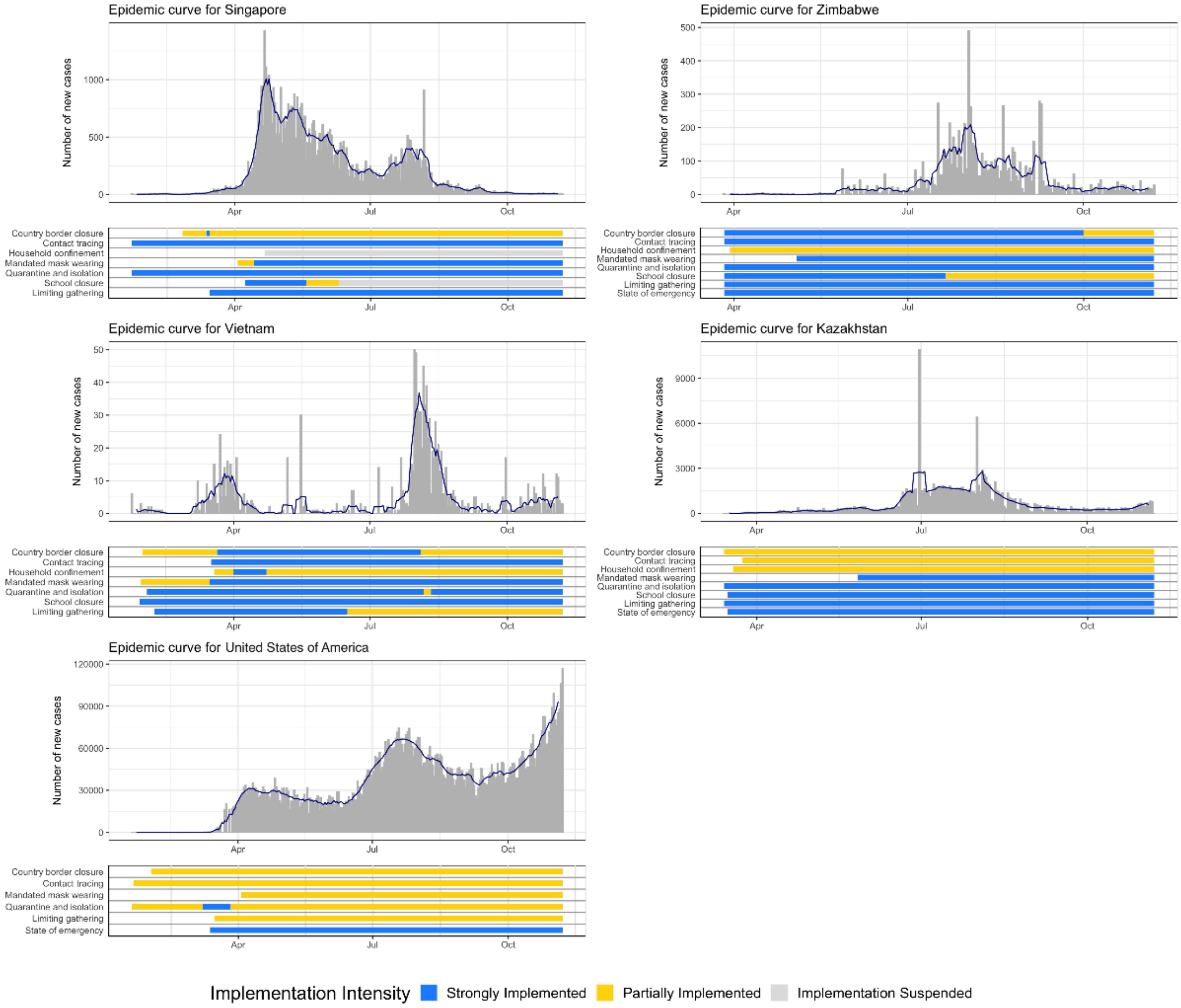
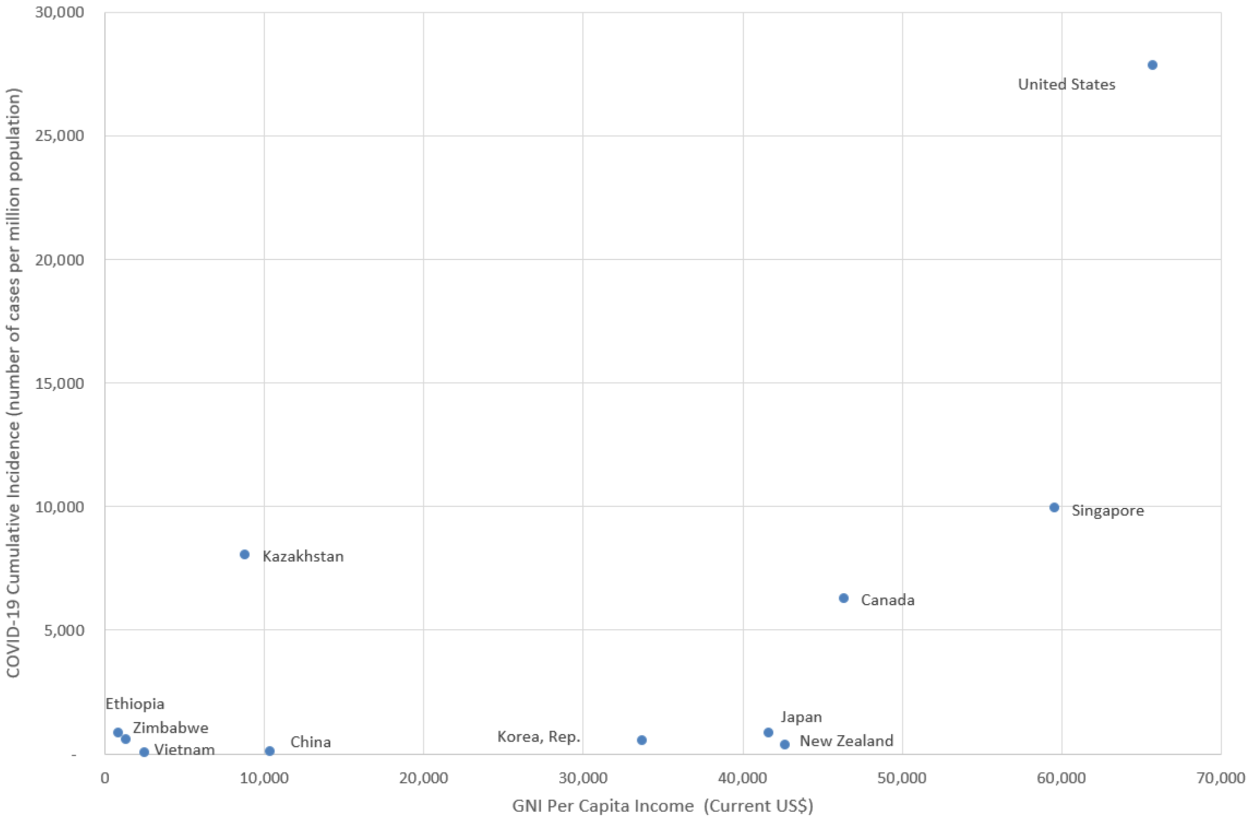


Figure 3. Cumulative COVID-19 incidence rates (January 1 to November 25, 2020) and national income levels. GNI: gross national income.



Discussion

Principal Findings

Efforts to control the COVID-19 pandemic have ranged from early, strict border closures and nationwide lockdowns to less stringent individual behavior change campaigns and public health recommendations. The exact mixture of PHSM implementation approaches, timings, and intensities has varied across regions and countries and often within countries depending on their size and governance structure. Public health experts have stated that the early and stringent implementation of mitigation strategies is key to pandemic control and results in greater reductions in the number of downstream cases and fatalities [9]. One study found that globally, the timing of PHSM implementation was significantly associated with a reduction in COVID-19 transmission rates, as measured by the R_t ratio [16]. Our analysis suggests that earlier PHSM implementation times as well as more stringent implementation may be related to lower caseloads and transmission durations across 11 countries. The package of 4 PHSMs that temporally coincided with decreased COVID-19 case counts and transmission durations (quarantine and isolation orders, school closures, household confinement, and limits on social gatherings) has been shown to be effective in other studies, thereby providing further evidence that these specific measures help to reduce the spread of the pandemic [7,8]. An advantage of our analysis is that the HIT-COVID data set includes a measure of implementation stringency for each individual PHSM (strongly, partially, or not implemented). Most other databases classify PHSM stringency according to the strictness of behavior-related PHSMs; thus, stringency is dependent on the type of PHSM as well as PHSM implementation [6].

Implementing effective COVID-19 PHSMs requires coherent national leadership and coordination as well as necessary resources. The US government’s pandemic management has been highly fragmented. Although a more unified response has been called for by US public health leaders, the United States has a strong history of state-level policy making, which creates logistical and cultural challenges to implementing stringent national PHSMs. Additionally, cultural distrust in public health and medicine may have contributed to implementing PHSMs later than what is recommended by public health experts. Finally, while the United States is a high-income country, low hospital workforce capacity, the lack of affordable health care, and the high prevalence of preexisting conditions may increase the population's susceptibility to contracting COVID-19 [17]. A lack of resources and intervention fatigue combined with the political pressure to reopen earlier than what public health officials have recommended may have contributed to an out-of-control pandemic that has infected over 31 million Americans and has left over 560,000 dead [1]. Our findings underscore that early, coordinated implementation; consistent enforcement; and high societal adherence to an adequate implementation duration were vital to controlling COVID-19 successfully in many countries.

Our finding of a positive relationship between national income and cumulative COVID-19 incidence raises further questions. Few studies have examined the impact of country-level income differences on COVID-19 outcomes. One study found a correlation between COVID-19 mortality and gross domestic product in 106 countries [18]. Another study found that the COVID-19 mortality rate ratio between older and middle-aged populations is higher in high-income countries than in low-income countries [19]. Finally, one analysis found that national income was positively associated with COVID-19 incidence and death rates across 210 countries; however, this paper has not been peer-reviewed [20]. Our result may be explained by the timing of PHSM implementation. According to Figure 1, lower-income countries implemented the package of 4 PHSMs early, making them more effective in mitigating COVID-19 transmission. Additionally, higher-income countries may face higher COVID-19 transmission rates due to the increased availability of international air travel. It is also possible that well-funded public health reporting systems and the availability of COVID-19 testing in higher-income countries are contributing factors. Some economists have argued that the estimates of COVID-19 morbidity and mortality rates in low- and middle-income countries (LMICs) are underestimated, as demographic simulations have suggested a much higher COVID-19 toll in LMICs, and that country-level income disparities are due to the pandemic not fully spreading through LMICs [21]. Finally, country-specific characteristics such as government structure, trust in public health and medicine, and the centralization of the pandemic response play a role in COVID-19 transmission and may be related to national income. Future research should further examine the relationship between country wealth and COVID-19 outcomes.

Our analysis has several limitations. Our sample size of only 11 countries limits the power of our analysis. We were not able to capture how inadequate policies exacerbate racial and ethnic inequities in COVID-19 outcomes. In the United States, the number of cases is 2.8 times higher among Indigenous and Latinx Americans and 2.6 times higher among Black Americans compared to that number among White Americans [22]. The age-adjusted mortality rate is 3.2 times higher among Black and Latinx Americans and 3.1 times high among Indigenous Americans compared to that rate among White Americans [23]. Higher rates of death and infection among people of color in other countries further highlight the influence of structural racism on health [24]. There is an urgent need for standardized, publicly available COVID-19 data that are disaggregated by race and ethnicity. Another limitation is that this study was a descriptive analysis, which precludes us from making conclusions about causal associations. Additionally, our population-level lens cannot account for individual-level behaviors, and we cannot differentiate the individual effects of PHSMs that were implemented concertedly in time and space. This may have contributed to the weak relationships observed between face mask policies and case counts. Finally, the PHSMs that were logged in the HIT-COVID database did not represent all PHSMs that were actually implemented during the study time period, as there may have been PHSMs that were not captured in the database.

Conclusion

The COVID-19 pandemic has thrown societies into disorder and has challenged us to rethink what characterizes a strong health system. Although adequate resources and robust health care systems are necessary for an effective pandemic response, our analysis highlights that rapid, decisive, stringent, national, and consistent public health interventions are crucial for preventing disaster and chaos. This descriptive analysis highlights country-level differences in PHSM implementation and COVID-19 transmission. Our work supports existing studies that have reported on the association between PHSM implementation timing and stringency and COVID-19 outcomes. Furthermore, this paper raises important questions for future research on the impact of socioeconomic factors on country-level outcomes of COVID-19 transmission.

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Conflicts of Interest

None declared.

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Abbreviations

HIT-COVID: Health Intervention Tracking for COVID-19
LMIC: low- and middle-income countries
PHSM: public health and social measure

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Original Paper

The Effect of Test Timing on the Probability of Positive SARS-CoV-2 Swab Test Results: Mixed Model Approach

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Abstract

Background: During the COVID-19 pandemic, swab tests proved to be effective in containing the infection and served as a means for early diagnosis and contact tracing. However, little evidence exists regarding the correct timing for the execution of the swab test, especially for asymptomatic individuals and health care workers.

Objective: The objective of this study was to analyze changes in the positive findings over time in individual SARS-CoV-2 swab tests during a health surveillance program.

Methods: The study was conducted with 2071 health care workers at the University Hospital of Verona, with a known date of close contact with a patient with COVID-19, between February 29 and April 17, 2020. The health care workers underwent a health surveillance program with repeated swab tests to track their virological status. A generalized additive mixed model was used to investigate how the probability of a positive test result changes over time since the last known date of close contact, in an overall sample of individuals who tested positive for COVID-19 and in a subset of individuals with an initial negative swab test finding before being proven positive, to assess different surveillance time intervals.

Results: Among the 2071 health care workers in this study, 191 (9.2%) tested positive for COVID-19, and 103 (54%) were asymptomatic with no differences based on sex or age. Among 49 (25.7%) cases, the initial swab test yielded negative findings after close contact with a patient with COVID-19. Sex, age, symptoms, and the time of sampling were not different between individuals with an initial negative swab test finding and those who initially tested positive after close contact. In the overall sample, the estimated probability of testing positive was 0.74 on day 1 after close contact, which increased to 0.77 between days 5 and 8. In the 3 different scenarios for scheduled repeated testing intervals (3, 5, and 7 days) in the subgroup of individuals with an initially negative swab test finding, the probability peaked on the sixth, ninth and tenth, and 13th and 14th days, respectively.

Conclusions: Swab tests can initially yield false-negative outcomes. The probability of testing positive increases from day 1, peaking between days 5 and 8 after close contact with a patient with COVID-19. Early testing, especially in this final time window, is recommended together with a health surveillance program scheduled in close intervals.

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KEYWORDS

close contact; COVID-19; health care workers; health surveillance; swab test timing

Introduction

COVID-19, caused by SARS-CoV-2 infection, manifests as an acute respiratory distress syndrome, which requires intensive care and can lead to difficulties in the management of cases and limited hospital beds. The COVID-19 pandemic has become a challenge for health care systems because of the large in-hospital diffusion of the pathogen [1,2]. The spread of the infection may involve patients sharing the same hospital ward (ward-based contact) but can also result from infectious health care workers (12%-29% of cases) [3,4].

The ongoing COVID-19 pandemic is placing a large strain on global health care, social, and economic systems. On April 7, 2021, John Hopkins University reported a total of 132,469,663 cases and 2,874,372 deaths worldwide [5].

Italy is one of the most affected countries with 3,686,707 registered cases (as of April 7, 2021), 5% of which were health care workers [5,6]. Asymptomatic cases play an important role in the nosocomial transmission of the disease [7]; they are estimated to vary from 5% to 80% of the total number of cases [8]. Personal protective equipment (PPE) such as universal face masks and preventive actions such as SARS-CoV-2 screening programs for hospitalized patients and workers have been introduced to limit the spread of the infection [4].

Contact tracing and active surveillance implemented through SARS-CoV-2 swab tests play an important role in the containment of the disease. Very few studies have investigated the “best time to test,” particularly in situations where a close contact was detected and most of them focused on symptomatic cases only.

This study aimed to estimate how the individual probability to test positive changes over time, from the date of the last known close contact until the end of individual follow-up evaluation, and to evaluate how different scheduled surveillance time intervals might impact disease prevention.

Methods

Population and Setting

The University Hospital of Verona (UHV) is a high-level facility that serves an area with 922,000 inhabitants and patients from other Italian regions. During the COVID-19 pandemic, it was one of the hub centers for the Veneto region.

According to the guidelines of the Italian Ministry of Health [9], the UHV established a taskforce [10] and conducted a health care surveillance program (HSP) to ensure the safety and well-being of patients and employees and the continuity of care.

All the employees of the UHV, the staff temporarily operating at UHV structures (contractors, PhD students, and internship holders) and the University of Verona staff operating at UHV facilities were involved in the HSP and were considered health care workers (HW) for the purpose of this study. Individuals involved in the HSP with an identifiable date of close contact with a patient with COVID-19 were included in the study. The definitions of close contact are presented in Textbox 1. The study period was approximately 2 months: February 29, 2020 (data on the first swab in our database), to April 17, 2020 (set date of data collection).

Textbox 1. Definition of close contact with a confirmed COVID-19 case according to the Veneto region (Italy) guidelines dated March 13, 2020 [11].

- A person cohabiting with a patient with COVID-19.
- A person who had direct physical contact with a patient with COVID-19.
- A person who had unprotected direct contact with the secretions of a patient with COVID-19.
- A person who had direct contact (face to face) with a patient with COVID-19 at a <2-meter distance, which lasted longer than 15 minutes.
- A person who has been in a closed environment (classroom, meeting room, or hospital waiting room) with a patient with COVID-19 for at least 15 minutes at a <2-meter distance.
- A health care professional or another person who provided direct assistance to a patient with COVID-19 or laboratory staff involved in handling samples of a patient with COVID-19 without the use of recommended personal protective equipment or using unsuitable personal protective equipment.

HSP

The HSP had 2 distinct pathways for symptomatic and asymptomatic HWs who had close contact with a COVID-19–positive individual. Symptomatic individuals were tested and quarantined at home until symptom resolution. For asymptomatic individuals, an oronasopharyngeal swab sample was collected as soon as possible and successively on days 7 and 14 from the date of contact, to ascertain the negative status of the HW. Specimens were collected, in accordance with national and international recommendations [12,13], from both the oropharynx and nasopharynx by trained physicians with assistance from a professional nurse. If an individual tested positive on the swab test, 14 days of fiduciary home isolation was recommended. After this period, 2 swabs were collected consecutively within 24 h. If both tests yielded negative findings, the HWs were considered to have recovered and were allowed to return to work.

Data Collection

At every sampling session, a short epidemiological questionnaire was administered to the HWs to collect the following data: presence of symptoms, nature of the contact (whether at the workplace or outside), age, ward working in, and personal contact details.

The AllplexTM2019-nCoV assay (Seegene Inc) was used to test the respiratory specimens. The virus was identified through multiplex real-time reverse transcriptase–polymerase chain reaction (RT–PCR) testing, which targeted 3 viral genes (E, RdRP, and N), with a detection limit of 4.8 copies/mL. The results were validated by the National Reference Laboratory of the National Health Institute [14]. Automated RNA extraction and RT–PCR were performed using Seegene NIMBUS (Seegene Inc). RT–PCR was performed using the CFX96TMDx platform (Bio-Rad Laboratories Inc) and subsequently interpreted using Seegene Viewer (Seegene Inc). Samples were considered positive at a cycle threshold (Ct) value of ≤40 for at least 1 of the 3 target genes. Microbiology laboratory data (swab results and dates) and data from the questionnaires were then merged into a unique database.

Ethics Statement

According to Decree-Law N.14 of March 9, 2020, personal data can be collected to guarantee public health and ensure the diagnosis and assistance of the infected individuals in the context of the COVID-19 emergency [15]. All data were collected exclusively for the purpose of the health surveillance program and were anonymized and presented in an aggregated format to ensure the privacy of the participants. The study conformed to the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Statistical Analysis

A data exploratory analysis was first conducted to investigate the characteristics of the HWs. Categorical data were compared using the chi-square test, and the Mann-Whitney (2-sample Wilcoxon) test was performed for continuous variables and to compare time-to-test positivity between groups of individuals (no censoring was carried out in this analysis; therefore, survival techniques could be discharged).

Generalized additive mixed models (GAMM) for binomially distributed data were used to investigate how the probability of a positive test result changes over time since the last known close contact date declared by the HW [16]. A continuous smooth function was used to model the effect of the number of days since close contact on the probability of testing positive and individual-specific random intercepts were included in the model to account for intraclass correlation of observations from among the same participants.

The same analysis was also performed to assess the probability of testing positive in the subset of individuals who eventually tested positive but initially presented a negative swab test finding. In addition to the aforementioned principal analyses, alternative surveillance time intervals were assumed to investigate how they might influence the results of our analysis. Specifically, for each individual, swabs following the first one, taken as soon as possible, were simulated at closer intervals (3 and 5 days) than the standard 7-day interval planned by the HSP. The length of surveillance between a testing date and the next one was "virtually" modified with a mathematical shift as shown below.

An index to enumerate individual swabs was generated as follows:

where *ds* and *dc* are the dates of the individual swab tests and of close contact, respectively, *i* identifies each of the individuals included in the study, and *t* is the index identifying each individual's test finding.

In our HSP, the fixed surveillance interval between swabs was 7 days. The *Iv* for the first swab (Iv_{i1}) was assumed to be 0 because it was considered unmodifiable by HSP timing.

Thereafter, we formulated a GAMM model introducing the index time as follows:

$$Y_i \sim \text{Bin}\ (n_i, \pi_i);\ \pi_i = \text{probability of a positive test}$$

$$\text{Logit}(\pi_{it}) = \beta_i[f\{(ds_{i1} - dc_i) + (Iv_{it} \times It)\}] + b_{i0} + \varepsilon_{it}$$

where ds_1 and *dc* are the date of the first swab and the date of close contact, respectively, *i* is the individual index, and *t* is the time observation index. *It* and *Iv* are the fixed surveillance interval time and the index visit, previously exposed, and $f\{(ds_{i1} - dc_i) + (Iv_{it} \times It)\}$ indicates a smooth function with penalized splines; furthermore, b_{i0} is the individual-specific random intercept in the model.

A *P* value of <.05 was considered significant. All analyses were performed using R software (version 3.5.2, The R Foundation).

Results

During the study period, 2071 of 6092 (34%) HWs currently employed had close contact with a confirmed patient with COVID-19. Among them, 191 (9.2%) yielded positive findings on oropharyngeal swab tests. This proportion was not significantly different for the sex (*P*=.25) and age (*P*=.31) of the individuals included in this study (Table 1). Among the COVID-19–positive individuals, 88 (46%) presented at least mild symptoms (such as cough, fever, dyspnea, sore throat, anosmia, and ageusia). The median time of symptom onset after close contact was 4.0 (IQR 1.0-6.3) days and was not significantly different for sex (*P*=.75) and age (*P*=.48).

In 25.7% of the individuals who tested positive (n=49), the first swab test after close contact yielded a negative result (Table 1). The occurrence of an initial negative swab test result was not associated with sex, age, or symptoms. In 9 of these individuals (4.7% of all infected HWs), the second swab test yielded a negative finding. The median time between close contact and the first swab test was 3 days for the group with an initial negative finding, whereas it was 4 days for those who tested positive on the first swab test (*P*=.06).

Table 1. Characteristics of health care workers at University Hospital of Verona (Italy) distinguished by SARS-CoV-2 swab test results and the presence of symptoms (data collected between February 29 and April 17, 2020).

Characteristics	Infected health care workers with an initial negative swab test finding after close contact with a patient with COVID-19			Positive swab test finding among health care workers after close contact with a patient with COVID-19			Symptomatic health care workers with COVID-19		
	Yes (n=49)	No (n=142)	*P* value[a]	Yes (n=191)	No (n=1880)	*P* value	Yes (n=88)	No (n=103)	*P* value
Sex, n (%)			.40			.25			.20
Male	15 (31)	55 (39)		70 (37)	607 (32)		37 (42)	33 (32)	
Female	34 (69)	87 (61)		121 (63)	1273 (68)		51 (58)	70 (68)	
Age (years), median (IQR)	40.9 (30.0-52.4)	47.9 (32.9-55.3)	.06	46.7 (31.8-54.8)	45.1 (32.2-53.2)	.31	48.9 (36.9-54.8)	41.5 (30.3-54.7)	.08
Symptoms, n (%)			.31	N/A[b]	N/A	N/A	N/A	N/A	N/A
Yes	19 (39)	69 (49)							
No	30 (61)	73 (51)							
Days from close contact to initial swab sample collection, median (IQR)	3.0 (1.0-6.0)	4.0 (2.0-8.0)	.06	N/A	N/A	N/A	N/A	N/A	N/A

[a] *P* values were computed using the chi-square test and the nonparametric Mann–Whitney *U* test.

[b] N/A: not applicable.

Since all HWs were checked over time with repeated swabs under the HSP, it was possible to calculate the proportion of false-negative findings from among the total number of individuals who tested negative (false omission rate). The false omission rate was 2.5%.

The median time from the date of individual close contact to the first positive finding on the swab test was estimated. In the overall sample of HWs, this median time was 7 (IQR 4-11) days. Considered separately, the median time for HWs who tested negative on their initial swab test and that for HWs who did not was 10 days and 4 days, respectively. No significant differences were observed in the time to the first positive finding on the swab test with respect to sex (*P*=.62), age (*P*=.47), or clinical manifestations (*P*=.39).

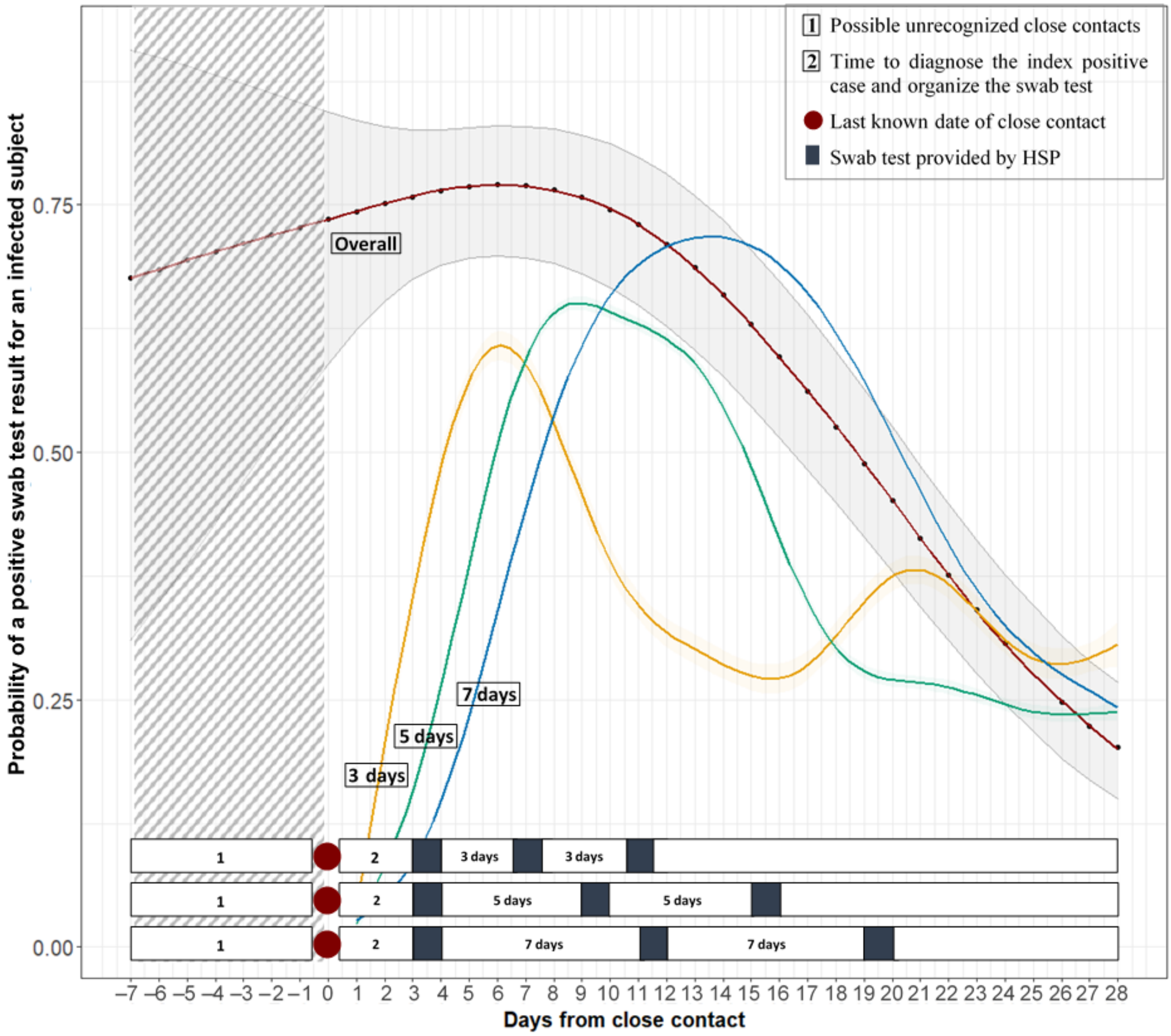
In the GAMM model that considered the whole group of COVID-19–positive individuals, the probability of a positive swab test result increased from 0.74 on day 1 to 0.77 on day 5 after close contact (Table 2). This probability peaked between the fifth and eighth days (0.77) and then decreased during subsequent days since close contact (Figure 1). All the predicted model probabilities for the first to the 21st day from close contact are indicated in Table 2.

Table 2. Predicted probabilities of the generalized additive mixed models for a positive swab test result related to the number of days since close contact in the whole group of infected health care workers at the University Hospital of Verona (model was fitted with data collected between February 29 and April 17, 2020).

Day	π (0.95% CI)
1	0.74 (0.62-0.84)
2	075 (0.65-0.83)
3	0.76 (0.67-0.83)
4	0.76 (0.69-0.83)
5	*0.77 (0.69-0.83)* [a]
6	*0.77 (0.69-0.83)*
7	*0.77 (0.69-0.83)*
8	*0.77 (0.69-0.83)*
9	0.76 (0.68-0.82)
10	0.75 (0.67-0.81)
11	0.73 (0.65-0.79)
12	0.71 (0.63-0.78)
13	0.69 (0.60-0.76)
14	0.66 (0.58-0.73)
15	0.63 (0.55-0.71)
16	0.60 (0.51-0.67)
17	0.56 (0.48-0.64)
18	0.53 (0.45-0.60)
19	0.49 (0.41-0.56)
20	0.45 (0.38-0.53)
21	0.41 (0.34-0.49)

[a] Italicized values indicate the days where the probability of testing positive for COVID-19 on the swab test peaks.

Figure 1. Graphical predictions from the generalized additive mixed models. The 4 curves represent the predicted probabilities of having a positive test related to the number of days since the last known date of close contact among all health care workers infected with SARS-CoV-2 (overall curve) and in the subgroups of those infected with SARS-CoV-2 with an initial negative swab test result in the 7-day standard surveillance interval and simulating 2 different time intervals of 3 and 5 days. The bars show the time course of the health surveillance program in the 3 different time intervals related to the probability curves. HSP: health surveillance program.



The same model was used to analyze the change over time of the probability of a positive swab test finding in the subset of HWs with an initial negative swab test result in the standard HSP 7-day interval and in the alternative "simulated schedule time" for surveillance intervals of 3 days and 5 days (Table 3).

In the 3 intervals (3, 5, and 7 days), the highest peak was observed on the sixth day, between the ninth and tenth days, and between the 13th and 14th days, respectively, with a probability of a positive swab test result of 0.61, 0.65, and 0.72, respectively (Figure 1). This probability then decreased with time in all surveillance interval models except for the 3 day interval, in which a secondary tail peak was obtained on the 21st day with a probability of 0.38. All the predicted model probabilities for the 3 assumed surveillance intervals and for days 1 to 28 from close contact are indicated in Table 3.

Table 3. Predicted probabilities of the generalized additive mixed model for a positive swab test result for COVID-19 in relation with the number of days since close contact with a patient with COVID-19, among infected health care workers from University Hospital of Verona (Italy) with an initial negative swab test result (the model was fitted with data collected between February 29 and April 17, 2020). Three different scenarios were included for the surveillance time interval (3, 5, and 7 days).

Day since close contact with a patient with COVID-19	3 days, π (0.95% CI)	5 days, π (0.95% CI)	7 days, π (0.95% CI)
1	0.07 (0.02-0.23)	0.03 (0.01-0.16)	0.03 (0.00-0.14)
2	0.17 (0.07-0.35)	0.07 (0.02-0.23)	0.05 (0.01-0.18)
3	0.34 (0.20-0.51)	0.15 (0.06-0.32)	0.09 (0.03-0.24)
4	0.50 (0.35-0.65)	0.26 (0.14-0.44)	0.15 (0.06-0.31)
5	*0.59 (0.45-0.72)* [a]	0.40 (0.25-0.56)	0.23 (0.12-0.41)
6	*0.61 (0.46-0.75)*	0.51 (0.37-0.66)	0.34 (0.20-0.51)
7	*0.58 (0.42-0.72)*	0.59 (0.45-0.72)	0.44 (0.30-0.60)
8	0.52 (0.36-0.67)	0.63 (0.48-0.76)	0.54 (0.39-0.67)
9	0.45 (0.31-0.61)	*0.65 (0.49-0.78)*	0.61 (0.47-0.73)
10	0.40 (0.27-0.54)	*0.65 (0.47-0.79)*	0.66 (0.51-0.78)
11	0.35 (0.24-0.49)	0.64 (0.45-0.79)	0.69 (0.54-0.81)
12	0.32 (0.20-0.46)	0.62 (0.43-0.77)	0.71 (0.55-0.83)
13	0.30 (0.18-0.45)	0.59 (0.40-0.75)	*0.72 (0.54-0.84)*
14	0.28 (0.16-0.45)	0.54 (0.37-0.71)	*0.72 (0.53-0.85)*
15	0.27 (0.14-0.46)	0.48 (0.33-0.64)	0.71 (0.52-0.85)
16	0.27 (0.14-0.47)	0.41 (0.28-0.57)	0.69 (0.49-0.84)
17	0.29 (0.14-0.50)	0.35 (0.23-0.50)	0.66 (0.46-0.82)
18	0.32 (0.15-0.55)	0.30 (0.19-0.45)	0.62 (0.43-0.78)
19	0.35 (0.15-0.61)	0.28 (0.16-0.43)	0.57 (0.39-0.74)
20	0.37 (0.16-0.65)	0.27 (0.15-0.43)	0.52 (0.35-0.68)
21	*0.38 (0.15-0.69)*	0.26 (0.14-0.44)	0.46 (0.31-0.62)
22	0.37 (0.12-0.71)	0.26 (0.14-0.45)	0.41 (0.27-0.56)
23	0.34 (0.10-0.72)	0.26 (0.13-0.45)	0.36 (0.24-0.51)
24	0.31 (0.07-0.73)	0.25 (0.12-0.45)	0.33 (0.21-0.48)
25	0.29 (0.06-0.74)	0.24 (0.10-0.46)	0.30 (0.18-0.45)
26	0.28 (0.05-0.75)	0.23 (0.09-0.47)	0.28 (0.16-0.43)
27	0.29 (0.04-0.78)	0.23 (0.08-0.50)	0.26 (0.14-0.42)
28	0.31 (0.04-0.82)	0.24 (0.08-0.54)	0.24 (0.13-0.41)

[a] Italicized values indicate the days where the probability of testing positive for COVID-19 on the swab test peaks.

Discussion

Principal Findings

Identification and tracking of close contacts are a fundamental strategy to prevent the spread of COVID-19. During the study period, approximately one-third of UHV HWs claimed that they had close contact with a patient with COVID-19. Among them, 9.2% tested positive on the oronasopharyngeal swab test. Other studies have reported similar results among HWs with regard to both the occurrence of close contacts and the prevalence of positive cases [17,18]. Nosocomial transmission of SARS-CoV-2 with outbreaks occurring in different wards has been reported in several countries [19,20].

In our study sample, approximately half of the HWs who tested positive were asymptomatic. The consistency of this finding with those of previous studies [21,22] may justify the need to test individuals regardless of clinical manifestation, especially in a health care setting, to avoid disease spread from asymptomatic cases [23].

The median time for the occurrence of symptoms, starting from the date of declared close contact, for symptomatic individuals was estimated to be 4 days. The incubation time of SARS-CoV-2 is still being debated: a meta-analysis conducted mostly on Chinese data estimated a mean incubation time of approximately 5 days [24], while the European Centre for Disease Prevention and Control reports a median incubation period between 5 and 6 days, ranging from 2 to 14 days [25].

RT–PCR analysis of oronasopharyngeal swab samples has been recognized as the most reliable test to identify and ascertain SARS-CoV-2 infection; however, the sensitivity and specificity of the swab test are still being discussed [26,27]. Two reviews reported sensitivities ranging between 63% and 98% [28,29]. The specificity of the test was reported to be higher (95%) [27].

In this study, 58 swab tests yielded negative findings before a positive finding was obtained in the subsequent test. The false-negative rate (the test does not initially detect the infection when one actually acquires it) in our sample was 22.3%. This result may have different explanations apart from the intrinsic sensitivity of the RT–PCR test. First, the rate of false-negative results may change in accordance with how long the infection has been acquired. The time between the date of the close contact and the date of the first specimen collection was not different between the 2 groups of positive and negative initial swabs, with comparable demographic characteristics, thus limiting the bias of an incorrect sampling timing (Table 1). However, some individuals may have presented a longer incubation period before the virus could be detected in a test, thus leading to false-negative results despite the infection already having been acquired. False-negative results are influenced even by the sampling quality of the swab. In particular, when the viral load is low, the specimen collection technique could be a source of diagnostic errors [30]. It is also worth noting that the RT–PCR assays used herein had a Ct of 40. The Ct is a semiquantitative value. A lower Ct value corresponds to a higher quantity of viral genetic material in the sample, which can be considered an approximation of the viral load. However, viruses have been isolated from laboratory cell cultures from samples exhibiting Ct values above 36 [31]. It may be possible that some of the samples, considered negative because of their high Ct, still had a very low quantity of viral genetic material, which increased in the subsequent days. In the study sample, the estimated probability of incorrectly ruling out a case of COVID-19 on the basis of a false-negative test was 2.5%. Long et al [32] reported similar results upon assessing 678 patients who underwent repeated testing. It must be considered that this probability is influenced by not only test sensitivity but also disease prevalence.

Starting from the assumption that false-negative results may be obtained, the median time to a positive swab test result was measured in the whole group and then separately, distinguishing between HWs with an initially negative finding and those with an initially positive finding on the swab test. The estimated median time from close contact to the first positive test was 7 days overall, 4 days in the group of HWs who presented an initial positive result, and 10 days for those who presented an initial negative finding on the swab test. This can be partly attributed to the HSP that planned a swab every 7 days for individuals with close contact. The surveillance time interval plays a crucial role in the detection of COVID-19–positive individuals and influences the spread of the infection.

As a repeated testing strategy is considered important to overcome false-negative results, especially in a health care setting [33,34], a GAMM model was applied to investigate how the probability of obtaining a positive swab test result may change over time from the last known date of close contact of that individual and ultimately to discern a possible “best time to test” after a close contact.

In our sample, the probability of a positive swab was 0.74 on day 1 and peaked (0.77) between days 5 and 8 after close contact. This high probability retrieved from the first day after close contact can be explained by the fact that the contact causing infection may have occurred on a previous date than the last one that was recognized and reported by the HW (Figure 1). Individuals who test positive have shown to be infective since the preclinical and subclinical stages of the disease [24,35,36], and it was reported that the replication rate of SARS-CoV-2 peaks 2 days post infection, with an increase in the virus titer detectable already in the first 24 h post inoculation [37]. Two studies conducted only on symptomatic individuals reported the maximum probability of a positive swab test result in the initial days following the onset of symptoms [34,38].

In our sample, 25.7% and 4.7% of infected HWs required 2 and 3 tests, respectively, to be confirmed as positive, consistent with a previous report [39]. Considering this group, the probability peak (0.72) was obtained approximately 13-14 days after close contact for the 7-day standard HSP surveillance interval.

When simulating a 3- and 5-day interval model, the probability of obtaining a positive swab test result peaked on the fifth to seventh and the ninth to tenth days, respectively. In the 3-day interval model, the time of the highest probability was similar to that estimated for the whole group of individuals who tested positive (Figure 1). The function for the 3-day interval shows 2 peaks, one between days 5-7 and another on day 21 after close contact. For screening intervals of 5 and 7 days, the function seems to include the 2 sets of swabs obtained on the same individual to ascertain positivity first and negativity thereafter, under a unique curve interval because of the wider intervals. Simulations of the screening time intervals narrower than the 7-day standard HSP surveillance interval have shown that the probability of testing positive can be detected earlier.

Limitations

One of the limitations of this study is that HWs have self-reported the dates of close contact, which may have led to recall bias errors. On the other hand, the HSP, by continuously monitoring HWs over time, permitted the registration of the updated last dates of close contact and to identify true-negative cases. HWs who tested positive at least once were considered true-positive cases, consistent with a previous report [38], even if the specificity of the swab test may have influenced the results.

Contact tracing has been one of the main strategies to keep the pandemic under control; however, only a few studies have investigated the relationship between close contact and a positive swab test result. Monitoring of HWs through swab testing in the hospital setting is particularly important because it may prevent large-scale disease spread.

Conclusions

This study is one of the first to explore the best scheduling time in an HSP for HWs. A call for algorithms has been made to detail the exact pathway to monitor the safety of HWs [40]. In a hospital setting, several unrecognized close contacts that cause infection may occur. Having shown that the probability of a positive swab test result for COVID-19 is already high in the first days and peaks between the fifth and eighth days after the last known close contact, early testing, especially within this time window would be advisable. Narrowing of surveillance intervals between swabs in the first 10 days might be recommended, since negative results may be obtained initially. Many European countries are currently facing a third wave of COVID-19. Ensuring the safety of patients and HWs and the continuity of care are fundamental in this situation. The correct use of the appropriate PPE is pivotal in preventing new infections; however, when an accidental close contact with a positive case occurs, it is mandatory to monitor HWs through swab testing. Many positive individuals may be asymptomatic or pauci-symptomatic; therefore, the recommendation is to test all HWs regardless of their clinical manifestations.

Authors' Contributions

In this study, RB, S Panunzi, and IC conceptualized and designed the study, were responsible for the data analysis, and made substantial contributions to drafting the manuscript. FM revised the manuscript critically and contributed substantially to the interpretation of the data. GLC, GS, IC, and RB made substantial contributions to data collection. S Porru was responsible for data management. ST revised the manuscript study critically and contributed to study conception.

Conflicts of Interest

None declared.

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Abbreviations

Ct: cycle threshold
GAMM: generalized additive mixed model
HSP: health surveillance program
HW: health care worker
PPE: personal protective equipment
RT–PCR: reverse transcriptase–polymerase chain reaction
UHV: University Hospital of Verona

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Original Paper

Correlation of Population SARS-CoV-2 Cycle Threshold Values to Local Disease Dynamics: Exploratory Observational Study

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Abstract

Background: Despite the limitations in the use of cycle threshold (CT) values for individual patient care, population distributions of CT values may be useful indicators of local outbreaks.

Objective: We aimed to conduct an exploratory analysis of potential correlations between the population distribution of cycle threshold (CT) values and COVID-19 dynamics, which were operationalized as percent positivity, transmission rate (R_t), and COVID-19 hospitalization count.

Methods: In total, 148,410 specimens collected between September 15, 2020, and January 11, 2021, from the greater El Paso area were processed in the Dascena COVID-19 Laboratory. The daily median CT value, daily R_t, daily count of COVID-19 hospitalizations, daily change in percent positivity, and rolling averages of these features were plotted over time. Two-way scatterplots and linear regression were used to evaluate possible associations between daily median CT values and outbreak measures. Cross-correlation plots were used to determine whether a time delay existed between changes in daily median CT values and measures of community disease dynamics.

Results: Daily median CT values negatively correlated with the daily R_t values ($P<.001$), the daily COVID-19 hospitalization counts (with a 33-day time delay; $P<.001$), and the daily changes in percent positivity among testing samples ($P<.001$). Despite visual trends suggesting time delays in the plots for median CT values and outbreak measures, a statistically significant delay was only detected between changes in median CT values and COVID-19 hospitalization counts ($P<.001$).

Conclusions: This study adds to the literature by analyzing samples collected from an entire geographical area and contextualizing the results with other research investigating population CT values.

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KEYWORDS

reverse transcription polymerase chain reaction; testing; cycle threshold; COVID-19; epidemiology; Rt; exploratory; correlation; population; threshold; disease dynamic; distribution; transmission

Introduction

As of February 16, 2021, the SARS-CoV-2 virus has infected more than 109 million people around the world and has been implicated in 2.41 million deaths [1]. In the United States alone, more than 486,500 deaths have been attributed to COVID-19 [1]. Reverse transcription polymerase chain reaction (RT-PCR) testing has become the predominant method for COVID-19 surveillance and diagnostic testing due to having higher sensitivity, higher specificity, and faster turnaround times compared to those of viral cultures [2,3]. RT-PCR tests detect viral genetic material in biological samples [4]. The cycle threshold (CT) value represents the number of polymerase chain reaction cycles that are required to detect a positive signal [5]. The CT value is inversely related to the viral load; a 3.3 increase in CT value indicates an approximately 10-fold decrease in the amount of viral genetic material present in a sample [5]. COVID-19 RT-PCR tests are generally considered positive only if they generate a result with a CT value that is lower than the recommended cutoff. In the United States, the Food and Drug Administration has approved emergency use authorizations for tests in which CT values of <37 can be considered positive [6].

CT values are lowest—indicating a larger amount of viral genetic material—early in the disease course. Indeed, numerous studies have reported that CT values tend to be highest prior to or during the earliest days following the onset of symptoms and decline as a disease progresses [7-11]. Lower CT values have been directly linked with higher infectivity, as shown by researchers' ability to cultivate live SARS-CoV-2 from samples [7,11-14] and the number of individuals infected by an index case [15]. In one study, SARS-CoV-2 could be cultivated from over 70% of samples with a CT value of <25 but could only be cultivated from less than 3% of samples with a CT value of ≥35 [16]. Singanayagam et al [11] found that in samples with a CT value of >35, the probability of such samples containing cultivable viruses declines to approximately 8%, and the correlations between CT values and the probability of samples containing cultivable viruses were similar in samples collected from symptomatic and asymptomatic individuals. CT values have also been reported to directly correlate with disease severity and mortality; CT values tend to be lower in patients with more severe disease presentations [13,17-19] and in hospitalized patients who ultimately die from COVID-19 [13,20].

There are however considerable limitations in the use of CT values for prognostication and treatment planning at the level of individual patients. Critics have noted that there may be significant variability in CT values based on the quantity of biological material collected on a testing swab as well as differences in RT-PCR reagents, equipment, and standards among laboratories [21]. CT values may also vary based on the gene target selected for RT-PCR or even based on the assay used to detect the same gene target [22]. In addition, RT-PCR only detects the presence of viral material and is unable to distinguish between live viruses and viral debris, which may linger for an extended period once an individual is no longer infectious [17]. CT values, when used as a semiquantitative measure of how much viral nucleic acid is present, are similarly limited. As a result of these constraints, clinicians and researchers continue to debate the utility of CT values for informing health care choices for individuals [5,21,22].

Despite the limitations in the use of individual-level CT values, measures of CT values across a population may provide a useful measure of COVID-19 dynamics in communities. It has been suggested that big data technology could be applied to the large amounts of data resulting from the pandemic in order to provide timely information for policy development [23]. As CT values have been reported to correlate with disease stage and infectivity, a higher proportion of low CT values in testing samples from a population may reflect epidemic growth in a community [24]. Preliminary analyses of simulation and surveillance testing data have suggested that decreases in the distribution of CT values in a population, as measured by the median CT value, may precede a local increase in transmission or positivity rates [24,25]. As such, the median CT value may be a useful measure for predicting a pandemic surge. This study describes an exploratory analysis of potential correlations between median CT values and COVID-19 dynamics, which were operationalized as percent positivity, transmission rate (R_t), and COVID-19 hospitalization count.

Methods

Sample Selection

The samples included in this study were collected between September 15, 2020, and January 11, 2021, as part of the ongoing diagnostic evaluation services provided by Dascena, Inc to residents in the state of Texas. In the greater El Paso area, a contractor for the El Paso Department of Public Health sent over 90% of collected samples to the Dascena COVID-19 Laboratory in Houston, Texas. All samples from the greater El Paso area that were processed by Dascena, Inc during the study period were included in our analysis. Supplementary analyses also included samples from Houston-Sugarland-Baytown, Dallas-Fort Worth-Arlington, and Austin-Round Rock. The Pearl Independent Institutional Review Board (IRB) approved this study with a waiver of informed consent (IRB Protocol 21-DASC-127).

This study included nasopharyngeal swabs, salivary samples, an anterior nares swab sample, and samples for which the type of biological specimen was not specified. The overwhelming majority of samples (147,720/148,410, 99.54%) were nasopharyngeal swabs. All biological samples were sent to the Clinical Laboratory Improvement Amendments–certified Dascena Laboratory. All samples were analyzed with the TaqPath COVID-19 Combi Kit (Thermo Fisher Scientific), and extraction was performed with a MagMAX RNA Isolation Kit (Thermo Fisher Scientific). The following three gene targets are used by these assays and may be the source of a positive result: the nucleocapsid gene, the spike gene, and the *ORF1ab* (open reading frames 1ab) gene [26]. RT-PCR was only conducted once for any unique sample. For each RT-PCR test, the CT value was recorded. Only samples that produced a valid CT value for a positive COVID-19 test (ie, at least 2 genes generating a positive signal with a CT value of ≤37) were used to determine daily median CT values and used in subsequent correlation analyses.

Data Processing and Measures

The following demographic data were available for testing samples: age, sex, race, ethnicity, and zip codes of residences. Testing samples from the greater El Paso area were selected based on the zip codes that were listed as part of the El Paso metropolitan statistical area (MSA) by the US Department of Labor, Office of Workers Compensation Program [27]. Daily percent positivity rate was calculated among all of the samples tested by Dascena from the greater El Paso area.

The effective reproduction number or R_t value was derived using the open-source algorithm from the rtcovidlive COVID-19 tracking website [28]. The algorithm is a Python script based on a Bayesian estimation model developed by Bettencourt and Ribeiro [29] with slight modifications for introducing gaussian noise to the prediction. Daily, new COVID-19 case data from individual counties were obtained from the COVID-19 Dashboard of the Center for Systems Science and Engineering at Johns Hopkins University [1], grouped by MSA, and fed into the rtcovidlive algorithm to generate a time series for R_t. The daily number of hospitalized individuals with COVID-19 in the El Paso area was derived from publicly available data produced by the Texas Department of State Health Services, which are grouped by trauma service area [30].

Comparative Analysis of Population-Level CT Values

In order to contextualize the results, a focused literature review using title and keyword searches was performed for peer-reviewed publications and preprint manuscripts on the use of CT value measurements across a population as a means of predicting or monitoring COVID-19 outbreaks. In total, 3 preprints were identified [24,25,31]. The data sets from this study and the preprints were then compared in terms of source population, the type of testing, sample size, the biological sample types included, the duration of the study period, the gene target(s) of RT-PCR tests, the CT-based value(s) measured, the metrics used to measure COVID-19 outbreaks, and the outcomes of the study.

Statistical Analysis

All analyses were conducted in Python [32] by using the following packages: pandas, matplotlib, plotly, scipy, and statsmodels. The daily median CT value among Dascena test samples, the daily R_t in the El Paso MSA, and the daily count of hospitalized individuals with COVID-19 in El Paso were plotted over time. Rolling 7-day averages of daily median CT values (with a minimum 5 days of data present in the window), the daily R_t, the daily number of COVID-19 hospitalizations, and the daily percent positivity rate among samples from El Paso that were sent to the Dascena Laboratory were also plotted over time. To better capture the dynamic change in percent positivity among Dascena test samples, the daily change in percent positivity was calculated from the 7-day rolling average for days in which more than 200 total tests were performed by the Dascena Laboratory. If fewer than 200 tests were performed on a particular day (eg, due to the holiday shutdown of collection sites), the percent positivity from the previous day was carried forward. The daily change in percent positivity was then plotted over time.

Scatterplots and linear regression were used to evaluate possible associations between the daily median CT value (nucleocapsid gene) and daily R_t, between the daily median CT value (nucleocapsid gene) and the daily count of COVID-19 hospitalizations, and between the daily median CT value (nucleocapsid gene) and the daily change in percent positivity among samples processed by Dascena. Since a considerable time delay was observed between changes in the daily median CT value (nucleocapsid gene) and the daily count of COVID-19 hospitalizations, a time lag of 33 days was applied to the hospitalization data prior to creating the scatterplot and conducting linear regression. Median CT values based on the nucleocapsid gene were selected because they have previously been cited in research on population CT values [24,30].

In order to evaluate whether a time delay existed between changes in the daily median CT value (nucleocapsid gene) and community outbreaks, cross-correlation plots were constructed between the daily median CT value and daily R_t, between the daily median CT value and the daily count of hospitalized patients with COVID-19, and between the daily median CT value and the daily change in percent positivity. In brief, a cross-correlation coefficient was obtained by dividing the correlation between two signals by the product of the auto-correlation of each of the two signals. The argmax of the cross-correlation coefficient is the dominant lag time between the two signals. As the purpose of our analysis was to investigate how the trough of daily median CT values correlated with the peak of the other signals, the following modifications were made to aid with visualization: (1) for each signal, the z-score was used instead of the absolute value; (2) the negative value of the z-score of the daily median CT value was used to ensure that a positive peak in the cross-correlation plots was present; and (3) 20% of positive samples were randomly sampled 5 times each day to estimate the variation in the cross-correlation between the daily median CT value and epidemiological signals. A 1-sample, two-tailed *t* test was used to determine if the mean lag differed statistically significantly from the 0.

Pairwise comparisons were performed via Pearson correlation (significance level of $P<.05$) to determine if any demographic factors that were associated with testing samples were significantly associated with R_t, COVID-19 hospitalization count, or percent positivity. The following demographic factors were investigated: the daily number of tests, daily median age, the daily percentage of samples from men, the daily percentage of samples from individuals who indicated that they were White, and the daily percentage of samples from individuals who indicated that they were of Hispanic ethnicity.

Results

In the greater El Paso area, 148,410 COVID-19 tests were sent to the Dascena Laboratory for processing, and 36,306 tests were positive. Of the 148,410 samples, 147,720 (99.54%) samples were nasopharyngeal swabs, 28 (0.02%) were salivary samples, 1 sample (0%) was an anterior nares swab, and 661 samples were biological specimens (0.45%) for which the type of specimen was not recorded. The median CT value (nucleocapsid gene) for nasopharyngeal samples was 23.14, which differed significantly from the median CT value (nucleocapsid gene; 25.58) observed for all other sample types ($P<.001$; Mood median test). The demographic characteristics of the entire population who were tested for COVID-19 are presented in Table 1.

Variability over time was observed in the median CT values and measures of COVID-19 dynamics in El Paso (Figure 1). As predicted in the a priori hypothesis, the daily median CT value negatively correlated with the daily R_t, daily count of COVID-19 hospitalization (with a time delay), and daily change in percent positivity among testing samples in the greater El Paso area (Figure 2).

A 32- to 34-day shift was observed between the median CT value and the daily count of hospitalized individuals with COVID-19 (Figure 3). Although the visual inspection of the daily median CT, daily R_t, and percent positivity plots over time

(Figure 1) suggested that peaks in R_t and percent positivity followed a trough in median CT, no statistically significant time delays were detected between the median CT value and change in percent positivity (*P*=.41) or R_t (*P*=.32). Pairwise comparisons revealed that several demographic factors of the testing samples were associated with COVID-19 outbreak measures (Table 2).

The data set in this study was substantially larger than those reported in comparator studies but differed in that it was not from a surveillance sample. Instead, this study used samples from individuals who required testing due to the presence of COVID-19 symptoms or required testing in the absence of symptoms (eg, for work or travel clearance). The median CT value was the most common measure of the population distribution of CT values across research studies to date, and R_t and percent positivity were the most common outbreak measures (Table 3).

Table 1. Demographic characteristics of the population from the greater El Paso area based on the COVID-19 tests submitted to the Dascena COVID-19 Laboratory between September 15, 2020, and January 11, 2021.

Characteristic	Value
Age (years), mean (SD)	36.92 (18.53)
Gender, n (%)	
Female	81,520 (54.93)
Male	66,270 (44.65)
Prefer not to answer	390 (0.26)
Unknown	230 (0.15)
Ethnicity and race, n (%)	
Hispanic	127,722 (86.06)
White (non-Hispanic)	6668 (4.49)
Black or African American (non-Hispanic)	1891 (1.27)
Asian or Pacific Islander (non-Hispanic)	879 (0.59)
Native American or Alaskan (non-Hispanic)	317 (0.21)
Other (non-Hispanic or prefer not to answer)[a]	10,933 (7.37)

[a] This category includes individuals who indicated “other” or “multiracial” (Black and White) for race or had no race and ethnicity data documented.

Figure 1. (A) Daily median CT values for SARS-CoV-2 positive samples. (B) Daily change in percent positivity for SARS-CoV-2 detection. (C) Daily SARS-CoV-2 R_t. (D) Daily count of hospitalized individuals with COVID-19. (E) The 7-day rolling average of the daily median CT values for SARS-CoV-2–positive samples. (F) The 7-day rolling average of percent positivity rates for SARS-CoV-2–positive samples. (G) The 7-day rolling average of daily SARS-CoV-2 R_t values. (H) The 7-day rolling average of the number of hospitalized individuals with COVID-19 in the greater El Paso area between September 15, 2020, and January 11, 2021. The red lines in graphs C and G signify an R_t value of 1. Red dots represent the global minimum for smoothed CT values and global maxima for smoothed epidemiological indicators. CT: cycle threshold; *ORF1ab*: open reading frames 1ab; R_t: transmission rate.

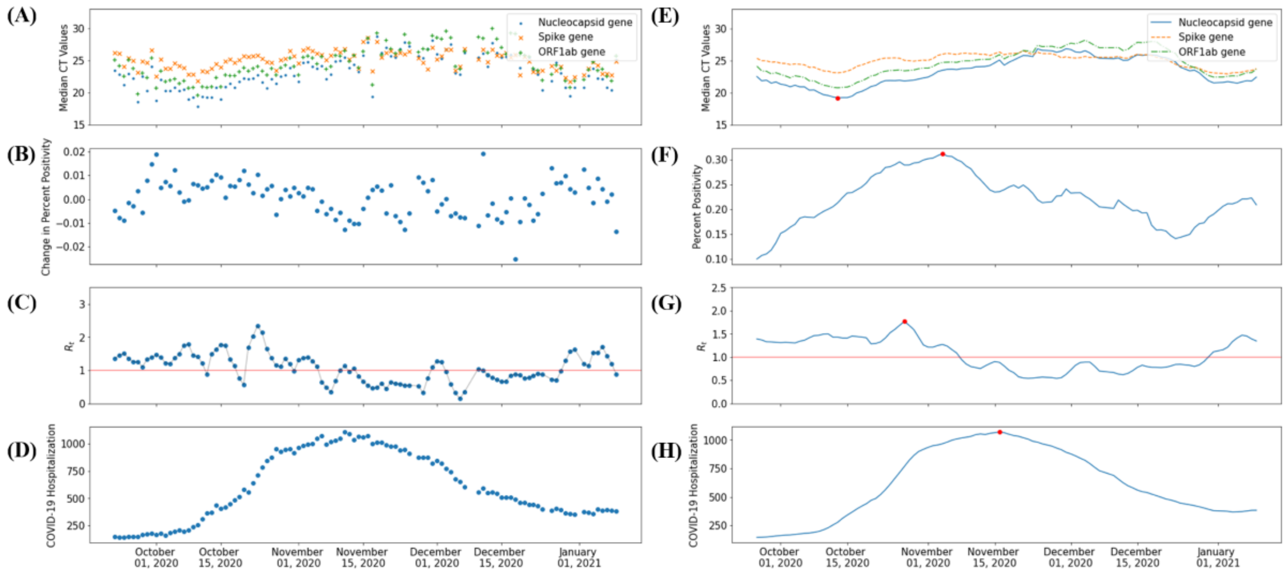


Figure 2. Linear regressions and scatter plots of (A) daily median CT values for SARS-CoV-2–positive samples versus daily transmission rate SARS-CoV-2 R_t, (B) daily numbers of hospitalized individuals with COVID-19, and (C) daily changes in percent positivity for SARS-CoV-2 detection in the greater El Paso area between September 15, 2020, and January 11, 2021. CT: cycle threshold; R_t: transmission rate.

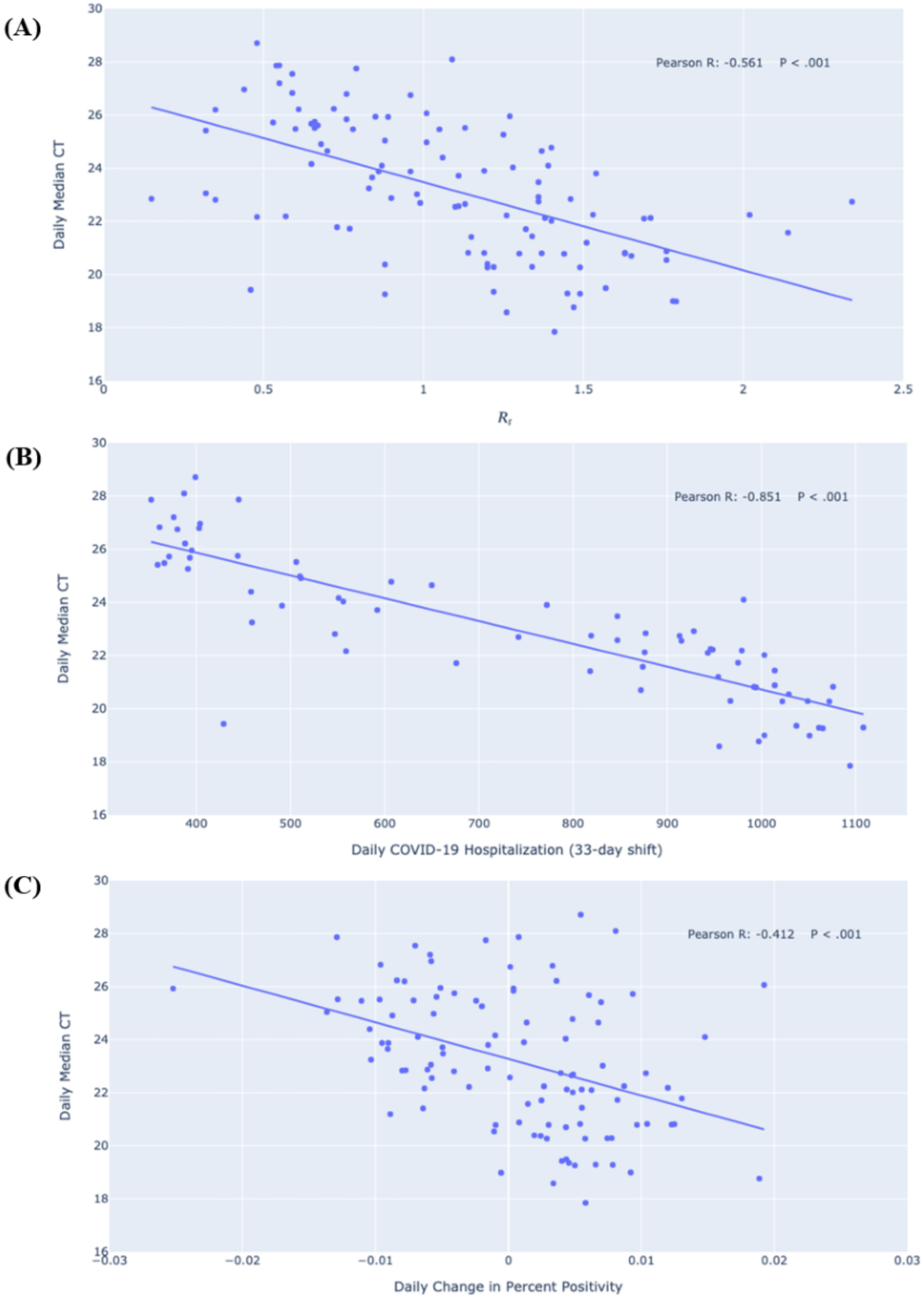
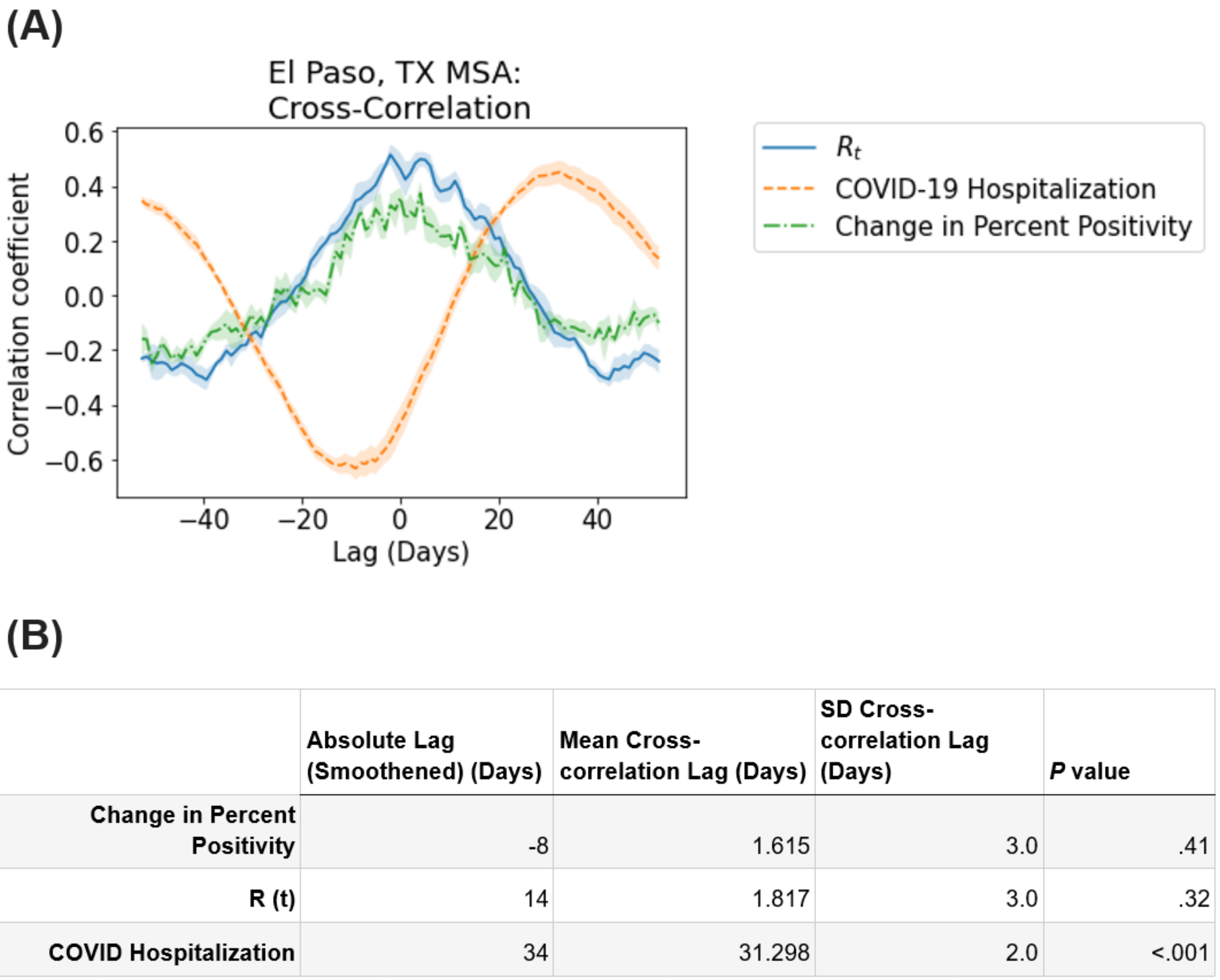


Figure 3. (A) Cross-correlation plot of daily median CT values for SARS-CoV-2–positive samples versus the daily SARS-CoV-2 R_t, daily number of hospitalized individuals with COVID-19, and daily change in percent positivity for SARS-CoV-2 detection in the greater El Paso area between September 15, 2020, and January 11, 2021. Lines represent the mean, while shaded areas indicate the SD across 5-fold sampling. (B) Lag between COVID-19 epidemiological signals and the daily median CT (nucleocapsid gene) values for SARS-CoV-2–positive samples. Absolute lag (smoothened) is the absolute time difference between the peak of each epidemiological signal and the trough of daily median CT values with a 7-day rolling average (red dots in Figure 1B). Mean cross-correlation lag and SD cross-correlation lag represent the mean and SD, respectively, among lags determined by the 5-fold sampling of daily median CT values and cross-correlation. The *P* value column shows the *P* values for determining whether the cross-correlation between daily median CT values and each epidemiological signal is statistically different from 0 (1-sample, two-tailed *t* test). CT: cycle threshold; MSA: metropolitan statistical area; R_t: transmission rate; TX: Texas.



	Absolute Lag (Smoothened) (Days)	Mean Cross-correlation Lag (Days)	SD Cross-correlation Lag (Days)	*P* value
Change in Percent Positivity	-8	1.615	3.0	.41
R (t)	14	1.817	3.0	.32
COVID Hospitalization	34	31.298	2.0	<.001

Table 2. Demographic factors of COVID-19 testing samples collected between September 15, 2020, and January 11, 2021, that were correlated with measures of COVID-19 outbreak dynamics during the sample collection period.

Measure of COVID-19 outbreak dynamics	Correlated variable	Correlation coefficient	*P* value
Daily R_t[a]	Daily median age	−.332	<.001
Daily changes in percent positivity	Daily percentage of samples from Hispanic individuals	.265	.006
Daily COVID-19 hospitalization (33-day shift)	Daily median age	−.451	<.001

[a] R_t: transmission rate.

Table 3. Comparison of studies that examine cycle threshold (CT) values of SARS-CoV-2–positive samples at the population level

Study characteristics	This study	Hay et al [24]	Walker et al [25]	El Zein et al [31]
Source population	El Paso, Texas metropolitan statistical area	Nearly all hospital admissions into Brigham & Women's Hospital in Boston, Massachusetts	United Kingdom's national COVID-19 Infection Survey, which provided a representative sample of the United Kingdom	All patients who tested positive for SARS-CoV-2 at the Detroit Medical Center
Type of testing	Testing based on symptoms or testing for nonsymptomatic purposes (eg, travel and work)	2 weeks of symptomatic testing and 4.5 months of surveillance testing	Surveillance testing	—[a]
Sample size	148,410 samples and 36,306 positive tests	—	843,85 samples and 1892 positive tests	708 hospitalized patients and 282 ambulatory patients
Biological sample types included	Mostly nasopharyngeal swabs and small numbers of anterior nares, salivary, or unknown sample types.	Nasopharyngeal swabs	Nose and throat swabs	Nasopharyngeal swabs
Timeframe (duration)	September 15, 2020, to January 11, 2021 (around 4 months)	April 3, 2020, to November 10, 2020 (around 7 months)	April 26, 2020, to October 11, 2020 (around 5.5 months)	April 4, 2020, to June 5, 2020 (around 2 months)
Gene target(s) of RT-PCR[b]	Nucleocapsid, spike, and *ORF1ab*[c] genes	—	Nucleocapsid, spike, and *ORF1ab* genes	Nucleocapsid gene
CT-based value(s)	Daily median CT value	Distribution, median, and skew of CT values	Mean and median CT values	High, medium, and low viral load (CT values of ≤25, 26-36, and ≥37, respectively)
Outbreak measure	R_t[d], count of individuals hospitalized with COVID-19, and change in percent positivity	R_t	Positivity rate	Mortality
Outcome(s) of study	Negative correlation between median CT and R_t, negative correlation between median CT and hospitalization count (with time delay), and negative correlation between median CT and percent positivity	Correlation between R_t and median and skewness of CT values among positive surveillance specimens	Declines in mean and median CT values preceded increases in positivity rates.	Downward trend in viral load coincided with a decrease in the number of deaths

[a] Not available.

[b] RT-PCR: reverse transcription polymerase chain reaction.

[c] *ORF1ab*: open reading frames 1ab.

[d] R_t: transmission rate.

Discussion

Principal Findings

In this study, we conducted an exploratory analysis of potential correlations between the population distribution of CT values for SARS-CoV-2–positive samples and COVID-19 dynamics. Our results show that the daily median CT value negatively correlated with three measures of COVID-19 dynamics, namely the daily SARS-CoV-2 R_t, the daily count of COVID-19 hospitalizations (with a time delay), and the daily change in percent positivity for SARS-CoV-2 detection among testing samples in the greater El Paso area (Figure 2).

At present, pandemic surges are largely predicted based on observed local case and mortality rates, which may lag behind changes in transmission rates by several weeks or be obscured by changes in testing capacity [24]. Given the ubiquitous availability of CT data and the pressing nature of the pandemic, interest has risen in exploring the possibility that the population distributions of CT values can be used as indicators of local outbreaks. This study adds to the growing literature on this topic by providing an analysis of median CT values from samples collected from an entire geographical area and contextualizing the results via a comparison to other research investigating the application of population-based CT values.

In the greater El Paso area, daily median CT values were found to negatively correlate with the daily percent positivity rate among samples, the daily R_t values extracted from community case rates, and the daily count of COVID-19 hospitalizations (with a delay). Of note, these associations were not observed in supplementary analyses (Figures S1, S2, and S3 in Multimedia Appendix 1) conducted for different Texas MSAs where substantially fewer tests, which covered a smaller proportion of the population (Table S1 in Multimedia Appendix 1), were processed. There appeared to be great day-to-day variability in the median CT values over time rather than consistent trends in the MSAs evaluated in supplementary analyses. This potentially reflects differences in the strength of signals that could be detected. In addition, substantial differences in the study populations may have contributed to the variable significance of the relationship between median CT value and outbreak measures among study sites. This hypothesis is supported by the observation of significant demographic differences between the El Paso MSA and the Texas MSAs evaluated in the supplementary analyses (Table S2 in Multimedia Appendix 1). This observation indicates that certain qualities of data sets that are used to measure population CT values may be important to their utility in approximating local COVID-19 pandemic surges.

Changes in the population distribution of CT values significantly (P<.001) preceded a rise in COVID-19 hospitalization counts in El Paso. However, contrary to the a priori hypothesis that changes in CT values would precede pandemic surges, the cross-correlation plots of median CT values, percent positivity rates, and R_t values did not strongly demonstrate such a relationship. It therefore remains unclear from the data whether changes in the population distribution of CT values preceded changes in community transmission or vice versa. Other studies evaluating population CT values of surveillance samples have reported that changes in CT values may precede traditional signs of an outbreak [24,25]. The inclusion of tests that were based on the presence of symptoms in the sample population may have influenced this association, such that a decline in CT values may be more closely linked to current case rates.

Strengths

The strengths of this study include the fact that all RT-PCR analyses were conducted at a single laboratory that used standardized testing protocols and that large samples of positive COVID-19 tests were acquired for the study site. The vast majority (147,720/148,410, 99.54%) of samples were nasopharyngeal swabs. As such, differences in median CT values based on sample type likely did not impact results. This study was not limited to a single medical center but included samples collected from an entire geographical area. This study compared median CT values to R_t values and hospitalization counts—traditional public health benchmarks that are used to define pandemic surges—thereby providing greater validity than what would be possible with only an internal comparison of different metrics for testing sample data. In addition, this study provided a novel examination of the features of RT-PCR testing data, which may contribute to and affect the usability of population-level metrics of CT values in predicting disease dynamics in a community.

Limitations

Although the study sample was large, other variables and forms of bias (eg, sampling bias) may have influenced the results. Indeed, differences in the comprehensiveness of the El Paso data set versus those in the supplementary site data sets (ie, the relative proportion of tests conducted by the Dascena laboratory versus those of other testing providers) may have contributed to the skew in the supplementary samples. Future directions for research on population-based CT values may therefore include analyzing whether significant differences in results can be detected in different subsamples of tested populations and evaluating methods for collating CT data across testing providers in a given geographic area.

No data on symptomatology were associated with samples at the time of collection. As such, these data did not allow us to distinguish between samples collected as part of a clinical evaluation of symptoms consistent with COVID-19 or those collected for other reasons (eg, clearance for work or travel). Prior research assessing the population distribution of CT values in relation to community outbreaks has explicitly used surveillance samples [24,25]. The variability in the observed correlations between the median CT value and outbreak measures in El Paso or those in other testing locations may partially reflect variability in the proportions of tests that were based on the presence of symptoms and tests for nonsymptomatic purposes in a given location. However, other differences between the testing site populations may also have contributed to the observed variability in the relationship between the median CT value and outbreak measures, such as differences in the demographics of the tested population. The research question of whether median CT values derived from all testing data, instead of those derived from surveillance-only testing data, may be reliably used to predict disease outbreaks remains unresolved and can only be addressed by using data sets in which symptomatology at the time of testing or reasons for testing may be linked to test results.

The samples used in this study were not collected expressly for the purposes of public health surveillance or research; therefore, the demographic composition of the sampled population varied from day to day. As indicated by Table 2, some aspects of the daily demographic composition of the tested population were found to correlate with epidemiological outcomes. Daily variability in the sampled population may therefore translate to variability in the strength of the associations between median CT values and measures of disease dynamics. However, these associations may also reflect underlying epidemiological trends, such as the disproportionately high rates of COVID-19 infection among Hispanic individuals [33], including those that occur during outbreaks. Additional research with real-world samples may build on this study by further exploring the relevance of demographic factors to the accuracy and utility of population-based CT measures.

Conclusions

As national, state, and local authorities continue to refine public health programs to track and contain the spread of SARS-CoV-2, it is imperative to optimize methods for predicting surges in community transmission. Greater lookahead times would enable local and state officials to enact public health policies for mitigating an anticipated pandemic surge and would provide health systems with the opportunity to initiate changes to their standard operating procedures, including activating reserve clinical personnel, procuring additional resources to the extent possible, and converting facilities to support additional patient flow. The population distribution of CT values, as measured by the median CT value, is a potential indicator for local outbreaks, which merits further investigation and may warrant the tracking of these quantitative data by public health departments.

Authors' Contributions

CFT processed the data, adapted the software code, conducted statistical analyses, generated figures, contributed to drafting the manuscript, and participated in critically reviewing and editing the manuscript. AG obtained and organized the data for study, reviewed software and statistical analyses, and contributed to the primary drafting and editing of the manuscript. AGS contributed to the critical review of the study design and analyses, the drafting of the manuscript, and the editing of the manuscript. QM and RD formulated the idea for this study, supervised analyses, and critically reviewed and edited the manuscript.

Conflicts of Interest

All authors whose affiliations are listed as “Dascena, Inc” (Houston, Texas, United States of America) are employees or contractors of Dascena, Inc. Dascena, Inc performed the SARS-CoV-2 detection testing for all of the samples used in this research study.

Multimedia Appendix 1
Supplementary materials.
[DOCX File , 994 KB - publichealth_v7i6e28265_app1.docx]

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Abbreviations

CT: cycle threshold
IRB: Institutional Review Board
MSA: metropolitan statistical area
***ORF1ab*:** open reading frames 1ab
R_t: transmission rate
RT-PCR: reverse transcription polymerase chain reaction

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Original Paper

How New Mexico Leveraged a COVID-19 Case Forecasting Model to Preemptively Address the Health Care Needs of the State: Quantitative Analysis

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Abstract

Background: Prior to the COVID-19 pandemic, US hospitals relied on static projections of future trends for long-term planning and were only beginning to consider forecasting methods for short-term planning of staffing and other resources. With the overwhelming burden imposed by COVID-19 on the health care system, an emergent need exists to accurately forecast hospitalization needs within an actionable timeframe.

Objective: Our goal was to leverage an existing COVID-19 case and death forecasting tool to generate the expected number of concurrent hospitalizations, occupied intensive care unit (ICU) beds, and in-use ventilators 1 day to 4 weeks in the future for New Mexico and each of its five health regions.

Methods: We developed a probabilistic model that took as input the number of new COVID-19 cases for New Mexico from Los Alamos National Laboratory's COVID-19 Forecasts Using Fast Evaluations and Estimation tool, and we used the model to estimate the number of new daily hospital admissions 4 weeks into the future based on current statewide hospitalization rates. The model estimated the number of new admissions that would require an ICU bed or use of a ventilator and then projected the individual lengths of hospital stays based on the resource need. By tracking the lengths of stay through time, we captured the projected simultaneous need for inpatient beds, ICU beds, and ventilators. We used a postprocessing method to adjust the forecasts based on the differences between prior forecasts and the subsequent observed data. Thus, we ensured that our forecasts could reflect a dynamically changing situation on the ground.

Results: Forecasts made between September 1 and December 9, 2020, showed variable accuracy across time, health care resource needs, and forecast horizon. Forecasts made in October, when new COVID-19 cases were steadily increasing, had an average accuracy error of 20.0%, while the error in forecasts made in September, a month with low COVID-19 activity, was 39.7%. Across health care use categories, state-level forecasts were more accurate than those at the regional level. Although the accuracy declined as the forecast was projected further into the future, the stated uncertainty of the prediction improved. Forecasts were within 5% of their stated uncertainty at the 50% and 90% prediction intervals at the 3- to 4-week forecast horizon for state-level inpatient and ICU needs. However, uncertainty intervals were too narrow for forecasts of state-level ventilator need and all regional health care resource needs.

Conclusions: Real-time forecasting of the burden imposed by a spreading infectious disease is a crucial component of decision support during a public health emergency. Our proposed methodology demonstrated utility in providing near-term forecasts, particularly at the state level. This tool can aid other stakeholders as they face COVID-19 population impacts now and in the future.

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KEYWORDS

COVID-19; forecasting; health care; prediction; forecast; model; quantitative; hospital; ICU; ventilator; intensive care unit; probability; trend; plan

Introduction

Since the novel coronavirus SARS-CoV-2 was identified and declared a global pandemic on March 11, 2020 [1], a key concern has been whether the demand for health care will exceed available resources. Early case reports clearly demonstrated that a large number of infections resulted in hospitalization, intensive care unit (ICU) admission, and breathing assistance via mechanical ventilation [2]. Further projection studies, which show plausible outcomes under defined scenarios [3], showed that COVID-19, the disease caused by SARS-CoV-2, had the potential to overwhelm existing capacity, especially given its limited treatment options [4-7]. In areas with limited resources and high rates of transmission, health care capacity has indeed been exceeded [8]. This threat has highlighted the need for continuous monitoring of hospital resources and for forecasting the impact of real-time changes in new cases on future strain of the health care system.

Real-time forecasting of infectious diseases has become a crucial component of decision support during public health emergencies. Since 2013, when the US Centers for Disease Control and Prevention (CDC) began hosting an annual influenza forecasting challenge [9], the field of infectious disease forecasting has grown. In the context of influenza, the task is for modelers to supply probabilistic forecasts of influenza-like illness for short-term targets, such as week-ahead incidence, at multiple geographical scales, using a variety of models and methods. From this effort, forecasting attempts for other diseases, such as chikungunya [10], Ebola [11], and West Nile [12], have proliferated in recent years, laying the groundwork for a rapid pivot to forecasting COVID-19 incident cases, deaths, and hospitalizations [13].

However, in the context of predicting impact on the health care system, the stress resulting from COVID-19 cases depends not only on the number of new hospitalized individuals but also on their overlapping periods of hospitalization. To the best of our knowledge, health care use forecasting in a probabilistic sense had not existed prior to the current COVID-19 pandemic. Hospitals had used historical data to make time series– and regression-based projections for long-term planning (ie, planning for the next 1 to 10 years). Generally, these projections examined a single relevant metric, such as average length of stay (ALOS) [14], discharges [15], demand for specific hospital specialties [16], or occupancy/bed need [17,18], and considered the impact of external trends, such as anticipated sociodemographic changes, through consideration of multiple scenarios [18]. Hospitals were also developing short-term forecasting tools of total occupancy or bed use [19-21], total occupancy as predicted by emergency department visits [22], and various emergency department metrics [23-26]. These short-term prediction efforts tended to approach the problem either from a hospital administration perspective, by focusing on operational measures informed by a single hospital's [19-22] or department's [23-26] historic data or surgery schedule [27], or from a research perspective by using hospital time series data as a use case for the development and assessment of novel statistical models [28-31] without regard to hospitals as complex systems in response to a burgeoning pandemic.

In response to the overwhelming demand from government agencies at the federal, state, and local levels to predict the immediate future burden of COVID-19, Los Alamos National Laboratory (LANL) first developed the COVID-19 Forecasts Using Fast Evaluations and Estimation (COFFEE) tool [32]. COFFEE generates short-term (1 day to 6 weeks ahead) forecasts of cumulative and incident confirmed cases and deaths for all US counties and states, as well as all countries with at least 100 confirmed cases and 20 deaths as reported by the Center of Systems Science and Engineering (CSSE) at the Johns Hopkins University (JHU) Coronavirus Resource Center dashboard [33]. To forecast the health care needs expected to arise from predicted cases, we additionally created the COVID-19 Hospitalization, Intensive Care, and Ventilator Estimator (CHIVE) forecasting tool, which combines forecasts every Monday and Thursday from COFFEE for the state of New Mexico, with current state-level data on hospitalizations, ICU bed use, and mechanical ventilator use. CHIVE is most useful as an actionable mid-term (ie, 2 to 4 weeks ahead) predictor of hospital resource use, enabling hospitals to order additional supplies and allocate existing staff and resources to best serve an expected influx of patients.

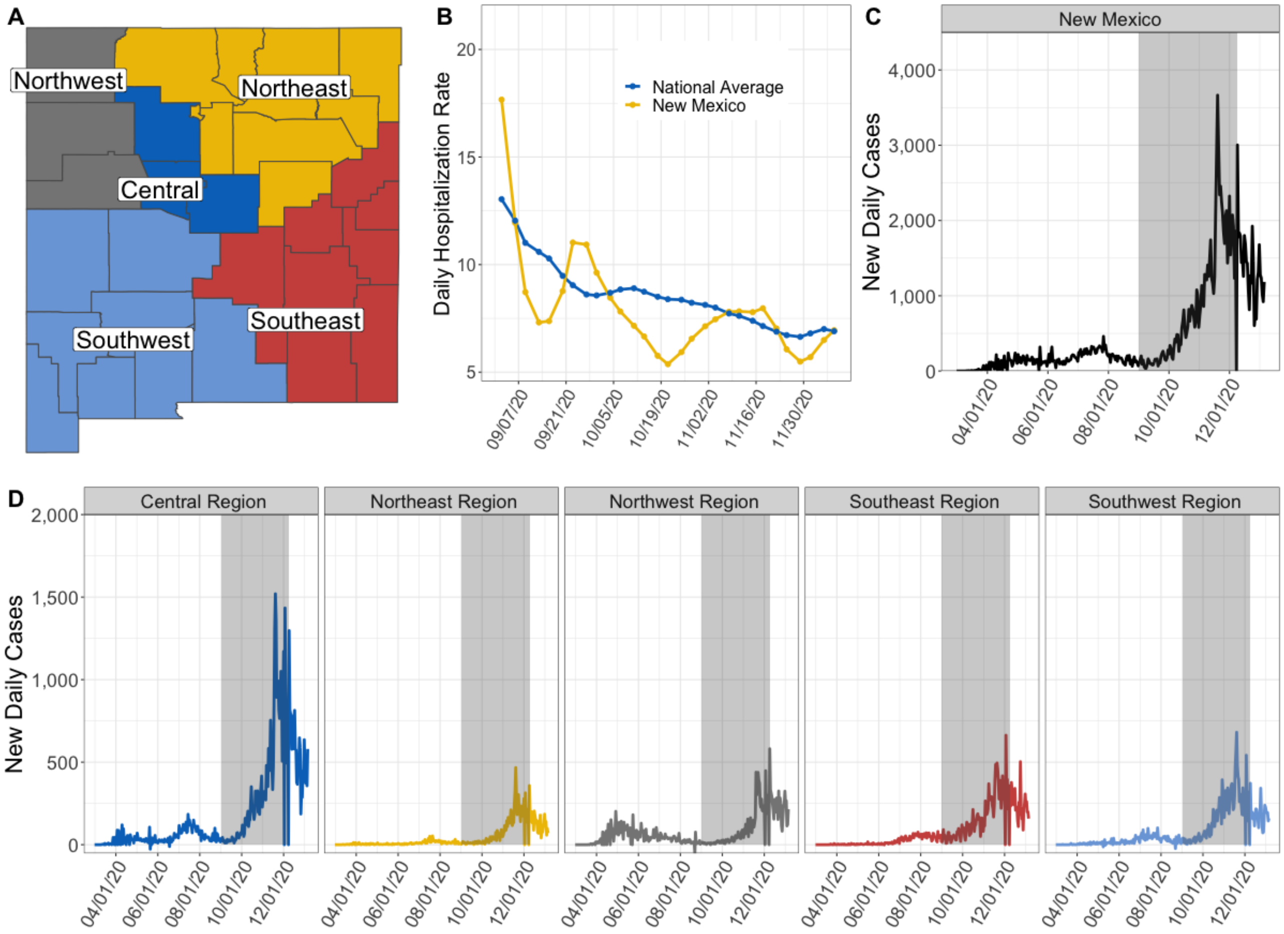
The aim of this modeling effort was to create a flexible forecasting tool to predict COVID-19–related health care use needs 2 to 4 weeks ahead, a time period identified by state and local stakeholders as being most useful for future planning. Here, we present the CHIVE methodology and characterize its performance over 29 forecasts made between September 1 and December 9, 2020, for New Mexico. This performance period includes both retrospective forecasts, as in, what the forecast would have been if the data were available, and those submitted in real time to the New Mexico Department of Health (NMDOH). The results of this study can provide a platform for other research groups or health departments to estimate health care needs and support decisions regarding resource planning and allocation.

Methods

Data

From November 4, 2020, to January 5, 2021, as a result of our partnership with NMDOH and Presbyterian Healthcare Services, we received access to the statewide number of COVID-19 confirmed/suspected inpatient hospitalizations, the number of patients in ICUs, and the number of patients on mechanical ventilation as reported in EMResource, a web-based tool for hospital resource reporting [34]. This data set contained retrospective data beginning from July 20, 2020. We also received individual hospital data on COVID-19 hospitalizations. For each day of data, we created regional level time series by summing the numbers of confirmed COVID-19 inpatient hospitalizations, patients in ICUs, and patients on mechanical ventilation across the hospitals within the counties assigned to each of NMDOH's five health regions (Figure 1A, Figure S1 in Multimedia Appendix 1).

Figure 1. New Mexico health regions, COVID-19 confirmed case time series from March 2020 to January 2021, and daily hospitalization rates from September to December 2020. (A) Division of New Mexico's 33 counties into five health regions. (B) The 2-week weighted daily hospitalization rate for New Mexico (yellow) compared to the national average (blue) (C). The number of new daily cases at the state level, with the grey box denoting the period of forecast performance evaluation. (D) The number of new daily COVID-19 cases for each of the five regions.



Daily Hospitalization Rate

Starting November 3, 2020, the United States Department of Health and Human Services began publishing a time series format of daily numbers of new hospitalizations by state [35], hereafter referred to as the HealthData.gov time series, with retrospective data for New Mexico going back to July 14, 2020. These data were released weekly.

We defined the daily hospitalization rate (DHR) as the ratio of new confirmed COVID-19 hospitalizations to new confirmed COVID-19 cases on the same day. To obtain the number of new confirmed COVID-19 hospitalizations from the HealthData.gov time series, we summed the previous day's admissions of adults and pediatric COVID-19 cases. We used the number of new cases as reported by the CSSE JHU Coronavirus Resource Dashboard [33] as the number of new confirmed individuals with COVID-19. We aligned the HealthData.gov admission data for day t with the JHU data of $t-1$ because the admission data are listed as the previous day. To account for data reporting anomalies (eg, "data dumps," days with zero reported hospitalizations or new cases), we calculated a 7-day rolling average of each quantity. The DHR on day t, therefore, is the 7-day rolling average of hospitalizations divided by the 7-day rolling average of new COVID-19 cases. Because the HealthData.gov time series only provides state-level numbers, we applied the same $DHR(t)$ to the regional forecasts.

The daily number of new hospitalizations in the future will impact the degree to which overlapping lengths of stay strain hospital resource capacity. To forecast the DHR into the future, $DHR(t)'$, we calculated a 2-week time-weighted average of the DHR and then assumed this DHR would persist throughout the forecast duration. Where $t= 0$ is the last day of the observed data, the weight of each DHR $(t - n)$ for $n = 0$: 13 was determined as

The DHR is a convenient ratio that is obtainable from available data. However, this metric is incorrectly defined because the denominator population is not included in the numerator population; thus, we used a 2-step modeling process to remove this inherent bias. Our goal was to create the most accurate forecast possible and not necessarily to maintain direct interpretation of the variables used in the model. A more traditional metric, such as case hospitalization rate, would require further inference about the lag between new cases and hospitalizations of those same cases, which is not necessary to achieve an accurate forecast.

Baseline Parameters of Health Care Use

The stress that COVID-19 places on New Mexico’s health care capacity depends not only on the rate of new hospitalizations but also on the amount of overlapping time during which individuals are hospitalized, which itself is dependent on the individual illness severity and length of stay for each patient. Therefore, we structured CHIVE around the probabilities that certain hospital events would occur (ie, ICU need) given hospitalization and the length of hospitalization given illness severity. Specifically, our model depended on four parameters: ALOS, ALOS for those admitted to the ICU or requiring mechanical ventilation, and percentages of those hospitalized and later admitted to the ICU and those hospitalized who were later placed on mechanical ventilation (Table 1). Early evidence showed that these parameters varied across age groups, and later evidence showed that they varied temporally as new treatment protocols were established [36]. For example, early in the pandemic, individuals were frequently placed on ventilators, leading to high percentages of hospitalized individuals on mechanical ventilation. In addition, it is uncertain how spatial variation in underlying health conditions and transmission intensity impact health care patterns.

Baseline parameters were estimated from data on New Mexico’s hospitalized COVID-19 cases from April 16 to June 15, 2020 [37]. In this time period, the ICU percentage of hospitalizations ranged from 37% to 53% and the percentage of patients on ventilation ranged from 22% to 36%. Rather than dynamically inferring the parameters with limited noisy data going forward, we used parameters that reflected these initial health care use trends in New Mexico, and we developed a postprocessing procedure (described in *Step 2: Postprocessing Based on Back-Fitting*) that adjusted the forecasts to time-varying trends without the need to determine new input values.

Table 1. New Mexico baseline parameters for COVID-19 health care use needs based on data from March to June 2020.

Parameter	New Mexico baseline	US range[a]
Average length of inpatient stay, days	5	4-6
Average length of stay for those admitted to the ICU[b] or on mechanical ventilator, days	14	11-14
Patients admitted to ICU among those hospitalized, %	42.8	23.8-36.1
Patients on mechanical ventilation among those hospitalized, %	28.2	12.0-22.1

[a] For comparison, we provide the best median estimate across age groups in the United States collected by the US Centers for Disease Control through August 8, 2020 [36].

[b] ICU: intensive care unit.

CHIVE Forecasting Model

To capture the heterogeneity in the severity of individual infections, we used probabilistic simulation. CHIVE works in two steps. In the first step, 4-week-ahead daily forecasts, $\theta_{t=1:28}$, of new confirmed cases from COFFEE [32] were used as input data to simulate 4 weeks of health care use. We simulated health care use based on the forecasted number of new cases, $\theta_{t=1:28}$, the weighted two-week average $DHR(t)'$, and the baseline parameters. The output of the simulation is a forecast for the numbers of occupied inpatient beds (H_1,..., H_{28}), ICU beds (IC_1,..., IC_{28}) and in-use ventilators (V_1,..., V_{28}) due to COVID-19. After simulating 1000 independent iterations of $H_{t=1:28}$, $IC_{t=1:28}$, and $V_{t=1:28}$, the second step adjusts the magnitudes of summary quantiles q of $H_{t=1:28}$, $IC_{t=1:28}$, and $V_{t=1:28}$, based on observed differences between the prior weeks’ baseline forecasts and the subsequently observed data.

Step 1: Model Baseline Simulations

For an independent iteration i of the simulator, we first sampled a trajectory of new COVID-19 cases, $\theta_{t=1:28}$, from the distribution specified by the 23 quantiles of $\theta_{t=1:28}$ in the COFFEE output. Let $p_i \sim Uniform(0,1)$ be the percentile of $\theta_{t=1:28}$ sampled. We drew $\theta_{t=1:28}$ such that p_i was the same for all t within iteration i.

For a day-ahead forecast $t + n$ where $t= 0$ is the last day of observed data, we generated our forecasts as follows:

1. Using a binomial distribution with the success probability equal to $DHR(t)'$, we sampled the number of new hospital admissions $y_{t+n,i}$ using the forecasted number of new confirmed cases $\theta_{t+n,i}$ on day $t+n$ as the number of trials.
2. We next sampled the number of new individuals admitted to the ICU, $u_{t+n,i}$, from a binomial distribution with $y_{t+n,i}$ trials and success probability equal to the ICU admission

percentage among those hospitalized. Similarly, we sampled the number of new individuals needing mechanical ventilation $w_{t+n,i}$ from a binomial distribution with $y_{t+n,i}$ trials and probability equal to the percent of all hospital admissions that require mechanical ventilation. We assumed that if $w_{t+n,i} \leq u_{t+n,i}$, all individuals requiring mechanical ventilation were also in an ICU; otherwise, we assumed that some non-ICU admissions also required mechanical ventilation. Thus, we calculated the number of new non-ICU or ventilator admissions (ie, general inpatient bed admissions), as $y'_{t+n,i} = y_{t+n,i} - \max(u_{t+n,i}, w_{t+n,i})$.

3. We next simulated the lengths of stay S for each new admission z. For admissions in an inpatient bed, we drew the lengths of stay from a Poisson distribution such that .
4. Because we assumed that the length of stay was similar between ICU patients and those on mechanical ventilation, we drew the lengths of stay for these critical care individuals from a Poisson distribution where . To obtain the lengths of stay for individuals in the group min $(u_{t+n,i}, w_{t+n,i})$, we sampled a subset without replacement from .
5. For all admissions observed up through $t+n$, we decreased the remaining length of stay for each individual by 1. The number of needed inpatient beds $H_{t+n,i}$ on $t+n$ was then the number of individuals who have a positive length of stay remaining. Similarly, we tracked $IC_{t+n,i}$ and $V_{t+n,i}$.

We repeated this process for 1000 random samples of $\theta_{t=1:28}$ and summarized the forecasts for day $t + n$ by a set of 23 quantiles q at levels 0.01, 0.025, 0.05, 0.10, … , 0.95, 0.975, and 0.99, such that we obtained $H_{\mathrm{t}=1:28,q=1:23}$, $IC_{\mathrm{t}=1:28,q=1:23}$ and $V_{\mathrm{t}=1:28,q=1:23}$.

This method makes several simplifying assumptions. First, it assumes instantaneous movement from confirmation of COVID-19 to hospitalization. Second, it assumes that a hospitalized individual requires the same category of health care for the duration of their stay. We argue that because the forecasting model is not meant to infer epidemiologic parameters, these simplifications reduce the need for introducing additional parameters when data may not exist to sufficiently estimate them.

Step 2: Postprocessing Based on Back-Fitting

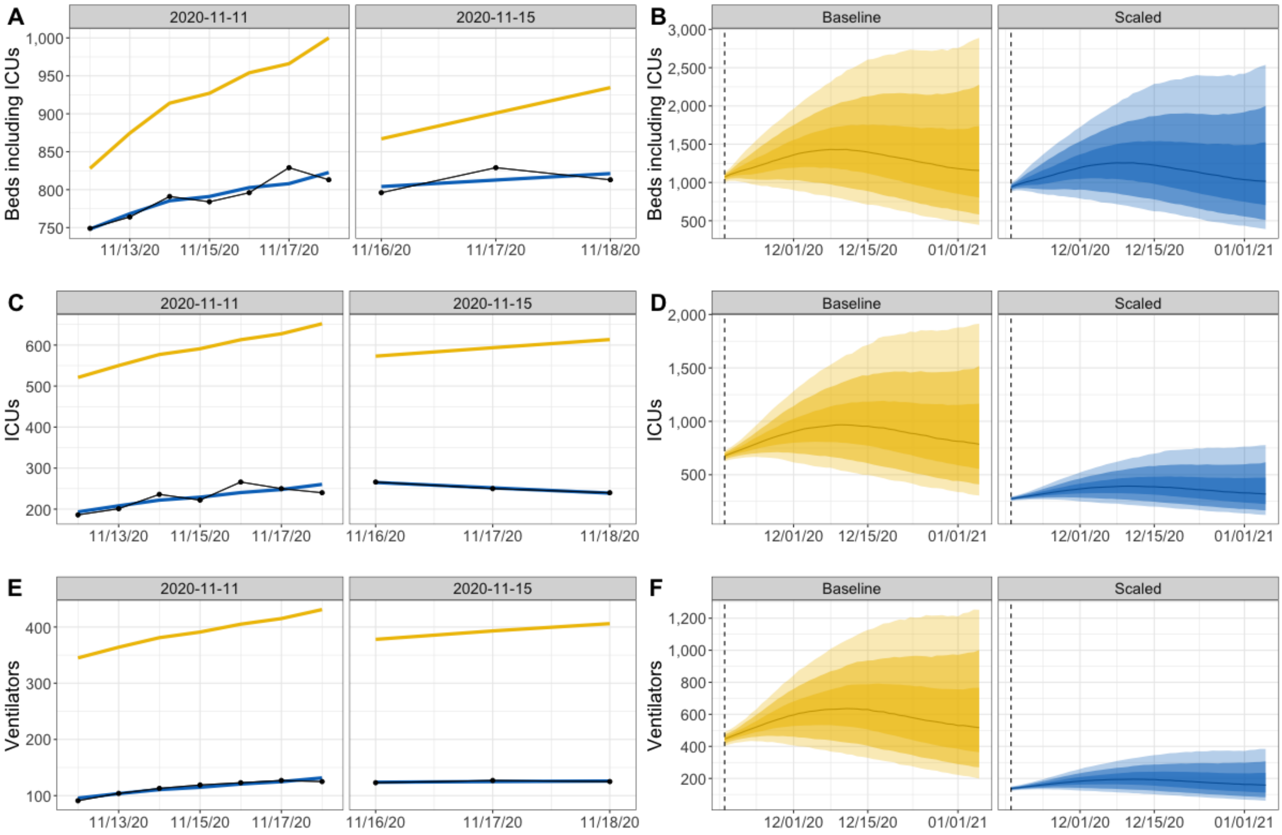
After generating the baseline 4-week forecasts $H_{\mathrm{t}=1:28,q=1:23}$, $IC_{\mathrm{t}=1:28,q=1:23}$, and $V_{\mathrm{t}=1:28,q=1:23}$, we adjust their magnitudes by finding scaling factors that bring the past week's baseline forecasts into alignment with the observed data (Table S1, Multimedia Appendix 1). In this way, we do not need to adjust the baseline parameters.

We fitted linear regression models from the forecasts generated over the past week to the observed data as follows for variable X, where X is either H, IC, or V (Figure 2):

1. Let t=0 be the day of the last observed data. For each forecast X_{t-n}, n=1,..., 7, we fit a linear regression model from the 50th percentile $X_{t-n,\, q=50}$ baseline trajectory to the eventually observed data $Y_{t-n:t}$, in the form $Y_{t-n} = \beta_{t-n} X_{t-n,q=50}$.
2. Across the forecasts, we take a time-weighted mean of the regression coefficients $\beta_{t-n:t}$, assigning weights as in Equation 1.
3. We multiply all baseline forecast quantiles by the weighted mean to obtain $X'_{t=1:28,q=1:23}$.

We found separately for inpatient beds, ICU beds, and in-use ventilators. All simulations and analyses were conducted using R, version 3.6.1 (R Foundation for Statistical Computing) [38].

Figure 2. Back-fitting procedure for the November 18, 2020, forecast for New Mexico. (A, C, E) For each forecast from over the week (the panels), a regression was fit (blue line) from the 50th percentile of the baseline forecasts (yellow line) to the observed data (black dots). A time-weighted average of the 2 regression coefficients from each panel was calculated separately for inpatient beds (A), ICU beds (C), and ventilators (E). (B, D, F) For the November 18 forecast, the *Baseline* forecast was multiplied by the time-weighted average of the regression coefficients to produce the *Scaled* forecast for the next four weeks. ICU: intensive care unit.



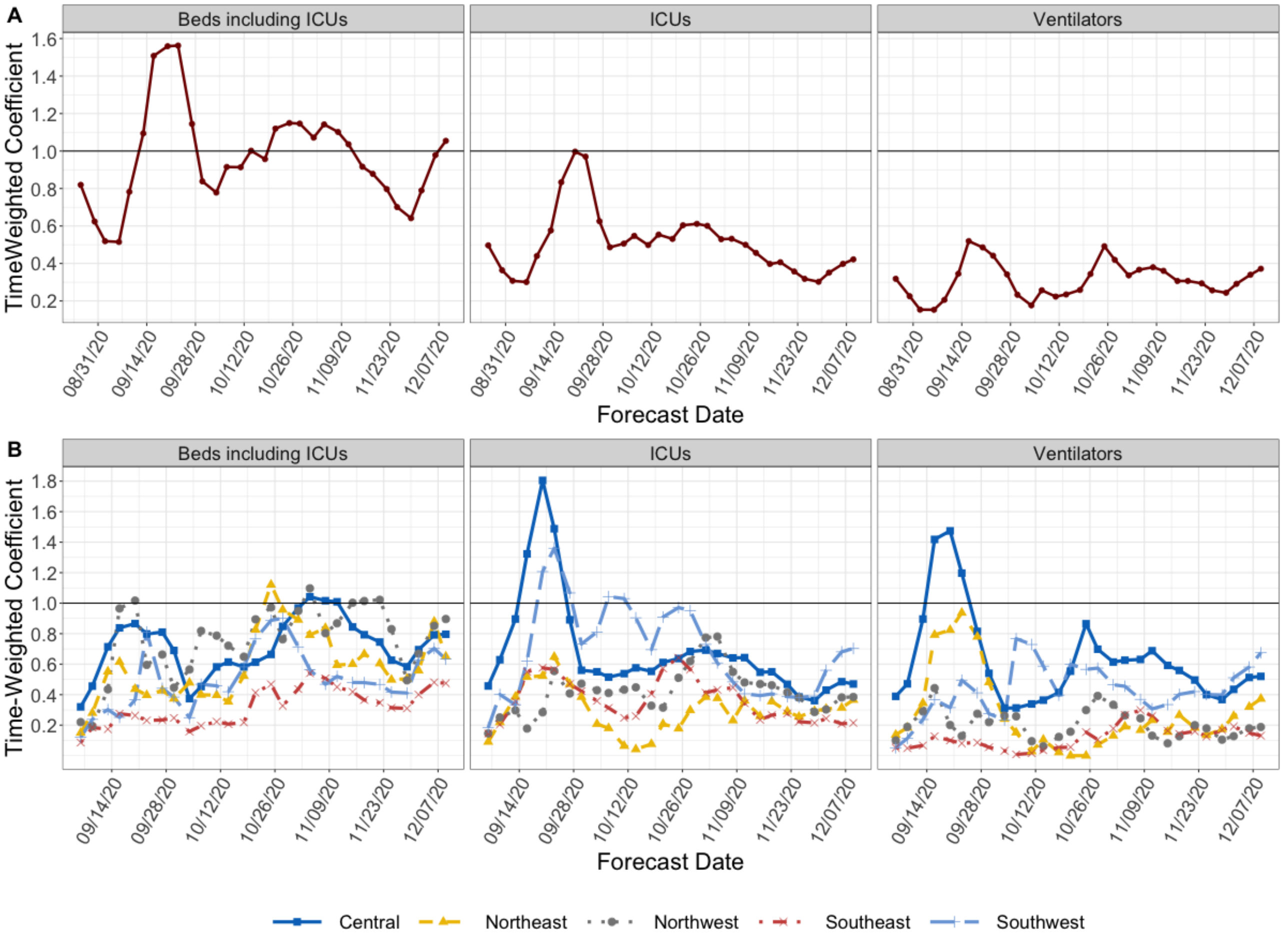
Results

Back-Fit Coefficients Are Dynamic by Time and Geography

At the state level, the 1-week weighted coefficients fluctuated through time (Figure 3A). All three health care use coefficients showed three peaks: one in early September, a second in late October, and a third in early December. During the first two peaks, the baseline forecasted number of inpatient beds was underestimated (coefficients greater than 1.0), while the baseline forecasts of ICU beds and individuals on ventilators were consistently overestimated (coefficients less than 1.0).

At the regional level, the baseline parameters most often produced forecasts that were overestimates for each of the five New Mexico regions (Figure 3B). In contrast to the state level, baseline forecasts of needed ICU beds and ventilators were underestimated for the Central region during mid-September. Across health care use categories, the coefficients for the Central region were closest to 1.0, indicating that the baseline parameters were the best match for this region. The coefficients for the Southeast region were consistently the smallest, indicating that the baseline parameters did not reflect health care trends in this region.

Figure 3. The fitted scaling coefficients from September to December, 2020, for hospital inpatient beds, ICU beds, and ventilators at the state level (A) and regional level (B). The solid black line represents a coefficient of 1.0, where the original 50th percentile forecast would be a good match for the eventual observed data. ICU: intensive care unit.



Forecasts Showed Higher Error at the Regional Level and for Ventilators

Using validation data through January 5, 2021, we compared the accuracy of the 4-week forecast horizons for the 29 forecasts made between September 1 and December 9, 2020 (Figure 4). To compare accuracy across health care use categories, regions, and time—where the observed magnitude varies widely—we looked at the weighted absolute percentage error (WAPE) while providing the mean absolute error (MAE) for context. The MAE is the difference between the median forecast (50th percentile) and the observed value. The WAPE is the sum of the absolute differences divided by the sum of the observed values over the 4-week forecast horizon. The WAPE can accommodate observed zero values, which occurred in our data at the regional level.

At the state level, the median forecasts were consistently 15% to 25% off for all three health care use categories for the 1- to 2-week horizon, and they showed an increase in error up through 4 weeks ahead (Table 2). Looking at the completed months during which a forecast was made, the October forecasts had the lowest overall mean WAPE of 20.0%, while the September forecasts had the highest WAPE of 39.7%. Of the three health care use categories, inpatient bed forecasts had the lowest overall WAPE (27.3%), while ICU beds had the highest (29.2%).

The regional level WAPEs similarly increased though the 3-week forecast horizon; however, for each forecast horizon, the regional WAPEs often exceeded their corresponding state-level WAPEs. Aggregated across forecast horizons and regions, the regional-level WAPE was 40.0% for inpatient hospitalizations, 40.4% for ICU units, and 40.0% for ventilators. However, because of smaller quantities, these errors translate to smaller absolute errors. For example, in the Northwest region, ventilator median forecasts were off by between 55% and 75% on average, corresponding to a raw difference of approximately 3 ventilators.

At the regional level, forecast error varied by location, month, and health care use category. All three health care use categories in the Central region had the lowest forecast WAPEs in October (hospital beds: 33.7%, ICU beds: 25.0%, ventilators: 28.6%), while the lowest forecast WAPEs for the Southwest regions all occurred in November (hospital beds: 39.8%, ICU beds: 42.7%, ventilators: 35.3%). For the remaining combinations of regions and health care needs, the results were split, with 66% of the lowest WAPEs occurring in November.

To understand how time series properties may have impacted the accuracy of the forecasts, we compared the monthly WAPE against the monthly volatility of the time series. The volatility, calculated as , is a measure that captures the noisiness of the observed time series data. We found no relationship between the volatility of a monthly time series and the WAPE. We also did not find a relationship between the WAPE and the total number of each health care use need in a particular month.

Figure 4. Reported health care use and example forecasts for New Mexico from October and November 2020. The numbers of concurrent hospitalization beds, ICU beds, and ventilators needed throughout hospitals in New Mexico from September 1 to December 29, 2020 (red points and line). Forecasts are day-ahead predicted medians (black line), and the 50%, 80% and 95% prediction intervals for 28 days (4 weeks). We show two examples, the first beginning on October 11, 2020, and the second beginning on November 25, 2020. ICU: intensive care unit.

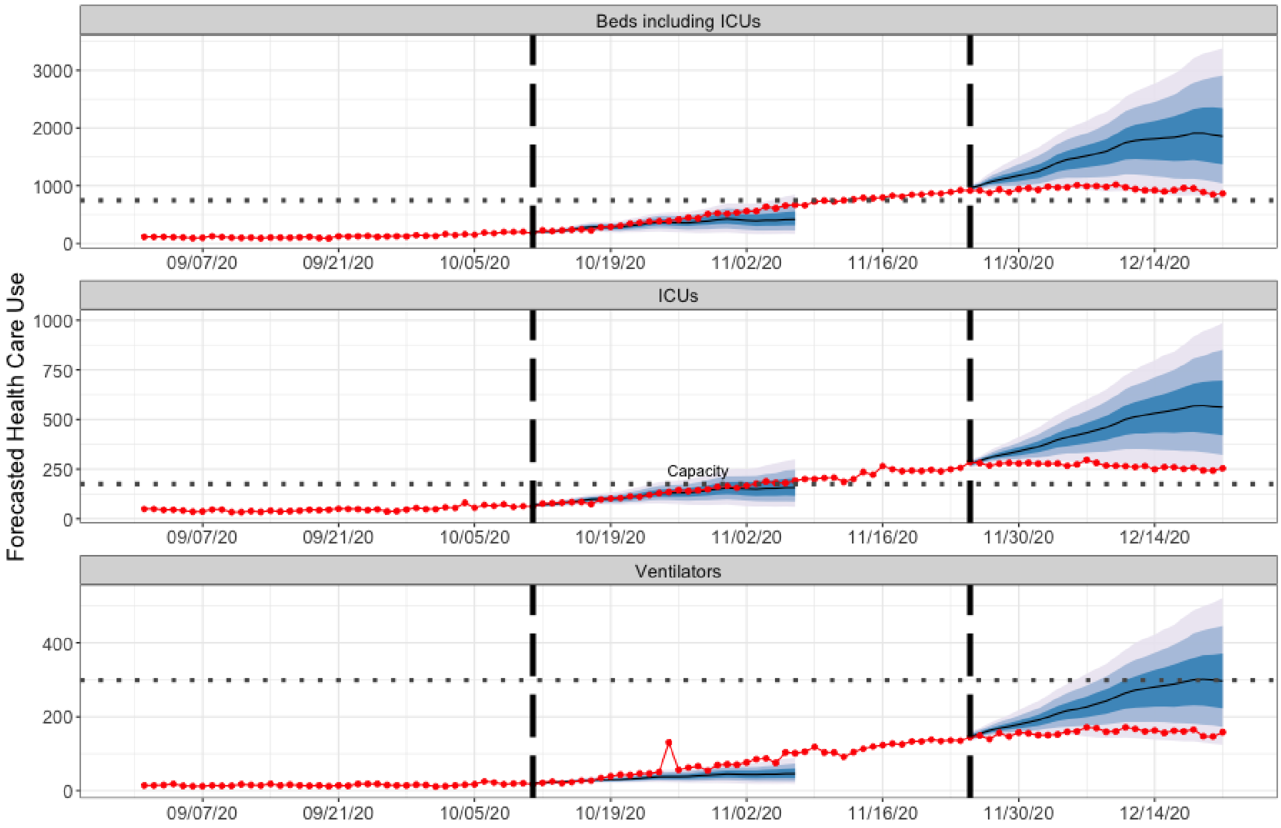


Table 2. The WAPEs and MAEs of the predicted forecasted median for COVID-19 health care use numbers reported for September 1 to January 5, 2020, in New Mexico.

Region[a] and type	Forecast horizon[b]							
	1 week ahead		2 weeks ahead		3 weeks ahead		4 weeks ahead	
	WAPE[c]	MAE[d] (SD)	WAPE	MAE (SD)	WAPE	MAE (SD)	WAPE	MAE (SD)
State								
Beds including ICUs[e]	0.170	81.8 (91.9)	0.244	130 (141)	0.307	179 (206)	0.334	210 (249)
ICUs	0.163	23.6 (22.4)	0.244	38.8 (39.4)	0.338	58.3 (64.1)	0.380	69.6 (81.0)
Ventilators	0.188	13.5 (13.6)	0.261	21.2 (21.9)	0.324	29.2 (31.4)	0.349	34.2 (40.3)
Central								
Beds including ICUs	0.175	27.3 (33.9)	0.267	46.9 (60.9)	0.381	74.0 (97.9)	0.486	103 (113)
ICUs	0.177	12.1 (13.7)	0.257	19.5 (23.4)	0.385	31.8 (39.7)	0.485	42.8 (50.6)
Ventilators	0.204	9.43 (10.7)	0.281	14.7 (17.3)	0.358	20.9 (26.2)	0.406	25.9 (32.6)
Northwest								
Beds including ICUs	0.283	12.8 (19.5)	0.335	17.9 (27.6)	0.425	26.5 (39.7)	0.480	34.0 (44.2)
ICUs	0.261	3.62 (4.09)	0.368	5.81 (7.07)	0.482	8.82 (11.3)	0.516	10.6 (14.2)
Ventilators	0.557	2.06 (2.17)	0.673	2.76 (2.80)	0.757	3.53 (4.30)	0.729	3.73 (5.44)
Southeast								
Beds including ICUs	0.240	8.89 (7.59)	0.310	12.5 (12.9)	0.394	17.1 (16.4)	0.468	21.9 (19.5)
ICUs	0.271	5.49 (4.55)	0.367	7.98 (7.64)	0.446	10.1 (10.2)	0.425	9.90 (10.1)
Ventilators	0.346	2.17 (2.21)	0.468	3.34 (3.43)	0.547	4.21 (4.55)	0.605	5.03 (4.86)
Southwest								
Beds including ICUs	0.251	15.1 (14.4)	0.413	26.9 (30.0)	0.595	41.0 (44.2)	0.618	45.0 (43.0)
ICUs	0.249	10.1 (9.47)	0.410	18.2 (21.1)	0.562	26.6 (33.5)	0.601	30.0 (34.4)
Ventilators	0.240	5.32 (5.04)	0.366	9.06 (9.40)	0.412	11.4 (10.6)	0.428	12.9 (9.95)
Northeast								
Beds including ICUs	0.306	10.4 (13.3)	0.417	15.7 (20.1)	0.584	24.6 (30.4)	0.672	30.8 (34.8)
ICUs	0.311	3.25 (3.64)	0.434	5.27 (6.16)	0.570	7.63 (9.51)	0.650	9.46 (10.3)
Ventilators	0.408	2.21 (2.34)	0.514	3.33 (3.15)	0.582	4.20 (3.83)	0.609	4.69 (4.11)

[a] Regions are listed in increasing order of overall WAPE across both the forecast horizon and health care categories.

[b] For each forecast horizon, we considered all daily forecasts within that week.

[c] WAPE: weighted absolute percentage error.

[d] MAE: mean absolute error.

[e] ICUs: intensive care units.

Prediction Intervals Start Off Narrow and Increase With Time

We assessed how well the forecasts were calibrated by measuring how often the observed data fell within a range of prediction intervals. If a forecasting model is well calibrated (ie, the prediction intervals are the correct width), the observed data should fall into the nominal prediction interval of the model with the expected frequency. For example, the observed data should fall into the 50% nominal prediction interval 50% of the time. Across the two geographic regions, prediction intervals were conservative (overconfident) at both the 50% and 90% prediction intervals. At the state level, the empirical coverage approached the nominal coverage by the 3- and 4-week-ahead forecast horizons (Figure 5, Table 3) for inpatient beds and needed ICU beds. However, across the regional levels and health care categories, the prediction intervals remained consistently narrow.

At the state level, we ranked the calibrations by comparing the relative absolute coverage error, as in, (nominal coverage – observed coverage)/nominal coverage. Between health care categories, the hospitalization forecasts were the best calibrated at both geographic scales, while the ventilator forecasts were the worst calibrated. At the regional scale, the Central region was the best calibrated model, while the Northeast region was the worst (Figure S3, Multimedia Appendix 1).

Figure 5. Coverage plot for New Mexico state-level forecasts at 4-week ahead horizons made between September 1 and December 9, 2020. Colored lines are labeled by their nominal coverage, while the position on the y-axis indicates its empirical coverage. If a forecast is well-calibrated, the empirical coverage should fall along the y-axis at its corresponding nominal coverage. ICU: intensive care unit.

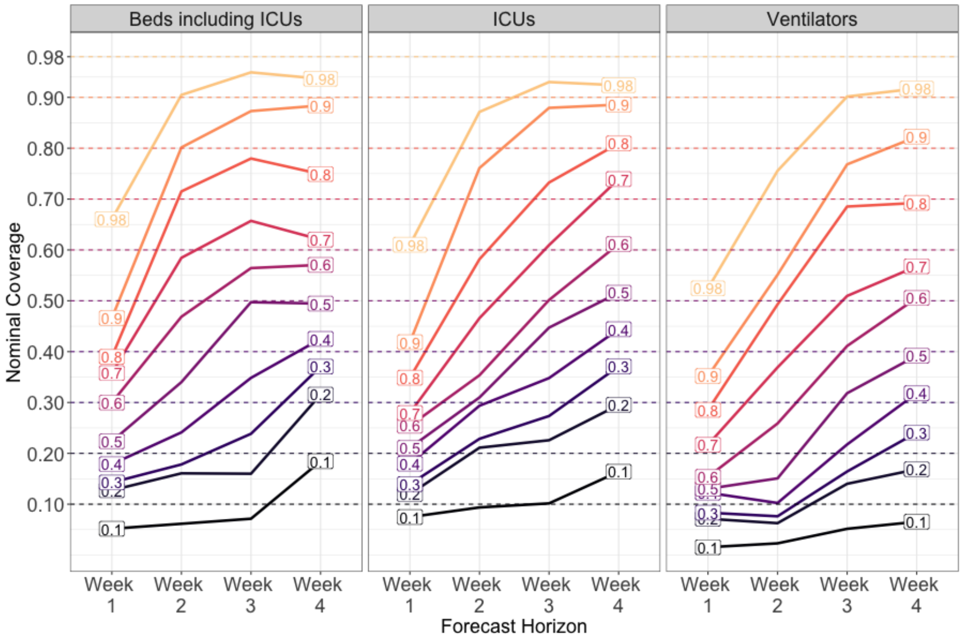


Table 3. Observed prediction interval coverage for COVID-19 health care use needs in New Mexico reported from September 1 to December 9, 2020.

Model and type	Measure (% coverage)	Observed prediction interval coverage			
		Forecast horizon			
		1 week ahead	2 weeks ahead	3 weeks ahead	4 weeks ahead
State					
Beds including ICUs[b]	50	0.22	0.34	*0.50* [a]	*0.50*
	90	0.47	0.80	*0.87*	*0.88*
ICU	50	0.21	0.31	*0.45*	*0.52*
	90	0.42	0.76	*0.88*	*0.89*
Ventilators	50	0.13	0.15	0.32	0.39
	90	0.35	0.55	0.77	0.82
Regional[c]					
Beds including ICU	50	0.27	0.33	0.36	0.30
	90	0.54	0.69	0.70	0.60
ICU	50	0.29	0.29	0.36	0.38
	90	0.57	0.65	0.70	0.71
Ventilators	50	0.20	0.23	0.27	0.33
	90	0.49	0.51	0.62	0.67

[a] Italicized quantities are within 5% of their nominal coverage.

[b] ICUs: intensive care units.

[c] Regional results are averaged across the five regions.

Discussion

Principal Findings

Given the uncertainty and unavailability of data regarding health care parameters associated with COVID-19, we chose to implement a naïve model and fitting procedure in which the main intent was to produce forecasts of the expected health care use levels up to 4 weeks into the future. Although COVID-19 case data have been widely available, hospitalization data have been consistently sparse and not always timely. Therefore, alternative approaches such as naive models may prove to be more robust in addressing these challenges. Our evaluations show that using a simple model and available forecasts of cases, one can forecast future health care use levels with sufficient accuracy for operational planning. During the pandemic, these data were used across local health care systems to determine staffing, equipment, and contingency plans, enabling superior preparation for surges in cases. Additionally, transport logistics were informed by our forecasts, ensuring that communities had the necessary capabilities to move patients to higher levels of care.

We found that CHIVE varied in its ability to accurately forecast across space, time, and health care needs. First, CHIVE was more accurate and better calibrated at the state level than for the five regions of New Mexico. We may have obtained this result because although CHIVE forecasts the expected *needed* number of beds, ICU beds, and ventilators, decision-making on the ground of individual treatment and new incoming patient diversions based on capacity, staffing resources, etc, will impact these numbers. These individual decisions will have more of an impact on the regional numbers than overall state numbers. Second, at both geographic scales, the forecasts of inpatient beds had the smallest error, possibly because of fewer unaccounted-for downstream effects that could impact the number of ICU beds and ventilators. Third, the forecasting model was most accurate at the 1-week forecast horizon but improved its uncertainty coverage at the 2-week forecast horizon. Finally, CHIVE performed well in October and November, when confirmed COVID-19 cases and new hospitalizations were rising. This finding suggests this method is flexible for different phases of the epidemic. Overall, our results suggest that the conditions for which CHIVE is most suited include forecasting the number of hospital inpatient beds at higher geographical scales in the 2-week horizon.

Both a strength and limitation of our method is that it is dependent on the LANL COFFEE model. First, the resolution of the case forecasts limits the resolution of the hospitalization forecasts. At the state and regional levels, the model is not resolved enough for individual hospital planning in its current form; however, it can still provide intuition about how rising case numbers translate to stresses on capacity. Real-time awareness of where cases are rising and the features of specific hospitals (ie, rural vs urban) by public health professionals can provide synergistic information that can translate to an indication of where capacity may be stressed and needs to be reinforced. Second, the coverage, or prediction interval widths, were consistently too small. Because the distribution of case forecasts was used as input, this may be a reflection of overconfident intervals of the COFFEE model. Finally, both COFFEE and CHIVE are agnostic to on-the-ground public health actions. For example, the Governor of New Mexico reimposed a strict lockdown on November 13, 2020, to curtail rising case numbers [39]. The forecast for November 25 (Figure 4) overpredicted the number of inpatient beds, ICU beds, and ventilators. This may be because the effects of the stay-at-home order had yet not been observed in the data, so neither COFFEE nor the postprocessing step of CHIVE anticipated the reduction in new cases at the start of December.

Separate from COFFEE, a limitation of our method is that new hospitalizations are assumed to be a fraction of newly confirmed cases; meanwhile, data have shown that there is a median of 6 days between symptom onset and hospitalization and of 3 days between symptom onset and administration of a SARS-CoV-2 test [36]. Future iterations of the model could consider identifying the correct lag. However, we assume that lag is also a dynamic parameter. Finally, ALOS and other average values used are poor representations of the underlying distributions of hospital stays, which are known to have very long tails [40].

Nonetheless, we believe that given the availability of COFFEE forecasts for many geographic regions, this simple method could be used as a situational awareness tool for many health care departments across the nation (and even worldwide), who would only need to have their locale's health care occupancy data available to supplement the forecasts of confirmed cases from COFFEE. For quantities that prove to be well calibrated, individual hospitals can use prediction intervals rather than point forecasts for their own needs. For example, if a hospital consistently sees their own caseloads around the lower 5% prediction interval, they can use this estimate for their individual needs. Alternatively, individual hospitals can use prediction intervals to determine their own risk avoidance by balancing the cost of unused beds versus going over capacity. In addition, this type of model could be used in nonpandemic settings where forecasts of disease burden take place, such as seasonal influenza.

The COVID-19 pandemic has highlighted the need for continued development of health care use forecasting. Seasonal hospitalization rates of influenza-like illnesses will be altered for years to come, compromising previous methodology that relied on historical time series to predict seasonal demand. Short-term forecasting may help state health departments and hospitals gain key situational awareness about what is expected in the near future. In addition, forecasting at a finer resolution, such as regions, can provide the opportunity for coordination of necessary resources. These modeling techniques may also prove helpful in addressing emergent needs in special and diverse populations that may otherwise go unmet and recognized. We see a strong and urgent need for continued collaboration between infectious diseases modelers, public health officials, and hospital managers. Although modelers can provide an outlook on transmission activity in the general population and translate transmission forecasts to incoming numbers and resources needed, hospital operations subject matter experts are best able to understand the limits of hospital capacities and resources, while public health officials can aid policy.

Conclusions

Although there is uncertainty in our forecasts, the proposed methodology is intended to provide estimates to decision makers and public health officials regarding the potential need of health care resources resulting from a burgeoning pandemic. Specifically, the results of this study can help research groups, departments of health, and ministries of health estimate future health care needs and support decisions regarding resource planning and allocation to ultimately reduce negative health care outcomes and save lives.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplemental figures and tables.
[DOCX File , 356 KB - publichealth_v7i6e27888_app1.docx]

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Abbreviations

ALOS: average length of stay
CDC: US Centers for Disease Control and Prevention
CHIVE: COVID-19 Hospitalization, Intensive Care, and Ventilator Estimator
COFFEE: COVID-19 Forecasts Using Fast Evaluations and Estimation
CSSE: Center of Systems Science and Engineering
DOE: Department of Energy
DHR: daily hospitalization rate
ICU: intensive care unit
JHU: Johns Hopkins University
LANL: Los Alamos National Laboratory
MAE: mean absolute error
NMDOH: New Mexico Department of Health
WAPE: weighted absolute percentage error

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Original Paper

A Wake-up Call for Burnout in Portuguese Physicians During the COVID-19 Outbreak: National Survey Study

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Abstract

Background: The COVID-19 outbreak has imposed physical and psychological pressure on health care professionals, including frontline physicians. Hence, evaluating the mental health status of physicians during the current pandemic is important to define future preventive guidelines among health care stakeholders.

Objective: In this study, we intended to study alterations in the mental health status of Portuguese physicians working at the frontline during the COVID-19 pandemic and potential sociodemographic factors influencing their mental health status.

Methods: A nationwide survey was conducted during May 4-25, 2020, to infer differences in mental health status (depression, anxiety, stress, and obsessive compulsive symptoms) between Portuguese physicians working at the frontline during the COVID-19 pandemic and other nonfrontline physicians. A representative sample of 420 participants stratified by age, sex, and the geographic region was analyzed (200 frontline and 220 nonfrontline participants). Moreover, we explored the influence of several sociodemographic factors on mental health variables including age, sex, living conditions, and household composition.

Results: Our results show that being female (β=1.1; t=2.5; P=.01) and working at the frontline (β=1.4; t=2.9; P=.004) are potential risk factors for stress. In contrast, having a house with green space was a potentially beneficial factor for stress (β=–1.5; t=–2.5; P=.01) and anxiety (β=–1.1; t=–2.4; P=.02).

Conclusions: It is important to apply protective mental health measures for physicians to avoid the long-term effects of stress, such as burnout.

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KEYWORDS

COVID-19; anxiety; coronavirus; depression; frontline; health care professionals; health care staff; obsessive compulsive disorder; SARS-CoV-2; stress

Introduction

The first case of COVID-19 caused by SARS-CoV-2 was reported in Wuhan, China, in December 2019 [1]. As on December 17, 2020, according to the World Health Organization, after COVID-19 was declared a pandemic, more than 72,000,000 cases were confirmed worldwide, with more than 1,600,000 deaths [2]. In Portugal, the first case was declared on March 2 [3,4], and as on December 17, 2020, a total of 358,296 confirmed cases and 5815 deaths were reported [5].

These numbers correspond to an infection rate of 3.48% and a mortality rate of 0.06% in the total Portuguese population (10,295,909 inhabitants) [6]. At the beginning of the first wave, on March 18, 2020, the Portuguese government declared a state of emergency to avoid virus transmission by applying confinement and social distancing measures [4,7,8]. The number of cases peaked in April 2020 during the first wave and started to decrease until September 2020, when a more severe wave began [4,5].

Recent studies conducted in Portugal during the COVID-19 outbreak reported that mental health status may depend on several protective and risk factors [9,10]. For example, women and younger individuals have greater levels of anxiety, while active workers have a better mental health status.

Medical health workers are among the professionals with a high risk of infection and demanding work conditions, involving lengthy and stressful shifts and situations involving life-or-death decision-making. Thus, they are prone to burnout syndrome and fatigue [11,12]. Recent studies conducted in China [13-19], Iran [20], and the United States [21] during the COVID-19 outbreak reported elevated levels of depression, anxiety, distress, and insomnia among health care workers, namely physicians and nurses. Moreover, certain literature reviews have further supported the impact of COVID-19 on the symptoms of anxiety and depression among health care professionals [22,23]. They have reported a prevalence rate between 18% and 70% for anxiety and between 17% and 40% for depression. Additionally, being a woman, having higher contact with patients with COVID-19, and working in more affected areas were considered risk factors for the psychosocial impact of this disease. Protective factors were associated with support from the family and health systems (eg, training and protective equipment).

Current recommendations and information from the media to avoid touching contaminated surfaces, to engage in frequent cleaning and washing behaviors, and to respect social distancing measures may exacerbate obsessive compulsive (OC) symptoms, namely the fear of contamination and excessive washing [24-28]. Health care professionals are required to work on site and have contact with patients with COVID-19, thus increasing their susceptibility to higher OC symptoms. Few studies have assessed OC symptoms in health professionals during the COVID-19 outbreak [17,18], thus indicating an increase in OC symptomatology.

In this study, we intend to investigate whether Portuguese physicians working at the frontline during the COVID-19 pandemic have worse mental health outcomes (depression, anxiety, stress, and OC symptoms) than their counterparts who are not at the frontline. Additionally, we aimed to explore what sociodemographic factors are potential risk or protective factors for mental health in this sample of health professionals. To our knowledge, this is the first study to explore the psychological impact of the COVID-19 pandemic on Portuguese health care professionals. Our findings may help develop and implement measures to support these professionals during the pandemic.

Methods

Study Design

The sample was selected by 2Logical (Lisbon, Portugal). The sample was randomly selected from the company's main database with information regarding all active physicians in Portugal, to create a final representative sample stratified by age, sex, and geographic region (n=549). A phone-based survey was first conducted with this sample to select participants willing to participate in the study. Consenting participants were invited to take a web-based survey during May 4-25, 2020, during the first wave of the COVID-19 pandemic in Portugal (English version available in Multimedia Appendix 1). At the time, 813 of the 22,749 total infected patients were receiving treatment for COVID-19 at the hospital, with 143 patients receiving intensive care [5]. Since Portugal has a total of 24,000 hospital beds available, including 430 beds in the intensive care unit, the health services were not operating at maximum capacity at the time [4,7]. However, Portugal has a low ratio of nurses per inhabitant, which may contribute to the burden of health care professionals during the pandemic [4,7]. Health care professionals from different fields (eg, internal medicine, anesthesiology, and pneumology) were assigned to intensive care services at this time [29]. Moreover, several emergency service units and COVID-19 community dedicated areas were established to treat patients [7]. Outpatient health care centers continued operating by replacing some presential appointments with telephonic or email contacts and by helping with the diagnosis, treatment, and follow-up of patients with COVID-19 [30,31].

Verbal informed consent was obtained from all subjects. All study procedures comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the tenets of the 2008 revision of the Helsinki Declaration of 1975. All procedures were approved by the Ethical Committee for Life Sciences of the University of Minho (Braga, Portugal; approval# 014/2020). Participants were not compensated for their participation in this study (Portuguese law# 21/2014).

The survey assessed information on age, sex, marital status, and geographic region of residence. The geographic region was categorized into low- and high-risk regions, based on the number of COVID-19 cases (high-risk regions were characterized as having ≥1,000 cases).

Data on living conditions were also acquired: if a participant was displaced from his/her regular habitation, type of current housing (apartment or house), house characteristics including the presence of green spaces and a balcony, the number of house habitants, and the presence of infants, children, teenagers, adults, elders, and pets in the current housing.

Additionally, the survey measured the levels of depression, anxiety, and stress with the 21-items Depression, Anxiety, and Stress Scale (DASS-21) and OC symptoms with the Obsessive-Compulsive Inventory-Revised (OCI-R). The DASS-21 scale assesses symptoms experienced in the prior week. This scale has 21 items with the following response options ranging 0="did not apply to me at all" to 3="applied to me very much or most of the time." The total score varies between 0 and 63. Each subscale (depression, anxiety, and stress) has 7 items and a total score ranging 0-21. Severe depression, anxiety, and stress symptoms correspond to scores higher than 10, 7, and 12, respectively [32]. The OCI-R measures OC symptoms in the previous month. This scale has 18 items divided into 6 categories (3 items each): hoarding, checking, ordering, neutralizing, washing, and obsessing. The answer for each item ranges from 0="not at all" to 4="extremely." The total score varies between 0 and 72, and scores above 20 indicate severe symptomatology [33].

Finally, participants were asked if they were working at the frontline and had direct contact with patients with COVID-19 and if they were currently in a quarantine period. Accordingly, participants were divided into two groups: participants working at the frontline during the COVID-19 pandemic (FRONT) and nonfrontline workers (NFRONT).

Statistical Analysis

Statistical analyses were conducted using the JASP software (version 0.12.2.0; JASP Team, University of Amsterdam). *P* values under .05 were considered significant.

For scalar variables, we assessed the assumptions of normality (the Shapiro–Wilk test) and homogeneity of variances (the Levene test) in each group. Between-group differences in parametric variables were estimated with the 2-tailed independent samples *t* test. The Mann–Whitney *U* test was applied for nonparametric variables. For categorical variables, we used the chi-square test to assess differences between groups.

We used multiple linear regression models to investigate which variables explained DASS-21 depression, anxiety, and stress scores and the OCI-R total score. We analyzed the following independent variables: age, sex, group, marital status, geographic region, house type, house green space, house balcony, number of house habitants, house infants, house children, house teenagers, house adults, house elders, and house pets. Since most of the sample was not under quarantine and was not displaced from their regular habitation, these variables were not included in the regression models (Table 1). Normality, linearity, and homoscedasticity assumptions were visually assessed with Q-Q plots and residuals vs predicted plots. The Durbin-Watson value was used to assess residuals correlations, and the tolerance and variance inflation factor values were analyzed to check for multicollinearity.

Results

A total of 549 physicians were contacted to participate in the study, of whom 420 (76.5%) responded to the survey. The participants who refused to be included in the study mainly declared a lack of interest or time. The physicians included in the study belonged to different specialties: general and family practice (n=155, 36.9%), internal medicine (n=62, 14.8%), pneumology (n=32, 7.6%), pediatrics (n=23, 5.5%), oncology (n=20, 4.8%), cardiology (n=18, 4.3%), psychiatry (n=17, 4.0%), gynecology (n=13, 3.1%), intensive medicine (n=12, 2.9%), infectiology (n=11, 2.6%), and other specialties (n=57, 13.6%) including hematology, endocrinology, immunoallergology, gastroenterology, dermatology, urology, neurology, rheumatology, orthopedics, and ophthalmology. In total, 68% of the participants worked in public settings, 11% in the private sector, and 21% in both public and private settings. A total of 200 participants were included in the FRONT group and 220 in the NFRONT group. Table 1 lists the main variables for both groups and the total sample.

When analyzing differences between the FRONT and NFRONT groups, we obtained significant outcomes for age, sex, house type, marital status, and the presence of children and adults in the house (Table 1). The FRONT group was younger than the NFRONT group (1 participant from the FRONT group was excluded from this analysis owing to incorrect data entered for age). Moreover, the FRONT group had a higher number of females than males in contrast with the NFRONT group. More frontline workers lived in an apartment rather than a house in contrast with the NFRONT group. Additionally, the number of frontline participants in a marriage or partnership was lower and the number of divorced and single individuals was higher than those in the NFRONT group. The number of participants living with children and adults was lower in the FRONT than in the NFRONT groups. The observed sociodemographic differences between the FRONT and NFRONT groups might be associated with age differences; older individuals might already be married or live with a partner and have children and a bigger house.

Table 1. Demographic data of the Portuguese physicians at the frontline and those not at the frontline during the COVID-19 pandemic (May 4-25, 2020), along with the statistics for between-group comparisons (Mann–Whitney *U* values for scalar variables and χ^2 values for categorical variables).

Characteristic	Frontline workers (n=200)	Nonfrontline workers (n=220)	Total (n=420)	Between-group statistics	
				Statistics	*P* values
Age (years), median (IQR)	47.0 (22.0)[a]	60.0 (21.2)	53.0 (23.0)	*U*=29,568.5; RBC[b]=0.3[c]	<.001
Sex, n (%)				$\chi^2(1)$=4.1	.04[c]
Female	107 (53.5)	96 (43.6)	203 (48.3)	N/A[d]	N/A
Male	93 (46.5)	124 (56.4)	217 (51.7)	N/A	N/A
In quarantine, n (%)				$\chi^2(1)$=0.5	.48
Yes	2 (1.0)	4 (1.8)	6 (1.4)	N/A	N/A
No	198 (99.0)	216 (98.2)	414 (98.6)	N/A	N/A
Geographic region, n (%)				$\chi^2(1)$=2.1	.14
High-risk	107 (53.5)	102 (46.4)	209 (49.8)	N/A	N/A
Low-risk	93 (46.5)	53.6 (118)	211 (50.2)	N/A	N/A
House displacement, n (%)				$\chi^2(1)$=0.4	.52
Yes	16 (8.0)	14 (6.4)	30 (7.1)	N/A	N/A
No	184 (92.0)	206 (93.6)	390 (92.9)	N/A	N/A
House type, n (%)				$\chi^2(1)$=5.8	.02
House	82 (41.0)	116 (52.7)	198 (47.1)	N/A	N/A
Apartment	118 (59.0)	104 (47.3)	222 (52.9)	N/A	N/A
Green space around the house, n (%)				$\chi^2(1)$=3.6	.06
Yes	110 (55.0)	141 (64.1)	251 (59.8)	N/A	N/A
No	90 (45.0)	79 (35.9)	169 (40.2)	N/A	N/A
Balcony in the house, n (%)				$\chi^2(1)$=0.4	.51
Yes	172 (86.0)	194 (88.2)	366 (87.1)	N/A	N/A
No	28 (14.0)	26 (11.8)	54 (12.9)	N/A	N/A
Marital status, n (%)				$\chi^2(3)$=8.4	.04[c]
Married/partnership	136 (68.0)	167 (75.9)	303 (72.1)	N/A	N/A
Divorced	38 (19.0)	27 (12.3)	65 (15.5)	N/A	N/A
Single	26 (13.0)	22 (10.0)	48 (11.4)	N/A	N/A
Widow	0 (0.0)	4 (1.8)	4 (0.9)	N/A	N/A
Number of house habitants, median (IQR)	2.0 (2.0)	2.0 (2.0)	2.0 (2.0)	*U*=23,987.5; RBC=0.09	.10
House infants, n (%)				$\chi^2(1)$=3.5	.06
Yes	13 (6.5)	26 (11.8)	39 (9.3)	N/A	N/A
No	187 (93.5)	194 (88.2)	381 (90.7)	N/A	N/A
House children, n (%)				$\chi^2(1)$=5.9	.02[c]
Yes	34 (17.0)	59 (26.8)	93 (22.1)	N/A	N/A
No	166 (83.0)	161 (73.2)	327 (77.9)	N/A	N/A
House teenagers, n (%)				$\chi^2(1)$=0.014	.91
Yes	29 (14.5)	31 (14.1)	60 (14.3)	N/A	N/A

Characteristic	Frontline workers (n=200)	Nonfrontline workers (n=220)	Total (n=420)	Between-group statistics	
				Statistics	*P* values
No	171 (85.5)	189 (85.9)	360 (85.7)	N/A	N/A
House adults, n (%)				$\chi^2(1)=5.0$	.03[c]
Yes	134 (67.0)	169 (76.8)	303 (72.1)	N/A	N/A
No	66 (33.0)	51 (23.2)	117 (27.9)	N/A	N/A
House elders, n (%)				$\chi^2(1)=0.2$	.64
Yes	39 (19.5)	39 (17.7)	78 (18.6)	N/A	N/A
No	161 (80.5)	181 (82.3)	342 (81.4)	N/A	N/A
House pets, n (%)				$\chi^2(1)=0.01$	.92
Yes	101 (50.5)	110 (50.0)	211 (50.2)	N/A	N/A
No	99 (49.5)	110 (50.0)	209 (49.8)	N/A	N/A

[a] One participant with missing information (incorrect data entry).

[b] RBC: rank biserial correlation effect size.

[c] Values are significant.

[d] N/A: not applicable.

Variables for age and sex differences between groups were used as covariates when assessing differences between FRONT and NFRONT groups for depression, anxiety, stress, and OC scores. The results of the analysis of covariance are displayed in Table 2. One participant from the FRONT group was excluded from this analysis owing to an incorrect data entry for age. We observed a significant effect of sex on the DASS-21 anxiety score. Female participants presented higher anxiety levels than males. Additionally, we observed significant effects of group, age, and sex on the DASS-21 stress score. FRONT physicians displayed higher stress levels than NFRONT participants. Younger participants had higher stress levels. Finally, females had higher stress levels than males.

Regarding the DASS-21 depression score, 15 (7.5%) participants in the FRONT group and 10 (4.5%) in the NFRONT group had severe symptoms (total sample=25, 5.9%). Regarding the DASS-21 anxiety score, 18 (9.0%) FRONT physicians presented severe symptoms compared to 13 (5.9%) NFRONT physicians (total sample=31, 7.4%). Regarding the DASS-21 stress score, 23 (11.5%) participants in the FRONT group had severe symptoms compared to 10 (4.5%) in the NFRONT group (total sample=33, 7.9%). Lastly, 39 (19.5%) FRONT physicians had severe OCI-R total scores as opposed to 36 (16.4%) in the NFRONT group (total sample=75, 17.9%) (Figure 1).

Regression models based on the DASS-21 anxiety ($F_{15,403}=1.84$; $P=.03$; $R^2=0.06$) and stress ($F_{15,403}=3.64$; $P<.001$; $R^2=0.12$) scores were significant, while those based on the DASS-21 depression ($F_{15,403}=1.54$; $P=.09$; $R^2=0.05$) and OCI-R ($F_{15,403}=0.64$; $P=.85$; $R^2=0.02$) scores did not reach significance. Regarding regression models that reached significance, having a green space at home helped reduce the DASS-21 anxiety ($\beta=-1.06$, SE 0.44; standardized $\beta=-0.17$; $t=-2.40$; $P=.02$) and stress ($\beta=-1.51$, SE 0.61; standardized $\beta=-0.16$; $t=-2.46$; $P=.01$) scores. Moreover, being female ($\beta=1.15$, SE 0.46; standardized $\beta=0.13$; $t=2.50$; $P=.01$) and being a frontline physician ($\beta=1.36$, SE 0.46; standardized $\beta=0.15$; $t=2.93$; $P=.004$) was associated with a high DASS-21 stress score (Figure 2).

Considering the effects of sex on the outcomes of the analysis of covariance and regression models for anxiety and stress, we used the regression models for DASS-21 anxiety and stress separately for males and females. DASS-21 anxiety models for males ($F_{14,202}=0.96$; $P=.50$; $R^2=0.06$) and females ($F_{14,187}=1.46$; $P=.13$; $R^2=0.10$) did not reach significance. The DASS-21 stress model reached significance for females ($F_{14,187}=2.45$; $P=.008$; $R^2=0.14$) but not for males ($F_{14,202}=1.41$; $P=.15$; $R^2=0.09$). Female FRONT physicians had higher levels of stress than their NFRONT counterparts ($\beta=1.59$, SE 0.65; standardized $\beta=0.18$; $t=2.45$; $P=.02$).

Table 2. Results of the analysis of covariance between Portuguese physicians at the frontline (n=200) and those not at the frontline (n=220) during the COVID-19 pandemic (May 4-25, 2020) with respect to the DASS-21[a] and OCI-R[b] scales, using age and sex as covariates.

Parameter	Values, mean (SD)	Between-group statistics	
		Statistics	*P* values
DASS-21 depression score			
Group		*F (1,415)*=2.7; η^2=0.065	.10
Frontline[c]	3.69 (4.12)	N/A[d]	N/A
Nonfrontline	2.78 (3.54)	N/A	N/A
Age	N/A	*F (1,415)*=1.9; η^2=0.004	.17
Sex		*F (1,415)*=0.7; η^2=0.001	.41
Female	3.54 (3.75)	N/A	N/A
Male	2.90 (3.92)	N/A	N/A
DASS-21 anxiety score			
Group		*F (1,415)*=1.8; η^2=0.004	.18
Frontline	2.50 (3.25)	N/A	N/A
Nonfrontline	1.89 (2.96)	N/A	N/A
Age	N/A	*F (1,415)*=1.4; η^2=0.003	.24
Sex		*F (1,415)*=4.7; η^2=0.011[e]	.03
Female	2.63 (3.20)	N/A	N/A
Male	1.77 (2.98)	N/A	N/A
DASS-21 stress score			
Group		*F (1,415)*=8.3; η^2=0.019[e]	.004
Frontline	6.47 (4.65)	N/A	N/A
Nonfrontline	4.69 (4.19)	N/A	N/A
Age	N/A	*F (1,415)*=6.8; η^2=0.016[e]	.009
Sex		*F (1,415)*=7.5; η^2=0.017[e]	.007
Female	6.45 (4.40)	N/A	N/A
Male	4.69 (4.44)	N/A	N/A
OCI-R total score			
Group		*F (1,415)*=1.8; η^2=0.004	.18
Frontline	13.12 (13.00)	N/A	N/A
Nonfrontline	11.70 (12.52)	N/A	N/A
Age	N/A	*F (1,415)*=0.9; η^2=0.002	.35
Sex		*F (1,415)*=0.4; η^2=0.001	.51
Female	12.68 (12.33)	N/A	N/A
Male	12.10 (13.17)	N/A	N/A

[a] DASS-21: 21-items Depression, Anxiety, and Stress Scale.

[b] OCI-R: Obsessive-Compulsive Inventory-Revised.

[c] One participant with missing information (incorrect data entry).

[d] N/A: not applicable.

[e] Values are significant.

Figure 1. DASS-21 and OCI-R scores of frontline (n=200) and nonfrontline (n=220) Portuguese physicians during the COVID-19 pandemic (May 4-25, 2020). Lines represent mean (SD) values. Points above the dotted line represent participants with severe symptoms. *Statistically significant differences between nonfrontline and frontline groups. DASS-21: 21-items Depression, Anxiety, and Stress Scale; OCI-R: Obsessive-Compulsive Inventory-Revised.

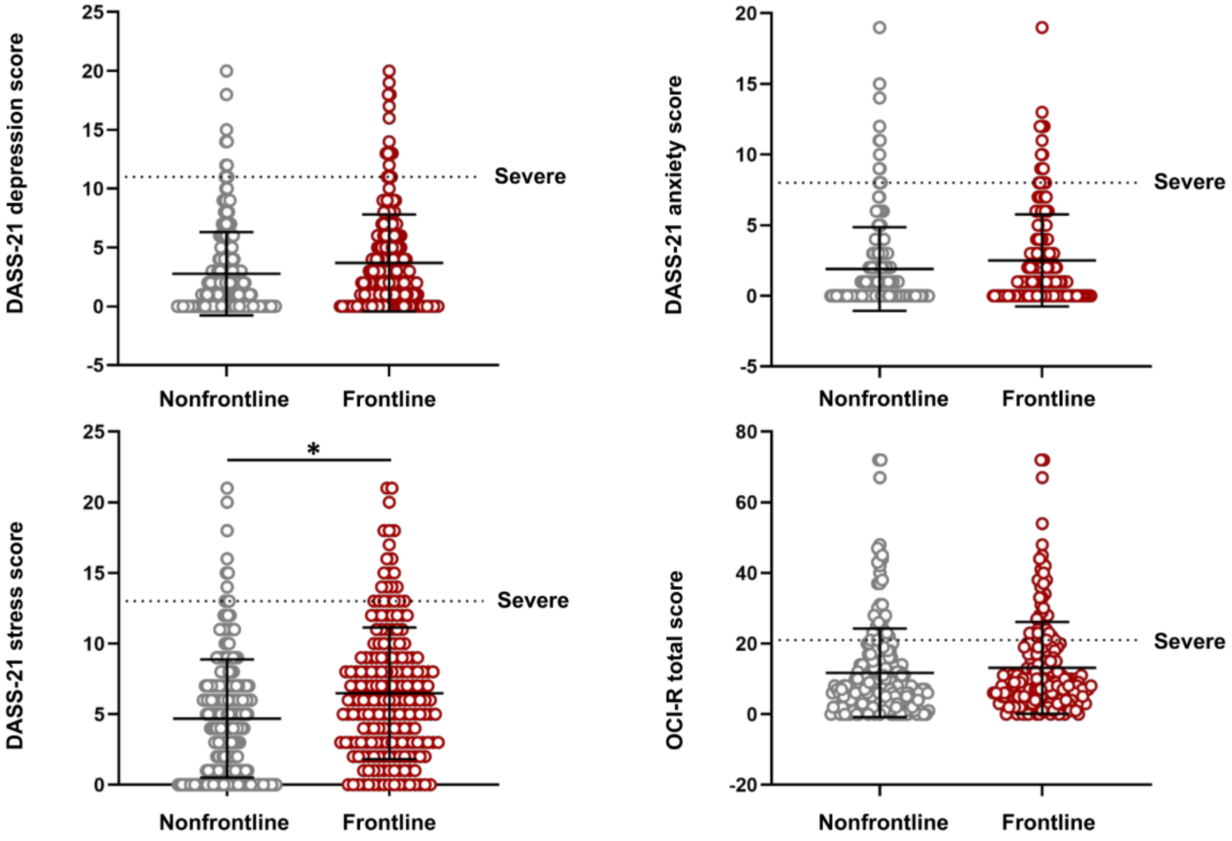
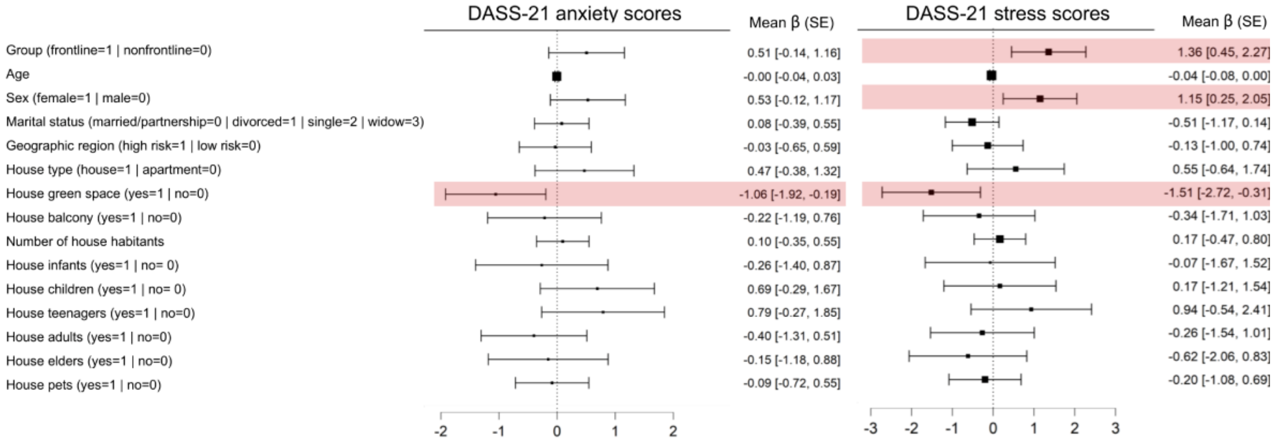


Figure 2. Significant variables in regression models for DASS-21 anxiety and DASS-21 stress scores of Portuguese physicians (n=420) during the COVID-19 pandemic (May 4-25, 2020). DASS-21 depression and OCI-R total models did not reach significance. The forest plot represents the mean unstandardized β (SE) values. The red boxes indicate statistical significance. One participant was excluded because of missing information for age (incorrect data entry). DASS-21: 21-items Depression, Anxiety, and Stress Scale; OCI-R: Obsessive-Compulsive Inventory-Revised.



Discussion

Principal Findings

In this study, we investigated whether the mental health of physicians working at the frontline during the COVID-19 pandemic is affected in comparison to other physicians. We found that frontline physicians have increased levels of stress. Furthermore, female physicians presented higher levels of stress and anxiety. Younger physicians also displayed augmented stress levels. Concurrent with these results, being female and working at the frontline are potential risk factors for stress, and having a house with green space is a potential protective factor for stress and anxiety.

These findings are consistent with those of our previous study on the general Portuguese population, which reported that being male, being older, and living in a house with green space appeared to be beneficial for mental health during the COVID-19 pandemic [10]. Moreover, previous studies have reported that women and younger individuals have a higher risk of mental disorders, including anxiety and mood disorders [34,35]. Furthermore, previous studies have reported negative associations between mental health variables (eg, stress and anxiety) and age among health care workers, indicating that older individuals might be more resilient to the psychological impact of COVID-19 [20,36,37]. Moreover, older physicians might cope better with stressful situations because they have more years of experience. On the other hand, older physicians might have been assigned to lower-exposure wards, considering the higher risk of more severe manifestations of COVID-19 with an older age [29]. Indeed, NFRONT participants were older than their FRONT counterparts in our study. Of note, age was not a significant variable in the stress regression model; this finding should be interpreted with caution. Parallel with our results, several recent studies reported that female medical workers have higher levels of anxiety and stress [13,18,20,21,36-38]. In addition to working outside of the house, women usually have more responsibilities within their household and with childcare than men. Moreover, they rely more on social support as a coping strategy for stress [39-41]. Thus, female physicians may have been exposed to more stressors during the COVID-19 pandemic because they might need to reconcile home, childcare, and work duties while having less social support from family and friends to follow social isolation guidelines, along with less support from spouses and their workplaces. Additionally, as a protective measure, schools and daycare centers for children were closed during the first wave of COVID-19 in Portugal [42], thus aggravating the lack of childcare support for women and possibly affecting their work schedule. On the other hand, in Portugal, more female physicians work in specialties including general and family practice and anesthesiology, internal medicine, and pneumology [43], which involve high contact with patients, while male physicians are more predominant in surgical fields, where several services were canceled during the pandemic [29]. This might also have contributed to the observed levels of anxiety and stress among female physicians. Lastly, having a house with green spaces, such as a garden, might help increase physical activity and provide outdoor relaxation periods, thus contributing to better mental health [44,45]. Thus, the effect observed for this variable might be a surrogate for high-quality leisure time.

Furthermore, in comparison with our previous results [10], frontline physicians presented a higher prevalence of severe OC symptoms (19.5%) than the general population (12.4%). However, we did not observe significant differences between FRONT and NFRONT physicians with respect to OC symptoms. Interestingly, the prevalence of severe OC symptoms in NFRONT physicians (16.4%) was also higher than that in the general population. Thus, COVID-19 might have an impact on OC symptoms among physicians in general, concurrent with previous reports [17,18]. The fear of self-infection or disease transmission among family members or coworkers because of working at health facilities with a high risk of infection may boost excessive washing and cleaning behaviors or contamination-related obsessive thoughts.

Furthermore, frontline workers in our study showed higher stress levels than other physicians and a higher prevalence of severe stress symptoms (11.5%) than the general population (9.3%) [10]. Previous studies have also reported increases in stress [36,37,46], distress [13], and burnout [11,12] symptoms among medical workers during the COVID-19 pandemic. These and other studies suggest that the fear of self-infection and disease transmission to family members, concern or grief for affected coworkers, social distance from family members, lack of proper COVID-19–related training and protective equipment, longer working hours, lack of sleep, and difficult life-or-death decision-making might be factors contributing to increased stress [38,46-51]. Other studies have also observed positive correlations between stress and the fear of infection and between stress and burnout symptoms among health care professionals [52]. Furthermore, previous outbreaks of other infectious diseases (eg, severe acute respiratory syndrome, Middle East respiratory syndrome, and A/H1N1 influenza) were associated with an increase in stress, distress, and burnout symptoms among health care professionals [53,54]. Long-term effects of augmented stress levels may translate to posttraumatic stress disorder and burnout, especially among frontline physicians [47,48,50,51,53,55].

Studies conducted in several countries have reported that health care professionals have elevated levels of anxiety and depression during the COVID-19 pandemic [22,23]. We did not observe evidence of increases in the symptoms of severe anxiety and depression in our sample when compared to a previous study on the general Portuguese population [10], and frontline workers were not different from other physicians in terms of these symptoms. These findings may be explained by the lower number of COVID-19 cases and the subsequent occurrence of the disease in Portugal when compared to countries that were among the first to be affected by this disease.

Limitations

This study has some limitations. We used a cross-sectional design, which prevents the inference of causality. The selection of participants was not free of putative bias because the physicians who consented to participate in the study might have better mental health indicators or a reduced workload (eg, by not working at the frontline) than the ones who refused to participate. Additionally, our conclusions cannot be applied to other health care professionals such as nurses who have had direct contact with patients with COVID-19. Since few physicians in our sample were in a quarantine period, we could not study the impact of this variable on mental health. Finally, other factors that were not considered in our analysis might have had a significant impact on mental health, including workload [19,21,46,52], history of psychiatric disorders [56], and the use of coping strategies (eg, use of substances, exercise, and mindfulness) [14,46]. Furthermore, we did not determine how long these physicians have been working at the frontline during the COVID-19 pandemic, whether they switched to other wards during the pandemic, whether they received psychological or psychiatric support [57], or whether they were facing difficulties in daily functioning at work or during social activities [58,59]. Thus, our findings should be interpreted with caution in consideration of these limitations.

Conclusions

This is the first study to provide evidence of increased stress levels in Portuguese physicians at the frontline of during the COVID-19 pandemic. We observed that female physicians are more susceptible to stress. Prolonged exposure to COVID-19–related stressors may lead to burnout syndrome. Thus, our results potentially provide essential guidelines for future preventive actions by health care systems, namely the establishment of proper rest periods, control of excessive workloads, the supply of basic needs (eg, personal safety and childcare), development of pandemic-related training programs, and the incorporation of protective measures for mental health (eg, virtual mindfulness-based interventions). Additionally, social contact with family and friends should not be overpowered by occupational demands [47-50].

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Authors' Contributions

All authors designed the study and drafted the manuscript. SF analyzed the data. NS, MPP, and PM supervised the study.

Conflicts of Interest

In the past 3 years, PM has received grants, CME-related honoraria, or consulting fees from Angelini, AstraZeneca, Bial Foundation, Biogen, DGS-Portugal, FCT, Janssen-Cilag, Gulbenkian Foundation, Lundbeck, Springer Healthcare, Tecnimede, and 2CA-Braga.

Multimedia Appendix 1
Table S1 - new supplementary table with survey information (round 2).
[DOCX File , 17 KB - publichealth_v7i6e24312_app1.docx]

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Abbreviations

DASS-21: 21-items Depression, Anxiety, and Stress Scale
FRONT: frontline physicians during the COVID-19 pandemic
OC: obsessive compulsive
OCI-R: Obsessive-Compulsive Inventory-Revised
NFRONT: nonfrontline physicians

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Original Paper

Community Mitigation of COVID-19 and Portrayal of Testing on TikTok: Descriptive Study

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Related Article:

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Abstract

Background: COVID-19 testing remains an essential element of a comprehensive strategy for community mitigation. Social media is a popular source of information about health, including COVID-19 and testing information. One of the most popular communication channels used by adolescents and young adults who search for health information is TikTok—an emerging social media platform.

Objective: The purpose of this study was to describe TikTok videos related to COVID-19 testing.

Methods: The hashtag #covidtesting was searched, and the first 100 videos were included in the study sample. At the time the sample was drawn, these 100 videos garnered more than 50% of the views for all videos cataloged under the hashtag #covidtesting. The content characteristics that were coded included mentions, displays, or suggestions of anxiety, COVID-19 symptoms, quarantine, types of tests, results of test, and disgust/unpleasantness. Additional data that were coded included the number and percentage of views, likes, and comments and the use of music, dance, and humor.

Results: The 100 videos garnered more than 103 million views; 111,000 comments; and over 12.8 million likes. Even though only 44 videos mentioned or suggested disgust/unpleasantness and 44 mentioned or suggested anxiety, those that portrayed tests as disgusting/unpleasant garnered over 70% of the total cumulative number of views (73,479,400/103,071,900, 71.29%) and likes (9,354,691/12,872,505, 72.67%), and those that mentioned or suggested anxiety attracted about 60% of the total cumulative number of views (61,423,500/103,071,900, 59.59%) and more than 8 million likes (8,339,598/12,872,505, 64.79%). Independent one-tailed *t* tests (α=.05) revealed that videos that mentioned or suggested that COVID-19 testing was disgusting/unpleasant were associated with receiving a higher number of views and likes.

Conclusions: Our finding of an association between TikTok videos that mentioned or suggested that COVID-19 tests were disgusting/unpleasant and these videos' propensity to garner views and likes is of concern. There is a need for public health agencies to recognize and address connotations of COVID-19 testing on social media.

(JMIR Public Health Surveill 2021;7(6):e29528) doi:10.2196/29528

KEYWORDS

TikTok; social media; COVID-19; testing; disgust; anxiety; content analysis; communication; infodemiology; infoveillance; public health; digital public health; digital health; community mitigation

Introduction

Testing is necessary for estimating community positivity rates and tracking the ongoing distribution of active COVID-19 cases by person, place, and time factors. The ongoing tracking of the distribution of the disease is one of the key strategies for community mitigation [1]. Testing is therefore centrally important in COVID-19 prevention. First identified in December 2019, COVID-19 quickly reached pandemic status, and the disease has had devastating consequences across the globe [2]. As of May 8, 2021, there have been 157,087,436 confirmed cases of COVID-19 and 3,274,092 deaths reported worldwide [2].

Due to the highly contagious nature of COVID-19, the importance of rapid and accurate testing cannot be understated [3]. The two main categories of COVID-19 tests are diagnostic tests for detecting current infection and antibody tests for detecting prior infection [4,5]. Molecular tests, including real-time reverse-transcription polymerase chain reaction tests and nucleic acid amplification tests, detect genetic material in SARS-CoV-2, while antigen tests detect proteins on the virus's surface; both tests are used to diagnose active infections [5,6]. In contrast to molecular and antigen tests, antibody and serology testing uses a blood sample to detect antibodies that were produced from a previous SARS-CoV-2 infection and cannot be used to diagnose current infection. Further, it is still unclear if the presence of antibodies results in future immunity to COVID-19 [4]. At present, antigen tests provide the fastest results (less than 1 hour), but a negative test cannot definitively rule out an active infection. Results from molecular tests are more accurate, and they may become available within 1 day or take up to 1 week; antibody test results are generally available within 1 to 3 days [7,8]. Improvements in diagnostic testing are evolving to identify active cases more rapidly and may help inform treatment [5-8]. At present, emergency use authorizations have been provided by the US Food and Drug Administration for different types of COVID-19 tests [9-11].

In molecular and antigen testing, samples are attained mostly via nasal or nasopharyngeal swabs, and a few molecular tests use saliva [5,12]. Molecular testing is the most accurate method for diagnosing current SARS-CoV-2 infections, as it can be used to detect the unique genetic sequence of SARS-CoV-2 [13]. Various companies and labs have developed a variety of molecular diagnostic tests, which may result in variation in the process of testing [14]. If an antigen test indicates a negative result (suggesting that there is no current infection), a molecular test can be used to avoid false-negative results [5,15]. At present, there is no COVID-19 test that is always 100% accurate [16], and individuals should choose a test based on their own situations and health care providers' recommendations [17].

Conducting rapid COVID-19 tests in high volume can lead to the timely identification and treatment of people with SARS-CoV-2 infection and help prevent disease transmission. It has been suggested that people with mild or no symptoms can transmit the virus [18], which further highlights the importance of the early identification and containment of people who are capable of transmitting disease. Testing can also help identify individuals who have been in contact with people with COVID-19, so that they can all be treated quickly. COVID-19 tests are an essential element of addressing the pandemic by helping researchers track the distribution of the disease, understand the contagious characteristics of the disease, and trace contacts [19,20]. Consequently, organizations such as the Centers for Disease Control and Prevention (CDC), Food and Drug Administration, and World Health Organization have been attempting to increase the availability and accessibility of COVID-19 tests.

The negative perceptions surrounding COVID-19 testing have persisted. These negative attitudes may stem from the discomfort of the testing process [21], compulsory testing, a fear of isolation, a worry of movement restriction [20,22,23], misconceptions about the virus or bad medical memory [24], fear or anxiety [25], and concerns related to accuracy [26,27]. Public fear and uncertainty have been recurrent themes of the COVID-19 pandemic.

Coronaphobia is defined as "as an excessive triggered response of fear of contracting the virus causing COVID-19, leading to accompanied excessive concern over physiological symptoms, significant stress about personal and occupational loss, increased reassurance and safety seeking behaviors, and avoidance of public places and situations, causing marked impairment in daily life functioning" [28]. It may contribute to fear, disgust, concern, and other negative attitudes toward COVID-19 tests. Although there is an abundance of information on COVID-19 being distributed, social media has been particularly popular in this context [29-32]. Social media has been found to have a significant potential influence on sources of information that are used by consumers, which in turn may influence perceptions and behaviors regarding COVID-19 prevention [33]. Despite this, research related to how COVID-19 testing is portrayed and discussed on social media is scarce.

One of the most popular social media platforms is TikTok, which has 689 million users across 150 countries and 100 million users in the United States [34]. In the United States, TikTok is most commonly used by those aged 10 to 19 years (32.5%), followed by 20- to 29-year-olds (29.5%) [34]. TikTok was the most downloaded mobile app in 2020 [35]. Similar to other social media platforms, there is an abundance of information related to COVID-19 on TikTok, including information that promotes health [36] and that which is misinformative [37]. It was found that 28% of TikTok users share COVID-19–related news [34]. Given the COVID-19 "infodemic," the popularity of TikTok, and the lack of related research, the purpose of this study was to describe content related to COVID-19 testing on TikTok.

Methods

This was a cross-sectional descriptive study that paralleled methods that were used in prior studies of TikTok [36-38]. By using discover mode and the hashtag #covidtesting, a sample of 100 videos was drawn in February 2021. This hashtag had the greatest number of views related to COVID-19 testing (around 191.2 million views at the time of this study). The content characteristics coded for each video included mentioning or displaying viral tests, antibody tests, nasal swabs, and test results; mentioning or suggesting that tests were disgusting/unpleasant and mentioning or suggesting anxiety, quarantine, and COVID-19 symptoms; and using music, dance or humor. In addition, the number and percentage of views, likes, and comments were recorded, and whether a video quoted a scientifically credible source was noted. All 100 videos were coded by a single reviewer (AP), while a second reviewer (CHB) coded a 10% random sample to demonstrate interrater reliability. The two coders' opinions differed on only 2 of the 150 data points (κ=0.97). The analysis was completed by using Microsoft Excel and included descriptive statistics and independent one-tailed *t* tests and chi-square tests (α=.05). As per the Institutional Review Board (IRB) at William Paterson University, studies without human subjects are not reviewed. The IRB at Teachers College, Columbia University deemed this study exempt from review.

Results

The 100 videos garnered more than 103 million views; 111,000 comments; and 12.8 million likes (Table 1). Only two content characteristics appeared in a majority of the videos—mentioning or displaying a viral test (88/100, 88%) or nasal swab (61/100, 61%). The 88 videos that mentioned or displayed a COVID-19 test garnered over 95% of the total cumulative number of views (98,303,500/103,071,900, 95.37%), over 92% of the total number of comments (102,898/111,817, 92.02%), and over 94% of the total number of likes (12,127,252/12,872,505, 94.21%), while the 61 videos that mentioned or displayed a nasal swab accumulated over 62% of the total number of views (64,010,600/103,071,900, 62.10%), over 76% of the total number of comments (85,222/111,817, 76.22%), and over 59% of the total number of likes (7,655,082/12,872,505, 59.47%). Few videos used dance (n=3) and mentioned or displayed an antibody or blood test (n=2), and only 1 video explicitly cited a scientifically credible source (Johns Hopkins Coronavirus Resource Center).

Table 1. Views, comments, and likes for COVID-19 testing–related videos on TikTok based on observed content characteristics.

Characteristic	Videos (N=100), n	Views (N=103,071,900), n (%)	Comments (N=111,817), n (%)	Likes (N=12,872,505), n (%)
Mentioned or displayed a viral test	88	98,303,500 (95.37)	102,898 (92.02)	12,127,252 (94.21)
Mentioned or displayed a nasal swab	61	64,010,600 (62.10)	85,222 (76.22)	7,655,082 (59.47)
Mentioned or displayed test results	30	22,207,200 (21.55)	17,960 (16.06)	1,550,191 (12.04)
Mentioned or suggested that tests are disgusting/Unpleasant	44	73,479,400 (71.29)	78,625 (70.32)	9,354,691 (72.67)
Mentioned or suggested anxiety	44	61,423,500 (59.59)	71,088 (63.58)	8,339,598 (64.79)
Mentioned or suggested quarantine	13	3,990,500 (3.87)	4835 (4.32)	783,443 (6.09)
Mentioned or suggested COVID-19 symptoms	11	26,825,700 (26.03)	27,050 (24.19)	2,523,617 (19.60)
Used music	47	29,610,600 (28.73)	43,148 (38.59)	4,186,839 (32.53)
Used humor	33	38,338,200 (37.20)	49,392 (44.17)	6,447,726 (50.09)

Even though only 44 videos mentioned or suggested that tests are disgusting/unpleasant and 44 mentioned or suggested anxiety, those that portrayed tests as disgusting/unpleasant garnered over 70% of the total cumulative number of views (73,479,400/103,071,900, 71.29%) and likes (9,354,691/12,872,505, 72.67%), and those that mentioned or suggested anxiety attracted around 60% of the total cumulative number of views (61,423,500/103,071,900, 59.59%) and more than 8 million likes (8,339,598/12,872,505, 64.79%). Independent one-tailed *t* tests (significance was set at $P<.05$) showed that suggesting anxiety had no statistical association with a video receiving views (P=.13), comments (P=.12), or likes (P=.10). However, mentioning or suggesting that testing was disgusting/unpleasant was associated with garnering views and likes, indicating that videos portraying a COVID-19 test as disgusting/unpleasant were more likely to receive a higher number of views and likes. Of the 33 videos that used humor, 23 (69.7%) mentioned or suggested that tests were disgusting/unpleasant ($P<.001$) and 23 (69.7%) mentioned or suggested anxiety ($P<.001$); hence, using humor was statistically associated with whether a video portrayed tests as disgusting/unpleasant and mentioned or suggested anxiety.

Discussion

There is a need for public health agencies to recognize and address the connotations associated with COVID-19 testing on social media. We found that mentioning or suggesting that COVID-19 tests are disgusting/unpleasant was associated with the number of TikTok views and likes. Although the cross-sectional nature of this study precludes causal inferences, our data suggest that portraying a test as a disgusting/unpleasant medical procedure may generate viewer interest and promote the endorsement of videos. This finding was unexpected and troubling but perhaps not surprising.

The behavioral immune system theory consists of psychological constructs and processes that are hypothesized to encourage disease prevention behaviors [39-41]. One component—disgust sensitivity—has been consistently associated with certain disease prevention behaviors [42], including germ aversion and pathogen disgust related to COVID-19 prevention [39,41]. Yet in our study, we found that mentioning or suggesting disgust/unpleasantness in TikTok videos about COVID-19 testing was associated with the cumulative number of views and likes.

The methodology for COVID-19 tests vary according to the test type, which in turn may influence perceptions regarding disgust/unpleasantness. For example, nasal swab testing involves inserting a soft nasal swab into the nostril (length of insertion: 1.5 cm for an anterior nasal swab and 2 cm for a midturbinate specimen). The CDC guidelines for nasal swab testing are as follows: “Slowly rotate the swab, gently pressing against the inside of your nostril at least 4 times for a total of 15 seconds. Get as much nasal discharge as possible on the soft end of the swab” [4]. This should be repeated for each nostril. It is important to note that a few molecular tests involve gathering saliva in a tube [5].

Disgust is known as an emotional precursor of avoiding unpleasant medical procedures [43]. It can be argued that disgust could potentially unite like-minded people in efforts to promote health [40]. From an evolutionary standpoint, disgust can be conceptualized as information that is best shared with others, given that the well-being of society hinges upon the mass avoidance of harmful experiences and aversive stimuli [44]. In videos that mentioned or suggested that COVID-19 tests are a disgusting/unpleasant experience, individuals might either intentionally or inadvertently endorse avoidance. It is thus plausible that viewers of TikTok videos may form an ad hoc community of sorts that is in agreement with avoiding COVID-19 testing. It may be this sense of community, and not the videos themselves, that are associated with the number of views and likes [45].

Another factor that may generate a high number of likes is the disclosure of an aversive experience, which may provide a sense of relief. Perhaps this is even more the case when this point of view is shared among members of a group, such as the many viewers of a TikTok video. In summary, a shared dislike of COVID-19 testing potentially gives rise to the positive emotions that are associated with membership in a group [46], leading to the liking of videos. It seems probable that a different, unidentified subset of TikTok viewers did not like the videos on COVID-19 testing. It has long been recognized that phobias are prone to informational transmission, meaning that emotions such as fear and disgust are propagated and exacerbated by way of news stories, media coverage, and similar informational sources [47]. Perhaps those who did not like COVID-19 testing–related videos on TikTok avoided these videos due to their preexisting fears of the medical procedure, knowing that viewing these videos could lead to the further exacerbation of coronaphobia [28,48].

The limitations of this study include its cross-sectional design, the small sample size, the restricted scope of data coded, and the inability to account for the algorithms that yielded the sample. A cross-sectional design is particularly important when it comes to social media studies, such as studies on TikTok, due to the constantly changing nature of information on this widely used communication channel. In addition, we do not know the extent to which the results would be different had a larger sample of videos been included. However, at the time of this study, the collective number of views for videos with the hashtag #covidtesting was 191.2 million, and the videos included in this study had over 103 million views. This study only included a limited range of coded information, which restricted the inferences that could be drawn. For example, there was no distinction between self-administered testing and clinical testing, as this would have required making assumptions, which could lead to inaccuracies. The algorithms that produced the sample are unavailable, as are the details on how these algorithms may change over time. Further, while view counts are registered on TikTok, there is no method for determining if a viewer observed the entirety of the video. Despite these limitations, this is the first study that examines TikTok videos related to COVID-19 testing and illustrates the importance of continuing research on this topic.

Authors' Contributions

CHB and CEB conceptualized the study. AP collected the data. JF conducted the data analysis. All authors contributed to manuscript production.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
IRB: Institutional Review Board

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Original Paper

A Rapid Assessment of the Impact of COVID-19 on Asian Americans: Cross-sectional Survey Study

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Abstract

Background: The diverse Asian American population has been impacted by the COVID-19 pandemic, but due to limited data and other factors, disparities experienced by this population are hidden.

Objective: This study aims to describe the Asian American community's experiences during the COVID-19 pandemic, focusing on the Greater San Francisco Bay Area, California, and to better inform a Federally Qualified Health Center's (FQHC) health care services and response to challenges faced by the community.

Methods: We conducted a cross-sectional survey between May 20 and June 23, 2020, using a multipronged recruitment approach, including word-of-mouth, FQHC patient appointments, and social media posts. The survey was self-administered online or administered over the phone by FQHC staff in English, Cantonese, Mandarin, and Vietnamese. Survey question topics included COVID-19 testing and preventative behaviors, economic impacts of COVID-19, experience with perceived mistreatment due to their race/ethnicity, and mental health challenges.

Results: Among 1297 Asian American respondents, only 3.1% (39/1273) had previously been tested for COVID-19, and 46.6% (392/841) stated that they could not find a place to get tested. In addition, about two-thirds of respondents (477/707) reported feeling stressed, and 22.6% (160/707) reported feeling depressed. Furthermore, 5.6% (72/1275) of respondents reported being treated unfairly because of their race/ethnicity. Among respondents who experienced economic impacts from COVID-19, 32.2% (246/763) had lost their regular jobs and 22.5% (172/763) had reduced hours or reduced income. Additionally, 70.1% (890/1269) of respondents shared that they avoid leaving their home to go to public places (eg, grocery stores, church, and school).

Conclusions: We found that Asian Americans had lower levels of COVID-19 testing and limited access to testing, a high prevalence of mental health issues and economic impacts, and a high prevalence of risk-avoidant behaviors (eg, not leaving the house) in the early months of the COVID-19 pandemic. These findings provide preliminary insights into the impact of the COVID-19 pandemic on Asian American communities served by an FQHC and underscore the longstanding need for culturally and linguistically appropriate approaches to providing mental health, outreach, and education services. These findings led to the establishment of the first Asian multilingual and multicultural COVID-19 testing sites in the local area where the study was conducted, and laid the groundwork for subsequent COVID-19 programs, specifically contact tracing and vaccination programs.

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KEYWORDS

COVID-19; Asian American; testing; mental health; barrier; behavior; impact; discrimination; inequality; disparity; experience; COVID; violence; culture; stress; anti-Asian violence

Introduction

COVID-19, a respiratory disease caused by SARS-CoV-2, was first identified in China in December 2019, and then quickly spread throughout the world. By March 2020, COVID-19 became a global pandemic, devastating many countries, including the United States. In California, many health care organizations have had to rapidly modify their services to telehealth and remote services in response to shelter-in-place orders and to minimize the spread of the virus. At the same time, Asian Americans have reported increased discrimination since the beginning of the outbreak due to anti-Asian rhetoric related to the virus originating in China [1].

The Asian American population is diverse in language, culture, and immigration history, which affects their experiences during the COVID-19 pandemic. Due to language barriers and limited data collection, disparities for this population often remain hidden [2]. During this pandemic, these issues may become exacerbated, and this population may run the risk of suffering in silence. Data from different geographic areas suggest that Asian Americans have high death rates among those who test positive for COVID-19 [3,4]. A study by the Kaiser Family Foundation of 50 million patients in the Epic health records system also found that Asian American patients, along with Black and Hispanic patients, have significantly higher rates of hospitalization and death due to COVID-19 compared to their White counterparts. However, there was little attention to COVID-19–related health disparities faced by Asian Americans [5].

Asian Health Services (AHS), a Federally Qualified Health Center (FQHC), provides medical, dental, behavioral health, and health education/outreach services in 14 languages to approximately 50,000 patients in Alameda County, California. When the pandemic emerged in March 2020, AHS quickly shifted to telehealth and remote services to minimize the risk of spreading the COVID-19 virus. Many AHS patients began to stay at home even before the state released a shelter-in-place order, and the streets of local areas with a high density of Asian Americans (eg, Oakland Chinatown) became empty. As in other Chinatowns and ethnic enclaves nationally [6] (Russo et al, unpublished data, 2020), many restaurants and other small businesses closed down. When AHS staff called to connect with patients via telehealth and general check-in appointments, they heard hundreds of patient stories about ongoing anti-Asian attacks and discrimination incidents, increased fear and isolation as many stayed in their homes, and growing mental health issues, including suicide attempts and domestic violence. As part of a rapid response to these patient narratives, AHS implemented telehealth services (medical, mental health, and dentistry) and continued to provide high-quality care throughout the COVID-19 pandemic, while concurrently responding to rising social needs, sounding the alarm on anti-Asian racism, and advocating for better data collection and disaggregation.

While California had implemented a shelter-in-place order, AHS observed that many patients and those in the local community were not coming out of their homes, even for necessities (eg, grocery shopping) and other essential services (eg, preventative health care appointments). At the same time, AHS observed low testing rates in Asian American communities, and suspected these low rates were due to barriers including language access, fear and stigma due to the rising anti-Asian landscape [7], and lack of information on resources. The purpose of this study was to describe the Asian American community's experiences during the COVID-19 pandemic, focusing on the Greater San Francisco Bay Area in California, and to better inform health care services provided at AHS.

Methods

We conducted a cross-sectional survey between May 20 and June 23, 2020, using a multipronged recruitment approach, including word-of-mouth through AHS social networks, the AHS patient pool (eg, wellness check-ins), and social media posts (eg, Facebook, WeChat). The survey was self-administered online or administered over the phone by AHS staff in English, Cantonese, Mandarin, and Vietnamese. The online survey was available in English, traditional Chinese, Vietnamese, and Korean (although we did not have any Korean respondents). The surveys were translated and reviewed by a certified translation vendor and then additionally reviewed by trained and experienced AHS staff, who are familiar with our target population. The 20-question survey included respondent demographics, COVID-19–related testing and preventative behaviors, economic impacts of COVID-19, experience with anti-Asian violence, and mental health challenges (Multimedia Appendix 1). The questions were mostly closed-ended. There was one open-ended question that allowed the respondent to share their experiences with "discrimination or violence (verbal, emotional, or physical)" due to their race/ethnicity. The survey instrument was designed by AHS health care staff, including several immigrant health researchers and a chief medical officer, and was pilot tested by four patients, two of whom had limited English proficiency. We used five questions from the California Health Interview Survey (CHIS), as the questions have been tested and validated [8]. CHIS is a web-based and telephone interview survey of over 20,000 Californian adults, teenagers, and children, and it is representative of the 58 counties in the state.

The survey included responses from individuals aged ≥12 years. We decided to use this age cutoff because AHS has several youth programs, which serve youth as young as 12 years of age. The AHS youth program staff conducted additional outreach to adolescents and young teens to understand the needs and experiences of Asian American youth during COVID-19.

This study was designed to be descriptive in design, so as to document and understand the COVID-19 experiences and behaviors of the AHS patient population, in order to inform the development of intervention and public response programs (eg, COVID-19 community testing sites). Our study is exempt from institutional review board (IRB) approval because we did not collect any personally identifiable information and the main purpose of the study was to examine FQHC health care services (ie, a public benefits program design rather than a research study); thus, we did not obtain written consent from participants. For the telephone-administered surveys, AHS staff verbally asked if patients were willing to voluntarily participate in the survey before administering the questions. For the online surveys, respondents voluntarily completed the survey and we emphasized in the survey text that the survey is voluntary and anonymous, and that we would not collect any personally identifiable information. We used descriptive statistics to summarize respondent characteristics and responses to the COVID-19 questionnaire.

Results

We surveyed 1279 individuals over a one-month period. The majority of respondents were women (760/1273, 59.7%), Chinese (1127/1278, 88.2%), foreign-born (1020/1254, 81.3%), and not fluent in English (718/1279, 56.1%); in addition, most participants resided in Oakland (586/1113, 52.7%; Table 1).

Only 3.1% (39/1273) were tested and there was a 5% (2/39) positivity rate among respondents who were tested (Table 2). The primary reasons that respondents reported for not getting tested were not finding a testing site (392/841, 46.6%) and not being concerned that they had been exposed to the virus (355/841, 42.2%). Respondents reported wearing a mask before (503/1270, 39.6%) and after (519/1270, 40.9%) it became required by the government. In addition, 70.1% (890/1269) reported avoiding leaving their house (eg, going to the grocery store, church, and school) to avoid COVID-19 infection.

Among respondents who reported experiencing economic impacts from COVID-19, 32.2% (246/763) reported losing their regular jobs and 22.5% (172/763) reported reduced hours or reduced income. About 12.7% (97/763) of respondents had financial difficulties related to paying their rent or mortgage and for basic necessities (eg, paying bills and tuition, affording groceries).

In terms of the mental health impact of the COVID-19 pandemic, 67.5% (477/707) of respondents reported feeling stressed, 22.6% (160/707) reported feeling depressed, and 15.8% (112/707) reported feeling restless or fidgety. Furthermore, 5.6% (72/1275) of respondents reported being treated unfairly because of their race/ethnicity, which was greater than the state average during this time period [9]. Among respondents who reported experiencing unfair treatment, only one person reported the incident.

For the open-ended question on “discrimination and violence,” there were 24 respondents who wrote comments. Most of the comments were about being yelled at or being given “dirty looks” for carrying the virus. One respondent shared, “I was called, ‘corona china’ from a random person and was told that from a cashier that Korean people are coming here with the virus. I reduced going out after these incidents.” Other respondents shared, “people have yelled at me while I am wearing a mask” or “people run when they see me wearing a mask.” Another respondent shared, “just going grocery shopping with my parents we always get mugged. Even in line to pay a woman had the audacity to call us racial slurs.”

Table 1. Demographic characteristics of Asian Health Services survey respondents, Greater San Francisco Bay Area, May-June 2020 (N=1279).

Characteristic	Particpants, n (%[a])
Gender (n=1273), n (%)	
Male	513 (40.3)
Female	760 (59.7)
Race/ethnicity (n=1278), n (%)	
Cambodian	20 (1.6)
Chinese	1127 (88.2)
Vietnamese	103 (8.1)
Other Asian	20 (1.5)
Two or more races	8 (0.6)
Age groups, years (n=1141), n (%)	
12-18	13 (1.1)
18-24	332 (29.1)
25-44	222 (19.4)
45-64	323 (28.3)
≥65	251 (22.0)
Birthplace (n=1254), n (%)	
United States	234 (18.7)
Foreign born	1020 (81.3)
Number of people per household (n=1278), average (SD)	3.5 (1.6)
English fluency (n=1279), n (%)	
Fluent or speak pretty well	388 (30.3)
Speak somewhat well	173 (13.5)
Do not speak English very well or at all	718 (56.1)
Residence (n=1113), n (%)	
Oakland	586 (52.7)
San Leandro	202 (18.1)
Alameda	79 (7.1)
San Francisco	41 (3.7)
Other cities in Alameda County	143 (12.8)
Other cities	62 (5.6)

[a] Percentages are based on nonmissing numbers.

Table 2. COVID-19 testing and preventative behaviors and COVID-19 impact on Asian Health Services survey respondents, Greater San Francisco Bay Area, May-June 2020.

Question	Participants, n (%[a])
Have you ever had or thought you might have had COVID-19?	
Yes	47 (3.7)
No	1229 (96.3)
Don't know/refused to answer	3
Were you ever tested for COVID-19?	
Yes	39 (3.1)
No	1234 (96.9)
Don't know/refused to answer	6
What was the reason why you did not get tested?	
I was not able to find a place that would test me.	392 (46.6)
I was told by a health professional that I did not need to get tested.	37 (4.4)
I was afraid that a positive test would require me to get health care, and I was worried about the cost.	20 (2.4)
I was afraid that using health care could affect my immigration status.	6 (0.7)
I was afraid of being discriminated against if others knew I was positive.	5 (0.6)
I thought if I could just isolate myself in my home, I would get better and not infect other people.	35 (4.1)
I was not concerned that I had been exposed to the virus.	355 (42.2)
Don't know/refused to answer	438
Did you ever receive a positive test result for COVID-19?	
Yes	2 (0.2)
No	1275 (99.8)
Don't know/refused to answer	2
Has anyone in your household that you live with ever tested positive for COVID-19?	
Yes	10 (0.8)
No	1252 (99.2)
Don't know/refused to answer	17
Have you experienced any of the following situations because of the COVID-19 outbreak?	
I have lost my regular job.	246 (32.2)
I have had a reduction in hours, or a reduction in income.	172 (22.5)
I have switched to working from home.	121 (15.9)
I have continued to report to work because I was an essential worker.	88 (11.5)
I have had difficulty in obtaining childcare, or had an increase in childcare expenses.	53 (6.9)
I have had financial difficulties with paying the rent or mortgage.	92 (12.1)
I have had financial difficulties with basic necessities, such as paying bills or tuition, affording groceries, etc.	97 (12.7)
I have been treated unfairly because of my race/ethnicity.	41 (5.4)
I have experienced other challenges (Specify: ______)	7 (0.9)
No response or none of the above	516
Have you had any experiences of discrimination or violence (verbal, emotional, or physical) due to your race/ethnicity during this COVID-19 outbreak?	
Yes	72 (5.6)
No	1203 (94.4)
Don't know/refused to answer	4

Question	Participants, n (%[a])
Have you reported your experience?	
Yes	1 (1.4)
No	71 (98.6)
Don't know/refused to answer	1207
Since the COVID-19 outbreak began, have you felt any of the following?	
Depressed	160 (22.6)
Hopeless	45 (6.4)
Stressed	477 (67.5)
Restless or fidgety	112 (15.8)
Other	12 (1.7)
Don't know/refused to answer	572
Have you talked to your doctor or a mental health professional about how you felt?	
Yes	69 (5.5)
No	1196 (94.5)
Don't know/refused to answer	14
Please indicate how long you have been wearing a mask.	
Wore a mask before shelter-in-place	503 (39.6)
Wore a mask when shelter-in-place started	519 (40.9)
Wore a mask after the government required us to do so	243 (19.1)
I do not wear a mask in public.	5 (0.4)
Don't know/refused to answer	9
Have you done other things to reduce your chances of getting infected with COVID-19?	
Avoid leaving my house to go to any public places (such as grocery stores, church, and school)	890 (70.1)
Avoid going to any of my health care appointments	105 (8.3)
Avoid taking public transportation	238 (18.8)
Other	36 (2.8)
Don't know/refused to answer	10

[a] Percentages are based on nonmissing numbers and definitive answers (ie, responses of “don’t know” and no response were not included in the total).

Discussion

The survey results underscore the different and interconnected needs of and issues in the Asian American community during the early stages of the pandemic. We found that Asian Americans reported low levels of COVID-19 testing (3%) and limited access to testing, high prevalence of mental health issues and economic impacts, and high prevalence of risk-avoidant behaviors (eg, not leaving the house) in the early months of the COVID-19 pandemic.

A high percentage of respondents reported they did not leave their homes, which likely reduced their risk of COVID-19 infection. However, another possible explanation for not leaving the home may be increased fear of unprovoked anti-Asian hate, harassment, and discrimination. Overall, 6% of respondents reported experiencing discrimination or violence. The quotes from some respondents also highlight the anti-Asian sentiment. The survey was conducted 2-3 months into the pandemic, relatively early on in the pandemic. We anticipate the prevalence of these experiences would increase over time. The data from this survey is consistent with the growing number of studies and reports on the rise in anti-Asian discrimination during the pandemic, which often involves physical violence and harassment [10-14].

The prevalence of perceived unfair treatment may also explain the high prevalence of self-reported mental health issues. Other studies have demonstrated the association between the increase of anti-Asian discrimination and poorer mental health among Chinese Americans and Asian Americans [10,15]. Within AHS, our mental health providers have shared that there is an increase in mental health utilization since the pandemic started. For example, our mental health appointments had previously typically not been fully booked, but since the pandemic started, our mental health appointments have been fully booked, and there was a decline in no-shows for appointments from 20% to close to zero. AHS mental health providers have noted that patients have shared their experiences of fear and trauma relating to both COVID-19 and anti-Asian hate, causing many patients to become fearful of leaving their homes. The social isolation experienced may also contribute to mental health impacts.

Our results highlight the low testing rate among AHS Asian American patients (3%). In comparison to testing rates in Alameda County during the same time period, where a majority of respondents reside, the testing rate across all racial groups was 174.3 per 1000 (17.4%), across all races, while the testing rate for Asian Americans was the lowest at 57.73 per 1000 (5.8%) [16]. Similarly, the Kaiser Family Foundation found COVID-19 testing rates were lower among Asian patients compared to White patients [5]. Furthermore, nearly half of respondents who did not get a test reported that they were not able to find a place to get tested. During the survey period, COVID-19 tests were difficult to access and even more difficult to access in Asian languages. Based on our work with this patient population and the broader literature base on Asian American health disparities, we hypothesize that language access was a major barrier to access to testing for Asian Americans and will remain a large barrier during the COVID-19 vaccination process if left unaddressed.

Our finding that the low testing rates were due to limited access to testing sites provided us with important data that we presented to our local government to justify the need for multilingual (eg, Cantonese, Mandarin, Vietnamese, Korean, Khmer, Tagalog, Burmese, Tongan, and Samoan) COVID-19 testing sites situated within neighborhoods with a higher density of Asian Americans (eg, Oakland Chinatown and Little Saigon of Oakland). Given the results of this survey, AHS has established several COVID-19 community testing sites that provide culturally appropriate services in multiple languages at several locations in Oakland and Fremont that have a higher density of Asian Americans. In addition, AHS launched a multilingual helpline to provide information and navigation assistance regarding the COVID-19 testing process, social services (eg, food and unemployment assistance), consultations for isolation and quarantine, and other case management and mental health referrals. Since the establishment of these services, the number of Asian Americans who receive COVID-19 testing has increased, and AHS has observed the successful use of the multilingual helpline to obtain services. The findings have also informed the establishment of a culturally and linguistically competent contact tracing program and vaccine rollout processes. AHS has seen high uptake of these services, including testing, contact tracing connections, and vaccinations, particularly among Asian American individuals with limited English proficiency; this is likely because AHS services have been developed and tailored to be culturally, linguistically, and geographically relevant, and are situated in neighborhoods where there are higher numbers of Asian Americans to increase access to these resources.

These findings are informative for other FQHCs serving similar populations, including the 32 community health centers across the nation within the Association of Asian Pacific Community Health Organization (AAPCHO), a network of community health organizations serving tens of millions of low-income Asian Americans as well as Native Hawaiian and Pacific Islanders across the country.

There are some limitations to our study. First, we cannot be certain that no individuals took the survey multiple times since we did not collect personally identifiable information. However, we did not provide any incentives for participation and do not believe there was any reason for respondents to take the survey multiple times. We also did not collect information that distinguishes respondents that completed the survey online from respondents who completed the survey administered by AHS staff. For the surveys that were administered by AHS staff, there is a potential for social desirability and misreporting. Thus, there is a possibility that there may be some differences in responses to these two methods of survey administration. Additionally, this survey was conducted at the beginning of the pandemic and for the purposes of improving FQHC services for a public benefits program design; therefore, we did not used a validated survey instrument. However, the development of survey questions was guided by health researchers and AHS staff familiar with the patient population, as well as questions from the CHIS, the largest state health survey in the United States. Furthermore, the survey was pilot tested by four patients who confirmed that questions were straightforward for English speakers and those with limited English proficiency and that the survey was feasible to complete during patient appointments. We did not use standardized discrimination questions because those instruments have not been well tested among Asian American populations with limited English proficiency. The COVID-19 pandemic is unprecedented in multiple ways, including the global morbidity and mortality impact, as well as the fact that Asian American communities have been targeted and blamed for causing the virus. At the time of our survey, there were no survey instruments that had been designed and tested to capture discrimination experiences during a pandemic. As health care providers who have served and advocated for the Asian American population since 1974, we designed questions that would allow us to capture our patients' experiences while being easy to comprehend and complete.

The survey findings highlight the ongoing need to use community-based approaches, including culturally and linguistically competent survey instruments, to document emerging issues in vulnerable populations to inform care and implement strategies to address disparities. At the time of our survey, there were no existing data to document COVID-19–related experiences among Asian Americans, and few peer-reviewed studies have been published on the Asian American experience one year into the pandemic [3,4,17,18]. As trusted health care providers who were hearing from hundreds of patients about the fear of infection and anti-Asian discrimination, the mental health impacts, and the lack of knowledge about resources due to language barriers, AHS implemented this survey, which informed our rapid response to COVID-19. The AHS experience can serve as a successful case study of evidence-based COVID-19 response efforts for other Asian American–serving FQHCs. The data on low testing, limited access to testing, and high mental health needs resulted in the establishment of culturally and linguistically competent COVID-19–related services (eg, testing, contact tracing, and vaccinations) and increased the overall utilization of the health services among Asian Americans during the pandemic.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey instrument.
[DOCX File , 21 KB - publichealth_v7i6e23976_app1.docx]

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Abbreviations

AHS: Asian Health Services
CHIS: California Health Interview Survey
FQHC: Federally Qualified Health Center
IRB: Institutional Review Board

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Original Paper

An Urban Population Health Observatory System to Support COVID-19 Pandemic Preparedness, Response, and Management: Design and Development Study

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Abstract

Background: COVID-19 is impacting people worldwide and is currently a leading cause of death in many countries. Underlying factors, including Social Determinants of Health (SDoH), could contribute to these statistics. Our prior work has explored associations between SDoH and several adverse health outcomes (eg, asthma and obesity). Our findings reinforce the emerging consensus that SDoH factors should be considered when implementing intelligent public health surveillance solutions to inform public health policies and interventions.

Objective: This study sought to redefine the Healthy People 2030's SDoH taxonomy to accommodate the COVID-19 pandemic. Furthermore, we aim to provide a blueprint and implement a prototype for the Urban Population Health Observatory (UPHO), a web-based platform that integrates classified group-level SDoH indicators to individual- and aggregate-level population health data.

Methods: The process of building the UPHO involves collecting and integrating data from several sources, classifying the collected data into drivers and outcomes, incorporating data science techniques for calculating measurable indicators from the raw variables, and studying the extent to which interventions are identified or developed to mitigate drivers that lead to the undesired outcomes.

Results: We generated and classified the indicators of social determinants of health, which are linked to COVID-19. To display the functionalities of the UPHO platform, we presented a prototype design to demonstrate its features. We provided a use case scenario for 4 different users.

Conclusions: UPHO serves as an apparatus for implementing effective interventions and can be adopted as a global platform for chronic and infectious diseases. The UPHO surveillance platform provides a novel approach and novel insights into immediate and long-term health policy responses to the COVID-19 pandemic and other future public health crises. The UPHO assists public health organizations and policymakers in their efforts in reducing health disparities, achieving health equity, and improving urban population health.

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KEYWORDS

causal inference; COVID-19 surveillance; COVID-19; digital health; health disparities; knowledge integration; SARS-CoV-2; Social Determinants of Health; surveillance; urban health

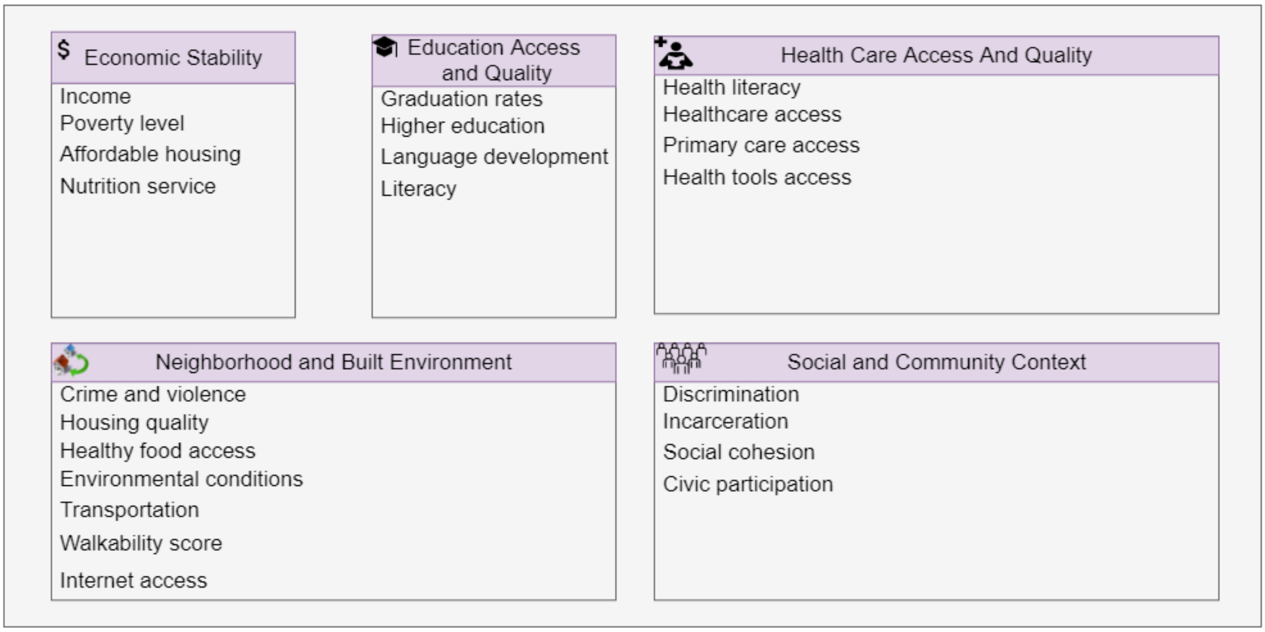
Introduction

Background

COVID-19 is a highly transmissible disease caused by SARS-CoV-2. COVID-19 has been one of the leading causes of death in many countries since December 2019 when it was first reported in Wuhan, China. As of May 5, 2021, there have been over 156 million confirmed cases of COVID-19 and more than 3.2 million deaths worldwide [1,2]. Currently, the United States is among the countries leading in the number of confirmed COVID-19 cases and deaths. According to the Institute for Health Metrics and Evaluation, by August 2021, there will be an estimated 600,000 COVID-19–related deaths in the United States [3]. COVID-19 illness can range from asymptomatic and mild to moderate and severe, with symptoms that include cough, shortness of breath, sore throat, fever, fatigue, and muscle pain. Underlying comorbid health conditions such as hypertension, diabetes, chronic obstructive pulmonary disease, cardiovascular disease, and cerebrovascular disease increase the risk of severe complications from COVID-19. These complications include acute respiratory failure, pneumonia, acute kidney or liver injury, blood clots, and possibly death [4,5].

Although COVID-19 adversely affects people’s lives in many respects, it disproportionally impacts certain groups and populations [6-11]. Researchers [12] are still exploring the dynamics of the COVID-19 pandemic in urban areas to understand the short- and long-term impacts of COVID-19 on urban environments, which may be densely populated. The socioeconomic and environmental risk factors and determinants are key to explain how urban life affects population health [13]. Underlying sociocontextual factors such as Social Determinants of Health (SDoH) could increase the prevalence of COVID-19 and COVID-19–related deaths in certain communities. A relatively new concept in health care, SDoH are defined by the World Health Organization as “the conditions of where a person is born, where they grow up, where they live, where they work, and where they age” [14]. SDoH is comprised of five domains: economic stability, education access and quality, neighborhood and built environment, health care access and quality, and social and community context [15,16]. Figure 1 illustrates several SDoH variables that are included in each domain, which are as follows. The economic stability domain encompasses the level to which an individual or group falls within the hierarchical societal structure, with variables that reflect the impact of socioeconomic conditions. The education access and quality domain consists of variables that influence the process of becoming educated. The neighborhood and built environment domain consists of variables that relate to the physical environment and have the potential to overlap with other domains, making them some of the most flexible domains. The health care access and quality domain include variables that reflect access to health care and describe how health information is interpreted to make appropriate and informed decisions. The social and community context domain encompasses variables that demonstrate the social setting an individual resides in and their community involvement. These SDoH are impacted by access to power, money, and other resources and are therefore considered to be the major driving force behind health inequities [14].

Figure 1. Five domains and variables of the Social Determinants of Health.



Our prior studies have explored associations between SDoH and several health outcomes [17-19]. Consequently, our findings underpin the importance of incorporating SDoH when implementing intelligent public health surveillance solutions to inform public health decisions. During the COVID-19 pandemic, the development of an intelligent surveillance platform that embeds SDoH indicators can improve equity in the uneven distribution of quality health care services (ie, testing and vaccination), inform health officials on the timing, phasing, and safety for reopenings, and address shortages of medical supplies, devices, and health care workers to alleviate the related health and economic crisis [20,21]. Such a platform would serve as an apparatus for actualizing effective intervention design and implementation to address health disparities, provide awareness to the general public, and improve public health decision-making and planning. Additionally, it can foster the consistent integration of surveillance data across jurisdictions to estimate the incidence and prevalence of different health conditions and related risk factors. Finally, it can be used for intelligent query-answering to formally interrogate hypothesis-driven research questions.

Objectives

In this study, we describe the design and development of the Urban Public Health Observatory (UPHO), a web-based knowledge-based surveillance platform that integrates multidimensional heterogenous data including SDoH indicators and population health data and provides near–real-time analysis and dashboarding of ongoing COVID-19–related comorbidities and mortalities. In particular, we aimed to (1) redefine the Healthy People 2030's SDoH taxonomy to classify SDoH indicators into 6 domains to characterize barriers that are specific to the COVID-19 pandemic and (2) design and develop a prototype for the UPHO surveillance platform.

Methods and Results

Classification of SDoH

According to the literature [6-11,22-33], SDoH are associated with COVID-19 transmission and mortality. For example, COVID-19–positive cases or death rates were impacted by SDoH, such as transportation or commuting patterns [29], housing density [22,25], poverty [23,24], health care access [24,27], environmental conditions [6], language barriers [11], occupation [7,23], and residence in rural areas. We argue that determining the correct SDoH variables to measure both health disparities and the spread of diseases is a crucial first step in developing an intelligent surveillance system [34]. While other recent studies have developed health surveillance platforms to facilitate COVID-19 pandemic management and recovery efforts [20,21], our study is unique in its adoption and refinement of the Healthy People 2030's SDoH taxonomy to include and classify SDoH indicators reported previously [6-11,22-33] into the following six domains: (1) SDoH that affect access to resources; (2) SDoH that increase disease exposure, susceptibility, and severity; (3) SDoH that affect adherence to local laws and health policies; (4) SDoH that are community characteristics; (5) SDoH that help increase awareness, knowledge dissemination, and health education; and (6) SDoH specific to neighborhood and built environment that can impact COVID-19–associated comorbidities (Table 1). We used this new SDoH classification as a guideline to collect and analyze the relevant socioeconomic indicators used in UPHO.

Table 1. Classification of Social Determinants of Health related to the COVID-19 pandemic.

Category	SDoH[a]

SDoH that affect access to resources	• Access to proper care:
	  • Distance (miles/hour) to the closest health care facility
	  • Transportation burden index
	• Access to healthy food sources:
	  • Distance to the nearest food market
	  • Proportion of people without access to a vehicle

SDoH that increase disease exposure	• Transportation:
	  • Proportion of people relying on public transportation
	  • Proportion of people relying on carpooling
	  • Proportion of people without access to a vehicle
	  • SafeGraph mobility data
	• Age groups:
	  • Dependents under 18, elderly over 65 years of age
	  • Proportion of single-parent households
	  • Households with dependents (children and elderly)
	  • How the different age groups spend their time
	• Occupation Type:
	  • Proportion of health care workers
	  • Proportion of frontline workers
	  • Proportion of single vs multiple household earners

SDoH that affect adherence to laws and policies	• Occupation Type:
	  • Proportion of health care workers
	  • Proportion of frontline workers
	  • Proportion of single-parent households
	• Population Density:
	  • Count of housing units
	  • Average household size
	  • Multifamily vs single-family residences

SDoH that are community characteristics	• Race, ethnicity, and immigration status
	  • Proportion of ethnic minorities
	  • Proportion of racial minorities
	  • Proportion of first-generation immigrants
	• Neighborhood quality:
	  • Social deprivation index
	  • Blight rating
	  • Proportion of people under the federal poverty line
	  • Proportion of unemployment
	  • Proportion of current or previously incarcerated people
	• Environmental or safety factors:
	  • Crime rates
	  • Distance to parks and community centers
	  • Distance to police or fire stations
	  • Proportion of green space coverage
	  • Air quality index

SDoH that enable increasing awareness, knowledge dissemination, and health education	• Digital access and digital inclusion:
	  • Proportion of people who have access to Wi-Fi or the internet
	  • Proportion of cellphone or smartphone users
	• Communication and language barriers:
	  • Proportion of first-generation immigrants
	  • Proportion of literate people
	• Education attainment:
	  • Proportion of people with a high school diploma
	  • Proportion of people with a 2-year college diploma
	  • Proportion of people with a baccalaureate diploma

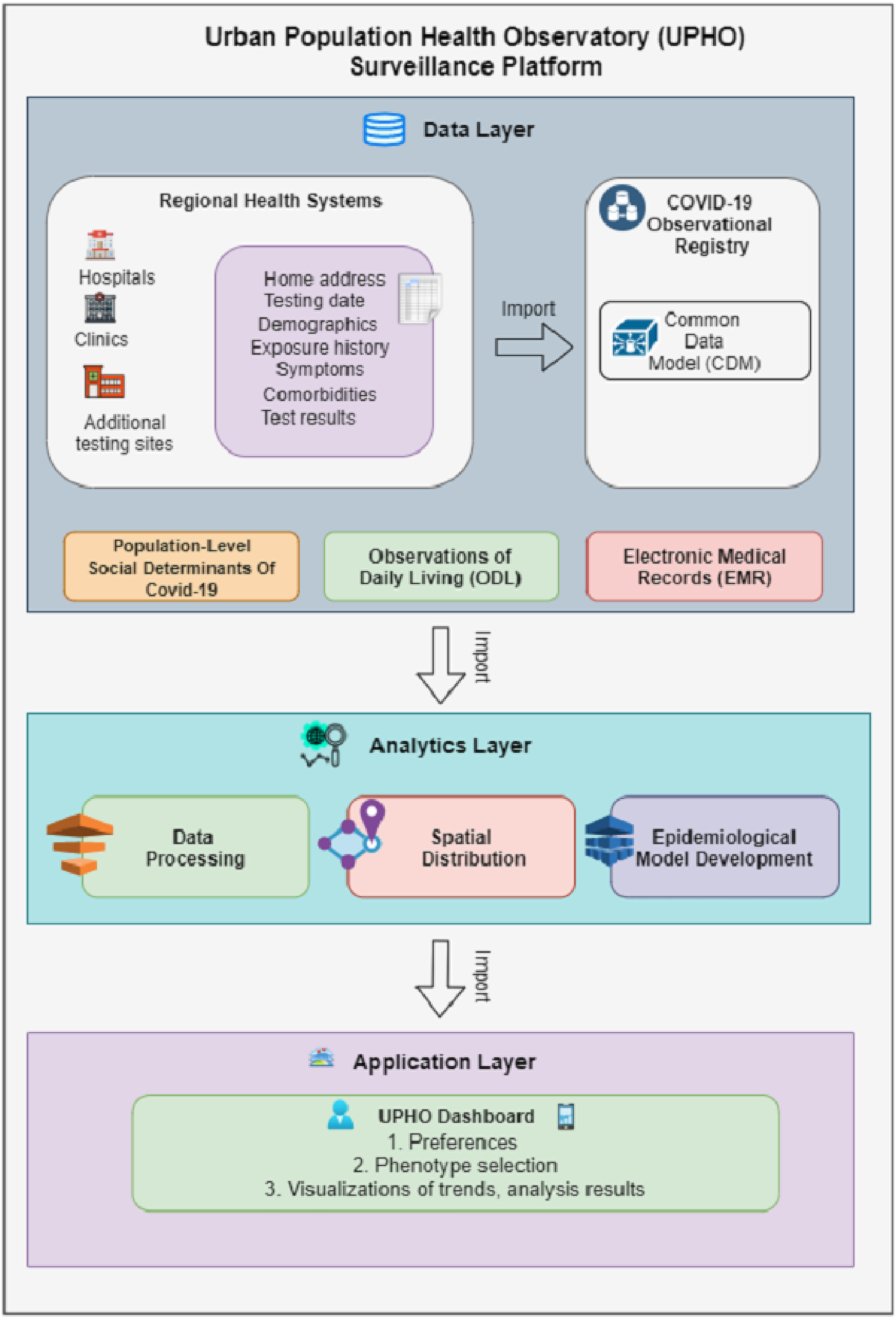
Category	SDoH[a]
SDoH specific to neighborhood and built environment that can impact COVID-19 associated co-morbidities	• Parcel or building characteristics • Social deprivation index • Blight rating • Proportion of residential addresses with backyards • Distance to parks and community centers • Proportion of green space coverage • Crime rates • Distance to market/fresh produce • Proportion of smokers

[a] SDoH: Social Determinants of Health.

UPHO: A Global Platform

We intend for the UPHO system to impact the health care infrastructure and services at multiple levels; for example, availability of timely, accurate, and complete public health surveillance systems; patient's engagement in self-care or management; competency in patient-centered diagnosis for COVID-19 and other diseases; and effective policy- and decision-making through the analysis of causal relationships among disease prevention, treatment options, and patient outcomes. The process of building UPHO involves (1) collecting and integrating data from several sources, (2) classifying the collected data into drivers and outcomes, (3) incorporating data science techniques for calculating measurable indicators from the raw variables, and (4) determining the extent to which interventions are identified or developed to mitigate drivers that lead to the undesired outcomes. The UPHO architecture is composed of three different layers (Figure 2): data, analytics, and application. The analytics layer extracts the information from the data layer and the applications layer extracts knowledge from the analytics layer. Here we have provided a detailed description of the design of the UPHO platform.

Figure 2. Layered architecture of the Urban Population Health Observatory platform from data to application.



UPHO Platform Design and Development

Data Layer

As shown in Figure 2, UPHO integrates data from several sources, including individual-level COVID-19 indicators collected from a regional registry, multidimensional population-level SDoH indicators, SDoH and epidemiological data, clinical data in the patients' electronic medical records, and patient-reported outcomes. These sources are discussed in detail below.

COVID-19 Observational Registry

The COVID-19 registry systematically collects individual-level COVID-19 indicator variables, including administered test results collected from several testing sites and self-reported outcomes collected from surveys. We performed data transfer between the different sites, including results from both surveys and diagnostic tests stored in the CSV format.

Population-Level Social Determinants of COVID-19

To obtain SDoH variables, we utilized data from the United States Census Bureau's 2018 American Community Survey [35], US Department of Agriculture, and PolicyMap [36] to obtain the variables in Table 1 at the level of the postal code, census tract, and census block group.

Individual-Level Observations of Daily Living

Individual-level anonymized data are collected through Internet of Things devices, including wearable devices or mobile global positioning system devices (SafeGraph [37] March 2020-current) that capture adherence to social distancing and shelter in place interventions. We collected social distancing metrics because social distancing and shelter-in-place orders were among the most effective early interventions during the pandemic. For that purpose, we utilized the publicly available SafeGraph [37] movement behavior data set, considering that the phased interventions started from March 30, 2020, through a phased reopening, including how often people visit specifically categorized public locations, the duration of their stay, and where they come from. This publicly available resource is collected anonymously from personal mobile phone usage. We utilized the data set to assess relationships among population movement behavior, transportation patterns, and COVID-19 transmission rates.

Electronic Medical Records (From Regional Hospitals)

This consists of COVID-19–associated clinical data including infection rates, diagnosis with other chronic conditions or comorbidities (eg, cancer, diabetes, and pregnancy), need for mechanical ventilation, escalation to the intensive care unit, and death.

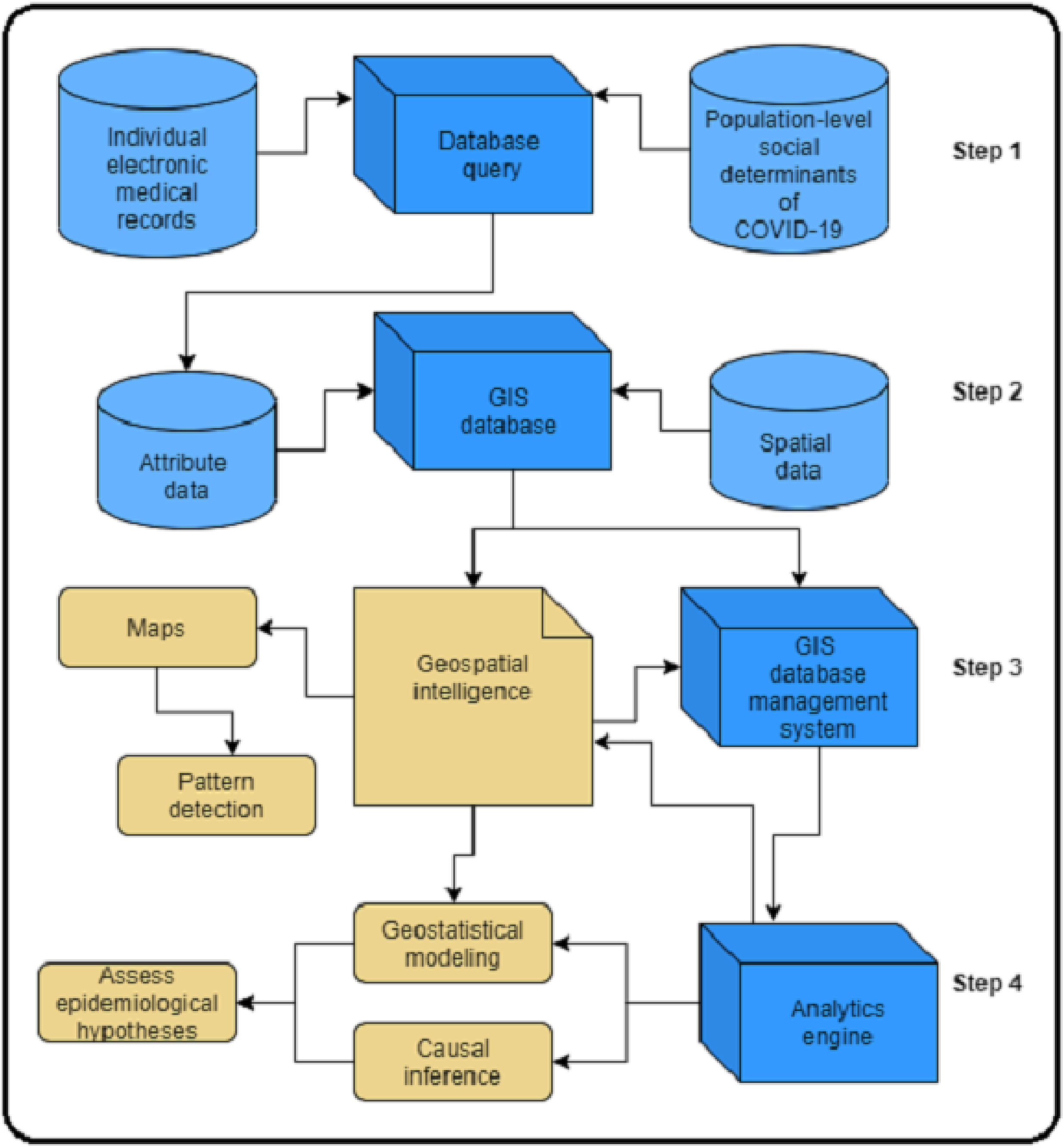
Analytics Layer

A core component of UPHO is the analytics layer, which is used for intelligent query-answering to formally propose hypothesis-driven research questions. In the following sections, we explain the different steps that we performed within the analytics layer.

Steps 1 and 2: Data Processing

Figure 3 provides a schematic representation of the UPHO analytic framework, which comprises a 4-fold process. Step 1 aligns and aggregates individual-level indicators of COVID-19 and population-level social determinants of COVID-19. The consolidated data set constructed in Step 1 is "attribute data" that merged with spatial data in a geographic information systems database in Step 2. These steps pave the way for geospatial intelligence analysis in steps 3 and 4.

Figure 3. The Urban Population Health Observatory analytics framework. GIS: geographic information system.



Step 3: Spatial Distribution

In step 3, we examined the spatial distribution to depict patterns. We conducted geospatial cluster analyses of COVID-19 transmission patterns, which includes neighborhood-level clusters and hotspots to identify high-risk groups. Hotspots are detected by implementing a spatiotemporal pattern mining, which expands the hotspot analysis to 3 dimensions by incorporating time.

Step 4: Epidemiological Model Development

In this step, we imported data from the geographic information systems' database management system into the analytics engine to perform geostatistical modeling and make causal inferences and to assess various epidemiological hypotheses. We have explained each operation below.

Step 4.1. Geostatistical Modeling and Causal Inference

Geostatistical Modeling

We examined the association among COVID-19 outcomes, SDoH, and policy adherence metrics at various levels of granularity, using global and local geostatistical modeling methods such as ordinary least squares regression and geographically weighted regression (GWR). Among implemented global and local models, we shall also depict which model better explains the association between COVID-19 outcomes and indicators. Global models such as the ordinary least squares regression model (Equation 1) assumes that the processes being modeled are stationary:

where Y is the COVID-19 outcome variable, β_k represents the parameters, X_k represents the observed values of the SDoH and policy adherence metrics variables k ($k=1,\dots,p$), and ε represents the random error term.

However, local models such as GWR (Equation 2) generate location-specific results that account for spatial nonstationarity:

where the term (u_i, v_i) represents the coordinates, β_0 (u_i, v_i) represents the intercept, and β_k (u_i, v_i) and X_{ik} are the parameters and observed values of the independent variable k ($k=1,\dots,p$), where i ($i = 1, 2, \dots,n$) represents the spatial location. β values are estimated using spatial weights. ε_i is the error term for location i.

In other words, the strength of GWR compared to global models is the ability to assess varying spatial associations among COVID-19 outcomes, SDoH, and policy adherence metrics.

Causal Inference

Causal inference is an important component of the UPHO analytic framework. One of the most challenging tasks in existing population health surveillance systems is encoding causal epidemiological information [38,39]. We utilize causal inference to examine the impacts of SDoH on disease spread and to evaluate the impact of the implemented interventions. Domain knowledge, Spearman rank correlation, and implementation of the Bradford Hill criteria have been used to assess the impacts of SDoH on disease spread, and the Bayesian structural time-series [40] has been used to evaluate the interventions.

Application Layer

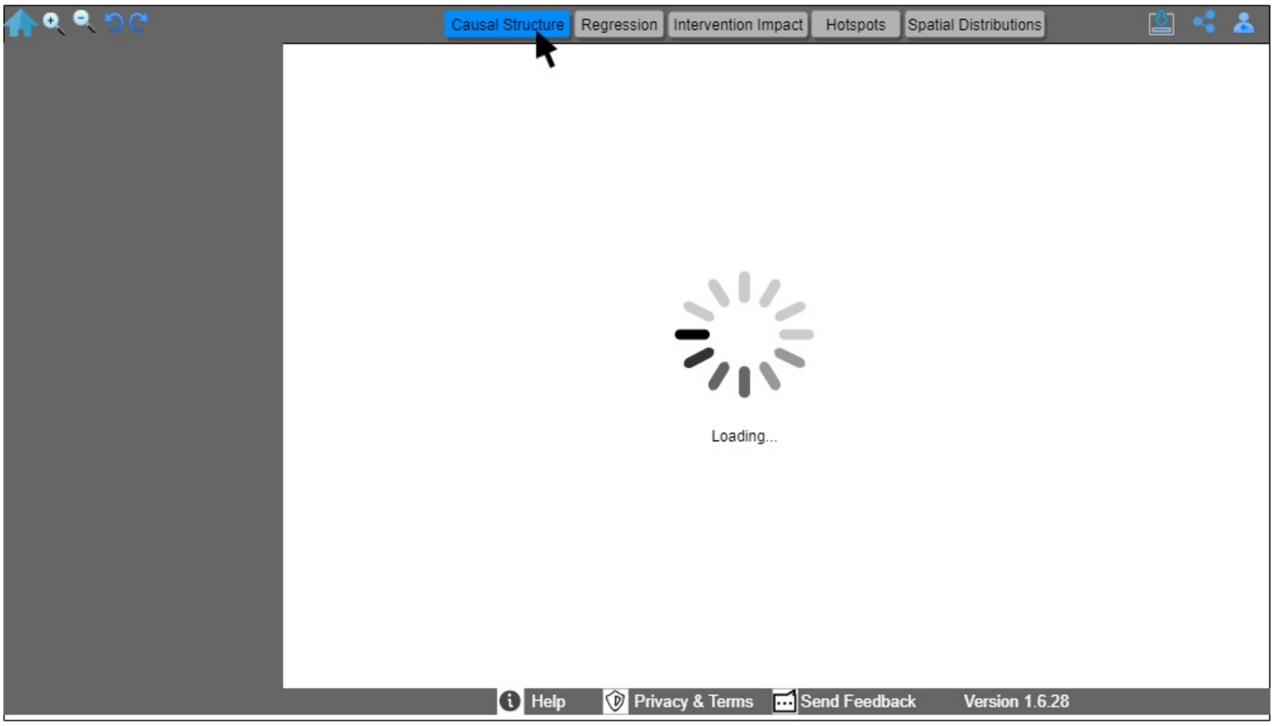
The application layer within the UPHO architecture (Figure 2) is where we leveraged the inferred knowledge to provide further insights to generate early warnings and inform policymakers. We visualized the results on a dashboard that queries the UPHO through its application programming interface and provides the features explained below.

Dashboard Prototype

The analytics layer (Figure 2) performs all analyses offline, including both global and local regression analyses. The results from the analytics layer are stored in a file-based repository that includes different geographic areas at different levels of granularity (eg, postal code, census tract, and census block group), along with their associated SDoH characteristics. It also includes the coefficient estimates between each SDoH and the different COVID-19 outcomes. The dashboard queries the repository of generated analytical results and renders the results on a tabbed view. The different tabs on the tabbed view reflect the 5 different analytics that users might aim to examine (Figure 4). Here we briefly explain the different features provided by this tabbed view and demonstrate some of them through a use case scenario in the following section.

- *F1: causal structure.* The user can use this tab to explore the causal structure with options of selecting different risk factor categories that reflect the social determinants of COVID-19 classification (Table 1).
- *F2: regression analysis*. The user will use this tab to select a level of granularity and explore both a simple association (global regression analysis) and varying spatial coefficient estimate distribution maps (including local regression analysis and GWR).
- *F3: intervention impact.* The user can use this tab to explore the causal impact of the intervention and temporal trends.
- *F4: hotspot analysis results.* The user can use this tab to explore interactive maps of high-risk groups.
- *F5: geospatial disease distribution*. The user can use this tab to select the geographic granularity of interest (eg, postal code, census tract, and block group) and the upstream social determinant risk factors (eg, crime, poverty, and transportation). This will allow the user to explore spatial variability maps.

Figure 4. A tabbed view of the 5 main features provided by the dashboard.



Use Case Scenarios

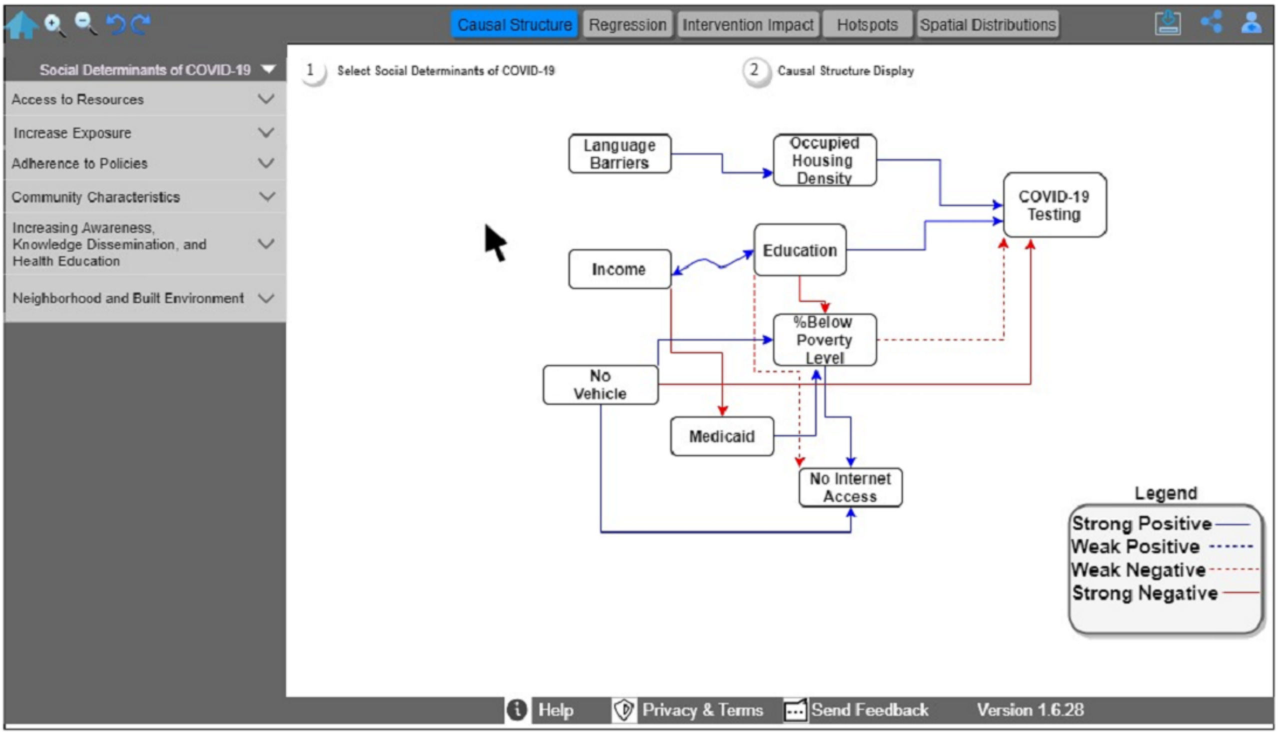
In this section, we have provided use case scenarios for each of the 4 different users to demonstrate the features available in the dashboard through the first scenario.

- *Scenario 1:* A public health official wants to launch a task force of physicians and nurses to run mobile testing or vaccination sites that will cater to areas that are socially disadvantaged and have low testing rates to reverse the trend of an infectious disease. Furthermore, she may wish to use neighborhood-level information (eg, the prevalence of positive cases, infection rates, number of testing and vaccination units, average household size, and the prevalence of multigenerational family residences) about temporal trends of COVID-19 to inform the reopening of facilities (eg, schools and restaurants) during or after the pandemic.
- *Scenario 2:* A primary care physician focuses on how SDoH from his patient’s neighborhood, such as distance to the nearest health facility, count of housing units, average household size, multigenerational family residence, increased prevalence of frontline workers, and reliance on public transportation, can influence his clinical diagnosis and management plans for patients presenting with COVID-19 symptoms at his clinic.
- *Scenario 3:* A patient uses SDoH characteristics obtained from her neighborhood population health data (eg, distance to the nearest health facility, food market, park or community center, walkability score, and crime rates) to develop self-care and management plans for type 2 diabetes, which renders her at an increased risk of severe COVID-19.
- *Scenario 4:* A caregiver with 2 children uses information from her parents-in-law’s neighborhood population health data (eg, the prevalence of positive cases, infection rates, hospitalization rates, and number of testing units) to decide whether to take her children to visit these in-laws for the Thanksgiving holiday.

We used scenario 1 to explore the capabilities of the UPHO surveillance platform and the dashboard features. In this scenario, the health official would be interested in only features F1, F3, and F5, to explore the causal pathways of testing, the geospatial distribution of administered COVID-19 tests and SDoH, and the temporal trend of daily COVID-19 cases in a geographical urban area. We used the UPHO user-centered platform to show how these 3 goals are achieved through the distinctive features of the dashboard.

First, the public health official signs in to the UPHO platform, which will determine her role and establish the appropriate access permissions. On logging in, the health official selects a specific chronic or infectious disease, in this case COVID-19, and the outcome of interest (eg, exploring the number of administered tests, recent cases, hospitalizations, or mortalities). If she selects COVID-19 testing as the outcome of interest, she can explore the causal structure as an analytical aim and the corresponding social determinants of COVID-19 of interest (F1; Figure 5). Through the causal structure, she will see the positive and negative correlations and their relative degrees.

Figure 5. Causal structure among COVID-19 testing and Social Determinants of Health within the Urban Population Health Observatory framework.



In Figure 5, the causal diagram shows a strong positive relationship among education, occupied housing density, and COVID-19 testing and a strong negative relationship between limited transportation and COVID-19 testing. By selecting new social determinants of COVID-19, the user can explore the causal information encoded in UPHO.

Thereafter, the public health official can explore the administered COVID-19 tests and the SDoH spatial distribution (F5, Figure 6). To that end, she selects the analytics aim of spatial distribution (F5), the specific level of granularity (step 1 in Figure 6), and the social determinant of COVID-19 variable(s) of interest (step 2 in Figure 6). The official can return to the home screen to select the COVID-19 cases as the outcome of interest and then the analytics aim of the intervention impact (F3, Figure 7). She can select “time-series” as a subaim (step 1 in Figure 7), and “daily” as a time measurement (step 2 in Figure 7). She has the option to stratify data by age, sex, or race. The dashboard reflects her selections by displaying an interactive time-series graph, which allows her to hover and explore COVID-19 cases and expand or shrink the graph. According to this example, COVID-19 cases would be declining in the urban area, thus providing evidence in support of the reopening of schools and restaurants in multiple phases while simultaneously considering the necessary safety measures.

Figure 6. Spatial distribution of administered COVID-19 tests and Social Determinants of Health.

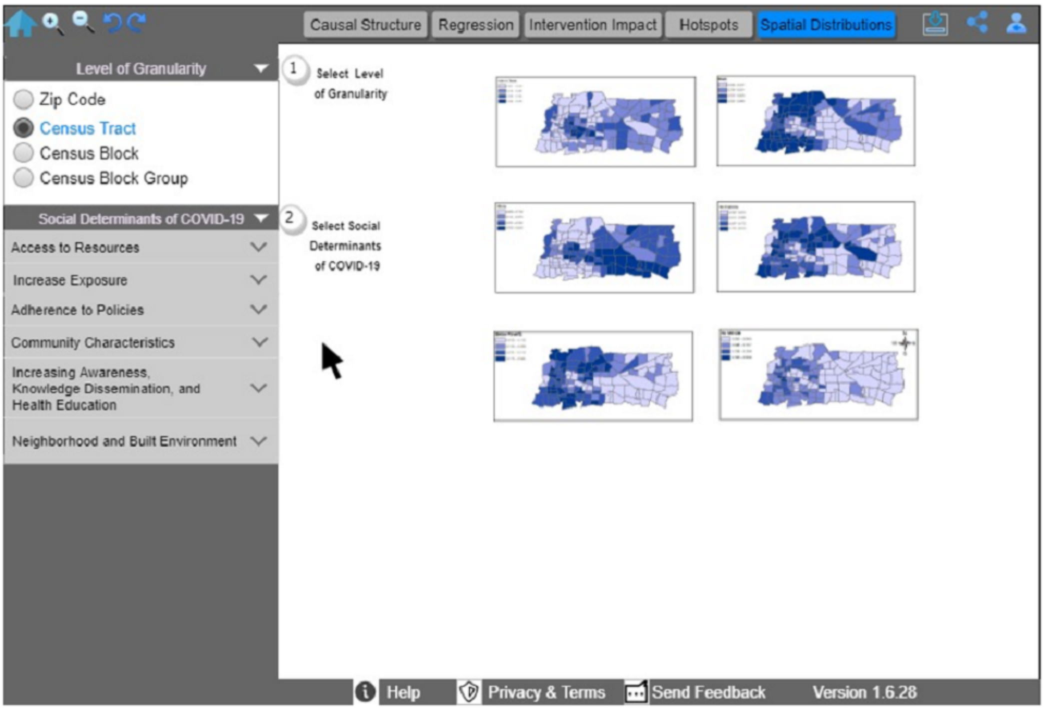
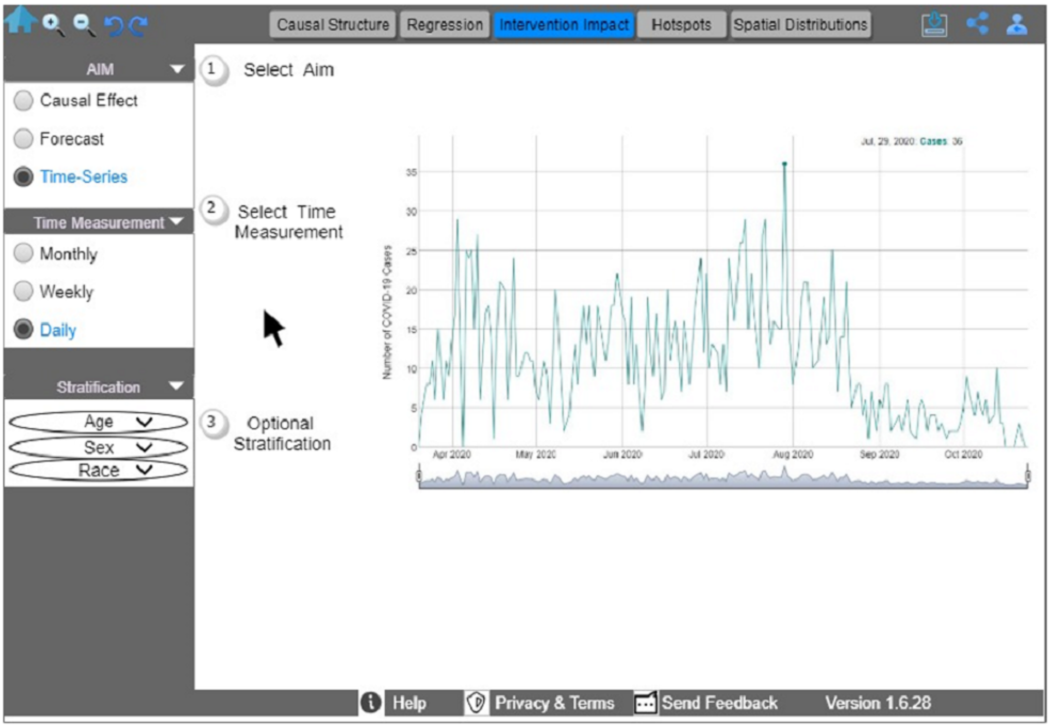


Figure 7. An interactive time-series graph that allows users to hover and explore COVID-19 cases, select the time measurement of interest, optionally stratify data on the basis of age, sex, or race, and expand or shrink the graph.



Discussion

Principal Findings

Many factors including SDoH increase the burden of COVID-19 on particular groups of the population. In the current study, we proposed the development of UPHO, a web-based urban population health observatory that can help mitigate the disparities of the disease burden of COVID-19 and to facilitate timely responses and better public health planning for equitable distribution of health care resources and services (eg, COVID-19 testing and vaccination). In this study, we redefined the Healthy People 2030's SDoH taxonomy into 6 thematic domains, and these SDoH indicators were integrated with other group-level and individual-level data sources within the UPHO platform. UPHO provides an innovative surveillance tool that systematically incorporates group-level SDoH indicators and population health data to facilitate informed decision-making necessary for preparedness, detection, rapid response, and management after disease outbreaks. The platform provides a reproducible, durable, and scalable model for data-driven, socially informed policymaking for recovery and future-readiness for COVID-19 and other large-scale pandemic events. UPHO enables precision observation and assessment, early detection, and health promotion [41] by disseminating evidence-based, accurate information and facilitating the public's access to timely health information to improve health literacy levels. It can also examine and depict causal pathways between upstream SDoH indicators and COVID-19 outcomes (including other infectious and chronic diseases). By performing local analysis to account for possible local variations, UPHO users can identify location-specific strategies to reduce transmissibility and the burden of diseases and increase the effectiveness of preventive interventions.

Furthermore, depending on the UPHO user's role (eg, public health organizations and primary care physicians) and interests, access can be gained to certain features within the dashboard. For instance, public health officials can visualize graphical representations of analytical results on the dashboard (eg, correlation plots, bar charts, hotspot maps, temporal graphs, and spatial distribution maps). Similarly, physicians may also utilize graphs and charts to summarize and provide context to data from patients' electronic health records, thereby allowing for better clinical decision-making and improved health care efficiency. The dashboard is not limited for use only by scientific investigators, epidemiologists, and health care professionals. Measures of SDoH from the dashboard can be accessible to both the general public and to government officials to identify neighborhood-level risk factors to inform decisions and policymaking. Accordingly, examples of the current and future applications of the UPHO platform include a policymaker who needs to make reliable, accurate, and informed decisions on school reopening and effective policy implementation during a disease outbreak or a clinician who uses information from a patient's postal codes for diagnostic reasoning, monitoring, and disease management. In addition to the epidemiological surveillance of infectious diseases such as COVID-19, the UPHO may also have utility in monitoring and learning about chronic diseases; for example, cancers in the urban population.

The platform implements an intelligent digital health solution that offers the appropriate security and access control mechanisms that are necessary to achieve protections on the privacy of health data.

Although this knowledge-based surveillance platform facilitates intelligent query-answering, there is some potential for improvement that could be considered for future studies. Relationships between upstream risk factors and health outcomes are important, but the addition of contextual knowledge would provide better insights. Consequently, future studies are required to incorporate a semantics layer into the UPHO platform, through which we will define domain ontologies and import some existing ontologies (eg, to study chronic conditions such as obesity [42]) to encode epidemiological knowledge, including concept hierarchies related to health indicators, concepts regarding statistical methods, and causal epidemiological axioms. The ontology will provide contextual knowledge that will help perform semantic inference. Together with the association results, the causal pathways from those inferences can render UPHO an integrated end-to-end analytics platform.

Conclusions

Social and environmental determinants have a disproportionate impact on minority and disadvantaged populations for COVID-19 infections and related illnesses. Although racial health inequalities have persisted throughout the health care system for years, the COVID-19 pandemic has exacerbated these disparities and made them more visible. Therefore, incorporating SDoH when implementing policies and interventions could facilitate COVID-19 response and management efforts. The UPHO surveillance platform provides a novel approach and novel insights to inform immediate or long-term health policy responses to the COVID-19 pandemic and other future public health crises. In summary, local COVID-19 registries systematically collect individual-level indicators from several regional testing and vaccination sites and align those indicators with population-level indicators, thereby providing decision support, measures for quality care, individual and population-level health reporting systems, and communication tools. The application of the UPHO could help reduce health disparities, thus achieving health equity and improving urban population health.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

GWR: geographically weighted regression
SDoH: Social Determinants of Health
UPHO: Urban Population Health Observatory

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Original Paper

The Interplay Between Policy and COVID-19 Outbreaks in South Asia: Longitudinal Trend Analysis of Surveillance Data

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Abstract

Background: COVID-19 transmission rates in South Asia initially were under control when governments implemented health policies aimed at controlling the pandemic such as quarantines, travel bans, and border, business, and school closures. Governments have since relaxed public health restrictions, which resulted in significant outbreaks, shifting the global epicenter of COVID-19 to India. Ongoing systematic public health surveillance of the COVID-19 pandemic is needed to inform disease prevention policy to re-establish control over the pandemic within South Asia.

Objective: This study aimed to inform public health leaders about the state of the COVID-19 pandemic, how South Asia displays differences within and among countries and other global regions, and where immediate action is needed to control the outbreaks.

Methods: We extracted COVID-19 data spanning 62 days from public health registries and calculated traditional and enhanced surveillance metrics. We use an empirical difference equation to measure the daily number of cases in South Asia as a function of the prior number of cases, the level of testing, and weekly shifts in variables with a dynamic panel model that was estimated using the generalized method of moments approach by implementing the Arellano–Bond estimator in R.

Results: Traditional surveillance metrics indicate that South Asian countries have an alarming outbreak, with India leading the region with 310,310 new daily cases in accordance with the 7-day moving average. Enhanced surveillance indicates that while Pakistan and Bangladesh still have a high daily number of new COVID-19 cases (n=4819 and n=3878, respectively), their speed of new infections declined from April 12-25, 2021, from 2.28 to 2.18 and 3.15 to 2.35 daily new infections per 100,000 population, respectively, which suggests that their outbreaks are decreasing and that these countries are headed in the right direction. In contrast, India's speed of new infections per 100,000 population increased by 52% during the same period from 14.79 to 22.49 new cases per day per 100,000 population, which constitutes an increased outbreak.

Conclusions: Relaxation of public health restrictions and the spread of novel variants fueled the second wave of the COVID-19 pandemic in South Asia. Public health surveillance indicates that shifts in policy and the spread of new variants correlate with a drastic expansion in the pandemic, requiring immediate action to mitigate the spread of COVID-19. Surveillance is needed to inform leaders whether policies help control the pandemic.

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KEYWORDS

7-day lag; acceleration; Bangladesh; Bhutan; COVID-19 surveillance; COVID-19; dynamic panel data; India; jerk; Maldives; Pakistan; South Asia; speed; Sri Lanka

Introduction

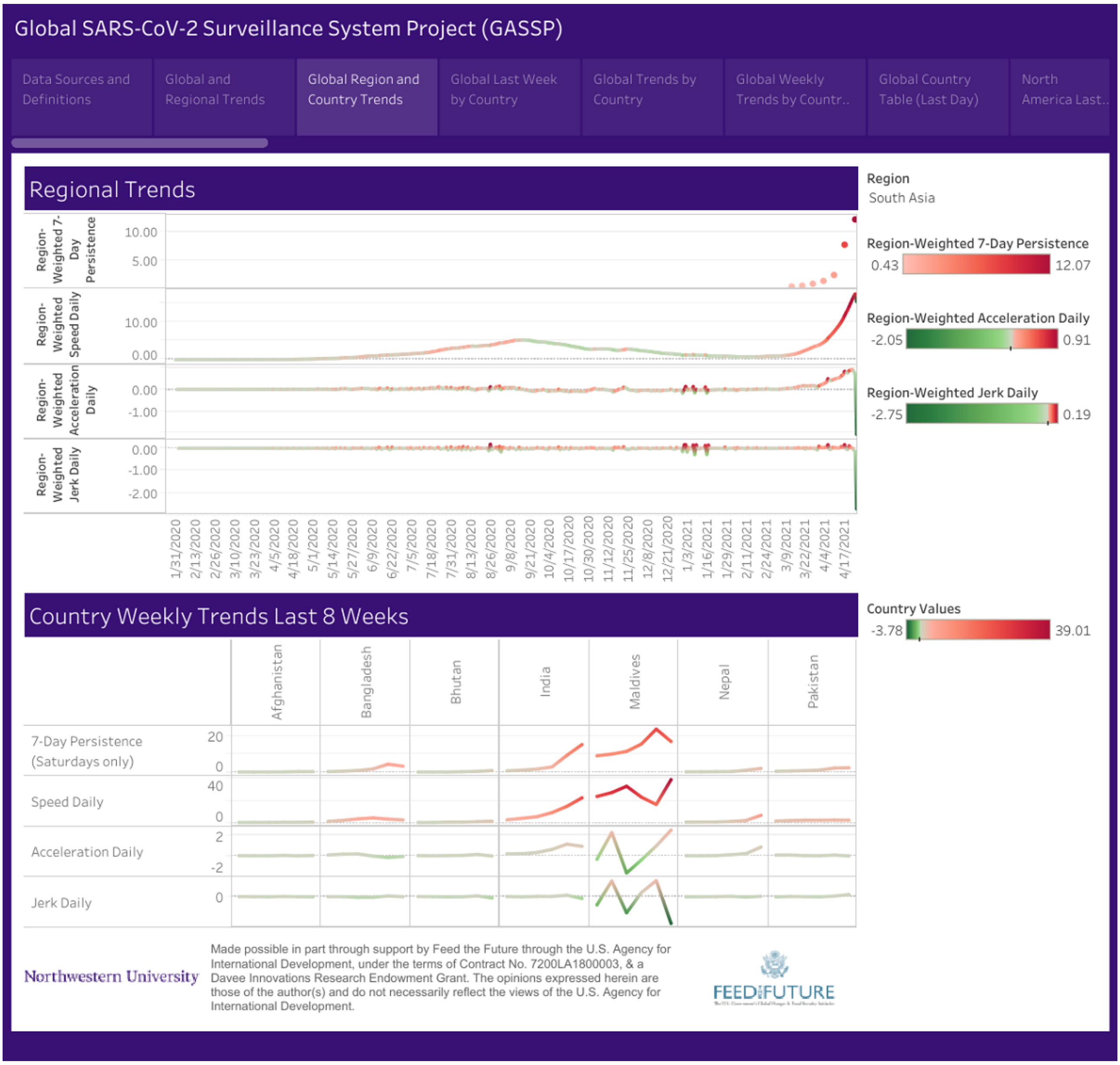
Background

The director general of the World Health Organization officially declared the outbreak of SARS-CoV-2, the virus that causes COVID-19, a pandemic on March 11, 2020 [1]. The first cases of COVID-19 in South Asia were reported in India on January 30, 2020 [2], while Pakistan confirmed its first 2 cases on February 26, 2020 [3]. In response, leaders worldwide weighed the costs of saving lives over saving livelihoods [4-6] by implementing the “Great COVID Shutdown.” While remanding citizens to their households strained the economies in Europe, Asia, and North America, the Great COVID Shutdown had a much more profound impact on low- and middle-income countries [7]. Low-income countries were disproportionately affected as their jobs and businesses were immediately obliterated, which resulted in abrupt increases in poverty and hunger [8-10].

The South Asian Association for Regional Cooperation, which comprises India, Pakistan, Bangladesh, Nepal, Sri Lanka, Maldives, Bhutan, and Afghanistan, met on March 15, 2020, to address the COVID-19 crisis [11,12]. South Asian countries began implementing mitigation efforts such as mask-wearing, social distancing, and closing schools and businesses in India, Bhutan, Bangladesh, and Sri Lanka in March 2020 [11]. By March 24, 2020, existing surveillance efforts in South Asia reported only 1536 cases and 22 deaths [13]. By April 2021, the number of observed COVID-19 cases and deaths in South Asian countries reached 18 million and 219,000, respectively [14], which indicated alarming growth. Figure 1 shows the timeline of COVID-19 events in South Asia.

Figure 1. Timeline of COVID-19 events in South Asia. SAARC: South Asian Association for Regional Cooperation, WHO: World Health Organization.

Figure 2. Weekly SARS-CoV-2 trends in South Asian countries (January 31, 2020 to April 25, 2021).



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In general, South Asia displayed a particularly unique trajectory since the onset of the pandemic. First, the region was slow to build their caseload, particularly when compared to other global regions in Europe, Central Asia, the Middle East, and the Americas [11]. Second, the significant uptick in COVID-19 transmissions in South Asia began accruing after international border lockdown policies were implemented to stop the spread of COVID-19, which forced migrant workers from South Asia to travel back to their home countries [15]. Globally, India is the largest source of migrant workers, followed by Bangladesh in sixth position and Pakistan in seventh position; this explains why India, Bangladesh, and Pakistan were the 3 most affected countries at the beginning of the pandemic in South Asia [16]. Migrant workers produce tremendous economic benefits; however, migration accelerates human interactions, which increases the spread of the disease. While human mobility has important benefits for economic growth, migration inadvertently leads to disease spread in a low-incidence setting. The movement of migrants toward their home countries before border lockdown measures were implemented, both internationally and within countries, was the largest mass migration since the 1947 partition of India, Pakistan, and Bangladesh [17]. The fear of migrants carrying COVID-19 rippled throughout South Asia, which subsequently only served to displace COVID-19 from the host countries of migrants to their home countries [18].

By early fall of 2020, India was on track to overtake the United States in the magnitude of COVID-19 transmissions but reversed course and cases declined after the implementation of strict stay-at-home policies in addition to other COVID-19 prevention policies [19]. The government of India also initiated social assistance packages to support the agricultural sector and provided direct and indirect relief to workers and households to minimize economic impacts [20]. Although there were short-term benefits and agriculture was the only sector that displayed positive growth (3.4%) in the first quarter of 2020 [21], the long-term impact of the lockdown could be negative.

By December 2020, the pandemic in the South Asian region was in decline owing to strict lockdowns and travel bans.

The easing of disease prevention policies in favor of economic, food security, social, and political concerns [22,23] along with the new SARS-CoV-2 strains or variants [24], resulted in explosive growth of the COVID-19 pandemic in early 2021, with India surpassing the United States' single-day records [25-29], thus overwhelming the health care system [30]. While global leaders must weigh policies that are aimed at protecting livelihoods, they also must consider their impact on lives and should be informed by ongoing systematic public health surveillance.

Objective

Our objective is to use COVID-19 surveillance to inform policy decisions regarding the pandemic; it is important to understand how South Asia differs between and within countries and from other global regions and to pinpoint where immediate action is needed to control the outbreaks. To that end, in addition to traditional surveillance metrics, we used dynamic panel modeling and the generalized method of moments, which correct for limitations in existing surveillance. Parallel work utilizing enhanced surveillance metrics has been completed for sub-Saharan Africa [31], the United States [32], the Middle East and North Africa [33], Central Asia [34], Europe [35], Latin America and the Caribbean [36], East Asia and the Pacific [37], Canada [38], and metropolitan regions [39].

Methods

Using application programming interfaces, we automatically extract data daily from the Foundation for Innovative New Diagnostics [40]. The Foundation for Innovative New Diagnostics compiles data from multiple sources across individual websites, statistical reports, and press releases. We also accessed data for the most recent 8 weeks from the GitHub repository [41]. This resulted in a panel of 8 countries with 62 days in each panel (n=496). We calculated traditional surveillance indicators as specified below. In addition, we used enhanced surveillance metrics, which perform better at measuring the dynamics of the pandemic and control for data contamination by using an empirical difference equation. We specified the number of new positive cases each day in each country as a function of the prior day's number of new cases, the number of new cases 7 days prior, the level of testing, and weekly shifts in variables that help determine whether the pandemic is expanding or contracting compared to prior weeks. This resulted in a dynamic panel model estimated using the generalized method of moments approach implementing the Arellano–Bond estimator in R [42,43].

Traditional surveillance indicators include the total number of cases and deaths, the 7-day moving average of new cases, and the 7-day moving average of deaths. Enhanced surveillance metrics [44,45] include the following: (1) speed: the weekly average number of new positive tests per day divided by the total country population and multiplied by 100,000; (2) acceleration: the weekly average of daily changes in the speed of the infection; (3) jerk: the change in the acceleration of the infection; and (4) the 7-day persistence effect on speed, which refers to the number of new cases reported on the present day, which are statistically attributable to new cases reported 7 days ago.

Results

Country-Specific Results of Regression Analysis

We grouped 8 countries including Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka in South Asia and present the results of regression analysis in Table 1. The weekly surveillance products are a function of these regressions.

The regression Wald statistic was significant (χ^2_6=10509826; *P*<.001). The Sargan test revealed nonsignificant findings, failing to reject the validity of overidentifying restrictions (χ^2_{513}=8; *P*>.99).

Table 1. Arellano–Bond dynamic panel data model of COVID-19 dynamics at the country level.

Variable	Coefficient	*P* value
7-day lag	0.424	<.001
7-day lag shift	0.617	.05
Wald statistic for regression, χ^2_6	10509826	<.001
Sargan statistic for validity, χ^2_{513}	8	>.99

Interpretation: Results of Regression Analysis for South Asia

The regression analyses indicate that we have a balanced panel and that we do not have overidentifying restrictions, which implies that this model fits the data. Further, regression analyses indicate a positive shift in the pandemic between April 12-18 and April 19-25, 2021.

Surveillance Results

Traditional and enhanced surveillance results for April 12-18, 2021, are presented in Table 2 and those for April 19-25, 2021, are presented in Table 3. Data of 5 prior weeks of COVID-19 surveillance trends are provided in Multimedia Appendix 1. Data dating back to the onset of the initial cases of COVID-19 in South Asia (January 2020), as well as other regions worldwide, are provided in our active surveillance system.

Table 2. Surveillance metrics for the week of April 12-18, 2021.

Country	7-day moving average of new cases	Total cases	7-day moving average of new deaths	Total deaths	Daily speed	Daily acceleration	Daily jerk	7-day persistence
Afghanistan	82	57,721	3	2539	0.21	–0.01	–0.01	0.21
Bangladesh	5188	715,252	89	10,283	3.15	–0.16	0.10	4.40
Bhutan	6	952	0	1	0.78	0.13	0.11	0.37
India	204,171	14,788,003	1125	177,150	14.79	1.12	0.20	9.41
Maldives	89	26,145	0	69	16.41	0.95	2.27	24.03
Nepal	562	283,658	5	3075	1.93	0.21	–0.06	1.00
Pakistan	5038	756,285	114	16,243	2.28	0.07	0.08	2.23
Sri Lanka	215	96,354	3	615	1.00	–0.08	–0.03	N/A[a]

[a] N/A: not applicable.

Table 3. Surveillance metrics for the week of April 19-25, 2021.

Country	7-day moving average of new cases	Total cases	7-day moving average of new deaths	Total deaths	Daily speed	Daily acceleration	Daily jerk	7-day persistence
Afghanistan	144	58,730	5	2572	0.37	0.03	0.04	0.22
Bangladesh	3878	742,400	96	10,952	2.35	–0.07	0.00	3.28
Bhutan	9	1018	0	1	1.22	–0.02	–0.19	0.81
India	310,310	16,960,172	2166	192,311	22.49	0.91	–0.25	15.41
Maldives	211	27,621	0	71	39.01	2.48	1.53	17.09
Nepal	1918	297,087	9	3136	6.58	0.84	0.05	2.01
Pakistan	4819	790,016	108	16,999	2.18	–0.01	–0.08	2.38
Sri Lanka	605	100,586	3	638	2.82	0.60	0.23	N/A[a]

[a] N/A: not applicable.

Overall, South Asia saw cases increasing steadily during the second wave of infections from March 8 to April 25, 2021, after steady declines in January and February 2021; however, country-level subanalysis with enhanced surveillance indicates that there are significant differences among South Asian countries (Multimedia Appendix 1).

In India, the 7-day moving average of daily new cases increased from 204,171 in the week of April 12-18, 2021, to 310,310 in the week of April 19-25, 2021, while the 7-day moving average of daily deaths increased from 1125 to 2166 per day during the same period, which indicates a 52% increase in new COVID-19 cases and a 92.5% increase in deaths per day. The speed increased from 14.79 new cases per day per 100,000 population in the week of April 12-18, 2021, to 22.49 new cases per day per 100,000 population in the week of April 19-25, 2021. An acceleration of 0.91 for the week of April 19-25, 2021, implies that the number of cases in India per 100,000 population is increasing by almost 1 case per day, although this rate is slightly lower than the acceleration of 1.12 reported in the prior week. Positive acceleration suggests the possibility of there being even more daily cases in the week of April 26-May 2, 2021, than in the week of April 19-25, 2021. The negative jerk indicates that although the rate of acceleration is decreasing, the acceleration remains positive. The reduction in India's case rate does not imply that the pandemic is receding, but rather only that the rate of explosive growth has slightly decreased. The 7-day persistence increased from 9.41 in the prior week to 15.41, which indicates that more than two-third of the new cases in the week of April 19-25, 2021, are statistically attributable to new cases in the prior week. This indicates a context of high transmissibility, which could be caused by a combination of policy shifts, superspreader events, or the presence of more contagious variants. India is now the epicenter of the COVID-19 pandemic [46], and indicators suggest that the pandemic will continue to worsen in India in the immediate future.

Maldives saw an increase in the 7-day moving average number of daily new COVID-19 transmissions from 89 to 211 and 0 new deaths between the weeks of April 12-18 and April 19-25, 2021. While this is an increase of 133%, the absolute caseload is small. The daily speed increased from 16.41 per 100,000 population in the week of April 12-18, 2021, to 39.01 per 100,000 population in the week of April 19-25, 2021, with an acceleration of 0.95 during the week of April 12-18, 2021, and a more rapid acceleration of 2.48 per 100,000 population during the week of April 19-25, 2021. The positive jerk of 1.53 indicates the increase in acceleration in addition to the speed at which the pandemic is expanding within Maldives. The 7-day persistence rate of 17.09 indicates that 44% of the new cases in the week of April 19-25, 2021, are statistically attributable to new cases in the prior week (ie, April 12-18, 2021). This indicates a context of high transmissibility; however, fewer cases are echoing forward.

Afghanistan saw a slight expansion in the pandemic from the week of April 12-18 to April 19-25, 2021, with an increase in speed from 0.21 to 0.37 per 100,000 population, and a shift from deceleration to an acceleration in pandemic growth of 0.03. This indicates a rising number of cases and increasing acceleration. The 7-day persistence of 0.22 in the week of April 19-25, 2021, compared to 0.21 in the week of April 12-18, 2021, indicates that new cases are statistically linked to cases in the prior week. The 7-day moving average of daily new cases increased from 82 to 144 over the same period. The ongoing growth is not ideal but does not signal alarming growth in the pandemic at this point.

Bangladesh saw a slight reduction in the pandemic from the week of April 12-18 to April 19-25, 2021, with a reduction in speed from 3.15 to 2.35 per 100,000 population, along with sustained deceleration. The 7-day moving average of daily new cases decreased from 5188 to 3878 cases between the weeks of April 12-18 to April 19-25, 2021. The 7-day persistence of 3.28 in the week of April 19-25, 2021, indicates that the cases this week are linked to those in the prior week and that the rate at which the cases are echoing forward is decreasing. Bangladesh is moving in the right direction.

Bhutan saw a slight expansion in the pandemic from the week of April 12-18 to April 19-25, 2021, with an increase in speed from 0.78 to 1.22 cases per 100,000 population; however, there was a shift from an acceleration of 0.13 to a deceleration –0.02. The 7-day persistence of 0.81 in the week of April 19-25, 2021, indicates that 46% of new transmissions are statistically linked to cases in the prior week. Since the caseload is small with 7-day averages of 6 new daily cases the week of April 12-18, 2021, increasing to 9 new cases in the week of April 19-25, 2021, Bhutan's current condition is less concerning than that of other countries in the region.

Nepal's speed is much lower than that of India or Maldives, but its daily speed of 6.58 new cases per 100,000 population in the week of April 19-25, 2021, is much higher than that of other countries in the region. This is an alarming increase in the daily speed from 1.93 per 100,000 population in the prior week for an increase in the 7-day moving average of new cases from 562 to 1918 per 100,000 population, a 3.4-fold increase in new transmissions. Acceleration increased from 0.21 in the week of April 12-18, 2021, to 0.84 in the week of April 19-25, 2021, indicating an increase in the rate of the pandemic. The 7-day persistence of 2.01 in the week of April 19-25, 2021, indicates that 50% of new cases are statistically linked to cases in the prior week. These indicators signal an alarming growth in Nepal.

Pakistan saw a very slight reduction in the pandemic from the week of April 12-18 to April 19-25, 2021, with a small reduction in speed from 2.28 to 2.18 cases per 100,000 population, and a shift from positive acceleration to deceleration in the pandemic. Pakistan's 7-day moving average of daily new cases slightly decreased from 5038 to 4819 over the 2-week period. The 7-day persistence of 2.38 in the week of April 19-25, 2021, indicates that approximately 94% of cases are statistically linked to cases in the prior week. The increase in persistence suggests an increasing clustering effect. Surveillance indicates that the pandemic is declining, but attention must be paid to the 7-day persistence as echoing cases are problematic, and more cases are echoing forward in Pakistan.

Sri Lanka, like Nepal, showed alarming growth in the pandemic from the week of April 12-18 to April 19-25, 2021, with an increase in speed from 1.00 to 2.82 cases per 100,000 population, which indicates a shift from a deceleration of –0.08 to an acceleration of 0.60 and a positive jerk. The necessary data needed to calculate the 7-day persistence are missing for Sri Lanka, but available surveillance measures indicate alarming growth.

Discussion

Principal Findings

Surveillance efforts have the capacity to inform leaders when policies are effective (and when they are not) [47] and are the foundation of public health [48]. However, for surveillance data to be most useful and actionable, they must be contextualized by the population and characteristics of the country in question. The most populous countries in South Asia are India, Pakistan, and Bangladesh. India is >6-fold larger than the next largest country in the region, Pakistan, and has an approximately 3-fold larger population than that of all other countries in the region combined. To that end, significant increases in the caseload and rates of transmission are alarming in a country with more than 1.3 billion people. In contrast, Bhutan has <1 million residents; hence, the speed of the pandemic is less concerning when the absolute number of cases are in single digits.

Traditional surveillance measures are useful but not sufficient to capture these distinctions, nor do they describe the dynamics of the pandemic. India and Maldives present a perfect case study with respect to the importance of using novel surveillance metrics. While India is more newsworthy because it ranks #1 in the absolute number of new COVID-19 cases, since its total population exceeds 1.3 billion people, the outbreak in Maldives is worse when controlling for population size. Explosive growth of the pandemic in Maldives does not affect as many individuals nor poses the same threat globally, as is the case of the outbreak in India; however, it is important to use the surveillance measures to identify the grave public health threat this outbreak poses to residents in Maldives and not let its relatively small size become overshadowed. The identification of concerning outbreaks, so they can be stymied, is imperative for the health of local regions.

Standard surveillance efforts provide a proxy for caseload (owing to asymptomatic and untested COVID-19–positive persons), which are helpful to understand the current levels of COVID-19 outbreaks; however, enhanced surveillance indicates how fast the outbreak is expanding and the alarming rates of explosive growth, as is the case in India. Speed, acceleration, jerk, and persistence are helpful metrics to compare the condition in each South Asian country relative to or within the region and to identify the need for sustaining actions or new interventions that lead to a reduction in the pandemic.

COVID-19 surveillance during the week of April 12-25, 2021, indicates that with the exception of Bangladesh and Pakistan, South Asia is experiencing an alarming outbreak of COVID-19. First, while there are many similarities in terms of development, the environment, and population structure, South Asian countries are heterogeneous in terms of their culture, economies, and susceptibility to the COVID-19 pandemic [49]. Second, migrant workers are central to disease control in South Asia, considering the large number of migrants in most South Asian countries [50]. Relaxing of the travel ban and reopening of borders have increased human interaction as migrants have passed through borders and used overcrowded public transportation to travel to their host countries, which has further fueled the COVID-19 outbreaks [18]. When South Asian leaders relaxed COVID-19 restrictions to reopen the economy [22], the pandemic markedly resurged [51] especially in India and South Asian island nations. Third, new variants B.1.1.7 (Alpha) and B.1.617.2 (Delta) harbor mutations that may have contributed to the significant impact of the current wave of COVID-19 in most South Asian countries [51]. The use of surveillance data to inform policy-level action to combat this outbreak must consider these local contexts.

Unfortunately, South Asia has experienced 2 waves of COVID-19, and all 8 countries still have active new transmissions on a daily basis, which leads to questions such as, "how will public health leaders know when the pandemic is receding?" or "are policies put in place to control the pandemic working?" Our findings indicate that adding enhanced surveillance to standard surveillance including measures of speed, acceleration, jerk, and persistence, can help to answer such questions. Additionally, enhanced surveillance metrics can help track pandemic growth factors that in turn help identify areas of concerning growth. While South Asia reversed its trajectory of the COVID-19 pandemic in late 2020 and early 2021, this trend decelerated and reversed course again, resulting in explosive growth in several South Asian countries, with Maldives and India experiencing the worst outbreaks.

By linking policies to the pandemic through systematic surveillance, it is evident when shifts result in outbreaks. Furthermore, surveillance informs public health leaders when it is safe to reopen the economy or change policy, thus establishing a delicate balance between saving lives while saving livelihoods. Undoubtedly, policymakers are faced with difficult decisions in their attempts to balance the health of their residents with the highly credible economic threat posed by the COVID-19 pandemic. It is estimated that an additional 75 million people fell below the poverty line owing to the COVID-19 pandemic in 2020, accounting for approximately 60% of the global increase in poverty in 2020 [52]. The dichotomy of lives versus livelihood may seem complex, but if people are alive, livelihoods can be addressed through appropriate policies. Dual focus on both improving pandemic surveillance and the needs of the health care system for protecting lives, and ensuring social protection for the agricultural sector and smallholder farmers for increased resilience, food, and nutritional security are needed.

COVID-19 cases had been decreasing steadily in South Asia since they peaked in late September 2020, but increased public gatherings and relaxing of public health restrictions led to the latest surge [53]. It is likely that currently implemented public health policies to stop the spread of COVID-19 were relaxed too soon after experiencing several weeks of decline in the number of active cases. For example, opening borders to allow migrant workers to travel back and forth between their host and home countries corresponded with an outbreak. Ideally, leaders should wait until the speed, acceleration, and jerk reach 0 before changing the policies on border openings, followed by careful surveillance to ensure that no hidden pockets of COVID-19 magnify into an outbreak. Alternatively, a staged approach to reopening is more realistic with subnational analysis for larger countries. For example, in areas where COVID-19 transmissions have stopped, allowing businesses to reopen to address economic concerns but banning travel to and from locations with active COVID-19 cases would result in fewer transmissions than a blanket retraction of all policies.

Limitations

Our findings are limited by the granularity in the country-level data. Data are reported on a national level for countries within South Asia, which precludes intranational analyses that would more closely reflect local regulations and better contextualize national trends. In addition, suboptimal public health infrastructure prevents data from being reported instantaneously and has severely limited the completeness of data from Sri Lanka. Multiple-day data are frequently collated into a single report, which may suggest almost 0 infections or deaths over a period of days, followed by a sudden spike in those same measures. Our analysis partially addresses this issue by calculating 7-day averages per 100,000 population for all metrics.

Comparison With Prior Work

We conducted similar studies based on dynamic panel data derived from other global regions [31-39,44,45] similar to South Asia.

Conclusions

The 7-day average number of cases and deaths, speed, acceleration, and persistence of new COVID-19 cases reveals an alarming outbreak in India and Maldives and concerning outbreaks in Afghanistan, Bhutan, Nepal, and Sri Lanka. While Bangladesh and Pakistan still have high daily caseloads, enhanced surveillance metrics indicate a reduction in their rates of novel infections. Because their daily caseload remains high, Bangladesh and Pakistan must remain vigilant in maintaining public health guidelines that will prevent additional outbreaks. Currently, these 2 countries are headed in the right direction.

While the United States still has the highest number of cumulative COVID-19 cases worldwide [32,54], the reality is that the United States only comprises 4% of the global population, while South Asia comprises 25% of the global population. India will fare much worse than the United States if the country fails to implement policies to mitigate the spread of COVID-19 or if public health restrictions in India remain as low as in 2020. Given the size of the region, prior and current outbreaks, a paucity of vaccines, and relaxed public health guidelines, South Asia in general, and India in particular, are set to exceed the United States' total caseload and deaths in the absence of massive intervention. The fact that India is surpassing the United States' daily record of new COVID-19 cases, combined with metrics including the pandemics' speed, acceleration, jerk, and persistence, indicates that India's alarming outbreak will only worsen. The current outbreak poses an immediate threat not only to the region, but also worldwide. Alarming outbreaks in South Asia are risky to any other region or country as COVID-19 can resurge and result in further outbreaks. The pandemic will not end anywhere until it ends everywhere [55].

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Tables S1-S5.
[DOCX File , 26 KB - publichealth_v7i6e24251_app1.docx]

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Viewpoint

The Anticipated Future of Public Health Services Post COVID-19: Viewpoint

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Abstract

In March 2020, the World Health Organization declared COVID-19 as a global pandemic. The COVID-19 pandemic has affected various public health functions and essential services in different ways and magnitudes. Although all countries have witnessed the effect of COVID-19, the impact differed based on many factors including the integrity and resiliency of the countries' health systems. This paper presents opinions and expectations of the authors about the anticipated changes in the future of public health at the global, regional, and national levels. The viewpoint is based on the current efforts and challenges that various stakeholders have carried out to control COVID-19 and the contribution from the literature on the future of public health. Numerous agencies and actors are involved in the fight against COVID-19 with variations in their effectiveness. The public health services showed weaknesses in most of the countries, in addition to the lack of adequate curative medicine settings. The pandemic highlighted the need for better governance and stronger and more resilient health systems and capacities. The COVID-19 experience has also emphasized the importance of coordination and collaboration among the countries and stakeholders. The COVID-19 pandemic might lead to a wide discussion to improve international and national approaches to prepare for and respond to similar events in terms of preparedness and response mechanisms and tools. Public health will not be the same as before COVID-19. New health priorities, approaches, and new agendas will be on the table of the global platforms and initiatives. More investment in research and technology to meet the demand for new vaccines and medicines, innovative methods like distance learning and working, more respect and remuneration to health professionals, and normalization of the public health and social measures that were induced during the COVID-19 pandemic are expected to be seen in future.

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KEYWORDS

COVID-19; public health; health system; health services

Introduction

As of February 6, 2021, more than 105.6 million COVID-19 cases and nearly 2.3 million deaths were reported from almost all countries worldwide [1]. Following the reported first cases of the COVID-19 pandemic, many countries applied variable public health and social measures to prevent and control the wider spread of cases. There are major concerns and uncertainties regarding not only when to return to "normal" activities but also the anticipation of what that *new normal* might be like [2]. Numerous agencies and actors have been involved in various public health interventions to fight against COVID-19 with variations in their effectiveness. This paper highlights the current efforts and interventions that are carried out by various stakeholders to control COVID-19. The objective is to initiate the discussion and share ideas about the future of public health post COVID-19 at the global, regional, and national levels.

COVID-19 Response: Leading Players and Partners

Many agencies have been involved in responding to and controlling the COVID-19 pandemic. The following sections provide an overview of the main players and partners, and their roles.

Ministries of Health

An obvious observation is that the ministries of health (MOH) have restored their leading role during their fight against COVID-19. For decades, such emergencies were essentially managed through the United Nations agencies and nongovernmental organizations (NGOs). The threat of COVID-19 has brought other government sectors closer to and more involved in the work of MOH [3]. However, many gaps were detected in the health system in most countries. In general, the public health services showed weaknesses in most of the cases, in addition to the lack of adequate curative medicine settings. An example was provided by the survey conducted by the World Health Organization (WHO), which showed that around 75% of countries reported a substantial degree of noncommunicable disease service disruptions [4].

The pandemic highlighted the need for better governance and stronger and more resilient health systems and capacities. It is time for the health systems to consider shifting the paradigm toward public health and preventive medicine. The COVID-19 pandemic has provided an opportunity to enhance coordination and collaboration among countries and stakeholders. Collaboration between the health care communities, public health professionals, subnational management, educational institutions, NGOs, transport, security agencies, and other line ministries is expected to continue in the future. Still, better coordination and collaboration are needed among various sectors that are involved in health interventions and response under the leading role of MOH.

World Health Organization

The WHO continues to provide its technical and logistic support to countries and the other UN agencies. It has developed and disseminated various protocols and tools for COVID-19 surveillance, case definition, planning, testing, isolation, quarantine, protection, and treatment. It has shipped millions of testing kits and equipment to needy countries [5,6]. In addition, the WHO has launched an academy to provide access to related training materials for health workforces [7].

The COVID-19 pandemic might lead to a discussion to improve the WHO's approach to prepare for and respond to similar events in terms of governance, mechanisms, and support systems, including the International Health Regulations. It is also expected that the new cooperation mechanisms and agreements among countries will be considered to improve the sharing of information and the early warning of similar threats [8].

Nongovernmental Organizations

Civil societies and NGOs have played a fundamental role in fighting COVID-19 at the local level [1]. Yet, civil societies are expected to play a bigger role in the accountability for funds to tackle the COVID-19 pandemic [3]. The main challenges encountered during their response are that not all of them are adequately structured to anticipate and adapt to a large-scale change in context. Besides, their business model is structured around preplanned projects and programs with identified deliverables and measurable outcomes. COVID-19 has put the NGOs under a funding crisis with a possible future decline in aid budgets and donations [9]. On the other hand, there are ongoing initiatives to establish a COVID-19 response investment vehicle. NGOs' liquidity funds may be necessary to ensure their sustainability. NGOs need to consider shifts in their mandates and priorities, and to build their capacities to deal with similar events.

Due to COVID-19, humanitarian access becomes a problem due to movement restrictions that might affect access to affected people and areas [10]. The impact on the conflict dynamics is expected to continue in many of the protracted conflict environments in which humanitarians operate. The support to the countries is challenged by accessibility to the various regions and outreach due to the restricted movement. However, this could be tackled through the model adopted by the Eastern Mediterranean Public Health Network, which managed to access those areas through its widespread network of Field Epidemiology Training Programs, rapid response teams (RRTs), and experts. Other NGOs and networks can build on this model, with the required adaptation, in their business model, partnerships, and approaches.

Private Sector

The private sector has contributed to many aspects like the provision of innovative solutions, including equipment, treatment, and vaccines. For example, in the United States, the private sector contributions to both diagnosis and treatment had led to a decrease in mortality by 44% and an increase in intensive care and nonintensive care hospital beds by 30% and 28%, respectively [11]. During the pandemic, the private sector shared its experience in organizing work and how business has been instrumental in addressing COVID-19 in a myriad of ways, including raising funds and supporting national responses; investing directly in primary health care (PHC); taking critical steps to protect their employees and communities; and leveraging their capabilities in manufacturing, communications, and supply of health commodities, especially personal protective equipment [12].

The contribution of the private sector to COVID-19 control efforts was mainly voluntary, mostly unorganized, and fragmented [13]. There is a need to establish a clear coordination mechanism with the government and NGOs. An additional requirement is a special platform or task force to engage the private sector in the national response to outbreaks like COVID-19 [14]. It is time to consider developing a legal frame for private contributions during emergencies to streamline the support with the national priorities [15]. It is wise to support the private sector post outbreak to ensure continuity of its effective support in future public health emergencies.

Global Initiatives and Platforms

The interest in empowering vulnerable people, communities, and countries is expected to rise again, as the world realized that the risk of one entity can affect the entire world. The Millennium Development Goals and Sustainable Development Goals (SDGs) could have better prepared countries for this crisis [15]. The world may need to stop and see how to accelerate the achievement of the SDGs and fix any shortcomings and challenges. Post COVID-19, it is expected that everyone will be mobilized around the UN 2030 Agenda and SDGs. COVID-19 might be used as a new excuse for isolationism and, hence, cutting development assistance for health and reframing global health because rich countries have had substantial economic losses [10]. It is also expected that the *north-south paradigm* will come to an end with a deepening division between north and south. New players will have key roles in global health policies and agendas like China and South Korea. Many scholars raised a serious question on whether we are going to see more health spending both at the domestic and the international levels. More investments are expected in prevention measures, higher salaries to medical staff, and improving their health insurance and increase in coverage [10]. Other scholars expect that infectious diseases will take center stage within the global agenda of future projects and initiatives [10]. To cope with the changing environment, the international organizations need to adopt new flexibilities and expanded mandates to match the needs of a pandemic and greater integration of the vertical programs.

Generally, more holistic, comprehensive, and coordinated approaches and strategic interventions become a necessity on the agenda of the multilateral and global initiatives [10]. Stronger intergovernmental and stakeholder platforms and networking are needed. Policies and strategies that directly or indirectly affect or are affected by the health of the public might be revised and updated. Moreover, countries and international partners need to revisit the health financing to tackle similar crises in the future [16].

Essential Public Health Functions

The COVID-19 pandemic has affected the various public health functions in different ways and magnitude [17]. Although all countries have witnessed the effect of COVID-19, the impact and response in those countries differ based on the integrity of their health systems. This paper tries to highlight the main challenges and the expected changes in selected essential public health services.

In a limited-income country like Pakistan, the COVID-19 outbreak has greatly challenged the health care system due to scarcity of basic health facilities at all levels, insufficient health policies, weak administration and governance, poor status of implementation of national policies, a less integrated system, and an indifferent attitude of the public toward protective measures [18].

Surveillance, Data Science, and Modeling

Disease surveillance is the backbone of any epidemic response, as it provides information about the sections of the population most at risk, which helps develop targeted interventions to contain the disease spread in the population [19]. In response to COVID-19, countries must adopt innovative solutions and new surveillance tools [20]. They need to run a robust real-time national integrated disease surveillance system with real-time data reported daily [21]. Using the latest technology, targeted smart lockdowns of high-risk areas with active daily sampling and daily monitoring led to a rapid decrease in cases. Examples are phone tracking data, closed-circuit television footage, and dashboards. However, there is still a need for innovative ideas, approaches, and tools to strengthen surveillance capacities. Countries should seriously consider adopting a comprehensive and integrated national surveillance system. This is to be linked to the event-based surveillance and participatory surveillance to intensify active surveillance. Additionally, the COVID-19 pandemic has taught us that we require a new dimension to privacy, protection of human rights, and ethics [22]. The use of digital technology in future epidemics and the lessons learned during COVID-19 will mitigate the effects of any future epidemics, as the health system is expected to be more strengthened, informed, and ready.

New Approaches for the Health System

A responsive health care system is needed to be able to mount an effective response to any health-related emergency. Countries need to have a clear holistic plan for preparedness and response. Globally, public health remains chronically underfunded, with spending further declined over the past 20 years. Despite the increased attention to public health, it remains unclear whether policy makers will increase investments in the public health infrastructure and workforce [23]. This pandemic has created the demand for better funding and investment in public health. The COVID-19 pandemic has tested the limits of the health care system in many countries. The pandemic has persuaded and forced the governments to inject much-needed funds into the health system. The health system has seen the allocation of unprecedented amounts of finances that have the potential to change the whole outlook of the health system, making it stronger and more responsive to the needs of populations. However, the government needs to create a *permanent budget cap exemption* mechanism for public health functions that are critical to prevent, detect, and respond to infectious diseases. This mechanism is a potential road for stable and increased funding for public health for the long term.

The countries have made use of their RRTs, which have effectively contributed to the detection and management of COVID-19. To respond to the pandemic, many countries required large numbers of trained medical staff. However, it was costly to do effective manual contact tracing efforts. In the United States, this required 100,000 workers and US $3.6 billion [24]. To tackle the shortcomings of traditional contact tracing, many countries worldwide have implemented or expressed interest in automated contact tracing services [25]. Although the advantages of automated contact tracing services can be attractive, governments still need to consider their technical shortcomings and the inherent trade-offs between privacy and efficacy when deciding whether to implement these technologies [26].

After COVID-19, the need to build automated contact tracing services and expand the investment to develop new rapid tests including immunity testing for antibodies is moving forward. The next phase of the pandemic may require the conduction of mass screening at the community level to better understand and hence manage the pandemic. The key questions here are can these be accomplished via the current health system and are our current health systems resilient enough to accommodate the new changes?

Public Health Services

The goal of all countries is to suppress the transmission of COVID-19 and provide care for all patients [23]. The COVID-19 pandemic has compromised the delivery of essential health services in various countries [27]. For example, the countries of the Eastern Mediterranean Region are challenged with the COVID-19 response, mainly in information sharing, expanding public health measures, protecting health workers, achieving behavior change, ensuring continuity of essential health services, and establishing reliable supply chains [28].

More efforts will be needed to develop and update the National Health Emergency Preparedness and Response Plan. Hospitals were overwhelmed and could not cope with the pandemic in most countries, including Western countries. Rethinking the role of hospitals and other institutions as hubs for care is required.

Many health systems collapsed due to a lack of the required competencies or due to the exhaustion of the working staff. More investment in PHC and shifting in the point of care, such as testing of common infectious diseases and on measures to prevent the spread of infections, are needed [17]. An appropriate mix of good quality hospitals, PHC services, and public health might be considered. A focus on sustainable service delivery is highly needed for bringing health care to patients, to eliminate doctor-patient visits whenever possible, for increasing the use of telemedicine, for manufacturing health commodities, and for strengthening supply chains [10]. PHC services near people's homes are so important and can be lifesaving. Improving access to vaccinations, screening, education, counseling, and supporting access to treatment are all essential [20]. The health systems are expected to focus on sustainable service delivery, with a significant increase in investment in emergency preparedness to cover the manufacture of health commodities and strengthen supply chains. Patrick Fine expects that health access and the role of social enterprise will be expanded. Among the expected changes in the provision of health services is that more basic services will be assigned for the community health workers to shorten the time of delivery [29]. Health tourism will abate, and instead, doctors are expected to fly to needy countries. Health insurance is expected to cover less and cost more [30].

Some forgotten or undermined health services like mental health and occupational health may see increasing attention [30]. During this pandemic, people were mentally suppressed, and the stigma associated with this disease created another mental crisis. COVID-19 will have a lasting impact on many people's mental health and well-being. To support people's recovery and resilience, public mental health and statutory mental health services, alongside the community welfare sector, will need to be resourced to meet increased demand and maintain a focus on vital preventative work.

On the other hand, public health laboratories play a vital role in protecting the health of people from emerging health threats. During a brief period of a few months, several public health labs have been established, all fully functional, properly equipped, and ably manned. This has again resulted in the strengthening of the lab capacity and health system. Further strengthening and digital linkage of this laboratory network will serve as a mechanism for laboratory-based surveillance of diseases other than COVID-19 as well. Therefore, the health system is expected to be well equipped to handle epidemics of any scale in the future.

Clearly defined legal powers and enforced public health law are needed to respond to outbreaks of contagious and serious diseases at the national level. To achieve this objective, countries need to update and refine their public health laws. This will ensure minimizing the transmission of infectious diseases. Besides, it is recommended to ensure the clarity of roles, relationships, and coordination mechanisms in health system governance and across governments.

Public Health Education and Priority Training

During the pandemic, health professionals across the health care system have worked tirelessly in the most challenging circumstances. The workforces have been a significant challenge that was observed during the response to COVID-19 [20]. Responding to the COVID-19 pandemic required an increase in the number of workforces [31]. Many health systems collapsed due to a lack of the required competencies or due to the exhaustion of the working staff. The COVID-19 pandemic could inspire young people to choose careers in public health. According to the Council for Public Health Education, to meet this increasing demand, there is a need for specialized training as part of professional development to ensure readiness for future similar challenges [32].

Medical and health curricula need to be updated and enriched to meet the emerging changes and needs in public health, both the core competencies as well as leadership and management skills. This is to be at the levels of undergraduate, postgraduate, and professional training. Distance training and e-learning become a necessity, and institutes and training providers must consider these modalities in their plans.

A good example of such specialized, on the job training for professionals is the Field Epidemiology Training Program. In fact, the aim of the Field Epidemiology Training Program is to improve the epidemiologic capacity of a country's public health workforce to detect and respond to health threats [33]. Hence more resources are to be allocated for establishing new Field Epidemiology Training Programs and strengthening the existing programs, with special focus on the frontline and intermediate levels. Hopefully, the pandemic will bring more respect and remuneration to health professionals, and health as a profession will be considered a high-risk job, and laws and regulations will need to be revisited.

Risk Communication

It was a challenge to advocate to the public and even the professionals on the importance of public health activities. Because of the COVID-19 pandemic, people, including decision makers, are now more open and receptive to the importance of *public health*. This momentum is needed to advocate more for public health agenda and adopt prohealth policies and secure more funding [27].

During the COVID-19 pandemic, health systems were challenged by a surplus of information. Some information was false and potentially harmful. Besides, the inaccuracy of the information and its fast distribution through various media channels made it more difficult for people to identify verified facts and advice from trusted sources. Misinformation rumors regarding COVID-19 become a substantial problem in epidemic responses [34]. Robust efforts were seen by the countries in this regard both in terms of a legal framework and an effective risk communication mechanism. Public awareness during the pandemic was ensured with the active involvement of print and electronic media and through community engagement programs. Many lessons were learned that will translate to improving the risk communication strategies and approaches for future pandemics.

Public health and social measures includes personal protective measures, environmental measures, physical distancing measures, and travel-related measures. These will continue and become more necessary [30]. There is a need to make good use of all community resources in future efforts [31]. Community health workers can play a role in community-based COVID-19 emergency response teams [29]. The public can be enabled to take part in the implementation of public health and social measures. Health education and health messages played a crucial role in controlling COVID-19. The public is used to relying on governments to provide advice and protect their well-being. However, many websites (official and informal), hotlines, webinars, and social media have been increasingly used by the public during the COVID-19 pandemic to get updated news and messages. This trend in relying more on community-based communication is expected to continue and become the default for future events [10].

Research and Innovative Public Health Solutions

Thousands of research articles have been published since the start of the COVID-19 pandemic. This is expected to grow especially with the research work that depends on big data. The Global Research Forum developed an initial COVID-19 Global Research Roadmap to guide a united COVID-19 agenda for research and development. Other funding opportunities are already there, and more are expected to come. The main areas for future research on COVID-19 could be research to support policy making and provide evidence-based solutions [19]; medical and technological research; and innovation to accelerate the production of the vaccines and treatments, tests, and equipment. Besides, expansion is expected in the use of technology to develop new tools to assist in executing public health functions (eg, surveillance functions, electronic and mobile phone–based data collection, and dashboards for logistic management systems) [10]. On the other hand, diagnostics based on artificial intelligence, cloud-based storage of medical records, integration of information in and outside the hospitals, and increased use of robotics have already been introduced to the health services [20]. Those will come under the bigger umbrella of telehealth and telemedicine [30]. Telehealth services were not new for developed communities, but its use was limited. Internet and Android apps increased the use of telehealth.

Different interventions and measures have been applied by various countries to respond to and control the COVID-19 pandemic. However, many questions were raised on the efficacy of those interventions and measures and how transparent they were. One can expect the need for evaluation studies to answer those questions and others like the accountability of the emergency operations and projects, COVID-19–related vaccination assessment, and social consequences and economic costs of public health and social measures.

Distant working becomes a reality with more use of technology like teleconferencing and videoconferencing systems, which requires confidence in digital security. Health "Immunity" Passports are expected to become mandatory for travel besides other measures like e-tickets, e-queuing, spacing, masks and gloves, and on-site testing [20].

Conclusion

Many countries applied various public health and social measures to prevent and control the spread of the disease. The pandemic highlighted the need for better governance and stronger health systems and capacities. It is recommended to consider shifting the paradigm toward public health and preventive medicine. In addition, the COVID-19 pandemic has shed light on the importance of coordination and collaboration among countries and stakeholders in different multilateral and global initiatives.

More efforts will be needed to encourage research and the use of technology to support policy making and provide evidence-based solutions. As health workforces show their crucial roles in managing public health emergencies like the COVID-19 pandemic, more efforts are needed to build their capacities and provide them with better working environments and motivating policies.

Following COVID-19, one can expect many changes in our daily life and activities. Although we are not sure about the *new normal* after COVID-19, we are sure about the fact that our lives and public health will not be the same as before. For agencies, systems, and individuals to survive after COVID-19, they must be resilient enough to cope with any expected changes.

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Conflicts of Interest

None declared.

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Abbreviations

MOH: ministries of health
NGO: nongovernmental organization
PHC: primary health care
RRT: rapid response team
SDG: Sustainable Development Goal
WHO: World Health Organization

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Original Paper

Epidemiology of Diphtheria in Yemen, 2017-2018: Surveillance Data Analysis

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Abstract

Background: As a consequence of war and the collapse of the health system in Yemen, which prevented many people from accessing health facilities to obtain primary health care, vaccination coverage was affected, leading to a deadly diphtheria epidemic at the end of 2017.

Objective: This study aimed to describe the epidemiology of diphtheria in Yemen and determine its incidence and case fatality rate.

Methods: Data were obtained from the diphtheria surveillance program 2017-2018, using case definitions of the World Health Organization. A probable case was defined as a case involving a person having laryngitis, pharyngitis, or tonsillitis and an adherent membrane of the tonsils, pharynx, and/or nose. A confirmed case was defined as a probable case that was laboratory confirmed or linked epidemiologically to a laboratory-confirmed case. Data from the Central Statistical Organization was used to calculate the incidence per 100,000 population. A *P* value <.05 was considered significant.

Results: A total of 2243 cases were reported during the period between July 2017 and August 2018. About 49% (1090/2243, 48.6%) of the cases were males. About 44% (978/2243, 43.6%) of the cases involved children aged 5 to 15 years. Respiratory tract infection was the predominant symptom (2044/2243, 91.1%), followed by pseudomembrane (1822/2243, 81.2%). Based on the vaccination status, the percentages of partially vaccinated, vaccinated, unvaccinated, and unknown status patients were 6.6% (148/2243), 30.8% (690/2243), 48.6% (10902243), and 14.0% (315/2243), respectively. The overall incidence of diphtheria was 8 per 100,000 population. The highest incidence was among the age group <15 years (11 per 100,000 population), and the lowest incidence was among the age group ≥15 years (5 per 100,000 population). The overall case fatality rate among all age groups was 5%, and it was higher (10%) in the age group <5 years. Five governorates that were difficult to access (Raymah, Abyan, Sa'ada, Lahj, and Al Jawf) had a very high case fatality rate (22%).

Conclusions: Diphtheria affected a large number of people in Yemen in 2017-2018. The majority of patients were partially or not vaccinated. Children aged ≤15 years were more affected, with higher fatality among children aged <5 years. Five governorates that were difficult to access had a case fatality rate twice that of the World Health Organization estimate (5%-10%). To control the diphtheria epidemic in Yemen, it is recommended to increase routine vaccination coverage and booster immunizations, increase public health awareness toward diphtheria, and strengthen the surveillance system for early detection and immediate response.

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KEYWORDS

diphtheria; epidemiology; incidence; case fatality rate

Introduction

Diphtheria is an acute bacterial disease caused by *Corynebacterium diphtheria* and presents most commonly as a membranous pharyngitis. Symptoms occur after an incubation period of 2 to 5 days [1]. The organism produces a toxin that causes necrosis of the tissues, leading to respiratory obstruction, heart failure, and death. Diphtheria was one of the most common causes of morbidity and mortality among children in the prevaccine era. The mortality rate associated with diphtheria was as high as 50% but dropped to about 15% after widespread use of diphtheria antitoxin treatment [2].

Throughout history, diphtheria has remained one of the most frightening infectious diseases globally, causing overwhelming epidemics with high case fatality rates and mainly affecting children. However, most cases in outbreaks, such as the large outbreak in the Russian Federation in the 1990s [3], and cases reported in the United States since 1980 involved individuals aged 15 years or older [4]. Individuals, particularly children, who are not vaccinated or are partially vaccinated are at risk of diphtheria. Moreover, adults are at high risk as immunity due to vaccination wanes over time [2].

After the introduction of the diphtheria vaccine in the United Kingdom and subsequently worldwide in the 1940s to 1950s [5], diphtheria was practically eliminated, and it became an uncommon disease worldwide. However, diphtheria remains an important health problem in countries with poor routine vaccination coverage. There is global concern that diphtheria is re-emerging. Several outbreaks of diphtheria have been reported from Eastern Europe [6], Southeast Asia, South America [7], and North Africa [8]. In countries of the Eastern Mediterranean Region (EMR), diphtheria continues to occur in the form of localized outbreaks. In 2017, 600 cases of diphtheria were reported in the countries of the EMR, including Islamic Republic of Iran (two cases), Iraq (two cases), Pakistan (560 cases), Sudan (two cases), Qatar (two cases), Afghanistan (one case), Saudi Arabia (one case), and Yemen (30 cases) [9].

In Yemen, the Expanded Program on Immunization (EPI) was established in 1977. The strategy for EPI was to reach 90% coverage at the national level for Penta-3. Although vaccines for major vaccine-preventable diseases are available free for the public under the EPI, vaccine-preventable diseases still cause nearly one-third of the total deaths among Yemeni children under 5 years of age. Before the conflict that began in late 2014, Yemen had a stable vaccination coverage reaching 70% to 80% of the target population; however, this significantly dropped after the war [10]. Vaccine-preventable diseases, such as measles, cholera, and diphtheria, saw a sudden surge after the beginning of the war [10]. Many sporadic outbreaks of diphtheria from different parts of the country were observed. Lately, in October 2017, a diphtheria outbreak occurred in Yareem district in Ibb governorate, and 11 cases were reported with a case fatality rate (CFR) of 27% [11].

The Diphtheria Containment Program was established in February 2018 as a response to the re-emergence of diphtheria in Yemen. Diphtheria mortality- and morbidity-related data are collected daily from health facilities using a case investigation form (Multimedia Appendix 1), which includes information on demographics, clinical signs and symptoms, outcomes, laboratory data, vaccination status, and case management. The recent diphtheria epidemic in Yemen has highlighted the need for diphtheria surveillance data analysis to be used to provide information, such case fatality, vaccination status, age-specific incidence rate, geographical area, and risk groups, for further epidemic preparedness. This study aimed to describe the epidemiology of diphtheria and determine its incidence and CFR.

Methods

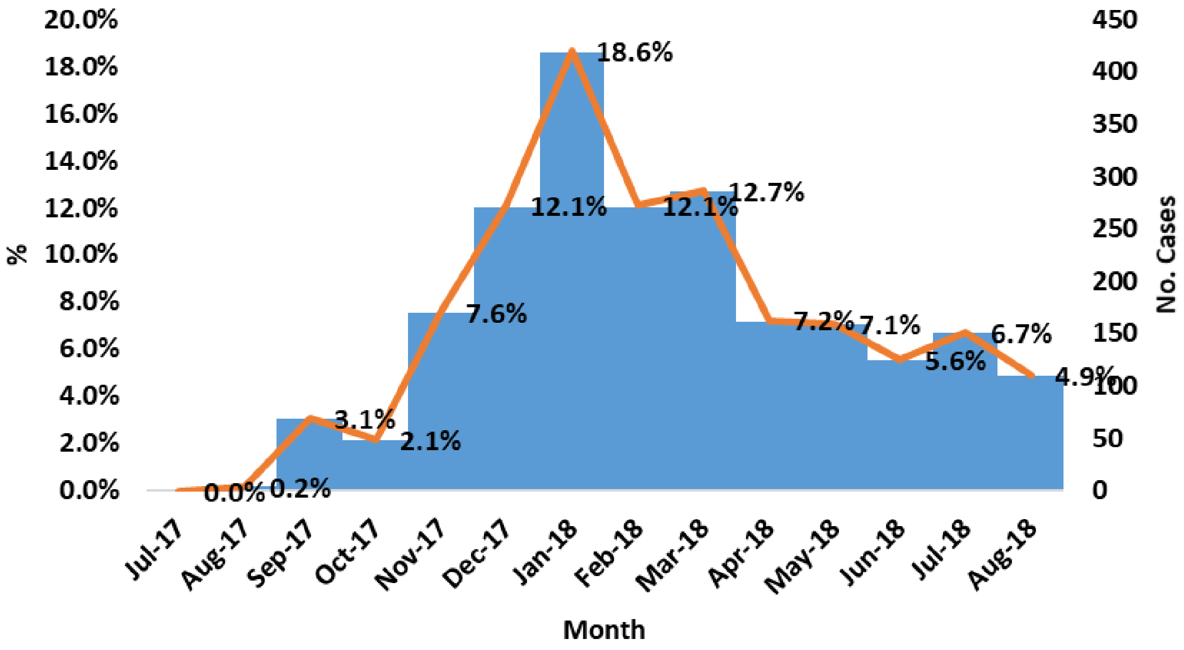
Data of patients with diphtheria were obtained from the diphtheria program in the form of a line list that was collected daily by the electronic Diseases Early Warning System. A probable case was defined as a case involving a person having laryngitis, pharyngitis, or tonsillitis and an adherent membrane of the tonsils, pharynx, and/or nose. A confirmed case was defined as a probable case that was laboratory confirmed or linked epidemiologically to a laboratory-confirmed case [12]. Data were reviewed and cleaned. For calculations of incidence rate, we used the population at risk from the Central Statistics Organization. Surveillance data were analyzed using Epi Info (Centers for Disease Control and Prevention) and Excel 2013 (Microsoft Corp). Data were described using simple descriptive methods, rate calculations, and graphs.

Results

Case Characteristics

A total of 2243 cases were reported during the period between July 2017 and August 2018. The number of cases gradually increased from July 2017, with the peak occurring in January 2018, and then decreased until August 2018 (Figure 1). About 49% (1090/2243, 48.6%) of the cases involved males and 51% (1153/2243, 51.4%) involved females. About 44% (978/2243, 43.6%) of the cases involved children aged 5 to 15 years. Diphtheria cases were reported from 215 districts in 20 governorates. Respiratory tract infection was the predominant symptom (2044/2243, 91.1%), followed by pseudomembrane (1822/2243, 81.2%).

Figure 1. The distribution of 2243 diphtheria cases reported during the period from July 2017 to August 2018 in Yemen.



Vaccination Status

Based on the vaccination status, the percentages of partially vaccinated, vaccinated, unvaccinated, and unknown status patients were 6.6% (148/2243), 30.8% (690/2243), 48.6% (10902243), and 14.0% (315/2243), respectively. Zero dose reporting gradually increased by age from 35% in age group <5 years to 74% in age group >45 years, while three doses of the vaccine decreased gradually with age.

Diphtheria Incidence Rate and the CFR

Table 1 shows the incidence rate of diphtheria per 100,000 population by age group and governorate. Table 2 shows the CFR. The overall incidence of diphtheria was 8 per 100,000 population at affected areas. The highest incidence was among the age group <15 years (11 per 100,000) and the lowest incidence was among the age group ≥15 years (5 per 100,000). The incidence rate varied widely across governorates. The highest incidence rate (20 per 100,000 population) was in Al Dhale’e, Ibb, and Sana’a, while the lowest incidence rate (7 per 100,000 population) was in other (n=17) governorates. The overall CFR among all age groups was 5%, and it was higher (10%) in the age group <5 years. The CFR was higher (22%) in difficult access governorates, including Raymah, Abyan, Lahj, Al Jawf, and Sa’adah.

Table 1. Diphtheria incidence by age and governorate in Yemen from 2017 to 2018.

Characteristic	Population (N=28,384,959)	Number of cases (N=2243)	Incidence (per 100,000 population)	*P* value
Age (years)				<.001
<15	12,688,111	1390	11	
15-35	9,836,674	681	7	
>35	5,860,174	172	3	
Governorates				<.001
Three governorates[a]	4,880,845	968	20	
Others (n=17)	23,504,114	1275	7	

[a] Al Dhale’e, Ibb, and Sana’a.

Table 2. Diphtheria case fatality rate by age and governorate in Yemen from 2017 to 2018.

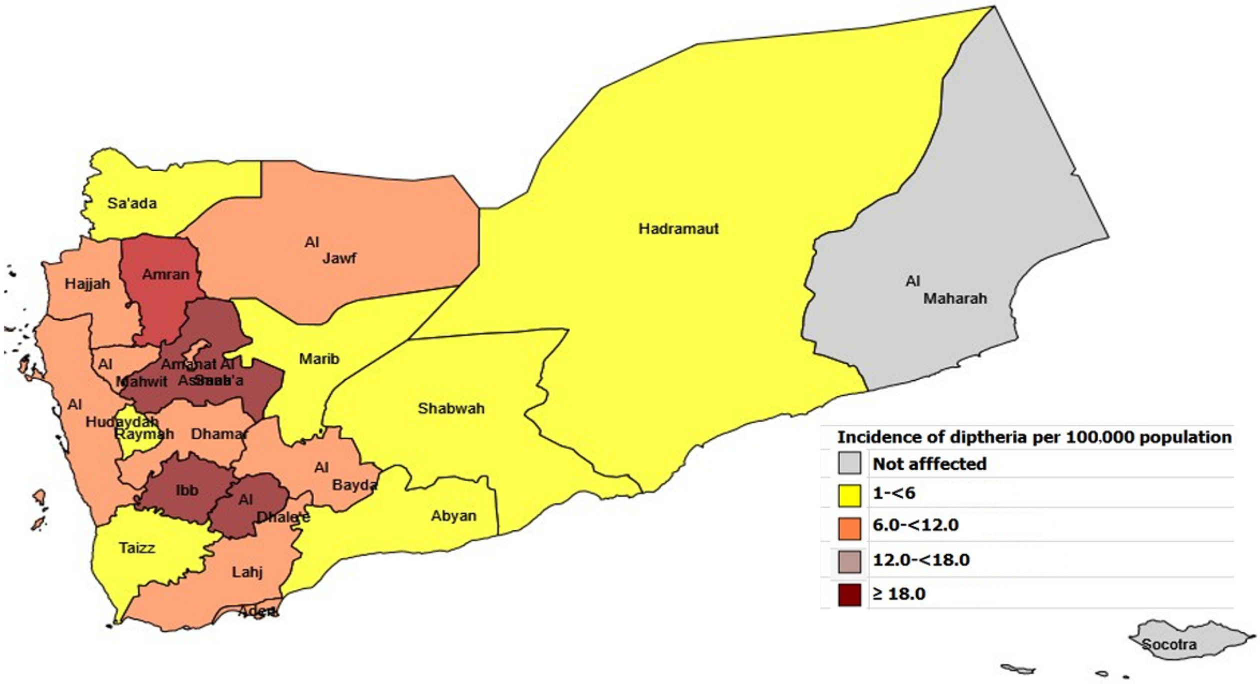
Characteristic	Number of cases (N=2243)	Number of deaths (N=120)	Case fatality rate	*P* value
Age (years)				<.001
<5	413	42	10%	
≥5	1830	78	4%	
Governorate				<.001
Difficult access[a]	92	20	22%	
Normal access	2151	100	10%	

[b] Raymah, Abyan, Sa'ada, Lahj, and Al Jawf.

Incidence Rate of Diphtheria by Place

Figure 2 provides a heat map showing that the incidence rate of diphtheria varied widely across governorates. The incidence shows that there was an increase in the number of diphtheria cases, with the highest rate of ≥18 per 100,000 population in Al Dhale'e, Ibb, and Sana'a, and the lowest rate of <6 per 100,000 population in Raymah, Shabwah, Taizz, and Abyan (Figure 2).

Figure 2. Incidence rate of diphtheria across governorates in Yemen.



Discussion

Principal Findings

Diphtheria has re-emerged after more than 30 years, and this has led to a huge public health concern in Yemen, which has a poor health system, low coverage of diphtheria vaccination, a low socioeconomic status, and population migration. Diphtheria has re-emerged as a deadly epidemic since the end of 2017. Our findings showed a notable rise in the number of diphtheria cases during the months between October 2017 and January 2018, which are considered winter months. This finding is consistent with the findings of previous studies in Yemen and Indonesia [11,13,14]. A decline in the cases after the peak started in February and continued until August 2018. This decline might be due to control of the spread as a result of vaccination campaigns that were implemented in February and May of 2018.

In terms of age distribution, previous reviews reported a shift in the age group affected by diphtheria to older children and adults [15,16], and this is similar to our finding that the age group 5-15 years was the most affected. However, this finding is not consistent with the findings of a previous study in Yemen [13], which found that children aged <5 years were more affected. This might be related to the immunization status of the population as well as the changing socioeconomic conditions in a given area [16].

Diphtheria outbreaks often occur because of low childhood vaccination, as well as lack of booster vaccinations for older children and adults [17]. This supports our findings that most affected cases were unvaccinated, which is consistent with the findings of previous studies in India and Indonesia reporting that mortality occurred in more than 70% of patients who did not receive complete immunization [14,18]. Our study confirms that raising immunity levels in the population through vaccination remains a critical tool for diphtheria control.

The incidence rate and CFR varied across governorates. This might be due to the variation of reporting. For example, Aden reported cases from all its districts, while Hadaramout reported cases from 7% of its districts. Improving reporting in all governorates will help in providing a complete picture of the epidemiology of diphtheria. The overall CFR was 5%, which is similar to the estimate reported in a previous study from India [19]. This estimation falls in the World Health Organization (WHO) reported range of 5% to 10%. However, five governorates that were difficult to access had a CFR twice that of the WHO estimate.

Conclusion

Diphtheria affected a large number of people in Yemen in 2017-2018. The majority of patients were partially vaccinated or not vaccinated. Children aged ≤15 years were more affected, with higher fatality among children aged <5 years. Five governorates that were difficult to access had a CFR twice that of the WHO estimate. To control the diphtheria epidemic in Yemen, it is recommended to increase routine vaccination coverage and booster immunizations, and strengthen the surveillance system for early detection and immediate response.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Diphtheria investigation form.
[PNG File , 227 KB - publichealth_v7i6e27590_app1.png]

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Abbreviations

CFR: case fatality rate
EMR: Eastern Mediterranean Region
EPI: Expanded Program on Immunization
WHO: World Health Organization

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Original Paper

The Rotavirus Surveillance System in Yemen: Evaluation Study

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Abstract

Background: Rotavirus (RV) kills over 185,000 children <5 years every year and is responsible for over one-third of all child diarrheal deaths worldwide. The Rotavirus Surveillance System (RVSS) in Yemen was launched in 2007 at five sentinel sites to monitor the impact of the vaccine on RV morbidity and mortality.

Objective: This study aimed to determine the usefulness of the RVSS, assess its performance, and identify the strengths and weaknesses of its implementation.

Methods: The Centers for Disease Control and Prevention’s updated guidelines on evaluating a public health surveillance system were used to evaluate the RVSS. In this assessment, qualitative indicators, such as usefulness, flexibility, stability, simplicity, and acceptability, were assessed through in-depth interviews with stakeholders at the central level and semistructured questionnaires with the sentinel site coordinators. The indicators for quantitative attributes—sensitivity, positive predictive value (PPV), completeness, and timeliness—were assessed by reviewing the results of laboratory samples and a random sample of case report forms. The scores for the indicators were expressed as poor (<60%), average (60% to <80%), and good (≥80%).

Results: The overall usefulness score of the RVSS was 73%, indicating an average rank. The RVSS was rated as having good flexibility (91%) and stability (81%), and average simplicity (77%) and acceptability (76%). In terms of quantitative attributes, the system was poor for sensitivity (16%), average for PPV (73%), and good for completeness (100%) and timeliness (100%).

Conclusions: Although the system attributes were flexible, stable, capable of providing quality data, and performing timely data reporting, some attributes still needed improvements (eg, usefulness, simplicity, acceptability, and PPV). There is a need for a gradual replacement of donor funds with government funds to ensure sustainability. The RVSS in Yemen strongly requires a progressive increase in the number of sites in governorates and sensitivity enhancement.

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KEYWORDS

Rotavirus; surveillance system; evaluation, Yemen

Introduction

Rotavirus (RV) is the major cause of vaccine-preventable severe and fatal diarrhea among young children [1]. Infection can be asymptomatic, cause mild to moderate gastroenteritis, or severe gastroenteritis with dehydration requiring hospitalization [2]. Recovery from a first RV infection usually does not lead to permanent immunity, and reinfection can occur at any age but with less severity than the first. The World Health Organization (WHO) identified an RV vaccine as the key strategy in reducing the RV-diarrhea burden. The monovalent (RV1) Rotarix and the pentavalent (RV5) Rota Teg are two safe and effective oral vaccines against RV infection in children [3].

Globally, nearly every child in the world gets infected with RV between 3 and 5 years of age. However, the highest rates of severe disease occur commonly at the age of 6 to 24 months [3,4]. Studies in the Eastern Mediterranean Region (EMR) have estimated approximately 65,000 child deaths each year due to RV infection. Mortality remains high in this region, especially in countries with a lower per capita income, such as Pakistan, Afghanistan, Sudan, Yemen, and Somalia [5]. The countries with a higher per capita income have few deaths, but the burden of severe RV disease is reflected in the many hospitalizations and clinic visits among children <5 years of age [5].

Yemen is a resource-limited country with acute gastroenteritis–related morbidity and mortality as the major health problem. The Ministry of Public Health and Population (MoPH&P) had introduced the RV vaccine into the routine immunization schedule in 2012. The vaccine is administered in two doses: the first dose is administrated at 6 weeks of age, and the second dose is completed by 10 weeks of age [6]. The introduction of the RV vaccine helped to decrease the burden of severe RV gastroenteritis and RV-associated mortality [7]. The RV hospitalization incidences in Yemen decreased from 43.8% in 2009 to 10.5% in 2014 [7].

The Rotavirus Surveillance System (RVSS) was launched in 2007 at five sentinel sites to monitor the impact of the vaccine on RV morbidity and mortality. The RVSS has never been evaluated before in Yemen. Therefore, this study aimed to determine the usefulness and performance of the RVSS, and identify the strengths and weaknesses of the system implementation.

Methods

Evaluation Design

The Centers for Disease Control and Prevention’s (CDC) updated guidelines on evaluating a public health surveillance system were used to evaluate the RVSS [8]. In this assessment, qualitative indicators of usefulness and other attributes of the system (eg, flexibility, stability, simplicity, and acceptability) were assessed through in-depth interviews with stakeholders at the central level, and semistructured questionnaires were used with the sentinel site coordinators. Furthermore, the indicators for quantitative attributes such as sensitivity, positive predictive value (PPV), completeness, and timeliness were assessed by reviewing the results of laboratory samples and a random sample review of case report forms. All the five sentinel sites covered by the RVSS (Yemen Swedish Hospital in Taiz, Al Wahda General Teaching Hospital in Aden, Al Sabeen Maternal Hospital in Sana’a, Al-Thawra Hospital in Ibb, and Al-Thawra Hospital in Al Hudaydah) were included and established for qualitative evaluation. The RVSS evaluation was conducted from October to December 2018.

Evaluation Approach

The RVSS stakeholders at the central level and the sentinel site coordinators were included in this study. Different data collection methods were used, such as a desk review of the RVSS documents, in-depth interviews with stakeholders at the central level, and semistructured questionnaires with the sentinel site coordinators. The evaluation involved reviewing the available documents such as operational manuals, monthly and annual reports, and databases. The documents were reviewed before interviewing the stakeholders to obtain information about the RVSS. Seven in-depth interviews were conducted with the stakeholders at the central levels to understand the RVSS implementation, as well as its usefulness, flexibility, stability, and strengths and weaknesses. The indicators for usefulness and other qualitative attributes were developed according to the CDC guidelines. A registers review was used to assess the quantitative attributes (sensitivity, PPV, completeness, and timeliness).

The indicators of attributes (usefulness, flexibility, and stability of the system) were assessed using questions with “yes” or “no” answers that were scored as 1 or 0, respectively. The level of simplicity and acceptability of the system was assessed on a 5-point Likert scale (1=strongly disagree, 2=disagree, 3=neutral, 4=agree, and 5=strongly agree).

For each indicator, the score percent was calculated as:

The overall attribute score percent was calculated as:

The sensitivity of the system was assessed by the proportion of stool samples of the suspected cases of RV gastroenteritis that tested positive for RV. The PPV was calculated as the proportion of the positive RV stool samples reported by the sentinel sites that tested positive at the National Central Public Health Laboratory (NCPHL). Timeliness was measured as the proportion of reports sent to the central level by the deadline. Missing data were measured by selecting the 1-year data and calculating the percentages of the missed variables. The data accuracy was assessed by comparing reports at the central level with the case report form. The ranking and scoring system used for the quantitative and qualitative attributes, as well as for the indicators of each attribute, were as follows: poor (<60%) average (60% to <80%), and good (≥80%).

Ethical Approval

The ethical review committee of MoPH&P advised that ethical approval for this evaluation protocol was not needed as it was part of the ongoing national evaluation activity. The stakeholders at the central level and the sentinel site coordinators were explained the aim of the study and were requested to participate. If they agreed, either an interview was conducted or a semistructured questionnaire was administered. Confidentiality of the collected data was maintained by limiting access to the research team only.

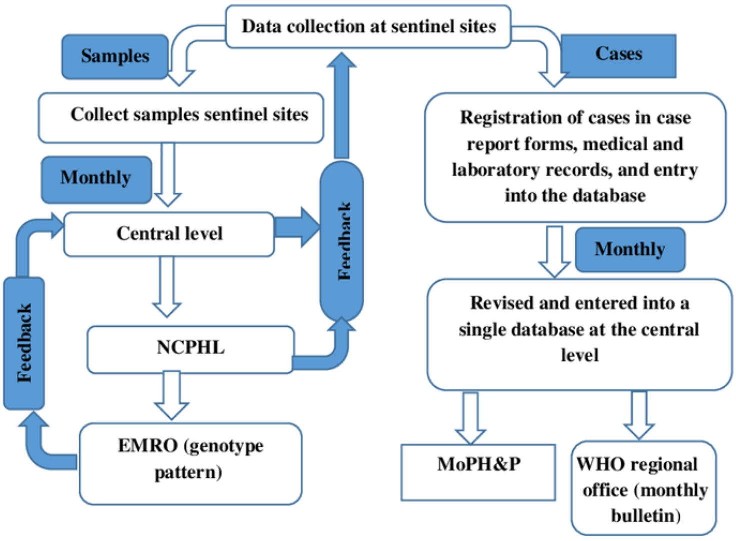
Results

Description of the RVSS

The MoPH&P established the RVSS in 2007 with technical and financial support from the WHO. After the RV vaccines were introduced in Yemen in 2012, the objectives of the RVSS were updated to include assessments of the vaccine impact on RV morbidity and mortality among children <5 years, as well as changes in RV epidemiology and circulating strains, and provide a basis for further epidemiologic research.

The RVSS required collecting data on individual cases of diarrhea among children <5 years of age. It was the active surveillance at the five sentinel sites. The potential data sources included inpatients in the Department of Pediatrics, the Emergency Department, and the Diarrhea Treatment Centers. A suspected case was a case with an acute (<14 days) watery diarrhea, defined as 3 or more loose or watery stools within a 24-hour period in a child <5 years of age admitted for diarrhea treatment into the hospital ward or the emergency unit at the sentinel sites. Children with bloody diarrhea and nosocomial infections were excluded. A confirmed case was a suspected case with the presence of RV in its stool confirmed by an enzyme immunoassay (EIA) or polymerase chain reaction (PCR)–based methods. Figure 1 shows the RVSS data collection flow chart.

Figure 1. Flow chart for RVSS data collection methods employed in phases 1 and 2. CDC: Centers for Disease Control and Prevention, EMRO: Regional Office for the Eastern Mediterranean, MoPH&P: Ministry of Public Health and Population, NCPHL: National Central Public Health Laboratory, RVSS: Rotavirus Surveillance System, WHO: World Health Organization.



In-depth Interviews With Stakeholders at the Central Level

Usefulness

Table 1 highlights that 5 out of 8 usefulness indicators achieved a good rank, while 2 indicators, development of the national policy strategy for the national immunization program and estimation of the RV magnitude, incidence, and mortality, achieved a poor rank. Another indicator, planning the resources, achieved an average rank. The overall usefulness indicated an average rank (n=41, 73%).

Table 1. The scores (score percent, %) and rank of the usefulness indicators as assessed by the central-level stakeholders.

Indicator	Score (%)	Rank
The system data provide an estimate of rotavirus magnitude, incidence, and mortality	2 (29)	Poor
The system data detect trends of rotavirus spread over time	7 (100)	Good
The system data recognize high-risk groups	7 (100)	Good
The system data plan the resources for prevention and control	5 (71)	Average
The system data update and develop the national policy strategy for the national immunization program	2 (29)	Poor
The system data assess the effect of interventions	6 (86)	Good
The system data estimate the needs of laboratory kits	6 (86)	Good
The system data are used as the basis for epidemiologic research	6 (86)	Good
Overall usefulness	41 (73)	Average

Flexibility

Table 2 shows that 5 out of 6 flexibility indicators achieved a good rank, while the indicator, "The system can accommodate any changes in funding," was ranked poor. The overall flexibility achieved a good rank (n=38, 91%).

Table 2. The scores (score percent, %) and rank of the flexibility indicators as assessed by the central-level stakeholders.

Indicator	Score (%)	Rank
The system can accommodate changes in the number of sentinel sites	7 (100)	Good
The system can accommodate any changes in funding	4 (57)	Poor
The system can accommodate changes in case definition	7 (100)	Good
The system can accommodate changes in reporting method	7 (100)	Good
The system can be adapted to integrate with other surveillance systems	6 (86)	Good
The system can accommodate changes in data with minimum cost and efforts	7 (100)	Good
Overall flexibility	38 (91)	Good

Stability

The study showed that 4 out of the 6 stability indicators achieved a good rank (Table 3). However, 2 indicators, the availability of planned resources for maintenance and the sustainability of the system if donors withdrew their support, achieved a poor rank. The overall stability ranked good (n=34, 81%).

Table 3. The scores (score percent, %) and rank of the stability indicators as assessed by the central-level stakeholders.

Indicator	Score (%)	Rank
No unscheduled system outages occurred during the last month	7 (100)	Good
No electrical power outage occurred during the last week	6 (86)	Good
There are planned resources for the maintenance of the system	4 (57)	Poor
The system is stable even after the sponsor's withdrawal of support	3 (43)	Poor
The system does not require time to manage data	7 (100)	Good
Reports are released regularly	7 (100)	Good
Overall stability	34 (81)	Good

Strengths and Weaknesses

The majority of stakeholders (n=6, 86%) reported the presence of a qualified medical team at the central and terminal levels as one of the strengths of the RVSS. Around half (n=4, 57%) respondents said the accuracy of data as an important strength:

Another strength was the continuity of data flow to the central level.

Regarding the weaknesses in the RVSS, all stakeholders said that a lack of financial support from the government and total dependence on the WHO for support were the major weaknesses of the system. The small number of surveillance sites was another reported weakness. One participant said:

Other weaknesses included delays in sending the feedback about the samples' results by the WHO Regional Office for the Eastern Mediterranean (WHO EMRO), lack of laboratory kits, and poor utilization of research findings.

Semistructured Questionnaire With the Sentinel Site Coordinators

The five sentinel site coordinators (all were females) responded to the semistructured questionnaire.

Simplicity

Table 4 shows that 8 out of 10 simplicity indicators (eg, case definition is available and easy to use, less time spent on collecting data, etc) achieved a good rank, while 2 indicators, the availability of laboratory tests and training, achieved a poor rank, and the overall simplicity was ranked average (n=193, 77%).

Table 4. The scores (score percent, %) and rank of the simplicity indicators as assessed by the sentinel site coordinators.

Indicator	Score (%)	Rank
The rotavirus case definition is available	25 (100)	Good
The rotavirus case definition is easy to use	24 (96)	Good
The case report form is available	24 (96)	Good
The case report form is easy to use	24 (96)	Good
Less time spent on collecting data	20 (80)	Good
Transmitting data to the enteral level is easy	22 (88)	Good
Follow-up of cases is easy	20 (80)	Good
Laboratory tests available in the health facility to confirm a diagnosis	5 (20)	Poor
You received training for rotavirus surveillance	22 (88)	Good
Training courses are conducted frequently	7 (28)	Poor
Overall simplicity	193 (77)	Average

Acceptability

Table 5 displays the 4 acceptability indicators used in the study. It was found that the indicators willingness to participate in the RVSS and responsiveness of the system to suggestions achieved a good rank. However, satisfaction with the RVSS and receiving feedback from the central level achieved average and poor ranks, respectively. The overall acceptability achieved an average rank (n=76, 76%).

Table 5. The scores (score percent, %) and rank of the acceptability indicators as assessed by the sentinel site coordinators.

Indicator	Score (%)	Rank
You are willing to participate in the Rotavirus Surveillance System	24 (96)	Good
You are satisfied with the surveillance system	17 (68)	Average
Received feedback report from the central level	12 (48)	Poor
Responsiveness of the system to suggestions	23 (92)	Good
Overall acceptability	76 (76)	Average

Assessment of Quantitative Attributes: Sensitivity, PPV, Completeness, and Timeliness

Of the 1787 cases suspected of having RV gastroenteritis at the sentinel sites, 1542 had their stool samples tested. Of the total cases tested for the stool samples, only 16% (n=244) samples tested positive for RV, indicating poor sensitivity. However, for PPV, about 73% (n=178) of the positive RV stool samples reported by the sentinel site tested positive at the NCPHL.

There were no missing variables when a random sample of 30 case report forms was reviewed. These forms were found to be consistent with the database. Therefore, completeness was 100% (n=30). All sentinel sites sent their reports by the fifth day of next month. Therefore, timeliness was also 100% (n=5).

Overall Performance of the RVSS

The overall RVSS performance was found to be average (Table 6).

Table 6. Summary of the overall performance of the Rotavirus Surveillance System (RVSS).

Attributes	Score (%)	Rank
Performance according to the central level	113 (81)	Good
Performance according to sentinel sites	269 (77)	Average
Performance of quantitative attributes	215 (57)	Poor
Overall RVSS performance	597 (69)	Average

Discussion

Principal Findings

The RVSS performance evaluation could enhance the usefulness of the surveillance data for public health action. In this evaluation, we assessed the attributes and operation of the RVSS in Yemen using the CDC's updated guidelines [8]. The RVSS data helped estimate the RV severity and provided a basis for epidemiologic research. However, it was reported that the RVSS data were used poorly to update and develop the national policy strategy for the national immunization program in Yemen. In contrast, the Australian Rotavirus Serotyping Program evaluation showed good usefulness of the system [9].

The flexibility of the RVSS was rated as good, and the system appeared to be able to adapt and accommodate new changes such as changes in the RV reporting method (phone reporting) and changes in the case definition. However, the system was found to be considerably donor dependent and could poorly accommodate any changes in funding. These observations were different from the evaluation results of the Australian Rotavirus Serotyping Program, which showed the system to be flexible and able to adapt to the changes [9]. Similarly, the RVSS evaluation in Kenya demonstrated the system to be flexible as it could incorporate new reporting sources [10].

The stability of the RVSS was rated good in this study. Although the system was stable and did not require time to manage the data, the system was considered poorly stable if the donors withdrew their support. The RVSS simplicity was rated average, while the case definition and the surveillance case report forms were reported to be available and easy to use. However, the laboratory tests in the health facility were not available to confirm a diagnosis. A comparison with the systems available in other countries showed that the Kenya RVSS scored better on simplicity [10].

The acceptability of the RVSS was rated as average, reflected by the stakeholders' willingness to participate in the RVSS and the responsiveness of the system to suggestions. However, the stakeholders' satisfaction with the RVSS and receiving feedback from the central level achieved average and poor rankings, respectively. For the last 2 years, the system did not receive any feedback reports from the WHO EMRO laboratories.

The sensitivity of the system was poor as only 16% of stool samples tested positive, which was contrary to a previous evaluation from Australia that found the system sensitive [9]. Moreover, the PPV in this evaluation was 73%, whereas a PPV of 98.5% was reported from the Kenyan RVSS evaluation [10]. Completeness was 100%, which was slightly higher than the results reported in the Kenya RVSS evaluation, where the completeness was 88% [10].

Our evaluation had several limitations. The assessment did not include one of the essential attributes of the system, representativeness, because the system depended on only five sentinel sites in five governorates and did not include the rest of the governorates or health facilities. Furthermore, we could not assess the timeliness regarding the feedback on the samples from the WHO EMRO during the period 2017-2018 because the WHO stopped receiving samples since 2017. Regarding the sensitivity and PPV, our evaluation was based only on the results of the 2017-tested samples. The sensitivity of the 2018 samples was not evaluated because the samples were not tested due to a lack of laboratory kits.

Conclusions

Although the system attributes were flexible, stable, capable of providing quality data, and performing timely data reporting, some attributes still needed improvement (eg, usefulness, simplicity, acceptability, and PPV). The system sustainability requires planning a gradual replacement of donor funds with government funds. Additionally, it is imperative that the NCPHL be upgraded with a RV genotype testing facility and has a scaled-up RVSS with more sites in governorates. There is a greater need for sensitivity enhancement of the RVSS. There is a need to ensure timely feedback from the WHO EMRO on the results of samples. Regular refresher training and feedback for health staff at the sentinel sites are recommended.

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Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
EIA: enzyme immunoassay
EMR: Eastern Mediterranean Region
MoPH&P: Ministry of Public Health and Population
NCPHL: National Central Public Health Laboratory
PCR: polymerase chain reaction
PPV: positive predictive value
RV: Rotavirus
RVSS: Rotavirus Surveillance System
WHO: World Health Organization
WHO EMRO: WHO Regional Office for the Eastern Mediterranean

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Original Paper

Incidence, Trend, and Mortality of Human Exposure to Rabies in Yemen, 2011-2017: Observational Study

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Abstract

Background: Rabies remains a neglected and poorly controlled disease throughout the developing world, particularly in Africa and Asia, where most human rabies deaths occur.

Objective: This study aimed to describe the epidemiology of rabies exposures, its trend, and its geographical distribution in Yemen.

Methods: Cumulative data from a rabies surveillance system for the period 2011-2017 were obtained from the National Rabies Control Program as paper-based annual reports. Data included the number of persons bitten by a suspected rabid animal, their gender and age, and the result of the animal’s laboratory test. Human cases were defined as those exposed to rabies virus bitten by a suspected rabid animal, exposed to a confirmed rabid animal and then received postexposure prophylaxis (PEP), and deaths occurred after exposure to a confirmed rabid animal after having rabies symptoms during 2011-2017.

Results: From 2011 to 2017, a total of 76,049 persons were bitten by a suspected rabid animal. Of these, 21,927 (28.83%) were exposed to positively confirmed rabid animals and then received PEP, and 295 (0.38%) rabies-related deaths occurred. Of all cases with rabies exposure, 50,882 (66.91%) were males. The most affected age group by animal bites (31,816/76,041, 41.84%), positive exposure (8945/21,927, 40.79%), and rabies deaths (143/295, 48.47%) was 5-14 years. Rabies vaccines and immunoglobulins quantities were least available in 2016 and 2017. The annual incidence rate of exposure to animal bites and rabies exposure was 50 and 14 per 100,000, respectively. The annual mortality rate was 2 per 1,000,000. The highest incidence rate of animal bites was in Dhamar (112 per 100,000) and Ibb (94 per 100,000), whereas the highest incidence of exposed cases was in Amanat Al Asimah (40 per 100,000) and Ibb (37 per 100,000). Mortality rate was the highest in Amanat Al Asimah (6 deaths per 1,000,000) followed by Ibb and Dhamar (4 deaths per 1,000,000 in both).

Conclusions: Rabies remains a worrying health problem in Yemen with higher percentage reported among children and males. Targeting school-age populations by education, communication, and information campaigns about preventive measures is strongly recommended. An electronic system should be introduced to improve reporting. It is important to have a sufficient supply of vaccines and immunoglobulins in control units, especially in the at-risk or impacted governorates. Future studies are suggested to determine incidences and risk factors of disease progression.

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KEYWORDS

rabies; incidence; trend; mortality

Introduction

Rabies is a zoonotic progressive neurological infection in humans and other mammals caused by the rabies virus, which belongs to the genus *Lyssavirus* (family: Rhabdoviridae) [1]. Over 99% of rabies cases are caused by bites of rabid dogs [1,2]. Rabies is a fatal disease with 2 clinical manifestations: furious (classical or encephalitic) and paralytic. Furious rabies accounts for nearly 80% of cases [3]. Initial symptoms are similar to those of many other illnesses including fever, headache, and general weakness or discomfort. As the disease progresses, more specific symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, hypersalivation, difficulty swallowing, and hydrophobia. There is no specific treatment for rabies, and as a result, death usually occurs within days of the onset of these symptoms. However, safe and effective animal and human vaccines are widely available for the prevention and control of rabies [3,4].

Rabies is classified as a poverty-related disease that affects disadvantaged populations with the vast majority of cases being reported in children under the age of 15 years [3]. Rabies remains a neglected disease and is poorly controlled throughout the developing world, particularly in Africa and Asia, where most rabies-related human deaths occur [5]. The disease is reported in 150 countries and territories and causes approximately 60,000 fatalities annually [2]. In Southern and Eastern Mediterranean countries, the burden due to dog-mediated rabies was estimated to be 1875 human deaths and 14,310 disability-adjusted life years per year in Central Asia and 229 human deaths and 1875 disability-adjusted life years per year in the Middle East [3]. However, estimates of burden have always been uncertain due to the lack of reliable data in many countries [2].

In Yemen, canines are the main reservoirs of this disease [4]. The incidence of rabies in Yemen is estimated to be 23 human cases per 1,000,000 population [6]. However, data are usually underestimated due to inadequate diagnosis and underreporting of human rabies in many areas of the country; in particular, laboratory test is only available for a suspected rabid animal, a direct fluorescent antibody test for observing rabies virus proteins in animal tissues, which is performed only in the Central Veterinary Laboratory (CVL). According to the Ministry of Public Health and Population and National Rabies Control Program (NRCP), approximately 50 deaths occur annually, and the number of dog bites was estimated to be 10,017 in 2017 [7]. Rabies postexposure prophylaxis (PEP) is available for humans only, and according to the CVL and NRCP, no vaccines are available for domestic animals [8].

The Rabies Surveillance System was set up in Yemen in the 1980s as a Rabies Control Unit in Sana'a city, and then in Ta'izz and Al Hudaydah. In 1990, the NRCP was established by the Ministry of Public Health and Population under the administration of the primary health care sector. The program now has 26 Rabies Control Units operating in 15 governorates out of the total 22 governorates in Yemen.

The reporting, however, remains a paper-based system. This study aimed to describe the epidemiology of human rabies exposure, its trend, and its geographical distribution in Yemen.

Methods

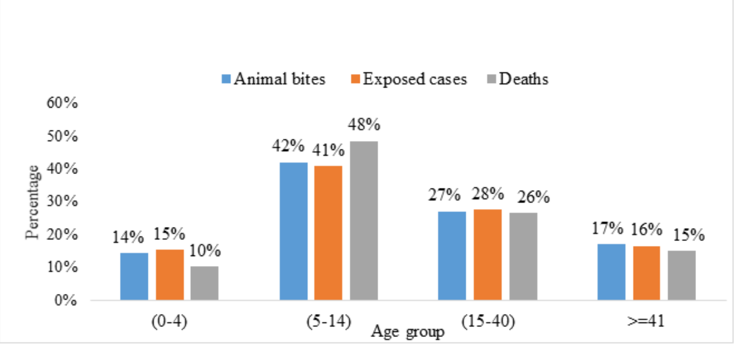
Cumulative data as paper-based annual reports from the Rabies Surveillance System for the period from 2011 to 2017 were obtained from the NRCP. Data included the number of persons bitten by a suspected rabid animal, their gender and age, and the result of the animal's laboratory test in the CVL. Quantities of vaccines and immunoglobulins for each control unit were also included. Human cases were defined as those exposed to rabies virus if bitten by a suspected rabid animal, exposed to a confirmed rabid animal and then received PEP, and deaths occurred after exposure to a confirmed rabid animal and having rabies symptoms during 2011-2017 [3]. Data were entered, cleaned, and analyzed using MS Excel and Epi Info 7.2. Percentages and rates were calculated. Total populations were obtained from the Yemen Central Statistical Organization and used to calculate the incidence rate/100,000 population.

Results

During the period 2011-2017, a total of 76,049 persons were bitten by a suspected rabid animal. Of those, 21,927 (28.83%) were exposed to positively confirmed rabid animals and then had PEP while 295 (0.38%) rabies deaths occurred. The annual average number of animal bites, exposed cases, and deaths was 10,846, 3132, and 42, respectively.

Of all cases with rabies exposure, 50,882/76,049 (66.91%) were males; in particular, children between ages 5 and 14 years were more impacted than other age groups: 31,816/76,041 (41.84%) had animal bites, 8945/21,927 (40.79%) had positive exposure, and 143/295 (48.47%) died (Figure 1).

Figure 1. Distribution of animal bites cases, exposed cases, and rabies deaths by age groups in Yemen between 2011 and 2017.

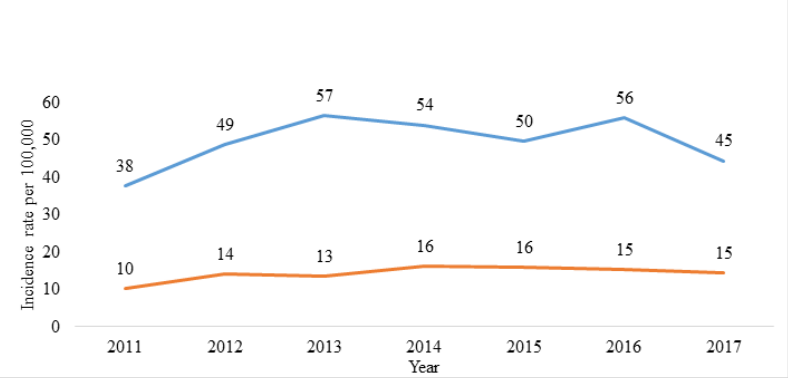


Available quantities of rabies vaccine and immunoglobulins varied by years; they were the least in 2016 and 2017, with 0 immunoglobulins vials available in 2017, whereas they were the highest in 2013 (data not shown).

The annual incidence rate of exposure to animal bites and rabies exposure was 50 per 100,000 population and 14 per 100,000 population, respectively, and the annual mortality rate was 2 per 1,000,000, population.

The incidence rate of animal bites was highest in 2013 and 2016. The incidence rate of rabies exposure increased from 10 per 100,000 in 2011 to 16 per 100,000 (highest rate) in both 2014 and 2015, but then decreased to 15 per 100,000 in both 2016 and 2017 (Figure 2).

Figure 2. Incidence rate of animal bites and exposed cases in Yemen from 2011 to 2017. Blue line: animal bites/100,000; orange line: exposed cases/100,000.



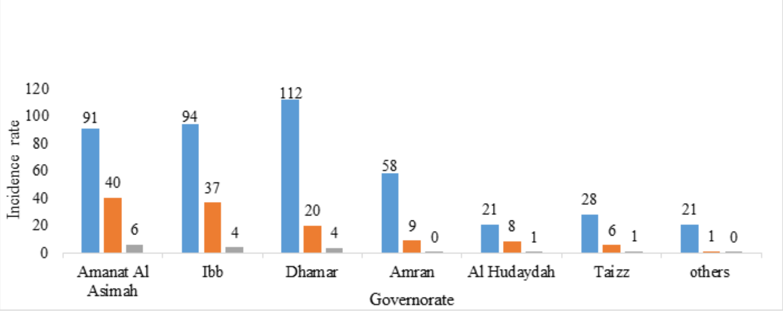
The highest number of deaths was reported in 2012 and 2017 (49 deaths in the 2 years). The highest mortality rate was reported in 2012, 2013, and 2017 (Table 1).

The highest incidence rate of animal bites was in Dhamar and Ibb with 112 and 94 per 100,000 population, respectively, and the highest incidence rate of rabies exposure was in Amanat Al Asimah and Ibb, with 40 and 37 per 100,000 population, respectively. Amanat Al Asimah had the highest mortality rate with 6 deaths per 1,000,000, followed by Ibb and Dhamar with 4 deaths per 1,000,000 population (Figure 3).

Table 1. Mortality rates from rabies in Yemen from 2011 to 2017.

Year	Population	Number of deaths	Mortality rate/1,000,000
2011	19,967,804	38	1.9
2012	20,610,108	49	2.4
2013	21,275,006	44	2.1
2014	21,963,378	43	2.0
2015	22,676,140	40	1.8
2016	23,414,249	32	1.4
2017	22,853,036	49	2.1

Figure 3. Incidence rate of animal bites, rabies exposed cases, and mortality rate by governorates in Yemen from 2011 to 2017. Blue bars: animal bites/100,000; orange bars: exposed cases/100,000; gray bars: deaths/100,000.



Discussion

Principal Findings

Rabies remains a neglected disease in Yemen. The present study highlights this health problem and provides information about the status of rabies exposure in Yemen.

Our results revealed that during the 7-year period (ie, from 2011 to 2017), the annual incidence rate of exposure to animal bites was 50 per 100,000, which was almost equal to the incidence rate in Oman (46.5 per 100,000 population) [9]. However, the incidence rate in our study was much lower than that in India (1700 per 100,000 population) [10], Iran (13.2 per 1000 population) [11], and Ghana (172 per 100,000 population) [12]. Unfortunately, this result may not reflect the actual status of exposure to animal bites in Yemen due to the underreporting of cases, which is attributed to low community awareness about the disease that in turn leads to very limited number of cases that actually receive proper medical care upon exposure.

The annual incidence rate of human rabies exposure was 14 per 100,000, which was lower than that reported in India, Ethiopia, and Vietnam [13-15], but higher than that in Thailand [16]. This difference is mainly due to variation in study methods employed, or it may well truly reflect the actual situation in these countries. By contrast, the low incidence of rabies exposure in Yemen compared with other counties is likely due to the underreporting of cases.

This study showed that the incidence rate remained unstable from 2011 to 2013, and then it increased from 2014 to 2016, which could be explained by the impact of political conflicts and the war in Yemen during these years. Because the war also affected both nonhealth and agricultural sectors, various measures of the municipality to control the population of street dogs and domestic animals (eg, sterilization) in rural and urban areas collapsed.

The highest number of deaths was in 2012 and 2017 (49 in both). This might be due to the improvement in the reporting system (2012) or to the scarcity of vaccines and lack of immunoglobulins due to siege and war (2017).

Globally, men are at higher risk than women, accounting for 50,882/76,049 (66.91%) of cases. This result was consistent with the findings of a previous study in Yemen [4]. This finding is also in agreement with those of previous studies in Oman, Iran, Ethiopia, India, Bhutan, and Nigeria [9,13,17-20]. The higher rate among men might be due to their increased outdoor activities in comparison to women.

According to the WHO, 40% of individuals impacted by rabies are children aged 4-15 years [21]. In our study, 40.79% (8945/21,927) of exposed individuals fall in this age group. A similar finding was reported in other developing countries such as Iraq and Tanzania [5,22]. The higher rate of being bitten in this age group is likely because children in this age group are more likely to play with, annoy, or approach the biting animals.

Our findings indicate the higher incidence of rabies in the main cities of Yemen, such as Amanat Al Asimah and Ibb. This result may due to improper recording of impacted cases from other governorates with poor health services, as suspected patients tend to visit referral hospitals in nearby governorates with better facilities. In particular, Dhamar recorded a high incidence, which may due to the poor and rural nature of the land.

Conclusion

Rabies remains a worrying health problem in Yemen, with a higher percentage of cases reported among children and males. The annual incidence of animal bites and rabies exposure was 50 and 14 per 100,000 population, respectively, and the annual mortality rate was 2 per 1000,000 population. Education, communication, and information campaigns about preventive measures by targeting school-age populations are strongly recommended. An electronic system should be introduced to improve reporting. It is important to have a sufficient supply of vaccines and immunoglobulins in control units, especially in the at-risk or impacted governorates. Moreover, vaccinating canines to avoid animal-to-human transmission are necessary. Finally, future studies are suggested to determine incidences and risk factors of disease progression.

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Conflicts of Interest

None declared.

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Abbreviations

CVL: Central Veterinary Laboratory
NRCP: National Rabies Control Program
PEP: postexposure prophylaxis

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