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COVID-19 Mask Usage and Social Distancing in Social Media Images: Large-scale Deep Learning Analysis

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Abstract

Background: The adoption of nonpharmaceutical interventions and their surveillance are critical for detecting and stopping possible transmission routes of COVID-19. A study of the effects of these interventions can help shape public health decisions. The efficacy of nonpharmaceutical interventions can be affected by public behaviors in events, such as protests. We examined mask use and mask fit in the United States, from social media images, especially during the Black Lives Matter (BLM) protests, representing the first large-scale public gatherings in the pandemic.

Objective: This study assessed the use and fit of face masks and social distancing in the United States and events of large physical gatherings through public social media images from 6 cities and BLM protests.

Methods: We collected and analyzed 2.04 million public social media images from New York City, Dallas, Seattle, New Orleans, Boston, and Minneapolis between February 1, 2020, and May 31, 2020. We evaluated correlations between online mask usage trends and COVID-19 cases. We looked for significant changes in mask use patterns and group posting around important policy decisions. For BLM protests, we analyzed 195,452 posts from New York and Minneapolis from May 25, 2020, to July 15, 2020. We looked at differences in adopting the preventive measures in the BLM protests through the mask fit score.

Results: The average percentage of group pictures dropped from 8.05% to 4.65% after the lockdown week. New York City, Dallas, Seattle, New Orleans, Boston, and Minneapolis observed increases of 5.0%, 7.4%, 7.4%, 6.5%, 5.6%, and 7.1%, respectively, in mask use between February 2020 and May 2020. Boston and Minneapolis observed significant increases of 3.0% and 7.4%, respectively, in mask use after the mask mandates. Differences of 6.2% and 8.3% were found in group pictures between BLM posts and non-BLM posts for New York City and Minneapolis, respectively. In contrast, the differences in the percentage of masked faces in group pictures between BLM and non-BLM posts were 29.0% and 20.1% for New York City and Minneapolis, respectively. Across protests, 35% of individuals wore a mask with a fit score greater than 80%.

Conclusions: The study found a significant drop in group posting when the stay-at-home laws were applied and a significant increase in mask use for 2 of 3 cities where masks were mandated. Although a positive trend toward mask use and social distancing was observed, a high percentage of posts showed disregard for the guidelines. BLM-related posts captured the lack of seriousness to safety measures, with a high percentage of group pictures and low mask fit scores. Thus, the methodology provides a directional indication of how government policies can be indirectly monitored through social media.

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KEYWORDS

COVID-19; mask detection; deep learning; classification; segmentation; social media analysis

Introduction

The outbreak of COVID-19 has the world in its grips. The World Health Organization declared it as a global pandemic on March 11, 2020 [1], and with exponentially rising cases, there are currently more than 32 million cases and 500,000 deaths in the United States (April 2021) [2]. Following World Health Organization health advisories, most countries have declared national emergencies, closed borders, and restricted public movement [3,4]. Masks have been found to reduce potential exposure risk from an infected person, proving to be a successful measure to suppress transmission and save lives [5-8]. Many studies have recognized the importance of community-wide use of masks for controlling the pandemic [9,10]. Social distancing measures have also been applied to prevent sick individuals from coming into contact with healthy individuals. These social distancing and mask use measures have proven successful in many countries like China [11,12]. Governments worldwide have adopted social distancing and mask use as primary nonpharmaceutical measures against the virus.

With over 32 million cases and 500,000 deaths as of April 2021, the United States is one of the largest countries to be hit by the virus. In the United States, many state governments had applied several stay-at-home and mask use measures as early nonpharmaceutical interventions. In the lead up to widespread vaccine deployment, the adoption of nonpharmaceutical interventions and their surveillance are critical for detecting and stopping possible transmission routes. Quantifying the effectiveness of such measures is a challenging task, which currently relies on on-ground surveys [13] or self-reported numbers [7]. However, these methods are cumbersome, thus leading to lags in data and the day-to-day evolution of a fast-moving pandemic.

The pervasive nature of social media provides a unique opportunity to create agile frameworks for assessing public health measures such as mask use. With its ease of access and global outreach, social media has a disproportionate influence on the dissemination of information during a pandemic [14]. In recent times of the pandemic, social media has become a popular platform for people to express their thoughts and opinions, and broadcast activities. The general public and authorities have been using hashtags like #CoronaOutbreak, #COVID19, and #mask to disseminate important information and health advisories, and this provides us with an opportunity to analyze behaviors and the impact of such advisories worldwide [15]. Indeed, social media has been extensively explored and analyzed for patterns that have emerged during the COVID-19 pandemic [16-19]. Signorini et al [20] examined Twitter based-information to track the swiftly evolving public sentiment regarding Swine Flu in 2011 and correlate the H1N1 virus subtype–related activity to track reported disease levels in the United States accurately.

During the pandemic, the United States also observed the Black Lives Matter (BLM) protests. The killing of George Floyd on May 25, 2020, sparked a series of protests [21] and agitations across the country. Protests are designed to stimulate public action for social justice. Such protests involve the physical gathering of people, making it difficult to adhere to social distancing and to wear masks. These protests provide an opportunity to observe how people react to public health–related preventive measures during such gatherings, but collecting the necessary data from the ground is a difficult task. Such protests have also gained high popularity and attraction through online social media [22,23].

Realizing the potential of social media in understanding such events, in this study, we used social media images from Instagram, a popular image-sharing social media platform, which has been used by researchers to study different public health emergencies [24]. Computer vision–based classifiers are necessary to check if a person is wearing a mask from an image. There exist 2 data sets previously published for mask classification tasks, namely, MAFA (Masked Faces) [25] and RMFD (Real-world Masked Face Dataset) [26]. The MAFA data set contains 35,805 masked images. Since the MAFA data set was curated and released in 2017, it could not capture different varieties and types of masks that have been in use during the pandemic period. The MAFA data set is biased toward 1 kind of mask; it majorly consists of medical staff wearing disposable medical-grade masks. The RMFD contains 7959 masked images with a variety of masks used during the COVID-19 period. However, a manual qualitative evaluation of the images revealed that the images were not suitable for analyzing high-quality social media images since most images were less than 50×50 resolution after cropping the face region. In addition to mask detection, analyzing the fit of the mask is a highly useful application. There is no previous work trying to analyze mask fit using semantic segmentation to the best of our knowledge.

Therefore, this study fills the gap with a pipeline designed to estimate the extent of mask behaviors by assessing mask use and mask fit from 2.04 million social media images obtained from 6 US cities. Along with geographical diversity among the cities, the 6 cities also have high population numbers. These cities were also found to have a high number of location-tagged posts on Instagram and hence were chosen as the locations of interest. We demonstrate the correlation of mask use and mask fit behaviors with COVID-19 burden, policy directives, and large-scale events, such as the nationwide BLM protests, in these 6 cities.

Methods

Data Sets

The study was approved by the institutional review board for adherence to ethical principles of research. The images were anonymized, and aggregated statistics for states were calculated. There was no attempt to recruit subjects, reidentify subjects, or link the images with other personal information in order to maintain confidentiality. Individual-level mask use adherence was not analyzed. Anonymized images were stored on secure servers as the following 3 different data set collections:

1. Mask-unmask classifier data set: This data set was used for training a model that classifies whether the person in the image is wearing a mask or not. For training, we needed images in

which people were wearing masks (masked images) and images in which people were not wearing masks (unmasked images) so that our model could learn to distinguish between the 2 categories. We collected around 30,000 images of people wearing masks from Google Search images using the tags "people wearing masks" and "children wearing masks." Images from Instagram were also collected with the tag explore feature, using the following 3 tags: "mask," "masked," and "covidmask." Although the tagging algorithms used by Google are expected to capture most of the images, some images may have been missed. There is further scope for expanding our set of tags chosen to capture the entire population of images in which people are wearing masks, which is a limitation of our current approach. However, this will need more research, as capturing other scenarios may also lead to noisier sets. After data collection, images with a width and height of at least 50 pixels were kept to ensure decent image quality. Then, Face Detector was used on these images to extract faces. The images of extracted faces were distributed among 5 annotators, and the annotators were asked to classify the faces as either "masked" or "unmasked." After the annotations, images of 9055 masked faces were obtained. For the unmasked face images, we created a random sample (without replacement) of 9055 faces from the VGGFace2 data set [27], which is a large-scale face recognition data set. The samples from VGGFace2 and the mask-unmask classifier data set were used to train the unmask-mask classifier, whose details are given in the Proposed Framework section.

2. Fit score data set: Out of 9055 masked faces that we obtained from the previous data set, we selected 504 images with different poses and a wide variety of mask designs. Then, we annotated these images using Label Studio [28] for getting pixel-level annotations of the mask region on the face. This data set was then used to train a semantic segmentation model, whose details are in the Proposed Framework section.

3. USA cities Instagram data set: For the analysis phase, we collected location-tagged public posts from Instagram between February 1, 2020, and May 31, 2020, for the following 6 cities: New York City, Seattle, Dallas, New Orleans, Minneapolis, and Boston. The first COVID case was reported in January 2020 [29], and till July 2020, the United States was still in the first wave of the COVID-19 pandemic [30]. Hence, the chosen time frame captures the beginning and growth of the COVID-19 pandemic in the United States. This collection was done for 6 major US cities, and these 6 cities were selected to represent different geographical sections of the country. We collected a total of 2.04 million public posts from these 6 cities. These posts were collected via Instagram's explore location feature. Instagram's GraphQL application programming interface was employed for the data collection. The tools used have been published as a python PyPI package [31]. We also collected 195,452 posts for New York City and Minneapolis from May 25, 2020, to July 15, 2020, which had major protests [32]. We curated a list of trending tags and keywords ("blm," "blacklivesmatter," "georgefloyd," "justiceforgeorgefloyd," "policebrutality," and "protest") during this period. We refer to the posts whose captions included these tags as BLM posts and the rest as non-BLM posts.

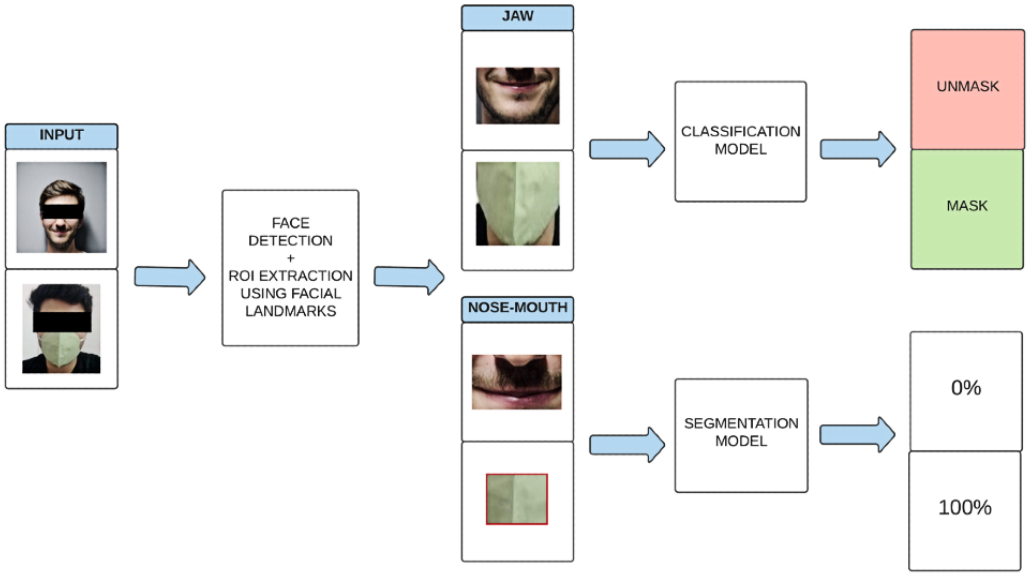
Proposed Framework

This article proposes a mask-unmask classification framework (for classifying masked and unmasked images) and a fit score analysis framework (for evaluating whether the masks are being worn effectively or not in the given image). The mask-unmask classification model is used to analyze the USA cities Instagram data set. The fit score analysis framework is just used for BLM posts to capture the mask use patterns during a huge social gathering.

Images obtained from sources mentioned in the previous section consisted of various individuals. Thereby, to detect face masks in these images, the first task of both frameworks was face detection. This was done using the pretrained model Retinaface [33], which is one of the top performing models on Face Detection on the WIDER Face (Hard) data set [34]. Next, facial landmarks were obtained using Dlib's implementation [35] (proposed by Kazemi et al [36]), which was used to extract the regions of interest (ROIs), as shown in Figure 1A. The landmarks 5-13, 31-36, and 49-68 (Figure 1B) were used to filter the face's jaw region. This jaw region obtained was then used as input in the classification model for the mask-unmask classification framework. The landmarks 32-36 and 49-68 (Figure 1B) were used to filter the nose-mouth region from the face. This nose-mouth region obtained was then used for calculating the fit score.

The jaw region was then classified on the basis of whether it contained a mask over it or not (Figure 1A) using a classification model. The following architectures were experimented with while training the mask-unmask classification model: MobileNet V2, Nas Net, EffecientNet B0, EffecientNet B1, EffecientNet B2, and DenseNet121. These architectures were selected since they have significantly fewer parameters than most other architectures (Multimedia Appendix 1). The input image size for all the models was 224×224. Transfer learning was used, and weight initialization of all models was done using ImageNet. All models were truncated at the last fully connected layer. The following layers were added: (1) average pooling with 5×5 pool size, (2) flatten layer, (3) dense layer with 128 hidden units and reLU activation, (4) dropout layer of 0.5, and (5) dense layer of 2 hidden units and Softmax activation. Adam optimizer with an initial learning rate of 1e-4 was used, and each model was trained for 30 epochs with a batch size of 64, with binary cross-entropy as the loss function. For training the classifier, the total data from the mask-unmask classifier data set consisted of 9055 masked and 9055 unmasked samples, which were split in an 80:20 ratio for training and validation sets. Five-fold cross-validation was used to evaluate the trained models' performance, and the different model results can be found in Multimedia Appendix 1.

Figure 1. (A) Face mask detection and mask fit calculation framework. The extracted jaws are passed to the trained mask-unmask classification model. The extracted nose-mouth region is given to the segmentation model to predict the masked region and calculate the fit score. (B) Facial landmarks detected on a face using Dlib. ROI: region of interest.



(A)

(B)

The evaluation indicated that EfficientNet B0 was the best performing model, with an overall accuracy of 0.98 (SD 0.01). EfficientNet [37] is a convolutional neural network architecture and scaling method that uniformly scales all depth/width/resolution dimensions. Efficient B0 has 5.3 million parameters with 18 layers. Its architecture consists of an initial 3×3 convolution layer, followed by a series of MBconv layers with different kernel sizes and number of channels. The series of MBconv layers are followed by a convolution layer, a pooling layer, and a fully connected layer. It uses linear activation in the last layer in each block to prevent loss of information from ReLU. Compared with conventional convolutional neural network models, the main building block for EfficientNet is MBConv, an inverted bottleneck conv, known initially as MobileNetV2. Before EfficientNet came along, the most common way to scale up ConvNet was by one of the following 3 dimensions: depth (number of layers), width (number of channels), and image resolution (image size). EfficientNet, on the other hand, performs compound scaling, that is, scaling of all 3 dimensions while maintaining a balance between all dimensions of the network. We used this trained model for further analysis using the mask-unmask classification framework.

To calculate the fit score of the appropriate region covering the nose and mouth regions of the face, we used a semantic segmentation-based model (Figure 1A). We defined the fit score as shown in Equation 1. Using the data from the fit score data set, we trained a U-Net–based model [38] for segmenting images of faces into the masked and unmasked regions. The model uses ResNet 32 and 50 encoders pretrained on ImageNet data [39]. The layers were trained progressively using cyclical learning rates [40]. Different model variations were experimented with using different encoders and input image sizes (Multimedia Appendix 2). Using the output of this model (true positive [TP] + false positive [FP]) and the nose-mouth region's facial landmarks, we calculated the fit score of an image of a face. The fit score is the percentage of ROI area covered by the mask on the face (Figure 1A). We employed the fit score analysis framework on BLM posts to understand how well people wore masks in groups during large events like protests. City-wise analysis was done to observe mask fit differences across major states of protest.

Statistical Tests

We used the Mann-Kendall trend test to look for monotonic increasing trends in the daily percentage of mask users.

We also used Pearson correlation, Spearman rank-sum correlation, and the Welch *t* test to perform our analysis. Although Pearson correlation assumes normal distribution for both variables [41], it has been shown to reveal hidden correlations even when data are not normally distributed [42].

We performed Pearson and Spearman correlations to decide whether the value of the correlation coefficient *r* between lagged COVID-19 cases and the daily percentage of people wearing masks is significantly different from 0 at a threshold of $P<.01$ [43].

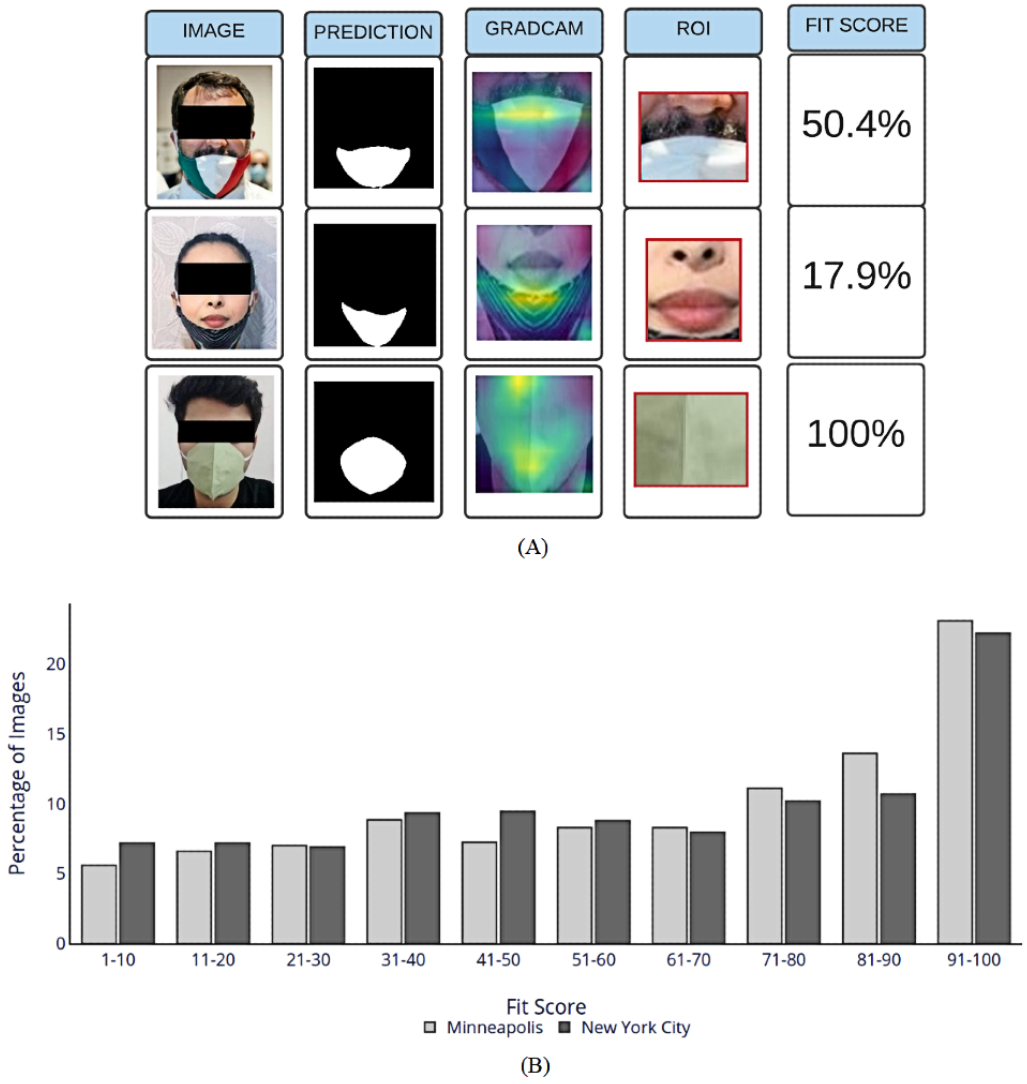
We then conducted the Welch *t* test to assess whether the daily posting is significantly affected by stay-at-home laws. The Welch *t* test requires normal distribution as a prerequisite, but since we were comparing mean values and our underlying series length was large (>30), this assumption could be bypassed [44]. We assessed the before and after posting effects of the application of stay-at-home laws in New York, Dallas, Seattle, Boston, Minneapolis, and New Orleans (Multimedia Appendix 3) [45-50]. We perform the Welch *t* test to test the following hypotheses for the 6 cities and calculate the *P* values with an alpha of .01: H0, $\mu0=\mu1$ (the daily percentage of group posting is not affected by the stay-at-home laws) and H1, $\mu0\neq\mu1$ (the daily percentage of group posting is affected by the stay-at-home laws), where $\mu0$ and $\mu1$ are the mean percentages of daily group posting.

In addition, we performed the Welch *t* test to test the effect on the percentage of masked faces from mask mandates for Boston, Minneapolis, and New York City (mask mandate dates for the other 3 cities did not lie in our chosen timeframe) (Multimedia Appendix 4) [45,51,52]. The hypotheses are as follows: H0, $\mu0=\mu1$ (the daily percentage of masked faces is not affected by the mask mandates) and H1, $\mu0\neq\mu1$ (the daily percentage of masked faces is affected by the mask mandates), where $\mu0$ and $\mu1$ are the daily mean percentages of masked faces. We calculated the associated *P* value for significance testing, with an alpha of .01.

Interpretability

To visually inspect what the trained EfficientNet B0 in the mask-unmask classifier had learned, we implemented GradCam [53] on the network. GradCam assesses which parts of the input image have the highest activation values, given a target class. In this case, we passed the jaw region (ROI) after facial landmark detection as the input image to the GradCam network for 3 examples (2 masked and 1 unmasked) (Figure 2A). We also inspected the segmentation model on the corpus of BLM posts collected from social media.

Figure 2. (A) GradCam analysis showing the activation of different regions on the jaw in the classification model. (B) Percentage of faces vs fit score for New York and Minneapolis for Black Lives Matter posts between May 25, 2020, and July 15, 2020. A total of 11,214 posts were analyzed. ROI: region of interest.



Results

The corresponding activation maps, mask predictions, and fit scores from GradCam analysis are shown in Figure 2A. Figure 2B shows the distribution of the fit scores for people wearing masks in BLM posts. Approximately 35% of the detected faces had a fit score ≥80% (the corresponding n/N values can be found in Multimedia Appendix 5). This means that the remaining 65% had some significant part of their nose/mouth region not covered.

The following paragraph presents the results of experiments conducted to evaluate the patterns of people wearing masks in the 6 cities across the selected time frame (February 1, 2020, and May 31, 2020). A total of 1.66 million faces were detected from all the posts across the 6 cities. Out of which, a total of 232,706 faces had masks. Table 1 shows the city-wise distribution of the detected faces and masks. We found that 1.16 million posts (around 57% of the total posts collected) had no faces, while 1.89 million (around 93%) of the total posts had no masked faces. One or more faces were detected in 0.87 million (43%) of the posts, of which 0.61 million (30%) had a single face detected and 0.26 million (13%) had multiple faces detected. In 0.14 million (7%) of the total posts, one or more masked faces were detected, out of which 0.12 million (6%) had a single masked face.

There was a decrease in group posting after the lockdown week. The average percentage of group pictures dropped from 8.05% to 4.65%. A sudden spike in group posting was observed around week 15 (Figure 3A).

A general increasing trend in the percentage of people wearing masks for all 6 cities was observed. The Mann-Kendall trend test showed a significant positive trend in the daily percentage of mask users for all 6 cities (corresponding *P* values can be found in Multimedia Appendix 6). New York City, Dallas, Seattle, New Orleans, Boston, and Minneapolis observed a month-wise increase of 5%, 7.4%, 7.4%, 6.5%, 5.6%, and 7.1%, respectively, between February 2020 and May 2020 (Figure 3C) (the corresponding n/N values can be found in Multimedia Appendix 7).

As shown in Figure 3B, the differences in group pictures between BLM and non-BLM posts were 6.2% and 8.3% for

New York City and Minneapolis, respectively. The differences in the percentage of masked faces in group pictures between BLM and non-BLM posts were 29.0% and 20.1% for New York City and Minneapolis, respectively (Figure 3F).

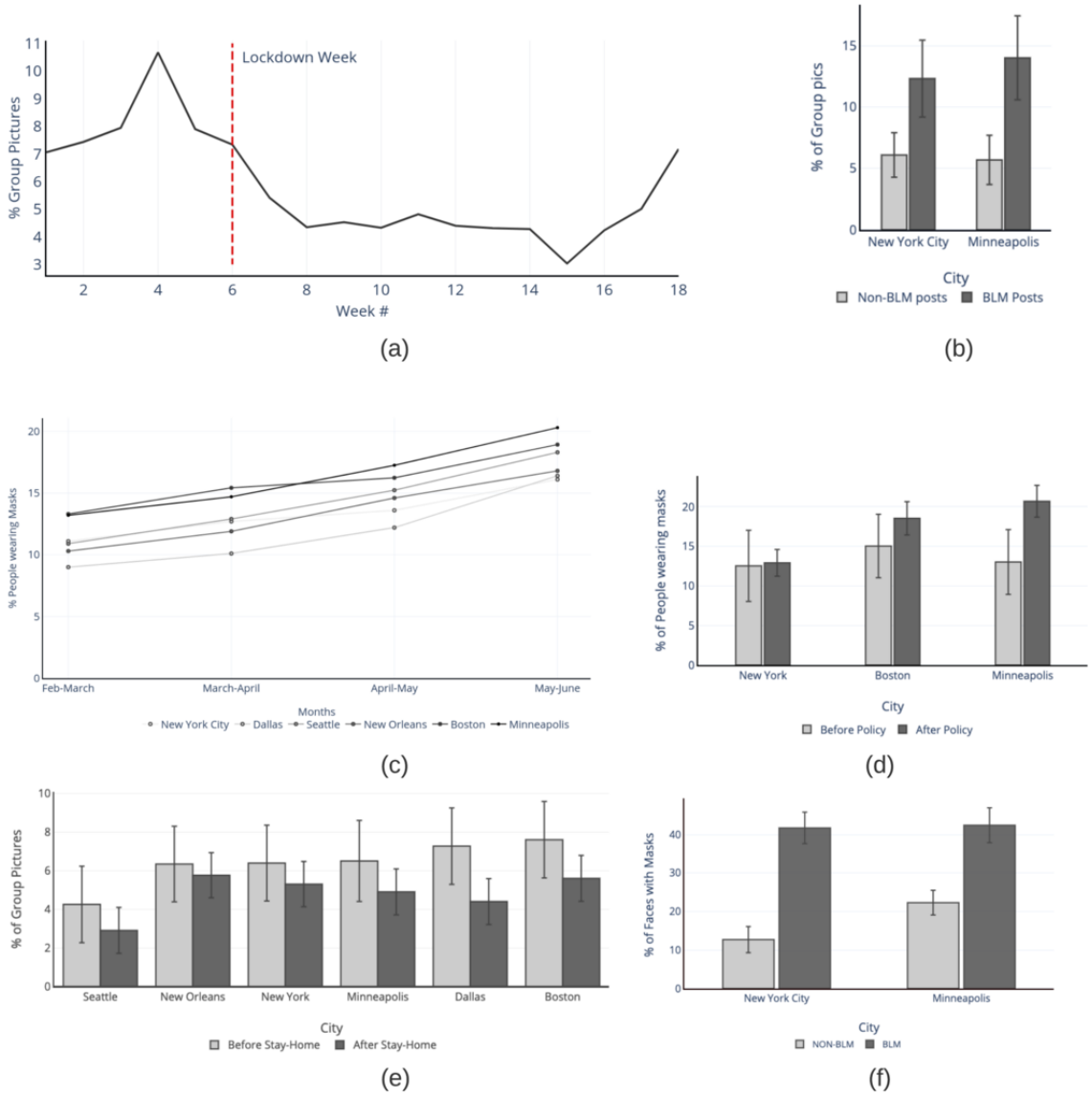
Figure 3D shows the average daily percentage of people wearing masks before and after the state mask mandates were applied for the 3 cities that implemented these mandates within our selected time range. Boston, Minneapolis, and New York City saw increases of 3.0%, 7.4%, and 1.0%, respectively, after applying mask mandates (the corresponding n/N values can be found in Multimedia Appendix 8). The average daily percentages of people wearing masks before and after the state mask mandates were applied were statistically different from one another for Boston and Minneapolis, with an alpha of .01, while the difference was not significant for New York City (test results can be found in Multimedia Appendix 9).

Boston, Minneapolis, New Orleans, Dallas, Seattle, and New York City saw decreases of 2.0%,1.6%, 0.6%, 2.8%, 1.3%, and 1.0%, respectively, in the average daily percentage of group pictures before and after the stay-at-home laws (the corresponding n/N values can be found in Multimedia Appendix 10) (Figure 3E). The average daily percentages of group posting before and after the stay-at-home laws were applied were statistically different from one another for all the 6 cities, with the alpha value set at .01 (test results can be found in Multimedia Appendix 11).

Table 1. City-wise distribution of the number of detected faces, number of detected masks, and number of masks per face through our framework, collected from Instagram between February 1, 2020, and May 31, 2020.

City	Total collected posts, n	Faces detected, n	Masks detected, n	Percentage of faces with masks
New York City	245,677	200,089	25,413	12.70
Dallas	540,500	444,194	48,119	10.83
Seattle	437,040	312,012	46,019	14.75
Minneapolis	220,999	152,822	30,385	19.88
New Orleans	315,082	321,591	39,420	12.26
Boston	283,757	238,770	43,350	18.15
Total	2,043,055	1,669,478	232,706	13.94

Figure 3. (A) Weekly percentages of group pictures detected from New York City, Seattle, Dallas, New Orleans, Minneapolis, and Boston between February 1, 2020, and May 31, 2020. A total of 2.04 million posts were analyzed. (B) Percentage of group pictures vs city for Black Lives Matter (BLM) and non-BLM posts between May 25, 2020, and July 15, 2020. A total of 192,854 posts were analyzed. (C) Monthly percentages of people wearing masks for each of the 6 cities, between February 1, 2020, and May 31, 2020. The data set was divided into months for each city, and the percentages of people wearing masks were computed. (D) Average daily percentage of people wearing masks before and after mask use guidelines for New York, Boston, and Minneapolis, between February 1, 2020, and May 31, 2020. A total of 750,433 posts were analyzed. (E) Average daily percentage of group pictures before and after stay-at-home laws for the 6 cities between February 1, 2020, and May 31, 2020. A total of 2.04 million posts were analyzed. (F) Percentage of people wearing masks in groups for BLM and non-BLM posts between May 25, 2020, and July 15, 2020. A total of 27,789 posts were analyzed.



Discussion

Principal Findings

The COVID-19 pandemic has given the entire research community and governments a chance to reflect on what kind of system needs to be in place to handle such catastrophes. A renewed focus is emerging in infodemiology [54], especially leveraging mass surveillance data [55,56]. Location tracking [57], periodic self-checks, and image recognition systems have been deployed by many governments [58-61] to get a handle on the pulse of the pandemic in their states. This study suggests another such approach, which can be applied to specific demographics to achieve similar near–real-time tracking of the pandemic's spread. Instagram and other social media platforms have been very successful in tracking the number of visits to public places [62]. In the context of COVID-19, public places are the focal points for the spread of the virus. It has been well-documented that face masks and social distancing are the 2 most effective nonpharmaceutical interventions to curb the spread of COVID-19 [7]. However, the use of masks and effective social distancing are often self-reported [63], without any proof to corroborate the claims. Models built on image data

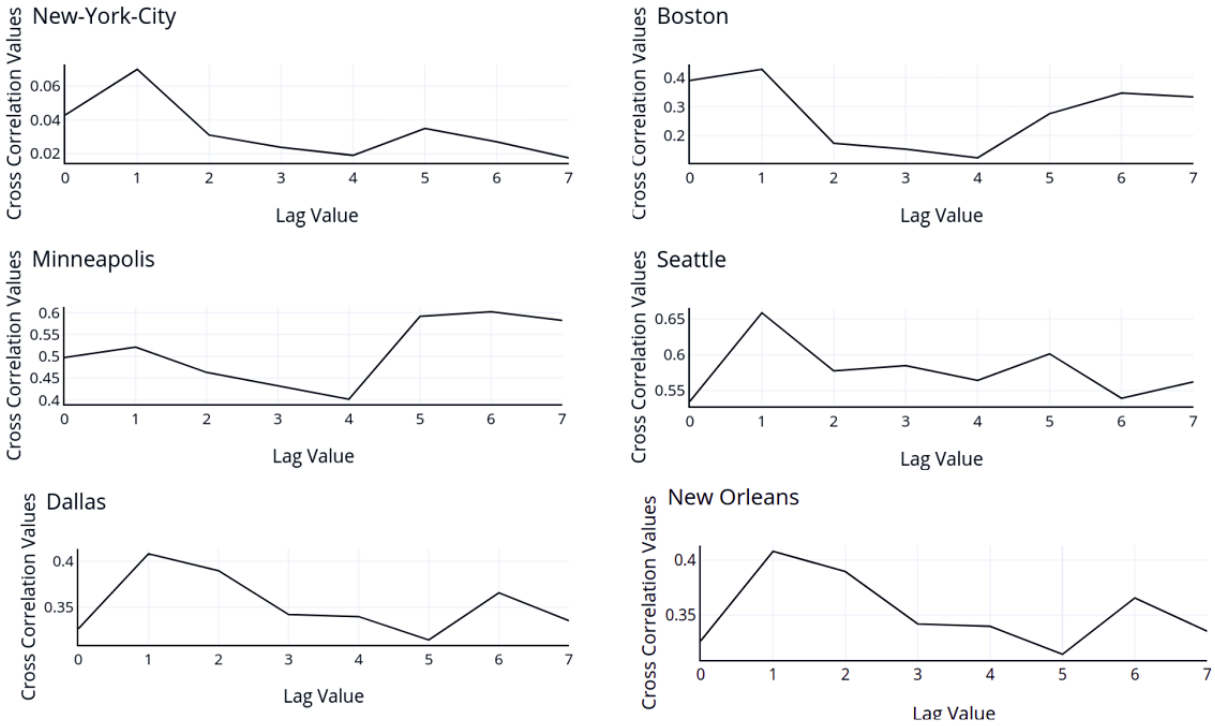
with location data [64] can be a powerful tool for the authorities to keep track of the pandemic's pulse.

An overall decrease in group posting was found as the pandemic grew and lockdowns were put in place. These group pictures posted online can be used as an estimator for the percentage of people spending time in groups. A sudden spike in group posting was found from May 16, 2020, to May 22, 2020 (week 15 of our timeline). This can be linked to the easing lockdown restrictions through weeks 13, 14, and 15 [65-68]. As the pandemic spread, the percentage of mask users saw a significant increasing trend for all the 6 cities through the months, suggesting that more people started wearing masks as the pandemic spread. Significant positive Spearman and Pearson correlations were found between the daily COVID-19 cases and the percentage of mask users for all the cities, except New York City, with an alpha of .01 (Multimedia Appendices 12 and 13). The maximum correlation was found to be with lag as 1 for all cities, except Minneapolis, as seen in Figure 4. As seen through social media, the stay-at-home state policies were successful as a significant decrease in group posting was observed on the adoption of stay-at-home laws for all 6 analyzed cities. After the mask use mandates were applied, a significant increase in the percentage of mask users was seen in Boston and Minneapolis, and a slight increase was observed in New York City. These results indicate adherence to nonpharmaceutical interventions in the 6 cities, with varying percentages of changes and effects. The trends of increasing mask use with the pandemic and positive changes with mask mandates corroborate with self-reported number-based survey methods in the United States [7]. Although a significant increase was seen in the percentages, the growth could have increased separately from the mandates. With an insignificant increase seen for New York City, supplemental public health interventions can be applied to maximize the adoption of such methods.

A large difference was observed in the percentage of group pictures between the posts that talked about the BLM protests. This difference can be explained by the huge collection of people in protests, with a lack of social distancing measures causing a high percentage of posts to involve group pictures. On the contrary, mask use was found to be much higher for BLM-related posts as compared to non-BLM posts. The mask fit score distribution of the protestors showed that only 35% of mask users had more than 80% of their nose/mouth region covered. This indicates that, while social distancing measures were not appropriately followed due to the nature of such large gatherings, protestors were more likely to wear a mask than the general public, but only a small percentage covered their faces properly, as seen through social media posts.

Models built on image data with location data can be powerful tools for authorities to keep track of the pandemic's pulse. This study provides a new method for governments and organizations to monitor policy decisions indirectly.

Figure 4. Pearson correlation between daily lagged cumulative cases and the percentage of masked photos between February 1, 2020 and May 31, 2020. The length of the series was 120. The lag was selected between 0 and 7 based on the highest correlation value.



Limitations

The images present in our data sets have a high definition and are in RGB mode. If the trained models have to be deployed in a new setting (eg, CCTV feed), certain image augmentation techniques like gray scaling and rescaling might be needed to fine-tune the models. For the analysis, we chose the image data from 6 major US cities by population and correlated the data with state-wide COVID-19 cases. Since these cities are some of the most populated cities of their respective states, it is

reasonable to assume that they will be the hotbeds of COVID-19 spread in their respective states.

The analysis was conducted using images obtained from the social media platform Instagram. We understand that these images might not represent the entire city population [69]. However, they do represent a wide demographic of internet users [70]. With recent studies conducted on geo-tagged text data present in Instagram posts [71], our assumption of a fair population representation in the Instagram data might not be too far-fetched. Among the mask users, celebrity posts (posts with likes greater than 10,000) contributed to only 0.2% of the total posts, which contained at least one mask, showing that the collected data mainly involved posts from the general population. However, we do acknowledge that capturing metadata for users while performing similar studies might yield a conclusive answer to the question of fair representation. Capturing and using metadata can be future work, which will build on our results.

Future Work

An addition to the modeling pipeline could be an indoor/outdoor environment detector, similar to that in the study by Zhou et al [72]. Another addition to the analysis could be selectively looking at the specific activity of users, who are deemed as "influencers" on the network. Their activity on the network can be analyzed in conjunction with the activity of their followers. This can help determine the role of social networks and the power of certain influential nodes in that network over other people's behavior during critical times such as a pandemic. Dynamic location relationships present in mobility data [73] can be further used to understand the pandemic's spread with higher location precision and even recognize malevolent actors in the system. A natural extension of this work is its replication across different social media platforms like Twitter, Facebook, and Baidu.

Conclusions

Models built on image data with location data can be powerful tools for authorities to keep track of the pandemic's pulse. This study examined 2.04 million posts collected from 6 US cities between February 1, 2020, and May 31, 2020, for adherence to mask use and social distancing, as seen through social media.

This study found a general increasing trend in mask use and a decreasing trend in group pictures as the pandemic spread. The stay-at-home laws caused a significant drop in group posting for all 6 cities, while the mask mandates caused a significant increase in mask use for 2 of the 3 cities analyzed. Although these results suggest an upward trend in the adoption of preventive methods, a large portion of nonadopters seen online indicates a need for supplemental measures to increase the effectiveness of such methods.

Posts related to protests were found to capture the lack of attention given to safety measures, with high percentages of detected group pictures and incorrect mask use. The methodology used provides a directional indication of how government policies can be indirectly monitored. The findings can help governments and other organizations as indicators for the successful implementation of nonpharmaceutical interventions for the COVID-19 pandemic.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Face mask detection model results.
[DOCX File , 13 KB - publichealth_v8i1e26868_app1.docx]

Multimedia Appendix 2
Face mask fit analyzer model results.
[DOCX File , 13 KB - publichealth_v8i1e26868_app2.docx]

Multimedia Appendix 3
Dates on which stay-at-home guidelines were enacted by the respective state governments.
[DOCX File , 13 KB - publichealth_v8i1e26868_app3.docx]

Multimedia Appendix 4
Dates on which mask mandates were enacted by the respective state governments.
[DOCX File , 13 KB - publichealth_v8i1e26868_app4.docx]

Multimedia Appendix 5
Underlying n and N values for Figure 2B.
[DOCX File , 13 KB - publichealth_v8i1e26868_app5.docx]

Multimedia Appendix 6
Test statistics and *P* values for the Mann-Kendall trend test for the daily percentage of mask wearers in 6 cities.
[DOCX File , 13 KB - publichealth_v8i1e26868_app6.docx]

Multimedia Appendix 7
Underlying n and N values for Figure 3C.
[DOCX File , 14 KB - publichealth_v8i1e26868_app7.docx]

Multimedia Appendix 8
Underlying n and N values for Figure 3D.
[DOCX File , 13 KB - publichealth_v8i1e26868_app8.docx]

Multimedia Appendix 9
Welch *t* test statistics and *P* values to test for equal means before and after the application of mask mandates.
[DOCX File , 13 KB - publichealth_v8i1e26868_app9.docx]

Multimedia Appendix 10
Underlying n and N values for Figure 3E.
[DOCX File , 13 KB - publichealth_v8i1e26868_app10.docx]

Multimedia Appendix 11
Welch *t* test statistics and *P* values to test for equal means before and after the application of stay-at-home orders.
[DOCX File , 13 KB - publichealth_v8i1e26868_app11.docx]

Multimedia Appendix 12
Pearson correlation coefficients and *P* values between lagged cumulative COVID-19 cases and the daily percentage of people wearing masks.
[DOCX File , 13 KB - publichealth_v8i1e26868_app12.docx]

Multimedia Appendix 13
Spearman correlation coefficients and *P* values between lagged cumulative COVID-19 cases and the daily percentage of people wearing masks.
[DOCX File , 13 KB - publichealth_v8i1e26868_app13.docx]

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Abbreviations

BLM: Black Lives Matter
MAFA: Masked Face
RMFD: Real-world Masked Face Dataset
ROI: region of interest

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Original Paper

Comparison of Online Patient Reviews and National Pharmacovigilance Data for Tramadol-Related Adverse Events: Comparative Observational Study

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Abstract

Background: Tramadol is known to cause fewer adverse events (AEs) than other opioids. However, recent research has raised concerns about various safety issues.

Objective: We aimed to explore these new AEs related to tramadol using social media and conventional pharmacovigilance data.

Methods: This study used 2 data sets, 1 from patients' drug reviews on WebMD (January 2007 to January 2021) and 1 from the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS; January 2016 to December 2020). We analyzed 2062 and 29,350 patient reports from WebMD and FAERS, respectively. Patient posts on WebMD were manually assigned the preferred terms of the Medical Dictionary for Regulatory Activities. To analyze AEs from FAERS, a disproportionality analysis was performed with 3 measures: proportional reporting ratio, reporting odds ratio, and information component.

Results: From the 869 AEs reported, we identified 125 new signals related to tramadol use not listed on the drug label that satisfied all 3 signal detection criteria. In addition, 20 serious AEs were selected from new signals. Among new serious AEs, vascular disorders had the largest signal detection criteria value. Based on the disproportionality analysis and patients' symptom descriptions, tramadol-induced pain might also be an unexpected AE.

Conclusions: This study detected several novel signals related to tramadol use, suggesting newly identified possible AEs. Additionally, this study indicates that unexpected AEs can be detected using social media analysis alongside traditional pharmacovigilance data.

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KEYWORDS

drug safety; pharmacovigilance; tramadol; social media; adverse effect

Introduction

Tramadol is a synthetic analgesic. It is a weak μ-opioid receptor agonist and is considered a different class of analgesic to conventional opioids [1,2]. Tramadol has earned a reputation for fewer side effects and lower rates of respiratory depression, overdose, and addiction due to its lower affinity with μ-opioid receptors than other opioids [3,4]. As a result, tramadol prescriptions have rapidly increased over the years [5-7] and it

is extensively prescribed for many types of pain [6-8]. However, there is insufficient empirical evidence that tramadol is safer than other opioids. Recent systematic reviews have revealed that tramadol is more likely to induce severe adverse events (AEs) such as seizures and hypoglycemia than other opioids [9-11]. Some studies suggest that tramadol has a similar or higher risk of long-term opioid use than other short-acting opioids [12,13]. Furthermore, a recent study found tramadol to be associated with increased mortality risk [14,15].

The traditional pharmacovigilance method of data acquisition from spontaneous reporting systems is often used to detect AEs [16]. However, this method is limited by under-reporting as it is known that fewer than 10% of AEs are reported [17]. Recently, internet-based AE detection has been used as a data-gathering tool complementary to traditional pharmacovigilance. Patients share their treatment experiences online, including drug side effects. Several studies have utilized online patient reviews for the purposes of pharmacovigilance [18,19].

In light of increasing evidence of risks associated with tramadol and the limitations of spontaneous reporting systems, this study aimed to explore new evidence for tramadol-related AEs using online patient reviews alongside national pharmacovigilance data. Additionally, we assessed the usefulness of online patient reviews in monitoring tramadol-induced AEs.

Methods

Data

The study used 2 data sources to collect information about tramadol-related AEs: (1) the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS); and (2) posts in a health forum, WebMD. First, we used FAERS data as traditional pharmacovigilance data to find new AE signals. Globally, the United States is the country with the highest number of opioid analgesics consumed [20], and FAERS is the representative spontaneous reporting system with the largest number of publications related to tramadol-related AEs [21,22]. FAERS contains information about AEs and medication error reports submitted to the FDA, coded in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Reporting to FAERS is voluntary for health care professionals and consumers, while it is mandatory for manufacturers [23]. Next, WebMD, one of the popular health forums, was chosen to obtain more detailed patient narratives of AE symptoms. The AEs were investigated using various types of social media such as social networking sites (Facebook, Twitter), blogs, forums, and comments [24]. Among them, the health forums have the advantage of effectively obtaining patient experiences online because they are specialized medical topics and have many patient users [25]. WebMD is a well-known health information service website in the United States that provides information on health and wellness topics, including drug information [26]. It also provides bulletin boards for posting personal reviews on specific drugs, frequently used as data sources for AE-related research [24,25].

Demographics

We used personal information on age and sex for FAERS and WebMD data sets; additionally, occurrence country was used for FAERS data in the analysis. FAERS provides various personal information, including age, sex, occupation, and country where the AEs occurred in the demographic file. All data sets were released after anonymization according to the privacy policy of the US Department of Health & Human Services [27]. WebMD displays the patient reviews of specific medications with nicknames, ages, and sex. WebMD also has its privacy policy fully complying with data protection regulations and developed to provide a safe space for sharing health-related information online [28]. We carefully considered data security and user privacy, and this study was ethically approved by the KNU Institutional Review Board (KNU-2021-0401)

FAERS Adverse Event Reports

We downloaded AE reports for January 2016 to December 2020 from the FAERS website [29]. From the 7,843,727 reports, we identified duplicate reports by case ID and selected the most recent to eliminate duplicate data. This left us with 6,874,999 reports. From these, tramadol-related AEs were retrieved for both single- and multi-ingredient drugs, including searches of the various brand names used in different countries as well as the generic drug name (n=92,135). Finally, we excluded AE reports in which tramadol was not reported as the primary or secondary suspected drug to rule out the potential misclassification of other drug-related AEs (n=29,345). The specific drug names and numbers of AE reports by year are summarized in Multimedia Appendix 1.

WebMD Adverse Event Reports

Online patient reviews of tramadol from September 2007 to August 2020 were gathered from the WebMD website using a Python web crawler. Patient review data were collected for tramadol HCL as well as combination drugs using both generic and brand names. A total of 3917 posts were automatically collected. Most of these pertained to tramadol HCL (n=2762). For the combination drugs, the majority of posts pertained to Ultram (Ultram, n=704; Ultram ER, n=134; Ultracet, n=177; tramadol HCL-acetaminophen, n=132; Conzip, n=8). Some of the posts only provided a rating of the drug. These were excluded and we retained only those posts with detailed descriptions. We then excluded posts that did not relate to drug-related AEs, such as drug prescription information and advertisements. Finally, we reviewed the remaining 2062 posts and assigned annotations according to the types of AEs described. The collected data were independently reviewed by 2 researchers (SP & J-WK), and symptoms considered as AE were manually assigned preferred terms (PTs) for AE types from MedDRA. If the PTs assigned by the 2 researchers did not match, a PT was agreed upon through discussion.

Statistical Analysis

To compare the distribution of tramadol-related AEs reported on FAERS with that of those reported on WebMD, we first categorized reports into respondent age groups. The age groups were children and adolescents (ages <19 years), adults (ages

19-64 years), and older adults (ages ≥65 years). The number of AEs was counted based on MedDRA's PTs in both data sets. Two or more PTs reported in a patient were counted as different AEs. The distribution of AEs was explored using the system organ classes (SOCs) of the MedDRA.

Additionally, we performed a disproportionality analysis of the FAERS data to identify the detection of tramadol-related AEs in traditional pharmacovigilance data. Disproportionality analysis is a comparison of observed and expected values; in this case, for tramadol-related AEs [30]. We calculated the proportional reporting ratio (PRR), the reporting odds ratio (ROR), and the information component (IC), which are commonly used as disproportionality measures. The threshold criteria for signal detection of adverse drug reactions were defined as PRR ≥2, ROR ≥2, and the observed number of tramadol-related AEs ≥3. The signal criterion for the IC measurements was when the lower limit of the 95% CI was greater than 0.

New signals were defined as AEs satisfying the signal criteria that were previously unknown or incompletely described. Their status as new was ascertained from tramadol label information. The drug labels were retrieved from a regulatory authority database (FDALabel, FDA, USA) and medical resources software systems (UpToDate, Wolters Kluwer Health; Micromedex, IBM). Medical events such as death, disability, hospitalization, or life-threatening consequences were classed as serious AEs. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc.).

Results

Table 1 shows the age and gender distributions of the patients with tramadol-related AEs from the WebMD and FAERS data sets. The majority of those who reported AEs on WebMD were adults aged 19-64 years. There were more reports from women than men. The FAERS data set showed a higher proportion of AEs reported by male and elderly patients. FAERS data had more missing values than WebMD data. The number of patient reports on FAERS was 10 times higher than on WebMD (n=2062 on WebMD; n=29,345 on FAERS). The majority of AEs in FAERS were reported from North America and Europe. The country distribution could not be presented on WebMD due to the lack of information.

Because some patients had multiple tramadol-related medical events, the number of AEs was greater than the number of patients. A total of 4288 and 123,393 AEs were reported on WebMD and FAERS, respectively. This corresponds to an average of 2.1 and 4.0 PTs per patient on the WebMD and FAERS systems, respectively. Table 2 shows the SOC of tramadol-related AEs for the 2 data sets. The SOC with a large number of AEs reported was largely consistent between the 2 data sets, although the frequency rankings were slightly different. There were many reports of psychiatric disorders, general disorders/administration site condition, nervous system disorders, and gastrointestinal disorders. However, the FAERS data included a higher percentage of injury, poisoning, and cardiac disorders. WebMD reports included a higher percentage of metabolism/nutritional disorders and eye disorders. FAERS and WebMD reported 22 and 27 SOCs, respectively, from a total of 27 possible MedDRA SOCs (data not shown).

Table 3 presents the distributions of AEs by MedDRA PTs of the WebMD and FAERS data sets in more detail. Drug inefficacy and drug dependence were the most frequently reported AEs on WebMD and FAERS, respectively. Patients from both data sets commonly reported drug dependence, nausea, vomiting, insomnia, dizziness, fatigue, anxiety, seizure, and pain. FAERS had a higher proportion of overdose, toxicity with various agents, death, and completed suicides. By contrast, WebMD reports included higher percentages of pruritus, constipation, and hyperhidrosis. Most reported AEs from both sources corresponded to those described on the drug labels. However, tramadol-related pain was not on these labels.

Table 1. Demographic characteristics of patients from the WebMD and FAERS[a] data sets.

Characteristics	WebMD, n (%)	FAERS, n (%)
Number of patients	2062 (100.0)	29,345 (100.0)
Age		
Less than 19 years old	12 (0.58)	1120 (3.82)
19-64 years old	1749 (84.82)	10,539 (35.91)
More than 64 years old	239 (11.59)	5523 (18.82)
Unknown	62 (3.01)	12,163 (41.45)
Gender		
Women	1359 (65.91)	14,928 (50.87)
Men	598 (29.00)	10,704 (36.48)
Unknown	105 (5.09)	3713 (12.65)
Occurrence country		
Africa	N/A[b]	96 (0.33)
Asia	N/A	1298 (4.42)
Europe	N/A	12,426 (42.34)
North America	N/A	14,997 (51.11)
Oceania	N/A	289 (0.98)
South America	N/A	141 (0.48)
Unknown	N/A	98 (0.33)

[a]FAERS: US Food and Drug Administration (FDA) Adverse Event Reporting System.
[b]N/A: not applicable.

Table 2. Classification of frequently reported tramadol-related adverse events from the WebMD and FAERS[a] data sets.

WebMD (N=4288)		FAERS (N=123,393)	
SOC[b]	Value, n (%)	SOC	Value, n (%)
Number of AEs	4288 (100.0)	Number of AEs	123,393 (100.0)
General disorders and administration site conditions	1360 (31.72)	Psychiatric disorders	23,340 (18.92)
Psychiatric disorders	900 (20.99)	General disorders and administration site conditions	16,899 (13.70)
Nervous system disorders	827 (19.29)	Injury, poisoning and procedural complications	15,764 (12.78)
Gastrointestinal disorders	568 (13.25)	Nervous system disorders	14,826 (12.02)
Skin and subcutaneous tissue disorders	239 (5.57)	Gastrointestinal disorders	9315 (7.55)
Investigations	80 (1.87)	Respiratory, thoracic and mediastinal disorders	4839 (3.92)
Musculoskeletal and connective tissue disorders	64 (1.49)	Musculoskeletal and connective tissue disorders	4729 (3.83)
Respiratory, thoracic, and mediastinal disorders	48 (1.12)	Investigations	4068 (3.30)
Metabolism and nutrition disorders	40 (0.93)	Skin and subcutaneous tissue disorders	3665 (2.97)
Eye disorders	32 (0.75)	Cardiac disorders	3274 (2.65)
Others	130 (3.03)	Others	22,674 (18.38)

[a]FAERS: US Food and Drug Administration (FDA) Adverse Event Reporting System.
[b]SOC: system organ classes of the Medical Dictionary for Regulatory Activities.

Table 3. Frequently reported tramadol-related adverse events from the WebMD and FAERS[a] data sets.

WebMD (N=4288)		FAERS (N=123,393)	
PT[b]	Value, n (%)	PT	Value, n (%)
Drug ineffective	599 (13.97)	Drug dependence	5547 (4.50)
Withdrawal syndrome	263 (6.13)	Overdose	3506 (2.84)
Insomnia	219 (5.11)	Toxicity to various agents	2824 (2.29)
Nausea	218 (5.08)	Drug hypersensitivity	2162 (1.75)
Drug dependence	197 (4.59)	Drug abuse	2053 (1.66)
Dizziness	197 (4.59)	Death	1840 (1.49)
Headache	171 (3.99)	Pain	1703 (1.38)
Somnolence	141 (3.29)	Nausea	1689 (1.37)
Pruritus	121 (2.82)	Drug ineffective	1673 (1.36)
Drug tolerance	105 (2.45)	Vomiting	1549 (1.26)
Vomiting	101 (2.36)	Completed suicide	1292 (1.05)
Abdominal pain (upper)	83 (1.94)	Somnolence	1247 (1.01)
Constipation	81 (1.89)	Dizziness	1046 (0.85)
Seizure	73 (1.70)	Depression	957 (0.78)
Fatigue	71 (1.66)	Confused state	954 (0.77)
Hyperhidrosis	68 (1.59)	Fall	920 (0.75)
Tremor	66 (1.54)	Anxiety	893 (0.72)
Feeling abnormal	64 (1.49)	Seizure	874 (0.71)
Pain	57 (1.33)	Fatigue	839 (0.68)
Anxiety	52 (1.21)	Headache	838 (0.68)
Euphoric mood	52 (1.21)	—	—
Others	1289 (30.06)	Others	88,987 (72.12)

[a]FAERS: US Food and Drug Administration (FDA) Adverse Event Reporting System.

[b]PT: preferred term of the Medical Dictionary for Regulatory Activities.

In Table 4, we present some examples of patient reports of tramadol-related pain from WebMD. Tramadol-related pain was of 2 types: pain caused by drug use and pain caused by drug discontinuation. The first 3 cases shown in the table are type 1, in which patients complained of pain after taking tramadol. Type 1 pain was primarily reported by patients who had been using tramadol for less than 1 year. The next 3 cases on the table are type 2, in which pain appears to be a symptom of withdrawal resulting from drug discontinuation, mostly in long-term tramadol users.

Table 4. Examples of patient reports of tramadol-related pain from WebMD.

Type	Gender	Age	Treatment duration	Medicine	Extracts text from review posts[a]
1	Female	45-54	1-6 months	Tramadol HCL	My doctor recommended this medication to me because of a pain I was experiencing. I went through a severe experience of drowsiness and more pain that I was even fainting. I had never used it again.
1	Female	65-74	Less than 1 month	Tramadol HCL	It helped for a couple days than my mouth & tongue broke out in sores and I started get upset stomach & worsen pain
1	Female	35-44	1-6 months	Ultram	I have cervical dystonia they gave me this pill that did nothing for pain. The pain got worse and worse finally on something different...
2	Female	25-34	1-6 months	Ultram	Wasn't for me. I can see how this could work for some but not for me. It took care of knee pain the first 2 days. The first day it even fixed a headache. After the third day, it did take the edge off but I still had stiffness and bruising type feeling on the knee. When off of the medicine, the pain was severe and sharp. Overall, it did work to help through the everyday but 3 flights up and down a few times a day isn't any match for this medicine.
2	Female	19-24	2 to less than 5 years	Tramadol HCL	I have been taking tramadol for the past 3 years and I agree that it does help with the pain. But after about the first year it stops working as well and you want to take more of the drug. It is very habit forming. There are too many withdrawal effects to mention. Sweating-freezing.. Diaharrea vomiting..sleep-less nights.. Pain in the legs.. Word of advice don't take this if you haven't already! You dont want the side effects! You will be sorry!
2	Female	45-54	10 years or more	Ultram	I can't stop taking it. The pain has got worse with this drug. The withdrawal is terrible. Side effects are flushing, sweating, irritable, over sensitive, pain, suicidal, can't spell (hehe)

[a]The reports are presented without correction in their original form as posted on the website.

In the FAERS data set, a total of 860 tramadol-related AEs satisfied all 3 of the signal detection criteria: PRR, ROR, and the lower limit of IC. Among them, 125 new signals not listed on the drug labels were found. The tramadol-related AEs and the PRR, ROR, and IC values are presented in Multimedia Appendix 2. The 3 tramadol-related AEs with the highest signal detection criteria values were ligament calcification (PRR=348.9; ROR=349.0; IC=4.1), hematidrosis (PRR=232.6; ROR=232.6; IC=3.1), and neurovascular conflict (PRR=139.6; ROR=139.6; IC=2.7). We also detected 20 new serious AE signals from the following 6 SOC categories: respiratory, vascular, gastrointestinal, infections, musculoskeletal, and nervous system disorders (Table 5). The vascular disorders category showed the largest criteria value of signal detection of the new serious AEs. Femoral artery aneurysm and iliac artery occlusion were included as serious AEs in this SOC category. Our results also included incidents of serious cardiotoxicity, intestinal twists or perforation, infections of the heart or lungs, and paralysis.

Table 5. New types of tramadol-related serious adverse events from the FAERS[a] data set.

SOC[b] and PT[c]	PRR[d]	ROR[e]	IC[f]
Respiratory, thoracic, and mediastinal disorders			
Diffuse alveolar damage	15.0	15.0	3.5
Cardiac disorders			
Toxic cardiomyopathy	22.9	22.9	3.0
Cardiorenal syndrome	10.0	10.0	2.8
Kounis syndrome	5.4	5.4	2.2
Vascular disorders			
Femoral artery aneurysm	74.8	74.8	3.9
Iliac artery occlusion	34.5	34.5	3.8
Gastrointestinal disorders			
Splenic artery aneurysm	15.8	15.8	2.5
Volvulus	4.0	4.0	1.8
Large intestine perforation	2.5	2.5	1.2
Infections and infestations			
Cardiac infection	5.5	5.5	2.0
Empyema	4.6	4.6	2.0
Endocarditis	3.5	3.5	1.7
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis	3.7	3.7	1.9
Nervous system disorders			
Cerebellar infarction	4.9	4.9	2.0
Toxic encephalopathy	3.2	3.2	1.6
Quadriplegia	4.5	4.5	2.0
Hemiplegia	2.7	2.7	1.4
Paraplegia	2.3	2.3	1.1
Paralysis	2.1	2.1	1.0

[a]FAERS: US Food and Drug Administration (FDA) Adverse Event Reporting System.

[b]SOC: system organ classes of the Medical Dictionary for Regulatory Activities.

[c]PT: preferred term of the Medical Dictionary for Regulatory Activities.

[d]PRR: proportional reporting ratio.

[e]ROR: reporting odds ratio.

[f]IC: information component.

Discussion

Principal Findings

It is necessary to identify unknown AEs to reduce drug-related health risks [31]. Many efforts have been made to systematically detect unknown AEs using both social media platforms and traditional pharmacovigilance systems [32,33]. The rich amount of publicly available health information that patients post online is an invaluable additional data source for postmarket safety surveillance [24,32]. Therefore, researchers have used data from both social media and pharmacovigilance systems to detect AEs, as each type of data source has its strengths and limitations [34-36].

FAERS is the national pharmacovigilance system used in the United States, while WebMD is among the social media platforms most frequently used in research to retrieve patient reviews of drug experiences. Thus, we used these 2 data sets to detect new tramadol-related AEs in this study. Our 2 data sets evidenced several AEs known to be symptomatic of serotonin syndrome, including altered mental status (eg, agitation, anxiety, hallucinations), autonomic instability (eg, arrhythmias, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (eg, hyperreflexia, tremor, rigidity), and gastrointestinal symptoms (eg, nausea, vomiting, diarrhea) [37,38]. However, there were qualitative differences in the reported tramadol-related AEs between the 2 data sets.

The FAERS data set produced a more diverse range of AEs than WebMD, in terms of both the range of severity and the affected organ systems. For example, reports of overdose, death, and completed suicide were only found on FAERS. FAERS reports also included 4 more SOCs in which tramadol-related AEs were reported than WebMD. Further, all but 1 (pain) of the new tramadol-related AEs detected was only found in the FAERS data set. Patients' reviews on WebMD were primarily concerned with mild AEs such as pruritus, constipation, and hyperhidrosis. These differences can be explained by the difference in sample sizes and AE reporters on the 2 sites. FAERS data had 10 times more reports of tramadol-related AEs than WebMD, allowing the inclusion of a wider range of AEs. This demonstrates the value of larger data sets when selecting social media platforms for drug-induced AE detection. Because AE reports on social media are only self-reported, serious AEs such as suicide and death cannot be reported on such platforms. However, because the risk perceptions associated with a given drug can differ between patients (mainly for WebMD) and health care professionals (mainly for FAERS), combining data from both populations may contribute to improved drug safety assessments.

The tramadol-related pain that was frequently reported in both data sets may be a previously unknown tramadol-related AE. The FDA drug label does not list pain among the potential tramadol-induced side effects. However, the statistical measures of disproportionality were over the threshold criteria of signal detection (PRR=2.2; ROR=2.2; IC=1.1). In addition, the patients' descriptions indicated increases in pain after taking tramadol. This is to be distinguished from both the persistence of existing pain due to an ineffective analgesic effect and pain caused by withdrawal following drug discontinuation. Increased pain might indicate opioid-induced hyperalgesia, which is increased sensitivity to pain caused by exposure to opioids [39]. There have been several reported cases of tramadol-induced hyperalgesia in previous studies [40,41]. Our result suggests that clinical assessments that consider opioid-induced hyperalgesia may be of value when patients complain of increased pain following tramadol treatment [42].

We detected 20 new serious AEs possibly related to tramadol. A clear distinction between the different types of serious AEs was difficult due to the diversity of AEs and related organ systems; however, most seemed to be broadly symptomatic of vascular diseases (eg, splenic artery aneurysm, femoral artery aneurysm, iliac artery occlusion) and their complications (eg, cerebellar infarction, quadriplegia, hemiplegia, paraplegia, paralysis). Our analysis also detected various coronary-related AEs. These results are not presented here because myocardial ischemia is already listed on the FDA drug label. The biological mechanisms that might explain an association between tramadol and vascular disease are not clear. A possible explanation is that tramadol mediates vascular homeostasis and thrombosis formation by inhibiting the reuptake of serotonin, affecting the platelet aggregation process [43]. Previous in vivo and in vitro studies have shown that tramadol use may enhance plasma coagulation and inhibit platelet disaggregation [44,45]. This finding from our analysis suggests that additional caution may be indicated before the use of tramadol in patients with vascular diseases as well as coronary artery disease.

Limitations

Our study had some limitations. First, our data may have produced nonrepresentative figures describing the occurrence of AEs due to limitations of spontaneous reporting systems such as under-reporting, selective reporting, biases in patient's drug preferences, and heterogeneity of the reports of different reporters [46]. Second, the results of our disproportionality analysis cannot prove a causal relationship. This method used the occurrence of AEs related to other drugs in the data as a proxy for the background incidence of AEs [47]. Thus, it may have been influenced by absolute report numbers. Third, posts from WebMD may have been misclassified into the wrong PTs due to a lack of clinical information. For example, if a patient complained that a coma occurred after taking tramadol, it cannot be medically confirmed that tramadol caused the coma without clinical information. Fourth, personal information from our data sets is based on voluntary reporting, and information has not been verified. Therefore, we could not rule out misinformation on demographics. Fifth, the user coverage may differ between 2 data sets, especially for the country profiles.

Conclusions

Despite the several study limitations, our study has 2 main strengths. First, this study found new tramadol-related signals. Based on the essential feature of pharmacovigilance signal [14], these findings have political implications for preventing drug-related health harms through the early detection of adverse drug reactions. Second, this study found the additional possible AE, pain, by comparing data from social media and conventional pharmacovigilance. Because pain is the main indication for analgesics, including tramadol, it is difficult to classify it as an AE without considering the patient's detailed symptom descriptions. Although FAERS is representative data for signal detection, detailed descriptions of AEs are not collected in this system. Thus, this study can be an example of the usefulness of patient drug reviews in social media in detecting unexpected AEs. However, the small sample size from WebMD prevented the detection of rare AEs by this means. To expand the utility of rare AE detection using social media, it would be necessary to use large amounts of social media data from several different sites, such as Twitter and Reddit. Social media data analysis using automatic natural language processing is a subject worthy of further research.

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Authors' Contributions

SP, Y-KS, and J-WK performed the data collection. SP and SC performed the data analysis. SP and J-WK wrote the paper, and all authors reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The number of tramadol-related adverse events in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data set.
[DOCX File , 16 KB - publichealth_v8i1e33311_app1.docx]

Multimedia Appendix 2
Signal detections of adverse events related to tramadol in the US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) data set.
[DOCX File , 31 KB - publichealth_v8i1e33311_app2.docx]

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Abbreviations

AE: adverse event
FAERS: US Food and Drug Administration (FDA) Adverse Event Reporting System
IC: information component
MedDRA: Medical Dictionary for Regulatory Activities
PRR: proportional reporting ratio
PT: preferred term of the Medical Dictionary for Regulatory Activities
ROR: reporting odds ratio
SOC: system organ classes of the medical dictionary for regulatory activities

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Original Paper

Patterns of Suicide Ideation Across Eight Countries in Four Continents During the COVID-19 Pandemic Era: Repeated Cross-sectional Study

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Abstract

Background: The COVID-19 pandemic and countries' response measures have had a globally significant mental health impact. This mental health burden has also been fueled by an infodemic: an information overload that includes misinformation and disinformation. Suicide, the worst mental health outcome, is a serious public health problem that can be prevented with timely, evidence-based, and often low-cost interventions. Suicide ideation, one important risk factor for suicide, is thus important to measure and monitor, as are the factors that may impact on it.

Objective: This investigation had 2 primary aims: (1) to estimate and compare country-specific prevalence of suicide ideation at 2 different time points, overall and by gender and age groups, and (2) to investigate the influence of sociodemographic and infodemic variables on suicide ideation.

Methods: A repeated, online, 8-country (Canada, the United States, England, Switzerland, Belgium, Hong Kong, Philippines, and New Zealand), cross-sectional study was undertaken with adults aged ≥18 years, with measurement wave 1 conducted from May 29, 2020 to June 12, 2020 and measurement wave 2 conducted November 6-18, 2021. Self-reported suicide ideation was derived from item 9 of the Patient Health Questionnaire-9 (PHQ-9). Age-standardized suicide ideation rates were reported, a binomial regression model was used to estimate suicide ideation indication rates for each country and measurement wave, and logistic regression models were then employed to relate sociodemographic, pandemic, and infodemic variables to suicide ideation.

Results: The final sample totaled 17,833 adults: 8806 (49.4%) from measurement wave 1 and 9027 (50.6%) from wave 2. Overall, 24.2% (2131/8806) and 27.5% (2486/9027) of participants reported suicide ideation at measurement waves 1 and 2, respectively, a difference that was significant (P<.001). Considerable variability was observed in suicide ideation age-standardized rates between countries, ranging from 15.6% in Belgium (wave 1) to 42.9% in Hong Kong (wave 2). Frequent social media usage

was associated with increased suicide ideation at wave 2 (adjusted odds ratio [AOR] 1.47, 95% CI 1.25-1.72; *P*<.001) but not wave 1 (AOR 1.11, 95% CI 0.96-1.23; *P*=.16). However, having a weaker sense of coherence (SOC; AOR 3.80, 95% CI 3.18-4.55 at wave 1 and AOR 4.39, 95% CI 3.66-5.27 at wave 2; both *P*<.001) had the largest overall effect size.

Conclusions: Suicide ideation is prevalent and significantly increasing over time in this COVID-19 pandemic era, with considerable variability between countries. Younger adults and those residing in Hong Kong carried disproportionately higher rates. Social media appears to have an increasingly detrimental association with suicide ideation, although having a stronger SOC had a larger protective effect. Policies and promotion of SOC, together with disseminating health information that explicitly tackles the infodemic's misinformation and disinformation, may importantly reduce the rising mental health morbidity and mortality triggered by this pandemic.

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KEYWORDS

pandemic; infodemic; psychosocial impacts; sense of coherence; suicide ideation; epidemiology; suicide; pattern; COVID-19; cross-sectional; mental health; misinformation; risk; prevalence; gender; age; sociodemographic

Introduction

Since the first known case was identified in Wuhan, China, the COVID-19 pandemic has led to globally significant physical and mental health sequelae [1,2] and extraordinary financial costs [3]. Inconsistent, continually evolving, and often swiftly implemented international and national response measures aimed at preventing the spread of COVID-19 have impacted all facets of society. Responses, while varied, commonly included stringent control measures such as lockdown and isolation periods, quarantine, restricted social gatherings and physical distancing, school and workplace closures, and domestic and international travel curtailments. The scale of global economic disruption from the COVID-19 pandemic has been unprecedented, resulting in countless business failures and job losses [3], despite multiple stimulus packages aimed at limiting the human and economic impacts of the pandemic [4]. Fear, anxiety, uncertainty, fatigue, together with the social and economic effects of the virus and associated countermeasures, have directly contributed to increased mental health burden [2,3]. This burden is unequally shared, disproportionately affecting vulnerable groups including young adults, students, ethnic minorities, and adults in socially or economically precarious situations [5,6]. In an effort to mitigate this mental health burden, many governments around the world have also implemented additional mental health support and financial measures [2].

The mental health burden of the COVID-19 pandemic has also been fueled by an infodemic—a rapid and far-reaching information overload, which includes misinformation and disinformation, that can serve to undermine or stymie public health responses [7-9]. The negative influence of excessive media exposure on mental health is receiving increasing attention and recognition [8-11], although its impact across the myriad of mental health and well-being domains has yet to be fully understood. In addition to national and international efforts aimed at readdressing this infodemic, such as a joint statement by the World Health Organization, the United Nations, and the United Nations Children's Fund among others [7], it has been opined that its effect can be buffered by individuals' and communities' psychological resources. Family functioning, social support, social participation, trust in agencies including health care institutions, and sense of coherence (SOC) are considered to be important resistance resources [7,9,12,13]. SOC develops over the life course, and those with a stronger SOC are able to understand, handle, and make sense of a stressful situation [9,12]. This likely increases individuals' capacities to use resistance resources to more effectively deal with the COVID-19 pandemic and associated circumstances [9,12,13]. On a population level, the infodemic is considered a major threat, with its promotion of noncompliance with public health measures; this reduces the effectiveness of these measures and ultimately enables the virus to continue to thrive [7]. On an individual level, it adds to confusion and strains mental health, already exacerbated by the pandemic. Therefore, it is essential to understand the importance of the infodemic, together with the factors and their role in mediating its effect.

Despite many national and international efforts, the global mental health burden of the COVID-19 pandemic is heavy [8], appears to be worsening [9], and is unequally shared within and between countries [8,9]. As a result, negative psychiatric and psychological responses are likely to be more prevalent, leading to poor mental health outcomes including, in the most severe cases, suicide. However, early findings from high-income and upper-middle-income countries suggest that the COVID-19 pandemic has not been associated with increases in population-level suicide rates [2]. Whether these findings remain true for lower-income countries or over longer timeframes, as the pandemic and associated global response measures continue, is open to conjecture and warrants future investigation. One mechanism for investigation is the monitoring of suicide ideation—a broad term used to describe a range of contemplations, wishes, and preoccupations with death [14]—an important risk factor for suicide [15]. Such monitoring is critical not only in alerting and informing governments and mental health agencies of a looming public health crisis but also to avert this already noted global issue with the aid of appropriate planning and prevention [16].

At the beginning of the pandemic, a cross-sectional convenience sampling study of suicide ideation among the general population across 10 countries between March 24, 2020 and April 30, 2020 (25,053 participants; 22.7% male) revealed significant differences between countries and among participants who were of younger age, male, married, and with various health beliefs

[17]. That study included adults aged ≥18 years from Hong Kong (n=11,368), Brazil (n=8375), China (n=956), the United Kingdom (n=845), Turkey (n=782), the United States (n=717), the Republic of Korea (n=658), Canada (n=508), Philippines (n=454), and Macau (n=186); overall suicide ideation within the previous 2 weeks was indicated by 15.7% of participants, derived from item 9 of the Patient Health Questionnaire-9 (PHQ-9) [18]. Suicide ideation ranged from 7.6% of participants in Brazil and the United Kingdom to 24.9% of participants in the Philippines [17]. However, the reliance on convenience sampling limited the external validity of these findings, and further tracking over time would provide much needed epidemiological information.

Using an 8-country, repeated-measure, cross-sectional study design, based on representative samples of adults and including several previously surveyed countries with the same PHQ-9 measurement instrument, this investigation had 2 primary aims: (1) to estimate and compare country-specific prevalence of suicide ideation at 2 different time points, overall and by gender and age groups, and (2) to investigate the influence of sociodemographic and infodemic variables on suicide ideation. In this paper, we contextualized findings with those published elsewhere to strengthen our understanding of suicide ideation across nations and people, to grasp the effect of the infodemic, and to provide empirical evidence that will ultimately be used to save lives.

Methods

Study Design

This was a repeated, 8-country, cross-sectional study, with measurement wave 1 conducted from May 29, 2020 to June 12, 2020 and measurement wave 2 conducted during November 6-18, 2020.

Participants

Study participants included adults aged ≥18 years residing in 1 of 8 countries from 4 continents (Canada, the United States, England, Switzerland, Belgium, Hong Kong, Philippines, and New Zealand) at the time of surveying.

Primary Measure

Our primary measure, self-reported suicide ideation, was derived from item 9 of the PHQ-9 [18]. The PHQ-9 asks: “Over the past 2 weeks, how often have you been bothered by the following problems?”, with item 9 asking “Thoughts that you would be better off dead or hurting yourself in some way.” Response options include (0) not at all, (1) several days, (2) over half the days, and (3) nearly every day. Suicide ideation responses were dichotomized into indicated (combining responses 1 through 3) and otherwise (response 0) categories. The PHQ-9 is available in multiple languages and has excellent internal consistency (Cronbach α=.89) and test-retest reliability (r=0.84) among primary care participants [18].

Sociodemographic, Pandemic, and Infodemic Variables

A detailed account of these variables and their definitions appears elsewhere [8]. In brief, gender identity was elicited with the following response options: male, female, another gender identity, I don't know/I prefer not to answer. Age in years was asked, with responses collapsed into the following groupings: 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, and ≥75 years. The usual household composition was defined as living alone, living with others including children, or living with others but without children; being an essential worker (eg, health care and social services, law enforcement, emergency services, provider of essential goods, educational institution) was indicated by a “yes” response. Those who worked in health care and social services were further partitioned from the other essential workers. The overarching goal of this interdisciplinary and international research project was to better understand how risk information is delivered and communicated by authorities and media and how it is received, understood, and used by the public. The perceived factors and threats caused by COVID-19 that are directly related to self were investigated, together with sources and trust in information [19]. Table 1 gives the names, descriptions, and response options of all utilized pandemic- and infodemic-related variables included in the survey. At both measurement waves, the questionnaire was validated by the project collaborators, then translated and made available in the English, French, German, Italian, and Chinese languages [8].

Table 1. Names, descriptions, and response options for the considered variables influenced by the pandemic.

Name	Descriptions	Response options
Self-isolation/quarantine	Having experienced self-isolation/quarantine, mandatory or voluntary	Yes because of symptoms or diagnosis of COVID-19, yes for other reasons, no
Financial losses	Having experienced financial losses of any kind due to COVID-19	Yes, no, unsure/ unknown
Threat perceived for oneself and/or family	Level of threat posed by the COVID-19 perceived for oneself and/or the family	Very low, low, moderate, high, very high
Threat perceived for country and/or world	Level of threat posed by COVID-19 perceived for the country and/or the world	Very low, low, moderate, high, very high
Being a victim of stigma	Being a victim of stigma or discrimination due to COVID-19	Yes, no, decline to answer
Level of information about COVID-19	Level would you rank your level of information about COVID-19	10-point scale: 1, very low level; 1-8, otherwise; 9-10, high level; 10, very high level
Trust in authorities score	Level at which you would rank your level of trust in (1) scientists, doctors, and health experts; (2) national health organizations; (3) global health organizations; (4) government	Each response rated on a 10-point scale: 1, very low level; 10, very high level; 4 scores summed, and partitioned into approximate quartiles based on measurement wave 1-response distributions
Internet-based social media as a regular source of information	Extent that social networks (eg, Facebook, Twitter, Instagram, other networks) are used to inform yourself about COVID-19	Mainly/always, often, sometimes, not much/never
Friends/family/co-workers as a regular source of information	Extent that friends/family/co-workers are used to inform yourself about COVID-19	Mainly/always, often, sometimes, not much/never
Sense of coherence	Measured using the 3-item Sense of Coherence (SOC-3) instrument [20,21], corresponding to comprehensibility, manageability, and meaningfulness; participants were asked (1) Do you usually see a solution to problems and difficulties that other people find hopeless? (2) Do you usually feel that your daily life is a source of personal satisfaction? (3) Do you usually feel that the things that happen to you in your daily life are hard to understand?	Each with response options: no (0), yes - sometimes (1), yes - usually (2); question (3) was reverse scored; then, the 3 scores were summed and dichotomized using the threshold: weaker (summed score of 0-4) or stronger (summed score of 5-6).

Procedure

A detailed description of the procedure and analyses involving these survey data to answer different research questions appears elsewhere [8,9]. Two polling firms, in collaboration with international partners, undertook recruitment and data collection using an online platform. Participants were randomly recruited from online panels using multiple sources, including traditional and mobile telephone methodologies (through a call center), social media (through Facebook and Instagram), and offline methods (through partner programs and campaigns such as friend recommendations). Quota sampling was used to ensure recruitment and representation of hard-to-reach groups. Once contacted and eligibility confirmed, a full explanation of the study purpose, methods of data management, and assurance of confidentiality was provided to potential participants prior to their agreement to participate in the online study. The survey was designed to take approximately 20 minutes to complete.

Selection of countries for inclusion was based on ensuring global continent diversity within a constrained budget and capturing different demographics, health systems and policies, and COVID-19 burdens and responses. Moreover, it was deemed necessary to invite country-specific lead investigators to provide context and ensure the survey was culturally fit-for-purpose. The core team came together from multiple existing professional connections, including the World Health Organization Thematic Platform for Health Emergency and Disaster Risk Management Research Network.

The implemented quota sampling was tailored for each country and based on that country's latest available census-derived population demographics. Strata comprised of age groups (18-24 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, ≥65 years), gender (female, male), and region (which was country-specific; eg, for Canada: Ontario, Québec, British Columbia, Alberta, Manitoba/ Saskatchewan, Atlantic provinces). A 70% minimum recruitment of the estimated stratum numbers for each characteristic (age, gender, and region) was targeted in order to ensure the best possible representation in the sample. The collected data were then weighted by the population demographic distributions to reach the final representative sample.

For each country, a minimum sample target was set at 1000 adults, except for Canada (the host country of the lead investigators), which was set at 1500. Common to broad-based, multipurpose epidemiology studies, a number of core principles and pragmatic considerations were invoked in selecting these sample sizes. They include (1) a largely balanced sample size for each country so that investigations of differences between countries has maximal statistical power, (2) the power to detect

differences in proportions of ≥10% or a relative risk of ≥1.2 exceeds 80% at the 2-tailed α=.05 within each country (these detectable differences are moderate to large and likely to be of clinical or meaningful significance), and (3) to maximize the number of different countries able to participate within a constrained budget.

Statistical Analysis

Reporting of study findings was informed by the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines [22]. Participant numbers and demographics by countries and measurement waves were initially described and compared using Pearson design-based *F* tests, which also accounted for sample weightings. Next, the crude overall PHQ-9 response distributions by measurement wave were described and compared using Pearson design-based *F* tests. Age-standardized suicide ideation rates across countries and measurement waves were then determined and compared. Direct standardization was employed, with the reference population drawn from the combined wave 1 and wave 2 samples and then stratified by age groups. This derived reference population was preferred, rather than adopting any standard population, due to the particular mix of lower- and higher-income countries included within this study. Age-specific observed rates stratified by age groups were then derived for each country and measurement wave separately, and the weighted average of the stratum-specific rates, together with measures of their variability, relative to the reference population was calculated. Analysis of variance was used to compare rates between countries for each measurement wave, and 2-sample Student *t* tests were employed to test the mean difference in age-standardized rates between measurement waves by country.

Treating countries as fixed effects, a binomial regression model with an identity link function was then used to estimate and compare rates of suicide ideation indication by gender and age groups for each country and measurement wave. The identity link function was chosen as multivariable-adjusted prevalences and their differences were of primary reporting interest [23]. In this model, gender, age group, country, and measurement wave main effects were initially considered together with all their 2-factor interaction term combinations. Backward stepwise elimination of nonsignificant interaction terms followed, determined by sequentially removing nonsignificant interaction terms yielding the highest Ward type III ^2P value, to derive the final model. The main effects and interaction terms in this final model represented a baseline combination of variables.

Binomial regression models with log link function were next considered to relate sociodemographic, pandemic, and infodemic variables to suicide ideation. However, despite using different maximization techniques (such as maximum likelihood optimization and iterated, reweighted least-squares optimization of the deviance) and starting value searches, some of these models failed to converge, which is a widely recognized issue [23]. Instead, more stable logistic models were employed. For the crude analysis, each variable and its interaction with measurement wave were added and investigated in a regression model that also included the baseline combination of variables. Finally, an adjusted analysis was conducted, whereby all considered sociodemographic, pandemic, and infodemic variables together with their interaction by measurement wave were simultaneously included in a regression model that also contained the baseline combination of variables. No main effect nor interaction term variable selection was undertaken for this adjusted analysis. A direct evaluation of the final model fit was unable to be conducted as most diagnostics are unavailable when the data include survey sampling weights. Instead, an indirect evaluation was conducted whereby the final model was rerun without these weights. The Hosmer-Lemeshow goodness-of-fit test was conducted using the conventionally employed 10 partitions [24]. This was followed by an area under the receiver operating characteristic curve (AUC) analysis. AUC is frequently employed as a summary measure of a model's predictive accuracy [25]. Adopting the recommendations of Hosmer and Lemeshow [24], an AUC of .5 suggests no discrimination, .7-.8 is considered acceptable, .8-.9 is considered excellent, and more than .9 is considered outstanding. All analyses were conducted using Stata SE version 16.0 (StataCorp, College Station, TX), accommodating the survey sampling weights and employing robust variance estimators. A 2-tailed α=.05 defined significance.

Ethics

This study sits within a broader program of research funded by the Canadian Institutes of Health Research, reviewed and approved by the Research Ethics Board of the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Estrie—Center hospitalier universitaire de Sherbrooke (CHUS; Human Ethics Committee [HEC] ref: 2020-3674). Informed consent was obtained from all participants before their participation, and the collection of information was carried out confidentially. Participants were able to withdraw at any time without penalty or need for explanation. The data sets did not carry any personally identifiable information. The study complied with the ethical standards for human experimentation as established by the Helsinki Declaration and Canada's HEC. All methods and reporting were performed in accordance with the HEC's relevant guidelines and regulations.

Results

Participants

The final sample totaled 17,833 adults: 8806 (49.4%) from measurement wave 1 and 9027 (50.6%) from wave 2. Overall, 51.6% (9204/17,833) were female, and 49.2% (8769/17,833) were aged between 18 years and 44 years. The sample numbers and weighted distribution (%) of participants' demographic characteristics by country and measurement wave appear in Table 2. Significant differences between countries were observed for age groups at measurement wave 1 (P<.001) and wave 2 (P<.001) but not for gender (P=.68 and P=.70 for measurement waves 1 and 2, respectively). Consistent with global demographic patterns, Filipino participants were younger than their non-Filipino counterparts.

Table 2. Participant numbers and weighted distribution (%) of their demographic characteristics by country and measurement waves 1 (surveyed between May 29, 2020 and June 12, 2020) and 2 (surveyed November 6-18, 2020).

Country	Gender[a], n (%)		Age (years), n (%)						
	Female	Male	18-24	25-34	35-44	45-54	55-64	65-74	≥75
Canada									
Wave 1 (n=1501)	723 (48.4)	772 (51.6)	163 (10.9)	247 (16.4)	243 (16.2)	269 (17.9)	262 (17.5)	246 (16.4)	72 (4.8)
Wave 2 (n=2004)	963 (48.3)	1031 (51.7)	218 (10.9)	329 (16.4)	324 (16.2)	359 (17.9)	350 (17.5)	340 (17.0)	84 (4.2)
United States									
Wave 1 (n=1065)	516 (48.5)	548 (51.5)	59 (5.5)	226 (21.2)	191 (17.9)	204 (19.1)	189 (17.8)	146 (13.7)	50 (4.7)
Wave 2 (n=1003)	478 (48.1)	517 (51.9)	81 (8.0)	187 (18.7)	180 (17.9)	192 (19.1)	178 (17.8)	71 (7.1)	114 (11.4)
England									
Wave 1 (n=1041)	508 (48.8)	532 (51.2)	116 (11.1)	181 (17.4)	170 (16.3)	186 (17.9)	151 (14.5)	190 (18.3)	47 (4.5)
Wave 2 (n=1000)	487 (48.8)	511 (51.2)	111 (11.1)	174 (17.4)	163 (16.3)	179 (17.9)	145 (14.5)	192 (19.2)	35 (3.5)
Belgium									
Wave 1 (n=1015)	494 (48.6)	521 (51.4)	63 (6.2)	208 (20.5)	139 (13.7)	210 (20.7)	171 (16.9)	186 (18.3)	37 (3.7)
Wave 2 (n=1014)	489 (48.4)	520 (51.6)	57 (5.6)	215 (21.2)	118 (11.6)	228 (22.5)	161 (15.9)	197 (19.4)	38 (3.7)
Switzerland									
Wave 1 (n=1002)	478 (47.7)	523 (52.3)	95 (9.5)	144 (14.4)	138 (13.8)	177 (17.6)	239 (23.9)	160 (16.0)	48 (4.8)
Wave 2 (n=1000)	477 (47.8)	522 (52.2)	95 (9.5)	144 (14.4)	138 (13.8)	176 (17.6)	171 (17.1)	226 (22.6)	49 (4.9)
Hong Kong									
Wave 1 (n=1140)	513 (45.1)	626 (54.9)	108 (9.5)	196 (17.2)	206 (18.1)	218 (19.1)	202 (17.7)	200 (17.5)	10 (0.9)
Wave 2 (n=1002)	451 (45.0)	550 (55.0)	95 (9.5)	172 (17.2)	181 (18.1)	192 (19.1)	177 (17.7)	171 (17.1)	13 (1.3)
Philippines									
Wave 1 (n=1041)	510 (49.4)	522 (50.6)	224 (21.6)	260 (25.0)	209 (20.1)	162 (15.5)	106 (10.2)	63 (6.1)	17 (1.6)
Wave 2 (n=1003)	489 (49.3)	503 (50.7)	216 (21.6)	251 (25.0)	201 (20.1)	156 (15.5)	126 (12.5)	47 (4.7)	6 (0.6)
New Zealand									
Wave 1 (n=1001)	484 (48.6)	512 (51.4)	122 (12.2)	184 (18.4)	163 (16.3)	175 (17.5)	157 (15.7)	149 (14.9)	50 (5.0)
Wave 2 (n=1001)	484 (48.6)	513 (51.4)	122 (12.2)	184 (18.4)	163 (16.3)	175 (17.5)	157 (15.7)	138 (13.8)	61 (6.1)

[a]25 participants at the measurement wave 1 and 42 participants at measurement wave 2 did not identify as being female (F) or male (M) or preferred not to answer this question, so had their gender set to missing.

Suicide Ideation

Overall Rates

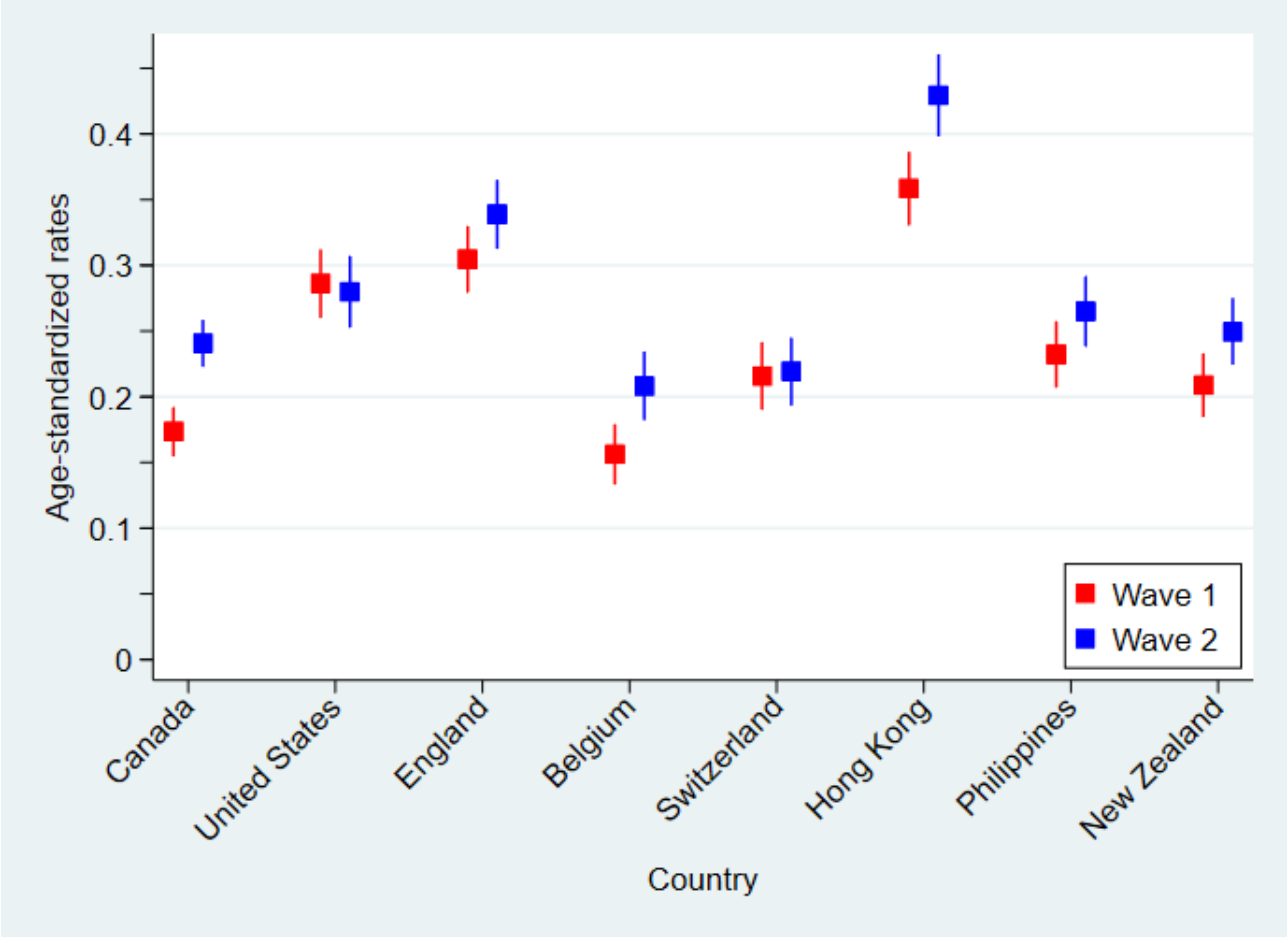
At measurement wave 1, 75.8% (6674.9/8806) of participants had no thoughts of being better off dead or hurting themselves in some way over the previous 2 weeks, whereas 14.7% (1247.9/8806) had these thoughts on several days, 6.4% (565.9/8806) had these thoughts over half the days, and 3.6% (317.3/8806) reported having these thoughts nearly every day. Approximately 5 months later, at the second measurement wave, 72.5% (6541.3/9027) of participants had no thoughts of being better off dead or hurting themselves in some way over the previous 2 weeks, 15.3% (1379.3/9027) had these thoughts on several days, 7.8% (706.6/9027) had these thoughts over half the days, and 4.4% (399.8/9027) reported having these thoughts nearly every day. These response distributions were significantly different between measurement waves (P<.001), with a 3.3% decrease in those having no thoughts of death of harm over the previous 2 weeks at measurement wave 2 compared with wave 1 and concomitantly, a 2.2% increase in those reporting having these thoughts nearly every day or over half the days.

Age-Standardized Rates

Figure 1 presents the age-standardized rates of the dichotomized suicide ideation variable across countries for measurement waves 1 and 2. Table S1 in Multimedia Appendix 1 gives the combined total age distribution of participants over measurement waves and countries used as the reference population for these age standardization calculations. Perusal of Figure 1 suggests that important differences in self-reported suicide ideation exist between countries and measurement waves. Analysis of variance confirmed this, with significant differences in age-standardized rates found between countries at measurement wave 1 (P<.001) and wave 2 (P<.001). Rates in Hong Kong participants, for instance, were significantly higher than all other countries at both measurement waves (all P<.001, except for P=.006 when compared with England participants at measure wave 1). When

comparing age-standardized rates of suicide ideation between measurement waves 1 and wave 2, significant increases were observed for participants in Canada (mean difference .067, 95% CI .041-.094; *P*<.001), Belgium (mean difference .052, 95% CI .017-.087; *P*=.004), Hong Kong (mean difference .071, 95% CI .029-.113; *P*<.001), and New Zealand (mean difference .041, 95% CI .006-.076; *P*=.02) but not for participants in the United States (*P*=.75), England (*P*=.07), Switzerland (*P*=.86), or the Philippines (*P*=.08).

Figure 1. Age-standardized rates and associated 95% CIs of suicide ideation by country for measurement waves 1 (surveyed between May 29, 2020 and June 12, 2020) and 2 (surveyed November 6-18, 2020).



Age- and Gender-Adjusted Comparison of Suicide Ideation Between Countries

As a result of the relatively small number of participants within the ≥75-year age group (see Table 1 and Multimedia Appendix 1, Table S1), they were combined with those aged 65-74 years to form the ≥65-year age category used henceforth. Initially, the statistical model of the binary measure of suicide ideation included the main effects of gender, age group, country, and measurement wave, together with all 2-factor interactions. However, the measurement wave × gender (step 1, *P*=.46) and measurement wave × country (step 2, *P*=.12) interaction terms were nonsignificant and were thus removed, leaving a model that included gender (*P*=.44), age group (*P*<.001), country (*P*<.001), measurement wave (*P*=.003), age group × gender (*P*<.001), country × gender (*P*=.003), age group × country (*P*<.001), and age group × measurement wave (*P*=.001). Due to its significant interactions with age group and country, the gender main effect was retained within the final model, despite not having a significant *P* value. Figure 2 and Table S2 in Multimedia Appendix 1 provide the estimated proportions of suicide ideation indication, together with associated 95% CIs, derived from this final model. These estimated proportions ranged from .040 (95% CI .010-.069) in measurement wave 1 and .030 (95% CI .001-.059) in wave 2 among women aged ≥65 years from Switzerland to .623 (95% CI .555-.690) in wave 1 and .692 (95% CI .618-.765) in wave 2 among women aged 18-24 years from England; see Table S2 in Multimedia Appendix 1.

Figure 2. Estimated proportion of participants self-reporting suicide ideation by country and measurement waves 1 and 2 stratified by age group, derived from the binomial regression model including age group, gender, country, measurement wave, and the measurement wave × age group, country × age group, country × gender, and age group × gender interactions. Females are denoted by red, males by blue, measurement wave 1 with hollow circles, and measurement wave 2 with solid circles. BEL: Belgium; CAN: Canada; ENG: England; HK: Hong Kong; NZ: New Zealand; PHL: Philippines; SWI: Switzerland; USA: United States.

Overall, among women, those aged 18-24 years had the highest estimated proportion of indications at both measurement waves (mean .389 and .458, respectively) and the greatest increase between measurement waves (mean change .069). Both the proportion of indications and the difference between measurement waves dampened with increasing age group. For men, those aged 25-34 years had the highest estimated indication proportion at both measurement waves (mean .414 and .468, respectively), somewhat higher than for those aged 18-24 years (mean .398 and .467, respectively). However, similar to female participants, the greatest increase in suicide ideation indications between measurement waves (mean change .069) occurred for those aged 18-24 years, and the proportion of indications and difference between measurement waves dampened with increasing age group; see Figure 2 and Table S2 in Multimedia Appendix 1. Notable in Figure 2 and Table S2 in Multimedia Appendix 1 are the relatively high proportions of participants experiencing suicide ideation from Hong Kong across all age groups, especially among those aged 45-54 years or ≥65 years.

Factors Affecting Suicide Ideation

The weighted frequency distributions of the potential risk and protective COVID-19–related factors for suicide ideation indication by measurement wave are presented in Table S3 in Multimedia Appendix 1. Logistic regression–estimated crude (OR) and adjusted (AOR) odds ratios and accompanying 95% CIs of suicide ideation associated with these factors by measurement wave appear in Table 3. The crude ORs were adjusted by gender, age group, country, and measurement wave main effects together with the age group × gender, country × gender, age group × country, and age group × measurement wave interaction terms identified in the previous section. In these analyses, both the main effect and interaction by measurement wave terms were significant for variables corresponding to self-isolation/quarantine (P<.001 and P=.02, respectively), financial losses (P<.001 and P=.003, respectively), and threat perceived for oneself and/or family (P<.001 and P=.008, respectively). However, significant main effect and nonsignificant interactions by measurement wave terms were identified for variables corresponding to being an essential worker (P<.001 and P=.66, respectively), being a victim of stigma (P<.001 and P=.09, respectively), trust in authorities score (P<.001 and P=.49, respectively), internet-based social media as a regular source of information (P<.001 and P=.13, respectively), friends/family/co-worker as a regular source of information (P<.001 and P=.33, respectively), and SOC (P<.001 and P=.24, respectively). This implies that these variables have a significant relationship with suicide ideation, which did not change between measurement waves. For the remaining variables, no significant relationships were observed.

Table 3. Estimated crude and adjusted odds ratios (ORs) and associated 95% CIs of suicide ideation associated with potential risk and protective COVID-19 related factors by measurement wave for the logistic model that included the entire sample over both measurement waves.

Factors	Crude OR (95% CI)[a]		Adjusted OR (95% CI)[b]	
	Wave 1	Wave 2	Wave 1	Wave 2
Household composition				
Alone	1 (reference)	1 (reference)	1 (reference)	1 (reference)
With children	0.93 (0.78-1.11)	1.02 (0.85-1.23)	1.03 (0.83-1.27)	1.05 (0.85-1.29)
With others	0.89 (0.75-1.06)	0.88 (0.74-1.05)	0.98 (0.81-1.20)	0.94 (0.77-1.13)
Essential worker				
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes: health	1.72 (1.45-2.04)	1.60 (1.33-1.91)	1.60 (1.31-1.96)	1.36 (1.10-1.69)
Yes: other	1.43 (1.24-1.65)	1.32 (1.14-1.52)	1.29 (1.09-1.53)	1.22 (1.03-1.44)
Self-isolation/quarantine				
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes: case/symptom-free	1.16 (1.01-1.32)	1.42 (1.24-1.63)	1.08 (0.93-1.26)	1.23 (1.05-1.44)
Yes: case or symptoms	3.16 (2.64-3.77)	2.84 (2.42-3.34)	2.39 (1.95-2.93)	1.91 (1.58-2.32)
Financial losses				
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	1.39 (1.23-1.57)	1.82 (1.62-2.06)	1.09 (0.95-1.25)	1.40 (1.22-1.60)
Unsure/unknown	1.95 (1.56-2.43)	2.85 (2.15-3.78)	1.79 (1.30-2.47)	2.42 (1.50-3.91)
Threat perceived for oneself and/or family				
High	1.84 (1.64-2.07)	1.47 (1.31-1.66)	1.66 (1.44-1.90)	1.31 (1.14-1.51)
Otherwise	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Threat perceived for country and/or world				
High	1.00 (0.88-1.13)	0.91 (0.80-1.04)	0.85 (0.73-0.98)	0.82 (0.70-0.96)
Otherwise	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Being a victim of stigma				
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	3.34 (2.88-3.87)	3.83 (3.27-4.49)	2.58 (2.17-3.06)	2.74 (2.26-3.31)
Decline to answer	1.64 (1.37-1.95)	2.24 (1.73-2.89)	1.15 (0.90-1.45)	1.23 (0.78-1.95)
Level of information about COVID-19				
High	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Otherwise	0.96 (0.85-1.08)	0.98 (0.86-1.11)	0.91 (0.79-1.06)	0.97 (0.83-1.13)
Trust in authorities score				
Q1 (low)	1.39 (1.19-1.63)	1.39 (1.19-1.63)	1.56 (1.29-1.89)	1.40 (1.15-1.71)
Q2	1.15 (0.98-1.36)	1.27 (1.08-1.50)	1.29 (1.06-1.57)	1.34 (1.10-1.63)
Q3	0.96 (0.81-1.13)	1.11 (0.95-1.31)	1.06 (0.87-1.28)	1.09 (0.90-1.32)
Q4 (high)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Internet-based social media as a regular source of information				
Often/always	1.35 (1.19-1.52)	1.54 (1.35-1.75)	1.11 (0.96-1.30)	1.47 (1.25-1.72)
Sometimes/never	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Friends/family/co-workers as a regular source of information				
Often/always	1.23 (1.10-1.38)	1.14 (1.01-1.28)	1.06 (0.92-1.23)	0.96 (0.83-1.11)
Sometimes/never	1 (reference)	1 (reference)	1 (reference)	1 (reference)

Factors	Crude OR (95% CI)[a]		Adjusted OR (95% CI)[b]	
	Wave 1	Wave 2	Wave 1	Wave 2
Sense of coherence				
Stronger (5-6)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Weaker (0-4)	3.96 (3.36-4.67)	4.56 (3.85-5.40)	3.80 (3.18-4.55)	4.39 (3.66-5.27)

[a]Adjusted for gender, age group, country, measurement wave, age group × gender, country × gender, age group × country, and age group × measurement wave.

[b]Adjusted for all variables included within this table, together with their interaction by measurement wave and the main effect and interactions terms included within the crude analysis.

When considered together in the adjusted analysis, the patterns of associations remained the same except that "friends/family/co-worker as a regular source of information" was no longer significant (main effect *P*=.38; interaction *P*=.32), "threat perceived for country and/or world" had a significant main effect (*P*=.03) but nonsignificant interaction (*P*=.80), and "internet-based social media as a regular source of information" had a nonsignificant main effect (*P*=.16) but significant interaction (*P*=.01), so that frequent users of social media were associated with significantly higher suicide ideation than infrequent users at measurement wave 2 (*P*<.001). Based on the magnitude of the *z* score, having a weaker SOC was associated with the highest likelihood of suicide ideation among the factors considered (AOR 3.80, 95% CI 3.18-4.55; *P*<.001 at wave 1, and AOR 4.39, 95% CI 3.66-5.27; *P*<.001 at wave 2), followed by identifying as being a victim of stigma (AOR 2.58, 95% CI 2.17-3.06; *P*<.001 at wave 1 and AOR 2.74, 95% CI 2.26-3.31; *P*<.001 at wave 2). Hong Kong participants were the most likely to report a weaker SOC. At measurement wave 1, 90.0% (1025.9/1140) of Hong Kong participants reported a weaker SOC compared with 66.9% (5130.4/7666) of participants in the other countries, while for measurement wave 2, the percentages were 90.3% (905.0/1002) and 67.3% (5402.7/8025), respectively.

In the adjusted model, re-analyzed without survey sampling weights, the Hosmer-Lemeshow goodness-of-fit was not significant (*P*=.38), and the AUC was .803 (95% CI .795-.810), which is on the cusp between acceptable and excellent. This indirect evidence suggests that the final model has adequate fit.

Discussion

Principal Findings

Suicide ideation is prevalent and increased significantly over time in the COVID-19 pandemic. Overall, 24.2% and 27.5% of adults aged ≥18 years reported at least one such thought at measurement waves 1 and 2, respectively. This is substantially higher than the 15.5% reported from a study undertaken approximately 2 months earlier than measurement wave 1 [17]. However, like the previous study, there was considerable variability between countries in the age-standardized rates of suicide ideation at measurement wave 1, ranging from 15.6% (95% CI 13.3%-17.9%) in Belgium to 35.8% (95% CI 33.0%-39.7%) in Hong Kong, and measurement wave 2, ranging from 20.8% (95% CI 18.2%-23.5%) in Belgium to 42.9% (95% CI 39.8%-46.1%) in Hong Kong. This significant increase in overall rates between studies likely reflects people's significant psychological deterioration over time, as observed within this study; the different composition of countries investigated; and the fundamentally different sampling strategies. Reliance on convenience sampling, particularly in surveys of mental health (where individuals with existing or severe mental illness are less likely to participate), is prone to substantial bias [26].

Hong Kong adults had demonstratively higher rates of suicide ideation than their counterparts in the comparator countries. This may reflect the cumulative effects of COVID-19 together with the political instability and social unrest of that time, which included the 2019-2020 Hong Kong protests [27]. These protests and the accompanying social unrest may have also directly contributed to the Hong Kong participants having consistently lower SOC levels (the greatest protective factor, over and above age and gender, against suicide ideation observed in this study) compared with the other investigated countries. Although the lower SOC levels may also be cultural, or even simply arise from different understandings of the questions in different cultures, it behooves further investigation.

Previously, a population-based prospective cohort of adults aged ≥18 years identified a major mental health burden during a time of social unrest in Hong Kong, although suicide ideation was identified in only 4.3% of their respondents using the same PHQ-9 instrument [28]. Also using the PHQ-9 item 9, another population-representative sample of Hong Kong residents aged ≥15 years conducted in July 2019 reported that 9.1% of their participants had suicide ideation [29]. These rates are significantly less than the 22.0% reported in a multinational study of suicide ideation [17] and the age-standardized rate of 35.8% reported here. Although the Hong Kong rate of suicide increased with the severe acute respiratory syndrome (SARS) outbreak in 2003, particularly among older adults, it has stabilized since to around 13.0/100,000 people per year [30]. This 2019 age-standardized rate for Hong Kong is higher than that in Canada or New Zealand, both estimated at 10.3/100,000 people per year, but less than that in the United States or Belgium, estimated at 14.5/100,000 and 13.9/100,000 people per year, respectively [30,31]. Thus, it could be argued that suicide and suicide ideation in Hong Kong may reflect culturally traditional patterns rather than a result of lower SOC [32].

Both age and gender were associated with suicide ideation. Apart from Hong Kong participants, rates decreased as age groups increased, a finding consistent with the literature [14,33]. Among those aged 18-24 years, 55-64 years, or ≥65 years, women in England, Belgium, and the Philippines had higher

estimated suicide ideation rates than men. Interestingly, according to the Worldometer [34], cumulative COVID-19 death rates for England (60.6 and 115.6 per 100,000 in June 2020 and November 2021, respectively) and Belgium (82.0 and 125.1 per 100,000 in June 2020 and November 2021, respectively) were highest among the countries investigated here, although the Philippines ranked sixth among the 8 countries. Women may have been differentially impacted or burdened by the relatively high mortality rates in England and Belgium, and the cultural expectations of Filipino women could contribute to these observations.

In all other countries and age groups, the reverse pattern was observed, with men having higher estimated rates than women. Arguably, apart from those aged 25-34 years, these gender differences were relatively small compared to the variations across age groups, countries, and measurement waves—suggesting that this extraordinary pandemic effect transcends previously documented gender differences. It is noteworthy that the reported results from the general population 2015 National Survey on Drug Use and Health in the United States showed similar variability between gender across age groups [33]. Strikingly and perhaps unsurprisingly, the factor with the most protective effect against suicide ideation, over age and gender, was having a stronger SOC. An increased SOC has previously been associated with lower rates of suicide ideation and attempts of suicide [35-37]. It also has been shown to be associated with lower rates of common psychopathological symptoms in this pandemic [8,9] and thus arguably, is an important underestimated resource in minimizing the COVID-19 psychosocial impact [8]. Health promotion strategies that strengthen SOC may provide a useful protective mechanism to assuage people's mental health burdens [38].

Although having a smaller effect size, another key finding was the rise and significance of internet-based social media as a regular source of information associated with suicide ideation in the adjusted analyses. In the first measurement wave, those who often or always used social networks as a regular source of information had an AOR of 1.11 (95% CI 0.96-1.30) compared with those who sometimes or never used social networks, a nonsignificant difference (P=.16). However, by measurement wave 2, the AOR had increased to 1.47 (95% CI 1.25-1.72), a difference that was significant (P<.001). Although social media can have a crucial role in disseminating health information and tackling infodemics and misinformation [39], frequent exposure to social media has been associated with mental health problems during the COVID-19 outbreak [40]. Interestingly, the deterioration in mental health associated with frequent social media use over the course of this pandemic has also been previously observed in 2 studies from China [40,41].

Strengths and Limitations

Although having salient strengths, such as the relatively large sample size, the timeliness of the recruitment and analysis, the spread of participants across 8 countries and 4 continents, and the repeated nature of the survey using consistent and psychometrically robust instruments, this study also has limitations. Arguably, the greatest potential weakness is the sampling mechanism and associated unmeasurable nonsampling bias. The employed sampling frame is more opaque than traditional or conventionally used frames. Participants were nonetheless randomly recruited from panels developed using multiple online and offline sources. Moreover, quota targeting sampling together with survey sampling weights were used to ensure approximately representative samples. In designing, attracting funding for, securing ethics for, and implementing this study, there was a pragmatic requirement to maximize expedited data collection, sample frame availability, cost effectiveness, and international reach while minimizing nonsampling bias. The selected approach sought to optimize these requirements and yield reliable and robust research data. However, despite considerable efforts undertaken to derive representative samples, some population groups may be underrepresented, including people without internet access or those with lower literacy levels [26]. In addition, people living with existing disabilities (including mental illness) are less likely to participate in online surveys compared with those without such disabilities and illnesses [26,42]. Although sampling weightings were adopted to ameliorate this effect, these adjustments may miss crucial elements of bias and cannot account for groups not included within the surveys.

Another potential weakness is the repeated cross-sectional rather than longitudinal study design, which negates any causal assertions. Moreover, individual participant changes over time cannot be investigated. However, assuming the sampling strategy and uptake remain consistent, valid population-level trend analyses can be conducted [43]. A careful statistical approach was employed here, which sought to disentangle systematic patterns from sampling variability, to investigate population-level, time-varying changes between measurement waves. Furthermore, ORs were reported rather than prevalence ratios (PRs). As suicide ideation was relatively common in this study, these ORs may overestimate their respective PRs and should not be interpreted as measures of relative risk [44]. Binomial regression models estimating PRs were initially entertained, but convergence issues arose. Instead, the more stable logistic models were employed without issue [23]. However, regardless of the regression model ultimately employed, the reported results may suffer from residual or unmeasured confounding effects [45]. For example, questions on the availability of face masks and protective clothing and the market flooding of ineffective counterfeit versions in Hong Kong [46] were not asked but are likely to contribute to poor mental health and suicide ideation of its people. Unmeasured confounding variables can result in substantial bias in the estimated exposure-outcome AOR, particularly if it is uncorrelated with the measured explanatory variables. Study replication using different suites of variables is needed to understand its effect. Another potential limitation is the PHQ-9 item 9 measure itself. It has been widely used and endorsed as a single measure to assess the prevalence of suicide ideation in research studies [47]. However, this stance is not uniformly shared, with some regarding it as an insufficient assessment tool for suicide risk and suicide ideation [48]. The lack of a universally accepted consistent definition of suicide ideation leads to ongoing challenges for researchers and others [14] and makes direct study comparisons difficult.

Conclusion

Globally, the COVID-19 pandemic era represents an extraordinary time for all societies, presenting extraordinary challenges and posing extraordinary and worsening mental health burdens on people. The high and increased rates of suicide ideation reported by participants across 8 countries in 4 continents reflect the cumulative effects of this pandemic and its associated burdens. Young adults and those in Hong Kong, in particular, have been deeply affected. SOC appears to be a potent protective force. A health promotion approach using a salutogenic orientation aimed at strengthening SOC may offer a new perspective for reducing suicide ideation. Moreover, with social media appearing to have an increasingly negative influence, it is critical for countries and health agencies to squarely redress rampant misinformation and disinformation communications. Suicide ideation is an important mental health indictor and risk factor for completed suicides. Policies and promotion of SOC, together with dissemination of health information that explicitly tackles the infodemic's misinformation and disinformation, may importantly contribute to reducing the rising mental health morbidity and mortality triggered by this pandemic.

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Authors' Contributions

PJS, MG, KKCH, EL, RL, CPYM, VM, TO, ZQ, and MR were involved in the study conceptualization, design, and implementation. MG (principal investigator) obtained the funding. PJS led the data analysis and drafting of the manuscript. All authors contributed to manuscript revisions prior to submission and during the review process. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tables S1, S2, and S3.
[PDF File (Adobe PDF File), 666 KB - publichealth_v8i1e32140_app1.pdf]

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Abbreviations

AOR: adjusted odds ratio
AUC: area under the receiver operating characteristic curve
CHUS: Center hospitalier universitaire de Sherbrooke
CIUSSS: Centre intégré universitaire de santé et de services sociaux
HEC: Human Ethics Committee
OR: odds ratio
PHQ-9: Patient Health Questionnaire-9
PR: prevalence ratio
SARS: severe acute respiratory syndrome
SOC: sense of coherence
STROBE: STrengthening the Reporting of OBservational studies in Epidemiology

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Original Paper

Health-Related Quality of Life Among Pregnant Women With Pre-pregnancy Smoking and Smoking Cessation During Pregnancy in China: National Cross-sectional Study

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Abstract

Background: Previous studies have hardly explored the influence of pre-pregnancy smoking and smoking cessation during pregnancy on the health-related quality of life (HRQoL) of pregnant women, which is a topic that need to be addressed. In addition, pregnant women in China constitute a big population in the largest developing country of the world and cannot be neglected.

Objective: This study aims to evaluate the HRQoL of pregnant women in China with different smoking statuses and further estimate the association between pre-pregnancy smoking, smoking cessation, and the HRQoL.

Methods: A nationwide cross-sectional study was conducted to determine the association between different smoking statuses (smoking currently, quit smoking, never smoking) and the HRQoL in pregnant women across mainland China. A web-based questionnaire was delivered through the Banmi Online Maternity School platform, including questions about demographics, smoking status, and the HRQoL. EuroQoL Group's 5-dimension 5-level (EQ-5D-5L) scale with EuroQoL Group's visual analog scale (EQ-VAS) was used for measuring the HRQoL. Ethical approval was granted by the institutional review board of the First Affiliated Hospital of Sun Yat-sen University (ICE-2017-296).

Results: From August to September 2019, a total of 16,483 participants from 31 provinces were included, of which 93 (0.56%) were smokers, 731 (4.43%) were ex-smokers, and 15,659 (95%) were nonsmokers. Nonsmokers had the highest EQ-VAS score (mean 84.49, SD 14.84), smokers had the lowest EQ-VAS score (mean 77.38, SD 21.99), and the EQ-VAS score for ex-smokers was in between (mean 81.04, SD 17.68). A significant difference in EQ-VAS scores was detected between nonsmokers and ex-smokers (P<.001), which indicated that pre-pregnancy smoking does have a negative impact on the HRQoL (EQ-VAS) of pregnant women. Compared with nonsmokers, ex-smokers suffered from more anxiety/depression problems (P=.001, odds ratio [OR] 1.29, 95% CI 1.12-1.50). Among ex-smokers, the increased cigarette consumption was associated with a lower EQ-5D index (P=.007) and EQ-VAS score (P=.01) of pregnant women. Compared to smokers, no significant difference was found in the ex-smokers' EQ-5D index and EQ-VAS score (P=.33).

Conclusions: Smoking history is associated with a lower HRQoL in pregnant Chinese women. Pre-pregnancy smoking is related to a lower HRQoL (EQ-VAS) and a higher incidence of depression/anxiety problems. Smoking cessation during pregnancy does not significantly improve the HRQoL of pregnant Chinese women. Among ex-smokers, the more cigarettes they smoke, the lower HRQoL they have during pregnancy. We suggest that the Chinese government should strengthen the education on quitting smoking and avoiding second-hand smoke for women who have pregnancy plans and their family members.

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KEYWORDS

health-related quality of life; pregnant women; smoking status; pre-pregnancy smoking

Introduction

Active smoking increases the risk of developing chronic diseases and malignancy, such as chronic obstructive pulmonary disease and lung cancer [1]. Until 2019, there were more than 1 million tobacco-caused deaths in China, and the hazards are expected to increase substantially in the next few decades [2-4]. Smoking has also been proven to impair reproductive function, and during pregnancy, it was identified as a risk factor for terrible clinical outcomes, such as stillbirth and abortion [5,6]. In China, although most of the women who smoke quit smoking when they are pregnant, the prevalence of smoking among pregnant women still reached 3.8% [7], which is higher than that of women in general (2.4%) [8]. In addition, the prevalence of smoking in women younger than 40 years old, who are at reproductive age, has increased significantly in recent years [7]. Therefore, the pregnant Chinese women's health-related quality of life (HRQoL) and its relationship to smoking needs to be explored.

The World Health Organization reported that tobacco use is a major risk factor for cardiovascular diseases, respiratory diseases, and cancers [9]. At the same time, nicotine withdrawal causes mental symptoms, including insomnia, anxiety, depression, and anhedonia [10]. In the general population, smoking cessation leads to a higher perceived quality of life [11]. However, among pregnant women, the health status of those quitting smoking after pregnancy was still worse than that of nonsmokers [12], and smoking-related health consequences occurred in most of the pregnant ex-smokers, which affected their somatic health [13]. A previous study addressed the effect of smoking before pregnancy [14], but it merely included smoking during the 3 months before conception as preconception smoking and did not explore the impact of pre-pregnancy on a wider circle of mental health. Furthermore, although the effect of smoking cessation has been explored in the general population [15], the exact effect of smoking cessation during pregnancy on the health status of pregnant women is still unclear. Therefore, it is necessary to evaluate the impact of pre-pregnancy smoking and smoking cessation during pregnancy on both physical health and mental health of pregnant women, especially in China, which is the largest country in the world.

The HRQoL is a multidimensional indicator for measuring people's physical, mental, emotional, and social health states in their lives over time. The HRQoL not only benefits the health perception at the individual level but also enables health agencies in legislation, community health planning, and business health projects [16]. The HRQoL of women who quit smoking during pregnancy can be used as an outcome indicator, which can facilitate the progression in pre-pregnancy smoking and smoking cessation management. Moreover, prevention is as important as cure in medicine, and knowing the impact of pre-pregnancy smoking and smoking cessation during pregnancy can help pregnant women prevent smoking-associated complications [17].

Considering its importance, we aim to explore the effect of pre-pregnancy smoking and smoking cessation during pregnancy on pregnant women's HRQoL in mainland China and compare the effects of pre-pregnancy smoking on pregnant women's HRQoL (5 health dimensions). Additionally, this study also explored the relationship between the number of cigarettes consumed and the HRQoL of pregnant women in mainland China.

Methods

Study Design

A nationwide cross-sectional study was performed to investigate pregnant women's HRQoL using a self-administrative questionnaire across mainland China. The questionnaire was designed based on the Global Tobacco Surveillance System and EuroQoL Group's 5-dimension (EQ-5D) questionnaire [18], which is a group of instrumental questionnaires to assess people's HRQoL, make cost-efficiency calculations, and evaluate economic issues in the public health field [19]. It has been proven that the Chinese version of the EQ-5D index can effectively measure the HRQoL of pregnant women [20]. In EQ-5D questionnaires, EuroQol Group's 5-dimension 5-level (EQ-5D-5L) scale and EuroQoL Group's visual analog scale (EQ-VAS) are more reliable and were used to measure the HRQoL in this study. The questionnaire includes a total of 10 fixed questions and 2 adaptive scales on 1 page, including demographics questions, smoking status questions, the EQ-5D-5L scale, and the EQ-VAS. A completeness check was applied, and participants were not allowed to submit the questionnaire until they responded to all the questions. Participants were not able to review or change their answers after submission.

Ethical approval was granted by the institutional review board of the First Affiliated Hospital of Sun Yat-sen University (ICE-2017-296). All procedures were conducted following the Declaration of Helsinki. All participants signed the informed consent documents before participation in this study.

Study Population and Recruitment

The web-based questionnaire was distributed through a national online platform (Banmi Online Maternity School) from August to September 2019. The Banmi Online Maternity School is a free platform that provides pregnancy knowledge for all internet users and serves more than 1 million users across China. The research group members of the Banmi Online Maternity School were the investigators. We advertised the survey with the wording "For providing you with more specific gestational health knowledge, we invite you to participate in this survey," and no incentive was provided. A total of 16,811 questionnaires from pregnant women aged from 16 to 60 years were included, and 328 (1.95%) of them were excluded due to the living location not being mainland China. The final sample comprised 16,483 pregnant women from mainland China. According to the standards of the Chinese Center for Disease Control and Prevention, the research was performed in 7 administrative regions of mainland China: (1) the Northeast (Heilongjiang, Jilin, and Liaoning), (2) the North (Beijing, Tianjin, Hebei, Shanxi, and Inner Mongolia), (3) Central (Hubei, Hunan, and Henan), (4) the East (Shanghai, Shandong, Jiangsu, Anhui, Jiangxi, Zhejiang, and Fujian), (5) the South (Guangdong, Guangxi, and Hainan), (6) the Northwest (Shanxi, Gansu, Ningxia, and Xinjiang), and (7) the Southwest (Chongqing, Sichuan, Guizhou, Yunnan, and Tibet).

Variables

Participants' sociodemographic information, including age, gestational age (weeks), address (provinces and cities), disposable income, smoking status, amount of cigarette consumption, smoking status of the spouse, and smoking duration (years), were collected. Previous studies have reported that maternal age, gestational age, and income level are related to people's HRQoL [21]. The independent variables in our study were the smoking status and cigarette consumption of pregnant women. To determine the smoking status, participants were provided with the following options: (1) currently smoking, (2) smoking only before pregnancy, and (3) never smoked. They were classified into (1) smokers, (2) ex-smokers, and (3) nonsmokers. Smokers and ex-smokers were further asked for the number of cigarettes they consumed per day and classified as mild (1-9 cigarettes), moderate (10-19 cigarettes), and heavy (>20 cigarettes) smokers [22].

Measurement

We use the EQ-5D instrument, which consists of the EQ-5D-5L scale and the EQ-VAS, to evaluate the HRQoL of pregnant women. The EQ-5D-5L scale assesses 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Further, each dimension is addressed by 5 levels: (1) none, (2) slight problem, (3) moderate problem, (4) severe problem, and (5) extreme problem/unable. All dimension levels were converted into 1, 2, 3, 4, or 5 in the given order. Next, an EQ-5D index for each participant was calculated using the EQ-5D-5L Crosswalk Index Value Calculator. The possible maximal EQ-5D index is in the range of –0.224-1, where 1 indicates the highest health status, 0 represents death, and negative indices indicate the health status considered worse than death [20,23,24]. The EQ-VAS was presented as a calibrated vertical line from 0 (worst) to 100 (best) [25]. Participants were asked to mark on the vertical line of the VAS based on their own perceptions of their health status. Generally, both a higher EQ-5D index and a higher EQ-VAS score indicate a better HRQoL.

Statistical Analysis

Data analysis was performed using STATA/SE version 14.0 for Windows (College Station, TX, USA). Normally distributed continuous variables were described using means and SDs. Nonnormal variables were presented as the median, and categorical variables were described using counts and percentages. Demographic data, including age, gestational age, address, smoking status, spouse's smoking status, EQ-5D index, and EQ-VAS score, were included. The EQ-5D index and the EQ-VAS score were the outcome variables, and they were not normally distributed. A 1-way ANOVA test was performed to compare the continuous variables and analyze their variances. The Bartlett test was used to determine unequal variances. The Tamhane T2 method was used for pairwise comparison tests of EQ-VAS scores between groups, and the chi-square test performed to analyze the proportion of spouse smoking among groups. To estimate the relationship between independent variables (demographics) and dependent variables (EQ-5D index and EQ-VAS score), we also ran an ordinary least squares regression, which minimized the sum of the squared residuals to obtain adjusted values of the dependent variables. For nonsmokers and smokers, an ordered logistic regression with odds ratios (ORs) and 95% CIs was run to assess the effects of independent factors on each dimension of EQ-5D indices. In the ordered logistic regression analysis, pre-pregnancy smoking was a dichotomous variable consisting of no smoking behavior (nonsmoker) and quitting smoking during pregnancy (ex-smoker). All tests were 2-sided, and $P<.05$ was considered statistically significant [20,26].

Bias

Because the HRQoL is related to individuals' perception of their position of life in the context of the culture and value systems in which they live, transnational culture differences will have an obvious impact on the HRQoL. Our study, which was conducted in China, avoided this potential difference [19]. We performed data desensitization before data cleaning and analysis. Although smoking status diversifies with educational levels and geographic factors, the large number of participants from many different areas in China in this study likely minimized selection bias. Since a completeness check was applied in the questionnaire-collecting process, the study has no nonresponse bias. Moreover, because only pregnant women who took part in the maternity school received questionnaires, the study has no ascertainment bias. The EQ-5D-5L scale and the EQ-VAS are subjective measurements of pregnant women's HRQoL. Therefore, self-reported bias is the main bias in this study.

Results

Participants

From August to September 2019, a total of 16,483 participants from 30 provinces were included (Table 1 and Figure 1). The

participants in our study were not characteristically different from the general pregnant women in China, except that those who had no access to the internet were not included.

Table 1. Demographics, EQ-5D[a] indices, and EQ-VAS[b] scores of pregnant women with different smoking statuses (N=16,483).

Characteristic	Smoker (n=93)	Ex-smoker (n=731)	Nonsmoker (n=15,659)	*P* value
Age (years), mean (SD)	26.45 (5.43)	26.18 (5.52)	28.25 (4.91)	<.001[c]
Gestational age (weeks), mean (SD)	21.17 (8.87)	20.50 (9.55)	21.12 (9.09)	.19
Spouse smoking, n (%)	87 (94)	607 (83.0)	8758 (56.0)	<.001[c]
Disposable income (CN ¥[d]), mean (SD)	28,589.01 (8680.59)	28,247.57 (8126.92)	29,978.01 (9321.93)	<.001[c]
Smoking duration (years), mean (SD)	19.53 (7.26)	20.37 (5.84)	—[e]	.20
EQ-5D index, mean (SD)	0.82 (0.14)	0.80 (0.12)	0.80 (0.13)	.16
EQ-VAS score, mean (SD)	77.38 (21.99)	81.04 (17.68)	84.49 (14.84)	<.001[c]

[a]EQ-5D: EuroQol Group's 5-dimension.

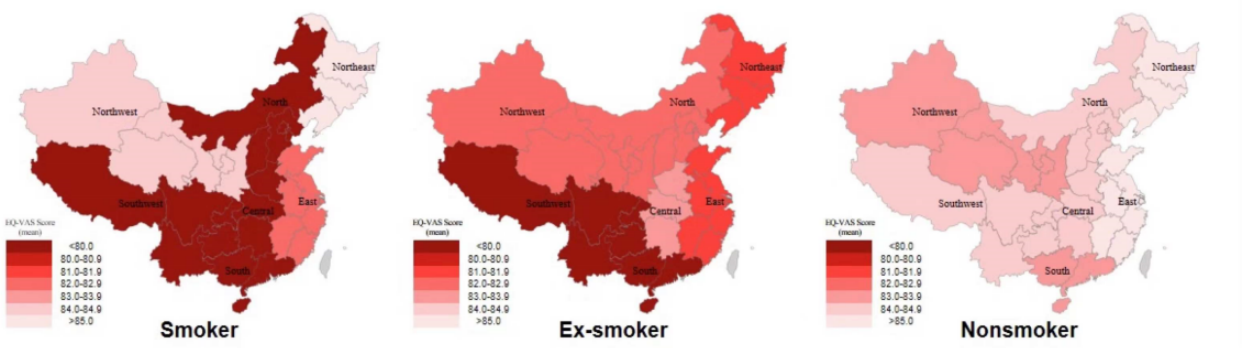
[b]EQ-VAS: EuroQoL Group's visual analog scale.

[c]*P*<.05.

[d]A currency exchange rate of CN ¥1= US $0.13971 was applicable per OANDA Rates in September 1, 2019.

[e]No result.

Figure 1. Geographical distribution of pregnant women's EQ-VAS scores of (A) smokers, (B) ex-smokers, and (C) nonsmokers across the 7 administrative regions in mainland China. EQ-VAS: EuroQoL Group's visual analog scale.



General Characteristics of Participants

Of the 16,483 participants, 93 (0.56%) were smokers, 731 (4.43%) were ex-smokers, and 15,659 (95%) were nonsmokers (Table 1). For the smoker group, the mean (SD) was 26.45 (5.43) years for age, 21.17 (8.87) weeks for gestational age, and 19.53 (7.26) years for smoking duration. Ex-smokers had an average gestational age of 20.50 (9.55) weeks and a smoking duration of 20.37 (5.84). Nonsmokers had an average gestational age of 21.12 (9.09) weeks.

Smokers, ex-smokers, and nonsmokers had an EQ-5D index of 0.82 (0.14), 0.80 (0.12), and 0.80 (0.13), respectively (Table 1). The EQ-VAS score was found to be statistically different among smokers (mean 77.38, SD 21.99), ex-smokers (mean 81.04, SD 17.68), and nonsmokers (mean 84.49, SD 14.84; all *P*<.001). Figures 1 and 2 reveal the EQ-VAS scores' distribution among pregnant Chinese women according to their geographic location and smoking status. Pregnant women who were nonsmokers had the highest, while the smokers had the lowest EQ-VAS scores. For nonsmokers, those living in Northeast and East China tended to have higher EQ-VAS scores, and those living in Northwest and South China had lower EQ-VAS scores. For smokers and ex-smokers, pregnant women living in Southwest and South China tended to have lower EQ-VAS scores. A significant difference was found in age, spouse smoking rate, and disposable income (all *P*<.001). Therefore, age, spouse smoking rate, and disposable income were adjusted in the analysis. After adjustment, the EQ-5D index was still not statistically different (*P*=.82), and the EQ-VAS score was still statistically different (*P*<.001) between pregnant women who were smokers, ex-smokers, and nonsmokers (Table 2). No significant difference was found in gestational age (*P*=.19) and the EQ-5D index (*P*=.16) among the 3 groups, and smoking duration showed no significant difference between smokers and ex-smokers (*P*=.20).

Figure 2. EQ-VAS distribution according to smoking status and IQR. EQ-VAS: EuroQoL Group's visual analog scale.

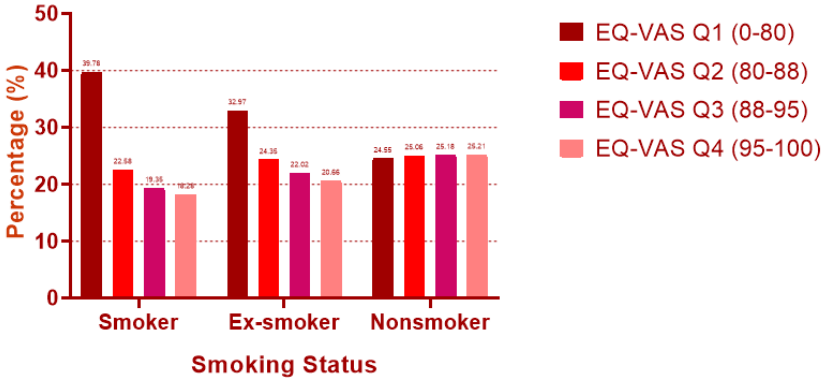


Table 2. EQ-5D[a] index and EQ-VAS[b] scores among smokers, ex-smokers, and nonsmokers (N=16,483).

Smoking status	Unadjusted value, mean (SD)	Age, per capita disposable income, and spouse smoking status adjusted, mean (SD)
EQ-5D index		
Smoker	0.82 (0.14)	0.80 (0.00)
Ex-smoker	0.8 (0.12)	0.80 (0.00)
Nonsmoker	0.8 (0.13)	0.80 (0.00)
P value	0.16	0.82
EQ-VAS		
Smoker	77.38 (21.99)	78.08 (0.13)
Ex-smoker	81.04 (17.68)	80.86 (0.05)
Nonsmoker	84.49 (14.84)	84.49 (0.01)
P value	<.001[c]	<.001[c]

[a]EQ-5D: EuroQol Group's 5-dimension.

[b]EQ-VAS: EuroQoL Group's visual analog scale.

[c]*P*<.05.

EQ-VAS Scores for Different Smoking Statuses

Table 3 presents the multicomparison of EQ-VAS scores between groups after the unequal variance test (*P*<.001). Significant differences were observed in the EQ-VAS scores, with of nonsmokers having the highest score of 84.49 (14.84). Specifically, their EQ-VAS scores were higher than those of smokers (mean difference=7.11, *P*=.01, 95% CI 1.56-12.66) and ex-smokers (mean difference=3.45, *P*<.001). However, no significant difference was found between smokers and ex-smokers (*P*=.33).

Table 3. Pairwise comparisons of pregnant women's smoking status and EQ-VAS[a] score between groups.

Pairwise groups	Mean difference	SE	95% CI	*P* value
Smoker vs ex-smoker	3.66	2.37	–2.09 to 9.41	.33
Smoker vs nonsmoker	7.11	2.28	1.56-12.66	.007[b]
Ex-smoker vs nonsmoker	3.45	0.66	1.86-5.04	<.001[b]

[a]EQ-VAS: EuroQoL Group's visual analog scale.

[b]*P*<.05.

Comparison of the Smoking Status in the 5 Dimensions of EQ-5D Index

Table 4 shows the frequency of the EQ-5D index in 5 dimensions by smoking status. In total, 3717 of 16,483 (22.55%) pregnant women reported health-related problems (levels 2-5) in the mobility dimension, 971 (5.89%) reported self-care problems, 3337 (20.25%) reported usual activity problems, 9298 (56.41%) reported pain and discomfort problems, and 8487 (51.49%) reported anxiety/depression problems. Results revealed that the main limited health dimension for pregnant women is pain/discomfort. According to the results in Table 4, the main health problem for ex-smokers and nonsmokers was pain/discomfort; among them, 429 of 731 ex-smokers (58.7%) and 8763 of 15,659 nonsmokers (55.9%) reporting related

problems. As the main health problem, depression/anxiety was reported by 52 of 93 smokers (56%).

Table 4. Frequency (%) of the EQ-5D[a] index of pregnant women with different smoking statuses (N=16,483).

EQ-5D dimension	Smoker, n (%)	Ex-smoker, n (%)	Nonsmoker, n (%)	Total, n (%)
Mobility				
Level 1	75 (81)	575 (78.7)	12,116 (77.4)	12,766 (77.45)
Level 2	18 (19)	125 (17.1)	2969 (19.0)	3112 (18.88)
Level 3	0	27 (3.7)	460 (2.9)	487 (2.95)
Level 4	0	4 (0.6)	58 (0.4)	62 (0.38)
Level 5	0	0 (0.0)	56 (0.4)	56 (0.34)
Self-care				
Level 1	87 (94)	689 (94.3)	14,736 (94.1)	15,512 (94.11)
Level 2	4 (4)	38 (5.2)	843 (5.4)	885 (5.37)
Level 3	0	1 (0.1)	58 (0.4)	59 (0.36)
Level 4	1 (1)	2 (0.3)	10 (0.1)	13 (0.08)
Level 5	1 (1)	1 (0.1)	12 (0.1)	14 (0.07)
Usual activity				
Level 1	80 (86)	606 (82.9)	12,460 (79.6)	13,146 (79.75)
Level 2	10 (11)	116 (15.9)	2875 (18.4)	3001 (18.21)
Level 3	0	7 (1.0)	245 (1.6)	252 (1.53)
Level 4	1 (1)	1 (0.1)	27 (0.2)	29 (0.18)
Level 5	2 (2)	1 (0.1)	52 (0.3)	55 (0.33)
Pain/discomfort				
Level 1	47 (51)	302 (41.3)	6836 (43.7)	7185 (43.59)
Level 2	42 (45)	385 (52.7)	8111 (51.8)	8538 (51.79)
Level 3	3 (3)	33 (4.5)	627 (4.0)	663 (4.02)
Level 4	1 (1)	10 (1.4)	68 (0.4)	79 (0.48)
Level 5	0	1 (0.1)	17 (0.1)	18 (0.11)
Depression/anxiety				
Level 1	39 (41)	309 (42.3)	7648 (48.8)	7996 (48.51)
Level 2	42 (45)	346 (47.3)	7086 (45.3)	7474 (45.34)
Level 3	11 (12)	56 (7.7)	750 (4.8)	817 (4.96)
Level 4	0	14 (1.9)	129 (0.8)	143 (0.87)
Level 5	1 (1)	6 (0.8)	46 (0.3)	53 (0.32)

[a]EQ-5D: EuroQol Group's 5-dimension.

Table 5 reveals the impact of risk factors on the 5 dimensions of EQ-5D-5L scale. Results indicated that increasing age and gestational age are positively related to mobility (both $P<.001$, OR 1.02, 95% CI 1.01-1.03; OR 1.04, 95% CI 1.03-1.04, respectively) and usual activity problems ($P=.01$, OR 1.01, 95% CI 1.00-1.02; $P<.001$, OR 1.03, 95% CI 1.03-1.04, respectively). Increasing age was negatively related to self-care ($P=.03$, OR 0.98, 95% CI 0.97-1.00), pain/discomfort ($P<.001$, OR 0.98, 95% CI 0.97-0.99), and anxiety/depression problems ($P<.001$, OR 0.98, 95% CI 0.97-0.98), while increasing gestational age was negatively related to them ($P<.001$, OR 1.08, 95% CI 1.07-1.09; $P<.001$, OR 1.02, 95% CI 1.02-1.02; and $P<.001$, OR 1.01, 95% CI 1.00-1.01, respectively). Spouse smoking (yes) was negatively related to self-care ($P<.001$, OR 0.79, 95% CI 0.69-0.90) and usual activity problems ($P=.001$, OR 0.88, 95% CI 0.81-1.95) but positively related to anxiety/depression problems ($P=.01$, OR 1.09, 95% CI 1.03-1.16). No correlation was found between disposable income and any health dimension. Pre-pregnancy smoking (yes) had a significant positive relationship with anxiety/depression problems ($P=.001$, OR 1.29, 95% CI 1.12-1.50).

Table 5. Ordered logistic regression analysis for each dimension in the EQ-5D[a] index of nonsmokers and ex-smokers (n=16,390).

Dimension	OR[b] (95% CI)	*P* value
Mobility		
Age	1.02 (1.01-1.03)	<.001[c]
Spouse smoking	1.00 (0.93-1.08)	.93
Disposable income	1.00 (1.00-1.00)	.002[c]
Gestational age	1.04 (1.03-1.04)	<.001[c]
Pre-pregnancy smoking[d]	0.99 (0.82-1.18)	.88
Self-care		
Age	0.98 (0.97-1.00)	.02[c]
Spouse smoking	0.79 (0.69-0.90)	<.001[c]
Disposable income	1.00 (1.00-1.00)	.15
Gestational age	1.08 (1.07-1.09)	<.001[c]
Pre-pregnancy smoking[d]	1.01 (0.73-1.41)	.93
Usual activity		
Age	1.01 (1.00-1.02)	.01[c]
Spouse smoking	0.88 (0.81-1.95)	.001[c]
Disposable income	1.00 (1.00-1.00)	0.37
Gestational age	1.03 (1.03-1.04)	<.001[c]
Pre-pregnancy smoking[d]	0.86 (0.70-1.05)	.13
Pain/discomfort		
Age	0.98 (0.97-0.99)	<.001[c]
Spouse smoking	1.00 (0.94-1.06)	.89
Disposable income	1.00 (1.00-1.00)	.001[c]
Gestational age	1.02 (1.02-1.02)	<.001[c]
Pre-pregnancy smoking[d]	1.09 (0.94-1.27)	.24
Anxiety/depression		
Age	0.98 (0.97-0.98)	<.001[c]
Spouse smoking	1.09 (1.03-1.16)	.006[c]
Disposable income	1.00 (1.00-1.00)	.001[c]
Gestational age	1.01 (1.00-1.01)	<.001[c]
Pre-pregnancy smoking[d]	1.29 (1.12-1.50)	.001[c]

[a]EQ-5D: EuroQol Group's 5-dimension.

[b]OR: odds ratio.

[c]*P*<.05.

[d]Pre-pregnancy smoking is a dichotomous variable consisting of no smoking behavior (nonsmoker, represented as 0) and quitting smoking during pregnancy (ex-smoker, represented as 1).

Amount of Cigarette Consumption and HRQoL

Table 6 shows the association of the EQ-5D index and EQ-VAS score with the amount of cigarette consumption per day among ex-smokers. Pregnant women who were ex-smokers were divided into 3 groups based on the amount of cigarette smoking. Significant differences across the 3 groups were found in both the EQ-5D index (*P*=.007) and the EQ-VAS score (*P*=.01). Moreover, both the EQ-5D index (mean 0.73, SD 0.16) and the EQ-VAS score (mean 67.93, SD 22.79) of heavy smokers were

lower than those of moderate smokers (mean 0.77, SD 0.11 and mean 79.38, SD 17.82, respectively), while mild smokers had the highest EQ-5D index (mean 0.80, SD 0.12) and EQ-VAS score (mean 81.53, SD 17.45).

Table 6. EQ-5D[a] index and EQ-VAS[b] score for pregnant ex-smokers (n=731).

	Mild smoker (n=638)	Moderate smoker (n=79)	Heavy smoker (n=14)	*P* value[c]
EQ-5D index, mean (SD)	0.80 (0.12)	0.77 (0.10)	0.73 (0.16)	.007
EQ-VAS, mean (SD)	81.53 (17.45)	79.38 (17.82)	67.93 (22.79)	.01

[a]EQ-5D: EuroQol Group's 5-dimension.

[b]EQ-VAS: EuroQoL Group's visual analog scale.

[c]$P<.05$.

Discussion

Principal Findings

Smoking history (whether before or during pregnancy) is related to a worse HRQoL for of pregnant women. Smoking cessation during pregnancy does not significantly improve pregnant women's HRQoL. Pre-pregnancy smoking is related to a worse HRQoL (EQ-VAS score) and a higher risk of anxiety/depression problems. In mainland China, pregnant smokers tend to have partners who are smokers. Moreover, the more cigarettes pregnant ex-smokers consume per day, the lower their HRQoL.

Limitations

We found a few limitations of our study. First, the study was conducted online, so pregnant women without access to the internet were not included. Second, this study divided participants only into 3 groups according to their smoking history. Although we adjusted the impact of age, spouse smoking rate, and disposable income on the HRQoL of participants, there are still many other endogenous factors that can affect pregnant women's HRQoL (eg, years of schooling, body mass index, chronic disease, abortion history) [27]. Future studies in this field should consider more factors that can affect pregnant women's HRQoL.

Comparison With Prior Works

Our results revealed that pregnant women with a smoking history, whether ex-smokers or smokers, have a lower HRQoL (EQ-VAS score) compared to nonsmokers. This result is similar to previous studies that reported that among women, smokers have a lower HRQoL compared to never-smokers [14,28]. A possible reason for this might be the harmful effect of pregnant women's smoking experience on their physical health, especially trachea and lung health [29]. Another possible explanation is the spouse smoking percentage, in which the ex-smoker group had a higher spouse smoking rate than the nonsmoker group and a lower spouse smoking rate than the smoker group. Pregnant women are exposed to a second-hand smoke environment if their spouses smoke, which results in detrimental effects on the pregnant women and can lead to asthma, lung cancer, ischemic heart disease, etc [30].

The significant difference between EQ-VAS scores of ex-smokers and nonsmokers revealed the negative effect of pre-pregnancy smoking on pregnant women's HRQoL in China. Before our study, few studies have addressed the effect of pre-pregnancy smoking on pregnant women's health. However, the only study in this field included only 3 months prior to conception as pre-pregnancy smoking, did not explore a wide range of mental issues, and reported that women who smoked during the 3 months prior to conception were more likely to report poor vitality than nonsmokers [31], which was similar to our results. However, our study provided information. Our study revealed that pre-pregnancy smoking is related to a worse HRQoL among pregnant women and showed a significant correlation between pre-pregnancy smoking and the anxiety/depression dimension. A possible reason for the overall health decline due to pre-pregnancy smoking is the health reduction caused by smoking, including a higher risk of cancer, heart disease, and stroke [32]. The significant negative impact of pre-pregnancy smoking on the anxiety/depression dimension might be due to the brain damage linked to smoking [33].

The insignificant EQ-VAS score difference between smokers and ex-smokers revealed that smoking cessation cannot significantly improve the HRQoL of pregnant women in China. This was similar to a previous study that investigated people but not pregnant women and concluded that quitting smoking alone does not improve an individual's HRQoL [28].

At the same time, the average EQ-5D index of pregnant women who were ex-smokers was not significantly different from that of other groups. Further analysis of the EQ-5D index revealed that the major problems for pregnant women in China are pain/discomfort problems. For smokers and nonsmokers, the anxiety/depression limitation is the most bothersome problem. Therefore, future policy planning in China should consider pain/discomfort care and mental health care during pregnancy.

Age was related to worsening mobility, which might be due to the decreasing mobility as people get older [34]. Gestational age was also related to worsening mobility, which can be explained by the limited movement for the heavier weight of pregnant women [35]. For the self-care dimension, age and gestational age were related to less self-care. A possible explanation for this is that older pregnant women or pregnant women of advanced gestational age tend to have more pregnancy care knowledge or even experience. Surprisingly, the spouse smoking rate was also related to less self-care. Future studies should explore the underlying reason. Our study also revealed that older pregnant women tend to report less pain/discomfort, which might be due to the tolerance to cutaneous pain increase with increasing age [36]. A correlation was also revealed between gestational age and pain/discomfort, although the

underlying reason is unclear and needs to be explored in future studies.

The spouse smoking rate was related to pregnant women's smoking status, in which the smoker group had the highest spouse smoking rate, the ex-smoker group had the second-highest spouse smoking rate, and the nonsmoker group had the lowest spouse smoking rate. This was similar to a previous study that concluded that smokers are more likely to have partners who smoke [37]. However, another study revealed that smoking exposure is associated with later depression/anxiety [38]. Following this, pregnant smokers are more likely to be exposed to both first- and second-hand smoke, and the risk of getting depressed or anxious increases even more. Therefore, local governments should advocate education of smoking cessation for both pregnant women and their families.

For ex-smokers, we found that the more cigarettes the women consumed before pregnancy, the lower their HRQoL, which is a new finding. Although a previous study explored the correlation between cigarette number and fetus health, no study has investigated the correlation between the cigarette consumption per day and the HRQoL of pregnant women [39]. Our study filled this gap.

The Banmi Online Maternity School is a free platform for all internet users and serves more than 1 million users in all the 31 provinces/municipalities across mainland China. Basically, it covers all pregnant women regardless of age, occupation, living location, past medical history, individual income, and other individual characteristics, except those who did not use the internet or pay attention to pregnancy care knowledge. Therefore, the characteristics of pregnant women in our study were not different from those of the regular pregnant women in China, except that our study did not include women who could not access the internet or did not pay attention to pregnancy care knowledge. Considering this information, the representativeness of the sample population is high. As of June 2019, the internet penetration rate in China was 61.2%, which was relatively low compared to that of South Korea and Japan, which ranged over 90% [40]. In the age of the internet, collecting information from those who do not know the internet demands a lot of human force and time and is difficult to implement. Future studies with larger groups and enough time might fill this gap.

Strengths

This study had a large sample size, with a total of 16,483 participants from 31 provinces/municipalities across mainland China. This study filled the gap, as the effect of pre-pregnancy smoking and smoking cessation on pregnant women's HRQoL was hardly addressed before, especially in China. This study is the first, to date, that horizontally compares pregnant Chinese women's HRQoL among smoking-before-pregnancy, smoking-during-pregnancy, and never-smoking groups and provides statistical evidence that the more cigarettes pregnant Chinese women consume, the lower their HRQoL. This study revealed that pregnant Chinese women who stop smoking after pregnancy are more likely to suffer from depression or anxiety compared to nonsmokers.

Conclusion

This study systematically explored the effect of the smoking period (whether before or during pregnancy), nicotine source (whether pregnant women themselves or their spouses), and the number of cigarettes consumed on the HRQoL of pregnant women. Smoking cessation during pregnancy does not significantly improve pregnant women's HRQoL. Pre-pregnancy smoking is related to a better HRQoL (EQ-VAS score). Pre-pregnancy smoking is also related to a higher risk of anxiety/depression problems. The more cigarettes pregnant ex-smokers consume per day, the lower their HRQoL. This study provides scientific guidance for the education of pregnant women and their families about protection of both mother and baby during pregnancy. Although nicotine might benefit pregnant women's physical health through the pain relief mechanism, its overall harmfulness for pregnant women's HRQoL (both physical and mental health) should not be neglected. We suggest that women who have labor plans or have already conceived quit smoking and do not resume smoking and avoid an environment with nicotine, especially if their spouses or other family members smoke. However, it is common sense that quitting smoking requires a strong mind and perseverance. Therefore, for those who cannot ban smoking at home, we suggest that they separate smoking family members from pregnant women to reduce the amount of nicotine to which the pregnant women are exposed. This can be achieved by establishing a contemporary smoking room or a pregnant woman room at home.

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Authors' Contributions

KH and SZ contributed equally. KH and W-KM contributed to the study design. KH and SZ analyzed the data and drafted the manuscript. HW contributed to the conduct of work and manuscript writing. SZ, CJPZ, BA, and ZW revised the manuscript. All authors approved the submission of the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EQ-5D: EuroQol Group's 5-dimension
EQ-5D-5L: EuroQol Group's 5-dimension 5-level
EQ-VAS: EuroQoL Group's visual analog scale
HRQoL: health-related quality of life
OR: odds ratio

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Original Paper

Measuring Problematic Internet Use, Internet Gaming Disorder, and Social Media Addiction in Young Adults: Cross-sectional Survey Study

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Abstract

Background: Digital technology use is nearly ubiquitous among young adults; this use provides both benefits and risks. The risks of technology use include maladaptive technology use or technology addiction. Several conceptualizations of these addictions have emerged, each with its own assessment tools. These conditions include problematic internet use (PIU), internet gaming disorder (IGD), and social media addiction (SMA). These conditions have been associated with health outcomes such as problematic alcohol use, sleep disorders, and mental illness. These maladaptive technology conditions have been most commonly studied in isolation from each other.

Objective: The aim of this study is to examine PIU, IGD, and SMA together to better inform future research approaches and provider screening practices for young adults.

Methods: This cross-sectional survey study was conducted using Qualtrics panel-based recruitment and survey hosting. We recruited US young adults aged 18-25 years. The survey assessed PIU, IGD, and SMA. Survey measures also included assessments of problematic alcohol use, sleep, depression, and anxiety. We evaluated the frequency of and overlap in positive screening scores among PIU, IGD, and SMA and modeled each condition using multivariate logistic regression. Finally, we calculated sensitivity and specificity, as well as the positive predictive value and negative predictive value of the screening tools using the most prevalent maladaptive technology type.

Results: Our 6000 participants had an average age of 21.7 (SD 2.5) years. Of these 6000 participants, 3062 (51.03%) were female, 3431 (57.18%) were Caucasian, 1686 (28.1%) were in a 4-year college program, and 2319 (38.65%) worked full time. The mean PIU score was 3.5 (SD 3.1), and 53.58% (3215/6000) of participants met the criteria for PIU. The mean IGD score was 2.7 (SD 2.6), and 24.33% (1460/6000) of participants met the criteria for IGD. The mean SMA score was 7.5 (SD 5.7), and 3.42% (205/6000) met the criteria for SMA. Across all 3 maladaptive technology use diagnoses, there were varied associations with demographic variables and similar overlap with health outcomes. The sensitivity of PIU screening to detect IGD was 82% and to detect SMA was 93%, whereas the specificity and positive predictive value were much lower (37%-54% specificity; 6%-37% positive predictive value).

Conclusions: This cross-sectional survey screened a large national sample of adolescents and young adults for PIU, IGD, and SMA to determine prevalence and overlap, demographic associations with each, and associations between these technology-related conditions and health outcomes. There was overlap across PIU, IGD, and SMA in some associated demographic variables and health outcomes. However, the patterns in the associated variables demonstrated unique qualities of each of these conditions.

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KEYWORDS

technology; young adults; addiction; social media; internet; video games; screening; surveillance; cross-sectional; survey; mobile phone

Introduction

Background

Adolescents and young adults (AYAs) are often considered digital natives as they are growing up in a highly immersive technological society. Most US adolescents own their own personal smartphones, providing constant access to communication, information, and social networks [1]. AYAs' frequent and consistent media use has both benefits and risks. Benefits include opportunities for creative expression and social support [2]. Risks include maladaptive technology use, including overuse and addiction. Following early efforts to conceptualize the meaning of maladaptive technology use, subsequent efforts have defined specific types of maladaptive technology use. In this paper, we focus on 3 common conceptualizations of maladaptive technology use: problematic internet use (PIU), internet gaming disorder (IGD), and social media addiction (SMA). These entities have most commonly been studied in isolation, limiting our ability to understand similarities and distinctions among these diagnoses. These 3 common conceptualizations of maladaptive technology use have commonalities in that they have often been associated with similar health conditions and commonly with mental health conditions [3-10]. Furthermore, although screening for problematic technology use is recommended by groups such as the American Academy of Pediatrics [11], screening efforts may be hampered if multiple assessments for different technologies are needed. Thus, an understanding of the intersection between types of maladaptive technology use and optimal screening tools is needed.

Early Studies of Maladaptive Technology Use: Conceptualizing Mechanisms of Maladaptive Use

Overview

Efforts toward understanding maladaptive technology use began in the 1990s, with a focus on the internet and its overuse. Two initial conceptualizations were based on the existing Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition disorders: substance abuse and dependency and pathological gambling [12,13]. From these early studies, 3 conceptualizations of maladaptive technology use emerged. One approach was broader, describing internet overuse as a general behavioral addiction [14,15]. A second approach was narrower, proposing a model that internet overuse should be more classified as an impulse control disorder with criteria defined as (1) maladaptive preoccupation with internet use characterized by either irresistible use or use that is excessive and longer than planned, (2) clinically significant distress or impairment, and (3) an absence of other explaining Axis 1 disorders [16]. A third approach proposed a cognitive behavioral model with focused attention on the impact of an individual's thoughts on their development of problematic behaviors. This approach also separated internet overuse into *generalized* overuse or multidimensional overuse of the internet and *specific* overuse [17]. Specific overuse was defined as dependence on a specific function of the internet.

Since these initial conceptualizations, the field has changed both through additional evidence and conceptualizations of maladaptive technology use and on changing technology. Conceptualizing maladaptive use has moved forward as inclusive of constructs beyond overuse and now includes constructs to represent risky use and individual impairment. Furthermore, studies have introduced conceptualizations of specific addictions related to new technologies, such as video games and social media. In most cases, these conceptualizations all center on these behaviors as "pathological forms of normal and necessary behaviors" [18]. The 3 common areas of study in the current literature include PIU, IGD, and SMA.

Problematic Internet Use

A 2012 study developed a conceptual framework for PIU using empirical data and defined it as "internet use that is risky, excessive or impulsive in nature leading to adverse life consequences, specifically physical, emotional, social or functional impairment" [19]. The prevalence of PIU is estimated to be 4% among adolescents [20] and 4%-6% among young adults in college [21-23]. PIU has been associated with both social and health consequences, including poor academic performance, stress, and fewer positive health behaviors [22]. Longitudinal studies have also suggested bidirectional relationships between PIU and other mental health conditions, such as depression [3,24-26].

Internet Gaming Disorder

Maladaptive video game use is most commonly referred to as IGD, given that most video gaming occurs on the web. In 2013, the American Psychological Association proposed IGD as a disorder in need of further study by [27]. Defining characteristics of gaming addiction include spending increasing amounts of time preparing for, organizing, and actually gaming [28]. Another literature review found that internet gaming could be defined by a series of negative cognitions, including the following: (1) a consistent overvaluation of rewards, activities, and identities; (2) a need to adhere to self-applied rules for playing and finishing games; (3) an overreliance on playing video games as a means of enhancing one's self-esteem; and (4) a means of social acceptance through either in-person gaming or web-based gaming. The estimated prevalence was described in a systematic review as 2% of children and adolescents affected by IGD, and the overall mean prevalence may reach 5.5% [29]. Negative consequences of IGD can include poor grades, academic problems, problematic alcohol use, depression, and negative self-esteem [8,10,29].

Social Media Addiction

SMA or addiction to social networking sites (SNSs) was defined in 2014 as "being overly concerned about SNSs, to be driven by a strong motivation to log on to or use SNSs, and to devote so much time and effort to SNSs that it impairs other social activities, studies or job, interpersonal relationships, and/or psychology health and well-being" [30]. Robust estimates of the prevalence of SMA are challenging, as most studies involve small and nonrepresentative samples of college students. In China, 2 studies reported 12% and 34% as the prevalence of SMA [7,31]. Studies on specifically Facebook addiction have reported prevalence rates between 1.6% and 8.6% [32,33]. SMA has been associated with sleep problems [34] and emotional problems, such as distress and depression symptoms [5,35].

Previous Associations With Maladaptive Technology Use

A previous study examined the relationships between several behavioral addictions, including internet addiction, video game addiction, and Facebook addiction and the 5-factor model of personality [36]. The study found >20 correlations between the 7 behavioral addictions measured in the study, all of which were positive. However, across the 5 factors of personality, the 3 constructs in this study (PIU, IGD, and SMA) were grouped together only via a negative association with conscientiousness. Another study of adults examined IGD and SMA and several measures of mental health symptoms. They found correlations between maladaptive technology use and mental health symptoms and a weak interrelationship between IGD and SMA [4]. These studies suggest connections between these maladaptive technology use constructs, as well as ways in which each may be unique.

Gaps in the Literature

Although tremendous strides have been made in the past several decades, several critical gaps remain in the literature. The divergent areas of focus for maladaptive technology use, including PIU, IGD, and SMA, mean that it remains unclear whether these diagnoses have similar associations with health outcomes. Although the literature has supported associations between PIU, IGD, and SMA and mental health conditions in particular, formal testing has not been conducted to evaluate the strength of these associations across these conditions. Furthermore, health care providers are increasingly called upon to screen for maladaptive technology use [11]. Thus, an understanding of how to approach initial screening and whether a single instrument or multiple scales are needed is important. This understanding is important to inform whether screening and treatment approaches need to be specific to certain technological platforms or broader.

Study Purpose

Building on these gaps in the literature, this study has 2 goals. The first goal is to understand the overlap in prevalence, demographic factors, and health outcomes across PIU, IGD, and SMA. If these 3 diagnoses are truly distinct, we would expect little overlap in a study population when screening for all 3. Furthermore, we would expect to see unique patterns in the associated demographic factors with PIU, IGD, and SMA. Finally, we would expect to see distinct associations with health outcomes. For this study, we will focus on health outcomes that have been studied in previous work with maladaptive technology use, including problematic alcohol use, sleep, depression, and anxiety [24,37-40].

The second goal of this study is to consider our findings and their impact on screening options for health care providers. If these 3 diagnoses are unique, then individual screening for PIU, IGD, and SMA is warranted. If there is overlap, it may be possible to identify a screening instrument with optimal sensitivity to facilitate universal screening. Then, when a positive screen emerges for a given patient, individual screening tools can be provided to improve specificity.

The aim of this study is to examine PIU, IGD, and SMA to better inform future research approaches and provider screening practices for young adults.

Methods

A web-based cross-sectional survey was conducted using Qualtrics panel-based recruitment and survey hosting. This study was approved by the University of Wisconsin institutional review board.

Participants and Recruitment

Our goal was to achieve a purposeful national sample of young adults to complete a closed web-based survey. Compared with traditional survey approaches, such as in-person, phone, or mail recruitment, web-based survey panels offer broader reach and lower costs in data collection [41]. We selected the web-based survey platform Qualtrics for several reasons. First, although web-based survey platforms do not use weighting, previous studies have shown that web-based survey approaches using tools such as Qualtrics can achieve demographic attributes that are typically within a 10% range of their corresponding values in the US population [42]. Second, we sought to recruit a diverse sample of young adults both in and out of school settings, so recruiting using traditional approaches, such as at a college campus, would not achieve that goal. Third, there is a strong and growing literature on the use of Qualtrics to recruit a sample of young people in the United States, including studies on media [43,44].

The target population for this study was 18-25-year-olds who were US residents and English-speaking. We established parameters for Qualtrics to recruit a sample consistent with race or ethnicity representative of the US census population for 18-25-year-olds who could speak or read in English [42]. Using these eligibility parameters, a Qualtrics survey manager recruited young adult panel participants using email and texting. Potential participants were directed to the web-based survey website to obtain more information. Potential participants were provided information about the survey including information about the length and topic of the survey. Participants completed informed consent before beginning the survey.

Survey Procedures

The survey was hosted on Qualtrics. Participants who provided consent were allowed to begin the survey. After informed

consent was obtained, each measurement tool was provided on a single webpage. Demographic information was collected on a single webpage. Participants were allowed to skip questions or scales if they were uncomfortable or did not want to complete certain items. Participants could move backward and forward in the survey before submitting the results.

Participants were provided Qualtrics points as an incentive for survey completion. Survey results were delivered to the investigative team without identifying information.

Survey Measures

Our 3 technology-related scales included assessments for PIU, IGD, and SMA.

Problematic Internet Use

The Problematic and Risky Internet Use Screening Scale (PRIUSS) [45] was developed based on the PIU conceptual framework [19]. The PRIUSS was validated for use among AYAs in English and Dutch [45-47]. The PRIUSS has 2 versions: a 3-item short screen designed as an initial screen to be followed by an 18-item full screen if the short screen is positive [48]. PIU was measured using the 3-item PRIUSS (PRIUSS-3) [46]. The scale asks participants to answer how often certain behaviors and experiences have happened in the past 6 months. For example, items include how often "do you feel irritated when you are away from the internet?" and "do you experience withdrawal when you are away from the internet?"

Internet Gaming Disorder

IGD was measured using the IGD Scale [49]. This 9-item scale asks participants to respond to whether they have had certain experiences in the past year. For example, items include "have there been periods when all you could think of was the moment that you could play a game?" and "have you felt unsatisfied because you wanted to play more?" Response options are yes and no. The cutoff for a positive score is ≥5 *yes* answers. The Cronbach α for this scale was .83.

Social Media Addiction

SMA was measured using the Bergan SMA Scale [37]. This scale has 6 items about the frequency of certain social media experiences over the past year. For example, statements include "You feel an urge to use social media more and more" and "You use social media in order to forget about personal problems." Response options are on a 5-point Likert scale from *very rarely* to *very often*. The initial scale was conceptualized as a Facebook Addiction Scale, which was shown to have good psychometric properties [36] and was subsequently expanded to represent a broader SMA scale. The Cronbach α for this scale was .87.

Health Behavior and Conditions

Our health behavior and condition measures included problematic alcohol use, sleep, depression, and anxiety.

Problematic Alcohol Use

Problematic alcohol use has been associated with maladaptive use in previous work [9,10,40,50]. We measured problematic alcohol use using the Alcohol Use Disorders Identification Test-Concise [51,52]. This 3-item scale asks participants about their alcohol consumption habits. For example, items include frequency of drinking alcohol and number of alcoholic drinks consumed on a typical day. Responses are on a 5-point Likert scale, with higher scores indicating greater consumption. Scores were allotted from 0 to 4 on a Likert scale for each question. The cutoff used to indicate hazardous drinking was 4 points for men and 3 points for women.

Sleep

Robust literature, including a systematic review and a meta-analysis [53], links maladaptive technology use to sleep issues [50,54,55]. Sleep was measured using the Epworth Sleepiness Scale [56]. This 8-item scale asks participants how likely they are to doze off or fall asleep in certain situations. For example, items include sitting and reading or as a passenger in a car for an hour without a break. Response options are on a Likert scale from 0 to 3, from no chance of dozing off to a high chance of dozing off. Higher scores indicate increased sleepiness; a score ≥11 represents higher sleepiness. The scale defines mild sleepiness as scores 11-14, moderate sleepiness as scores 15-17, and severe sleepiness as scores 18-24.

Depression

Depression has consistently been associated with maladaptive technology use across multiple studies [3,5,7,8,24,52,57-59]. For this study, depression was measured using the Patient Health Questionnaire [60-62]. This 9-item scale asks participants how often they have experienced the given symptoms in the past 2 weeks. For example, items include "little interest or pleasure in doing things" and "feeling down, depressed or hopeless." Response options used a 4-point Likert scale ranging from *not at all* to *nearly every day*. The scale defines mild depression as scores of 6-10, moderate depression as scores of 11-14, moderately severe depression as scores of 15-19, and severe depression as scores of 20 and above.

Generalized Anxiety Disorder

Anxiety has been linked to maladaptive technology use in previous work [3,8,57,58]. Anxiety was measured using the Generalized Anxiety Disorder–7 scale [63]. This 7-item scale asks participants how often they have experienced the given symptoms in the past 2 weeks. For example, items include "feeling nervous, anxious or on edge" and "trouble relaxing." Response options used a 4-point Likert scale ranging from *not at all* to *nearly every day*. Scores for this scale include mild anxiety as scores 6-10, moderate anxiety as scores 11-15, and severe anxiety as scores of ≥16.

Demographic measures included age, gender, and race and ethnicity. We asked the participants about the highest grade they had completed, with answer options including some high school, high school graduate, some college, technical school or associate arts degree, college degree, some graduate school, completed a graduate degree, and others. We asked about current education or employment status as well (eg, part-time or full-time employment).

Analysis

Statistical analyses were conducted using SAS software (SAS Institute Inc), version 9.4. All *P* values were 2-tailed, and $P<.05$

was used to indicate statistical significance. Descriptive statistics were summarized as frequencies and percentages or means and SDs.

Age was categorized as younger (18-20-year-olds) versus older (21-25-year-olds) AYAs. Race or ethnicity was categorized for analyses based on 2 goals. One goal was to leverage statistical power by collapsing some groups with smaller proportions of participants. This categorization led to several larger groups. Our second goal was to ensure that the groups identified in previous studies as at risk for problematic technology use were included in the analyses. Thus, we then reviewed previous studies of problematic technology use [7,64] to ensure that at-risk groups from these studies were included as distinct groups for analysis. Our final list of groups included Asian, Caucasian or White, Hispanic or Latino, African American, and others. The highest grade completed was dichotomized to include college education versus no college. Employment was dichotomized as any employment (full or part-time) versus not employed. Current schooling was dichotomized as in school (full or part-time) versus not in school.

To address our first study aim, we evaluated the frequency of and overlap in positive screening scores among PIU, IGD, and SMA. We calculated the proportions of participants who met the clinical criteria for PIU, IGD, and SMA using those scales' validated score cutoffs.

To determine associations between demographic variables and maladaptive technology use diagnoses, as well as maladaptive technology use and health behavior and conditions, we used multivariate logistic regression.

Finally, we calculated the typical measures to assess the value of screening tests in clinical settings [65]. These typically include sensitivity, which is the ability of a test to correctly classify an individual as having a condition or the likelihood that a test is positive in a true positive case. These also include specificity, which is the ability of a test to correctly classify an individual as being without a condition or the likelihood that a negative test is a true negative. Positive predictive value (PPV) is the percentage of participants with a positive test to be positive cases, and negative predictive value (NPV) is the percentage of patients with a negative test who do not have the condition. An optimal screening test often relies on high levels of specificity and a high NPV to avoid missing a possible positive case. Screening tests are often followed by diagnostic tests, and an optimal diagnostic test often relies on high levels of sensitivity and PPV to correctly identify cases. We calculated the sensitivity and specificity of the screening tools using the most prevalent maladaptive technology type, defining that condition as the gold standard for this study.

Results

Overview

Our 6000 participants had an average age of 21.7 (SD 2.4) years. Of the 6000 participants, 3062 (51.03%) were female, 3431 (57.18%) were Caucasian, 1686 (28.1%) were in a 4-year college program, and 2319 (38.65%) worked full-time. Table 1 provides the demographic data.

Table 1. Demographic information of young adult participants recruited using Qualtrics panels (N=6000).

Variables	Values
Age (years), mean (SD)	21.7 (2.4)
Gender, n (%)	
Female	3062 (51.03)
Male	2841 (47.35)
Other	91 (1.5)
Race or ethnicity, n (%)	
Caucasian or White	3431 (57.18)
Asian	304 (5.07)
Hispanic or Latino	502 (8.37)
Black or African American	793 (13.22)
Other	957 (15.95)
Highest grade completed, n (%)	
Some high school	101 (1.68)
High school graduate	2149 (35.82)
Some college	1682 (28.03)
Technical school or associate arts degree	311 (5.18)
College degree	1123 (18.72)
Some graduate school	232 (3.87)
Completed graduate degree	314 (5.23)
Other	68 (1.13)
Current education or employment, n (%)	
Part-time work	1853 (30.88)
Full-time work	2319 (38.65)
Part-time school	486 (8.1)
Full-time school	1263 (21.05)

Descriptive Data

Descriptive data for all measures are provided in Table 2. Descriptive data included mean scores across the maladaptive technology instruments. Findings included a mean score for problematic alcohol use of 2.6 (SD 2.6), mean score for depression of 9.4 (SD 7.2), mean score for anxiety of 8.4 (SD 6.1), and mean score for sleep of 9.07 (SD 5.2).

Table 2. Descriptive data from young adult participants.

Variables	Mean (SD; range)
PIU[a]	3.5 (3.1; 0-12)
IGD[b]	2.7 (2.6; 0-9)
SMA[c]	7.5 (5.7; 0-24)
Problematic alcohol use	2.6 (2.6; 0-12)
Depression	9.4 (7.2; 0-27)
Anxiety	8.4 (6.1; 0-21)
Sleep	9.1 (5.2; 0-24)

[a]PIU: problematic internet use.

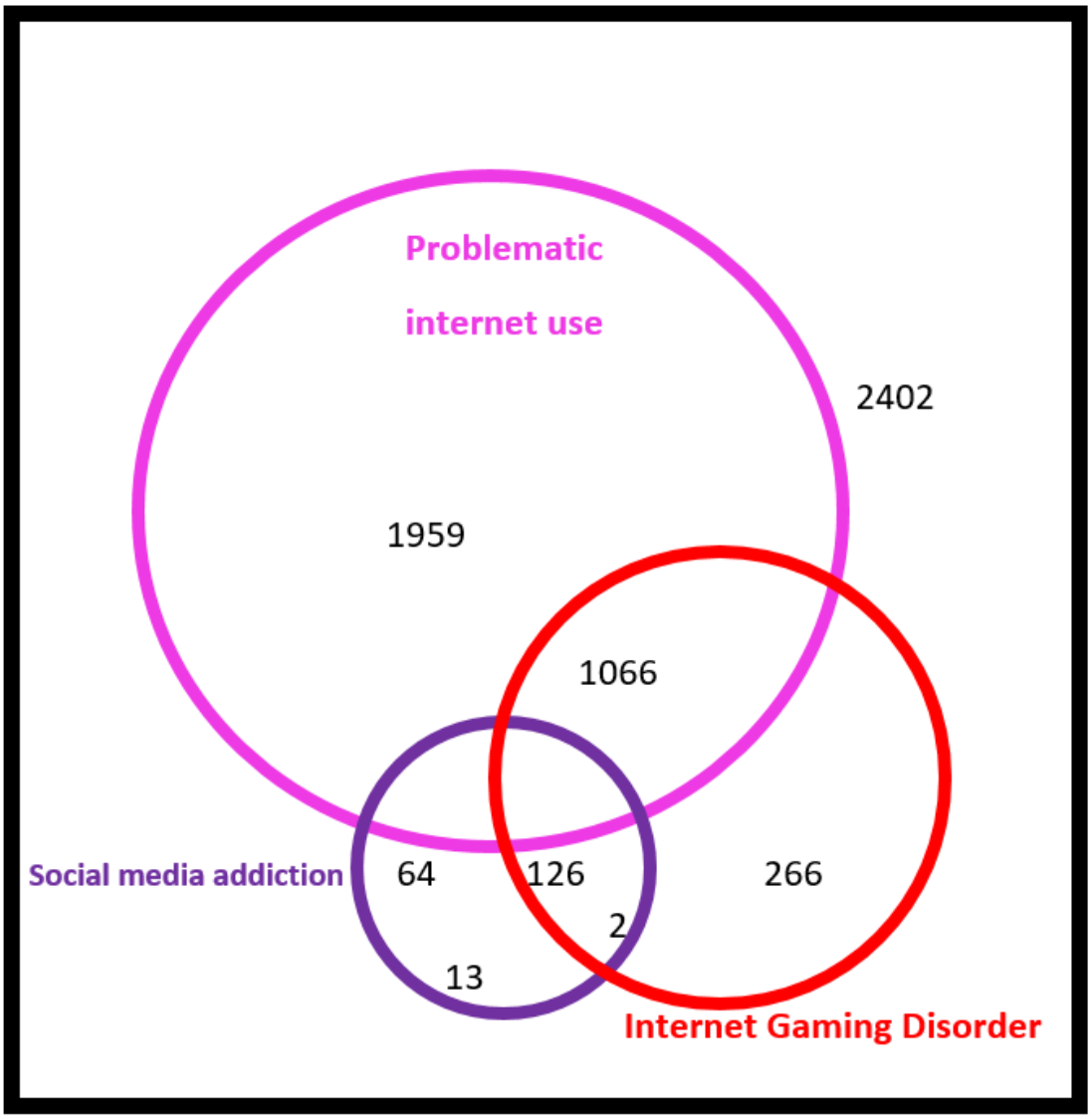
[b]IGD: internet gaming disorder.

[c]SMA: social media addiction.

Prevalence of PIU, IGD, and SMA

For PIU, the mean PRIUSS score was 3.5 (SD 3.1), and 53.58% (3215/6000) of participants met the criteria for PIU. The mean IGD score was 2.7 (SD 2.6), and 24.33% (1460/6000) met the criteria for IGD. The mean SMA score was 7.5 (SD 5.7), and 3.42% (205/6000) met the criteria for SMA. Of the 6000 participants, 1959 (32.65%) met the criteria for only PIU, 266 (4.43%) met the criteria for only IGD, and 13 (0.22%) met the criteria for only SMA. Approximately 40.03% (2402/6000) did not meet the criteria for any of these diagnoses. Figure 1 represents the overlap in screening rates for PIU, IGD, and SMA.

Figure 1. Overlap in screening rates for problematic internet use, internet gaming disorder and social media addiction among a young adult population.



Associations With Demographic Variables Across PIU, IGD, and SMA

There were varied associations with demographic variables across all 3 maladaptive technology use diagnoses. There were no noted differences across younger and older AYAs in our study population for PIU, IGD, or SMA. Males were more likely to meet the criteria for PIU (odds ratio [OR] 1.2, 95% CI 1.0-1.4) and IGD (OR 2.9, 95% CI 2.5-3.5) than females. There was no gender association noted for SMA.

In evaluating race and ethnicity, Asian participants were more likely to meet the criteria for PIU than Caucasian participants (OR 1.7, 95% CI 1.3-2.4). Similar findings were present for IGD; Asian participants were more likely to meet the criteria for IGD than Caucasian participants (OR 1.6, 95% CI 1.2-2.2). Hispanic participants were also more likely to meet the criteria for IGD than non-Hispanic Caucasian participants (OR 1.3, 95% CI 1-1.7).

Higher educational levels were positively associated with PIU (OR 1.4, 95% CI 1.2-1.6) and SMA (OR 1.4, 95% CI 1-2) compared with lower educational levels. Being employed was positively associated with IGD (OR 1.3, 95% CI 1.2-1.5) than not being employed. Multimedia Appendix 1 illustrates these associations.

Health Outcomes: Association With PIU, IGD, and SMA

For health behavior and condition variables, problematic alcohol use was positively associated with PIU, IGD, and SMA. Sleep issues were associated with PIU and IGD across all 3 sleep outcomes (mild, moderate, and severe sleepiness), whereas SMA was only associated with severe sleepiness (OR 4.6, 95% CI 2.9-7.2). Depression screening showed a similar pattern: there were associations with PIU and IGD across all categories of depression, although SMA was only associated with severe depression (OR 2.5, 95% CI 1.3-5.3). Anxiety also showed a similar pattern. Anxiety was associated with PIU and IGD across all categories of anxiety, and SMA was only associated with severe anxiety (OR 5.2, 95% CI 2.5-10.9). Multimedia Appendix 1 shows these associations.

Screening for Maladaptive Technology Use

Given that PIU was the most prevalent maladaptive technology use diagnosis, we tested PIU as our defined gold standard in this study and its capacity to predict IGD and SMA. The sensitivity of PIU for detecting IGD was 82% (95% CI 80%-84%), and the specificity was 54% (95% CI 53%-56%). The PPV was 37% (95% CI 35%-39%), and the NPV was 90% (95% CI 89%-91%). Thus, the overall accuracy was 61% (95% CI 60%-62%).

The diagnostic accuracy of PIU for predicting SMA included sensitivity of 93% (95% CI 88%-96%), with a specificity of 47% (95% CI 46%-48%). The PPV was 6% (95% CI 5%-7%), and the NPV was 99% (95% CI 99%-100%). The overall accuracy was 48% (95% CI 47%-50%).

Discussion

Principal Findings

This cross-sectional survey screened a large national sample of AYAs for PIU, IGD, and SMA to determine prevalence and overlap, demographic associations with each, and associations between these technology-related conditions and health outcomes. There was overlap across PIU, IGD, and SMA in some associated demographic variables as well as health outcomes. However, the patterns in the associated variables demonstrated unique qualities of each of these conditions.

Prevalence Differences in PIU Compared With IGD and SMA

Our first finding was that PIU was the most prevalent condition among our study population, and screening for PIU captured many of the participants who screened positive for IGD and SMA. Given that PIU is more nonspecific than IGD's focus on video games and SMA's focus on social media, this finding may seem logical. There is overlap in the emotions and behaviors asked in each of the scales for PIU, IGD, and SMA; however, the PRIUSS asked participants to consider their internet use more broadly. Placing these findings in the context of previous work, we can consider the early conceptualizations of problematic technology use. Our findings align with an early cognitive behavioral model with focused attention on the impact of an individual's thoughts on their development of problematic behaviors. This approach separated internet overuse into *generalized* overuse or multidimensional overuse of the internet and *specific* overuse [17]. Specific overuse was defined as dependence on a specific function of the internet. We found that PIU, a more generalized condition, was the most prevalent of the 3 conditions and that IGD and SMA as more specific conditions were endorsed by smaller groups than PIU. These findings suggest that this generalized or specific model may provide insights into the mechanisms for the current state of problematic technology conditions.

Prevalence of PIU Compared With Previous Studies

It is notable that prevalence rates for PIU in this study, using a brief screening tool, indicated that just over half of participants screened positive for PIU using the short PRIUSS-3 screen. Previous studies of college students using the longer PRIUSS-18 have suggested prevalence rates among 4-year college students of around 4% [21]. As these are 2 different but related instruments with different purposes, this is likely the main reason for the higher prevalence of screening at risk for PIU in this study. The PRIUSS-3 was designed to maximize sensitivity at the expense of specificity. As a screening tool for identifying individuals who would benefit from further screening, this tool has demonstrated 100% sensitivity and 69% specificity [48]. This design approach and screening purpose of the PRIUSS-3 is the most likely explanation for why the prevalence rates were higher compared with previous work.

A second consideration is whether these prevalence findings represent differences based on our broad study population of young adults. This study recruited a general population of young adults across the United States, a different approach than that of many previous studies that have focused on specific populations of college students [66-68]. This study's focus on young adult populations may also explain the increased rates of IGD compared with previous studies.

A third possible consideration is whether our findings suggest an increasing prevalence of PIU within society over time. It can be argued that an increasing number of daily activities now occur on the web, such as shopping, viewing recipes, or learning new skills. Thus, the continued infringement of the internet into lives may lead to increasing reliance or dependence on web-based connections. However, given the stark differences in the prevalence for this study compared with others using the PRIUSS-18 and studying 4-year college student populations, this final consideration is not likely able to fully address or explain our findings.

Correlations Between PIU, IGD, SMA and Health Outcomes

We found strong correlations between PIU and the mental illnesses of anxiety and depression in the 0.4 range, and similar findings for SMA were found. Correlations for gaming and anxiety and depression were lower, in the 0.27-0.34 range. For correlations with alcohol use, we found lower correlations with all our technology diagnoses; the highest correlation was with PIU at 0.21. For sleep, correlations were similar across PIU, IGD, and SMA, all in the 0.3 range. These findings support screening for depression and anxiety concomitantly with

maladaptive technology use. These findings also illustrate subtle differences among PIU, IGD, and SMA, such as how participants who screened positive for IGD also demonstrated a lower correlation for anxiety compared with depression, which differed from the pattern for PIU and SMA. These findings should be explored in future studies.

Limitations

This study's results may not generalize beyond a study population of young adults recruited via Qualtrics. Recruiting from a web-based panel meant that we could designate the study population size and criteria; however, it limited our ability to assess external validity. However, the Qualtrics platform and panels have been used in previous technology-focused studies [44], and panel recruitment has been shown to closely approximate US populations [42]. A second limitation is that our measures were assessed using self-report and thus may be subject to social desirability bias and recall bias.

Given that our study is cross-sectional and not longitudinal, we cannot conclude the directionality of these correlations. It is possible that our study illustrates preferential web-based activities among young adults with depression or anxiety. Furthermore, our study did not test or posit mechanisms by which problematic technology use and health conditions may be related. Although previous literature has identified associations between problematic technology use and certain conditions, an exploration of the mechanisms to support these associations remains understudied. This area of inquiry will be important for future work.

Finally, our study represents a unique approach for measuring multiple maladaptive technology conditions in a single study; thus, placing the findings in the context of existing literature is more challenging because of this unusual approach. Future studies should consider longitudinal study designs incorporating more than one measure of maladaptive technology use to further understand the similarities and differences across these conditions.

Implications

Despite these limitations, our study has several intriguing implications. The first implication is that the findings suggest that PIU, IGD, and SMA are more alike than different. We found some small differences with demographic factors, which may support group or cultural differences rather than different underlying mechanisms for these types of maladaptive technology use. Across our health outcomes, we found similar positive correlations across PIU and SMA with anxiety and depression, with IGD showing some small differences.

One clinical implication centers on our finding that PIU was the most common condition and that screening for PIU captured many participants who screened positive for IGD and SMA. Given that PIU was identified as having sensitivity to detect IGD and SMA at the levels of 82% and 98%, respectively, it is likely that screening for PIU may be a valid approach to detect concerns related to technology. Then, if the screen is positive, follow-up screening could include specific evaluations for IGD or SMA depending on the patient's history. As the PRIUSS-3 is designed to optimize sensitivity, this tool is likely a reliable candidate for this type of initial screening. Furthermore, as the PRIUSS-3 includes 3 questions, this brief screening tool could be incorporated into clinical flows without undue patient or clinic staff burden.

Our study found that PIU, IGD, and SMA were also commonly associated with positive screens for depression and anxiety. Thus, another clinical implication is that for clinics that do not conduct routine depression and anxiety screening for all patients, a positive screen for PIU should also prompt a screen for depression and anxiety. Early and ongoing screening for PIU may be a potential approach for identifying young adults at risk for other mental illnesses, and it may prompt further evaluation.

Conclusions

In conclusion, our study advances the understanding of PIU, IGD, and SMA by demonstrating their strong overlap in meeting diagnostic criteria and similarities in demographic risk factors. We also found similarities in health behavior and conditions across PIU and SMA in particular. If these 3 conditions were truly distinct, we would anticipate little overlap in a population when screening for all 3 maladaptive technology conditions. We can conclude that PIU, IGD, and SMA are more similar than different. Finally, we identified that an efficient screening approach might be to conduct initial screening for PIU, followed by technology-specific screening assessments and screening for depression and anxiety.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Associations between demographic factors and health outcomes with maladaptive technology conditions.
[DOCX File , 16 KB - publichealth_v8i1e27719_app1.docx]

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Abbreviations

AYA: adolescent and young adult
IGD: internet gaming disorder
NPV: negative predictive value
OR: odds ratio
PIU: problematic internet use
PPV: positive predictive value

PRIUSS: Problematic and Risky Internet Use Screening Scale
SMA: social media addiction
SNS: social networking site

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Original Paper

Ecological Momentary Assessment of Physical Activity and Wellness Behaviors in College Students Throughout a School Year: Longitudinal Naturalistic Study

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Abstract

Background: The Wellness Environment app study is a longitudinal study focused on promoting health in college students.

Objective: The two aims of this study were (1) to assess physical activity (PA) variation across the days of the week and throughout the academic year and (2) to explore the correlates that were associated with PA, concurrently and longitudinally.

Methods: The participants were asked to report their wellness and risk behaviors on a 14-item daily survey through a smartphone app. Each student was provided an Apple Watch to track their real time PA. Data were collected from 805 college students from Sept 2017 to early May 2018. PA patterns across the days of the week and throughout the academic year were summarized. Concurrent associations of daily steps with wellness or risk behavior were tested in the general linear mixed-effects model. The longitudinal, reciprocal association between daily steps and health or risk behaviors were tested with cross-lagged analysis.

Results: Female college students were significantly more active than male ones. The students were significantly more active during the weekday than weekend. Temporal patterns also revealed that the students were less active during Thanksgiving, winter, and spring breaks. Strong concurrent positive correlations were found between higher PA and self-reported happy mood, 8+ hours of sleep, ≥1 fruit and vegetable consumption, ≥4 bottles of water intake, and ≤2 hours of screen time (P<.001). Similar longitudinal associations found that the previous day's wellness behaviors independently predicted the following day's higher PA except for mood. Conversely, the higher previous-day PA levels were associated with better mood, more fruit and vegetable consumption, and playing less music, but with higher liquor consumption the next day.

Conclusions: This study provides a comprehensive surveillance of longitudinal PA patterns and their independent association with a variety of wellness and risk behaviors in college students.

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KEYWORDS

young adulthood; wellness; substance use; Apple Watch

Introduction

Research has shown that physical activity (PA) has numerous health and wellness benefits across the life span [1-4]. Despite this, few American college students meet public health recommendations for 150 minutes of moderate and vigorous PA per week [5,6]. Indeed, approximately 40% to 56% of college students participate in PA less than 2 times a week [7].

College students also fail to meet the guidelines for a total of 10,000 steps per day [8,9].

Being able to monitor individuals' PA plays an important role on PA promotion initiatives [10]. Wearable technologies, such as the Apple Watch (Apple Inc), provide valid estimates of steps, PA time, and energy expenditure under laboratory and free-living conditions, providing opportunities for individuals to self-monitor their behaviors [11-13]. Public health professionals have indicated that wearable devices may be a cost-effective intervention method for PA behavior change to improve health outcomes and facilitate high levels of interest and motivation for PA [14]. However, studies examining the effectiveness of wearable devices in college students are conflicting. Kim et al [15] found that wearing an activity monitor for 15 weeks did not improve PA relative to a control group. However, Pope et al [16] implemented a 12-week, combined smartwatch and health education intervention on a sample of college students, aimed to improve PA, and found statistically significant increases in moderate-to-vigorous physical activity (MVPA) and improvements in other health behaviors or outcomes. The PA level among college students varied dramatically from daily 6-10 minutes to 46-57 minutes, depending on how the PA was measured [15,16].

PA tends to correlate with other health and risk behaviors; therefore, multicomponent approaches to improve health behaviors and lower-risk behaviors may yield greater effectiveness compared with targeting 1 behavior alone [17,18]. The intercorrelation between PA and other health behaviors such as sleep, diet, and water consumption have been extensively explored in both cross-sectional and longitudinal studies where positive associations have been reported [19-21]. Conversely, the associations of risk behaviors such as smoking and alcohol consumption with PA have shown mixed results [22-24].

The longitudinal pattern and correlates of PA in college students may better inform future intervention work for designing ecological and multicomponent health behavior programs [25]. To the best of our knowledge, no study has examined yearlong trajectories of PA using the Apple Watch and correlated the objective PA with other salient health and risk behaviors. Therefore, the primary purpose of this study was to document objective PA trajectories, assessed using the Apple Watch during the 2017-2018 academic year, in a sample of college students. The secondary purpose of this study was to assess the concurrent and longitudinal associations of PA and other health and risk behaviors.

Methods

Participants

All participants were from the University of Vermont (UVM) Wellness Environment (WE) study during the 2017-18 academic year. Less than half of the recruited students were assigned to the WE group, and the remainder were assigned to the control group. WE is a neuroscience-inspired health promotion program that incentivizes students to adopt healthy lifestyles. All of the recruited participants had access to a smartphone app, developed to incentivize higher PA, consume a healthy snack after workout, drink more water, and engage in mindfulness activities. WE students were provided resources that included gym access located in the residence halls, group fitness classes, mindfulness classes, and fitness and nutrition mentors.

Study inclusion criteria included full-time UVM undergraduates aged 18-25 years with an iPhone 5 (Appl Inc) or newer (for app compatibility and connection to Apple Watch). A total of 1952 students were originally recruited, and 805 participants (222 Male, 574 Female, and 9 students who chose not to disclose their gender) were included in this study. The study protocol was approved by the UVM Institutional Review Board.

Instruments and Assessment

Apple Watch

All participating students received either a Series 0 or Series 1 Apple Watch. The Apple Watch is equipped with heart rate sensor, accelerometer, and gyroscope to track steps, heart rate, exercise minutes, active and resting energy expenditure, sedentary breaks, distance traveled, and stairs climbed. The students were asked to wear the Apple Watch during the 2017-2018 academic year.

Daily Surveys

A 14-item survey was distributed to all participants each night (opening from 7 PM to midnight) via the WE study app on their iPhone or Apple Watch. The survey collected data from 6 wellness behaviors (ie, minutes of exercise, minutes of mindfulness, minutes of music played or sang, fruits and vegetables consumed, hours of sleep, and amount of water consumed) and 7 risk behaviors (ie, cigarette use, consumption of alcoholic drinks, illicit drug use, shots of liquor, number of nonprescribed pills, marijuana use, and hours of screen time). Data informing the overall mood of the day (happy, ok, or sad day) were also included. The daily survey was not a previously validated survey but has been cross-validated with other validated surveys [26]. The participants' demographic data were also collected at baseline. Apple Watch and daily survey data collected from Oct 9, 2017, to May 13, 2018, were used in the current study, resulting in 216 days of data.

Data Processing and Analysis

The data were analyzed in 2020. Daily step data were accessed via Apple's HealthKit application programming interface and screened for compliance. A daily step total of 2000 was used as the wear time cut-off point [27]. The students who had a minimum of 50 valid days of Apple Watch data and completed at least 50% of the daily surveys were included in the final sample. The inclusion criterion of 50 days was the median compliance rate that 50% of the participants (n=1952) had at least 50 days of valid Apple Watch data. Descriptive statistics for demographic variables including age, inclusion in wellness program, gender, race, and year in college as well as average daily steps were computed.

Concurrent associations of daily steps with each wellness or risk behavior were tested first using a general linear mixed effects univariable model (1 behavior as a single predictor). This was followed using a multivariable model (all behaviors entered the same time as multiple predictors) with all 13

wellness and risk behaviors, except for exercise, tested simultaneously.

Longitudinal, reciprocal associations between daily steps and health or risk behaviors were tested with cross-lagged analysis to explore whether the previous-day health and risk behaviors predict the next-day PA and vice versa. The intraclass correlation coefficient was 23.4% in the unconditional model, indicating that 23.4% of the variance in daily steps was between the participants. Thus, all analyses of the daily surveys accounted for repeated, correlated observations within individuals. An autoregressive covariance structure was used, and demographic variables were controlled for all of the mixed models [28]. All analyses were conducted with SAS 9.4 (SAS Institute) software with an alpha value set at $P<.05$.

Results

Sample Description

A total of 805 participants with at least 50% daily survey completion and 50 days of valid steps data were included in the analytic sample, which resulted in 77,857 total participant-days' worth of observations. The analytic sample included in the study did not differ from the baseline sample (N=1871) in terms of demographic distribution (ie, academic year, gender, involvement in the WE program, and race). The average number of observations per participant throughout the 2017-18 academic year was 97 days (SD 48, range 50-212). Overall, the majority of the study sample were female (72.1%), Caucasian (85.4%), and freshman (60.8%) or sophomore (21.8%) (Table 1). No statistical differences were found in the average steps between races, academic class standing, and involvement in the WE program. The only significant difference was that female participants had higher average steps than males ($P<.001$).

Table 1. Average daily steps stratified by sample characteristics.

Characteristics and populations		Other values		
		Mean steps	95% CI	*P* value
Gender, n (%)				
Male	222 (27.9)	8488	(8227-8749)	Reference
Female	574 (72.1)	8904	(8739-9069)	<.001
WE[a] status, n (%)				
Wellness Environment	351 (43.6)	8833	(8624-9042)	Reference
College as usual	454 (56.4)	8731	(8545-8917)	.47
Academic year, n (%)				
First year of college	486 (60.8)	8826	(8650-9010)	Reference
Second year of college	174 (21.8)	8800	(8538-9131)	.98
Third year of college	113 (14.1)	8539	(8160-8902)	.15
Fourth year of college	26 (3.3)	8588	(7908-9456)	.71
Race, n (%)				
Caucasian	677 (85.4)	8770	(8624-8927)	Reference
African American	12 (1.5)	9030	(7992-10,072)	.63
Asian	53 (6.7)	8714	(8231-9361)	.95
Latina or Latino	22 (2.8)	8571	(7851-9452)	.77
Native American	4 (0.5)	8388	(6307-10,469)	.72
Pacific Islander	3 (0.4)	11,223	(8827-13,620)	.05
Other	22 (2.8)	8672	(7796-9472)	.74

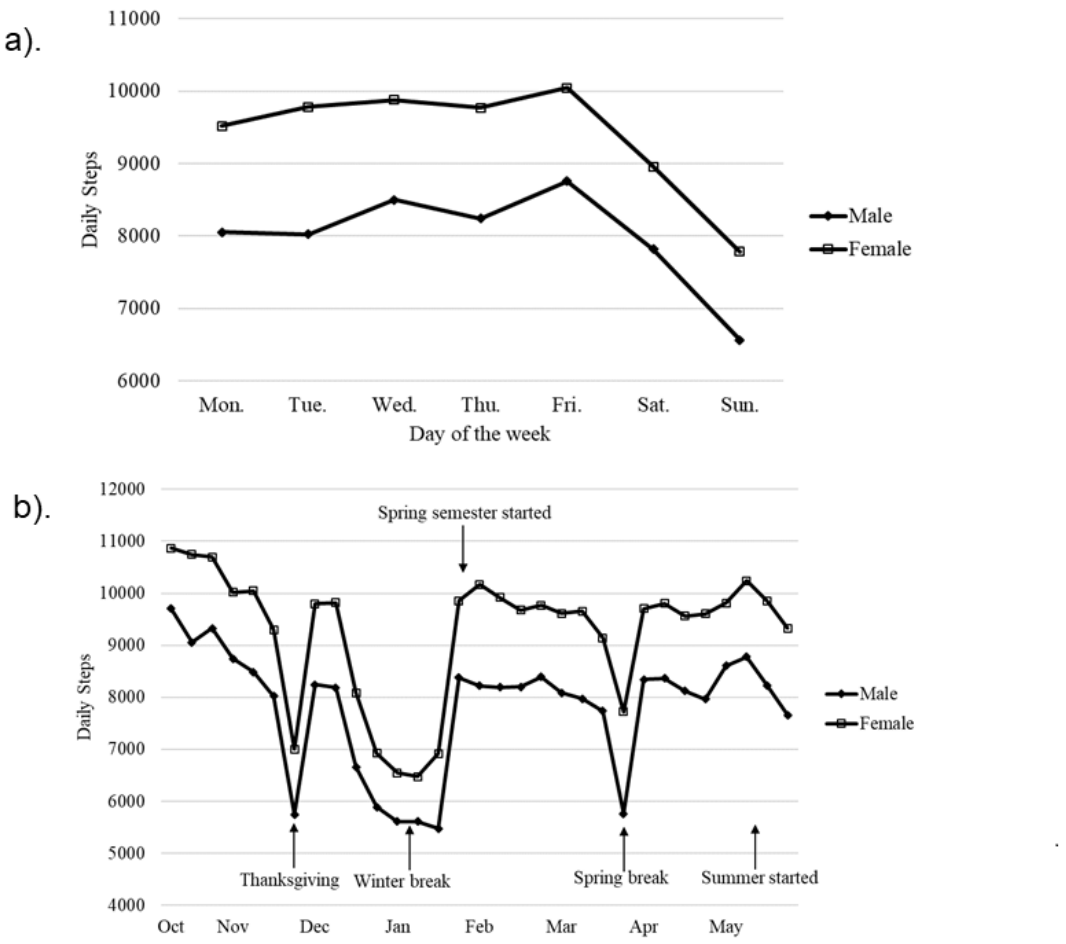
[a]WE: Wellness Environment.

Prevalence of Daily Steps

Steps were tracked daily and across the entire year (Figure 1). The participants were more active during the weekdays (Monday to Friday, ranged from 8989 to 9566), and their daily steps were approximately 1000 fewer on Saturdays (8533, SD 286) and an additional 800 fewer steps on Sundays (7327, SD 286) compared with weekday steps. A larger variation was found across the school year. Step counts were significantly lower during school breaks including Thanksgiving (6999, SD 338), winter break (6471, SD 345), and spring break (7725, SD 341). The most active period was the first 3 weeks of the study, which ranged from 10,697 to 10,864 steps daily. Gender difference attenuated during the weekends and breaks. Compared with males, female participants accumulated about 1500 more steps during weekdays and over 1100 more steps on Saturdays and Sundays.

Note that the daily steps were averaged into weekdays with data from the entire academic year (Figure 1a), and the daily steps were averaged into study weeks (Figure 1b).

Figure 1. The prevalence of daily steps across day of the week (a) and the academic year (b) by gender.



Concurrent Associations of Daily Steps With Wellness or Risk Behaviors

The association of daily steps with 1 wellness or risk behavior (Multimedia Appendix 1: Supplemental Table 1) in the univariable model was similar to that of the steps with multiple behaviors in the multivariable model (Table 2). Higher levels of PA were associated with happy mood (>650 daily steps) and other health behaviors, including ≥1 servings of fruits and vegetables, ≥4 glasses of water, and ≥1 minute of mindfulness practice (P<.001). A dose-response association was also found between PA with fruit and water consumption. Nonacademic screen time was negatively associated with daily steps in that a difference of over 2000 steps was found between the participants who spent 0-2 hours and 7+ hours on screen (P<.001).

Moreover, 3 out of 6 substance abuse behaviors (ie, liquor, cannabis, and nonprescribed pills) were significantly associated with PA (P<.001). For 30 minutes of self-report exercise, there was approximately 1700 additional steps estimated by Apple Watch (P<.001). The cumulative wellness items had a positive association with daily steps (P<.001). The participants were most active when they had 0 risk behaviors (9338 steps; 95% CI 8748-9928) followed by those who engaged 2 and more risk behaviors (8855 steps; 95% CI 8257-9452) and then 1 risk behavior (8508 steps; 95% CI 7918-9099).

Table 2. Healthy and risky behaviors predicting daily steps within the multivariate model.

Healthy and risky behaviors[a]	Estimated steps	95% CI	*P* value
Mood			
Sad	8535	(7774-9295)	Reference
Ok	8622	(7867-9378)	.17
Happy	9189	(8434-9944)	<.001
Sleep (hours)			
<4	9194	(8419-9969)	.51
4-7	9125	(8372-9879)	Reference
8+	8027	(7273-8780)	<.001
Fruit, n			
0	8169	(7412-8927)	Reference
1-3	8798	(8044-9552)	<.001
4+	9378	(8619-10,138)	<.001
Water, n			
0-3	8105	(7349-8861)	Reference
4-6	8824	(8069-9579)	<.001
7+	9416	(8655-10,177)	<.001
Screen time (hours)			
0-2	9848	(9094-10,601)	Reference
3-6	8859	(8104-9613)	<.001
7+	7639	(6871-8408)	<.001
Mindfulness (minutes)			
0	8386	(7632-9141)	Reference
1-9	9009	(8251-9767)	<.001
10+	8951	(8191-9711)	.02
Music (minutes)			
0	8752	(7996-9508)	Reference
1-30	8731	(7974-9487)	.64
31+	8863	(8106-9620)	.04
Alcohol			
No	8811	(8057-9565)	Reference
Yes	8753	(7992-9513)	.41
Liquor			
No	8487	(7733-9242)	Reference
Yes	9077	(8313-9840)	<.001
Marijuana			
No	8674	(7919-9430)	Reference
Yes	8890	(8128-9651)	.01
Cigarettes			
No	8724	(7973-9474)	Reference
Yes	8840	(8042-9638)	.52
Illicit drugs			
No	8881	(8219-9544)	Reference

Healthy and risky behaviors[a]	Estimated steps	95% CI	*P* value
Yes	8682	(7660-9704)	.64
Nonprescribed pills			
No	9169	(8434-9904)	Reference
Yes	8395	(7542-9248)	<.001
Gender			
Male	8519	(7729-9308)	Reference
Female	9045	(8287-9803)	<.001
WE[b] status			
Wellness Environment	8712	(7918-9506)	Reference
College as usual	8852	(8097-9607)	.44
Academic year			
First year of college	9074	(8333-9816)	Reference
Second year of college	8752	(7967-9537)	.12
Third year of college	8644	(7819-9468)	.09
Fourth year of college	8658	(75552-9764)	.36
Race			
Caucasian	8360	(7797-8922)	Reference
African American	8596	(7264-9927)	.71
Asian	8429	(7626-9232)	.83
Latina or Latino	8435	(7383-9487)	.87
Native American	8110	(5914-10,305)	.82
Pacific Islander	11,039	(8502-13,575)	.03
Other	8506	(7391-9622)	.77

[a]Demographic factors were controlled in the model.

[b]WE: Wellness Environment.

Longitudinal Associations of Daily Steps With Wellness of Risk Behaviors

The previous-day behaviors predicting the next day's PA were tested using both univariable (Multimedia Appendix 1: Supplemental Table 2) and multivariable models (Table 3). The results indicated that each of the self-reported behaviors independently predicted the next day's PA. As shown in Table 3, the previous-day fruit and vegetable consumption, water consumption, and mindfulness practice had significantly positive associations with the following day's PA. The students who had 1-3 and 4+ servings of fruit and vegetables accumulated 656 and 375 more following-day steps compared with students who had no fruit and vegetable consumption, respectively (*P*<.001). Similarly, the students who had 7+ bottles of water accumulated 335 and 215 additional following-day steps compared with those who had 0-3 and 4-6 bottles of water (*P*<.001). The previous-day screen time was a negative predictor of the following-day PA. The students who had 3-6 hours and 7+ hours of screen time accumulated 203 and 506 fewer following-day steps compared with those who had 0-2 hours of screen time (*P*<.001). The students with any mindfulness practice had 300-400 additional following-day steps compared with those who had no mindfulness practice (*P*<.001). However, Students who were happy or played music predicted lower following-day PA compared with those who had a sad mood or played no music. Previous-day cigarettes and illicit drugs did not significantly predict the following day's PA (Table 3). Conversely, higher previous-day PA levels were associated with less following-day exercise, higher fruit and vegetable consumption, less playing music, and higher liquor consumption (*P*<.05, Table 4).

Table 3. Previous-day healthy and risky behaviors predicting daily steps in multivariate model.

Previous-day healthy and risky behaviors[a]	Estimated steps	95% CI	*P* values
Steps	0.2	(0.19-0.21)	<.001
Mood			
Sad	8788	(8033-9543)	Reference
Ok	8812	(8064-9559)	.75
Happy	8487	(7740-9234)	<.001
Sleep (hours)			
<4	8600	(7827-9373)	.27
4-7	8736	(7991-9481)	Reference
8+	8751	(8005-9497)	.70
Fruit, n			
0	8383	(7633-9134)	Reference
1-3	8664	(7918-9411)	<.001
4+	9039	(8286-9792)	<.001
Water, n			
0-3	8544	(7796-9292)	Reference
4-6	8664	(7916-9411)	.03
7+	8879	(8124-9634)	<.001
Screen time (hours)			
0-2	8932	(8187-9677)	Reference
3-6	8729	(7983-9476)	<.001
7h+	8426	(7661-9191)	<.001
Mindfulness (minutes)			
0	8460	(8140-9642)	Reference
1-9	8891	(9066-10,036)	<.001
10+	8737	(7983-9490)	<.001
Music (minutes)			
0	8803	(8055-9551)	Reference
1-30	8697	(7947-9446)	.04
31+	8587	(7837-9336)	<.001
Alcohol			
No	8945	(8200-9691)	Reference
Yes	8446	(7690-9202)	<.001
Liquor			
No	8921	(8175-9668)	Reference
Yes	8470	(7710-9230)	<.001
Marijuana			
No	8804	(8055-9553)	Reference
Yes	8587	(7832-9342)	.03
Cigarettes			
No	8612	(7869-9355)	Reference
Yes	8779	(7973-9586)	.44
Illicit drugs			

Previous-day healthy and risky behaviors[a]	Estimated steps	95% CI	*P* values
No	8678	(8071-9286)	Reference
Yes	8713	(7587-9839)	.95
Nonprescribed pills			
No	8932	(8207-9657)	Reference
Yes	8459	(7577-9340)	.13
Gender			
Male	8535	(7766-9304)	Reference
Female	8857	(8107-9606)	.03
WE[b] status			
Wellness Environment	8595	(7821-9370)	Reference
College as usual	8796	(8050-9542)	.18
Academic year			
First year of college	8852	(8114-9590)	Reference
Second year of college	8664	(7897-9431)	.27
Third year of college	8444	(7650-9239)	.05
Fourth year of college	8822	(7824-9820)	.94
Race			
Caucasian	8482	(7858-9105)	Reference
African American	8472	(7290-9654)	.99
Asian	8494	(7715-9274)	.96
Latina or Latino	8256	(7290-9221)	.56
Native American	7969	(6139-9799)	.56
Pacific Islander	10,529	(8414-12,644)	.05
Other	8667	(7657-9678)	.65

[a]Demographic factors were controlled in the model.

[b]WE: Wellness Environment.

Table 4. Previous day daily steps predicting healthy and risky behaviors within the univariable model.

	Previous day steps as predictor[a]		
Outcomes	Coefficient	95% CI	*P* value
Mood	-0.0049	(-0.013, 0.0031)	.07
Sleep	-0.0001	(-0.0079, 0.0077)	.98
Exercise	-0.010	(-0.018, -0.0027)	.01
Fruit	0.011	(0.0033, 0.018)	.01
Water	0.0047	(-0.0032, 0.013)	.24
Screen time	0.0070	(-0.001, 0.015)	.09
Mindfulness	-0.0080	(-0.018, 0.0016)	.10
Music	-0.0096	(-0.018, -0.0014)	.02
Alcohol	0.013	(-0.0003, 0.027)	.06
Liquor	0.027	(0.015, 0.038)	<.001
Marijuana	0.0095	(-0.007, 0.026)	.25
Cigarettes	0.011	(-0.013, 0.035)	.36
Illicit drugs	0.029	(-0.006, 0.063)	.11
Nonprescribed pills	-0.011	(-0.038, 0.017)	.45

[a]Demographic factors were controlled in the models.

Discussion

Principal Findings

This paper provided a unique and comprehensive profile of objectively measured daily PA and self-reported health and risk behaviors using ecological momentary assessment over 7 months within 1 academic year among college students. We found PA variations between the weekday and weekend and between school days and academic breaks. Gender differences in PA were attenuated during the weekend and academic breaks. Compared with risk behaviors, stronger and independent associations were found between PA and several wellness behaviors including self-report exercise minutes, fruit and vegetable consumption, sleep, water consumption, and mood states.

Although consumer monitors provide the potential to track PA in real time during longer time periods, few studies have reported continuously monitored PA levels (ie, for more than a few weeks) in adult or youth populations. Several studies have applied consumer monitors such as Fitbit (Fitbit Inc) or Misfit (Misfit Inc) in intervention studies lasting from 12 weeks to 6 months, but the majority of the studies have used research-based activity monitors (eg, Actigraph) and only reported baseline and posttest MVPA [15,29]. Three intervention studies used Fitbit and reported the real-time steps or MVPA data over 1 year [30], 12 weeks [31], and 8 weeks [32]. Although direct comparisons to this study are precluded due to the sample and setting differences, there may have been possible behavioral reactivity within in the first 2 or 3 weeks of wearing the device [30-32]. No other prior ecological momentary assessment of PA studies in college students were identified.

Similar to 2 other recent intervention studies with college students using wearables [15,16], around 70% of the participants in this study were female. Mixed results were found in the literature about gender differences and PA levels among college students. The majority of previous research using self-report data suggested that males were more active than females; however, studies using objectively measured PA found either no gender differences or females being more active than males [33-35]. Our study showed that female participants were more active than their male counterparts during the week and across the school year. Possible explanations for these differences could be that males tend to overestimate their PA levels in the self-report data, and they tend to engage in resistance training, which is a nonambulatory activity that may not be captured by the Apple Watch [11,36].

Our study also found that the participants were more active during structured days (ie, school days) than unstructured days (ie, academic breaks and weekends). A few other studies also observed that college students were more active during weekdays than weekends [33,34]. For example, Clemente et al [37] found that both male and female Portuguese college students were more active during weekdays than weekend days. However, this finding was expected because most students had to walk to or around campus during weekdays [34]. Despite this, we did not find empirical studies that examined the seasonal patterns of objective PA in a college sample, which may be due to prior measurement constraints such as the lack of technology to continuously monitor PA over several months with research-based monitors.

Besides environmental changes, university students, especially first-year students, undergo social, academic, emotional, and physiological changes that may influence their lifestyle and behaviors such as higher stress levels leading to increased drug

and alcohol abuse [38]. Young adults had the highest prevalence (13.1%) of major depressive episodes compared with other adult age groups, according to the data from 2017 National Survey on Drug Use and Health [39]. Several randomized controlled trials indicated the small-to-moderate therapeutic effects of exercise on depression and anxiety disorders [40,41]. Our study indicated that students who had higher PA had better current and next day mood. Encouraging college students to engage in PA or exercise could be an effective way to cope with academic and interpersonal stress during the transition from high school to college.

The magnitude of association of PA and other wellness and risk behaviors remained generally consistent in the univariable and multivariable models, supporting the independent association between PA and wellness and risk behaviors in college students. For PA and health behaviors, fruit, vegetable, and water consumption were positively correlated with PA levels while screen time was negatively associated with PA, which have been confirmed by other cross-sectional studies [20,21,42]. However, the significant temporal link between PA and fruit or vegetable consumptions found in our study contradicted the findings of previous studies in the literature [19]. Congruent with prior research, our study also found that PA levels decreased from freshman to senior year. This indicates the importance of offering health behavior education and promotion programming to freshmen, targeting several health and risk behaviors [42-44]. Unlike other studies [20,35,42], our study did not find significant associations between PA and risk behaviors. Notwithstanding, PA was identified as a protective factor for alcohol and substance use behaviors in our temporal analysis. A possible explanation is that the majority of the study sample were freshmen who live on campus, half of whom reside in WE housing where students sign a contract not to consume alcohol in their dorm. Thus, those students who wanted to consume alcohol needed to walk to bars, parties, and stores, increasing their daily step count.

Strengths and Limitations

To the best of our knowledge, this is the first study using an ecological momentary approach to assess multiple wellness behaviors in 1 academic year among college students. The study assessed real time and objective PA within a real-world setting over a full academic year in addition to the tracking of other wellness and risk behaviors. Academic breaks and weekends were identified as inactive periods for college students, which allows targeted interventions to be designed to enhance the health of young adults during this critical life transition period. The successful deployment of the study app allowed us to collect 13 different wellness behaviors and mood states simultaneously on a daily basis. This enabled us to study the different wellness behaviors' independent and dependent associations as well as concurrent and longitudinal associations with PA.

There are a number of limitations in this study. First, the study sample was generally homogeneous with a majority of participants being female and Caucasian at a single university in Northeastern United States. Second, the Apple Watch provided objectively measured step count data, but no wear time data were available to assess. Considering the possible linear association of longer wear time and higher number of steps accumulated, the activity level could be skewed for students who wore the Apple Watch longer and slept less. Third, the wellness and risk behaviors were measured by self-report daily survey items with fixed response sets.

Implications and Contribution

The independent associations explored between PA and a variety of other health-related behaviors indicated that promoting one behavior will not necessarily influence other behaviors. This study provided novel information on specific patterns of college students' objective PA, wellness, and risk behaviors over an academic year.

Conflicts of Interest

This study was supported by a research grant from the Conrad Hilton Foundation. The funding source had no involvement in the study design, data collection, analysis and interpretation of data, writing of the report, or the decision to submit the article for publication. YB had full access to all the data in the study, performed all statistical analyses, and takes responsibility for the integrity of the data and the accuracy of the data analysis. WEC receives research support from the National Institute of Mental Health, National Institute on Drug Abuse, and the National Institute for Child Health and Development. JH receives research grants from the Conrad Hilton Foundation and Apple Corp.

Multimedia Appendix 1
Healthy and risky behaviors predicting daily steps within the univariable model. Previous day healthy and risky behaviors predicting daily steps within the univariable model.
[DOCX File , 21 KB - publichealth_v8i1e25375_app1.docx]

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Abbreviations

MVPA: moderate-to-vigorous physical activity
PA: physical activity
UVM: University of Vermont
WE: Wellness Environment

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Original Paper

Participant Engagement and Reactance to a Short, Animated Video About Added Sugars: Web-based Randomized Controlled Trial

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Abstract

Background: Short, animated story-based (SAS) videos are a novel and promising strategy for promoting health behaviors. To gain traction as an effective health communication tool, SAS videos must demonstrate their potential to engage a diverse and global audience. In this study, we evaluate engagement with a SAS video about the consumption of added sugars, which is narrated by a child (a nonthreatening character), a mother (a neutral layperson), or a physician (a medical expert).

Objective: This study aims to (1) assess whether engagement with the sugar intervention video differs by narrator type (child, mother, physician) and trait proneness to reactance and (2) assess whether the demographic characteristics of the participants (age, gender, education status) are associated with different engagement profiles with the sugar intervention video.

Methods: In December 2020, after 4013 participants from the United Kingdom completed our randomized controlled trial, we offered participants assigned to the placebo arms (n=1591, 39.65%) the choice to watch the sugar intervention video (without additional compensation) as posttrial access to treatment. We measured engagement as the time that participants chose to watch the 3.42-minute video and collected data on age, gender, education status, and trait reactance proneness. Using ordinary least squares regression, we quantified the association of the demographic characteristics and trait reactance proneness with the sugar video view time.

Results: Overall, 66.43% (n=1047) of the 1576 participants in the 2 placebo arms voluntarily watched the sugar intervention video. The mean view time was 116.35 (52.4%) of 222 seconds. Results show that view times did not differ by narrator (child, mother, physician) and that older participants (aged 25-59 years, mean = 125.2 seconds) watched the sugar video longer than younger adults (aged 18-25 years, mean = 83.4 seconds). View time remained consistent across education levels. Participants with low trait reactance (mean = 119.3 seconds) watched the intervention video longer than high-trait-reactance participants (mean = 95.3 seconds), although this association did not differ by narrator type.

Conclusions: The majority of participants in our study voluntarily watched more than half of the sugar intervention video, which is a promising finding. Our results suggest that SAS videos may need to be shorter than 2 minutes to engage people who are young or have high trait proneness to reactance. We also found that the choice of narrator (child, mother, or physician) for our video did not significantly affect participant engagement. Future videos, aimed at reaching diverse audiences, could be customized for different age groups, where appropriate.

Trial Registration: German Clinical Trials Register DRKS00022340; https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00022340

International Registered Report Identifier (IRRID): RR2-10.2196/25343

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KEYWORDS

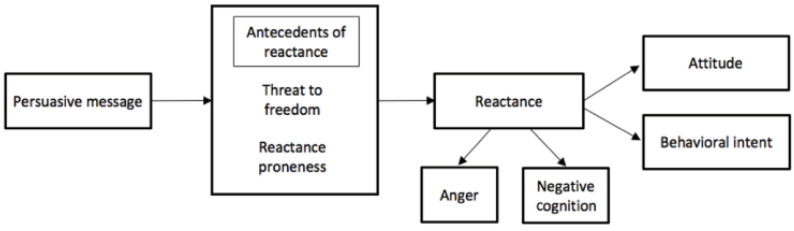
added sugar; prevention; sugar consumption; short and animated story-based video; informational video; randomized controlled trial; social media; participant engagement; health promotion; United Kingdom; entertainment; patient education; healthy eating; preventive health; health messaging

Introduction

Engaging the public in the care and maintenance of their own health constitutes a longstanding challenge for health communicators, health educators, and public health agencies worldwide [1,2]. Innovative strategies, including the use of pictures [3], digital storytelling, and entertainment-education [4], have all shown promise for increasing engagement in public health campaigns. Research has shown that packaging health recommendations in a relatable story can be more effective than traditional media approaches that frame health messages as informational arguments [5]. More recently, social media has emerged as an important platform for communicating evidence-based health messages and potentially improving health outcomes [2,6]. Aligned with this innovative direction, short, animated story-based (SAS) videos draw from entertainment-education media, communication theory, and the animated entertainment industry to promote compelling, evidence-based health messages that are optimized for "viral spread" over social media channels [7,8]. Under 4 minutes in length and using culturally de-identified character portrayals, SAS videos are designed to be accessible and adaptable across different global regions, languages, and literacy levels [7,9]. However, to gain further traction as a health communication tool, SAS videos must demonstrate their potential to catalyze engagement across diverse audiences.

As with all persuasion strategies, optimal engagement with SAS videos may be limited by a motivation to reject the health message—a phenomenon known as reactance [10]. As a theoretical construct, reactance consists of 4 main components: (1) freedom, which individuals possess insofar as they are aware of it and can enact it; (2) threat to freedom, which is anything that makes it difficult to enact that freedom; (3) reactance, which is the motivation to reestablish the freedom if that freedom is eliminated or threatened with elimination; and (4) direct restoration, which involves the freedom of the individual to perform a forbidden act [11]. In the communications literature, Dillard and Shen [11] and Zhang [12] have proposed the Intertwined Process Cognitive-Affective Model, which describes the pathways through which a persuasive message can provoke reactance (Figure 1). The model includes 2 antecedents to reactance: threat to freedom and trait reactance proneness, which is a personal trait or propensity to experience reactance [13], reactance itself (comprising anger and negative cognition), and its outcomes (attitude and behavioral intent). Previous research on reactance in the health sciences has led to the development of several strategies to reduce reactance in areas such as the use of e-cigarettes [14], littering [15], alcohol [16], and eating behaviors [17], among others [5,18-22]. Of these strategies, we are most interested in the narrator's characteristics (eg, the claim to expertise, intended motive, the threat level of the narrator) that are likely to arouse reactance to health messages.

Figure 1. The Intertwined Process Cognitive-Affective Model of reactance [11],[12].



In a recent study, we investigated whether a child narrator reduced reactance to a SAS video about the consumption of added sugars [23]. In the video, the 2 main characters, a mother and her preadolescent daughter, engage in food-related activities, such as shopping for groceries and cooking dinner. Through a narrative, they present educational content on the health problems associated with the addition of excess sugars in commonly available foods. Using a web-based experiment platform, we randomized 4013 participants to the same sugar video narrated by the daughter (a nonthreatening character), the daughter's mother (a neutral layperson), or the family physician (an expert with medical authority). We then compared the differences in reactance to the 3 narrators relative to a SAS video with a health message about sunscreen use (the content placebo) and a SAS video with a non-health-related message about earthquakes (the placebo). We hypothesized that the child narrator would arouse the least reactance to the sugar intervention message.

In this study, we investigate the role of trait reactance proneness and demographic factors in voluntary engagement with the sugar intervention video narrated by the child, the mother, or the physician. The participants (n=1576) are those who were initially randomized to the content placebo (the sunscreen SAS

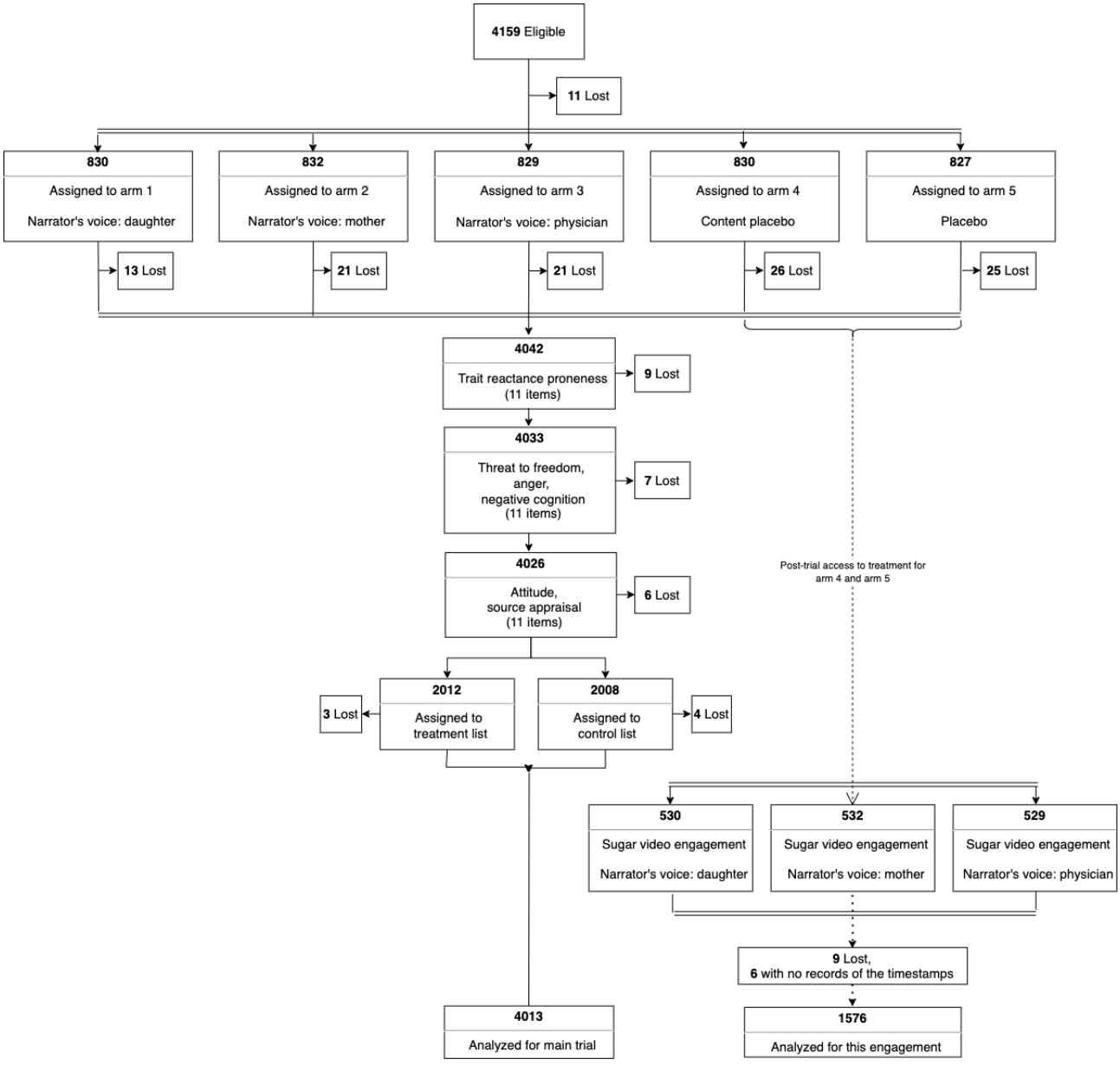
video) or the placebo (the earthquake SAS video) arms in the main trial and who were then offered the intervention video as posttrial access to treatment [24]. We define engagement as the duration of time that the participants spent watching the 3.42-minute intervention video. We hypothesized that participants with lower trait reactance proneness would spend more time watching the intervention videos, with the child-narrated video having the longest view time (assuming it would arouse the least reactance). In addition, given that SAS videos are designed for social media, we hypothesized that younger participants (aged 18-24 years) would watch the intervention video longer than older participants (aged 25-59 years). Findings from our study could inform the future design and delivery of effective, spreadable SAS videos aimed at promoting health in diverse audiences.

Methods

Study Design and Participants

This was a randomized controlled trial (RCT) with posttrial access to the treatment stage [23]. In the main trial, participants were randomly assigned (1:1:1:1:1) to 3 different intervention arms (arms 1-3), a content placebo arm (arm 4), and a placebo arm (arm 5). In each intervention arm, respondents watched a SAS video about sugar consumption, narrated by 3 different voices: a preadolescent daughter (arm 1), the daughter's mother (arm 2), and the family physician (arm 3). In the content placebo arm, participants watched a SAS video with a non-sugar-related message about sunscreen use; in the placebo arm, participants watched a non-health-related video about earthquakes (Figure 2). At the end of the trial, participants randomized to the content placebo and placebo arms were given the option to watch the sugar intervention video. If these participants agreed, they were then randomized 1:1:1 to the sugar video narrated by the child, the mother, or the physician.

Figure 2. Flowchart depicting the study methodology.



Both trials (main and post) were hosted and run on the Gorilla platform (Cauldron Science Limited) [25] and participants were recruited through Prolific (Prolific Academic Ltd) [26]. Inclusion criteria included being between the ages of 18 and 59 years (male, female, or other), being able to speak English, and residing in the United Kingdom. More details on the sample size determination can be found in Multimedia Appendix 1. The study and its outcomes were registered with the German Clinical Trials Register [27] on July 24, 2020 (#DRKS00022340). Ethical approval was obtained from the Heidelberg University's ethics committee on March 18, 2020 (#S-088/2020). No harm or adverse events were observed, given the online format of the trial.

Randomization and Blinding

The Gorilla algorithm randomly assigned participants to the 5 arms in the main trial and to the 3 intervention arms in the posttrial stage. Since the recruitment took place on the Prolific platform, it was not possible to identify or link data back to the participants. Participants responded to the survey questions and submitted their responses anonymously through the Gorilla platform. Both the study subjects and the investigators had no knowledge regarding the allocation status of the participants.

Informed Consent

All participants underwent a process of informed consent on the Prolific platform. The consent form explained the purpose of the study, the risks and benefits of the research, and how to contact the study investigators. By clicking the link, participants agreed to participate in our study and were redirected to the Gorilla platform, where additional information was given. Participants could leave the research study at any time.

Procedures

Here, we provide some basic details of the main trial to give context to our posttrial study. Further details of the main trial and its procedures can be found elsewhere [23].

At the beginning of the main trial, participants were asked to answer demographic questions about their age, gender, and highest educational attainment. Participants were then randomized to the sugar intervention arm, the content placebo arm, or the placebo arm, where they watched a SAS video from start to finish.

The sugar intervention video was narrated in English, with a duration of 3 minutes and 42 seconds. Its aim was to boost knowledge about the health consequences of consuming added sugars [28-30]. The video presented the WHO recommendations for daily sugar consumption, the health risks associated with excess consumption, and some strategies for reducing sugar in an individual's daily diet. The characters were deliberately represented without distinguishable cultural identifiers, to enhance cross-cultural appeal, while the soundtrack was designed to arouse emotion and enhance engagement. We, the coauthors, decided to compare the child narrator with the mother and family physician narrators. In the content placebo arm, respondents watched an animated video delivering a non-sugar-related health message about tanning and the use of sunscreen [31]. In the placebo arm, participants watched a non-health-related video about the causes and characteristics of earthquakes [32]. Both content placebo and placebo videos were animated, short (3.42 minutes), and narrated by a single character. We chose these nonintervention videos to be as similar as possible to the sugar intervention video but with no sugar content (the content placebo video about sunscreen use) and no health message (the placebo about earthquakes). Although both placebo and content placebo videos were chosen with caution, they were taken from external sources, and we, therefore, could not modify the design of those videos. After watching the SAS video, participants answered questions about their proneness to trait reactance.

For this study, participants who were randomized to the content placebo video or placebo video were then given the option to watch the sugar intervention video (posttrial access to treatment). Participants could watch the sugar video or end the study without watching the sugar video. If participants chose to watch the sugar video, they were asked on the next page to click the Play button or click the Finish button at any time to end the survey. The participants were informed that they would not be compensated for the additional time taken to watch the sugar video.

Measures

The primary outcome of this study was participant engagement, measured as the total time (in seconds) spent watching the SAS sugar video. We also collected data on the participants' age, gender, and educational status. We further considered the role of the participants' propensity toward reactance and its effect on view time. To measure trait reactance proneness, participants answered 11 questions based on the Hong Psychological Reactance Scale [27]. The questions comprised 4 major factors: emotional response to restricted choice, reactance to compliance, resisting influence from others, and reactance to advice and recommendations. Possible responses were arranged along a 5-point scale, anchored by strongly disagree (1) and strongly agree (5).

Statistical Analysis

To quantify the participants' engagement, we used the graphical experiment builder in Gorilla that records a timestamp whenever a new screen is displayed. In our case, Gorilla registered the moment when the participant reached the instruction screen of the final task as the first timestamp, the moment when they entered the video screen as the second timestamp, and the moment when they ended the experiment as the third timestamp. Gorilla also recorded loading delays of more than 10 seconds.

Participants who spent less than 3 seconds on the video screen were grouped together with participants who did not watch the SAS video. Among participants who chose to watch the SAS video, we quantified the length of time spent watching the sugar video. We defined the dependent variable *engagement time* as the difference between the third timestamp and the second timestamp. The resulting variable was reported in seconds between 0 (ie, the respondent watched 0 seconds of the SAS video) and 222 (ie, the respondent watched the entire SAS video). We used 5 ordinary least squares regression models to investigate which sociodemographic factors and narrator's voice

were associated with engagement time. Model 1 included narrator, a categorical variable that equaled 1 if the participant was randomly assigned to watch the sugar video narrated by the preadolescent daughter, 2 if the narrator's voice of the video was the mother's, and 3 if it was the physician's. Models 2-4, respectively, added age, gender, and education completed, which were all categorical variables. We included each categorical variable nonparametrically in our model as a set of dummies. Model 5 added the participants' trait reactance proneness mean score, which is a continuous variable between 0 and 5. The methodology for calculating the participant's trait reactance proneness mean score is described in the study protocol [23].

We dropped observations that had missing values and performed all statistical analyses using Stata software version 14.2.

Results

Principal Findings

Between December 9, 2020, and December 11, 2020, we recruited 4159 participants for the main RCT. The main trial design is shown in Figure 2 and described elsewhere [23]. Of the 4159 participants, 1591 (38.25%) were assigned to 1 of the 2 placebo videos, of which 15 (0.94%) had missing data. Of the final sample of 1576 participants, 957 (60.7%) were female and 504 (32%) were between the ages of 25 and 34 years. In addition, over 1292 (82%) of participants had obtained at least a bachelor's degree. Table 1 shows the summary statistics of the sociodemographic variables by trial arm and narrator's voice (child, mother, physician). The *P* values stem from chi-squared tests and provide evidence that the randomization was successful.

Table 1. Characteristics of 1576 participants from the United Kingdom, with data on engagement with a short, animated video about added sugars in a web-based RCT[a], December 2020.

Demographics	Content placebo arm (790 observations)			Placebo arm (786 observations)		
	Narrator 1 (child), n (%)	Narrator 2 (mother), n (%)	Narrator 3 (physician), n (%)	Narrator 1 (child), n (%)	Narrator 2 (mother), n (%)	Narrator 3 (physician), n (%)
Age (years), *P*=.68[b]						
18-24	57 (22.8)	64 (22.5)	63(24.7)	69(25.1)	68(28.2)	71 (26.3)
25-34	83 (33.2)	93 (32.6)	80 (31.4)	89 (32.4)	74 (30.7)	85 (31.5)
35-44	57 (22.8)	67 (23.5)	51 (20.0)	58 (21.1)	50 (20.7)	59 (21.8)
45-54	37 (14.8)	41 (14.4)	49 (19.2)	41 (14.9)	36 (14.9)	39 (14.4)
55-59	16 (6.4)	20 (7.0)	12 (4.7)	18 (6.5)	13 (5.4)	16 (5.9)
P value[c]	N/A[d]	.77	N/A	N/A	.99	N/A
Gender, *P*=.72[b]						
Female	155 (62.0)	167 (58.6)	153 (60.0)	179 (65.1)	142 (58.9)	161 (59.6)
Male	95 (38.0)	117 (41.0)	98 (38.4)	92 (33.4)	98 (40.7)	107 (39.6)
Other	0 (0.0)	1 (0.3)	4 (1.6)	4 (1.4)	1 (0.4)	2 (0.7)
P value[c]	N/A	.19	N/A	N/A	.31	N/A
Education status, *P*=.87[b]						
Primary school	6 (2.4)	4 (1.4)	3 (1.2)	2 (0.7)	3 (1.2)	5 (1.8)
High school	37 (14.8)	45 (15.8)	38 (14.9)	39 (14.2)	42 (17.4)	45 (16.7)
BA, some college	155 (62.0)	176 (61.7)	166 (65.1)	184 (66.9)	152 (63.1)	160 (59.3)
MA/PhD	52 (20.8)	60 (21.0)	48 (18.8)	50 (18.2)	44 (18.3)	60 (22.2)
P value[c]	N/A	.19	N/A	N/A	.54	N/A

[a]RCT: randomized controlled trial.

[b]The *P* value comes from a Chi-squared test comparing the distribution of the respective covariates between the two study arms.

[c]The *P* value comes from a Chi-squared test comparing the distribution of the respective covariates between the three different narrators.

[d]N/A: not applicable.

A total of 1047 (66.43%) of the 1576 participants chose to watch the sugar video. Among these participants, the average time spent watching the sugar video was 116.35 (52.4%) of 222 seconds. Figure 3 displays the average view time by the

narrator's voice (child, mother, physician), age, gender, and education status. Results show that the average view times did not significantly differ between the child, mother, and physician trial arms. Moreover, older participants (aged 25-59 years, mean = 125.2 seconds) watched the sugar video longer than younger adults (aged 18-25 years, mean = 83.4 seconds). Specifically, after adjusting for sociodemographic factors, participants aged 25-34 years watched 32.92 seconds longer than younger participants (reference category), participants aged 35-44 years watched 46.96 seconds more, participants aged 45-54 years watched 47.50 seconds more, and participants aged 55-59 years watched 46.78 seconds more (P<.001, Table 2, model 5). Although not statistically significant, female participants tended to watch the video almost 8 seconds longer than males (Table 2, column 5). After adjusting for our set of covariates, we observed that the view time did not significantly vary across different educational levels (Table 2, column 5). Results show that participants with higher levels of reactance proneness were likely to watch the SAS video for a shorter period. A 1 unit increase in the reactance proneness mean score was associated with a 10.86-second decrease in the SAS view time (P=.07, Table 2, model 5).

To see view time as a function of trait reactance proneness for the child, mother, and physician narrators, adjusted for education level, please see Multimedia Appendix 1. The lack of significance suggests that the relationship of the reactance proneness mean score on the view time did not vary by the narrator's voice. Figure 4 shows the interaction between trait reactance proneness and the narrator's voice, and it reveals that participants with high trait reactance (scores of 4 or more) watched, on average, 95.3 seconds of the video, while those with low or moderate levels of trait reactance (scores of 3 or less) watched, on average, 119.3 seconds.

Figure 3. Participant view times (n=1047) of a short, animated video about sugar intake by narrator's voice, sociodemographic characteristics, and trait proneness reactance. Note: The whiskers represent the 95% CIs of view time.

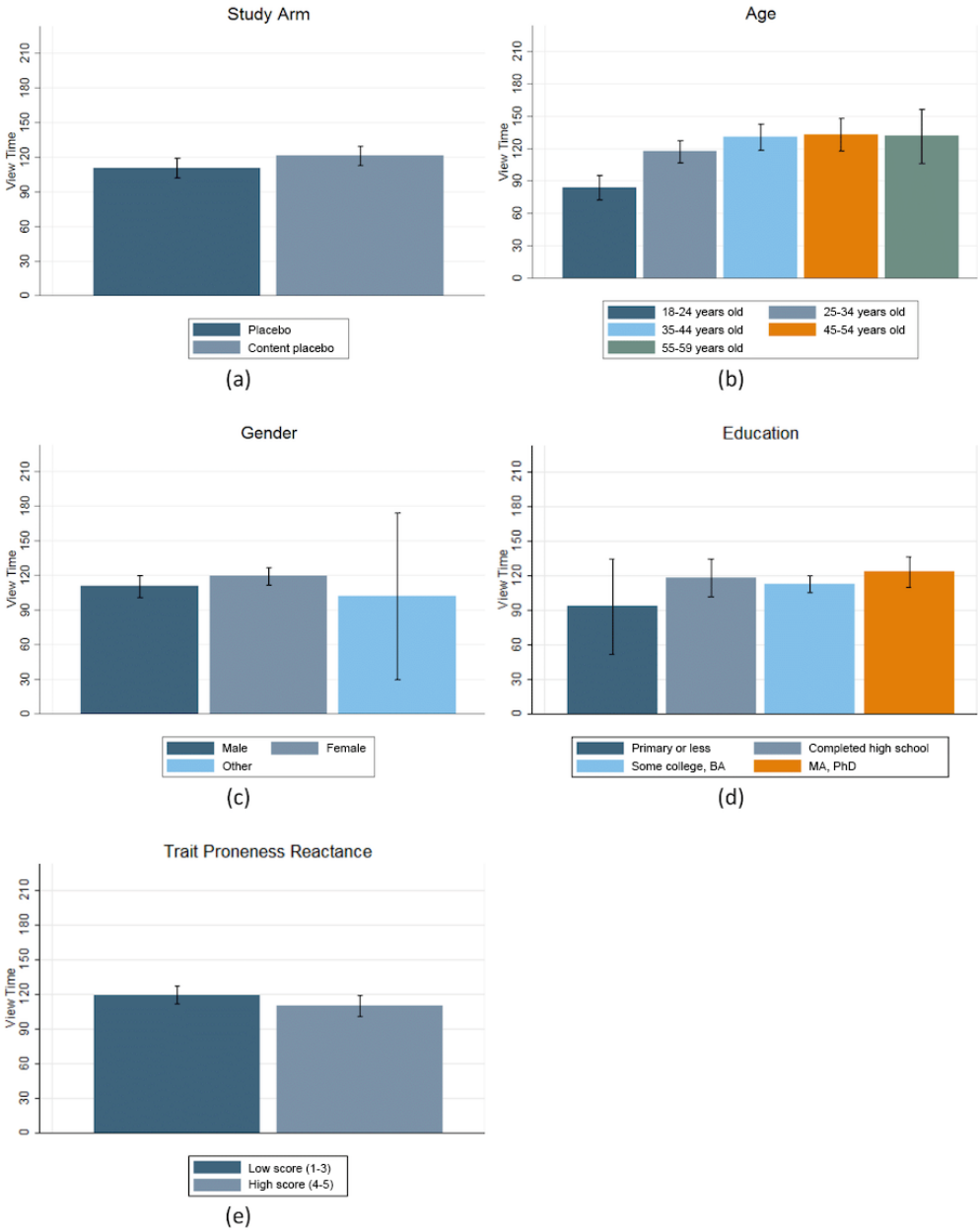


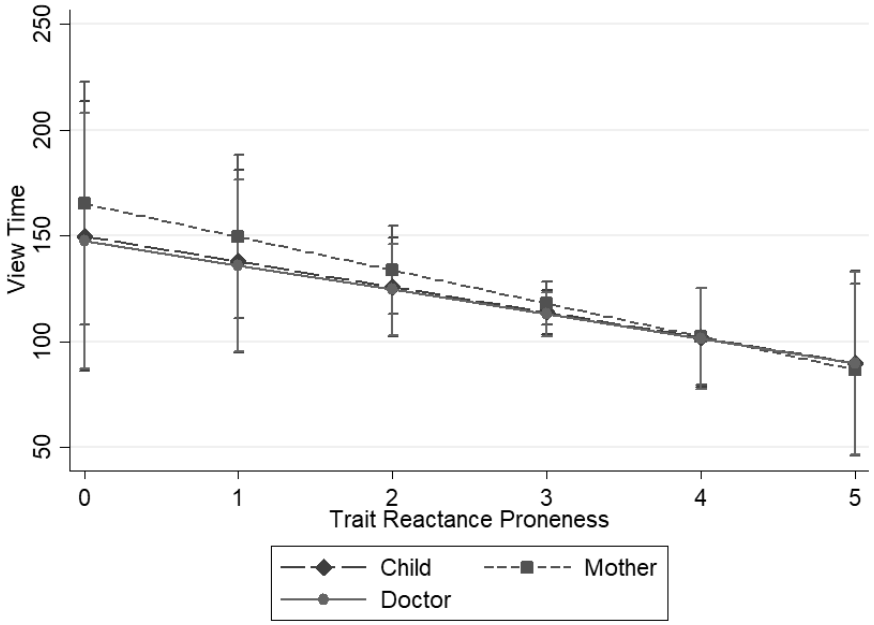
Table 2. Linear regression coefficients of factors (narrator's voice, sociodemographic characteristics, reactance proneness) associated with engagement with a short, animated video about added sugars (n=1047).

Factors	Model 1 (SE, *P* value)	Model 2 (SE, *P* value)	Model 3 (SE, *P* value)	Model 4 (SE, *P* value)	Model 5 (SE, *P* value)
Narrator (Ref[a]: daughter)					
Narrator 2: mother	5.217 (7.362, .48)	4.196 (7.250, .56)	4.820 (7.255, .51)	4.807 (7.265, .51)	3.995 (7.262, .58)
Narrator 3: physician	0.023 (7.429, .99)	–1.080 (7.306, .88)	–0.616 (7.307, .99)	–0.849 (7.304, .91)	–1.582 (7.295, .83)
Age (years; Ref: 18-24)					
25-34	—[b]	33.44 (7.873, <.001)	33.60 (7.857, <.001)	33.42 (8.022, <.001)	32.92 (8.026, <.001)
35-44	—	46.62 (8.546, <.001)	47.41 (8.546, <.001)	47.22 (8.622, <.001)	46.96 (8.624, <.001)
45-54	—	49.28 (9.609, <.001)	48.99 (9.591, <.001)	48.77 (9.575, <.001)	47.50 (9.592, <.001)
55-59	—	47.80 (13.959, .001)	48.68 (13.886, <.001)	47.77 (13.977, .001)	46.78 (13.897, .001)
Gender (Ref: female)					
Female	—	—	10.21 (6.109, .095	10.47 (6.134, .09)	10.02 (6.129, .102)
Other	—	—	–6.822 (33.142, .84)	–6.874 (33.296, .84)	–7.537 (34.051, .83)
Education status (Ref: primary school)					
High school	—	—	—	28.63 (22.411, .202)	25.43 (22.257, .25)
BA, some college	—	—	—	21.54 (21.230, .31)	19.61 (21.037, .35)
MA/PhD	—	—	—	27.02 (21.977, .22)	23.90 (21.844, .27)
Trait reactance proneness	—	—	—	—	–10.86 (5.871, .07)
n	1047	1047	1047	1047	1047

[a]Ref: reference group.

[b]Not applicable.

Figure 4. Predicted view times (n=1047) by narrator's voice of a short, animated video about sugar intake. Note: The whiskers represent the 95% CIs at predicted trait proneness values.



Discussion

Principal Findings

In this web-based RCT, we assessed participant engagement with a SAS video about added sugar consumption. We hypothesized that participants with higher levels of trait reactance proneness would watch the SAS video for a shorter period and that younger participants (aged 18-24 years) would have higher engagement with the sugar intervention when compared with older participants (aged 25-59 years). Overall, 66.43% (1047/1576) of the participants voluntarily watched the sugar intervention video with an average view time of 116.35 (52.4%) of 222 seconds. We observed that participants with

low levels of trait reactance proneness watched the video longer, whereas contrary to our expectations, older participants watched the intervention video longer than younger participants.

As stated, our results show that the majority of the 1576 participants chose to engage with the intervention video and watched, on average, more than half of the video. In recent years, an ever-increasing number of offerings, including high-budget entertainment productions, have competed to occupy our leisure time. The degree of voluntary engagement seen in this study, despite a comparatively low-budget, SAS health video, underscores the potential for this health communication modality. The engagement documented in our study also far exceeds patient engagement with print-based health communication materials distributed in health care settings [33]. In 1 such study, Williams et al [33] found that only 15% of participants reported voluntarily reading written materials provided by their doctors.

We examined the role of trait reactance proneness on participants' view time, which has been shown to be an obstacle to successful health promotion campaigns [34]. Because individuals with high levels of reactance have a need to maintain or restore their perceived or actual personal freedoms, we assumed that high levels of reactance would negatively affect the view time. Indeed, we observed that view time was less for participants who scored high in trait reactance proneness regardless of the narrator. Specifically, the findings reveal that participants high in reactance watched, on average, less than 100 seconds of the SAS video, irrespective of the narrator. This result is in line with the literature on trait reactance proneness, which details that the outcomes of reactance are detrimental to health communication campaigns and noncompliance in instructive interventions. Bensley and Wu [35], for instance, found that high-threat messages recommending either abstinence or controlled drinking create a reactance effect, as demonstrated by negative ratings and higher consumption. It follows that individual differences in trait reactance must be clearly considered while designing an SAS intervention. Future videos should aim at being as concise as possible and potentially less than 2 minutes long in order to engage those with high levels of reactance or proneness to reactance.

In the main trial, we investigated the role of the narrator on reactance to the sugar video. Since previous studies have shown that individuals may perceive doctors as coercive or overly directive [36], we first hypothesized that a child narrator would be perceived as a nonthreatening health messenger, thereby arousing less reactance. In the main trial, we found no evidence that the child narrator attenuated reactance to the sugar reduction message when compared with the physician and mother narrators [37]. Consistent with previous results [37], our findings from the posttrial stage show that the implementation of different narrator voices did not influence participants' view time, suggesting that their level of reactance was not altered. These findings suggest that using a child narrator may neither reduce reactance nor increase engagement with SAS videos. Other variables, such as content length, may be more important to optimize for different target audiences.

Since the SAS video was designed for rapid distribution on social media channels, we expected higher participation from younger participants (aged 18-25 years). Surprisingly, we found that older people (ages 25 years and more) watched the video, on average, longer than younger participants. This result might be explained by the perceived vulnerability among older adults, that they are more likely to suffer from health problems that are associated with an excessive consumption of added sugar. Furthermore, longer viewing times in older adults might also be connected to differences in information processing or the perceived seriousness and involvement in the study. Younger participants (ie, emerging adults in this case) are less risk averse and more accustomed to engaging with extremely short forms of content [38,39]. Another reason might be that younger people, who constantly engage with social media, might find animated health videos less entertaining or novel than older people, who spend considerably less time on social media [40]. This is echoed also in the notion that younger people have shorter attention spans, potentially driven by an increased availability of a plethora of online content, rendering them a challenging target audience [41]. This finding is consistent with the results of a recent online study we conducted on participant engagement with a short, animated video about COVID-19 prevention [42], where, too, younger participants viewed the video for a shorter amount of time, on average. This suggests that older participants, rather than younger participants, could benefit the most from SAS health videos delivering a story that unfolds a little more slowly than many contemporary social media posts. To optimally engage different target audiences, future SAS videos could be customized for different age groups.

Strengths

A key strength of this study was the use of an RCT design, which allowed us to reduce any systematic differences and bias through randomization. In addition, the use of an online recruitment platform helped us reach a large sample size, ensuring the quality and reliability of the results. We are not aware of any other study that had such a large sample size and used a similar experimental approach to examining participant engagement in the field of public health. Arguably, this posttrial stage of our RCT enabled us to capture participants' voluntary willingness to watch a SAS video without any financial compensation. Although this condition is similar to the real world, we acknowledge that participants' responses may have been affected by their awareness of being in a scientific study and that their actions were being recorded for scientific purposes. Nevertheless, outside of a scientific study setting, we report anecdotal evidence of willingness to engage in our sugar intervention video. After our RCT, the child-narrated version of the video was posted on the creator's (author MA) YouTube channel, where it reached 3700 views in the first 48 hours after its release.

Limitations

Our study had several limitations. Given the online setting of our study, we were not able to determine whether participants actively watched the intervention video (it may have been playing in the background while the participant was engaged in other activities). Given the posttrial phase of our study, we

were only able to evaluate the role of demographic factors and trait proneness reactance on participant engagement with the sugar intervention video. We acknowledge that other factors could have affected the time that participants spent watching the sugar intervention video, such as the perceived threat of the message, the perceived threat to health, the perceived risk of adopting an alternative behavior, and anger and negative cognition toward the sugar message (see Figure 1). In future research, we could address this limitation by considering how engagement with SAS videos is affected by these factors, which are typically included in health communication models and research [43-46]. Another limitation is that our online sample was relatively well educated, with 1308 of 1576 (83%) participants having at least some college education (BA, MA, PhD or equivalent), which is slightly higher when compared to the UK national average [47]. Indeed, several studies have observed that online samples report higher education than one finds in representative samples. Nevertheless, our study's educational composition is similar to a recent online research on COVID-19 knowledge in the United States and the United Kingdom [48] and 1 study conducted on COVID-19 prevention [42]. In this study, we did explore the effect of education on participants' view time. We first assumed that participants with higher education are more receptive to health education campaigns and more likely to seek health information [49,50]. Our results reveal there was no statistically significant difference in terms of engagement time across the different educational levels. Thus, although the high education status may be a limitation, we do not believe this has significantly affected our results and conclusions.

Conclusion

SAS videos demonstrate potential for engaging diverse audiences and thereby enhancing the distribution of health education messages. Designed to be emotionally arousing and culturally neutral, SAS videos can facilitate public health efforts to promote healthy behaviors and meet audiences where they are across the media landscape. The evidence from this study demonstrates promising engagement with the SAS health messaging modality, across diverse audiences. As these audiences spend increasingly more time online, the need for innovative approaches to engaging them also increases. Even the most accurate and clear health messages have little value if they fail to reach their target viewers. For this reason, researchers and health communicators of the future will need to understand how to optimally engage their audiences and research in this field should be a high priority.

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Authors' Contributions

CF, MA, and AV wrote the paper. CF, AV, and VH undertook the statistical analysis. MA designed, produced, and created all 3 sugar videos (child, mother, physician). AV, VH, and CF contributed to the questionnaire development. AV and TB designed the trial. All authors provided comments and feedback. The data that support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no competing interests. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Multimedia Appendix 1
Supplementary Materials.
[DOCX File , 27 KB - publichealth_v8i1e29669_app1.docx]

Multimedia Appendix 2
CONSORT-EHEALTH checklist (V. 1.6.1).
[PDF File (Adobe PDF File), 2461 KB - publichealth_v8i1e29669_app2.pdf]

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Abbreviations

RCT: randomized controlled trial
SAS: short, animated story-based

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Original Paper

Risk Factors of Dengue Fever in Urban Areas of Rawalpindi District in Pakistan During 2017: A Case Control Study

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Abstract

Background: During August 2017, increased numbers of suspected dengue fever cases were reported in the hospitals of Rawalpindi district. A case control study was conducted to determine the risk factors among urban areas, dengue serotype, and recommend preventive measures.

Objective: The objective of the investigation was to determine the risk factors among urban areas, dengue serotype, and recommend preventive measures.

Methods: A case was defined as having acute febrile illness with one or more of the following symptoms: retro-orbital pain, headache, rash, myalgia, arthralgia, and hemorrhage. The cases were residents of Rawalpindi and were confirmed for dengue fever from August 30, 2017, to October 30, 2017. All NS1 confirmed cases from urban areas of Rawalpindi were recruited from tertiary care hospitals. Age- and sex-matched controls were selected from the same community with a 1:1 ratio. Frequency, univariate, and multivariate analyses were performed at 95% CI with $P<.05$ considered statistically significant.

Results: Totally 373 cases were recruited. The mean age was 36 (SD 2.9) years (range 10-69 years), and 280 cases (75%) were male. The most affected age group was 21-30 years (n=151, attack rate [AR] 40%), followed by 31-40 years (n=66, AR 23%). Further, 2 deaths were reported (case fatality rate of 0.53%). The most frequent signs or symptoms were fever (n=373, 100%), myalgia and headache (n=320, 86%), and retro-orbital pain (n=272, 73%). Serotype identification was carried out in 322 cases, and DEN-2 was the dominant serotype (n=126, 34%). Contact with a confirmed dengue case (odds ratio [OR] 4.27; 95% CI 3.14-5.81; $P<.001$), stored water in open containers at home (OR 2.04; 95% CI 1.53-2.73; $P<.001$), and travel to a dengue outbreak area (OR 2.88; 95% CI 2.12-3.92; $P<.001$) were the main reasons for the outbreak, whereas use of mosquito repellents (OR 0.12; 95% CI 0.09-0.18; $P<.001$) and regular water supply at home (OR 0.03; 95% CI 0.02-0.04; $P<.001$) showed protective effects. The geographical distribution of cases was limited to densely populated areas and all the 5 randomly collected water samples tested positive for dengue larvae.

Conclusions: Stored water in containers inside houses and subsequent mosquito breeding were the most probable causes of this outbreak. Based on the study findings, undertaking activities to improve the use of mosquito repellents and removing sources of breeding (uncovered water stored indoors) are some recommendations for preventing dengue outbreaks.

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KEYWORDS

dengue fever; outbreak; Rawalpindi; risk factors; stored water; urban

Introduction

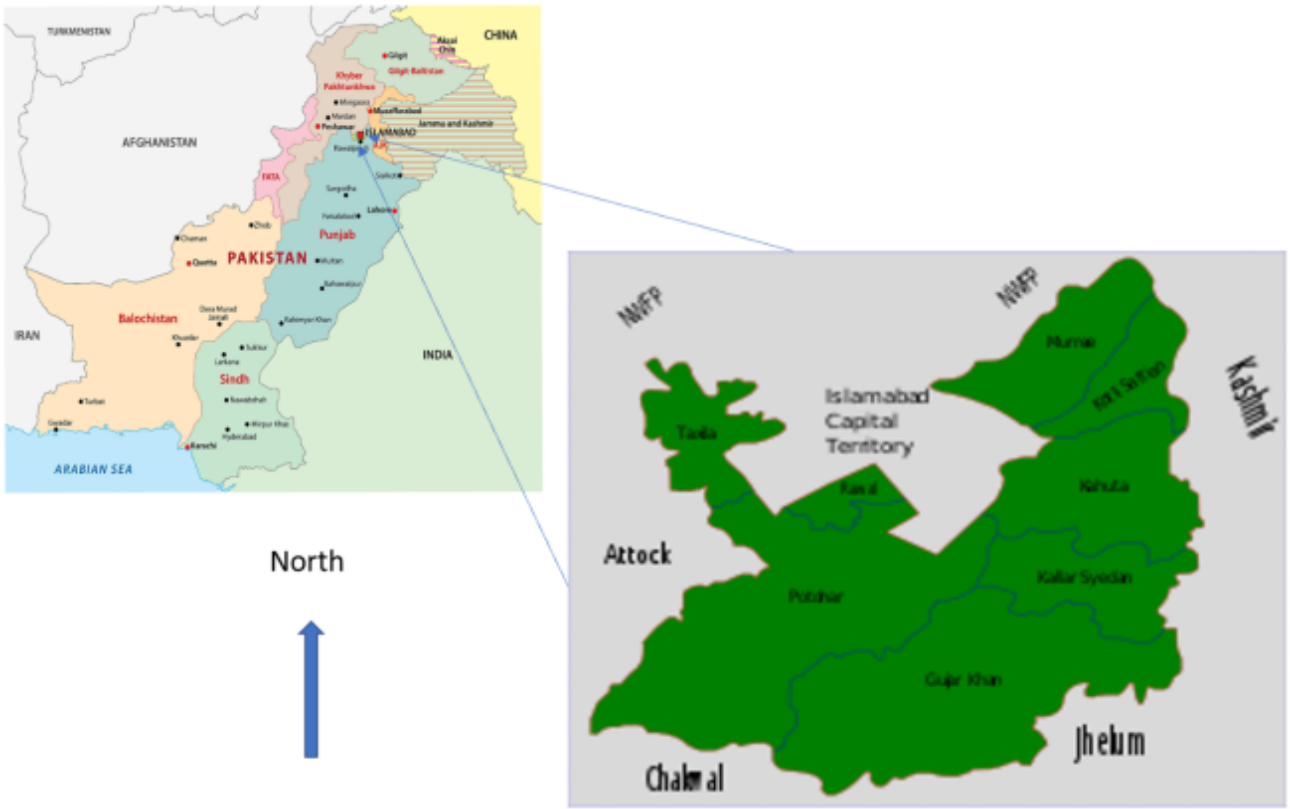
Dengue is a viral infection that is transmitted to the host by the mosquito vector Aedes aegypti. Symptoms vary from flu-like ones to potential lethal complications including hemorrhages. Currently, there are 4 distinct serotypes of the virus that are identified as causing dengue (DEN-1, DEN-2, DEN-3, and DEN-4). Infection from one serotype provides lifelong immunity against that serotype [1]. Clinical manifestations of dengue virus infection range from asymptomatic infection to dengue fever (DF), dengue hemorrhagic fever, or dengue shock syndrome, and these may affect other organs such as the liver, kidneys, brain, or heart [2,3].

Approximately 390 million dengue infections occur annually. However, only 96 million infections manifest clinically [4]. An estimated 3.9 billion people are at risk of contracting this disease worldwide [5]. Since 1994, Pakistan is facing dengue outbreaks [6,7]. The first confirmed case of DF in Pakistan was reported in Karachi city in 1994 [8]. There has been a dramatic rise in dengue cases, and numbers have increased from 4500 cases in Karachi in 2005 to 21,204 cases in 2010 nationally. During 2011, there were 14,000 confirmed cases and 300 deaths in Lahore district only due to DF. However, even these data do not portray the true situation in the country, as the actual burden is expected to be much higher than reported [9]. Later, in 2018, DF was added to the list of priority diseases in Pakistan [10]. In 2019, 19,000 cases were reported at the National Institute of Health [11] and the toll rose to 52,000 until a Public Health Emergency Operations Center coordinated with all departments to control the outbreak 2 weeks earlier compared to the previous year's outbreaks [12]. In 2020, the case burden in Pakistan tripled, including COVID-19, measles, and DF [13]. As no specific medicine or vaccine has been developed for DF, the only method to control this disease is through prevention (vector control) using long-lasting insecticide-treated materials effective for more than 5 years. Similarly, homes, offices, and schools can be protected from Aedes aegypti using bed and window nets, which is the cheapest method of controlling the disease [14,15]. Hospital admissions for dengue infection start increasing from August (monsoon season in Pakistan), and the same pattern is prevailing in other neighboring countries such as India and Bangladesh [16].

During August 2017, an outbreak was announced by the health authorities of Rawalpindi district. To design and employ effective preventive and control strategies against the disease, it was necessary to identify the risk factors of the disease prevailing in the district and share these results with the public health authorities for targeted control strategies.

This investigation was conducted to determine the risk factors associated with DF among patients from urban areas of Rawalpindi to estimate the prevalent serotype in this outbreak and recommend measures for prevention. Rawalpindi is a metropolitan city neighboring the capital Islamabad, and as the disease is considered an urban disease, we decided to examine these factors among dengue cases coming from the urban areas of this district. Figure 1 shows the geographical location of Rawalpindi district.

Figure 1. Geography of district Rawalpindi, Pakistan.



Methods

Records of the tertiary care hospitals of the district were obtained, and the history of recent influxes of migrants like internally displaced population was also ruled out.

A case control study was designed to determine the risk factors associated with this disease. All patients visiting the tertiary care hospitals of Rawalpindi with acute febrile illness and any 3 symptoms among retro-orbital pain, headache, rash, myalgia, arthralgia, and hemorrhagic manifestations between August 30 and October 30, 2017, were admitted according to the guidelines provided by the provincial health department [17]. Blood samples were collected from the patients enrolled according to the criteria set by the Public Health Laboratory Division of the National Institute of Health and were tested for dengue IgM, IgG, and NS1.

All laboratory-confirmed cases were recruited from the inpatient departments of the hospitals. A functional case was defined as the onset of acute febrile illness with one or more of the following symptoms: retro-orbital pain, headache, rash, myalgia, arthralgia, and hemorrhagic manifestations from August 30 to October 30, 2017, which was in accordance with the case definition established by the Department of Health. The residential addresses of the patients were collected, and age- and sex-matched controls were enrolled from the same community with a 1:1 ratio. The controls were defined as residents from the neighborhood of the cases who had not experienced acute febrile illness from August 30 to October 30, 2017, and had not been diagnosed as having DF by any physician or laboratory during this time.

An institutional review board exception was obtained from the National Institute of Health in Islamabad. After obtaining informed written consent translated to Urdu and reading out the same to the respondents where necessary, a close-ended, structured, and pretested questionnaire was used to collect data from cases and controls regarding general characteristics and possible risk factors (Multimedia Appendix 1). Information was collected on indoor or outdoor insecticidal sprays within the last 10 days in their area. Water samples were collected from 5 randomly selected places with stagnant water and from water stored indoors for detection of larvae. Water samples were sent to the Institute of Public Health in Lahore for dengue larvae detection. Samples were also collected for serotyping and sent to the provincial laboratory of the Institute of Public Health with permission from the district health authorities.

Frequency, univariate, and multivariate analyses were performed using statistical software Epi Info 7 (Centers for Disease Control and Prevention). An epidemic curve was constructed to demonstrate the distribution of cases over time. The cases were plotted on a spot map to understand the geographical distribution of the cases in the area. Age- and gender-wise infection rates were calculated. The odds ratios (ORs) were calculated for different exposures at 95% CI and $P<.05$ was considered statistically significant.

Results

The outbreak started on August 29, 2017, and it started declining on October 30, 2017, peaking during the last week of September and first week of October, as shown in Figure 2. Totally 373 cases were enrolled from tertiary care hospitals, as confirmed by their respective laboratories through NS1 tests.

The mean age of the confirmed cases was 36 (SD 2.9) years (range 10-69 years) with a male-to-female ratio of 3:1. Most of the cases were in the age group of 21 to 30 years (n=151, attack rate [AR] 40%), followed by the age group of 31 to 40 years (n=66, AR 23%). Further, 2 deaths were reported (case fatality rate=0.53%). The most frequent symptom was fever (n=373, 100%), followed by myalgia (n=320, 86%), headache (n=320, 86%), and retro-orbital pain (n=272, 73%). Serotype identification was carried out for 322 cases. DENv-2 (n=126, 39%) was the most prevalent serotype followed by DENv-3 (n=96, 30%), DENv-4 (n=58, 18%), and DENv-1 (n=42, 13%). Table 1 presents the statistics.

Most patients had leukopenia (mean 4.5 [SD 5.06]) whereas hemoglobin levels were within normal limits (13.76 [SD 2.5]).

Out of the 373 confirmed cases, 237 were contacts of a confirmed case (OR 4.27; 95% CI 3.14-5.81; $P<.001$) and 219 stored water in open containers (OR 2.04; 95% CI 1.53-2.73; $P<.001$). Further, 189 people traveled to an area with dengue outbreak (OR 2.88; 95% CI 2.12-3.92; $P<.001$). Regular water supply at home (OR 0.03; 95% CI 0.02-0.04; $P<.001$) and regular use of mosquito repellents (OR 0.12; 95% CI 0.09-0.18; $P<.001$) proved effective in preventing dengue. In contrast, previous visits to hospitals (OR 0.83; 95% CI 0.57-1.21; $P=.34$) showed no significant association with dengue infection, as observed in Table 2.

The geographical distribution of dengue cases showed the typical characteristics of dengue mosquitos, limiting their activity within pockets of densely populated areas and avoiding crossing of highways in urban dwellings. Water samples taken from 5 randomly selected stagnant water places and from water stored indoors for detecting larvae tested positive for larvae.

Figure 2. Epidemic curve showing the time distribution of dengue cases in Rawalpindi during 2017 (N=373).

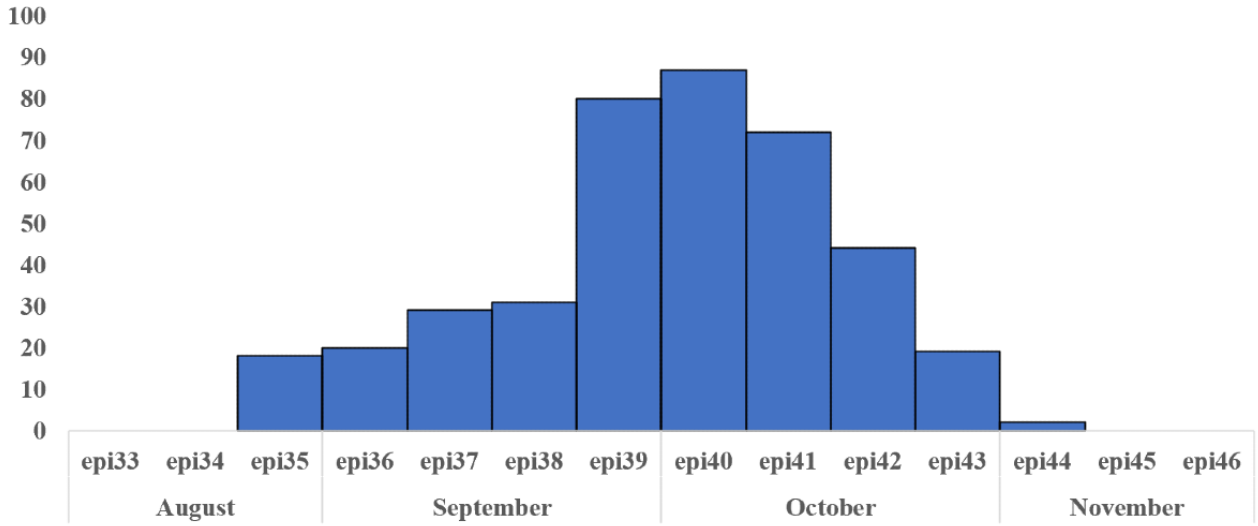


Table 1. Statistics of dengue cases in Rawalpindi during 2017 (N=373).

Characteristics	n (%)
Sex	
Male	278 (75)
Female	95 (25)
Age group (years)	
10-20	96 (26)
21-30	151 (40)
31-40	66 (18)
41-50	39 (10)
≥50	21 (7)
Signs or symptoms	
Fever	373 (100)
Myalgia	320 (86)
Headache	320 (86)
Retro-orbital pain	272 (73)
Serotype (n=322)	
DENv[a]-1	42 (13)
DENv-2	126 (39)
DENv-3	96 (30)
DENv-4	58 (18)

[a]DENv: dengue virus

Table 2. Factors associated with dengue infection among residents of Rawalpindi during 2017 (N=373).

Risk factors	Cases	Controls	OR[a]	95% CI	*P* value
Contact with a confirmed case	237	108	2.35	3.14-5.81	<.001
Stored water in open containers at home	219	153	2.04	1.53-2.73	<.001
Travel to areas with dengue outbreak	189	98	2.88	2.12-3.91	<.001
Regular water supply at home	64	322	0.03	0.02-0.04	<.001
Regular use of mosquito repellant	48	199	0.12	0.09-0.18	<.001
Previous visit to a hospital	300	310	0.83	0.57-1.21	.34

[a]OR: odds ratio.

Discussion

Principal Findings

This study showed that males were more affected than females, and the young age group of 21 to 30 years was the most severely affected (AR=40%). Stored water in containers inside houses and subsequent mosquito breeding were the most probable causes of the outbreak and the use of mosquito repellents had a protective effect. Dengue affects all age groups including infants and adults [17]; however, children usually tolerate this infection better than adults [18]. Our results support this finding, as there were only 3 children under 10 years of age admitted during this outbreak and none in infancy.

Simmons et al found that in mild dengue cases, laboratory analysis shows no significant changes except for abnormal leukocyte counts and moderate elevation of the hepatic amino-transferase enzyme activity [19]. This phenomenon was observed in our study too, where there was no significant difference between the laboratory parameters of the cases and controls.

In our study, the case fatality rate was 0.53%, showing that timely medical care and symptomatic management saved lives. Gubler states that the case fatality can be reduced to less than 1% with correct and timely treatment [20]. Akhter emphasizes that even patients with complications can be cured if given supportive and adequate treatment [21]. This explains the low case fatality during this outbreak, as the government had referral hospitals (Holy Family Hospital, Rawalpindi) and had devised the diagnosis and management criteria for all suspected, confirmed, and complicated DF cases at primary and secondary care hospitals.

According to the classification schemes of the World Health Organization, leukopenia in patients with febrile illness is one of the key findings when suspecting dengue infection [22]. In the present study, most of the patients presented low leukocyte levels and relatively better hemoglobin levels. The average leukocyte count was 4.5 among the admitted dengue patients. Other studies have documented that case fatality rates of dengue increase when infection occurs in patients with other acute or chronic diseases like asthma, diabetes, and hypertension [23,24].

Vector control is crucial in preventing DF. Along with the availability of impregnated bed nets, other measures like window curtains and water container covers treated with long-lasting insecticide have been tested in dengue endemic countries [25]. Only 48 individuals out of 373 were using mosquito repellents or any kind of protection against mosquitos; however, in the control group, 199 used mosquito repellents and this proved protective.

There are 4 distinct dengue virus serotypes that cause dengue (DEN-1, DEN-2, DEN-3, and DEN-4) [1]. During this outbreak, 322 blood samples were tested. DEN-2 (n=126, 39%) was the most prevalent serotype, followed by DEN-3 (n=96, 30%), DEN-4 (n=58, 18%), and DEN-1 (n=42, 13%). In previous outbreaks of dengue reported from different cities of Pakistan, DEN-2 remained the prominent serotype. In the dengue outbreaks in 2008 and 2009, DEN-2, 3, and 4, and DEN-2 and 3 were prominent, respectively [26]. Similarly, according to dengue case data from Sheikhupura and Gujranwala districts, DEN-2 was the most prevalent, followed by the DEN-1 serotype 1 [27].

Most of the cases were males with a male-to-female ratio of 3:1. This finding confirms those of previous studies [28,29]. Male predominance may be due to multiple reasons. Males are usually responsible for taking children early in the morning to school, and they go out for work. They are also responsible for bringing food and other items in the evening. As it was summer, males usually wore thin clothes with half sleeves, thus becoming more vulnerable to mosquito bites. In comparison, females stay at home and according to the local culture, they are well covered. Fatima reported the same findings where 73% of the cases comprised males and the mean age of the subjects was 34 years with a range of 5 to 80 years [30]. Similar results were obtained in our investigation where the mean age was 36 years (range 10-69 years).

The presence of stored water in homes, usually in open containers, for domestic use was observed because of intermittent water supply. Storing water was found to be a risk factor for spreading DF. Out of the 373 dengue cases, 307 had intermittent water supply and 219 were storing water at home for domestic and drinking purposes (OR 2.04, *P*<.001), and 196 had stagnant water pools, ponds, or passages near their homes. Fatima reported that the source of water supply is a risk factor for DF [30]. This finding supports the findings of another study from Vietnam [31]. This study also states that the absence of taps was strongly associated with DF. Apart from stored water in homes, open wells were the major source of water supply for the study population and both factors promoted vector breeding. Phoung et al highlight the same issue, identifying that mosquito

larvae in water containers and gardens near houses are the most important risk factors for dengue transmission [32].

Recently, Wang et al have described that there are several risk factors that correlate with dengue hemorrhagic fever, including viral, epidemiological, human, and abiotic factors [33]. Another study conducted among young children has revealed the same risk factors as those identified in our study. Among the people in the study population, those storing water in their homes and consistently covered the storage containers did not develop dengue as opposed to those who did not. Similarly, the positivity of the dengue virus was significant (P<.001) among children who did not regularly wear long-sleeved shirts and full pants [34].

Consequently, different prevention and control activities were performed during the outbreak, including awareness campaigns about DF, filling of stagnant water reservoirs, and discouraging water storage at home. Insecticide-treated bed nets were distributed, and their use was demonstrated.

Recommendations

1. Enhance community health sessions to increase awareness about DF and its preventive measures among the general public.
2. District administrations must prioritize filling of stagnant water reservoirs and discourage water storage in open containers.
3. Promote the use of mosquito repellents.
4. Provide and distribute impregnated bed nets and demonstrate their use.
5. Sensitize the local community elders, schoolteachers, and influential persons about the seriousness of the issue and obtain their support.

Limitations

Owing to time constraints and limited monetary resources, all environmental and serotyping tests were not carried out.

Conclusions

Dengue is a re-emerging disease. There are multiple factors that can contribute to the development of this disease. Owing to the overall change in the global environment and deteriorating conditions like poverty, access to basic necessities of life, health care, and conflicts in most of the developing countries, dengue is now an endemic disease. More focused studies will be required to pinpoint the risk factors along with efforts to use a multisectoral approach to control and prevent this disease.

An effective surveillance system, such as Integrated Disease Surveillance and Response, will help reduce dengue cases through timely detection of outbreaks and response strategies based on the collected information. A surveillance system with supported multisector coordination will facilitate prevention of the disease. Further, focused studies will be valuable for devising control plans.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire provided to the participants of the study.
[DOCX File , 14 KB - publichealth_v8i1e27270_app1.docx]

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Abbreviations

AR: attack rate
DF: dengue fever

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Original Paper

Added Value of Electronic Immunization Registries in Low- and Middle-Income Countries: Observational Case Study in Tanzania

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Abstract

Background: There is growing interest and investment in electronic immunization registries (EIRs) in low- and middle-income countries. EIRs provide ready access to patient- and aggregate-level service delivery data that can be used to improve patient care, identify spatiotemporal trends in vaccination coverage and dropout, inform resource allocation and program operations, and target quality improvement measures. The Government of Tanzania introduced the Tanzania Immunization Registry (TImR) in 2017, and the system has since been rolled out in 3736 facilities in 15 regions.

Objective: The aims of this study are to conceptualize the additional ways in which EIRs can add value to immunization programs (beyond measuring vaccine coverage) and assess the potential value-add using EIR data from Tanzania as a case study.

Methods: This study comprised 2 sequential phases. First, a comprehensive list of ways EIRs can potentially add value to immunization programs was developed through stakeholder interviews. Second, the added value was evaluated using descriptive and regression analyses of TImR data for a prioritized subset of program needs.

Results: The analysis areas prioritized through stakeholder interviews were population movement, missed opportunities for vaccination (MOVs), continuum of care, and continuous quality improvement. The included TImR data comprised 958,870 visits for 559,542 patients from 2359 health facilities. Our analyses revealed that few patients sought care outside their assigned facility (44,733/810,568, 5.52% of applicable visits); however, this varied by region; facility urbanicity, type, ownership, patient volume, and duration of TImR system use; density of facilities in the immediate area; and patient age. Analyses further showed that MOVs were highest among children aged <12 months (215,576/831,018, 25.94% of visits included an MOV and were applicable visits); however, there were few significant differences based on other individual or facility characteristics. Nearly half (133,337/294,464, 45.28%) of the children aged 12 to 35 months were fully vaccinated or had received all doses except measles-containing vaccine–1 of the 14-dose under-12-month schedule (ie, through measles-containing vaccine–1), and facility and patient characteristics associated with dropout varied by vaccine. The continuous quality improvement analysis showed that most quality issues (eg, MOVs) were concentrated in <10% of facilities, indicating the potential for EIRs to target quality improvement efforts.

Conclusions: EIRs have the potential to add value to immunization stakeholders at all levels of the health system. Individual-level electronic data can enable new analyses to understand service delivery or care-seeking patterns, potential risk factors for underimmunization, and where challenges occur. However, to achieve this potential, country programs need to leverage and strengthen the capacity to collect, analyze, interpret, and act on the data. As EIRs are introduced and scaled in low- and middle-income countries, implementers and researchers should continue to share real-world examples and build an evidence base for how EIRs can add value to immunization programs, particularly for innovative uses.

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KEYWORDS

immunization; immunization information system; electronic immunization registry; digital health; eHealth

Introduction

Background

With the increasing digitalization of health systems worldwide, there is growing interest and investment in electronic immunization registries (EIRs). EIRs are "confidential, computerized, population-based systems that collect and consolidate vaccination data from vaccination providers for better immunization strategies" [1]. EIRs are designed to provide a consolidated patient record to health care workers at the point of care to enable the delivery of the appropriate vaccines at the appropriate time. At the population level, EIRs can provide aggregate data on vaccination coverage to inform resource allocation and program operations. In this way, EIRs aim to improve the immunization delivery system to reach every child by supporting more effective, efficient, and data-driven care [2,3].

Vaccine coverage has historically been the primary metric for evaluating immunization programs. As an increasing number of low- and middle-income countries (LMICs) have begun implementing EIRs, vaccine coverage has been measured as a key outcome for assessing EIR effectiveness. Pre–post studies in Vietnam, Bangladesh, and Pakistan have demonstrated significant increases in child vaccination coverage after the introduction of EIRs that included SMS text message reminders and, in addition, in Pakistan, decision support systems [4-6].

In addition to improving vaccine coverage, other benefits of EIRs have been identified for individuals, immunization program performance and management, research, and population health [7,8]. For example, EIRs store patient vaccine history at the individual level, can help identify defaulters and reduce dropout rates at the program level, and provide data to support resource allocation and strategic planning at the population level [8]. Across levels, EIRs that capture individual-level data provide an opportunity to redefine traditional vaccine indicators and conduct more timely, granular analyses to support decision-making [9]. EIRs enable immunization programs to explore outcomes of interest beyond vaccine coverage, including longitudinal outcomes at the population and individual levels. As EIRs are costly to introduce and maintain, it is important for decision-makers to consider all possible benefits to justify the investment [10,11].

In some settings where EIRs are being considered or introduced, immunization coverage may already be high and, therefore, not an appropriate metric for EIR added value. The Early-Stage Digital Health Investment Tool was developed to assist ministries of health in determining their readiness to introduce a digital health tool, such as an EIR, by assessing the core building blocks of digital health [12]. In practice, country health systems with sufficient readiness are likely those that have already achieved relatively high vaccination coverage. In these contexts, improved vaccination coverage may not be the primary goal of introducing EIRs.

Objective

The aims of this study are to (1) conceptualize additional ways that EIRs can add value to immunization programs and (2) assess the feasibility and potential value-add using Tanzania as a case study.

Methods

Overview

This study comprised 2 sequential phases. First, a comprehensive list of ways EIRs can potentially add value for immunization programs was developed through stakeholder interviews. Second, the added value was evaluated using Tanzania Immunization Registry (TImR) data for a prioritized subset of program needs.

Phase 1

Conceptual Framework

A comprehensive list of common barriers that country immunization programs face in achieving coverage and equity goals was used to identify the ways in which EIRs can add value. The list was adapted from a July 2019 Gavi workshop on *Improving Data use in Immunization* in which approximately 40 participants from the Gavi Secretariat, core and extended partners, and country representatives identified and categorized barriers. For each common barrier, the study team (EC, TKR, and LW) identified ways that EIRs could help address the barrier based on their expertise and implementation experience.

Data Collection and Analysis

Stakeholder interviews were conducted to refine the framework of the immunization program barriers and potential EIR solutions. Stakeholders were purposively selected based on their expertise in research, policy, or implementation of EIRs. A total of 7 stakeholders participated in semistructured web-based interviews facilitated by the study team (EC) from November 2019 to January 2020. A total of 4 stakeholders were government officials from countries in Sub-Saharan Africa, identified through the BID (Better Immunization Data) Learning Network [13]. A total of 3 stakeholders were from international public health agencies, donors, or implementing organizations. Summary notes from the interviews were used to refine the conceptual framework. A follow-up web-based survey (using SurveyMonkey, Momentive, Inc) was sent to a wider group of EIR experts (including interviewees) in January 2020, asking respondents to prioritize topics from the conceptual framework for further analyses. Survey responses from 17 individuals were used, in conjunction with the interview data, to prioritize the 4 topics for phase 2 analyses.

Phase 2

Setting

Data from Tanzania's EIR were analyzed to illustrate how an EIR can add value to each of the prioritized topic areas. The Government of Tanzania partnered with the BID Initiative, funded by the Bill & Melinda Gates Foundation and launched in 2013, to design and implement a package of solutions to improve immunization data quality and use [14]. An EIR was an essential component of the solution package. EIR design began in 2014 and went through iterations culminating in TImR, which is built on the OpenIZ platform (now known as SanteDB, SanteSuite) [15]. The Government of Tanzania has led a staged rollout of TImR to facilities across districts and regions. As of December 31, 2020, TImR was rolled out to 3736 facilities across 15 of 25 regions in mainland Tanzania and included 1.6 million client records.

Data Sources

Immunization, facility, and patient data were extracted from the TImR system with permission from the Government of Tanzania. Data were deidentified after extraction, and all analyses were conducted using deidentified data. The development and implementation of the TImR system have been discussed in detail elsewhere [15-17]. Population density data were extracted at the ward level from WorldPop's United Nations–adjusted GeoTIFFs at 100×100 km spatial resolution using Database of Global Administrative Areas (GADM) administrative shapefiles and matched to facilities based on facility geocodes [18,19]. Subject matter experts were consulted on the construction of analysis variables (eg, missed opportunities for vaccination [MOVs]). Data were processed and analyzed using Alteryx (version 2020.3; Alteryx, Inc), R (version 4.0.0; R Foundation for Statistical Computing), Tableau (version 2020.2; Tableau Software, Inc), and STATA (version 14.2; StataCorp LLC).

Ethics Approval

This study received nonresearch determination from the PATH. The Government of Tanzania and the PATH have data-sharing permissions in place that guided the use of TImR data for this study.

Data Restrictions

The analyses focused on services provided between 2017 and 2019 and the vaccine doses that were included in the official Tanzania vaccine schedule, specifically Bacillus Calmette–Guérin (BCG); oral polio vaccine (OPV); diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b (Penta); pneumococcal conjugate vaccine (PCV); rotavirus (Rota); and measles-containing vaccine (Table 1). Data were further restricted to doses received while the TImR system was live (ie, doses logged in the system at the time of service or shortly afterward). Doses retroactively entered to complete patient medical records were included in the continuum of care analysis only. This analysis included back-entered doses for patients with at least one live TImR entry to capture the full picture of their vaccine history. A total of 3 regions (Mtwara, Rukwa, and Ruvuma) with <50 visits recorded in TImR by December 31, 2019, were excluded. In addition, patient IDs with >3 instances of a given vaccine dose (eg, OPV-1) were assumed to be dummy patient IDs used to log vaccinations provided during mass immunization campaigns and were excluded from the analysis. Patient IDs with up to 3 instances of a given dose were assumed to result from data entry errors.

Table 1. Tanzania vaccine schedule.[a]

Vaccine dose	Scheduled visit number	Age eligibility
BCG[b]-0 and OPV[c]-0	1	Birth or first contact
OPV-1, Penta[d]-1, PCV[e]-1, and Rota[f]-1	2	6 weeks
OPV-2, Penta-2, PCV-2, and Rota-2	3	10 weeks
OPV-3, Penta-3, and PCV-3	4	14 weeks
MCV[g]-1	5	9 months
MCV-2	6	18 months

[a]Inactivated polio vaccine immunization was excluded from our analyses as it was introduced partway through the analysis period. It would normally be received during visit 4 at the age of 14 weeks.

[b]BCG: Bacillus Calmette–Guérin.

[c]OPV: oral polio vaccine.

[d]Penta: diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b.

[e]PCV: pneumococcal conjugate vaccine.

[f]Rota: rotavirus.

[g]MCV: measles-containing vaccine.

Definitions

Outcomes

Missed Opportunities for Vaccination

MOVs were assessed at the visit level using the World Health Organization (WHO) definition: "any contact with health services by an individual (child or person of any age) who is eligible for vaccination (e.g., unvaccinated or partially vaccinated and free of contraindications to vaccination), which does not result in the person receiving one or more of the vaccine doses for which he or she is eligible" [20]. Dose eligibility was based on patient age, prior doses received, and time since the last dose of the vaccine sequence (if applicable). The MOV variable was constructed both as a binary (any MOV in a visit or not) and count (number of vaccine-specific MOVs per visit). Binary coding was used for the regression models, which motivated the use of logistic regression.

Vaccine Dropout

Vaccine-specific dropout for multidose vaccines was defined as receiving the first but not the last dose in the vaccine schedule (eg, receiving PCV-1 but not PCV-3). OPV dropout was defined as receiving OPV-0 or OPV-1 and not OPV-3; children who did not receive OPV-0 by the age of 2 were eligible for OPV-1 without receiving OPV-0; therefore, either vaccine can be treated as the starting dose. We also assessed dropout between birth doses and first follow-up visit, defined as receiving either of the birth doses (BCG or OPV-0) but none of the first follow-up visit doses (OPV-1, Penta-1, PCV-1, and Rota-1). Finally, we assessed overall dropout, which is defined as receiving at least one scheduled vaccine dose but not completing the full 14-dose schedule. The dropout variables were constructed as binaries (meeting criteria for dropout or not), motivating the use of logistic regression in the models.

Assigned Facility and Nonassigned Visits

Children are assigned a home facility when they are registered in the TImR system based on their preferences and where they plan to receive care. A nonassigned visit is a visit to any health facility other than the assigned visit. This variable was constructed as a binary variable (visit at home facility or not), motivating the use of logistic regression in the models.

Predictors

Dose Timeliness

A dose was considered timely if it was received within 7 days of the scheduled date (Table 1). In practice, in Tanzania, a child is generally considered a defaulter after 7 days past their scheduled date.

Urbanicity

A facility was designated as urban if the ward in which it is located had a population density of at least 500 persons per square km and rural if otherwise [21]. A patient was assumed to live in an urban area if their assigned facility, presumably near their residence, was designated as urban or rural, if otherwise.

Stockout

Facility stock use, including days of 0 stock, is recorded in TImR by facility and vaccine type. Vaccine-specific stockout was defined as any period in which the stock balance for a given vaccine was zero. A composite indicator was also constructed for the proportion of days with a stockout, with the number of days with a stockout for a primary vaccine (BCG, OPV, PCV, Penta, Rota, or measles-containing vaccine [MCV]) as the numerator and the number of days with facility stock data in the TImR system for each primary vaccine as the denominator.

Age

Age was defined in two ways: static age at the time of data extraction (December 31, 2019) and age at the time of a given visit. The 2 age variables were coded into 1-year categories up to the age of 5 years (ie, <12 months, 12-23 months, 24-35 months, 36-47 months, and 48-59 months), which is the upper limit of standard eligibility for most of the vaccines of interest.

Regression Models

For all analyses, we used mixed-effects logistic regression to assess the factors associated with the various outcomes. In all models, relevant patient and facility characteristics were included as fixed effects, and nested random intercepts for region, district, and facility ID were used to account for clustering.

Results

Phase 1: EIR Added Value

Textbox 1 lists ways that EIRs can help address common barriers faced by immunization programs in achieving coverage and equity. EIRs can add value through existing functionalities (eg, the ability to identify underimmunized children) and through functionalities that may not be a core component of existing systems (eg, the ability to serve as a platform for remote, virtual supportive supervision).

On the basis of stakeholder input, 4 topics were prioritized for phase 2 analyses:

1. Denominators and population movements, including patient movement between facilities or geographic areas for care
2. MOVs, including their frequency and any associated characteristics
3. Continuum of care, including which children drop out and when in the vaccination schedule
4. Continuous quality improvement (CQI), including trends or outliers in data quality or service delivery, to inform targeted quality improvement efforts

The remainder of this section provides an overview of the TImR data and then provides results on each of the 4 priority topic areas to illustrate how EIR data can be used to better understand denominators and population movement, MOVs, continuum of care, and CQI.

Textbox 1. Immunization barriers and potential electronic immunization registry–based solutions.

Lack of understanding about what drives immunization demand

- EIR data can identify un- or underimmunized children and explore drivers of their vaccination status (eg, geography, demographic characteristics, and facility type).
- EIR data can be used to analyze at what point children drop out of the continuum of care.
- EIRs can have embedded decision support to guide health workers in delivering tailored messages or services to increase acceptance and uptake.

Overly complex processes

- EIRs can be designed to streamline data capture and reduce the burden of data entry.
- EIRs can be designed to meet decision-making needs for end users.

Skill level and availability of human resources

- Access to data through EIRs can empower and motivate users and strengthen agency.
- If EIRs are designed with individual health worker log-ins, EIRs can track human resources based on active health worker profiles.
- EIR data can identify error rates of individual health workers and link them to additional training or supportive supervision.
- EIRs can have embedded training resources or capacity assessments.
- EIR data can be used to forecast service delivery needs by facility or district to optimize the distribution of human resources and session times.

Geographic and social barriers to access

- EIR data can identify un- or underimmunized children to explore whether they are concentrated in certain geographic areas and if they have shared demographic characteristics to inform targeted outreach.
- EIRs can track an individual's vaccinations across public and private sector facilities.

Microplanning challenges

- EIRs can capture more accurate, timely, and complete denominators to inform microplanning.
- EIR data can be used to understand population movement or health-seeking behaviors to inform microplanning (eg, how common it is for children to move between multiple facilities).

Inadequate introduction of new vaccines

- EIR data on current vaccine delivery can be used to forecast the necessary stock and human resources to introduce new vaccines.

Inadequate governance structures and capacities

- The process of designing and introducing an EIR can help clarify and document governance structures related to immunization data.
- EIR data can provide more accurate denominator estimates to inform costing and budgeting for the EPI.

A lack of resilience in leadership

- EIRs can encourage continuous quality improvement by highlighting trends, outliers, or patterns that may require adaptive management.
- EIRs provide more timely, detailed data compared with traditional paper-based reporting, which enables timely, responsive action from leaders.
- EIRs can provide a platform for remote, web-based supportive supervision.

Gaps in information systems

- EIRs can show which facilities are entering data or not and factors associated with reporting.
- EIRs can be designed to mimic health worker workflows to streamline data collection and reporting practices.

Poor quality of stock data from health facilities

- EIR service delivery data can be triangulated to see how consistent it is with vaccine stock data and to forecast stock needs.
- EIR service delivery data can be used to inform decisions about vial size (eg, whether smaller vial sizes are needed in some areas to reduce waste).

Poor quality of service delivery

- EIRs can identify service delivery patterns to optimize health worker allocation and session timing to match demand.
- EIRs that capture check-in time and vaccination time can calculate patient wait times.

- EIRs can identify missed opportunities for vaccination.
- EIRs can include stock reorder alerts to reduce stockout frequency.

Vaccine safety and effectiveness

- EIR data triangulated with patient-level data on adverse events following immunization or surveillance data can answer questions about the effectiveness of vaccines given at different times.

Phase 2: Tanzania Case Study

The sample size for the individual analyses varied because of differing inclusion criteria and missing data. In full, our sample comprised 2,444,803 vaccine doses over 958,870 visits for 559,542 patients. These visits occurred in 2359 health facilities covering 57 districts in 10 regions. The median (IQR) number of provided doses per facility per month was 40 (9-123), and the median number of visits was 17 (4-49). Table 2 provides participant demographics and facility characteristics.

Table 2. Patient and facility characteristics.[a]

Level and covariate	Number of visits, n (%)	Number of patients, n (%)	Number of facilities, n (%)
Patient			
Sex			
Female	472,782 (49.35)	275,605 (49.31)	N/A[b]
Male	485,195 (50.65)	283,361 (50.69)	N/A
Age (as of December 31, 2019)			
<12 months	235,387 (24.55)	153,857 (21.61)	N/A
12-23 months	300,948 (31.39)	183,618 (25.8)	N/A
24-35 months	300,646 (31.35)	143,976 (20.23)	N/A
36-47 months	106,673 (11.12)	64,360 (9.04)	N/A
48-59 months	13,389 (1.4)	12,153 (1.71)	N/A
≥5 years	1,828 (0.19)	153,857 (21.61)	N/A
Age (at time of visit; months)			
<12	833,349 (86.91)	N/A	N/A
12-23	111,259 (11.6)	N/A	N/A
24-35	10,138 (1.06)	N/A	N/A
36-47	2811 (0.29)	N/A	N/A
48-59	1283 (0.13)	N/A	N/A
Urbanicity (of patient)			
Rural	624,726 (66.2)	365,459 (66.38)	N/A
Urban	318,972 (33.8)	185,106 (33.62)	N/A
Facility			
Facility type			
Dispensary	343,525 (60.39)	1,953 (82.79)	343,525 (60.39)
Health center	152,496 (26.81)	311 (13.18)	152,496 (26.81)
Hospital	72,786 (12.8)	95 (4.03)	72,786 (12.8)
Urbanicity (of facility)			
Rural	621,375 (65.78)	364,817 (65.67)	1873 (81.01)
Urban	323,284 (34.22)	190,689 (34.33)	439 (18.99)
TImR[c] use duration (as of December 31, 2019)			
0-5 months	5038 (0.53)	N/A	104 (4.45)
6-11 months	282,993 (29.63)	N/A	1041 (44.56)
1 year	183,826 (19.25)	N/A	625 (26.76)
≥2 years	483,201 (50.59)	N/A	566 (24.23)
Region			
Arusha	270,099 (28.25)	112,963 (20.22)	271 (11.56)
Dar es Salaam	3062 (0.32)	2726 (0.49)	48 (2.05)
Dodoma	96,059 (10.05)	61,033 (10.93)	321 (13.69)
Geita	25,807 (2.7)	21,152 (3.79)	123 (5.25)
Kilimanjaro	93,231 (9.75)	52,367 (9.37)	294 (12.54)
Lindi	12,532 (1.31)	10,101 (1.81)	162 (6.91)
Morogoro	86,815 (9.08)	61,697 (11.04)	298 (12.71)

Level and covariate	Number of visits, n (%)	Number of patients, n (%)	Number of facilities, n (%)
Mwanza	152,914 (15.99)	113,953 (20.4)	318 (13.56)
Njombe	11,469 (1.2)	9645 (1.73)	184 (7.85)
Tanga	204,246 (21.36)	113,002 (20.23)	326 (13.9)

[a]Some categories will add up to more or less than the total number of visits, patients, or facilities because of missing data or patients having repeat visits or visits at multiple facilities.

[b]N/A: not applicable.

[c]TImR: Tanzania Immunization Registry.

Denominators and Population Movement

Overview

This analysis explored population movement, that is, care seeking at alternative (nonassigned) facilities, which affects the accuracy of facility denominators. Of 810,568 total visits, 765,835 (94.48%) were at a child's assigned facility, 15,575 (1.92%) were at a nonassigned facility within 5 km of the child's assigned facility, 14,147 (1.82%) at facilities located >5 km from the assigned facility but within the same district, 12,267 (1.51%) in a different district within the same region, and 2926 (0.36%) in a different region. Figure 1 summarizes attendance by region for all visits and visits to nonassigned facilities. Although children were similarly likely to seek care at their assigned facility across regions, patterns of care seeking to nonassigned facilities varied. For example, of visits to nonassigned facilities, children in Dar Es Salaam region were most likely to seek care within 5 km (64/85, 75%), whereas children in Geita were most likely to seek care outside of the region (131/187, 70.1%).

Table 3 explores visits at assigned and nonassigned facilities based on patient and assigned facility characteristics. There was little variation in the likelihood of a visit being at a nonassigned facility based on patient sex, assigned facility ownership, or assigned facility type. As expected, patients assigned to urban facilities and patients whose assigned facility had a higher number of facilities within 5 km were more likely to visit nonassigned facilities. Older children were more likely to visit nonassigned facilities; however, this could be an artifact of older children having more visits (and thus more opportunities to visit other facilities) or being more likely to have moved since being entered into the TImR system (ie, no longer residing near their assigned facility). Patients assigned to facilities newer to the TImR system were less likely to visit nonassigned facilities.

Figure 1. Visits to assigned and nonassigned facilities.

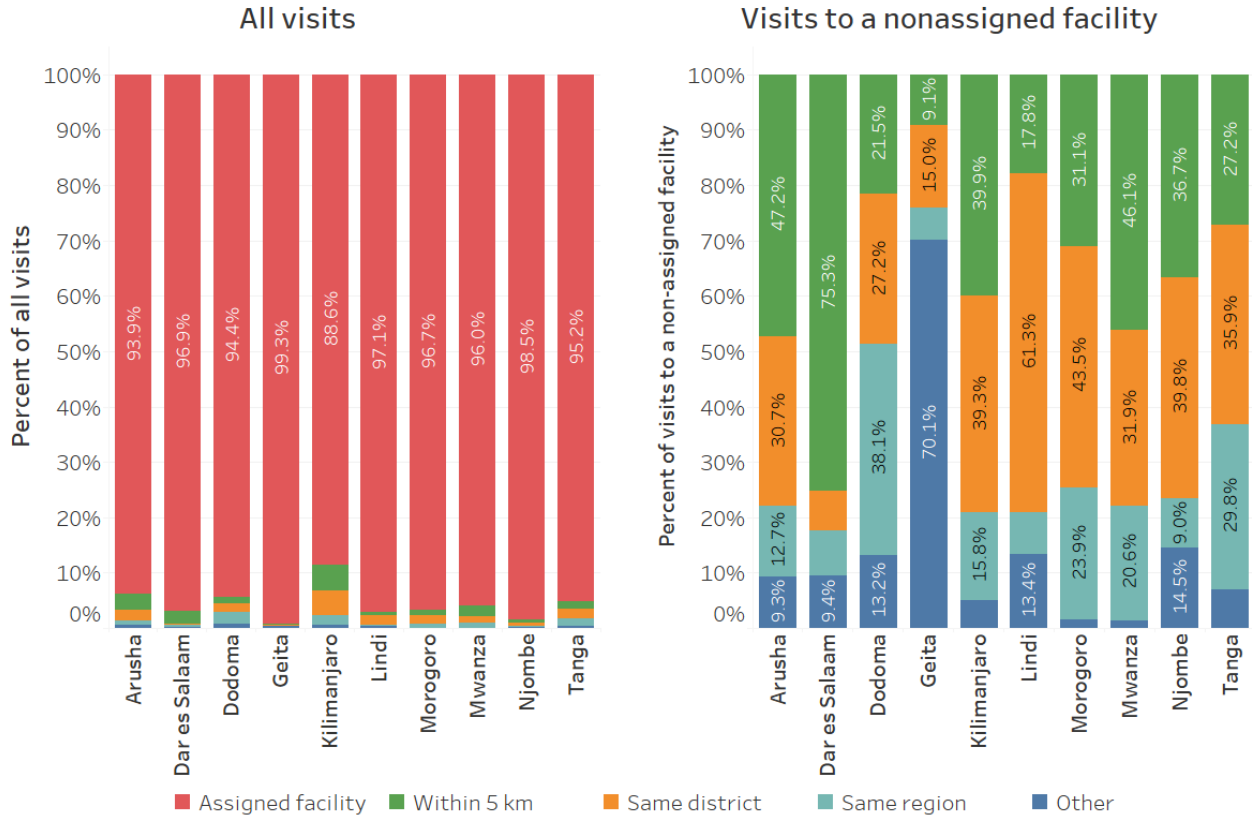


Table 3. Visits to assigned and nonassigned facilities by patient and assigned facility characteristics (N=810,568).

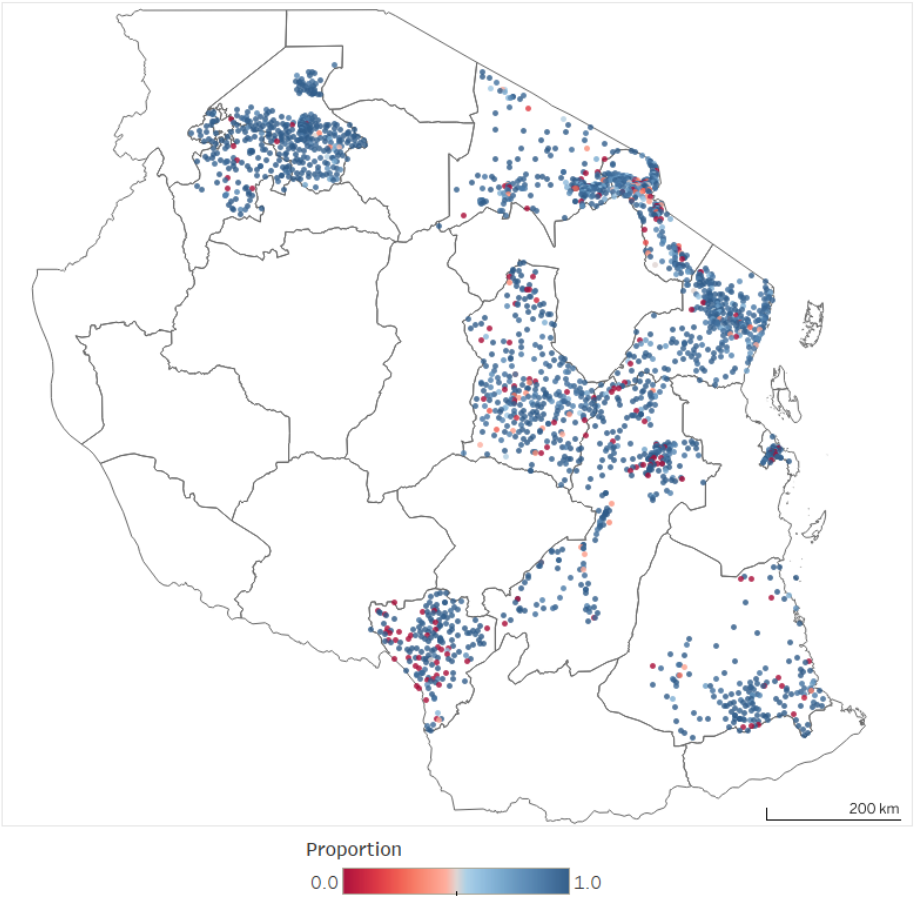
Covariate	Total visits, n	At nonassigned facility, n (%)	At assigned facility, n (%)
Sex			
Female	400,507	22,028 (5.5)	378,479 (94.5)
Male	409,164	22,504 (5.5)	386,660 (94.5)
Age at time of visit (months)			
<12	232,653	10,935 (4.7)	221,718 (95.3)
12-23	296,680	16,317 (5.5)	280,363 (94.5)
24-35	220,613	12,796 (5.8)	207,817 (94.2)
36-47	53,190	3989 (7.5)	49,201 (92.5)
48-59	5908	520 (8.8)	5388 (91.2)
Assigned facility type			
Dispensary	490,965	25,530 (5.2)	465,435 (94.8)
Health center	223,344	13,401 (6.0)	209,943 (94.0)
Hospital	96,259	5679 (5.9)	90,580 (94.1)
Assigned facility urbanicity			
Rural	598,804	25,150 (4.2)	573,654 (95.8)
Urban	205,070	19,482 (9.5)	185,588 (90.5)
Assigned facility ownership			
Private	148,088	9922 (6.7)	138,166 (93.3)
Public	655,786	34,101 (5.2)	621,685 (94.8)
Assigned facility TImR[a] duration (at time of visit)			
0-5 months	461,325	20,760 (4.5)	440,565 (95.5)
6-11 months	196,127	14,513 (7.4)	181,614 (92.6)
1 year	133,746	8693 (6.5)	125,053 (93.5)
≥2 years	19,370	697 (3.6)	18,673 (96.4)
Number of facilities within 5 km of assigned facility			
0	277,803	9167 (3.3)	268,636 (96.7)
1	157,322	7551 (4.8)	149,771 (95.2)
2-5	171,457	13,888 (8.1)	157,569 (91.9)
>5	192,290	20,767 (10.8)	171,523 (89.2)

[a]TImR: Tanzania Immunization Registry.

Spatial Variation in Assigned Facility Attendance

Figure 2 shows the proportion of all visits by children assigned to a given facility that occurred at the assigned facility. Facilities with low attendance appeared to cluster in northern Kilimanjaro, southeastern Arusha, southeastern and urban Mwanza, and coastal and central Tanga.

Figure 2. Proportion of visits at assigned facilities by facility geocode.



Model Results

Table 4 shows results from the logistic regression model with a given visit to a nonassigned facility as the outcome of interest. Children assigned to public facilities and health centers or hospitals, facilities with a longer duration of TImR use, and facilities in areas with higher health facility density were significantly more likely to visit a nonassigned facility. Children attending facilities with a greater number of recorded visits were significantly less likely to visit a nonassigned facility. Interestingly, the relationship with age was no longer monotonic after adjusting for other covariates. As compared with children aged ≤12 months, children aged 1 to 2 years were less likely to visit a nonassigned facility, whereas those aged 3 to 4 years were more likely.

Table 4. Population movement regression model results.

Covariate	Unadjusted model		Adjusted model	
	OR[a] (95% CI)	*P* value	aOR[b] (95% CI)	*P* value
Sex				
Female	Reference	N/A[c]	Reference	N/A
Male	0.98 (0.96-1.00)	.08	0.99 (0.97-1.01)	.21
Age (months)				
<12	Reference	N/A	Reference	N/A
12-23	0.71 (0.69-0.74)	<.001	0.79 (0.76-0.82)	<.001
24-35	0.64 (0.61-0.66)	<.001	0.87 (0.83-0.91)	<.001
36-47	0.85 (0.81-0.89)	<.001	1.30 (1.23-1.37)	<.001
48-59	1.20 (1.08-1.33)	<.001	1.89 (1.69-2.11)	<.001
Assigned facility urbanicity				
Rural	Reference	N/A	Reference	N/A
Urban	1.42 (1.11-1.82)	.01	0.93 (0.74-1.18)	.56
Assigned facility ownership				
Private	Reference	N/A	Reference	N/A
Public	N/A	N/A	1.37 (1.13-1.66)	.001
Assigned facility type				
Dispensary	Reference	N/A	Reference	N/A
Health center	1.16 (0.94-1.43)	.17	1.71 (1.41-2.07)	<.001
Hospital	1.53 (1.07-2.21)	.02	2.13 (1.52-2.98)	<.001
Assigned facility stockout (% of days)	1.00 (1.00-1.01)	.48	1.00 (0.99-1.01)	.94
Total assigned visits (log)	0.28 (0.26-0.32)	<.001	0.24 (0.21-0.27)	<.001
Assigned facility TImR[d] duration				
0-5 months	Reference	N/A	Reference	N/A
6-11 months	2.40 (1.17-4.94)	.02	1.55 (1.44-1.68)	<.001
12-23 months	2.84 (1.17-6.88)	.02	7.29 (6.75-7.87)	<.001
≥2 years	2.15 (0.88-5.28)	.09	8.15 (7.48-8.89)	<.001
Number of facilities within 5 km of assigned facility				
0	Reference	N/A	Reference	N/A
1	1.62 (1.50-1.76)	<.001	2.03 (1.97-2.09)	<.001
2-5	8.38 (7.75-9.05)	<.001	2.06 (1.98-2.15)	<.001
>5	9.55 (8.76-10.40)	<.001	1.48 (1.35-1.64)	<.001

[a]OR: odds ratio.

[b]aOR: adjusted odds ratio.

[c]N/A: not applicable.

[d]TImR: Tanzania Immunization Registry.

Missed Opportunities for Vaccination

Overview

MOVs, where the patient did not receive at least one vaccine for which they were eligible, were observed in 23.69% (226,525/956,195) of visits. Although we found little variation in the likelihood of an MOV based on sex, there was notable heterogeneity across age groups, facility urbanicity, facility type, and duration of TImR use at the facility (Table 5). The higher likelihood of an MOV among younger patients may be an artifact of the higher number of scheduled doses in the first year of life, and therefore, greater opportunity for missed doses.

Table 5. Visits with missed opportunities for vaccination (MOVs) by vaccine type and patient and facility characteristics.[a]

Covariate	Number of visits	Visits with an MOV by vaccine, n (%)						
		Any vaccine	Penta[b]	OPV[c]	BCG[d]	MCV[e]	Rota[f]	PCV[g]
Overall	956,195	226,525 (23.69)	60,364 (6.31)	58,040 (6.07)	54,924 (5.74)	5781 (0.60)	95,651 (10.00)	63,684 (6.66)
Sex								
Female	471,406	111,636 (23.68)	29,692 (6.30)	28,570 (6.06)	27,234 (5.78)	2794 (0.59)	47,011 (9.97)	31,358 (6.65)
Male	483,896	114,582 (23.68)	30,594 (6.32)	29,409 (6.08)	27,583 (5.70)	2953 (0.61)	48,488 (10.02)	32,236 (6.66)
Age group (months)								
<12	831,018	215,576 (25.94)	55,453 (6.67)	53,492 (6.44)	51,461 (6.19)	2080 (0.25)	95,651 (11.51)	58,627 (7.05)
12-23	110,968	9298 (8.38)	4376 (3.94)	4027 (3.63)	2913 (2.63)	2973 (2.68)	—[h]	4492 (4.05)
24-35	10,123	1239 (12.24)	374 (3.69)	350 (3.46)	354 (3.5)	609 (6.02)	—	417 (4.12)
36-47	2805	293 (10.45)	114 (4.06)	125 (4.46)	145 (5.17)	83 (2.96)	—	104 (3.71)
48-59	1281	119 (9.29)	47 (3.67)	46 (3.59)	51 (3.98)	36 (2.81)	—	44 (3.43)
Visited facility type								
Dispensary	563,186	138,714 (24.63)	38,917 (6.91)	34,295 (6.09)	30,271 (5.37)	3646 (0.65)	61,852 (10.98)	43,948 (7.80)
Health center	270,290	58,821 (21.76)	14,359 (5.31)	16,463 (6.09)	15,233 (5.64)	1465 (0.54)	22,830 (8.45)	14,035 (5.19)
Hospital	122,719	28,990 (23.62)	7088 (5.78)	7282 (5.93)	9420 (7.68)	670 (0.55)	10,969 (8.94)	5701 (4.65)
Visited facility urbanicity								
Rural	620,214	156,768 (25.28)	41,729 (6.73)	41,956 (6.76)	35,968 (5.8)	4178 (0.67)	67,467 (10.88)	47,301 (7.63)
Urban	322,199	65,247 (20.25)	16,588 (5.15)	14,540 (4.51)	18,082 (5.61)	1540 (0.48)	26,318 (8.17)	15,165 (4.71)
Visited facility TImR[i] duration (at time of visit)								
0-5 months	600,234	130,595 (21.76)	23,894 (3.98)	37,593 (6.26)	36,829 (6.14)	2340 (0.39)	53,416 (8.90)	36,747 (6.12)
6-11 months	197,188	50,634 (25.68)	18,569 (9.42)	11,582 (5.87)	10,329 (5.24)	1321 (0.67)	21,660 (10.98)	12,598 (6.39)
1 year	135,342	37,630 (27.8)	15,231 (11.25)	7277 (5.38)	5864 (4.33)	1827 (1.35)	17,584 (12.99)	11,410 (8.43)
≥2 years	19,705	6576 (33.37)	2430 (12.33)	1140 (5.79)	1188 (6.03)	248 (1.26)	2871 (14.57)	2641 (13.40)
Visited facility stockout (% days)								
<10%	666,531	155,134 (23.27)	40,379 (6.06)	41,754 (6.26)	34,730 (5.21)	3990 (0.60)	66,733 (10.01)	46,524 (6.98)
10%-19%	153,392	36,516 (23.81)	9888 (6.45)	8543 (5.57)	10,200 (6.65)	960 (0.63)	15,191 (9.90)	8672 (5.65)
20%-29%	77,730	21,007 (27.03)	6297 (8.10)	4226 (5.44)	7103 (9.14)	490 (0.63)	7957 (10.24)	4291 (5.52)
≥30%	54,072	12,203 (22.57)	2998 (5.54)	3031 (5.61)	2683 (4.96)	306 (0.57)	5090 (9.41)	3552 (6.57)

[a]Vaccine-specific percentages do not add up to the total missed opportunity for vaccination (MOV) percentage as patients can have MOVs for multiple vaccine types in a single visit.

[b]Penta: diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b.

[c]OPV: oral polio vaccine.

[d]BCG: Bacillus Calmette–Guérin.

[e]MCV: measles-containing vaccine.

[f]Rota: rotavirus.

[g]PCV: pneumococcal conjugate vaccine.

[h]Children are not considered eligible for rotavirus immunization after the first year of life.

[i]TImR: Tanzania Immunization Registry.

Of the 557,674 children included in the analysis, 167,115 (29.97%) had ≥1 MOVs. The mean number of MOVs per child was 0.61 (SD 1.20). Among the 167,115 children with an MOV, 85,697 (51.28%) had ≥1 MOV (range 1-15). Of 338,439 recorded MOVs, rotavirus was the most likely to have an MOV (accounting for 28.26% of all MOVs; n=95,650), followed by PCV (18.82%, 63,682), Penta (17.84%, 60,363), OPV (17.15%, 58,039), BCG (16.23%, 54,924), and MCV (1.71%, 5781). The lower MOV proportion for MCV was likely because of fewer

visits where children were age-eligible for MCV (aged at least 9 months).

MOV Reasons

The TImR system allows providers to indicate the reasons why a scheduled and eligible dose was not provided. However, the reason will only be noted if a dose is knowingly not given and thus is absent for doses for which providers did not recognize the patient's eligibility. For eligible doses that the provider logged as missed, the data indicated the mechanisms behind MOVs.

Table 6 details MOV reasons by vaccine type. Of 338,439 recorded MOVs, 183,623 (54.26%) had a listed reason: 177,624 (52.48%) were because of facility stockout, 2474 (0.73%) because of medical contraindication, 3184 (0.94%) because of being *late* (generally meant to indicate that the child is too old to start the vaccine sequence), 178 (0.05%) because of guardian refusal, and 163 (0.05%) because of expired stock. These reasons varied by vaccine type, with roughly three-quarters of Penta and PCV MOVs because of stockout but less than half for BCG, MCV, and rotavirus MOVs. Rotavirus MOVs were more likely to result from medical contraindications (913/95,650, 0.95%) compared with MOVs of the other vaccine types, whereas MCV had the highest likelihood of being missed because of guardian refusal (15/5781, 0.26%).

Table 6. Reasons for missed opportunities for vaccination (MOVs).

Vaccine type	Number of recorded MOVs	MOV reason (MOVs for given vaccine type), n (%)					
		Stockout	Medical contraindication	Late	Refusal	Expired stock	No reason provided
Overall	338,439	177,624 (52.48)	2474 (0.73)	3184 (0.94)	178 (0.05)	163 (0.05)	154,816 (45.74)
Rota[a]	95,650	34,315 (35.88)	913 (0.95)	761 (0.8)	34 (0.04)	38 (0.04)	59,589 (62.3)
OPV[b]	58,039	37,056 (63.85)	296 (0.51)	1118 (1.93)	37 (0.06)	31 (0.05)	19,501 (33.6)
Penta[c]	60,363	46,133 (76.43)	309 (0.51)	558 (0.92)	36 (0.06)	62 (0.1)	13,265 (21.98)
PCV[d]	63,682	47,712 (74.92)	434 (0.68)	834 (1.31)	39 (0.06)	37 (0.06)	14,626 (22.97)
BCG[e]	54,924	24,430 (44.48)	126 (0.23)	513 (0.93)	40 (0.07)	11 (0.02)	29,804 (54.26)
MCV[f]	5781	2694 (46.6)	12 (0.21)	117 (2.02)	15 (0.26)	5 (0.09)	2938 (50.82)

[a]Rota: rotavirus.

[b]OPV: oral polio vaccine.

[c]Penta: diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b.

[d]PCV: pneumococcal conjugate vaccine.

[e]BCG: Bacillus Calmette–Guérin.

[f]MCV: measles-containing vaccine.

Model Results

Results from the any-vaccine MOV and OPV-specific MOV models were selected as illustrative examples of interest and are shown in Table 7. Unadjusted results can be found in Multimedia Appendices 1 and 2. Age group and TImR duration were significantly associated with any MOV and OPV-specific MOVs. Compared with children aged <1 year, older children were substantially less likely to experience MOVs in both models. This may be because of the greater opportunity for MOVs at younger ages because of more scheduled doses in the first year of life. Interestingly, TImR use duration at the time of visit showed opposite directionality between the models, with longer TImR implementation associated with a higher likelihood of any MOV but lower likelihood of OPV-specific MOVs, suggesting that there may be different mechanisms leading to MOVs by vaccine type.

Table 7. Missed opportunity for vaccination (MOV) regression model results.

Covariate	Any MOV		OPV[a] MOV	
	aOR[b] (95% CI)	*P* value	aOR (95% CI)	*P* value
Sex				
Female	Reference	N/A[c]	Reference	N/A
Male	1.00 (0.99-1.01)	.90	1.00 (0.98-1.02)	.88
Age (months)				
0-11	Reference	N/A	Reference	N/A
12-23	0.19 (0.18-0.19)	<.001	0.41 (0.40-0.43)	<.001
24-35	0.25 (0.23-0.26)	<.001	0.33 (0.29-0.37)	<.001
36-47	0.19 (0.17-0.22)	<.001	0.40 (0.33-0.49)	<.001
48-59	0.18 (0.15-0.22)	<.001	0.33 (0.24-0.46)	<.001
Urbanicity				
Rural	Reference	N/A	Reference	N/A
Urban	0.90 (0.75-1.08)	.25	0.96 (0.73-1.26)	.78
Ownership				
Private	Reference	N/A	Reference	N/A
Public	1.02 (0.88-1.18)	.85	0.89 (0.71-1.12)	.31
Facility type				
Dispensary	Reference	N/A	Reference	N/A
Health center	0.89 (0.77-1.03)	.11	1.13 (0.91-1.40)	.28
Hospital	0.99 (0.76-1.28)	.91	0.92 (0.62-1.36)	.68
Facility TImR[d] duration (at time of visit)				
0-5 months	Reference	N/A	Reference	N/A
6-11 months	1.61 (1.58-1.63)	<.001	0.90 (0.88-0.93)	<.001
12-23 months	2.27 (2.22-2.31)	<.001	0.73 (0.71-0.76)	<.001
≥2 years	3.15 (3.03-3.27)	<.001	0.67 (0.62-0.72)	<.001

[a]OPV: oral polio vaccine.

[b]aOR: adjusted odds ratio.

[c]N/A: not applicable.

[d]TImR: Tanzania Immunization Registry.

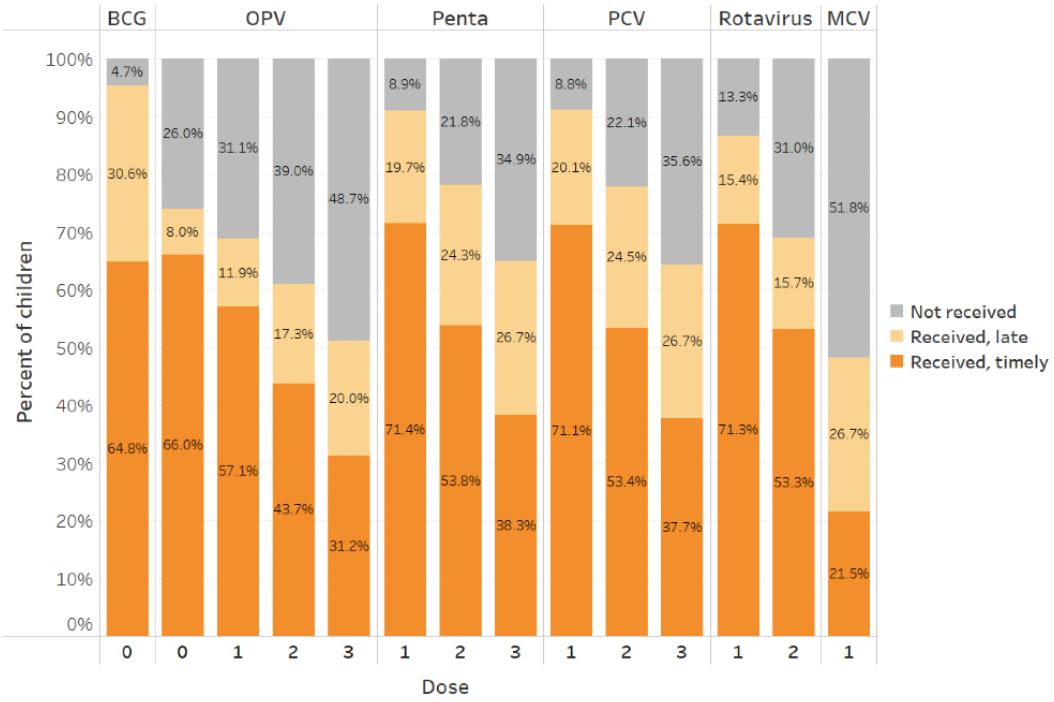
Continuum of Care

This analysis explored the vaccine dropout. To ensure common eligibility for doses, this analysis was restricted to children aged 12 to 47 months at the end of 2019 and focused on the 14 doses scheduled for the first year of life (ie, through MCV-1; Table 1).

Immunization Coverage

Overall, 93,619 (31.79%) of 294,464 children in our sample were fully immunized for doses scheduled in the first year of life (inclusive of OPV-0), with a further 39,718 (13.48%) receiving all scheduled doses, except for MCV-1. Figure 3 shows the doses received and timeliness by vaccine type and dose. As expected, there was a drop-off in coverage with later doses in each vaccine sequence. Timeliness also decreased monotonically with later doses in a sequence.

Figure 3. Vaccine coverage and dose timeliness. BCG: Bacillus Calmette–Guérin; MCV: measles-containing vaccine; OPV: oral polio vaccine; PCV: pneumococcal conjugate vaccine.



Vaccine Dropout

Table 8 details dropout rates across patient characteristics. For multidose vaccine-specific dropout, OPV had the highest rate (66,798/217796, 30.67%), followed by PCV (78,767/268,582, 29.33%), Penta (76,659/268,315, 28.57%), and Rota (52,086/255,337, 20.4%). Rotavirus may have had a lower dropout rate because there were only 2 doses in the sequence. There were common trends for all outcomes, such as older children and private facilities showing lower levels of dropout for all types of dropouts. However, some trends were outcome-/vaccine-specific, such as rural facilities showing higher levels of dropout for all vaccines except OPV. Most of these differences were marginal except for dropout by age group.

Table 8. Dropout by patient and facility characteristics.

Covariate	Children dropped out, n (%)					
	Penta[a]	OPV[b]	Rota[c]	PCV[d]	Birth or first	Overall dropout
Overall	76,659 (28.57)	66,798 (30.67)	52,086 (20.4)	78,767 (29.33)	16,414 (5.79)	194,765 (66.14)
Sex						
Female	37,591 (28.47)	32,735 (30.6)	25,547 (20.31)	38,652 (29.23)	8073 (5.78)	95,793 (66.1)
Male	38,962 (28.66)	33,955 (30.69)	26,466 (20.45)	40,006 (29.4)	8262 (5.75)	98,633 (66.14)
Age group (months)						
12-23	51,057 (31.9)	46,743 (34.42)	34,951 (22.84)	52,795 (32.87)	12,159 (6.99)	124,599 (69.99)
24-35	25,602 (23.65)	20,055 (24.46)	17,135 (16.75)	25,972 (24.06)	4255 (3.88)	70,166 (60.26)
Assigned facility type						
Dispensary	46,833 (27.82)	38,737 (28.63)	32,216 (20.08)	48,415 (28.72)	8338 (4.72)	118,279 (64.57)
Health center	21,375 (29.52)	20,176 (33.41)	14,236 (20.62)	21,790 (30.06)	5161 (6.74)	54,369 (68.01)
Hospital	8451 (30.69)	7885 (35.68)	5634 (21.77)	8562 (31.15)	2915 (9.63)	22,117 (70.55)
Assigned facility urbanicity						
Rural	51,651 (28.88)	41,372 (30.23)	35,904 (21.19)	53,075 (29.68)	10,448 (5.54)	131,395 (67)
Urban	23,375 (27.46)	23,778 (30.94)	15,051 (18.44)	24,077 (28.25)	5711 (6.34)	59,872 (64.1)
Assigned facility ownership						
Private	14,514 (30.83)	11,976 (32.64)	9272 (20.78)	14,567 (30.89)	3072 (6.16)	35,856 (68.61)
Public	61,289 (28.03)	53,867 (30.13)	42,184 (20.26)	63,223 (28.9)	13,186 (5.71)	156,847 (65.54)

[a]Penta: diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b.

[b]OPV: oral polio vaccine.

[c]Rota: rotavirus.

[d]PCV: pneumococcal conjugate vaccine.

Immunization Typologies

To better understand vaccination profiles, we constructed immunization archetypes using all possible combinations of eligible scheduled doses. Patients were fit into these archetypes based on their immunization history. Table 9 shows the 10 most common archetypes by vaccine doses received. After being fully vaccinated and fully vaccinated except for MCV-1, the third most common typology was receiving all doses except for the OPV sequence (19,322/294,464, 6.56% of children), followed by dropping out between the second and third visits (13,270/294,464, 4.51%) or between the third and fourth visits (13,102/294,464, 4.45%), and receiving only the birth doses (BCG and OPV-0; 10,156/294,464, 3.45%).

Table 9. Immunization typologies (10 most common).

Vaccine and dose														Children, n (%)
BCG[a]	OPV[b]				Penta[c]			PCV[d]			Rota[e]		MCV[f]	
0	0	1	2	3	1	2	3	1	2	3	1	2	1	
R[g]	R	R	R	R	R	R	R	R	R	R	R	R	R	93,619 (31.79)
R	R	R	R	R	R	R	R	R	R	R	R	R	NR[g]	39,718 (13.49)
R	NR	NR	NR	NR	R	R	R	R	R	R	R	R	R	19,322 (6.56)
R	R	R	NR	NR	R	NR	NR	R	NR	NR	R	NR	NR	13,270 (4.51)
R	R	R	R	N	R	R	NR	R	R	NR	R	R	NR	13,102 (4.45)
R	R	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	10,156 (3.45)
R	NR	NR	NR	NR	R	R	R	R	R	R	R	R	NR	10,064 (3.42)
R	NR	NR	NR	NR	R	NR	NR	R	NR	NR	R	NR	NR	5587 (1.9)
R	NR	NR	NR	NR	R	R	NR	R	R	NR	R	R	NR	3861 (1.31)
R	R	R	R	NR	R	R	NR	R	R	NR	R	NR	NR	3842 (1.31)

[a]BCG: Bacillus Calmette–Guérin.

[b]OPV: oral polio vaccine.

[c]Penta: diphtheria, tetanus, pertussis, hepatitis B, and *Haemophilus influenzae* type b.

[d]PCV: pneumococcal conjugate vaccine.

[e]Rota: rotavirus.

[f]MCV: measles-containing vaccine.

[g]"R" indicates a given dose was received, while "NR" indicates the dose was not received.

Visit Dropout

To understand dropout between different scheduled visits, we analyzed the proportion of children that had received any vaccine from each of the 5 scheduled touchpoints with the immunization system in the first year of life (Table 1). Overall, 96.29% (283,548/294,464) of children received at least one of the birth doses (BCG or OPV-0), 93.16% (274,314/294,464) received at least one of the visit 2 doses (OPV-1, PCV-1, Penta-1, or Rota-1), 80.98% (238,450/294,464) received at least one visit 3 dose, 67.52% (198,812/294,464) received at least one visit 4 dose, and 48.21% (141,948/294,464) received the visit 5 dose.

Model Results

The results from the Penta and overall dropout models were selected as illustrative examples of interest and are shown below. Unadjusted results can be found in Multimedia Appendices 3 and 4. As shown in Table 10, older age was significantly associated with a lower likelihood of both Penta and overall dropout (ie, starting but not finishing the 14-dose schedule). In the overall dropout model, urban facilities were associated with a significantly lower likelihood of overall dropout, and public facilities were associated with a higher likelihood. These trends were not observed in the Penta dropout model.

Table 10. Dropout regression model results.

Covariate	Penta dropout		Overall dropout	
	aOR[a] (95% CI)	*P* value	aOR (95% CI)	*P* value
Sex				
Female	Reference	N/A[b]	Reference	N/A
Male	1.02 (1.00-1.04)	.06	1.01 (0.99-1.03)	.21
Age (months)				
12-23	Reference	N/A	Reference	N/A
24-35	0.23 (0.22-0.23)	<.001	0.19 (0.19-0.19)	<.001
Assigned facility urbanicity				
Rural	Reference	N/A	Reference	N/A
Urban	0.86 (0.71-1.04)	.11	0.83 (0.70-0.99)	.03
Assigned facility ownership				
Private	Reference	N/A	Reference	N/A
Public	1.04 (0.90-1.22)	.57	1.15 (1.00-1.33)	.047
Assigned facility type				
Dispensary	Reference	N/A	Reference	N/A
Health center	0.95 (0.81-1.10)	.49	1.04 (0.91-1.22)	.58
Hospital	1.19 (0.91-1.54)	.20	1.27 (1.00-1.61)	.06
Assigned facility stockout (% of days)	1.00 (1.00-1.01)	.12	1.00 (1.00-1.01)	.28

[a]aOR: adjusted odds ratio.

[b]N/A: not applicable.

Continuous Quality Improvement

EIRs provide data for the rapid assessment of CQI improvement measures. These assessments can help improve service provision by identifying areas in need of targeted training or other quality improvement interventions. As shown in Table 11, 10% of facilities account for most of the issues, suggesting that targeted interventions to identified facilities could greatly improve care. These results use absolute numbers and, therefore, will be biased toward facilities with higher patient loads and longer TImR implementation durations. In practice, CQI analyses would likely be restricted to specific months or quarters, reducing any duration bias. Absolute figures can also offer greater efficiency by targeting CQI interventions to providers or facilities with the highest absolute number of issues.

Table 11. Continuous quality improvement.

All facilities (n=2345)	Issues accounted for, n (%)		
	Visits to a nonassigned facility[a] (n=44,733)	Visits with an MOV[b] (any vaccine; >n=226,525)	Children who have dropped out (full dropout; n=194,765)[a]
10% (n=134)	36,307 (81.16)	126,226 (55.72)	112,895 (57.96)
25% (n=586)	42,937 (95.99)	180,752 (79.79)	159,584 (81.94)
50% (n=1172)	44,715 (99.96)	215,989 (95.35)	188,281 (96.67)
75% (n=1758)	44,733 (100)	225,569 (99.58)	193,971 (99.59)

[a]Aggregated by child's assigned facility.

[b]MOV: missed opportunity for vaccination.

Discussion

Principal Findings

EIRs can add value in multiple ways. Access to individual-level data that captures all touchpoints with the immunization program allows for new analyses that can benefit immunization programs, national and regional ministry staff, health care providers and administrators, funders, and other stakeholders [8,9,22]. Descriptive statistics can be used to rapidly monitor service provision and vaccination coverage or inform quality improvement efforts. Longitudinal and spatial analyses can be used to understand temporospatial changes in care and coverage. Risk factor analyses can be used to identify patient and facility

characteristics associated with immunization issues (eg, dropout). These analyses can be targeted to the relevant stakeholder groups. For example, facility-level statistics for a given district can inform targeted supportive supervision, and national-level coverage trends can enable evidence-based policy development. EIRs also allow for more cost-effective and rapid synthesis of immunization data; many of these descriptive statistics and analyses would not be possible using the aggregate data available in the routine health information system or would require significant additional funding, time, and other resources for survey data collection [9]. The analyses presented in this study are intended to illustrate the types of insights that EIR data can provide to immunization programs.

Denominators and Population Movement

Inaccurate population denominators are a common challenge for monitoring coverage, improving implementation, and informing planning, such as projecting vaccine stock and staffing needs. A recent scoping review of immunization data quality in LMICs found that denominators were often inaccurate, infrequently adjusted, and inconsistent between the district and national levels [23]. Population denominators are influenced by migration, urbanization, and refugee crises, among other population dynamics that can have large effects at the local level [24]. Population denominators are further complicated by children seeking care at different facilities over time. The Strategic Advisory Group of Experts working group on the quality and use of global immunization and surveillance data identified inaccurate denominators as a common challenge and noted the lack of guidance on how to improve the accuracy of denominators and track mobile populations [25].

EIRs greatly simplify tracking patients who seek care at multiple facilities, enabling a more nuanced understanding of population movement across both geography and time and allowing for more robust coverage estimates. The use of the TImR data allowed us to explore both the magnitude of and factors associated with seeking care at facilities other than the patient's assigned, or *home*, facility. Our analysis revealed that a small subset of patients sought care outside their assigned facility (44,733/810,568, 5.52%); however, this varied by region; facility urbanicity, type, ownership, patient volume, and duration of TImR system use; density of facilities in the immediate area; and patient age. In addition, where patients seeking care varied by region, patients in some regions were more likely to travel to other districts and regions for care. For example, children who did not attend their assigned facility in Geita were most likely to attend a facility outside of the region, potentially because of population mobility associated with mining in the region. These insights can help inform resource allocation. EIRs also greatly simplify tracking patients who seek care at multiple facilities, decreasing the likelihood of missed or redundant doses. Although a small number of children in the Tanzania case study sought care outside their assigned facilities, some areas would have a much larger nomadic or mobile population. For example, in Cameroon, children born at home, immigrants, emigrants, and nomadic populations are not accurately accounted for when planning outreach vaccination sessions, which contributes to delaying or not vaccinating an estimated 30% to 70% of the population in some districts [26].

Missed Opportunities for Vaccination

Identifying and avoiding MOVs is an important and cost-effective method for achieving greater vaccination coverage. The challenge is in identifying when, where, and among which children or facilities MOVs are experienced to address them. Integration of clinical decision support systems within EIRs can automate the determination of child dose eligibility and alert the provider, which has been shown to reduce MOVs for routine childhood immunizations [27,28]. In addition, by collating vaccination history with child and facility characteristics, EIRs naturally allow for exploration of MOVs across these characteristics and by different vaccines. Our analysis of the TImR data showed that MOVs were highest among children aged <12 months (as mentioned, potentially because of the higher number of scheduled doses in the first year of life); however, there were few significant differences by other individual or facility characteristics. Other studies of countries in Sub-Saharan Africa have identified additional demographic and socioeconomic characteristics associated with increased odds of MOVs, including high birth order, high number of under 5 children in the house, lack of maternal education, lack of media access, and household and neighborhood poverty [29,30]. Although these data were not captured in TImR, they could be captured by an EIR to enable new analyses and equity insights [8,31].

This information can be used by providers to identify children who may be at higher risk of experiencing an MOV. In addition, it can be used by managers to identify providers and facilities with higher rates of MOVs for supportive supervision or refresher training or identify areas with high rates of vaccine hesitancy for outreach campaigns. In addition, EIRs can provide insight into the mechanisms behind MOVs, such as stock issues and vaccine-specific hesitancy. Where data were available, stockouts were the primary reason for MOVs, whereas mechanisms such as vaccine hesitancy and medical contraindications were relatively rare. The TImR data also showed that rotavirus was the most likely to have an MOV, which may indicate that eligibility requirements should be reviewed or refresher training provided. For additional insights, analysis of EIR data can be complemented by other tools such as those included in the WHO MOV strategy toolkit [20].

Continuum of Care

Identifying where in the vaccine schedule some children drop out and why they drop out is another key challenge for achieving high levels of vaccine coverage. Understanding which vaccine doses and child and facility characteristics are associated with failure to complete a vaccine sequence or the full vaccine schedule can help inform service provision, training, and quality improvement measures at the facility, regional, and national levels. In the TImR data, nearly half of children aged 12 to 35 months were fully vaccinated or had received all doses except MCV-1 of the 14-dose under-12-month schedule (ie, through MCV-1). Among children who did not complete the vaccine schedule, levels of dropout varied by vaccine. Facility characteristics associated with dropout also varied by vaccine; for example, assigned facility urbanicity was significantly associated with a lower likelihood of overall dropout (ie, starting

but not finishing the 14-dose schedule) but not Penta-specific dropout, suggesting that the mechanisms behind dropout may vary by vaccine. Continuum of care analyses could be further expanded if the EIR data were linked to a birth registration system. In the Tanzania case study, 5.79% (16,414/283,548) of children dropped out between birth and the first immunization dose; however, this may be an underestimation if some children are not registered at birth. In countries with a strong civil registration and vital statistics system, linking the EIR to birth registration or an antenatal care registry could expand the continuum of care analysis. Using EIRs to explore immunization typologies can also provide insight into which vaccines and visits require greater care. For example, in the TImR data, 6.56% (19,322/294,464) of children were fully vaccinated through MCV-1 except for the 3 to 4 OPV doses, highlighting the need for greater research into barriers to OPV coverage.

CQI Analysis

The CQI analysis showed that most issues (eg, MOVs) came from a minority of facilities. EIRs enable decision-makers at the national and subnational levels to quickly assess and identify providers, facilities, or geographic areas for targeted quality improvement measures, thereby improving the quality of care and increasing improvement in intervention effectiveness.

Added Value of EIRs

These analyses were designed to show the potential of EIRs to allow for a more nuanced, rapid, and cost-effective evaluation of vaccine program data to facilitate data use for decision-making. For example, automated dashboards of key indicators (eg, vaccine-specific coverage, stockouts, and child dropout) can inform planning and clinical practice at the facility level without the need for on-site data analysis. Providers can also use EIRs to simplify the tracking of individual patients, particularly those seeking care at multiple facilities, to improve the quality of care and reduce issues such as MOVs [27,28]. The integration of EIRs with SMS text messaging services to automate appointment and outreach to children at risk of defaulting has been shown to reduce dropout rates for routine childhood immunizations [4]. At the district and regional levels, the evaluation of underperforming facilities can be used for targeted supportive supervision and supplemental training. At the national level, up-to-date data on geographic and spatial trends in vaccine coverage can be used to inform nationwide campaigns, resource allocation, or policy development.

Designed well, EIRs can democratize immunization data. However, they require the necessary support to function effectively. The Early-Stage Digital Health Investment Tool has identified 6 building blocks for effective digital health systems: human capacity, investments and funding, data capture and use, infrastructure, standards and interoperability, and governance and policy [12]. Strong building blocks can maximize the effectiveness of EIR systems; however, this can pose a challenge in some low- and middle-income settings where 1 or several of these building blocks may be lacking. The WHO estimates that 50% of low-income and 24% of lower-middle–income countries have strong institutional capacity or involvement in data analysis at the national ministry [22]. With technical capacity often centralized at the national level, these figures are even lower at the subnational level. Furthermore, 54% of low-income and 41% of lower-middle–income countries are rated nascent, limited, or moderate in their capacity to have data and evidence drive policy and planning [22]. Implementing robust and routinized data frameworks, including EIRs, can address gaps in data availability and provide mechanisms to harness the data to drive evidence-based policy and planning. Automation and tailoring of data output to specific end users (eg, facility-level indicator dashboards for providers) can simplify data analysis and interpretation. However, effective use of EIR data for decision-making will require health care workers and administrators at all levels to have the skills, motivation, and autonomy to understand and act on the data [16,17]. Leadership at the national and regional levels should prioritize capacity building to enable the health system to make use of EIR data [32].

EIR is a solution that aims to improve immunization program performance. The efficiency and impact of EIRs can be maximized by introducing them in combination with other interventions, such as capacity strengthening for data use, vaccine stock management systems, data governance frameworks, or SMS text messaging reminders for caregivers. Interventions that use multiple mechanisms to address various barriers to data use have been found to be more successful in achieving immunization data use and action [33].

Limitations

The TImR results are intended to illustrate the ways EIRs can add value to immunization programs by providing actionable information for health care providers and managers. The results are not intended to be generalizable to Tanzania as a whole because of several data limitations. First, regions and districts implemented TImR at various points in time, meaning that some geographies are over- or underrepresented in the results. Second, and relatedly, only a subset of regions in Tanzania have introduced TImR; therefore, immunization services delivered outside the TImR coverage area are not captured in the results. Third, children who may live within the TImR coverage area but have not had a touchpoint with the immunization delivery system (also known as *zero dose children*) or were not registered at birth are not captured in the results. Fourth, this study did not assess data completeness, and any incomplete data (eg, providers not entering all immunizations into TImR) may limit the accuracy of the results. Fifth, prior studies of the TImR data have shown reduced system use over time, potentially biasing results toward facilities with greater capability to maintain reporting systems [16]. Sixth, as mentioned earlier, the analyses were limited to data captured in TImR. Although these data can be powerful for diagnosing issues, they do not capture all patient, facility, or geographic characteristics that may influence immunization delivery and can be limited in explaining trends. For example, MOVs may be underestimated as this study only captures MOVs during immunization visits and not during nonimmunization visits [34,35]. As noted earlier, some characteristics shown to be associated with MOVs were not captured in TImR. Triangulation with other data sources or targeted follow-up data collection can help answer the *why* questions. Finally, the lens used in this study was the assessment

of the potential added value of EIRs. This study does not attempt to highlight the challenges associated with implementing or maintaining EIRs, although many such challenges have been identified elsewhere [1,3,8,9,17,36].

Conclusions

EIRs have the potential to add substantial value to immunization stakeholders at all levels of the health system beyond measuring vaccine coverage. Individual-level data captured through EIRs can enable new analyses to understand immunization service delivery or care-seeking patterns, potential risk factors for underimmunization, and where challenges occur. Notably, most issues (eg, occurrence of MOVs, visits to a nonassigned facility, and number of defaulters) occur in a minority of facilities, highlighting the potential for EIRs to inform targeted quality improvement efforts. However, to achieve this potential, country programs need to leverage and strengthen their capacity for collecting, analyzing, and interpreting the data. Measures and analyses should be prioritized to match the needs and capabilities of the immunization program. Ideally, the prioritized measures should be integrated into routine systems to facilitate ongoing CQI efforts. As EIRs are introduced and scaled in LMICs, implementers and researchers should continue to share real-world examples and build an evidence base for how EIRs can add value to immunization programs, particularly for innovative uses.

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Conflicts of Interest

TKR provided funding for this research in her role as a senior program officer at the Bill & Melinda Gates Foundation.

Multimedia Appendix 1
Complete missed opportunity for vaccination (any vaccine) regression model results.
[DOCX File , 16 KB - publichealth_v8i1e32455_app1.docx]

Multimedia Appendix 2
Complete missed opportunity for vaccination (oral polio vaccine) regression model results.
[DOCX File , 17 KB - publichealth_v8i1e32455_app2.docx]

Multimedia Appendix 3
Complete dropout (Penta) regression model results.
[DOCX File , 16 KB - publichealth_v8i1e32455_app3.docx]

Multimedia Appendix 4
Complete dropout (overall) regression model results.
[DOCX File , 15 KB - publichealth_v8i1e32455_app4.docx]

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Abbreviations

BCG: Bacillus Calmette–Guérin
BID: Better Immunization Data
CQI: continuous quality improvement
EIR: electronic immunization registry
GADM: Database of Global Administrative Areas
LMIC: low- and middle-income country
MCV: measles-containing vaccine
MOV: missed opportunity for vaccination
OPV: oral polio vaccine
TImR: Tanzania Immunization Registry
WHO: World Health Organization

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Original Paper

Individuals With SARS-CoV-2 Infection During the First and Second Waves in Catalonia, Spain: Retrospective Observational Study Using Daily Updated Data

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Abstract

Background: A description of individuals with SARS-CoV-2 infection comparing the first and second waves could help adapt health services to manage this highly transmissible infection.

Objective: We aimed to describe the epidemiology of individuals with suspected SARS-CoV-2 infection, and the characteristics of patients with a positive test comparing the first and second waves in Catalonia, Spain.

Methods: This study had 2 stages. First, we analyzed daily updated data on SARS-CoV-2 infection in individuals from Girona (Catalonia). Second, we compared 2 retrospective cohorts of patients with a positive reverse-transcription polymerase chain reaction or rapid antigen test for SARS-CoV-2. The severity of patients with a positive test was defined by their admission to

hospital, admission to intermediate respiratory care, admission to the intensive care unit, or death. The first wave was from March 1, 2020, to June 24, 2020, and the second wave was from June 25, 2020, to December 8, 2020.

Results: The numbers of tests and cases were lower in the first wave than in the second wave (26,096 tests and 3140 cases in the first wave versus 140,332 tests and 11,800 cases in the second wave), but the percentage of positive results was higher in the first wave than in the second wave (12.0% versus 8.4%). Among individuals with a positive diagnostic test, 818 needed hospitalization in the first wave and 680 in the second; however, the percentage of hospitalized individuals was higher in the first wave than in the second wave (26.1% versus 5.8%). The group that was not admitted to hospital included older people and those with a higher percentage of comorbidities in the first wave, whereas the characteristics of the groups admitted to hospital were more alike.

Conclusions: Screening systems for SARS-CoV-2 infection were scarce during the first wave, but were more adequate during the second wave, reflecting the usefulness of surveillance systems to detect a high number of asymptomatic infected individuals and their contacts, to help control this pandemic. The characteristics of individuals with SARS-CoV-2 infection in the first and second waves differed substantially; individuals in the first wave were older and had a worse health condition.

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KEYWORDS

epidemiology; SARS-CoV-2; COVID-19; timeline; comparison; pandemic; waves; population characteristics

Introduction

Since the first case of pneumonia caused by SARS-CoV-2 in December 2019, the pandemic struck the world with, probably, one of the most challenging outbreaks in the 21st century [1]. Nearly 90 million confirmed cases and nearly 2 million COVID-19–related deaths have occurred on all continents until January 11, 2021, as reported by the World Health Organization [2].

The first cases in Europe were detected in Italy and spread throughout the continent before societies realized the severity of the situation [3,4]. Health systems were suddenly burdened with individuals infected by this highly transmissible new disease, to the point of collapse in certain countries [5]. Strict lockdown measures were applied in most countries to decrease the number of cases and ensure adequate care for patients in critical condition [6]. These measures had a certain effectiveness, and the first COVID-19 wave faded away during the summer in Europe [7], only to give way to a second wave shortly after, with the easing of restrictions and presumably the initiation of the school term [8,9], although later reports questioned this [10-12], as well as the transfer of social life into indoor spaces [13]. The steady second increase of cases in Europe was initially evident in Spain from where it spread again, although this time at a slower pace, even within the Spanish regions [14]. After all, health systems had a short period to organize their structure if a second wave hit in the autumn, as was the case.

The arrival of the pandemic caught the health systems quite unaware and unprepared, and uncertainty had a synergic effect with the lack of knowledge about the new virus, the infection, and the disease [15-17]. As it spread, at the assistance level, the optimal actions to be taken were unclear [18]; at the management level, administrations had to adapt primary care and hospital health services; and at the informative level, the sources were neither prepared nor connected enough, and did not have methods to obtain reliable and complete data on SARS-CoV-2 infection [15,16]. Information systems on SARS-CoV-2 infection had to be built from scratch during the first wave and refined during the second wave.

Although much has been learnt about the virus and its transmissibility, many gaps in knowledge remain, including the comparison of the first wave and the entire second wave, which has received limited attention [19,20], and the consideration of individuals with various degrees of severity. Inquiry into such differences would improve our understanding of the effectiveness of the applied measures, and thus, it would help plan and improve the optimal public health strategies to tackle or at least alleviate the consequences of this infection. The evidence suggests that the context plays an important role in the presentation and spread of this infection [7,21]. Indeed, contributing factors and their weights may vary due to climatic conditions, government actions, culture, and behavior of the population, or could differ in patients attended in primary care settings and in hospitals [7,21]. At the time the study was conducted, Catalonia was facing the end of the second wave and foreseeing the possibility of the initiation of a third wave in the subsequent months [22]. A detailed epidemiological framework by country was recommended to consider the conditions for deployment of massive testing within the strategies to control this epidemic [22]. Accordingly, this study aimed to describe and compare the first and second waves of the SARS-CoV-2 epidemic in Catalonia (Spain). Particularly, we sought to report the daily counts, incidences, and numbers of hospitalized patients with this infection, and to compare the characteristics of cases in the first and second waves considering various degrees of severity.

Methods

Overview

This study was structured in 2 stages. First, in the general population, we examined the number of positive SARS-CoV-2 tests in each wave. Second, within the population with a positive test, we compared the characteristics of 2 retrospective cohorts, 1 for each wave. The first wave lasted from March 1, 2020, to

June 24, 2020, and the second from June 25, 2020, to December 8, 2020.

Analysis of the General Population

Enrollment included individuals from the province of Girona (Catalonia, Northern Spain), within the area of influence of Hospital Universitari de Girona Doctor Josep Trueta and Parc Hospitalari Martí i Julià from Salt (Girona).

For each wave, we counted the number of individuals with corresponding test results and the number of tests per diagnosis. On a daily basis, we tallied the number of individuals with a positive test from the general population, the daily empiric reproduction number at day 7 (ρ7; the empiric reproduction number is related to the reproduction number [23]), and the incidence rate of positive cases at 14 days. Pseudonymized data for these analyses were obtained from the primary care and hospital records.

Comparison of Cohorts of Individuals With a Positive SARS-CoV-2 Test Result

The cohorts included individuals with a confirmed SARS-CoV-2 infection whose episode was closed, hereinafter also referred to as cases. Confirmed SARS-CoV-2 infection was defined by a positive test result, either using real-time reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 [24] (requiring a cycle threshold under 39 as per laboratory standards in the daily routine of the 2 hospitals included in this study) or using a rapid antigen test [25-27]. The index date was the date of the positive test result, except where there was a COVID-19–related registry in the primary care center within 7 days before the positive test result, in which case the index date was the date of the visit instead. An episode was followed up to 30 days after a positive test result in the primary care records, if there was no record of hospital discharge; if there was a record, it was considered up until the time of discharge. For cases defined from the primary care records, death was considered if it occurred up until 30 days after a positive diagnostic test; for cases defined from hospital records, death was considered up until the time of discharge. Data records were obtained up to January 8, 2021.

For each wave, we characterized the cases (individuals with confirmed SARS-CoV-2 infection) using pseudonymized data registered in clinical health records from primary care. We considered the following variables up to the index date: age, sex, vascular risk factors (smoking, high alcohol consumption, obesity, diabetes mellitus, dyslipidemia, and hypertension), other comorbidities (atrial fibrillation, heart failure, ischemic heart disease, peripheral arterial disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, sleep apnea, chronic kidney disease, malignant neoplasms, dementia, and depression), and treatment with acetylsalicylic acid. We also recorded previous influenza and pneumococcal vaccination, and calculated the Charlson index for every participant [28]. The Charlson index is a validated method to classify comorbidity, weighting the amount and severity of comorbid diseases in an integrated score that predicts 1-year mortality risk [29,30].

Censoring was applied at the time of closing the case. The highest degree of severity at censoring was the outcome. It was defined by admission to hospital, or lack of it, and department of admission (for admitted participants). Outcomes were considered by increasing severity as follows: mild infection (not admitted to a hospital), admitted to a conventional hospital (neither in intermediate respiratory care [IRC] nor in the intensive care unit [ICU]), admitted to IRC (ie, requiring noninvasive ventilation), admitted to the ICU (ie, requiring invasive ventilation), or death. Allocation of participants to the hospital departments was determined from pseudonymized inpatient administrative data, whereas allocation as mild infection (not admitted to hospital) was determined from pseudonymized hospital emergency records and from the primary health records.

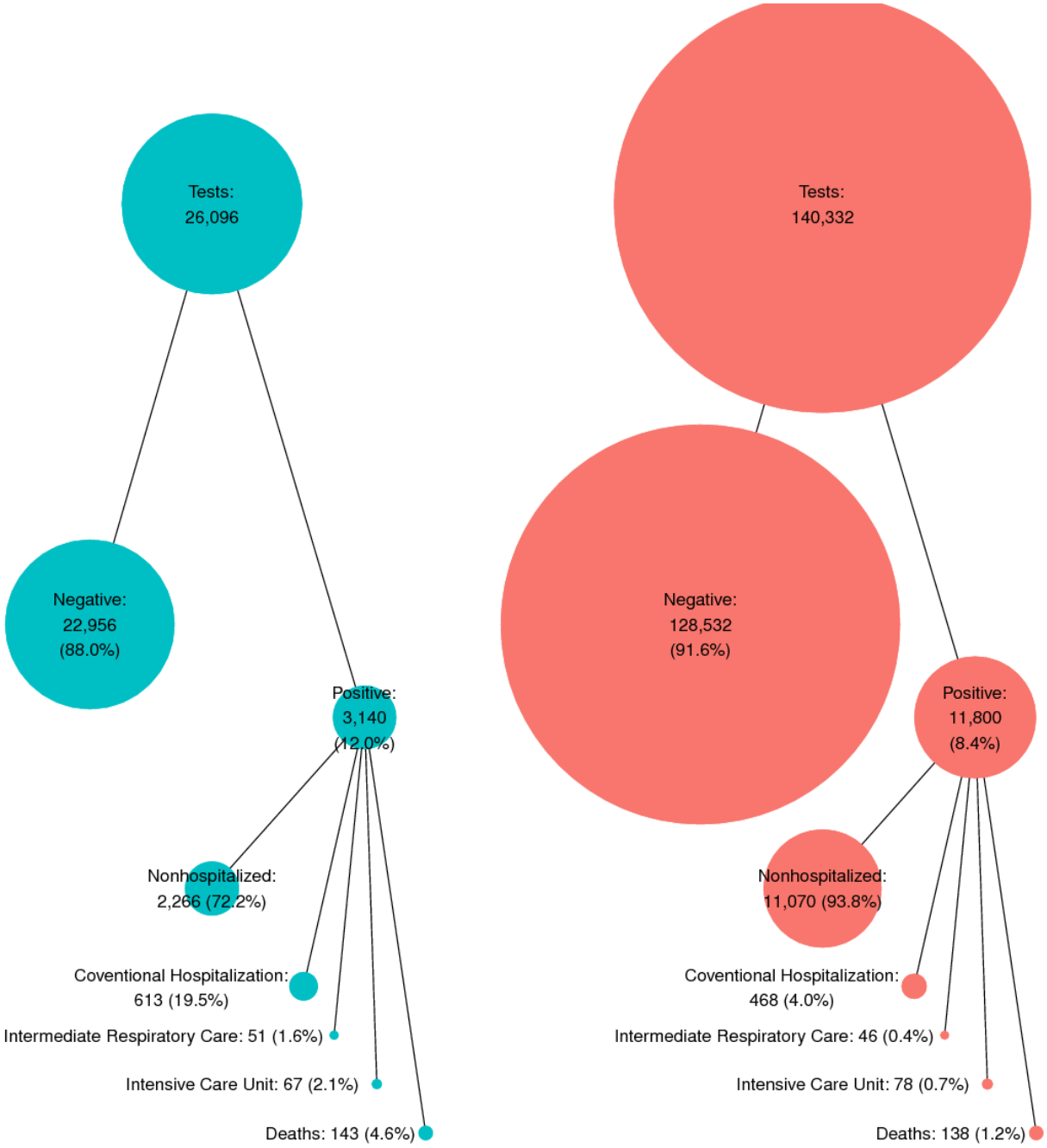
For each wave, we estimated the cumulative incidence of the outcomes (degrees of severity) at 30 days. We also counted the total and daily numbers of individuals in hospital within cases (individuals with confirmed SARS-CoV-2 infection). For each degree of severity (outcome), baseline characteristics described cases in the first and second waves using the mean (SD) for continuous variables, and the cumulative number (percentage) for categorical variables; comparison of these characteristics was carried out using the Student *t* test for continuous variables and the Fisher exact test for categorical variables. The level of significance was set at .05. We also calculated the absolute differences of the means (95% CIs) for continuous variables and the odds ratios (ORs) (95% CIs) for categorical variables in the second wave with respect to the first. All analyses were performed using R software (version 4.0.3; R Foundation for Statistical Computing) [31].

Results

Overview

Figure 1 provides a general overview of the 2 stages in this study. On the one hand, it shows the counts of positive tests in the general population; on the other hand, it shows the number of individuals for each outcome among those with a positive test.

Figure 1. Comparison of the number and percentage of suspected and confirmed cases in the first (from March 1, 2020, to June 24, 2020) and second (from June 25, 2020, to December 8, 2020) SARS-CoV-2 waves in Girona (Catalonia).

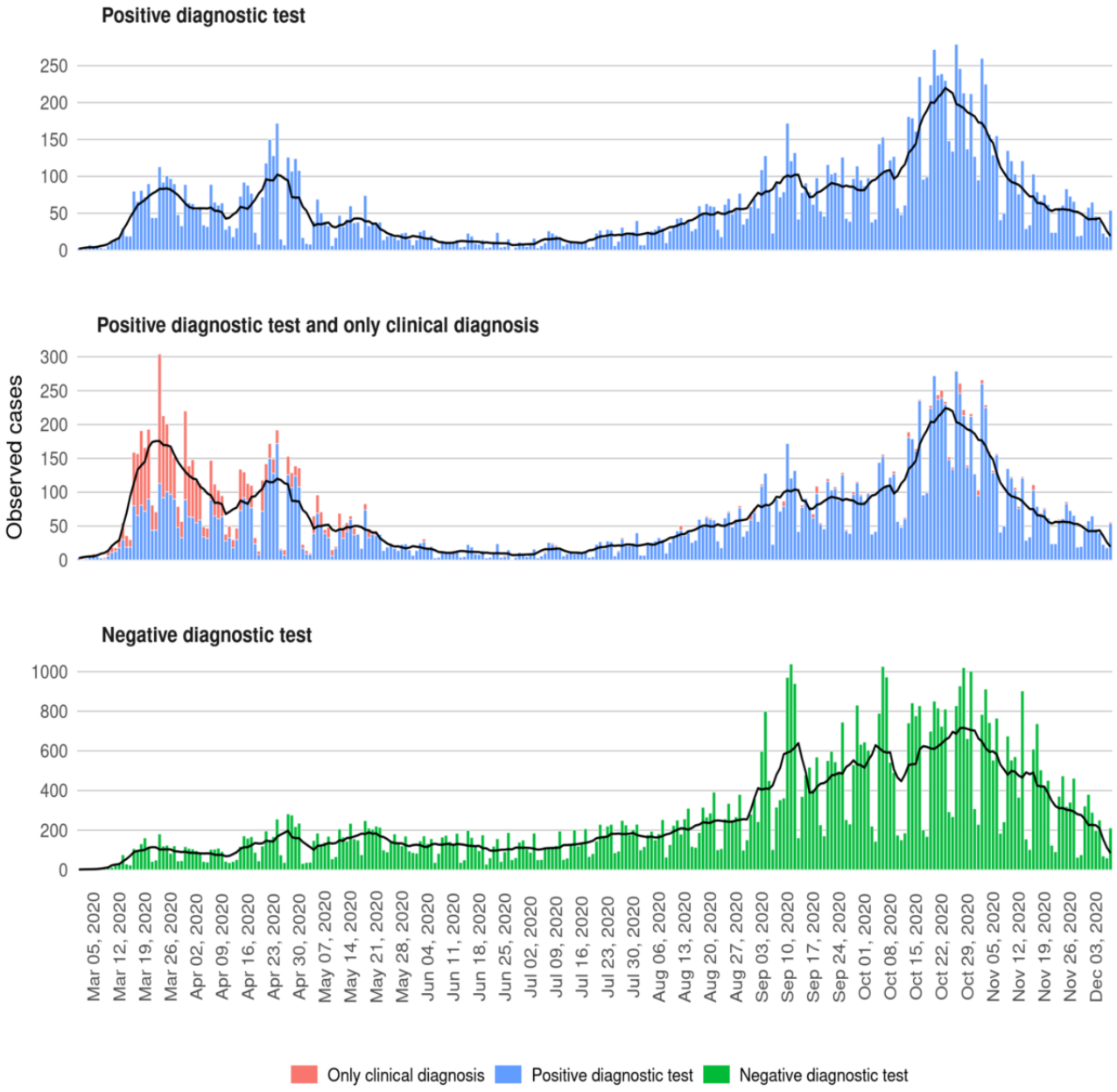


Analysis of the General Population

Total counts showed that the first wave had much lower numbers of positive cases (over 3000) than the second (nearly 12,000), but had a higher percentage of positive tests with respect to all suspected individuals (12.0% in the first wave versus 8.4% in the second) (Figure 1). The number of tests per case was 8.3 in the first wave (a total of 26,096 tests and 3140 cases) and 11.9 in the second wave (a total of 140,332 tests and 11,800 cases).

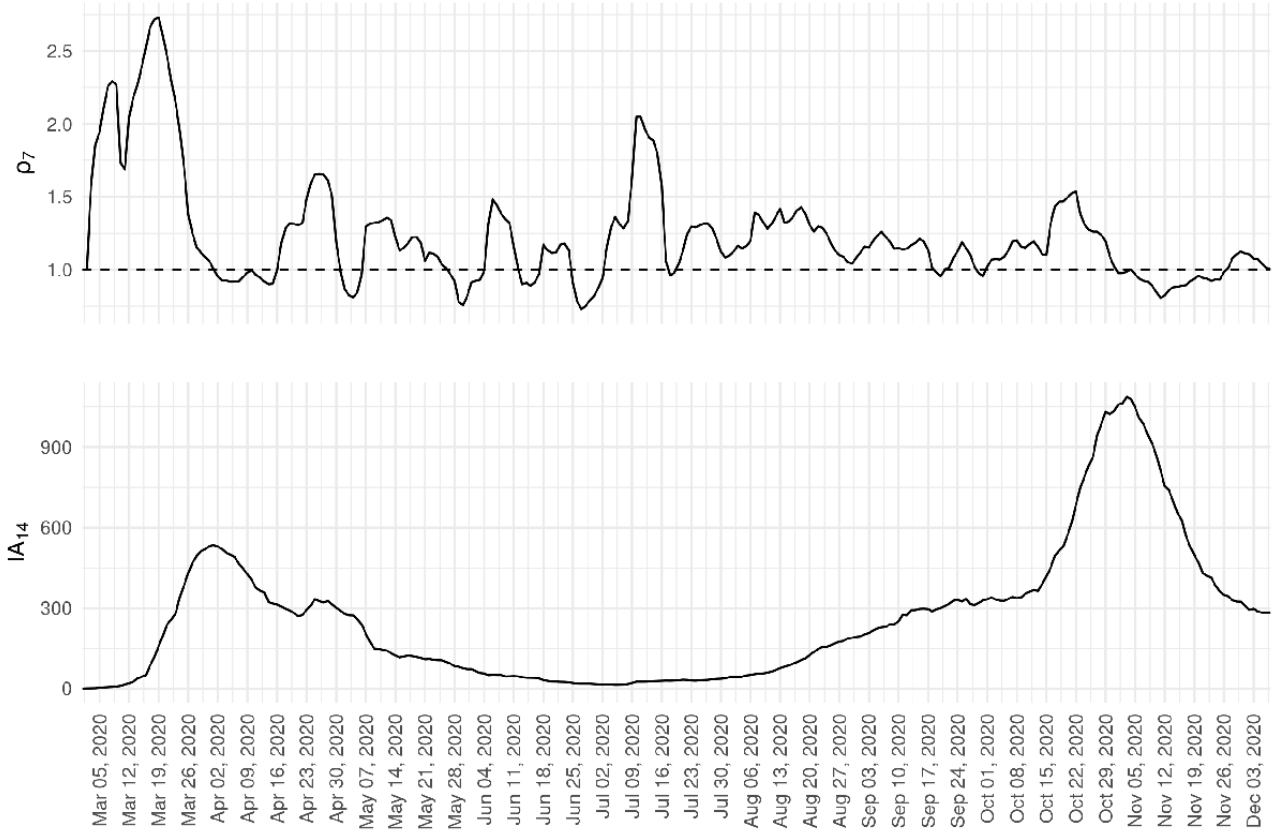
Two waves could be clearly distinguished in the timeline of COVID-19 cases. The first wave of the overall population (hospitalized and nonhospitalized) showed an increase of cases in March (Figure 2). Then, the number of cases decreased until the beginning of summer (at the end of June), when a slow increasing trend appeared again (Figure 2). The second wave was longer, and many more positive cases were detected in that period (nearly 4-fold) (Figure 1). However, when we considered an additional group of possible cases, that is, individuals with no confirmatory test but with symptoms compatible with COVID-19 (indicated as only clinical diagnosis in Figure 2), the situation became more even (Figure 2). Figure 2 also shows that the number of daily negative diagnostic test results was much higher in the second wave.

Figure 2. Daily number of individuals with a positive and/or negative SARS-CoV-2 test in Girona (Catalonia) from March 1, 2020, to December 8, 2020.



SARS-CoV-2 transmission in the community was also monitored with the cumulative incidence rate of SARS-CoV-2 infection at 14 days and with the transmission rate at 7 days, indicated by the empiric reproduction number (ρ7) (Figure 3). At the beginning of the first wave, the ρ7 value increased, followed by an increase in the incidence rate. Social distancing and ultimately strict lockdown led to a drop in the ρ7 value; when it was under 1, the incidence started to decrease. The decrease went on as far as the ρ7 value was predominantly under 1. However, at the end of June, the ρ7 reached a value over 1 and remained there, which led to a slow but constant increase in the incidence rate and subsequently to the second wave.

Figure 3. Daily evolution of the empiric reproduction number (7 days; ρ7) and cumulative incidence rate (14 days; IA14) of positive cases in Girona (Catalonia), from March 1, 2020, to December 8, 2020.

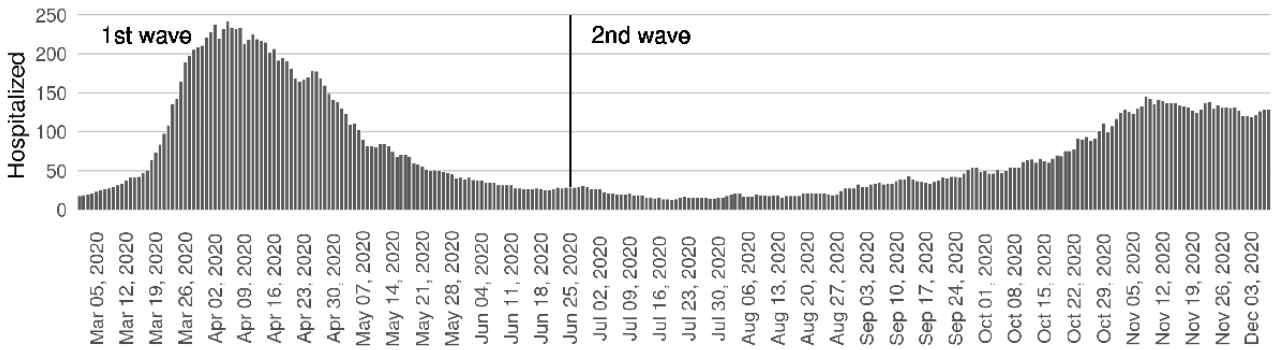


Comparison of Cohorts of Individuals With a Positive SARS-CoV-2 Test

Figure 1 shows the cumulative incidence at 30 days for each outcome within each wave, with respect to all individuals with a positive test result (cases). The first wave contained a lower percentage of individuals with mild SARS-CoV-2 infection (nonhospitalized) and higher percentages of individuals who were in a conventional hospital, who were admitted to IRC, who were admitted to the ICU, and who passed away (including in-hospital and out-of-hospital deaths).

Hospitalized cases amounted to 818 out of 3140 cases in the first wave and 680 out of 11,800 cases in the second, with cumulative incidences at 30 days of 26.1% and 5.8%, respectively. During the first wave, 613 patients (a cumulative incidence at 30 days of 74.9%, with respect to all hospitalized) were in a conventional hospital, 51 (6.2%) were in IRC, 67 (8.2%) were in the ICU, and 87 (10.6%) passed away. The corresponding figures among hospitalized cases during the second wave were 468 (68.8%), 46 (6.8%), 78 (11.5%), and 88 (12.9%), respectively. The daily number of individuals in hospital showed a much steeper increase during the first wave than the second, the initiation of which was more progressive (Figure 4).

Figure 4. Daily number of individuals with a positive SARS-CoV-2 test in hospital over time (from March 1, 2020, to December 8, 2020) in Girona (Catalonia).



Comparison of the baseline characteristics (individuals with a positive test [cases]) showed that individuals with mild SARS-CoV-2 infection (no hospital admission) were almost 10 years older in the first wave (P<.001) (Table 1). The absolute difference in the mean age between the second wave and the first supported statistical significance (Multimedia Appendix 1); the absolute difference was −8.67 (95% CI −9.71 to −7.63). Regarding other degrees of severity, the mean ages of individuals with conventional hospitalization and individuals admitted to the ICU were slightly higher in the second wave (P=.04 and P=.02, respectively) (Tables 1 and 2). The 95% CI of the absolute differences supported statistical significance; they were 2.5 (95% CI 0.15-4.85) and 5.15 (95% CI 0.66-9.64), respectively. As for the rest of the population characteristics, the percentage of individuals with other comorbidities and risk factors in the first wave was mostly higher than in the second, in the group with no hospital admission (Table 1), with significant P values. These results were supported by ORs under 1 and with significant 95% CIs (Multimedia Appendix 1). Characteristics in the rest of the groups (hospitalized) were similar in the first and second waves, with few exceptions (Tables 1 and 2). In the second wave, the group admitted to a conventional hospital had a higher percentage of individuals with dyslipidemia, hypertension, and cerebrovascular disease, and receiving acetylsalicylic acid (Table 1). These results were supported by ORs over 1 and with significant 95% CIs (Multimedia Appendix 1). The group admitted to IRC included a higher percentage of individuals receiving acetylsalicylic acid in the second wave (Table 2), and the OR comparing the second wave with the first wave was 3.01 with significance and a 95% CI of 1.63-5.77. The group admitted to the ICU had a higher percentage of individuals with diabetes and a higher Charlson index in the second wave (Table 2), with significant P values and significance of the 95% CIs of the ORs and the absolute differences. Finally, the group of deceased individuals had a higher percentage of patients with atrial fibrillation, previous pneumococcal vaccination, and treatment with acetylsalicylic acid in the second wave (Table 2). The P values for the differences and the 95% CIs of the ORs supported statistical significance.

Table 1. Comparison of the baseline characteristics of individuals with a positive SARS-CoV-2 test from Girona (Catalonia) in the first (March 1, 2020, to June 24, 2020) and second (June 25, 2020, to December 8, 2020) SARS-CoV-2 waves in the no admission and admission but no intermediate respiratory care or intensive care unit groups.

Variable	No admission			Admission but no IRC[a] or ICU[b]		
	1st wave (n=2266)	2nd wave (n=11,070)	*P* value	1st wave (n=613)	2nd wave (n=468)	*P* value
Age, mean (SD)	54.5 (22.3)	45.8 (26.3)	<.001	58.6 (18.9)	61.1 (20.0)	.04
Men, n (%)	703 (31.0)	5223 (47.2)	<.001	300 (48.9)	235 (50.2)	.71
Smoker, n (%)	393 (23.9)	1910 (26.5)	.10	92 (17.9)	54 (13.7)	.24
Exsmoker, n (%)	140 (8.5)	603 (8.4)	.10	74 (14.4)	61 (15.5)	.24
Alcohol consumption of high risk, n (%)	35 (1.5)	115 (1.0)	.048	19 (3.1)	15 (3.2)	.99
Obesity, n (%)	538 (23.7)	2404 (21.7)	.16	248 (40.5)	205 (43.8)	.23
Diabetes, n (%)	194 (8.6)	575 (5.2)	<.001	117 (19.1)	110 (23.5)	.08
Dyslipidemia, n (%)	420 (18.5)	1192 (10.8)	<.001	169 (27.6)	158 (33.8)	.03
Hypertension, n (%)	574 (25.3)	1475 (13.3)	<.001	220 (35.9)	215 (45.9)	.001
Atrial fibrillation, n (%)	102 (4.5)	145 (1.3)	<.001	44 (7.2)	33 (7.1)	.99
Heart failure, n (%)	63 (2.8)	51 (0.5)	<.001	23 (3.8)	19 (4.1)	.87
Ischemic heart disease, n (%)	64 (2.8)	146 (1.3)	<.001	38 (6.2)	37 (7.9)	.28
PAD[c], n (%)	52 (2.3)	91 (0.8)	<.001	24 (3.9)	24 (5.1)	.37
Cerebrovascular disease, n (%)	52 (2.3)	84 (0.8)	<.001	15 (2.4)	29 (6.2)	.003
COPD[d], n (%)	65 (2.9)	137 (1.2)	<.001	44 (7.2)	33 (7.1)	.99
Asthma, n (%)	132 (5.8)	539 (4.9)	.06	42 (6.9)	24 (5.1)	.25
Sleep apnea, n (%)	56 (2.5)	210 (1.9)	.08	33 (5.4)	33 (7.1)	.30
Chronic kidney disease, n (%)	167 (7.4)	217 (2.0)	<.001	61 (10.0)	65 (13.9)	.05
Malignant neoplasms, n (%)	175 (7.7)	358 (3.2)	<.001	69 (11.3)	52 (11.1)	.99
Dementia, n (%)	232 (10.2)	208 (1.9)	<.001	44 (7.2)	35 (7.5)	.91
Depression, n (%)	199 (8.8)	530 (4.8)	<.001	73 (11.9)	44 (9.4)	.20
Previous flu vaccination, n (%)	598 (26.4)	1254 (11.3)	<.001	183 (29.9)	142 (30.3)	.89
Previous pneumococcus vaccination, n (%)	533 (23.5)	1739 (15.7)	<.001	199 (32.5)	179 (38.2)	.05
ASA[e], n (%)	57 (2.5)	190 (1.7)	.01	17 (2.8)	37 (7.9)	<.001
Charlson index, mean (SD)	2.3 (2.0)	2.0 (1.8)	<.001	2.8 (2.3)	2.8 (2.2)	.86

[a]IRC: intermediate respiratory care.

[b]ICU: intensive care unit.

[c]PAD: peripheral arterial disease.

[d]COPD: chronic obstructive pulmonary disease.

[e]ASA: acetylsalicylic acid.

Table 2. Comparison of the baseline characteristics of individuals with a positive SARS-CoV-2 test from Girona (Catalonia) in the first (March 1, 2020, to June 24, 2020) and second (June 25, 2020, to December 8, 2020) SARS-CoV-2 waves in the admission to intermediate respiratory care, admission to the intensive care unit, and deceased groups.

Variable	Admission to IRC[a]			Admission to the ICU[b]			Deceased		
	1st wave (n=51)	2nd wave (n=46)	*P* value	1st wave (n=67)	2nd wave (n=78)	*P* value	1st wave (n=143)	2nd wave (n=138)	*P* value
Age, mean (SD)	64.6 (14.7)	61.7 (15.4)	.35	56.2 (13.1)	61.3 (14.2)	.02	81.0 (12.4)	81.7 (11.3)	.61
Men, n (%)	34 (66.7)	30 (65.2)	.99	48 (71.6)	63 (80.8)	.24	73 (51.0)	69 (50.0)	.90
Smoker, n (%)	5 (10.4)	6 (14.3)	.83	6 (10.7)	6 (9.0)	.49	17 (13.8)	17 (14.2)	.46
Exsmoker, n (%)	8 (16.7)	6 (14.3)	.83	10 (17.9)	18 (26.9)	.49	13 (10.6)	19 (15.8)	.46
Alcohol consumption of high risk, n (%)	0 (0.0)	0 (0.0)	N/A[c]	2 (3.0)	3 (3.8)	.99	7 (4.9)	6 (4.3)	.99
Obesity, n (%)	30 (58.8)	25 (54.3)	.15	33 (49.3)	39 (50.0)	.79	50 (35.0)	53 (38.4)	.50
Diabetes, n (%)	16 (31.4)	7 (15.2)	.09	9 (13.4)	25 (32.1)	.01	47 (32.9)	51 (37.0)	.53
Dyslipidemia, n (%)	17 (33.3)	17 (37.0)	.83	22 (32.8)	27 (34.6)	.86	55 (38.5)	65 (47.1)	.15
Hypertension, n (%)	24 (47.1)	24 (52.2)	.69	24 (35.8)	39 (50.0)	.09	101 (70.6)	106 (76.8)	.28
Atrial fibrillation, n (%)	9 (17.6)	3 (6.5)	.13	1 (1.5)	1 (1.3)	.99	18 (12.6)	35 (25.4)	.009
Heart failure, n (%)	4 (7.8)	2 (4.3)	.68	0 (0.0)	1 (1.3)	.99	11 (7.7)	17 (12.3)	.23
Ischemic heart disease, n (%)	8 (15.7)	4 (8.7)	.36	3 (4.5)	8 (10.3)	.22	14 (9.8)	21 (15.2)	.21
PAD[d], n (%)	1 (2.0)	1 (2.2)	.99	3 (4.5)	3 (3.8)	.99	11 (7.7)	6 (4.3)	.32
Cerebrovascular disease, n (%)	2 (3.9)	1 (2.2)	.99	2 (3.0)	1 (1.3)	.60	11 (7.7)	12 (8.7)	.83
COPD[e], n (%)	10 (19.6)	6 (13.0)	.42	2 (3.0)	4 (5.1)	.69	15 (10.5)	19 (13.8)	.47
Asthma, n (%)	3 (5.9)	4 (8.7)	.70	2 (3.0)	3 (3.8)	.99	4 (2.8)	11 (8.0)	.06
Sleep apnea, n (%)	9 (17.6)	3 (6.5)	.13	5 (7.5)	6 (7.7)	.99	7 (4.9)	7 (5.1)	.99
Chronic kidney disease, n (%)	9 (17.6)	7 (15.2)	.79	3 (4.5)	6 (7.7)	.51	42 (29.4)	46 (33.3)	.52
Malignant neoplasms, n (%)	9 (17.6)	4 (8.7)	.24	7 (10.4)	13 (16.7)	.34	51 (35.7)	42 (30.4)	.38
Dementia, n (%)	2 (3.9)	1 (2.2)	.99	0 (0.0)	2 (2.6)	.50	46 (32.2)	38 (27.5)	.43
Depression, n (%)	7 (13.7)	3 (6.5)	.32	4 (6.0)	6 (7.7)	.75	22 (15.4)	26 (18.8)	.53
Previous flu vaccination, n (%)	19 (37.3)	17 (37.0)	.99	14 (20.9)	15 (19.2)	.84	84 (58.7)	79 (57.2)	.81
Previous pneumococcus vaccination, n (%)	24 (47.1)	16 (34.8)	.30	17 (25.4)	26 (33.3)	.36	85 (59.4)	107 (77.5)	.001
ASA[f], n (%)	0 (0.0)	4 (8.7)	.047	3 (4.5)	7 (9.0)	.34	12 (8.4)	24 (17.4)	.03
Charlson index, mean (SD)	2.8 (2.4)	1.9 (1.2)	.07	1.7 (1.1)	2.7 (2.7)	.03	3.1 (2.3)	3.5 (2.7)	.23

[a]IRC: intermediate respiratory care.

[b]ICU: intensive care unit.

[c]N/A: not applicable.

[d]PAD: peripheral arterial disease.

[e]COPD: chronic obstructive pulmonary disease.

[f]ASA: acetylsalicylic acid.

Discussion

Principal Findings

We compared the epidemiology and characteristics of individuals with SARS-CoV-2 infection in the first and second waves in Catalonia. The first wave struck more suddenly, and although SARS-CoV-2–positive individuals were less numerous, the percentage with respect to all suspected individuals was higher than in the second wave. Moreover, individuals with a positive diagnostic test were healthier in the second wave, as indicated by the lower proportion of individuals who required hospitalization (26.1% in the first wave versus 5.8% in the second) and the lower percentage of patients with comorbidities among nonhospitalized patients. However, these lower percentages might also be attributed to the younger age of the population in the second wave, because younger individuals tend to have a better health condition. Once in hospital, the differences in age and comorbidities between the first and second waves were much less prominent.

During the first wave, no screening for the general population was performed, simply because there was no time to organize screenings and tests were not available for everyone. In March and April 2020, RT-PCR tests were performed for patients admitted to the hospital and for health workers, and up to early June, screenings were directed at old people in nursing homes, centers for disabled individuals, supervised flats, and penitentiaries. These screenings represented one-third of all PCR tests carried out during the first wave (ie, PCR tests were prioritized for the most vulnerable populations). However, if we consider the number of clinically diagnosed cases in the first wave (individuals who were considered to have COVID-19 based on signs and symptoms, but in whom no diagnosis test was performed), the number of individuals with COVID-19 appears similar. Even conceding that the infection spread was just starting during the period included in the first wave, it is likely that a large number of asymptomatic cases were unnoticed in that wave. This idea is supported by previous reports [32] and is coherent with our results. Figure 2 and Figure 4 show that hospitalized cases were more numerous and the number increased more abruptly in the first wave than in the second wave (Figure 4), but the number of daily overall cases detected with diagnostic tests was much lower in the first wave (Figure 2).

In the second wave, surveillance and health systems were more organized and proactive, especially in areas where the transmission rate increased, which allowed a huge amount of screening tests to be carried out. This volume of tests during the second wave would explain the much higher number of positive cases (almost 4-fold) than in the first wave. The lower percentage of positive cases in the second wave shows the efforts and success of the screening systems to find, test, and isolate contacts when needed. This is another crucial aspect in the epidemiology comparing the first and second waves in this pandemic (the means to diagnose the infection, the consideration of a person as a case, the availability of diagnostic tests, and the capacity of the surveillance systems to organize screenings and preventive measures at a large scale) [33].

In hospitals, the situation was also very different during the 2 waves. The first wave arrived so suddenly that the system collapsed, and the criteria to allocate and treat patients according to severity kept changing and were different from the second wave. During the second wave, the population, especially vulnerable individuals, knew how to protect themselves, which smoothened the increase of cases, and thus, the situation in hospitals was tense but the system did not collapse. The criteria to allocate and treat patients were more established, and health professionals could be more proactive to admit and treat patients with milder forms of the disease.

Within hospitalized patients, the second wave included a higher percentage of individuals with certain conditions in the group of patients with conventional hospitalization (dyslipidemia, hypertension, cerebrovascular disease, or treatment with acetylsalicylic acid), those with admission to the ICU (diabetes), or those who passed away (atrial fibrillation, pneumococcus vaccination, and treatment with acetylsalicylic acid). This could be partly explained because of a slightly higher age average. Finally, the second wave lasted longer than the first, which resulted in a fairly similar total number of patients in IRC, those in intensive care, and those who passed away in both waves.

Strengths and Limitations

We had access to daily updated and reliable data that could be structured for analysis up to a date that included the second wave. Moreover, we could assess all individuals with a diagnostic test for SARS-CoV-2 (ie, with a negative or positive result), which allowed a complete description of the situation, since a high number of positive mild cases could be, as the case actually was, due to an increase in the number of tests performed. However, we acknowledge that in February and March 2020, clinical diagnosis or the definition of close contacts was determined according to epidemiological criteria from countries that first reported COVID-19 cases (China [34] and Italy [35]); thus, many patients who must have been positive were not identified as such, and some close contacts were overlooked. Additionally, antigen tests were not available in the first wave and were only available in the second wave. In this second wave, the tests were performed in certain situations, like screening in schools or in symptomatic individuals, and the criteria to apply them changed to adapt and avoid too much pressure on the health systems. We decided to include them in the analysis to be able to account for all individuals who tested positive and appraise the performance of the screening.

Comparison With Prior Work

A Letter to the Editor on an analysis from Japan reported higher pressure on the health system, higher proportion of individuals with comorbidities, and older mean age in the first wave, in line with our results. However, they could not include data to complete the second wave, and thus, there is a possibility that future findings differ from their results at the time of publication [19]. Nevertheless, comparison of results in Japan and the south of Europe remains of high interest. Indeed, preparedness for the pandemic differed between countries before [36] and during the spread of the pandemic. Some countries had some time to equip themselves for the second wave, but they could not adapt readily enough to it, with subsequent burden on the health

system and thus the population [32]. Further analyses that compare the first and second waves in other countries would be very useful to determine expected common characteristics and differences. A couple of previous reports characterized the first wave in Spain, as in April and August 2020 [37,38]. The authors of a report from the Working Group for the Surveillance and Control of COVID-19 observed a much higher percentage of hospitalized patients among individuals who tested positive in a diagnostic test when compared with our study (45% versus 11%), which could be explained by the definition of a case. They considered a person as a case if they had symptoms of severe acute respiratory infection and had travelled to COVID-19–affected areas or had epidemiological links with COVID-19 laboratory-confirmed cases [37]. Finally, an analysis of the first wave in Catalonia studied data from the primary care setting to compare the characteristics of individuals with and without COVID-19, and deceased and living patients with COVID-19; our results in the first wave for nonhospitalized individuals and for deceased patients are comparable to the findings in this study [38].

Conclusions

Screening systems for SARS-CoV-2 infection were scarce during the first wave, but were more adequate during the second wave, reflecting the usefulness of surveillance systems to detect a high number of asymptomatic infected individuals and their contacts, to help control this pandemic. Individuals infected by SARS-CoV-2 differed substantially during the first and second waves in Catalonia. Infected individuals were older and had more comorbidities in the first wave, and more of them needed hospitalization. Hospitals collapsed in the first wave, but tension was lower in the second wave, which contributed to better care for a broader spectrum of the population.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Absolute differences and odds ratios for the baseline characteristics of individuals with a positive SARS-CoV-2 test result from Girona (Catalonia) on comparing the second SARS-CoV-2 wave (June 25, 2020, to December 8, 2020) to the first wave (March 1, 2020, to June 24, 2020).
[DOCX File , 22 KB - publichealth_v8i1e30006_app1.docx]

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Abbreviations

ρ7: empiric reproduction number at day 7
ICU: intensive care unit
IRC: intermediate respiratory care
OR: odds ratio
RT-PCR: reverse-transcription polymerase chain reaction

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Original Paper

The Role of Information and Communications Technology Policies and Infrastructure in Curbing the Spread of the Novel Coronavirus: Cross-country Comparative Study

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Abstract

Background: Despite worldwide efforts, control of COVID-19 transmission and its after effects is lagging. As seen from the cases of SARS-CoV-2 and influenza, worldwide crises associated with infections and their side effects are likely to recur in the future because of extensive international interactions. Consequently, there is an urgent need to identify the factors that can mitigate disease spread. We observed that the transmission speed and severity of consequences of COVID-19 varied substantially across countries, signaling the need for a country-level investigation.

Objective: We aimed to investigate how distancing-enabling information and communications technology (ICT) infrastructure and medical ICT infrastructure, and related policies have affected the cumulative number of confirmed cases, fatality rate, and initial speed of transmission across different countries.

Methods: We analyzed the determinants of COVID-19 transmission during the relatively early days of the pandemic by conducting regression analysis based on our data for country-level characteristics, including demographics, culture, ICT infrastructure, policies, economic status, and transmission of COVID-19. To gain further insights, we conducted a subsample analysis for countries with low population density.

Results: Our full sample analysis showed that *implied telehealth policy*, which refers to the lack of a specific telehealth-related policy but presence of a general eHealth policy, was associated with lower fatality rates when controlled for cultural characteristics (P=.004). In particular, the fatality rate for countries with an implied telehealth policy was lower than that for others by 2.7%. Interestingly, *stated telehealth policy*, which refers to the existence of a specified telehealth policy, was found to not be associated with lower fatality rates (P=.30). Furthermore, countries with a government-run health website had 36% fewer confirmed cases than those without it, when controlled for cultural characteristics (P=.03). Our analysis further revealed that the interaction between implied telehealth policy and training ICT health was significant (P=.01), suggesting that implied telehealth policy may be more effective when in-service training on ICT is provided to health professionals. In addition, credit card ownership, as an enabler of convenient e-commerce transactions and distancing, showed a negative association with fatality rates in the full sample analysis (P=.04), but not in the subsample analysis (P=.76), highlighting that distancing-enabling ICT is more useful in densely populated countries.

Conclusions: Our findings demonstrate important relationships between national traits and COVID-19 infections, suggesting guidelines for policymakers to minimize the negative consequences of pandemics. The findings suggest physicians' autonomous use of medical ICT and strategic allocation of distancing-enabling ICT infrastructure in countries with high population density to maximize efficiency. This study also encourages further research to investigate the role of health policies in combatting COVID-19 and other pandemics.

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KEYWORDS

health policy; telehealth; physical distancing; disease transmission; COVID-19

Introduction

First identified in December 2019, the novel COVID-19 outbreak has rapidly spread worldwide. As of September 23, 2021, the World Health Organization (WHO) reported that over 229.8 million people were infected worldwide, with over 4.7 million deaths caused by COVID-19 [1]. Furthermore, on December 19, 2020, a mutant of COVID-19, labeled B.1.1.7, was found, causing further havoc specifically in European countries. Consequently, the UK Prime Minister Boris Johnson imposed another lockdown that was even stricter than the previous lockdowns [2]. This kind of catastrophic pandemic is not unprecedented. From 1918 to 1919, the H1N1 influenza A virus emerged and went on to infect approximately 40% of the global population, with a mortality rate of more than 2% [3]. The H1N1 flu persists to this date, over 100 years since its first appearance, and has undergone significant genetic mutations. Virologists expect COVID-19 to follow a similar pattern [4,5]. As such, the prevalence of pandemics and genetic mutations is not a one-off phenomenon. Other outbreaks with disruptive social and economic consequences are probable [6], demanding research on how to control the spread of a virus in its early stages.

With this urgent need in mind, it is noteworthy that the infection and fatality rates as well as the speed of transmission have varied widely across countries. Countries, such as Israel, Singapore, South Korea, and Taiwan, are regarded as relatively successful in curbing transmission [7], whereas European countries and the United States experienced an explosive increase in the number of confirmed cases [1]. It is known that minimizing physical contact between individuals without disturbing their daily lives and improved medical practices are crucial in managing the spread of infectious diseases in general [8]. First, as a means of reducing physical contact and enabling social distancing, national information and communications technology (ICT) infrastructure, such as e-commerce and high speed internet connection, has played a key role in many countries [8,9]. Second, the possible importance of medical ICT policies and infrastructure has also been recognized. For example, effective use of telehealth practices has been credited with the successful management of other infectious diseases, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), pointing to a possible role for telehealth in controlling pandemics [10]. In addition, other medical ICTs, such as computerized physician order entry (CPOE) and e-prescribing, have been acknowledged as drivers of health care improvements in quality and efficiency [11]. Third, countries differed significantly across other dimensions, such as implementation of early lockdown and conformity to government policies because of their cultural differences, which could have affected their success in social distancing.

Therefore, to gain broader insights, there is a need for country-level analysis of the national-level characteristics that mitigate the spread of COVID-19 through successful distancing and improved medical practices. Nevertheless, previous studies on the spread of COVID-19 tended to have narrower scopes, such as individuals, several cities, a single country, or a single continent, rather than a global focus [12-17]. Although there are some exceptions, those studies were still limited in the number of countries, possibly due to difficulty in data collection, for investigation [15,16]. For instance, the latest cross-country study on the effect of threat or coping appraisal on distancing compliance was conducted by comparing 5 countries only [18]. In addition, prior research also focused on how the demographic, cultural, or political factors of a country affected COVID-19 infection [19-22], but did not include ICT-related factors.

To address such a research gap, the primary objective of this study was to identify what national characteristics have a major impact on curtailing contagious diseases during the relatively early days of the pandemic. In particular, we focused on the role of distancing-enabling ICT infrastructure (DistancingICT) and medical ICT infrastructure and policy (MedicalICT) in containing COVID-19 infection, fatality rates, and transmission speed.

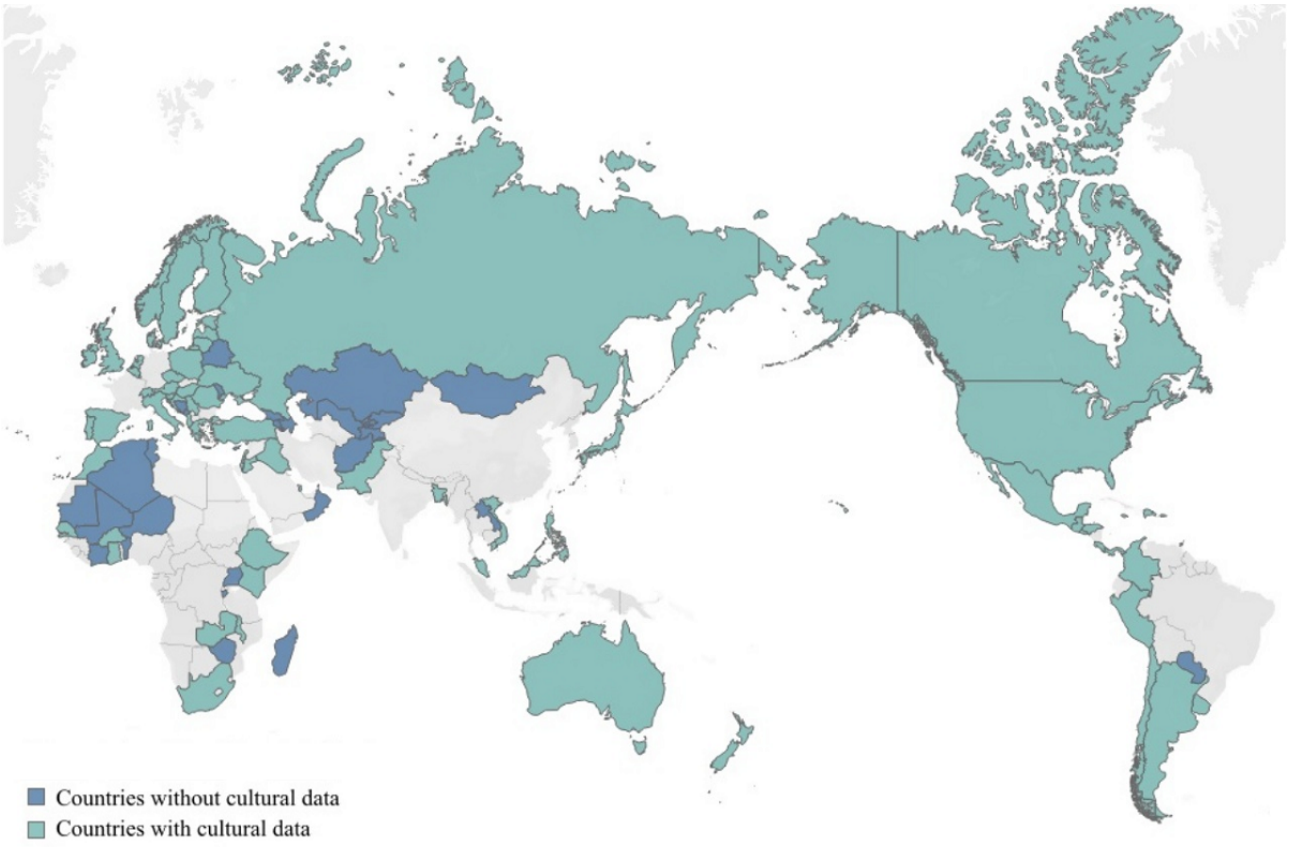
Methods

Data Collection

The main sources of country-level data used in this study included the United Nations, the World Bank, the WHO, Worldometers, Our World in Data (OWID), Ookla, Hofstede Insights, and Wikipedia. Among these, Worldometers is a reference site that provides real-time statistics on diverse topics. As a widely used source of research, media, and teaching, OWID is an online scientific publication institute that focuses on global issues such as poverty and disease. Ookla provides analyses of internet access performance metrics. Hofstede Insights provides culture scores of each country based on Hofstede's cultural dimension theory [23], and is widely used in academic research. For example, to predict growth of COVID-19 confirmed cases across several countries, Hofstede dimensions are used to account for cultural factors [24]. Wikipedia is used only to determine which countries enforced national lockdowns in the early days of COVID-19. The accuracy of enforcement and the dates of enforcement were further confirmed through research in the media. All the data were collected between July and August 2020. This sampling strategy allows us to analyze the determinants of COVID-19 transmission during the early days of the pandemic.

We limited our analysis to the countries that reported statistics related to the spread of COVID-19. For example, countries without accurate statistics on deaths as of July 28, 2020, were excluded. China, the country at the epicenter of COVID-19, was excluded because the patterns of disease spread and governmental control differ greatly from those in other countries. By matching the data for the social, economic, and demographic statuses of countries, as well as their physical distancing and health care–related ICT infrastructure, our final data set consisted of 98 countries. The countries included in our analysis are shown in Figure 1.

Figure 1. Map chart of the countries used in the analysis.



We focused on the following 3 dependent variables that represented the early state of the spread of COVID-19 in each country: (1) the cumulative number of infections, (2) the fatality rate, and (3) the number of days from initial infection to the 1000th infection. The first dependent variable represents the cumulative number of COVID-19 infections per country as of July 28, 2020. The second dependent variable is the fatality rate, which is the death toll over the cumulative number of infections. The third dependent variable is the transmission speed of COVID-19 in its initial stage. This is represented for each country by the number of days from the date of the first confirmed case to the date of the 1000th confirmed case. For the third dependent variable, countries with fewer than 1000 cases as of July 28, 2020, were excluded due to the difficulty of calculating the speed of transmission.

The 2 main categories of our main independent variables were DistancingICT and MedicalICT. For DistancingICT, we chose the following 2 variables based on findings of previous research: rate of credit card ownership and broadband internet speed. Research and Markets reported that during the COVID-19 pandemic, North America's online sales surged, and credit cards were the top payment method for these online sales [25]. Previous studies further support the relationship between e-commerce and credit card usage. Meyll and Walter surveyed more than 25,000 US households and confirmed that individuals using mobile payments are likely to use credit cards [26]. Given this direct relationship between e-commerce and credit card usage, we identified credit cards as a major enabler of distancing as they serve as alternatives to offline shopping. Broadband internet speed also assists individuals to comply with stay-at-home orders during COVID-19 [27]. Next, the MedicalICT variables involved the availability of a national telehealth policy or strategy; availability of government-supported multilingual health internet websites that provide information; institutions with health care ICT training; and national electronic health records (EHRs). These variables represent MedicalICT because the variables relate to either reliable online sharing of medical information (government health internet sites and national EHRs) or the effective use of existing medical ICT technology (national telehealth policy and health care ICT training).

In particular, national telehealth policy is divided into the following 2 types: implied and stated. An *implied telehealth policy* means that a country does not have a specific national telehealth policy or strategy, and such a policy is referred to in the overall national eHealth policy. Australia, Finland, and the United States are examples of such countries. The United Kingdom and Norway, on the other hand, have separate telehealth policies. For instance, the Norwegian Ministry of Health commissioned the Norwegian Centre for Telemedicine to foster telehealth services, while assuring "the necessary actions to secure a successful dissemination of the services" [28]. As such, countries with a specific national telehealth policy or strategy, apart from a national eHealth strategy, are accounted for as "stated" telehealth policy in our model. Although the term telehealth and eHealth are at times used interchangeably, they differ in the purpose of use. While telehealth indicates usage of ICT to promote long-distance care, eHealth indicates usage of ICT for health in general. For example, in the United States, before COVID-19, telehealth was only for people who needed

long-distance care due to limited access to nearby hospitals [29,30], while eHealth was widely applied to patients regardless of hospital accessibility. Accordingly, reimbursement on telehealth has not been prioritized or sufficiently instituted, as compared to that on general eHealth [30]. As such, telehealth, comparably, lacked clearly stated guidance before the pandemic.

Our control variables were selected based on the results of prior research that primarily focused on how the demographic, cultural, or political factors of a country affected COVID-19 infections [19-22]. The larger the scale of these countries' economies, the greater their potential for economic activities, such as job hunting and international exchanges, that increase the opportunities for infections. Thus, we included gross domestic product (GDP) at purchasing power parity (PPP) and unemployment rate as controls for the economic statuses of countries. Moreover, because several studies have indicated that high temperatures and humidity may influence the infection rate of COVID-19, we included annual rainfall and temperature as controls [31]. Similarly, we added other controls, such as the proportion of senior citizens, early implementation of a national lockdown, and population density, to our model, along with 2 culture-related variables, individualism and uncertainty avoidance. Overall, we selected additional control variables that are identified as important determinants of the spread of contagious viruses in the literature. Detailed explanations of our main variables and additional control variables are summarized in Table 1.

Table 1. Variable descriptions.

Variable name	Description (by country)	Source	Year measured
Dependent variable			
Total cases[a]	Number of individuals infected by COVID-19	Worldometers	2020
Fatality rate[a]	Death rate against the number of confirmed cases (0-100)	Worldometers	2020
Number of days[b]	Number of days elapsed from the first confirmed case to the 1000th confirmed case	Our World in Data	2020
Control variable			
GDP[c] PPP[d]	GDP by PPP in billions	World Bank	2019
Unemployment rate	Unemployment rate (0-100)	World Bank	2019
Population density	People per square km of land area	World Bank	2019
Percent aged 60 or over	Percentage of people aged 60 or older	United Nations	2019
Annual rainfall	Average annual rainfall in mm	World Bank	2019
Annual temperature	Average annual temperature in °C	World Bank	2019
Early lockdown	Implementation of a national lockdown within 1 month of the first confirmed case (dichotomous)	Wikipedia, Press	2020
Individualism	Cultural dimension score for preference for a loosely knit social framework in which individuals are expected to take care of only themselves and their immediate families (0-100)	Hofstede[e]	2015
Uncertainty avoidance	Cultural dimension score for degree to which the members of a society feel uncomfortable with uncertainty and ambiguity (0-100)	Hofstede	2015
ICT[f] infrastructure enabling physical distancing			
Credit card ownership	The percentage of respondents who report having a credit card (aged 15+)	World Bank	2017
Broadband speed	Broadband internet speed in Mbps	Ookla	2019
Medical ICT infrastructure and policy			
Telehealth policy (stated)	Country with a stated telehealth policy or strategy (1: yes, 0: otherwise)	World Health Organization	2015
Telehealth policy (implied)	Country with no specific telehealth policy or strategy but is referred in an overall eHealth policy or strategy (1: yes, 0: otherwise)	World Health Organization	2015
Government health websites	Government-supported health internet sites providing information (1: available, 0: not available)	World Health Organization	2015
Training ICT health	Institutions offering in-service training to health professionals on ICT for health (1: available, 0: not available)	World Health Organization	2015
National EHR[g]	Country with a national EHR (1: available, 0: not available)	World Health Organization	2015

[a]Data collected as of July 28, 2020.

[b]Data collected as of August 9, 2020.

[c]GDP: gross domestic product.

[d]PPP: purchasing power parity.

[e]Definitions for Hofstede variables were obtained online [32].

[f]ICT: information and communications technology.

[g]EHR: electronic health record.

Empirical Analysis

For each dependent variable, we specified our models as follows:

$$log\ (Total\ Cases_i) = \alpha_1 + \beta_{11} Control_i + \beta_{12} DistancingICT_i + \beta_{13} MedicalICT_i + \varepsilon_{1i} \quad \textbf{(1)}$$

$$Fatality\ Rate_i = \alpha_2 + \beta_{21}Control_i + \beta_{22}DistancingICT_i + \beta_{23}MedicalICT_i + \varepsilon_{2i} \quad \textbf{(2)}$$

$$log\ (Number\ of\ Daysi) = \alpha_3 + \beta_{31}Control_i + \beta_{32}DistancingICT_i + \beta_{33}MedicalICT_i + \varepsilon_{3i} \quad \textbf{(3)}$$

where *i* denotes an individual country.

For simplicity, an ordinary least squares estimator was used to estimate the coefficients. The variables of main interest were DistancingICT and MedicalICT. The positive coefficient values of DistancingICT and MedicalICT in equations 1 and 2 demonstrate that the variables increased the total number of confirmed cases and the fatality rate. In contrast, the positive coefficients of DistancingICT and MedicalICT in equation 3 represent a slower transmission speed. In all 3 models, we used the same set of control variables, including GDP PPP, unemployment rate, population density, elderly population ratio, annual rainfall, annual temperature, and early lockdown. For normality, we log transformed all the variables, including total cases and number of days, that displayed skewed distributions and were nonnegative.

For each dependent variable, our baseline model included all the main independent variables and controls, but without the 2 culture-related variables of individualism and uncertainty avoidance. In the second model, we added these culture-related variables to the baseline model. We performed this separate estimation because the content for the culture-related variables was not available for all 98 countries. Thus, adding them to the model reduced the sample size from 98 to 69. In the third model, we added several interaction terms to check for possible interaction effects between MedicalICT variables. To ensure that independent variables in the analysis were not correlated, we calculated variance inflation factor (VIF). All the independent variables had VIF values less than 10, which indicates no multicollinearity violations [33]. Lastly, robust standard errors were used to address any possible heteroskedastic error.

We also conducted a subsample analysis in which we removed countries with high population density. A prior study showed positive correlation between population density and COVID-19 infection [14]. Residents of densely populated countries inevitably have interactions and contacts with more people offline, whereas loosely populated countries can reduce such possibilities when the infrastructure is built up. Moreover, less populated countries may not have sufficient localized medical services, thus requiring more medical ICT infrastructure than other countries. The needs and utilization of ICT would significantly vary by population density as well. Thus, to determine if our results might be biased by the inclusion of countries with higher population density, we conducted an additional analysis with only countries with lower population density.

Results

Main Analysis

The descriptive statistics for the variables used in this analysis and their correlations are presented in Table 2 and Multimedia Appendix 1, respectively.

Table 2. Summary statistics.

Variable name	Mean (SD) value	Minimum value	Maximum value
Dependent variable			
Total cases, n (98 countries)	113,021.2 (464,974.3)	20	4,498,343
Fatality rate, % (95 countries)	3.32 (3.18)	0.05	15.26
Number of days, n (91 countries)	51.02 (29.30)	11	139
Control variables			
GDP[a] PPP[b], US $ billions (98 countries)	734.76 (2,290.02)	9.03	21,427.70
Unemployment rate, % (98 countries)	6.55 (4.68)	0.09	28.18
Population density, persons/km^2 (98 countries)	256.50 (919.32)	2.11	8737.02
Percentage aged 60 or older, % (98 countries)	15.32 (8.85)	3.19	34.02
Annual rainfall, mm (98 countries)	78.85 (54.56)	1.53	244.87
Annual temperature, °C (98 countries)	16.74 (8.57)	−4.97	29.29
Early lockdown, dichotomous (98 countries)	0.36 (0.48)	0	1
Individualism, numeric score (68 countries)	42.85 (23.57)	6	91
Uncertainty avoidance, numeric score (68 countries)	66.97 (22.67)	8	100
Distancing-enabling ICT[c] infrastructure			
Credit card ownership rate, % (98 countries)	21.23 (22.25)	0	83
Broadband speed, Mbps (98 countries)	45.47 (36.40)	4.18	191.93
Medical ICT infrastructure			
Telehealth policy (stated), dichotomous (98 countries)	0.22 (0.42)	0	1
Telehealth policy (implied), dichotomous (98 countries)	0.37 (0.49)	0	1
Government health websites, dichotomous (98 countries)	0.61 (0.49)	0	1
Training ICT health, dichotomous (98 countries)	0.82 (0.39)	0	1
National EHR[d], dichotomous (98 countries)	0.47 (0.50)	0	1

[a]GDP: gross domestic product.

[b]PPP: purchasing power parity.

[c]ICT: information and communications technology.

[d]EHR: electronic health record.

The results for regressions with robust standard error are shown in Tables 3-5. For each dependent variable (number of confirmed cases [Table 3], fatality rate [Table 4], and transmission speed [Table 5]), model 1 was the baseline model, while model 2 added culture-related variables as controls. Model 3 included all the control variables as well as the interaction effects between distancing ICT and medical ICT variables ($DistancingICT_i \times MedicalICT_i$). As mentioned above, in the case of *Number of Days*$_i$, countries with no reported cases of the 1000th infection as of July 28, 2020, were excluded from the analysis. As for the goodness of fit, R^2 for *Total Cases*$_i$ was higher than that for *Fatality Rate*$_i$ and *Number of Days*$_i$, indicating that the national characteristic variable used in the analysis explains the cumulative number of infected better than the 2 other dependent variables. For *Total Cases*$_i$, the R^2 values for the 3 models were 61.5%, 73.3%, and 75.4%, respectively. Considering that the R^2 averages of *Fatality Rate*$_i$ and *Number of Days*$_i$ were 44.5% and 37.0%, respectively, the overall explanatory power of the models for *Total Cases*$_i$ exceeded that of the 2 others. Therefore, national characteristics account for a significant portion of the differences in the cumulative number of confirmed cases by country.

Table 3. Main regression results for the full sample with the dependent variable log (total cases).

Variable	Model 1[a] (baseline model), regression coefficient (SE)	*P* value	Model 2[b] (including culture), regression coefficient (SE)	*P* value	Model 3[c] (interaction effects), regression coefficient (SE)	*P* value
General variable						
log (GDP[d] PPP[e])	1.136 (0.116)	<.001	1.124 (0.122)	<.001	1.104 (0.133)	<.001
Unemployment rate	0.033 (0.016)	.04	0.015 (0.018)	.40	0.019 (0.019)	.32
log (population density)	0.250 (0.129)	.06	0.278 (0.150)	.07	0.359 (0.162)	.03
Percentage aged 60 years or older	−0.027 (0.014)	.06	−0.054 (0.019)	.006	−0.055 (0.020)	.007
log (annual rainfall)	−0.253 (0.169)	.12	−0.023 (0.246)	.93	−0.115 (0.258)	.66
Annual temperature	−0.021 (0.012)	.07	−0.030 (0.015)	.06	−0.035 (0.016)	.03
Early lockdown	−0.018 (0.151)	.91	0.04 (0.158)	.80	−0.06 (0.179)	.74
Individualism	N/A[f]	N/A	0.005 (0.006)	.42	0.005 (0.006)	.37
Uncertainty avoidance	N/A	N/A	0.007 (0.004)	.08	0.006 (0.004)	.15
Distancing-enabling ICT[g] infrastructure						
Credit card ownership rate	−0.002 (0.005)	.64	0.0002 (0.005)	.97	−0.0002 (0.005)	.97
log (broadband speed)	0.068 (0.316)	.83	0.156 (0.335)	.64	0.104 (0.364)	.78
Medical ICT infrastructure						
Telehealth policy (stated)	0.055 (0.179)	.76	0.192 (0.191)	.32	0.861 (0.648)	.19
Telehealth policy (implied)	−0.003 (0.152)	.98	−0.098 (0.166)	.56	−0.13 (0.433)	.77
Government health websites	−0.221 (0.161)	.17	−0.440 (0.193)	.03	−0.675 (0.278)	.02
Training ICT health	0.174 (0.183)	.35	0.096 (0.205)	.64	0.276 (0.311)	.38
National EHR[h]	0.179 (0.137)	.20	0.094 (0.144)	.52	0.206 (0.231)	.38
Interaction						
Telehealth policy (stated)×government health websites	N/A	N/A	N/A	N/A	−0.049 (0.443)	.91
Telehealth policy (implied)×government health websites	N/A	N/A	N/A	N/A	0.527 (0.351)	.14
Telehealth policy (stated)×training ICT health	N/A	N/A	N/A	N/A	−0.567 (0.758)	.46
Telehealth policy (implied)×training ICT health	N/A	N/A	N/A	N/A	−0.241 (0.417)	.57
Telehealth policy (stated)×national EHR	N/A	N/A	N/A	N/A	−0.117 (0.442)	.79
Telehealth policy (implied)×national EHR	N/A	N/A	N/A	N/A	−0.25 (0.442)	.52
Constant	−8.285 (1.347)	<.001	−8.577 (1.579)	<.001	−8.140 (1.745)	<.001

[a]Model 1: 98 observations; R^2=0.615; adjusted R^2=0.55.

[b]Model 2: 69 observations; R^2=0.733; adjusted R^2=0.65.

[c]Model 3: 69 observations; R^2=0.754; adjusted R^2=0.64.

[d]GDP: gross domestic product.

[e]PPP: purchasing power parity.

[f]N/A: not applicable.

[g]ICT: information and communications technology.

[h]EHR: electronic health record.

Table 4. Main regression results for the full sample with the dependent variable fatality rate.

Variable	Model 1[a] (baseline model), regression coefficient (SE)	*P* value	Model 2[b] (including culture), regression coefficient (SE)	*P* value	Model 3[c] (interaction effects), regression coefficient (SE)	*P* value
General variable						
log (GDP[d] PPP[e])	1.635 (0.571)	.005	1.573 (0.670)	.02	1.993 (0.711)	.007
Unemployment rate	−0.042 (0.077)	.59	−0.019 (0.095)	.84	0.043 (0.099)	.67
log (population density)	0.036 (0.623)	.95	1.579 (0.805)	.06	1.962 (0.843)	.03
Percentage aged 60 or older	0.143 (0.07)	.04	0.045 (0.101)	.66	0.025 (0.103)	.81
log (annual rainfall)	0.198 (0.835)	.81	2.373 (1.325)	.08	2.224 (1.346)	.11
Annual temperature	−0.011 (0.058)	.85	−0.033 (0.082)	.69	−0.041 (0.082)	.62
Early lockdown	−0.617 (0.737)	.41	−1.000 (0.860)	.25	−0.535 (0.931)	.57
Individualism	N/A[f]	N/A	0.138 (0.031)	<.001	0.141 (0.031)	<.001
Uncertainty avoidance	N/A	N/A	0.034 (0.022)	.13	0.036 (0.022)	.11
Distancing-enabling ICT[g] infrastructure						
Credit card ownership rate	0.0002 (0.023)	.99	−0.057 (0.027)	.04	−0.074 (0.028)	.01
log (broadband speed)	−1.287 (1.513)	.40	−1.199 (1.799)	.51	−0.015 (1.893)	.99
Medical ICT infrastructure						
Telehealth policy (stated)	−0.715 (0.888)	.42	−1.093 (1.042)	.30	−1.03 (3.367)	.76
Telehealth policy (implied)	−1.176 (0.743)	.12	−2.684 (0.903)	.004	−6.231 (2.242)	.008
Government health websites	−0.053 (0.800)	.95	−1.721 (1.058)	.11	−2.985 (1.473)	.05
Training ICT health	−0.37 (0.904)	.68	−0.091 (1.100)	.93	0.029 (1.611)	.99
National EHR[h]	−0.508 (0.655)	.44	0.888 (0.780)	.26	−0.206 (1.208)	.87
Interaction						
Telehealth policy (stated)×government health websites	N/A	N/A	N/A	N/A	2.896 (2.315)	.22
Telehealth policy (implied)×government health websites	N/A	N/A	N/A	N/A	1.7 (1.832)	.36
Telehealth policy (stated)×training ICT health	N/A	N/A	N/A	N/A	−0.595 (3.934)	.88
Telehealth policy (implied)×training ICT health	N/A	N/A	N/A	N/A	1.654 (2.162)	.45
Telehealth policy (stated)×national EHR	N/A	N/A	N/A	N/A	−1.256 (2.293)	.59
Telehealth policy (implied)×national EHR	N/A	N/A	N/A	N/A	3.419 (2.009)	.10
Constant	−13.999 (6.791)	.04	−24.255 (8.600)	.007	−30.459 (9.241)	.002

[a]Model 1: 95 observations; R^2=0.271; adjusted R^2=0.143.

[b]Model 2: 68 observations; R^2=0.496; adjusted R^2=0.338.

[c]Model 3: 68 observations; R^2=0.569; adjusted R^2=0.358.

[d]GDP: gross domestic product.

[e]PPP: purchasing power parity.

[f]N/A: not applicable.

[g]ICT: information and communications technology.

[h]EHR: electronic health record.

Table 5. Main regression results for the full sample with the dependent variable log (number of days).

Variable	Model 1[a] (baseline model), regression coefficient (SE)	*P* value	Model 2[b] (including culture), regression coefficient (SE)	*P* value	Model 3[c] (interaction effects), regression coefficient (SE)	*P* value
General variable						
log (GDP[d] PPP[e])	−0.130 (0.044)	.005	−0.08 (0.055)	.15	−0.061 (0.058)	.29
Unemployment rate	−0.001 (0.006)	.84	−0.001 (0.007)	.87	0.004 (0.008)	.61
log (population density)	−0.068 (0.047)	.16	−0.089 (0.064)	.17	−0.079 (0.066)	.24
Percentage aged 60 or older	0.005 (0.005)	.30	0.01 (0.008)	.23	0.003 (0.008)	.71
log (annual rainfall)	0.032 (0.063)	.62	−0.05 (0.104)	.63	−0.057 (0.105)	.59
Annual temperature	0.010 (0.005)	.03	0.008 (0.007)	.21	0.006 (0.007)	.36
Early lockdown	−0.096 (0.055)	.09	−0.118 (0.069)	.09	−0.118 (0.075)	.13
Individualism	N/A[f]	N/A	−0.002 (0.002)	.46	−0.002 (0.002)	.46
Uncertainty avoidance	N/A	N/A	−0.003 (0.002)	.17	−0.002 (0.002)	.26
Distancing-enabling ICT[g] infrastructure						
Credit card ownership rate	−0.0003 (0.002)	.88	−0.001 (0.002)	.56	0.0004 (0.002)	.88
log (broadband speed)	−0.125 (0.113)	.27	−0.208 (0.140)	.14	−0.260 (0.146)	.08
Medical ICT infrastructure						
Telehealth policy (stated)	0.002 (0.066)	.98	0.009 (0.081)	.91	−0.328 (0.260)	.21
Telehealth policy (implied)	0.001 (0.055)	.99	0.042 (0.071)	.56	−0.357 (0.183)	.06
Government health websites	0.017 (0.061)	.78	0.047 (0.085)	.59	0.067 (0.117)	.57
Training ICT health	0.055 (0.070)	.44	0.042 (0.091)	.65	−0.203 (0.128)	.12
National EHR[h]	−0.029 (0.049)	.55	0.018 (0.062)	.77	0.038 (0.096)	.70
Interaction						
Telehealth policy (stated)×government health websites	N/A	N/A	N/A	N/A	−0.015 (0.183)	.94
Telehealth policy (implied)×government health websites	N/A	N/A	N/A	N/A	0.02 (0.144)	.89
Telehealth policy (stated)×training ICT health	N/A	N/A	N/A	N/A	0.415 (0.304)	.18
Telehealth policy (implied)×training ICT health	N/A	N/A	N/A	N/A	0.506 (0.188)	.01
Telehealth policy (stated)×national EHR	N/A	N/A	N/A	N/A	−0.013 (0.178)	.94
Telehealth policy (implied)×national EHR	N/A	N/A	N/A	N/A	−0.107 (0.159)	.50
Constant	3.131 (0.520)	<.001	3.078 (0.690)	<.001	3.163 (0.723)	<.001

[a]Model 1: 91 observations; R^2=0.341; adjusted R^2=0.219.

[b]Model 2: 65 observations; R^2=0.329; adjusted R^2=0.105.

[c]Model 3: 65 observations; R^2=0.440; adjusted R^2=0.146.

[d]GDP: gross domestic product.

[e]PPP: purchasing power parity.

[f]N/A: not applicable.

[g]ICT: information and communications technology.

[h]EHR: electronic health record.

Our results suggest that medical ICT policy, rather than the ICT infrastructure itself, is negatively associated with the fatality rate. For example, the coefficient for implied telehealth policy was −2.684 and significant (*P*=.004) (Table 4), that is, the fatality rate for countries with an implied telehealth policy was lower than that for others by 2.7 percentage points. Moreover,

the coefficient for the rate of credit card ownership was −0.057 and significant (*P*=.04) (Table 4), suggesting that credit card usage could have lessened the fatality rate. However, broadband internet speed was not associated with any of the 3 measures of transmission of COVID-19. Lastly, the presence of a government-run health website showed a negative and significant relationship with the total number of confirmed cases (β=−0.440; *P*=.03) (Table 3). This implies that countries with government-run health websites had 36% fewer confirmed cases than those without it.

The effects of DistancingICT and MedicalICT on the transmission speed of COVID-19 were not statistically significant. For the interaction terms, although most coefficients were insignificant, the interaction between implied telehealth policy and training ICT health was significant (β=0.506; *P*=.01) (Table 5). Therefore, an implied telehealth policy may be more effective when in-service training on ICT is provided to health professionals (β=−0.357+0.506=0.149).

Despite this not being the main focus of the study, it would be meaningful to examine the effects of other control variables in light of the lack of country-level empirical studies on the spread of COVID-19. Interestingly, early lockdowns, contrary to expectations, were statistically uncorrelated with the total number of infections and the fatality rate. Moreover, the coefficients for GDP with the total number of confirmed cases and the fatality rate were 1.136 (*P*<.001) and 1.635 (*P*=.005), respectively (Table 4). Population density was positively associated with the total number of cases and the fatality rate, but temperature was negatively associated with the total number of infections. Lastly, the ratio of the elderly population and the total number of infections showed a negative relationship (β=−0.027; *P*=.06) (Table 3).

As for the cultural dimensions of COVID-19, our results suggested no significant relationship between the fatality rate and uncertainty avoidance, 1 of the 2 cultural dimensions from Hofstede Insights. However, individuals' tendency to care only for themselves and their immediate family, as represented by individualism, showed a positive relationship with the fatality rate (β=0.138; *P*<.001) (Table 4).

Additional Analysis

Although it has not been long since the COVID-19 outbreak and the transmission mechanism of the virus has not yet been clarified, it is apparent that human-to-human interaction increases the risk of infection [14,34]. Moreover, prior research has found a positive association between dense populations and infection rates [14], possibly because high density enhances the probability of an individual's exposure to the virus. However, people in such areas could be more aware of the risk, consequently taking precautions or complying with government regulations to avoid an epidemic. Moreover, highly concentrated urbanization is more likely to offer entrenched contact-free systems (eg, delivery and retail kiosks) than less populated regions, thus stagnating or reducing the spread of the virus. As such, the effect of DistancingICT or MedicalICT may vary substantially between countries with high and low population densities. Therefore, we conducted a further regression analysis on countries outside of the top 30% in population density in our sample. The results of the further analysis are shown in Tables S1-3 in Multimedia Appendix 2.

The key results are not remarkably different. Telehealth policy, rather than technology itself, may promote efficient management of COVID-19's aftermath regardless of population density. Unlike other national traits, the presence of telehealth policy (stated and implied) showed a negative association with the fatality rate when we omitted countries in the top 30% of population density from our sample. These consistent results highlight the importance of telehealth policy development in infection containment. However, it is noteworthy that credit card ownership was no longer significant. It is conceivable that countries with lower population density also have lesser rates of offline physical interaction, thus lowering the need for credit cards and online shopping.

Discussion

Principal Findings

In this study, we conducted exploratory research on the role of national characteristics, especially in regard to ICT and medical ICT infrastructure and concomitant policies that enable physical distancing, in the cumulative number of confirmed cases, fatality rates, and initial transmission speed of COVID-19. The findings suggested that medical ICT policies, especially when in-service training on ICT is provided, could potentially reduce the fatality rate. Government health websites were negatively associated with the total number of confirmed cases. Moreover, possession of a credit card was observed to decrease the fatality rate.

Discussion of the Findings

The analysis results countered general intuition that ICT infrastructure should play a crucial role in slowing COVID-19 transmission. Overall, we found that the relationship between ICT infrastructure and COVID-19 infection or its consequences was less than expected. Nevertheless, there are some important findings to highlight.

First, the presence of a telehealth policy manifested a negative correlation with the fatality rate. Surprisingly, only implied telehealth policy, but not stated telehealth policy, showed a statistically significant correlation with the fatality rate. This raises the possibility that an implied telehealth policy may be more effective than a stated one because setting specific guidelines as in a stated policy sets boundaries that hinder clinicians' flexible decision-making or system utilization in a crisis [35]. The result remained consistent even when countries with high population concentrations were excluded. Moreover, it is important to note that the telehealth policy becomes more relevant when in-service training on ICT is provided. Such an interaction result is aligned with WHO Digital Health Guidelines that state "Extensive training on the technology and operating the device should be done before introducing the system for use directly with clients" [36]. It is also notable that government health websites had a negative and significant relationship with the total number of confirmed cases. Consistent with preceding studies [37,38], it advocates governmental online communication in case of disease outbreaks to facilitate efficient interconnection between specialists from various fields.

Otherwise, prompt and precise communication attempts by the government could enhance information transparency and build trust among the public, increasing the likelihood of public compliance with suggested guidelines including vaccine acceptance [39].

Second, our findings suggest that possession of a credit card, a widely used payment method for e-commerce [25,26], is related to a lower fatality rate. The results varied when countries with higher population density were omitted; this could happen because of either uneven development of contact-free systems in areas of lower density or prevention of crowding through widespread interventions such as contact tracing [40]. Nonetheless, such a finding denotes how credit card ownership facilitates distancing compliance via online commerce. Alternatively, credit cards could have advanced financial inclusion and cushioned the financial burden even in challenging times. For instance, cardholders, especially those with a low income, have benefited from financial assistance programs, including deferred payments, waived late fees, and even skipped payments, from credit card issuers [41]. With financial assistance, perceived burden would have been decreased, fostering adherence to suggested guidelines [42].

Third, we had interesting findings from the control variables on the spread of COVID-19 and its aftermath. Early lockdown enforcement displayed no relationship with COVID-19 transmission, although policymakers intuitively assumed that compulsory restriction of contacts would be helpful in diminishing the total number of infections, fatality rate, and speed of transmission. Such intuitions are inferred from their actions to tighten stay-at-home restrictions [27]. Our result is consistent with the outcome of a preceding analysis that stated infection control was apparently effective before the mandate, and thus, voluntary social behavior, rather than legal enforcement, is more crucial in combating a pandemic [43,44].

Stronger individualistic culture exhibited a higher fatality rate, whereas uncertainty avoidance showed no association with the fatality rate. Related to individualism, a recent study clarified the role of individualism-collectivism on the perceived risk of COVID-19 and sense of responsibility [45]. In essence, individuals with strong collectivistic orientation perceived greater fear because of their higher physical and social interconnection with others [45]. Moreover, collectivism-oriented people, due to their strong sense of integrity and responsibility within the society, were willing to follow containment guidelines, whereas individualism-oriented people were not willing to follow guidelines [46]. This finding is in line with preceding research that identified a relationship between pathogen risk and societal individualism [47]. Societal collectivism, which is more prevalent in Eastern cultures, did "[serve] as a natural guard against disease transmission" [48].

A previous study also revealed that countries with relatively high uncertainty avoidance were less likely to engage in public gathering, potentially decreasing the number of infections and the fatality rate [21]. However, in this study, such an effect was not observed. The discrepancy could stem from different data collection periods. Huynh conducted an analysis at the initial stage of COVID-19, from February 16, 2020, to March 29, 2020 [21], but we used COVID-19 transmission data until July 28, 2020. It is challenging to refrain from public gatherings for several months; the impact of uncertainty avoidance would be weakened eventually.

The analysis result indicates that GDP is positively related to the number of total cases and the fatality rate. It is plausible that economically active countries, as represented by higher GDP, involve more interactions between individuals, causing an inevitable increase in the number of infections. Alternatively, in larger economies, the number of confirmed cases may reflect better testing because these countries have the economic capacity to conduct more tests. Lastly, a higher proportion of the elderly population was correlated with a fewer number of infections in total. The perceived risk of infection among elders might have influenced stay-at-home compliance, thus reducing physical contact and infections.

Implications for Research and Practice

The results of this study have several implications. Theoretically, the findings contribute to the effect of ICT infrastructure and policy in epidemics. Prior studies have examined ICT adoption intention of health care workers or how ICT use improves public health or physical wellness in general [49-52]. Moreover, past research on ICT and health have paid attention to how ICT mitigates various health-related challenges by providing access to health-related information and fostering communication between patients and physicians [53-55]. For example, previous research found that telephone usage for health care lowered depression rates [53] and increased immunization rates [54]. However, they rarely showed interest for ICT use in the context of epidemics, possibly due to its unlikelihood. Similarly, previous research on ICT policy in health care mainly focused on the "limitations concerning design and implementation of policies" of public health improvement. Considering that ICT, by its nature, enables faster communication to the public, it is surprising that the effect of ICT on epidemics, which are widespread and abrupt, was not investigated sufficiently. In this study, we have addressed this void by examining the relationship of ICT policy with total cases, fatality rate, and transmission speed under the pandemic circumstance. Therefore, by expanding the scope of the role of ICT on people's health, this study contributes to the literature on ICT and health-related challenges.

Practically, this study advocates autonomous use of medical ICT, rather than playing it by the book. Contrary to the assumption that detailed and rigorous policy statements limit or prevent a wide range of health threats, such as smoking habits and cardiovascular diseases [56,57], the findings indicate that stated medical ICT policy is in fact less likely to taper the fatality rate than implied medical ICT policy. It is plausible that relatively less restrictions are helpful for better medical services because for jobs with high variety tasks, such as medical practice, increased autonomy boosts the job performance of workers [58]. This finding is relevant in the broader context of the digital health field and provides significant empirical insights that could improve the outcome of long-distance medical care and guide future clinical decision support system (CDSS)-related strategies. This finding is aligned with WHO guidelines, which

suggest that "health workers may deviate from the recommendations" of a CDSS based on physicians' own rationale [36], although an algorithm-based CDSS is conventionally perceived as competent. As such, policymakers need to consider the independent and flexible decision-making of physicians in the context of medical ICT usage.

Regarding distancing-enabling infrastructure, this study showed that the government should prioritize providing ICT infrastructure that enables physical distancing in densely populated areas. As the budget for ICT infrastructure is limited, the government should strategically allocate funds to achieve the greatest benefit. Especially, strategic budgeting is vital in developing countries where tax revenue is relatively insufficient. Because our findings show that differences in population density yield different outcomes of ICT implementation, governors can consider investing in populous areas first, in order to maximize the benefit with limited resources.

Conclusions

Despite our findings on the relationship between national characteristics and disease dispersion, our study is not without limitations. Although we included most established countries, we were not able to include all countries in our analysis. Consequently, the sample size for regression was small. In addition, the data for medical ICT infrastructure and the rate of credit card ownership were not up-to-date. Therefore, their impacts during the observation period may not have been accurately estimated. However, it is important to note that ICT policy and infrastructure have a delayed "lag" effect on country-level outcomes because people need to adopt, trust, and alter their behaviors in line with new technologies and policies [59]. For instance, a recent study on the role of ICT in women's health outcomes showed that the maternal fatality rate was lowered while modern medical care seeking behavior increased after kiosks were implemented and used for some years [59]. In addition, although we included broadband speed in the model, broadband coverage may also play a distinct role. For instance, high broadband speed offers fast communication online, advocating real-time information sharing in dire situations such as COVID-19 [9]. On the other hand, broadband coverage enables seamless internet connectivity with personal devices; when individuals get out of the service range at some point, they would not get broadband access. While lack of decent broadband coverage indicates inability to use the internet, lack of decent broadband speed denotes unattainability of prompt communication with others. Nevertheless, the correlation between broadband coverage and speed was high (correlation=0.79). Accordingly, only one of them was used for our analysis to avoid a multicollinearity problem. Moreover, there are other potential confounders, such as mask adherence, that were not included in our study. However, we believe that our culture-related variables, such as individualism and uncertainty avoidance, may account for such confounders [60]. Lastly, because the COVID-19 pandemic has not ended, the long-term effect of ICT infrastructure and ICT policies could not be examined.

By conducting an analysis at the country level, we ensured the generalizability of our work and developed tentative guidelines to control the spread of infectious diseases. We have especially emphasized the importance of medical telehealth policies that contribute to reduce the consequences of COVID-19. By collecting updated COVID-19 data, future research can clarify the long-term effects of the aforementioned national traits. We hope that this study will broaden the scope of research on the impact of ICT infrastructure and policies, and give guidance for better policy-making in the health care domain.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Pairwise correlations (N=98).
[DOCX File , 21 KB - publichealth_v8i1e31066_app1.docx]

Multimedia Appendix 2
Regression results for the sample with less population density (lower 70%).
[DOCX File , 40 KB - publichealth_v8i1e31066_app2.docx]

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Abbreviations

CDSS: clinical decision support system
DistancingICT: distancing-enabling ICT infrastructure
EHR: electronic health record
GDP: gross domestic product
ICT: information and communications technology
MedicalICT: medical ICT infrastructure and policy
OWID: Our World in Data
PPP: purchasing power parity
VIF: variance inflation factor
WHO: World Health Organization

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Original Paper

Has Omicron Changed the Evolution of the Pandemic?

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Abstract

Background: Variants of the SARS-CoV-2 virus carry differential risks to public health. The Omicron (B.1.1.529) variant, first identified in Botswana on November 11, 2021, has spread globally faster than any previous variant of concern. Understanding the transmissibility of Omicron is vital in the development of public health policy.

Objective: The aim of this study is to compare SARS-CoV-2 outbreaks driven by Omicron to those driven by prior variants of concern in terms of both the speed and magnitude of an outbreak.

Methods: We analyzed trends in outbreaks by variant of concern with validated surveillance metrics in several southern African countries. The region offers an ideal setting for a natural experiment given that most outbreaks thus far have been driven primarily by a single variant at a time. With a daily longitudinal data set of new infections, total vaccinations, and cumulative infections in countries in sub-Saharan Africa, we estimated how the emergence of Omicron has altered the trajectory of SARS-CoV-2 outbreaks. We used the Arellano-Bond method to estimate regression coefficients from a dynamic panel model, in which new infections are a function of infections yesterday and last week. We controlled for vaccinations and prior infections in the population. To test whether Omicron has changed the average trajectory of a SARS-CoV-2 outbreak, we included an interaction between an indicator variable for the emergence of Omicron and lagged infections.

Results: The observed Omicron outbreaks in this study reach the outbreak threshold within 5-10 days after first detection, whereas other variants of concern have taken at least 14 days and up to as many as 35 days. The Omicron outbreaks also reach peak rates of new cases that are roughly 1.5-2 times those of prior variants of concern. Dynamic panel regression estimates confirm Omicron has created a statistically significant shift in viral spread.

Conclusions: The transmissibility of Omicron is markedly higher than prior variants of concern. At the population level, the Omicron outbreaks occurred more quickly and with larger magnitude, despite substantial increases in vaccinations and prior

infections, which should have otherwise reduced susceptibility to new infections. Unless public health policies are substantially altered, Omicron outbreaks in other countries are likely to occur with little warning.

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KEYWORDS

Omicron; SARS-CoV-2; public health surveillance; VOC; variant of concern; Delta; Beta; COVID-19; sub-Saharan Africa; public health; pandemic; epidemiology

Introduction

Background

The Omicron (B.1.1.529) variant was identified in Botswana on November 11, 2021 [1]. This novel variant has an unprecedented average of 50 mutations, including around 30 mutations in the spike protein. In vitro studies and epidemiological surveys suggest that Omicron is able to spread more rapidly, but more information is needed to define transmission rates, determine if it evades vaccine-elicited or natural immunity, and determine if it influences disease severity or pathogenesis [2]. More data are needed to fill in these critical knowledge gaps to best inform public health practices as Omicron continues to spread [3].

Omicron Compared to Other Variants

After the first cases of Omicron were identified in Botswana, it first spread to several countries in sub-Saharan Africa (SSA) and has since spread globally [4]. Since then, Omicron has been identified in more than 140 countries [5,6]. Preliminary investigations estimate that Omicron may have infected 3-6 times as many people as the Delta variant over this same time period [3,7-10]. Given that most outbreaks of new variants have occurred during periods of low incidence, it is hard to estimate how Omicron will behave in competition with other variants in regions of high incidence. Preliminary data from Europe suggest Omicron may outcompete Delta, though it is unclear if these variants are targeting the same population [11]. Specifically, it is not clear if vaccinations or prior infections impact the infectivity and/or transmissibility of Omicron to the same extent as other variants. Although viral reproduction rates may provide some proxy of transmission risk, no studies have yet been completed that stratify Omicron's risk in different populations. To that end, this study employs surveillance data and empirically tested transmission metrics in the first countries to experience outbreaks in SSA to determine how Omicron compares to the first wave of SARS-CoV-2 virus as well as its subsequent variants of concern, including Alpha, Beta, and Delta.

Variants of Concern

Since late 2020, variants of the SARS-CoV-2 virus that pose increased risks have been identified, named, and monitored [12]. A variant that poses increased risk to human health is classified as a variant of interest (VOI) if it has genetic changes that affect transmission, severity, immune system protection, or treatment effectiveness and is associated with community spread [12]. VOIs that result in an increase in transmissibility or disease severity, or that are not controlled through public health, vaccination, or medical therapy interventions, are designated as variants of concern (VOC) [12]. Since May 2021, VOIs and VOCs have been named by the World Health Organization using the Greek alphabet. One VOC, Beta, originated in SSA, with the earliest documented sample in South Africa in May 2020. VOC designation was not declared for the Beta variant until December 18, 2020 [12]. The most recent VOC, Omicron, was identified in multiple locations in November 2021 and was officially designated a VOC on November 26, 2021 [12].

Omicron in Southern African Countries

Since its debut more than 2 months ago, Omicron has been sequenced all over the world and appears to be responsible for driving several outbreaks of SARS-CoV-2 or causing existing outbreaks to accelerate [13,14]. Because the acceleration of daily transmissions has often been driven by multiple variants within a given country's outbreak, such as in the case of the United States or the United Kingdom [15-17], it is difficult to disentangle the individual burden each variant places on a given population [18].

On November 11, 2021, the date that Omicron was first sequenced in Botswana, the rate of new SARS-CoV-2 transmissions in the United Kingdom was 34,427 cases per day. Estimates are based on a 7-day moving average, or a rate of 50.47 daily new cases per 100,000 population [4]. This transmission rate is more than 5 times that of an outbreak; the Centers for Disease Control and Prevention (CDC) defines an outbreak as 10 daily new cases per 100,000 population. Omicron was identified in the United Kingdom while they were already in the middle of an outbreak that involved other VOCs. Conversely, with the exception of Botswana, none of the countries in the south of SSA were in an outbreak. In fact, the average daily speed for SSA or daily new transmissions was 0.17 per 100,000 population, and that rate was decelerating by 0.08 cases per day during the week that Omicron was first sequenced in Botswana. This is consistent with previously reported outbreaks in most SSA countries, which occurred at periods of low incidence and thus were driven largely by one variant at a time. Therefore, SSA countries provide an opportunity to understand how Omicron affects an entire population compared to other VOCs without having to differentiate the involvement of other variants within an outbreak.

Objective

The objective of this study is to examine the status of the SARS-CoV-2 pandemic in SSA and to model novel transmission metrics to determine if Omicron is more transmissible than other VOCs.

Methods

Novel Surveillance Metrics

This report will present both standard and new validated surveillance and transmission metrics [19-29] on the status of the SARS-CoV-2 pandemic in SSA countries over the past 3 weeks. The Foundation for Innovative New Diagnostics [30] compiles data from multiple sources across individual websites, statistical reports, and press releases; data for the most recent 8 weeks were accessed from the GitHub repository [31]. This produced a panel of 47 countries with 120 days for each country (n=5640). An empirical difference equation was specified in which the number of positive cases in each country at each day is a function of the prior number of cases and weekly shift variables that measure whether the contagion was growing faster/slower/at the same rate compared to the previous weeks. The dynamic panel model was estimated using the generalized method of moments approach by implementing the Arellano-Bond estimator in R (version 4.1.1; R Foundation for Statistical Computing) with the *plm* package (version 2.4-1) [32,33].

Arellano-Bond estimation of difference equations has several statistical advantages over R naught [26,28,34-38]: (1) it allows for statistical examination of the model's predictive ability and the validity of the model specification, (2) it corrects for autocorrelation and heteroscedasticity, (3) it has good properties for data with a small number of time periods and large number of countries, and (4) it corrects for omitted variable issues and provides a statistical test of correction validity. With these advantages, the method is applicable to ascertain and statistically validate changes in the evolution of the pandemic within a period of a week or less, including changes in the reproduction rate [27]. Empirically, we validated this technique based on the predictive ability of past data that resulted in the derivation of speed, acceleration, jerk, and 7-day persistence, which follow the definitions and methods described by Oehmke and colleagues [27,34].

Traditional surveillance indicators include total cases and deaths, 7-day moving average of new cases, and 7-day moving average of deaths. Enhanced surveillance metrics [26-28] 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 the day-over-day change in the speed of infection), (3) jerk (the week-over-week change in the acceleration rate of transmissions), and (4) seven-day persistence effect on speed, which refers to the number of new cases reported today that are statistically attributable to new cases reported 7 days ago. We measure the transmission inflation factor by dividing the rate of new cases each week by the rate of new cases on December 3 [4]. Although standard surveillance metrics identify the presence and severity of an outbreak, they do not explain whether an outbreak is contracting, escalating, or imminent. Our additional transmission metrics do.

We also used an extension of the sample to examine how Omicron may have shifted the evolution of the pandemic. To compare Omicron outbreaks to those caused by earlier VOCs, we also included Arellano-Bond estimates for the entire year of 2021. We controlled for cumulative vaccinations and infections because SSA countries had far fewer vaccinations and infections at the time of earlier outbreaks compared to the current Omicron outbreaks. An interaction term between an indicator for the emergence of Omicron with the 1- and 7-day lags of cases provides a test for whether Omicron has shifted the nature of persistence in the pandemic.

Publicly Available Molecular Data

Data on the number of sequenced variants over time per country were obtained from publicly available sequences in Global Initiative on Sharing Avian Influenza Data (GISAID) [39]. We collected clade designations from sequences using Nextclade nomenclature [40] and lineage designations using Pangolin nomenclature for SARS-CoV-2 [41,42]. Additionally, we contrasted prevalence data with the compiled data available in outbreak.info [43].

Modeling

We first plotted the spike in cases by variant and country. To compare trends in the rate of new infections under each variant, we standardized the point at which a country eclipses the CDC threshold of an outbreak as day 0. Within each country, we followed the rate of SARS-CoV-2 infections in the 4 weeks up to an outbreak threshold and in the 4 weeks afterward, subject to the limits of the most recent available data. This standardization allows for a comparison of the speed, acceleration, and magnitude of the Omicron outbreaks relative to those driven by earlier VOCs.

Because these trend comparisons do not control for differences in population vaccinations and prior infections during the various outbreaks, we added these mediators as control variables in a dynamic panel regression. We modeled the rate of new infections as a function of infections on the previous day and previous week. These lagged infection rates measure persistence in the pandemic, or the extent to which cases today echo forward into tomorrow and next week.

The model contains an indicator variable equal to 1 if the calendar date was on or after November 1, 2021, and equal to 0 if the calendar date was earlier. This indicator is meant to capture a conservative estimate of the time window in which the Omicron variant originated. Interactions between this indicator and infections on the previous day and week provide a test for whether Omicron shifted the trajectory of the pandemic. The model also controlled for cumulative vaccinations and infections in the country population, and included an indicator for weekend dates, which are subject to spotty data reports.

We used the Arellano-Bond estimator to generate coefficient estimates, along with their standard errors, for a sample period covering January 1, 2021, through December 31, 2021. This time period covers the recent Omicron outbreaks as well as outbreaks driven by other VOCs.

Results

Table 1 provides standard surveillance metrics along with our novel metrics of transmission for 7 data points between December 3, 2021, and January 17, 2022. For a complete surveillance and transmission table that includes daily figures for all SSA countries over the past 7 weeks, current through January 17, 2021, please refer to Multimedia Appendix 1 [4].

The daily speed of the pandemic is defined as the number of new cases per day per 100,000 population. If we use the CDC threshold for an outbreak or a threshold of 10 daily new cases per 100,000 population, these eight countries in our study group were in an outbreak sometime between December 3, 2021, and January 17, 2022: Botswana, Eswatini (formerly known as Swaziland), Gabon, Lesotho, Namibia, South Africa, Zambia, and Zimbabwe (Figure 1) [4]. In the truncated Table 1, we excluded Cabo Verde, Comoros, and Seychelles because outbreaks in small densely populated island nations included other VOCs when Omicron entered into the equation. Although Zambia, Namibia, and Botswana currently remain in an outbreak (with a daily rate of new cases per 100,000 population of 11.6, 13.5, and 46.6, respectively), Gabon, Lesotho, South Africa, Eswatini, and Zimbabwe's outbreaks have ended and continue to cycle down at a daily rate of 7.6, 6.3, 9.1, 7.4, and 4.1, respectively.

To put the outbreaks in perspective, we standardized the data using December 3, 2021, as the base rate of daily cases. The inflation factor is the rate of new cases on any given day divided by the base rate on December 3, 2021. By early December, Omicron was driving the escalation of new cases in sub-Saharan countries. Eswatini and South Africa's Omicron escalation of cases were first to develop and they are the only two countries whose baselines have returned to their December 3, 2021, baselines. The rate of new cases increased for Botswana, Gabon, Lesotho, Namibia, South Africa, Eswatini, Zambia, and Zimbabwe at their apex in the outbreak by 26.8-fold, 22.4-fold, 39.7-fold, 24.9-fold, 3.4-fold, 12.2-fold, 176-fold, and 31.9-fold, respectively.

Our novel transmission metric, 7-day persistence, is based on a 120-day panel of data and measures the number of new cases per day per 100,000 that are a function of novel infections 7 days earlier. Essentially, it measures how outbreaks and transmissions echo forward. Measuring the persistence rate of SARS-CoV-2 avoids the limitations and data bias in the measurement of R naught, such as sampling error and missing data [26,27]. It is the echoing forward of transmissions that explains the underlying condition that causes a clustering of new cases. Persistence is a transmission metric that is the first to signal a potential outbreak because it is based on 120 days of data versus the 7 days used in standard surveillance. As an example, Botswana showed an upward trend in persistence 2 weeks before its Omicron outbreak had reached the CDC threshold of 10 cases per 100,000 population (Table 1). The increase in speed itself only became evident about 7 days before the threshold was reached. Persistence continues to increase for an additional week after the apex of the outbreak as it is the echo forward of cases.

Our model also calculates the weekly rate of acceleration and jerk. The acceleration rate helps to identify countries that are at the beginning, middle, or end of an outbreak, even if a country still has relatively few new SARS-CoV-2 cases per day. In addition, these transmission metrics can inform when a spike in cases is still accelerating and at risk for exponential growth or when an outbreak is slowing, reaching its apex, or decelerating from day to day, whereas the jerk measures shifts in the rates of acceleration week over week.

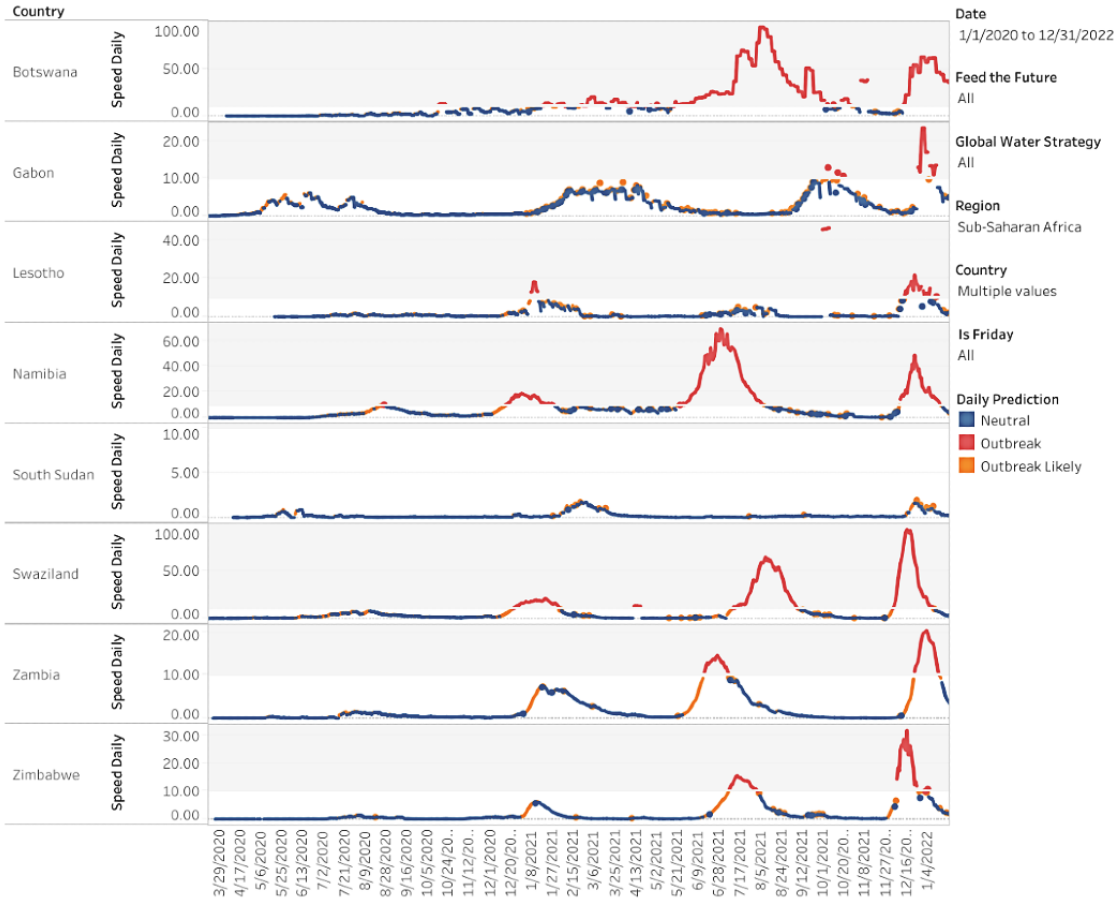
Exponential growth measures the expansion and contraction of the outbreak. At their zenith, Eswatini and Namibia had the largest weeks of exponential growth at 454.8 and 268.1, respectively.

Table 1. Standard and novel surveillance metrics for the first countries to experience an Omicron-only outbreak, December 3, 2021-January 17, 2022.

Country and date	New cases 7-day moving average	New cases/100,000 7-day moving average	Inflation factor	7-day persistence	Acceleration weekly	Jerk weekly	Exponential growth potential weekly
Botswana							
3-Dec-2021	56	2.3	1.0	1.0	–3.0	8.7	–7.0
10-Dec-2021	113	4.7	2.0	3.9	16.5	19.4	23.3
17-Dec-2021	539	22.5	9.6	5.6	124.6	108.1	140.0
24-Dec-2021	1304	54.4	23.2	30.0	223.4	98.9	291.7
31-Dec-2021	1502	62.7	26.8	73.2	57.8	–165.6	159.2
7-Jan-2022	1478	61.7	26.3	85.2	–7.0	–64.8	–55.2
14-Jan-2022	1118	46.6	19.9	30.4	–105.2	–98.2	–185.3
Gabon							
3-Dec-2021	24	1.1	1.0	0.6	–4.9	–1.6	–6.0
10-Dec-2021	23	1.0	1.0	1.7	–0.4	4.6	–1.6
17-Dec-2021	27	1.2	1.1	1.2	1.4	1.8	3.4
24-Dec-2021	42	1.9	1.8	1.6	4.6	3.2	7.7
31-Dec-2021	537	23.6	22.4	2.5	152.0	147.4	158.3
7-Jan-2022	306	13.4	12.7	32.2	–71.0	–223.0	–81.7
14-Jan-2022	173	7.6	7.2	6.6	–40.7	30.3	–46.6
Lesotho							
3-Dec-2021	12	0.5	1.0	0.1	2.5	2.9	3.1
10-Dec-2021	87	4.0	7.3	0.9	24.4	21.9	26.3
17-Dec-2021	264	12.2	22.3	4.7	57.4	33.0	70.2
24-Dec-2021	471	21.8	39.7	16.1	67.0	9.6	101.2
31-Dec-2021	116	5.4	9.8	29.0	–115.0	–182.1	–65.8
7-Jan-2022	320	14.8	27.0	7.2	66.2	181.3	83.0
14-Jan-2022	136	6.3	11.5	7.2	–59.7	–126.0	–51.4
Namibia							
3-Dec-2021	51	2.0	1.0	0.1	10.9	9.5	12.3
10-Dec-2021	246	9.5	4.8	3.3	52.8	41.9	59.3
17-Dec-2021	495	19.1	9.7	11.2	67.3	14.6	94.9
24-Dec-2021	1269	49.0	24.9	25.5	209.4	142.1	268.1
31-Dec-2021	628	24.3	12.3	65.9	–173.3	–382.7	–171.6
7-Jan-2022	506	19.6	9.9	33.0	–33.0	140.3	–67.3
14-Jan-2022	350	13.5	6.9	9.6	–42.2	–9.1	–63.2
South Africa							
3-Dec-2021	6982	11.6	1.0	2.2	67.3	58.1	74.0
10-Dec-2021	15,467	25.8	2.2	19.1	98.9	31.6	133.6
17-Dec-2021	23,437	39.0	3.4	30.2	92.9	–6.0	159.3
24-Dec-2021	16,654	27.7	2.4	51.7	–79.1	–172.0	–123.9
31-Dec-2021	9311	15.5	1.3	37.0	–85.6	–6.5	–96.4
7-Jan-2022	7932	13.2	1.1	20.9	–16.1	69.5	–38.6
14-Jan-2022	5461	9.1	0.8	6.5	–28.8	–12.7	–42.8
Eswatini							

Country and date	New cases 7-day moving average	New cases/100,000 7-day moving average	Inflation factor	7-day persistence	Acceleration weekly	Jerk weekly	Exponential growth potential weekly
3-Dec-2021	91	7.7	1.0	0.2	50.8	49.0	52.4
10-Dec-2021	573	48.9	6.3	12.7	288.3	237.6	314.2
17-Dec-2021	1101	93.9	12.2	57.3	314.7	26.4	454.8
24-Dec-2021	725	61.9	8.0	124.1	–224.1	–538.8	–311.5
31-Dec-2021	308	26.3	3.4	82.5	–249.2	–25.1	–214.1
7-Jan-2022	152	12.9	1.7	35.4	–93.3	155.8	–91.9
14-Jan-2022	87	7.4	1.0	6.3	–38.9	54.4	–44.8
Zambia							
3-Dec-2021	21	0.1	1.0	0.0	0.4	0.4	0.5
10-Dec-2021	66	0.3	3.2	0.2	1.7	1.3	2.0
17-Dec-2021	530	2.8	25.8	0.4	17.2	15.5	18.3
24-Dec-2021	2071	10.9	100.7	3.8	57.0	39.9	66.1
31-Dec-2021	3620	19.1	176.0	14.9	57.3	0.3	87.6
7-Jan-2022	3429	18.1	166.7	26.3	–7.1	–64.4	–30.0
14-Jan-2022	2203	11.6	107.1	9.0	–45.4	–38.3	–60.8
Zimbabwe							
3-Dec-2021	515	3.4	1.0	0.1	22.3	22.4	23.1
10-Dec-2021	2625	17.4	5.1	5.6	97.9	75.6	109.2
17-Dec-2021	4821	31.9	9.4	20.5	101.9	4.0	150.9
24-Dec-2021	1881	12.5	3.7	42.4	–136.4	–238.2	–109.1
31-Dec-2021	1503	10.0	2.9	16.7	–17.5	118.8	–35.0
7-Jan-2022	1146	7.6	2.2	13.5	–16.6	1.0	–29.7
14-Jan-2022	622	4.1	1.2	3.7	–24.3	–7.8	–26.5

Figure 1. First sub-Saharan countries to experience an Omicron outbreak.



How Do Omicron Outbreaks Compare to Other VOC Outbreaks?

We examined the daily speed of the pandemic or the number of daily new cases per 100,000 population and found that Gabon, Lesotho, South Africa, Eswatini, Zambia, and Zimbabwe have already set new 2-year outbreak records in the first 4 weeks of the outbreak, in December 2021. All the countries in Figure 1 whose current outbreaks are driven by Omicron, except Botswana, had more new daily infections than during every other outbreak caused by either the original SARS-CoV-2 variant, Beta, or Delta. Most of these countries recorded peak speeds during the outbreak of the Delta variant; however, the exponential growth of Omicron cases has reversed course and contracted. It is remarkable that not only did Omicron result in record highs, but also those highs took fewer days to reach.

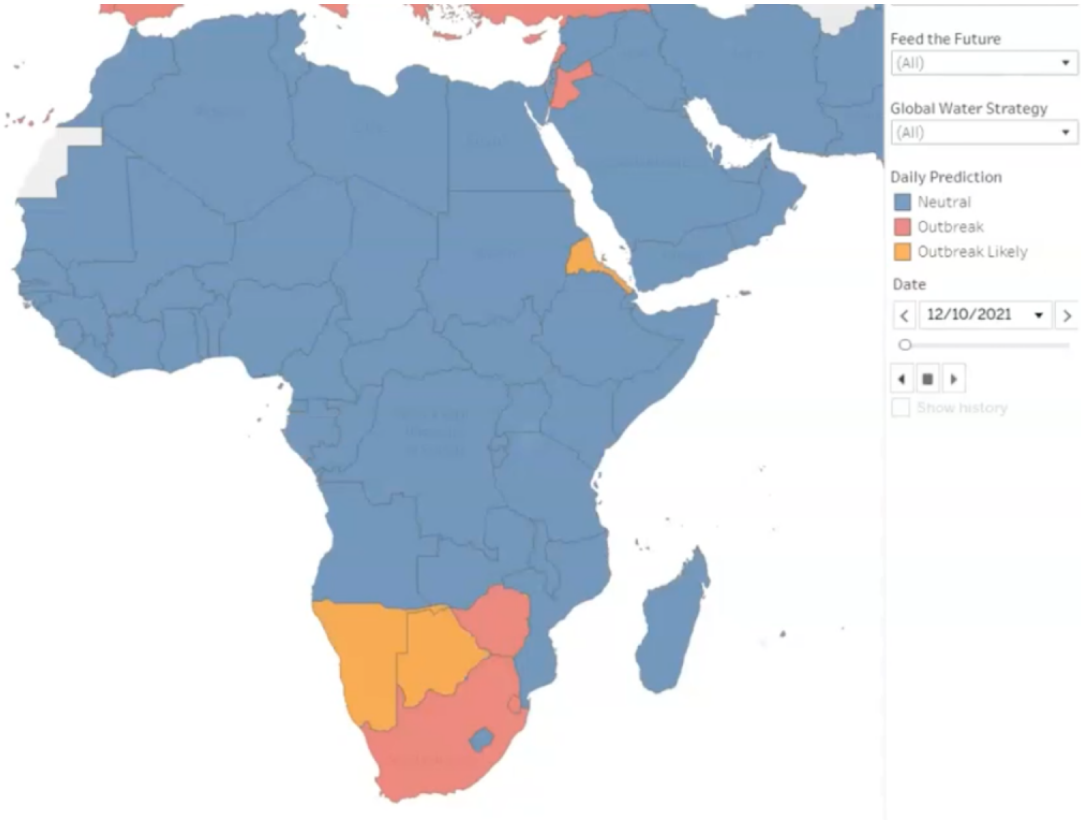
For some of the countries currently in an outbreak, such as Botswana and Zambia, the rate of increase is slowing, which means even though these countries are in an outbreak, the increase in daily new cases slowed between the last week in December and the first week in January 2022, compared to the prior 4 weeks. In contrast, sub-Saharan countries where Omicron began transmitting and escalating later are not slowing (Multimedia Appendix 1). Not only did the 7-day moving average, rate of new cases, and daily new cases increase more rapidly with Omicron than with other VOCs, but the rate itself increased when compared to the prior 2-4 weeks.

Figure 2 demonstrates how the SARS-CoV-2 pandemic transmitted through Africa after the Omicron variant was identified. Countries that light up as orange have been experiencing a surge in cases for 7 consecutive days. Blue countries indicate neutral growth for 24 hours and countries in red exceed the outbreak threshold of 10 daily new cases per 100,000 population. Since November 11, 2021, a number of countries in Africa had outbreaks forming, especially those countries in the south of the continent [4]. The figures for each country, presented below, differentiate between the VOCs.

The evolution of Omicron in the first 8 African countries to experience an Omicron-only outbreak—Botswana, Eswatini, Gabon, Lesotho, Namibia, South Africa, Zambia, and Zimbabwe—are depicted in the figures presented below. To compare the evolution of infections to outbreaks driven by earlier VOCs, a value of 0 on the x-axis denotes the moment a country eclipses the CDC threshold of 10 new cases per 100,000 population. This standardization allows for a visual comparison of outbreaks that have occurred on different calendar dates within a country.

The solid lines refer to the speed, or rate of new cases, of the current Omicron-driven outbreak. In each of Botswana, Eswatini, Gabon, Lesotho, Namibia, South Africa, Zambia, and Zimbabwe, the speed of the pandemic has accelerated faster under Omicron than prior VOCs, as depicted by dashed lines.

Figure 2. A screen capture of a dynamic map of transmission of the SARS-CoV-2 pandemic through Africa after the Omicron variant was identified. Full video can be viewed here: [44].



In Botswana (Figure 3), the outbreaks from SARS-CoV-2, Beta, and Delta roughly followed the same initial pattern in new cases. Surprisingly, in fact, the progression of SARS-CoV-2 and Beta were similar enough to be almost indistinguishable at the scale of the plot. Data for the country are not always available on a daily basis, so the trend lines contain steps. The Omicron outbreak began with fewer transmissions than Delta, Beta, and the original SARS-CoV-2 variants. Still, before Omicron, every outbreak built slowly over the course of several weeks before peaking. Though not depicted over the time scale, the eventual peaks of Delta, Beta, and SARS-CoV-2 were roughly 96, 20, and 12. The return to sub-outbreak speed was variable because the Beta outbreak had yet to truly subside before the Delta outbreak started. Speed just barely fell to below the CDC threshold before the Delta outbreak.

The Omicron outbreak, in contrast, occurred within less than a week. Speed quickly jumped from roughly 5 to 25 daily new transmissions per 100,000 population. Within 2 weeks, the speed had jumped to 60. If SSA countries with earlier Omicron outbreaks that have subsided are an indication, Botswana may be near its peak speed. The comparison of peak speeds between Omicron and Delta outbreaks is confounded, however, because the Beta outbreak had yet to truly subside before the Delta outbreak began.

The Omicron outbreak in Eswatini also quickly accelerated from near zero new cases per 100,000 population to a peak of 95 within approximately 2 weeks (Figure 4). The peak is over 1.5 times higher than the previous peak in the Delta outbreak, and 4 times higher than the peak in either of the previous Beta outbreaks. We note that because sequencing data are limited, the assignment of the initial 2 outbreaks to the Beta variant is our own assumption.

Figure 3. Botswana outbreaks by variant of concern.

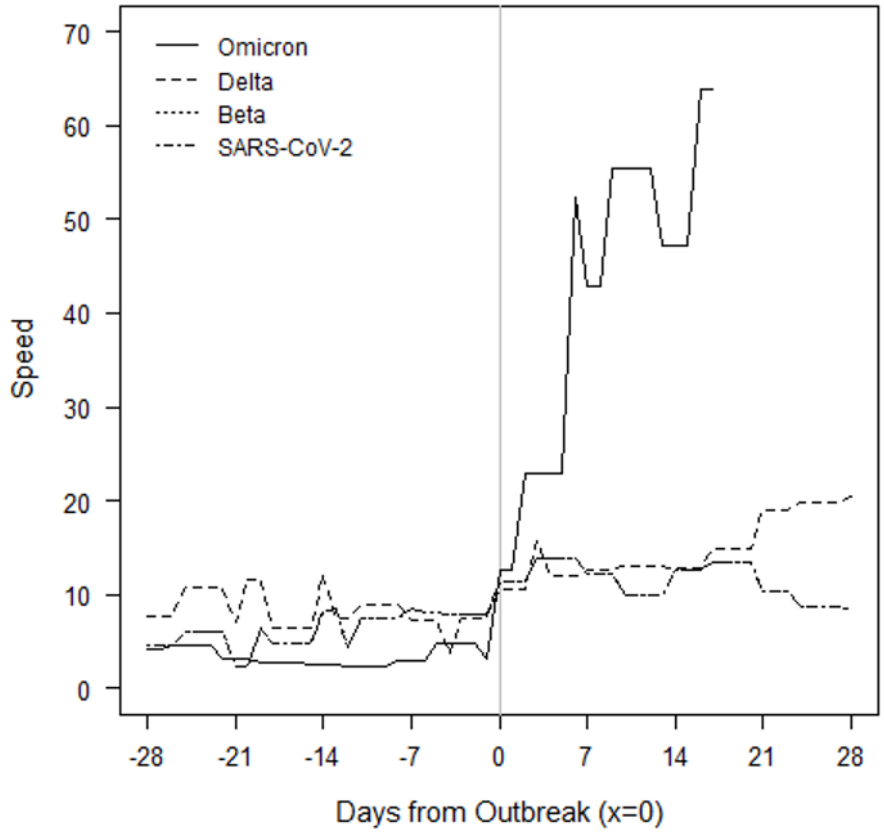
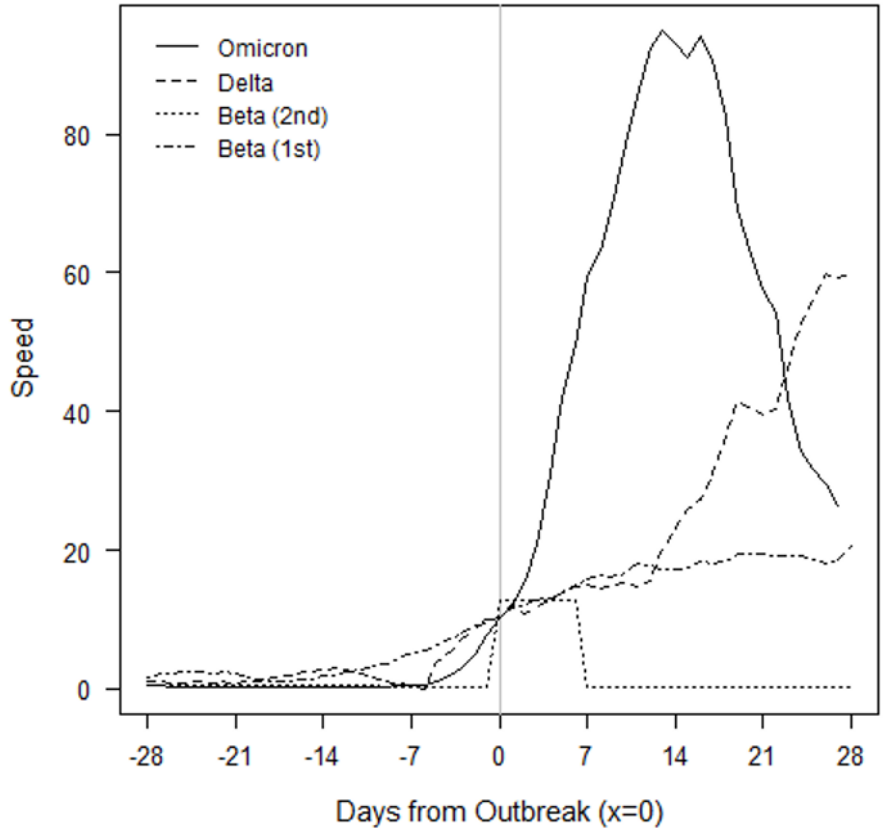


Figure 4. Eswatini outbreaks by variant of concern.



Gabon has seen an even higher acceleration of new cases in the Omicron outbreak (Figure 5). From a speed of near zero, the country reached a speed of 25 within less than a week. This peak is already twice that of the earlier Delta outbreak, and acceleration may continue if other SSA countries whose Omicron outbreaks have begun to subside provide any

indication. In those countries, the rate of new cases accelerated for at least 2 weeks before the Omicron outbreak began to subside.

The Omicron and Beta outbreaks in Lesotho followed a broadly similar trajectory, though the duration of the peak speed in Omicron was higher (Figure 6). Each outbreak yielded a peak speed of roughly 20. This similarity of outbreaks by VOC is shared by South Africa. The similarity is perhaps unsurprising because Lesotho has borders contained entirely within South Africa.

Figure 7 depicts the outbreaks for Namibia. Each prior outbreak built slowly over the course of several weeks, while Omicron began with fewer cases than other outbreaks. The initial SARS-CoV-2 outbreak was fleeting, and speed declined immediately after the outbreak threshold was reached. The Beta and Delta outbreaks continued to show positive acceleration for roughly 2 weeks after the CDC threshold was reached. We note that while we attribute the January 2021 outbreak to the Beta variant, which was first detected in the country on January 15, 2021, this attribution is an assumption because sequencing data are limited. Omicron provided slightly more warning than it did for Botswana, but speed jumped dramatically over the course of a week, from roughly 5 to 20, then to 50 within another 10 days. The Omicron outbreak has since subsided as quickly as it rose. The peak speed of 50 is lower than the peak speed of 70 the country eventually reached under the Delta outbreak. However, like in Botswana, the Delta outbreak came at the tail of the Beta outbreak. Speed never fell below 5 between the two, which may confound a comparison of the Omicron and Delta outbreaks.

Figure 5. Gabon outbreaks by variant of concern.

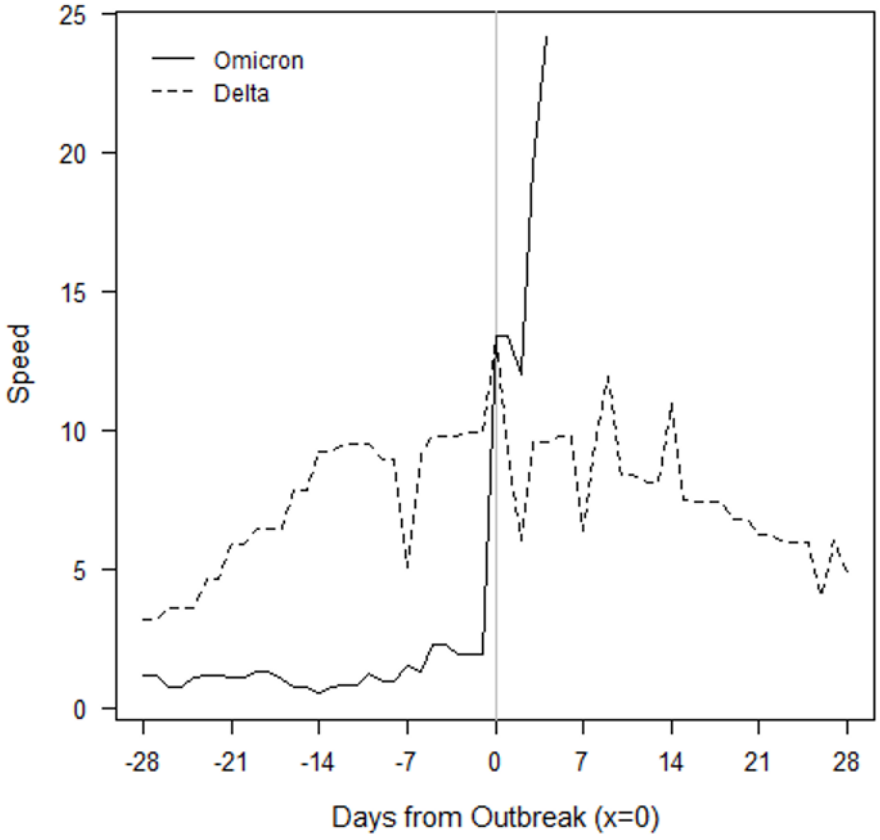


Figure 6. Lesotho outbreaks by variant of concern.

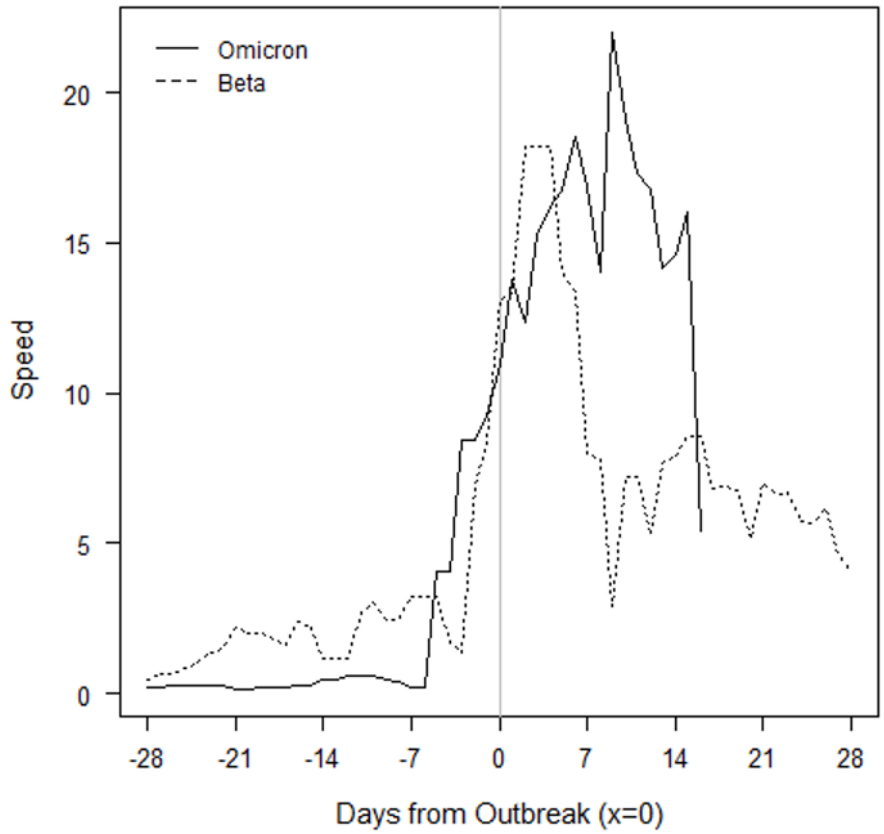
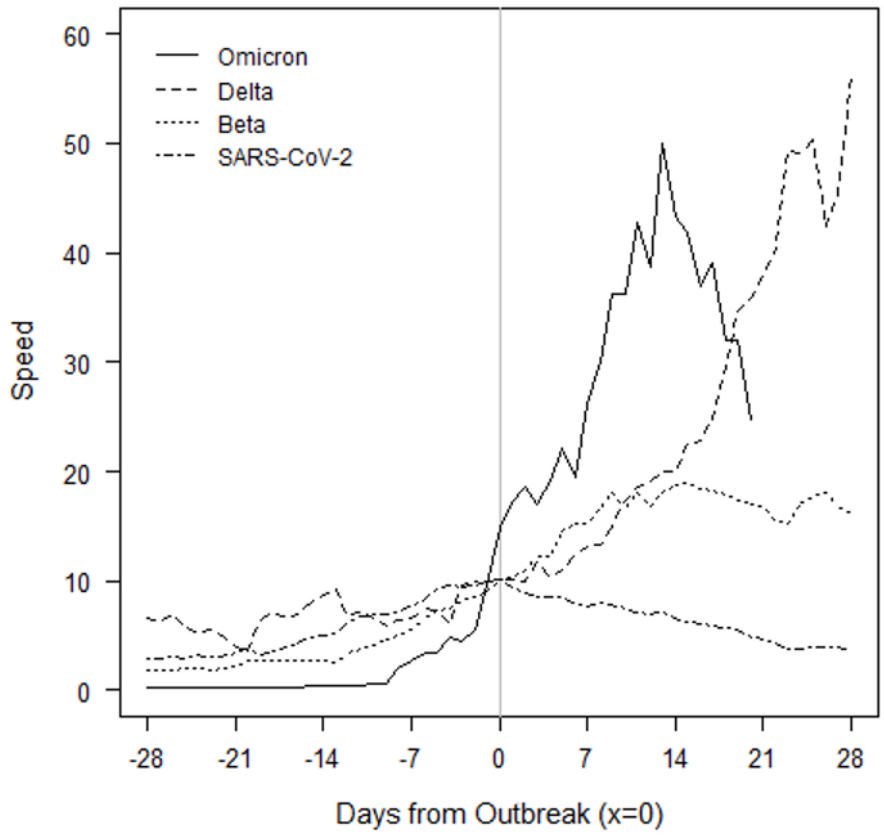


Figure 7. Namibia outbreaks by variant of concern.



South Africa saw a more rapid acceleration in new infections in the Omicron outbreak relative to prior VOCs (Figure 8). The prior outbreaks followed similar patterns. They built slowly over the course of several weeks, but they continued to rise for 2-5 weeks after the CDC outbreak threshold was reached. The Omicron outbreak gave roughly a week and a half of warning.

Acceleration has been much faster, and peak speed was higher: 40 in Omicron versus 33, 31, and 20 in Delta, Beta, and SARS-CoV-2, respectively. Speed fell to below 20 by the end of December 2021 and dipped below the outbreak threshold by 0.09 cases per 100,000 population by the second week of January 2022.

Figure 9 depicts the outbreaks in Zambia. The earlier Delta outbreak built slowly over 4 weeks before the country eclipsed the outbreak threshold. Speed slowly rose to 15 over the next 2 weeks before subsiding at roughly the same rate at which it grew. The Omicron outbreak only gave 2 weeks of warning, and within 1 week of surpassing the outbreak threshold, speed had already reached 20.

Zimbabwe only had one prior outbreak with which to compare Omicron, which is notable because the country started with a lower rate of transmissions in the Omicron outbreak than it did in the Delta and Beta surges in transmissions (Figure 10). Although Beta caused an increase in cases around the start of 2021, speed did not rise enough to reach the CDC outbreak threshold. Delta reached the outbreak threshold after a 3- to 4-week rise in transmissions. Omicron gave only a week's warning before reaching the threshold and reached a speed over twice the peak of Delta. Again, speed has fallen at roughly the rate at which it grew, but speed reversed its downward trend over the most recent 2 days of data.

Importantly, the raw numbers in Figures 3-10 do not control for cumulative vaccinations or infections. The rate of acceleration under Omicron is even more alarming given the difference in cumulative vaccinations and infections under the Omicron outbreaks and those driven by earlier VOCs. For example, South Africa had reached nearly 12 million total vaccinations by the threshold of the Omicron outbreak, but the country had only surpassed 1.5 million vaccinations by the threshold of the earlier Delta outbreak. The respective numbers for total infections at the start of each outbreak were roughly 3 million and 1.7 million.

Regression analysis provides estimates of the relationship between two variables after controlling for others. We completed Arellano-Bond dynamic panel estimates for SSA over the full calendar year 2021. A dynamic model is required because new SARS-CoV-2 infections are certainly a function of prior infections. The estimation also controls for time-invariant, unobservable characteristics, which may differ by country. We extended the sample period used for surveillance metrics to cover the start of 2021. The extension was needed to examine how Omicron outbreaks compare to those from other VOCs earlier in the year. Note that for countries with complete data for the year, the time period T is slightly higher than 365 days because the model incorporates lags of variables.

The dependent variable is the rate of new cases per 100,000 population. The key independent variable, *after_nov_21*, is an indicator for whether the calendar date is on or beyond November 1, 2021. Because the exact date of origin for Omicron is unknown, this date is meant to be a conservative estimate of the time window in which it originated. However, results are robust to recoding the variable with nearby dates.

Figure 8. South Africa outbreaks by variant of concern.

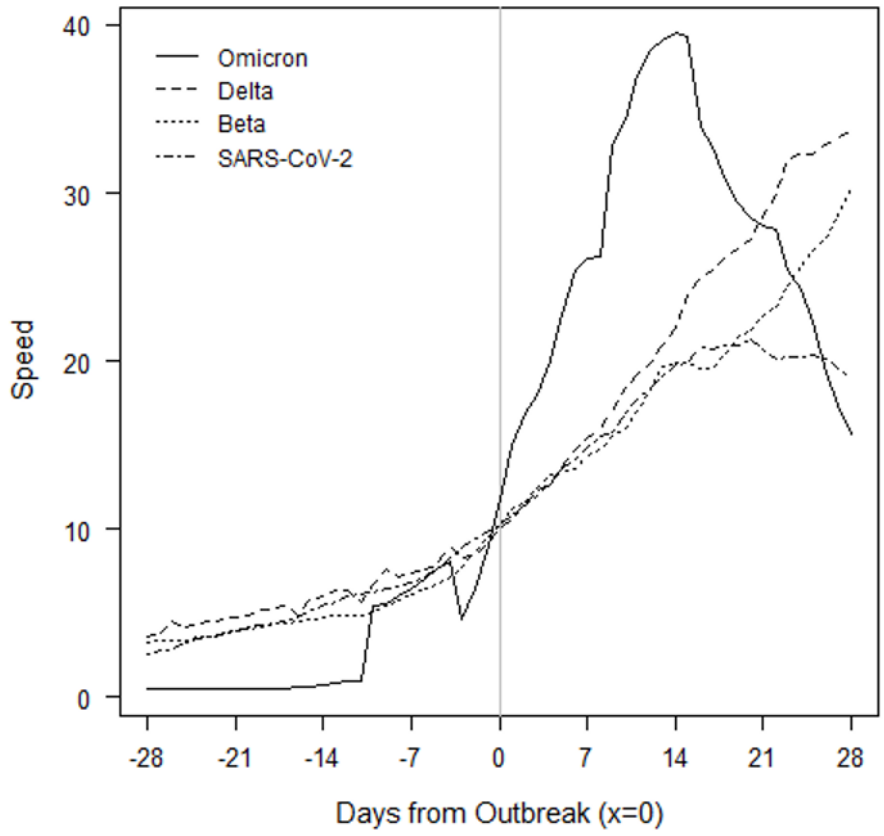


Figure 9. Zambia outbreaks by variant of concern.

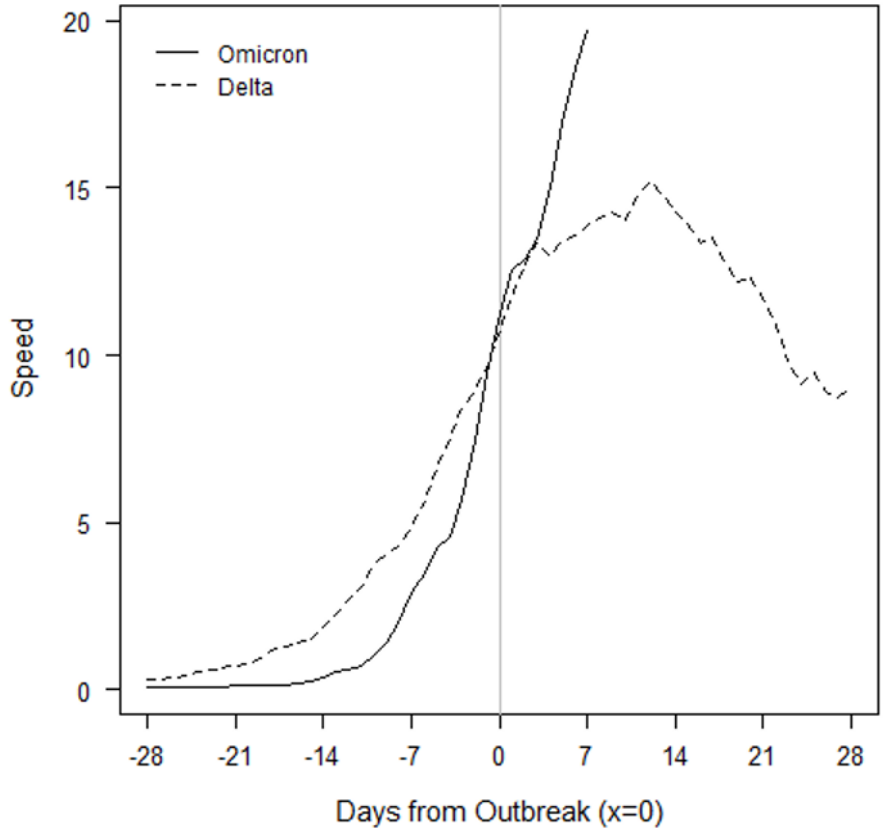
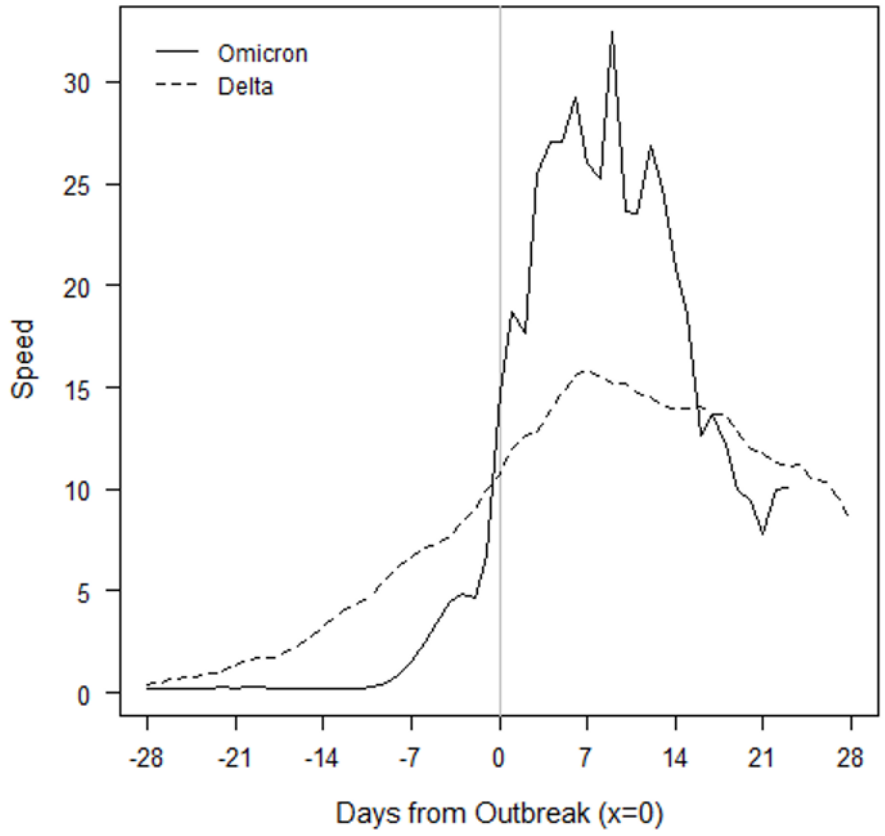


Figure 10. Zimbabwe outbreaks by variant of concern.



The first and seventh lag of the rate of new cases (*lag.pos.1* and *lag.pos.7*, respectively) provide measures of persistence in the pandemic. Their coefficients describe how new cases echo forward from day to day and week to week, respectively. The regression estimates also control for cumulative cases (*cum_cases*), cumulative vaccinations (*cum_vacc*), and an

indicator variable for weekend dates (*weekend*), as data reports are less consistently released on weekends.

Because *after_nov_21* is interacted with the lagged rate of new cases, the coefficient on *after_nov_21* by itself does not provide a useful interpretation. To be precise, the coefficient provides the estimated change in the average rate of new cases after November 2021 for a country with 0 previous cases.

However, the interaction between *after_nov_21* and the 1- and 7-day lags of cases (*lag.pos.1*, *lag.pos.7*) confirms that Omicron has changed the evolution of the pandemic. The positive, statistically significant coefficients on the interaction terms mean Omicron has strengthened persistence in the pandemic compared to earlier VOCs. After controlling for vaccinations and prior infections, 1- and 7-day persistence have increased by 1 and 0.52, respectively, since the start of November 1, 2021.

We also note that several SSA countries stand on the precipice of outbreak. The ability to identify a statistical impact of Omicron this early in its spread suggests its true effect may be stronger than the initial results indicate.

The coefficient on *cum_vacc* shows the protective effect of vaccinations at the population level. Over the course of 2021, every vaccination reduces the expected transmission rate by 0.002. The effect is statistically significant at the .05 level. Although its magnitude appears modest, keep in mind the dependent variable measures the *daily* rate of new infections per 100,000.

The positive coefficient on *cum_cases* may come as a surprise if prior infections reduce susceptibility. However, the mechanical correlation between cumulative cases and new infections in an outbreak seems to mask any possible reductions in susceptibility.

Finally, the Arellano-Bond estimator relies on instrumental variables. Although their validity cannot be directly tested, the Sargan test of overidentification restrictions yields a *P* value near 1, which suggests the instruments are valid (Table 2).

Table 2. Arellano-Bond dynamic panel data estimates[a].

Variable	Coefficient (SE)	*P* value
after_nov_21	–2.68 (1.02)	.009
lag.pos.1	–0.68 (0.14)	<.001
lag.pos.7	0.31 (0.31)	.31
weekend	–1.12 (0.45)	.01
cum_cases	0.008 (0.001)	<.001
cum_vacc	–0.002 (0.001)	.03
after_nov_21 × *lag.pos.1*	0.52 (0.16)	.001
after_nov_21 × *lag.pos.7*	1.29 (0.28)	<.001

[a]Unbalanced panel: n=43, *t*=359-366, N=15,731. Sargan test: X^2_{4656}=44 (*P*>.99). Autocorrelation test (1): normal=–1.28 (*P*=.20). Autocorrelation test (2): normal=–0.89 (*P*=.37).

Discussion

Principal Findings

Omicron has spread much faster than any previous VOC in SSA. Given the speed of spread, the variant provides relatively little warning of an outbreak based on current surveillance infrastructure and metrics. Although previous VOCs typically provided at least 14-21 days of warning and an average of 35 days, Omicron has driven outbreaks in SSA from a speed of almost zero new cases to 10 per 100,000 population within 7-10 days. The longest warning period of transmission escalation thus far appears to be roughly 10 days, as seen in South Africa, Zambia, and Zimbabwe.

Additionally, Omicron outbreaks have a greater magnitude in terms of the number of new SARS-CoV-2 infections. For the first group of southern African countries to go into outbreak, the peak rate of new transmissions averaged roughly 1.5-2 times the peak of earlier VOCs (Figures 3-10). Botswana and Namibia saw higher peaks under Delta than Omicron, but those comparisons may be confounded because the Delta outbreaks occurred on the tail end of earlier Beta outbreaks.

At the population level, the observed ability for Omicron to outperform prior VOCs is worrisome because total vaccinations and prior infections are higher now than they were when the other VOCs caused outbreaks. Even in countries outside of SSA with high vaccination rates, there have been sharp increases in the spread of SARS-CoV-2 infections caused by Omicron [45]. In the United Kingdom, Omicron has been shown to be associated with a 5.41-fold higher risk of reinfection compared to Delta, confirming relatively low levels of immunity from prior infections [46]. Similar reinfection rates have been reported in South Africa [47]. Both vaccinations and prior infections are expected to reduce susceptibility in the population. However, our findings suggest that the degree of protection may be lessened against Omicron (Table 2).

The results therefore highlight the enhanced transmissibility of Omicron compared to other VOCs. Still, the results do not precisely identify the extent to which Omicron may evade vaccines or immunity from prior infections. The data are too early to inform whether Omicron outbreaks are driven by new infections or reinfections in either the vaccinated or unvaccinated population [47].

Likewise, the coming weeks will provide critical information on the effect of Omicron outbreaks on deaths and hospitalizations. Recent data from the United Kingdom indicate SARS-CoV-2 infections from the Omicron variant may not be any less severe than the Delta variant [46], which contradicts observations from South Africa that suggest Omicron infections are less severe than earlier VOC infections [48,49]. Early laboratory data also show significant reductions in the ability of SARS-CoV-2 antibodies to neutralize the Omicron variant compared to the original virus, among those vaccinated with 2 doses of the Pfizer/BioNTech vaccine [47]. In one study in California, investigators found Omicron increased the risk of hospitalization 4- to 5-fold and increased the risk of symptomatic disease 7- to 10-fold for mRNA vaccine recipients, with similar relative effects for recently vaccinated individuals or individuals with waned antibody titers [49]. Thus, the significantly higher speed and magnitude of an Omicron outbreak, coupled with more extensive vaccine escape [47] and possibly comparable pathogenicity, could signal a potential to significantly overwhelm hospital capacity with a larger number of infected persons within a shorter window of time [45].

In addition to southern Africa being the region where Omicron was first identified, it offers an ideal natural experiment for a comparison of isolated outbreaks driven by Omicron versus prior VOCs. The impact of Omicron may be different for countries already in the midst of current outbreaks driven by another VOC. For example, the United States and the United Kingdom are currently experiencing upsurges in Omicron cases amid ongoing Delta outbreaks. Future work will examine the interaction of VOCs within an outbreak and Omicron's potential for a viral sweep.

Limitations

Our study reports on data current up through January 17, 2022. Adverse outcomes are likely to increase because the Omicron outbreak has not had sufficient time to realize morbidity, mortality, severity, transmissibility, and evasiveness. Our data are limited by the granularity of country reporting. Data are reported on a national level for countries within SSA, 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 limits the completeness of data. Multiple days of data are frequently bundled into a single report, which may give the impression of zero infections or deaths over a period of days followed by a sudden spike in those same measures. Our data address this issue by calculating 7-day averages per 100,000 population. However, inconsistent reporting in combination with large new daily cases reports can also artificially suppress the 7-day average and mask the true impact of increasing cases over that period.

Comparison With Prior Work

We conducted prior surveillance estimates and SARS-CoV-2 research on speed, acceleration, jerk, and persistence, relying on dynamic panel data in SSA and other global regions [20,21,23,24,26-29,34,38,50-52].

Conclusions

Without question, Omicron is more transmissible than prior VOCs [49]. The analysis of outbreaks by VOC in southern African countries shows Omicron transmits at least 2-3 times faster at a country level than prior VOCs. Despite starting from a lower daily rate of SARS-CoV-2 transmissions, Omicron results in worse outbreaks in terms of magnitude by a factor of 1.5-2 on average. However, as Eswatini, Lesotho, Namibia, South Africa, and Zimbabwe have shown, the outbreaks may also subside as quickly as they grow. Still, as outbreaks grow, local surveillance infrastructure may not be able to keep up with the greater number of persons seeking testing for symptoms or exposure. Extensive media coverage of the Omicron variant may also be promoting behavioral changes that could slow the outbreak. Conversely, populations experiencing pandemic fatigue could disregard reports of new outbreaks, relaxing preventative behaviors and leading to additional transmissions. Finally, the recently concluded holiday season likely increased human interactions as it did a year ago. The results presented in this study suggest it takes fewer cases of Omicron to initiate an outbreak than Delta, Beta, Alpha, and the original SARS-CoV-2. Even if Omicron results in lesser disease severity than prior VOCs, hospitals may expect a high caseload of patients because Omicron is highly transmissible. The world should plan how to flatten the curve given the speed, acceleration, jerk, and persistence of Omicron.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Daily SARS-CoV-2 surveillance complete file.
[DOCX File , 102 KB - publichealth_v8i1e35763_app1.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
GISAID: Global Initiative on Sharing Avian Influenza Data
SSA: sub-Saharan Africa
VOC: variant of concern
VOI: variant of interest

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Original Paper

Reasons for Nonuse, Discontinuation of Use, and Acceptance of Additional Functionalities of a COVID-19 Contact Tracing App: Cross-sectional Survey Study

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Abstract

Background: In several countries, contact tracing apps (CTAs) have been introduced to warn users if they have had high-risk contacts that could expose them to SARS-CoV-2 and could, therefore, develop COVID-19 or further transmit the virus. For CTAs to be effective, a sufficient critical mass of users is needed. Until now, adoption of these apps in several countries has been limited, resulting in questions on which factors prevent app uptake or stimulate discontinuation of app use.

Objective: The aim of this study was to investigate individuals' reasons for not using, or stopping use of, a CTA, in particular, the Coronalert app. Users' and nonusers' attitudes toward the app's potential impact was assessed in Belgium. To further stimulate interest and potential use of a CTA, the study also investigated the population's interest in new functionalities.

Methods: An online survey was administered in Belgium to a sample of 1850 respondents aged 18 to 64 years. Data were collected between October 30 and November 2, 2020. Sociodemographic differences were assessed between users and nonusers. We analyzed both groups' attitudes toward the potential impact of CTAs and their acceptance of new app functionalities.

Results: Our data showed that 64.9% (1201/1850) of our respondents were nonusers of the CTA under study; this included individuals who did not install the app, those who downloaded but did not activate the app, and those who uninstalled the app. While we did not find any sociodemographic differences between users and nonusers, attitudes toward the app and its functionalities seemed to differ. The main reasons for not downloading and using the app were a perceived lack of advantages (308/991, 31.1%), worries about privacy (290/991, 29.3%), and, to a lesser extent, not having a smartphone (183/991, 18.5%). Users of the CTA agreed more with the potential of such apps to mitigate the consequences of the pandemic. Overall, nonusers found the possibility of extending the CTA with future functionalities to be less acceptable than users. However, among users, acceptability also tended to differ. Among users, functionalities relating to access and control, such as digital certificates or "green cards" for events, were less accepted (358/649, 55.2%) than functionalities focusing on informing citizens about the spread of the virus (453/649, 69.8%) or making an appointment to get tested (525/649, 80.9%).

Conclusions: Our results show that app users were more convinced of the CTA's utility and more inclined to accept new app features than nonusers. Moreover, nonusers had more CTA-related privacy concerns. Therefore, to further stimulate app adoption and use, its potential advantages and privacy-preserving mechanisms need to be stressed. Building further knowledge on the forms of resistance among nonusers is important for responding to these barriers through the app's further development and communication campaigns.

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KEYWORDS

COVID-19; SARS-CoV-2; coronavirus; contact tracing; proximity tracing; mHealth; mobile app; user acceptability; surveillance; privacy

Introduction

Since the emergence of SARS-CoV-2, the subsequent pandemic has been managed by governments worldwide by implementing wide-ranging policies. These include measures that disrupt human mobility, such as full and partial lockdowns, limiting the number of individuals' physical contacts, and accompanying testing, tracing, and quarantine strategies. Traditionally, contact tracing has been implemented primarily through call centers, where agents interview individuals who have been diagnosed with COVID-19 and people who crossed paths with them [1]. However, contact tracing conducted by a call center has several limitations [2,3]. Therefore, a growing number of countries have developed contact tracing apps (CTAs) that offer users the possibility to keep track of their proximity with other app users and receive warnings if users were close to someone who tested positive for COVID-19 [4]. In most countries where CTAs have been implemented, the use of these apps is voluntary. However, limited uptake levels have been reported [5]. In Europe, uptake levels have been reported as ranging from less than 1% to almost half of the population [6]. Yet, the effectiveness of a CTA depends on the population's uptake. Modeling studies have quantified the impact of CTA adoption on the spread of the virus. One study found that at least 56% of the population should use a CTA in order to contribute to the mitigation of the pandemic [7]. Even if this threshold is not met, lower uptake levels are able to reduce infection rates and, therefore, use of a CTA could be an effective complement to manual contact tracing. For instance, in a model including 15% of the population using a CTA, exposure notification would reduce the number of infections by 8% [8]. However, the impact of CTAs further depends on measures that are in place, such as nonpharmaceutical measures to mitigate the epidemic (eg, displacement restrictions), the adoption of individual preventive behaviors (eg, physical distancing and isolation compliance for infected individuals), the testing capacity, and easy access to testing facilities to increase early case detection [9].

In Belgium, the CTA Coronalert was launched in September 2020. The app was developed based on the DP-3T (Distributed Privacy Preserving Proximity Tracing) architecture. This was combined with the Exposure Notification interface provided by Google and Apple [10]. The app has been downloaded 2.7 million times, representing almost one-third of Belgian smartphone users [11] (details on how the specific CTA works is summarized in Multimedia Appendix 1). The system offers important privacy safeguards: it only serves to detect close contacts of COVID-19–infected persons, does not track location, and does not link information with personal data [12]. As this system is based on the DP-3T protocol and has also been implemented in a large number of European Union (EU) countries and US states [5], cross-border interoperability has been developed so the app can be used in other countries that use the same system. But for such an app to function optimally, its widespread adoption by the population is crucial.

Previous research focusing on COVID-19 CTAs has concentrated on predictors of app adoption and sociodemographic differences between adopters and nonadopters. Some studies found higher CTA adoption or adoption intention among males, younger respondents, individuals with a higher income, and individuals living in urban areas [13-15]. Studies found that several factors stimulate app uptake, such as current and potential users' attitudes toward the contribution of the app in diminishing the spread of the virus (ie, perceived usefulness or performance of the app) and positive social influence to use the app (ie, subjective norm). CTAs' perceived safety and privacy also impacted its use or use intention. Moreover, individuals' engagement in pandemic-related behavioral adjustments, their trust in government, and their trust in health authorities influenced app uptake [1,15-23]. Respondents who had a personal experience with COVID-19, either as a patient or with relatives who were diagnosed with COVID-19, or those who perceived health consequences in case of infection were more inclined to install the app [15,23,24]. Moreover, research has pointed toward concerns regarding the implementation of CTAs. Users' perceived security and privacy risks were found to decline app uptake intention [1,14]. Although research has focused on uptake motives and predictors, as well as perceived risks of a CTA, few studies have focused on concerns that fuel nonadoption or discontinuation of use [18,24,25].

Therefore, this paper aims to address an important gap in the literature regarding the nonuse of health-related apps, the relevance of which has become especially apparent in the COVID-19 crisis. As such, this study focuses on potential sociodemographic differences between adopters and nonadopters and reasons for nonuse. More particularly, we focus on the reasons for (1) not downloading the app, (2) having downloaded but not activated the app, and (3) discontinuation of use by uninstalling the app. Moreover, attitudinal differences between nonusers and users were assessed in terms of individual and societal expected outcomes of a CTA.

A second gap that is addressed concerns insight into citizens' attitudes toward plausible expanding functionalities of CTAs over the course of the pandemic. Therefore, respondents were confronted with potential new features that are not currently integrated in Coronalert but have been implemented in other countries' CTAs or are being discussed as potential useful additional options to stimulate app uptake and continued use. In this regard, several authors have raised concerns about governments extending personal data collection and use beyond what was originally envisioned in the context of the pandemic (ie, "function creep") [26,27]. Whereas there are crucial legal aspects connected to the implementation of CTAs and their functionalities [28], the perspective of the end user and the important role of public acceptance cannot be ignored. Therefore, assessing users' attitudes toward additional data-gathering features of CTAs seems crucial.

Given that population-based research regarding these app functionalities is scarce [29,30], we investigated how users and nonusers differ in their attitudes toward these potential features. For instance, the app could indicate that its holder did not have close contact with another user who tested positive for COVID-19, in order to gain access to public places or other locations. Also, other credentials could be integrated, such as vaccination certificates or results of COVID-19 antibody testing. The verifiers (eg, employers and event organizers) could then ask the holders to present this proof to gain access [31]. Still, the implementation of such "green certificates" have been subject to many criticisms, and several scholars have pointed to the necessary ethical and privacy-related considerations in this regard [31-33].

Therefore, to contribute to the research on digital contact tracing, this study has three main objectives. First, we investigate the thresholds for adoption of CTAs. Second, the potential difference between users and nonusers in terms of CTAs' perceived impact is examined. Third, we study users' and nonusers' openness to potential functionalities that could be included in CTAs.

Methods

Procedure and Sample

This study was conducted in Flanders, the Dutch-speaking part of Belgium. An online survey was administered to 18- to 64-year-old respondents. Data were collected between October 30 and November 2, 2020. In that period, the following COVID-19 measures were in place: citizens were allowed to have close contact with a maximum of one person who is not part of one's own household; citizens were allowed to have private meetings with a maximum of four persons, the same persons within a period of 2 weeks; markets and shops were open; cafés and restaurants were closed, but takeaway and delivery were allowed; telework became the norm for all professional activities that allow it; professional sport competitions could not welcome spectators; indoor events (cultural, religious, etc) could accept a maximum of 200 participants and there were adapted rules for indoor sport activities; and a curfew was in force from 12 AM until 5 AM.

The recruitment of respondents was organized by a professional research agency that manages a panel consisting of 300,000 members in Belgium. Panel members who choose to participate in a survey are not remunerated for their participation but enter in a contest organized by the agency to win vouchers of €50 maximum. Respondents were recruited specifically for the purpose of this study.

A sample of 1850 respondents was recruited with the following eligibility criteria: (1) being a resident of Belgium, (2) being aged between 18 and 64 years, and (3) speaking Dutch. To achieve a heterogeneous sample, we followed a stratified sampling procedure. Based on Belgian federal statistics, we stratified the data a priori regarding gender, age, and education level so that the proportion of the sample's strata would reflect the proportion of the Flemish population. In total, 8000 panel members were emailed an invitation to participate; the invitation included a short description of the study and a link redirecting respondents to an online survey set up specifically for this study. When 1850 respondents were reached in accordance with the strata, based on gender, age, and education level, data collection was truncated. This was made possible because every panel member's sociodemographic profile is known by the agency. The researchers had no access to the identity of the participants, and the questionnaire did not request any form of identification that could have inconvenienced respondents or jeopardized their anonymity toward the researchers. Afterward, we confirmed eligibility of the respondents and correspondence with the predefined strata based on sociodemographic variables included in the questionnaire.

After informing the respondents of the study's objectives and requesting their informed consent, the respondents were confronted with a paragraph briefly explaining the key features of the Coronalert app (ie, the use of Bluetooth to detect proximity and the anonymous disclosure of users' COVID-19–positive status to other users who have been in their proximity). This study was part of a larger research project concerning predictors of app adoption and use. Prior to the online data collection among the panel members, the survey's introduction and the whole questionnaire were assessed by three researchers to check the clarity of the questions and the brief explanation.

This study was approved by the Ethical Commission of Ghent University, which supervises the privacy and confidentiality measures taken in each conducted study as well as how data are stored after data collection.

Measures

Besides the sociodemographic characteristics of gender, age, education level, and employment status, we also questioned the medical condition of respondents. The latter was assessed by asking respondents if they suffered from one or more diseases (eg, heart, lung, or kidney diseases; diabetes; cancer; reduced immune system; and high blood pressure) that could be a risk factor when positive for COVID-19.

The employment categories of Statbel, the Belgian federal statistics institute, were used, based on the International Standard Classification of Occupations. This classification was shortened by grouping several categories, and "flexi-job" was added as a supplementary category, as it is a relatively new employment category.

Respondents were asked about the reasons why they did not install, installed but did not activate, or uninstalled the app. Next, we assessed respondents' attitudes toward CTAs' potential impact (8 items). Several statements were presented that were related to the societal and individual implications of mobile contact tracing. Respondents were asked whether they agreed or not with the implications of CTAs, using 5-point Likert scales. In addition, acceptance of potential features and applications of the Coronalert app was measured (11 items using 5-point Likert scales). The submitted options were based on functionalities that are already integrated into specific apps or discussed as potential options [34]; these can be divided in two categories: (1) information and advice and (2) control and

access. The first category groups the following advice to users: recognizing symptoms of COVID-19 infection; being informed about infection levels in one's neighborhood, but also being able to get advice from a health professional; and being able to make an appointment to be tested. The second set of options includes the use of the app as a kind of "corona pass," to show that one has not been in contact with a person infected with COVID-19 or to allow authorities using the app to check movements of infected persons. Users' and nonusers' attitudes were measured on a 5-point Likert scale, ranging from 1 (not agree) to 5 (agree). The study's questionnaire is included in Multimedia Appendix 2.

Analytical Strategy

Several analyses were performed to describe differences between users and nonusers of Coronalert, regarding both sociodemographic variables and different attitudes. Prior to the main analyses, all three categories of nonusers (ie, respondents who did not install the app, those who downloaded but did not activate the app, and those who uninstalled the app) were merged into a single group of nonusers. As such, a dichotomous variable of use versus nonuse was created for subsequent analyses. All analyses were performed using SPSS Statistics for Macintosh (version 28; IBM Corp).

First, chi-square analyses and *t* tests were performed to test between-group differences among users and nonusers regarding sociodemographic variables. Afterward, descriptive analyses were performed to assess the different reasons for not using the app. Subsequently, potential differences between users and nonusers were assessed concerning the Coronalert app's potential impact; users' and nonusers' acceptance of new app functionalities was also assessed. Chi-square tests and *t* tests were used for testing categorical and continuous between-group differences, respectively. Cohen *d* was reported and interpreted, along with *P* values, to assess the effect size and presence of significant effects, respectively. Cohen [35] recommends values of 0.10, 0.30, and 0.50 to delimit small, medium, and large effects, respectively.

Results

Overview

The study sample's composition and descriptive statistics are presented in Table 1. In total, 1850 respondents participated in the survey, including 50.4% (933/1850) women. The mean age of the respondents was 45.29 (SD 14.42) years, 39.6% (n=732) had a university or higher education college degree, 39.2% (n=726) had a higher secondary education degree, and 21.2% (n=392) had a lower secondary education degree.

Chi-square tests revealed no significant differences between users and nonusers regarding gender, education level, employment type, and reported health risks. In addition, an independent-samples *t* test indicated no significant differences in terms of age between users and nonusers.

Table 1. Study sample and characteristics of users and nonusers of the COVID-19 contact tracing app Coronalert in Belgium.

Characteristic	Total sample (N=1850)	Users of Coronalert (n=649)[a]	Nonusers of Coronalert (n=1201)[a]	Chi-square (*df*)	*t* test (*df*)	*P* value
Participants, n (%)	1850 (100)	649 (35.1)	1201 (64.9)	N/A[b]	N/A	N/A
Gender, n (%)						
Male	917 (49.6)	317 (34.6)	600 (65.4)	0.2 (1)	N/A	.65[c]
Female	933 (50.4)	322 (35.6)	601 (64.4)			
Age in years, mean (SD)	45.29 (14.42)	45.24 (14.68)	45.32 (14.28)	N/A	0.115 (1848)	.47
Education level, n (%)						
Lower secondary education	392 (21.2)	135 (34.4)	257 (65.5)	0.3 (2)	N/A	.87
Higher secondary education	726 (39.2)	252 (34.7)	474 (65.3)			
Higher education	732 (39.6)	262 (35.8)	470 (64.2)			
Type of employment, n (%)						
Worker	439 (23.7)	154 (35.1)	285 (64.9)	0.9 (3)	N/A	.84
White-collar worker, civil servant, or executive	1120 (60.5)	396 (35.4)	724 (64.6)			
Self-employed or liberal profession	248 (13.4)	82 (33.1)	166 (66.9)			
Flexi-job[d]	43 (2.3)	17 (39.5)	26 (60.5)			
Health risks[e], n (%)						
Yes	694 (37.5)	259 (37.3)	435 (62.7)	3.8 (2)	N/A	.15
No	1006 (54.4)	333 (33.1)	673 (66.9)			
I don't know	150 (8.1)	57 (38.0)	93 (62.0)			

[a]Percentages are based on the total values in the "Total sample" column.

[b]N/A: not applicable; this statistic was not calculated for this item; the *t* test was used for the age variable and the chi-square test was used for all other variables.

[c]Statistics for a set of variables are reported on the top line of that group.

[d]Flexi-job is a specific employment status where people can work additional hours (in the hospitality industry) on favorable terms, even when already retired or employed elsewhere.

[e]Participants with health risks suffer from one or more diseases that can be a risk factor when positive for COVID-19.

Reasons for Nonuse of Coronalert

In total, 64.9% (1201/1850) of respondents were not using the CTA at the time of the study. The data revealed three types of nonusers: 82.5% (991/1201) had not installed the app, 12.0% (144/1201) downloaded the app but never activated it, and 5.3% (64/1201) had installed the app, but already deleted it from their smartphone. Respondents were questioned about the reasons why they did not install, installed but did not activate, or uninstalled the app. These reasons are summarized in Table 2.

The most important reason for not installing the app was the lack of advantages respondents found in using Coronalert (308/991, 31.1% of the respondents who did not install the app). This was followed by worries about privacy (290/991, 29.3%) and dreading stress when using the app, as reasons for not installing it. Not having a smartphone (183/991, 18.5%) or having an older smartphone model (93/991, 9.4%) were also reasons given by the respondents for not installing the app. A total of 1 in 7 respondents (138/991, 13.9%) saw little value in the app, as they were convinced that they had a low risk of contracting the virus. Reasons for not installing the app that were related to governments' involvement in the app included worries about how the government would use the collected data (189/991, 19.1%) and that the government would be able to follow users' movements (80/991, 8.1%). Technical issues, such as experiencing problems when installing the app (46/991, 4.6%), being afraid they would experience difficulties when installing it (63/991, 6.4%), or being afraid that the app would drain the battery (96/991, 9.7%), were less frequently selected as reasons.

A total of 1 in 10 nonusers (144/1201, 11.9%) downloaded the app but did not activate it. The top reasons for these nonactivators included worries about how the government would treat their data (50/144, 34.7%), general privacy concerns (34/144, 23.6%), difficulties in using the app (27/144, 18.8%), or seeing few advantages in using it (16/144, 11.1%).

Another category of respondents deleted the app, although they first decided to install it on their smartphones (64/1201, 5.3% of our nonusers sample). The three most-cited reasons included the following: seeing too few advantages in using it (24/64, 37.5%), experiencing difficulties in using it (16/64, 25.0%),

and being afraid the app would impact their smartphone's battery consumption (12/64, 18.8%).

While a majority of respondents did not install Coronalert, almost 1 in 5 stated that they may decide to install the app in the future (183/991, 18.5%). The main reasons they gave for not yet having adopted this contact tracing technology were related to their smartphone, which was an older model that was not compatible with the app (43/183, 23.5%); not being in the possession of a smartphone (34/183, 18.6%); and having experienced technical issues or not seeing advantages in mobile contact tracing in the context of current COVID-19–related movement restrictions (both 29/183, 15.8%).

Table 2. Reasons for nonuse of the COVID-19 contact tracing app Coronalert in Belgium.

Reasons for nonuse of the app	Not installed (n=991), n (%)	Installed, but not activated (n=144), n (%)	Uninstalled (n=64), n (%)
I don't have a smartphone	183 (18.5)	N/A[a]	N/A
I have an older smartphone	93 (9.4)	N/A	N/A
I experienced a technical problem	46 (4.6)	17 (11.8)	6 (9.4)
I run little risk of contracting the coronavirus	138 (13.9)	12 (8.3)	6 (9.4)
I am afraid that my smartphone battery will drain fast	96 (9.7)	17 (11.8)	12 (18.8)[b]
For me, the app is too difficult to install	63 (6.4)	27 (18.8)[c]	16 (25.0)[c]
I find too few advantages in using the app	308 (31.1)	16 (11.1)	24 (37.5)
I am worried about how the government will use the obtained data	189 (19.1)	50 (34.7)	11 (17.2)
I am afraid that my privacy is not guaranteed when I use the app	290 (29.3)	34 (23.6)	5 (7.8)
I worry that the government will be able to follow my movements	80 (8.1)	11 (7.6)	0 (0)
I do not trust the app	176 (17.8)	6 (4.2)	6 (9.4)
Using the app would cause me stress	208 (21.0)	17 (11.8)	10 (15.6)[d]
I see only few advantages in using the app due to the current measures that make fewer activities outside of home possible	93 (9.4)	27 (18.8)	6 (9.4)

[a]N/A: not applicable; these questions were not submitted to respondents without a smartphone or those with an older smartphone.

[b]The item was adapted to fit the context of stopping the use of Coronalert: "I have the impression that my battery drains more rapidly."

[c]The item was rephrased as "For me, the app is too difficult to use."

[d]The item was rephrased as "Using the app stresses me."

Differences Between Nonusers and Users as to Coronalert's Potential Impact

As shown in Table 3, the most important contributions of the app for users were as follows: helping the government in its fight against the pandemic (530/649, 81.7%), a CTA is more rapid than traditional contact tracing in detecting and warning infected users (481/649, 74.1%), the app diminishes the spread of the virus (445/649, 68.6%), the app rapidly alerts users of risky contacts (408/649, 62.9%), and a CTA detects risky contacts while preserving users' privacy (384/649, 59.2%). Overall, these top five reasons regarding Coronalert's usefulness were cited less frequently by nonusers of the app, who seemed to be less convinced by the potential impact of the app. An independent-samples *t* test did report a significant difference, with a large effect size (t_{1848}=–15.37, *P*<.001 [2-tailed]; Cohen *d*=0.76, 95% CI 0.66-0.86) between app users and nonusers concerning the impact of Coronalert on diminishing the spread of the virus. Users of the app were more convinced of the impact of CTAs than nonusers. Moreover, Coronalert users were more assured than nonusers that the app would inform them more rapidly of potential infections than would traditional contact tracing. This significant difference had a large effect size (t_{1624}=–16.99, *P*<.001 [2-tailed]; Cohen *d*=0.78, 95% CI 0.67-0.87). In general, users were more persuaded that a CTA would inform them rapidly if they had a risky contact (t_{1848}=–2.55, *P*<.01 [2-tailed]; Cohen *d*=0.13, 95% CI 0.03-0.22). Users were also more convinced that by using a CTA, one would take more precautionary measures not to spread the virus than nonusers, but the difference had a medium effect size (t_{1848}=–6.40, *P*<.001 [2-tailed]; Cohen *d*=0.31, 95% CI 0.21-0.41). Users were more strongly convinced that using the app helps the government to fight the virus. The difference between nonusers and users had a strong effect size (t_{1716}=–20.81, *P*<.001 [2-tailed]; Cohen *d*=0.92, 95% CI 0.82-1.02). Finally, users were more convinced than nonusers that the CTA respects users' privacy. However, a small effect size was found (t_{1848}=–3.62, *P*<.001 [2-tailed]; Cohen *d*=0.17, 95% CI 0.08-0.27).

Table 3. Attitudes toward the potential impact of the COVID-19 contact tracing app Coronalert in Belgium.

Questions and responses	Total sample (N=1850)	Nonusers of Coronalert (n=1201)	Users of Coronalert (n=649)	*t* test (*df*)	*P* value	Cohen *d*
By using Coronalert, one collaborates in diminishing the spread of the coronavirus						
Response score, mean (SD)[a]	N/A[b]	3.03 (1.14)	3.86 (1.01)	–15.37 (1848)[c]	<.001[c]	0.76[c]
Response, n (%)						
Not agree	175 (9.5)	159 (13.2)	16 (2.5)			
Rather disagree	211 (11.4)	161 (13.4)	50 (7.7)			
Not agree/not disagree	626 (33.8)	488 (40.6)	138 (21.3)			
Rather agree	520 (28.1)	267 (22.2)	253 (39.0)			
Agree	318 (17.2)	126 (10.5)	192 (29.6)			
By using Coronalert, one is more wary when having face-to-face contacts						
Response score, mean (SD)	N/A	3.02 (1.15)	3.10 (1.14)	–1.520 (1848)	.13	0.07
Response, n (%)						
Not agree	247 (13.4)	171 (14.2)	76 (11.7)			
Rather disagree	253 (13.7)	156 (13.0)	97 (14.9)			
Not agree/not disagree	694 (37.5)	466 (38.8)	228 (35.1)			
Rather agree	476 (25.7)	296 (24.6)	180 (27.7)			
Agree	180 (9.7)	112 (9.3)	68 (10.5)			
By using Coronalert, users know rapidly when they have been in contact with someone who is infected with the coronavirus						
Response score, mean (SD)	N/A	3.47 (1.12)	3.61 (1.08)	–2.551 (1848)	.01	0.13
Response, n (%)						
Not agree	157 (8.5)	116 (9.7)	41 (6.3)			
Rather disagree	135 (7.3)	79 (6.6)	56 (8.6)			
Not agree/not disagree	449 (24.3)	305 (25.4)	144 (22.2)			
Rather agree	811 (43.8)	527 (43.9)	284 (43.8)			
Agree	298 (16.1)	174 (14.5)	124 (19.1)			
By using Coronalert, one will take more precautionary measures not to spread the coronavirus						
Response score, mean (SD)	N/A	2.82 (1.22)	3.19 (1.15)	–6.396 (1848)	<.001	0.31
Response, n (%)						
Not agree	288 (15.6)	233 (19.4)	55 (8.5)			
Rather disagree	346 (18.7)	213 (17.7)	133 (20.5)			
Not agree/not disagree	581 (31.4)	403 (33.6)	178 (27.4)			
Rather agree	447 (24.2)	246 (20.5)	201 (31.0)			
Agree	188 (10.2)	106 (8.8)	82 (12.6)			
By using Coronalert, one helps the government in its fight against the coronavirus						
Response score, mean (SD)	N/A	3.12 (1.16)	4.09 (0.83)	–20.810 (1716)	<.001	0.92
Response, n (%)						
Not agree	150 (8.1)	150 (12.5)	0 (0)			
Rather disagree	181 (9.8)	143 (11.9)	38 (5.9)			
Not agree/not disagree	560 (30.3)	479 (39.9)	81 (12.5)			
Rather agree	592 (32.0)	275 (22.9)	317 (48.8)			
Agree	367 (19.8)	154 (12.8)	213 (32.8)			

Questions and responses	Total sample (N=1850)	Nonusers of Coronalert (n=1201)	Users of Coronalert (n=649)	*t* test (*df*)	*P* value	Cohen *d*
Coronalert detects contacts with persons who are infected with the coronavirus, respecting the privacy of the app users						
Response score, mean (SD)	N/A	3.51 (1.17)	3.71 (1.15)	–3.618 (1848)	<.001	0.17
Response, n (%)						
Not agree	166 (9.0)	117 (9.7)	49 (7.6)			
Rather disagree	64 (3.5)	46 (3.8)	18 (2.8)			
Not agree/not disagree	615 (33.2)	417 (34.7)	198 (30.5)			
Rather agree	545 (29.5)	354 (29.5)	191 (29.4)			
Agree	460 (24.9)	267 (22.2)	193 (29.7)			
Coronalert is quicker than contact tracing by phone, to check the contacts of people who are infected with the coronavirus						
Response score, mean (SD)	N/A	3.28 (1.09)	4.06 (0.85)	–16.985 (1624)	<.001	0.78
Response, n (%)						
Not agree	115 (6.2)	115 (9.6)	0 (0)			
Rather disagree	103 (5.6)	80 (6.7)	23 (3.5)			
Not agree/not disagree	666 (36.0)	521 (43.4)	145 (22.3)			
Rather agree	573 (31.0)	321 (26.7)	252 (38.8)			
Agree	393 (21.2)	164 (13.7)	229 (35.3)			
Using Coronalert helps to prevent loved ones from being infected with the coronavirus						
Response score, mean (SD)	N/A	3.33 (1.23)	3.41 (1.22)	–1.307 (1848)	.19	0.07
Response, n (%)						
Not agree	214 (11.6)	146 (12.2)	68 (10.5)			
Rather disagree	173 (9.4)	108 (9.0)	65 (10.0)			
Not agree/not disagree	558 (30.2)	377 (31.4)	181 (27.9)			
Rather agree	539 (29.1)	338 (28.1)	201 (31.0)			
Agree	366 (19.8)	232 (19.3)	134 (20.6)			

[a]Mean scores were calculated for nonusers and users of the app separately.

[b]N/A: not applicable; mean scores were not calculated for the entire sample.

[c]This value was calculated using the mean scores for users and nonusers of the app and not the frequencies of individual responses.

Differences Between Nonusers and Users as to Coronalert's Potential Applications

As highlighted before, almost one-third of respondents (308/991, 31.1%) who did not install the app saw few advantages in using it. Therefore, complementary functionalities that respond to potential users' needs could stimulate adoption and continued use.

In general, users of Coronalert were more in favor of the potential options that were proposed than respondents who did not use the app (Table 4). Users were most in favor of being informed that they visited a place where one or several persons had later been diagnosed with COVID-19 (547/649, 84.3%), being able to make an appointment to get tested (525/649, 80.9%), getting advice on how to protect oneself (458/649, 70.6%), having contact with a health professional (473/649, 72.9%), receiving statistics about the impact of the virus (eg, number of infections and hospitalizations; 453/649, 69.8%), being informed about the number of infections in one's neighborhood (438/649, 67.5%), or getting access to a questionnaire to assess COVID-19 symptoms (431/649, 66.4%).

All differences between users and nonusers in their support for the proposed new functionalities were significant, with medium to strong effect sizes. In particular, Coronalert users were significantly more in favor of being informed that they visited a place where one or several persons had later been diagnosed with COVID-19 (t_{1565}=–13.62, *P*<.001 [2-tailed]; Cohen *d*=0.54, 95% CI 0.45-0.64), being able to make an appointment with a health professional to get tested (t_{1579}=–13.33, *P*<.001 [2-tailed]; Cohen *d*=0.64, 95% CI 0.53-0.73), getting advice on how to protect oneself (t_{1418}=–10.03, *P*<.001 [2-tailed]; Cohen *d*=0.37, 95% CI 0.25-0.44), and being able to get in contact with a health professional (t_{1438}=–11.43, *P*<.001 [2-tailed]; Cohen *d*=0.54, 95% CI 0.44-0.64). Also, a majority were in favor of viewing statistics about the evolution of the impact of the virus (eg, infections and hospitalizations; t_{1527}=–14.91, *P*<.001 [2-tailed]; Cohen *d*=0.69, 95% CI 0.60-0.80), gaining information about the number of infections in one's neighborhood (t_{1239}=–7.55,

P<.001 [2-tailed]; Cohen *d*=0.38, 95% CI 0.29-0.48), or getting access to a questionnaire to assess COVID-19 symptoms (t_{1848}=–9.61, *P*<.001 [2-tailed]; Cohen *d*=0.46, 95% CI 0.37-0.56).

Concerning potential functionalities of Coronalert with a focus on control and access, findings are more mixed. Among users of the app, the implementation of these functionalities seems more debated, as often only half of this group agreed on the future implementation of these functionalities. For example, about half of the users agreed on a "green screen" functionality to access events (358/649, 55.2%), schools (357/649, 55.0%), and offices (322/649, 49.6%). A narrow majority were in favor of using the app to control the whereabouts of people who are infected with COVID-19 (339/649, 52.2%). While overall acceptability of these control functionalities were lower compared to the information-related options, users were still significantly more likely to accept these functionalities compared to nonusers (access to events: t_{1248}=–10.73, *P*<.001 [2-tailed]; Cohen *d*=0.53, 95% CI 0.44-0.63; access to schools: t_{1282}=–11.06, *P*<.001 [2-tailed]; Cohen *d*=0.55, 95% CI 0.45-0.64; access to offices: t_{1225}=–10.55, *P*<.001 [2-tailed]; Cohen *d*=0.53, 95% CI 0.43-0.62; control of whereabouts: t_{1179}=–9.20, *P*<.001 [2-tailed]; Cohen *d*=0.47, 95% CI 0.37-0.56).

Table 4. Attitudes toward potential applications of the COVID-19 contact tracing app Coronalert in Belgium.

Questions and responses	Total sample (N=1850)	Nonusers of Coronalert (n=1201)	Users of Coronalert (n=649)	*t* test (*df*)	*P* value	Cohen *d*
Information and advice						
Through a questionnaire that is integrated in the app that questions users about symptoms, you should be able to assess if you are infected with the coronavirus						
Response score, mean (SD)[a]	N/A[b]	3.27 (1.12)	3.79 (1.12)	–9.61 (1848)[c]	<.001[c]	0.46[c]
Response, n (%)						
Not agree	150 (8.1)	123 (10.2)	27 (4.2)			
Rather disagree	159 (8.6)	93 (7.7)	66 (10.2)			
Not agree/not disagree	620 (33.5)	495 (41.2)	125 (19.3)			
Rather agree	544 (29.4)	317 (26.4)	227 (35.0)			
Agree	377 (20.4)	173 (14.4)	204 (31.4)			
Through the app, you should be able to be informed about how many individuals in your neighborhood are infected with the coronavirus						
Response score, mean (SD)	N/A	3.25 (1.14)	3.70 (1.24)	–7.551 (1239)	<.001	0.38
Response, n (%)						
Not agree	186 (10.1)	122 (10.2)	64 (9.9)			
Rather disagree	177 (9.6)	131 (10.9)	46 (7.1)			
Not agree/not disagree	538 (29.1)	437 (36.4)	101 (15.6)			
Rather agree	592 (32.0)	342 (28.5)	250 (38.5)			
Agree	357 (19.3)	169 (14.1)	188 (29.0)			
Through the app, you should be able to be informed that you visited a place where one or several persons were present who were infected with the coronavirus						
Response score, mean (SD)	N/A	3.55 (1.34)	4.21 (0.93)	–13.62 (1565)	<.001	0.54
Response, n (%)						
Not agree	134 (7.2)	116 (9.7)	18 (2.8)			
Rather disagree	54 (2.9)	37 (3.1)	17 (2.6)			
Not agree/not disagree	443 (23.4)	366 (30.5)	67 (10.3)			
Rather agree	693 (37.5)	440 (36.6)	253 (39.0)			
Agree	536 (29.0)	242 (20.1)	294 (45.3)			
Through the app, you should be able to receive advice on how you can better protect yourself against the coronavirus						
Response score, mean (SD)	N/A	3.38 (1.8)	3.92 (1.01)	–10.03 (1418)	<.001	0.37
Response, n (%)						
Not agree	154 (8.3)	123 (10.2)	31 (4.8)			
Rather disagree	115 (6.2)	83 (6.9)	32 (4.9)			
Not agree/not disagree	577 (31.2)	449 (37.4)	128 (19.7)			
Rather agree	534 (28.9)	311 (25.9)	223 (34.4)			
Agree	470 (25.4)	235 (19.6)	235 (36.2)			
Through the app, you should be able to receive general information on the spread of the coronavirus (eg, weekly averages of infections, hospitalizations, and deaths)						
Response score, mean (SD)	N/A	3.16 (1.33)	4.04 (1.13)	–14.91 (1527)	<.001	0.69
Response, n (%)						
Not agree	254 (13.7)	226 (18.8)	28 (4.3)			
Rather disagree	108 (5.8)	76 (6.3)	32 (4.9)			
Not agree/not disagree	541 (29.2)	405 (33.7)	136 (21.0)			

Questions and responses	Total sample (N=1850)	Nonusers of Coronalert (n=1201)	Users of Coronalert (n=649)	*t* test (*df*)	*P* value	Cohen *d*
Rather agree	411 (22.2)	265 (22.1)	146 (22.5)			
Agree	536 (29.0)	229 (19.1)	307 (47.3)			
Through the app, you should be able to make an appointment to be tested for the coronavirus						
Response score, mean (SD)	N/A	3.47 (1.23)	4.20 (1.03)	–13.33 (1579)	<.001	0.64
Response, n (%)						
Not agree	176 (9.5)	154 (12.8)	22 (3.4)			
Rather disagree	90 (4.9)	62 (5.2)	28 (4.3)			
Not agree/not disagree	416 (22.5)	342 (28.5)	74 (11.4)			
Rather agree	553 (29.9)	351 (29.2)	202 (31.1)			
Agree	615 (33.2)	292 (24.3)	323 (49.8)			
Through the app, you should be able to get in contact with a health professional to ask advice related to the coronavirus						
Response score, mean (SD)	N/A	3.29 (1.30)	3.97 (1.19)	–11.43 (1438)	<.001	0.54
Response, n (%)						
Not agree	230 (12.4)	190 (15.8)	40 (6.2)			
Rather disagree	124 (6.7)	79 (6.6)	45 (6.9)			
Not agree/not disagree	465 (25.1)	374 (31.1)	91 (14.0)			
Rather agree	499 (27.0)	310 (25.8)	189 (29.1)			
Agree	532 (28.8)	248 (20.6)	284 (43.8)			
Control and access						
Public authorities should be able to follow the whereabouts of people who are infected with the coronavirus						
Response score, mean (SD)	N/A	2.63 (1.36)	3.30 (1.56)	–9.20 (1179)	<.001	0.47
Response, n (%)						
Not agree	533 (28.8)	388 (32.3)	145 (22.3)			
Rather disagree	166 (9.0)	98 (8.2)	68 (10.5)			
Not agree/not disagree	516 (27.9)	419 (34.9)	97 (14.9)			
Rather agree	281 (15.2)	157 (13.1)	124 (19.1)			
Agree	354 (19.1)	139 (11.6)	215 (33.1)			
The organizer of an event should be able to require participants to show through the Coronalert app on their smartphone that they were not in contact with someone who is infected with the coronavirus						
Response score, mean (SD)	N/A	2.74 (1.33)	3.47 (1.43)	–10.73 (1248)	<.001	0.53
Response, n (%)						
Not agree	427 (23.1)	332 (27.6)	95 (14.6)			
Rather disagree	205 (11.1)	124 (10.3)	81 (12.5)			
Not agree/not disagree	529 (28.6)	414 (34.5)	115 (17.7)			
Rather agree	334 (18.1)	191 (15.9)	143 (22.0)			
Agree	355 (19.2)	140 (11.7)	215 (33.1)			
An employer should be able to require employees to show through the Coronalert app on their smartphone that they were not in contact with someone who is infected with the coronavirus						
Response score, mean (SD)	N/A	2.60 (1.32)	3.32 (1.45)	–10.55 (1225)	<.001	0.53
Response, n (%)						
Not agree	499 (27.0)	382 (31.8)	117 (18.0)			
Rather disagree	193 (10.4)	122 (10.2)	71 (10.9)			
Not agree/not disagree	553 (29.9)	414 (34.5)	139 (21.4)			

Questions and responses	Total sample (N=1850)	Nonusers of Coronalert (n=1201)	Users of Coronalert (n=649)	*t* test (*df*)	*P* value	Cohen *d*
Rather agree	297 (16.1)	165 (13.7)	132 (20.3)			
Agree	308 (16.6)	118 (9.8)	190 (29.3)			
A school should be able to require students to show through the Coronalert app on their smartphone that they were not in contact with someone who is infected with the coronavirus						
Response score, mean (SD)	N/A	2.70 (1.37)	3.46 (1.43)	–11.06 (1282)	<.001	0.55
Response, n (%)						
Not agree	461 (24.9)	366 (30.5)	95 (14.6)			
Rather disagree	197 (10.6)	113 (9.4)	84 (12.9)			
Not agree/not disagree	510 (27.6)	397 (33.1)	113 (17.4)			
Rather agree	309 (16.7)	167 (13.9)	142 (21.9)			
Agree	373 (20.2)	158 (13.2)	215 (33.1)			

[a]Mean scores were calculated for nonusers and users of the app separately.

[b]N/A: not applicable; mean scores were not calculated for the entire sample.

[c]This value was calculated using the mean scores for users and nonusers of the app and not the frequencies of individual responses.

Discussion

This study found that, one month after its launching, one-third of a stratified sample of the Flemish population used Coronalert. Our analyses showed that there were no significant differences among users and nonusers of the Coronalert app in terms of age, gender, education level, professional activity, and health condition. This contrasts with previous work [18] on the topic and suggests that other, possibly attitudinal, factors are at play. Previous research already highlighted the importance of potential users' attitudes toward the impact of using a CTA, but also potential concerns about privacy and how users perceive social norms concerning CTA usage [1].

We identified three types of nonusers of the app: those who never installed the app, those who installed but never activated the app, and those who deleted the app after installing. Considering the first group, the most important reasons for not installing the app were a lack of perceived advantages, privacy concerns, and feared stress when using the app. Fewer respondents referred to technical reasons, such as not having a smartphone or having an incompatible or older model, or being convinced that they run little risk of contracting the virus. These results partly correspond, but also contrast, with other research focusing on nonadoption motives. An Australian study found that for those who refused to download the app, privacy concerns constituted the most important reason, followed by technical problems [25]. A multi-country study confirmed that one of the main factors that may hinder app uptake are concerns over privacy and cybersecurity [17]. In research conducted in Switzerland and France, the lack of usefulness was the most important reason, but privacy and security concerns were also mentioned as important reasons [18,36]. Technical reasons were less stressed by this study's respondents, but were highlighted in other studies [18,25]. Nevertheless, making the app compatible with older smartphones could be important to enhance its use, as 9.4% (93/991) of this study's respondents had compatibility issues. Still, an important proportion of respondents (183/991, 18.5%) did not possess a smartphone and, therefore, were excluded from using this contact tracing technology. To be able to reach members of this population who are interested in digital contact tracing but do not possess a compatible smartphone, an adapted contact tracing system could be proposed that complements the use of CTAs, namely Bluetooth tokens [37,38]. This system could help cover people without a smartphone or those who prefer not to use a CTA [39].

In contrast with the study by von Wyl et al [18] among Swiss citizens, more Belgian respondents were concerned about the app's battery use. Moreover, lack of trust in government was expressed by a limited number of Swiss respondents. By contrast, more Belgian respondents feared the government's use of the collected data (189/991, 19.1%). In addition, almost one-fifth of nonusers (176/991, 17.8%) stated that they do not trust the app. Concerns of government surveillance at the end of the pandemic was also an important reason for not installing the app in a five-country survey [17]. In other words, nonadopters need to be convinced of how users' privacy is protected. Stressing the data-minimizing solution that has been adopted not only protects users' privacy rights but also stimulates broader support in the population [40]. Therefore, increasing the readability of the privacy policy could reassure potential users and increase app adoption [41].

Another important reason given by nonusers was feared stress when using the app (208/991, 21.0% of current nonusers). Therefore, clear explanations should be given in the app, as well as in video animations on the app's website, regarding the steps to take when confronted with a message that one has had a high-risk exposure. At this stressful moment, users need assistance in carefully taking the right steps to get tested and engage in protective measures. However, user statistics of Coronalert revealed that 37% of all app users who received a positive COVID-19 test result—in total, some 20,000 users—confirmed their status through the app, which automatically and anonymously informed close contacts that

they have been near someone who has tested positive [42]. In other words, almost two-thirds did not engage in this essential step to warn other users. Therefore, more accompaniment is needed when users are confronted with this stressful news, to encourage them to engage in warning other users. In general, more information is needed about how the app functions, as other research found there are some important misconceptions about the possibilities and limits of contact tracing technology [25].

The study also found out that some potential users still need to be convinced of the app's potential impact. In total, 31.1% (308/991) of individuals who did not install the app saw limited advantages in using it. Although some contact restricting measures were in place when the survey was fielded, the app could still prove its usefulness in tracing risky contacts in shops and other public places that were open. Stressing the potential impact of the app is important to augment individuals' uptake intention. Previous research found that the strongest predictor of app use intention among potential users was their expectations concerning the performance of the app to augment their knowledge of potential confrontation with a COVID-19–positive contact and how it could help circumvent the spread of the virus [1]. Therefore, testimonials from users and influencers on general media and social media could be used to inform nonusers about their positive experience with the app [1,18,39,43]. In Belgium, public broadcasters and other media have explained Coronalert's functioning. However, when launching the app and at the time of this survey, only textual information was included on the website and on the app explaining the app's functioning. No video animations were available on the website or on the app that clearly explained how Coronalert functions [44]. This contrasts with other countries, where video animations clearly explain how the implemented CTA works and also touch on sensitive issues, such as privacy [45].

This study's results further show that a small part of the sample (144/1850, 7.8%) have installed the app on their smartphone, but eventually decided not to activate it. This group, who were first convinced to download Coronalert but then hesitated to use it, could be further informed about the advantages of app use. Additionally, some of their concerns could be countered by explaining how the app protects users' privacy by not identifying nor individually locating users; at the same time, the advantages one has in using the app could be stressed in order to dispel their doubts. Moreover, Coronalert and other CTAs are increasingly interoperable in EU member states [46]. This could be stressed as an important advantage when traveling.

Another category of respondents first downloaded the app but eventually uninstalled it from their smartphone (64/1850, 3.5%). They gave similar reasons to those of the nonadopters. For instance, respondents who uninstalled the app stated that they experienced difficulties using the app. It would, therefore, be important for app developers to gain in-depth insight into the issues that former users have experienced. Moreover, additional usability research could be conducted, as previous research among potential users found issues related to the understandability of CTAs, doubts concerning their usefulness and privacy, and which follow-up actions were expected after a risk exposure notification [47]. Moreover, previous research analyzing media content concerning the implementation of CTAs has identified thresholds and challenges experienced by users and showed the need to intensify communication about the benefits of using the apps [48]. By scraping social media and analyzing app users' reviews, comments, and reported technical issues, developers could collect input to address reported issues and further develop CTA functionalities [4,49]. Also, by conducting in-depth interviews with potential users and analyzing media coverage on CTAs, the framing of the app's functionalities and discussed issues can be detected [50].

The study further found that nonusers were significantly less convinced than users of several potential contributions of the app during this pandemic. While a majority of users (445/649, 68.6%) were convinced that it can contribute to diminishing the spread of the virus, only one-third (393/1201, 32.7%) of nonusers agreed. Users were also more convinced that the app helps the government in its fight and is quicker than traditional contact tracing, while, at the same time, respecting individuals' privacy. This corroborates the already-stressed importance of making the impact of using Coronalert more concrete and visible and, at the same time, showing how the system respects users' privacy. Communication campaigns could stress specific individual and societal advantages of contact tracing. Moreover, research into the reasons that could trigger nonusers to adopt the app could be used to lower thresholds for nonadopters. For instance, vulnerable groups (eg, senior citizens and individuals with comorbidities) and groups with a high potential to spread the virus, because they are frequently in contact with other people outside their household, could be targeted by specific campaigns to drive them to adopt the app [51].

Finally, this study also assessed the potential support for additional functionalities. Among both users and nonusers, functionalities that focus on information were considered more acceptable than options concerning control and access. For example, users were most in favor of being informed that they had visited a place where people were present who had been diagnosed with COVID-19. This would need adaptations of the current system, as location is not recorded. An alternative would be to have check-ins in public places, so visitors would be informed if they have been in proximity with confirmed COVID-19 cases [52]. Moreover, a majority of users and nonusers were in favor of expanding the app's mobile health functionalities, by including more information and advice on how to prevent infection and recognize symptoms as well as being able to get in touch with a health professional for advice.

While the possibility of using the app as a green card for events, school, and workplace access was most favored in the "control and access" category, overall acceptance was rather low. Among the users, only half of the respondents agreed that this kind of functionality should be implemented. Among nonusers, acceptance was even lower, with a big majority of the respondents indicating that they are not in favor of this option. These results correspond to a US study that found that a minority of young adults were willing to accept digital surveillance prior to participating in activities in public places (eg, concerts and restaurants) [53]. The EU Digital COVID Certificate includes information on citizens' vaccination, test, and recovery status

[54]. However, our results indicate that public support among Flemish citizens for such implementations is low. In sum, governments and app developers need to strike the right balance between finding appealing new functionalities that stimulate app uptake and sustained use, while addressing privacy and other issues voiced by potential users [3].

Several limitations apply to this study. First, although our sample's strata were based on the proportions reported by the country's official statistics concerning age, gender, and education level, we may have missed specific groups, more particularly, individuals who are disadvantaged in terms of income, health status, or other characteristics. Relatedly, it is possible that our sample was prone to self-selection bias, given that members of the panel were free to participate in the study. However, we aimed to counter this bias by relying on a stratified sampling procedure, following federal statistics of the sociodemographic profile of Belgian citizens. Second, as the pandemic and subsequent measures still develop, further research is needed on app use intention, actual usage, and discontinuation of use in time periods where more or less restricting measures are in place. Therefore, it could be important to conduct longitudinal research or comparative research between countries that have different levels of COVID-19–related measures, as motivations to adopt CTAs may fluctuate depending on the measures in place that limit social contact. Further comparative research could also be encouraged to address the reasons for nonadoption or discontinuation of use. By conducting research in countries with different political systems, the role of trust in government and other institutions involved in the development and deployment of CTAs could be further investigated [17]. Finally, this study focused on public support for new functionalities in one country. Future research might investigate which specific combination of functionalities works best in which countries and among which specific target groups [3].

Conflicts of Interest

None declared.

Multimedia Appendix 1
How the contact tracing app (CTA) Coronalert works.
[DOCX File , 14 KB - publichealth_v8i1e22113_app1.docx]

Multimedia Appendix 2
Questionnaire concerning Coronalert.
[DOCX File , 23 KB - publichealth_v8i1e22113_app2.docx]

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Abbreviations

CTA: contact tracing app
DP-3T: Distributed Privacy Preserving Proximity Tracing
EU: European Union

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Original Paper

COVID-19 Vaccine Hesitancy and Acceptance Among Individuals With Cancer, Autoimmune Diseases, or Other Serious Comorbid Conditions: Cross-sectional, Internet-Based Survey

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Abstract

Background: Individuals with comorbid conditions have been disproportionately affected by COVID-19. Since regulatory trials of COVID-19 vaccines excluded those with immunocompromising conditions, few patients with cancer and autoimmune diseases were enrolled. With limited vaccine safety data available, vulnerable populations may have conflicted vaccine attitudes.

Objective: We assessed the prevalence and independent predictors of COVID-19 vaccine hesitancy and acceptance among individuals with serious comorbidities and assessed self-reported side effects among those who had been vaccinated.

Methods: We conducted a cross-sectional, 55-item, online survey, fielded January 15, 2021 through February 22, 2021, among a random sample of members of Inspire, an online health community of over 2.2 million individuals with comorbid conditions. Multivariable regression analysis was utilized to determine factors independently associated with vaccine hesitancy and acceptance.

Results: Of the 996,500 members of the Inspire health community invited to participate, responses were received from 21,943 individuals (2.2%). Respondents resided in 123 countries (United States: 16,277/21,943, 74.2%), had a median age range of 56-65 years, were highly educated (college or postgraduate degree: 10,198/17,298, 58.9%), and had diverse political leanings. All respondents self-reported at least one comorbidity: cancer, 27.3% (5459/19,980); autoimmune diseases, 23.2% (4946/21,294); chronic lung diseases: 35.4% (7544/21,294). COVID-19 vaccine hesitancy was identified in 18.6% (3960/21,294), with 10.3% (2190/21,294) declaring that they would not, 3.5% (742/21,294) stating that they probably would not, and 4.8% (1028/21,294) not sure whether they would agree to be vaccinated. Hesitancy was expressed by the following patients: cancer, 13.4% (731/5459); autoimmune diseases, 19.4% (962/4947); chronic lung diseases: 17.8% (1344/7544). Positive predictors of vaccine acceptance included routine influenza vaccination (odds ratio [OR] 1.53), trust in responsible vaccine development (OR 14.04), residing in the United States (OR 1.31), and never smoked (OR 1.06). Hesitancy increased with a history of prior COVID-19 (OR 0.86), conservative political leaning (OR 0.93), younger age (OR 0.83), and lower education level (OR 0.90). One-quarter (5501/21,294, 25.8%) had received at least one COVID-19 vaccine injection, and 6.5% (1390/21,294) completed a 2-dose series. Following the first injection, 69.0% (3796/5501) self-reported local reactions, and 40.0% (2200/5501) self-reported systemic reactions, which increased following the second injection to 77.0% (1070/1390) and 67.0% (931/1390), respectively.

Conclusions: In this survey of individuals with serious comorbid conditions, significant vaccine hesitancy remained. Assumptions that the most vulnerable would automatically accept COVID-19 vaccination are erroneous and thus call for health care team members to initiate discussions focusing on the impact of the vaccine on an individual's underlying condition. Early self-reported side effect experiences among those who had already been vaccinated, as expressed by our population, should be reassuring and might be utilized to alleviate vaccine fears. Health care–related social media forums that rapidly disseminate accurate information about the COVID-19 vaccine may play an important role.

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KEYWORDS

COVID-19; vaccine; hesitancy; cancer; autoimmune diseases; vaccination; comorbidities; SARS-CoV-2; survey; cross-sectional; survey; incidence; safety; vulnerable; perception; attitude

Introduction

The rapid development of safe and effective vaccines against SARS-CoV-2 may stem the global COVID-19 pandemic. However, vaccine hesitancy—the reluctance or refusal to vaccinate—has emerged as a major worldwide public health concern, especially as it may impair the ability to reach herd immunity status [1-5]. An Ipsos poll of 15 countries for the World Economic Forum conducted in January 2021 reported vaccine acceptance rates ranging from 86% in Brazil to only 46% in Russia, with the United States ranking 12th (63% vaccine acceptance) [6]. Over time, COVID-19 vaccine acceptance has increased. Serial tracking polls by the Kaiser Family Foundation conducted in the United States reported that, as of July 2021, 70% of adults had either "received" or "will receive as soon as possible" the vaccine, up from 55% in February 2021 and 34% in early December 2020 [7,8]. However, antivaccination sentiment remained constant over this timeframe, with 14% stating that they would "definitely not get vaccinated" and 3% agreeing "only if required" [8]. Although the more virulent coronavirus Delta variant has increased the rapidity of vaccination uptake among individuals who were "waiting to see," only 2% of those who refused vaccines were influenced by its emergence [8]. Multiple studies have explored reasons for COVID-19 vaccine hesitancy, with vaccine-specific concerns (side effects and efficacy), a need for more information, racial/ethnic biases, political views, general antivaccine attitudes or beliefs, and a lack of trust being most commonly cited [4,5,7-12].

Individuals with comorbid conditions have been disproportionately affected by COVID-19. A US review of nearly 500,000 commercially insured COVID-19 patients noted that, although only 51.7% had pre-existing conditions, 83.3% of the COVID-19–related deaths occurred among those with comorbidities. The risk of dying from COVID-19 was strongly correlated with the number of comorbidities, nearly doubling with a single comorbid condition and increasing 8-fold with 5 or more conditions [13]. Persons with developmental disorders, congenital and acquired neurologic disabilities, cancers (especially lung cancer, leukemia, and lymphoma), sickle cell disease, chronic kidney disease, heart failure, and diabetes appear to be at a particularly high risk for COVID-19–related mortality [13,14]. Hypertension, obesity, chronic lung diseases, and chronic liver diseases have also been associated with more severe COVID-19 disease [15-18].

COVID-19 vaccine allocation policies have prioritized individuals with serious comorbidities [19]. However, since regulatory clinical trials of COVID-19 vaccines excluded those with immunocompromising conditions and those receiving immunosuppressive therapies, few patients with cancer and autoimmune diseases were enrolled [20,21]. Thus, with limited vaccine safety and efficacy data available, but noting the increased mortality risk, patients with comorbidities may have conflicted COVID-19 vaccine attitudes. We therefore initiated an internet-based survey drawing from our international health-oriented social network to explore issues surrounding COVID-19 vaccine hesitancy in these vulnerable populations. Additionally, we sought to explore early self-reported side effect experiences among those who had already been vaccinated, as this might provide information useful to combating hesitancy.

Methods

Study Design and Participants

Survey participants were recruited from Inspire (Arlington, VA), an online health community of over 2.2 million individuals with comorbid conditions and their caregivers. Members anonymously engage with others with similar conditions through discussion posts and direct messaging. The community, with members residing in over 100 countries, represents over 3600 comorbid conditions including cancer, autoimmune diseases, rare diseases, and other chronic conditions.

When individuals join Inspire, they are given the opportunity of opting in to receive invitations for research projects. For this study, email invitations were sent on a daily basis to a computer-generated random sample of members who had agreed to receive research survey requests. Prior to participating in this study, individuals completed a consent form (approved by WCG IRB, Puyallup, WA) that detailed the purpose of the research. Participants were able to withdraw at any time throughout the survey. Participants were not compensated. Duplicate responses were removed by review of unique tokens assigned to participants.

Measures

The survey consisted of 55 items, with initial responses leading to a potential addition of 8 follow-up questions. The survey was implemented using Alchemer, a web-based survey tool. Survey logic, programming, testing, and data validation were done via Alchemer. Items used to assess vaccine perception and hesitancy were adapted from Pew Research Center's American Trends Panel 2020 survey, with additional questions added and linguistic adjustments [22]. Demographic, health conditions, and treatment-related questions were adapted from Inspire's standard question sets. Behavioral and political leaning questions were adapted and modified from the Kaiser Family Foundation's vaccine perception survey [7]. A dichotomous conservative political leaning variable was created from the multi-option political leaning question to include in the logistic regression analysis. This was done by grouping participants into either conservative political leaning or nonconservative political leaning categories.

Independent measures in the survey detailed demographics including age, education level, political leaning, ethnicity,

income, residence (country of residence; if in the United States, state of residence), patient history of disease including specific disease, current treatment status if a cancer patient, and gender. Dependent measures included plans to receive the vaccine and attitudes and concerns toward the COVID-19 vaccines.

Interest in obtaining the vaccine was evaluated through the question, "Do you plan to get the COVID-19 vaccine when one is available?" This item was evaluated with options of "I already got it," "I've tried but have not been able to get it," "Definitely," "Probably," "Unsure," "Probably not," and "Definitely not." For the purpose of analysis, participants who responded with "Definitely not," "Probably not," or "Unsure" were considered to be "vaccine hesitant." Participants indicating the other responses, including those who had already received the COVID-19 vaccine, were considered to be "vaccine acceptant."

Attitudes and concerns about the vaccine were elicited through the question, "What are your concerns about the vaccine? Check all that apply." The possible responses included the following: "I do not believe I need it," "I do not think it was developed responsibly," "I do not trust the government has insured that the vaccines are safe and effective," "I do not trust vaccines in general," "I do not trust the COVID-19 vaccine in particular," "I am concerned that the COVID-19 vaccine is too new," "I want to see how others respond first," "Concerns over the role of politics in the development process," "It is too difficult to get vaccinated," "I am concerned with contracting the coronavirus from the vaccine," "I am concerned about the side effects or discomfort," and "I have religious objections."

As concerns about side effects may contribute to COVID-19 vaccine hesitancy and since immunocompromised individuals were largely excluded from COVID-19 vaccine trials, we sought to obtain additional information about the experiences of individuals who had received the vaccine. Specifically, we included questions about the type of vaccine received and which (if any) side effects were experienced. The list of reportable symptoms and effects from the vaccine included on the survey were adapted from the Pfizer/BioNTech BNT162b2 mRNA COVID-19 Vaccine FDA Briefing Report [23]. Potential localized side effects included pain at the injection site, swelling at the injection site, redness at the injection site, itching at the injection site, and other. Potential systemic side effects included fever, chills, headache, joint pain, muscle/body aches, fatigue, nausea, vomiting, diarrhea, abdominal pain, rash, and other.

Statistical Plan

Two-way cross tabulations were used to summarize sociodemographic variables, behavioral and public health belief variables, and comorbid disease variables across vaccine hesitancy. Pearson chi-squared tests were performed to assess for statistical significance in the differences between groups. Univariate logistic regression analyses were performed to assess independent relationships between several variables and the dichotomous vaccine acceptance variable.

Multivariate logistic regression analysis was performed to assess the relationship between multiple predictor variables and the dichotomized vaccine acceptance variable. Two-sided, design-based tests and an alpha level of .05 was used to evaluate statistical significance in all chi-squared, F test, and logistic regression analyses. No backward selection was used, and all variables remained in the model regardless of their significance level. All data management and analysis were conducted using SPSS Version 28 (IBM Corp, Armonk, NY).

Study Funding

This study was funded by Inspire, which was responsible for the study design; the collection, analysis, and interpretation of the data; and the decision to approve publication of the finished manuscript.

Results

Survey Respondent Demographics

Invitations to participate in this survey were sent to 996,500 members of the Inspire health community between January 15, 2021 and February 22, 2021. Responses to the survey request were received from 21,943 individuals (2.2%), of which 17,115 completed the entire survey (1.7% of those invited and 78.0% of respondents). The median age range of respondents was 56-65 years, which appeared older than the Inspire community median age range of 40-49 years. The survey respondents were mostly female (15,696/20,685, 75.9%), similar to the general Inspire community (77%). There was minimal self-identification as belonging to a racial or ethnic minority within the respondent population.

Inspire's membership is made up of both individuals with declared illnesses and their caregivers. However, caregivers who wished to participate in this study separate from their loved ones were instructed to complete a separate survey based on their own attitudes and to document their own health status. All participants (21,943/21,943, 100%) in this project indicated at least one comorbid condition. A cancer diagnosis was self-reported by 27.3% (5459/19,980) of responding participants, 23.2% (4946/21,294) had an autoimmune disease, and 35.4% (7544/21,294) were diagnosed with a chronic lung disease.

Respondents were highly educated, with 58.9% (10,198/17,298) holding college or postgraduate degrees. Political leanings were diverse, with 31.6% (5683/17,967) self-declaring liberal tendencies, 20.7% (3711/17,967) self-declaring as conservative, 24.3% (4357/17,967) self-declaring as independent, and 23.5% (4216/17,967) preferring not to declare. Respondents lived in 123 countries, with 74.2% (16,277/21,943) residing in the United States, 8.5% (1855/21,943) in Canada, 8.1% (1781/21,943) in the United Kingdom, 3.1% (688/21,943) in Australia, and the remaining 6.1% (1342/21,943) in Europe, Central, South America and the Caribbean, the Middle East, the Russian Federation, Africa, or the Far East.

COVID-19 Vaccine Hesitancy in the Study Cohort

Among the 21,294 individuals with cancer, autoimmune diseases, or other serious diseases who responded to survey questions about their attitudes on vaccination, 18.6% (3960/21,294) indicated COVID-19 vaccine hesitancy, including 10.3% (2190/21,294) who declared that they would not receive the vaccine, 3.5% (742/21,294) who stated that they would probably not, and 4.8% (1028/21,294) who were not sure

whether they would agree to be vaccinated. By contrast, 25.8% (5501/21,294) respondents reported that they had already received at least one COVID-19 vaccine injection by February 22, 2021. Of the US participants, 29.6% (4813/16,277) had already undergone vaccination. Among participants from other countries, 688 had undergone vaccination including 68% of participants living in Israel, 27% in the United Kingdom, 4% in Canada, and none in Australia. Additionally, 6.9% (1462/21,294) had tried but had been unable to obtain the vaccine, 43.9% (9342/21,294) definitely planned to undergo vaccination, and 4.8% (1029/21,294) indicated that they probably would undergo vaccination, leading to an overall vaccine acceptance of 81.4% (17,334/21,294).

Factors Independently Associated With COVID-19 Vaccine Hesitancy

As shown in Table 1, multiple demographic factors were associated with vaccine hesitancy in the simple logistic regression analysis. Younger age was associated with increased vaccine hesitancy. In this survey of Inspire members with serious illnesses, 62.8% (12,707/20,225) of respondents were greater than 55 years of age, and in this subgroup, only 13.8% (1757/12,707) were vaccine hesitant compared with 25.1% (1889/7518) among those younger in age (P<.001). Although few self-reported a non-white racial or ethnic category, those who did report were more likely to be vaccine hesitant. The Inspire respondent members were highly educated, with 58.9% (10,198/17,298) possessing a college degree—a cohort who had vaccine hesitancy of 13.7% (1396/10,198) compared with 22.5% (1597/7100) among those with less formal education (P<.001). Respondents had diverse political leanings, but those with more conservative political leanings were more likely to express vaccine hesitancy. Respondents living outside the United States were more likely to be vaccine hesitant (998/4579, 21.8%) compared with those from the United States (2904/16,596, 17.5%; P<.001).

Opinions about public health policy also shaped vaccine hesitancy attitudes. In our study population of individuals with severe illnesses, 96.2% (18,376/19,468) reported routinely wearing masks. Although a greater proportion of mask wearers reported vaccine acceptance than those who reported not wearing masks, 18.4% (3444/18,736) of mask wearers remained vaccine hesitant. Most (16,269/21,294, 78.2%) respondents routinely received an influenza vaccination—a cohort with a vaccination acceptance prevalence of 91.6% (14,905/16,269) compared with the 45.9% (2083/4545) acceptance prevalence among those who did not routinely receive an influenza vaccine (P<.001). Respondents who did not feel that the media reported scientific data accurately had a slightly higher prevalence of vaccine hesitancy (635/3084, 20.6%) compared with those that did believe media information was scientifically accurate (1924/10,465, 18.4%; P=.006) Among those who responded “No” or “Probably not” to the question “Do you trust the vaccine was developed responsibly?”, 98.4% (1512/1537) and 91.0% (575/632), respectively, reported being vaccine hesitant (P<.001; Table 2).

Table 1. Vaccine hesitancy by age, gender, ethnicity, education level, and political leanings among individuals with serious comorbidities (n=21,294) using Inspire between January 15, 2021 and February 22, 2021.

Characteristic	Overall sample (n=21,294), n (%)	COVID-19 vaccine received or definitely or probably will receive the vaccine (n=17,334), n (%)	Definitely or probably will not receive the vaccine or unsure about receiving the vaccine (n=3960), n (%)
Age[a](years)			
<26	381 (1.9)	289 (75.9)	92 (24.1)
26-35	1315 (6.5)	928 (70.6)	387 (29.4)
36-45	2513 (12.4)	1871 (74.5)	642 (25.5)
46-55	3309 (16.4)	2541 (76.8)	768 (23.2)
56-65	5288 (26.2)	4340 (81.1)	948 (17.9)
66-75	5591 (27.6)	4961 (88.7)	630 (11.3)
>75	1828 (9.0)	1649 (90.2)	179 (9.8)
Gender[b]			
Male	4989 (24.1)	4237 (84.6)	752 (15.4)
Female	15,696 (75.9)	12,802 (81.5)	2894 (18.5)
Race/ethnicity[c]			
White	17,354 (89.2)	14,487 (83.5)	2867 (16.5)
Black or African American	514 (2.6)	391 (76.1)	123 (23.9)
Hispanic or Latino	614 (3.2)	509 (82.9)	105 (17.1)
Asian	627 (3.2)	520 (82.9)	107 (17.1)
Hawaiian/Pacific Islander	22 (0.1)	15 (67.2)	7 (31.8)
Native American/Alaskan	132 (0.7)	88 (66.7)	44 (33.3)
Other	479 (2.5)	337 (70.4)	142 (29.6)
Prefer not to answer	706 (3.6)	306 (43.4)	400 (56.6)
Education level[d]			
High school or less	1640 (9.5)	1246 (75.9)	394 (24.1)
Vocational or associate degree	2546 (14.7)	1955 (76.8)	591 (23.2)
Some college	2914 (16.8)	2302 (79.0)	612 (21.0)
College degree	4448 (25.7)	3748 (84.3)	700 (15.7)
Postgraduate	5750 (33.2)	5054 (87.9)	696 (12.1)
Political leaning[e]			
Liberal	5683 (31.6)	5401 (95.0)	282 (5.0)
Conservative	3711 (20.7)	2653 (71.5)	1058 (28.5)
Independent	4357 (24.3)	3520 (80.8)	837 (19.2)
Prefer not to answer	4216 (23.5)	3185 (75.5)	1031 (24.5)

[a]n=20,225.

[b]n=20,685.

[c]n=19,465.

[d]n=17,298.

[e]n=17,967.

Table 2. Responses to the question, "Do you plan to get the COVID-19 vaccine when one is available?", as an indicator of vaccine hesitancy, by mask wearing, routine influenza vaccination, belief in media coverage accuracy, and trust in responsible development among individuals with serious comorbidities (n=21,294) using Inspire between January 15, 2021 and February 22, 2021.

Characteristic	Overall sample (n=21,294), n (%)	Responses	
		"I already got it," "I've tried but have not been able to get it," "Definitely," "Probably", n (%)	"Unsure," "Probably not," "Definitely not", n (%)
Mask wearing[a]			
Always/sometimes wears a mask	18,736 (96.2)	15,292 (81.6)	3444 (18.4)
Rarely/never wears a mask	732 (3.8)	557 (76.1)	175 (23.9)
Routine influenza vaccine[b]			
Usually gets a flu vaccine	16,269 (78.2)	14,905 (91.6)	1364 (8.4)
No flu vaccine	4545 (21.8)	2083 (45.9)	2462 (54.1)
Media information scientifically accurate[c]			
Yes or generally yes	10,465 (53.8)	8541 (81.6)	1924 (18.4)
No or generally no	3084 (15.8)	2449 (79.4)	635 (20.6)
Mixed	5910 (30.3)	4852 (82.1)	1058 (17.9)
Do you trust the vaccine was developed responsibly[d]			
Yes	12,498 (61.2)	12,292 (98.4)	206 (1.6)
Probably so	3900 (19.1)	3494 (89.6)	406 (10.4)
Not sure	1837 (9.0)	750 (40.8)	1087 (59.2)
Probably not	632 (3.1)	57 (9.0)	575 (91.0)
No	1537 (7.5)	25 (1.6)	1512 (98.4)

[a]n=19,468.

[b]n=20,814.

[c]n=19,459.

[d]n=20,409.

Of the survey respondents, 9.0% (1906/21,294) self-reported a prior history of COVID-19 infection, and an additional 5.1% (1085/21,294) believed that they had experienced symptoms suggestive of COVID-19 without confirmation (or were unsure). Although current guidelines recommend vaccination despite prior infection, 34.7% (1039/2991) of these individuals were vaccine hesitant. By contrast, among the more than 17,000 respondents who claimed no prior exposure to SARS-CoV-2, only 15.8% (2758/17,460) were vaccine hesitant (P<.001; Table 3).

Table 3. Responses to the question, "Do you plan to get the COVID-19 vaccine when one is available?", as an indicator of vaccine hesitancy, among individuals with serious comorbidities (n=21,294) who used Inspire between January 15, 2021 and February 22, 2021, according to prior COVID-19 infection history (n=20,451).

Previous COVID-19 infection status	Overall sample (n=20,451), n (%)	Responses	
		"I already got it," "I've tried but have not been able to get it," "Definitely," "Probably", n (%)	"Unsure," "Probably not," "Definitely not", n (%)
Had COVID-19	1906 (9.0)	1209 (63.4)	697 (36.6)
Unsure if had COVID-19	1085 (5.1)	743 (68.5)	342 (31.5)
Did not have COVID-19	17,460 (85.4)	14,702 (84.2)	2758 (15.8)

Vaccine Hesitancy in Specific High-Risk Comorbid Populations

Among the 5459 individuals with cancer, 13.4% (731/5459) indicated vaccine hesitancy, including 13.2% (193/1463) of those who were currently receiving treatment and 13.5% (538/3996) of those who had completed prior treatment. Those who were not being treated for cancer had a vaccine hesitancy prevalence of 20.3% (2954/14,521). The difference in vaccine hesitancy proportions between those being treated for cancer and those not being treated for cancer was statistically significant (*P*<.001). Among participants with autoimmune diseases, 19.4% (962/4946) self-reported vaccine hesitancy compared with 18.0% (2943/16,348) of those not being treated for an autoimmune disease who reported vaccine hesitancy (*P*=.02). Of the respondents with chronic lung disease, 17.8% (1344/7544) reported vaccine hesitancy compared with 19.0% (2616/13,750) of those not being treated for chronic lung disease (*P*=.03). Vaccine hesitancy was also expressed by 19.7% (598/3041; *P*=.03) of those diagnosed as obese, 18.0% (963/5358; *P*=.99) diagnosed with hypertension, and 19.0% (266/1400; *P*=.30) of individuals living with type 2 diabetes, with comparisons against respondents who did not indicate these comorbidities (Table 4).

Table 4. Responses to the question, "Do you plan to get the COVID-19 vaccine when one is available?", as an indicator of vaccine hesitancy, among individuals with serious comorbidities (n=21,294) using Inspire between January 15, 2021 and February 22, 2021.

Characteristic	Overall sample (n=21,294), n (%)	Responses	
		"I already got it," "I've tried but have not been able to get it," "Definitely," "Probably", n (%)	"Unsure," "Probably not," "Definitely not", n (%)
Cancer[a]			
Yes, in treatment	1463 (7.3)	1270 (88.8)	193 (13.2)
Yes, past treatment	3996 (20.0)	3458 (86.6)	538 (13.5)
No cancer	14,521 (72.7)	11,567 (79.7)	2954 (20.3)
Autoimmune disease			
Yes	4946 (23.2)	3984 (80.6)	962 (19.4)
No	16,348 (76.8)	13,405 (82.0)	2943 (18.0)
Chronic lung disease			
Yes	7544 (35.4)	6200 (82.2)	1344 (17.8)
No	13,750 (64.6)	11,134 (81.0)	2616 (19.0)
Hypertension			
Yes	5358 (25.2)	4395 (82.0)	963 (18.0)
No	15,936 (74.8)	13,068 (82.0)	2868 (18.0)
Type 2 diabetes			
Yes	1400 (6.6)	1134 (81.0)	266 (19.0)
No	19,894 (93.4)	16,353 (82.2)	3541 (17.8)
Obesity			
Yes	3041 (14.3)	2443 (80.3)	598 (19.7)
No	18,253 (85.7)	14,968 (82.0)	3285 (18.0)

[a]n=19,980.

Univariate Logistic Regression Analysis of COVID-19 Vaccine Acceptance

In the univariate logistic regression analysis, having received a routine influenza vaccine was associated with COVID-19 vaccine acceptance (odds ratio [OR] 1.24). Those who reported routinely receiving an influenza vaccine had 1.24 times the odds of being COVID-19 vaccine acceptant. Those who reported having trust that the COVID-19 vaccine was developed responsibly had 2.07 times the odds of being vaccine acceptant (OR 2.07). Those who reported being previously infected with COVID-19 had 0.93 times the odds of being vaccine hesitant (OR 0.93). Those who reported an independent political leaning or liberal political leaning had 1.12 and 1.14 times the odds, respectively, of being vaccine acceptant when compared with those who reported a conservative political leaning. Respondents residing within the United States had 1.03 times the odds of reporting vaccine acceptance than those living outside the United States. Those with an age higher than the median age of the study had 1.12 times the odds (or a 12% increase in odds) of reporting vaccine acceptance compared with those below the median age, while those at the median age had 0.99 times the odds of being vaccine acceptant compared with those below the median age. Moreover, those with some college education had

1.03 times the odds of being vaccine acceptant compared with those with a high school degree or less, while those with at least a 4-year degree had 1.04 times the odds of being vaccine acceptant compared with those with a high school degree or less. Smoking status was not significantly associated with vaccine acceptance. Men had 0.98 times the odds of being vaccine acceptant than women. Those diagnosed with cancer had 1.03 times the odds of being vaccine acceptant compared with those not diagnosed with cancer, and those who reported mask wearing had 1.02 times the odds of being vaccine acceptant (Table 5).

Table 5. Univariate logistic regression of vaccine acceptance among individuals with serious comorbidities (n=21,294) using Inspire between January 15, 2021 and February 22, 2021.

Variable	Odds ratio (95% CI)	*P* value
Routine influenza vaccine	1.24 (1.23-1.25)	<.001
Trust in responsible development of COVID vaccine	2.07 (2.05-2.09)	<.001
Prior COVID infection	0.93 (0.92-0.94)	<.001
Political leaning		
Conservative political leaning (reference)	-[a]	-
Independent	1.12 (1.10-1.13)	.003
Liberal leaning	1.14 (1.12-1.15)	<.001
Residence (United States vs outside the United States)	1.03 (1.02-1.04)	<.001
Age		
Age below the median (reference)	-	-
Median age	0.99 (0.98-0.99)	<.001
Age above the median	1.12 (1.11-1.13)	<.001
Education level		
High school and less (reference)	-	-
Some college, associate degree	1.03 (1.03-1.04)	<.001
At least a college degree	1.04 (1.02-1.06)	<.001
Smoking status	1.01 (1.00-1.02)	.17
Gender	0.98 (0.97-0.99)	.001
Cancer diagnosis	1.03 (1.02-1.04)	.001
Mask wearing	1.02 (1.01-1.03)	<.001

[a]Reference category.

Multivariate Logistic Regression Models of COVID-19 Vaccine Acceptance

To understand the impact of these independent variables on vaccine acceptance, a multivariate logistic regression analysis was performed to predict those who had received or planned to receive their vaccination by February 20, 2021. Overall, our model was a statistically significant predictor of vaccine acceptance, with an adjusted R^2 of 0.525, meaning our model explained 52.5% of the variance in vaccine acceptance. Results of the multivariate logistic regression analysis are shown in Table 6. The Pearson goodness-of-fit test yielded a χ^2_{1474} of 1500.56, which was considered insignificant (P=.31). The deviance goodness-of-fit test yielded a χ^2_{1474} of 1374.86, which was also considered insignificant (P=.97). These results suggest good model fit.

Table 6. Multivariate logistic regression analysis of vaccine acceptance among individuals with serious comorbidities (n=21,294) using Inspire between January 15, 2021 and February 22, 2021.

Variable	Odds ratio (95% CI)	*P* value
Routine influenza vaccine	1.08 (1.07-1.08)	<.001
Trust in responsible development of COVID vaccine	1.86 (1.84-1.88)	<.001
Prior COVID infection	0.97 (0.96-0.98)	<.001
Political leaning		
Independent	1.02 (1.01-1.03)	<.001
Liberal	1.06 (1.05-1.07)	<.001
Residence (United States vs outside the United States)	0.98 (0.98-0.99)	<.001
Age		
Median age	1.01 (0.99-1.02)	.07
Above the median age	1.02 (1.01-1.03)	<.001
Education level		
Some college	1.00 (0.99-1.01)	.56
College and graduate school	0.99 (0.98-1.01)	.68
Smoking status	1.01 (1.00-1.02)	.004
Gender	1.00 (0.99-1.02)	.67
Cancer diagnosis	1.00 (0.99-1.00)	.45
Mask wearing	0.10 (0.99-1.01)	.96

Factors associated with vaccine acceptance after controlling for other covariates included routine influenza vaccination, political leaning, age (below the median versus median range versus above the median), country of residence (in the United States versus living outside the United States), prior COVID-19 infection, and trust in responsible development of the COVID-19 vaccine. Routine receipt of influenza vaccination remained a positive predictor of COVID-19 vaccine acceptance after controlling for other covariates, with an OR of 1.08, meaning participants who reported regularly receiving the flu shot had 1.08 times the odds of being vaccine acceptant. Trust in responsible development of the vaccine was also a significant predictor of COVID-19 vaccine acceptance, with an OR of 1.86, meaning that those who reported having trust in the development of the vaccine had 1.86 times the odds of receiving it than those that reported not having trust in the development. Those residing in the United States (OR 0.98) had 0.98 times the odds of accepting the vaccine than those living outside the United States. Those who reported never smoking also had slightly greater odds of vaccine acceptance (OR 1.01). By contrast, vaccine acceptance was less likely with a history of prior COVID-19 infection (OR 0.97). After controlling for other variables, those reporting an independent political leaning had 1.02 times the odds of being vaccine acceptant compared with those who reported a conservative political leaning, and those who reported a liberal political leaning had 1.02 times the odds of being vaccine acceptant than those who reported a conservative political leaning. Age remained a statistically significant predictor of vaccine acceptance after controlling for other variables. Those with an age higher than the median age of the study had 1.02 times the odds of reporting vaccine acceptance compared with those below the median age, while those at the median age had 1.01 times the odds of being vaccine acceptant compared with those below the median age. When controlling for other variables, gender was no longer a statistically significant predictor of vaccine acceptance. The same is true for education level, cancer diagnosis, and mask wearing.

Concerns About Vaccines

Of the 3960 respondents who indicated COVID-19 vaccine hesitancy, apprehension regarding the newness of the vaccine was the most commonly cited reason for hesitancy, expressed by 53.1% (2104/3960) of hesitant respondents. Concerns about the safety of the vaccine and a general distrust of the development process (including governmental oversight) also were common (Table 7).

Table 7. Concerns about the COVID-19 vaccine among the vaccine-hesitant individuals (n=3960) using Inspire between January 15, 2021 and February 22, 2021.

Responses to the question: "What are your concerns about the vaccine? Check all that apply."	Overall (n=3960), n (%)	United States (n=2817), n (%)	Outside the United States (n=1143), n (%)
I am concerned the COVD-19 vaccine is too new.	2104 (53.1)	1532 (54.4)	572 (50.0)
I do not trust the government has ensured that the vaccines are safe and effective.	1900 (48.0)	1365 (48.5)	535 (46.8)
I am concerned about side effects and discomfort.	1738 (43.9)	1219 (43.4)	519 (45.5)
I do not trust the COVID-19 vaccine in particular.	1571 (39.7)	1126 (40.0)	445 (38.9)
I have concerns over the role of politics in the development process.	1533 (38.7)	1112 (39.4)	421 (36.8)
I want to see how others respond first.	1319 (33.3)	974 (34.6)	345 (30.2)
I do not think it was developed responsibly.	1313 (33.2)	922 (32.7)	391 (34.2)
I do not believe I need it.	869 (22.0)	589 (20.9)	280 (24.5)
I do not trust vaccines in general.	832 (21.0)	591 (21.0)	292 (25.5)
I have religious objections.	331 (8.4)	262 (9.3)	69 (6.0)
I am concerned with contracting the coronavirus from the vaccine.	327 (8.3)	221 (7.8)	106 (9.3)
It is too difficult to get vaccinated.	86 (2.2)	74 (2.6)	12 (1.0)

Early Experience With COVID-19 Vaccination in High-Risk Populations

As of the study cutoff, 5501 (5501/21,294, 25.8%) survey respondents had received at least one COVID-19 vaccination (Pfizer-BioNTech: 2640/5501, 48.0%; Moderna: 2586/5501, 47.0%; Oxford-AstraZeneca: 55/5501, 1.0%; other/unknown: 220/5501, 4.0%). A 2-injection series was completed by 6.5% (1390/21,294) of respondents. Following the first injection, 69.0% (3796/5501) self-reported experiencing local adverse events, and 40.0% (2200/5501) self-reported systemic reactions. Pain at the injection site was the most commonly self-reported side effect. Fatigue and myalgias were the most commonly self-reported systemic side effects. Among those who had received 2 vaccine injections (n=1390), the frequencies of self-reported local and systemic reactions increased following the second injection, to 77.0% (1070/1390) and 67.0% (931/1390), respectively (Figures 1 and 2).

Figure 1. Self-reported localized reactions to COVID-19 vaccination among individuals with cancer, autoimmune diseases, or other serious comorbidities and/or their caregivers (n=5501 who received an initial vaccine dose; n=1390 who completed a 2-dose series).

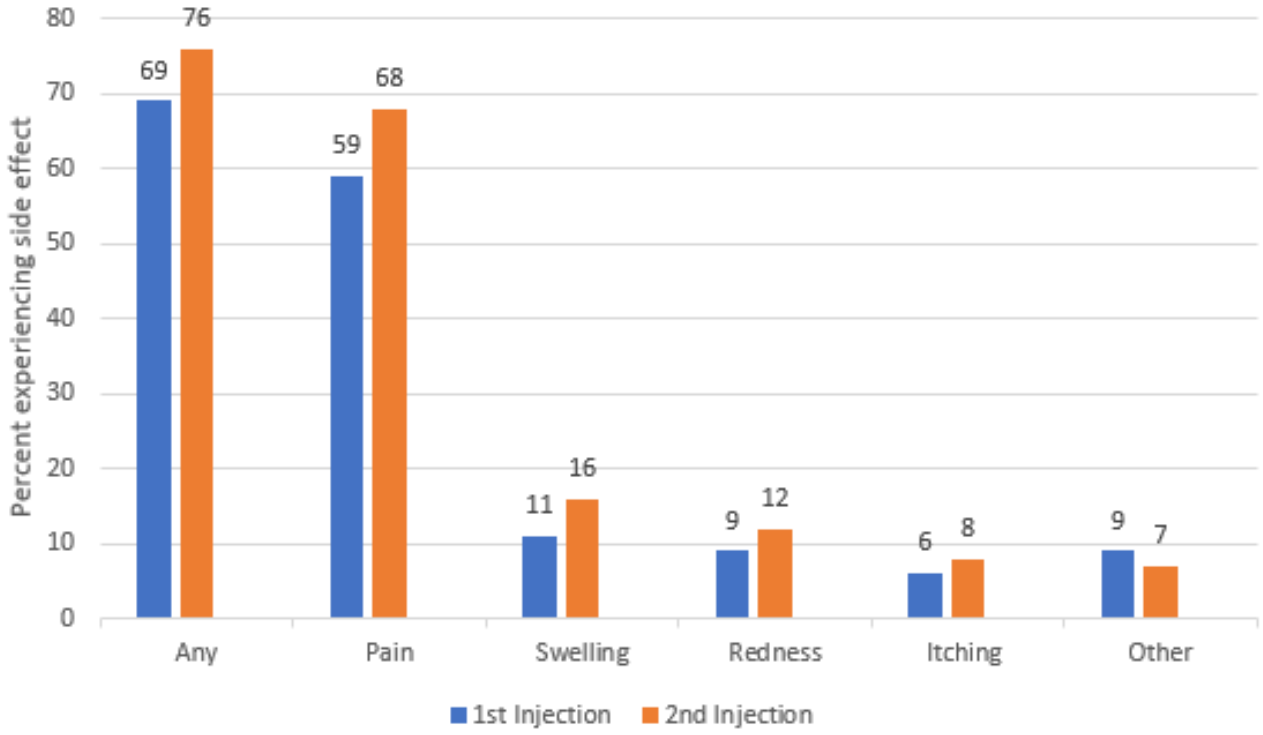
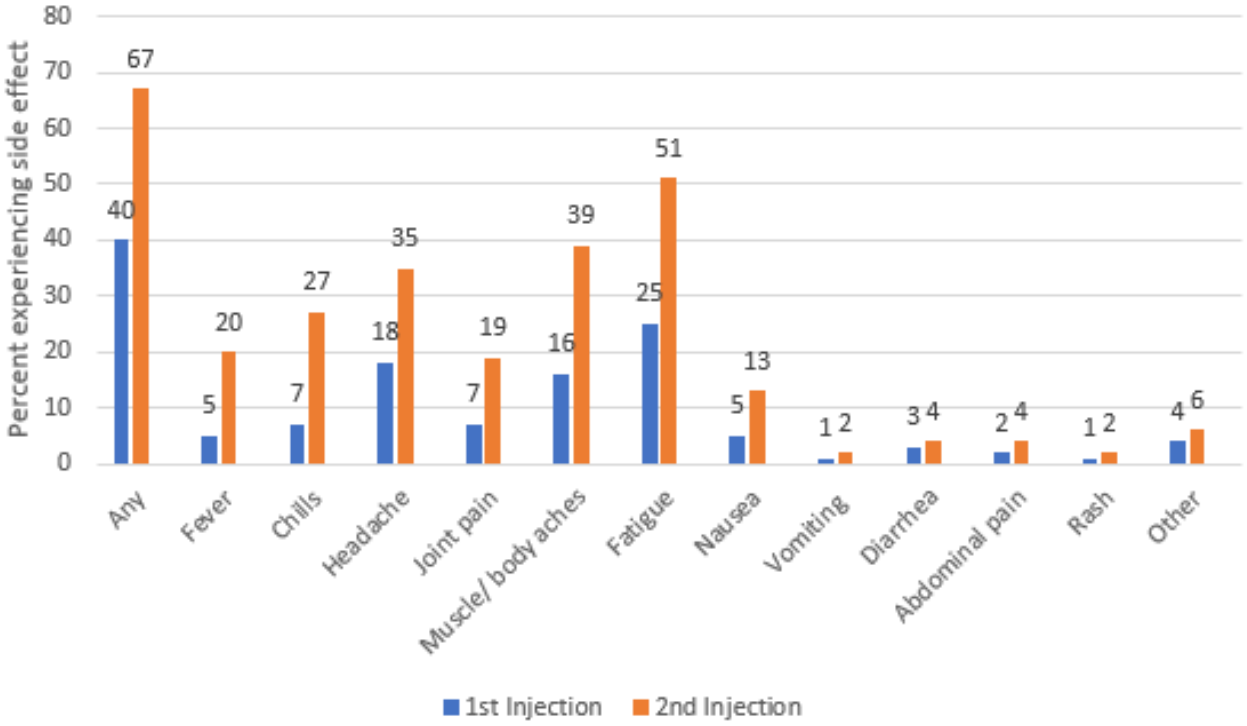


Figure 2. Self-reported systemic reactions to COVID-19 vaccination among individuals with cancer, autoimmune diseases, or other serious comorbidities and/or their caregivers (n=5501 who received an initial vaccine dose; n=1390 who completed a 2-dose series).



Among respondents who had received a vaccination with the Pfizer-BioNTech (n=2640) or Moderna (n=2586) vaccines, the initial injection led to overall self-reported localized side effects among 65.0% (1716/2640) and 75.0% (1939/2586), respectively. Local reactions increased to 72.0% (480/667) and 85.0% (368/433) with the second booster Pfizer-BioNTech and Moderna injections, respectively. A more dramatic increase in self-reported systemic side effects was noted with the second injection, with overall systemic effects rising from 37.0% (977/2640) to 62.0% (413/667) and 40.0% (1034/2586) to 77.0% (333/433), with the Pfizer-BioNTech and Moderna vaccines, respectively.

Of the 5459 cancer patients who responded to the survey, 30.0% (1638/5459) had received 1 injection, and 6.0% (325/5459) completed both vaccine injections. In this cancer population, 64.5% (1057/1638) self-reported local reactions, and 34.1% (559/1638) self-reported systemic reactions to the first injection; with the second injection, 72.3% (235/325) experienced local reactions, and 59.1% (192/325) experienced systemic reactions. The types of reactions mirrored the overall study population. Of the 5186 individuals with autoimmune disorders, 23.9% (1239/5186) had received 1 vaccination, and 6.0% (311/5186) had completed the series. In this immunocompromised population, with the first injection, local reactions were described by 69.0% (855/1239), and systemic reactions were described by 41.3% (512/1239); with the second vaccine injection, local reactions were described by 78.1% (243/311), and systemic reactions were described by 67.2% (209/311). Among the 1878 respondents with chronic lung diseases who received the vaccine, with the first injection, 67.2% (1262/1878) self-reported local reactions, and 39.9% (794/1878) self-reported systemic reactions; with the second vaccine injection, local reactions occurred in 76.8% (288/375), and systemic reactions occurred in 69.1% (259/375). Similar patterns were noted among respondents with obesity (1st dose: 539/777, 69.4% had local reactions, and 334/777, 43.0% had systemic reactions; 2nd dose: 154/202, 76.2% had local reactions, and 152/202, 75.2% had systemic reactions), hypertension (1st dose: 947/1420, 66.7% had local reactions, and 550/1420, 38.7% had systemic reactions; 2nd dose: 272/366, 74.3% had local reactions, and 243/366, 66.5% had systemic reactions), and type 2 diabetes (1st dose: 253/376, 67.3% had local reactions, and 159/376, 42.3% had systemic reactions; 2nd dose: 74/95, 77.9% had local reactions, and 75/95, 78.9% had systemic reactions).

Discussion

In this survey of nearly 22,000 individuals with serious comorbid conditions conducted shortly after vaccine regulatory approvals, 8 in 10 respondents reported a willingness to receive the COVID-19 vaccine. This high level of vaccine acceptance in a community of vulnerable individuals who regularly seeks medical information through participation in an online health forum compares favorably with reports in public opinion polls drawn from general populations taken at the same timeframe [6,7]. Additionally, as of late February 2021, 29.6% (4813/16,277) of US participants in the survey stated that they had already received at least one COVID-19 vaccine injection, which compared favorably with the 18% vaccination prevalence in US adults at that time [24]. Our survey thus appears to confirm a strong desire for protection against SARS-CoV-2 in vulnerable populations, although vaccine allocation prioritization may have also influenced these findings.

However, almost 1 in 5 respondents to our survey, all of whom had comorbidities, reported COVID-19 vaccine hesitancy. This

was a similar hesitancy prevalence as reported in general population polls at the time [6,7]. Among patients with cancer, autoimmune diseases, and chronic lung diseases, 13.4%, 19.4%, and 17.8%, respectively, expressed hesitancy. This is very concerning given that individuals with cancer and other serious comorbidities have experienced an increased proportion of the mortality from the pandemic [13-18]. Furthermore, since our survey enrolled from a medically savvy population who participate in online health forums, we were surprised by these results. The lack of inclusion of immunocompromised individuals within regulatory clinical trials may have contributed to the safety concerns expressed by 43.9% of vaccine-hesitant respondents [20,21]. However, other factors, many of which were similar to concerns raised by the general public, were deemed important by our respondents. Thus, it appears that our study population fell into 2 polarizing cohorts: one group that was more eager to undergo vaccination as a consequence of coexisting illnesses and increased mortality risks and a second group that was COVID-19 vaccine hesitant and influenced by broad social vaccine concerns.

We identified multiple factors that were independently associated with vaccine hesitancy. Lack of trust in COVID-19 vaccine development, including the rapidity and politicization of the process, was expressed by our comorbid cohort but is a view not unique to our population [12]. Generalized distrust of vaccines and avoidance of influenza vaccines were additional broad concerns that transcend comorbid status. Conservative political leaning, lower education level, and younger age are also commonly cited in public opinion polls [7,8,10,11,25]. Individuals who had already contracted COVID-19 avoided vaccination, possibly believing natural immunity alone was protective [26].

Few studies have specifically explored issues of COVID-19 vaccine hesitancy among patients with severe comorbid conditions or strategies to increase acceptance in high-risk populations. As these individuals already have ongoing health care contact, the potential influence of their physicians should not be ignored. A Korean study noted that, although only 61.8% of their cancer patients were initially willing to receive the COVID-19 vaccine, acceptance increased by 30% if their oncologist recommended it [27]. Similarly, a Tunisian study noted that a discussion about the impact of COVID-19 upon cancer treatments and outcomes was projected to have the single greatest impact on reducing hesitancy [28]. An online survey of 540 Mexican women with breast cancer also noted a 3-fold increase in the likelihood of accepting vaccination following their oncologists' recommendation [29]. Unfortunately, a physician's recommendation does not always change opinions. Nearly 40% of French cancer patients who were vaccine hesitant did not feel that their oncologist was qualified to advise them on COVID-19 vaccination and instead preferred to rely on personal judgements [30]. Nonetheless, the specialist physician possesses unique insights into potential impacts of vaccination on the patient's underlying disease, a fear that must be allayed, as expressed by a cohort of patients with autoimmune rheumatic disease [31]. A UK randomized trial demonstrated that emphasizing the personal benefits of vaccination reduced hesitancy to a greater extent than information about collective benefit. Where perception of risk from vaccines is most salient, which is likely among high-risk comorbid populations, decision making frequently becomes centered on the personal [32].

Establishing trust in science and vaccine development is critical to reducing vaccine hesitancy. Despite our population having ongoing contact with the health care system (by virtue of their underlying diseases) and routinely engaging in an online health-related forum, we noted that issues regarding trust were expressed by over 40% of vaccine-hesitant respondents. A survey of nearly 6000 US health care workers, older adults, frontline essential workers, other essential workers, and individuals with a high-risk chronic condition conducted in early 2021 identified that lack of trust in the vaccine approval and development processes was the most important trust issue. Other domains of trust (in vaccine safety and efficacy, in health care providers, in sources of information, and generalized trust) were of lesser importance [33]. Similar results were noted in an online survey of over 1000 Italians who responded that vaccine acceptance was driven by a trust in science, acceptance of prior vaccines, and an understanding that COVID-19 is more serious than influenza [34].

The potential role of social media in combating the COVID-19 pandemic cannot be underestimated. This study was sponsored by an online health community whose international membership shares medical information and personal experiences via hundreds of disease-specific forums. Our motivation for designing the study was to increase our membership's knowledge and encourage discussions regarding COVID-19 vaccine experiences. The rapid enrollment of nearly 22,000 respondents with serious diseases over a 5-week period, with thousands more viewing the online results, attests to the potential influence of the worldwide web on health issues. An infodemiology study of over 650,000 "tweets" from November 2020, prior to the release of vaccines, identified that the main themes driving vaccine hesitancy were concerns of safety, efficacy, freedom, and mistrust in institutions (either the government or multinational corporations) [35]. A qualitative coding methodologic review of antivaccine social media noted that the most frequent narratives centered on "corrupt elites" and rhetoric appealing to the vulnerability of children [36]. As rumors and conspiracy theories are common, tracking COVID-19 vaccine misinformation in real time and engaging with social media to disseminate correct information can be an important safeguard against misinformation [37]. Health care–related patient platforms, such as Inspire, where individuals with concerns can obtain understandable COVID-19–related medical information relevant to their other medical conditions should play an important role in decreasing vaccine hesitancy.

As noted in our survey, COVID-19 vaccine acceptance and hesitancy are a global issue. Respondents residing outside the United States were more likely to exhibit vaccine hesitancy, but the reasons for concerns about vaccination appeared similar. A systematic review of World Health Organization regions noted great variability in acceptance of the vaccine, with lowest rates in Hong Kong and the Democratic Republic of the Congo, 2 countries with recent political instability. In contrast, China, Indonesia, and Malaysia all reported hesitancy prevalence below 10%, potentially a reflection of their early experiences with

SARS-CoV-2. Across Europe, hesitancy varied greatly from 20% in the United Kingdom to almost 60% in Italy [38]. Other reports have indicated higher acceptance of vaccination in lower- and middle-income countries [39,40]. As evidenced by the 123 nations represented in our respondent population, the internet represents a powerful potential tool for dissemination of information about COVID-19 vaccination across boundaries.

Limited data exist regarding the safety and effectiveness of COVID-19 vaccination among immunocompromised individuals (with the exception of individuals infected with HIV) since they were excluded from the regulatory phase 3 trials. Therefore, we expected safety concerns to dominate vaccine hesitancy concerns in our survey [41]. To address this, we requested information about side effect profiles among respondents who had undergone vaccination with the goal of sharing this information with our online membership in the hope that this would reduce vaccine hesitancy. Indeed, early experience with vaccinations, as self-reported by the over 5000 respondents who had already been vaccinated, should be reassuring to individuals with serious comorbidities. Side effect profiles were similar to adverse event reports from the regulatory trials, although overall generally lower in frequency [23,42]. Whether this is a reflection of the weaker immune status of our population or a result of differences in reporting styles (online survey vs research-grade clinical trial monitoring) is unknown. However, an interesting finding was that the prevalence of self-reported systemic reactions to the initial vaccination appeared to be much lower than those reported in the clinical regulatory trials but increased, closer to the general population results, with the booster. This pattern of side effect intensity (as a surrogate for immune responsiveness) suggests that booster vaccines may be required in immunocompromised individuals or that confirmation of antibody response may be necessary. Regardless, given the side effect profiles noted in our survey, the recommendations to vaccinate individuals with potential immune dysfunction despite a lack of clinical trial data appear justified, although future studies to document vaccine efficacy in these populations are needed.

We recognize several limitations to our study. The survey was conducted in January 2021 and February 2021, shortly after the release of the COVID-19 vaccine, and represents attitudes from a single time point. As additional information about the safety and efficacy of vaccination becomes available to our participants, we expect that attitudes might change. Indeed, serial tracking polls conducted by the Kaiser Family Foundation have noted an increase in the acceptance of vaccination over time, although most of the changes in attitudes have occurred among the “wait and see” populations, with little movement among the vaccine-hesitant cohort [8]. Nonetheless, it is probable that our findings do not represent current opinions. Additionally, ORs determined by logistic regression analysis do not approximate relative risk or prevalence ratios since the outcome variable of vaccine hesitancy was not rare in our study population [43]. Additionally, the Inspire community membership is 77% female with a median age of 40-49 years. Given the composition of Inspire’s community, survey respondents were not intended to represent a random sampling of the general population or any outside demographic. We also obtained a low (2.2%) response rate to our online survey, and thus, our findings might not be representative of our membership population. It is possible that the most vocal opinions were overexpressed. We noted a dichotomous response, with a larger cohort desiring vaccination (more than the general population) but also a significant vaccine-hesitant cohort, with few respondents in the middle. It is interesting that our vaccine hesitancy prevalence and concerns mirror those of general population opinion polls, indicating that vulnerable populations are susceptible to antivaccination social issues. Additionally, although we noted several factors that appeared to be associated with vaccine hesitancy or acceptance, a cause-and-effect relationship should not be inferred on the basis of our survey. Finally, we did not investigate methods to reduce vaccine hesitancy in this study but plan to add items to ongoing online surveys of our membership with this goal.

In summary, our online survey highlights a high level of acceptance of COVID-19 vaccines among vulnerable individuals. However, the finding that 1 in 5 remains vaccine hesitant is of concern and points to a need for additional efforts. Although governmental mandates or financial incentives are being considered, educational efforts must continue [44,45]. Among individuals who have serious comorbid diseases and thus are already connected to the health care system, direct conversations by the medical specialist team about the impact of the COVID-19 vaccine have been demonstrated to reduce hesitancy and should be intensified. As demonstrated by our survey, it cannot be assumed by physicians that the most medically vulnerable automatically accept vaccination. Disinformation about the COVID-19 vaccines is common on social media sites and fosters hesitancy [46]. Our intent is to share our study results with the ≥2 million members of the Inspire health community, harnessing the internet to increase vaccine acceptance by demonstrating tolerable vaccine side effects among individuals with serious comorbid conditions. A website detailing the survey questions and updated daily with results is available to the general public [47].

Conflicts of Interest

None declared.

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Abbreviations

OR: odds ratio

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