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Contents

Original Papers

Review

Corrigenda and Addenda

Original Paper

Automated Real-Time Collection of Pathogen-Specific Diagnostic Data: Syndromic Infectious Disease Epidemiology

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Abstract

Background: Health care and public health professionals rely on accurate, real-time monitoring of infectious diseases for outbreak preparedness and response. Early detection of outbreaks is improved by systems that are comprehensive and specific with respect to the pathogen but are rapid in reporting the data. It has proven difficult to implement these requirements on a large scale while maintaining patient privacy.

Objective: The aim of this study was to demonstrate the automated export, aggregation, and analysis of infectious disease diagnostic test results from clinical laboratories across the United States in a manner that protects patient confidentiality. We hypothesized that such a system could aid in monitoring the seasonal occurrence of respiratory pathogens and may have advantages with regard to scope and ease of reporting compared with existing surveillance systems.

Methods: We describe a system, BioFire Syndromic Trends, for rapid disease reporting that is syndrome-based but pathogen-specific. Deidentified patient test results from the BioFire FilmArray multiplex molecular diagnostic system are sent directly to a cloud database. Summaries of these data are displayed in near real time on the Syndromic Trends public website. We studied this dataset for the prevalence, seasonality, and coinfections of the 20 respiratory pathogens detected in over 362,000 patient samples acquired as a standard-of-care testing over the last 4 years from 20 clinical laboratories in the United States.

Results: The majority of pathogens show influenza-like seasonality, rhinovirus has fall and spring peaks, and adenovirus and the bacterial pathogens show constant detection over the year. The dataset can also be considered in an ecological framework; the viruses and bacteria detected by this test are parasites of a host (the human patient). Interestingly, the rate of pathogen codetections, on average 7.94% (28,741/362,101), matches predictions based on the relative abundance of organisms present.

Conclusions: Syndromic Trends preserves patient privacy by removing or obfuscating patient identifiers while still collecting much useful information about the bacterial and viral pathogens that they harbor. Test results are uploaded to the database within a few hours of completion compared with delays of up to 10 days for other diagnostic-based reporting systems. This work shows that the barriers to establishing epidemiology systems are no longer scientific and technical but rather administrative, involving questions of patient privacy and data ownership. We have demonstrated here that these barriers can be overcome. This first look at the resulting data stream suggests that Syndromic Trends will be able to provide high-resolution analysis of circulating respiratory pathogens and may aid in the detection of new outbreaks.

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KEYWORDS

epidemiology; patients; privacy; communicable disease; internet; pathology, molecular

Introduction

Surveillance Landscape

The availability of real-time surveillance data that can monitor the spread of infectious diseases benefits public health [1-3]. At present, tracking of respiratory or foodborne outbreaks relies on a variety of methods ranging from automated real-time electronic reporting to manual Web entry of test results. Systems such as the Centers for Disease Control and Prevention's (CDC) FluView [4], National Respiratory and Enteric Virus Surveillance Systems (NREVSS) [5], National Electronic Disease Surveillance System [6], Global Emerging Infections Surveillance (GEIS) [7], and others, although Web-based, still require manual entry of data from laboratories, resulting in data that are often incomplete or not current.

Syndrome-based surveillance systems [8-10] include BioSense (extraction of symptomatic data from electronic health records [11]), Google Flu (tracking of internet search queries [12] but recently discontinued [13]), and Flu Near You (voluntary reporting [14]). Additionally, numerous next generation, syndromic surveillance systems, for example, pharmacy sales records [15,16], Twitter conversations [17,18], and Wikipedia hits [19,20] have come online in the past 5 years. However, these systems cannot report the specific pathogen causing an increase in a particular set of symptoms. Finally, there are more localized efforts such as GermWatch in Utah [21] and the Electronic Clinical Laboratory Reporting System (ECLRS) in New York [22] that draw from hospital information systems (HISs) and laboratory information systems (LISs). This disparity in technologies and data collection methods results in incomplete surveillance.

Comprehensive Testing

Comprehensive and uniform diagnostic test data will aid in the identification of potential outbreaks. A combination of broad respiratory pathogen testing and an internal electronic surveillance system enabled the rapid dissemination of data across the largest health care system in New York, the North Shore-LIJ Health System (now Northwell Health), during the influenza A H1N1-2009 pandemic in the New York City area. Pathogen-specific molecular testing permitted rapid (1) notification to state epidemiologists, (2) tracking of the virus so that health care resources could be managed effectively, and (3) evaluation of influenza diagnostics [23,24]. Today, with the threat of emerging pathogens such as Middle East respiratory syndrome coronavirus (CoV), avian influenza, enterovirus (EV) D68, and Ebola virus, real-time surveillance programs are critical [25,26].

It is not always possible to accurately diagnose the causative agents of most infectious diseases from symptoms alone because of overlapping clinical presentation. Thus, to achieve maximal utility, infectious disease surveillance systems should move beyond syndrome-based reporting and be pathogen-specific and comprehensive, reporting on as many of the common pathogens for a particular syndrome as possible. Sensitive and specific automated molecular diagnostic systems that detect up to 4 different pathogens in a single sample have been available from in vitro diagnostic (IVD) manufacturers for some time [27,28]. However, adoption of IVD platforms with broad multiplexing capability has become widespread only in the last few years. Commercially available systems that can detect most of the known etiological agents for respiratory, gastrointestinal (GI), and other multipathogen syndromes [29-31] include the BioFire (Salt Lake City, UT) FilmArray System ([32]; Multimedia Appendix 1); the GenMark (Carlsbad, CA) eSensor XT-8 [33] and ePlex [34]; and the Luminex (Austin, TX) xTAG [35], nxTag [36], and Verigene systems [37].

Sharing of Patient Data

Multianalyte diagnostic tests provide the raw data needed for real-time pathogen-specific syndromic surveillance, but there remain a number of obstacles to sharing these results (reviewed in [38]). The obstacles largely center on information privacy and network security. A real-time surveillance system using diagnostic test results requires safeguards for protected health information (PHI). Medical records and devices have become attractive targets for cyber attackers in recent years [39], which has made hospitals and clinics reluctant to connect their local area networks (LANs) to the internet. Releasing patient test results requires the removal of PHI or authorization from the patient. Studies have shown that deidentification of patient data is not as simple as removing all specific identifiers because in the age of big data, under the right circumstances, it is possible to reassociate patients and their data using publicly available information [40-43].

We describe here the implementation of a real-time pathogen-specific surveillance system that overcomes the PHI concerns noted above. BioFire Syndromic Trends deidentifies, aggregates, and exports test results from FilmArray Instruments in use in US clinical laboratories [44]. Although data from all commercially available FilmArray panels [45] are exported to the Trend database, we focus here on the Respiratory Panel (RP) that can detect 17 viral (adenovirus, Adeno; coronavirus, CoV [OC43, 229E, NL63, HKU-1]; human metapneumovirus, hMPV; human rhinovirus/enterovirus, HRV/EV; influenza A, Flu A [subtyping H1N1, 2009 H1N1, H3N2]; influenza B, Flu B; parainfluenza viruses, PIVs [1-4]; and respiratory syncytial virus, RSV) and three bacterial (*Bordetella pertussis, Chlamydia pneumoniae, and Mycoplasma pneumoniae*) pathogens [32,46,47].

With more than 362,000 patient results for the FilmArray RP test alone, the Trend database has many of the properties associated with big data as it applies to infectious disease [48]. After describing how the dataset can be cleaned of nonpatient tests, we make some observations on the seasonality of the different respiratory pathogens and the occurrence of codetection (more than one organism is detected in one test). Relatively little is known about rates of multiple concurrent respiratory infections and their overall impact on the health of the patient. Finally, we apply the ecological concept of species diversity [49] to observe a correlation between the abundance of each pathogen and the rate at which codetections (more than one positive result per test) occur in the tested population.

Methods

Origin of Syndromic Trends

FilmArray Trend was originally implemented to provide BioFire customers with an up-to-date view of the respiratory and GI pathogens circulating at their institution. From the perspective of an IVD manufacturer, the most uniform and thus the simplest method of accomplishing this is to follow a bottom-out approach to data export in which the FilmArray sends data to a cloud database managed by the manufacturer, and Web views of these data are available by clinicians at the hospital that generated the data (solid lines in Figure 1) rather than a top-out approach (dashed lines in Figure 1) in which the data are extracted from the hospital information system. This method provides the clinical institution with a tool to perform pathogen-specific surveillance for very little cost.

Patient Privacy When Exporting FilmArray Test Results

The Expert Determination study of the Trend data export algorithm (Multimedia Appendix 2) established that FilmArray patient results have been adequately deidentified. Therefore, a data use agreement (DUA), rather than business associates agreements (see Multimedia Appendix 2 for the difference between the two agreements) could be executed with each of the collaborating institutions (Multimedia Appendix 1). The DUAs define for the clinical laboratory how BioFire will manage and make use of the Trend data. The Trend client software residing on the FilmArray computer queries the FilmArray test result local database and exports the results to an Amazon Web Services database (Multimedia Appendix 1). The Trend client software performs deidentification on the FilmArray computer before export, as detailed in Multimedia Appendix 2. Health care providers (HCPs) are granted access to their institution's Trend data by the laboratory director. As Web access to view the data is restricted to the local site, deidentification of geographic indicators is not required. However, in the implementation of the public Trend website, which presents FilmArray test results from around the United States, we have further aggregated the data with respect to geographic origin and obfuscated the date of the test (Multimedia Appendix 2). As only deidentified data are exported from the clinical institutions, no PHI is sent to or stored on the cloud server.

Test Utilization Rate and Pathogen Detection Rate

The FilmArray RP test utilization rate (TUR) metric is defined as the non-normalized number of RP patient test results generated each week across the Trend sites (computed as a centered 3-week moving average). To calculate the pathogen detection rate (as displayed in Figure 2 [second data view] and on the Trend website), we compute the rate for each organism at each institution as a centered 3-week moving average. To adjust for the capacity differences between sites, a national aggregate is calculated as the unweighted average of individual site rates. Only data from sites contributing more than 30 tests per week is included to avoid noise from small numbers of tests. Because the calculation of pathogen detection rate includes results from patients with multiple detections, the detection rate for all organisms can, in theory, add up to greater than one. In practice, this does not occur.

Comparison With the Centers for Disease Control and Prevention Influenza-Observed Rate of Detection

The CDC FluView rate of Flu A and Flu B detections, as well as the reported incidence of weighted influenza-like illness (ILI), are taken from the CDC website [4]. Only the CDC data from the Department of Health and Human Services regions that contained Trend pilot sites (Multimedia Appendix 1) were used for calculating the rate of influenza detections.

Calculation of Codetection Rates and Related Measures

Pathogen codetections are defined as FilmArray tests in which two or three organisms are detected. We also calculated two other measures that relate to codetections: the circulating pathogen number and the measure of interspecific encounter (MIE). Both of these time series measures are calculated for each site and week, a centered 5-week moving average is computed, and then an unweighted average of all sites is used to create a national aggregate. The 5-week moving average is used to reduce noise because of small numbers of samples within a week at some sites.

More specifically, the circulating pathogen number is simply the count of the unique organisms detected at a site during a 1-week period. MIE is calculated from the frequencies of each organism at a site (number of positive test results for an organism divided by the number of FilmArray tests performed at that site). To reduce noise, we only include site data if more than 10 FilmArray tests were performed in that week. If $P_1 ... P_N$ are the percentage detection of the N different organisms circulating at a single site over a single week, then MIE is defined as shown in equation 1:

Conceptually, MIE is an attempt to estimate the likelihood that a patient infected with one organism may be infected with another unique organism circulating in the population at a given period in time, resulting in a coinfection.

Figure 1. Schema for export of in vitro diagnostic (IVD) test results to an external database. Bottom-Out and Top-Out approaches for data export are indicated by solid and dashed lines, respectively. Some institutions have developed their own systems for aggregating and displaying infectious disease data (indicated by internal website). HIS: hospital information system; LIS: laboratory information system; CDC: Centers for Disease Control and Prevention; NREVSS: National Respiratory and Enteric Virus Surveillance Systems.

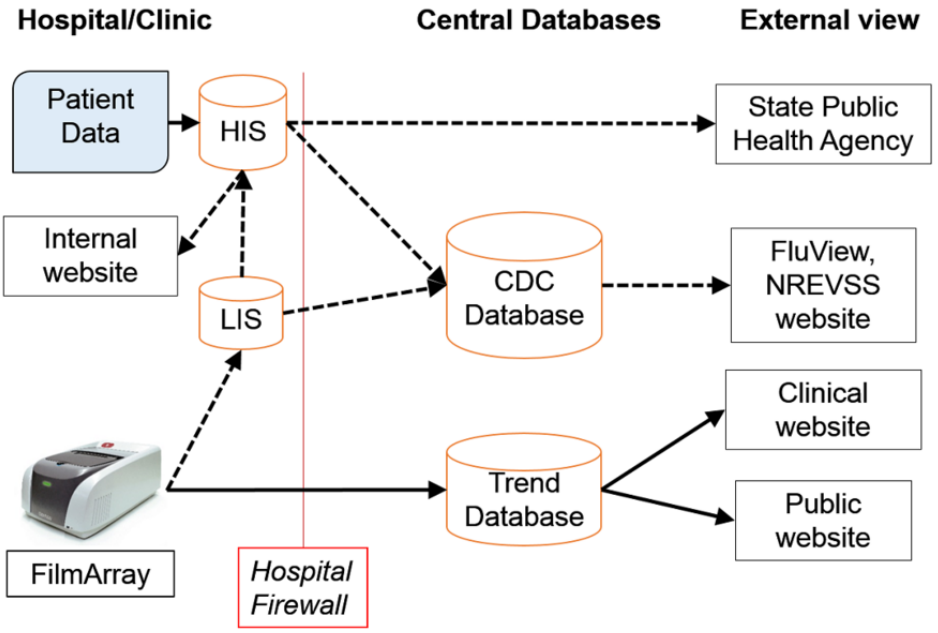


Figure 2. Detection of respiratory panel (RP) organisms over time across all sites. Detection of FilmArray RP pathogens in the Trend dataset displayed as stacked area graphs. All data views have the same time period (July 2013 through July 2017). (First data view) Count of each organism. The test utilization rate (TUR) metric (purple line, units are FilmArray RP tests performed) and count of FilmArray RP tests that are negative (white are between pathogen count and TUR) are indicated. The y-axis values are not indicated as this is considered proprietary information. (Second data view) Pathogen detection rates for all organisms. (Third data view) Pathogen detection rates for the subset of organisms that show seasonality (see Results and the legend for the list of organisms). (Fourth data view) Human rhinovirus (HRV) or enterovirus (EV) detection rates. The CDC weighted influenza-like illness (ILI; scaled up tenfold to be visible against the pathogen data) is indicated (black line) in the third and fourth data views. Organisms follow the same color scheme in all panels; the order of organisms in the legend (down then across) matches that of the stacked area graph top to bottom.

Results

Sending FilmArray Data Directly to the Cloud

The most general and efficient way to aggregate test results from the FilmArray instrument in a clinical laboratory is to follow a bottom-out approach to data export (Figure 1; Multimedia Appendix 1). In this scheme, the FilmArray instrument (at the bottom of the information hierarchy) directly sends data via the internet to a single cloud database where it can be viewed by HCPs at the originating institution. This data export pathway contrasts with a top-out approach (Figure 1) in which diagnostic test results are pushed from the instrument up through the LIS, to the HIS (at the top of the information hierarchy) and, finally, a subset of this information is forwarded to cloud-based databases.

Initial testing of the Trend export mechanism was performed in collaboration with the clinical laboratories of the Medical University of South Carolina. This trial allowed us to develop and test auto-export functions and deidentification protocols for the Trend software. The deidentification requirement of the Health Insurance Portability and Accountability Act (HIPAA) of 1996, specifically the Safe Harbor provision, requires the removal of 18 enumerated variables that could directly or indirectly identify an individual [50]. In accord with this requirement, the first stage study did not export test identifiers or free-form text fields and only returned the year of the test. The initial dataset provided low-resolution information but was a useful platform to evaluate the proposed system. Further development to enable export of higher resolution data required the design of routines that would adhere to an alternative HIPAA deidentification strategy, namely, the Expert Determination approach, which requires a risk assessment demonstrating that the chance of reidentifying an individual is sufficiently small [51]. The Expert Determination process identified and made recommendations for fields that could facilitate disclosure of PHI (Multimedia Appendix 2). A summary of the Expert Determination results detailing the risk of Trend data in regard to replicability, availability, and distinguishability is shown in Multimedia Appendix 2.

All sites (Multimedia Appendix 1) submitted the Trend project for review by their local institutional review board; all but one of the 20 review boards deemed the project exempt because of the absence of PHI export. Thus, the security requirements for the database and the controls necessary for storage and transport of deidentified data are significantly reduced.

Following the protocol established by Expert Determination review, the Trend software delays the export of results until the number of tests queued for export exceeds a minimum threshold for each type of FilmArray panel. In practice, this results in an average time to export of less than 2 hours from each site that has multiple instruments. A total of 99.11% (74,912/75,585) of the test results exported automatically occurred within 24 hours of test completion.

Characteristics of the FilmArray Sites Used in the Trend Pilot Study

The 20 sites contributing to the Trend pilot project (Multimedia Appendix 1) have the same average number of instruments; six (range: 1-22) as for all US FilmArray customers. The Trend pilot sites have been using the FilmArray RP test for an average of 3.8 years (range: 1-6) before June 2017. The size of the institutions participating ranges from 300 to 6400 beds, with the majority being large hospitals, and health care networks with an average of 1100 beds. Six (30%, 6/20) sites are pediatric hospitals, and one is a reference laboratory. Fifteen (75%, 15/20) of the sites have uploaded archived FilmArray RP test results to the Trend database, with eight (40%, 8/20) reporting results dating back to 2012. Unless stated otherwise, the data presented here cover the period from July 2013 to July 2017.

The algorithm used to diagnose the cause of respiratory disease varies by site. More than half of the Trend sites do not enforce an institutional respiratory testing protocol and, even within sites that have a required protocol, some discretionary use of FilmArray RP is allowed. Without detailed records from each institution’s HIS, it is not possible to determine whether the FilmArray RP was used as a front line test or as a reflex test (typically following a negative result for influenza and RSV).

Cleaning Nonpatient Test Results From the Trend Database

To determine the prevalence of respiratory pathogens, we needed to expunge the Trend database of test results that are not derived from clinical patient samples. Nonpatient results come from a variety of sources including verification testing, routine quality control (QC), and proficiency testing (PT; Multimedia Appendix 3). Despite this complexity, the majority of nonpatient test results can be identified and distinguished from the patient-derived data because of the high number of positive organism calls in a single test and because of the temporal aspects of verification and control testing (Multimedia Appendix 3 shows one such identification method). QC tests are estimated to account for half of all FilmArray RP results in which more than three organisms are detected. In addition to the exclusion of tests temporally associated with validation events, all results with four or more positives were removed from further analysis (approximately 1% of the filtered total). This includes the small fraction of test results with exactly four organisms (Multimedia Appendix 3, Tests after event removal column) because the minority are derived from patient testing.

Detection of Respiratory Pathogens in Trend Samples From 2013 to 2017

The detection counts and pathogen detection rates derived from the Trend dataset for each organism in the FilmArray RP are shown in Figure 2. Other views of these data, including percent detection of individual organisms or combinations of organisms, are available on the BioFire Syndromic Trends public website [44]. The FilmArray RP TUR (see Methods) and the individual organism detection counts increased over this period because the Trend clinical sites increased their utilization of the FilmArray RP tests (Figure 2, first data view). Seasonal fluctuations can also be seen within this growth pattern, with use increasing up to four-fold each winter when compared with the previous summer. HRV/EV, the most common pathogen detected group, is identified in approximately one-fourth of all samples tested each year (Multimedia Appendix 4). Other pathogens detected in approximately one-tenth of the samples include RSV, the PIVs, ADV, influenza, and hMPV. *M pneumoniae*, *C pneumonia*, and *B pertussis* are detected in a small percentage (one-fiftieth) of all samples. The average percentage of each organism is relatively constant over the 4 years of data in the Trend database (Multimedia Appendix 5).

The pathogens' seasonal variability measured by percent detection can be classified into at least three groups. Group 1: the majority of organisms follow the classical respiratory season (October-March) and increase by more than ten-fold above their baseline detection rate (Figure 2, third data view). These include the CoVs, Flu A, Flu B, hMPV, the PIVs, and RSV (PIV3 is a slight exception to this rule in that it peaks in the summer months and has a winter peak that is only detected regionally; data not shown). Within this group, all but five viruses demonstrate significant fluctuations from year to year; Flu B, hMPV, OC43, and PIV3 and RSV experience relatively consistent annual peaks. Group 2: HRV/EV is in a class by itself in that it is detected in a high percentage of tests over time (minimum of one-tenth of tests in winter) and experiences moderate peaks of two- to three-fold outside the respiratory season baseline in the early fall and spring (Figure 2, fourth data view). Group 3: the bacteria and Adeno are present at a relatively constant rate (Multimedia Appendix 6). The CDC FluView reported rate of ILI tracks moderately well with the group 1 organisms (cross-correlation of 0.85) and not with HRV/EV or with Adeno and the bacteria.

Comparison of Trend With Centers for Disease Control and Prevention Measures of Influenza

The CDC FluView network [4] gathers information about influenza prevalence from a large number of public health and clinical laboratories in the United States. FluView is considered the gold standard for these measures. We compared the Trend detection rates for Flu A (all subtypes) plus Flu B with the FluView Influenza (A and B) from September 2015 to July 2017 (Figure 3). The analysis was restricted to this time period because of a change in the CDC's reporting of flu prevalence in the fall of 2015. A cross-correlation of 0.974 was observed between the Trend Flu A or B percent detection and FluView reported influenza prevalence. Notably, the onset, peak, and duration of the influenza season coincide between the two measures.

Respiratory Panel Codetections

We found that approximately 38,000 FilmArray RP tests in the Trend dataset had two or three codetections. The most common codetections observed are those involving HRV/EV, which is the pathogen with the overall highest rate of detections (Figure 4, first data view). The codetection rate within each organism varies widely (from one-tenth to one-half; Figure 4, second data view). Although an additional pathogen was detected in half of the Adeno and CoV positive samples, codetections were observed in only one-tenth of the samples positive for either Flu A or Flu B (Figure 4, second data view).

Figure 3. Trend influenza detection rate compared with Centers for Disease and Prevention's (CDC) influenza activity. Percent of combined FilmArray Flu A (all subtypes) and Flu B detections (blue line) and CDC-reported influenza prevalence (black lines). CDC data are aggregated only from regions with participating Trend sites.

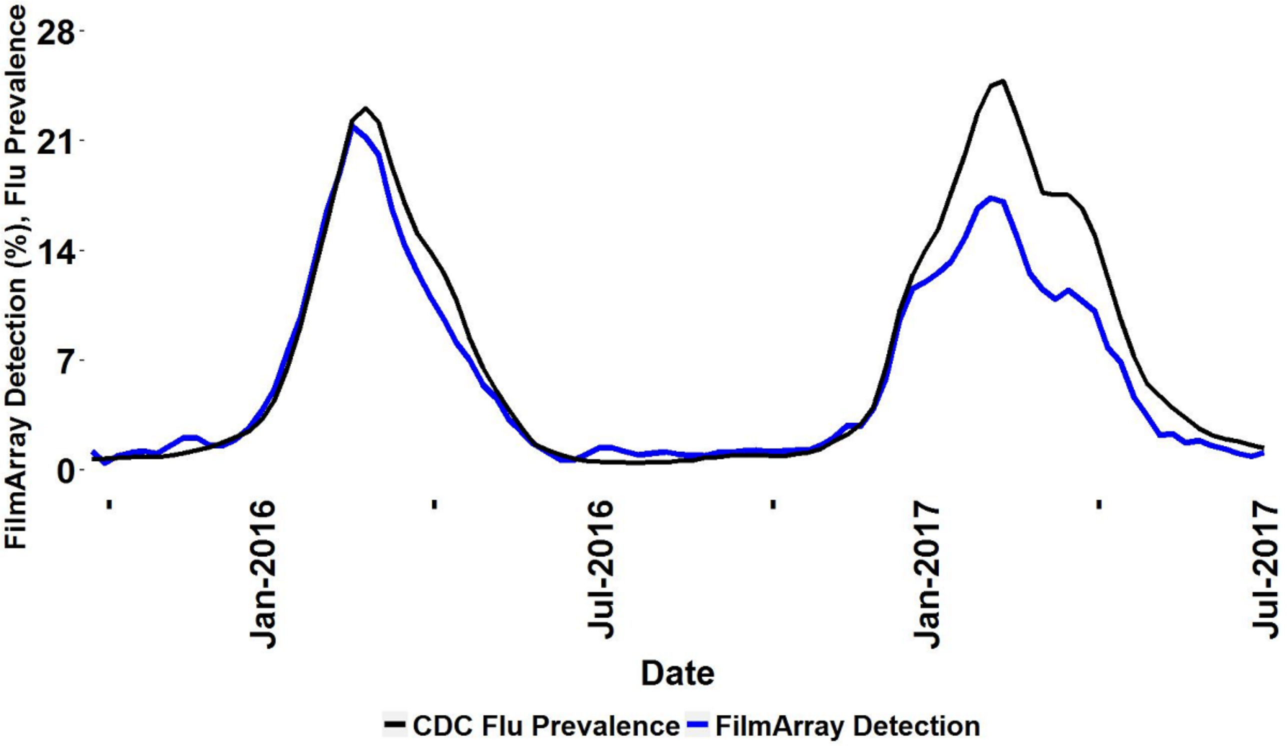


Figure 4. Detection rates for all organisms compared with codetections. Percent total positive detections for each organism in the respiratory panel (RP) Trend dataset is presented in stacked bars, showing the rate of detection of a single organism (first data view, blue) and those involved in a codetection (first data view, black). Data are calculated for each site during the period from July 2013 to July 2017, when available, and then aggregated. (Second data view) Percentage of each organism involved in a codetection is shown. Bars are colored by pathogen family (CoV, purple; bacteria, blue; PIVs, green; Flu A, yellow).

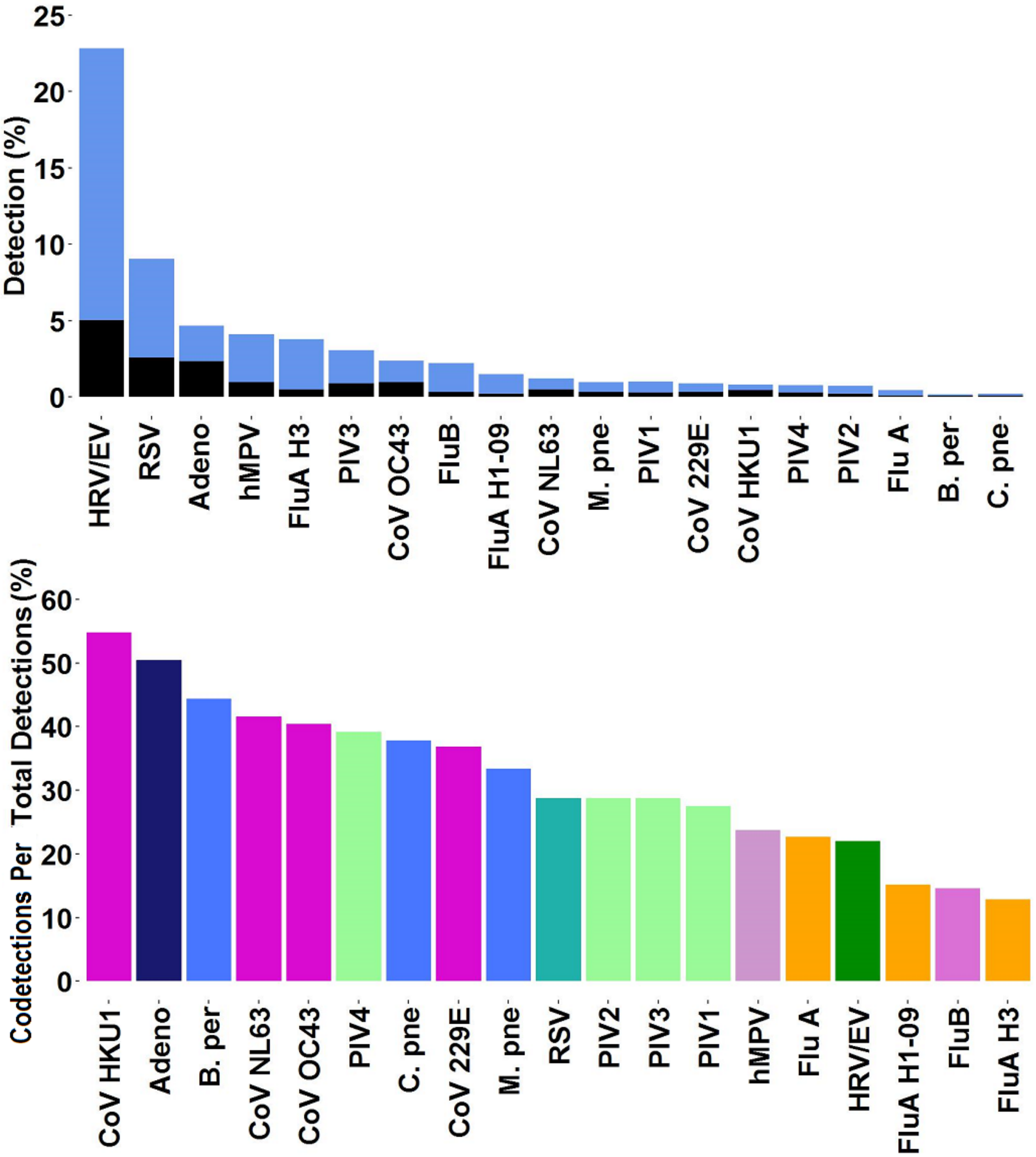
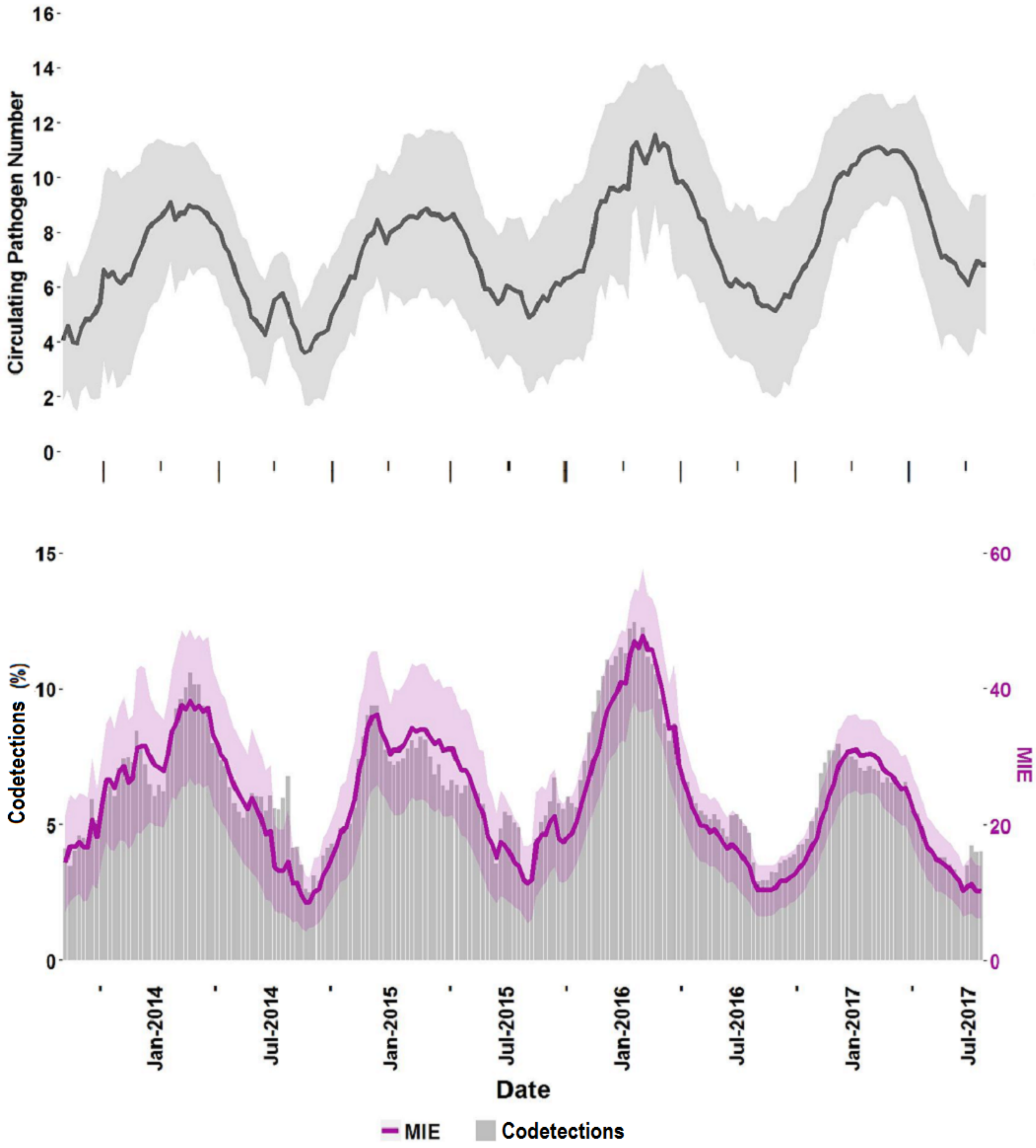


Figure 5. Seasonal variation in pathogen diversity and codetections. (First data view) Average circulating pathogen number (black line) and one SD computed across all Trend sites (gray area). (Second data view) Rate of codetections in the respiratory panel (RP) Trend dataset (gray bars, left axis), the measure of interspecific encounter (MIE) index (purple line, right axis), and MIE CIs (shaded purple area).



Trend data have high temporal, spatial, and organism-specific resolution. These three properties allow for a novel evaluation of codetections. The observed rates of codetections should be influenced by the number of circulating pathogens detected by the FilmArray RP test at a particular site. Figure 5, first data view, shows the average number of unique organisms detected at each site in a given week (see Methods: Calculation of codetection rates). This number fluctuates from a summer low of four to a winter high of 11 pathogens. Figure 5, second data view (gray bars), shows that the total rate of organism codetections in the Trend dataset fluctuates annually, with peak rates occurring in the winter months. The average rates have been as high as one in 8 tests in the winter of 2016 and as low as one in 50 in the summer of 2014.

From the Trend data, an MIE can be calculated as the probability of a codetection, weighted by the prevalence of each circulating pathogen at a site. Although the value of the MIE metric is higher than the actual codetection rate, it correlates well (Figure 5, second data view, purple line compared with the gray bars has a cross-correlation of 0.9488 at a lag of 0). The magnitude adjustment between MIE and the observed codetections is calculated by the slope of the linear regression of the two metrics (Multimedia Appendix 7) and has a value of 4.05 (R^2=.9003).

Discussion

Properties of Trend Data

This study describes BioFire Syndromic Trends, a new system for real-time reporting of widespread pathogen-specific syndromic data. Even in its pilot phase, the Trend database already has many of the features that characterize big data [48]. The Vs of big data—volume (amount), velocity (speed of acquisition), veracity (accuracy), variety (diversity of information), and value (utility)—should be kept in mind as we consider the properties of Trend in clinical and public health settings.

The Trend RP dataset is growing at an average rate of >400,000 pathogen test results per month (>20,000 patient tests with 20 pathogens). Connecting the first 20 clinical sites has provided insight into the principal concerns that will be raised by the legal, information technology, and administrative departments of the HCPs that house FilmArray instruments. It should be possible, therefore, to expand the Trend installed base by 10- to 20-fold over the next few years. Similarly, the existence of Trend should enable other IVD manufacturers to build their own Trend-like systems with greater acceptance on the part of their customers, thereby allowing a more global and comprehensive surveillance perspective.

The data in Figure 2 are similar to previous demonstrations of the seasonality associated with different respiratory viruses [52-55]. What is novel is that these data are generated automatically, on site, and in close to real time compared with other surveillance systems. Nearly all of the test results are exported to the Trend database within 24 hours of being generated. As part of the deidentification protocol, sequential FilmArray RP tests of the same type are put into the same time bin. This has the effect that test results are exported faster during periods of peak use, such as during the peak of the respiratory season or during an outbreak. Trend should be instrumental at a local level to determine the start of a respiratory season; many hospitals make significant changes to their operations based on this event; however, at present, data collection to track the respiratory season is often slow and manual, or semiautomated at best.

The key to implementing Trend clinical sites was to demonstrate that FilmArray test results can be exported without the risk of breaching PHI confidentiality either directly or through some combination of the data that were exported. Trend successfully used the Expert Determination process as prescribed by the HIPAA guidelines (see Multimedia Appendix 2), which greatly simplified the data sharing agreement between BioFire Diagnostics and the clinical site and allowed HCPs to use Trend without risk of inadvertently disclosing PHI.

The software architecture underlying the Trend system is both simple and secure: (1) no changes to the institutional firewall or LAN are needed; (2) the Trend database cannot reach back and query the FilmArray computer because of the institutional firewall, which is set to outbound data only; and (3) Trend software can only submit data to the cloud database and cannot query the database (Multimedia Appendix 1). Yet, despite this security, authorized users of the Trend database can mine the deidentified data to look for novel patterns in respiratory pathogen epidemiology.

The Costs and Benefits of Bottom-Out Data Export System

The goal of an epidemiological surveillance network is to infer which infectious diseases are circulating in the general population based on testing a sample of patients [56]. Different surveillance systems have different biases in their data; biases that perturb the ability to predict true population prevalence.

Although the removal of all PHI has great benefits in terms of implementation, it also has several shortcomings that complicate interpretation of the data. First, Trend cannot account for the variability in the diagnostic testing algorithms applied to the selection of samples to be tested by the FilmArray instruments. During the respiratory season, HCPs may prescreen patients with other diagnostic tests including rapid antigen or molecular assays for influenza and RSV or commercial and laboratory-developed molecular tests for a mix of other respiratory pathogens. Depending upon the sensitivity of these upstream tests, more than half of influenza and RSV for the subset of the patients screened would be excluded from the Trend dataset if the front line test is positive. This testing protocol may skew the actual prevalence of not only influenza and RSV but all other individual respiratory pathogens and coinfections detected by the FilmArray. In some institutions, testing is reserved for hospitalized patients and others at risk for developing complications of respiratory tract infections, including the very young, very old, and immunocompromised patients. So Trend data may represent a less healthy patient population and not necessarily general community prevalence. Conversely, there are sites that perform a significant number of tests for the outpatient setting. This may create variability among the clinical sites' percent positivity and introduces a challenge to comparing pathogen intensity between sites.

The uncertainties surrounding the testing algorithm and the precise patient population tested should not interfere with determining the onset, peak, and duration of the pathogen season at each institution. These limitations on the data are likely to be common among almost all current surveillance systems for similar reasons. Given these concerns, the agreement between the percent positivity of Flu A or B as determined by Trend and the percent positivity reported by CDC FluView Influenza is striking (Figure 3), supporting the validity and utility of the Trend data.

The second source of concern in the Trend dataset is a consequence of the removal of sample identification such that we cannot directly determine whether the sample was from a patient or was a nonclinical sample (verification test, QC, or PT) and should be removed from further epidemiological analysis. We estimate that nonpatient testing makes up approximately one-fiftieth of the total FilmArray RP tests. Automated detection algorithms remove roughly one in 25 of the total RP tests, including approximately half of the nonclinical samples. With the exception of the four positive tests, the clinical samples removed by filtering should be a random sampling of all patient tests. The remaining nominal fraction of nonpatient tests has essentially no impact on the Trend evaluation of pathogen prevalence, but they do make it more difficult to perform high-resolution analysis of pathogen codetections. This is especially true for codetections of low prevalence organisms where QC positives are likely to be more common than real positives. Future updates to the FilmArray software will simplify the process by which the instrument operator can tag tests of nonpatient samples, thereby largely eliminating the need to filter such test results from the Trend database before analysis.

The Seasonality and Coinfections of Respiratory Pathogens

The total positivity rate of the FilmArray RP test varies from a low of approximately one-third of tests in the summer months to a high of three-fourths of the tests in December and January. Figure 5, second data view, shows that the average number of different circulating pathogens at a single institution can vary from eight up to 11 during the winter months. Even during the peak periods of ILI, many respiratory infections are due to other viruses (Figure 2, third data view) that can present clinically in a similar fashion [57,58]. Therefore, the presumption of an influenza infection based on reported influenza percent positivity, without diagnostic testing for the virus, can lead to the inappropriate use of antiviral agents [59]. Conversely, without comprehensive testing, a negative influenza or RSV test can lead to the prescription of an unnecessary antibiotic. Trend data can be a valuable aid for antimicrobial stewardship programs because it provides real-time information regarding the causes of respiratory infections and highlights the prevalence of viral infections.

As previously observed [55], the viruses that share the winter seasonality of influenza demonstrate annual or biennial behavior. It is possible that the viruses that share an influenza-like seasonality but do not show a two-year cycle (RSV and hMPV) are actually alternating strains, but the FilmArray RP Test does not detect this difference (eg, the FilmArray RP does not differentiate between RSV A and RSV B). Adeno and the bacteria show constant occurrence through the year; HRV is in a unique class with peaks in the fall and spring.

Detection of multiple respiratory viruses in the same patient has been reported before. In the Trend dataset, the rate of dual and triple codetections was approximately 7.94% (28,741/362,101), with HRV/EV as the organism most commonly observed in a codetection. Some viruses such as ADVs and the CoVs are detected in the presence of another organism approximately half of the time (Figure 4). In principle, a FilmArray RP positive result may represent detection of residual pathogen nucleic acid from a previous infection that has resolved. However, several studies suggest that coinfections are associated with more severe disease [60-62] (see also discussion in [63]). In such cases, information about multiple detections can provide infection control practitioners with data that can assist in bed management and in the assessment of risk for nosocomial infections in a patient population that has been segregated by the occurrence of a common pathogen. Such information can prevent the introduction of a new pathogen associated with cohorting patients during busy respiratory seasons [64-66].

The question of whether different respiratory pathogens interfere with, or facilitate, growth in a human host is of some interest and not well understood. With the right data, it can be studied at the population [67], individual [68], and cellular level [63]. Because the Trend data still include some nonpatient tests, we have chosen not to analyze every possible dual or triple infection individually. Rather, we have taken a global approach and compared the overall rate of observed codetections with MIE, which is a measure of the diversity of viruses circulating in a specific region and time period. MIE is similar, but not identical, to Probability of Interspecific Encounter (PIE [69]), also referred to as the Gini-Simpson index (1-D, where D is the Simpson's index), which is used in ecology as a measure of the species diversity of a region. Similarly, the circulating pathogen number of Figure 5, first data view, is identical to the Species Richness measure of ecology. We calculate MIE using frequencies (P_i) of pathogen positivity per FilmArray test and note that the sum of all pathogen frequencies can add up to more than unity because of codetections or be less than unity because of the presence of negative tests. In this regard, MIE differs from PIE because it is not a probability measure.

Figure 5, second data view, shows that the observed rate of codetections is a constant fraction of MIE (approximately one-quarter as indicated by the linear regression of Multimedia Appendix 7). This observation suggests that, in the aggregate, respiratory pathogens are appearing in coinfections at a rate that can be predicted by their observed abundance. The data, however, may be biased by the patient population tested and the type of respiratory disease. The data also does not rule out that there are particular respiratory pathogens that occur more or less often in mixed infections than predicted by their individual percent positivity rates [63,70]. As we improve our ability to remove nonpatient test results from the Trend dataset, we will be able to characterize specific virus codetection rates and their significance [54,55,67,68,71,72].

Applications of Trend Data

As with weather forecasting, there is both a theoretical and a practical interest in predicting the next few weeks or months of the respiratory season [73-76]. Trend contributes to infectious disease forecasting efforts because the data are timely and comprehensive. As the number of sites participating in Trend increases, it will be possible to localize the reported infections to smaller geographical regions. At a high enough density of Trend sites, patterns of movement of respiratory pathogens across the United States will become visible in a way that has not been easily observed before now.

The Trend RP data show the percentage contribution of each pathogen to what is currently being detected by FilmArray RP testing (Figure 2, second data view) [44]. This analysis does not take into account changes in the rate of testing over a given season; information that should provide additional data regarding disease intensity and severity. In contrast, the simple metric, TUR, describes the non-normalized rate of FilmArray test usage and serves as a surrogate for the level of syndromic disease that HCPs observe (Figure 2, first data view).

TUR suffers from two defects. First, it is closely linked to the sales of the FilmArray test and thus is proprietary data that BioFire does not share (Google took a similar position in regard to releasing the search queries used by Google Flu Trends [12]). Second, TUR is driven by both the demand for testing and the growth in FilmArray product adoption and increasing acceptance and usage by HCPs. A useful step beyond TUR would be a normalized rate that can adjust for the underlying growth of testing unrelated to the intensity and duration of the respiratory disease season. An increase in a normalized TUR metric may indicate the prevalence of circulating respiratory viruses and the intensity of respiratory disease overall. Likewise, an increase in the normalized metric, concomitant with an increase in negative tests, may indicate the occurrence of an outbreak caused by an emerging pathogen.

Public health agencies, which include local and state health departments and the CDC, are specifically exempt under a HIPAA provision that allows clinical laboratories to disclose PHI to the agencies for specified public health purposes [77]. The exemption includes follow-up studies on reportable infectious diseases. Real-time pathogen-specific syndromic surveillance systems such as Trend will allow state health departments to more rapidly identify, acquire, and test residual samples from potential outbreaks. Conversely, perceived outbreaks may actually be coincidental multi-organism seasonal surges, and rapid analysis by Trend-like systems could prevent timely and costly outbreak investigation.

Given the movement in health care technology toward greater vertical integration of a hospital's data, the bottom-out approach exemplified by Trend will face more competition from top-out approaches (Figure 1, see, eg, GermWatch in Utah, [21]) because these systems can capture patient information (eg, age, gender, and patient address) that is critical for more detailed epidemiological analysis. However, combining PHI with the diagnostic test result in the top-out approach makes these systems more complex and difficult to implement and may limit participation by health care institutions. Ironically, bottom-out data export systems have a role to play in the development of top-out systems because bottom-out export provides a rapid and efficient means to quality check the data flowing from top-out systems. Trend data could also be combined with data derived from other automated diagnostic platforms [78,79]. This work might best be accomplished by a third party that is viewed as independent and impartial. For example, in the case of data originating in the United States, a federal institution or a private foundation could host a database to which IVD manufacturers would contribute their different syndromic test results. The benefits of a more complete view of circulating pathogens should outweigh the complexities of combining data from different platforms.

Future Outlook

Syndromic Trends is a novel surveillance tool for simultaneously monitoring multiple syndromic diseases that has demonstrated promise in expanding our knowledge of the epidemiology of infectious diseases. Indeed, the close correlation of seasonal respiratory viruses tracked by Trend with reported CDC ILI highlights the major contributory role of multiple respiratory pathogens beyond influenza to ILI. The national and global expansion of Trend will provide a comprehensive tool to study the impact of coinfections, understand the role of previously underappreciated pathogens, and clarify true disease epidemiology. Finally, systems such as Trend will be essential for the rapid identification of disease anomalies indicating potential emergent outbreaks, thereby providing an independent tool for public health surveillance.

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Conflicts of Interest

LM, ANF, RKN, CVC, JDJ, KMR, CCG, and MAP are present or former employees of bioMérieux, Inc, or its subsidiaries. bioMérieux markets the FilmArray System and Trend. FSN, PHG, DJ, VD, AL, JDB, SS, KAS, HS, RS, SJ, JAD, JCW, KL, FM, SLR, MA-R, PDF, GAS, SJM, SVS, and BMA are research contractors of BioFire Diagnostics for the development of the BioFire Syndromic Trends system. CCR and JFM are members of the Syndromic Trends Working Group. BAM is a paid consultant of BioFire Diagnostics.

Multimedia Appendix 1

BioFire Syndromic Trends System.

[PDF File (Adobe PDF File), 132KB - publichealth_v4i3e59_app1.pdf]

Multimedia Appendix 2

Deidentification of Patient data for Infectious Disease Epidemiology.

[PDF File (Adobe PDF File), 127KB - publichealth_v4i3e59_app2.pdf]

Multimedia Appendix 3

Cleaning Trend Data.

[PDF File (Adobe PDF File), 141KB - publichealth_v4i3e59_app3.pdf]

Multimedia Appendix 4

Detection of FilmArray RP Organisms by Type.

[PDF File (Adobe PDF File), 196KB - publichealth_v4i3e59_app4.pdf]

Multimedia Appendix 5

Detection of FilmArray RP Organisms by Year.

[PDF File (Adobe PDF File), 402KB - publichealth_v4i3e59_app5.pdf]

Multimedia Appendix 6

Detection of Adenovirus and the Three Bacteria.

[PDF File (Adobe PDF File), 216KB - publichealth_v4i3e59_app6.pdf]

Multimedia Appendix 7

Linear Regression of MIE and Observed Codetections.

[PDF File (Adobe PDF File), 207KB - publichealth_v4i3e59_app7.pdf]

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Abbreviations

Adeno: adenovirus
CDC: Centers for Disease Control and Prevention
CoV: coronaviruses
DUA: data use agreements
ECLRS: Electronic Clinical Laboratory Reporting System
Flu: influenza
GEIS: Global Emerging Infections Surveillance
HCP: health care provider
HIPAA: Health Insurance Portability and Accountability Act
HIS: hospital information system
hMPV: human metapneumovirus
HRV/EV: human rhinovirus/enterovirus
ILI: influenza-like illness
IVD: in vitro diagnostic
LAN: local area network
LIS: laboratory information system
MIE: measure of interspecific encounter
NREVSS: National Respiratory and Enteric Virus Surveillance Systems
PHI: protected health information
PIE: probability of interspecific encounter
PIV: parainfluenza virus
PT: proficiency testing
QC: quality control
RP: respiratory panel
RSV: respiratory syncytial virus
TUR: test utilization rate

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Original Paper

Cross-Jurisdictional Data Exchange Impact on the Estimation of the HIV Population Living in the District of Columbia: Evaluation Study

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Abstract

Background: Accurate HIV surveillance data are essential to monitor trends to help end the HIV epidemic. Owing to strict policies around data security and confidentiality, HIV surveillance data have not been routinely shared across jurisdictions except a biannual case-by-case review process to identify and remove duplicate cases (Routine Interstate Duplicate Review, RIDR). HIV surveillance estimates for the District of Columbia (DC) are complicated by migration and care seeking throughout the metropolitan area, which includes Maryland and Virginia. To address gaps in HIV surveillance data, health departments of DC, Maryland, and Virginia have established HIV surveillance data sharing agreements. Although the Black Box (a privacy data integration tool external to the health departments) facilitates the secure exchange of data between DC, Maryland, and Virginia, its previous iterations were limited by the frequency and scope of information exchanged. The health departments of DC, Maryland, and Virginia engaged in data sharing to further improve HIV surveillance estimates.

Objective: This study assessed the impact of cross-jurisdictional data sharing on the estimation of people living with HIV in DC and reduction of cases in the RIDR process.

Methods: Data sharing agreements established in 2014 allowed for the exchange of HIV case information (eg, current residential address) and laboratory information (eg, test types, result dates, and results) from the enhanced HIV/AIDS Reporting System (eHARS). Regular data exchanges began in 2017. The participating jurisdictions transferred data (via secure file transfer protocol) for individuals having a residential address in a partnering jurisdiction at the time of HIV diagnosis or evidence of receiving HIV-related services at a facility located in a partnering jurisdiction. The DC Department of Health compared the data received to DC eHARS and imported updated data that matched existing cases. Evaluation of changes in current residential address and HIV prevalence was conducted by comparing data before and after HIV surveillance data exchanges.

Results: After the HIV surveillance data exchange, an average of 396 fewer cases were estimated to be living in DC each year from 2012 to 2016. Among cases with a residential status change, 66.4% (1316/1982) had relocated to Maryland and 19.8% (392/1982) to Virginia; majority of these had relocated to counties bordering DC. Relocation in and out of DC differed by mode of transmission, race and ethnicity, age group, and gender. After data exchange, the volume of HIV cases needing RIDR decreased by 74% for DC-Maryland and 81% for DC-Virginia.

Conclusions: HIV surveillance data exchange between the public health departments of DC, Maryland, and Virginia reduced the number of cases misclassified as DC residents and reduced the number of cases needing RIDR. Continued data exchanges will enhance the ability of DC Department of Health to monitor the local HIV epidemic.

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KEYWORDS

HIV; surveillance; data sharing; public health; cross-jurisdictional

Introduction

Both the National HIV/AIDS Strategy released by the White House Office of National AIDS Policy in 2010 [1] and the 2016 District of Columbia 90/90/90/50 Plan to End the HIV Epidemic by 2020 [2] include key goals and outcome measures that depend on having an accurate population estimate of the number of individuals diagnosed and living with HIV. The four main aims of the District of Columbia (DC) Plan included the following: 90% knowing their HIV status, 90% engagement in HIV care, 90% viral suppression among those who enter care, and 50% reduction in new HIV diagnoses by 2020. Because the National HIV/AIDS Surveillance System (NHSS) aims to document all people diagnosed with HIV in the United States, the system is uniquely poised to provide a foundational denominator for these outcomes. Participants in NHSS consist of state and local health departments with public health authority to collect data on people living with HIV (PLWH). Thus, it is incumbent upon the participants of NHSS to provide the most up-to-date HIV prevalence data possible. In addition, having up-to-date HIV surveillance data would make data-to-care strategies, which use surveillance data to identify PLWH who are not achieving optimal health outcomes, more efficient [3].

NHSS supports the systematic collection of HIV and AIDS cases in the United States by 59 jurisdictions (states and territories), including the DC [4]. The data collected in NHSS are utilized to monitor the HIV epidemic, inform care, treatment, and prevention efforts and enable local health departments to report to the United States Centers for Disease Control and Prevention (CDC). Data are collected and maintained on local instances of the NHSS's data collection system, the enhanced HIV/AIDS Reporting System (eHARS), which is a browser-based application. In addition to HIV-related diagnostic and clinical laboratory data, demographic data, risk information, treatment facility, and residential address are collected from health care providers and stored in eHARS. Each NHSS participant shares deidentified data with CDC monthly [5].

The Routine Interstate Duplicate Review (RIDR) process facilitates the identification and exchange of information across jurisdictions concerning individuals diagnosed with HIV who are documented in the eHARS databases of different jurisdictions. Although the main purpose of this process is deduplication, resident addresses may be exchanged, allowing jurisdictions to further refine their local estimates of PLWH. Certain authorized personnel at the state, county, and local health departments are permitted to discuss cases if there is an indication that the individual may have been in another state's surveillance system. The Council of State and Territorial Epidemiologists provides a platform for jurisdictions to maintain an up-to-date list of the personnel identified to conduct RIDR.

Migration and population growth have challenged the understanding of who is living with HIV in DC. The US Census Bureau reported that between 2010 and 2016, the population of DC increased by an estimated 79,447 (13.2%) persons, and the Washington-Arlington-Alexandria Metropolitan Statistical Area population increased by an estimated 525,745 (8.8%) persons [6]. In addition to overall growth, according to the American Community Survey, between 2011 and 2015, approximately 24,530 persons moved out of DC to the surrounding counties of Prince George's and Montgomery County, Maryland, Arlington and Fairfax County, Virginia, and Alexandria [7], and the racial majority of those who moved out of DC to those jurisdictions were black at 44.3% (10,868/24,530). The vast majority of black persons and Hispanic and Latino persons who left DC moved to Prince George's County, Maryland, whereas the majority of the white persons who left DC moved to Montgomery County, Maryland. The overall population shifts make understanding the migration patterns of PLWH in the DC metropolitan area more challenging.

Residential address information is collected by NHSS, but it may not be updated beyond the initial case report collected at the time of HIV diagnosis. A lack of current residential addresses can stymie data-to-care efforts, which utilize residential address to re-engage people out of care; surveillance epidemiologists have found that the bulk of the effort is spent on updating addresses in eHARS, increasing the time to re-engagement [8]. Based on data in DC eHARS, PLWH may appear to be out of care but could have moved to a nearby county outside of DC and switched their care to a non-DC health care provider.

In 2013, the health departments of DC, Maryland, and Virginia met with Georgetown University to discuss the concept of sharing data across jurisdictions to expand the scope and timeliness of HIV surveillance data. By 2014, the three jurisdictions had agreed to share HIV surveillance data with each other and executed data sharing agreements (DSAs). DSAs included elements such as the frequency of sharing data, what variables would be shared, data security measures, and the format in which data would be transmitted. In 2014, National Institutes of Health funded Georgetown University to conduct a pilot study on a privacy sharing device for disease surveillance data known as the Black Box, in which the three jurisdictions participated. The Black Box pilot-tested a proof of concept that an encrypted, intermediary technology could receive surveillance data from the three health departments and securely report the probability of matches back to each jurisdiction. The pilot was successful in identifying multiple matches across the jurisdictions [8]. After seeing the success of the Black Box pilot and building upon the trust that was built during the setup of the Black Box pilot, the health departments of DC, Maryland, and Virginia recognized the need for more variables and routine exchanges of data to occur separately from relying upon the Black Box technology.

Starting in 2016, the health departments of DC, Maryland, and Virginia began to hold monthly conference calls that focused on the implementation of a routine exchange of HIV surveillance data (independent of the Black Box) between the three jurisdictions. Goals of the data exchange included the following: increasing information utilized to assess the HIV care continuum through the exchange of laboratory data; increase the ability to deduplicate cases through the exchange of personally identifiable surveillance data (ie, first name, last name, and date of birth); and increase the accuracy of the estimation of PLWH in DC by utilizing current residential information received through the data exchange. The objectives of this evaluation were to assess the impact of cross-jurisdictional data sharing on the estimation of PLWH in DC and reduction of cases needing review in the RIDR process.

Methods

Cross-Jurisdictional Operations Coordination and Governance Structure

Discussions about the concept of cross-jurisdictional exchanges of HIV data between DC Department of Health, Maryland Department of Health, and Virginia Department of Health began in January 2013. At the outset, all three jurisdictions needed substantial organizational and leadership buy-in and support from the general counsels to execute DSAs. In addition, following the execution of DSAs, key stakeholders in the surveillance divisions provided more nuanced input to plan for implementation. Beginning in 2016, the three jurisdictions established the DC, Maryland, and Virginia Regional (DMV) HIV Surveillance group, which comprised the leadership of the three jurisdictions' HIV surveillance units, epidemiologists, eHARS data managers, and case surveillance coordinators. The group scheduled monthly calls to plan and review progress. In between the monthly calls, a subcommittee of epidemiologists from each health department developed the specific procedures of the data exchange, including the data elements to be shared, the frequency of exchanges, and validation of results. Variables chosen to be part of the exchange included case information, HIV diagnostic testing, viral load, CD4 results, and genotype sequence data (Multimedia Appendix 1).

Data Extraction and Exchange Procedures

Each jurisdiction used the same SAS v9.4 (SAS Institute, Inc, Cary, North Carolina, USA) code to extract data from their respective instances of eHARS. The data files were encrypted and uploaded to a secure file transfer protocol site hosted by Maryland Department of Health. The epidemiologists who conducted the data extraction notified the respective jurisdictions of the uploaded data and provided encryption passwords to designated personnel. Upon receipt of the shared files, each jurisdiction assessed data quality and communicated about data gaps and inconsistencies.

The initial data exchange included data entered into eHARS from January 1, 2015, to March 31, 2017. The data sent by jurisdictions included cases for which the state listed for residence at HIV diagnosis, residence at AIDS diagnosis, HIV diagnosing facility, AIDS diagnosing facility or laboratory facility state matched the receiving jurisdiction. During this initial exchange, DC Department of Health received 56,451 laboratory results from Maryland Department of Health and 15,090 from Virginia Department of Health. DC Department of Health provided Maryland Department of Health with 82,683 laboratory results and provided Virginia Department of Health with 97,467 (Table 1).

Table 1. Laboratory results exchanged by the jurisdictions.

Results received by and sent to jurisdictions sent by DC[a]	Jurisdiction (n) Virginia	Maryland
Laboratory results received	15,090	56,451
Laboratory results sent	97,467	82,683

[a]DC: District of Columbia.

Table 2. Data matching criteria.

Match Level	Matching criteria
Match 1	If First Name, Last Name, Date of Birth
Match 2	Else if, First Name (First 6 Letters), Last Name, Date of Birth
Match 3	Else if, Last Name (First Letter), Last Name (Letters 3 through 8), First Name (Letters 2 through 8), Date of Birth
Match 4	Else if, Last Name (First Letter), Last Name (Letters 3 through 8), First Name (Letters 2 through 8), Birth Month, Birth Year
Match 5	Else if, Last Name (First Letter), Last Name (Letters 3 through 8), First Name (Letters 2 through 8), Birth Day, Birth Year
Match 6	Else, if Last Name, First Name (Letters 1 through 2), Date of Birth
Match 7	Else, if Last Name (Letters 1 through 3), First Name (Letters 1 through 3), Date of Birth
Match 8	Else if, Last Name (Letters 1 through 4), First Name (Letters 1 through 4), Birth Year
Match 9	Else if, First Name (Letters 1 through 3), Last Name (Letters 1 through 3), Birth Month, Birth Year
Match 10	Else if, First Name (Letters 1 through 3), Last Name (Letters 1 through 3), Birth Day, Birth Year
Match 11	First Name (Letters 1 through 3), Last Name (Letters 1 through 3), Birth Month, Birth Year

Data Matching Procedures

Each jurisdiction used their own matching procedures and algorithms to assess whether the person-level data received during the exchange matched persons currently in their eHARS system. DC Department of Health used an 11-key algorithm in SAS (Table 2) to match incoming data from exchange with existing persons in DC eHARS. The first match key assessed exact matches, which consisted of first name, last name, and date of birth, whereas the other match key criteria allowed for slight variation in how the surveillance information may have been recorded.

Estimating People Living With HIV in the District of Columbia

Calculations of the number of PLWH vary by jurisdiction. For the purpose of this study, DC estimated the number of PLWH based on evidence of a DC residential address within the previous 5 years and having associated laboratory data present within the same time period; for example, when estimating PLWH for 2016, persons with a DC address within the past 5 years who also had laboratory records between 2012 and 2016 would be included in the estimate. This is consistent with how the DC prevalence estimate was presented at the Annual Epidemiology and Surveillance Report from DC [9]. DC recognizes that this may differ from HIV prevalence estimates published by CDC; however, owing to the high amount of population movement in and out of DC, it is believed this would produce a more accurate estimate.

Routine Interstate Duplicate Review

RIDR is a process coordinated by CDC, in which a Soundex match is conducted on national data to identify potential duplicates within the system. Soundex is a coded index associated with how a name sounds versus how a name is spelled. Jurisdictions receive lists semiannually and typically correspond with one another by telephone to ascertain whether or not the persons identified are same or different. Staff from each jurisdiction record a duplicate review status in eHARS and exchange new current residential addresses and recent laboratory information [5]. Updating these data enable jurisdictions to identify persons who have moved between jurisdictions. Information received from the data exchange was utilized to update RIDR information on matched persons without the need to conduct manual RIDR processes.

Data Analysis

The current residential address is calculated and updated in eHARS from incoming case reports and laboratory data obtained from health care providers, laboratories, or other health departments.

Analytic datasets were derived before and after uploading exchanged data from Maryland and Virginia into DC eHARS; these became the pre-exchange and postexchange datasets. The main outcomes of this analysis were the change in the estimate of PLWH in DC and the reduction in the number of cases needing RIDR between DC and Maryland and between DC and Virginia after the data exchange.

Results

Changes in Residential Jurisdiction

After the HIV surveillance data exchange between DC and Maryland and Virginia, there were 396 fewer persons estimated to be living with HIV in DC each year between 2012 and 2016, as seen in Figure 1. There was an average −3.1% difference (pre-exchange versus postexchange) over this time period.

Figure 1. People living with HIV in Washington, District of Columbia (DC), 2012-2016, before and after HIV surveillance data exchange between DC, Maryland, and Virginia.

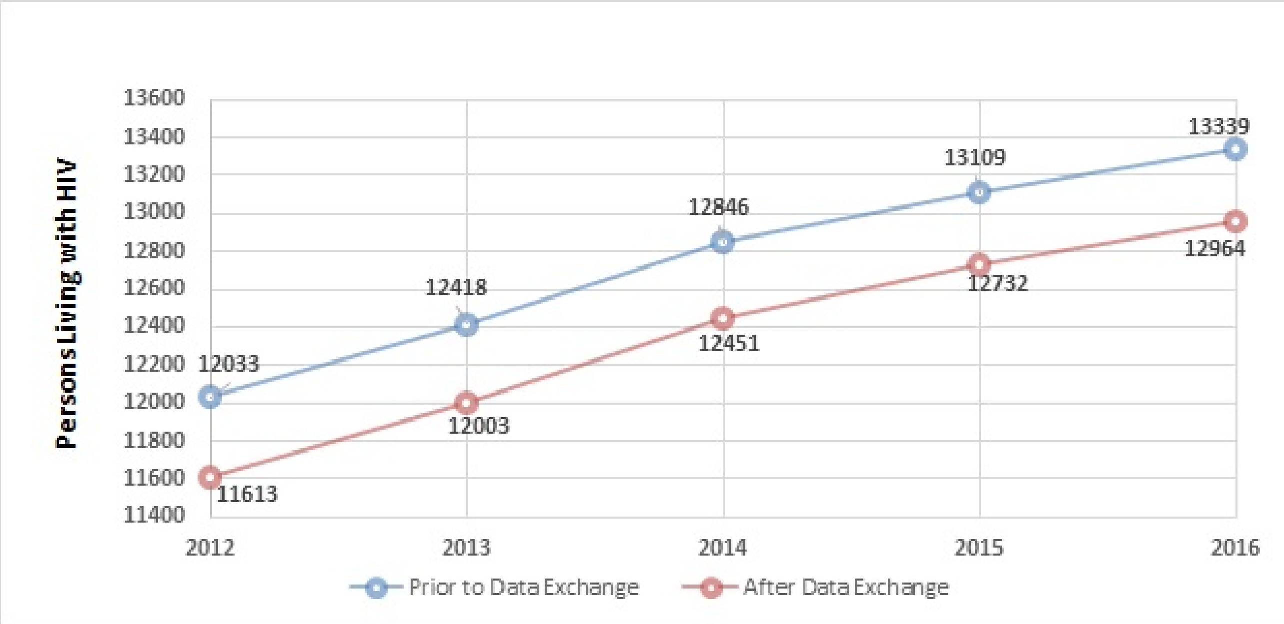

Figure 2. Distribution of persons with a change in residential jurisdiction, 2016.

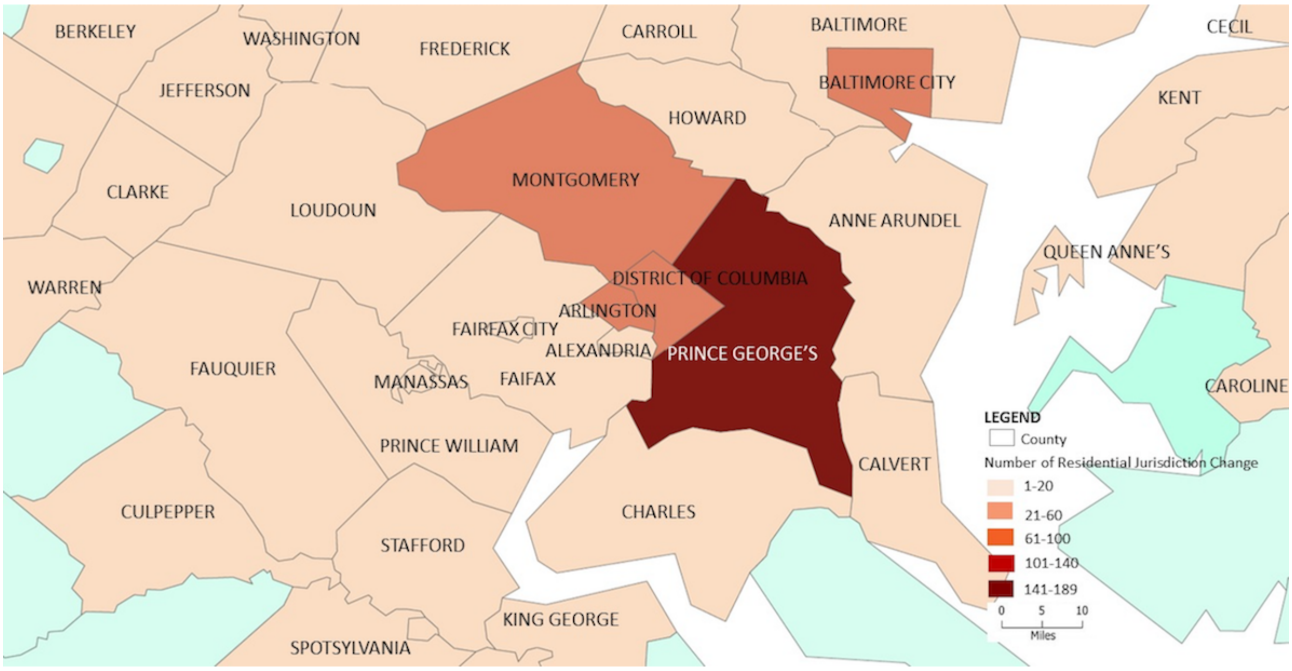

Table 3. Updated current state of residence after HIV surveillance data exchange between the District of Columbia, Maryland, and Virginia, by Jurisdiction, 2016.

Residential state	People living with HIV with a change in residential jurisdiction (N=426), n (%)
California	1 (0.2)
District of Columbia	43 (10.1)
Delaware	1 (0.2)
Maryland	284 (66.7)
Mississippi	1 (0.2)
North Carolina	1 (0.2)
New Jersey	1 (0.2)
New York	7 (1.6)
Ohio	1 (0.2)
Oklahoma	1 (0.2)
Pennsylvania	1 (0.2)
Texas	1 (0.2)
Virginia	83 (19.5)

Of the 426 persons who were found to have a non-DC residence in 2016, the majority had an address in Maryland (284/426, 66.7%) or Virginia (83/426, 19.5%). Most of the individuals who appear to have moved out of DC were in one of the adjacent counties: Prince George's County, Maryland (n=138), Montgomery County, Maryland (n=34), and Arlington County, Virginia (n=23). Figure 2 geospatially depicts the persons whose current residence changed owing to information received in the data exchange with most people shown to be living closely along the border of DC. It was also found that 43 people changed their residence from either Maryland or Virginia to DC (Table 3).

Most people with a change in residential jurisdiction were male. Males represented 74.7% (212/284) of those with a new residential address in Maryland and 79.5% (66/83) of persons with a new address in Virginia. Among those whose residential jurisdiction changed to DC, 83.7% (36/43) were male. Just under 50% of migrants to Maryland (137/284, 48.2%) had a mode of transmission of men who have sex with men (MSM) or MSM and injection drug use (MSM/IDU). Similarly, when assessing migrants by mode of transmission, MSM and MSM/IDU represented the majority of persons who migrated to Virginia (47/83, 56.6%). When assessing those with an evidence of a change in residency to either of the three jurisdictions, among those with a mode of transmission of IDU, there were relatively similar distributions by jurisdiction at 9.3% (4/43) to DC, 8.5% (24/284) to Maryland, and 8.4% (7/83) to Virginia. Similar results were found when assessing heterosexual contact, wherein 29.9% (85/284) of persons with a new Maryland residence, 26.5% (22/83) of persons with a new Virginia address, and 23.3% (10/43) of persons with a new DC address had heterosexual contact as a mode of transmission. Changes of address among racial or ethnic categories showed significant differences with black persons or African Americans making up a larger percentage of those who migrated to DC (31/43, 72.1%) and Maryland (234/284, 82.4%) compared with Virginia (48/83, 57.8%). Additionally, Hispanic and Latino persons represented a higher proportion of persons moving to Virginia (12/83, 14.5%) than those who moved to DC (4/43, 9.3%) or Maryland (19/284, 6.7%). White persons represented a smaller proportion of those who moved to Maryland (21/284, 7.4%) when compared with DC (8/43, 18.6%) and Virginia (20/83, 24.1%). When looking at age groups, persons with a residential change into DC were more likely to be over 40 years old, whereas persons aged between 25 and 39 years represented the majority of persons with a residential change to Maryland (148/283, 52.2%) and Virginia (48/83, 57.8%) (Table 4).

Table 4. Demographic characteristics of people living with HIV with a change in residential jurisdiction, by state, 2016.

Characteristics	People living with HIV with a change in residential jurisdiction			People living with HIV in DC[a] (N=12,964), n (%)
	DC (N=43), n (%)	Maryland (N=284), n (%)	Virginia (N=83), n (%)	
Gender				
Female	7 (16.3)	70 (24.6)	15 (18.1)	3395 (26.2)
Female to male	0 (0.0)	2 (0.7)	0 (0.0)	72 (0.6)
Male	36 (83.7)	212 (74.6)	66 (79.5)	9352 (72.1)
Male to female	0 (0.0)	0 (0.0)	2 (2.4)	145 (1.1)
Mode of transmission				
MSM[b]	24 (55.8)	127 (44.7)	42 (50.6)	5650 (43.6)
IDU[c]	4 (9.3)	24 (8.5)	7 (8.4)	1372 (10.6)
MSM/IDU	0 (0.0)	10 (3.5)	5 (6.0)	404 (3.1)
Heterosexual contact	10 (23.3)	85 (29.9)	22 (26.5)	3689 (28.5)
Risk not identified	4 (9.3)	31 (10.9)	7 (8.4)	1703 (13.1)
Other[d]	1 (2.3)	7 (2.5)	0 (0.0)	146 (1.1)
Race or ethnicity				
White	8 (18.6)	21 (7.4)	20 (24.1)	2076 (16.0)
Black	31 (72.1)	234 (82.4)	48 (57.8)	9670 (74.6)
Hispanic	4 (9.3)	19 (6.7)	12 (14.5)	884 (6.8)
Other[e]	0 (0.0)	10 (3.5)	3 (3.6)	334 (2.6)
Age group				
0-12	1 (2.3)	5 (1.8)	0 (0.0)	22 (0.2)
13-19	2 (4.7)	17 (6.0)	4 (4.8)	60 (0.5)
20-24	7 (16.3)	48 (16.9)	11 (13.3)	331 (2.6)
25-29	7 (16.3)	47 (16.5)	21 (25.3)	908 (7.0)
30-39	9 (20.9)	101 (35.6)	27 (32.5)	2452 (18.9)
40-49	12 (27.9)	49 (17.3)	16 (19.3)	2963 (22.9)
50-59	5 (11.6)	15 (5.3)	4 (4.8)	3957 (30.5)
>=60	0 (0.0)	2 (0.7)	0 (0.0)	2268 (17.5)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)

[a]DC: Dictrict of Columbia.

[b]MSM: men who have sex with men.

[c]IDU: injection drug use.

[d]Other mode of transmission includes perinatal transmission, hemophilia, blood transfusion, and occupational exposure (health care workers).

[e]Other race includes mixed-race individuals, Asians, American Indians, Native Hawaiians, Pacific Islanders, and unknown races.

Table 5. January 2017 Routine Interstate Duplicate Review (RIDR) cases resolved by the District of Columbia, Maryland and Virginia region HIV surveillance data exchange.

Total HIV cases identified by Centers for Disease Control and Prevention	Maryland (N=171), n (%)	Virginia (N=82), n (%)
RIDR cases resolved by data exchange	127 (74.3)	67 (81.7)
Remaining HIV cases needing RIDR	44 (25.7)	15 (18.3)

Changes in Routine Interstate Duplicate Review

RIDR activities are typically conducted through the exchange of case information via the telephone. Telephonic RIDR resolution activities between DC and Maryland and DC and Virginia were not conducted prior to the data exchange. The HIV surveillance data exchange among DC, Maryland, and Virginia allowed for RIDR information to be exchanged electronically and decreased the number of cases identified by RIDR needing manual resolution by 74.3% (127/171) between DC and Maryland and by 81.7% (67/82) between DC and Virginia (Table 5). This has had a significant impact in reducing the workload of health department staff in all three jurisdictions. Additionally, the data sharing process has contributed to an overall reduction in the number of persons needing resolution between the three jurisdictions because duplicates were identified earlier than with the biannual RIDR process. For the July 2017 RIDR list produced by CDC, DC Department of Health saw a reduction in resolution case volume of 61.4% between DC and Maryland and 43.9% between DC and Virginia compared with the January 2017 RIDR list.

Discussion

Although the overall population estimates between 2012 (635,630) and 2016 (684,336) in DC increased by 7.1% [6], based on our analysis, between 375 and 420 PLWH migrated out of DC each year over the past five years. This represents a −3.1% change in PLWH in DC over this time period. Although this percent decrease is relatively small, the absolute number of persons deemed to be living in a different jurisdiction represents a significant amount of surveillance personnel effort that would have been exerted in re-engagement in care efforts. There are many factors that may contribute to migration in and out of DC, but they are beyond the scope of this paper. However, it is interesting to note that the majority of individuals diagnosed with HIV who moved out of DC stayed within the surrounding counties (Prince George's County and Montgomery County in Maryland, and Fairfax County, Arlington County, and Alexandria City in Virginia), which are part of the DC Ryan White Part A Eligible Metropolitan Area. Individuals who are Ryan White-eligible would still be able to access services offered in the Part A geographic area. However, other services they may need, such as Medicaid or the AIDS Drug Assistance Program, would need to be accessed from their new residential jurisdiction because they are distributed by states only.

We demonstrated a significant reduction in cases needing to be resolved via the labor-intensive RIDR process after the implementation of the data exchange. Cross-jurisdictional HIV surveillance data exchange is feasible and could be of great benefit to other areas of the United States where there are substantial movement across states or jurisdictions. The protocol used in the DMV HIV surveillance data exchange has made DC Department of Health HIV surveillance operations more efficient.

Testing and treatment methods with new advanced biomedical interventions have become the cornerstone of strategies to reduce new HIV infections. The 90/90/90/50 Plan to End the HIV Epidemic by 2020 in the District of Columbia set goals to ensure that 90% of persons with HIV know their status, 90% of persons diagnosed with HIV are retained in HIV care and treatment, and 90% of persons on treatment are virally suppressed, resulting in a 50% reduction in cases by 2020 over the baseline year of 2015 [10]. To meet these measures, a robust surveillance system is needed to identify new cases of HIV and monitor HIV care markers with an accurate denominator. The DMV HIV surveillance data exchange has enabled DC Department of Health to more accurately identify persons residing within the jurisdiction to better track and assess health outcome measures.

Data-to-care efforts in DC have focused on locating PLWH who appear to be out of care based on clinical and surveillance data [11]. Prior to the DMV HIV surveillance data exchange, individuals who moved out of DC may have appeared to be out of care, but they relocated their residence and health care. Data exchange resulted in updated residential addresses and reduced the number of people potentially needing re-engagement in care. The updated address data will significantly assist the data-to-care efforts in DC with more accurate location information of people who may be in need of outreach, re-engagement, treatment adherence, and other enabling or support services. The data exchange also updated laboratory data, which is critical to understanding who may need more intensive public health interventions, such as individuals with low CD4 cell counts or high viral load levels. The use of updated residential address and laboratory data in this way affirms the utility of collecting this information from PLWH. Future analyses may include pre- and postexchange comparison of engagement in care and viral suppression among PLWH in DC.

Data exchange was limited to three states with moderate HIV prevalence. The DMV HIV surveillance data exchange may be enhanced by exchanging data with other nearby states, such as New York, New Jersey, Pennsylvania, and North Carolina, with high levels of RIDR overlap with cases in DC. This was explored in a separate project (Black Box RIDR Resolution project) funded by CDC, in which additional states participate to identify potential matched cases in a secure and confidential manner, and the recently funded CDC-RFA-PS18-1805-Secure Data Sharing Tool awarded to Georgetown University. Additional limitations include in the validity of the accuracy of the matching algorithm. The 11-key matching algorithm was validated to be extremely accurate at the higher levels (match levels 1-4), although there is potential for mismatching at the lower levels (match levels 6-11).

The DMV HIV surveillance data exchange has demonstrated that conducting standardized matches of data across jurisdictions is feasible and provides timely resolution of duplicate cases that might otherwise require time-intensive, one-to-one conversations between health department staff. Other states, particularly jurisdictions in which PLWH may seek care across jurisdictional boundaries, may benefit from pursuing DSAs to conduct HIV surveillance data exchanges. More accurate epidemiologic data may be used for improving funding decisions around care and prevention programs, particularly in areas with significant levels of population movement and migration.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Detailed variables extracted from eHARS.

[PDF File (Adobe PDF File), 48KB - publichealth_v4i3e62_app1.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
DC: District of Columbia
DMV: District of Columbia, Maryland and Virginia region
DSA: data sharing agreement
eHARS: enhanced HIV/AIDS Reporting System
IDU: injection drug use
MSM: men who have sex with men
NHSS: National HIV/AIDS Surveillance System
PLWH: people living with HIV
RIDR: Routine Interstate Duplicate Review

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Original Paper

Facial-Aging Mobile Apps for Smoking Prevention in Secondary Schools in Brazil: Appearance-Focused Interventional Study

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Abstract

Background: Most smokers start smoking during their early adolescence, often with the idea that smoking is glamorous. Interventions that harness the broad availability of mobile phones as well as adolescents' interest in their appearance may be a novel way to improve school-based prevention. A recent study conducted in Germany showed promising results. However, the transfer to other cultural contexts, effects on different genders, and implementability remains unknown.

Objective: In this observational study, we aimed to test the perception and implementability of facial-aging apps to prevent smoking in secondary schools in Brazil in accordance with the theory of planned behavior and with respect to different genders.

Methods: We used a free facial-aging mobile phone app (“Smokerface”) in three Brazilian secondary schools via a novel method called mirroring. The students’ altered three-dimensional selfies on mobile phones or tablets and images were “mirrored” via a projector in front of their whole grade. Using an anonymous questionnaire, we then measured on a 5-point Likert scale the perceptions of the intervention among 306 Brazilian secondary school students of both genders in the seventh grade (average age 12.97 years). A second questionnaire captured perceptions of medical students who conducted the intervention and its conduction per protocol.

Results: The majority of students perceived the intervention as fun (304/306, 99.3%), claimed the intervention motivated them not to smoke (289/306, 94.4%), and stated that they learned new benefits of not smoking (300/306, 98.0%). Only a minority of students disagreed or fully disagreed that they learned new benefits of nonsmoking (4/306, 1.3%) or that they themselves were motivated not to smoke (5/306, 1.6%). All of the protocol was delivered by volunteer medical students.

Conclusions: Our data indicate the potential for facial-aging interventions to reduce smoking prevalence in Brazilian secondary schools in accordance with the theory of planned behavior. Volunteer medical students enjoyed the intervention and are capable of complete implementation per protocol.

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KEYWORDS

dermatology; smoking; apps; photoaging; face; skin; tobacco; tobacco cessation; tobacco prevention

Introduction

Background

Smoking is the leading global cause of preventable death, causing nearly 6 million deaths per year worldwide. A 2011 study of the tobacco-related burden in Brazil found that smoking was accountable for 147,072 deaths (403 deaths per day), 157,126 myocardial infarctions, and 63,753 cases of cancer. It generated 2.69 million disability-adjusted life years and cost the Brazilian health system US $7.37 billion in 2011 alone [1].

Most smokers start smoking during their early adolescence, often with the idea that smoking is glamorous, with the associated health consequences too far in the future to imagine. According to the Adolescent Cardiovascular Risk Study, almost 600,000 adolescents smoke regularly in Brazil and most of them tried their first cigarette between 15 and 17 years of age [2].

The earlier a person starts smoking, the higher the chance of becoming a regular smoker and developing associated diseases. As most smokers start smoking during early adolescence, it is imperative to develop, test, and validate tobacco control strategies that focus on this group through an age-appropriate and innovative approach. Most educational interventions for adolescents have focused on increasing awareness of tobacco-induced diseases [2]. These mostly fail to show sustainable effects [3].

Research on School-Based Tobacco Prevention Interventions in Brazil

In Brazil, a 2015 randomized controlled trial at the Federal University of the State of São Paulo investigating different school-based interventions to reduce the use of various psychotropic substances among 1316 students showed mixed effects for different drugs/settings with study design limitations precluding interpretation [4].

Furthermore, a study on educational interventions among school adolescents analyzed the effectiveness of an educational program on smoking developed by the Brazilian Cancer Institute. The researchers selected 32 random schools from a total of 46 public schools in the city of Pelotas and randomized them to control and intervention schools. The total sample was 2200 students in the 7th and 8th grades (13-14 years old). They used questionnaires before and after interventions and collected urine samples in order to detect nicotine. Although the results showed no change in tobacco use reduction, they improved the students' knowledge on passive smoking [5].

Despite these studies, data on school-based tobacco prevention interventions conducted remain scarce.

Education Against Tobacco

Founded in Germany in 2012, Education Against Tobacco is a global network of medical students that aims to provide science-based and age-appropriate preventions to a large number of adolescents and at the same time sensitizes prospective physicians to the importance of delivering smoking cessation advice and engaging themselves in tobacco control activities after their graduation [6-10]. The network currently involves 80 medical schools in 14 countries, with 3500 medical students educating more than 50,000 secondary school students in the classroom setting per year, while using and optimizing apps and strategies. In Brazil, Education Against Tobacco was founded in 2016 and is already present in 15 medical schools in the country.

In a recent paper, we introduced facial-aging mobile apps that alter a person's selfie (a self-portrait taken with a mobile phone camera) to predict future appearance if that person smokes [11]. These apps are considered a new opportunity for smoking prevention after their effectiveness was first demonstrated by Burford et al [12,13]. They are also used in other behavioral change settings, such as skin cancer prevention [14,15]. In the clinical setting, they were recently made available in waiting rooms to motivate patients to address quitting with their doctor [16] or to improve UV protection [17]. In addition to this, many dermatology publications have called for a novel public health approach in light of new findings on the facial-aging effects of smoking [18]. Facial-aging approaches indicate relevance for teenagers as evidenced by numerous publications demonstrating and investigating their influence on behavior [6,19-24]. In contrast, it is notable that the tobacco industry itself tried to establish the link between attractiveness and smoking by commercial advertising in the past [25].

We recently implemented a facial-aging mobile app ("Smokerface") in German secondary schools via a method called mirroring [26]. We "mirrored" the students' altered 3-dimensional (3D) selfies on mobile phones or tablets via a projector in front of their entire grade. Using an anonymous questionnaire, we then measured sociodemographic data as well as the perceptions of the intervention on a 5-point Likert scale among 125 students of both genders (average age 12.75 years). A majority of the students perceived the intervention as fun (77/125, 61.6%), claimed that the intervention motivated them not to smoke (79/125, 63.2%), and stated that they learned new benefits of nonsmoking (81/125, 64.8%).

Theoretical Considerations on Photoaging Interventions in Adolescence

The self-concept of appearance, which photoaging interventions harness, is the strongest predictor of self-esteem in adolescents of both genders [27,28]. In the most recent publication by Baudson et al involving a sample of 2950 adolescents from a broad range of secondary schools, it was noted that this is especially true for students from lower educational schools and girls [28]. An explanation for the general effectiveness of such an intervention is given by the theory of planned behavior, according to which the subjective norm (ie, "my friends think that smoking makes you unattractive"), the attitudes (consisting of beliefs, ie, "smoking leads to unattractiveness"), and the perceived behavioral control (ie, "I can resist if somebody offers me a cigarette") influence both the behavioral intentions of a person and their behavior. Photoaging interventions may affect all three of these predictors, and the mirroring intervention specifically had a strong influence on the subjective norm in a recent pilot study [26].

This study investigated if effects are different for female/male participants and if the results of our novel facial-aging intervention are reproducible in Brazil, a country where data on tobacco prevention programs remain scarce. Additionally, a process evaluation investigated whether local volunteering medical students are capable of complete intervention implementation.

Methods

Participants

We included a total sample of 306 students in Grade 7 in our cross-sectional study with an average age of 12.97 years (age range 12-16; 172/306, 56.2% female; 134/306, 43.8% male) attending three regular public secondary schools in the city of Ponte Nova in southeast Brazil (total of 15 classes). Informed consent was obtained from the parents. A large majority of participants (257/306, 84.0%) reported that they owned a smartphone.

Setting

The mirroring approach was implemented via local medical students from the Education Against Tobacco nonprofit organization who were attending the Federal University of Ouro Preto in Brazil [7-9]. Two medical students per classroom conducted the interventions with approximately 20 students at a time (average 20.4 students, SD 4.4). To increase students' participation in the mirroring intervention, students were encouraged to download the app ("Smokerface") before our visit, via a letter 3 days in advance. When we visited the schools, 34.3% (105/306) of students already had the facial-aging app on their mobile phone.

Intervention

The mirroring intervention consists of a 45-minute app-based module in the classroom setting. Mirroring means that the student's altered 3D selfies on their mobile phones or tablets are "mirrored" via a projector in front of the whole class, for example, sneezing or coughing (Multimedia Appendix 1). In front of their peers and teachers, they could display their image as a nonsmoker/smoker 1, 3, 6, 9, 12, or 15 years in the future (see Figures 1 and 2). Multiple device displays can be projected simultaneously, which we used to consolidate the altering measures with graphics (eg, to explain wrinkle formation). We implemented mirroring with 10 Galaxy Tab A tablets (Samsung) via Apple's AirPlay interface using the Android app "Mirroring360" (Splashtop Inc).

In the first 10 minutes, the displayed face of one student volunteer was used to show the app's altering features to their peer group, providing an incentive for the rest of the class to try the app.

In the following 15 minutes, students were encouraged to try the app on their own device or one of the tablet computers provided for students not owning a mobile phone or without the app. The number of provided tablet computers was calculated so the phase would take up to 12 minutes at the most, factoring in a utilization time of about 4 minutes per student. By this calculation, 25 minutes of the mirroring intervention and 10 provided tablets were sufficient to have every student within a grade of 40 pupils successfully photoaged at least once.

This was followed by a 15-minute interactive discussion of the remaining functions of the app: facial changes, quitting via the free Smokerstop app, and impaired growth, strength, and sagginess of women's breasts. These topics are strictly in line with the explanatory graphics within the app (Figures 3 and 4).

Postsurvey

In the last 5 minutes of the time in the classroom, the perception of the intervention by students was measured directly after the intervention via 10 items in an anonymous survey on a 5-point Likert scale: (1) one item on change of intentions ("My 3D selfie motivates me not to smoke"), (2) two items on the perceived reactions of the peer group ("My classmates think I look better as a non-smoker" and "The reactions of my classmates motivate me not to smoke"), (3) three items on future app-use and app-sharing ("I plan to try this app again in the future," "I want to have the Smokerface app on my phone" and "I plan to show this app to other people"), (4) four items addressing global feedback ("The intervention was fun," "I learned new benefits of nonsmoking," "Smokerface app motivates other people to quit smoking," and "Smoking would have negative effects on my appearance").

The medical students filled out a brief process evaluation consisting of six items capturing the complete implementation of the intervention as well as how the medical students perceived its effectiveness when in class.

Figure 1. Effect view of the Smokerface app on an iOS iPad; normal aging without smoking for 15 years.

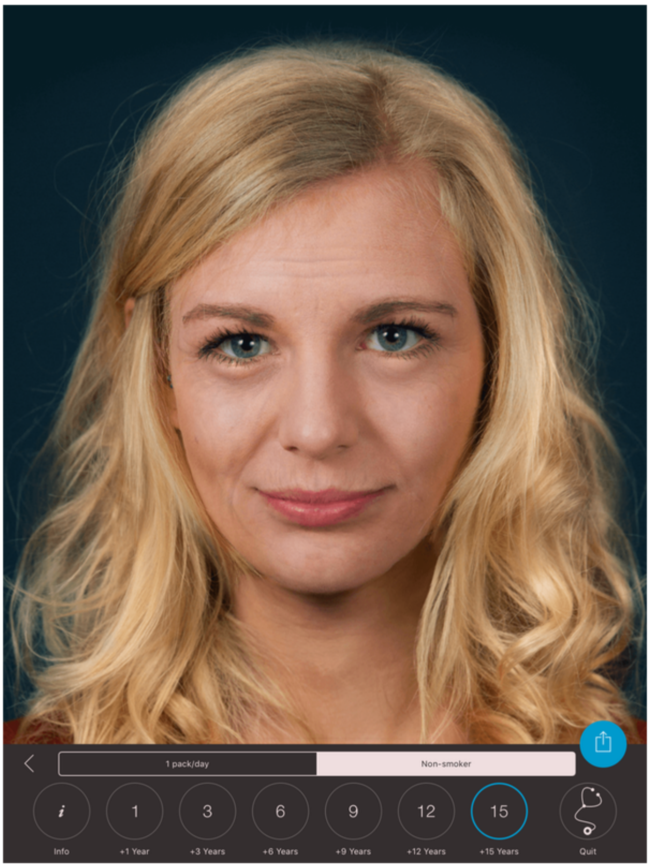


Figure 2. Effect view of the Smokerface app on an iOS iPad; aging with smoking one pack of cigarettes a day for 15 years.

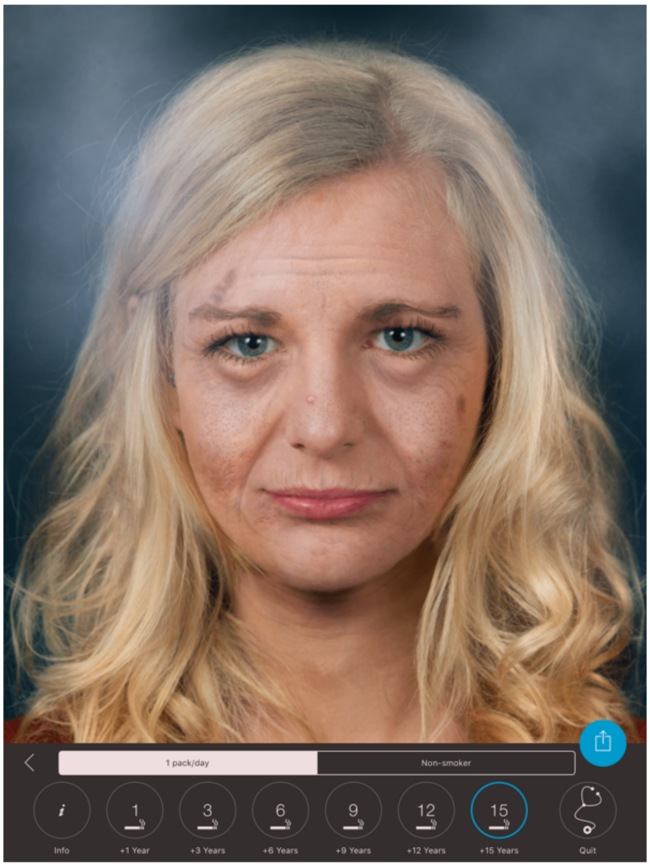


Figure 3. Infographic within the Smokerface app on the dermatologic short-term/long-term consequences of smoking.

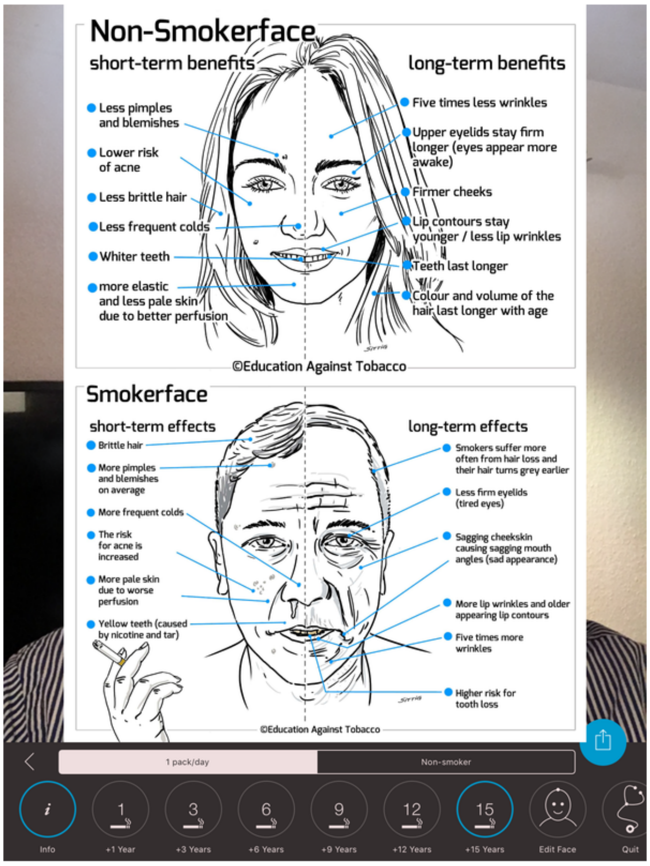
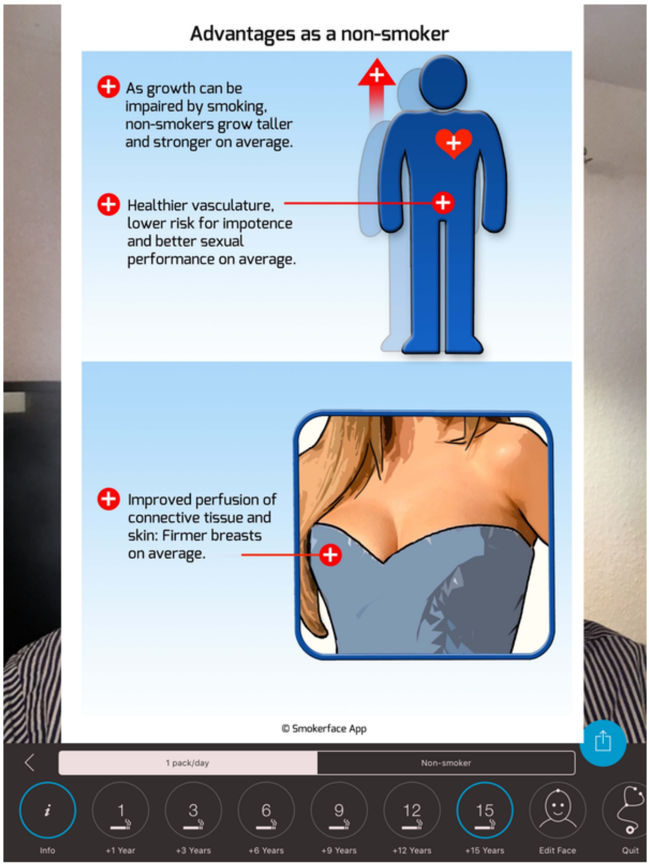


Figure 4. Infographic within the Smokerface app on the consequences of smoking on growth/strength and the firmness of women breasts.



Results

All data were analyzed and illustrated in regards to overall perceptions of the intervention within the whole sample (Figure 5) but also to identify gender differences (Figure 6).

Motivation Not to Smoke

We measured 94.4% (289/306) agreement on the item measuring the increase of motivation not to smoke: 94.4% agreed/fully agreed that their 3D selfie motivates them not to smoke while only 1.6% (5/306) disagreed or strongly disagreed and 4% were not sure (Figure 5). These results did not vary notably in males compared to females: in males, 92.4% (124/134) agreement and 1.5% (2/134) disagreement and, in females, 95.9% (165/172) agreement and 1.8% (3/172) disagreement (Figure 6).

Perceived Subjective Norm During the Mirroring Intervention

The two items measuring the reactions of the peer group towards the individual selfie showed positive peer pressure to become or to remain a nonsmoker. The majority of students agreed/totally agreed that their classmates prefer them as nonsmokers (266/306, 86.9%) and that their classmates' reaction to the 3D selfie motivates them not to smoke (264/306, 86.2%) (Figure 5). The results were similar between different genders on the first item ("My classmates think I look better as a nonsmoker"). However, females had a higher rate of agreement on the second item ("The reactions of my classmates motivate me not to smoke"): 81.2% (109/134) agreement and 9.0% (12/134) disagreement in males compared to 90.0% (155/172) agreement and 1.2% (2/172) disagreement in females (Figure 6).

App Reuse and Sharing

We measured more than 70% agreement in all three items measuring intention to reuse or share the Smokerface app. The majority of the students expressed a desire to show the app to other people (271/306, 88.7% agreement and 10/306, 3.4% disagreement), would like to have the app on their mobile phones (215/306, 70.3% agreement and 27/306, 8.9% disagreement), and planned to try the app on themselves again later on (221/306, 72.4% agreement and 19/306, 6.2% disagreement). These results did not vary notably in males versus females.

Global Feedback

Almost all participants expressed that they perceived the intervention as fun: 99.3% (304/306) agreement, 0.0% (0/306) disagreement, and 0.7% (2/306) neutral (Figure 5). Almost all also stated that they learned new benefits of nonsmoking: 98.0% (300/306) agreement versus 1.3% (4/306) disagreement (Figure 5). A large majority also reported that they agree/totally agree that smoking would have negative effects on their appearance (305/306, 99.7%) and that the Smokerface app motivates people to quit smoking (275/306, 89.8%). These results were similar between males and females, except for a higher female agreement on the item "Smokerface app motivates other people to quit smoking": 84.3% (113/134) agreement and 3.7% (5/134) disagreement in males versus 94.1% (162/172) agreement and 1.8% (3/172) disagreement in females (Figure 6).

Figure 5. Survey results of the whole sample.

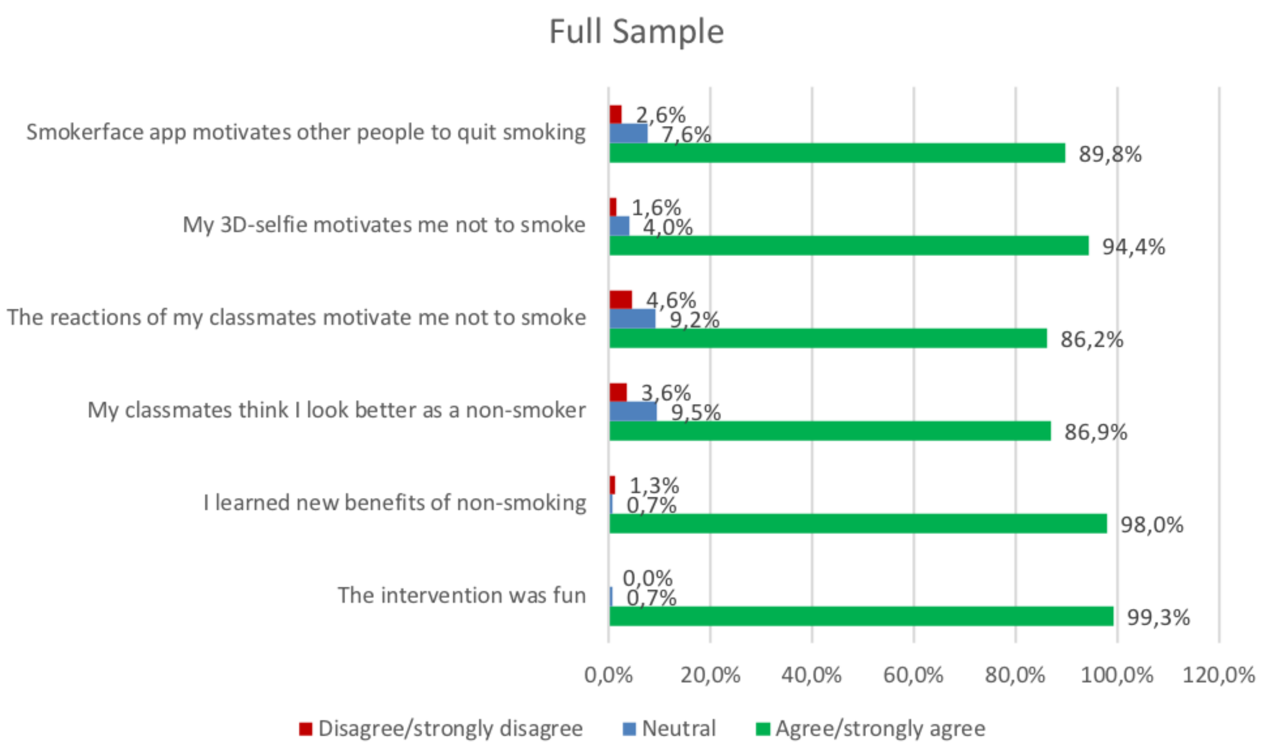
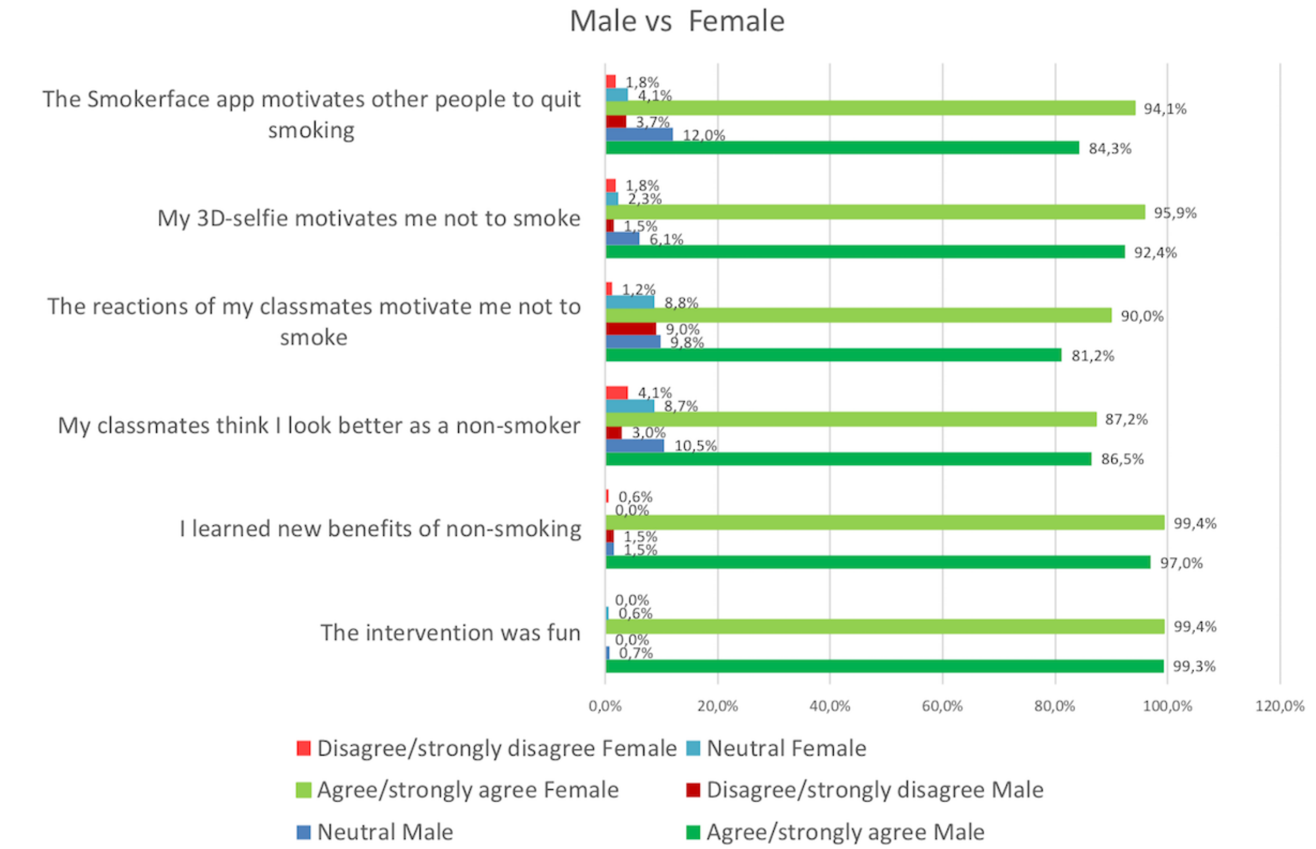


Figure 6. Survey results of male versus female participants.



Data Obtained From Medical Students

Our process evaluation conducted among all of the six volunteering medical students via a short questionnaire after every classroom visit revealed that 100% of the secondary school students received the mirroring intervention as outlined in the methods section. All of the medical students were able to have empathic communication with the students, regarded the intervention as enjoyable, and said it motivated them to deliver smoking cessation advice to future patients.

Discussion

Principal Considerations

Mobile apps are used, evaluated, and optimized in smoking cessation settings [29-52] while the number of completed randomized trials remains scarce. Mobile phone apps in school-based prevention settings present a potential new way of delivering effective interventions that remain with the pupils after the classroom visit is finished. In Brazil specifically, approximately 85% of Brazilian adolescents and young adults (10- to 24-year-olds) owns a smartphone according to the Brazilian Institute of Geography and Statistics.

The Intervention in the Context of the Theory of Planned Behavior

The theoretical background of the participant-centered mirroring intervention includes increasing perceived self-efficacy of using the app, which has been proven to encourage repetitive use and is associated with the effectiveness of an intervention according to the theory of planned behavior [53]. Accordingly, 72.4% of the students fully agreed or agreed directly after the intervention that they wanted to use the app again on their own despite the one-time-use nature of the app and the fact that most of them had used the app at least twice already. By causing direct peer group and teacher reactions to the intervention itself, the subjective norm is affected, which also predicts adolescent smoking [53].

The theory of planned behavior identifies perceived behavioral control as the strongest predictor of smoking onset (eg, if students think they could refuse a cigarette successfully). To this end, an age-appropriate reason not to smoke was integrated into the student community by both the name of the app, “Smokerface”, and the fact that it was installed on most students’ devices. A majority (89.8%) of the students stated that the app was an appropriate tool to convince peers to quit smoking when asked after the intervention. Also, many students would refer to smokers as “smokerfaces” or stated that they did not want to be a “smokerface,” which is an age-appropriate reason to decline a cigarette if offered by a peer.

Gender Differences

Both genders agreed in most categories, which is consistent with recent literature suggesting that appearance aspects play a major role for self-esteem in male as well as in female adolescents. While females tend to be more susceptible to appearance aspects in the past, the differences between the two sexes appear to assimilate [28,54,55].

Still, in this study a larger fraction of female participants agreed that the Smokerface app motivates other people to quit smoking (84.3% agreement in males vs 94.1% agreement in females; Figure 6) and also perceived the reactions of their classmates as a stronger motivation for abstinence (81.2% agreement in males vs 90.0% agreement in females; Figure 6), indicating a higher perception in females of subjective norms reinforcing the importance of their outward appearance.

Limitations

Our results stem from anonymous self-reports via paper-and-pencil questionnaires filled out after the intervention. While anonymity decreases social desirability bias in self-reports, they may not be regarded as objective as externally measurable markers (eg, cotinine saliva or carbon monoxide testing). Furthermore, handing out the questionnaires after the intervention rather than before might have provoked a social desirability bias despite anonymity. In addition, cross-sectional data without a control group or follow-up cannot determine effectiveness. Thus, the authors plan to conduct a randomized trial [24].

Conclusion

The facial-aging intervention was effective in generating an increased motivation to stay away from tobacco in Brazilian adolescents. The predictors measured indicated an even higher prospective effectiveness in southeast Brazil than in Germany (over 90% of agreement in Brazil vs over 60% of agreement in Germany on the items that measured motivation to remain abstinent) in accordance with the theory of planned behavior. Medical students are capable of complete implementation of the intervention. A randomized controlled trial measuring prospective effects in Brazil is planned as a result of this study [24].

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Authors' Contributions

TJB invented the intervention, wrote the manuscript, and performed the statistical analysis. BBS and TJB drafted the design of the study. BBS organized the intervention, coordinated the logistics of the study, data collection, data entry, translated all classroom materials, wrote parts of the manuscript, and reviewed its final version. FPAAP, GMM, TFCR, MG, MVH, AJO, AHE, DAG, WS, CvK, CB, PCRPC, JLS, JA, and AA contributed to the design of the study, data collection, data analyses, and proofread the manuscript. All authors declare responsibility for the data and findings presented and have full access to the dataset.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Animated effect view (coughing) of the Smokerface app.

[MP4 File (MP4 Video), 2MB - publichealth_v4i3e10234_app1.mp4]

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Original Paper

Twitter-Based Influenza Detection After Flu Peak via Tweets With Indirect Information: Text Mining Study

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Abstract

Background: The recent rise in popularity and scale of social networking services (SNSs) has resulted in an increasing need for SNS-based information extraction systems. A popular application of SNS data is health surveillance for predicting an outbreak of epidemics by detecting diseases from text messages posted on SNS platforms. Such applications share the following logic: they incorporate SNS users as social sensors. These social sensor–based approaches also share a common problem: SNS-based surveillance are much more reliable if sufficient numbers of users are active, and small or inactive populations produce inconsistent results.

Objective: This study proposes a novel approach to estimate the trend of patient numbers using indirect information covering both urban areas and rural areas within the posts.

Methods: We presented a TRAP model by embedding both direct information and indirect information. A collection of tweets spanning 3 years (7 million influenza-related tweets in Japanese) was used to evaluate the model. Both direct information and indirect information that mention other places were used. As indirect information is less reliable (too noisy or too old) than direct information, the indirect information data were not used directly and were considered as inhibiting direct information. For example, when indirect information appeared often, it was considered as signifying that everyone already had a known disease, leading to a small amount of direct information.

Results: The estimation performance of our approach was evaluated using the correlation coefficient between the number of influenza cases as the gold standard values and the estimated values by the proposed models. The results revealed that the baseline model (BASELINE+NLP) shows .36 and that the proposed model (TRAP+NLP) improved the accuracy (.70, +.34 points).

Conclusions: The proposed approach by which the indirect information inhibits direct information exhibited improved estimation performance not only in rural cities but also in urban cities, which demonstrated the effectiveness of the proposed method consisting of a TRAP model and natural language processing (NLP) classification.

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KEYWORDS

influenza surveillance; location mention; Twitter; social network; spatial analysis; internet; microblog; infodemiology; infoveillance

Introduction

Background

The increased use of social networking platforms entails more widely shared personal information. Twitter, a microblogging platform that enables users to communicate by updating their status using 140 or fewer characters, has attracted the attention of many researchers and service developers as a valuable personal information resource. Consequently, various approaches for analyzing social data (called as *social monitoring*

[1]) have been presented so far. These approaches have presented an important shared premise that Twitter users can be human sensors for event detection [2], and the feasibility of these approaches has been demonstrated on various occasions such as earthquakes [2-4], political elections [5-7], stock market fluctuations [8], and outbreaks of various infectious diseases [9-33]. Among them, the study of social monitoring of health-related information shared on the internet is referred to as *infodemiology* [1,34] and gathers much attention in terms of practical needs.

Objective

This study particularly examined such applications for detecting disease epidemics, by taking advantage of the swiftness of the information transmission on Twitter. Numerous Twitter-based disease detection and prediction systems have been developed worldwide. However, these systems have several weaknesses. One significant deficit is population distribution imbalance owing to the fact that most social networking service (SNS) users reside in urban areas, resulting in analysts facing difficulty getting sufficient amounts of data from rural areas. For example, user population of Japan is strongly concentrated in a few central cities such as Tokyo and Osaka. Specifically, the population of Tokyo is estimated to be 13.515 million (about 11% of Japan's total population) [35]. Other users live outside these areas, in less populated regions of Japan. This population bias results in difficulties in obtaining consistent performance. Figure 1 shows the geographic distribution in Japan of 7,666,201 influenza-related tweets for the period from 2012 to 2015. The distribution is skewed because rural areas have fewer young people than the cities. For instance, the number of young in-migrants (aged 15-29 years) from other areas to Tokyo was 20.56% as of 2014. The other areas except Osaka and Nagoya basically suffer from an exodus of young people [36]. Therefore, fewer SNS users are available in the rural areas.

To overcome this skewed distribution problem, information from a broader range of targets than that used in earlier studies can be utilized. One solution is to use indirect information [37,38] that had been discarded in previous studies related to Twitter-based disease surveillance [15,26-31,39]. Examples of such indirect information are as follows:

1. *My friend in Hokkaido caught the flu.*
2. *NEWS: Classes in Hokkaido have been suspended because of the flu.*

The fundamental idea is presented in Figure 2. Although tweets are concentrated in the urban areas, indirect information covers wider areas. However, indirect information is unreliable (sometimes too noisy or too old). In example (1) above, it is unknown when the *friend* caught the flu. And in example (2), the flu had already spread to the area. Due to the difficulties presented above, previous studies did not use such indirect information to any significant degree.

An example of tweet timelines and a patient timeline is presented in Figure 3. Note that each timeline is normalized based on the maximum value of a season. Direct information (black dashed line) shows a similar timeline to the patient timeline (gold standard; red area). However, before the peak of epidemics, the amount of direct information increases a bit, leading to overestimation errors. In addition, after the peak of epidemics, the amount of direct information decreases, leading to underestimation errors. On the other hand, the timeline of the linear combination of direct and indirect information (blue line) shows complex phenomena: it has many and sometimes sudden peaks (eg, February 27, 2013), which would be caused by news spreading and so on. Apparently, indirect information is difficult to use.

To aggregate direct information and indirect information in a sophisticated way, this study employed a different approach that specifically examines the relation between indirect information and the human motivation to tweet. The approach considers that after the peak of epidemics, the topic of influenza goes out of fashion, inhibiting the motivation of people to tweet about the flu. Consequently, a more similar timeline (red line) to the patient timeline (gold standard; red area) than that of the direct information timeline can be obtained as shown in Figure 3. It also could screen out sudden peaks of the amount of indirect information.

Another difficulty is the detection of the degree of the propagated information. This study specifically examines the amount of indirect information because it indicates that people in different places also know about the event. Consequently, this study made the following assumption: the degree of propagation (popularity) is correlated with the amount of indirect information. According to the previous study by Aramaki et al [15], most people report influenza information precisely in the early stage of an influenza season. However, as the indirect information is propagated widely, most people know about the influenza epidemic and become insensitive to the event. We designate such deactivated people as trapped sensors. This study investigates the degree to which this model improves the performance of the event detection.

The objective of this study was to handle indirect information to estimate the trend of the number of influenza patients in each area and each season. This estimation would be useful in satisfying practical needs not only in the industry but also of individual consumers, such as the supply control of vaccines and products for disease prevention or treatment. To study this, we built a state-of-the-art Twitter-based influenza surveillance system. Our contributions are 2-fold:

1. We reconfirmed the contribution of existing techniques. The existing techniques mainly consist of 2 main parts: tweet classification based on natural language processing (NLP) techniques and the use of direct information comprising global positioning system (GPS) information and profile information (PROF).
2. Subsequently, we evaluated the proposed model that aggregates indirect information to direct information.

Although a Twitter platform based on the Japanese language is used in this study, the proposed model for aggregating social sensors is universal, as they do not depend on a specific platform or language because no platform and language-specific technique are used. Note that the proposed model does not always work better under all conditions; we at least showed that our results targeted larger number of areas (47 areas) compared with previous studies to achieve a higher accuracy on an average.

Figure 1. Population bias in Twitter-based influenza surveillance. According to the geographic distribution in Japan of 7,666,201 influenza-related tweets for the period from 2012 to 2015, most Twitter users are in urban cities (such as Tokyo and Osaka). Other cities are adversely affected by a shortage of data that biases influenza detection there.

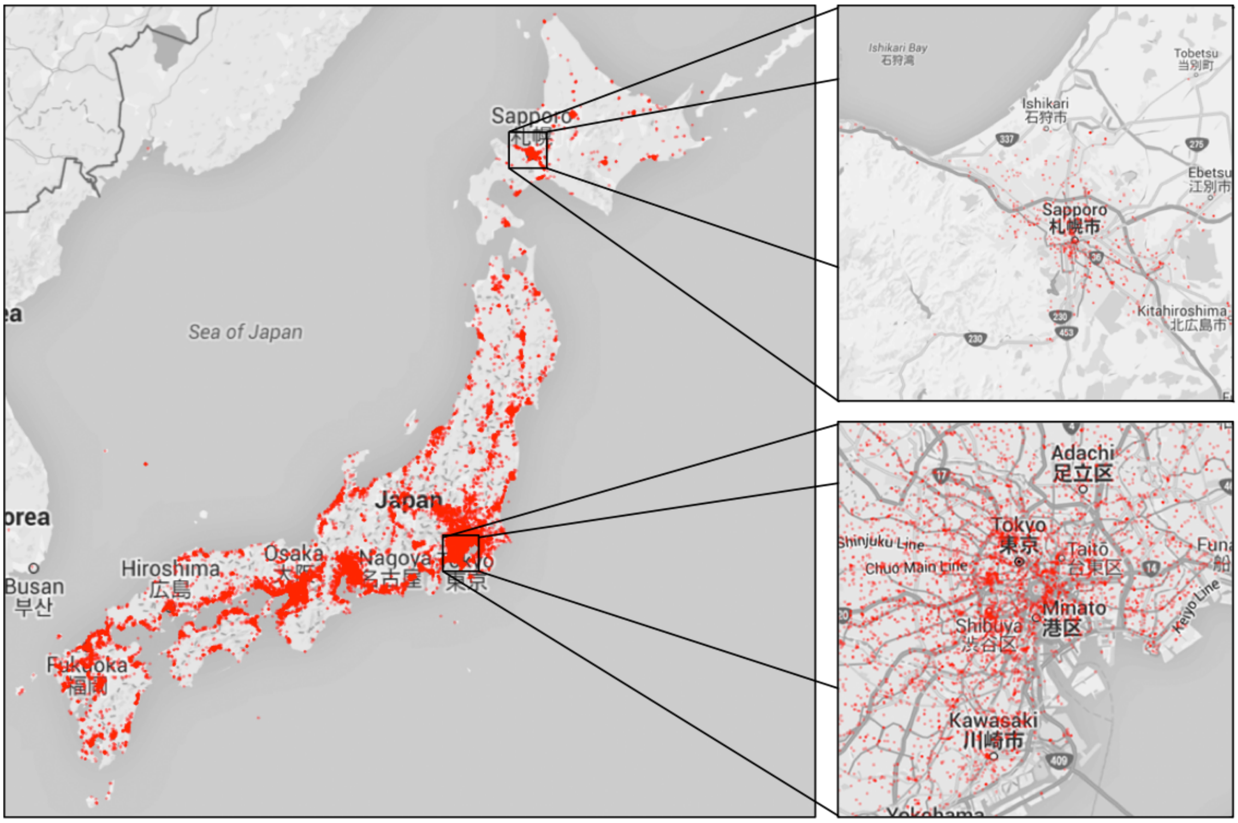


Figure 2. Most social sensor–based approaches consider people as sensors (center and right). Whereas previous social sensors exploited only direct information, the proposed method uses indirect information (right).

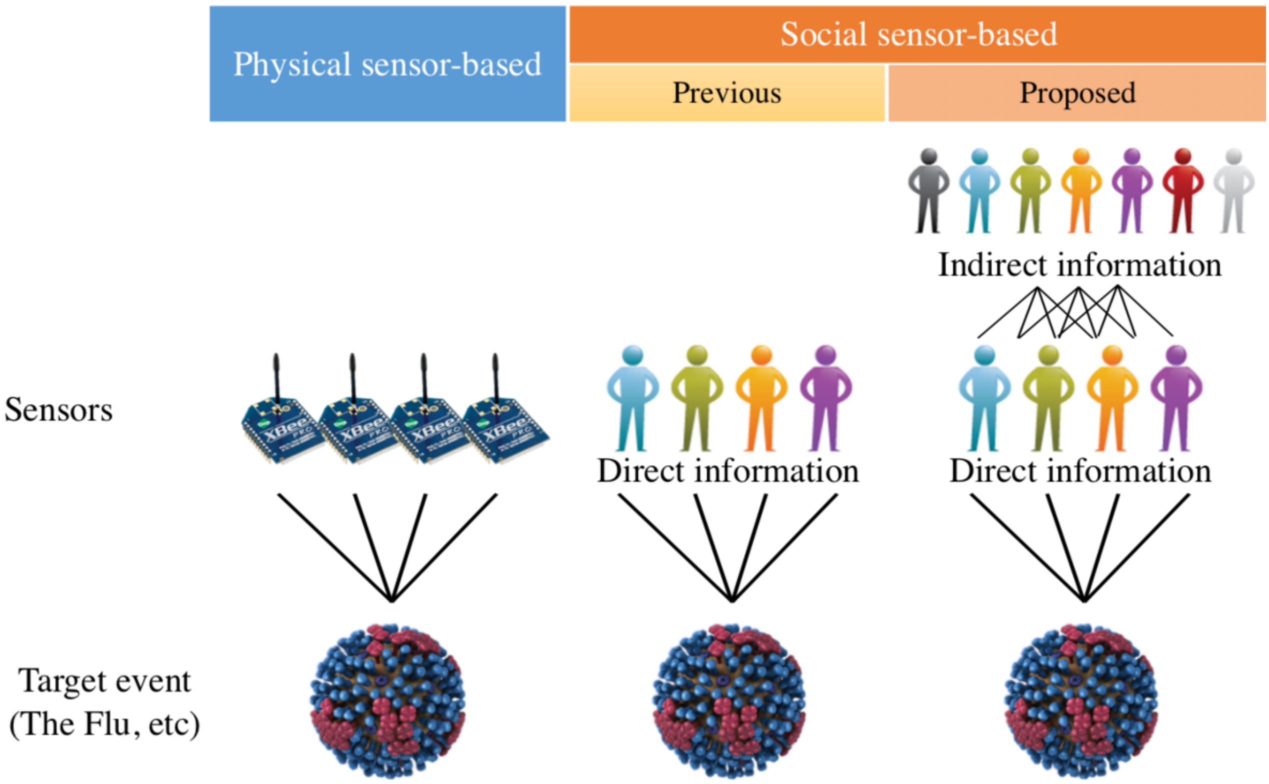
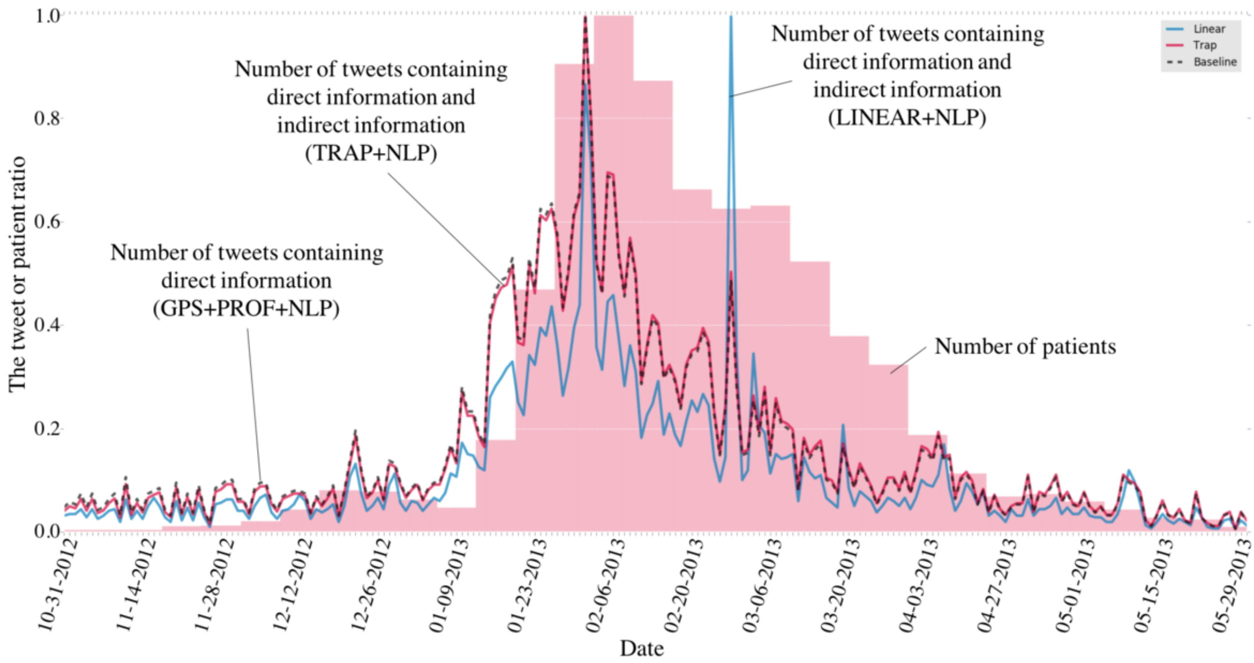


Figure 3. Amounts of direct and indirect information in a tweet timeline in Hiroshima from November 1, 2012 to May 31, 2013. The black dashed line shows the timeline of direct information (BASELINE+PROF+NLP), the blue line shows the timeline of direct information and indirect information that are aggregated in a naive way (LINEAR+NLP), the red line shows the timeline of direct information and indirect information that are aggregated by the proposed model (TRAP+NLP), and the red area shows gold standard timeline. The x-axis shows the date, and the y-axis indicates the tweet ratio and the patient ratio (normalized by the max value in the season). GPS: global positioning system; PROF: profile information; NLP: natural language processing.



Methods

System Overview

The system consisted of 3 modules to analyze given tweet data: a positive or negative (P or N) classification module, a location detection module, and a data aggregation module. For the aggregation, we used 2 methods using 3 types of location information: a LINEAR model and a TRAP model.

Tweet Data Collection

We collected the influenza-related tweets written in Japanese via the Twitter streaming application programming interface (API) for 5 years (from August 2, 2012 to March 1, 2016). All tweets comprised an influenza-related Japanese keyword *I-N-FU-RU* (*flu* in Japanese). These data include noise tweets, which are tweets that do not index an influenza patient. An example of such noise tweets is *influenza vaccination*. To filter out such influenza-negative tweets, the NLP module determines whether a given tweet is positive or negative.

Natural Language Processing Module: Positive or Negative

This module judges whether a given tweet is of an influenza patient (positive) or not (negative). This task is a sentence binary classification such as spam email filtering. This module applied a binary classification based on support vector machine under the bag-of-words representation. In the implementation, the same classification model was used as in the study by Aramaki et al [15]. To construct the model, 5000 tweets as a training set were assigned one of the two labels: positive or negative (P or N) by human annotators. In this labeling, tweets that met the following 2 conditions are regarded as a positive case:

- *Condition 1:* Area—Although a tweet seems to report a positive case, it may be not about a Twitter user himself or herself but about others. In such a case, we assume that one or more people with influenza would be likely to be present around the Twitter user. Here, we regard *around* as a distance in the same city. For cases in which the distance is unknown, we regard it as negative. Due to this annotation policy, the retweet type message is also negative.
- *Condition 2:* Tense—The tense should be present tense (current) or recent past. Here, we define the *recent past* as the prior 1-day period: *the previous day.*

The training set consisted of pairs of sentences and a label (positive or negative). Samples of tweets with labels are shown as follows:

1. BBC News: Okinawa has an influenza pandemic—(P, I)
2. Okinawa suffers a major outbreak of influenza—(P, D)
3. Retweet: My mother got the flu today—(P, I)
4. I got an influenza shot today—(N, D)
5. Doctor said influenza will be late in this season—(N, I)

Note that P/N denotes positive (P) or negative (N); D/I denotes Direct information (D) or Indirect information (I). We use retweet, too, in the same manner as normal tweets (non-retweet tweets).

For classifying a test set of tweets, we split each Japanese sentence into a sequence of words using a Japanese morphological analyzer MeCab (ver.0.98) [40] with IPADic (ver.2.7.0) [41]. The parameters for support vector machine including a polynomial kernel (d=2) were used in the study by Aramaki et al [15].

Location Detection Module (Direct or Indirect)

We used 3 types of location information extracted from each tweet: direct information, which includes GPS information and profile information, and indirect information or referred location.

Direct Information: Global Positioning System (GPS) Information

A tweet contains GPS-based data if a Twitter user allows the use of the location function. However, most users turn this functionality off for privacy reasons. Currently, the ratio of tweets with GPS information is only 0.46% (35,635/7,666,201) in our dataset.

Direct Information: Profile Information (PROF)

Several Twitter users describe their address in their profile (PROF). We regard the Twitter user as near the profile address. The proportion of tweets with profile location is 26.23% (2,010,605/7,666,201). This information was used in the study by Aramaki et al [15]. To disambiguate the location names, we used a geocoding service [42] provided by Google Maps [43]. Specifically, we sent queries about Twitter users' locale to Google Maps and obtained results in JavaScript Object Notation format. We wrote a simple parser in Python to parse these returned results to get information about the country.

Indirect Information: Referred Location

Several tweets contain the location name in the contents, such as "My friend in Hokkaido caught the flu." This study used this indirect information. To detect the location name in the contents, we used a location name list consisting of area names and famous landmarks. The proportion of tweets with indirect information was 4.73% (362,349/7,666,201).

Thus, we use the location if the GPS information is available. Otherwise, if a user profile information includes address data, then we use that information. The address data are geocoded by the geocoding service, API, provided by Google. Otherwise, if the content of the tweet contains a location name (area names), we consider it as the indirect information in the area. Consequently, a tweet is classified into GPS, PROF, or indirect information. Note that this classification is partly inclusive, as a tweet is classified into GPS or PROF exclusively, and then the tweet including location name is also counted as indirect information inclusively.

Aggregation Module (LINEAR or TRAP)

A difficulty hindering the combination of different resources is the question of how to combine them. This study investigated 2 methods: (1) simple aggregation (LINEAR model) and (2) TRAP model, which is proposed for implementing our assumption that people prefer to report new information and that they are insensitive to already-propagated information.

LINEAR Model

A simple method to use indirect information is to aggregate different types of information. In this model, we weigh the direct information as more important than the indirect information.

We formalize the number of patients $I_{\mathrm{LINEAR}}(a,t)$ in area a at day t as follows:

$I_{LINEAR}(a,t) = w_{GPS} \cdot GPS(a,t) + w_{PROF} \cdot PROF(a,t) + w_{IND}\Sigma_{b\in A} IND(a,b,t)$ **(1)**

Where, $GPS(a,t)$ is the number of tweets with GPS information, $PROF(a,t)$ is the number of tweets with profile information, $IND(a,b,t)$ is the number of tweets with indirect information, and w_{GPS}, w_{PROF}, and w_{IND} are weight parameters.

TRAP Model

This model includes the following 2 assumptions:

1. People prefer a new event and are, therefore, insensitive to an already-propagated event.
2. The degree of propagation (popularity) is correlated with the amount of indirect information.

The first assumption derives from human nature—people hesitate to inform others of an already-known fact. For example, if the Twitter stream is full of repeated influenza information, then such a situation dampens enthusiasm to tweet similar information.

The second assumption comes from the features of Twitter. Most indirect information consists of retweet or news information that tends to delay the direct information. The volume of this type of information corresponds to the volume of people who never tweet.

On the basis of these 2 assumptions, in the early stage of a season, most social sensors are *activated* to report influenza precisely (see Figure 4). Because the indirect information spreads widely, most people become *deactivated* to the event (Figure 4). We designated such deactivated people as trapped sensors. Under these circumstances, although the number of influenza tweets is small, the number of patients might be larger than the tweet volume, because a trapped sensor might disregard influenza.

We formalize the number of patients $I_{TRAP}(a,t)$ in area a at day t using a popularity function, $pop(a,t)$, as follows:

$I_{TRAP}(a,t)=(I_{LINEAR}[a,t]) / (w_{USERS}\cdot N_a - w_{TRAP}\cdot \log(pop[a,t] + 1)$ (2)

$pop(a,t)=\Sigma^{t}_{d=1}IND(a,d)$

Where $I_{LINEAR}(a,t)$ is the linear model and variable N_a is a set based on the number of potential active tweeting users defined by the number of tweets. A function, $pop(a,t)$, returns a cumulative number of the indirect information by the day t in a season, indicating the degree of popularity of attention of a crowd to influenza in the area a. w_{USERS} and w_{TRAP} are weight parameters.

Figure 4. Concept image of TRAP model. (a) People actively report the influenza before epidemics. (b) However, most people lose interest in sharing the direct information after epidemics because much indirect information already exists. In the proposed model, we call such people Trapped Sensors.

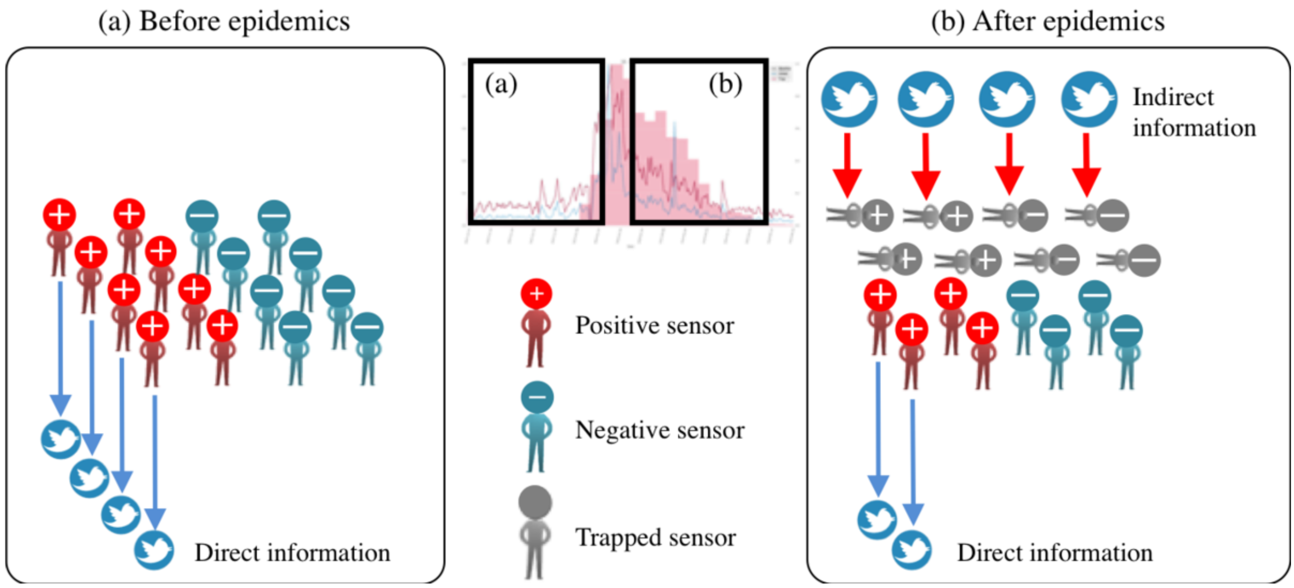


Table 1. Data description.

Season	Duration	Number of tweets (size)
SEASON 2012	November 1, 2012-May 31, 2013	1,959,610 (729.4 MB)
SEASON 2013	November 1, 2013-May 31, 2014	501,542 (143.7 MB)[a]
SEASON 2014	November 1, 2014-May 31, 2015	2,736,685 (808.2 MB)
ALL	August 2, 2012-March 1, 2016	7,666,201 (2.275 GB)

[a]We were unable to collect sufficient tweets on January 17, 2014 and January 18, 2014 in SEASON 2013 because of Twitter application programming interface specification changes. In addition, the number of tweets throughout this season was consistently smaller than the other seasons.

Evaluation

Datasets

These results were obtained by using the Japanese infectious disease data consisting of 2 types of data: one is Twitter data for the proposed system, and the other is the timeline report of the number of influenza patients.

Tweet Data

Our data comprised a collection of influenza-related tweets spanning 5 years. Human annotators annotated the collected tweet data into positive or negative labels, and using the support vector machine-based classification model constructed in the previous work [15] trained with a sample of 5000 randomly selected tweets from an influenza tweet corpus from November 2008, we classified our collected data into positive or negative label. For more precise information regarding the classifier and the training set, please see the previous report by Aramaki et al [15].

Because influenza epidemics appear in the winter, we split the data as follows:

1. SEASON 2012: November 01, 2012 to May 31, 2013
2. SEASON 2013: November 01, 2013 to May 31, 2014
3. SEASON 2014: November 01, 2014 to May 31, 2015

Statistics of the tweet data are presented in Table 1. Note that we were unable to collect sufficient tweets in SEASON 2013 because of changes in Twitter API specification, and we only used what we collected.

Gold Standard Data

We used the number of influenza cases as the gold standard data. In Japan, the Infectious Disease Surveillance Center [44] gathers statistics of patients diagnosed with influenza by rapid influenza diagnostic tests from about 5000 clinics and releases summary reports called the Infectious Diseases Weekly Reports [45]. The report presents the number of influenza patients for each Japanese prefecture (47 areas) in a week. Therefore, this test set enables week-based evaluation in 47 areas.

Models

We compared the 4 methods described below.

TRAP

TRAP is the proposed model. It detects disease epidemics by considering the balance between direct information (GPS information and profile information) and indirect information (referred location). In this study, we set N_a to a value based on the number of potential active tweeting users for equation 2. Afterward, we set the weight parameters w_{USERS} and w_{TRAP} to 0.1 and 2.0, respectively, based on the results of preliminary experiments.

LINEAR

LINEAR is a model that uses GPS information, profile information, and indirect location information together. In this study, weight parameters w_{GPS}, w_{PROF}, and w_{IND} in equation 1 were set to 1.0. Note that these values are not optimal parameters. This study set the weighting parameters based on heuristic and preliminary experimental results. To examine optimal parameters for improving the validity of our model is one of the future works.

BASELINE+PROF

This is a baseline model presented in the study by Aramaki et al [15]. The approach uses GPS information and profile location:

$I_{BASE\,+\,PROF}(a,t)=GPS(a,t) + PROF(a,t)$ (3)

BASELINE

This is a simple baseline that uses only GPS information:

$I_{BASE}(a,t)=GPS(a,t)$ (4)

In addition to evaluation of the effectiveness of the positive or negative classification (NLP technique), we also conducted with or without the test. Thus, with the various combinations, 8 methods (4×2) were evaluated (see Multimedia Appendix 1).

Evaluation Metric

The evaluation metric used in this study is the correlation (Pearson correlation coefficient) between the gold standard values and the estimated values. This metric is also used in the previous study [33]. The correlation-based evaluation is unbiased under the assumption of equal population sizes. Therefore, we can calculate the correlation coefficient, *r*, for a given data array consisting of the gold standard data (the number of patients) and the values that a model estimated based on the number of tweets.

We regard strong positive correlation as high performance, which comes from the previous studies [15,33]. Specifically, we defined a strong positive correlation as r>.7, moderate positive correlation as .4<r ≤.7, and weak positive correlation as 0<r ≤.4.

Results

Overview

Evaluation was performed for 4 durations: (1) SEASON 2012, (2) SEASON 2013, (3) SEASON 2014, and (4) SEASON-TOTAL (all; 1-3). Thus, 1504 (8 methods×47 areas×4 durations) correlation coefficients were calculated.

Table 2 presents the results obtained. Table 2 and Table 3, respectively, present the correlation coefficients of models with and without NLP for the gold standard data. Note that most of the correlation coefficients (99.60%,1498/1504) were positive, and a high negative correlation was not observed. Specifically, we discuss these results in terms of contributions of NLP-based classification, profile information, and data aggregation by LINEAR model and TRAP model.

Table 2. Values of the correlation coefficient (*r*) of methods with natural language processing.

Target and method	SEASON 2012	SEASON 2013	SEASON 2014	SEASON-TOTAL
All areas				
TRAP+NLP[a]	.76[b]	.70[b]	.69[b]	.70[b]
LINEAR+NLP	.70	.55	.53	.50
BASELINE+PROF[c]+NLP	.74[d]	.68	.67	.69
BASELINE+NLP	.33	.37	.48	.36
High-population areas (Top 10)				
TRAP+NLP	.80[b]	.77[b]	.72[b]	.75[b]
LINEAR+NLP	.78[d]	.65	.64	.64
BASELINE+PROF+NLP	.80[b]	.77[b]	.71[d]	.75[b]
BASELINE+NLP	.55	.60	.63	.53
Low-population areas (Top 10)				
TRAP+NLP	.75[b]	.66[b]	.71[b]	.69[b]
LINEAR+NLP	.62	.46	.48	.43
BASELINE+PROF+NLP	.70	.61	.65	.64
BASELINE+NLP	.21	.26	.35	.25

[a]NLP: natural language processing.

[b]Highest correlation coefficient in each target area and each SEASON.

[c]PROF: profile information.

[d]High correlation (*r*>.7).

Table 3. Values of correlation coefficient (*r*) of methods without natural language processing.

Target and method	SEASON 2012	SEASON 2013	SEASON 2014	SEASON-TOTAL
All areas				
TRAP	.72[a]	.63[a]	.67[a]	.65[a]
LINEAR	.65	.48	.53	.48
BASELINE+PROF[b]	.69	.59	.66	.64
BASELINE	.29	.34	.48	.35
High-population areas (top 10)				
TRAP	.75[a]	.69[a]	.71[a]	.70[a]
LINEAR	.72[c]	.60	.63	.61
BASELINE+PROF	.75[a]	.69[a]	.70	.70[a]
BASELINE	.44	.56	.63	.50
Low-population areas (top 10)				
TRAP	.71[a]	.61[a]	.64	.60[a]
LINEAR	.58	.41	.46	.40
BASELINE+PROF	.65	.52	.65[a]	.59
BASELINE	.20	.23	.35	.25

[a]Highest correlation coefficient in each target area and each SEASON.

[b]PROF: profile information.

[c]High correlation ($r>.7$).

Contribution of Natural Language Processing–Based Classification (TRAP Vs TRAP+NLP)

To evaluate the contribution of NLP for positive and negative classification, we compared the results of TRAP in Table 3 and TRAP+NLP in Table 2. Although both methods are strongly correlated with the gold standard data, TRAP+NLP (*r*=.70 in SEASON-TOTAL) is predominantly higher than TRAP (*r*=.65). This result demonstrates the contribution of NLP.

In addition, TRAP+NLP and all other models with NLP (BASELINE+NLP, BASELINE+PROF+NLP, and LINEAR+NLP) achieved better detection performance using the NLP classifier.

Although methods with NLP worked well to estimate influenza epidemics, almost half of the tweets were removed. This might indicate that the NLP-based classification used in this domain (influenza or not) is basically simple, so it must be improved.

Contribution of Profile Information (BASELINE+NLP Vs BASELINE+PROF+NLP)

To evaluate the contribution of profile information, we compared BASELINE+NLP with BASELINE+PROF+NLP. As shown in Table 2, the correlation coefficient of BASELINE+PROF+NLP (*r*=.69 in SEASON-TOTAL) is much higher than that of BASELINE+NLP (*r*=.36) through all SEASONs. This fact suggests that the profile information is highly related to improving the performance in detecting influenza epidemics. However, BASELINE+NLP achieved lower correlation in this study than in Aramaki et al [15]. One of the possible reasons would be that the model did not consider an area (prefecture)-level estimation, so it did not work well in several areas that did not have enough number of tweets.

As described above, both NLP classification and profile information improved the performance to detect influenza epidemics. This result shows that the combination of these techniques (BASELINE+PROF+NLP) achieved higher performance.

Contribution of Indirect Information in LINEAR Model (BASELINE+PROF+NLP Vs LINEAR+NLP)

To evaluate the contribution of indirect information in the LINEAR model, we compared the performance of BASELINE+PROF+NLP with LINEAR+NLP. Although the performance of both methods was medium, the correlation coefficient of LINEAR+NLP (*r*=.50 in SEASON-TOTAL) is lower than that of BASELINE+PROF+NLP (*r*=.69) through all SEASONs, as shown in Table 2. This point indicates the difficulty inherent in detecting influenza epidemics solely by adding indirect information in a naive manner.

Contribution of Indirect Information in TRAP Model (BASELINE+PROF+NLP Vs TRAP+NLP)

To evaluate the proposed model, the TRAP model, we compared the respective performances of TRAP+NLP and BASELINE+PROF+NLP, which were better than LINEAR+NLP.

In fact, TRAP+NLP exhibited the highest correlation coefficient among the models, indicating that it achieved the best performance for influenza epidemic detection on the gold standard data. This, in turn, suggests that TRAP model methods effectively contribute to the exploitation of both direct and indirect information from social sensors to detect disease epidemics accurately.

Discussion

Few Tweets After Flu Peak

The fact that the TRAP model outperforms the LINEAR model indicates that when influenza becomes a hot topic, people do not talk about it, which shows the aspect of human nature in which people become bored quickly with the news. Similar phenomena have also been presented from a psychological viewpoint. Most studies showed rapid propagation of rumors (especially bad news) and their short life [46-48]. Among various SNSs, Twitter is an extremely *fast* media. Therefore, the life of news on this platform might be shorter than other existing news. In other words, people might hesitate to tweet an already-known fact.

This model has sufficient room for application to additional studies. For example, we simply regard the simulation of the referred tweet as news. Better methods using other media, such as news website information, are reasonable. The manner of estimation of the potential tweet users can also be improved by considering more realistic data.

Effectiveness of Each Module

From results obtained from the experiment presented in the previous section, we observed the following 3 findings:

1. Effectiveness of NLP-based classification.
2. Effectiveness of direct information and indirect information.
3. Effectiveness of data aggregation by TRAP model.

We first reconfirmed the 2 findings that were already studied in the previous work [15]—the effectiveness to apply NLP-based tweet classification and the effectiveness to use direct information. Then, we evaluated the effectiveness to use indirect information, in addition to direct information and to embed this information into TRAP model that are the main contributions of this paper.

Another novelty of this study is high-resolution geographic analysis. Therefore, we discuss the above effectiveness for each area throughout this section. Multimedia Appendix 2 portrays temporal changes of the gold standard data (red bar plot) and results of TRAP+NLP (red line), LINEAR+NLP (gray line), and BASELINE+PROF+NLP (blue line) for 3 SEASONs in 47 areas in Japan. Note that our evaluation was conducted by comparing the correlations between a tweet timeline and a patient timeline in an area. We assumed that the comparison would not be biased if the population sizes were comparable.

Effectiveness of Natural Language Processing–Based Classification

We determined the effectiveness of NLP-based classification by comparing the performance of the methods with NLP for the top-10 high-population areas in Table 2 with the performance of the methods without NLP for the top-10 low-population areas in Table 3. The rank of the population of areas is presented in Multimedia Appendix 3.

In urban areas such as Tokyo and Osaka, the TRAP model (without NLP) performance was sufficiently high. In fact, the correlation coefficient of TRAP was equal to or higher than .7. For the other results, all correlation coefficient values were higher than .5, reflecting medium correlation.

However, in more rural areas such as Shimane and Toyama, no significant improvement was observed when NLP was used. In particular, little difference in performance was found between BASELINE+NLP and BASELINE. However, NLP never worsened the performance, which motivates the use of NLP.

Effectiveness of Profile Information and Propagated Information

The proposed method used 3 types of location information: GPS information, profile information (as used by previous studies), and referred location. We discussed the effects of exploiting the referred location (as indirect information), as well as GPS information and profile information (as direct information). From Table 2, we observed that the indirect information might not be as important in high-population areas such as Tokyo and Osaka. For example, BASELINE+PROF+NLP realized a high correlation (r>.7) in urban areas on an average. In such areas, even BASELINE+NLP only using GPS information had medium correlation.

In contrast, using indirect information was effective in rural areas. Although BASELINE+PROF+NLP was determined as just medium correlation (r ≤.7) through all SEASONs, TRAP+NLP showed high correlation in SEASON 2012 and SEASON 2014, as shown in Table 2. The results for SEASON 2013 might be affected by the lack of tweet data, as shown in Table 1.

This result might be caused by a common pattern by which much direct information is available in urban areas. In contrast, because a sufficient amount of direct information is not available from rural areas, there is some lack of exploitation of indirect information.

Effectiveness of Data Aggregation by TRAP Model

We can discuss the effectiveness of the TRAP model by comparing the correlation coefficients of the top-10 high-population areas and that in the top-10 low-population areas in Table 2.

In urban areas, the performance of 2 methods related to the TRAP model (TRAP+NLP and TRAP) was the highest among the others. The correlation coefficients of the 2 methods related to the LINEAR model (LINEAR+NLP and LINEAR) were less than .7, except in SEASON 2012. For example, for Tokyo (AREA13) and Osaka (AREA27) in Multimedia Appendix 2, TRAP+NLP matched the gold standard data well. In contrast, LINEAR+NLP has some gaps. These results confirm the effectiveness of TRAP model for tweets in urban areas.

In rural areas, the performance of the methods related to the TRAP model (TRAP+NLP and TRAP) was also the highest. Most of the correlation coefficients were higher than .6. In particular, the performance of TRAP+NLP in the rural areas was higher than that of the LINEAR+NLP in the urban areas on an average. For example, for Shimane (AREA32) and

Toyama (AREA18) in Multimedia Appendix 2, the results of both TRAP+NLP and LINEAR+NLP in SEASON 2012 matched the gold standard well. However, the results in other SEASONs have partial gaps. The results of LINEAR+NLP are affected by the small number of tweets. For such areas, we improve the performance by adjusting the weight parameters adequately.

Overall, we confirmed the effectiveness of aggregation using the TRAP model that does not treat the 3 types of location information in the same manner but instead distinguishes referred location as indirect information and uses it differently.

Relation Between Volume of Tweets and Performance

The relation between population and the detection performance presents an important finding. Multimedia Appendix 3 presents the relation between population (blue bar plot) of each area and performance (lines). The population is the number of tweets. The performance is the correlation coefficient. This figure compares TRAP+NLP (red line) with BASELINE+PROF+NLP (dotted black line).

The results show that the performance of TRAP+NLP was higher than that of BASELINE+PROF+NLP in urban areas. Specifically, the top 17 high-population areas (from Tokyo [AREA13) to Ibaraki [AREA8]) exhibited high correlation (r>.7). In these areas, more than 400 tweets were emitted.

However, other areas have large performance variances. Although both methods sometimes stagnate at the same performance level, in most cases, TRAP+NLP outperforms BASELINE+PROF+NLP. In Aomori (AREA2), Nagano (AREA17), Oita (AREA44), Nagasaki (AREA42), and Yamanashi (AREA16), the TRAP model achieved higher performance (r>.7) than that of the BASELINE+PROF+NLP (r ≤.7). One typical example is Aomori of SEASON 2012 and SEASON 2013. The graph of Aomori in Multimedia Appendix 2 shows that TRAP+NLP was able to detect a high level of continuous epidemic in SEASON 2013, indicating the effectiveness of the TRAP model. However, as described previously, sometimes it was unable to detect tweets after an epidemic. This remains a subject of future work.

Although the TRAP model achieved higher performance than BASELINE+PROF+NLP, the performance was of a medium level (.4<r≤.7) in Niigata (AREA15), Fukui (AREA 20), Tochigi (AREA 9), Mie (AREA24), Iwate (AREA 3), Kagoshima (AREA 46), and 10 other areas. For example, the graph of Fukui in Multimedia Appendix 2 shows that TRAP+NLP was unable to detect the sequential influenza epidemics in SEASON 2012. There were gaps in other SEASONs. Therefore, the average performance through all SEASONs was medium. TRAP model exhibited poorer performance than BASELINE+PROF+NLP in SEASON 2013 in only one (Kumamoto [AREA 43]) area (see Kumamoto in Multimedia Appendix 2). One of the reasons is medical treatment failure in Kumamoto in the SEASON. That was domestic news, but tons of news on the failure appeared in Twitter stream, causing the bias.

The results show the strong advantages of TRAP+NLP in high-population areas. More importantly, TRAP+NLP never shows worse performance, except in one area. These findings are expected to contribute to similar SNS-based surveillance.

Parameter Optimization

An important issue was the optimization of parameters used in the model. TRAP model required 5 parameters, w_{GPS}, w_{PROF}, w_{IND}, w_{USERS}, and w_{TRAP}, as shown in the equations 1 and 2. As for the 2 parameters w_{GPS} and w_{PROF}, we set to 1.0, as comparative models, BASELINE and BASELINE+PROF, set the same weightings. Accordingly, we also set w_{IND} to 1.0, so the choice of these weightings would be reasonable.

We optimized the other 2 parameters, w_{USERS} and w_{TRAP}, in preliminary experiments. We observed changes in the correlation coefficients of high-population areas (top 10) and low-population areas (top 10) by adding 0.01 to the parameter value w_{USERS} from 0 to 1.0. As a result, 80% of areas (16/20) were found to have a high correlation (r>.7) when w_{USERS} was 0.05 and more. The observation for the parameter w_{TRAP} was conducted in the same way. Specifically, we tested by adding 1.0 to the parameter value w_{TRAP} from 0 to 3.0. Consequently, we set w_{USERS} and w_{TRAP} to 0.1 and 2.0, respectively, so that this pair could achieve the best performance.

Limitations and Future Direction

The proposed method has several limitations. First of all, we have methodological limitations when crawling Twitter data and detecting tweet location. Our Twitter crawling method relies on a specific keyword *I-N-FU-RU* (*flu* in Japanese). Further research should crawl all tweets of each person so that we can conduct more detailed analyses, including moving trajectory analysis of a person, a recovery process analysis, and so on. Furthermore, this study handles only the location name as indirect information, but various expressions have been used in indirect messages. Therefore, it would be required to apply location estimation techniques for improving the accuracy of this model.

We also have limitations to use self-reported data by social media users. Generally, social media users are biased toward young- to middle-aged demographics so that their data may not represent the population of interest. In addition, social media data are influenced by a variety of user-dependent factors and surroundings. Thus, this study focused on propagated information about the flu and attempted to embed the sensitivity of social sensors in each stage during epidemics of the flu into a model. However, the sensitivity of social sensors can be affected by multiple factors. For example, if a severe case or death case was reported in a particular subgroup of the population, this event would affect and resensitize trapped sensors. Although this study assumed a straightforward case that a trapped sensor had never been resensitized in a season, there is room for considering relations between the (re)sensitivity of social sensors and the gravity of events.

Table 4. Area resolution of surveillance.

Location	Target (number of areas)	Data size (million tweets)
Aramaki [15]	Japan (1)	300
Achrekar [26]	United States (10)	1.9[a]
Culotta [27]	United States (1)	0.5
Kanouch [28]	Japan (1)	300
De Quincy [29]	Europe (1)	0.14
Doan [30]	United States (1)	24[a]
Szomszor [31]	Europe (1)	3

[a]Indicates the number of users in millions.

To improve the detection performance for disease epidemics, it is important to implement functions that enable consideration of various effects related to geographic relations among areas: adjacency (neighborhood or not), accessibility (easy to access or not), and isolation (island or not). Furthermore, this study was conducted to elucidate the current situation of disease epidemics. To predict the spread of disease, we need to develop a method through integration with various prediction models. This would enable us to identify outbreaks of infectious diseases with high accuracy before a wider outbreak.

Comparison With Prior Work

Social Sensors for Health-Related Events

Social media are used to detect various events, such as earthquakes [2-4], political elections [5-7], and stock prices in a market [8]. Among the various applications, the study on health-related event detection referred to as *infodemiology* [1,34] has been gaining much attention from researchers in areas such as air pollution [49], Web-based doctor reviews [50], West Nile virus [9], cholera [10], *Escherichia coli* outbreak [11], dengue fever outbreak [12], and influenza [1,13-33]. One review of the literature reported that half of the SNS-based surveillances are related to influenza (15 of 33 papers) [25]. That is true because influenza is a major worldwide public health concern. In particular, unexpected influenza pandemics, which have been experienced 3 times already in the twentieth century (eg, *Spanish flu*), are global issues.

Twitter is the most frequently used social medium for influenza detection [13-33]. Studies have consistently demonstrated a high correlation between the number of influenza patients and the actual influenza-related tweets. However, most studies targeted only country-level detection. Furthermore, detailed surveillance of areas is rarely conducted, as shown in Table 4. One reason is the volume shortage of tweets in small areas. Therefore, it remains unknown whether a small rural area can achieve the same high performance. One advantage of this study is its investigation performance in areas with small populations.

Location Estimation

Location estimation including estimation of the place of residence of someone is an important issue in this study. Although the simplest and most reliable method is to use GPS information, many difficulties can arise. For instance, many users turn off this functionality to maintain the privacy of their information. As a result, location estimation from the SNS original text is necessary. Related studies identified 2 difficulties in location estimation of SNS texts: detecting a location name in tweet messages and disambiguating the location names.

To address these challenges, a collection of location names is necessary. Usually, Wikipedia is used as the basis of a location name dictionary. We also used a location name dictionary obtained from Japanese Wikipedia. As for the location name disambiguation, several methods have been studied [51]. Location-indicative words from tweet data are found by calculating the information gain ratios. Earlier research effort shows that words improve the user location estimation performance. They concluded that the procedure requires little memory: it is fast. Moreover, lexicographers can use it to extract location-indicative words. A probabilistic framework was developed to quantify the spatial variation manifested in search queries [52], which brings them to spatial probabilistic distribution models. One study [53] estimated geographic regions from unstructured, nongeo-referenced text by computing a probability distribution over the surface of the Earth. Another study [54] estimated a city-level user location based purely on the content of tweets, which might include reply tweet information, without the use of any external information, such as a gazetteer or internet protocol (IP) information. Two unsupervised methods [55] have been proposed based on notions of nonlocalness and geometric localness to prune noisy data from tweets. One report [56] described language models of locations using coordinates extracted from geotagged Twitter data. Although this study used geocoding services provided by Google, incorporating such techniques can support future studies.

Conclusions

This paper proposed a novel approach that uses not only direct information but also indirect information that mentions other places for disease epidemic prediction. We assumed a model by which the indirect information inhibits direct information. In the experiments performed for high-resolution areas (prefecture level), the proposed approach exhibited improved detection performance not only in rural cities but also in urban cities, which demonstrated the effectiveness of the proposed method consisting of a TRAP model and NLP classification.

This model offers sufficient room for additional study. For example, although this study handles only location name as indirect information, various expressions have been used in indirect messages. Therefore, applying location estimation techniques could improve the accuracy of this model. Another limitation of this study is the Twitter crawling method that relies on a specific keyword *I-N-FU-RU*. This method cannot allow the collection of a timeline of tweets of a person. If we crawled all tweets of each person, it could conduct more detailed analyses, including moving trajectory analysis of a person, a recovery process analysis, and so on.

Future work will study worldwide influenza surveillance. Furthermore, we plan to apply this method to other epidemic surveillances and to establish a novel method by integrating various models to exploit their prediction accuracy.

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Authors' Contributions

SW and EA conceived and designed the model and method, in addition to analyzing the data. SW, EA, and YK prepared the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Models used for data aggregation. Note that NLP is the positive/negative classifier, GPS is GPS information, PROF is profile information, and IND is indirect information.

[PNG File, 30KB - publichealth_v4i3e65_app1.png]

Multimedia Appendix 2

Temporal changes of positive influenza tweets for 3 SEASONs in 6 prefectures in Japan. The x-axis shows the date from the beginning of SEASON 2012 to the end of SEASON 2014, whereas the y-axis shows the tweet ratio and the patient ratio (normalized by the max value in each season). The red line shows the timeline of direct information and indirect information that are aggregated by the proposed model (TRAP+NLP), and the red area shows gold standard timeline. The black dotted line shows the timeline of direct information (BASELINE+PROF+NLP). The blue line shows the timeline of direct information and indirect information that are aggregated in a naive way (LINEAR+NLP). PROF: profile information; NLP: natural language processing.

[PNG File, 30KB - publichealth_v4i3e65_app2.png]

Multimedia Appendix 3

Relation of the number of tweets (blue bar) and correlation coefficient of TRAP+NLP (red line) and BASELINE+PROF+NLP (dotted black line) for each area. Areas are ordered by populations based on the number of tweets. The x-axis shows the area; the y-axis indicates the correlation coefficient (left side) and the number of tweets (right side). In most areas, the proposed approach (TRAP+NLP) shows a higher correlation ratio than the conventional system. PROF: profile information; NLP: natural language processing.

[PNG File, 30KB - publichealth_v4i3e65_app3.png]

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Abbreviations

API: application programming interface
GPS: global positioning system
NLP: natural language processing
PROF: profile information
SNS: social networking service

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Original Paper

Bringing Real-Time Geospatial Precision to HIV Surveillance Through Smartphones: Feasibility Study

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Abstract

Background: Precise measurements of HIV incidences at community level can help mount a more effective public health response, but the most reliable methods currently require labor-intensive population surveys. Novel mobile phone technologies are being tested for adherence to medical appointments and antiretroviral therapy, but using them to track HIV test results with automatically generated geospatial coordinates has not been widely tested.

Objective: We customized a portable reader for interpreting the results of HIV lateral flow tests and developed a mobile phone app to track HIV test results in urban and rural locations in Rwanda. The objective was to assess the feasibility of this technology to collect front line HIV test results in real time and with geospatial context to help measure HIV incidences and improve epidemiological surveillance.

Methods: Twenty health care workers used the technology to track the test results of 2190 patients across 3 hospital sites (2 urban sites in Kigali and a rural site in the Western Province of Rwanda). Mobile phones for less than US $70 each were used. The mobile phone app to record HIV test results could take place without internet connectivity with uploading of results to the cloud taking place later with internet.

Results: A total of 91.51% (2004/2190) of HIV test results could be tracked in real time on an online dashboard with geographical resolution down to street level. Out of the 20 health care workers, 14 (70%) would recommend the lateral flow reader, and 100% would recommend the mobile phone app.

Conclusions: Smartphones have the potential to simplify the input of HIV test results with geospatial context and in real time to improve public health surveillance of HIV.

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KEYWORDS

HIV surveillance; smartphones; mobile phones; geospatial data

Introduction

For the HIV/AIDS epidemic to be curtailed in a sustainable fashion, it will be critical to increase diagnosis, awareness, and tracking of HIV infections among the hardest hit, resource-constrained countries. Precise measurements of HIV incidences at a subnational level are instrumental in mounting an effective global response [1], but the most reliable methods currently require labor-intensive population surveys.

For HIV diagnostics, HIV rapid tests (which use lateral flow test technology) are widely used for primary screening. These tests are low cost, readily available, and can be performed in field settings, but they have shown lower specificity and sensitivity during field conditions as compared to laboratory evaluations, suggesting that there may be user variability in performing and reading the test results. Furthermore, test results are currently first entered by hand into a book and later transcribed into a computer. This process can introduce data entry errors and slows availability of the data for use by health care providers and officials. There exists an opportunity, using the latest technologies in mobile devices, to accurately record HIV test results to improve efficiency in clinic operations, improve surveillance and management of the disease at a systems level, and ultimately reduce turnaround time to commencement of antiretroviral therapy (ART). For example, the availability of real-time HIV testing data could allow public officials to rapidly identify local outbreaks of the disease and implement a timely and effective public health response.

Africa accounts for 70% of the world's population living with HIV and close to two-thirds of newly infected individuals [2]. Currently, the region experiences uneven access to HIV tests, long turnaround time of HIV testing, delayed time initiation of ART, and poor retention and adherence with therapy [3]. The high HIV incidences across sub-Saharan Africa mount pressure on decentralized services, which have been underutilized [4,5], in allowing infected individuals to know their status with subsequent linkage to care. Increasing the capability of decentralized testing will be critical in an effort to allocate resources to people and places of greatest need [6,7] to achieve an HIV-free generation (a goal of United Nations sustainable development plans by 2030 [8]).

In Rwanda, detailed household surveys have indicated higher HIV incidences than previously estimated [9] and point to the need for more rapid and detailed characterization of incident infections in planning for an effective national strategy for at-risk populations. HIV incidence in Rwanda seemed to decline after the 1990s with the provision of ART [9,10]. While 160,000 people in Rwanda receive treatment with ART [11], a recent study highlighted the need to understand HIV incidence at a more granular level than currently available in order to reduce HIV infections in the country [9]. More specifically, the study highlights the need for understanding HIV incidence subnationally and within different populations [12], in contrast to using uniform national models for planning HIV programs at local levels that could present many biases [13]. In Rwanda, a relatively low national HIV incidence (compared to other sub-Saharan Africa countries) masks wide variations across groups and demographics [14].

Novel mobile phone technologies are being developed and tested to expand HIV care to decentralized settings [8,15-17]. While some examples include mobile devices and diagnostics to increase adherence to medical appointments [18-21] and to ART therapy [22-28], most mobile health technologies for HIV [29] focus on short message service (SMS) texting. While potentially useful for different aspects of HIV management, these studies did not focus on tracking of HIV test results, let alone doing so with geospatial coordinates provided by mobile phones. Technologies associated with smartphones (ie, mobile phones with enhanced computing power that can run native software programs and can connect to the internet) and mobile phone apps have only been tested recently [30]. Despite the potential of geospatial data on mobile phones, there are few studies on leveraging this information to track HIV incident infections in real time. If such geospatial data could be collected, they could enable HIV test results to be linked to geospatial coordinates. Studies in South Africa and Lesotho found that visualization of georeferenced data (collected by analyzing existing sources of information or by field surveys equipped with Global Positioning System [GPS] receivers, respectively) has the potential to efficiently guide HIV program operations [31,32]. In neither study were the objectives to link geospatial information to HIV test results or to obtain the GPS coordinates using mobile phones.

In this study, we paired a portable reader for interpreting the results of HIV lateral flow tests with a mobile phone app to track HIV test results in urban and rural locations in Rwanda. In a point-of-care setting, a health care worker performs an HIV rapid test. The technology tested in this study first enables the health care worker to use a customized lateral flow reader (LFR) to read the results of the HIV rapid test as positive or negative. Second, the health care worker can instantly record within a mobile app the HIV test result, and the result can be sent instantly or at the next point of internet connection to the cloud. After integration to a relational database stored on the cloud, the results are immediately viewable with geospatial context and in real time by health officials who can allocate resources to local clinic workers efficiently in order to stop HIV outbreaks at their onset. The results from the study aim to lay the foundation for a scalable method to improve the efficiency and quality of identifying HIV incidences quickly in developing countries.

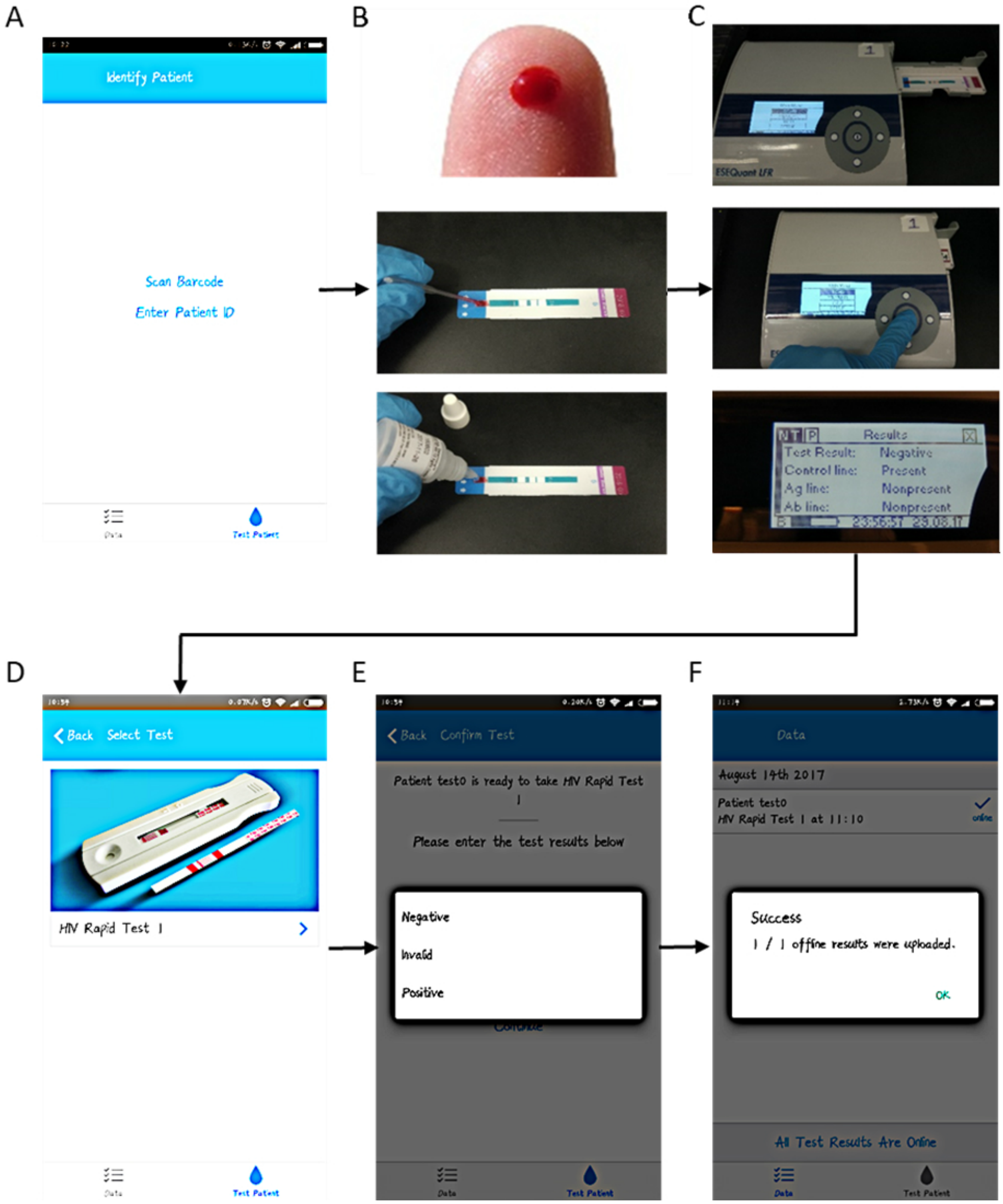
Methods

Development and Customization of Lateral Flow Reader Hardware

We purchased 4 ESEQuant LFR readers (Qiagen Inc) for digital interpretation of band intensities in lateral flow tests. The LFR machines consist of 2 parts: main body and drawer. On the main body, the screen and 5 buttons control the program that runs the tests and displays the test results. For the drawer, we designed and manufactured (via a 3D printer) a custom white holder to fit the exact size of an Alere Ab/Ag combo test strip (Abbott) for analysis. The customized LFR can read the control/Ab/Ag lines shown on an Alere Ab/Ag combo test strip and display the results.

The LFR can either work separately or remotely when connected to a personal computer. In remote mode, several important parameters such as incubation time, scanning positions, detecting range, and detection limitation can be controlled by the software and programmed into the reader. Using lateral flow tests with HIV-positive and HIV-negative samples for calibration, we customized the spatial positions of the 3 stripes of the Ab/Ag/control lines. A built-in peak detection function of the software would determine within the designated spatial positions whether a line would be classified as present. We calibrated all the LFRs with our customized method and provided the readers to the testing sites for use (Figure 1 A-C).

Figure 1. Step-by-step illustration of clinical testing. (A) App instructs user to perform an Alere HIV rapid test. (B) User performs a finger prick and places a drop of blood on the lateral flow strip. (C) The HIV test is placed in a lateral flow test reader, which scans the test and produces a reading. Here, the test result is negative, and the control line is present to indicate a valid test. (D) App displays the HIV rapid test model to be selected. (E) The patient ID and test results are entered into the app. (F) Results are uploaded to the cloud either at the time of test or later when internet is available.



Design and Coding of Mobile Software

To develop a mobile app to electronically record and transmit test results (Figure 1 D-F), we coded the app by using a cross-platform development tool called React Native. React Native allowed us to port the application, written in Javascript, to both iOS and Android devices (although all mobile phones used in this study were Android) while using platform-specific, native implementations of features such as GPS location and networking.

The mobile app used local storage drivers to save HIV test results to the device in the absence of internet connection. Once a connection was established, test results could be uploaded to our internal PostgreSQL database running on Google's Cloud

Compute platform. PostgreSQL is an open-source relational database with an emphasis on extensibility and standards compliance. As a database server, its primary functions are to store data securely and return that data in response to requests from other software applications. We also added an intermediary Node.js webserver running on Heroku to mediate the communication between the mobile device and database. A single HIV test result contained the following information: patient ID, test ID, result (positive, negative, or invalid), time, latitude, and longitude.

We used Knowi, an online data visualization tool, to view HIV test results and create geographic heatmaps of patient test results. Knowi connected directly to our internal database using read-only database credentials. Knowi enables visualization, warehousing, and reporting automation from PostgreSQL along with other unstructured and structured data sources.

Ethics Review Approval

The study protocol was approved by the Rwanda National Ethics Committee. Documents on patient consent, health care worker consent, data confidentiality, patient questionnaire, and health care worker questionnaire were approved by the committee. The questionnaire for health care workers collected information on the usability of the technology, while the questionnaire for patients queried the demographics of the patients. In addition, the consent form and questionnaire for patients were translated into Kinyarwanda to facilitate interactions with patients who were not fluent in English.

Study Setting

The study took place at 3 sites in Rwanda over 4 weeks in February and March 2018. The 2 urban sites in Kigali were Masaka District Hospital (DH) and Kibagabaga DH. One rural site was Kabaya DH in the Ngororero District of the Western Province of Rwanda. Kabaya DH has a capacity of 144 beds and serves 188,902 inhabitants and is geographically difficult to access due to the lack of reliable roads and bridges, especially in the rainy season.

Recruitment and Training of Health Care Worker Participants

At the 2 urban sites, we invited clinical and laboratory staff to participate in the study. For the 2 sites in Kigali, 4 health care workers in each facility (8 total) participated. In Masaka DH, 3 nurses and 1 lab technician participated (2 male, 2 female). In Kibagabaga DH, 2 nurses, 1 lab scientist, and 1 midwife participated (4 females). At Kabaya, we invited clinical and laboratory staff to participate in the study, and 12 health care workers at Kabaya participated: 5 A1 nurses, 2 A2 nurses, 4 lab technicians, and 1 midwife (8 male, 4 female). (A1 refers to completion of 3 years of postsecondary school, while A2 refers to completion of only secondary school.)

Health care worker participants were trained in the following modules: overview of project (background, aims, and procedure), review of health care worker consent form and data confidentiality agreements, demonstration of LFR, demonstration of mobile app, review of patient consent form (translated) and questionnaires for patients (translated) and health care worker, and review of study plan. At the conclusion of the trial, laboratory and clinical staff were interviewed using the health care provider questionnaire.

Recruitment of Patients

Patients for the 3 sites came through maternity/gynecology and outpatient departments and were scheduled to be tested for HIV (Alere Determine HIV Combo+ Stat Pak, Abbott Laboratories) through provider-initiated testing. All such adult patients (aged 21 years and older) during the study period were invited by health care workers to enroll. Individual interviews were held in a private space provided by the health facility to protect subject confidentiality. After the study was introduced to the patient, potential participants were informed in their mother tongue about the objectives of the study and the fact that their participation was voluntary. They were informed that they are free to choose not to participate in the study or withdraw at any time with no explanation required, and they will not suffer any negative consequences for their decision. With guidance from health care workers, those who agreed to participate reviewed and signed an informed consent form in Kinyarwanda, their mother tongue, and were provided 1000 RWF (US $1.15) as compensation for their time. Completed consent forms were stored separately from study documents, and names were not recorded on any data documents reviewed in the study.

Operation of Technology

Health care workers performed the Alere Determine HIV-1/2 combo tests with a finger-pricked patient blood sample. The completed test strip was placed into the customized and precalibrated LFR, and the LFR digitally displayed (unambiguously, as opposed to visual interpretation) a positive or negative result. Results of the HIV tests as visually interpreted were also recorded with pen and paper, and discrepancies relative to the LFR result noted.

Next, the provider input a deidentified patient ID and test result (positive, negative, or invalid) into the mobile app. We purchased locally available mobile phones for the study. The mobile phones were from Impress (Vertex; 60,000 RWF [US $69]). As described previously, the mobile app assists in the registration of patient test results alongside the location of testing down to the street level. The data input by the health care worker, alongside the GPS information, were saved into the phone's memory. The health care worker either uploaded this information to the cloud database immediately (if internet connectivity was available) or later (when internet connection became available). Internet connectivity, which can be intermittent, was not required for the test results to be recorded.

After each testing procedure, patients were interviewed by the health care worker using the patient questionnaire in Kinyarwanda.

Results

User Statistics

After approval of the study protocol by the Rwanda National Ethics Review Committee, we worked with the Directors General of the 3 sites to conduct the trial. Four health care workers at each urban site and 12 at the rural site were trained in the objectives of the trial and the details of the protocol, including issues related to patient consent and confidentiality. From these sites, we enrolled 513 patients at Masaka DH and 596 patients in Kibagabaga DH, for a total of 1109 patients across the 2 sites. For our rural site, we enrolled 1081 patients at Kabaya DH. Remarkably, 100% of eligible patients who were approached agreed to participate at Kabaya DH (similar to the 2 urban sites).

The trial took place over a 4-week period in spring 2018 Table 1. Of the patients whose HIV results were tracked, 91.51% (2004/2190) of the results came with a phone-generated GPS location. (We were also able to manually add the GPS location for the remaining patients since we knew the location of the testing.) The results that did not come with automatic GPS coordinates came primarily earlier in the trial, when the location settings on the phone were not set properly. The problems were mostly resolved after switching "Turn on Location" to on and restarting the phone. Also, a reading of result showed "invalid" if the Alere test was untested, or more likely, if the drawer of the reader was empty. The few invalid results came early in the trial when 3 health care workers did not place the HIV test into the reader or sufficiently firmly press the test down into the housing; after a quick reminder of the procedure during the first 2 weeks, there were no more invalid results. Of the valid tests, the LFR produced the same readings as visual interpretation in 100% of the cases (2166/2166), with 0 discrepancies.

Table 1. Summary of the trial data.

Sites	Participants, n	Recordings without GPS[a], n (%)	Recordings with GPS, n (%)	Invalid recordings, n (%)	Recordings showing positive HIV, n (%)
Masaka	513	62 (12.1)	451 (87.9)	4 (0.8)	39 (6.5)
Kibagabaga	596	32 (5.4)	564 (94.6)	0 (0.0)	9 (1.5)
Kabaya	1081	92 (8.5)	989 (91.5)	20 (1.9)	23 (2.1)
Total	2190	186 (8.5)	2004 (91.5)	24 (1.1)	71 (3.2)

[a]GPS: Global Positioning System.

Table 2. Demographics of patients at each site. Questionnaires that did not record a gender or report the testing of HIV were excluded from the analysis.

Characteristics	Masaka DH[a]	Kibagabaga DH	Kabaya DH
Subjects, n	513	596	1081
Questionnaires analyzed (correctly filled out), n	507	593	1057
Female, n (%)	459 (90.5)	593 (84.5)	668 (63.2)
Own mobile phone, n (%)	345 (68.0)	506 (85.3)	755 (71.4)
Own smartphone or internet-enabled phone, n (%)	40 (7.9)	123 (20.7)	78 (7.4)
Means of transportation to hospital, n (%)			
Motorcycle	233 (46.0)	161 (27.2)	29 (2.7)
Public transportation	93 (18.3)	291 (49.1)	120 (11.4)
Walk	147 (29.0)	66 (11.1)	889 (84.1)
Time to travel to hospital: less than 2 hours, n (%)	443 (87.4)	551 (92.9)	888 (84.0)
Employed (yes), n (%)	125 (24.7)	178 (30.0)	467 (44.2)
Annual income, RWF[b] (USD)			
1st quartile	333,000 (383)	500,000 (575)	60,000 (69)
Median	400,000 (460)	900,000 (1035)	255,000 (296)
3rd quartile	765,000 (879)	1,200,000 (1379)	716,250 (823)
Literacy level			
Tertiary (A1/A0/Bachelor), n (%)	23 (4.5)	35 (5.9)	58 (5.5)
Secondary (S1-S6), n (%)	186 (36.7)	256 (43.2)	249 (23.6)
Primary (P1-P8), n (%)	265 (52.3)	264 (44.5)	311 (29.4)
Informal (none), n (%)	33 (6.5)	38 (6.4)	439 (41.5)

[a]DH: District Hospital.

[b]RWF: Rwandan franc.

From analysis of a survey (Table 2), across the 2 urban sites, the patients at Kibagabaga DH are higher in median income (χ^2_1=39.2, P<.001, by the Mood median test), literacy (χ^2_3=7.86, P=.49), and ownership of mobile phones (χ^2_1=45.4, P<.001) and smartphones (χ^2_1=32.0, P<.001). At the rural site, the patients at Kabaya DH consisted of more males than at the urban sites (there was a campaign for male circumcision at the time of the trial). In general, the rural patients were less likely to own mobile phones (χ^2_1=11.2, P=.001) and smartphones (χ^2_1=31.7, P<.001), walk to the hospital, and while they were more likely to be employed (χ^2_1=62.1, P<.001), they had lower median income (χ^2_1=35.0, P<.001, by the Mood median test) and literacy (χ^2_3=376.9, P<.001) than those at the 2 urban sites (chi-squared tests comparing the rural site to both of the urban sites combined). For example, 41.53% (439/1057) of patients at Kabaya DH had no formal literacy.

Across all 3 sites, the percentage of patients who own mobile phones was high (at least 68% at each site), but only a smaller percentage (at most 20%) owned mobile phones that could surf the internet.

Real-Time Geographical Dashboard to Street Resolution

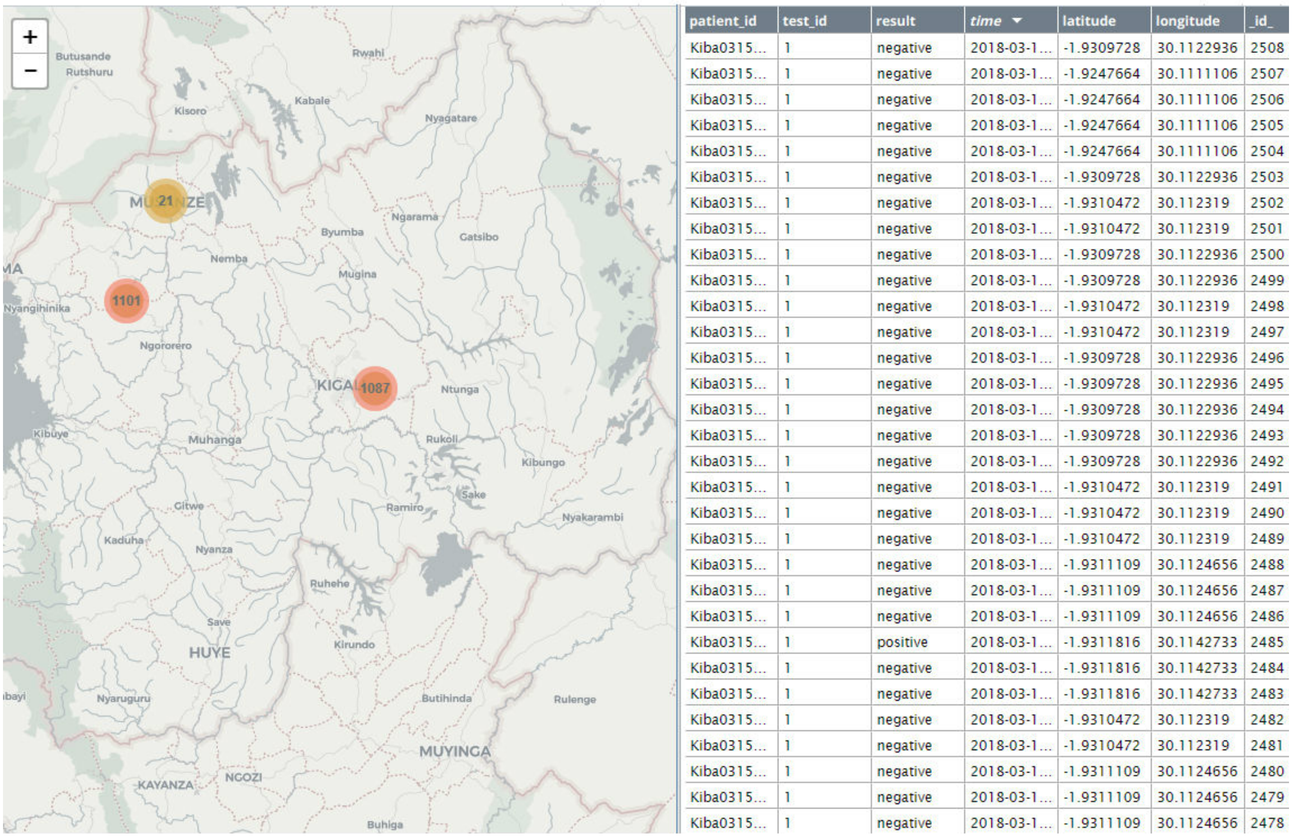
The mobile app registered each HIV test result. As shown in the map of Rwanda (Figure 2), the results were viewable on the dashboard immediately.

As shown in the map, 1087 results were recorded in Kigali and 1122 results in Northwest Rwanda. When zooming into Kigali, one can focus on the 2 sites of Masaka and Kibagabaga separately. First, with Masaka (Figure 3), one can see the HIV test results, including multiple subsites (as performed by different health care workers) at the site, down to street-level resolution. Clicking on 1 of the numbers revealed each of the HIV test results. Similar geographical resolution was achieved with Kibagabaga (Figure 3), showing several test locations as performed by health care workers. In addition, zooming in on the map of Northwest Rwanda showed test results at Kabaya DH to street-level resolution as performed by the 12 health care workers (Figure 3).

Survey of Health Care Workers

At the end of the trial, we performed surveys of the patients and health care workers. A summary of the results of the survey of health care workers is shown in Table 3.

Figure 2. Real-time dashboard of HIV tests tracked in Rwanda. On the map to the left, tests done in Kigali and northwest Rwanda are shown. The right shows the log of the tests as they are recorded.



patient_id	test_id	result	time	latitude	longitude	_id_
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2508
Kiba0315...	1	negative	2018-03-1...	-1.9247664	30.1111106	2507
Kiba0315...	1	negative	2018-03-1...	-1.9247664	30.1111106	2506
Kiba0315...	1	negative	2018-03-1...	-1.9247664	30.1111106	2505
Kiba0315...	1	negative	2018-03-1...	-1.9247664	30.1111106	2504
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2503
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2502
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2501
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2500
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2499
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2498
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2497
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2496
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2495
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2494
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2493
Kiba0315...	1	negative	2018-03-1...	-1.9309728	30.1122936	2492
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2491
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2490
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2489
Kiba0315...	1	negative	2018-03-1...	-1.9311109	30.1124656	2488
Kiba0315...	1	negative	2018-03-1...	-1.9311109	30.1124656	2487
Kiba0315...	1	negative	2018-03-1...	-1.9311109	30.1124656	2486
Kiba0315...	1	positive	2018-03-1...	-1.9311816	30.1142733	2485
Kiba0315...	1	negative	2018-03-1...	-1.9311816	30.1142733	2484
Kiba0315...	1	negative	2018-03-1...	-1.9311816	30.1142733	2483
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2482
Kiba0315...	1	negative	2018-03-1...	-1.9310472	30.112319	2481
Kiba0315...	1	negative	2018-03-1...	-1.9311109	30.1124656	2480
Kiba0315...	1	negative	2018-03-1...	-1.9311109	30.1124656	2479
Kiba0315...	1	negative	2018-03-1...	-1.9311109	30.1124656	2478

Figure 3. Real-time dashboard of the 3 sites to street resolution. (A) Masaka District Hospital: HIV test results at Masaka District Hospital (left); zoomed region of the red box in left image (middle); clicking on the number 40 showed each of the test results (right). (B) Kibagabaga District Hospital: HIV test results at the site (left) and zoomed image on the red box on the left, showing fine distinction of test locations to street resolution (right). (C) Kabaya District Hospital: HIV test results at the site(left) and xoomed image on the red box on the left, showing fine distinction of test locations to street resolution (right). Colors of each cluster indicate the number of samples (green=1 to 10; yellow=11 to 99; red=100 or above).

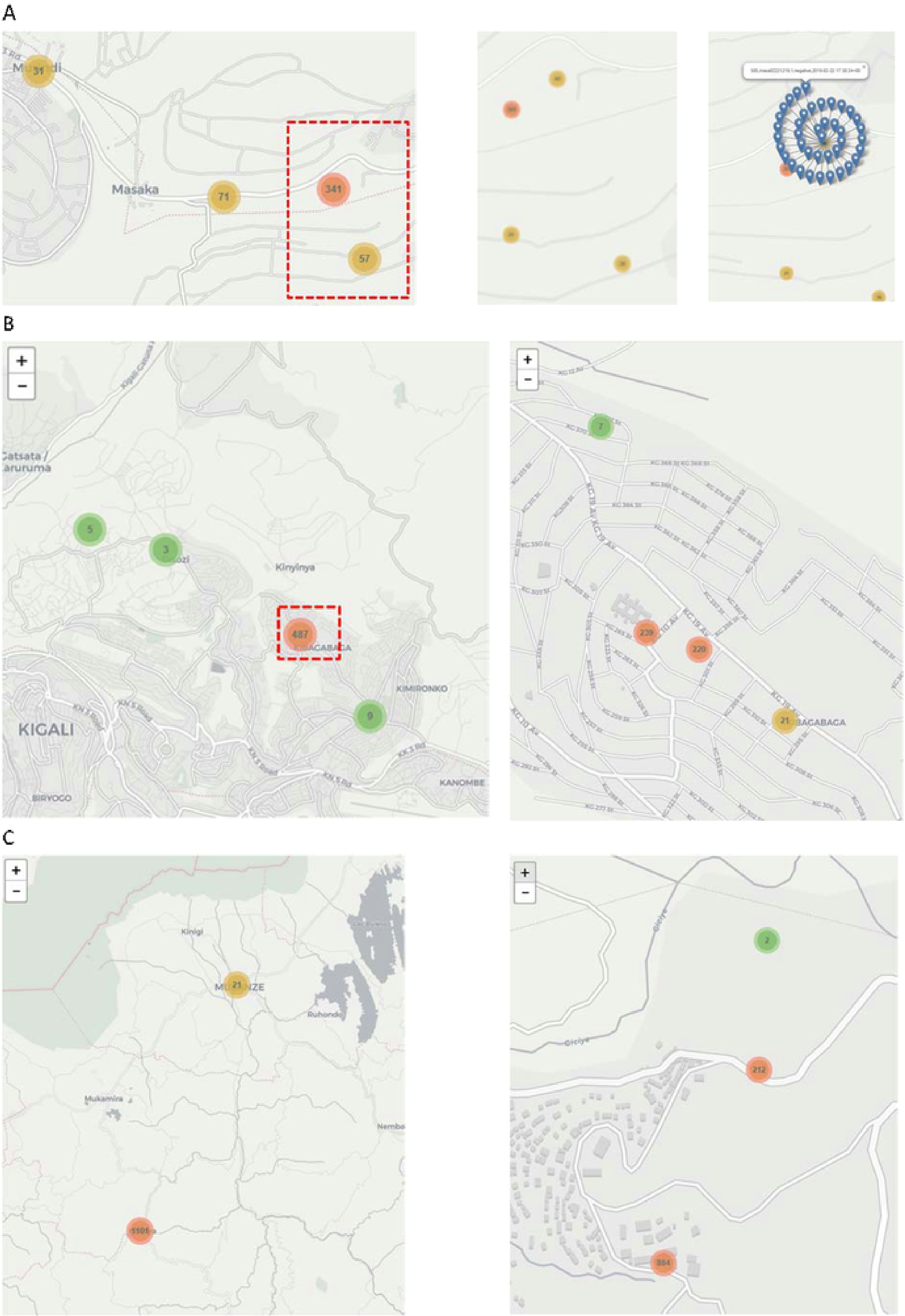


Table 3. Results of survey of health care workers.

Topics	Responses answering yes, n (%)
Rapid HIV testing	
Were you trained in HIV rapid testing?	20 (100)
Do you find it difficult to interpret the results of rapid tests?	2 (10)
Experience with lateral flow reader	
Have you used the Junco LFR[a]?	8 (40)
How many patients with the Junco LFR?	103
Do you feel the LFR made HIV testing easier?	15 (75)
Do you feel the LFR made HIV testing faster?	17 (85)
Do you feel the LFR made HIV testing more difficult?	3 (15)
Do you feel the LFR made HIV testing slower?	3 (15)
Would you like to use the LFR again during HIV testing?	16 (80)
Would you recommend the LFR to others?	14 (70)
Mobile app	
Did you find the mobile app easy to use?	19 (95)
Would you prefer to use the mobile app over paper records?	19 (95)
Would you use the mobile app again during HIV testing?	20 (100)
Would you recommend the app to others?	20 (100)
Mobile phone	
Do you own a mobile phone?	20 (100)
Do you own a smartphone?	19 (95)

[a]LFR: lateral flow reader.

The 20 health care workers were highly satisfied with the technology. They were most favorable toward the mobile app, finding it easy to use and preferable over paper records. No internet was needed at the time of performing the test (connectivity was required to upload the results, either immediately or later). All of respondents would use the mobile app again during HIV testing and recommend the app to others. While they were provided mobile phones for the trial, 100% of the health care workers owned phones, with 95% (19/20) owning smartphones and using the phones for internet surfing.

The health care workers were slightly less enthusiastic about the LFR. Overall, 80% (16/20) would like to use the LFR again during HIV testing, and 70% (14/20) would recommend it to others. The health care workers at Kabaya were more enthusiastic about the LFR: 83% (10/12) would like to use the LFR again during HIV testing, and 83% (10/12) would recommend it to others.

Survey of Patients

We also conducted and tabulated the results of a survey of the patients across the 3 sites. Results were recorded by pen and paper and later transcribed into a computer. A summary of the results is shown in Table 4.

Across the 3 sites, 42.7% (253/593) to 71.0% (360/507) of patients received their test results within 30 minutes, with a sizeable percentage (lowest of 26.6% [135/507] at Masaka DH to highest of 48.2% [286/593] at Kibabaga DH) waiting past 30 minutes. At the 2 urban sites, 68.0% (345/507) to 85.3% (506/593) of patients owned cell phones (with most using them for calling, texting, and listening to music). At the rural site, 71.43% (755/1057) of patients owned cell phones (with most using them for calling and texting).

Table 4. Results of survey of patients.

Variable/question	Masaka DH[a]	Kibagabaga DH	Kabaya DH
Subjects, n	513	596	1081
Questionnaires analyzed (correctly filled out), n	507	593	1057
Study subject sex, n (%)			
Female	459 (91.5)	501 (84.5)	668 (63.2)
Male	48 (9.5)	02 (15.5)	389 (36.8)
Have you had a laboratory examination on your blood today? (yes), n (%)	507 (100)	593 (100)	1054 (99.7)
For which laboratory examinations was your blood drawn today? n (%)			
HIV	507 (100)	592 (99.8)	1042 (98.6)
How long did it take you to get the laboratory results? n (%)			
Less than 30 minutes	360 (71.0)	253 (42.7)	681 (64.4)
30 minutes to 1 hour	70 (13.8)	193 (32.5)	225 (21.3)
1 to 2 hours	58 (11.4)	63 (10.6)	101 (9.6)
Over 2 hours	7 (1.4)	30 (5.1)	37 (3.5)
Not stated	12 (2.4)	54 (9.1)	13 (1.2)
Do you own a mobile phone? n (%)	345 (68.0)	506 (85.3)	755 (71.4)
If yes, what type? n (%)			
Basic phone (text, calling, no internet)	293 (57.8)	408 (68.8)	662 (62.6)
Smartphone (can download apps) or internet-enabled phone (check email, browse internet)	40 (7.9)	97 (16.4)	69 (6.5)
Model not specified	12 (2.4)	1 (0.2)	24 (2.3)

[a]DH: District Hospital.

Discussion

Principal Findings

We have demonstrated a technology that successfully recorded HIV test results. We paired a portable reader for interpreting the results of HIV lateral flow tests with a mobile phone app to track over 2000 HIV test results in urban and rural locations in Rwanda and could immediately view the HIV test results with geospatial context and in real time. While most health care workers felt the LFR was effective and would use it again for HIV tests, some workers felt it slowed the process. Also, the LFR experienced some operational issues that were resolved within a week. All were satisfied with the mobile app.

The use of mobile phones for HIV diagnostics has so far been limited, with most of the work focused on the outdated SMS messaging technique. There may be a perception that apps require constant internet connectivity and expensive smartphones and are not amenable to aiding HIV diagnostics in developing countries. Our technology does not require constant internet connectivity and makes use of the full power of apps on low-cost (less than $70 USD) smartphones, which over 90% of the health care workers personally own (depending on the demographics). The technique was judged to have high user acceptability, with 100% of the health care workers recommending the app.

While this study was not designed to accurately measure prevalence, we note that the Kigali sites reported 4.3% prevalence, compared to 5.6% in urban population (and 6.1% in Kigali) as previously reported [9]. (The lower apparent prevalence in Kibagabaga DH, being located in Gasabo district, may reflect more patients visiting from rural areas than Masaka DH, located in Kicukiro district.) In our study, the rural site of Kabaya DH reported 2.1% compared to 2.6% as previously reported for rural population [9].

Limitations

The technology was effective. Overall, 92% of the HIV test results had autogenerated GPS coordinates (with a much higher percentage in the last 3 weeks after the phones were set correctly). The results suggest that this technology can effectively scale (especially if use of an LFR is not required) to the whole country compared to expensive and labor-intensive community cohort–based questionnaires by leveraging the power of mobile phones. However, pointing to the limitations of this study, several important steps still need to be addressed before significant public health impact can be achieved: patient records will need to be integrated with existing electronic health record systems before such a technology can replace (rather than complement) current patient records, and replacement of the functions of the LFR with the app could streamline workflow and increase usability. Also, the reliance on manual entry of the data could still introduce errors, although currently the LFR keeps a backup log of the results (so the results can be cross-checked using the time stamp), and in the future, a picture of the rapid test will be taken and kept on record for cross-validation of results. Finally, to increase the success rate of using the technology, including among users of different levels of education and technical proficiencies, we could ask for a successful skills demonstration after the training and before starting the trial.

Conclusions

Toward the Joint United Nations Programme on HIV/AIDS 90-90-90 targets for HIV patients and diagnostics, we tested a mobile phone–based technology for tracking HIV incidences in Western Rwanda and at rural locations, where unexpected incidences emerged [9]. In rural settings, the LFR was perceived to work faster compared to the existing workflow (100% in rural sites to 63% urban sites) and was recommended more highly (83% rural sites to 50% urban sites). The app was uniformly praised for its speed of use and effectiveness, garnering 100% recommendation.

For the way forward, we are buoyed by the effectiveness of our technique and the uniform enthusiasm especially for the app (100% enthusiasm from all 20 health care workers). We plan to expand a version of the app that would obviate the need for an LFR, which could improve the scalability of the method to improve public health surveillance of HIV and other infectious diseases. The results from the study aim to lay the foundation for a scalable method to improve the efficiency and quality of identifying HIV incidences quickly in developing countries. In the future, this technology could also be applied to HIV home testing, with 10% of our surveyed patients already owning compatible mobile phones. We will work to scale this technology in Rwanda and beyond, which, at low marginal cost, leverages the power of mobile phones to track HIV incidences in real time and with proper spatial context.

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Conflicts of Interest

SKS has financial interest in Junco Labs. APN, BU, DMK, JN, QF, AE, and JH are employees or contractors of Junco Labs.

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Abbreviations

ART: antiretroviral therapy
DH: District Hospital
GPS: Global Positioning System
LFR: lateral flow reader
SMS: short message service

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Review

eHealth Literacy in People Living with HIV: Systematic Review

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Abstract

Background: In the era of eHealth, eHealth literacy is emerging as a key concept to promote self-management of chronic conditions such as HIV. However, there is a paucity of research focused on eHealth literacy for people living with HIV (PLWH) as a means of improving their adherence to HIV care and health outcome.

Objective: The objective of this study was to critically appraise the types, scope, and nature of studies addressing eHealth literacy as a study variable in PLWH.

Methods: This systematic review used comprehensive database searches, such as PubMed, EMBASE, CINAHL, Web of Science, and Cochrane, to identify quantitative studies targeting PLWH published in English before May 2017 with eHealth literacy as a study variable.

Results: We identified 56 unique records, and 7 papers met the eligibility criteria. The types of study designs varied (descriptive, n=3; quasi-experimental, n=3; and experimental, n=1) and often involved community-based settings (n=5), with sample sizes ranging from 18 to 895. In regards to instruments used, 3 studies measured eHealth literacy with validated instruments such as the eHealth Literacy Scale (eHEALS); 2 studies used full or short versions of Test of Functional Health Literacy in Adults, whereas the remaining 2 studies used study-developed questions. The majority of studies included in the review reported high eHealth literacy among the samples. The associations between eHealth literacy and health outcomes in PLWH were not consistent. In the areas of HIV transmission risk, retention in care, treatment adherence, and virological suppression, the role of eHealth literacy is still not fully understood. Furthermore, the implications for future research are discussed.

Conclusions: Understanding the role of eHealth literacy is an essential step to encourage PLWH to be actively engaged in their health care. Avenues to pursue in the role of eHealth literacy and PLWH should consider the development and use of standardized eHealth literacy definitions and measures.

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KEYWORDS

eHealth literacy; HIV; systematic review; mobile phones

Introduction

HIV is a major global health issue with an estimated 36.7 million people living with HIV (PLWH) worldwide [1]. In the United States, 1.1 million individuals are estimated to have HIV [2]. With the advent of antiretroviral therapy (ART), HIV has become a chronic condition requiring self-management, including the adherence to ART and keeping regular HIV care appointments [3]. However, PLWH often do not adhere to their treatment regimen; only 30% are ART adherent to the point of achieving viral suppression [4].

eHealth, “a medical and public health practice supported by a Web-based platform,” is a popular innovation in self-management of chronic conditions and includes mobile phones, tablet computers, and personal computers [5]. Web-based electronic communication technology is a relatively new source of health information that requires a new set of health literacy skills. Internet access is now nearly unlimited with 89% of US adults using the internet to access health information and gain social support [6]. This eHealth not only increases the access to health information but also expands social support and coping strategies by linking people together largely through a network of commercial, educational, and governmental websites as well as social media [7]. The utility of eHealth as an effective health communication and educational tool for self-management of chronic conditions has already been demonstrated [8]. In addition, evidence indicates that eHealth interventions offer great promise to promote care across the HIV treatment cascade, including prevention [9], medication adherence [10,11], and quality of life [12].

eHealth literacy refers to one’s ability “to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to address or solve a health problem” [13]. In this era of eHealth, PLWH represent an important population in which to intervene on eHealth literacy as electronic health sources is a more feasible and cost-effective means to improve the adherence to HIV care continuum, treatment outcomes, and promote health for PLWH [14]. Hence, this study aims to critically appraise the types, scope, and nature of studies designed to address eHealth literacy as a study variable in PLWH.

To the best of our knowledge, this is the first systematic review to address eHealth literacy in PLWH. Although previous systematic reviews have addressed eHealth literacy in college students [15], underserved populations [16], or older adults [17], eHealth literacy tools [18], Web-based health literacy interventions [19], computer-based interventions and applications [20], and eHealth policy issues [21], none were focused on PLWH. We aim to explain the definitions of eHealth literacy used in each study, describe theoretical and measurement approaches pertaining to eHealth literacy, and evaluate the study findings on eHealth literacy in association with target behavior or health outcomes in PLWH to identify gaps and areas for potential future research.

Methods

Review Design

We conducted a systematic review of quantitative evidence designed to assess eHealth literacy as a study variable in PLWH. Owing to the heterogeneity relative to study designs and statistical analysis approaches among the included studies, we synthesized the study findings rather than conducting a meta-analysis.

Study Eligibility

Studies were screened to assess their relevance for our review. Specifically, the following inclusion criteria were used papers that used a quantitative study design (including descriptive, correlational, quasi-experimental, or experimental); papers including eHealth literacy as a study variable; and papers including participants with HIV or AIDS. Our initial search was not limited by the age of study participants or sex to maximize the breadth of the study findings. In addition, we included any study that reported quantitative findings relevant to the review question. Studies from around the globe were included, as were studies conducted in various settings, including community or health system settings.

Notably, only studies written in English were included. Studies were excluded if full-texts were unavailable (ie, conference abstracts), they were not quantitative designs, or they reported protocol only with no measured outcomes.

Search and Identification Process

In consultation with a medical librarian, peer-reviewed journal papers were searched systematically in PubMed, EMBASE, CINAHL, Scopus, Web of Science, and Cochrane databases using variations of MeSH terms—methodological interest (ie, measurement of eHealth literacy as a study variable), population of interest (ie, PLWH), and study design of interest (ie, quantitative) to identify relevant papers published in English before April 27, 2017. In addition, a manual search of reference lists in selected papers was completed. Multimedia Appendix 1 provides a full search strategy for the database searches. Papers and abstracts were excluded if they did not address the population, design, or variable of interest.

Data Extraction and Quality Assessment

At the conclusion of the study selection process, 1 reviewing author extracted data from the studies using a standard template. The initial data extraction captured both the study characteristics (eg, setting, participants, type of study design, and eHealth literacy measure) and key findings from each study. In addition, other team members reviewed the studies and extracted data relating to key findings. Extracted findings were compared and discussed until all discrepancies were resolved.

We assessed the rigor of the underlying evidence base for the review by developing an overview of key methodological characteristics, including the study design, sample size and strategy, study setting, and year of publication. No studies were excluded on the basis of the quality assessment. Rather, the quality assessment process was conducted independently by 2 raters using the Joanna Briggs Institute quality appraisal tools based specifically on study designs, randomized controlled trials (RCTs) [22], quasi-experimental [22], and cross-sectional [23] studies to identify strengths and weaknesses in study methodologies and guide the interpretation and assessment of study findings.

Results

Selection of Studies

Figure 1 presents a detailed outline of the paper selection process. Our initial database search in April 2017 resulted in 116 citations. After removing duplicates, 56 titles with abstracts were reviewed independently for relevance by 2 authors (among HH, LES, and SG). The third author resolved conflicts in the inclusion of papers. Overall, 26 papers passed on to the next full-text review process. Of 26 full-text papers that were reviewed independently by 2 authors, 7 were deemed eligible. Reasons for exclusion included study design not quantitative (n=6), patient population not PLWH (n=5), duplicated paper (n=2), eHealth literacy not measured (n=2), full paper not found (n=2), and wrong format of paper (ie, not a journal paper; n=2).

Quality Assessment: Characterizing the Evidence Base

Overall, the studies appraised in this review achieved, at least, the assessment criteria, but the quality varied across individual studies. Although 1 RCT scored 8 of 13 [24] and 1 of 3 quasi-experimental studies scored 6 of 9 [25], they exhibited strengthened validity of causal inferences by comparing the control and intervention groups. In addition, 2 quasi-experimental studies scored 6 of 9 [26,27] and lacked a comparison group to determine pre-post intervention effects. One cross-sectional study earned a perfect score of 8 of 8 [28]; the remaining 2 earned 4 and 6, respectively [29,30]; potential confounding factors were not identified in these 2 studies. In addition, 2 of 7 studies did not use a validated standard measure of eHealth literacy but collected participants' basic literacy skills [24,29].

Furthermore, an interrater agreement rate was calculated [31]. The resulting statistic indicated substantial agreement (average interrater agreement rate, 69%) [32]. For items where discrepancies occurred between raters, we resolved them by interrater discussion. Table 1 shows consensual scores of the quality assessment.

Figure 1. Literature review flowchart.

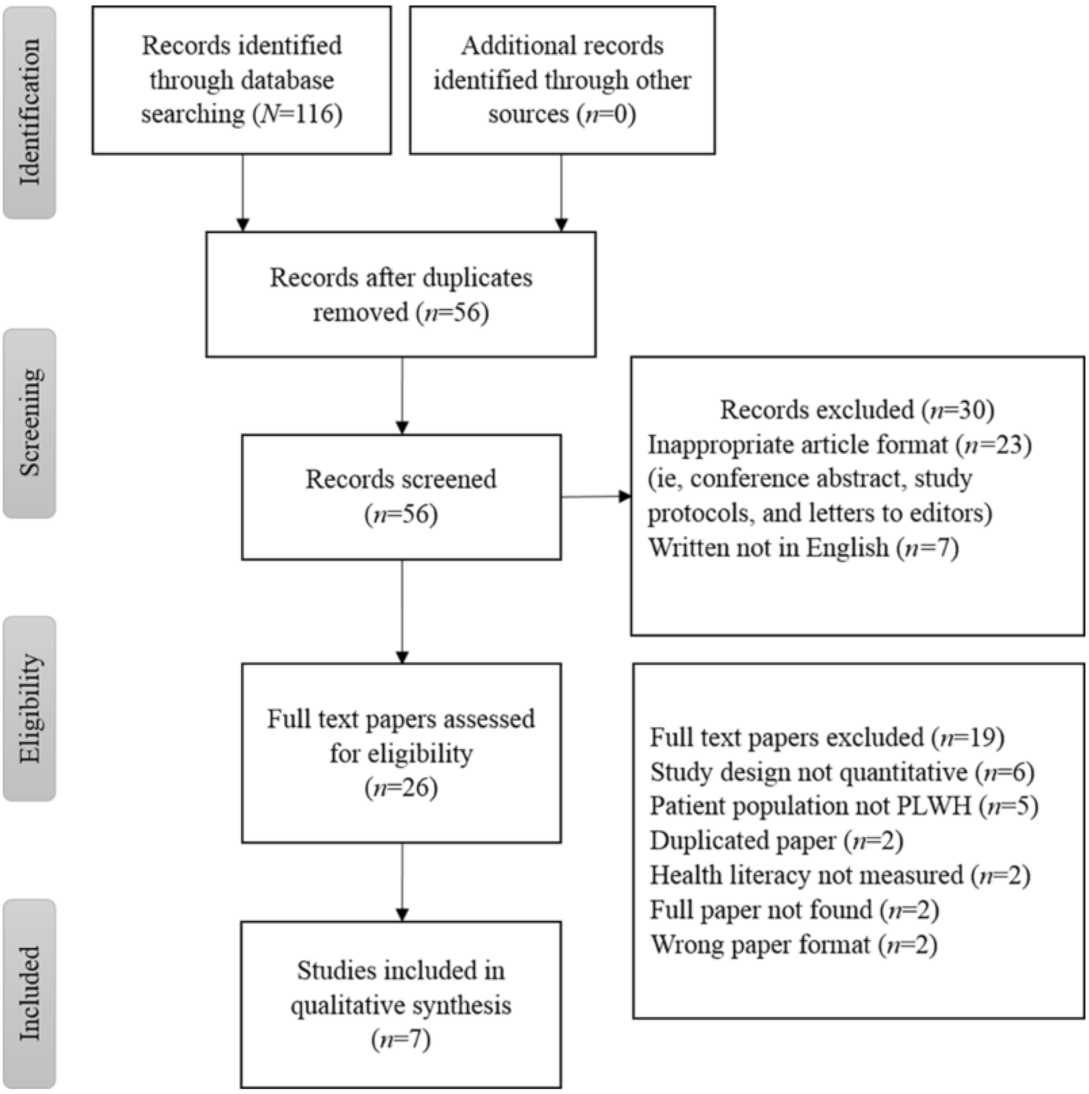

Table 1. Quality assessment.

Study items	Siedner et al [24] (n=8)	Ownby et al [26] (n=6)	Robinson et al [27] (n=6)	Woods et al [25] (n=6)	Blackstock et al [28] (n=8)	Kim et al [29] (n=4)	Krishnan et al [30] (n=6)
Randomized controlled trial							
1. Was true randomization used for assignment of participants to treatment groups?	✔						
2. Was allocation to treatment groups concealed?							
3. Were treatment groups similar at the baseline?							
4. Were participants blind to treatment assignment?							
5. Were those delivering treatment blind to treatment assignment?							
6. Were outcomes assessors blind to treatment assignment?							
7. Were treatment groups treated identically other than the intervention of interest?	✔						
8. Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	✔						
9. Were participants analyzed in the groups to which they were randomized?	✔						
10. Were outcomes measured in the same way for treatment groups?	✔						
11. Were outcomes measured in a reliable way?	✔						
12. Was appropriate statistical analysis used?	✔						
13. Was the trial design appropriate, and any deviations from the standard randomized controlled trial design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	✔						
Quasi-experimental studies							
1. Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about which variable comes first)?		✔	✔	✔			
2. Were the participants included in any comparisons similar?				✔			
3. Were the participants included in any comparisons receiving similar treatment or care, other than the exposure or intervention of interest?							
4. Was there a control group?				✔			
5. Were there multiple measurements of the outcome both pre and post the intervention or exposure?		✔	✔				
6. Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?		✔	✔				
7. Were the outcomes of participants included in any comparisons measured in the same way?		✔	✔	✔			
8. Were outcomes measured in a reliable way?		✔	✔	✔			
9. Was appropriate statistical analysis used?		✔	✔	✔			
Cross-sectional studies							
1. Were the criteria for inclusion in the sample clearly defined?					✔	✔	✔
2. Were the study subjects and the setting described in detail?					✔	✔	✔

Study items	Siedner et al [24] (n=8)	Ownby et al [26] (n=6)	Robinson et al [27] (n=6)	Woods et al [25] (n=6)	Blackstock et al [28] (n=8)	Kim et al [29] (n=4)	Krishnan et al [30] (n=6)
3. Was the exposure measured in a valid and reliable way?					✔		✔
4. Were objective, standard criteria used for measurement of the condition?					✔		✔
5. Were confounding factors identified?					✔	✔	
6. Were strategies to deal with confounding factors stated?					✔		
7. Were the outcomes measured in a valid and reliable way?					✔		✔
8. Was appropriate statistical analysis used?					✔	✔	✔

Overview of Studies Included in the Review

Tables 2 and 3 summarize the main characteristics of studies included in this review. All 7 included studies were published from 2010 to 2016. Of these, 4 studies were conducted in the United States [25-28], 2 in Uganda [24,29], and 1 in Peru [30]. Various study designs used were cross-sectional [28-30], quasi-experimental [25-27], and RCT [24]. Of note, 2 studies identified a theoretical or conceptual framework used in their research [24,26].

Study participants were recruited from a variety of settings as follows: community-based HIV/AIDS organizations [26,28-30], HIV hospital settings [24,27], and both community-based and hospital settings [25]. Overall, HIV-infected adults aged >18 years were included; 1 study included only people who had advanced immunosuppression ($CD4^+$ [cluster of differentiation 4] T-cell count <350 cells/mm^3 and taking ARTs for, at least, 4 years) [29], 1 included women only [28], and 1 involved men who have sex with men and transgender women [30]. The sample sizes ranged from 18 to 895.

Among studies that included women, most had a majority of female participants (56%-100%) but 2 [25,26] included only 9% and 29% of females in their study samples, respectively. Studies in the United States tended to include a large proportion of African American or black (57%-63%) participants [25-28] in which more than half (54.3%) of the study sample was Caucasian. All but 1 study [30] reported low educational levels with 37%-65% of participants having less than high school education. The baseline access to mobile phones, computers, and the internet was fairly high among participants in the United States, Uganda, and Peru. In the United States, 87.3%-88.9% used a smartphone, [25,28], 58.7%-88.9% used a home computer or tablet [25,28], 72.2% had regular access to the internet [27], and 66.7% used the internet daily [25]. Similarly, in Uganda, 81.8%-82.8% of study participants owned a mobile phone [24,29]. Krishnan et al reported that 59.6% of participants in Peru had access to a standard cell phone, 30.1% had access to a smartphone, 37.3% used landlines, and 35.4% accessed a laptop or desktop computer [30].

Definition and Assessment of eHealth Literacy

In this review, 5 of 7 studies defined eHealth literacy. Most studies [25-28] defined eHealth literacy as the capacity to find, process, understand, and apply health information to make appropriate health decisions. Blackstock et al [28] specified that this information must come from an electronic source. Kim et al [29] simply defined health literacy as the ability to read and write.

In addition, 3 studies conducted in the United States [25,27,28] measured eHealth literacy using the eHealth Literacy Scale (eHEALS), a self-evaluation tool comprising 8 items with a 5-point Likert scale. eHEALS measures the participants' level of knowledge, comfort, and skills in utilizing the internet or electronic health information to solve health problems [33]. In addition to assessing the ability to utilize internet-based health information using eHEALS, Woods et al [25] determined participants' general literacy, numeracy levels, and HIV-associated knowledge using a battery, including the Test of Online Pharmacy Skills (TOPS), Test of Online Health Records Navigation (TOHRN), Rapid Estimate of Adult Literacy in Medicine), HIV Knowledge 18, Expanded Numeracy Scale, Short Assessment of Health Literacy, Test of Functional Health Literacy in Adults (TOFHLA) reading comprehension, and Newest Vital Sign.

Moreover, Ownby et al [26] used the full-length version of TOFHLA [34] to measure basic reading and numeracy abilities to understand the verbal and written information commonly used in actual health care settings. Krishnan et al [30] used a short version of TOFHLA [35] in Spanish for screening patient literacy levels in health care settings in Peru. In Uganda, Siedner et al [24] and Kim et al [29] evaluated the feasibility and effect of a mobile phone-based short message service (SMS) text message intervention on the adherence to HIV treatment. eHealth literacy was assessed by study-tailored questions by asking participants to read a full sentence in their local language at enrollment; for example, "Are you able to read and/or write?" along with mobile phone availability [24,29].

Table 2. Overview of included studies.

Study	Study design, sample size, and setting	Study purpose	Study framework	Sample characteristics	Definition of eHealth literacy
Blackstock et al, 2016 [28]	Cross-sectional, N=63, February-April, 2014; 6 community-based organizations providing social and clinical services to people living with HIV	To examine the relationship between eHealth literacy and HIV transmission risk behaviors in internet-using women with HIV	No study framework reported	100% female; median age, 49 (IQR[a] 44-54) years; 54.0% (34/63) non-Hispanic black; 36.5% (23/63) Hispanic; 38.1% (24/63) <high school education; 85.7% (54/63) prescribed ART[b]; 87.3% (55/63) owned a cell phone; 58.7% (37/63) had a computer or tablet	"The ability to find, understand, & evaluate health information from electronic sources and apply this information to a specific health problem" (Norman and Skinner, 2006 [13])
Kim et al, 2015 [29]	Cross-sectional, June 2012-August 2013, N=895, AIDS Support Organization	To determine the proportion of people living with HIV who are literate and also use mobile phones in rural Uganda	No study framework reported	76.4% (684/895) female; median age, 44 (IQR 44-50) years; 65% (581/895) <high school education; median time on HIV medications, 6.8 (IQR 5.8-7.7) years; 82.8% (741/895) owned a mobile phone; 73.0% (653/895) can read and write	Ability to read and write
Krishnan et al, 2015 [30]	Cross-sectional, N=359, no specified date, 3 sites at 2 nongovernmental organizations providing health care	To examine the use of communication technology and acceptance of mHealth among HIV-infected Peruvian men who have sex with men and TGW[c] to gauge the feasibility of an mHealth-enabled HIV-risk reduction program	No study framework reported	77.7% (279/359) male; 13.3% (48/359) TGW; mean age, 34 (SD 8.11) years; 2.2% (8/359) <high school education; 53.3% (131/246) completed college; 87.2% (313/359) currently on ART; 59.6% (214/359) had access to a standard cell phone; 30.1% (108/359) had access to a smartphone; 37.3% (134/359) used landlines; 35.4% (127/359) accessed a laptop or computer	Definition of eHealth literacy not reported
Ownby et al, 2012 [26]	Quasi-experimental, N=124, May 2010-December 2011, Urban and suburban HIV clinics	To evaluate whether an Information-Motivation-Behavioral Skills Model–based electronic intervention can improve health literacy and medication adherence	Information-Motivation-Behavioral Skills model	29% female (36/124); mean age, 47.1 (SD 8.69) years; 63% (78/124) black; 37% (46/124) <high school education; mean, 11.6 (SD 7.18) years on ART; mean Test of Functional Health Literacy in Adults score, 88.48 (SD 14.16)	"The degree to which individuals have the capacity to obtain, process, & understand basic health information & services needed to make appropriate health decisions" (Nielsen-Bohlman et al, 2004 [36])
Robinson et al, 2010 [27]	Quasi-experimental, N=18, July, 2008, HIV-positive care center in a hospital setting	To determine if computer skills and internet health educational intervention will improve the perceived knowledge of internet health resources and confidence using the internet for health questions	No study framework reported	55.6% (10/18) female; mean age, 46 (range 34-69) years; 61.1% (11/18) African American; 27.8% (5/18) Caucasian; 44.4% (8/18) high school education or less; 72% (13/18) have regular internet access; 23% (3/13) sought health information in the internet in the past 3 months	The "capacity to acquire, understand & use information in ways which promote & maintain good health"
Siedner et al, 2015 [24]	Experimental, N=385, HIV clinic of the Mbarara Regional Referral Hospital	To identify predictors of uptake of a mHealth app and evaluate the efficacy of various short message service text message formats to optimize the confidentiality and accessibility	Concepts derived from the Technology Acceptance Model and the Unified Theory of Technology Acceptance and Use of Technology	65.2% (251/385) female; median age 32 (IQR 26-39) years; 62.4% (240/385) primary education or less; 67.5% (260/385) could read a complete sentence; 81.8% (315/385) had a mobile phone	Definition of eHealth literacy not reported

Study	Study design, sample size, and setting	Study purpose	Study framework	Sample characteristics	Definition of eHealth literacy
Woods et al, 2016 [25]	Cross-sectional, N=67, neuroAIDS research center, which recruits from local HIV clinics and community-based organizations	To evaluate the effects of HIV-associated neurocognitive disorders on 2 internet-based tests of health care management	No study framework reported	9.0% (6/67) female; 68.7% (46/67) HIV+ and 31.3% (21/67) HIV- mean age 45.5 (SD 9.2) years; 53.7% (36/67) Caucasian; 19.4% (13/67) Hispanic; mean education level 13.2 (SD 2.5) years; 95.7% (44/46) prescribed ART; 86.6% (58/67) use a home computer; 76.1% (51/67) own a smartphone; 67.2% (45/67) use the internet daily	"The capacity to obtain, communicate, process, & understand basic health information & services to make appropriate health decisions" (Patient Protection & Affordable Care Act, 2010 [37])

[a]IQR: interquartile range.

[b]ART: antiretroviral therapy.

[c]TGW: transgender women.

Characteristics of eHealth Literacy Among People Living With HIV

Overall, varying scales with differing scoring systems were used to determine the level of eHealth literacy. High eHealth literacy scores among PLWH ranged from 52.4% to 87% in study samples with the majority of studies finding high eHealth literacy among 65%-80% of participants. Such a wide variance arose because high literacy was defined differently in each study, ranging from the ability to read a complete sentence [24] to a TOFHLA score >75 [26], and an eHEALS score greater than the median [28]. Kim et al [29] simply asked about the ability to read and write and reported on differences in participant demographic characteristics by literacy; they found that men are more likely to be literate and use a cell phone than women, AOR 2.81 (95% CI 1.83-4.30), and employed participants are more likely to be literate and use a cell phone than those with no income, AOR 2.35 (95% CI 1.23-4.49).

The acceptability of eHealth interventions was measured in 3 studies [27,29,30]. Nearly all (91.7%) patients with high eHealth literacy supported their providers' use of SMS text messaging communication for reminders or to check health status in contrast to only 38.8% of PLWH who were not literate or did not own a cell phone (P<.001) [29]. Daily electronic medication adherence reminders were preferred over weekly or monthly [30]. Furthermore, perceptions of the ability to use the internet and eHealth literacy levels increased significantly after administration of a brief computer and eHealth class (P<.05 and P<.01, respectively) [27].

eHealth Literacy and Health Outcomes in People Living With HIV

In this review, 6 of 7 studies examined the associations between eHealth literacy and a variety of health outcomes in PLWH. The 2 studies that measured the relationship between eHealth literacy and HIV-related behavior reported conflicting results. In Blackstock et al [28], higher eHealth literacy was found to be associated with more significant HIV transmission risk behaviors among women living with HIV, including vaginal or anal intercourse without a condom and illicit drug use in the past 30 days, adjusted for income and perceived health status, AOR 3.90 (95% CI 1.05-14.56). The authors suggested the complexities of eHealth literacy across unique social contexts as a possible explanation for the unexpected finding.

In contrast, following an electronically delivered health literacy intervention targeting HIV-related health literacy on medication adherence, participants in Ownby et al [26] self-reported increased knowledge about barriers to adherence and medication misconceptions (P=.02) as well as adherence behavioral skills, including using reminders, scheduling medications with other daily activities, and soliciting social support (P=.02). Data were collected 3 months apart; however, no control group was included in this study.

Siedner et al [24] examined participant retention in HIV care by measuring attendance at return-to-clinic appointments in accordance with instructions. Following an intervention that involved providing test results through SMS text messages, 60.8% of participants returned to the clinic when provided instructions through SMS text messages [24]. The ability to read a complete sentence on enrollment was independently associated with an accurate identification of the message sent, AOR 4.54 (95% CI 1.42-14.47; P=.01), and return to the clinic within 7 days of the first transmitted SMS text message, AOR 3.81 (95% CI 1.61-9.03; P=.002) [24]. In addition, the ability to access an SMS text message on enrollment was independently associated with returning to the clinic within 7 days of the SMS text message notification, AOR 4.90 (95% CI 1.06-22.61; P=.04) [24].

Table 3. Overview of the included studies.

Study	Measurement of eHealth Literacy (Validity or Reliability)	HIV-Related Health Outcome	Main Findings
Blackstock et al, 2016 [28]	eHEALS[a] Dichotomized at the median (high vs low health literacy; alpha=.88)	HIV transmission risk behaviors, including condomless vaginal or anal intercourse, and any illicit drug use in the previous 30 days	Higher eHealth literacy, AOR[b] 3.90 (95% CI 1.05-14.56), significantly associated with HIV transmission risk behaviors, adjusted for income and self-perceived health status.
Kim et al, 2015 [29]	Study questions: “Are you able to read?” and “Are you able to write?” (validity or reliability not reported)	Viral suppression (CD4[c] count), adherence to ART[d]	Literate mobile phone users had lower adherence to ART (84.2% vs 90.6%; *P*=.007) and more favorable perception of utilizing reminders to support the adherence to treatment (57.1% vs 36.7%; *P*<.001) than those who were either illiterate, did not have a mobile phone, or both. There was no difference between literate mobile users and other study participants in the virological suppression.
Krishnan et al, 2015 [30]	Short Test of Functional Health Literacy in Adults (validity or reliability not reported)	ART adherence	No significant differences were found in communication technology use and mHealth acceptance among participants with alcohol use disorders, depression, and suboptimal ART adherence.
Ownby et al, 2012 [26]	TOFHLA[e]<59, inadequate; 60-74, marginal; >75, adequate (validity or reliability not reported)	Medication adherence	Changes in the adherence only approached the statistical significance. Knowledge and behavioral skills increased over the course of the study.
Robinson et al, 2010 [27]	eHEALS (validity or reliability not reported)	HIV-related health outcome not measured	A significant improvement from the baseline to immediately following the intervention was observed in perceived eHealth literacy levels (mean summary score 19 vs 32, *P*<.01) and perceptions of ability to use the internet (*P*<.05).
Siedner et al, 2015 [24]	Participants were asked to read a complete sentence in the local language (validity or reliability not reported)	Retention in care defined as a return to the clinic within 7 days of the first SMS[f] text message for those with abnormal results or on the date of the scheduled appointment for those with normal results	The ability to read a complete sentence on enrollment was independently associated with accurate identification of the message sent, AOR 4.54 (95% CI 1.42-14.47), and return to the clinic within 7 d of the first transmitted SMS text message, AOR 3.81 (95% CI 1.61-9.03). An ability to access an SMS text message on enrollment was independently associated with returning to the clinic within 7 days of an abnormal SMS text notification, AOR 4.90 (95% CI 1.06-22.61).
Woods et al, 2016 [25]	TOPS[g]; TOHRN[h]; eHEALS; Rapid Estimate of Adult Literacy in Medicine; HIV Knowledge 18; Expanded Numeracy Scale; TOFHLA; Short Assessment of Health Literacy; Newest Vital Sign (validity or reliability not reported)	CD4 count and HIV plasma viral load	Lower TOPS scores were associated with fewer years of education (ρ=.49, *P*=.003), higher HIV viral load (correlation=−.47, *P*=.006), less frequent computer and internet use (*P*<.05) and not owning a smartphone (*P*<.05); lower TOHRN scores were associated with lower education (ρ=.40, *P*=.01), higher HIV viral load (ρ=–.032, *P*=.045), less frequent internet use (*P*<.05), and anxiety related to computer use (*P*<.05).

[a]eHEALS: eHealth Literacy Scale.

[b]AOR: adjusted odds ratio.

[c]CD4: cluster of differentiation 4.

[d]ART: antiretroviral therapy.

[e]TOFHLA: Test of Functional Health Literacy in Adults.

[f]SMS: short message service.

[g]TOPS: Test of Online Pharmacy Skills.

[h]TOHRN: Test of Online Health Records Navigation.

The relationship between eHealth literacy and HIV treatment adherence was mixed. Literacy was inversely associated with ART adherence, which was measured by Kim et al [29] as the self-reported number of missed doses per month (86.4% adherence among literate PLWH with a phone vs 90.6% adherence among not literate PLWH or those with no phone; AOR=1.76; 95% CI 1.12-2.77; *P*=.007). Krishnan et al [30] found no significant differences between patients with optional and suboptimal adherence in their access to communication technology overall; however, a significant difference was observed for mHealth acceptance among participants with and without optimal ART adherence (*P*<.01); for example, participants with poor adherence were less likely to be interested in anonymous internet interaction with a health professional to discuss HIV-related issues compared with participants with optimal adherence (*P*<.001) [30]. Ownby et al [26] attempted to improve the rates of adherence with an electronically delivered health literacy intervention; after this intervention, the adherence increased by 2.3% overall, resulting in the statistical significance among participants who were <95%, <90%, and <85% adherent (*P*=.01,.009,.04, respectively) but not among those in adherence categories of ≤75% [26]. These conflicting results about the relationship between the adherence and eHealth literacy might have been, in part, because of the complexities of measuring the adherence primarily with self-report as well as the nuanced differences between participants exhibiting high- and low-level adherence.

Because only 2 studies assessed participants' HIV viral load under dissimilar study settings, we were unable to determine the association between eHealth literacy and HIV viral suppression [25,29]. Woods at al [25] reported, among a small sample of 46 HIV-infected participants with and without HIV-associated neurocognitive disorders, poorer performance in Web-based health care navigation tasks was associated with fewer years of education (ρ=.49, *P*=.003), higher plasma HIV viral load (ρ=–.47, *P*=.006), less frequent computer and internet use (*P*<.05), not owning a smartphone (*P*<.05), and higher anxiety related to using a computer (*P*<.05). According to Kim et al [29], in a large-scale study (n=895) with participants having advanced immunosuppression, however, the proportion of participants with an HIV viral load of >1000 copies/mL did not differ between literate phone owners (9%) and phone users who could not read and write (5.7%, *P*=.09).

Discussion

Although there has been limited reporting on eHealth literacy targeting PLWH, available studies addressing eHealth literacy in PLWH varied in their scope, methodology, and outcomes. The studies included in the systematic review provide some evidence for the role of eHealth literacy in relation to diverse HIV-related health outcomes, including HIV transmission risk, retention in care, treatment adherence, and virological suppression. Even though eHealth literacy was generally high and majority of those individuals included in the samples were receptive to the use of SMS text messaging communication [29], findings were mixed with instances of eHealth literacy both promoting as well as hindering health outcomes.

In descriptive studies, eHealth literacy was either inversely associated with HIV transmission prevention behaviors, ART adherence, or viral load [25,28,29] or unrelated to the adherence [30]. In contrast, eHealth literacy showed promise in promoting increased HIV knowledge and HIV-related behavioral skills, return visits when linked to care, and in bolstering the adherence in studies using quasi-experimental or experimental designs [24,26]. Each of these factors is critical in maintaining positive outcomes related to knowledge and behaviors [26].

Negative outcomes in retention in care and treatment adherence may be attributed to general literacy challenges and access to phones, laptops, and desktop devices [24,30]. In addition, the findings may be attributable to methodological biases associated with the studies included in the review. Specifically, although 1 RCT [24] and 1 of 3 quasi-experimental studies [25] had strengthened the validity of causal inferences by comparing control and intervention groups, the baseline differences between participants' characteristics in both groups were unclearly reported. In addition, 2 quasi-experimental studies [26,27] lacked a comparison group to determine pre-post intervention effects. Thus, the relationships among eHealth literacy and linkage to care [24], Web-based health care navigation tasks [25], medication adherence [26], and internet health literacy and confidence [27] could not be attributed to the potential causal effect. Moreover, 2 of 7 studies did not use a validated standard measure of eHealth literacy but collected participants' basic literacy skills [24,29]. Self-reported literacy may result in not only the limited accuracy of data collected but also social desirability bias [38].

This review has revealed several gaps in the existing evidence base; gaps that collectively point to what we argue should be key parts of the eHealth literacy research agenda going forward. The most important gap and a critical focus of future research is the use of validated instruments to measure eHealth literacy, which do not appear in these studies. Much of the research we reviewed used some form of eHealth literacy assessment but with no evidence of validity and reliability or proxy measures for eHealth literacy. Future eHealth literacy research should adopt more rigorous instrumental approaches to addressing eHealth literacy as a new way of promoting and facilitating self-management in PLWH. In addition, there exists a limited explanation of definitions of eHealth literacy used in the literature. Hence, the selection of study instruments was minimally justified within the reviewed studies, highlighting the need for adopting a validated eHealth literacy framework to better understand and promote healthy behaviors and outcomes of PLWH. Finally, this review highlighted a critical methodological gap and area for future improvement—the need for ensuring a rigorous study design with adequate sample size, use of validated eHealth literacy measures and theoretical framework, and the use of diverse study samples of PLWH; for example, because >90% of adolescents and young adults use the internet daily [39], youth needs to receive more attention in eHealth literacy research as they may have a different level of eHealth literacy than older adults. Finally, because qualitative studies or mixed-methods studies provide diversified, in-depth perspectives, the combination of quantitative and qualitative data would contribute to the development of a complete understanding of the eHealth literacy among PLHW.

Although the strengths of this review's design included its inclusive search strategy that ensured extensive coverage, standardized data extraction, and iterative analysis, there are several limitations. First, despite our expanded search criteria, only a small number of studies met the inclusion criteria because of a lack of published studies. Second, the heterogeneity in the quality and quantity of data reported in the studies included in the review. Finally, we were unable to include studies in languages other than English, thereby limiting the generalizability of our findings.

In conclusion, the importance of eHealth literacy among PLWH has only recently begun to be addressed. In the areas of HIV transmission risk, retention in care, treatment adherence, and virological suppression, the role of eHealth literacy remains partially understood. Understanding the role of eHealth literacy among PLWH is an essential next step in self-management of HIV and AIDS. Avenues to pursue in the role of eHealth literacy and PLWH should include the development and use of standardized eHealth literacy measures. Additionally, examining the role of eHealth literacy longitudinally from prevention to viral suppression could yield knowledge regarding at what point, from diagnosis through management, are the best points to intervene with eHealth literacy strategies. Finally, elucidating the other factors that potentially contribute to eHealth literacy, such as access and general literacy, could yield valuable findings going forward.

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Conflicts of Interest

None declared.

Multimedia Appendix 1

Search strategy.

[PDF File (Adobe PDF File), 40KB - publichealth_v4i3e64_app1.pdf]

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Abbreviations

AOR: adjusted odds ratio
ART: antiretroviral therapy
CD4: cluster of differentiation 4
eHEALS: eHealth Literacy Scale
IQR: interquartile range
PLWH: people living with HIV
RCT: randomized controlled trials
SMS: short message service
TOFHLA: Test of Functional Health Literacy in Adults
TOHRN: Test of Online Health Records Navigation
TOPS: Test of Online Pharmacy Skills

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Original Paper

Using Geosocial Networking Apps to Understand the Spatial Distribution of Gay and Bisexual Men: Pilot Study

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Abstract

Background: While services tailored for gay, bisexual, and other men who have sex with men (gbMSM) may provide support for this vulnerable population, planning access to these services can be difficult due to the unknown spatial distribution of gbMSM outside of gay-centered neighborhoods. This is particularly true since the emergence of geosocial networking apps, which have become a widely used venue for meeting sexual partners.

Objective: The goal of our research was to estimate the spatial density of app users across Metro Vancouver and identify the independent and adjusted neighborhood-level factors that predict app user density.

Methods: This pilot study used a popular geosocial networking app to estimate the spatial density of app users across rural and urban Metro Vancouver. Multiple Poisson regression models were then constructed to model the relationship between app user density and areal population-weighted neighbourhood-level factors from the 2016 Canadian Census and National Household Survey.

Results: A total of 2021 app user profiles were counted within 1 mile of 263 sampling locations. In a multivariate model controlling for time of day, app user density was associated with several dissemination area–level characteristics, including population density (per 100; incidence rate ratio [IRR] 1.03, 95% CI 1.02-1.04), average household size (IRR 0.26, 95% CI 0.11-0.62), average age of males (IRR 0.93, 95% CI 0.88-0.98), median income of males (IRR 0.96, 95% CI 0.92-0.99), proportion of males who were not married (IRR 1.08, 95% CI 1.02-1.13), proportion of males with a postsecondary education (IRR 1.06, 95% CI 1.03-1.10), proportion of males who are immigrants (IRR 1.04, 95% CI 1.004-1.07), and proportion of males living below the low-income cutoff level (IRR 0.93, 95% CI 0.89-0.98).

Conclusions: This pilot study demonstrates how the combination of geosocial networking apps and administrative datasets might help care providers, planners, and community leaders target online and offline interventions for gbMSM who use apps.

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KEYWORDS
service access; geosocial networking apps; gay and bisexual men; spatial distribution; gay neighborhoods

Introduction

In British Columbia, Canada, HIV and other sexually transmitted infections continue to disproportionately impact gay, bisexual, and other men who have sex with men (gbMSM) [1,2]. Yet, because the spatial geography of gbMSM may not correlate with that of the broader population, it remains difficult to ensure that sexual health and other services are optimally tailored for these individuals [3]. Previous research examining the social geography of gbMSM has shown that their spatial distribution is nonrandom [4] within the general population. For example, research suggests that the marginalization of sexual minorities along with other forces has given rise to gay neighborhoods—areas that often have a higher than expected concentration of gay men, gay-centered amenities, and homonormative cultural artifacts [5]. However, changing attitudes toward gbMSM in Western society have supposedly reshaped these communities, leading to changes in where these men live, work, and socialize [6]. Additionally, current literature indicates that the introduction of geosocial networking apps, which allow gbMSM to use smart devices to connect with other gbMSM within their geographic proximity, has reduced the need for traditional gay enclaves to facilitate connection [7,8]. These changes challenge the assumption that sexual health services tailored for gbMSM are only needed (or appropriate) within these historically gay neighborhoods [9]. Further compounding the difficulty of targeting app users, their spatial geography may not correlate with that of the wider gbMSM population. For example, previous research has found that only 10% of rural gbMSM sought sex online, compared with 56% in medium sized cities, 50% in suburban areas, and 48% in urban centers [10]. However, dating and online hookup apps largely appeared on the scene in 2009, after this research was conducted; therefore, it is unclear whether these patterns hold true today. These realities make it difficult to identify where and how sexual health services can best meet the needs of app users who are at elevated risk for HIV and other sexually transmitted infections.

Methods in examining app user density have not been widely explored. This study is the first of its kind in Canada and is only preceded by the work of Delaney et al [3], who used similar methods in estimating app user density in Atlanta, Georgia. In their pilot, the authors used a geosocial networking app designed for gbMSM to manually sample 2666 app users across 79 sampling locations. Sampling locations were selected by starting at the home of 1 of the researchers and driving along road networks to create 2-mile sampling intervals throughout the city. In areas where app user density was greater than 50 users per 2-mile radius, they recorded the maximum distance to the 50th closest user and traveled to the next sampling point outside of that buffer. This sampling strategy resulted in 79 data collection points across the city, many of which overlapped. The data were then smoothed using ArcGIS's kernel density tool (Esri) [11] to create a density map of app users. While Delaney's objectives were primarily descriptive, our study seeks to modify and leverage their sampling methods to estimate the spatial density of app users across Metro Vancouver and identify the independent and adjusted neighborhood-level factors that predict app user density. The latter of these 2 objectives has not yet been explored despite studies in other research contexts suggesting that neighborhood-level factors are related to the health and behavior of gbMSM [12,13].

Methods

Study Setting

This pilot study took place in Metro Vancouver, a regional district of British Columbia, Canada (see Figure 1). Metro Vancouver is a favorable location for examining the delivery of sexual health services as it offers a highly supportive environment for sexual minorities and for people living with HIV [14-16]. Since the late 1990s, the province has provided HIV medications and testing services free of charge, with much of the HIV treatment services being administered centrally by the British Columbia Centre for Excellence in HIV/AIDS [16]. Further, the province has led the way in several global initiatives, including the Joint United Nations Programme on HIV/AIDS 90-90-90 worldwide strategy for HIV prevention [17]. Further, Metro Vancouver is an ideal location to consider app use and the spatial variation in gender and sexual minority populations, as it has an active lesbian, gay, bisexual, and transgender (LGBT) community, evidenced by its hosting of an annual gay pride parade, several community-based organizations for lesbian, gay, bisexual, transgender, and queer people, gay bathhouses and bars, and other attractive amenities. Many of these attractions are in the downtown West End (Vancouver's historically gay neighborhood), however smaller municipalities such as New Westminster are also home to gay bathhouses and gay-owned businesses.

Data Collection

App User Density

Like Delaney et al [3], we used a popular geosocial networking app designed for gbMSM and primarily used by people looking for casual sexual partners, dates, or relationships [7]. While several similar apps exist—targeting a wide range of gbMSM subgroups—the app selected for our study was chosen because it is among the most popular apps for gbMSM [18]. When creating or editing their profile, users of this app can elect to provide a picture and headline for their profile, which is displayed in a grid alongside other users, organized by increasing Euclidian distance [19]. Only active or recently active (ie, within 1 hour) profiles are displayed. Tapping on each photo reveals volunteered information, composing a user's profile. Further, and of greatest relevance to this study, users are also asked whether they would like to grant access to their location data, which in turn is displayed to other users as real-time Euclidian distance [19]. We should note that the app used in this pilot study is not necessarily representative of all apps used by gbMSM, and we expect that future analyses will explore and compare the results from available platforms. Nevertheless, using this platform, we modified Delaney's data collection method by systematically sampling app users across a grid of predetermined data collection points throughout Metro Vancouver (see Figure 2). The first collection point was selected randomly from a location in Metro Vancouver, and the grid was created by calculating the coordinates for points at 2-mile intervals. Rather than physically traversing the city, as in Delaney et al [3], this approach allowed us to estimate app user density by putting the coordinates of each sampling location into our phone and then counting the number of profiles within a 1-mile radius of each sampling location. This distance was chosen because the app allows users to see the distance (in feet) of other app users up to a 1-mile radius, beyond which the distance of other users is measured with less precision (in miles). As we were only counting the number of users within each sampling radii, no data were collected from user profiles. Collection of other profile data was avoided as an extra precaution beyond traditional ethics guidelines due to the need for further ethical guidance on the use of internet-embedded, publicly available geotagged data for public health and research purposes [20].

As some users did not display their location on their profile, we did not count users who withheld their location and were listed on our screen such that it was unclear whether they were within 1 mile of our virtual sampling location (although we did count users without location information when their inclusion was unambiguous). Recognizing that the desire for greater privacy might vary spatially, this limitation has the potential to underestimate the number of users at some sampling locations (eg, where discreet users worry that they might be identified based on their location). In evaluating the extent to which this limitation impacted our results, we sampled 500 profiles across 5 spatially diverse sampling locations and found that 25.4% (127/500, range 19 to 32) of users did not provide location information. Of these, 5.5% (7/127, range 0 to 3) were listed such that their privacy settings made their inclusion ambiguous (ie, less or greater than 1 mile). The remaining 120 participants did not provide location information but were listed such that dichotomizing their location (eg, 1 mile or more, less than 1 mile) was not difficult (ie, they appeared earlier in the distance-ordered list of users than the farthest participant within 1 mile, thus indicating they resided within 1 mile).

As previous research has shown that app use is higher in the evening and on weekdays [21], data were collected between 5:45 pm and 11:00 pm, Monday through Wednesday, in the last week of November 2016. Dates were selected to represent a normal weekday (eg, no holidays or LGBT events). To further control for variance in use across time (ie, peak hours), we used a random number generator to randomize the order in which geographic locations were sampled. As users can access apps from anywhere (eg, work, home, bars, bathhouse), it is likely that some users access the app from multiple locations throughout their day or week; therefore, individuals were blocked so that they were not counted multiple times. When accessing the app platform, we used a blank profile and did not respond to private messages.

Figure 1. Study setting.

Figure 2. Sampling strategy for mapping app user density. Dotted line represents 1-mile radius around each sampling location. Numbers represent the order in which location was sampled.

Neighborhood Factors

Recognizing that social and demographic factors have previously been associated with app use [22-25], risky sexual behavior [4,26-29], and neighborhood residence among gay and bisexual men [28,30-32], selected sociodemographic variables for each dissemination area were derived from the 2016 Canadian Census using the Census Analyzer developed by Computing in the Humanities and Social Sciences at the University of Toronto. Additional information on this data source is available elsewhere [33]. Brief definitions for each variable included in our study are provided in Textbox 1. Selection of included variables was made based on their ubiquity in administrative datasets and scientific surveys, thus improving the reproducibility of our study [34]. Furthermore, measuring urbanity, gender, age, ethnicity, socioeconomic status, family situation, and immigration status, the selected variables represented a variety of factors which have regularly been associated with health-related outcomes [35-40].

Statistical Analysis

Spatial data were generated in ArcMap version 10.5 (Esri), and statistical modeling was conducted in R version 3.4.4 (The R Foundation). Bivariate and multivariable Poisson regression models were used to identify neighborhood-level factors associated with greater app user density. The spatial unit of analysis for this regression was the 1-mile sampling radius around each virtual sampling point. For each unit, app user density, rounded to the nearest integer, was calculated by dividing the number of app users observed at each sampling location by the land area within the 1-mile sampling radius. As explanatory variables were on the dissemination area level, we created a combined area and population-weighted average for each factor, which took into account the population size of each dissemination area as well as the proportion of the dissemination area within each sampling radius [41]. Final multivariable models were constructed by initially including all candidate variables of interest and then optimizing the Akaike information criterion (AIC) by backwards elimination. As our sampling method may have biased the app user density of location, we forced inclusion of an interaction term that controlled for time of day (ie, before 8 pm, 8 pm or later) and day of week (ie, Monday, Tuesday, or Wednesday). As a widely used variable selection method [42], particularly for exploratory analyses such as those conducted in our study, this backwards elimination procedure allowed us to identify the relatively best fitting statistical model achievable from our candidate variables, thus simultaneously improving the reproducibility of our study procedures and ensuring the optimal inclusion of candidate variables under conditions where closely related measures (eg, income and education) might limit model accuracy or performance. Comparing the final multivariable model to 1 including only population density and our time-day interaction term, we used a likelihood ratio test [43] and a Bonferroni outlier test [44], the latter of which allowed us to assess the relative performance of the models and detect geographic areas of interest with statistically unexpected app user densities.

Textbox 1. Definitions of census dissemination area level characteristics.

- Population density (per 100): total population of all persons living in each dissemination area divided by the land area of the dissemination area. Modeled as a per 100 resident increase in persons per km^2.
- Percentage of residents who are male: percentage of residents in each dissemination area who are male.
- Average age of male residents: average age of male residents in each dissemination area.
- Median income of male residents (per Can $1000 [US $1300]): median annual income of male residents in each dissemination area. Modeled as per Can $1000 increase in annual income.
- Percentage of male residents not married: percentage of male residents in each dissemination area who were not married and not living with a common-law partner, including those who were never married, separated, divorced, or widowed.
- Percentage of male residents with a postsecondary education: percentage of male residents in each dissemination area who have credentials beyond that of a high school diploma, including trade and apprenticeship certificates, college degrees, and university degrees.
- Percentage of male residents living below the low income cutoff (LICO) level: proportion of male residents in each dissemination area living below the Canadian Census Bureau’s LICO level (ie, those with after-tax income levels more than 20 percentage points below that required to afford food, shelter, and clothing in the dissemination area in which they reside).
- Percentage of males who are unemployed: percentage of male residents in each dissemination area who are unemployed.
- Percentage of male residents who are immigrants: percentage of male residents in each dissemination area who were born outside of Canada.
- Percentage of male residents who are visible minorities: percentage of male residents in each dissemination who are non-Caucasian in race or nonwhite in color and who are not indigenous.
- Average household size of residents: average number of persons who occupy the same dwelling unit and do not have a usual place of residence elsewhere in Canada or abroad.

Model fit was assessed using the McFadden likelihood-based pseudo r^2 and by reviewing other postmodel evaluation criteria (such as the distributions of residuals). The Office of Research Ethics at Simon Fraser University waived ethics approval, as we collected only publicly accessible data (ie, counted the number of profiles near each sampling location) and did not engage users.

Results

A total of 2021 app user profiles were counted within 1 mile of 263 sampling locations. Figure 3 presents the population density of each dissemination area, and Figure 4 presents the observed app user densities at each sampling buffer. Table 1 provides descriptive statistics for each dissemination area–level characteristic examined in our model and the bivariate associations with app user density.

In our simplified model examining the association between app user density and population density (controlling for time and day of sampling), each 100-person increase in population density was associated with a 6.2% increase in app user density (incidence rate ratio [IRR] 1.06, 95% CI 1.06-1.07). As suggested by an increase in model fit (pseudo r^2 .650 to .760), the results of a likelihood ratio test (P<.001), and a 4-fold reduction in the number of outliers (Figure 5) identified by a Bonferroni model outlier test (ie, 4 to 1), an AIC optimized model including all dissemination area characteristics of interest had superior performance relative to this population density–only model.

As shown in Table 2, this expanded model showed that app user density was positively associated with population density, average age of male residents, proportion of male residents who were not married, proportion of males with a postsecondary education, proportion of male residents who were immigrants, proportion of males living below the low income cutoff (LICO) level, and average household size of residents.

Figure 3. Population density of dissemination areas in Metro Vancouver, colored by quantiles.

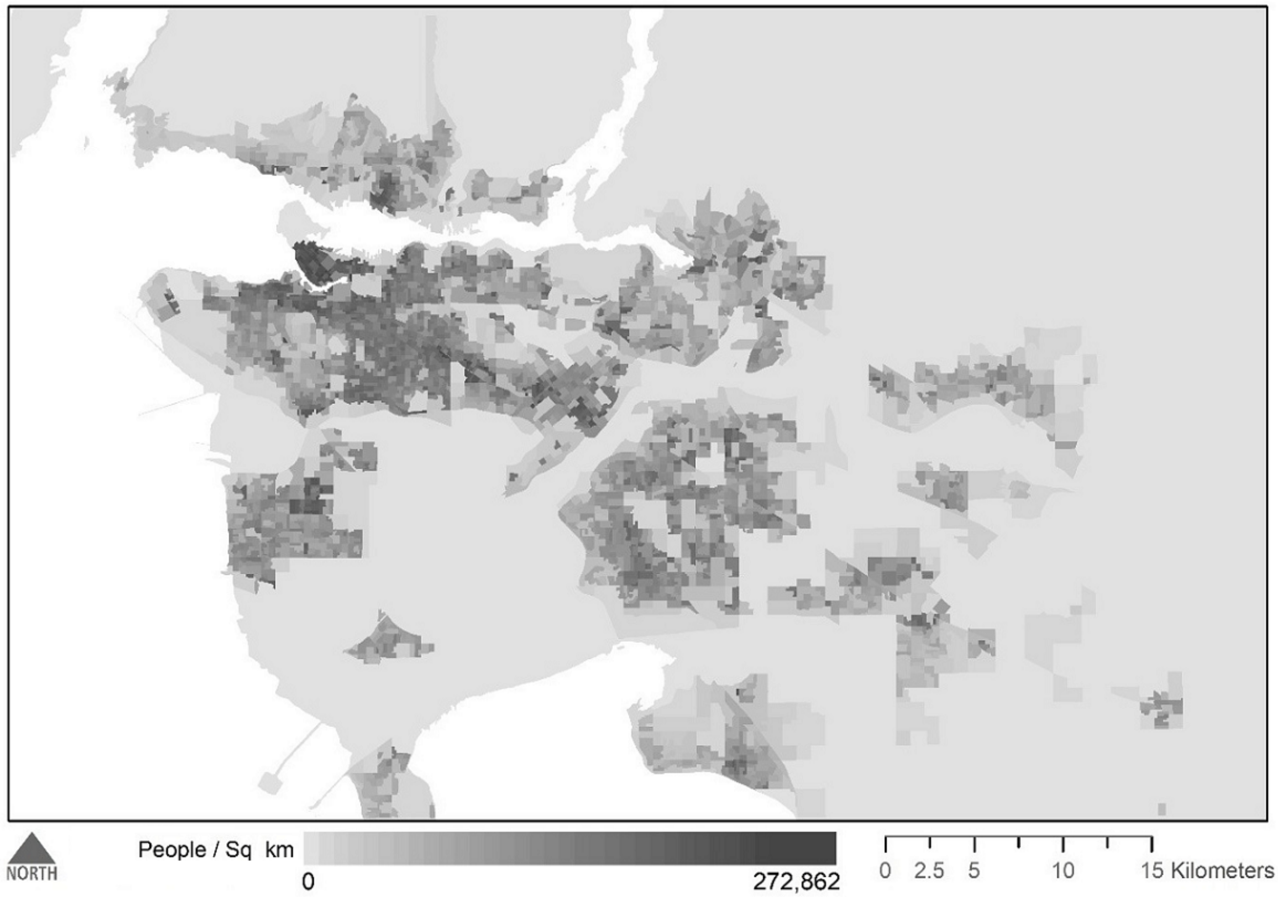

Figure 4. Observed density of app users, colored by natural breaks.

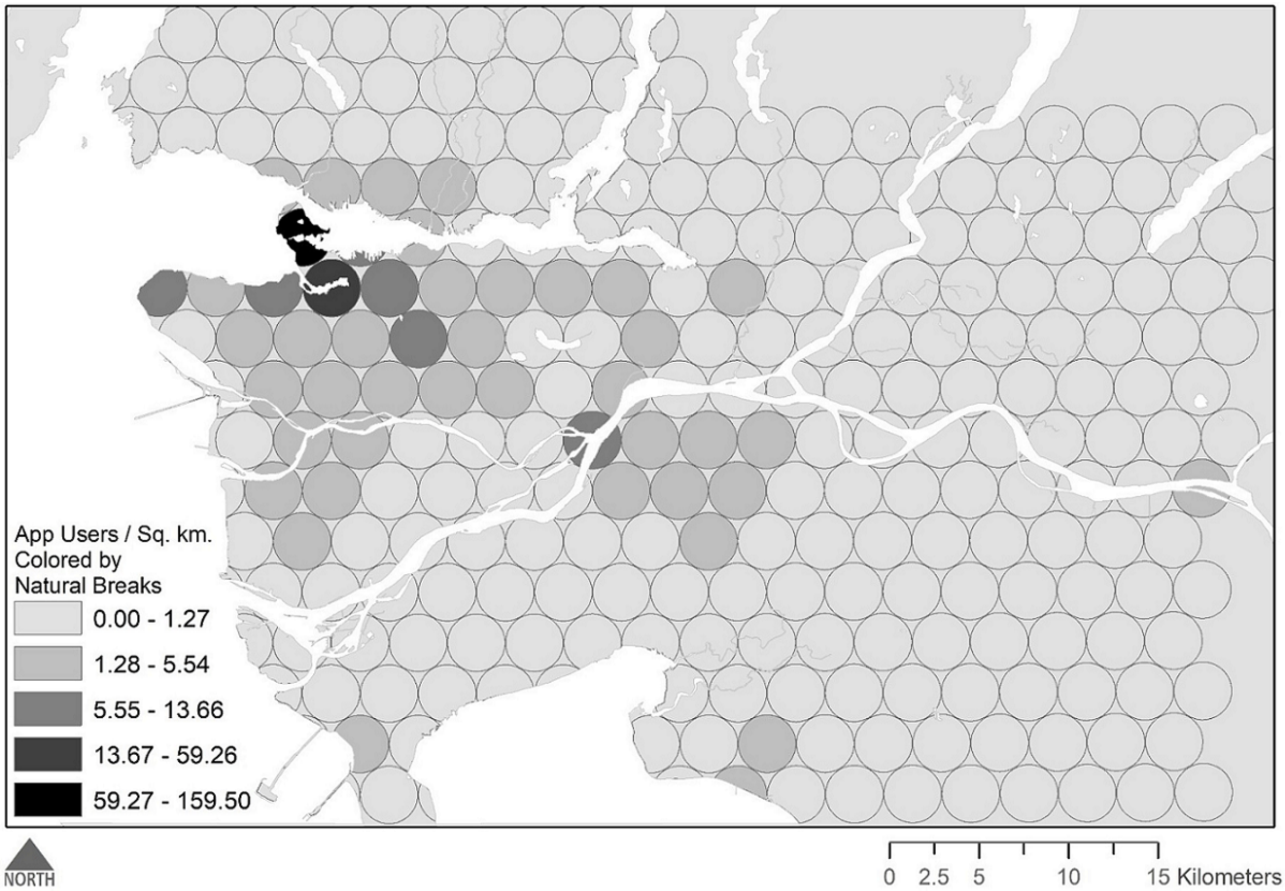

Table 1. Descriptive statistics and bivariate associations with app user density for areal population-weighted dissemination area–level characteristics.

2016 Census variable	Median (Q1-Q3)	*P* value
Population density (persons/km^2)	331.6 (59.2-1807.0)	<.001
Percentage of residents who are male	49.3 (48.6-50.5)	<.001
Average age of male residents (years)	41.1 (38.2-44.1)	.581
Median income of male residents (Can $)	48,567 (42,816-55,826)	<.001
Percentage of male residents not married	35.4 (30.9-40.5)	<.001
Percentage of male residents with a postsecondary education	57.6 (48.9-62.0)	<.001
Percentage of males who are unemployed	5.1 (3.4-6.1)	<.001
Percentage of male residents living below LICO[a] level	7.0 (4.9-11.1)	<.001
Percentage of male residents who are immigrants	27.2 (18.4-38.8)	<.001
Percentage of male residents who are visible minorities	26.0 (12.4-46.8)	<.001
Average household size of residents	2.8 (2.6-3.0)	<.001

[a]LICO: low income cutoff.

Figure 5. Model outliers in population density–only model (light and dark gray) and final multivariate model (dark gray only).

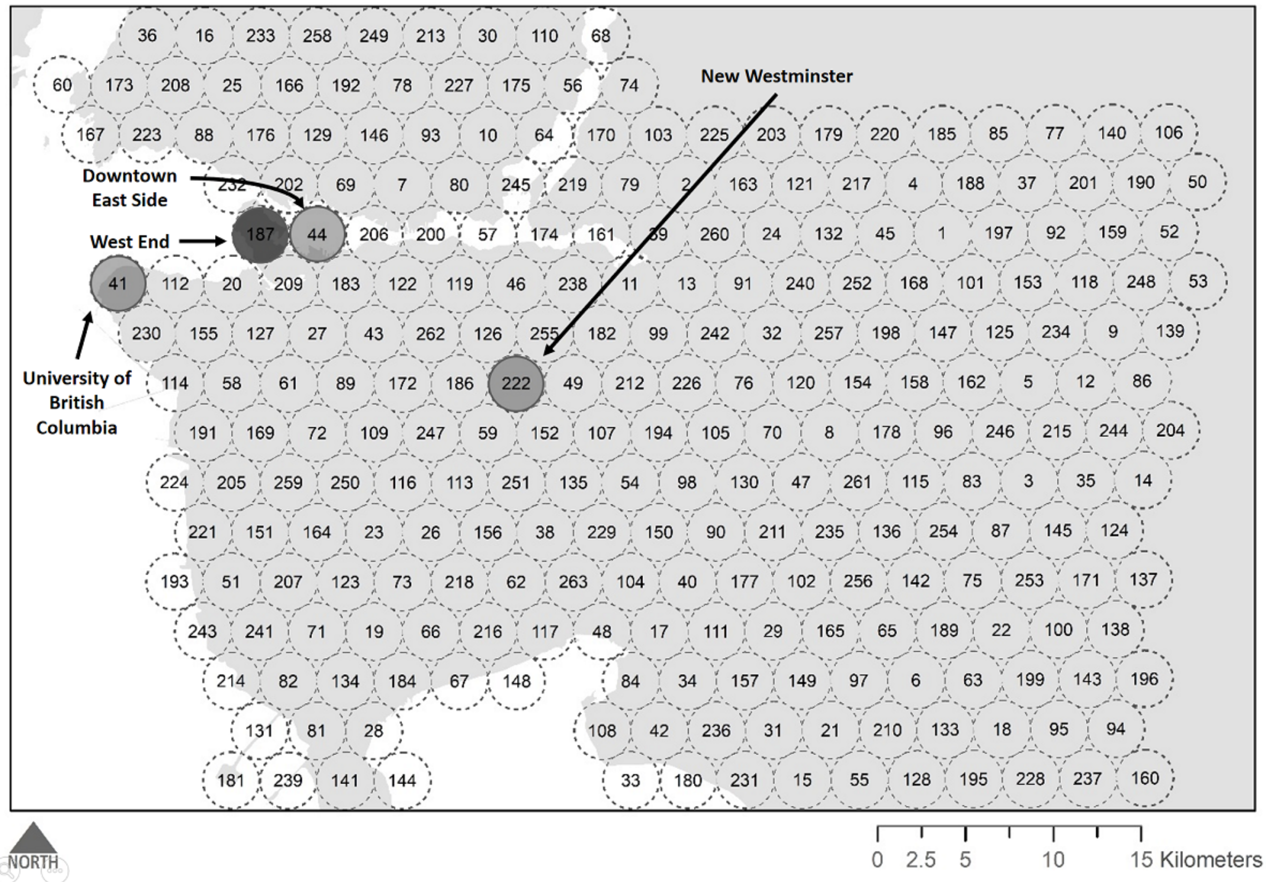

Table 2. Multivariate Poisson regression examining areal population-weighted dissemination area–level characteristics associated with sampling area app user density.

Variable	Incidence rate ratio (95% CI)
Population density (per 100)	1.03 (1.02-1.04)
Average age of male residents	0.93 (0.88-0.98)
Median income of male residents	0.96 (0.92-0.99)
Percentage of male residents living below LICO[a] level	0.93 (0.89-0.98)
Percentage of male residents with a postsecondary education	1.06 (1.03-1.10)
Percentage of male residents who are immigrants	1.04 (1.004-1.07)
Percentage of male residents not married	1.08 (1.02-1.13)
Average household size of residents	0.26 (0.11-0.62)
Sampling time	
Monday: before 8:00 pm	Reference
Monday: 8:00 pm or later	2.16 (1.24-3.83)
Tuesday: before 8:00 pm	2.00 (1.07-3.79)
Tuesday: 8:00 pm or later	2.28 (1.44-3.77)
Wednesday: before 8:0 pm	1.15 (0.44-2.67)
Wednesday: 8:00 pm or later	1.13 (0.67-1.94)

[a]LICO: low income cutoff.

Discussion

Principal Findings

Using a popular geosocial networking app designed for gbMSM, we sampled over 2000 profiles that were within 1 mile of 263 randomly selected sampling sites in Metro Vancouver, Canada. While our methodology extends those originally piloted by Delaney et al [3], this study is novel in its use of this approach to evaluate the relationship between app user density and other neighborhood-level factors. In doing so, this pilot study supports the use of geographic information systems in aiding public health specialists to understand the spatial distribution of app users. With that said, we acknowledge that the associations identified in our study may be the result of ecological fallacy. Addressing this possibility, we also recognize that several of the factors associated with app user density in this pilot study have also been shown to predict app use among gbMSM at the person level.

Beginning with the social geography of app use, we note that each 100-person increase in population density was associated with a 6% increase in app user density in unadjusted models and a 3% increase when accounting for other factors. Furthermore, we see in Figures 4 and 5 that app user density is dramatically higher in downtown Vancouver, particularly in the historically gay neighborhood of Davie Village. This, along with increased app user density in New Westminster (the location of several LGBT-friendly amenities including a gay bathhouse), shows that app user density tracks the distribution of other gay-centric amenities quite well, perhaps indicating that the social geography of online sex seeking has changed from the patterns observed earlier in the internet's history, when online sex seekers were more likely to identify as bisexual, be closeted, live outside major urban centers, and be disconnected from the gay community [45]. If true, these patterns agree with recent community-based research among gbMSM in Metro Vancouver that suggests that online sex-seeking gbMSM actually spend more time with other gbMSM and are equally as likely to participate in the gay community compared with those who do not seek sex online [46]. With that said, these findings should not be interpreted to mean that rural gbMSM do not use online venues. To do so would be to conflate app use with app user density, the latter of which being a composite measure that includes both the spatial distribution of gbMSM and the prevalence of app use among these men. As such, we note that previous studies have shown that rural men rely on internet-enabled technologies to connect with one another, particularly in rural localities where gbMSM are stigmatized [47]. Interpreted with respect to this, it is possible that app user density is higher in urban areas due to both a preference among gbMSM to live in these areas [48] and the increased motivation for app use proffered by greater opportunities to meet nearby partners [49-51]. Regarding the first hypotheses, we should comment that a growing body of literature has come to question unidirectional migration patterns (ie, from rural to urban) of LGBT people [6,52,53], and research regarding the latter highlights how different motivations for technology use (eg, to meet nearby partners for casual sex) may motivate urban MSM to specifically use apps. With these varied perspectives in mind, we acknowledge that the relationship between online sex seeking, identity, disclosure, and community connectedness remain important areas of study for the health and social sciences [54].

More squarely within the focus of our pilot study, we found that each 1% increase in the proportion of males who were not married and each 1-person increase in average household size were associated with a respective 8% increase and 74% decrease in app user density. The opposing effects here are consistent on face value: with increasing household size being negatively associated with an increasing proportion of residents who are married. Likewise, given that previous research has shown that the technographics of online dating are heavily biased toward single and nonmonogamous users [22], an increasing proportion of single residents in a given neighborhood is expectedly associated with increasing app user density.

As with measures assessing marital status and household size, the observation that each 1-year increase in the average age of the male population was associated with a respective 7% decrease in app user density is unsurprising. Again, the technographics of app use tend to skew toward young gbMSM [46,55]. Thus, neighborhoods with a greater proportion of young men (and a lower average age) would be expected to have more app users. However, again referring to Figures 4 and 5, we can see that the outliers identified by our pilot study included the sampling area in which the University of British Columbia is located. Underscoring this spatial observation, we also documented a 6% increase in app user density for each 1% increase in the proportion of males who had a postsecondary education. This finding too is supported by recent person-level research in Metro Vancouver that has shown an association between greater educational attainment and online sex seeking [22]. Likewise, studies have documented higher educational attainment among adult sexual minorities [56]. Together, these disparate findings are suggestive of nuanced interrelationships between residential location, app use, educational attainment, and age. However, these cannot be fully explained by our findings here and require additional research regarding the life course of gay and bisexual men.

Moving to other closely related sociodemographic measures, our study found that each 1% increase in the proportion of males who were living below the LICO level and each Can $1000 (US $1300) increase in the median income of males were associated with a 7% and 4% decrease in app user density, respectively. As these associations present seemingly contradictory findings, we should first point out that median income and the proportion of residents living below the LICO threshold represent considerably different neighborhood and household conditions despite both serving as measures of socioeconomic status [57]. Median incomes are the median total income residents receive throughout a year. LICO thresholds are the income levels in each dissemination area below which a household would devote at least 20% more than the average family would on basic necessities (ie, food, clothing, and shelter) [58]. An increasing proportion of people living below LICO thresholds can indicate an increasing proportion of impoverished residents as well as an increasing cost of living in a given neighborhood. Therefore, the negative associations between app user density and these 2 measures may indicate that app user density is lower in both cash-strapped neighborhoods (regardless of overall income levels) and those where incomes are depressed. In either case, these trends may be associated with greater constraints placed on the time of residents or attributable to differing lifestyles of residents in these neighborhoods. Supporting this interpretation, previous research examining the association between individual income and app use found that app use on weekdays (during which this study was conducted) is associated with having lower income [21]. As such, caution should be taken when interpreting these findings, as patterns of app user density on weekends might eliminate or reverse this association. In any case, further qualitative research may be needed to understand how app use, neighborhood residence, and socioeconomic status relate to one another.

The same is likely true regarding the final measure included in our multivariable model. Indeed, as is often the case with research addressing multiple intersecting identities [59], to our knowledge little attention has been specifically devoted to the diverse phenomenon of app use among immigrant gbMSM or those living in semisegregated immigrant neighborhoods [60], yet in our study we found that each 1% increase in the proportion of males who were immigrants was associated with a 4% increase in app user density. It is possible that immigrants rely on apps as ways to connect with other gay men, perhaps due to the lack of LGBT venues available to them in ethnically segregated neighborhoods [61] or, alternatively, due to their desire to explore their sexuality discreetly [60]. In either case, this association highlights the importance of diversifying sexual health services and ensuring that they are accessible to those living outside traditional gay villages that often have the reputation of being for wealthy, white, gay men and their straight allies [62,63].

Implications

Given the findings outlined, future studies are needed to assess the generalizability of these piloted methods and determine the generalizability of these results outside Metro Vancouver. Laying groundwork for such a validation, our pilot study provides a proof of concept for methods that might be used by public health leaders to optimize the delivery and focus of HIV prevention services by targeting populations at elevated risk for HIV transmission using administrative and geotagged data. While we are not aware of any studies that have leveraged this type of data to improve the delivery of HIV services (ie, location of new services, mobile testing vans) to high-risk neighborhoods, some work has shown that administrative data can be used to identify neighborhoods at risk for other adverse health outcomes [26]. Combining spatial data from various sources (such as dating apps) with administrative data may, therefore, provide an important opportunity for knowledge translation in the context of sexual health, allowing providers to deliver health care services to at-risk neighborhoods. This is especially true for jurisdictions that have invested in mobile testing services [64], online-initiated testing services [65], or other flexible health promotion programs. Further, by planning HIV care using a neighborhood-level perspective [66], public health and community leaders can better justify support for targeted interventions that can address the varied context-specific needs and concerns of local communities [4].

Limitations

That said, the findings discussed are limited by several potential biases. First, and perhaps most importantly, readers should be aware that sociodemographic census-level factors may not reflect the characteristics of the app users sampled here. Second, because our explanatory variables are averaged across several dissemination areas, the accuracy of our estimates may be limited. However, because dissemination areas are administrative boundaries that are not necessarily reflective of the natural gradation of the characteristics, it is unclear to what extent these units might have biased our results. Future studies should employ a more purposeful sampling design that might better capture app user density within natural communities. Third, our data do not describe from where sampled users are accessing apps (eg, from bars or their home). Therefore, the data generated for this study do not necessarily reflect the residential location of gbMSM but rather where they use the apps on a typical weekday evening. Importantly, while the time and days selected for sampling were purposeful, the effects of sampling error may introduce bias into our study design. To account for this, we randomly assigned the order in which location points were sampled. However, it is still possible that temporal patterns of app use vary by some nonrandom factor (eg, daily routines). Indeed, it is not entirely clear how patterns of app use might vary across the day or week. Future analyses should explore these temporal patterns to determine why and to what degree app use varies across time and under what conditions gbMSM use apps. Fourth, this study was conducted using only a single app. While the app we selected is among the most popular apps for gbMSM [18], few studies have examined differences between apps that are targeted to and as a result taken up by specific subcultures or subgroups within the gay community. It is therefore possible that the spatial density of app users is reflective of only a subset of gbMSM who use apps to find sexual partners. Future work should investigate whether our results are reproducible with other apps such as those targeting older men, ethnic minority men, or men interested in “kink.” That said, previous research has shown that there is a large amount of overlap in the apps used by gbMSM. For instance, 1 study reported a median number of apps per user as 3.11 [21]. Fifth, as our multivariable model had a pseudo r^2 of .76, omitted variables not accounted for in this study may also affect app user density. These likely include factors that are difficult to measure using administrative data or are at least rarely measured in these data sources, such as sexual orientation, prevalence of HIV, the social climate toward sexual minorities in a given neighborhood, or a person’s ability to meet sexual partners via other venues. Similarly, our models have yet to be validated for other settings and given that they were developed as exploratory, proof-of-concept models, further research is needed before these or similar models are used authoritatively to inform the deployment of health resources. Therefore, future studies should seek out other datasets and data sources from which models might be derived, thus providing a more complete and empirically valid picture of the ecological factors associated with app user density (eg, male population density vs general population density, same-sex households).

Conclusions

Findings from this pilot study highlight the potential utility of using geographic information systems to better understand the spatial density of gbMSM, particularly among those who use geosocial networking apps and live in urban settings. While additional analyses are needed to validate the modeling techniques explored here and understand the impact of various sampling decisions (eg, time of day, choice of app provider), our findings suggest that these methods may be useful for public health and community leaders hoping to better understand the communities of gbMSM they serve.

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Conflicts of Interest

None declared.

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Abbreviations

AIC: Akaike information criterion
gbMSM: gay, bisexual, and other men who have sex with men
IRR: incidence rate ratio
LGBT: lesbian, gay, bisexual, and transgender
LICO: low income cutoff

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Original Paper

Overlap of Asthma and Chronic Obstructive Pulmonary Disease in Patients in the United States: Analysis of Prevalence, Features, and Subtypes

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Abstract

Background: Although asthma and chronic obstructive pulmonary disease (COPD) are clinically distinct diseases, they represent biologically diverse and overlapping clinical entities and it has been observed that they often co-occur. Some research and theorizing suggest there is a common comorbid condition termed asthma-chronic obstructive pulmonary disease overlap (ACO). However, the existence of ACO is controversial.

Objective: The objective of this study is to describe patient characteristics and estimate prevalence, health care utilization, and costs of ACO using claims-based diagnoses confirmed with medical record information.

Methods: Eligible patients were commercial US health plan enrollees; ≥40 years; had asthma, COPD, or ACO; ≥3 prescription fills for asthma/COPD medications; and ≥2 spirometry tests. Records for a random sample of 5000 patients with ACO were reviewed to validate claims-based diagnoses.

Results: The estimated ACO prevalence was 6% (estimated 10,250/183,521) among 183,521 full study patients. In the claims-based cohorts, the comorbidity burden for ACO was greater versus asthma but similar to COPD cohorts. Medication utilization was higher in ACO versus asthma and COPD. Mean total health care costs were significantly higher for ACO versus asthma but similar to COPD. In confirmed diagnoses cohorts, mean total health care costs (medical plus pharmacy) were lower for ACO versus COPD but similar to asthma (US $20,035; *P*=.56). Among confirmed cases, where there was medical record evidence, smoking history was higher in ACO (300/343, 87.5%) versus asthma cohorts (100/181, 55.2%) but similar to COPD (68/84, 81%).

Conclusions: ACO had more comorbidities, medication utilization, and costs than patients with asthma or COPD but differences were not seen after confirmation with medical records.

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KEYWORDS

COPD; asthma; asthma-COPD overlap; ACO; claims data; medical records; diagnosis validation

Introduction

Obstructive lung disease is a significant public health problem. Combined, airway diseases such as asthma and chronic obstructive pulmonary disease (COPD) affect up to 15% of adults in the United States, cause more than a million hospitalizations, and over 15 million lost work days [1]. The global effects of combined asthma and COPD are even more dramatic—300 million people are affected by COPD, and up to 300 million by asthma. COPD, the third leading cause of death worldwide, is associated with an estimated 3 million deaths per year, and asthma with 200,000 deaths per year [2].

Although asthma and COPD are clinically distinct diseases, they represent biologically diverse and overlapping clinical entities. Clinicians have been studying asthma and COPD in relation to each other for more than half a century, since the formulation of the Dutch hypothesis in 1961 [3,4]. Asthma and COPD overlap [5] commands considerable attention and is discussed comprehensively in guidelines such as the Global Initiative for Asthma [6] and the Global Initiative for Lung Disease for COPD [7].

Asthma-COPD overlap (ACO; previously referred to as asthma-COPD overlap syndrome) is characterized by persistent airflow limitation consistent with COPD, together with several distinguishing features of asthma [7]. Prevalence estimates for ACO range from 5.5% to 55% [8-14] and the large discrepancy islikely attributable to differences in diagnostic criteria for asthma and COPD [5] and other factors, including age and gender [15]. Despite a growing body of literature, no standard exists to identify the syndrome and there is no consensus definition [16]. The result is a mixed picture of overlapping symptoms, patient characteristics, and comorbidities not reliably differentiated from asthma and COPD [17].

The literature suggests that, compared with asthma or COPD, ACO is associated with more rapid decline in lung function, more frequent exacerbations, increased health care resource utilization, worsening quality of life, and higher mortality rates [16,18,19]. This profile, however, relies on diversely defined populations and prevalence estimates [15,17,20] and might have dubious diagnostic utility.

The treatment responses of patients with ACO could be important for clinical decisions, suggesting potential value in additional, more precise characterization of this disease entity [5,15]. Little epidemiologic research has critically evaluated patterns of clinical diagnosis using the commonly used overlapping International Classification of Diseases, Ninth Revision (ICD-9) code patterns for asthma and COPD which can suggest possible ACO, indicating an important gap in knowledge. Such patterns of diagnosis might provide additional clues to better characterize the disease entity. A better understanding of the features of ACO might lead to improved diagnosis and treatment of this entity and improvements in public health for those patients affected by airways disease

Respiratory diseases, notably asthma and COPD, have resulted in immense clinical and economic challenges for public health [21,22]. Health services vigilantly investigate and seek to understand the epidemiological trends of respiratory diseases in the US, historically striving to maintain a state of readiness to respond [23-25]. While infectious respiratory conditions remain a major concern, changing environmental conditions and stresses from expanding industrial, military, and agricultural activities require greater vigilance and laboratory, hospital, and rehabilitation resources. Increasingly prevalent and worsening asthma and COPD, and by extension ACO, could strain the clinical and financial resources of public health services in the US and globally [26]. Better characterization and more accurate diagnosis will help in in the management of ACO, and in the development of better preventive public health strategies to decrease the impact of this clinical entity.

To help to address this gap in knowledge about ACO, this medical record based observational study employed a more rigorous research design—stricter inclusion criteria, plus confirmation of ICD-9 code-based identification of ACO with medical record review—than prior similar claims-based studies. The objective was to estimate the prevalence of ACO in a population of asthma or COPD patients, and describe patterns using an enhanced dual identification approach. Additionally, this study sought to describe medication utilization and health care costs of patients with ACO compared to patients with only asthma or COPD.

Methods

Data Source

Data were queried from the HealthCore Integrated Research Database, a single payor health insurance repository of administrative claims data for approximately 43 million members at the time of study. Applicable regulations and the Health Insurance Portability and Accountability Act were followed strictly; the study was approved by the New England Institutional Review Board.

Study Design and Patient Population

This retrospective cohort study used administrative claims data and medical record reviews between January 1, 2006 and October 31, 2015 (see Multimedia Appendix 1). The index date (first date patients met inclusion criteria) occurred during the intake period, which was between 1 January 2007 and 31 October 2014. Study patients were health plan members, ≥40 years old on index date, and with 12 months pre- and postindex health plan eligibility. Three cohorts were examined (asthma, COPD, or ACO) based on having (1) ≥2 diagnoses (≥30 days apart) for asthma (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 493) or COPD (ICD-9 CM codes 491, 492, and 496), (2) ≥2 procedure codes (≥30 days apart) for asthma-related or COPD-related procedures, (3) ≥3 Generic Product Identifier (GPI)-defined prescription fills (≥30 days apart) for asthma or COPD medication, and (4) ≥2 Current Procedural Terminology codes for spirometry tests. Asthma- and COPD-only cohorts had neither diagnostic nor procedure codes for the other disorder. Patients meeting criteria for both asthma and COPD constituted the claims-positive ACO cohort. Patients with a preindex cancer diagnosis were excluded.

Medical Record Review

ACO was confirmed for the purposes of this study by medical record review of 5000 randomly selected claims-positive patients with ACO during 2015-2016, whose outpatient records were abstracted using a standardized form. COPD was confirmed by persistent airflow obstruction (forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] less than 0.70) at symptom baseline. Positive computed tomography documentation of emphysema was not required but considered supportive of COPD diagnosis. Medical record confirmation of asthma included any two of the following: allergic rhinitis, chronic sinusitis or eczema, positive skin test or desensitization to environmental allergens, medical history of asthma before age 40 years, or family history of asthma [16]. Smoking status was assessed by medical record review. Patients with medical record features consistent with COPD or asthma as described above we considered to have medical record "confirmed" diagnoses of these disorders, and those with medical record features of both COPD and asthma were considered to have "confirmed ACO" Spirometry criteria for reversibility were not used because reversibility has been shown to occur with COPD as well as asthma, so therefore cannot be used to differentiate COPD from asthma [27].

Outcome Measures

Demographic variables were measured on the index date. The Deyo-Charlson Comorbidity Index (DCI) [28] score provided a baseline of illness burden. Smoking history was determined from Current Procedural Terminology codes for tobacco cessation counseling (99406, 99407) and use disorder (ICD-9-CM 305.1; V1582). Asthma and COPD medication utilization was assessed with GPI codes. All-cause medical and pharmacy costs were assessed for the 12-month post-index period. Total health care costs included inpatient, emergency department, outpatient, and pharmacy expenditures. Costs were adjusted to 2016 values using the consumer price index for US medical care services [29].

Statistical Analysis

The study population was characterized with descriptive statistics. Frequencies and percentages were reported for categorical variables; means, medians, and standard deviations for continuous variables. Correspondence analysis was conducted to graphically describe the overlap of asthma and COPD ICD-9 codes with medical records [30-32]. Correspondence analysis is conceptually similar to principal component analysis, but applies to categorical rather than continuous data. In a similar manner to principal component analysis, it provides a means of displaying or summarizing a set of data in two-dimensional graphical form. Comparisons among cohorts for response measures were conducted using paired-comparison *t* tests for continuous variables or *Z* tests for percentage differences for categorical variables. Generalized linear model analyses (GLM) using a log link with gamma distribution were used for cost analyses. The GLM is a flexible generalization of ordinary linear regression that allows for response variables that have error distribution models other than a normal distribution. The GLM generalizes linear regression by allowing the linear model to be related to the response variable via a link function and by allowing the magnitude of the variance of each measurement to be a function of its predicted value. Alpha was set at .05, 2-sided, for statistical significance.

Results

Overview

A total of 2,219,034 patients had ≥1 claim for asthma and/or COPD; of those, 20,459 met the inclusion and exclusion criteria and had claims-positive ACO; similarly, 17,156 had claims-positive COPD; and 145,906 had claims-positive asthma (see Multimedia Appendix 1).

Prevalence

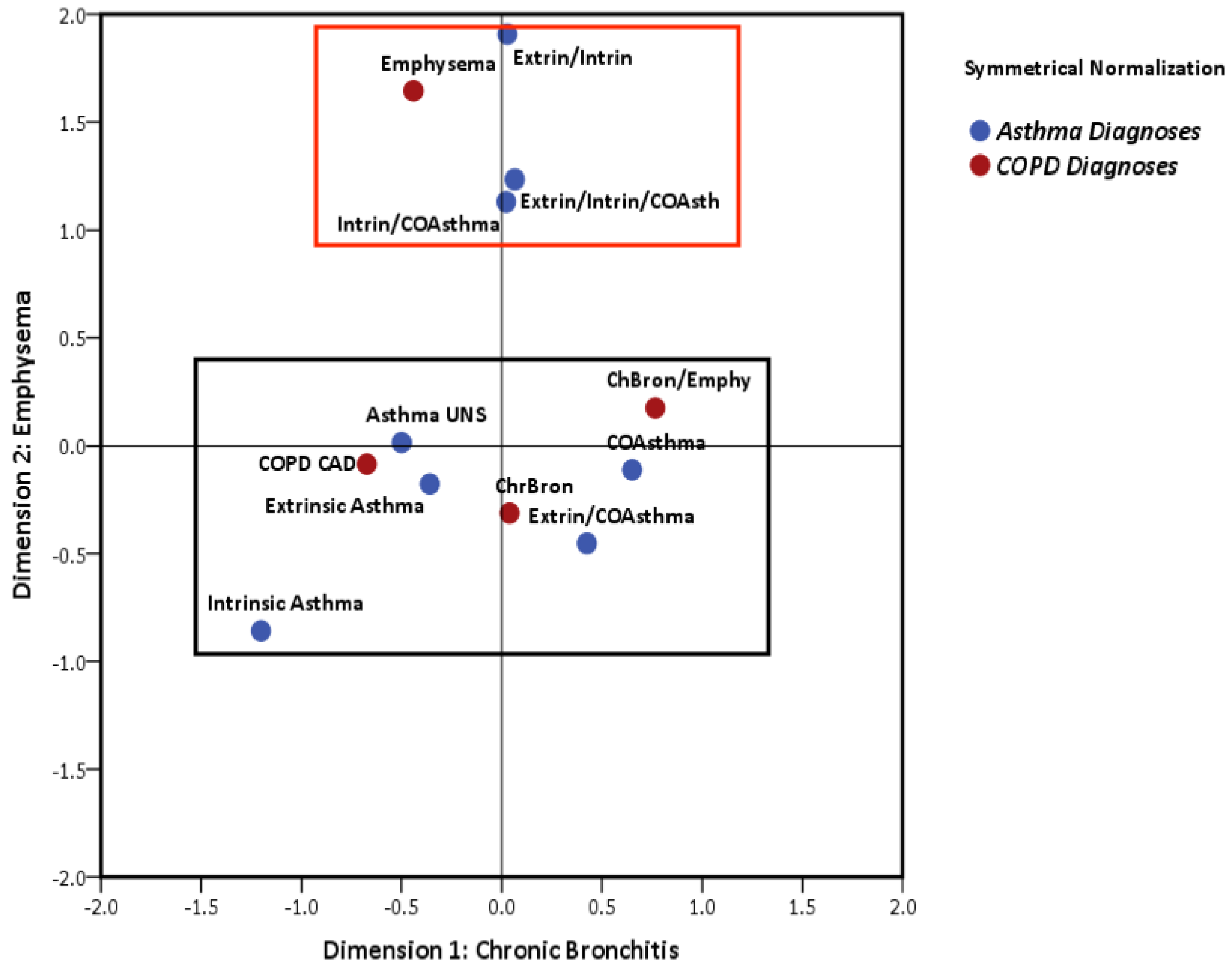
Of the 5000 ACO patients randomly selected for medical record review, 3038 were excluded because of missing records, providers not located, or providers not complying with requests. From the 1962 available records, 1181 were excluded because of absent spirometry results or FEV_1/FVC values. The remaining 781 successful medical record reviews confirmed ACO in 391 (50.1%) of the patients; 206 (26.4%) with confirmed asthma only; and 106 (13.6%) with confirmed COPD only (see Multimedia Appendices 1 and 2). A total of 78 patients were excluded from analyses as their medical records supported neither an asthma nor COPD diagnosis. We assumed that the proportions of confirmed ACO diagnoses would be similar for patients with medical record reviews compared to study patients overall. Extrapolating the 50.1% ACO confirmation rate to the full claims-positive ACO cohort (20,459 patients) yielded 10,250 patients meeting the confirmation criteria. Dividing this numerator (10,250 patients) by the total number of patients found with ≥1 criterion for asthma or COPD (183,521 patients) resulted in an estimated ACO prevalence of approximately 6%.

Description of Overlapping Asthma and Chronic Obstructive Pulmonary Disease Diagnoses

Most confirmed ACO patients had several overlapping asthma diagnoses; however, the only overlapping COPD ICD-9 code diagnoses were chronic bronchitis and emphysema (see Multimedia Appendix 3). The most common cross ACO ICD-9 codes were chronic bronchitis mixed with chronic obstructive asthma (51/391, 13.0%), COPD chronic airway disorder occurring with unspecified asthma (50/391, 12.8%), chronic bronchitis comorbid with unspecified asthma (49/391, 12.5%), and patients with both COPD chronic bronchitis and COPD emphysema, as well as chronic obstructive asthma (46/391, 11.8%).

Correspondence analysis confirmed the ACO population. The χ^2 value was 55.08 (*P*<.001), indicating significant cross-asthma-COPD diagnostic patterns. A 2-dimensional solution accounted for 51.1% of the total variance; dimension 1 for 29.1% and dimension 2 for 22% of total variance (Figure 1). Of the COPD ICD-9 diagnoses codes, chronic bronchitis, chronic airway disease (CAD), and comorbid chronic bronchitis and emphysema diagnoses occurred most frequently; and chronic bronchitis was the most central to the COPD code for the primary cluster of patients. CAD and comorbid chronic bronchitis and or emphysema patterns occurred together less frequently; the codes were about two standard deviations apart. Frequently occurring overlapping asthma symptoms included extrinsic asthma, both unspecified and chronic obstructive forms, also reflecting substantial variation (Figure 1), and heterogeneity in dual diagnosis patterns within ACO. Dimension 2 defined a distinct set of codes comprising multiple mixed asthma diagnoses and emphysema, while differentiating a group of infrequent joint diagnoses with little in common with core ACO characteristics. Few patients (6.1%) were captured in the second cluster.

Figure 1. Correspondence analysis biplot of ICD-9-CM subtypes of ACO condition patients. The x- and y-axes are in z-scale metric. Rectangles define two distinct dimensions of patients. The black rectangle encapsulates the historical view that chronic bronchitis is most central to the condition. Note there is variation along x-axis indicating within cluster heterogeneity. The red rectangle captures a distinct dimension that is 1.5 SD distance from the core cluster. This cluster is comprised of multiple mixed asthma diagnoses and emphysema. Overall, there is substantial symptom variation within the ACO condition. Intrin: intrinsic asthma; Extrin: extrinsic asthma; COA: chronic obstructive asthma; Asthma UNS: asthma unspecified; Emphy: COPD emphysema; ChBron: COPD chronic bronchitis; COPD CAD: COPD chronic airway obstruction.



Cohort Characteristics and Comorbid Illnesses

A comparison of the mean ages of the claims-based cohorts suggested ACO patients were older (68.4 years, SD 11.4) than asthma patients (53.4 years, SD 9.5) but similar to those with COPD (67.0 years, SD 10.8). In the confirmed cohorts, all groups were of similar age: ACO (68.2 years, SD 11.0), COPD (71.4 years, SD 9.3), and asthma (67.9 years, SD 11.1). Women were the majority in the claims-positive cohorts for both ACO (13,155/20,459, 64.30%) and asthma (99,362/145,906, 68.10%), but not for COPD (8012/17,156, 46.70%). This difference was not observed in the confirmed cohorts with women being the majority in all groups (ACO 232/391, 59.3%; COPD 62/106, 58.5%; and asthma 148/206, 71.8%).

Comorbidity severity (DCI scores) was similar in the claims-positive ACO and COPD cohorts (mean DCI 1.5 for both cohorts, SD 1.7; *P*=.87), but higher than the claims-positive asthma cohort (mean DCI 0.4, SD 0.9; *P*<.001; Tables 1 and 2). In the confirmed diagnosis cohorts, however, comorbidity severity was lower for ACO (mean DCI score 1.3, SD 1.5) versus the COPD cohort (mean DCI score 1.9, SD 2.0; *P*=.007), but similar to the asthma cohort (mean DCI score 1.5, SD 1.6; *P*=.11).

Smoking History

Smoking was significantly less common in the claims-positive ACO cohort (4133/20,459, 20.2%) versus the COPD cohort (5215/17,156, 30.40%; *P*<.001) but more common than in the claims-positive asthma cohort (6128/145,906, 4.20%; *P*<.001; Tables 1 and 2). No significant difference was seen among the confirmed diagnosis cohorts for claims-assessed smoking: ACO (90/391, 23%) and asthma (35/206, 17.0%; *P*=.27) and COPD (26/106, 24.5%; *P*=.68) cohorts. The difference between the confirmed asthma and confirmed COPD cohorts was statistically significant (*P*=.047). Among the chart reviewed subjects, there was no information on previous or current smoking behavior for 25/206 (12.1%) confirmed asthma cases, 22/106 (20.8%) confirmed COPD cases, and 48/391 (12.3%) confirmed ACO cases. Therefore, the denominators for chart reviewed smoking behavior was 181 for confirmed asthma, 84 for confirmed COPD, and 343 for confirmed ACO.

Table 1. Demographic characteristics and comorbidities for the claims positive cohort.

Demographics	Asthma (n=145,906)	COPD[a] (n=17,156)	ACO[b] (n=20,459)	*P* value		
				Asthma vs ACO	COPD vs ACO	Asthma vs COPD
Age (years), mean (SD)	53.4 (9.5)	67.0 (10.8)	68.4 (11.4)	<.001	<.001	<.001
Female, n (%)	99,362 (68.1)	8012 (46.7)	13,155 (64.3)	<.001	<.001	<.001
Comorbidity						
DCI[c], mean (SD)	0.4 (0.9)	1.5 (1.7)	1.5 (1.7)	<.001	.86	<.001
Smoking						
Claims-assessed, n (%)	6128 (4.2)	5215 (30.4)	4133 (20.2)	<.001	<.001	<.001

[a]COPD: chronic obstructive pulmonary disease.

[b]ACO: asthma-COPD overlap.

[c]DCI: Deyo-Charlson Comorbidity Index.

Table 2. Demographic characteristics and comorbidities confirmed diagnosis cohort (based on the random sample of 5000 patients randomly drawn for the claims-positive asthma-chronic obstructive pulmonary disease [COPD] overlap [ACO] cohort).

Demographics	Asthma (n=206)	COPD (n=106)	ACO (n=391)	*P* value		
				Asthma vs ACO	COPD vs ACO	Asthma vs COPD
Age (years), mean (SD)	67.9 (11.1)	71.4 (9.3)	68.2 (11.0)	.69	.003	.003
Female, n (%)	148 (71.8)	62 (58.5)	232 (59.3)	.003	.88	.017
Comorbidity						
DCI[a], mean (SD)	1.5 (1.6)	1.9 (2.0)	1.3 (1.5)	.11	.007	.10
Smoking						
Claims-assessed, n (%)	35 (17)	26 (25)	90 (23)	.27	.68	.047
Chart-assessed, n (%)	100 (55.2)[b]	68 (81)[c]	300 (87.5)[d]	<.001	<.001	<.001
Not documented[e], n (%)	25 (12.1)	22 (20.8)	48 (12.3)	.67	.001	.001

[a]DCI: Deyo-Charlson Comorbidity Index.

[b]n=181.

[c]n=84.

[d]n=343.

[e]Smoking not documented in medical record.

Thus, the medical record data indicated the confirmed ACO cohort (300/343, 87.5%) had significantly higher percentage of past or present smoking than the confirmed COPD (68/84, 81%; *P*<.001) and confirmed asthma cohorts (100/181, 55.2%; *P*<.001). A significantly greater proportion of patients in the confirmed COPD cohort had a history of smoking, compared with the confirmed asthma cohort (*P*<.001).

Medication Utilization

Use of asthma and COPD medications was higher among patients in the claims-positive ACO cohort compared with patients in the claims-positive asthma and COPD cohorts (Tables 3 and 4). The only exceptions were the use of long-acting muscarinic antagonists (LAMA), which was higher in the claims-positive COPD (6391/17,156, 37.25%) cohort than in the ACO cohort (6138/20,459, 30.0%; *P*<.001), and long-acting beta2-agonists (LABA) were higher in the COPD cohort (635/17,156, 3.7%) compared to ACO (716/20,459, 3.5%; *P*=.04). Inhaled corticosteroid (ICS) use was not statistically significantly different between the claims-positive asthma and claims-positive ACO cohorts (25,242/145,906; 17.3% vs 3805/20,459; 18.6%; *P*=.09). The claims-positive COPD and ACO cohorts had similar use of short-acting beta-agonist and short-acting muscarinic antagonists (SABA/SAMA; 2728/17,156; 15.9% vs 3110/17,156; 15.2%, respectively; *P*=.76) and SAMA (652/17,156; 3.8% vs 859/20,459; 4.2%, respectively; *P*=.32). In contrast, asthma and COPD medication use was largely similar among patients in the confirmed ACO cohort compared with the confirmed asthma and COPD cohorts (Tables 3 and 4). Compared with the confirmed ACO cohort, the confirmed asthma cohort had lower use of ICS/LABA (59.6% vs 44.7%, respectively; *P*=.001), LAMA (34.0% vs 18.0%, respectively; *P*<.001), SABA/SAMA (18.4% vs 11.2%, respectively; *P*=.02), and LABA (4.6% vs 1.5%, respectively; *P*=.01). Only the use of LAMA was lower in the confirmed ACO cohort compared with the confirmed COPD cohort (34.0% vs 44.3%, respectively; *P*=.05), and only ICS use was higher in the confirmed ACO cohort than in the confirmed COPD cohort (21.2% vs 12.3%, respectively; *P*=.04).

Table 3. Chronic obstructive pulmonary disease (COPD) or asthma medication use during the 12-month follow-up period for the claims positive cohort.

Asthma or COPD medication	Asthma (n=145,906), n (%)	COPD (n=17,156), n (%)	ACO[a] (n=20,459), n (%)	*P* value[b]		
				Asthma vs ACO	COPD vs ACO	Asthma vs COPD
SABA[c]	82,583 (56.6)	7463 (43.5)	12,337 (60.3)	<.001	<.001	<.001
OCS[d]	51,067 (35.0)	7377 (43.3)	11,518 (56.3)	<.001	<.001	<.001
ICS[e]/LABA[f]	49,024 (33.6)	6554 (38.2)	11,191 (54.7)	<.001	<.001	<.001
LTRA[g]	39,103 (26.8)	926 (5.4)	5729 (28.0)	.001	.001	<.001
ICS	25,242 (17.3)	1269 (7.4)	3805 (18.6)	.091	<.001	<.001
SABA/SAMA[h]	3648 (2.5)	2728 (15.9)	3110 (15.2)	<.001	.76	<.001
LABA	3210 (2.2)	635 (3.7)	716 (3.5)	<.001	.04	.01
LAMA[i]	1605 (1.1)	6391 (37.2)	6138 (30.0)	<.001	<.001	<.001
SAMA	1167 (0.8)	652 (3.8)	859 (4.2)	<.001	.32	<.001

[a]ACO: asthma-COPD overlap.

[b]Significance calculated using a *Z* test for differences in column proportions.

[c]SABA: short-acting beta2-agonist.

[d]OCS: oral corticosteroid.

[e]ICS: inhaled corticosteroid.

[f]LABA: long-acting beta2-agonist.

[g]LTRA: leukotriene receptor antagonist.

[h]SAMA: short-acting muscarinic antagonist.

[i]LAMA: long-acting muscarinic antagonist.

Table 4. Chronic obstructive pulmonary disease (COPD) or asthma medication use during the 12-month follow-up period for the confirmed diagnosis cohort (based on the random sample of 5000 patients randomly drawn for the claims-positive asthma-COPD overlap [ACO] cohort).

Asthma or COPD medication	Asthma (n=206), n (%)	COPD (n=106), n (%)	ACO (n=391), n (%)	*P* value[a]		
				Asthma vs ACO	COPD vs ACO	Asthma vs COPD
SABA[b]	119 (57.8)	68 (64.2)	249 (63.7)	.16	.93	.28
OCS[c]	112 (54.4)	63 (59.4)	228 (58.3)	.36	.84	.39
ICS[d]/LABA[e]	92 (44.7)	59 (55.7)	233 (59.6)	.001	.47	.07
LTRA[f]	68 (33.0)	23 (21.7)	109 (27.9)	.19	.20	.04
ICS	40 (19.4)	13 (12.3)	83 (21.2)	.60	.04	.11
LAMA[g]	37 (18.0)	47 (44.3)	133 (34.0)	<.001	.05	<.001
SABA/SAMA[h]	23 (11.2)	17 (16.0)	72 (18.4)	.02	.57	.22
SAMA	5 (2.4)	3 (2.8)	21 (5.4)	.09	.28	.98
LABA	3 (1.5)	5 (4.7)	18 (4.6)	.047	1.0	.04

[a]Significance calculated using a *Z* test for differences in column proportions.
[b]SABA: short-acting beta2-agonist.
[c]OCS: oral corticosteroid.
[d]ICS: inhaled corticosteroid.
[e]LABA: long-acting beta2-agonist.
[f]LTRA: leukotriene receptor antagonist.
[g]LAMA: long-acting muscarinic antagonist.
[h]SAMA: short-acting muscarinic antagonist.

Table 5. All-cause health care costs during follow-up.

All-cause health care costs	Asthma	COPD[a]	ACO[b]	*P* value[c]		
				Asthma vs ACO	COPD vs ACO	Asthma vs COPD
Claims positive cohort						
Patients, n	145,906	17,156	20,459	—	—	—
Total costs (US $), mean (SD)	10,103 (18,987)	25,546 (54,118)	25,307 (42,735)	<.001	.690	<.001
Inpatient	1836 (13,419)	11,251 (45,205)	10,311 (35,065)	<.001	.003	<.001
Emergency department	397 (1518)	506 (1707)	701 (2456)	<.001	<.001	<.001
Outpatient	4682 (9503)	8,826 (21,557)	9050 (18,602)	<.001	.475	<.001
Prescription	3188 (5079)	4963 (7438)	5594 (8652)	<.001	<.001	<.001
Confirmed diagnosis cohort						
Patients, n	206	106	391	—	—	—
Total costs (US $), mean (SD)	20,311 (23,122)	27,132 (34,680)	19,419 (23,353)	.560	.001	.007
Inpatient	5973 (16,080)	13537 (28,003)	7026 (18,258)	.497	.030	.011
Emergency department	587 (1945)	462 (1113)	743 (2548)	.274	.083	.411
Outpatient	9393 (14,460)	8614 (13,596)	6257 (7020)	.002	.007	.132
Prescription	4358 (3590)	4518 (3594)	5393 (8579)	.008	.086	.705

[a]COPD: chronic obstructive pulmonary disease.
[b]ACO: asthma-COPD overlap.
[c]Significance calculated using a *Z* test for differences in column proportions.

Health Care Costs

Mean total health care costs 12 months postindex were significantly higher for patients in the claims-positive ACO cohort compared with the claims-positive asthma cohort (US $25,307 vs US $9966, respectively; *P*<.001), but similar to the claims-positive COPD cohort (US $25,198; *P*=.69; Table 5). Mean costs in the claims-positive ACO cohort were significantly higher than the claims-positive asthma cohort for inpatient (US $10,171 vs US $1811, respectively; *P*<.001), emergency department (US $691 vs US $391, respectively; *P*<.001), outpatient (US $8927 vs US $4618, respectively; *P*<.001), and prescription expenditures (US $8534 vs US $3145, respectively; *P*<.001). Mean costs in the claims-positive ACO cohort were lower than in the claims-positive COPD cohort for inpatient costs (US $10,171 ACO vs US $11,098 COPD; *P*=.003) but higher for emergency department costs (US $692 ACO vs US $499 COPD; *P*<.001).

When mean total costs were compared among the confirmed cohorts, however, the ACO cohort had significantly lower costs than the COPD cohort (US $19,155 vs US $26,762, respectively; *P*=.001) but similar to those of the asthma cohort (US $20,035; *P*=.56). The confirmed ACO cohort had lower mean costs than the confirmed asthma cohort for outpatient (US $6172 ACO vs US $9265 asthma; *P*=.002) and prescription costs (US $5320 ACO vs US $4299 asthma; *P*=.008), and lower mean costs than the confirmed COPD cohort for inpatient (US $6930 ACO vs US $13,353 COPD; *P*=.03) and outpatient costs (US $6172 ACO vs US $8497; *P*=.007).

Discussion

Principal Results

The prevalence of ACO in this study population was estimated at 6%, determined by a claims-based definition combined with medical record review to further support the diagnosis. We extrapolated the proportion of medical record confirmed ACO diagnoses from the medical record review (50.1%) to the wider claims-based asthma, COPD, and ACO study population. Medical record review added specificity to ACO diagnoses versus claims alone. Historically in claims-based studies of ACO patients were considered as meeting the definition for ACO if patients had a minimum number of ICD code diagnosis for both COPD and asthma on different occasions. Given the substantial overlap in asthma and COPD symptoms, patients could be diagnosed with either condition by clinicians, this may reflect some degree of ambiguity regarding which clinical diagnosis patients actually are manifesting, therefore reflecting a diagnostic challenge rather than a true clinical overlap syndrome. We have attempted to clarify this situation by going beyond the ICD-9 codes in a sample of patients to identify those patients who meet the traditional claims-based attribution of ACO, but also have corroborating information in the medical record that features of both asthma and COPD actually exist and the ICD-9 codes are to some degree supportable. We were therefore able to define a group of patients who had ICD-9-based characterization of ACO, COPD, and asthma but also ICD-9- and medical record review-based characterization as ACO, COPD, and asthma; and, consequently, compare these two groups. This provided useful information on the condition of ACO but also on the role of claims-based research in the future study of this syndrome.

Current or past tobacco smokers were at higher risk for ACO. Greater proportions of both claims-positive COPD and ACO patients smoked, and the confirmed ACO cohort had a significantly higher percentage of past or present smoking than the confirmed COPD and the confirmed asthma cohorts. Van den Berg and Aalbers suggested two ACO clinical phenotypes: never-, ex-, or current smokers with a history of asthma who have incompletely reversible airflow obstruction; and smokers or ex-smokers with COPD who display increased bronchodilator reversibility [17]. Our data underscored the key association of smoking with ACO as likely contributing to the evolution of the persistent airflow limitation feature of this clinical entity. The difference between confirmed ACO and confirmed asthma was largely the evidence of persistent airflow limitation based on FEV_1/FVC.

Results from the correspondence analysis question the rationale for including patients with diagnosed emphysema in future studies as they have little in common with the majority of ACO patients. Diagnoses most central to ACO were chronic bronchitis, chronic airway disease, chronic obstructive asthma, asthma not otherwise specified, and extrinsic asthma. Additionally, symptom patterns can present differently. The overlapping diagnostic codes reflecting bronchitis or airway disease may suggest bronchitis symptoms (cough, phlegm production, etc) are more suggestive of ACO versus COPD. This merits further study.

Demographic and comorbidity profiles were similar for confirmed ACO and COPD cohorts. The claims-positive ACO cohort had a greater comorbidity burden than the claims-positive asthma cohort, demonstrating differences between claims-based and medical record-confirmed definitions of ACO. Likewise, evidence in the claims-based cohorts showed greater use of most asthma and COPD medications for ACO patients versus the other two cohorts but results for confirmed cohorts did not show as many significant differences. ICS/LABA, LAMA, SABA/SAMA, and LABA usage was greater in the confirmed ACO versus the confirmed asthma cohort; use of ICSs was greater compared with confirmed COPD cohort, suggesting that ACO might be more responsive to ICSs. The results indicate that ACO patients are prescribed the same amount—or more—asthma and COPD medications as patients with asthma or COPD alone.

Higher ACO versus asthma costs were seen across inpatient, emergency department, outpatient, and pharmacy categories. Costs were lower, however, for all categories for COPD versus ACO patients, except for emergency department services where ACO-attributable costs were significantly greater than COPD-attributable costs. Costs were different in the confirmed cohorts. ACO patients had significatly lower costs than COPD patients, and similar to those in the asthma cohort. Confirmed ACO patients had lower mean costs relative to asthma patients for outpatient and pharmacy services, as well as confirmed COPD patients for inpatient and outpatient services. Possible reasons may include greater treatment responsiveness and less severe disease versus the COPD cohort, although our study was not designed to provide any further clarification.

Limitations

Despite the strengths inherent in its design, these study results must be viewed against important limitations. Data were from commercially insured patients and results may not be generalizable more broadly. Almost two-thirds (60.1%) of the accessed medical records were excluded primarily because spirometry results or provider FEV_1/FVC values were missing. Missing data also constrained ACO identification in the claims-positive ACO population.

Comparisons With Prior Studies

The 6% prevalence estimate of ACO in the study population was lower than in earlier studies, which ranged from 12% to 55% [8,10,12,13,16] but was consistent with the 5.5% estimate from the Majorca Real-Life Investigation in COPD and Asthma study [14], and in line with the 4% to 12% estimates of other recent studies [9,11]. These discrepancies between our study and prior studies might be attributed, in part, to the quantity and quality of available medical records. Only 40% of medical records accessed were complete and usable in confirming the ACO diagnosis and may have provided insufficient information to confirm 49.9% of claims-positive ACO cases. If this was accurate, and assuming that all ACO diagnoses were confirmed by medical record review (100%), under this scenario the estimated ACO prevalence would be 11%, which is consistent with a prior observational study [11].

Our findings of a greater comorbidity burden, medication use, and costs in the claims-positive ACO cohort compared with the claims-positive asthma and COPD cohorts were consistent with prior studies [18]. However, the lower costs observed in the confirmed ACO cohort differed from prior studies that showed ACO patients with higher resource utilization and costs [18,33-35]. This suggests a striking method effect upon results across studies. Costs are critical in public health activities, and they have important implications for all stakeholders. Like the Gerhardsson de Verdier et al claims-based study, which showed costs doubling for ACO versus asthma patients, our study showed an increase (almost 3-fold) for ACO versus asthma alone at 12-months' follow-up but were similar for ACO and COPD patients in that time frame.

Conclusions

ACO and asthma patients had similar demographic profiles, and ACO and COPD patients had similar comorbidity burdens. Health care costs for ACO, asthma, and COPD patients were in the same range, but ACO patients received slightly more medication versus asthma or COPD patients. Medical record confirmation of ACO suggested a lower prevalence and other differences than claims-based identification. Such methods-based variations should be considered in future studies.

Acknowledgments

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Conflicts of Interest

RMT is an employee of HealthCore, Inc; MD, who is currently an employee of Teva Pharmaceuticals, Inc, was an employee of AstraZeneca at the time of the study. BD is an employee of AstraZeneca.

Multimedia Appendix 1

Study design.

[PDF File (Adobe PDF File), 49KB - publichealth_v4i3e60_app1.pdf]

Multimedia Appendix 2

Patients with chart-confirmed asthma and/or chronic obstructive pulmonary disease.

[PDF File (Adobe PDF File), 21KB - publichealth_v4i3e60_app2.pdf]

Multimedia Appendix 3

Correspondence table for overlap among ICD-9 subtype diagnoses for medical record confirmed ACO population.

[PDF File (Adobe PDF File), 30KB - publichealth_v4i3e60_app3.pdf]

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Abbreviations

ACO: asthma-COPD overlap
CAD: chronic airway disease
COPD: chronic obstructive pulmonary disease
DCI: Deyo-Charlson Comorbidity Index
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GPI: generic product identifier
GLM: generalized linear model
ICD-9: International Classification of Diseases, Ninth Revision
ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification
ICS: inhaled corticosteroid
LABA: long-acting beta2-agonists
LAMA: long-acting muscarinic antagonists
LTRA: leukotriene receptor antagonist
OCS: oral cotricosteroid
SABA: short-acting beta-agonist
SAMA: short-acting muscarinic antagonist

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Corrigenda and Addenda

Correction: The Association Between Commonly Investigated User Factors and Various Types of eHealth Use for Self-Care of Type 2 Diabetes: Case of First-Generation Immigrants From Pakistan in the Oslo Area, Norway

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Correction of: http://publichealth.jmir.org/2017/4/e68/

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The authors of "The Association Between Commonly Investigated User Factors and Various Types of eHealth Use for Self-Care of Type 2 Diabetes: Case of First-Generation Immigrants From Pakistan in the Oslo Area, Norway" (JMIR Public Health Surveill 2017;3(4):e68) would like to make changes to the following areas in the Results section:

1. Table 6
   - The label "(h) Keeping track of health information" should be replaced with "(i) Self-assessment of health".
   - The label "(i) Self-assessment of health" should be replaced with "(h) Keeping track of health information".
   - Heading of column "Log odds ratio" should be replaced with "Estimate".
2. In the "Association Between User Factors and eHealth Use" sub-section, in the last paragraph, the second last sentence is "The *health* component is negatively related to closed online communication about T2D with a few acquaintances (d), and there is an indication of a positive relation between the *health* component and the use of Web applications and mobile apps for active decision making on T2D self-care by self-assessing of health status (*P*=.05)." This should be replaced with: "The *health* component is negatively related to closed online communication about T2D with a few acquaintances (d), and there is an indication of a positive relation between the *health* component and the use of Web applications and mobile apps for active decision making on T2D self-care by tracking of health information (*P*=.05)."

The errors were caused by an inadvertent mistake on labeling results of statistical analysis before drafting the manuscript and the oversight of the missing label for the result of the Poisson regression analysis. As the results of both logistic regression analysis and Poisson regression analysis are presented in the same table, the label "Estimate" should be used to express the results in the most appropriate manner.

Although the errors concern changes in results, the changes do not impact on the conclusion.

Regarding the missing label for the result of the Poisson regression analysis, the method is clearly stated in the Methods section, and thus we consider that the impact of this change is minor.

The correction will appear in the online version of the paper on the JMIR website on August 27, 2018, together with the publication of this correction notice. Because this was made after submission to PubMed, Pubmed Central, and other full-text repositories, the corrected article also has been re-submitted to those repositories.

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Original Paper

Estimating the Population Size of Female Sex Workers in Three South African Cities: Results and Recommendations From the 2013-2014 South Africa Health Monitoring Survey and Stakeholder Consensus

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Abstract

Background: Robust population size estimates of female sex workers and other key populations in South Africa face multiple methodological limitations, including inconsistencies in surveillance and programmatic indicators. This has, consequently, challenged the appropriate allocation of resources and benchmark-setting necessary to an effective HIV response. A 2013-2014 integrated biological and behavioral surveillance (IBBS) survey from South Africa showed alarmingly high HIV prevalence among female sex workers in South Africa's three largest cities of Johannesburg (71.8%), Cape Town (39.7%), and eThekwini (53.5%). The survey also included several multiplier-based population size estimation methods.

Objective: The objective of our study was to present the selected population size estimation methods used in an IBBS survey and the subsequent participatory process used to estimate the number of female sex workers in three South African cities.

Methods: In 2013-2014, we used respondent-driven sampling to recruit independent samples of female sex workers for IBBS surveys in Johannesburg, Cape Town, and eThekwini. We embedded multiple multiplier-based population size estimation methods into the survey, from which investigators calculated weighted estimates and ranges of population size estimates for each city's female sex worker population. Following data analysis, investigators consulted civil society stakeholders to present survey results and size estimates and facilitated stakeholder vetting of individual estimates to arrive at consensus point estimates with upper and lower plausibility bounds.

Results: In total, 764, 650, and 766 female sex workers participated in the survey in Johannesburg, Cape Town, and eThekwini, respectively. For size estimation, investigators calculated preliminary point estimates as the median of the multiple estimation methods embedded in the IBBS survey and presented these to a civil society-convened stakeholder group. Stakeholders vetted all estimates in light of other data points, including programmatic experience, ensuring inclusion only of plausible point estimates in median calculation. After vetting, stakeholders adopted three consensus point estimates with plausible ranges: Johannesburg 7697 (5000-10,895); Cape Town 6500 (4579-9000); eThekwini 9323 (4000-10,000).

Conclusions: Using several population size estimates methods embedded in an IBBS survey and a participatory stakeholder consensus process, the South Africa Health Monitoring Survey produced female sex worker size estimates representing approximately 0.48%, 0.49%, and 0.77% of the adult female population in Johannesburg, Cape Town, and eThekwini, respectively. In data-sparse environments, stakeholder engagement and consensus is critical to vetting of multiple empirically based size estimates procedures to ensure adoption and utilization of data-informed size estimates for coordinated national and subnational benchmarking. It also has the potential to increase coherence in national and key population-specific HIV responses and to decrease the likelihood of duplicative and wasteful resource allocation. We recommend building cooperative and productive academic-civil society partnerships around estimates and other strategic information dissemination and sharing to facilitate the incorporation of additional data as it becomes available, as these additional data points may minimize the impact of the known and unknown biases inherent in any single, investigator-calculated method.

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KEYWORDS

female sex workers; population size estimation; integrated biological and behavioral surveillance surveys; South Africa; HIV

Introduction

Female sex workers (FSWs) have long been recognized as a key population at a high risk for HIV infection [1,2]. In the context of a generalized HIV epidemic in South Africa, individual and structural factors such as poverty, stigma, discrimination, and criminalization of sex work contribute to FSWs' vulnerability to HIV and complicate efforts to control the HIV epidemic in the sex worker population [3]. Although South Africa still criminalizes sex work, FSW populations are a visible, mobilized, and economically significant population across the country, including the major metropolitan areas that are centers of industrial and trade-based employment, provincial cities and towns, and rural areas, particularly those traversed by the country's well-developed national highway network that links Atlantic and Indian Ocean port cities to the South African interior as well as the landlocked countries to South Africa's north [4]. FSWs work in diverse settings, including along major transport routes, at public venues such as urban street corners, parks, bars, and taverns, as well as in more closed spaces such as private homes, where they mainly interact with clients using social media platforms [4].

HIV surveillance data, including population size estimates (PSEs) on the South African FSW population, are limited. Studies conducted in the 1990s and 2000s observed that as many as half of all sampled sex workers were HIV positive, but these studies did not include PSEs [5,6]; recent South African initiatives aimed to meet the HIV needs of key populations, including those sponsored by the US President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund), have highlighted the need for reliable, methodologically rigorous PSEs for key populations generally and FSWs in particular. In 2013, fieldwork undertaken by the South African National AIDS Council (SANAC) and sponsored by the Global Fund estimated that there were roughly 150,000 FSWs in South Africa or nearly 1% of the adult female population aged 15-49 years [7]. Despite the explicit inclusion of FSWs in South Africa's national HIV strategic plans since at least 2007, prior to 2016, these efforts had not been informed by rigorously collected surveillance or survey data to quantify HIV treatment or biomedical prevention for the FSW population.

In 2013-2014, in partnership with South Africa's National Department of Health (NDOH) and SANAC, PEPFAR and the US Centers for Disease Control and Prevention (CDC) sponsored a collaboration between the University of California San Francisco, Anova Health Institute, and the Wits Reproductive Health and HIV Institute to conduct the South Africa Health Monitoring Survey (SAHMS), an integrated biological and behavioral surveillance (IBBS) survey, in South Africa's three largest cities of Johannesburg, Cape Town, and eThekwini. The SAHMS aimed to estimate HIV prevalence and associated risk, prevention, and health-seeking behaviors among FSWs as well as to estimate the size of the FSW population in each of the three metropolitan areas. HIV prevalence and behavioral results have been reported elsewhere [2]. Briefly, we estimated that 71.8% (95% CI 56.5-81.2) of FSWs in Johannesburg, 39.7% (95% CI 30.1-49.8) in Cape Town, and 53.5% (95% CI 37.5-65.6) in eThekwini were HIV infected. Among HIV-positive FSWs, only 26.9% in Johannesburg, 23.6% in Cape Town, and 35.3% in eThekwini were on antiretroviral treatment.

As there is no "gold standard" for estimating the size of key populations, we adapted CDC-recommended best practices [8] by integrating multiple multiplier-based methods of estimating the size of the FSW population at each site into the IBBS surveys and by engaging in a participatory process to achieve stakeholder consensus PSEs. In this paper, we have described these survey methods, PSE methods and results, and the consensus process through which FSW stakeholders adopted PSEs and plausible ranges (PRs) for purposes of strategic planning, policy making, advocacy, and programming.

Methods

Sample Size and Precision

The SAHMS was a cross-sectional HIV bio-behavioral surveillance study with a target sample size of 500 FSWs in each city. We used respondent-driven sampling (RDS) methods [9-12] that have been subsequently adapted for key populations HIV surveillance and population size estimation purposes [13-19]. We have described elsewhere how RDS recruitment operated in the SAHMS [2]. Briefly, each city's sample was recruited independently of the others'. Recruitment of each sample began with 1-3 seeds identified by stakeholders and study staff during pre-IBBS formative assessment; each seed recruited up to 3 additional FSWs from their social and professional networks, who recruited up to 3 additional FSWs, and so on in Markov chains, as shown in Table 1.

The study procedures consisted of a behavioral survey and biological testing for HIV. All participants who wanted to know their HIV status were offered rapid HIV testing services (HTS). Eligible candidates were those who were born biologically female; aged 16 years or older; had exchanged sex for money with someone other than a primary partner in the previous 30 days; and had lived, worked, or socialized in the urban area where they were recruited for the previous 6 months. Participants provided written informed consent for study procedures and separate written informed consent for rapid HTS (per South African guidelines). HIV-positive FSWs were referred to FSW-competent, nonstigmatizing clinical care. Survey data collection commenced in July 2013 and concluded in February 2014.

Laboratory and statistical analyses of biological and behavioral survey data followed the Strengthening the Reporting of Observational Studies in Epidemiology RDS guidelines [20], and the full description of laboratory methods has been provided in the SAHMS final report [2]. In the next sections, we have described the background and methodological approach to each population size estimation method.

Wisdom of the Crowds

The theoretical assumption of "wisdom of the crowds" (WOTC) asserts that a reasonable estimate of the size of a population may be derived from aggregating responses from survey participants [21]. The SAHMS included the following question: "Approximately how many other women who have sex for money do you think live in and around [survey city]?" To improve response reliability, the question was asked twice within the survey. The final estimate was reached by taking the average of the two median estimates and ranges.

Unique Object Multiplier

The unique object multiplier is a 2-step method commonly used in conducting population size estimation of key populations. The first step involves distributing unique, memorable objects in advance of the survey throughout the study area to the members of the population of interest. The objects were determined through stakeholder consultation in each city. In eThekwini, lavender-colored bracelets were distributed, while compact make-up kits were used in Johannesburg and Cape Town. In each city, study staff and stakeholder volunteers distributed objects to FSWs throughout the study area a few weeks prior to survey launch, varying days and times in order to achieve the largest distribution.

To avoid distribution biases and errors in the first step of this process, we relied on the advice of individual volunteers and staff who were familiar with the local FSWs, or who were themselves local FSWs, to minimize the possibility that individuals would receive multiple objects or that objects would be distributed to nonpopulation members. The numbers of objects distributed at a particular time and geographic area (eg, street intersection, brothel) were recorded and varied to ensure that different individuals and subpopulations would be encountered in each object distribution event. Finally, with each brief interaction, staff screened women to verify their FSW status and whether they had previously received the object.

The second step was an item in the survey instrument: "In the previous 6 months, did you receive an object, like the one I am showing you now?" with the interviewer holding up an example of the object distributed. The proportion of survey respondents who answered "yes" to the question was used to calculate the RDS-adjusted size estimate for this method. The calculation used for this method was N=n/p; where "N" is the PSE, "n" the number of objects distributed in the population, and "p" the proportion of participants who reported receiving an object in the survey.

Unique Event Multiplier

The 2-step principles and calculation for the unique event multiplier are similar to the unique object. In the first step, in advance of the survey launch in each city, staff and stakeholders sponsored a memorable launch event, with the theme and name of the event determined through stakeholder input in each city and the event publicized through FSW stakeholders and social networks. Staff and stakeholders counted each woman who entered the event and screened all women to confirm FSW status. Each count was recorded; discrepancies between counters were resolved through discussion until a count deemed to be reasonable was arrived at by all counters. In the second step, survey participants were asked if they attended the event, with the event identified by its name and date. To calculate an RDS-adjusted PSE, we used the previously mentioned formula N=n/p: here "n" is the number in attendance at the event and "p" the proportion of the survey sample who reported having attended the event.

Service Multiplier

In this 2-step process, staff first obtained de-duplicated counts of FSWs who utilized any clinical HIV or community-based service (eg, HIV testing, attendance at an advocacy workshop) from partnering stakeholder organizations between January 1 and June 16, 2013. In Johannesburg, these were visits to Esselen Street Clinic, a clinic operated by clinical staff at the Wits Reproductive Health and HIV Institute, where the visiting population primarily comprises sex workers; in Cape Town and eThekwini, these were either having attended a "Creative Space" advocacy workshop organized by the Sex Worker Education and Advocacy Taskforce or having received HTS through the TB/HIV Care Association, who provide mobile testing to FSWs. In the second step, the survey asked participants whether they had received the particular service between January 1 and June 16 (with January 1 referenced as "New Year's Day" and June 16 as "Youth Day," a South African public holiday and, therefore, a salient recall endpoint). With the same N=n/p multiplier formula; here "n" is the number of de-duplicated FSWs reported by the service provider and "p" is the proportion of participants who reported receiving services from the given provider.

Table 1. Respondent-driven sampling sample size and recruitment statistics for three samples of female sex workers in South Africa.

Site	Sample size	Seeds	Waves to equilibrium	Total waves	Mean network size
Johannesburg	764	5	7	17	20.67
Cape Town	650	6	10	29	16.98
eThekwini	766	3	6	16	11.40

Calculation of Preliminary Population Size Point Estimates

Study investigators calculated a point estimate for the FSW population in each city that was the median of a plausible range of individual point estimates derived from the sources described above. Investigators excluded point estimates as implausible in calculating the median if they were outside of an obvious range of reasonableness—for example, a preliminary point estimate could not be less than the survey sample size in each city, or it would suggest that more than half the adult female population were engaged in sex work. The investigators adopted the median of the plausible estimates as the preliminary PSE, with the largest reasonable point estimate as an upper plausibility bound and the lowest reasonable point estimate as the lower plausibility bound.

Modified Delphi Process and Adoption of Consensus Population Size Estimates

Using this range of estimates, investigators then invited input on the preliminary PSEs, including their *a priori* exclusion of implausible results, from a stakeholder committee following a consensus process described by colleagues in the San Francisco Department of Public Health [22] and previously implemented in Tanzania [23] and Ghana [24]. The study investigators convened a meeting with stakeholders who were familiar with the three FSW populations to present the preliminary PSEs and associated upper and lower plausible bounds. The stakeholder group included representatives of NDOH, civil society human rights advocacy and health services organizations represented on the SANAC, and other academic experts. The PSE and crude data were distributed to stakeholders in advance of an in-person stakeholder meeting.

At this meeting, investigators reviewed all the individual PSE methods outlined above, discussed the variation between and limitations of each method, and identified their *a priori* implausible estimates. Upon achieving consensus on the plausible range of PSEs, the investigators calculated preliminary median PSEs and upper and lower plausible bounds. Preliminary PSEs were also compared with census data from 2011 to back-calculate the proportion of the adult female population engaging in sex work in each city to demonstrate where the estimate lay within a range of reasonableness, including comparison to other PSE studies and assumptions from other contexts. In this case, the group considered PSEs derived from a 2013 national rapid assessment of the sex worker population commissioned by SANAC and presented by Konstant et al [7] to assess whether the preliminary median PSEs and PRs were sensitive to the previous results. (Briefly, the rapid assessment's multimethod approach consisted of mapping and enumeration, interviews with sex workers, focus group consultations with key informants, and fieldwork counts conducted by stakeholder fieldworkers. Results were reported as counts and proportions of the adult female population aged above 15 years.

Finally, the investigators facilitated a stakeholder group discussion to compare the preliminary median PSEs and plausibility ranges against stakeholders' own experiences of engagement with the FSW population through existing prevention or treatment programs. This process provided the opportunity to reconsider any point estimates that investigators had excluded *a priori*. At the conclusion of the meeting, the group was invited to reject, amend and recalculate, or adopt the preliminary PSEs as consensus PSEs.

Data Analysis

We calculated HIV prevalence and other uni- and bivariable proportions using the RDS Analysis Tool version 7.1.46 and the SPSS version 23.0. Each sample's results were analyzed, weighted, and reported independently of the others. We estimated the size of the FSW population in each city following best practices that recommend multiple methods and "multiple multipliers" [8] and following a 2-phase data triangulation and consensus-based process.

Results

Sampling or Recruitment

We recruited 2180 FSWs across the three sites. In Johannesburg, recruitment began in August 2013 and continued for 25 weeks, recruiting a total of 764 women through 5 seeds. The Cape Town site launched in July 2013 and was open for 28 weeks, with a final sample of 650 through 6 seeds. The eThekwini study site began recruiting participants in September 2013 and was operational for 22 weeks, with 766 women included in the final sample recruited through 3 seeds.

PSEs for each city and the survey counts on which they are based, for example, the count of participants in the survey who recalled receiving the unique object, have been listed by estimation method in Table 2. In Johannesburg, the WOTC produced the lowest estimate at 3000 FSWs (range 3000-3500) and was ultimately deemed implausibly low by consensus and excluded from calculation of the median. The unique object had the highest estimate at 10,895 FSWs (95% CI 582-25,018). The unique event produced an estimate of 4500 FSWs (95% CI 272-not applicable). The service multiplier result was deemed an unreasonably low estimate as it produced an estimate equal to the survey sample size. Previously published literature has estimated the Johannesburg FSW population at 10,894 [7].

In Cape Town also, WOTC produced the lowest point estimate at 1500 FSWs (range 1000-1750) and unique object the highest at 23,750 FSWs (95% CI 783-59,375). This value was deemed outside the range of plausibility by stakeholder consensus and was excluded from calculation of the median. The unique event multiplier result was 7500 FSWs (95% CI 1380-37,500). The two service multiplier results in Cape Town were 4579 FSWs (95% CI 3153-6869) and 2551 FSWs (95% CI 1708-3585). Previously published literature has estimated the Cape Town FSW population at 7351 [7].

In eThekwini, the WOTC estimate was 4000 FSWs (range 3000-5000). The unique object multiplier result was 11,200 FSWs (95% CI 326-34,000). The unique event resulted in an estimate of 747 FSWs. However, this estimate was judged to be highly implausible since it was well below the de-duplicated data provided by service providers and, therefore, excluded from the final analysis. This is very likely attributable to a misunderstanding regarding the unique event attendance question among eThekwini survey participants. The two service multiplier estimates were 12,840 FSWs (95% CI 7379-33,879) and 9323 FSWs (95% CI 5255-17,515). Prior literature has estimated the FSW population in this city at 6145 [7].

The Modified Delphi consensus process meeting with stakeholders endorsed the investigator recommendations on preliminary point estimates (median of all estimates), resulting in the exclusion of unreasonable results from calculating the median. In Cape Town, WOTC was dismissed as implausible based on program data and expert opinion. The point estimate became the median of the remaining estimates, rounded up. Stakeholders were given the option of accepting the highest and lowest plausible estimate as the PR; in Cape Town and eThekwini, they relied on expert opinion to round the upper boundary down.

Population Size

Table 2 presents preliminary and consensus PSEs and PR results, including the proportion of the adult female population represented by the consensus PSEs and PRs. We have included Konstant et al’s results to demonstrate the sensitivity of the IBBS-derived consensus PSEs to previous estimates [7].

Table 2. Consensus population size estimates of South African female sex workers (FSWs) in the South Africa Health Monitoring Study 2013-2014.

City and method	FSW count, n	Sample proportion, p	Point estimate, N (95% CI or range)	Final estimate, n (%)[a]	Plausible results, range (%)
Johannesburg					
Wisdom of the crowds	N/A[b]	N/A	3000[c]		
Unique object	1351	0.124	10,895 (582-25,018)		
Unique event	27	0.006	4500 (272-N/A)		
Service multiplier	261	0.341	765[c]		
Literature	N/A	N/A	10,894	7697 (0.48)	5000-10,895 (0.31-0.69)
Cape Town					
Wisdom of the crowds	N/A	N/A	1500[c]		
Unique object	950	0.04	23,750[c]		
Unique event	75	0.01	7500 (1380-37,500)		
Service multiplier 1	577	0.126	4579 (3153-6869)		
Service multiplier 2	398	0.156	2551 (1708-3585)		
Literature	N/A	N/A	7351	6500 (0.49)	4579-9000 (0.35-0.69)
eThekwini					
Wisdom of the crowds	N/A	N/A	4000 (3000-5000)		
Unique object	952	0.075	11,200 (326-34,000)		
Unique event	56	0.085	747[c]		
Service multiplier 1	642	0.05	12,840 (7379-33,879)		
Service multiplier 2	578	0.062	9323 (5255-17,515)		
Literature	N/A	N/A	6145	9323 (0.77)	4000-10,000 (0.33-0.83)

[a]% adult female population.

[b]N/A: not applicable.

[c]Implausible estimate not used in the calculation of median preliminary population size estimate.

Discussion

Principal Results

The SAHMS study, and the PSEs derived from it, fill a critical strategic information gap by providing conservative yet robust PSEs of FSWs in South Africa's three largest cities of Johannesburg, Cape Town, and eThekwini, producing point estimates of 7697, 6500, and 9323, respectively.

Strengths

This study is, to our knowledge, the first published study of its kind for South Africa where the incorporation of stakeholder consensus into the analysis of IBBS data was an integral component of the population size estimation methodology. Indeed, the service multiplier methods could not be implemented without significant stakeholder engagement, and stakeholder endorsement of the PSE results as plausible is critical to the PSEs' utility. In this case, stakeholder endorsement of these PSEs was critical to NDOH and SANAC developing, launching, and costing the National Sex Worker HIV Plan 2016-2019 [25] as well as setting realistic and data-informed FSW prevention and treatment targets for South Africa's HIV/STI National Strategic Plan 2017-2022 [26]. While these planning processes were entirely independent of SAHMS data collection or its PSE processes, stakeholders' decision that surveillance data and PSEs were reliable enough to inform strategic planning was only possible because they were meaningfully and consistently engaged with the data collection and interpretation process.

Comparison With Prior Work

The estimates derived from our methodology in these cities are largely consistent with 2013 estimates by Konstant et al, derived from different methodologies [7]. While stakeholders acknowledged that the PSEs appeared to be lower than they had expected (a result also reported by Konstant et al), stakeholders were persuaded to rely on these results as they were based upon empirical methodologies that were consistently and transparently applied to the IBBS PSE data. Thus, these consensus PSEs were acknowledged by stakeholders to be data informed and usable for their purposes of programmatic planning and benchmarking.

Limitations

We are aware that the major critique and limitation of the individual methods we used, as well as the consensus process through which final PSEs were calculated and adopted, are that the methods and process are subject to significant and frequently unmeasurable biases, making it difficult to impossible to assess PSE accuracy and subjects' precision to subjective biases. In fact, we substantially agree and would contend that while greater accuracy is of course a goal, it is unlikely to be achieved through a single method with enough rigor to achieve scientific consensus on bias and accuracy anytime soon. The virtue of the individual PSE methods and the consensus process described in this paper lies in their utility to public health planning and action. Individually, the multiplier methods that we selected for inclusion in the SAHMS are available, easy to implement, rigorous enough to be reproducible, and—critically—transparent in their limitations and are generally easily understood by stakeholders. Moreover, numbers that do not align with stakeholder opinion or experience are not likely to be adopted or utilized, which essentially throws good money after bad. None of this should be interpreted as our endorsement of methodological sloppiness or indiscriminate guessing; it is simply a recognition that lives are at stake and avoidable infection, illness, and death should be prioritized over methodological debates in the meantime.

These FSW PSEs are also subject to several methodological and implementation-related limitations. As discussed previously, reasonable people may disagree on whether the results are accurate or precise *enough*, and we acknowledge that there is no empirical way to validate consensus point PSEs. Nearly every step in the process is vulnerable to biases introduced through both random and human error; as facilitators of the consensus process, investigators have a duty to be ruthlessly and transparently skeptical of *all* results in light of other available evidence and stakeholder experience so that reversion to the mean of empirically collected and analyzed data is privileged over indiscriminate guessing. In particular, we are aware of the emerging consensus in the scientific community that Delphi methods such as WOTC have become less necessary or desirable to be included in multimethods comparisons. We report it here only because it was a method considered by this stakeholder group in 2016, and the purpose of this paper is to describe stakeholder consensus methodology and the results generated through it, more than to validate or invalidate any individual PSE methodology. We are aware of the major empirical limitations of similar Delphi methods; they have been perhaps less robust than, for example, multiplier methods. We substantially agree, and there may be enough, more empirical and robust, methodologies now available that a recommendation to exclude them in the future would not be unwarranted. This said, we note that as implemented and analyzed in SAHMS, WOTC produced the lowest point PSEs compared with the capture-recapture multiplier methods, considered more empirically based.

These consensus PSEs are primarily informed by point estimates from the more empirically satisfying and theoretically reproducible multiplier methods, yet we caution that even these point estimates must be understood and qualified as being subject to several biases embedded in these methods. For example, it is not possible to independently validate that unique object or event counts include only individuals who are true population members. Additionally, given the requirement that multiplier counts be independent of survey counts, even the most rigorous implementation of multiplier and survey methods cannot guarantee plausible results as demonstrated by Cape Town's object multiplier. Self-report bias may have been introduced in multiplier methods relying on socially desirable affirmative answers to questions about, for example, being in possession of a make-up kit (object) or getting HIV tested in the last 6 months (service). Additionally we observed relatively low attendance at each of the three unique events, and in the case of eThekwini, the number of attendees recaptured through RDS recruitment produced an implausible result nearly equal to the site's achieved sample size (ie, ~100% recapture). For all these reasons, it is advisable to discuss proposed multiplier method procedures with the population during presurvey assessments such as phrasing of recapture survey questions to avoid misunderstandings and biased responses. Furthermore, it is important to monitor and document the implementation of both sides of the capture-recapture methods carefully. In the absence of these recommendations, it may otherwise not be possible for investigators or stakeholders to make reasoned, qualitative judgments about the plausibility of the individual results or the range of preliminary PSE results.

Additionally, it is debatable as to whether venue-based nonprobability and quasi-probability methods may provide more reliable population size data for purposes of estimating unmet HIV program needs; in particular, Rao et al's [27] side-by-side comparison of the advantages and limitations of RDS with venue-based nonprobability sampling provides critical perspective on clearly defining a target population, if assessing unmet service delivery needs for service delivery is among the intended outcomes or uses of PSE data. We acknowledge the potential advantages of such methods particularly in resource-limited settings, especially because strategic information-gathering resources are finite and increasingly constrained, but we believe that currently, even in a human rights-protecting legal environment such as South Africa's, stigma and discrimination, as well as sex workers' well-founded fears of legal jeopardy and human rights violations by law enforcement (sex work itself remains criminalized), may prevent some FSWs (and other key populations members) with substantial unmet needs from being visible at selected, relatively public hotspots where they might be systematically enumerated. Similarly, nonservice delivery venues where FSWs are likely to be enumerated (eg, brothels, the internet) may be more difficult for investigators to access than for RDS recruitment to penetrate. The chief advantage of RDS with key populations—that it relies on network ties within a population to populate the sample—requires that it be implemented with substantial baseline knowledge of the population's characteristics and needs. Here stakeholder perspectives are critical to informing investigators' perspectives, and population members may also properly be considered stakeholders in a consensus process, even if they are not sitting in a conference room with service provider and other types of stakeholders, whose perspectives may inherently be biased toward those who are countable and have already been reached. In this sense, failure to demonstrate substantial network transition out of service provider-related networks suggests either optimal service coverage of the population (highly improbable in sex work-criminalized environments) or methods-implementation limitations that must be identified and acknowledged in analysis.

Successive sampling (SS)-PSEs are possible to calculate from RDS data [28] and, on their face, may appear more methodologically and empirically satisfying. We did not include SS-PSEs here only because these have not been vetted by this stakeholder group, and the participatory stakeholder process is the subject of this paper as much as the estimates it produced. We endorse SS-PSE's inclusion in multiple-method comparisons of future surveillance and population size estimation work in South Africa and elsewhere. SAHMS II, which will be fielded in 2018-19, will calculate SS point estimates and present these for consideration by stakeholders for calculating a mean PSE and reaching consensus PSEs. SS-PSE accuracy and precision are dependent on well-monitored field implementation of RDS and proper post-hoc accounting of bias in RDS recruitment data. For this reason, we could not recommend reliance on any single method and continue to endorse vetting and triangulation of multiple empirical methodologies by stakeholders and technical experts in a participatory process.

Lessons Learned

At the end of the day, a PSE has no inherent value unless it is adopted and used consistently by all stakeholders in government, civil society, and Global Health financing partners. Investigators cannot hope to achieve anything like accuracy without the granular knowledge that local stakeholders possess regarding FSWs and similarly stigmatized and hidden key populations; stakeholders cannot make this judgment of a PSE result unless they judge the method of producing it to be reasonable, transparent, and competently applied. Ultimately, our method places great responsibility in the hands of technical advisors who must navigate advocacy, service provider, and political interests while privileging empirically derived data in weighing what is and is not a reasonable result, even when this is inconvenient. The authors hope to have ably discharged this duty both in reporting these first consensus-based PSEs for South African FSWs and in describing the process through which the consensus was achieved. Because the identification of a "gold standard" methodology that can consistently produce a single, accurate result for key populations like FSWs continues to elude us all, we recommend this approach that incorporates multiple empirical methods into a "multiple multipliers" comparison and facilitates participatory data triangulation to achieve stakeholder consensus PSEs. Presently, HIV strategic planning efforts in South Africa and throughout the world involve costing of the proven but expensive biomedical prevention and treatment technologies that are essential to achieving real and lasting impact on the high-prevalence, high-incidence epidemics experienced by FSWs and other key populations. The experience of South Africa suggests that these consensus PSEs have provided a necessary and useful baseline from which to launch an evidence-informed assault to end key populations' HIV epidemics.

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Authors' Contributions

MAG, AEM, and TL performed the analysis and interpretation and drafted the manuscript. All the other authors reviewed, commented, and issued the final approval of the version to be published. MS is an independent consultant (Johannesburg, South Africa).

Conflicts of Interest

None declared.

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Abbreviations

CDC: US Centers for Disease Control and Prevention
FSW: female sex worker
HTS: HIV testing services
IBBS: integrated biological and behavioral surveillance
NDOH: National Department of Health
PEPFAR: President's Emergency Plan for AIDS Relief
PR: plausible range
PSE: population size estimate
RDS: respondent-driven sampling
SAHMS: South Africa Health Monitoring Survey
SANAC: South African National AIDS Council
SS: successive sampling
WOTC: wisdom of the crowds

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Original Paper

Using Predictive Analytics to Identify Children at High Risk of Defaulting From a Routine Immunization Program: Feasibility Study

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Abstract

Background: Despite the availability of free routine immunizations in low- and middle-income countries, many children are not completely vaccinated, vaccinated late for age, or drop out from the course of the immunization schedule. Without the technology to model and visualize risk of large datasets, vaccinators and policy makers are unable to identify target groups and individuals at high risk of dropping out; thus default rates remain high, preventing universal immunization coverage. Predictive analytics algorithm leverages artificial intelligence and uses statistical modeling, machine learning, and multidimensional data mining to accurately identify children who are most likely to delay or miss their follow-up immunization visits.

Objective: This study aimed to conduct feasibility testing and validation of a predictive analytics algorithm to identify the children who are likely to default on subsequent immunization visits for any vaccine included in the routine immunization schedule.

Methods: The algorithm was developed using 47,554 longitudinal immunization records, which were classified into the training and validation cohorts. Four machine learning models (random forest; recursive partitioning; support vector machines, SVMs; and C-forest) were used to generate the algorithm that predicts the likelihood of each child defaulting from the follow-up immunization visit. The following variables were used in the models as predictors of defaulting: gender of the child, language spoken at the child's house, place of residence of the child (town or city), enrollment vaccine, timeliness of vaccination, enrolling staff (vaccinator or others), date of birth (accurate or estimated), and age group of the child. The models were encapsulated in the predictive engine, which identified the most appropriate method to use in a given case. Each of the models was assessed in terms of accuracy, precision (positive predictive value), sensitivity, specificity and negative predictive value, and area under the curve (AUC).

Results: Out of 11,889 cases in the validation dataset, the random forest model correctly predicted 8994 cases, yielding 94.9% sensitivity and 54.9% specificity. The C-forest model, SVMs, and recursive partitioning models improved prediction by achieving 352, 376, and 389 correctly predicted cases, respectively, above the predictions made by the random forest model. All models had a C-statistic of 0.750 or above, whereas the highest statistic (AUC 0.791, 95% CI 0.784-0.798) was observed in the recursive partitioning algorithm.

Conclusions: This feasibility study demonstrates that predictive analytics can accurately identify children who are at a higher risk for defaulting on follow-up immunization visits. Correct identification of potential defaulters opens a window for evidence-based targeted interventions in resource limited settings to achieve optimal immunization coverage and timeliness.

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KEYWORDS

machine learning; artificial intelligence; immunizations; dropouts; predictive analytics

Introduction

Despite the availability of free routine immunizations in low- and middle-income countries (LMICs), many children are not completely vaccinated, are vaccinated late for age, or drop out from the course of the immunization schedule. According to the World Health Organization (WHO) and United Nations International Children's Emergency Fund (UNICEF) immunization coverage estimates, the mean dropout rates for Bacillus Calmette–Guérin (BCG) and the second dose of measles-containing vaccine are 34.6% (SD 20.4%) in low-income countries and 28.6% (SD 20.4%) in GAVI-eligible LMICs [1]. Studies have reported consistent findings in which the coverage rates of earlier vaccines are significantly higher than the coverage for vaccines that are administered later on in the immunization schedule, [2,3] with the highest dropout occurring between the diphtheria-tetanus-pertussis (DTP3) dose and the first dose of measles vaccine [2]. A probable explanation is the relatively long time interval (35.5 weeks) between the administration of the DTP3 vaccine (14 weeks) and measles vaccine (9 months), which increases the likelihood of mothers forgetting about the vaccination appointment or not having the time to make scheduled visits for immunizations [3].

Despite individual efforts by governments to improve coverage and reduce dropout rates, vaccinators lack readily available on-site information tools to target children who are at highest risk of dropout or late vaccination. To achieve full universal coverage and improve the timeliness of individual vaccine doses, low-resource countries can model and visualize the risk on large datasets, including that at the individual level during immunization visits, to identify and target children who are at a high risk of dropping out or delaying the next vaccine dose.

In the era of big data, when the collection of massive amounts of reliable data has become inexpensive and easy, predictive analytics is being utilized in a wide variety of settings. The fields of business, marketing, and finance were among the earliest adopters of predictive analytics. One well-known application is credit scoring, a predictive model that analyzes a particular customer’s information, such as credit history, to assess the potential risk of lending money to that customer. Web-based retailers, such as Amazon, also utilize powerful predictive algorithms to tailor item recommendations for the individual experience of their users [4].

Predictive analytics technology uses mathematical and computational statistical modeling, machine learning, and multidimensional data mining techniques [5] to accurately forecast future immunization outcomes based on existing data and to predict parental adherence to routine childhood immunization schedules. What makes predictive analytics powerful and so widely applicable is the fact that the systems can iteratively learn and improve over time [5] to achieve the desired quality of predictive performance. These systems use traditional statistical methods, such as the calculation of the area under the system’s receiver operating characteristic (ROC) curve, to measure the system’s predictive performance [6]. It was not until electronic medical records and big data in health care became more widely adopted that opportunities for using predictive analytics in health began to increase [7]. A machine learning algorithm built to optimize the management of patients with chronic kidney disease in the United States was able to identify the most probable data-driven clinical pathway and predict the upcoming required intervention with an accuracy of 50%-75% [8]. A proof-of-concept study at the Department of Medicine at Yale University created a random forest model and “trained” it to predict the in-hospital mortality rate of patients with sepsis. The model used local data from the hospital, and it had an area under the curve (AUC) with a 95% CI of 0.86 (range 0.82-0.90), outperforming all traditional analytic models used as controls with statistically significant results [9]. In addition to anticipating outcomes based on the population level, predictive analytics have also been used to forecast individual outcomes. Researchers at the University of Texas, Houston, developed three machine learning algorithms to predict suicidality among individuals with mood disorders based on their medical and sociodemographic data. All three models had >50% accuracy in distinguishing someone as an individual who had attempted to commit suicide from someone who had not [10].

According to WHO, in 2015 [11], a child born in a low-income country was 11 times more likely to die before reaching the age of 5 years than a child born in a high-income country, highlighting the crucial link between demographic and socioeconomic factors influencing health outcomes. Our hypothesis is as follows: a child’s likelihood to miss or not show up on time for a vaccination visit is correlated with certain demographic and background characteristics, such as socioeconomic status, gender, maternal education, ethnicity, and location. We have leveraged the power of “big data” collected through a digital immunization registry to develop a predictive analytics algorithm that tags children who are most likely to miss their follow-up immunization visits. Through statistical modeling, we can use immunization and demographic data to classify whether a child showing up at the immunization center is at high or low risk of missing subsequent immunization visits. This research aimed to develop and validate the accuracy of the predictive analytics algorithm in identifying children who were likely to default from subsequent immunization visits for any vaccine included in the routine immunization schedule. We also sought to determine which predictive analytics model has the highest predictive accuracy. Although our research was based on previous studies about behavioral predictive analytics models, this will be the first to examine parental adherence to routine childhood immunization schedules in developing countries.

Methods

Study Population and Data Source

Vaccination data were abstracted from the Zindagi Mehfooz Digital Immunization Registry, a mobile phone-based registry program initially supported by the United Nations Foundation and currently scaled in Sindh province with support from WHO. The registry software was developed based on an android platform, and it has various features, including web interface, mobile phone-based data access and entry, radio frequency identification and quick response code-based identification, interactive short message service (SMS) reminders, electronic decision support system that guides vaccinators for routine and catch-up immunizations, and geographic information system for tracking of vaccinators. The retrospective data subset had 49,439 records from 21 immunization centers in two cities (Karachi, Sindh and Muzaffargarh, Punjab) collected from May 2012 to April 2016. We excluded a total of 1885 records from the total dataset; among these, 326 records were excluded based on invalid dates for age or immunizations and three were not included because the children had died. Moreover, 1556 were excluded because they only had measles-2 immunization record, which is the last recommended immunization dose, and there were no further follow-up visits.

The cohort of children included in the model had visited the immunization center for one of the six routine immunization visits. These children had complete records of the core variables used in the analysis. During data extraction, transformation, and cleaning stage, the information on demographic and vaccine-related variables was obtained as raw data. The variables for model prediction were used from routinely collected data on the Expanded Program on Immunization (EPI) for administering recommended immunizations to children aged below 2 years. The variables that did not add any contextual information (child’s name, address, and contact number) were filtered out, whereas the rest were utilized in the model (Textbox 1). Figure 1 summarizes the main procedures of the study.

Data Analysis or Prediction Objective

Our primary objective was to validate the functionality of the predictive analytics model through predicting the likelihood of each child defaulting from subsequent immunization visits for any vaccine included in the routine immunization schedule.

Modeling

We used support for recursive partitioning, support vector machines (SVMs), random forests, and C-forest models in the predictive analytics component. These models were encapsulated in the predictive engine, which identified the most appropriate method to use in a given case based on the following standard measures: accuracy, precision (positive predictive value), sensitivity, specificity, and negative predictive value.

Recursive Partitioning

Recursive partitioning is a statistical method that creates a binary decision tree that classifies the classes of the target attribute by recursively splitting the training data into subsets until a certain criterion is met. The advantage of recursive partitioning algorithm is its performance on larger datasets and flexibility in prioritizing sensitivity and specificity. However, the disadvantages include overfitting data and the lack of support for continuous variables. Furthermore, the problem of overfitting can be resolved with the use of tuning parameters [12].

Support Vector Machines

SVMs are based on a discriminative classification technique that forms a tree-like graph of learned classification rules. This model is extremely efficient for binomial target attributes, and it performs well on datasets with a high number of attributes, regardless of training data size. This study uses LibSVM implementation [13,14].

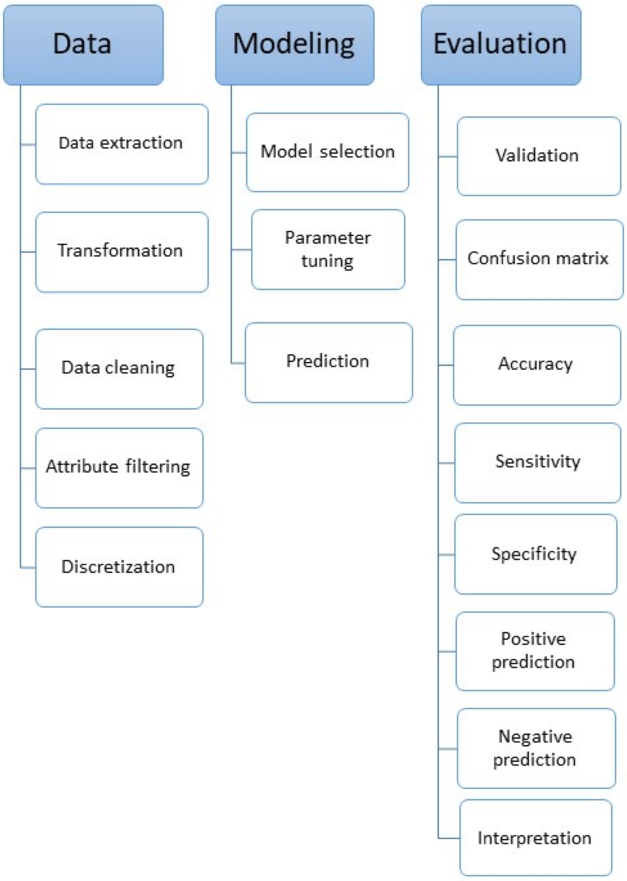
Random Forests

Random forests are an extension of the decision tree model. The random forest grows several trees against each classification rule, each providing a classification of a target object. The decision is made through voting. The benefit of using random forests is their higher accuracy on larger datasets and their capability to handle high-dimensional data without the need of using the dimensionality reduction step. Random forests are also good at locating outliers and scaling data to reduce error due to bias. Breiman’s implementation [15,16] of the random forest has been used in this study.

Textbox 1. List of predictors from the routinely collected immunization data

1. Gender of the child
2. Language spoken at the child’s house
3. Place of residence of the child (town or city)
4. Enrollment vaccine
5. Timeliness of vaccination
6. Enrolling staff (vaccinator or others)
7. Date of birth (accurate or estimated)
8. Age group of the child (<1 month, 1 month, 2 months, 3 months, 4 months, 6 months, 9 months, 1 year, 1.5 years, 2 years, 3 years, and >3 years)

Figure 1. Procedures of the Study.



C-Forest

C-Forest is based on conditional inference trees, which estimate a regression relationship by binary recursive partitioning in a conditional inference framework. C-Forest can work on multivariate target variables as well, which is not supported by the recursive partitioning model by default. This study used an algorithm proposed by Hothorn, Hornik [17].

Parameter Tuning

In this step, the default parameters of the algorithms were tuned on different values until the most optimal setting, for example, the values of the parameters that provide the best accuracy for the model, had been reached. These parameters were different for each algorithm; for example, in the random forest model, we discovered that the default value for the number of trees to grow (50) was insufficient. Thus, we tested different values and chose 150 as the optimal value. Another example from the recursive partitioning is complexity parameter in which we determined the algorithm if the complexity parameter was set to 0.01; then, a node should had split further only when the goodness of fit was improved to at least 0.01 due to this split. We learned that the default value (0.01) was appropriate and changing it did not improve the results.

For parameter tuning, the training dataset was further split into two parts: training set and validation set. Classifiers were trained on training set and tuned upon the test set. Then, the final accuracy was measured on the validation set in which the outcome of the target variable was hidden from the classification algorithm. Although parameter tuning could improve accuracy (often extremely marginal), this was an optional step.

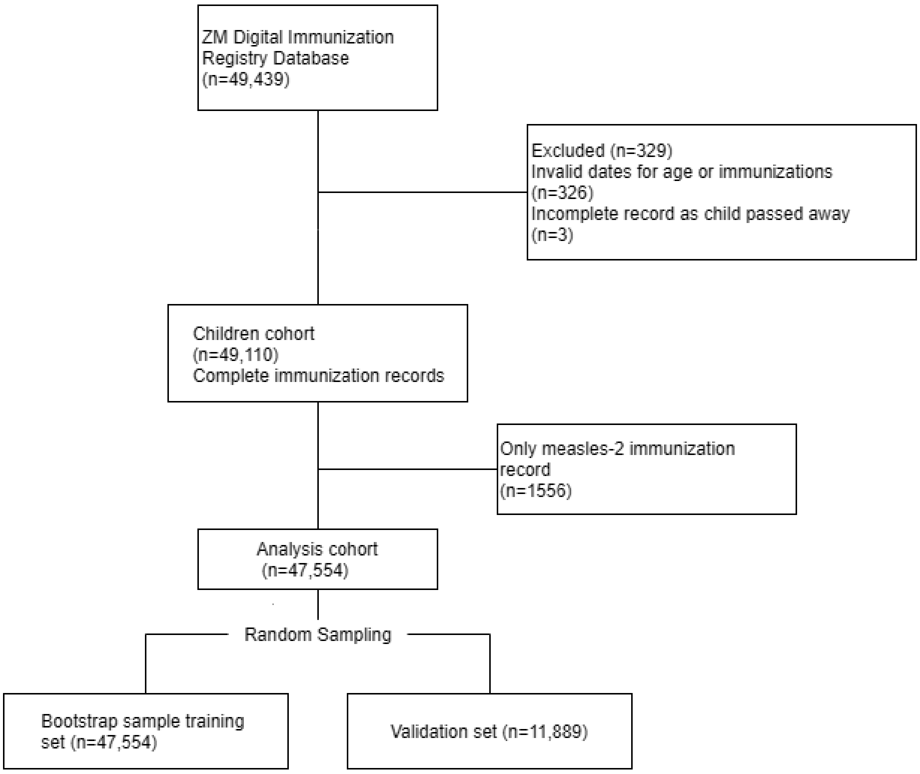
Evaluation

For evaluating the algorithm, we carried out bootstrapping to generate training and validation dataset. To avoid affecting the performance of the model, the validation dataset was not included as part of the training set. The validation dataset was generated as follows:

1. Extracting a sample of size equal to the dataset with replacement
2. Storing all observations from the dataset for validation, which were not selected during sampling
3. Repeating the sampling until the size of the validation set is one-fourth (11,889) of the original dataset size (47,554).

This validation dataset set was neither used during training nor for parameter tuning. It was only used for model evaluation. Random sampling with replacement from the original sample was performed until the training subsample equivalent to the same size as the original sample was achieved. All the left-over records, which were not selected in the training set, were placed together in the validation subsample, as seen in Figure 2. The test set was separated initially, and no parameter tuning was performed on this set to ensure the simulation of real-world data population. These test data were later used to test the accuracy of the other parameters of each model by predicting the target class.

Figure 2. Derivation procedure for extracting training and validation cohort data. ZM: Zindagi Mehfooz.



Accuracy, which is defined as the percentage of total correct predictions, is considered the first parameter in the evaluation of any machine learning algorithm: accuracy = (T_P + T_N) / (T_P + T_N + F_P + F_N), where T_P refers to all correct positive classifications, T_N indicates all correct negative classifications, F_P represents all false positive classifications, and F_N refers to all false negative classifications. The other parameters included the following: sensitivity = T_P / (T_P + F_N), specificity = T_N / (T_N + F_P), precision (positive predictive value) = T_P / (T_P + F_P), and negative predictive value = T_N / (T_N + F_N). The rationale behind using multiple parameters is that accuracy is not the de facto model in every case; for example, in the case of predicting immunization, we might prefer an algorithm with high sensitivity over another algorithm with higher accuracy. Furthermore, the overall prediction accuracy of all machine learning models was measured using the area under the ROC curve (C-statistic). ROC curve is a plot of true positive rate [T_P / (T_P + F_N)] against the false positive rate [F_P / (F_P + T_N)], and AUC determines the predictive performance of the model.

Results

The baseline characteristics of the children in the test and validation cohorts are shown in Table 1. Both subsets had similar characteristics in terms of the selected variables. The mean enrollment age was 12.9 weeks, and the highest enrollment was carried out during the BCG vaccination visit. The baseline demographic characteristics of the participants excluded from the analysis (n=256) were not significantly different from those included in the final analysis (N=47,554). Out of 11,889 cases in the validation dataset, the actual number of children who defaulted was 6155.

Figure 3 provides a visual illustration of the outcomes of all models showing the number of true positives, true negatives, false positives, and false negatives.

According to the four outcomes produced, the recursive partitioning model predicted that 45.90% (5457/11,889) children would default; among them, 83.43% (4553/5457) children did default, which accounts for 83.4% of the total default population. Likewise, it was predicted that 54.10% (6432/11,889) children would return for the next vaccination; among them, 75.09% (4830/6432) children did return. In the support vector machine model, the total population of children who defaulted was 7310 (7310/11,889, 61.48%); among them, 5473 defaulted, which accounts for 74.87% (5473/7310) of the total default population. Likewise, it predicted that 38.51% (4579/11,889) children would return for vaccination; among them, 85.11% (3897/4579) did return. Meanwhile, the random forest model predicted that the total number of children who defaulted will be 70.89% (8428/11,889); among them, 69.34% (5844/8428) did default. Likewise, it predicted that 29.11% (3461/11,889) children would return for vaccination; among them, 91.01% (3150/3461) did return. Lastly, the C-forest model predicted that 63.34% (7530/11,889) would default; among them, 73.98% (5571/7530) did default. Likewise, it predicted that 36.66% (4359/11,889) children would return for vaccination; among them, 86.20% (3775/4359) did return. These results produced accuracy rates of approximately 78.9%, 78.8%, 75.6%, and 78.6% for recursive partitioning, SVMs, random forests, and C-forest, respectively (Table 2).

Table 1. Baseline characteristics of the training and validation data cohorts.

Characteristics of the participants	Training cohort (N=47,554)	Validation cohort (N=11,889)
Enrollment age (weeks), mean (SD)	12.92 (15.9)	12.93 (15.9)
Gender (female), n (%)	20,425 (42.95)	5049 (42.47)
Enrollment vaccine, n (%)		
BCG[a]	24,744 (52.03)	6195 (52.11)
Pentavalent-1	8955 (18.83)	2236 (18.81)
Others	13,855 (29.14)	3458 (29.08)
Language spoken, n (%)		
Urdu	846 (1.78)	208 (1.75)
Unknown	46,561 (97.91)	11,644 (97.94)
Others	147 (0.31)	37 (0.31)
Place of residence (town), n (%)		
Korangi	41,225 (86.69)	10,296 (86.60)
Muzafargarh Town	1693 (3.56)	445 (3.74)
Others	4636 (9.75)	1148 (9.66)
Place of residence (city), n (%)		
Karachi	45,415 (95.50)	11,334 (95.33)
Muzafargarh	1996 (4.20)	519 (4.37)
Others	43 (0.30)	36 (0.30)
Timeliness of vaccination[b], n (%)		
BCG		
Early	16 (0.07)	4 (0.07)
Late	17,126 (70.19)	4254 (69.61)
Timely	7258 (29.75)	1852 (30.32)
Pentavalent-I		
Early	11 (0.12)	1 (0.02)
Late	8892 (99.73)	2220 (99.78)
Timely	13 (0.15)	4 (0.18)
Pentavalent-II		
Early	9 (0.22)	2 (0.20)
Late	4099 (99.15)	996 (99.20)
Timely	26 (0.63)	6 (0.60)
Pentavalent-III		
Early	14 (0.38)	3 (0.34)
Late	4338 (99.31)	883 (99.21)
Timely	11 (0.30)	4 (0.45)
Measles-I		
Early	6 (0.14)	1 (0.09)
Late	4338 (99.20)	1113 (99.02)
Timely	29 (0.66)	10 (0.89)
Age group		
<1 month	5465 (11.49)	1386 (11.66)

Characteristics of the participants	Training cohort (N=47,554)	Validation cohort (N=11,889)
1-9 months	35,972 (75.64)	8949 (75.27)
>1 year	6117 (12.86)	1554 (13.07)

[a]BCG: Bacillus Calmette–Guérin.

[b]Excludes records with invalid dates.

Figure 3. Flow diagram of all the study predictive models.

Table 2. Performance of the study models predicting the likelihood of defaulting from the follow-up immunization visits. Higher C-statistics results in better algorithm discrimination.

Model	Area under the curve C-statistic	95% CI
Recursive partitioning	0.791	0.784-0.798
Support vector machines	0.786	0.777-0.792
Random forests	0.750	0.742-0.756
C-Forest	0.782	0.775-0.789

Overtime, through using artificial intelligence (AI), because more data are captured, the system will continue to self-learn from accumulated records, recognizing influential variables, self-selecting statistical models, and continually upgrading itself to achieve the highest predictive accuracy. However, the recursive partitioning model outperforms the rest of he models in terms of overall accuracy rates, but since the performance of a classifier does not directly depend on the accuracy rate alone, therefore, we analyzed other performance metrics, such as sensitivity, specificity, positive predictive value, and negative predictive value. Table 3 presents the outcomes for all the performance metrics.

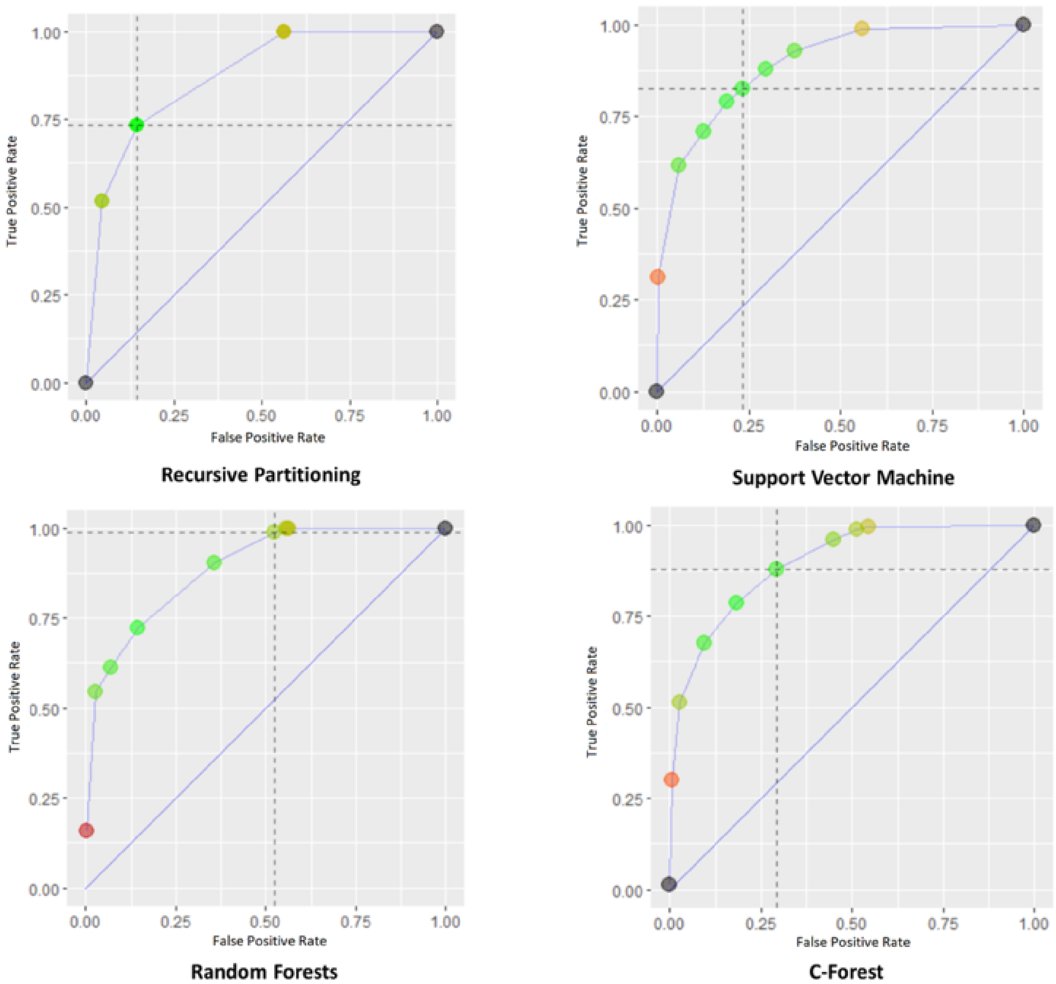
According to Table 3, the random forest model outperforms all the other models with a sensitivity rate of 94.9%, although it has the lowest accuracy rate. The random forest model predicted that majority of the population will default, that is, it has predicted that (70.88% of the whole population, 8428/11,889) will default. Moreover, it can correctly identify the maximum number of children who defaulted (5844 out of 8428 children actually defaulted). The random forest model's high sensitivity permits the recognition of almost all children who will not receive subsequent vaccinations (94.9%). By contrast, the recursive partitioning model produces the highest specificity at 84.2% and lowest sensitivity at 74.0%, indicating that it can identify the maximum number of children who will adhere to their vaccination schedule. The recursive partitioning model produces moderate results for both sensitivity and specificity at 74.0% and 84.2%, respectively, and it had the highest accuracy rate at 78.9%. Figure 4 shows the individual performance metrics for each model as illustrated in the ROC.

The random forest model correctly predicted 8994 cases, yielding a sensitivity and specificity of 94.9% and 54.9%, respectively. The C-forest model, SVMs, and recursive partitioning models improved the prediction by achieving 352, 376, and 389, additional correct cases, respectively, over the predictions made using the random forest model. However, looking across the models, as accuracy of the models increased, the sensitivity decreased from 94.9% (for random forest model) to 74.0% (for recursive partitioning model), whereas specificity went up from 54.9% (for random forest model) to 84.2% (for recursive partitioning models). All models had a C-statistic of 0.750 or above, and the recursive partitioning model algorithm had the highest statistic (AUC 0.791, 95% CI 0.784-0.798; Table 2).

Table 3. Performance metrics of all the study predictive models.

Model	Accuracy (%)	Sensitivity (%)	Specificity (%)	Precision (%)	Negative predicted value (%)
Recursive partitioning	78.9	74.0	84.2	83.4	75.1
Support vector machines	78.8	88.9	68.0	74.9	85.1
Random forests	75.6	94.9	54.9	69.3	91.0
C-Forest	78.6	90.5	65.8	74.0	86.6

Figure 4. Receiver operating characteristic for all the study predictive models.



Discussion

Principal Findings

We have demonstrated the feasibility and validity of the predictive analytics algorithm in identifying children who were likely to default from subsequent immunization visits, and the algorithm yielded a 79.1% accuracy rate. This information could empower policy makers, immunization programs, and vaccinators to reduce dropouts and improve immunization coverage, timeliness, and equity through the targeted use of evidenced-based interventions at an individual or community level. Reduced immunization coverage and losses to follow-up do not allow communities to fully take advantage of the benefit of routine childhood immunization programs.

Because the approach is becoming a topic of interest, results from initial formative studies on the use of predictive analytics in a variety of settings are now being assessed. Our findings are in accordance with those reported from other studies that have used AI technology within the health domain to predict future outcomes. The success rates of predictions from other studies are similar; for example, a model conducting risk profiling of patients who are likely to develop chronic kidney disease using gradient tree-based algorithm had an AUC statistic of 0.871, and statistically significant (*P*<.001) differences were observed in disease outcomes in the high-, medium-, and low-risk groups [18]. Similarly, in another study that predicted cardiovascular risk, the predictions produced by the machine learning algorithm using a variety of models were better (AUC 0.745, 95% CI 0.739-0.750) than those produced by the existing risk prediction algorithms [19]. These findings corroborate the potential of predictive analytics to revolutionize the current practices of preventing disease and promoting better health care.

This formative study tested the feasibility of an array of statistical models to make predictions showing the variability of results depending upon our outcome of interest. The random forest model had the best performance with results expected to further improve as more data is collected because the system learns overtime as a result of machine learning. Other studies that have used different predictive models also reinforce the finding that one of the models is typically the highest achieving model compared with others depending on the outcome of interest [19]. The selection of variables for the predictive model was limited to the information collected during routine immunizations. Machine learning will also proactively interpret and identify new data patterns in routinely collected data, significantly improving the accuracy of individual risk classification over time. However, collecting additional variables, including household income, ethnicity, maternal tetanus vaccination status, and maternal and paternal education status, may further enhance the predictive accuracy.

Operationally, developing countries are in the process of using digital immunization registries (DIRs), which provide an extremely rich source of patient information [20], creating an opportunity for effectively using machine learning and predictive analytics to identify children who are most likely to default from their immunization schedule. From a technical standpoint, predictive analytics has high interoperability, which helps it to be easily linked to any DIR or electronic health record to strengthen the health systems and empower the vaccinators. This feature further enhances the utility of this module given the high appeal for interoperability to enable cooperative progress in public health through linking heterogeneous data [21].

To further enhance the ease of use, the front end of the module is designed for nonprogrammers, and it does not require technologically skilled users, making it easy to implement and sustain in low-resource settings. From an operational perspective, the utilization of predictive analytics does not require large investments in resources or trainings. With the expanding presence of DIRs, the technological platform for large-scale implementation is already in place, and the user interface can be tailored to meet local requirements. The self-learning algorithm quickly adapts to context, adjusting variables, models, and standard measures as needed.

Financially, the returns to be gained from optimal resource allocation and reduced expenditure on vaccine-preventable diseases are substantially greater than the set-up cost, ensuring a high return on investment per dollar spent. Although a high-dropout may mean that a large proportion of the population must be targeted at the start, the offset in the required funding may be substantial for LMICs. Other clinical studies that used AI for predicting future outcomes also highlight the reduction in economic burden through early detection and treatment of disease [22]. The health department and local government could ultimately benefit through savings incurred owing to the allocation of resources to population segments that require them the most. Wasting of the limited resources of the government could be reduced if not eliminated. Furthermore, the health department could make substantial savings in the treatment costs for vaccine-preventable diseases.

In addition, machine learning techniques have also been proven to improve resource allocation decisions. For instance, a study examining patient admission decisions in tertiary care hospitals has revealed that a machine learning Bayesian model could lead to more efficient resource allocation decisions when deciding which patients to admit in the hospital. Similarly, in our context, predictive analytics can identify children at high risk for overburdened frontline health workers and as a result, evidence-based interventions, such as center-based counseling, out-reach services, and repeated SMS reminders, can be targeted toward this cohort leading to optimal resource allocation.

Our idea constitutes an unconventional approach for improving the timeliness of routine immunization and reducing missed opportunities; in an era where a collection of massive amounts of reliable data has become cheap and easy, predictive analytics is considered a cutting-edge innovation with only limited application in the field of health service delivery despite its strong impact and potential. Machine learning, particularly deep learning, is now being used to predict the patients' chances of relapse, early deterioration, and developing diseases, such as cancer and automated diagnosis of eye disease, as recently shown by Google. However, in the field of immunization, predictive modeling is a novel idea, and its potential in revolutionizing immunization service delivery is yet to be identified.

To achieve the key goal of the global vaccine action plan 2011-2020, for example, meet the 90% national vaccination coverage and 80% coverage rate for all vaccines by 2020 in every district, we need to focus on strategies that reduce dropouts and expand coverage. As presented in this paper, predictive analytics can help in the identification of children who are likely to default or dropout from the course of the immunization schedule; therefore, communities where incomplete immunization rates are prevalent will benefit the most from targeted concentration of efforts promoting the goal of universal health equity. Although this paper provides a plausible causal pathway in which the information gained through this model can lead to health system improvement, more rigorous evaluations must be conducted to fully determine the programmatic effectiveness of this model from an implementation perspective.

Limitations

The limitation of our model was the exclusion of the records containing invalid dates for age or immunizations. Although the imputation method was used to deal with invalid or missing data in the machine learning models because this was a feasibility study, the data models were utilized only on complete records. Furthermore, it is relevant to mention that we have evaluated the predictive analytics algorithm on only one outcome, particularly the likelihood of a child to default from subsequent immunization visits. There are other parameters in which the algorithm could be evaluated, such as the likelihood of completing the full immunization schedule. However, to keep the approach simple, other approaches were considered beyond the scope of this study, and this must be further evaluated. The predictive analytics will be beneficial for communities with high access and underutilized services because the model is based on initial contact with vaccinator or health care worker, and communities with low access may only benefit indirectly when herd immunity is achieved. The other limitation of the study is the generalizability of data to other populations. Developing this model for other populations would require recalibration and adjustment to account for other disparities as well as the inclusion of relevant prediction variables.

Conclusion

The expansion of DIRs in lower- and middle-income countries is creating a unique opportunity to analyze and interpret data to generate real-time actionable insight in expanding immunization services and coverage. This feasibility study showed that predictive analytics can accurately identify individual children who are likely to default from subsequent immunization visits. Predictive analytics can strengthen immunization programs by facilitating the targeted implementation of interventions aimed at reducing the dropouts.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
AUC: area under the curve
BCG: Bacillus Calmette–Guérin
DIR: digital immunization registries
DTP3: diphtheria-tetanus-pertussis
EPI: Expanded Program on Immunization
FN: false negative
IRD: Interactive Research and Development
LMIC: low- and middle-income countries
ROC: receiving operating characteristic
SMS: short message service
SVM: support vector machines
TP: true position
UNICEF: United Nations International Children's Emergency Fund
WHO: World Health Organization

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Original Paper

User-Driven Comments on a Facebook Advertisement Recruiting Canadian Parents in a Study on Immunization: Content Analysis

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Abstract

Background: More people are searching for immunization information online and potentially being exposed to misinformation and antivaccination sentiment in content and discussions on social media platforms. As vaccination coverage rates remain suboptimal in several developed countries, and outbreaks of vaccine-preventable diseases become more prevalent, it is important that we build on previous research by analyzing themes in online vaccination discussions, including those that individuals may see without actively searching for information on immunization.

Objective: The study aimed to explore the sentiments and themes behind an unsolicited debate on immunization in order to better inform public health interventions countering antivaccination sentiment.

Methods: We analyzed and quantified 117 user-driven open-ended comments on immunization posted in the Comments section of a Facebook advertisement that targeted Canadian parents for recruitment into a larger study on immunization. Then, 2 raters coded all comments using content analysis.

Results: Of 117 comments, 85 were posted by unique commentators, with most being female (65/85, 77%). The largest proportion of the immunization comments were positive (51/117, 43.6%), followed by negative (41/117, 35.0%), ambiguous (20/117, 17.1%), and hesitant (5/117, 4.3%). Inaccurate knowledge (27/130, 20.8%) and misperceptions of risk (23/130, 17.7%) were most prevalent in the 130 nonpositive comments. Other claims included distrust of pharmaceutical companies or government agencies (18/130, 13.8%), distrust of the health care system or providers (15/130, 11.5%), past negative experiences with vaccination or beliefs (10/130, 7.7%), and attitudes about health and prevention (10/130, 7.7%). Almost 40% (29/74, 39%) of the positive comments communicated the risks of not vaccinating, followed by judgments on the knowledge level of nonvaccinators (13/74, 18%). A total of 10 positive comments (10/74, 14%) specifically refuted the link between autism and vaccination.

Conclusions: The presence of more than 100 unsolicited user-driven comments on a platform not intended for discussion, nor providing any information on immunization, illustrates the strong sentiments associated with immunization and the arbitrariness of the online platforms used for immunization debates. Health authorities should be more proactive in finding mechanisms to refute misinformation and misperceptions that are propagating uncontested online. Online debates and communications on immunization need to be identified by continuous monitoring in order for health authorities to understand the current themes and trends, and to engage in the discussion.

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KEYWORDS

Facebook; immunization; vaccination; antivaccination movement; social media

Introduction

The Role of the Internet in Vaccine Hesitancy

The World Health Organization (WHO) and its group of experts have identified vaccine hesitancy as an important issue facing immunization programs in the developed world [1]. This has been evident in Canada and other developed nations such as the United States and countries in Europe that have reported an increase in the number of outbreaks of vaccine-preventable diseases [2-7].

Many factors influence vaccine noncompliance or hesitancy; however, the role of the internet due to the abundance of online antivaccination sentiment and activists has been reported as an important concern [8-13]. A significant association was established between using the internet to search for vaccine information and negative parental perception of the risk of childhood immunizations [14]. More people are searching for health information online, including information on immunization [15,16]. Health professionals are concerned that parents seeking vaccine information online are being exposed to misinformation and antivaccination sentiment via websites and online communications on social media platforms [8,11,12,17]. Over the past decade, social media sites have gained popularity in Canada, where 67% of Canadian internet users are using social media on a daily basis [16], with most users being under the age of 35 years [18]. In Canada, Facebook is reported as the most popular social media platform, with usage rates higher than global and US averages [19,20]. Health information communicated in interactive platforms is of questionable accuracy, as it is often exchanged without the participation of health professionals or health organizations [17,21]. This exchange of misinformation online has the potential to influence parents' decision to vaccinate their children [12,14,22,23] and may be contributing to suboptimal vaccination coverage among Canadian children [24] and increases in vaccine-preventable disease rates [25-28]. Results from the last Childhood National Immunization Coverage Survey show that 70% of Canadian parents surveyed reported being concerned about potential side effects of vaccines, and 37% believed that vaccines can cause disease [24]. A recent study by Dubé et al reported that vaccine experts perceive a decline in vaccination rates and that vaccine hesitancy is an important issue to address in Canada [29]. Furthermore, participants reported that dissemination of negative information online and lack of knowledge about vaccines were key issues in the causes of vaccine hesitancy in Canada [29].

Many studies have analyzed content from vaccine-critical websites and blogs found via search engines, as well as content posted on participative websites, chat rooms, and social media platforms such as Twitter, Facebook, YouTube, and Myspace [30]. These studies have identified similar themes, such as vaccine safety and effectiveness, alternative medicine, civil liberties, conspiracy theories, morality and misinformation, and mistrust of health professionals as the predominant arguments in the antivaccination movement [10,30,31]. Techniques such as skewing science, shifting hypotheses, and attacking critics have been reported as tactics of the online antivaccination community arguing against vaccination [11]. Themes underlying vaccine hesitancy can change over time and by place [13,29]; therefore, as coverage rates remain suboptimal in Canada and outbreaks of vaccine-preventable diseases become more prevalent, it is critical that we continue to build on previous research by analyzing themes in online vaccination discussions. Most research has focused on analyzing the content of discussions on sites or platforms that individuals would find via active research on immunization [30]. However, there is a gap in research in analyzing vaccine information that individuals may see without actively searching for information and could influence decisions on vaccination [30]. Ward et al proposed that future research on vaccine criticism on the internet should include analysis of more complex and interactive ways of information circulation, such as posts, likes, links, and retweets [30]. Furthermore, there is a need for more research to better understand vaccination sentiments specifically among Canadian parents.

From December 12, 2013 to January 11, 2014, we posted 6 different Facebook advertisements linked to a Web-based survey on childhood immunizations to the Facebook News Feeds of Canadian parents as part of a larger research study [32]. The advertisements reached over 100,000 Canadian parents who matched the following inclusion criteria: (1) located in Canada, (2) 18 years of age or older, (3) parent of a child aged 0 to 15 years, and (4) displaying a profile in French or English. Overall, women represented the majority of Facebook users reached by the advertisements and who also clicked on the advertisement to the Web-based survey [32]. Two advertisements (Figure 1 and Figure 2) had the highest number of views from unique Facebook users reaching 74,572 users and 38,643 users, respectively, and the highest click-through rates to our online survey [32]. Further details on the methods and results of this recruitment strategy are available [32]. The advertisements did not provide any information on immunization, did not try to solicit discussion, and were not posted, shared, liked, or promoted by the researchers. The advertisements did not provide any information on immunization, did not try to solicit discussion, and were not posted, shared, liked, or promoted by the researchers. The Comments section of the advertisements was accessible, and this created an unsolicited and spontaneous discourse where users posted comments on immunization to the 2 most viewed advertisements (Figures 1 and 2).

Figure 1. The most popular Facebook advertisement posted to Canadian parents' News Feeds from December 12, 2013 to January 11, 2014.

Figure 2. The second most popular Facebook advertisement posted to Canadian parents' News Feeds from December 12, 2013 to January 11, 2014.

Objective

This study investigated a unique interactive debate on Facebook resulting from the above Facebook advertisements to recruit parents in immunization research. Our objective was to qualitatively analyze and quantify the content of users' posts to describe the main vaccination sentiments and themes of an online immunization debate of Facebook users who commented on our posted advertisements, in order to better understand the vaccination debate and to identify underlying themes. We addressed this by asking 2 questions. First, what are the main vaccination sentiments (eg, anti- or provaccination) in the online debate? Second, what are the main themes on vaccination by type of sentiment? This study will add to the body of research on online vaccination discussions by analyzing a posting not intended for interaction that individuals could see without actively searching for information on immunization. The results will assist health professionals in understanding some of the content on vaccine information being shared online in order to help guide messaging and the development of online interventions.

Methods

Content Analysis

In this study, we qualitatively analyzed and quantified the content of open-ended comments posted by Facebook users. On January 11, 2014, at the end of the 4-week recruitment period, we captured and saved all user comments posted in the Comments section of the Facebook advertisements. We included all comments in French or English that contained any message on immunization. We excluded any comments that did not pertain to immunization (eg, comments on the advertisement itself, "lol"). We did not capture any identifying information from the Facebook users, and we removed the advertisement (along with the posted comments) from Facebook immediately at the end of the recruitment period; thus, no captured comments can be directly or indirectly linked to any Facebook user.

Data Analysis

After comment capture, 2 raters (JLT and BL) independently coded the comments on the type of message, the sex of the user, the main message of the comment, and the claims made in the comment. To increase validity, the 2 raters independently categorized the comments and resolved any difference to reach 100% consensus based on discussion and a clear framework previously established [33-35]. A third rater was available if consensus was not attainable.

We measured user interaction by the number of "likes" for specific comments. Commentators either simply made comments or provided a link to vaccine information online. Thus, we classified the type of comment as comment only, comment with link to accurate information or trustworthy source, or comment with link to inaccurate information or nontrustworthy source. We classified trustworthy sources as links to government or reputable associations or scientists. We classified accurate information as websites with information or statistics from government sources or peer-reviewed studies. We classified remaining links as nontrustworthy or inaccurate. We determined the sex of the commentator by using the user's name, photo, or comment and classified sex as not clear if one or both raters had any uncertainty.

We categorized the main message of the comments as positive, negative, hesitant, or ambiguous. We coded the comments as positive if the central message supported vaccination, portraying it positively (eg, describing the benefits or safety of vaccination, promoting vaccinations, describing the risks of not vaccinating or low risk of vaccinating) [36]. We coded comments as negative if the central message portrayed vaccination negatively (eg, emphasizing the risk of vaccination, opposing vaccination, promoting distrust in vaccine science, making allegations of conspiracy or collusion) [36]. If the central message portrayed indecision or uncertainty on the risks or benefits of vaccination (eg, questions or concerns about risk or safety, requests for information or links, questions regarding others' decision to vaccinate), we coded the comments as hesitant. If the main message was not clear, we coded the comment as ambiguous. We then used two separate coding schemes to subcategorize the content: one for the negative, hesitant, and ambiguous comments and one for the positive comments.

We subcategorized the claims in the negative, hesitant, and ambiguous comments based on the themes of determinants of vaccine hesitancy suggested by the WHO's Strategic Advisory Group of Experts Working Group (SAGE WG) on Immunization [37,38]. The SAGE WG matrix organizes vaccine sentiment into three domains: contextual influences, such as socioeconomic barriers, mistrust in the pharmaceutical industry, or religious values; individual and social group influences, such as personal knowledge or perceptions of risk; and vaccination and vaccination-specific issues, such as the vaccination schedule or characteristics of the vaccine; each main theme contains specific subcategories [37-39]. We categorized claims about vaccination within the comments according to the major themes and subthemes; claims could be classified into one or more themes and subcategories within the themes. We chose the SAGE WG matrix as the coding framework because it was developed by experts to include all known and potential determinants of vaccine hesitancy based on a thorough systematic review and expert opinion [37,38]. We created a category of other for any claim not covered by the SAGE WG matrix as determined by rater consensus [40]. The material was read several times prior to coding to ensure it fit the preconceived framework and to identify any other themes. Definitions of the framework categories were researched and discussed between the raters prior to coding. Both raters manually coded and discussed material from a random sample of respondents prior to independent coding.

The SAGE WG coding framework did not accurately capture the themes in the positive comments; thus, we categorized the claims in the positive comments based on broad themes in the data, with both raters independently generating categories and reaching consensus to develop the final coding scheme [33-35,40]. No new codes arose after approximately 40% of the comments were assessed.

The 2 raters independently categorized all comments (negative and positive) and claims within the comments, and achieved over 95% consensus. The raters met once to discuss items where consensus was not reached and achieved 100% consensus based on discussion and preestablished frameworks and criteria [33-35].

We conducted descriptive statistics to quantify respondent characteristics, main messages, and identified themes. Raters conducted content analysis with NVivo 10 qualitative data analysis software (QSR International) and quantified the analysis with descriptive statistics using Microsoft Office Excel 2007 (Microsoft Corporation). We obtained ethical approval from the University of Toronto’s Office of Research Ethics, Toronto, ON, Canada (REF#29309).

Results

Respondent Characteristics, Main Messages, and User Interaction

The advertisements generated 117 comments by 85 unique Facebook users after we excluded 9 comments not meeting the inclusion criteria. Of the 85 commentators, 77% (65/85) were female, 14% (12/85) were male, and for 9% (8/85) the sex was not clear. The majority of the comments were comments only (103/117, 88.0%), and 11.9% (14/117) posted links to websites. Of the 14 website links, 2 were from trustworthy sources, with 1 linked to a trustworthy source with accurate information (a government website with official statistics) and 1 linked to an online news story with accurate information posted from a government source. The main message of 43.6% (51/117) of comments was positive, followed by 35.0% (41/117) negative, 17.1% (20/117) ambiguous, and 4.3% (5/117) hesitant. Comments with the most interaction (20 or more likes) had mostly positive main messages (8/9, 89%) and 1 negative. The following 2 redacted positive comments had the most interaction (43 and 40 likes, respectively) and highlighted the predominant theme within the positive comments: the benefits of vaccines versus the risk for children and others in becoming infected with the disease (indicated as theme 1 in the comments below). In addition, the 2 other most identified themes were represented within these comments: parents who do not vaccinate their children are uneducated (theme 2), and vaccines do not cause autism (theme 3). Note that we redacted comments solely for the purpose of omitting words and sentences inconsequential to the context and analysis.

> *Vaccinating your children is the best way to prevent them (and others) from getting viruses and diseases...you are essentially protecting them from the awful signs and symptoms of the disease...the benefits out way the risks (Theme 1). Why do you think small pox was eradicated? Bc enough people around the world got the vaccine for it and it had no one to spread to, therefore: eradicated!!! There is NOT as many people unvaccinated as vaccinated, 80% of the population vaccinate their children...that # is decreasing bc of people’s lack of knowledge...Your not idiots for vaccinating your children you are just uneducated about biomedical facts! (Theme 2)*
>
> *What about the infants and people who are immuno-compromised who CANT vaccinate? They depend on those people who CAN vaccinate to be protected and not spread these things!! (Theme 1) I have a child with autism, and do NOT believe vaccines have ANYTHING to do with it! That has been disproven! (Theme 3)*

Lack of knowledge or awareness was the most prevalent theme in the negative comments, as suggested by the misinformation on immunity and transmission of disease contained within the following most liked (40 likes) negative redacted comment:

> *If their was a breakout of tuberculosis, polio...the vaccinated children would not be amune! If a vaccine protects you & your children, why...are all the vaccinated children catching it? There is absolutely no evidence that outbreaks start from unvaccinated people!...Every time there’s an outbreak there’s as many vaccinated as unvaccinated people catching the disease. There is absolutely no protection from a disease from taking a vaccine!*

Themes in the Negative, Hesitant, and Ambiguous Comments

In the 66 negative, hesitant, or ambiguous comments, 130 claims were made on factors affecting vaccination decisions. Individual and social group influence was the predominant theme in the claims within the posted comments (85/130, 65.4%). Within this theme, 20.8% (27/130) of the claims displayed lack of knowledge or awareness on immunization (including misinformation and the belief in their own research and knowledge), with the majority (22/27, 81%) providing inaccurate information or misperceptions on immunization and some explicitly stating their belief in the credibility or accuracy of their knowledge and research (5/27, 19%). Approximately 18% (23/130, 17.7%) of the claims revealed a low perception of the risk of disease and need for the vaccine or a high perception of risk of adverse events associated with vaccination. Table 1 displays the identified themes according to the WHO SAGE WG matrix on vaccine hesitancy.

Themes in the Positive Comments

In the 51 positive comments (and 2 hesitant comments with positive claims), we identified 74 claims on factors affecting vaccination decisions. Within these comments, the majority (29/74, 39%) of the positive claims stated concerns over nonvaccinating parents putting their children and others at risk of disease and death or stated how the benefits outweigh the potential risks, followed by claims that nonvaccinating parents are uneducated, unintelligent, or selfish (13/74, 18%) (Table 2).

Table 1. Negative, hesitant, and ambivalent claims posted by Facebook users on Facebook advertisements categorized by themes (n=130).

Themes	n (%)	Examples of claims within comments
Contextual influences	19 (14.6)	
Mistrust in pharmaceutical industry or government transparency	18 (13.8)	• Pharma wanna make money...Bottom line is that vaccination is all about $$$$$... • The chances of your child dying from these diseases is highly unlikely. There is SO much gov involvement...
Religious values	1 (0.8)	• I come from a Mennonite background where we were not vaccinated.
Individual and group influences	85 (65.4)	
Lack of knowledge or awareness (misinformation and belief in own knowledge or research)	27 (20.8)	• Lmao the courts admitted to vaccines causing autism...But they did it quietly! If I find the article I will post it on here...I do not vaccinate my children and never will...liquid mercury is metal you are injecting into your children... • The argument that an epidemic would break out if children were not vaccinated is proven incorrect by every Amish/Mennonite community that is thriving today. Recent studies have shown startling evidence that links autism directly to vaccines along with decreased brain function. If you would like sources to this I can provide them. • All sorts of diseases have been directly linked to vaccines including and especially autism...I hope wise people everywhere choose to educate themselves before making this decision. • From my observations, limited as they are, the immunized ones tend to be the ones lacking basic immunity.
Risk or benefit of vaccination (perceived, heuristic)	23 (17.7)	• ...so in my opinion he still would have a chance of getting these illnesses if I vaccinated him so I don't see the point in giving him something that WILL harm him for a CHANCE that he might not get sick...There are some vaccinations that (my) children will not get (like chicken pox) as I think it is an unnecessary risk... • There is absolutely no protection from a disease from taking a vaccine! But there are many people who die from vaccines every year! • Don't fool yourself. EVERY TIME you vaccinate there is a risk, even of death. It is up to you to decide if that risk is what is right for your child. For some children it might be worth it, but for other children it isn't worth it...There are risks and there are children that are much better off without vaccines.
Health system and providers (trust and personal experience)	15 (11.5)	• Ask your doctor?! No Doctor is God. They are all trained to say the same thing. The truth is none of us know the truth. • Any health care professional will side with pro vaccine idea. I will not vaccinate my son. Do you even know what your injecting in your kid?
Beliefs and attitudes about health and prevention	10 (7.7)	• My children have needed to see a doc approximately never in their lives. They are a testament to a holistic lifestyle and natural immunity. My observations of most kids that have been vaccinated is that they seem to be endlessly ill and have had multiple courses of antibiotics in their short lives!!
Experience with past vaccination	10 (7.7)	• My son had convulsions after getting vaccinated, that was 19 years ago and no vaccines again.
Vaccination or vaccination-specific issues	5 (3.8)	
Role of health care professionals	3 (2.3)	• ...my paediatrician & general practitioner both disagree with vaccinating...
Vaccination schedule	2 (1.5)	• None of this 3 in 1...Dangerous injecting 2-4 shots in a kid at one time...
Other	21 (16.2)	
Parents' right to choose and not be judged	18 (13.8)	• I think every parent has the right to chose what is best for their child. I don't think it's right for other parents or people to judge others for what they decide!!! • I find it incredibly interesting that so many people are bothered by someone else's choice to vaccinate or not vaccinate. If you get vaccinated, who cares if someone else doesn't, it's not your life....Everyone needs to take a chill pill... • Defend your vaccines all you want but don't call us idiots for not taking them!
Requesting information or sources	3 (2.3)	• Do you have any sources for your input?

Table 2. Positive claims posted by Facebook users on Facebook advertisements categorized by themes (n=74)[a,b].

Themes	n (%)	Examples of claims within comments
Vaccines prevent disease risk or benefit	29 (39)	• No vaccine is 100% but those vaccinated can fight the illness more effectively. Herd immunity only works when we vaccinate. I wonder if some peoples opinions would change if we lived in a country where vaccination was not common, and these diseases were common... • Some parents have chosen to opt out and Polio, Whooping Cough and Diptheria are recurring. This puts us all at risk. The benefits outweigh the risks. We do not want these diseases to return with a vengeance! • I personally could not live with myself if my child got very sick or died from a preventable disease to which we have access to free immunizations for...Now of course I vaccinated my kids because they can protect them from death...If they were bad...Or caused autism they would have been out of the market and not given by doctors don't you think? I have 4 kids ranging from 18 to ten months. It's worth the risk getting vaccinated. I've seen what whooping cough and polio do to people. I promise, those who've had polio will probably get their kids vaccinated.
Parents who do not vaccinate are uneducated or unintelligent	13 (18)	• If you're going to be an idiot and not immunize, at least make sure you're a well educated idiot... • Wow, it never ceases to amaze me how ignorant and just plain dumb some people are... • It's idiots who don't vaccinate their kids that cause outbreaks...people think that they know more than the medical community. • I find people who don't vaccinate are some of the most uneducated nut jobs...
Follow the advice of health care providers and trustworthy sources	12 (16)	• ...get your information from reputable sites ie health canada or the cdc. Stay away from those "crunchy granola" opinion- based websites • Research does not include google off siting an article you found on Facebook. These people don't even know the definition of a peer reviewed research paper or study...and if you can't tell the difference you should try and trust that the medical professionals who do know... • ...everyone should read official statistics and not internet mumbo jumbo. The internet has so much bs that it can make anyone's perception a reality... • Yup our society rallies around a former porn star/actress looking to continue her 15 minutes of fame instead of putting our trust in our medical and science community...Sad state of society I'd say!
Vaccines do not cause autism	10 (14)	• Jenny McCarthy made the Hollywood rounds stating her son got autism from his vaccines...Since then it has been proven her son doesn't even have autism nor do vaccines cause autism... • I have a child with autism, and do NOT believe vaccines have ANYTHING to do with it! That has been disproven! • The jury is not out on autism. The verdict is no link...
I am provaccine or vaccinate	10 (14)	• Be smart...Vaccinate • Myself, I am a believer in vaccinations but that's just what I believe is right for my kids...

[a]We included 2 hesitant comments with positive claims in the analysis.

[b]Total percentage does not equal 100% due to rounding.

Discussion

Principal Findings

The majority of comments were clearly pro- (51/117, 43.6%) or antivaccination (41/117, 35.0%) with few comments vocalizing vaccine hesitancy (4.3%). Themes in the online debate followed those identified in the literature and mostly captured in the SAGE WG framework [30,37]. As reported in other studies analyzing online vaccination messages [31,37,41], information in the negative comments was often inaccurate and the risks of immunization were misperceived. Mistrust in the pharmaceutical industry, the government, and health system was also a recurring theme in the online debate and previously identified as an important theme in studies analyzing vaccine-critical websites [10,21,30,31]. The right to choose without being judged was expressed within many negative comments yet not identified in the SAGE WG framework. This theme could have emerged in response to several judgments made within the positive comments on the level of intelligence or education of nonvaccinators. However, the theme of civil liberties or parents' right to choose has been reported in previous studies analyzing vaccine opposition website content [10,30,31,41]. Slightly more positive comments were posted than negative or hesitant, and positive comments received the most interaction. Although the majority of the positive comments did not provide any links or obvious information from health authorities, there was encouragement to seek out trusted sources and people. No commentator self-identified as a health professional. The debate also highlighted the persistence of the myth linking vaccines to autism. Seeman et al [42] also reported this persistent inaccuracy on the safety of the measles-mumps-rubella (MMR) vaccine in an online survey of Canadian parents, and Nicholson and Leask [21] reported that one-third of the participants in an online MMR vaccine discussion forum were critical of the vaccine, with the risk of adverse effects and autism and concerns with vaccine ingredients as the major themes. Furthermore, a recent Canadian survey reported that 28% of adults reported to believe that there is or be uncertain about a link between vaccines and autism [43].

As we targeted the advertisements at Canadian parents, most of the commentators likely represented this demographic. Most of the commentators were female, but we expected this, as the Facebook campaign biased the advertisement reach toward a female population [32]. The 2 most popular advertisements reached over 100,000 Canadian parents on Facebook [32]; thus, the posted comments would have been visible to other targeted and potentially vaccine-hesitant Canadian parents who chose not to respond, as well as an unknown number of individuals not targeted by the campaign. These online debates should be of concern to public health authorities, as the spread of misinformation and misperceptions can reach large audiences with the potential to negatively influence vaccine-hesitant and provaccine individuals [22]. In addition, the analysis of the online debate revealed the lack of knowledge and spread of misinformation on a platform not intended to solicit discussion. The presence of public health authorities online is limited to top-down dissemination of information with limited engagement in online debates. This lack of public health involvement online could potentially enable the unabated spread of antivaccination sentiment and misinformation that potentially affect vaccination decisions among hesitant and provaccine parents.

Identified themes, such as the perceived risk of adverse events versus the risk of disease, and misinformation on autism and other disorders, immunity, and vaccine ingredients, could be addressed with more communication messages tailored to the issues in the online discussions. Although some antivaccination activists may never be swayed by evidence, it is important for health authorities to provide information to those with genuine concerns or questions, and engage in online debates rapidly in a nonjudgmental and transparent manner. Parents' right to choose and not be judged was an important theme among the negative comments. The issue of freedom and individual rights versus the notion of social good is a fundamental ethical issue in immunization programs and needs to be given careful thought in our communications on issues such as mandatory vaccination and exemption rights. Passive interventions such as increasing knowledge or reminder recalls have been shown to be the least effective in addressing vaccine hesitancy [44], and there is a need for more dialogue-based approaches targeted to specific subpopulations with an intended focus on social networks [44]. In a recent randomized controlled trial, Glanz et al [45] found that Web-based information delivered on vaccines via social media platforms during pregnancy can have a positive impact on parental vaccine decisions. However, communication strategies on immunization via social media are still not well understood, and caution must be used to prevent legitimizing vaccine hesitancy [46]. Social media can be an important communication tool for public health; however, the content of online debates needs to be better monitored to identify the predominant themes, the type of misinformation, or specific requests for information, and to understand the determinants among Canadian parents [46,47]. This study adds to this body of research and highlights the major themes in one online debate, as well as the need for ongoing monitoring due to the extent of misinformation being shared.

Although online monitoring is essential, we need to better understand who should be engaging online to rebut misinformation and spread accurate and scientifically valid information on immunization. Mistrust in health care professionals and the government has been reported as an important determinant in vaccine hesitancy [30,37,48,49]; thus, alternative spokespeople (eg, influential mommy bloggers or celebrities) may need to be considered in the delivery of expert-based information. However, a recent survey of Canadian adults reported that the majority trust physicians and public health officials for timely and credible vaccine information, while popular celebrities were the least trusted [43]. Further research is needed to determine the extent of public health involvement, and what interventions or messaging and by whom would have the most impact online. MacDonald et al [50] reported that no simple strategy exists in overcoming vaccine hesitancy and that health care workers and immunization program managers need to "become adept at recognizing and tackling hesitancy in all of its incarnations." This includes detecting vaccine hesitancy in populations and subgroups, having communication plans to address antivaccination misinformation, and actively supporting vaccine acceptors [50]. Online silence from public health authorities could give the impression of agreement with antivaccination information or sentiment [50]. Adversarial approaches could be counterproductive [51]; thus, public health departments need to be proactive in their social media strategies by promoting the safety of vaccines and addressing misinformation with targeted and tested interventions and messaging [13,17,50]. As such, it would also be useful to develop a common matrix that captures the arguments of those engaging in online discussions to influence nonvaccinators and vaccine-hesitant individuals (ie, provaccinators) and to further research their impact. Furthermore, health authorities and researchers should consider the ethical implications of nonengagement when using interactive online platforms for public health communications and interventions.

Limitations

This study was limited in that the analysis was of one online debate and not necessarily representative of the main themes in all online immunization debates. Furthermore, the target audience was self-selected Canadian parents on an online social media platform, and we collected the presented data in 2013 and 2014. Thus, the results are not generalizable to a larger population, and the themes underlying vaccine hesitancy may have changed for this population, as they can be context specific, varying across time, place, or vaccine [13,37]. Thus, it is imperative that the online conversation be continually monitored in various subgroups and over time in order to identify current themes and trends to tailor public health communications on immunization to specific audiences. Although we did not intend the advertisement to elicit discussion on vaccines and clearly requested users to complete an online survey, it is possible that the advertisement unintentionally provoked discussion by asking for thoughts on vaccines. The type of messaging used should be considered when posting online advertisements, and the Comments section should be deactivated when appropriate and feasible. It is also important to note that we could have overestimated the total number of individual commentators (85 unique Facebook users), as it was not possible to verify whether the same individual had multiple accounts under different user names.

Conclusion

The presence of over 100 comments posted on advertisements not intended as a discussion forum illustrates not only the strong sentiments associated with immunization but also the arbitrariness of platforms used for online debates. This unsolicited online debate is evidence of the importance of monitoring online discussions and of using technology capable of identifying immunization discussions among Canadian parents, as interactions are not just limited to vaccine-critical websites or groups and can occur via several platforms. The random nature of online debates will present a challenge for health authorities in terms of monitoring and engagement. Monitoring will need to include data mining with algorithms for keywords on immunization to quickly identify and engage in all public online communications on immunization. Health authorities need to identify methods to better leverage online platforms and networks in order to build trust, increase knowledge and access to information, and contest misinformation and misperceptions. It would also be important to consider appropriate jurisdictional responsibilities among health authorities for online surveillance and communications in immunization discussions.

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Conflicts of Interest

None declared.

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Abbreviations

MMR: measles-mumps-rubella
SAGE WG: Strategic Advisory Group of Experts Working Group
WHO: World Health Organization

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