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Original Paper

Entomological Surveillance of the Invasive Aedes Species at Higher-Priority Entry Points in Northern Iran: Exploratory Report on a Field Study

Seyed Hassan Nikookar[1], PhD; Alireza Maleki[2], BSc; Mahmoud Fazeli-Dinan[1], PhD; Razieh Shabani Kordshouli[1], BSc; Ahmadali Enayati[3], PhD

[1] Department of Medical Entomology and Vector Control, Health Sciences Research Center, School of Public Health, Mazandaran University of Medical Sciences, Sari, Iran

[2] Guilan University of Medical Sciences, Rasht, Iran

[3] Department of Medical Entomology and Vector Control, School of Public Health and Health Sciences Research Center, Mazandaran University of Medical Sciences, Sari, Iran

Corresponding Author:
Ahmadali Enayati, PhD
Department of Medical Entomology and Vector Control
School of Public Health and Health Sciences Research Center
Mazandaran University of Medical Sciences
Khazar Abad Road (Km-17th)
Sari, P.O. Box 48175-1553
Iran
Phone: 98 9111522209
Email: aenayati1372@gmail.com

Abstract

Background: Arboviral diseases such as dengue, Zika, and chikungunya are transmitted by *Aedes aegypti* and *Ae albopictus* and are emerging global public health concerns.

Objective: This study aimed to provide up-to-date data on the occurrence of the invasive *Aedes* species in a given area as this is essential for planning and implementing timely control strategies.

Methods: Entomological surveillance was planned and carried out monthly from May 2018 to December 2019 at higher-priority entry points in Guilan Province, Northern Iran, using ovitraps, larval collection, and human-baited traps. Species richness (*R*), Simpson (*D*), evenness (*E*), and Shannon-Wiener indexes (*H*) were measured to better understand the diversity of the *Aedes* species. The Spearman correlation coefficient and regression models were used for data analysis.

Results: We collected a total of 3964 mosquito samples including 17.20% (682/3964) belonging to the *Aedes* species, from 3 genera and 13 species, and morphologically identified them from May 2018 to December 2019. *Ae vexans* and *Ae geniculatus*, which showed a peak in activity levels and population in October (226/564, 40.07% and 26/103, 25.2%), were the eudominant species (*D*=75.7%; *D*=21.2%) with constant (C=100) and frequent (C=66.7%) distributions, respectively. The population of *Ae vexans* had a significant positive correlation with precipitation (*r*=0.521; *P*=.009) and relative humidity (*r*=0.510; *P*=.01), whereas it was inversely associated with temperature (*r*=−0.432; *P*=.04). The Shannon-Wiener Index was up to 0.84 and 1.04 in the city of Rasht and in July, respectively. The rarefaction curve showed sufficiency in sampling efforts by reaching the asymptotic line at all spatial and temporal scales, except in Rasht and in October.

Conclusions: Although no specimens of the *Ae aegypti* and *Ae albopictus* species were collected, this surveillance provides a better understanding of the native *Aedes* species in the northern regions of Iran. These data will assist the health system in future arbovirus research, and in the implementation of effective vector control and prevention strategies, should *Ae aegypti* and *Ae albopictus* be found in the province.

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KEYWORDS

mosquito surveillance; Aedes; biodiversity; Guilan; Northern Iran

Introduction

Background

Mosquitoes are the most important medical insects because they transmit various pathogens to humans and animals [1]. Mosquitoes are found in temperate and tropical regions of the world and beyond the Arctic Circle. The family *Culicidae* includes 3591 valid species, which are classified into 2 subfamilies and 113 genera [2]. The genera *Anopheles*, *Culex*, and *Aedes* are the most important taxa in this family. The genus *Aedes* has the highest number of species, with 33 species of uncertain subgeneric status and 900 species classified into 72 subgenera [1]. Members of the genus *Aedes* are vectors of at least 22 arboviruses, including some of the most human health–threatening viruses such as the chikungunya, dengue, and Zika viruses [3].

Aedes aegypti and *Ae albopictus* are the main vectors of these arboviral diseases. *Ae aegypti* is a domestic species with highly synanthropic behavior, originating from the forests of Africa, and is currently found in most tropical and subtropical regions around the world [4,5]. *Ae albopictus* is native to the forests of Southeast Asia that subsequently spread to the Americas, Europe, Africa, Australia, and several islands in the Pacific Ocean over the past 30 to 40 years, following global trade, especially in used tires [6,7].

Over the past 2 decades, the Asian tiger mosquito, *Ae albopictus*, and yellow fever mosquito, *Ae aegypti*, have been reported in several countries of the Mediterranean basin, including Afghanistan, Armenia, Oman, Pakistan, Saudi Arabia, Yemen, and Turkey (which is located near the Mediterranean basin) [8,9]. Dengue and chikungunya outbreaks have recently been reported in Pakistan, Saudi Arabia, Yemen, and Oman [8-10], raising concerns about the probable influx of these species in Iran [11]. As anticipated, in 2014, the first specimens of *Ae albopictus* were collected from Sistan and Baluchestan Province in neighboring Pakistan [12]. More importantly, *Ae aegypti* has also been revealed in the Lengeh and Khamir ports in Hormozgān Province during the last couple of years [9], which has caused great concern for the country. This may result in outbreaks of arboviral diseases in Iran, where *Ae aegypti* and *Ae albopictus* are established. Therefore, it strongly emphasizes the necessity for regular implementation of entomological surveillance programs at points of entry to detect the presence of invasive *Aedes* species and to estimate the risk of incidence of vector-borne diseases throughout the county, especially in Guilan Province.

Over the past few decades, Guilan Province has made tremendous efforts in social development and urbanization, the expansion of agricultural projects, water resources, and the tourism industry. There are several ports of entry, including the Anzali and Astara international ports, which link it to Eurasia through the Volga Don Canal [13], and Rasht Sardar Jangal International Airport in the province. Suitable weather conditions and a spectacular natural landscape make the province an important national and international holiday destination in Northern Iran, factors that predispose the province to the risk of invasive *Aedes* species.

Objectives

Therefore, given the concern about the possible entry of these species from neighboring northern countries as well as the geographical and ecological suitability of Guilan Province, this study aims to conduct and establish an initial entomological surveillance of invasive species of *Aedes* in line with the national search for *Ae aegypti* and *Ae albopictus*. In doing so, apart from early detection of the entry of these invasive species, capacity building of the workforce of the Health Deputy and other organizations such as seaports and airports of Guilan Province, as well as providing a data set for the fauna of *Aedes* in Northern Iran were among the purposes of this research.

As no biodiversity studies on *Aedes* species in Guilan Province, Northern Iran, have been conducted so far, assessment of the biodiversity of *Aedes* mosquitoes is one of the aims of this study.

Methods

Study Area

Guilan Province is located in northwestern Iran between 36°34′ and 38°27′ N latitude and 48°34′ and 50°36′ E longitude and has mostly coastal, plain, foothill, and mountainous areas with a population of 2,531,000 and an area of approximately 14,042 km^2 The province is surrounded by the Republic of Azerbaijan and the Caspian Sea to the north, Ardebil Province to the west, Mazandaran Province to the east, and Zanjan Province to the south. The center of the province, Rasht City, is known internationally as the “City of Silver Rains” and among Iranians as the “City of Rain.” The maximum and minimum absolute temperatures are 37 °C and −19 °C, respectively, and the average temperature is 15 °C (30-year data from Guilan Synoptic Station) [14]. The average relative humidity at 06:30 AM was 94%, and at noon it was 72%. The average annual rainfall is approximately 1401 mm [15]. A moderate climate and abundance of water have turned the province into an ideal place for mosquitoes to thrive. Rice is a major crop in this province. The city of Astara in the far western part of Guilan Province is the most active transit port and the third most active border of the country between Iran and the Caucasus region, and is thus in a position that can support the entry of invasive *Aedes* into the country.

Specimen and Data Collection

This study was started in 2017 in Guilan Province because of its strategic importance in the region in terms of the entry of invasive species into the country from the northern belt, by training the field work teams, organizing the study, and preparing the materials. The actual sampling was carried out bimonthly from May 2018 to December 2019, according to the seasonal activity of the species in the region. The specimens were identified to the species level, and the results were analyzed in 2020; this was followed by the drafting of the manuscript. Sampling was performed in 3 cities that harbored the main entry points, namely the Rasht International Airport and the Anzali and Astara seaports in Guilan Province. In each of these cities, the main entry point and 2 other locations in the vicinity were included in the sampling. This totals the sampling locations in each city (Rasht, Anzali, and Astara) to 3 locations (Multimedia

Appendix 1), as suggested by the Iran Centers for Disease Control and Prevention surveillance guidelines for invasive *Aedes* vectors [9]. The specimens were collected using three methods: ovitrap, larval collection, and human-baited trap. A total of 27 staff members from the Guilan health centers were recruited and trained to perform sampling.

Ovitrap Surveillance

The ovitraps were black 1 L plastic cylindrical buckets (12 cm in diameter × 15 cm in height) and wooden paddles (3 cm × 12 cm × 0.5 cm each) placed vertically inside the trap as a substrate for oviposition. A 10% solution of *Orayza sativa* or *Cynodon dactylon* was used as a natural attractant in the ovitraps. They were placed bimonthly (once in the first half of the month and once in the second half of the month) outdoors and indoors at a height of <1.5 m, protected from rain and direct sunlight, out of reach of children and pets at selected points at each point of entry (100 ovitraps in total), and visited 72 hours later. The suspected paddles were collected and transferred to the laboratory for counting and species identification after being kept for 2 to 3 days at room temperature before hatching (Figure 1). It should be mentioned that the ovitraps were mostly placed in roofed areas such as corners of buildings and roofed parking lots and inside buildings to protect them from rain, but for ovitraps that were placed in roofless environments, small gable roofs at a height of 30 cm were set up above each ovitrap. If this was not possible and rainwater entered the ovitrap, the excess water was automatically removed through a hole placed at the one-third mark from the upper end of the ovitrap.

Figure 1. Ovitrap used to collect eggs of the invasive *Aedes* species (original photo).

Larval Surveillance

Larval surveys were performed in the preferred natural and artificial habitats of invasive *Aedes* species using a standard 350 mL dipper. In small breeding sites where dippers could not be used, the sampling was performed using plastic pipettes. Sampling was always conducted by the same individual in the morning (from 8 AM to noon) or afternoon (from 4 PM to 6 PM) for approximately 30 minutes at each larval habitat. Approximately 10 to 30 dips were performed in each larval habitat, depending on their size. The collected larvae were preserved in glass vials containing lactophenol solution and transferred to the laboratory for being mounted on microscopic slides using Berlese medium before morphological identification.

Human-Baited Catches

Daily biting was done each fortnight near breeding sites and human dwellings at each station (Multimedia Appendix 1) in the study cities. A total of 6 participants were randomly divided into 3 groups (each consisting of a human bait and a collector) for the 3 sampling stations in each city. The study was performed from 7 AM to 8 PM, with a break of 15 minutes every 3 hours. To avoid unnecessary biting, the participants were covered in net jackets in areas where the landing of mosquitoes was not taking place. The participants laid down and exposed their legs and hands from knee to ankle and elbow to wrist. The collector aspirated any mosquito that landed and gently expelled it into a paper cup covered with netting. The mosquitoes collected each hour were killed by freezing for at least 15 minutes at −20 °C, pinned, and identified using recent morphological keys [16]. It should be noted that before starting the collection, the aim of the research was explained to the participants and they were included in the study after providing informed consent.

Ethics Approval

The study protocol was approved by the ethical committee of the Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1397.3475) and the study was performed according to the Iran Centers for Disease Control and Prevention surveillance guidelines for invasive *Aedes* vectors [9].

Dominance and Distribution of the *Aedes* Species

Dominance (D) and distribution (C) structures were also calculated for each of the species in the area according to the method proposed by Nikookar et al [17]. According to the obtained D and C values, 5 classes were considered to show the intensity of distribution and dominance.

Biodiversity and Rarefaction Analysis

Indices of species richness, evenness, dominance, community heterogeneity, and sufficiency of sampling efforts were computed using the following formulas at the spatial and temporal scales:

Margalef (D_{Mg}=S-1lnN), Menhinick (D_{Mn}=SN), Simpson dominance (D=λ=i=1SPi2)), evenness (J or E or Pielou index) – (J=H'H'max=H'logS), Shannon indices ($H=\Sigma p_i \times \ln p_i$) and rarefaction curve (E(Sn)=i=1S[1-N-NinNn]), where N represents the total number of individuals in the sample, S represents the number of species in the sample, N_i is the number of individuals of species number i; P_i=niN, where P_i is the proportion of individuals observed in the ith species, n_i is the number of individuals in the ith taxon, and H′ is the Shannon-Wiener function [18-20].

It should be mentioned that the steep slope to the left of the curve indicates that many species have not yet been discovered, whereas reaching the asymptotic line indicates a reasonable number of specimens. Therefore, more intensive sampling efforts are likely to result in only a small number of additional species [20].

Statistical Analysis

All statistical analyses were performed using SPSS (version 20, IBM Corp). The normality of the data was tested using the Shapiro-Wilk test, as the data were not normally distributed. Spearman correlation analysis was used to evaluate the relationship between the frequency of occurrence of *Aedes* species and climatic variables in the region. A regression model was also used to show the transparency and intensity of the relationship by using an R^2 estimate.

Results

Species Composition

A total of 3964 mosquito specimens, including 2103 (53.05%) larvae and 1861 (46.94%) adults belonging to 3 genera, with 4 species being larvae, and 13 species being adults, were collected from Guilan Province, Northern Iran, from May 2017 to December 2017. Of these, 1.81% (38/2103) larvae and 21.82% (406/1861) adults belonged to the subfamiliy Anophelinae, and 98.19% (2065/2103) larvae and 78.18% (1455/1861) adults were from the subfamily Culicine (Table 1).

The highest number and percentage of samples were collected in Anzali (1412/3964, 35.62% of the total captured specimens), whereas the lowest number was collected in Astara (1158/3964, 29.21%). No *Anopheles* larvae were found in the studied counties, except for *Anophelesplumbeus* (Table 1).

Ae vexans was the most abundant species collected from all counties. *Ae vexans* was caught with maximum and minimum relative abundances in Anzali (256/1412, 18.13%) and Rasht (132/1394, 9.50%; Table 1). *Ae geniculatus*, *Ae echinus*, and *Ae pulchritarsis* were only collected as adults, with the former being the second most abundant *Aedes* species in this study.

Table 1. Numbers and percentage of mosquito species recorded at higher-priority entry points of Guilan Province, Northern Iran, from May 2018 to December 2019.

Species	Rasht		Anzali		Astara		Total	
	Larvae, n (%)	Adult, n (%)	Larvae, n (%)	Adult, n (%)	Larvae, n (%)	Adult, n (%)	Larvae, N (%)	Adult, N (%)
Anopheles maculipennis sl	—[a]	11 (1.8)	—	18 (2.5)	—	19 (3.5)	—	48 (2.6)
Anopheles pseudopictus	—	136 (22.3)	—	172 (24.2)	—	36 (6.6)	—	344 (18.5)
Anopheles hyrcanus	—	5 (0.8)	—	—	—	—	—	5 (0.5)
Anopheles sacharovi	—	—	—	—	—	9 (1.7)	—	9 (0.3)
Anopheles plumbeus	38 (4.8)	—	—	—	—	—	38 (1.8)	—
Culex pipiens	579 (74)	132 (21.6)	595 (84.8)	124 (17.5)	511 (82.7)	166 (30.5)	1685 (80.1)	417 (22.4)
Culex theileri	—	7 (1.1)	—	—	—	179 (32.8)	—	186 (10)
Culex tritaeniorhynchus	140 (18)	140 (23)	14 (2)	182 (25.6)	25 (4)	42 (7.7)	179 (8.5)	364 (19.6)
Culex torrentium	1 (0.1)	—	3 (0.4)	3 0.4()	—	—	4 (0.2)	3 (0.2)
Aedes vexans	25 (3.1)	107 (17.5)	90 (12.8)	166 (23.4)	82 (13.3)	94 (17.2)	197 (9.4)	367 (19.7)
Aedes geniculatus	—	58 (9.5)	—	45 (6.4)	—	—	—	103 (5.5)
Aedes echinus	—	14 (2.3)	—	—	—	—	—	14 (0.7)
Aedes pulchritarsis	—	1 (0.1)	—	—	—	—	—	1 0.05
Total	783 (100)	611 (100)	702 (100)	710 (100)	618 (100)	540 (100)	2103 (100)	1861 (100)

[a] No sample was collected.

Monthly Population Trends of the *Aedes* Species

The highest total number of larvae (n=110) and adults of the (n=143) *Aedes* species was found in October, while the lowest number was found in August for larvae (10/197, 5.07%) and July for adults (8/485, 1.6%; Figure 2). The population density of *Ae vexans* adults in Rasht and Astara counties began to increase in May, disappeared from sampling in August, reached its greatest peak in October, and then gradually decreased. In Anzali, the species had a different population trend, appearing with 2 peaks, one in early May (48/55, 87%) and another at the beginning of autumn (45/59, 76%; Table 2). The highest number and percentage of *Ae vexans* larvae were recorded in October in Rasht (15/110, 13.6%) and Anzali (70/110, 63.6%) and in November in Astara (32/110, 76.2%; Table 3).

The *Ae geniculatus* species was active in all months except for August in Rasht and July and August in Anzali, although the species was not observed during the monthly sampling efforts in Astara. The highest population of the species was found in May in Rasht (17/42, 40%). After May, the population of the species decreased gradually in June and July, disappeared in August, and then increased and reached a smaller peak in October. The population of this species showed its highest peak in June (14/28, 50%) and October (14/59, 24%) in Anzali (Table 2). The population fluctuations of other species are shown in Table 2.

The fluctuations that occurred between May and December in the populations of *Ae vexans* and *Ae geniculatus*, the most abundant species in the province, are shown in Figure 3.

Figure 2. The total number of *Aedes* specimens collected by month at higher-priority entry points of Guilan Province, Northern Iran, from May 2018 to December 2019.

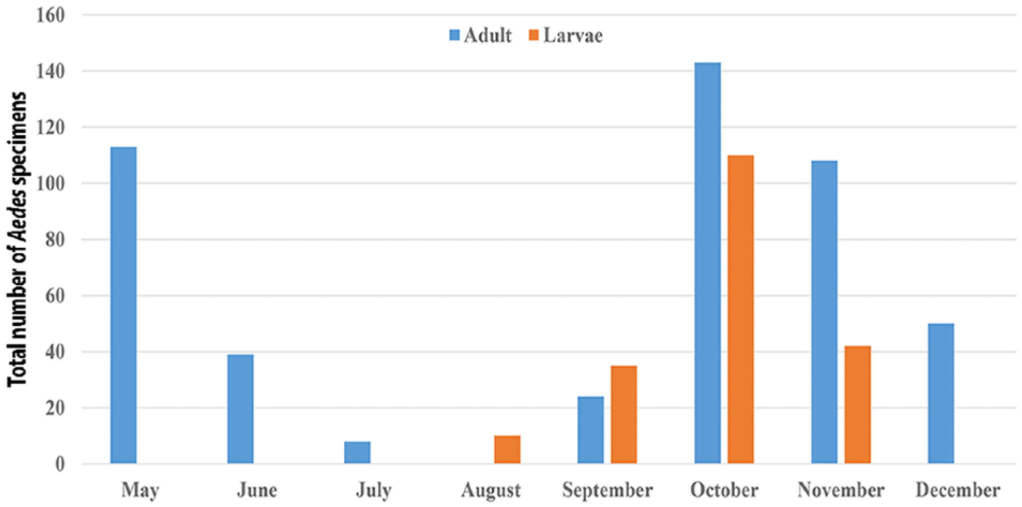


Table 2. Monthly population fluctuations of adult *Aedes* species collected at higher-priority entry points of Guilan Province, Northern Iran, by collection month, 2018 to 2019.

County and species	May, n (%)	June, n (%)	July, n(%)	August, n (%)	September, n (%)	October, n (%)	November, n (%)	December, n (%)
Rasht								
Aedes vexans	18 (42.8)	3 (27.3)	2 (25)	—[a]	4 (36.4)	35 (72.9)	30 (75)	15 (75)
Aedes geniculatus	17 (40.5)	6 (54.5)	4 (50)	—	5 (45.4)	12 (25)	10 (25)	4 (20)
Aedes echinus	7 (16.7)	2 (18.2)	2 (25)	—	2 (18.2)	—	—	1 (5)
Aedes pulchritarsis	—	—	—	—	—	1 (2.1)	—	—
Total	42 (100)	11 (100)	8 (100)	—	11 (100)	48 (100)	40 (100)	20 (100)
Anzali								
Aedes vexans	48 (87.3)	14 (50)	—	—	6 (75)	45 (76.3)	33 (84.6)	20 (90.9)
Aedes geniculatus	7 (12.7)	14 (50)	—	—	2 (25)	14 (23.7)	6 (15.4)	2 (9.1)
Total	55 (100)	28 (100)	—	—	8 (100)	59 (100)	39 (100)	22 (100)
Astara								
Aedes vexans	16 (100)	—	—	—	5 (100)	36 (100)	29 (100)	8 (100)
Total	113 (23.3)	39 (8.04)	8 (1.64)	—	24 (4.95)	143 (29.48)	108 (22.26)	50 (10.30)

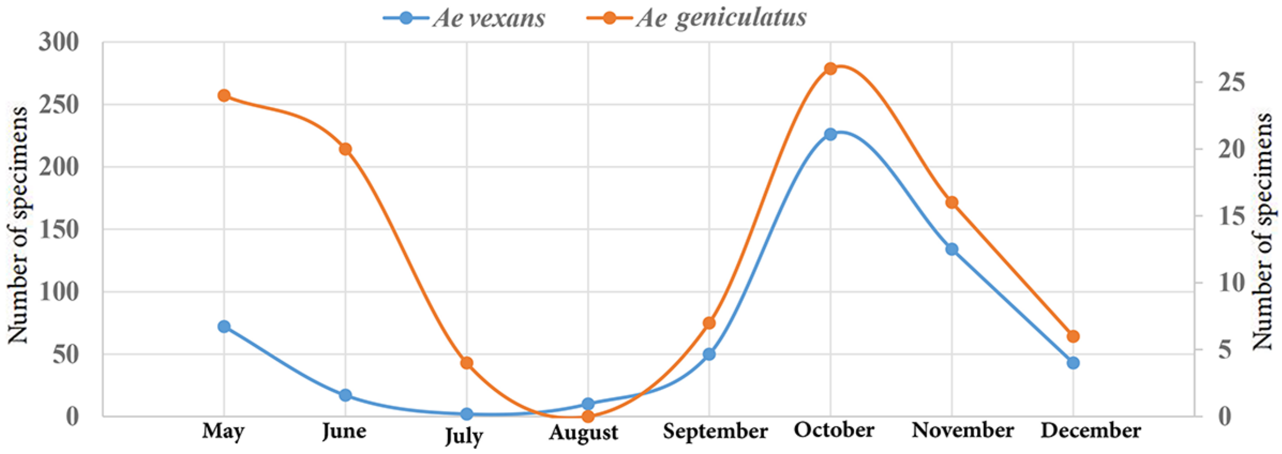
[a] No sample was collected.

Table 3. Monthly population fluctuations of larvae *Aedes* species collected at higher-priority entry points of Guilan Province, Northern Iran, by collection month, 2018 to 2019.

County	Species	May, n (%)	June, n (%)	July, n (%)	August, n (%)	September, n (%)	October, n (%)	November, n (%)	December, n (%)
Rasht	*Aedes vexans*	—[a]	—	—	10 (100)	—	15 (13.6)	—	—
Anzali	*Aedes vexans*	—	—	—	—	10 (28.57)	70 (63.6)	10 (23.8)	—
Astara	*Aedes vexans*	—	—	—	—	25 (71.43)	25 (22.7)	32 (76.2)	—
Total	—	—	—	—	10 (5.1)	35 (17.8)	110 (55.8)	42 (21.3)	—

[a] No sample was collected.

Figure 3. Monthly population trends of the most abundant species, *Aedes vexans* and *Ae geniculatus*, at higher-priority entry points of Guilan Province, Northern Iran, from May 2018 to December 2019.



Dominance and Distribution of the *Aedes* Species

Ae vexans was an eudominant species (D=75.7%), with a constant distribution (C=100%) in both larvae and adult forms. *Ae geniculatus* showed eudominance and a frequent distribution of up to D=21.2% and C=66.7%, respectively, compared with other species. *Ae echinus* was subdominant (D=2.9) and had a sporadic distribution of up to C=11.1%. Because *Ae pulchritarsis* specimens were collected at low frequencies, its distribution and dominance structures are not discussed (Table 4).

Table 4. The dominance and distribution values of larvae and adults of *Aedes* species collected at higher-priority entry points of Guilan Province, Northern Iran from May 2018 to December 2019.

	N (%)	Dominance (%)	Dominance criteria	Distribution (%)	Distribution criteria
Adults					
Aedes vexans	367	75.7	Eudominant	100	Constant
Aedes geniculatus	103	21.2	Eudominant	66.7	Frequent
Aedes echinus	14	2.9	Subdominant	11.1	Sporadic
Aedes pulchritarsis	1	0.2	Subrecedent	11.1	Sporadic
Larvae					
Aedes vexans	197	100	Eudominant	100	Constant

Biodiversity in Spatial and Temporal Scales

The biodiversity indices of *Aedes* species at spatial and temporal scales are shown in Tables 5 and 6. The Shannon-Wiener Index was calculated to be up to 0.84 and 1.04 in Rasht and July, respectively. Maximum richness (S) was found in Rasht (S=4) and in all months except in August and November. Menhinick (D_{Mg}) and Margalef (D_{Mn}), as indices of species richness, had the highest numerical values in Rasht (D_{Mg}=0.27; D_{Mn}=0.56) and July (D_{Mg}=1.06; D_{Mn}=0.96). The highest values of evenness (J') were recorded in Anzali (J'=0.76) and in July (J=0.94). The maximum Simpson diversity index was found in Anzali (D=0.74) and jointly in October and November (D=0.80), indicating the strong influence of the eudominant species, *Ae vexans*, on other species in the area.

Table 5. Biodiversity indices of *Aedes* species in Guilan Province, Northern Iran, by spatial scale, 2018 to 2019.

Species	Rasht	Anzali	Astara
Richness (*S*)	4	2	1
Abundance (*N*)	205	301	176
Menhinick (D_{Mg})	0.27	0.11	0.07
Margalef (D_{Mn})	0.56	0.17	0
Shannon-Weiner (*H*)	0.84	0.42	—[a]
Simpson (*D*)	0.49	0.74	—
Evenness (*J*)	0.58	0.76	—

[a] Not computable.

Table 6. Biodiversity indices of *Aedes* species in Guilan Province, Northern Iran, by temporal scale, 2018 to 2019.

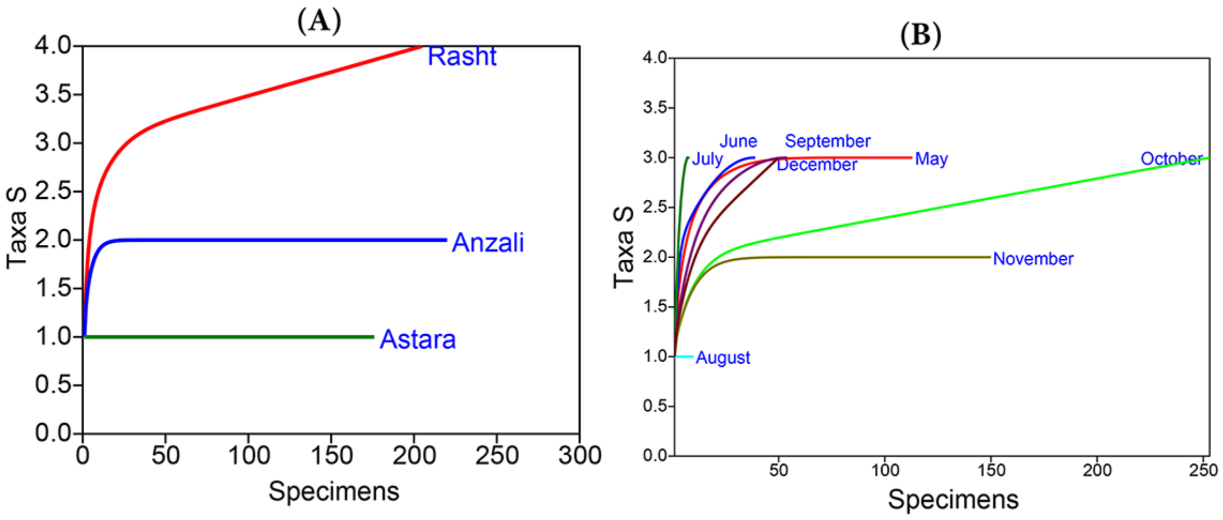
Species	May	June	July	August	September	October	November	December
Richness (*S*)	3	3	3	1	3	3	2	3
Abundance (*N*)	113	39	8	10	59	253	150	50
Menhinick (D_{Mg})	0.28	0.48	1.06	0.31	0.39	0.18	0.16	0.42
Margalef (D_{Mn})	0.42	0.54	0.96	0	0.49	0.36	0.19	0.51
Shannon-Weiner (*H*)	0.73	0.85	1.04	—[a]	0.50	0.35	0.33	0.73
Simpson (*D*)	0.57	0.45	0.37	—	0.73	0.80	0.80	0.75
Evenness (*J*)	0.69	0.78	0.94	—	0.55	0.47	0.70	0.52

[a] Not computable.

Rarefaction Analysis

The rarefaction curves showed the stability of the number of species in each sample (the horizontal axis shows the number of individuals and the vertical axis shows the number of expected species yielded from the method). It almost reached the asymptotic line at all spatial and temporal scales, except in Rasht and in October, where more sampling efforts were needed to increase the richness (Figure 4).

Figure 4. Refraction curve at 95% CI, based on species richness at spatial (A) and temporal (B) scales, 2018 to 2019. Taxa S refers to species richness or number of species.



Effects of Meteorological Factors on the Population of the *Aedes* Species

A significant positive correlation was observed between the population of *Ae vexans* and mean rainfall (*r*=0.521; *P*=.009) and humidity (*r*=0.510; *P*=.011). The mean temperature had a significant negative effect on the *Ae vexans* population (*r*=−0.443; *P*=.035). In addition, no significant relationship was observed between the population of other *Aedes* species and meteorological factors (Table 7).

The tested regression model described low R^2 values of 0.27, 0.26, and 0.18 between the *Ae vexans* population and mean rainfall, humidity, and temperature, respectively (Figure 5).

Figure 6 shows that after rainfall, with a lag time of approximately 15 days, the *Ae vexans* population increases significantly.

Table 7. Correlation coefficient between *Aedes* species population and meteorological factors at higher-priority entry points of Guilan Province, Northern Iran, from May 2018 to December 2019.

Species	Mean temperature (°C)	Mean humidity (mm)	Mean rainfall (%)
Aedes vexans			
Coefficient	−0.432	0.510	0.521
P value	.04	.01	.009
N	24	24	24
Aedes geniculatus			
Coefficient	−0.138	0.170	0.272
P value	.52	.43	.20
N	24	24	24
Aedes echinus			
Coefficient	0.073	−0.170	0.036
P value	.74	.43	.87
N	24	24	24
Aedes pulchritarsis			
Coefficient	−0.111	0.172	0.217
P value	.61	.42	.31
N	24	24	24

Figure 5. Regression relationships between *Aedes vexans* and meteorological factors at higher-priority entry points of Guilan Province, Northern Iran, from May 2018 to December 2019.

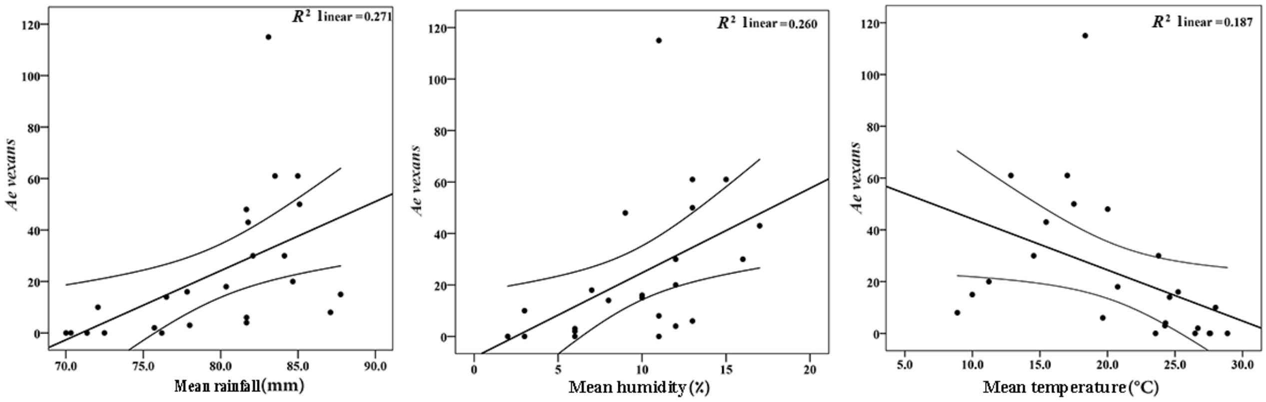
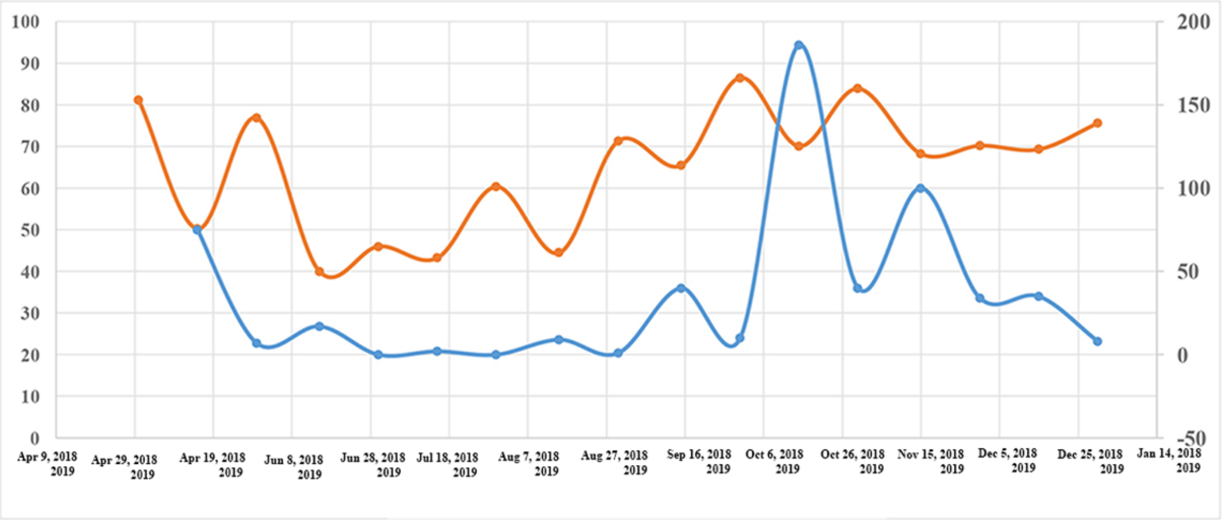


Figure 6. Lag phase between rainfall and population frequency of *Aedes vexans*, Guilan Province, Northern Iran.



Discussion

Species Composition, Dominance, and Distribution

The introduction, establishment, and spread of invasive *Aedes* species are of great public health concern, mostly because of their ability to transmit a variety of arboviruses [21]. Surveillance is important to detect the occurrence and establishment of uncommon or invasive species, evaluate the risk of pathogen transmission, plan vector control programs, and understand the ecology of circulating vectors and the diseases they transmit in the region [22]. This is the first comprehensive surveillance of *Aedes* species focusing on *Ae aegypti* and *Ae albopictus* at higher-priority entry points in Guilan Province, Northern Iran, performed according to the Iran Centers for Disease Control and Prevention surveillance guidelines for invasive *Aedes* vectors [9]. In total, 3 genera and 13 species of mosquitoes were collected in this study. Furthermore, 5 species belonging to the genus *Anopheles*, 4 species of the genus *Culex*, and 4 species of the genus *Aedes* were collected from the study areas. Although species other than *Aedes* are also important vectors of some pathogens, only the *Aedes* species are discussed here.

Ae aegypti and *Ae albopictus* were not found in the sampling efforts at the points of entry and high-risk sites in this study. It is worth mentioning that historically, *Ae aegypti* was observed in the Khuzistan and Bushehr provinces of southern Iran [23-25]. However, this species was not observed in Iran from 1954 to 2019. Malaria eradication programs in Iran, which began in 1957, could be a reason for its disappearance. Recently, *Ae aegypti* has been detected in the ports of Khamir and Lengeh, as well as Bandar Abbas in Hormozgān Province [9], which makes its re-establishment plausible and poses a potential risk of its spread to other parts of the country.

The Asian tiger mosquito, *Ae albopictus*, was found for the first time in Iran in the districts of Nik-shahr, Sarbaz, and Chabahar in Sistan and Baluchestan Province [12]. It has been the most invasive mosquito species worldwide over the past 30 years [6]. This thermophilic species is adapted to a more temperate climate by producing diapausing eggs and has a strong tendency to expand, as the species was observed in 28 European countries, established itself in 20 of them [26,27]. It should be noted that extensive entomological surveillance has failed to reproduce observations of *Ae albopictus* after its first presence in Iran. This reflects the fact that *Ae albopictus* may not have been able to establish itself in the area [28].

Ae vexans was the eudominant species with a constant distribution in both the larval and adult stages. The species was classified as a dominant species with varying distributions, including sporadic [17], moderate [29], and infrequent [30]. In comparison with our research, *Ae vexans* was introduced as a satellite species with a sporadic distribution [31]. It is widely distributed throughout the Holarctic region and is native to Eastern Europe, the Americas, Africa, and Asia [32,33]. It was introduced as the most prevalent species of *Aedes* in Northern Iran [17,34], which is in accordance with the findings of this study.

The floodwater mosquito *Ae vexans* is an opportunistic feeder that can feed on birds and mammals, facilitating zoonotic transmission [35]. Apart from being known as a biting pest, the species is known to be a competent vector for St Louis encephalitis virus, Snowshoe hare virus, Jamestone Canyon virus, Tahyna virus, Batai virus, and the dog heartworm parasite *Dirofilaria immitis* [36]. *Ae vexans* is considered the primary vector of Rift Valley fever phlebovirus in Africa [37], and its transmissibility has been experimentally confirmed in field populations of the Americas continent [38]. Zika virus has recently been detected in the salivary glands of *Ae vexans* caught in the field [39]. *Ae vexans* is assessed as a potential secondary vector of West Nile virus [35] and has been considered as a main "bridge vector" owing to its preferred blood-feeding habits of both humans and birds. Owing to the high abundance of the species, the potential role in virus transmission, and the existence of wetlands for migratory birds as the reservoir hosts in the study area, the ecological aspects of *Ae vexans* could be the focus of future research.

Ae geniculatus was recorded in the dominant class with a frequent distribution. The species has been reported to be dominant in the forest habitats of the northern regions of Iran (without reporting any dominance and distribution indices) [40,41]. Similar to invasive *Aedes*, this species is known as the tree trunk hole mosquito, breeds in natural containers in woodlands and in man-made containers in semiurban and semidomestic environments [42]. *Ae geniculatus* is a Palearctic species, opportunistic feeder, competent vector for *Dirofilaria immitis* and *repens* [42,43], and chikungunya [44]. The species was not collected during sampling efforts from Astara County in this study, which may be because of the lack of preferred habitats and differences in selected sampling sites during the monitoring period. Because there is little data regarding the biology, ecology, and pathogens transmitted by the species in Iran, further research is needed to increase the knowledge on these issues in the future.

Ae echinus was a subdominant species with an infrequent distribution and was found only in Rasht County in our investigation. The differences in the sites selected during the study were probably a limiting factor. The species is distributed in the Mediterranean region, North Africa, Asia and Southern Europe, Greece, Algeria, Morocco, Spain, and France [45]. *Ae echinus* specimens were collected for the first time in Sari, Mazandaran Province by Janbaksh in 1955 [46], and in the counties of Rezvanshahr, Shaft, Fuman, and Masal of Guilan Province by Azari-Hamidian in 2002 [47] as larvae. By contrast, in this study and another study in Northern Iran [41], this species was observed only in the adult form.

Ae pulchritarsis specimens were collected at a low frequency. All *Aedes* species collected in the study are native to the northern regions of the country, as shown in the checklist of mosquitoes in Northern Iran [17,48].

Monthly Population Trends of the *Aedes* Species

Climate can accelerate or delay the development of mosquitoes and the availability of breeding sites [49]. An overall trend of a lower number of *Aedes* mosquitoes being observed in the drier months (June to September) than during the wetter months (October to May) was evident (Figure 2). The results of this study showed that the most prevalent species, *Ae vexans* and *Ae geniculatus*, were mostly observed in the autumn, when it can be the most appropriate starting to start monitoring the population dynamics of these species. This finding was further supported by Wagner and Mathis [50]. The population fluctuations of these species began in May, peaked in October, and gradually disappeared after December. There is not much data about the seasonal activity of *Aedes* species in Iran. The maximum population densities of *Ae geniculatus* and *Ae vexans* were reported in September and October, respectively, in Mazandaran Province, Northern Iran [41,51]. The highest activity peaks of *Ae vexans* were documented in June [29] and August [52] in the Iğdır Plain of the Aras Valley, Turkey. The difference between the results of this study and the findings in other regions may be explained by the topography, climate, and sampling sites selected, which affect the bionomics of *Aedes* mosquitoes.

Effects of Meteorological Factors on the Population of the *Aedes* Species

Ae vexans population showed a significant positive correlation with mean rainfall and humidity and a negative correlation with mean temperature. In concordance with our findings, many studies have shown the effects of meteorological factors on the *Aedes* population dynamics [51,53-56]. The researchers believed that rainfall was the most influential climatic variable for the *Aevexans* population, sometimes with a lag phase, by creating temporary pools as the preferred habitat for floodwater species. This study was not designed to and did not aim to address the analysis of lag time, but according to Figure 6, it seems that there is probably a lag time of at least 15 days from the beginning of the rainfall to the observation of an increase in the population of *Ae vexans*. In agreement with our findings, there was a lag time of at least 10 and 15 days in the early rainy season and 20 days after the end of the rainy season between the peak of rainfall and abundance of the species. Some studies have also shown that there is a complex relationship between rainfall and the *Ae vexans* population trend; in 2005, rainfall had a negative effect on the population density of *Ae vexans*, and in 2006, it had a positive effect [57]. These findings suggest that seasonal activities should be evaluated over several years to gain a better understanding of the lag time between population trends and climatic factors as well as the impact of other variables.

Temperature can be considered a survival-limiting factor for populations of the *Aedes* species [56]; this is supported by this study. Relative humidity was positively and significantly correlated with the population dynamics of *Ae vexans* [55], which is in agreement with our investigation. However, there was no positive or negative correlation between the abundance of other *Aedes* species and meteorological factors.

Biodiversity and Rarefactions Analysis

There were differences in the biodiversity of *Aedes* species at the spatial and temporal scales in the study area, as shown by the maximum values of the Shannon-Weiner index in Rasht and in July. Suitable habitat conditions for mosquitoes to reproduce and thrive could be a reason for this high diversity. Some studies have shown that lower biodiversity in a community might lead to a faster rate of emergence and re-emergence of infectious diseases [58-60]. They believed that there was a link between high biodiversity and reduced risk of vector-borne diseases, which underscores the importance of biodiversity studies. This is in agreement with the opinions of other researchers.

The highest levels of richness were observed in Rasht; these values were the same in all months except in August and November. Given that species richness is affected by sampling intensity, a standard rarefaction curve was used to confirm the adequacy of sampling efforts at temporal and spatial scales by reaching the asymptotic line. Rarefaction curve analysis showed that further sampling efforts are required to achieve maximum richness in Rasht and in October.

Evenness is presented as how individuals are distributed in a community, with the highest rates observed in Anzali and in July. Although there was high evenness in Anzali, the greatest diversity was observed in Rasht. This is because the biodiversity index is influenced by 2 other factors, that is, species richness and dominance. Low or high rates of these factors can affect the biodiversity index [18,61]. There are no specific data related to the biodiversity of *Aedes* species in Iran, and only a few studies have sporadically measured the biodiversity indices of mosquitoes in Neka city, Mazandaran Province, by Nikookar et. al [18]; in Bashagard district, southern Iran by Hanafi-Bojd et al [62]; in Abhar County, Azerbaijan Province by Paksa et al [63]; and in Chaharmahal and Bakhtiari Province by Omrani and Azari-Hamidian [64], highlighting the need for more studies in this regard.

As there is no proper vaccine available for *Aedes*-borne diseases (dengue, Zika fever, and chikungunya) to date, and because of the relatively high insecticide resistance in *Aedes* vectors, the main control intervention would be source reduction. Therefore, community participation is a key important factor that has shown varying degrees of success in disease prevention [65]. Raising people’s awareness through social media, holding educational workshops [66,67], and using mobile phone–based monitoring apps to produce risk maps [68] can be useful in community-based vector control.

Conclusions

According to the findings of this study, although Guilan Province has the potential for hosting the invasive vectors, *Ae aegypti* and *Ae albopictus*, these species were not found in this region during the monitoring period. However, entomological surveillance of *Aedes* mosquito fauna is important at entry points and high-risk sites for the timely identification of the entry of invasive species. *Ae vexans*, which is a potential vector of medical and veterinary importance, actively circulates in autumn in Guilan Province, Northern Iran. Other important *Aedes* species have also been identified in the study areas. Our data can be useful to health policy makers in designing and implementing appropriate surveillance and control measures for *Aedes* mosquitoes.

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Authors' Contributions

The conceptualization and designing for this study were done by AE and SHN, and they also worked toward fixing the methodology of the work. AM and RSK collected the data, SHN and MF-D analyzed the results, and the validation of the results was confirmed through discussions between AE and SHN. SHN wrote the first version of the manuscript, all the authors reviewed it, and AE edited and confirmed the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Ecogeographical characteristics of sampling sites where mosquitoes were collected in Guilan Province, Northern Iran.
[DOCX File , 14 KB - publichealth_v8i10e38647_app1.docx]

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Original Paper

Pilot Influenza Syndromic Surveillance System Based on Absenteeism and Temperature in China: Development and Usability Study

Zhen Yang[1], PhD; Chenghua Jiang[2], PhD

[1]School of Medicine, Tongji University, Shanghai, China
[2]Dongfang Hospital, Tongji University, Shanghai, China

Corresponding Author:
Chenghua Jiang, PhD
Dongfang Hospital
Tongji University
No 1239 Siping Road, Yangpu District
Shanghai, 200092
China
Phone: 86 18917266778
Email: jchtongji@163.com

Abstract

Background: Shortcomings of the current school-based infectious disease syndromic surveillance system (SSS) in China include relying on school physicians to collect data manually and ignoring the health information of students in attendance.

Objective: This study aimed to design and implement an influenza SSS based on the absenteeism (collected by face recognition) and temperature of attending students (measured by thermal imaging).

Methods: An SSS was implemented by extending the functionality of an existing application. The system was implemented in 2 primary schools and 1 junior high school in the Yangtze River Delta, with a total of 3535 students. The examination period was from March 1, 2021, to January 14, 2022, with 174 effective days. The daily and weekly absenteeism and fever rates reported by the system (DAR1 and DFR; WAR1 and WFR) were calculated. The daily and weekly absenteeism rates reported by school physicians (DAR2 and WAR2) and the weekly positive rate of influenza virus (WPRIV, released by the Chinese National Influenza Center) were used as standards to evaluate the quality of the data reported by the system.

Results: Absenteeism reported by school physicians (completeness 86.7%) was 36.5% of that reported by this system (completeness 100%), and a significant positive correlation between them was detected (r=0.372, P=.002). When the influenza activity level was moderate, DAR1s were significantly positively correlated among schools (r_{ab}=0.508, P=.004; r_{bc}=0.427, P=.02; r_{ac}=0.447, P=.01). During the influenza breakout, the gap of DAR1s widened. WAR1 peaked 2 weeks earlier in schools A and B than in school C. Variables significantly positively correlated with the WPRIV were the WAR1 and WAR2 of school A, WAR1 of school C, and WFR of school B. The correlation between the WAR1 and WPRIV was greater than that between the WAR2 and WPRIV in school A. Addition of the WFR to the WAR1 of school B increased the correlation between the WAR1 and WPRIV.

Conclusions: Data demonstrated that absenteeism calculation based on face recognition was reliable, but the accuracy of the temperature recorded by the infrared thermometer should be enhanced. Compared with similar SSSs, this system has superior simplicity, cost-effectiveness, data quality, sensitivity, and timeliness.

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KEYWORDS

influenza; syndromic surveillance system; face recognition; infrared thermometer; absenteeism; temperature

Introduction

School-aged children are vulnerable to influenza. The incidence of influenza among children aged 5-14 years during the influenza season ranges from 17.31% to 46.61% [1]. School-aged children also contribute to the amplification of virus transmission. Epidemiologic evidence suggests that influenza first occurs among school-aged children and that once infected, this population transmits the virus among family members and subsequently to the general population [2,3]. An infected student spreads the virus to an estimated 2.4 (95% CI 1.8-3.2) other children within a school [4]. Incidence rates in adults who reside with school-aged children may be 2 to 3 times higher than the incidence rates in similar adults who do not reside with school-aged children [5].

Absenteeism is an influenza surveillance indicator recommended by the World Health Organization and an important determinant adopted in the school-based syndromic surveillance system (SSS). In 1979, Peterson et al [6] demonstrated the effectiveness of school absenteeism for influenza surveillance. Since then, several studies have discussed the value of absenteeism surveillance from different perspectives. Compared to other methods, the main advantages of absenteeism surveillance include noninvasiveness, no requirement of clinical testing, low cost, simple operation, and good representation. Additionally, absenteeism surveillance can be used to accurately estimate the economic burden of influenza and its impact on education and promote effective cooperation between the health and education departments [6-12]. However, absenteeism itself is not a direct manifestation of the clinical symptoms of the disease, but only an approximate estimate of the illness. Therefore, it is sensitive but lacks specificity [10]. Baer et al [11] suggested that the greatest value of absenteeism surveillance may lie in “situational awareness” rather than “early detection.”

Absenteeism can be divided into three types: all-cause absence, illness absence, and syndrome-specific absence [13]. These 3 indicators have high specificity, but they increase the workload of the school. The SSS must balance specificity and the burden on the school [12]. Otherwise, the schools will be uncooperative, and the system will be eventually rejected [11,14,15]. Reducing the burden to maintain and improve the compliance of schools is an important challenge for the effective operation of such systems. Researchers have continuously been focusing on three main technical approaches to address this challenge: (1) improving the automation of data collection and changing the data collection method from manual statistics to fingerprint [14] or smart card methods [16]; (2) improving the convenience of data transmission, with data transmission changing from postcards, telephone, and fax [6] to email [10], and then to widely used network platforms [7-9,11,14-16]; (3) diversifying data reporters, with the reporter usually being a school physician or teacher and some systems requiring parents to report information [15,17] or encouraging students to participate in reporting the information [18].

Public health emergencies of infectious diseases emerging from schools account for 85.64% of the total number of all annual national public health emergencies [19]. Therefore, school-based SSSs are particularly significant in China. The SARS outbreak in 2003 and the H1N1 pandemic in 2009 prompted many places in mainland China to build systems for school-based infectious disease symptom surveillance [15,20-22], but the continuous operation of such systems is challenging. First, although the government formulated the school infectious disease reporting standard as early as 2012 [23] and issued several documents emphasizing the reporting of epidemic information in schools during the COVID-19 pandemic [24,25], absenteeism statistics are still not mandatory for schools. Second, the severe shortage of school physicians exacerbates the problem. Only 33.1% of primary and secondary schools are equipped with school physicians, with 1 school physician serving 2800 students on average; the proportions of school physicians in central and western regions, rural areas, and low-grade schools are even lower [26]. Therefore, the system based on manual information reports struggles to stimulate enthusiasm in schools [16]. Finally, Chinese people attach significant importance to studying, and parents worry that absence will delay the learning progress of their children. Consequently, they will send their children to school even if they are ill [27], which increases the possibility of misjudging the epidemic situation of infectious diseases just by calculating absenteeism.

Using artificial intelligence and information technology instead of manual methods to collect absenteeism data while considering the health information of students in attendance is highly important to solve the current development dilemma of SSS in China. To this end, an SSS was designed and trial-operated, which realized synchronous acquisition of identity, absenteeism, and temperature data based on face recognition and thermal imaging. The system has been in operation at 3 sentinel schools in the Yangtze River Delta region since November 2020. Data from these 3 schools collected by the system between March 2021 and January 2022 were exported to investigate 2 aspects. First, the alternative method of manually collecting absenteeism data explored in previous studies has produced a large amount of erroneous data [14]. Simultaneously, although infrared temperature measurement technology is widely used in the screening of suspected cases of infectious diseases in the population [28], instruments as well as environmental and individual factors can easily interfere with its accuracy [29-31]. Therefore, the completeness and accuracy of the collected data need to be verified. Second, body temperature is the first clinical symptom of most infectious diseases, and its advantage in influenza SSS has been confirmed by Miller et al [32]. Theoretically, multisource data can improve the accuracy of the perception of infectious disease information by the surveillance system [33]. The monitoring effectiveness of the combination of nonclinical symptoms (absenteeism) and clinical symptoms (fever) is another issue that requires investigation.

Methods

Reporting System

The proposed SSS was based on an app called “Xiao Lian Xing” (XLX) [34], which can be downloaded for free on Alipay (Alibaba Group Holding Co, Ltd). The app integrates face recognition technology and infrared temperature measurement technology to realize intelligent management of school public health. Its workflow is shown in Figure 1.

The operating company signed service agreements with the school and its superior management organization. According to the agreement, the school organized for the parents to register an account in Alipay with a smart phone (registration was completely voluntary), and then input information about the child, such as the name, gender, ID, school name, class, and face image into the account. Parents can also use the account to check the attendance and temperature of their children. The system collected student attendance and temperature data through terminal devices, which were composed of 2 modules, namely a face recognition system (identification accuracy ≥99.99%, Sunmi Technology Group Co, Ltd) and an infrared thermometer (measuring accuracy of ±0.5˚C, Hikvision Digital Technology Co, Ltd). The 2 modules were connected using a self-designed software for synchronous input and upload of the identity, attendance, and temperature. The data processing center was responsible for processing the data uploaded by each terminal and relaying the analysis results of absenteeism and fever at different levels to family users (ie, parents or other guardians), school users (ie, teachers, school health workers, and administrators), and school district management department users.

Terminal devices were generally arranged at the school gate. After students arrived at school every day, they went to the device for testing. Face recognition of the students was performed, and their identity information, attendance information, and facial temperature were automatically recorded by the instrument. Only students who were identified and had a normal temperature were admitted directly, whereas students with fever (temperature≥37.3˚C) were processed separately. To ensure that every student was subjected to instrument testing, the school arranged for staff on duty to supervise the children. Daily information on student attendance and temperature was transmitted to the cloud data center in real time. The data processing center generated a daily statistical report of the check-in and body temperature (with infrared images) of students in real time (Figure 2), summarized and analyzed the data, and gave feedback on the results at different levels (individual, classes, schools, school districts, etc).

Figure 1. Workflow of the Xiao Lian Xing system.

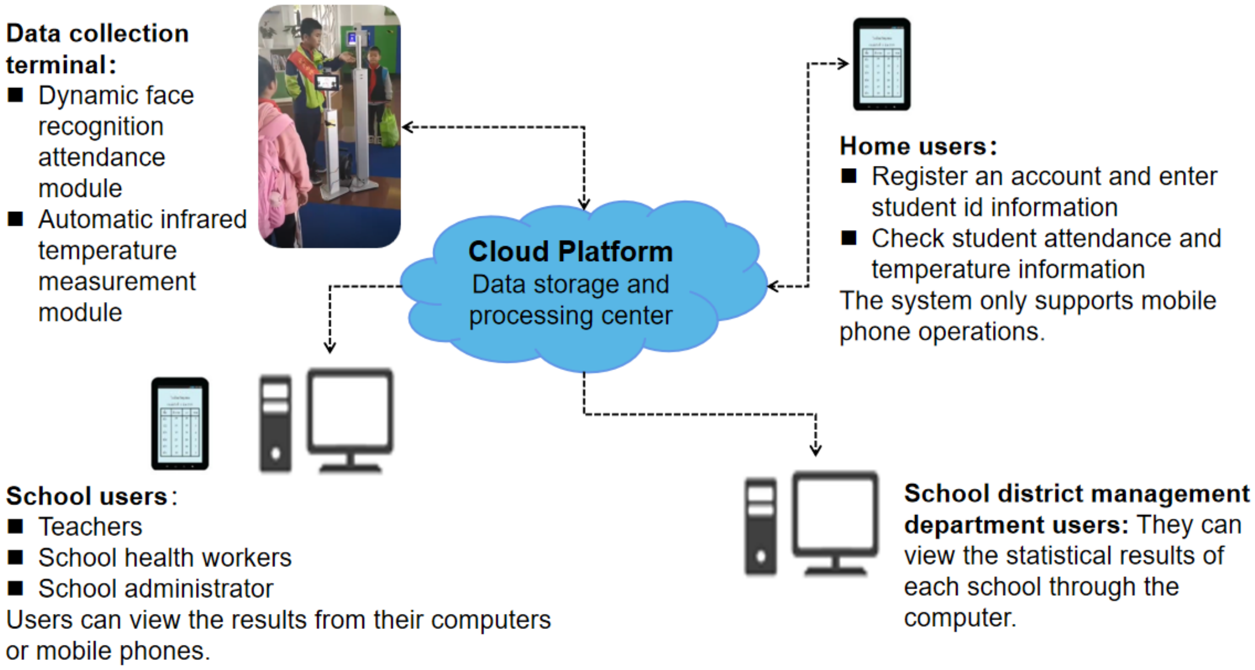


Figure 2. Statistical interface of student daily absenteeism and body temperature.

签到日期 2022-01-13 2022-01-13

签到状态 全部

School	Name	ID	Grade	Class	Date	Time	Attendance	Temperature	Health code
****** 小学	*****	330108***** ***091X	一年级	三班	2022-01-13	09:00:54	正常	38.1℃	绿码
****** 小学	*****	330783***** ***0443	一年级	二班	2022-01-13	08:46:34	正常	37.3℃	绿码
****** 小学	*****	360402***** ***1928	二年级	二班	2022-01-13	08:31:57	正常	37.2℃	绿码

Red letters indicate body temperature ≥ 37.3℃

Study Population and Data Collection

The study population comprised 3 schools in the Yangtze River Delta region. Schools A and B were primary schools. School A, located in Xiaoshan District, Hangzhou city, Zhejiang Province, began to use version 1.0 of the system (only face recognition) in November 2020 and version 2.0 (face recognition and infrared thermometer) in March 2021. School B, located in Binjiang District of Hangzhou city, began to pilot version 2.0 of the system in March 2021; it allowed students to use smart cards to check-in and began to fully use version 2.0 in September 2021. School C is a junior high school located in Pudong District, Shanghai, and it started to use version 2.0 of this system in October 2021.

The surveillance period was divided into 2 phases, namely, phase I, from March 1, 2021, to June 25, 2021, and phase II, from September 1, 2021, to January 14, 2022. The effective surveillance times of these phases were 83 and 91 days in total, respectively. In phase I, the numbers of students in school A and B were 1861 and 1100, respectively. In phase II, the numbers of students in schools A, B, and C were 1954, 1154, and 427, respectively, with a total of 3535 students. The system collected the following data for each school: total number of enrolled students, number of daily absentees, and number of daily students with fever. By default, students who failed to check-in within 1 hour after the specified arrival time were counted as absenteeism cases, where students whose body temperature was ≥37.3˚C were counted as fever cases.

The absenteeism reported by physicians in schools A and B (school C has no record of the school physician) was collected as the reference standard to evaluate the quality of absenteeism reported by the system. Absenteeism reported by the school physicians was defined as “the student is not in school that day.” The data reported by school physicians were collected from September 1, 2021, to January 14, 2022. To verify the reliability and feasibility of the surveillance system for infectious diseases, influenza was selected as the target disease. The reference criteria for influenza activities were obtained from the weekly influenza surveillance report released by Chinese National Influenza Center [35]. These weekly report statistics show the weekly positive rate of influenza virus (WPRIV) tests in southern and northern China. The WPRIV was calculated as the ratio of the number of virus-positive samples to the total number of samples submitted [36]. As both Hangzhou and Shanghai are in southern China, only the data of the southern region in the weekly report were used. The corresponding surveillance weeks ranged from the ninth week of 2021 to the fifth week of 2022. During this period, the influenza virus strain circulating in southern China was mainly type B.

Ethics Approval

Data used in this study were anonymized, so the Tongji University Review Board classified this study as nonhuman subject research, and it was exempted from approval.

Data Analysis

The daily absence rate (DAR) of the 3 schools was calculated as follows:

The DAR is divided into two categories: system-reported (DAR1) and school physician–reported (DAR2). The correlation coefficient of the 2 variables was then calculated. According to relevant literature [9,12], the data were considered abnormal if DAR1 exceeded 10%. The abnormal causes relating to the school were investigated, and if they were noninfectious factors, the abnormal data were statistically treated in an appropriate manner. Then, the DAR time series diagrams of the 3 schools were drawn (Figure 3), the Pearson correlation of the DARs among the 3 schools was calculated, and the morphological differences among their DAR curves were compared. We compared the correlation and trend of DAR1 and DAR2 (Figure 4).

Second, according to the time series diagram of DAR1 (Figure 3), the starting date was determined as the date when the DAR1 of each school began to stabilize, and then the daily fever rate (DFR) of each school was calculated after this date. When the DFR deviated by 3 SDs from the mean value, the infrared images of students in the system were examined. If the problem was operational, the corresponding DFR was used as the missing value and was replaced with the mean of the DFR for the previous and next days of that date. Absenteeism and fever were assumed to represent different severity degrees of influenza symptoms, with absenteeism representing severe symptoms and attendance with fever representing mild symptoms. Therefore, the denominators of both the DAR and DFR were set as the number of total enrollments. The calculation formula of the DFR was as follows:

The DFR time series diagrams of the 3 schools are shown in Figure 5; the morphological differences among their DFR curves were compared, and the Pearson correlation of the DFRs among the 3 schools was calculated.

Third, based on the DAR and DFR, the weekly absenteeism rate (WAR) and weekly fever rate (WFR) for the three schools were calculated as follows:

The time series diagrams of the WAR and WFR of the 3 schools were produced, and their coincidence with the time series diagram trends of the WPRIV was compared (Figures 6-8).

Finally, the following statistical process was performed: (1) The sums of the WAR and WFR of each school were calculated. (2) Based on the data of school A, the data of school B were added at the beginning of week 37; then the data of school C were added again in week 45, and then the combined WAR and WFR were combined based on the weight of the total enrollment in each school. (3) The sums of the combined WAR and WFR were calculated. Simultaneously, the current time was set to *t*; then the WPRIV sequence was advanced by 1 week (*t– 1*), 2 weeks (*t–2*), and 3 weeks (*t–3*). The correlation of the WPRIV with the aforementioned WARs and WFRs and their sum was calculated under these 4 conditions to investigate the reliability, accuracy, and timeliness of different types of data derived from this system for influenza activity surveillance.

Figure 3. Time series of daily absenteeism rates reported by the systems of schools A, B, and C.

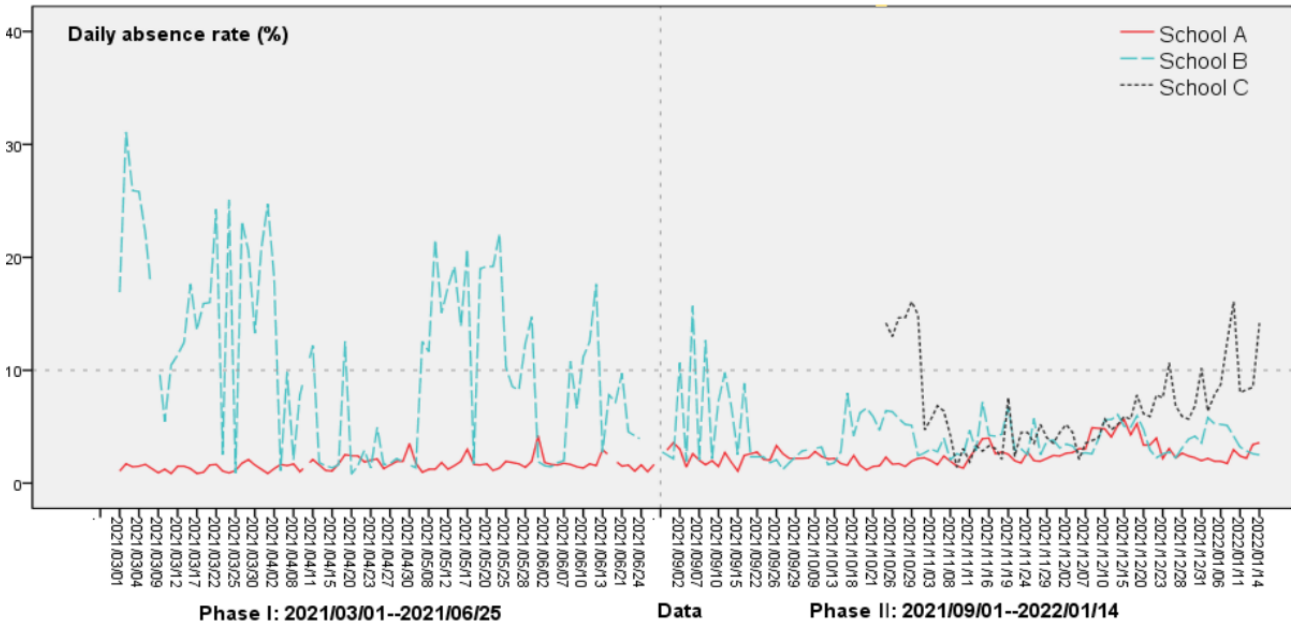


Figure 4. Time series of daily absenteeism rates reported by the system (DAR1) and school physicians (DAR2). DAR: daily absenteeism rate.

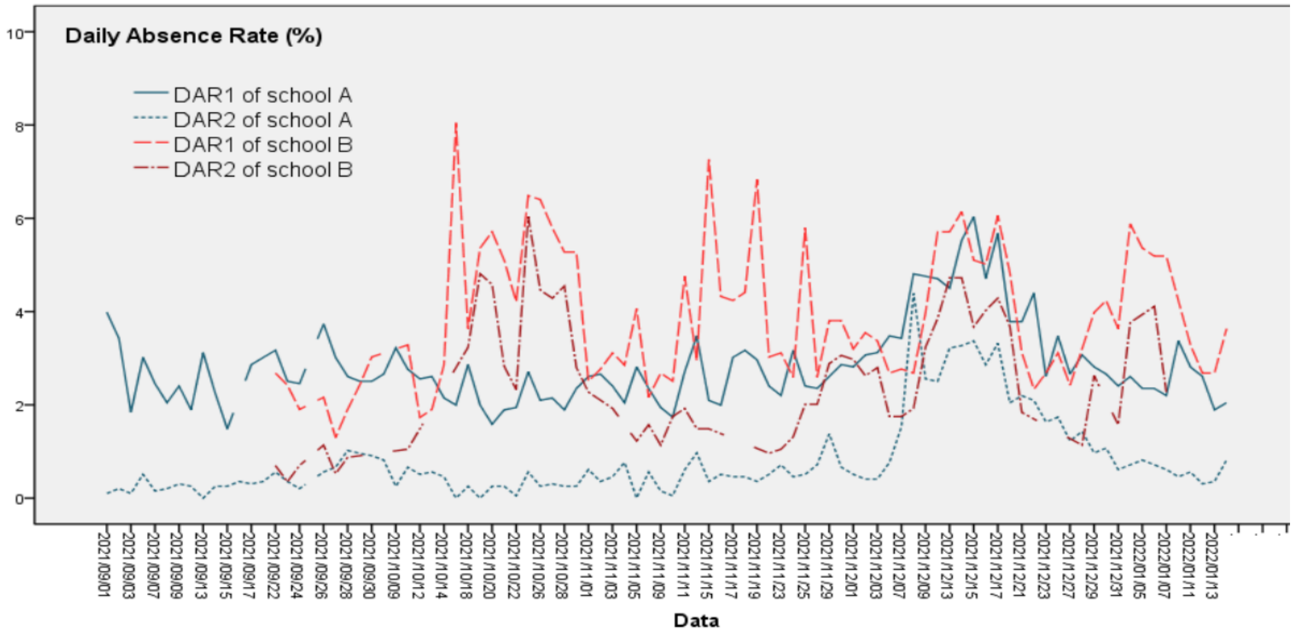


Figure 5. Time series of daily fever rates in 3 schools.

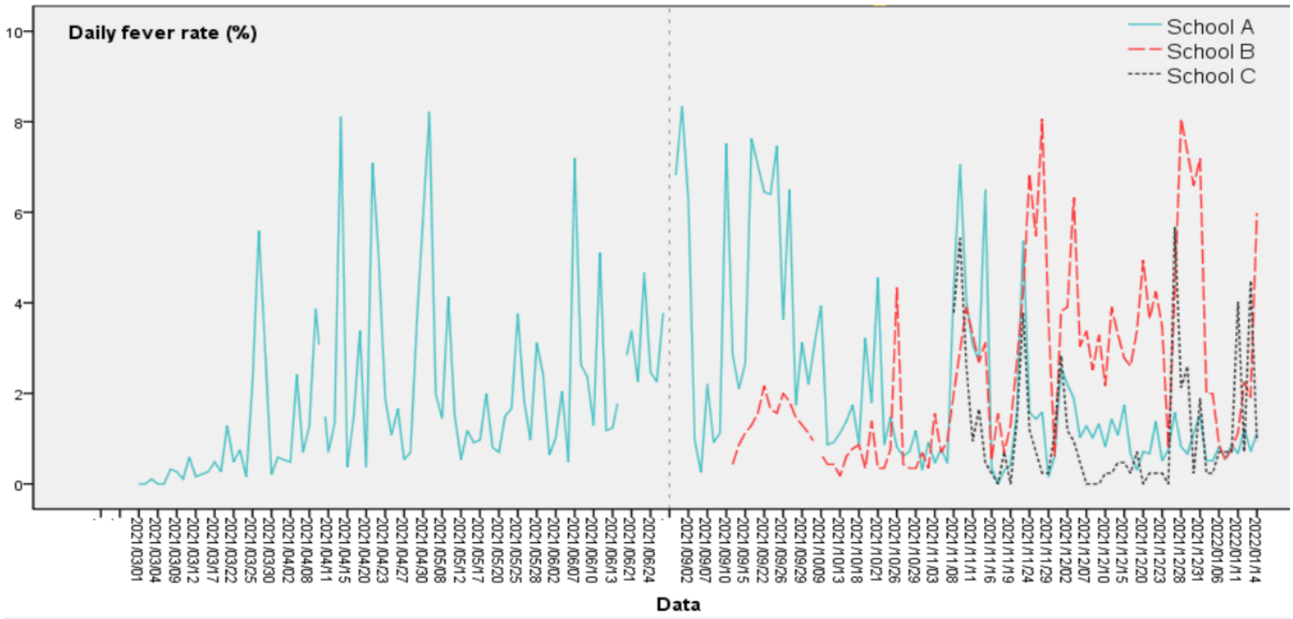


Figure 6. Weekly positive rates of influenza virus, weekly absenteeism rates, and weekly fever rates of school A.

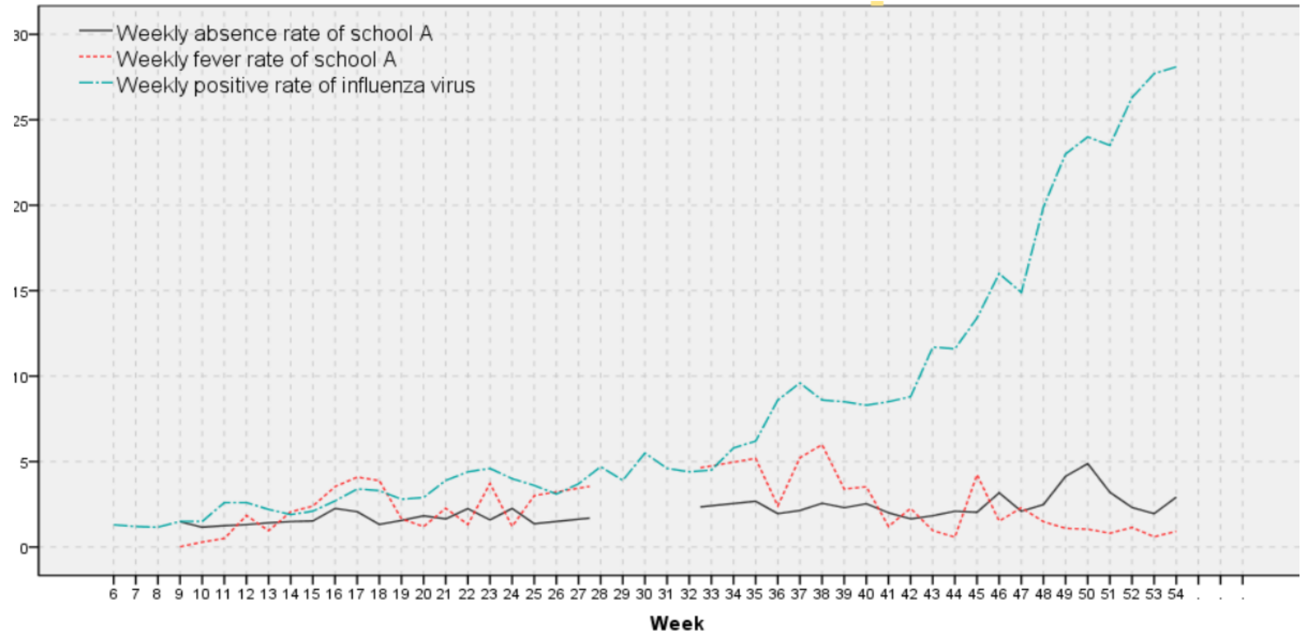


Figure 7. Weekly positive rates of influenza virus, weekly absenteeism rates, and weekly fever rates of school B.

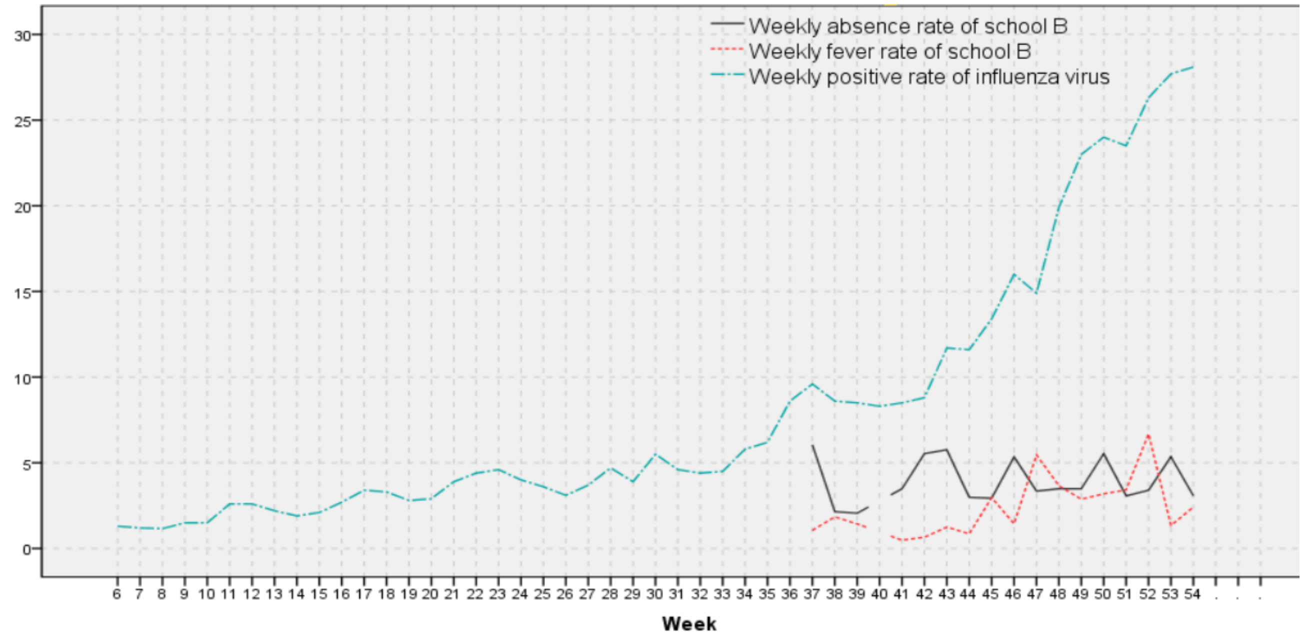
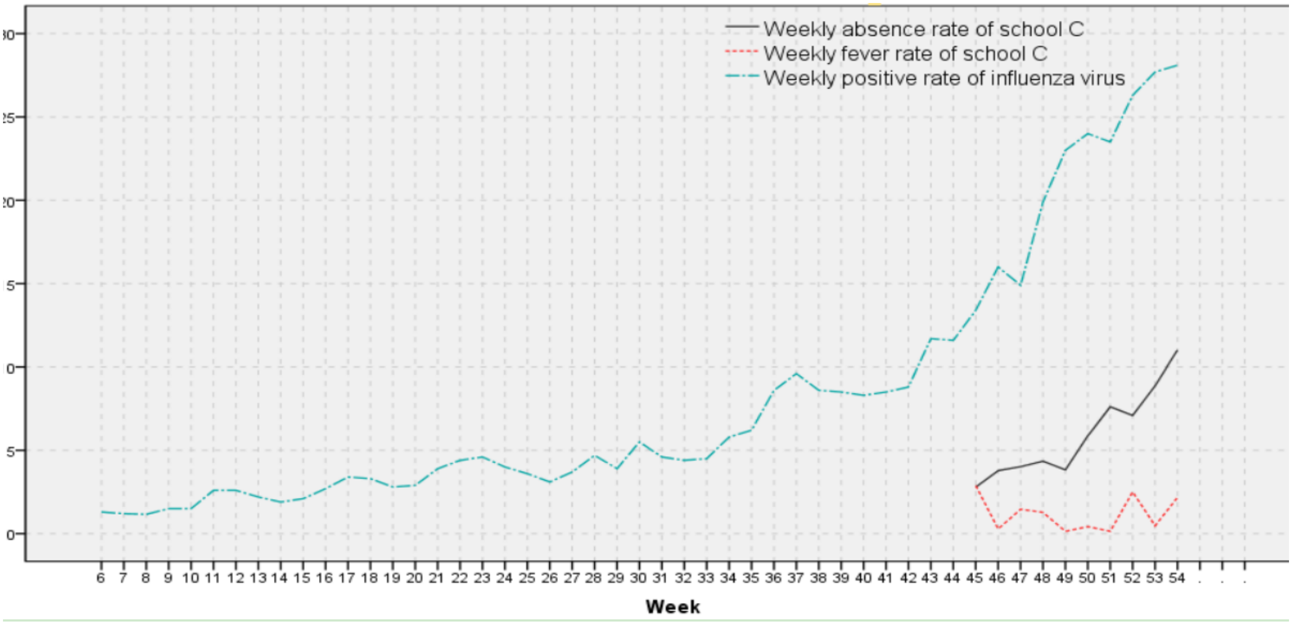


Figure 8. Weekly positive rates of influenza virus, weekly absenteeism rates, and weekly fever rates of school C.



Results

Analysis of DAR1

In phase I, all 2961 students in schools A and B had registered accounts in the system. In phase II, the total number of students in the 3 schools was 3535, with 3530 students (99.86%) having registered accounts (Table 1). The DAR of school A remained relatively stable throughout the surveillance period, without surpassing the 10% critical threshold (Figure 3). The DAR of school B fluctuated sharply in phase I, but the overall trend was decreasing. In phase II, after about 2 weeks, the DAR curves of schools B and A were similar. The DAR of school C varied considerably during the first 2 weeks of system commissioning and began to stabilize about 2 weeks later. The DAR of school C exceeded 10% on 4 days, December 24, December 31, January 7, and January 10, 2022. These 4 days were weekends or holidays.

The DAR1s of the 3 schools were very similar along with the trends over the 30 monitoring days from November 8 to December 20 (Figure 3). During this time, 3 pairs of absenteeism rates, namely schools A and B (r_a=0.508, *P*=.004), B and C (r_b=0.427, *P*=.017), and A and C (r_{ac}=0.447, *P*=.012), were moderately positively correlated. After December 20, the DARs at the 3 schools showed different trends, with the differences between school C and the other 2 schools being significantly different.

Table 1. Daily absenteeism rates and daily fever rates of 3 schools reported by the system in phases I and II.

School	Total number	Number of enrollments	Rate of enrollment (%)	Daily absenteeism rate (%)			Daily fever rate (%)		
				Minimum	Maximum	Mean	Minimum	Maximum	Mean
Phase I									
A	1861	1861	100	0.86	4.19	1.63	0	8.22	1.87
B	1100	1100	100	0.82	31.09	11.14	N/A[a]	N/A	N/A
Phase II									
A	1954	1954	100	1.07	5.63	2.55	0	8.34	2.12
B	1154	1153	99.91	1.21	15.70	4.23	0.17	8.07	2.44
C	427	423	99.06	1.42	16.08	6.75	0	5.67	1.19

[a] N/A: not applicable.

Correlation Analysis of DAR1 and DAR2

Between September 1, 2021, and January 14, 2022, students from school A were expected to attend school for 92 days and students from school B for 90 days. Both the system and the school physician of school A recorded 92 days of data. A total of 5128 absences were reported by the system, whereas a total of 1476 absences were reported by the school physicians, with the latter accounting for 28.78% of the former. In school B, the system recorded 3452 absences over 90 days, whereas the school physician recorded 1691 absences over 66 days (73.3% completeness), with the number reported by school physicians being 48.99% of the number reported by the system.

A significant positive correlation between DAR1 and DAR2 in school A was detected (*r*=0.809, *P*<.001), and their change trends were highly consistent. In school B, DAR1 and DAR2 were also significantly positively correlated (*r*=0.766, *P*<.001), but there was a notable gap between them in November 2021 (Figure 4). The abovementioned data show that the absence reported by school physicians (completeness 86.7%) was only 36.5% of the absence reported by the system (completeness 100%), and that a significant positive correlation between the 2 was present (*r*=0.372, *P*=.002).

Analysis of DFR

The DFR calculation time for school A started from March 1, 2021 (week 9), for school B from September 13, 2021 (week 37), and for school C from November 8, 2021 (week 45). The infrared image investigation of the system confirmed that high-temperature objects were placed next to the infrared thermometer in school A on 2 days (April 30, September 18), and on 1 day (April 1), the thermometer was unable to measure temperatures owing to physical failure. In school B, there were 2 days (November 11 and December 29) when a high-temperature object was placed next to the thermometer. The DFR of these 5 days was regarded as a missing value and replaced with the mean of the DFR for the previous and next days.

Overall, the DFR curve of school A resembles a parabola with a downward opening (Figure 5). This trend was similar to the daily average temperature change trend in this area during the surveillance period. During the 30 days from September 13 to October 29, the DFR of school A was always higher than that of school B, and after October 29, this relationship was gradually reversed. The DFR curves of schools C and A were closer, and the DFRs of these 2 schools were also significantly positively correlated (r_{ac}=0.493, *P*<.001). Although no significant correlation was detected between schools A and B (r_{ab}=–0.023, *P*=.84), and schools B and C (r_{bc}=0.091, *P*=.54), the DFR curves of the 3 schools were consistent in some wave peaks and troughs.

Correlation Analysis of WAR1, WFR, and WPRIV

The WAR1s and WFRs for the 3 schools were calculated, and their time series diagrams were plotted. The WAR1 of school A was consistent with the trend of the WPRIV (Figure 6), that is, both the WAR1 and WPRIV gradually increased over time. After week 42, influenza activity levels spiked, with the first peak of WAR1 of school A presenting in week 46 (1 week earlier than WPRIV), and the second peak in week 50 (the same time as the WPRIV). The first peak of the WFR1 in school A was at week 45 (2 weeks earlier than the WPRIV).

School B showed a peak of the WAR1 in weeks 42 and 43 (Figure 7). Investigation on this aspect showed that the school had problems with the health codes of some students; therefore, school B prudently allowed 4 classes of grade 1 to study at home. The second WAR1 peak of school B was in week 45, and the third one was in week 50. These 2 peak times were the same as those of school A, but school B had another WAR1 peak in week 53, which was different from school A. As the level of influenza activity increased, the WFR1 of school B peaked at week 45 (same as in school A), week 47, and week 52.

The surveillance weeks of school C were few, and the WAR1 of school C has been on the rise throughout the surveillance period (Figure 8), which was highly consistent with the trend of the WPRIV. The 3 peaks of the WFR1 in school C were in week 45 (same as school A and B), week 47, and week 52 (same as school B). On combining with Figures 5-7, the mismatch trend of the WAR1 and WFR became evident. This phenomenon was especially apparent in school B. For example, the WARs peaked in weeks 46, 50, and 53, whereas the corresponding WFRs were at a low point. For weeks 45, 47, and 52, the WFRs peaked, whereas the WAR1s were at their troughs.

Among the WAR1s reported by the system, only the WAR1 of schools A and C was significantly positively correlated with the WPRIV. At *t*–3, the correlation coefficient between the WAR1 of school A and WPRIV was the highest, whereas at *t*, the correlation coefficient between the WAR of school C and WPRIV was the highest (Table 2). Although the WAR of school B was not significantly correlated with the WPRIV in the 4 conditions, the variation trend of the correlation coefficients was similar to that in school A. Only the WFR of school B was significantly positively correlated with the WPRIV, and the maximum coefficient was at *t*–3. The addition of the WAR1 to the WFR produced an increased correlation with the WPRIV only in the sum of school B. The WAR1 of school A reported by the school physician was significantly positively correlated with the WPRIV, with the maximum coefficient located at *t*–3. The correlation coefficients between the WAR1 and WPRIV that were calculated based on system-reported data were higher than those calculated based on data reported by school physicians in each condition. The WAR1 of school B reported by both the school physician and the proposed system was not significantly correlated with the WPRIV in any of the 4 conditions.

Table 2. Correlation analysis of weekly absenteeism rate, weekly fever rate, and weekly positive rate of influenza virus.

Variables	Weekly positive rate of influenza virus							
	t	*P* value	*t–1*	*P* value	*t–2*	*P* value	*t–3*	*P* value
Data reported by the system								
Weekly absence rate of school A	0.662	<.001	0.638	<.001	0.654	<.001	0.674	<.001
Weekly absence rate of school B	0.334	.21	0.268	.32	0.391	.13	0.442	.09
Weekly absence rate of school C	0.771	.009	0.728	.02	0.444	.2	0.222	.54
Weekly fever rate of school A	–0.368	.03	–0.367	.03	–0.387	.02	–0.363	.03
Weekly fever rate of school B	0.492	.05	0.589	.02	0.557	.03	0.618	.01
Weekly fever rate of school C	0.229	.47	0.307	.33	0.056	.86	–0.002	>.99
Weekly absence and fever rate of school A	0.058	.74	0.045	.79	0.038	.83	0.069	.69
Weekly absence and fever rate of school B	0.6	.01	0.635	.008	0.687	.003	0.767	.001
Weekly absence and fever rate of school C	0.686	.03	0.664	.04	0.317	.37	–0.333	.35
Data reported by school physicians								
Weekly absence rate of school A	0.58	.007	0.55	.01	0.59	.006	0.648	.002
Weekly absence rate of school B	0.429	.11	0.406	.13	0.4	.14	0.379	.16

Discussion

Principal Findings

In 2017, Groseclose and Buckeridge [37] proposed a surveillance system evaluation framework comprising 12 indicators, namely simplicity, acceptability, representativeness, stability, data quality, timeliness, flexibility, security, sensitivity, predictive value positive, cost-effectiveness, and standard use. Comparison of the proposed system with existing similar systems showed its advantages in in terms of simplicity, cost-effectiveness, data quality, sensitivity, and timeliness.

This system is simple to operate and has a low construction cost. The simplicity of the proposed surveillance system is reflected in four aspects: data availability and type, organization and type, data exchange and conversion, and personnel operation and training [37]. Sickness absence surveillance based on manual data collection requires the data reporter to have extensive medical expertise. Therefore, the reporter is required to be a school physician or a part-time worker with adequate medical training. On the other hand, the operation of the proposed system does not require professional personnel, but it only requires students to stand in front of the instrument in accordance with the standard for 1 second so that all symptom data can be automatically obtained. In this way, the system is highly cost-effective in terms of workforce. Moreover, contrary to the government-led SSS, which involves high investment for platform research and development, the proposed system is built based on the mature network platform and is thus cost-effective.

The absenteeism reported by the system was complete and accurate, and the completeness of the temperature was high, but the accuracy needs to be improved. Fingerprints, smart cards, or face recognition were used to guarantee that every student in attendance is checked and accurately identified. Lawpoolsri et al [14] attempted to use fingerprints instead of manual collection but failed after many students missed and checked wrongly. In this study, the proportion of students registering system accounts was close to 100%, the accuracy of face recognition technology was more than 99.99%, and the school also arranged personnel to supervise the students during check-in. Data showed that the absenteeism reported by the system was highly positively correlated with that reported by school physicians, and the completeness of the former was higher than that of the latter. The system also needs to confidently guarantee that the temperature of each identified student is accurately measured. As face recognition and infrared temperature measurement were almost synchronized, the completeness of temperature was adequate, but its accuracy needs to be improved. The accuracy of thermal imaging is affected by the instrument, environment, and individual factors [29-31]. In this study, only the temperature of school B met the monitoring requirements. The instruments in school B were installed indoors and strictly supervised by students. These measures are helpful to reduce improper measurement behavior and improve the accuracy. Future research will focus on the construction and installation of instruments and implementation of the operation standards.

The proposed system showed good sensitivity. The surveillance sensitivity includes case detection, outbreak detection, and case definition [37]. Existing systems focus on students who are absent from school [6-12,14-18,20-22], whereas others also consider students who visit the school health room [9,10]. During an influenza outbreak, about 20% of the population shows symptoms, but only about 2% require physician consultation [38]. Students do not miss school or consult school physicians unless they are seriously ill. Because of academic pressure, it is common for Chinese students to attend school sick, and about 74.7% of those who took sick leave were absent for less than 1 day [26]. This is a potential explanation for the number of absences reported by school physicians being only about 36.5% of the number reported by the system in this study. The correlation between the WAR of school A reported by the system and the WPRIV was higher than that between the WAR reported by school physicians and the WPRIV, thus appearing to support this conclusion. Data showed that in the influenza outbreak season, the DFR in some schools was up to 8%. By adjusting the absenteeism criteria and combining temperature screening, the presented system is more sensitive to case and outbreak detection than existing systems.

The results also showed good timeliness rates. The data of this system were transmitted in real time and analyzed automatically. Parents, teachers, and administrators were able to instantly access the attendance and temperature status of an individual, class, and school. Baer et al [11] proposed that the surveillance value of absenteeism lies more in situational awareness than in early detection, which may need to be revised when applied to China. This study revealed that absenteeism in the 3 schools was significantly positively correlated when influenza activity levels were low, which was not consistent with the findings of Schmidt et al [8] stating that absenteeism is very similar across age groups. With the increase in influenza prevalence, absenteeism in primary schools was the first to peak, and absenteeism in middle schools reached the first peak 2 weeks later, which is consistent with the findings of Mook et al [39]. Subsequently, the gap in the absenteeism timing among schools increased, even between 2 primary schools; at this point, the claim of Schmidt et al [8] does apply. The addition of temperature data increased the timeliness of the system. The results showed that temperature could predict influenza up to 3 weeks earlier when the temperatures of students were accurately measured. Combined with the study of Miller et al [32], the timeliness advantage of temperature in influenza surveillance may indeed exist. Therefore, it is extremely critical to standardize instrument placement and operation procedures in the future to further improve the reliability and accuracy of temperature data.

Limitations

First, although thermal infrared imaging is simple, its accuracy is easily influenced by environmental factors [29]. Because of the need for COVID-19 prevention, some schools introduced the proposed system. Nonetheless, these schools attach different importance levels to epidemic prevention and control, which in turn leads to different levels of hardware support and operation supervision. These disparities led to differences in data quality, especially temperature data, which hindered further analysis of these data. Second, COVID-19 was a prevailing issue during the surveillance period. Although it facilitated the roll-out of the system to a certain extent, the number of COVID-19 cases in the surveillance area was too small to be the target disease. However, because influenza was selected as the target infection, the status data for the influenza epidemic in general are distorted by the pressure of COVID-19 prevention. Consequently, some of the presented results need to be re-evaluated without considering the impact of COVID-19. Finally, although the system has been authorized by the government to collect sensitive personal information, possible changes to the national personal information and privacy protection policy in the future will substantially affect the operational stability of the system.

Conclusions

Comparison of the proposed system with existing similar systems showed its advantages in terms of simplicity, cost-effectiveness, data quality, sensitivity, and timeliness. This study showed that the absenteeism recorded using face recognition technology was reliable, but the accuracy of the temperature recorded by infrared thermometers should be enhanced. The implementation of the influenza SSS based on absenteeism and temperature data was feasible. When influenza activity levels were moderate, a significant positive correlation between the DARs was detected; however, as the levels increased, the gap among the DARs gradually increased and peaked about 2 weeks earlier in primary schools than in junior high schools. The introduction of temperature measurement substantially strengthened the surveillance timeliness, allowing detection of influenza outbreaks up to 3 weeks earlier than traditional systems. This study demonstrated a feasible way to solve the challenge of developing a surveillance system and promote the automation of symptom data acquisition in the surveillance system.

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Conflicts of Interest

None declared.

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Abbreviations

DAR: Daily absence rate
DFR: Daily fever rate
SSS: Syndromic surveillance system
WAR: Weekly absence rate
WFR: Weekly fever rate
WPRIV: Weekly positive rate of influenza virus

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Original Paper

Provider-Initiated HIV Testing in Puerto Rico from Data of the National HIV Behavioral Surveillance–Heterosexual Cycle (NHBS-HET) 2016: National Cross-sectional Survey

Vivian Colón-López[1,2*], MPH, PhD; Derick Pérez-Guzmán[3*], BA; Maureen M Canario De La Torre[3*], MPH; Nadia Centeno-Alvarado[3*], MPH; Ivony Y Agudelo-Salas[3*], MSc; Yadira Rolón[4*], MSc; Sandra Miranda[4*], MSc; Maria Pabón[4*], MA; Jorge Rodríguez-Lebrón[4*], MSc; Gladys Girona Lozada[4*], MSc

[1]Cancer Control and Population Sciences Program, Comprehensive Cancer Center, University of Puerto Rico, San Juan, Puerto Rico

[2]Evaluation Program, Health Services Administration, Graduate School of Public Health, Medical Sciences Campus, University of Puerto Rico, San Juan, Puerto Rico

[3]Data Analysis and Publication Core, Comprehensive Cancer Center, University of Puerto Rico, San Juan, Puerto Rico

[4]HIV/AIDS Surveillance Program, Puerto Rico Health Department, San Juan, Puerto Rico

[*]all authors contributed equally

Corresponding Author:
Vivian Colón-López, MPH, PhD
Cancer Control and Population Sciences Program
Comprehensive Cancer Center
University of Puerto Rico
Edificio Centro Comprensivo de Cáncer de la Universidad de Puerto Rico,
Segundo Piso Oficina # 225, Paseo José C Barbosa
San Juan, 00935
Puerto Rico
Phone: 1 787 772 8300 ext 1225
Email: vivian.colon@upr.edu

Abstract

Background: According to the Centers for Disease Control and Prevention and World Health Organization guidelines, all individuals aged 13-64 years should get screened for HIV infection as part of their routine medical examinations. Individuals at high risk should get tested annually.

Objective: This study aimed to identify the sociodemographic, health care, and sexual behavioral characteristics of provider-initiated HIV testing using data from the Puerto Rico National HIV Behavioral Surveillance 2016 cycle, directed toward heterosexual individuals at increased risk of HIV infection.

Methods: A sample of 358 eligible participants were recruited through respondent-driven sampling, where sociodemographic characteristics, health care use, and HIV test referral were used to assess a description of the study sample. Pearson chi-square and Fisher tests were used to evaluate proportional differences. Multivariate logistic regression models were performed to determine the association between independent variables and HIV test referral. Adjusted prevalence ratios by sex and age with their 95% CIs were determined using a statistical significance level of .05.

Results: Despite 67.9% (243/358) of participants showing high-risk sexual behavioral practices and 67.4% (236/350) reporting a low perceived risk of HIV infection among those who visited a health care provider within the last 12 months, 80.7% (289/358) of the study sample did not receive an HIV test referral at a recent medical visit. Multivariate analysis showed that the estimated prevalence of the participants who received an HIV test referral among those who reported being engaged in high-risk sexual behaviors was 41% (adjusted prevalence ratio .59, 95% CI .39-.91; *P*=.02) lower than the estimated prevalence among those who did not engage in high-risk sexual behavior.

Conclusions: This sample of Puerto Rican adults reported a significantly lower prevalence of receiving an HIV test referral among heterosexual individuals at increased risk of HIV infection who engaged in high-risk behaviors. This study further emphasizes the need for health care providers to follow recommended guidelines for HIV test referrals in health care settings.

Promotion practices in the future should include enhancing referral and access to HIV tests and implementing preventive measures to counteract the HIV epidemic in Puerto Rico.

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KEYWORDS

HIV; HIV testing; heterosexual; health care provider; Puerto Rico; National HIV Behavioral Surveillance; NHBS; behavioral surveillance system; HIV infection; Centers for Disease Control and Prevention; CDC; respondent-driven sampling

Introduction

Heterosexual contact is the second most common route of HIV transmission in the United States [1]. Data from the Puerto Rico HIV Surveillance System reported that heterosexual contact was the most prevalent mode of HIV transmission, accounting for 36% of the total cases in 2016. The vast majority (70%) of HIV-diagnosed cases were men. However, among heterosexual individuals, women were the most affected by this transmission route, accounting for approximately 62% of those cases [2]. In Puerto Rico, studies have shown a high prevalence of high-risk sexual behaviors among men and women [3], where more than half (60%) of heterosexual men and women have ever been tested for HIV in their lifetime (unpublished Puerto Rico National HIV Behavioral Surveillance [NHBS] data, 2010 cycle).

According to the 2006 guidelines from the Centers for Disease Control and Prevention (CDC) on HIV testing, all individuals aged 13-64 years should be screened for HIV infection as part of their routine medical examinations. Individuals at high risk should get tested annually [4]. The World Health Organization and the Joint United Nations Program of HIV/AIDS recommend that health care providers offer patients opt-out HIV testing and counseling. Specifically, it is suggested that HIV testing be offered to patients regardless of the presence or absence of clinical symptoms of HIV infection and the patient's motive(s) for seeking health advice [5]. This effort, known as provider-initiated HIV testing (PIHT), has resulted in an increased number of patients being tested [6,7].

Despite the previous recommendations, the rigorous application of this practice is not seen in most health care scenarios [8]. Previous studies have identified barriers that might account for the lax implementation of PIHT [9,10]. Some barriers include the lack of time during routine visits, the health care provider's beliefs that their patients would feel uncomfortable discussing HIV infection, a patient's idea that their previous results (before the last 12 months) remain valid, and the provider's (or patient's) sense that such a conversation would be inappropriate because of a poor doctor-patient relationship [7-11]. However, further studies have reported that such barriers could be overcome through provider initiatives such as adopting a sensitive attitude when engaging patients in discussing HIV testing and making educational reinforcement on HIV [12,13].

The number of individuals tested for HIV in 2010 still falls short of the expected number [14]. The burden of HIV infection in heterosexual individuals at high risk in Puerto Rico and the current low–HIV testing uptake highlights the need for understanding the correlates and characteristics of PIHT. This study aimed to identify the sociodemographic, health care, and sexual behavioral characteristics of PIHT using data from the Puerto Rico–NHBS. Insights into PIHT profile may help develop strategies for the early identification of new HIV cases, contributing to better patient care and outcomes.

Methods

Data Source

The NHBS is a cross-sectional survey performed in the United States and its jurisdictions that collects data related to high-risk behavioral practices for HIV infection in 3 different populations: men who have sex with men, persons who inject drugs, and heterosexual individuals at increased risk of HIV infection [15]. NHBS procedures and methods can be found elsewhere [15]. The NHBS performs consecutive surveys in each cycle, in which the abovementioned populations are studied separately in rounds composed of independent cycles.

Participation in this project was completely anonymous and voluntary, which involved completing a face-to-face interview using a standardized questionnaire in Spanish that gathered information about HIV-associated risk behaviors. Additionally, the participants were offered a voluntary HIV test through the interview process, which they could opt out of while still completing the survey. The interviewers described these activities through informed consent to the participants before they began the questionnaire. Participants who completed the NHBS survey and those who agreed to the HIV test received a stipend for their time (US $20 for the survey and US $20 for the HIV test). NHBS staff did not require any personal information from the participants to protect their privacy and confidentiality. Blood specimens and questionnaires were linked by Survey ID numbers only.

Ethics Approval

The Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus reviewed and approved this study (A0910115).

Recruitment

Data used for this analysis correspond to the Puerto Rico NHBS–Heterosexual Cycle's 4th round (PR-NHBS-HET4) conducted in 2016. Recruitment for PR-NHBS-HET4 was performed through respondent-driven sampling (RDS). The implementation of RDS began with a limited number of initial recruits known as "seeds," which are people who work with the target population and can adequately identify other participants with the ideal characteristics of the NHBS project.

The participating areas were included within the San Juan metropolitan statistical area. The estimated sample size for PR-NHBS-HET4 was 500 participants. Inclusion criteria for seeds and participants were the following: (1) be aged 18-60 years, (2) have had vaginal or anal sex with a person of the opposite sex in the 12 months before the interview date, (3) have not previously participated in any other PR-NHBS-HET cycle, (4) live in 1 of the participating San Juan metropolitan statistical area municipalities, (5) identify as male or female, (6) be able to complete the interview in Spanish or English, (7) have not injected drugs in the 12 months before the interview date, and (8) have a low income as established by the Department of Health and Human Services poverty guidelines or have low educational attainment—no greater than high school education [16,17]. During the PR-NHBS-HET4 cycle, a total of 609 interviews were conducted. Of these participants, 114 were excluded from the study because they did not meet the inclusion criteria, leaving 495 participants—9 of whom were seeds. For this analysis, we restricted the sample to those who visited a health care provider within the last 12 months, leaving 358 participants as the final sample that had complete data on the main outcome of this study.

Measurements

Variables for sociodemographic characteristics, health care use, HIV testing, and PIHT were assessed per the NHBS core questionnaire [18]. To collect the main outcome data, the participants responded to the question, "At any of those times you were seen [by a doctor, nurse, or other health care provider], were you offered an HIV test?" The participant's response was dichotomized into 2 categories, "Yes" or "No." Variables such as educational level, annual household income, employment, and marital status were dichotomized for data analysis. Risk perception was assessed using dichotomized categories (low–risk perception of getting infected with HIV and high–risk perception of getting infected with HIV). A high-risk sexual behavior scale was performed if the study participant reported engaging in at least one of the following in the past 12 months: (1) any exchange of sex for drugs or money; (2) having sex with more than one sexual partner; (3) having sex with a partner who "probably" or "definitely" had other sex partners, concurrently; (4) having sex with a partner who had "probably" or "definitely" injected drugs; (5) having sex with a partner who "probably" or "definitely" had male-to-male sexual contact (only female respondents); and (6) having sex with a partner whose HIV status was "positive" or "indeterminate."

Data Analysis

The univariate analysis assessed descriptive measurements for sociodemographic characteristics, high-risk sexual behaviors, and the use of health care services. The bivariate analysis consisted of Pearson chi-square and Fisher exact tests to describe the proportional differences of the variables related to sociodemographic characteristics, HIV testing, high-risk behaviors, and PIHT. To assess the association between selected independent variables and PIHT, a logistic regression analysis was conducted with those variables that showed statistical significance in association with the bivariate analysis. Logistic regression models were performed for each independent variable separately. Crude prevalence ratios and adjusted prevalence ratios (PR_a) by sex and age are presented with 95% CIs and a statistical significance level established at .05. To estimate PR_a, we assessed the interaction terms in the logistic model using the likelihood ratio test. All statistical analysis was performed with Stata statistical software (version 17; StataCorp LLC).

Results

Sociodemographic Characteristics

Most (250/358, 69.8%) of the sample were women. The respondents' median age was 39 (SD 12.01) years. The majority (307/358, 85.8%) of the respondents reported having medical insurance at the time of the interview (Table 1).

Table 1. Provider-initiated HIV testing in heterosexual individuals at increased risk of HIV infection, Puerto Rico National HIV Behavioral Surveillance Cycle 2016 (N=358).

Characteristic	Total sample, N	Received HIV test referral, n (%)	Did not receive HIV test referral, n (%)	*P* value[a]
All participants	358	69 (19.3)	289 (80.7)	
Sex (N=358)[b]				
Male	108	19 (17.6)	89 (82.4)	.60
Female	250	50 (20)	200 (80)	
Age (years; N=358)				
18-29	102	26 (25.5)	76 (74.5)	.06
30-60	256	43 (16.8)	213 (83.2)	
Education (N=358)				
High school or less	246	50 (20.3)	196 (79.7)	.46
Some college or more	112	19 (17)	93 (83)	
Employed (N=358)				
No	226	38 (16.8)	188 (83.2)	.12
Full time or part time	132	31 (23.5)	101 (76.5)	
Marital status (N=358)				
Married or partnered	151	33 (21.8)	118 (78.2)	.29
Separated, divorced, widowed, or never married	207	36 (17.4)	171 (82.6)	
Currently insured (N=358)				
No	51	9 (17.7)	42 (82.3)	.75
Yes	307	60 (19.5)	247 (80.5)	
Lacked health care due to cost (N=358)				
No	304	63 (20.7)	241 (79.3)	.10
Yes	54	6 (11.1)	48 (88.9)	
Had a usual source of care (N=358)				
No	23	3 (13)	20 (87)	.59
Yes	335	66 (19.7)	269 (80.3)	
Ever tested for HIV (N=358)				
No	81	4 (4.9)	77 (95.1)	<.001
Yes	277	65 (23.5)	212 (76.5)	
Low–risk perception of getting infected with HIV in the next 12 months (n=350)				
No	114	18 (15.8)	96 (84.2)	.40
Yes	236	46 (19.5)	190 (80.5)	
Engaged in high-risk sexual behavior[c] (N=358)				
No	115	29 (25.2)	86 (74.8)	.050
Yes	243	40 (16.5)	203 (83.5)	
Men who engaged in high-risk sexual behavior[c] (n=108)				
No	30	7 (23.3)	23 (76.7)	.33
Yes	78	12 (15.4)	66 (84.6)	
Women who engaged in high-risk sexual behavior[c] (n=250)				
No	85	22 (25.9)	63 (74.1)	.095
Yes	165	28 (17)	137 (83)	

[a] Chi-squared test–reported *P* value.

[b] Denominators vary because of nonresponse in the form of missing values.

[c] Defined as engaging in at least one of the following: (1) any exchange of sex for drugs or money; (2) having sex with more than one sexual partner; (3) having sex with a partner who "probably" or "definitely" had other sex partners, concurrently; (4) having sex with a partner who had "probably" or "definitely" injected drugs; (5) having sex with a partner who "probably" or "definitely" had had male-to-male sexual contact (only female respondents); and (6) having sex with a partner whose HIV status was positive or indeterminate.

Use of Health Care Services and HIV Testing

Of those participants who reported having visited their health care providers within the last 12 months, only 19.3% (69/358) received an HIV test referral from their health provider. More than half (277/358, 77.4%) of the participants reported having been tested for HIV infection at least once at some point in their lifetime. Of this group, only 30.8% (69/224) of the respondents had tested within the 12 months before the interview. When asked to relate the primary reasons for not getting tested for HIV in the past 12 months, 33.6% (94/280) of the participants' most frequent answer was being afraid of having HIV. Regarding risk perception, 236 (67.4%) out of 350 participants reported perceiving themselves as having a low risk of getting HIV in the next 12 months (Table 1).

Sociodemographic Characteristics, HIV Testing, High-Risk Sexual Behaviors, and PIHT

Table 1 shows significant differences between the participants who received an HIV test referral from their providers and those who did not. Individuals who reported being aged 30-60 years tended to have a significantly higher prevalence of not receiving an HIV test referral from their providers (*P*=.06). Statistically significant differences between participants who reported having ever been tested for HIV and provider recommendations were observed (*P*<.001). Significant differences were also observed among individuals who had engaged in high-risk sexual behaviors. Those who reported higher risk sexual practices had a lower HIV test referral from their provider (*P*=.050). The difference in the proportion of women who reported engagement in high-risk sexual behaviors achieved marginal significance (*P*=.095). Additionally, women received significantly more HIV test referrals than men, despite no significant differences between the 2 groups in reported high-risk sexual behaviors (post hoc analysis; *P*=.25).

Factors Associated With PIHT

Multivariate logistic regressions models adjusted for age and sex showed that the estimated prevalence of the participants who received an HIV test referral among those who reported being engaged in high-risk sexual behavior is 41% (PR_a .59, 95% CI .39-.91; *P*=.02) lower than those who did not engage in high-risk sexual behavior (Table 2). Moreover, the prevalence of getting an HIV test referral by their health care provider among women who engaged in high-risk sexual practices is 43% (PR_a .57, 95% CI .35-.93; *P*=.02) lower than women who reported not being engaged in high-risk sexual behavior. Lastly, the prevalence of receiving a referral for HIV testing by a provider among individuals who reported being tested for HIV in their lifetime is 6 times (CI 95% 2.12-15.28; *P*=.001) the prevalence of getting a referral of HIV testing among those who have not been tested for HIV throughout their life (Table 2).

Table 2. Multivariate analysis of variables associated with provider-initiated HIV testing, Puerto Rico National HIV Behavioral Surveillance Cycle 2016 (N=358).

Variable	Received HIV test referral, n (%)	Did not receive HIV test referral, n (%)	Crude prevalence ratio (95% CI)	*P* value	Adjusted prevalence ratio[a] (95% CI)	*P* value
Engaged in high-risk sexual behavior[b] (N=358)[c]						
No (n=115)	29 (25.2)	86 (74.8)	Reference	.048	Reference	.02
Yes (n=243)	40 (16.5)	203 (83.5)	.65 (.43-.99)		.59 (.39-.91)	
Women who engaged in high-risk sexual behavior[b] (n=250)						
No (n=85)	22 (25.9)	63 (74.1)	Reference	.09	Reference	.02
Yes (n=165)	28 (17)	137 (83)	.66 (.40-1.07)		.57 (.35-.93)	
Ever tested for HIV (N=358)						
No (n=81)	4 (4.9)	77 (95.1)	Reference	.002	Reference	.001
Yes (n=277)	65 (23.5)	212 (76.5)	4.75 (1.79-12.65)		5.70 (2.12-15.28)	

[a] Adjusted by sex and age.

[b] Defined as engaging in at least one of the following: (1) any exchange of sex for drugs or money; (2) having sex with more than one sexual partner; (3) having sex with a partner who "probably" or "definitely" had other sex partners, concurrently; (4) having sex with a partner who had "probably" or "definitely" injected drugs; (5) having sex with a partner who "probably" or "definitely" had had male-to-male sexual contact (only female respondents); and (6) having sex with a partner whose HIV status was positive or indeterminate.

[c] Denominators vary because of nonresponse in the form of missing values.

Discussion

Principal Findings

This study aimed to examine the characteristics and behaviors of PIHT referrals among heterosexual individuals at increased risk using data from PR-NHBS-HET4. Findings show that most study participants had medical insurance coverage and had visited a health care provider in the past year. Despite their documented access to health services, among those who visited a health care provider within the past 12 months, 80.7% reported they did not receive an HIV test referral from their provider.

Comparison With Prior Work

The estimated number of participants who reported not receiving an HIV test referral from a health provider in this study is higher than those reported using Virginia's NHBS data (58%) [8]. This result shows a gap in implementing HIV testing guidelines in health care settings and the need to promote provider HIV screening among heterosexual adults at increased risk of HIV infection [4]. Our study showed that participants who engaged in high-risk sexual behavior were less likely to receive an HIV screening referral. Main barriers including insufficient time, burdensome consent process, lack of knowledge or training, lack of patient acceptance, pretest counseling requirements, competing priorities, and inadequate reimbursement have been identified in a comprehensive literature review [19]. Moreover, similar to other studies, our results showed that many participants perceived themselves to be at low risk of getting infected with HIV [20,21]. This low–risk perception may offer insight into the discrepancy between the number of individuals who seek health services and those who receive an HIV test referral, as having a low perception of risk has been previously linked to a decreased uptake of HIV testing [22,23]. Despite this gap, findings also revealed that women received significantly more HIV test referrals than men, despite no significant differences between the 2 groups in reported high-risk sexual behaviors, which is an observation consistent with the literature [24,25]. This difference between men and women could be partially explained by prenatal care since routine HIV testing during pregnancy has been a long-standing recommendation in the United States [26].

In 2007, the Joint United Nations Program of HIV/AIDS and the World Health Organization issued new guidelines on HIV testing. Even with the rules laid out by international organizations, there have been challenges in the implementation, considering that policies regarding HIV testing are decided by each nation or state individually [27]. Therefore, studies show the variation in HIV test referrals across states and the discrepancy between global expectations and local realities [28,29]. Particularly in Puerto Rico (where either governmental or private insurance covers most of the population) [30], efforts to increase HIV test referrals have recently been supported by public policy. Law Number 45 of May 2016 mandates that HIV testing be referred to patients as part of their routine care. Specifically, individuals aged 13-64 years who are at low risk of infection are to be referred for an HIV test as part of their routine medical testing at least once every 5 years. Individuals at high risk of infection must be referred for an HIV test annually. Additionally, Article 3 of this legislation explicitly states that medical insurance policies, whether private or government-issued, must include an annual HIV test in their primary health insurance coverage [31].

Considering the Puerto Rican public policy regarding HIV test referrals and our findings, we observe a gap that echoes the difficulty in implementing HIV prevention efforts. To bridge this gap, efforts related to HIV stigma education in health care settings [32] and CDC-funded HIV testing events are examples of effective strategies to increase HIV testing uptake. In addition, further identification of predictors of refusal to participate in PIHT can provide more insight into the barriers that limit the scope and referrals of HIV testing in health care settings in Puerto Rico [33].

Limitations

Among the limitations of this study, we consider the study's design as one of them. As a cross-sectional study, the impact of the evaluated variables on PIHT over time cannot be assessed. Other limitations include using self-reported information gathered during face-to-face interviews that could have introduced a social desirability bias. The studied population limits the generalizability of the result to other populations with different sociodemographic profiles. Contrarily, however, an advantage of the study is the use of RDS, which has been proven to be a reliable methodology for reaching and recruiting minority populations [34,35]. Recent data for NHBS-HET is available; unfortunately, the variables of interest (eg, HIV risk perception and the high-risk sexual behavior of men and women having unprotected sex with an HIV-positive partner) are not similar in their construction, which limits the opportunity to conduct a merged analysis of different periods. Despite the limitations, this behavioral surveillance system has successfully provided the necessary information for monitoring the implementation of the CDC's HIV testing guidelines. It has made it possible to better understand the patient-driven HIV testing habits, patient health care access, and risk behaviors of the members of this population, with a particular focus on the Puerto Rican heterosexual individuals at increased risk of HIV infection population. Lastly, compared to other studies, our results are limited due to the scope of PIHT in the literature. Most recent studies evaluated PIHT jointly with referral and counseling, indicating that patients are receptive to this joint approach. These studies had documented the overall high levels of acceptability of PIHT when offered in addition to referrals and counseling [6,7]. As this study was based on PR-NHBS data collection procedures, counseling—which has been included in other studies—was not offered to the extent of providing continual care for the patient.

Conclusions

In summary, findings from this study show low adherence practices for HIV test referrals in health care settings in Puerto Rico. Increasing adherence to such guidelines among heterosexual individuals at increased risk of HIV infection is critical to ensuring the early diagnosis of unidentified HIV cases, which would lead to better patient care and outcomes that will support the development of more effective awareness and prevention measures [7,36]. Future studies should explore the communication dynamics between the patient and provider in discussing preventative screening. Specifically, a qualitative component should be added to evaluate reasons for opting out of HIV tests, identify barriers to PIHT, and collect information relevant to social factors that affect PIHT (eg, stigma, HIV awareness, the doctor-patient relationship, etc). As policies are enacted to support the implementation of HIV testing referred to patients as part of their routine care, implementation studies should explore the effectiveness of PIHT communication and strategies for increasing adherence to HIV test referral guidelines in different health care settings in Puerto Rico.

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Authors' Contributions

VC-L, YR, and JR-L contributed to the manuscript’s conceptualization, analysis interpretation, and manuscript writing. MMCDLT, NC-A, and IYA-S contributed to the manuscript’s conceptualization, analysis execution, and manuscript writing. YR, SM, MP, and GGL contributed to the manuscript’s conceptualization and analysis interpretation. DP-G contributed to the analysis re-evaluation, analysis interpretation, data results, and discussion evaluation.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
NHBS: National HIV Behavioral Surveillance
PIHT: provider-initiated HIV testing
PR-NHBS-HET4: Puerto Rico National HIV Behavioral Surveillance–Heterosexual Cycle 4th round
PR_a: adjusted prevalence ratio
RDS: respondent-driven sampling

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Original Paper

Prediction of COVID-19 Infections for Municipalities in the Netherlands: Algorithm Development and Interpretation

Tjeerd van der Ploeg[1], PhD; Robbert J J Gobbens[1,2,3,4], RN, MScN, PhD

[1]Faculty of Health, Sports and Social Work, Inholland University of Applied Sciences, Amsterdam, Netherlands
[2]Zonnehuisgroep Amstelland, Amstelveen, Netherlands
[3]Department Family Medicine and Population Health, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[4]Tranzo, Tilburg School of Social and Behavioral Sciences, Tilburg University, Tilburg, Netherlands

Corresponding Author:
Tjeerd van der Ploeg, PhD
Faculty of Health, Sports and Social Work
Inholland University of Applied Sciences
De Boelelaan 1109
Amsterdam, 1081 HV
Netherlands
Phone: 31 653519264
Email: tvdploeg@quicknet.nl

Abstract

Background: COVID-19 was first identified in December 2019 in the city of Wuhan, China. The virus quickly spread and was declared a pandemic on March 11, 2020. After infection, symptoms such as fever, a (dry) cough, nasal congestion, and fatigue can develop. In some cases, the virus causes severe complications such as pneumonia and dyspnea and could result in death. The virus also spread rapidly in the Netherlands, a small and densely populated country with an aging population. Health care in the Netherlands is of a high standard, but there were nevertheless problems with hospital capacity, such as the number of available beds and staff. There were also regions and municipalities that were hit harder than others. In the Netherlands, there are important data sources available for daily COVID-19 numbers and information about municipalities.

Objective: We aimed to predict the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants per municipality in the Netherlands, using a data set with the properties of 355 municipalities in the Netherlands and advanced modeling techniques.

Methods: We collected relevant static data per municipality from data sources that were available in the Dutch public domain and merged these data with the dynamic daily number of infections from January 1, 2020, to May 9, 2021, resulting in a data set with 355 municipalities in the Netherlands and variables grouped into 20 topics. The modeling techniques random forest and multiple fractional polynomials were used to construct a prediction model for predicting the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants per municipality in the Netherlands.

Results: The final prediction model had an R^2 of 0.63. Important properties for predicting the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants in a municipality in the Netherlands were exposure to particulate matter with diameters <10 μm (PM10) in the air, the percentage of Labour party voters, and the number of children in a household.

Conclusions: Data about municipality properties in relation to the cumulative number of confirmed infections in a municipality in the Netherlands can give insight into the most important properties of a municipality for predicting the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants in a municipality. This insight can provide policy makers with tools to cope with COVID-19 and may also be of value in the event of a future pandemic, so that municipalities are better prepared.

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KEYWORDS

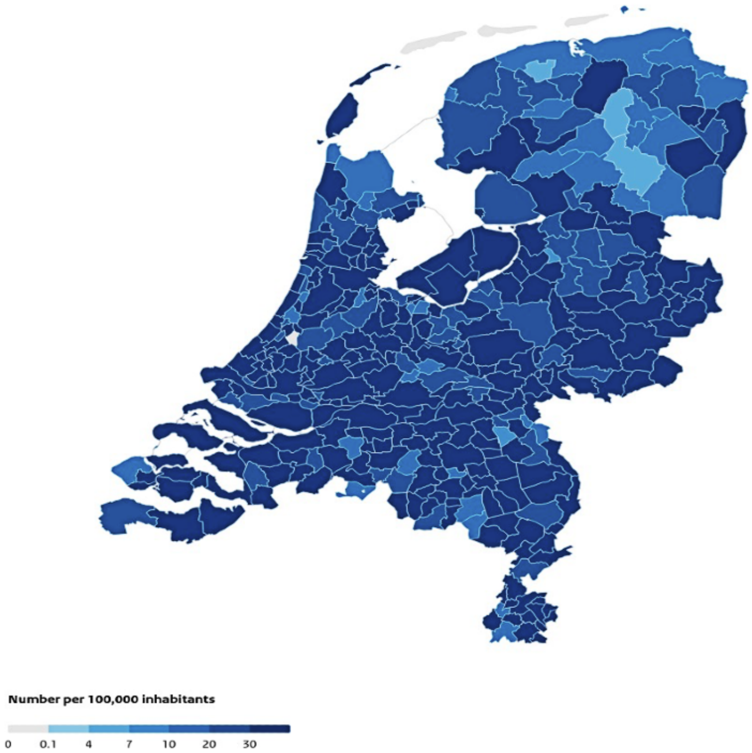
municipality properties; data merging; modeling technique; variable selection; prediction model; public health; COVID-19; surveillance; static data; Dutch public domain; pandemic; Wuhan; virus; public; infections; fever; cough; congestion; fatigue; symptoms; pneumonia; dyspnea; death

Introduction

COVID-19 was first identified in December 2019 in the city of Wuhan, China. The World Health Organization [1] declared the outbreak a public health emergency of international concern on January 30, 2020, and a pandemic on March 11, 2020. The virus quickly spread and is still among us. After infection, symptoms such as fever, a (dry) cough, nasal congestion, and fatigue can develop. COVID-19 can have many adverse outcomes such as a reduction in the quality of life of children, adolescents [2], and older adults, especially when they have to live in a lockdown [3]. In some cases, the virus causes severe complications such as pneumonia and dyspnea and can result in death. In a retrospective study among critically ill patients with COVID-19 admitted to intensive care units in Italy, both the mortality rate and absolute mortality were high [4].

At the end of February 2020, the first COVID-19 case in the Netherlands was confirmed. In June 2020, 46,000 cases had been identified. On May 9, 2021, 1,406,517 infections were confirmed [5]. However, the distribution of the confirmed infections over the Dutch municipalities was not uniform. There were differences between the municipalities with respect to the number of confirmed infections (see Figure 1). This finding raised the question of why some municipalities were hit so hard by COVID-19. A cross-sectional study conducted in the United States showed that states that have denser populations, lower socioeconomic status, and lower mean age are associated with higher incidence rates of COVID-19 [6].

Figure 1. Cumulative confirmed infections per municipality (reproduced with permission from the National Institute for Public Health and the Environment [5]) .



Some studies identified the degree of air pollution, especially the presence of particulate matter with diameters <10 µm (PM10) and nitrogen dioxide (NO_2), as an important factor for the high number of confirmed infections [7]. Currently, older adults face the most threats and challenges, not only in the Netherlands but also in many countries. Although all age groups are at risk of contracting COVID-19, older adults are more vulnerable to developing severe illness due to physiological changes that come with aging and potential underlying health conditions [1].

A Dutch study hypothesized that religious gatherings and the number of confirmed infections were associated [8]. This study showed that in the Dutch bible belt, church attendance was strongly related to the number of confirmed infections. However, in Southern Netherlands, a traditionally Catholic part of the Netherlands, nominal church membership mattered more than church attendance. Based on these findings, the study concluded that religious gatherings probably facilitated the spread of the virus in both a direct and indirect way.

Differences between urban and rural areas were found in a Brazilian study, demonstrating that in urban areas, more people were infected with COVID-19 [9]. However, in a sample of 5009 American adults, it was shown that rural residents were less likely to participate in COVID-19–related preventive behaviors, including working from home and wearing a face mask in public [10]. Thus, more infections in rural areas would be expected.

An American study identified political party affiliation as a factor associated with the spread of COVID-19 [11]. In this study of young adults, who lived predominantly in Los Angeles County or elsewhere in California, self-reported Republican political party affiliation was associated with less frequent physical distancing and participating in social recreational activities that may perpetuate the COVID-19 pandemic.

We aimed to predict the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants in a municipality using the properties of 355 municipalities in the Netherlands. In the Netherlands, the National Institute for Public Health and the Environment [5] and the Central Agency for Statistics [12] are important data sources for daily COVID-19 numbers and information about municipalities, respectively. With these data, we can gain insight into the relationship between municipality properties and the cumulative number of confirmed infections per 10,000 inhabitants in a municipality. This insight can provide policy makers with tools to cope with COVID-19 and may also be of value in the event of a future pandemic, so that municipalities are better prepared. It is even conceivable that different protective measures may need to be taken in municipalities or regions.

Methods

Data Collection

Our aim was to predict the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants in a municipality using the properties of 355 municipalities in the Netherlands. Therefore, we retrieved data from the National Institute for Public Health and the Environment and the Central Agency for Statistics and merged these data into a database consisting of 335 municipalities and variables with respect to the municipality topics as listed in Textbox 1, supplemented with the cumulative number of confirmed infections per 10,000 inhabitants in a municipality. All variables within the topics were expressed as numbers or fractions.

Textbox 1. Municipality topics.

Topics

- Age distribution
- Dependency ratio
- Ethnicity
- Degree of urbanization
- Cause of death
- Household type
- Education level
- Social benefit
- Number of cars or motor bikes
- Number of facilities
- Health
- Number of caregivers
- Mean distances to facilities
- Political party preference
- Labor force participation
- Number affiliated to sports club
- Exposure to air pollution
- Illiteracy
- Benchmark scores for the municipalities
- Religion

Outcome Variable and Modeling

The outcome variable in this study was the cumulative number of confirmed infections per 10,000 inhabitants in a municipality in the period from January 1, 2020, to May 9, 2021. We used a technique based on random forest (RF) for backward variable selection (VARSELRF) [13] to select important variables for the prediction of the outcome. Next, we used RF for the calculation of the importance of the selected variables [14]. The selected variables were then used for the construction of a multiple fractional polynomials (MFP) model for predicting the outcome. The MFP modeling technique offers the opportunity for building models with functions of the relevant explanatory variables and is more flexible than linear regression [15].

Description of the Modeling Techniques

RF Modeling Technique

RF is an ensemble classifier that consists of many decision trees. In the case of classification, RF outputs the class that is the mode among the classes from individual trees. In the case of regression, RF outputs the value that is the mean of the values outputted from individual trees. Each tree is constructed using a bootstrap sample from the original data. A tree is grown by recursively partitioning the bootstrap sample based on the optimization of a split rule. In regression problems, the split rule is based on minimizing the mean squared error, whereas in classification problems, the Gini index is commonly used. At each split, a subset of candidate variables is tested for the split rule optimization, similar to recursive partition modeling [16]. For prediction, a new sample is pushed down the tree. This procedure is iterated over all trees in the ensemble. Key parameters are the number of trees and the number of candidate variables [14].

VARSELRF Modeling Technique

VARSELRF is a variable selection technique based on RF with backward stepwise elimination of variables that are not important [13,17]. This variable selection technique returns very small sets of predictor variables and will not return sets of variables that are highly correlated, because they are redundant.

MFP Modeling Technique

The MFP modeling technique is a collection of functions targeted at the use of fractional polynomials for modeling the influence of continuous predictor variables on the outcome in regression models, as introduced by Royston and Altman [18] and modified by Sauerbrei et al [15,19]. It combines backward elimination with a systematic search for a transformation to represent the influence of each continuous predictor variable on the outcome.

Performance Measures

We used the R^2 statistic, the root of the mean squared error (RMSE), and the normalized RMSE (NRMSE) as measures for the performance of the prediction model. The R^2 measures how well the predictor variables can explain the variation in the outcome variable. The RMSE measures the typical distance between the predicted value from the prediction model and the value of the outcome variable. The NRMSE is the ratio of the RMSE of the prediction model and the RMSE of the model with no predictor variables ($RMSE_0$).

In the formulas, y represents the actual values, $\hat{y}$ represents the prediction for the actual values from the prediction model, $\bar{y}$ represents the mean value of the actual values, and n represents the number of cases. An R^2 value toward 1 indicates good performance, whereas an R^2 value toward 0 indicates bad performance. An NRMSE value toward 0 indicates good performance [20].

Data Analysis

For all analyses, we used R statistical software (version 3.4.4; R Foundation for Statistical Computing) [21].

Ethical Consideration

For this study, no ethical approval was required because the granularity of the data was at the municipality level.

Results

Table 1 shows percentiles with respect to the cumulative number of confirmed infections, hospital admissions, and deaths per 10,000 inhabitants. The median (50% percentile) of the cumulative number of confirmed infections per 10,000 inhabitants—our outcome variable—was 884. Of the 335 municipalities, 25% (n=84) had 1022 cumulative confirmed infections per 10,000 inhabitants or more.

Table 1. Cumulative numbers per 10,000 inhabitants (May 9, 2021).

Percentile	Confirmed infections, n	Hospital admissions, n	Deaths, n
2.5%	511	6	3
25%	757	11	7
50%	884	15	9
75%	1022	20	13
97.5%	1278	32	21

Table 2 shows the top 10 municipalities with respect to the cumulative number of confirmed infections, hospital admissions, and deaths per 10,000 inhabitants. It is noteworthy that the top 10 municipalities for confirmed infections did not overlap with the top 10 municipalities for hospital admissions and deaths. It is also noteworthy that the first 3 municipalities for confirmed infections are known as Christian municipalities and that the first 3 municipalities for hospital admissions are located in the southern part of the Netherlands.

Table 3 shows the selected variables of the VARSELRF modeling technique and the ranking by importance score with the RF modeling technique. The importance scores were calculated by the RF modeling technique; a higher score means that the variable is more important. The variables “Exposure to PM10” and “Labour party PvdA” had the highest importance scores compared to the other variables in Table 3.

Table 4 shows the coefficients of an MFP model with the selected variables. The R^2 of the model was 0.63 as calculated by (1), and the NRMSE of the model was 0.61 as calculated by (4).

For example, suppose that 20% of people in a municipality voted for the Liberal party Democraten 66. Using the transformation of this predictor variable and the coefficients in Table 4, the contribution of this predictor variable to the prediction of the cumulative number of confirmed infections per 10,000 inhabitants is then calculated as:

Similarly, the contributions of the other predictor variables can be calculated with the transformations of the predictor variables and their coefficients in Table 4. Table 5 shows the characteristics, example values, and the contributions of the predictor variables. By summing the contributions in Table 5 and the intercept in Table 4, the prediction of 837 cumulative confirmed infections per 10,000 inhabitants is obtained using the example values.

Table 2. Top 10 municipalities with cumulative numbers per 10,000 inhabitants (May 9, 2021).

Municipality	Cumulative number per 10,000 inhabitants, n
Confirmed infections	
Bunschoten	1873
Hardinxveld-Giessendam	1428
Maasdriel	1348
Edam-Volendam	1336
Tubbergen	1310
Bladel	1309
Zaltbommel	1291
Horst aan de Maas	1285
Katwijk	1279
Nederweert	1278
Hospital admissions	
Boekel	38
Peel en Maas	38
Cranendonck	37
Oudewater	37
Bernheze	35
Gouda	35
Uden	33
Gemert-Bakel	32
Landerd	32
Eijsden-Margraten	30
Deaths	
Bernheze	25
Zandvoort	25
Cranendonck	24
Krimpen aan den IJssel	23
Laren	23
Boxtel	22
Gouda	22
Heemstede	22
Boekel	21
Capelle aan den IJssel	21

Table 3. Selected variables (May 9, 2021).

Variables	Variable importance score
Exposure to PM10[a]	13,083
Labour party PvdA[b]	8544
Animal welfare party PvdD[c]	4164
Denomination or philosophical grouping	3578
Age-class 20-25 (years)	3445
Households with children	3361
Liberal party D66[d]	3166
Catholic	3034
Green party GroenLinks	3023

[a] PM10: particulate matter with diameters <10 µm.

[b] PvdA: Partij van de Arbeid.

[c] PvdD: Partij voor de Dieren.

[d] D66: Democraten 66.

Table 4. Coefficients of the multiple fractional polynomials model (May 9, 2021).

Variables with transformations	Coefficient
Intercept	−355.78
$(\text{Exposure to PM10}^{a}/10)^{1}$	669.95
$(\text{Households with children}/100)^{1}$	696.71
$(\text{Liberal party D66}^{b}/10)^{-2}$	64.89
$(\text{Liberal party D66}/10)^{-2} \times \log[(\text{Liberal party D66} / 10)]$	25.51
$(\text{Age-class 20-25}/10)^{-2}$	−34.98
$(\text{Catholic}/100)^{1}$	282.44
$(\text{Denomination or philosophical grouping}/100)^{1}$	−344.94
$(\text{Animal welfare party PvdD}^{c})^{-2}$	195.17
$(\text{Labour party PvdA}^{d}/10)^{1}$	−74.90
$(\text{Green party GroenLinks}/10)^{1}$	−109.32

[a] PM10: particulate matter with diameters <10 µm.

[b] D66: Democraten 66.

[c] PvdD: Partij voor de Dieren.

[d] PvdA: Partij van de Arbeid.

Table 5. Characteristics predictor variables and example values.

Variables	Minimum	Mean	Maximum	Example values	Contribution
Exposure to PM10[a]	15.1	18.6	21.4	19.0	1272.9
Households with children	19.0	35.4	57.6	37.1	258.5
Liberal party D66[b]	0.5	10.8	23.2	20.0	20.6
Age-class 20-25 (years)	3.2	5.5	16.2	4.1	−208.1
Catholic	0.4	32.2	88.3	63.0	177.9
Denomination or philosophical grouping	19.9	57.5	98.1	68.6	−236.6
Animal welfare party PvdD[c]	0.2	2.7	6.0	2.4	35.0
Labour party PvdA[d]	0.2	5.2	10.6	4.8	−36.1
Green party GroenLinks	0.2	7.1	20.3	8.4	−91.6

[a] PM10: particulate matter with diameters <10 µm.

[b] D66: Democraten 66.

[c] PvdD: Partij voor de Dieren.

[d] PvdA: Partij van de Arbeid.

Discussion

Overview

The COVID-19 pandemic has endangered human lives all over the world. It has led to health care problems (physical, psychological, and social). The World Health Organization points out that measures such as self-isolation and quarantine may lead to an increase in loneliness, depression, anxiety, and self-harm or suicidal behavior [22]. In addition, COVID-19 puts a lot of pressure on the health care system and ensures an economic slowdown in all countries involved [23]. In this study, we aimed to study the properties of 355 municipalities in the Netherlands for predicting the cumulative number of confirmed COVID-19 infections per 10,000 inhabitants in a municipality.

Relevant static data per municipality were collected from data sources that were available in the Dutch public domain, and these data were merged with the dynamic daily number of infections in the period from January 1, 2020, to May 9, 2021 [5,12]. We used the VARSELRF [13] technique (based on RF) to select important variables, followed by MFP modeling to develop a prediction model for the cumulative number of confirmed infections per 10,000 inhabitants in a municipality.

Principal Findings

Our prediction model explained 63% of the variance of the dependent variable (cumulative number of confirmed COVID-19 infections per 10,000 inhabitants). This finding means that our prediction model is useful for predicting the cumulative number of confirmed infections per 10,000 inhabitants in a municipality in the Netherlands. In our study, we used 20 municipality topics for developing a prediction model. The most important predictors were exposure to PM10, being a Labour party voter, and the number of children in households.

Comparison With Prior Work

A systematic review identified 7 models for the identification of people at risk for COVID-19 in the general population. In these models, the most frequently included predictors were age, comorbidities, vital signs, and image features [24].

In our study, exposure to PM10 had the highest importance score out of all predictors. Other studies also observed significant associations of PM10 with COVID-19 infections [25,26]. Social distancing led to a 35.56% and 20.41% decrease, relative to the previous year, in the mean of PM10 and NO_2, respectively [27]. However, a systematic review showed that exposure to particulate matter with diameters <2.5 µm and NO_2 provided a more important contribution to triggering COVID-19 spread and lethality than PM10 [28]. All findings indicate reducing air pollution as a current public health problem, as well as in a more sustainable post–COVID-19 world [27].

Our study showed that being a Labour party (Partij van de Arbeid) voter can be considered an important predictor of the cumulative number of COVID-19 infections per 10,000 inhabitants. One explanation could be that voters for left-wing parties conformed more to government rules (eg, social distancing) than voters for right-wing parties (who have more distrust about government actions) [29]. Labour party voters are also generally older [30]. Support for the Labour party is stronger in the northern areas of the Netherlands. We recommend further studies focusing on the characteristics of these party voters, including lifestyle characteristics, to better understand the association with the cumulative number of COVID-19 infections per 10,000 inhabitants.

In this study, the number of children in households was an important predictor of the cumulative number of COVID-19 infections per 10,000 inhabitants. This finding may be due to school attendance [31]. However, a study among 300,000 adults showed that the risk of COVID-19 requiring hospital admission was reduced as the number of children in households increased [32]. Moreover, no association was found between exposure to children and COVID-19 [32]. This finding is confirmed by a systematic review, which concluded that it is unlikely that children are the main drivers of this pandemic [33]. Additionally, in this study, the top 10 municipalities for confirmed infections did not overlap with the top 10 municipalities for hospital admissions and deaths as we had expected. This finding indicates that there is no association between the cumulative number of COVID-19 infections per 10,000 inhabitants and both adverse outcomes, which stands in contrast to other studies [4,34,35]. From the top 10 municipalities for hospitalizations and deaths, 3 municipalities appeared on both lists. This result was expected, as only people with severe COVID-19 complaints are admitted to hospital, and these people will have an increased risk of death [36]. COVID-19 vaccines can be considered the most promising means of reducing the spread of this virus. Thus, it is crucial that many people get vaccinated. A scoping review including 22 studies showed that gender, age, education, and occupation were associated with vaccine acceptance [37]. In addition, trust in authorities, vaccine efficacy, vaccine safety, having a current or previous influenza vaccination, and perceived risk of a COVID-19 infection were also associated with COVID-19 acceptance [37]. It is important for all countries to address the barriers to vaccine acceptance, so that maximum vaccine coverage can be achieved. This step requires the commitment of all stakeholders, from policy makers to health care professionals and scientists.

Limitations

Some limitations of our study should be mentioned. Our prediction model was only based on data of municipalities in the Netherlands, so the external validity of the model is limited. The model may not be usable elsewhere in the world. This limitation will certainly apply to countries outside of Europe that have a different culture, health care, and political systems and inhabitants with different sociodemographic and health characteristics. Unfortunately, other prediction models of COVID-19 have a similar problem [24,38]. For preventing and combatting COVID-19, it is vital to apply these prediction models on different data sets and check changes in the behavior of the models from one country to another. A second limitation refers to the presence of several COVID-19 variants [39]. The Omicron variant emerged in 2021, and the developed prediction model may not be applicable to this variant. A third limitation is that variables such as the presence of childcare for families impacted by COVID-19 or other public health factors were not available in our data set. This limitation will be taken into account for follow-up research.

Conclusions

In conclusion, collecting data about municipality topics in relation to the cumulative number of confirmed infections in a municipality can give insight into the most important topics for predicting the number of cumulative confirmed infections per 10,000 inhabitants for a municipality in the Netherlands. In the prediction model, the most important topics were exposure to PM10, being a Labour party voter, and the number of children in households. The findings contribute to increasing our knowledge on COVID-19 and can provide policy makers with tools to cope with COVID-19. This study may also be of substantive value in the event of a future pandemic, so that municipalities are better prepared. It is even conceivable that different protective measures may need to be taken in municipalities or regions.

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Data Availability

The data set used and analyzed during the current study is available from the corresponding author on reasonable request.

Authors' Contributions

TvdP and RJJG wrote the main manuscript, and TvdP prepared all figures and tables and performed all analyses. TvdP and RJJG reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

MFP: multiple fractional polynomials
NO_2: nitrogen dioxide
NRMSE: normalized root of the mean squared error
PM10: particulate matter with diameters <10 µm
RF: random forest
RMSE: root of the mean squared error
VARSELRF: variable selection based on random forest

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Original Paper

Global Variations in Event-Based Surveillance for Disease Outbreak Detection: Time Series Analysis

Iris Ganser[1,2], MSc; Rodolphe Thiébaut[2,3], MD, PhD; David L Buckeridge[1], MD, PhD

[1]McGill Clinical and Health Informatics, School of Population and Global Health, McGill University, Montreal, QC, Canada

[2]INSERM U1219 Bordeaux Population Health Research Center, INRIA, 2 Université de Bordeaux, Bordeaux, France

[3]Service d'Information Médicale, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France

Corresponding Author:
David L Buckeridge, MD, PhD
McGill Clinical and Health Informatics
School of Population and Global Health
McGill University
2001 McGill College Avenue, Suite 1200
Montreal, QC, H3A 1G1
Canada
Phone: 1 514 934 1934 ext 32991
Email: david.buckeridge@mcgill.ca

Abstract

Background: Robust and flexible infectious disease surveillance is crucial for public health. Event-based surveillance (EBS) was developed to allow timely detection of infectious disease outbreaks by using mostly web-based data. Despite its widespread use, EBS has not been evaluated systematically on a global scale in terms of outbreak detection performance.

Objective: The aim of this study was to assess the variation in the timing and frequency of EBS reports compared to true outbreaks and to identify the determinants of variability by using the example of seasonal influenza epidemic in 24 countries.

Methods: We obtained influenza-related reports between January 2013 and December 2019 from 2 EBS systems, that is, HealthMap and the World Health Organization Epidemic Intelligence from Open Sources (EIOS), and weekly virological influenza counts for the same period from FluNet as the gold standard. Influenza epidemic periods were detected based on report frequency by using Bayesian change point analysis. Timely sensitivity, that is, outbreak detection within the first 2 weeks before or after an outbreak onset was calculated along with sensitivity, specificity, positive predictive value, and timeliness of detection. Linear regressions were performed to assess the influence of country-specific factors on EBS performance.

Results: Overall, while monitoring the frequency of EBS reports over 7 years in 24 countries, we detected 175 out of 238 outbreaks (73.5%) but only 22 out of 238 (9.2%) within 2 weeks before or after an outbreak onset; in the best case, while monitoring the frequency of health-related reports, we identified 2 out of 6 outbreaks (33%) within 2 weeks of onset. The positive predictive value varied between 9% and 100% for HealthMap and from 0 to 100% for EIOS, and timeliness of detection ranged from 13% to 94% for HealthMap and from 0% to 92% for EIOS, whereas system specificity was generally high (59%-100%). The number of EBS reports available within a country, the human development index, and the country's geographical location partially explained the high variability in system performance across countries.

Conclusions: We documented the global variation of EBS performance and demonstrated that monitoring the report frequency alone in EBS may be insufficient for the timely detection of outbreaks. In particular, in low- and middle-income countries, low data quality and report frequency impair the sensitivity and timeliness of disease surveillance through EBS. Therefore, advances in the development and evaluation and EBS are needed, particularly in low-resource settings.

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KEYWORDS

event-based surveillance; digital disease detection; public health surveillance; influenza; infectious disease outbreak; surveillance; disease; outbreak; analysis; public health; data; detection; detect; epidemic

Introduction

Infectious diseases continue to threaten populations worldwide, as demonstrated clearly during the novel coronavirus (SARS-CoV-2) pandemic. Infectious disease surveillance produces crucial information for public health professionals to make good emergency response decisions and implement effective countermeasures to contain outbreaks [1,2]. Traditional disease surveillance (or indicator-based surveillance [IBS]) relies on laboratory test results transmitted through public health networks [3,4], but these systems are focused on only a few diseases, can have a considerable reporting time lag, and lack sensitivity, especially for novel pathogens [5-7]. Event-based surveillance (EBS) was developed to complement IBS to enable near real-time detection of infectious disease outbreaks [3]. To identify possible outbreaks, EBS attempts to detect unusual patterns related to potential events, which precede the official confirmation of disease outbreaks [2,8]. For this purpose, EBS systems use unstructured and mainly internet-based data such as web-based news articles [9,10].

In addition to early disease activity detection, surveillance for events has the potential to augment the sensitivity of IBS in regions with few medical centers or lower health-seeking behaviors [11]. The usefulness of EBS in resource-limited settings has been demonstrated by its ability to detect dengue fever [12] and Ebola outbreaks [13,14] before detection by official bodies. Furthermore, resource-limited regions stand to benefit the most from EBS, as they are disproportionately affected by infectious diseases [15] and may have limited resources to implement IBS systems. However, due to the unstructured and unverified nature of the gathered data, EBS systems face considerable challenges, with the overarching problem being the accurate discrimination of true signals from an immense amount of noise [16,17]. EBS systems are also highly dependent on the internet coverage in the countries of operation and filtering of languages. This may lead to a considerable variation in EBS performance across geographical settings, which, together with the inherent uncertainty of the information gathered, suggests that EBS systems should be carefully evaluated in a representative set of countries. However, despite their widespread use, EBS systems tend to be used in an ad hoc and informal way. This type of use could explain why there is not much published evidence about the variation in EBS system performance across countries. Rather, most available literature focus on the adequate classification of health-related events from web-based sources or the implementation of innovative functionalities [18-20].

Therefore, as the first objective, we aimed to document the global variation in the sensitivity and timing of the information obtained through EBS for outbreak detection. We applied a systematic monitoring approach to data derived from 2 EBS systems in a representative set of countries and used seasonal influenza outbreaks as the test case. As our second objective, we identified factors driving the observed differences in detection across countries. The identification of factors that influence performance is important to identify ways to improve EBS, especially in resource-poor settings.

Methods

Data

For this study, 24 countries from 15 influenza transmission zones were chosen to evaluate EBS performance on a global scale: Argentina, Australia, Brazil, Bulgaria, China, Costa Rica, Ecuador, Egypt, France, Germany, Greece, India, Iran, Mexico, Nigeria, Russia, Saudi Arabia, South Africa, Sweden, Thailand, Uruguay, United Kingdom, United States, and Vietnam. These countries were selected to represent a broad spectrum of geographical locations, languages, and income brackets and were sampled randomly from all influenza transmission zones.

FluNet: The Reference

FluNet is a web-based tool created by the World Health Organization (WHO) for disseminating virologic influenza surveillance data and serves as the reference to evaluate EBS systems. FluNet provides publicly available counts of laboratory-confirmed influenza cases per country, aggregated per week, from all participating global influenza surveillance and response system (GISRS) countries, other national influenza reference laboratories, which are collaborating with GISRS, and from WHO regional databases [21]. FluNet data were collected from January 2013 to December 2019, except for Saudi Arabia, where FluNet data were only available as of January 2017. The beginning of the study period was chosen to be January 2013 so that the effects of the 2009 pandemic would not influence the analysis.

Ethical Considerations

As FluNet is an active international surveillance tool and its data are published in an aggregated manner in the open domain, the approval of a research ethics board was not required for this research.

HealthMap Data

HealthMap provides real-time surveillance of infectious diseases by collecting data from web-based news aggregators such as Google News, expert-moderated systems such as Program for Monitoring Emerging Diseases-Mail, and validated alerts from official sources [10,19]. Any news article that passed through HealthMap's filtering algorithm from January 2013 to July 2019 and related to "human influenza" was considered an influenza report. Duplicate reports were identified by a unique ID number assigned to each report and removed together with reports concerning countries' overseas territories (9012 and 62 out of 31,796 total events, respectively), resulting in a total of 22,722 unique reports. To match gold standard data, daily report counts from HealthMap were aggregated into a weekly format, resulting in a total of 341 weekly data points spanning 6.5 years.

Epidemic Intelligence From Open Sources Data

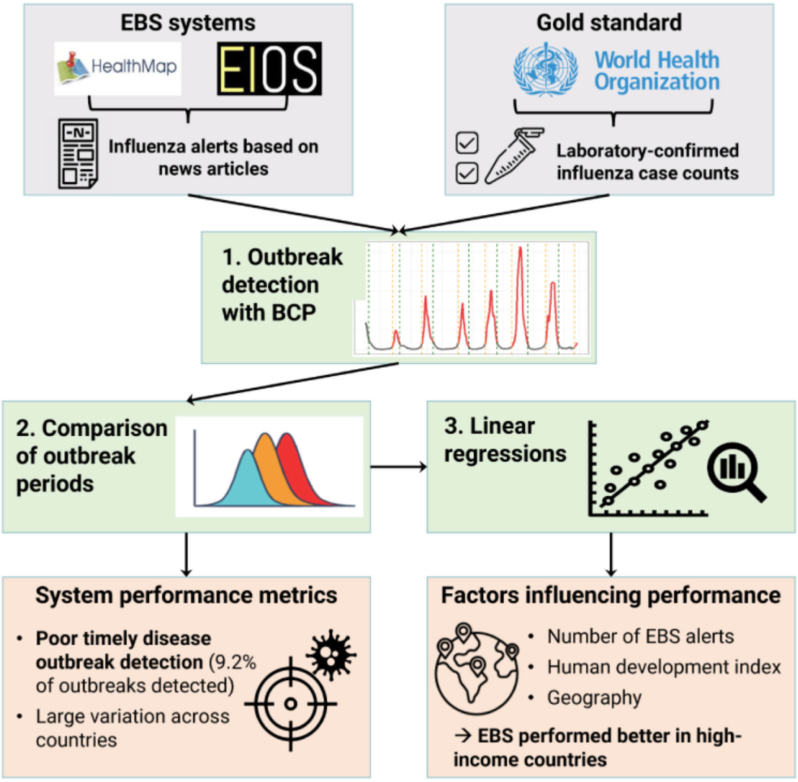
In 2017, the WHO implemented the Epidemic Intelligence from Open Sources (EIOS) system as a collaboration between multiple public health organizations, acting on a global scale to provide timely public health surveillance [22]. EIOS integrates data from multiple EBS systems, including HealthMap, and performs report deduplication before uploading to the platform. Daily event data were provided from November

11, 2017 (the day of EIOS implementation) through December 2019. All EIOS reports for the 24 countries of interest with the keywords “Influenza virus not identified,” “H1N1,” “H1N1v,” “H1N2,” “H1N2v,” “H2N1,” “H2N2,” “H3N2,” and “H3N2v” were retrieved and aggregated into weeks, totaling 109 weeks.

Outbreak Detection Methodology and Workflow

Our overall workflow is illustrated in Figure 1. Outbreaks were detected retrospectively in all 3 data sets based on media report frequency or confirmed influenza case counts by using Bayesian change point (BCP) analysis. The date of outbreak onset had to be detected in gold standard as well as in EBS data because FluNet did not provide a consistent epidemic indicator. Although not initially developed for infectious disease outbreaks [23,24], change point analysis has been used to determine the start points of influenza epidemics [25,26]. Essentially, change point methods identify points in time series before and after which distributional parameters differ significantly. To do this, the BCP algorithm breaks a time series into blocks, calculates the mean and variance of these blocks, and derives the probability of each break point being a change point. All BCP analyses were conducted using the R package bcp, version 4.0.3 [23,27], which is based on the method described by Barry and Hartigan [24]. The posterior mean and variance, and from this, the probability of each time point being a change point, were estimated with 600 Markov Chain Monte Carlo iterations, and the first 100 Markov Chain Monte Carlo iterations were discarded as burn-in. Only 600 iterations were used, as convergence was reached quickly after the first iterations. The priors p0 (change point probability) and w0 (signal-to-noise ratio) were kept at their default value of 0.2. As multiple change points were flagged by BCP analysis during outbreaks, we applied additional criteria to determine the start and end points of influenza outbreaks. In short, epidemic start and end points were the first and last change points in the rising and descending curves, respectively. See Multimedia Appendix 1 for a more detailed description of the BCP method and our outbreak detection algorithm.

Figure 1. Illustration of the workflow. BCP: Bayesian change point analysis; EBS: event-based surveillance.



Performance Evaluation Metrics

The epidemic intervals detected using HealthMap and EIOS reports were compared to the intervals detected using FluNet to calculate sensitivity (the proportion of all outbreaks in the gold standard data detected by the EBS systems), positive predictive value (PPV, the proportion of all outbreaks detected in the EBS data corresponding to an outbreak in the gold standard), specificity (the proportion of all weeks without an outbreak in the EBS data, during which no outbreak was detected in the gold standard data), timeliness, and timely sensitivity for each EBS system separately by country. The metric of timely sensitivity describes the ability of a system to detect an outbreak before or around the same time as traditional surveillance systems and is defined as outbreak detection by EBS within a window of 2 weeks before and after the start of an outbreak in the gold standard. Our rationale for choosing this time interval around the outbreak onset in the gold standard data is that the reporting lag of IBS data for influenza usually exceeds 2 weeks; so, this is the timeliness advantage possibly gained by EBS. Moreover, we hypothesized that a true outbreak could be detected 2 weeks before outbreak onset in the gold standard data, but not earlier than that, to avoid detection of false positives. Timeliness was defined as the proportion of outbreak duration remaining at detection to circumvent the problem of nondetected outbreaks [28].

In the equation above, alert refers to a detected outbreak in the EBS system data. n (weeks) is the total number of weeks in the study for the respective system (341 for HealthMap and 109 for EIOS). Accuracy was calculated as the sum of correctly classified weeks over the number of all weeks.

Regressions and Variable Selection Process

We conducted multivariable regressions to identify the independent effect of country-specific factors (independent variables) on the performance metrics (dependent variables), while controlling for all other factors included in the model. Highly correlated independent variables were removed from the models until the variance inflation factors were below the conservative threshold of 4 [29]. Influential variables were selected in a forward selection process based on the Akaike information criterion. By checking the residual plots of our final models, we confirmed that all model assumptions were met.

Country-specific variables examined as explanatory variables were the total number of media reports over the data collection period, the maximum counts of media reports per week, global region (temperate Northern hemisphere, temperate Southern hemisphere, or tropical), language (official language English yes/no), latitude, longitude, human development index (HDI), Press Freedom Index (PFI), the total number of internet users, and HealthMap filter language (yes/no). Latitude and longitude were assigned to the centroid of each country. Country languages could only be explored as a binary indicator of English as the official language or not because of sparse strata. Geography was explored as a categorical variable (temperate vs tropical) and as a continuous variable (latitude/longitude). HDI rankings from 2018 and the total number of internet users per country in 2017 were obtained from the United Nations Development Programme [30]. PFI values from 2018 were obtained from *Reporters without Borders* [31]. The PFI ranges from 1 to 100, with lower values indicating higher press freedom. All regression models were fit using the R software version 3.6.3 [32], including the packages MASS version 7.3-51.6 [33] and glmnet version 4.0 [34]. Effect estimates are reported as point estimates and 95% CIs, and *P* values are provided for orientation only. In 2 sensitivity analyses, we selected variables based on least absolute shrinkage and selection operator regressions and excluded the 3 countries with low FluNet data quality (Nigeria, Thailand, and Vietnam).

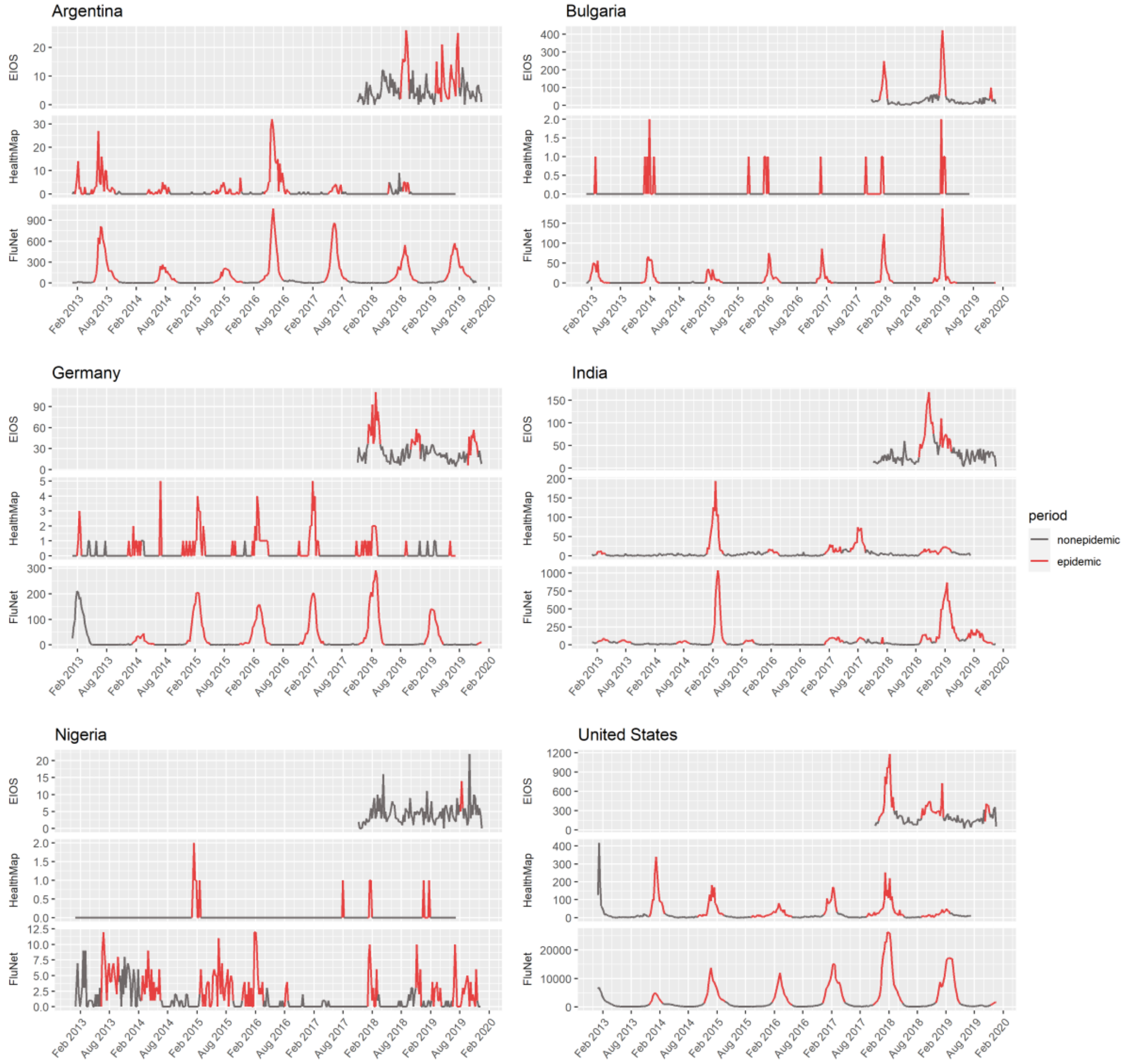
Results

Sample Characteristics

Laboratory-confirmed positive influenza counts over 7 years from FluNet were compared to HealthMap reports over 6.5 years and EIOS reports over 2 years. In most countries, the numbers of influenza-positive specimens provided by FluNet were high enough to allow a good distinction between epidemic and nonepidemic periods. In Nigeria, Thailand, and Vietnam, the signal-to-noise ratio was very high due to a low total number of tested individuals and positive results. The number of EBS signals varied by country, and EIOS collected more annual reports than HealthMap due to its aggregation of sources (Multimedia Appendix 2). Few HealthMap reports were collected in 12 countries (Bulgaria, Costa Rica, Ecuador, Germany, Greece, Iran, Nigeria, Saudi Arabia, South Africa, Sweden, Thailand, and Uruguay), in which HealthMap did not filter for news articles in the respective official languages.

Figure 2 illustrates the report frequency over time for FluNet, HealthMap, and EIOS for selected countries. HealthMap reports in countries with frequent reporting generally coincided with influenza epidemics in FluNet data (eg, Argentina, India, United States). In contrast, EIOS reports appeared to be less synchronized with FluNet counts and tended to have a lower signal-to-noise ratio. It is apparent from these plots that there are substantial differences in influenza activity and EBS signals across countries.

Figure 2. Time series of weekly reports relating to influenza from Epidemic Intelligence from Open Sources and HealthMap and weekly virological influenza counts from FluNet for selected countries from January 2013 to December 2019. Epidemic periods found with Bayesian change point analysis for each system are highlighted in red, and nonepidemic periods are shown in grey. EIOS: Epidemic Intelligence from Open Sources.



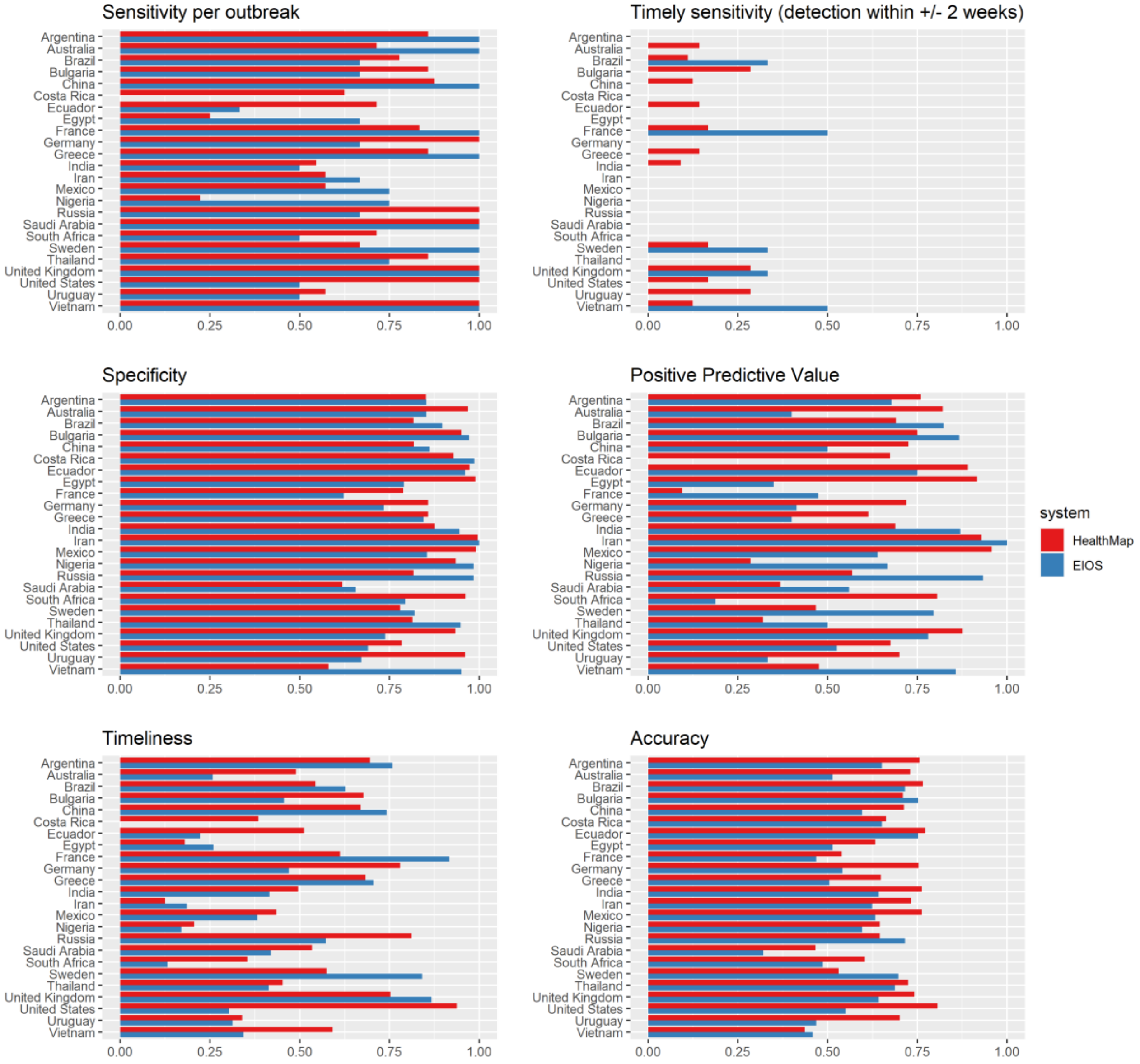
Evaluation of System Performance

Overall, 22 out of 238 (9.2%) outbreaks in the data sets were detected within a time interval of 2 weeks before or after outbreak onset in the gold standard data. HealthMap and EIOS did not detect any outbreaks in a timely manner in 12 (50%) and 19 (79%) out of 24 countries, respectively (Figure 3). HealthMap showed the best timely outbreak detection in Bulgaria, the United Kingdom, and the United States, with 2 out of 7 (29%) detected outbreaks each. EIOS showed a timely sensitivity of 50% in France and Vietnam, corresponding to 1 out of 2 outbreaks detected on time and 33% (1 out of 3 outbreaks detected on time) in Brazil, Sweden, and the United Kingdom. In contrast, the sensitivity of EBS systems was much higher than the timely sensitivity, with 100% of outbreaks detected at any time during the outbreak in 6 countries by HealthMap and 9 countries by EIOS. However, the between-country variation was large. Likewise, PPV and timeliness were very heterogeneous across countries: HealthMap had a PPV <50% in 4 countries and >75% in 9 countries, while EIOS's PPV ranged from 0% in Costa Rica to 100% in Iran, with 8 countries <50% and 8 countries >75%. Timeliness was especially poor in EIOS, where the proportion of outbreak duration remaining at detection was <50% in 15 countries. This means that most EBS alerts were raised more than halfway through the outbreak, by which point the outbreak would likely be detected through other means.

To gain a more comprehensive understanding of system performance, accuracy was calculated as a metric combining sensitivity and specificity (Figure 3). HealthMap's accuracy was the highest in the United States (81%), Ecuador, and Brazil (both 77%), and the lowest in Saudi Arabia (47%) and Vietnam (44%). EIOS showed the highest accuracy in Brazil and Russia (both 75%), Bulgaria, and Ecuador (both 72%), and the lowest accuracy in Saudi Arabia (46%) and Vietnam (32%) as well.

As an illustrative example, HealthMap showed consistently high evaluation metrics in the United States because HealthMap reports were well synchronized with seasonal influenza epidemics reflected in FluNet counts (Figure 2 and Multimedia Appendix 3). In a country with no clear influenza seasonality, such as India, HealthMap's timeliness and sensitivity were lower than that in the United States (timeliness: 50% vs 94%, sensitivity: 55% vs 100%, respectively), but overall accuracy was not markedly reduced (76% vs 81%, respectively) because of high specificity (88% vs 78%, respectively). In contrast, EIOS detected many epidemic signals in the United States in the nonepidemic season of 2018, which decreased its performance metrics relative to India, where EIOS had equal sensitivity (both 50%) but higher specificity (95% vs 69%, respectively). Clearly, a set of country-specific factors must lead to these differences in system performance between the United States and India.

Figure 3. HealthMap and Epidemic Intelligence from Open Sources performance metrics for the detection of influenza outbreaks from January 2013 to July 2019 (HealthMap) or from November 2017 to December 2019 (Epidemic Intelligence from Open Sources). All metrics were calculated with FluNet data as reference. EIOS: Epidemic Intelligence from Open Sources.


Sensitivity per outbreak

Timely sensitivity (detection within +/- 2 weeks)

Specificity

Positive Predictive Value

Timeliness

Accuracy

Identification of Factors Influencing the System Performance

Next, we identified factors associated with the variation of performance indicators across countries stratified by system. It was not possible to identify predictors of timely sensitivity for either system since assumptions of linear regressions were not met and logistic regressions were problematic, as some of the explanatory variables showed perfect separation. Only a moderate amount of the variation in the metrics was explained by the variables examined, as the R^2 values ranged between 0.144 and 0.587. In HealthMap (Table 1), higher sensitivity was associated with a higher total number of reports and higher HDI. Increasing press freedom (corresponding to a lower PFI) and English as the official language were associated with a lower sensitivity of HealthMap. Higher sensitivity of EIOS (Table 2) was independently associated with higher latitude and lower press freedom. In contrast, a higher HDI reduced HealthMap's specificity while increasing PFI decreased specificity. EIOS's specificity was markedly higher in tropical regions than in temperate regions. None of the examined variables was significantly associated with HealthMap's PPV, while a country's latitude and PFI influenced EIOS's PPV. Timeliness of outbreak detection was associated with a higher number of reports, higher HDI, and increasing latitude in HealthMap, and with higher number of reports, increasing latitude, and not having English as the official country language in EIOS. Both sensitivity analyses showed very similar results to those of the main analysis.

Table 1. Effect of country-specific covariates on HealthMap performance in detecting influenza outbreaks from January 2013 to July 2019.

Outcome, covariate	Category/increment	Coefficient (95% CI)	*P* value	Adjusted R^2
Sensitivity				0.456
Log (total reports)	1 log	0.039 (–0.012 to 0.091)	.13	
Human development index	1 score	0.017 (0.008 to 0.025)	<.001	
Press freedom index	1 score	0.003 (–0.001 to 0.008)	.10	
Official language (reference: not English)	English	–0.128 (–0.313 to 0.057)	.16	
Positive predictive value				
Specificity				0.144
Human development index	1 score	–0.004 (–0.009 to 0.001)	.11	
Press freedom index	1 score	–0.003 (–0.005 to –0.0003)	.03	
Timeliness				0.504
Log (total reports)	1 log	0.047 (0.013 to 0.082)	.009	
Human development index	1 score	0.007 (–0.001 to 0.015)	.08	
Latitude	1°	0.004 (–0.001 to 0.009)	.12	

Table 2. Effect of country-specific covariates on the performance of Epidemic Intelligence from Open Sources in detecting influenza outbreaks from November 2017 to December 2019.

Outcome, covariate	Category/increment	Coefficient (95% CI)	*P* value	Adjusted R^2
Sensitivity				0.229
Latitude	1°	0.008 (0.002 to 0.014)	.02	
Press freedom index	1 score	0.005 (–0.0003 to 0.010)	.06	
Positive predictive value				0.587
Global region (reference: Temperate Northern)	Temperate Southern	–0.008 (–0.219 to 0.203)	.94	
Global region (reference: Temperate Northern)	Tropical	0.481 (0.271 to 0.692)	<.001	
Latitude	1°	0.012 (0.006 to 0.018)	<.001	
Press freedom index	1 score	0.003 (–0.001 to 0.007)	.10	
Specificity				0.284
Global region (reference: Temperate Northern)	Temperate Southern	–0.019 (–0.137 to 0.099)	.74	
Global region (reference: Temperate Northern)	Tropical	0.143 (0.046 to 0.240)	.006	
Timeliness				0.430
Log (total reports)	1 log	0.074 (–0.015 to 0.164)	.09	
Official language (reference: not English)	English	–0.212 (–0.520 to 0.095)	.17	
Latitude	1°	0.008 (0.003 to 0.014)	.006	

Discussion

Main Findings

To our knowledge, this study is the first to rigorously evaluate 2 EBS systems, HealthMap and EIOS, against a gold standard on a global scale, permitting the quantification of global variation in EBS performance and identification of country-specific factors determining this variation. High generalizability was guaranteed because 24 countries from 15 influenza transmission zones worldwide were included with multiple outbreak patterns of seasonal influenza.

We introduced the metric of timely sensitivity to assess the ability of each system to detect infectious disease outbreaks before or around the same time as traditional surveillance systems. Contrasting sensitivity with timely sensitivity highlights the discrepancy between the proportion of outbreaks that the systems provide information on (175/238, 73.5%) and the proportion of outbreaks where EBS could have led to early detection (22/238, 9.2%). These results demonstrate that monitoring report frequency in EBS may be insufficient for outbreak detection, and they suggest the need to reconsider assumptions about how EBS systems should be used to achieve timely outbreak detection across countries.

As we documented a significant variability in sensitivity, PPV, and timeliness of outbreak detection across countries, we analyzed several covariates as the potential drivers of this variability. We found that the number of reports gathered explained the performance variability of both systems, while a higher HDI improved HealthMap's sensitivity and timeliness but decreased PPV. The most important predictor of EIOS performance was a country's geographic location, with higher sensitivity, timeliness, and PPV, but reduced specificity in countries further away from the equator, indicating that EIOS is better in detecting clearly seasonal epidemic patterns. Surprisingly, EBS filter language was not found to be a determinant of between-country variation. Overall, the results suggest that both EBS systems had the best performance in high-income countries, although the systems failed to detect a considerable number of outbreaks in a timely manner in these countries. These results do not necessarily conflict with the findings that EBS does confer a timeliness advantage over traditional surveillance systems in the detection of Ebola or dengue fever [12-14].

The important influence of the number of gathered reports on system performance is likely due to measured and unmeasured factors. Unexpectedly, in our data set, there were no significant correlations between the total number of reports and a country's HDI or PFI. Unmeasured factors that would explain this finding could be the country-specific news landscape, which news sources are included in news aggregators filtered by the EBS systems, and local internet availability and usage. With growing connectedness in low-income countries, the opportunity for the usage of social media arises. For example, during the Ebola epidemic in Western Africa in 2014/2015, monitoring of Twitter activity was retrospectively shown to produce earlier alerts than alerts by official bodies [14,35]. However, using social media as a data stream for disease surveillance raises additional challenges such as limited representativeness of the general public by social media users and a strong potential for misinformation [36,37].

Social media surveillance is an interesting way to complement current EBS [38,39], but from an evaluation perspective, it is imperative to first understand the performance of individual data streams before analyzing combined data sources. Since the number of gathered reports has an important influence on system performance, the usefulness of setting thresholds on report numbers for alerting EBS system users could be an interesting avenue to explore. For example, to contextualize information, alerts based on low reports numbers could be flagged and provided with a warning that EBS system information is likely unreliable because it is based on too little information.

Comparison With Prior Work

Although there are many approaches to digital disease surveillance in general and digital influenza surveillance [40,41], in particular, we focused our evaluation on the utility of 2 EBS systems, which are based on digital news media. We focused on these systems as they are used routinely in public health practice internationally and within many countries. Given their regular use, it is important to develop a sound evidence base to guide their effective implementation and operation. In addition to EBS, many other approaches to digital disease surveillance have been proposed, including surveillance of web-based search queries, social media, or participatory online systems specifically for influenza. Although some of these approaches have gained attention, they are not widely used in public health practice [42]. One example is Google Flu Trends, a system developed by Google researchers using web-based search queries to nowcast regional influenza activity, which was found to correlate well with IBS systems and predict influenza-like illness incidence accurately [5]. However, Google Flu Trends was discontinued after it failed to detect the A/H1N1 pandemic and overestimated the 2012-13 influenza season [40,41,43]. Monitoring social media, mainly Twitter, has also shown potential for predicting disease outbreaks in multiple studies and correlates well with IBS data [44,45], but its use has been sporadic, often with a focus on large gatherings.

In one of the few published studies to quantify the performance of implemented EBS systems, Barboza et al [46] found that HealthMap detected H5N1 outbreaks worldwide on average 12 days before their gold standard with a detection rate of 43% and a PPV of 12% (compared to 75% and 66% in our study, respectively). Discrepancies may be due to differences in study design, as the authors of that paper took the first report of an H5N1 outbreak as the epidemic start point and used different gold standards. Interestingly, in the same study, the authors simulated a virtual system by aggregating data from 6 sources and assessed its performance [46]. This virtual combined system achieved a 93% detection rate of H5N1 outbreaks but only a 7% PPV as compared to a lower mean sensitivity (73%) but higher mean PPV (60%) of EIOS—the realization of a combined system—in our study. In another study, Barboza et al [18] also identified system type, filter language, outbreak region, and type of infectious disease as determinants of system performance but did not assess how the effect of these determinants varied by country.

Limitations of This Study

Despite the use of influenza in other evaluations of EBS systems [46], there are limits to how well findings from such evaluations generalize to other infectious disease outbreaks due to the clear seasonality, high prevalence, and consequent potential lack of newsworthiness of influenza. Moreover, influenza shares important keywords for digital disease detection with other conditions of interest such as the common cold. Consequently, we expect our results may underestimate EBS performance because outbreaks of common infections such as influenza are likely more difficult to detect through EBS compared to less frequent and more newsworthy infectious diseases such as Ebola. Indeed, as EBS detection mechanisms might differ between communicable diseases more generally, we suggest separate performance evaluations of EBS systems for the detection of other types of diseases, using this study as a blueprint. For example, in the case of a hemorrhagic fever such as Ebola, EBS systems might give a greater lead in detection over traditional surveillance systems due to large reporting delays and poor data availability [13,14,47]. However, quantitative evaluation of EBS for diseases such as hemorrhagic fevers is hampered by the small number of outbreaks and the limited availability of gold standard data, particularly early in an outbreak. For these reasons and given the small number of EBS evaluation studies, we aimed to first advance the understanding of EBS performance by using a disease with sufficient report numbers to make valid statistical inferences. Traditional influenza surveillance through FluNet provides such a gold standard with high report numbers and almost global coverage.

However, there were some limitations to FluNet for this evaluation. Most notably, epidemic intervals were not labelled explicitly in these data; therefore, we had to apply a statistical method to detect influenza outbreaks, allowing these intervals to labelled in the gold standard data. Although this approach appeared to work well for most countries, the performance was not good in Nigeria, Thailand, and Vietnam due to the low number of reported cases and the inherently more irregular influenza activity in these countries. Moreover, as FluNet influenza counts represent only people having sought health care, the total amount of influenza activity is underestimated, and differences in health care resources and surveillance activities may influence the number of specimens reported. A further complication is that some countries modify their testing and surveillance strategies over the course of an epidemic [48]. For instance, France reported influenza cases to FluNet only from the beginning of October to the beginning of May of each year.

Examples of other gold standard data used to evaluate EBS include the Centers for Disease Control and Prevention Influenza-like Illness Surveillance Network [5], WHO reports on H5N1 [46], and the Centers for Disease Control and Prevention Yellow Book [12]. All these data are dependent on health care–seeking behaviors or passive reporting from health care providers. Moreover, WHO and Yellow Book reports experience delays as they require official notification by a national authority. In fact, one could argue that a proper gold standard for influenza (or any other disease) does not exist, as all IBS systems are affected by delays, overreporting, and underreporting [49,50] and frequently capture only those cases seeking medical care [51]. The lack of a reliable gold standard for comparing the performance of EBS systems not only leads to differential results in the evaluation metrics for multiple systems but also creates problems when comparing the same system across diseases and regions. Given the challenges in identifying a suitable gold standard, we believe that the FluNet is a reasonable choice as it displays many characteristics of a good gold standard: (1) influenza cases are laboratory-confirmed, so FluNet is highly specific and has a high PPV for cases. These features are more important for determining the start and end of the epidemic than sensitivity (ie, absolute case counts), as laboratory-confirmed case counts accurately reflect the start and end points of epidemic periods, which is the information of interest in the gold standard in this case; (2) case count numbers are sufficiently high to make valid statistical inferences; (3) FluNet data cover a wide range of countries allowing measurement across many regions and seasons; and (4) our retrospective data extraction avoids the introduction of errors due to data delays and corrections. Moreover, the automated epidemic detection process we chose to apply likely differs from how EBS systems are used in practice. However, detection of outbreaks with BCP was a standardized way of looking at report frequency.

The variation of the performances of the systems could be explored but was limited. Since data were only available for 24 countries, regressions had to be performed with a small number of degrees of freedom and low numbers of countries per category in the categorical variables. Therefore, it was not possible to disentangle the effect of all variables in every situation.

Finally, the aggregation of daily EBS reports into weekly counts was an important limitation affecting our capacity to ascertain timely sensitivity, but it was necessary to guarantee comparability with the gold standard data. Similarly, as the EBS data were aggregated per country, they did not capture any regional diversity within countries. This is especially problematic for noncontiguous landmasses and large countries spanning diverse climatic regions such as Brazil and China, with different epidemic properties of influenza [48], but again necessary to guarantee comparability.

Conclusion

As the SARS-CoV-2 pandemic has made clear, infectious diseases will continue to be major risks for global health security. The results from this study can help to guide development toward better EBS to prevent future large outbreaks. As demonstrated by the poor timely outbreak detection in this study, advances in the use and evaluation of EBS are needed.

Our analysis documented considerable performance variations across settings. Depending on what exists as routine public health surveillance, related infrastructure, and media landscape, there are situations where EBS can currently be useful, especially in high-income countries for seasonal influenza epidemic surveillance. Efforts need to be made to better understand the determinants of outbreak detection through EBS, particularly in low- and middle-income countries, as current EBS systems were found to be a disadvantage in tropical regions and regions with lower HDI. The inequalities created by biases in EBS, such as low media and internet coverage and low newsworthiness of tropical diseases, should be explored in future research, and the needs of resource-poor settings should be met through further development of EBS.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary methods.
[DOCX File , 21 KB - publichealth_v8i10e36211_app1.docx]

Multimedia Appendix 2
Mean annual report numbers relating to influenza outbreaks in HealthMap (from January 2013 to July 2019) and Epidemic Intelligence from Open Sources (from November 2017 to December 2019). EIOS: Epidemic Intelligence from Open Sources.
[PNG File , 283 KB - publichealth_v8i10e36211_app2.png]

Multimedia Appendix 3
Evaluation metrics of HealthMap (from January 2013 to July 2019) and Epidemic Intelligence from Open Sources (from November 2017 to December 2019) for the detection of influenza outbreaks in the United States and India. EIOS: Epidemic Intelligence from Open Sources.
[PNG File , 175 KB - publichealth_v8i10e36211_app3.png]

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Abbreviations

BCP: Bayesian change point
EBS: event-based surveillance
EIOS: Epidemic Intelligence from Open Sources
GISRS: global influenza surveillance and response system
HDI: human development index
IBS: indicator-based surveillance
PFI: Press Freedom Index
PPV: positive predictive value
WHO: World Health Organization

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Original Paper

Spatiotemporal Distribution of HIV Self-testing Kits Purchased on the Web and Implications for HIV Prevention in China: Population-Based Study

Ganfeng Luo[1*], PhD; Lingyun Su[2*], MS; Anping Feng[1*], MSc; Yi-Fan Lin[1*], PhD; Yiguo Zhou[1], MSc; Tanwei Yuan[1], MSc; Yuqing Hu[1], MPH; Song Fan[3], PhD; Yong Lu[4], PhD; Yingsi Lai[5], PhD; Qian Shi[6], PhD; Jun Li[7], PhD; Mengjie Han[8], MPH; Huachun Zou[1], PhD

[1]School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, China
[2]US-China Health Summit, Beijing, China
[3]School of Public Health, Southwest Medical University, Luzhou, China
[4]School of Public Health, the Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education, Guizhou Medical University, Guiyang, China
[5]School of Public Health, Sun Yat-sen University, Guangzhou, China
[6]School of Geography and Planning, Sun Yat-sen University, Guangzhou, China
[7]School of Computer Science, China University of Geosciences, Wuhan, China
[8]National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China
[*]these authors contributed equally

Corresponding Author:
Huachun Zou, PhD
School of Public Health (Shenzhen)
Sun Yat-sen University
No. 66, Gongchang Road, Guangming District
Shenzhen, 518107
China
Phone: 86 2087335651
Email: zouhuachun@mail.sysu.edu.cn

Abstract

Background: HIV self-testing (HIVST) holds great promise for expanding HIV testing. Nonetheless, large-scale data on HIVST behavior are scant. Millions of HIVST kits are sold through e-commerce platforms each year.

Objective: This study aims to analyze the spatiotemporal distribution of the HIVST kit–purchasing population (HIVSTKPP) in China.

Methods: Deidentified transaction data were retrieved from a leading e-commerce platform in China. A joinpoint regression model was used to examine annual trends of the HIVSTKPP rates by calculating average annual percentage change. Bayesian spatiotemporal analysis was performed to locate hot spots with HIVSTKPP rates. Spatial autocorrelation analysis and space-time cluster analysis were conducted to identify clusters of HIVSTKPP. High-high clusters of HIVSTKPP can be identified by spatial autocorrelation analysis, and high-high clusters indicate that a region and its surrounding region jointly had a higher-than-average HIVSTKPP rate. Spatial regression analysis was used to elucidate the association between the number of HIV testing facilities, urbanization ratio (the proportion of urban population in the total population), and gross domestic product per capita and the HIVSTKPP.

Results: Between January 1, 2016, and December 31, 2019, a total of 2.18 million anonymous persons in China placed 4.15 million orders and purchased 4.51 million HIVST kits on the web. In each of these 4 years, the observed monthly size of the HIVSTKPP peaked in December, the month of World AIDS Day. HIVSTKPP rates per 100,000 population significantly increased from 20.62 in 2016 to 64.82 in 2019 (average annual percentage change=48.2%; *P*<.001). Hot spots were mainly located in municipalities, provincial capitals, and large cities, whereas high-high clusters and high-demand clusters were predominantly detected in cities along the southeast coast. We found positive correlations between a region's number of HIV testing facilities, urbanization ratio, and gross domestic product per capita and the HIVSTKPP.

Conclusions: Our study identified key areas with larger demand for HIVST kits for public health policy makers to reallocate resources and optimize the HIV care continuum. Further research combining spatiotemporal patterns of HIVST with HIV surveillance data is urgently needed to identify potential gaps in current HIV-monitoring practices.

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KEYWORDS

HIV self-testing; spatiotemporal patterns; China; e-commerce platform

Introduction

Background

HIV is a growing public health challenge in China, with the annual rate of persons with newly diagnosed HIV rising from 3.66 per 100,000 in 2007 to 9.35 per 100,000 in 2020 [1,2]. At the end of 2020, there were 1.053 million people living with HIV and 351,000 cumulative reported HIV-related deaths in China [2]. Although HIV testing services are widely available in China [3,4], only an estimated 68.9% of the people living with HIV were aware of their serostatus [5], which is far below the Joint United Nations Program on HIV and AIDS target of 95% of the people living with HIV knowing their HIV status [6]. Many high-risk groups, including men who have sex with men (MSM), sex workers, and people who use drugs, are reluctant to seek venue-based HIV testing services because of concerns about confidentiality, stigma, discrimination, and inconvenience [7]. Determining how to improve the HIV detection rate and promote the identification of people living with HIV has always been the focus and difficulty of AIDS epidemic prevention and control efforts.

HIV self-testing (HIVST) holds great promise for expanding HIV testing [8]. China's 13th Five-Year Plan for HIV Prevention and Control, a national policy framework for HIV response adopted in 2017, encouraged innovative strategies to expand HIV testing, including distribution of HIVST kits through web-based platforms [9]. E-commerce platforms such as Amazon and eBay as well as Taobao and Jingdong in China are central to how people shop and purchase goods, including HIVST kits [10]. These platforms reach billions of registered users across high-, middle-, and low-income countries [10]. HIVST kits are easily available through e-commerce platforms in China [11], with >1 million kits sold on the web in 2018 [12]. Web-based purchasing of HIVST kits is common among some populations at high risk of HIV acquisition. One-third of MSM in China have purchased HIVST kits on the web [7]. In addition, a recent study showed that of 591 individuals who ever purchased HIVST kits on the web in China, 64.7% (220/340) of the heterosexual respondents, 69.9% (112/161) of the homosexual respondents, and 72% (65/90) of the bisexual respondents had engaged in unprotected sex in the last 6 months [12]. In other words, the web-based HIVST kit–purchasing behavior largely indicates that recent high-risk sexual behavior is a factor in HIV acquisition.

Spatiotemporal Analyses

In recent decades, spatiotemporal analyses have been applied to HIV surveillance and outbreak investigation among different populations [13-16]. Applying these same principles to analyze the spatiotemporal evolution of HIVST kit–purchasing patterns can provide insight into the distribution of those at potential high risk for HIV and in need of HIVST and HIV care [17]. This information can be used to identify gaps in HIV prevention and optimize allocation of resources [17]. Identifying associations between HIVST kit purchasing and macroscopic factors such as number of HIV testing facilities, urbanization ratio (the proportion of urban population in the total population), and gross domestic product (GDP) may help in the development of interventional strategies or policy responses contextualized to different settings.

No previous publication has analyzed the spatiotemporal distribution of HIVST, and the effect of expanding HIVST based on China's 13th Five-Year Plan for HIV Prevention and Control remains unclear. In this study, we used transaction data collected from a leading e-commerce platform to analyze the spatiotemporal patterns of the HIVST kit–purchasing population (HIVSTKPP) to uncover clusters of HIVST kit purchasing and evaluate associations with macroscopic factors in China.

Methods

Data Collection

Records of the sales of HIVST kits between January 1, 2016, and December 31, 2019, were retrieved from a leading e-commerce platform in China [17]. To protect the consumers' privacy, the name of the e-commerce platform is not being disclosed. The extracted variables included (1) anonymized ID details; (2) purchase date; (3) shipping province, city, and provincial-controlled county; and (4) purchase quantity. In addition, IP addresses were not included in the original data set.

The size of the resident population, urbanization ratio, and GDP per capita (CN¥ 10,000 [US $1410]) for each shipping province, city, and provincial-controlled county were drawn from the Statistical Yearbook of China [18]. The number of HIV testing facilities in each area was collected from the Chinese Center for Disease Control and Prevention (CCDC) [19]. Maps were obtained from the National Catalogue Service for Geographic Information [20].

Data Management

All personal identifiable information was removed or deidentified. All data were maintained entirely within a sandbox environment of the e-commerce platform.

Inclusion and Exclusion Criteria

To minimize the impact of bulk or proxy purchasing of HIVST kits, we only included those persons who had purchased ≤48 kits cumulatively over the entire study period. We only included records with shipping addresses within mainland China. Orders shipped to Hong Kong, Macao, Taiwan, and overseas were excluded.

Definition of HIVSTKPP

In our study, HIVSTKPP refers to anonymous persons who purchased HIVST kits from a leading e-commerce platform for their own use for HIV testing in China between January 1, 2016, and December 31, 2019.

Statistical Analysis

The rate of HIVST kit purchasing per 100,000 population was calculated by dividing the number of anonymous persons who bought the kits by the total population in an area. When calculating the HIVSTKPP rate, we only included each anonymous person's latest recorded purchase to avoid duplication. In this study, anonymous person was defined as a unique individual by anonymized user ID of the e-commerce platform. Data were analyzed at the regional, provincial, city, and provincial-controlled–county levels.

In China, 31 provinces are aggregated into 7 regions (North China, Northeast China, East China, Central China, South China, Southwest China, and Northwest China) based on geography, climate, economy, history, and ethnicity by the Chinese government (Textbox 1).

The geographical distribution of these 7 regions and 31 provinces is presented in Figure 1. In addition, 4 municipalities (Beijing, Shanghai, Tianjin, and Chongqing cities) belong to provincial administrative units. The 31 provinces and their capitals are presented in Textbox 2.

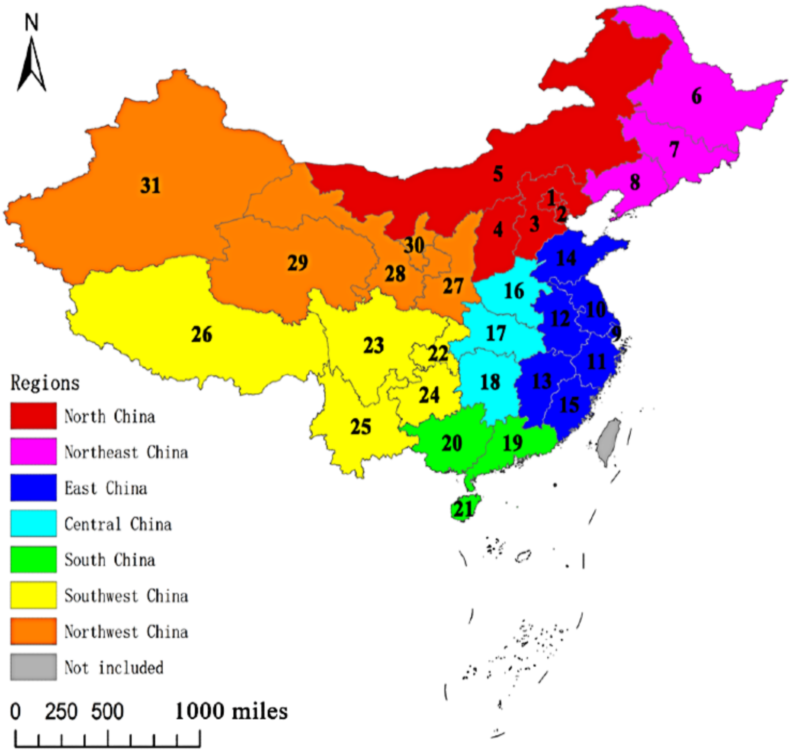
Time series analysis [21] and joinpoint regression analysis [22] were performed to examine seasonal patterns of the monthly size of the HIVSTKPP and annual trends of the HIVSTKPP rates, respectively. A spatial autocorrelation model was constructed to evaluate the spatial distribution patterns (clustered, dispersed, and random) of the HIVSTKPP [23,24]. Four types of local spatial clusters can be identified by a spatial autocorrelation model: high-high, low-low, high-low, and low-high [13]. High-high and low-low clusters indicate that a city and its surrounding region jointly had higher-than-average and lower-than-average HIVSTKPP rates, respectively. A high-low cluster represents a city with an above-average HIVSTKPP rate surrounded by cities with below-average rates, whereas a low-high cluster represents a city with a below-average HIVSTKPP rate surrounded by cities with above-average rates. Temporal-spatial clustering analysis was implemented to identify high-risk (higher demand for HIVST kits) and low-risk (lower demand for HIVST kits) clusters of HIVSTKPP over space and time simultaneously [25,26], and we set a maximum spatial cluster size of 50% of the population at risk and a maximum temporal cluster size of 50% of the study period to scan for spatial clusters with high and low rates in our study. A Bayesian spatiotemporal model was constructed to detect hot spots and cold spots of the HIVSTKPP [27]. Spatial lag model or spatial error model (SEM) and geographically weighted regression model were constructed to assess the global and local spatial correlation between the size of the HIVSTKPP and 3 factors (number of HIV testing facilities, urbanization ratio, and GDP per capita [CN¥ 10,000 {US $1410}]), respectively [13,28]. Details of the statistical analysis can be found in Multimedia Appendix 1 [1-3,6-9,17,18,29-39].

Textbox 1. The 7 regions and 31 provinces of mainland China.

Regions and provinces

- North China
- Beijing, Tianjin, Hebei, Shanxi, and Inner Mongolia
- Northeast China
- Heilongjiang, Jilin, and Liaoning
- East China
- Shanghai, Jiangsu, Zhejiang, Anhui, Jiangxi, Shandong, and Fujian
- Central China
- Henan, Hubei, and Hunan
- South China
- Guangdong, Guangxi, and Hainan
- Southwest China
- Chongqing, Sichuan, Guizhou, Yunnan, and Tibet
- Northwest China
- Shaanxi, Gansu, Qinghai, Ningxia, and Xinjiang

Figure 1. Geographical distribution of 7 regions and 31 provinces in mainland China. The 31 provinces are as follows: 1, Beijing; 2, Tianjin; 3, Hebei; 4, Shanxi; 5, Inner Mongolia; 6, Heilongjiang; 7, Jilin; 8, Liaoning; 9, Shanghai; 10, Jiangsu; 11, Zhejiang; 12, Anhui; 13, Jiangxi; 14, Shandong; 15, Fujian; 16, Henan; 17, Hubei; 18, Hunan; 19, Guangdong; 20, Guangxi; 21, Hainan; 22, Chongqing; 23, Sichuan; 24, Guizhou; 25, Yunnan; 26, Tibet; 27, Shaanxi; 28, Gansu; 29, Qinghai; 30, Ningxia; and 31, Xinjiang.



Textbox 2. Mainland China's 31 provincial capitals.

Provinces and capitals

- Beijing: Beijing municipality
- Tianjin: Tianjin municipality
- Hebei: Shijiazhuang city
- Shanxi: Taiyuan city
- Inner Mongolia: Hohhot city
- Heilongjiang: Harbin city
- Jilin: Changchun city
- Liaoning: Shenyang city
- Shanghai: Shanghai municipality
- Jiangsu: Nanjing city
- Zhejiang: Hangzhou city
- Anhui: Hefei city
- Jiangxi: Nanchang city
- Shandong: Nanchang city
- Fujian: Fuzhou city
- Henan: Zhengzhou city
- Hubei: Wuhan city
- Hunan: Wuhan city
- Guangdong: Guangzhou city
- Guangxi: Nanning city
- Hainan: Haikou city
- Chongqing: Chongqing municipality
- Sichuan: Chengdu city
- Guizhou: Guiyang city
- Yunnan: Kunming city
- Tibet: Lhasa city
- Shaanxi: Xi'an city
- Gansu: Lanzhou city
- Qinghai: Xining city
- Ningxia: Yinchuan city
- Xinjiang: Urumqi city

Ethics Approval

This study was conducted with the approval of the institutional review board and ethics committee of Sun Yat-sen University (SYSU-SPH2021026). We did not identify or reidentify any individual, purposefully or inadvertently, in our analysis.

Results

HIVST Kit–Purchasing Patterns

Between January 1, 2016, and December 31, 2019, a total of 2.18 million anonymous persons in China placed 4.15 million orders and purchased 4.51 million HIVST kits on the web. HIVST kits were delivered to 366 cities and provincial-controlled counties (Table 1). The mean number of HIVST kits sold per month was 94.01 thousand, and the mean number of HIVST kits sold per day was 3.09 thousand. Of the 2.18 million anonymous persons who purchased HIVST kits, 1.39 million (63.79%), 0.41 million (18.73%), and 0.16 million (7.39%) anonymous persons purchased HIVST kits on 1, 2, and 3 occasions between January 1, 2016, and December 31, 2019, respectively; in addition, 1.33 million (60.88%), 0.43 million (19.59%), and 0.17 million (7.66%) anonymous persons purchased 1, 2, and 3 kits, respectively (Table 2). The average annual HIVSTKPP rate between January 1, 2016, and December 31, 2019, was 39.16 (SD 19.90) per 100,000 (Table 1).

Table 1. The number of purchasers, purchases, and HIV self-testing kits sold as well as the HIV self-testing kit–purchasing population rate between January 1, 2016, and December 31, 2019, in mainland China.

Year	Purchasers (N=2,180,284), n (%)	Purchases (N=4,148,429), n (%)	Kits (N=4,512,353), n (%)	Population (thousand; N=5,568,220), n (%)	Rate[a]
2016	285,107 (13.08)	641,566 (15.47)	750,752 (16.64)	1,382,710 (24.83)	20.62
2017	369,140 (16.93)	832,775 (20.07)	924,661 (20.49)	1,390,080 (24.96)	26.55
2018	618,498 (28.37)	1,203,435 (29.01)	1,282,882 (28.43)	1,395,380 (25.06)	44.32
2019	907,539 (41.62)	1,470,653 (35.45)	1,554,058 (34.44)	1,400,050 (25.14)	64.82

[a] The rate of HIV self-testing kit purchasing per 100,000 population was calculated by dividing the number of purchasers by the total population in an area. The rate for the 4-year period from January 1, 2016, to December 31, 2019, was 39.16.

Table 2. The number of purchasers with ≥1 purchases and the number of purchasers of ≥1 HIV self-testing kits between January 1, 2016, and December 31, 2019, in mainland China.

Variable	Values (N=2,180,284), n (%)
Purchases	
1	1,390,790 (63.79)
2	408,471 (18.73)
3	161,192 (7.39)
4	78,898 (3.62)
5	43,773 (2.01)
6	27,069 (1.24)
7	17,708 (0.81)
8	12,174 (0.56)
9	8804 (0.4)
10	6469 (0.3)
HIV self-testing kits	
1	1,327,298 (60.88)
2	427,037 (19.59)
3	167,042 (7.66)
4	88,952 (4.08)
5	49,154 (2.25)
6	31,585 (1.45)
7	20,195 (0.93)
8	14,508 (0.67)
9	10,689 (0.49)
10	8364 (0.38)

Temporal Trends in the HIVSTKPP

The observed annual HIVSTKPP markedly increased from 0.29 million anonymous persons in 2016 to 0.91 million anonymous persons in 2019 (Figure 2). The observed HIVSTKPP showed a clear periodic pattern, with 46.31% (1,009,704/2,180,284) of the anonymous persons purchasing HIVST kits between September and December (Figures 3-5). The maximum monthly number was observed in December for all provinces (Figure 5 and Figure 6).

Figure 2. Temporal trend of the size of the HIV self-testing kit–purchasing population (HIVSTKPP) by year and month between January 1, 2016, and December 31, 2019, in mainland China.

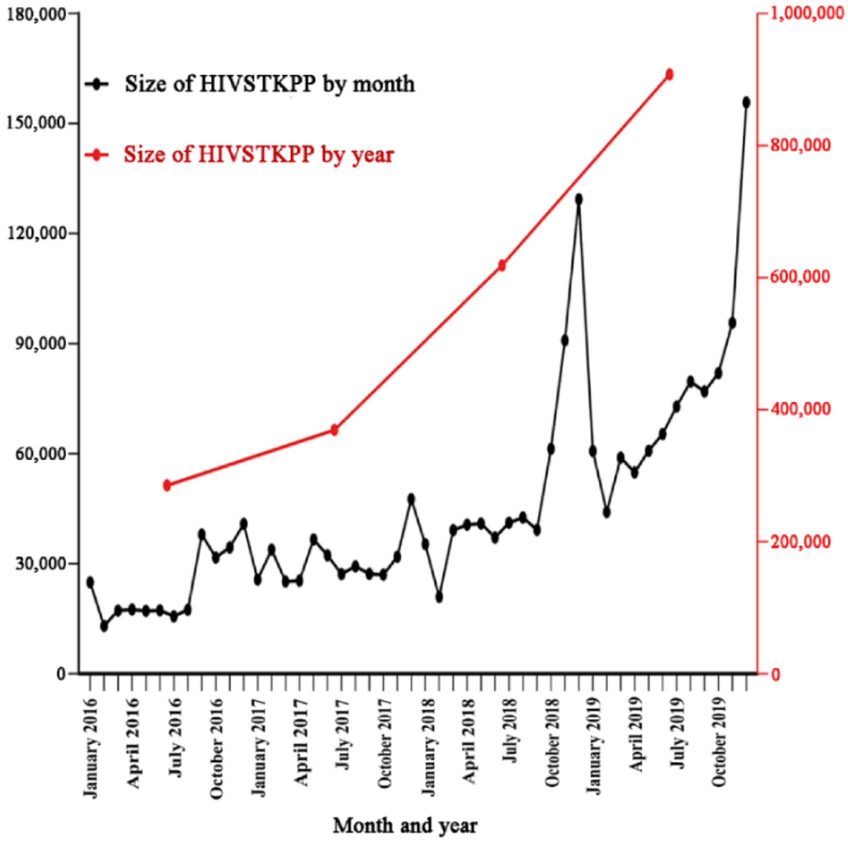


Figure 3. The seasonal and trend decomposition using Loess of the size of the HIV self-testing kit–purchasing population by month from January 1, 2016, to December 31, 2019, in mainland China.

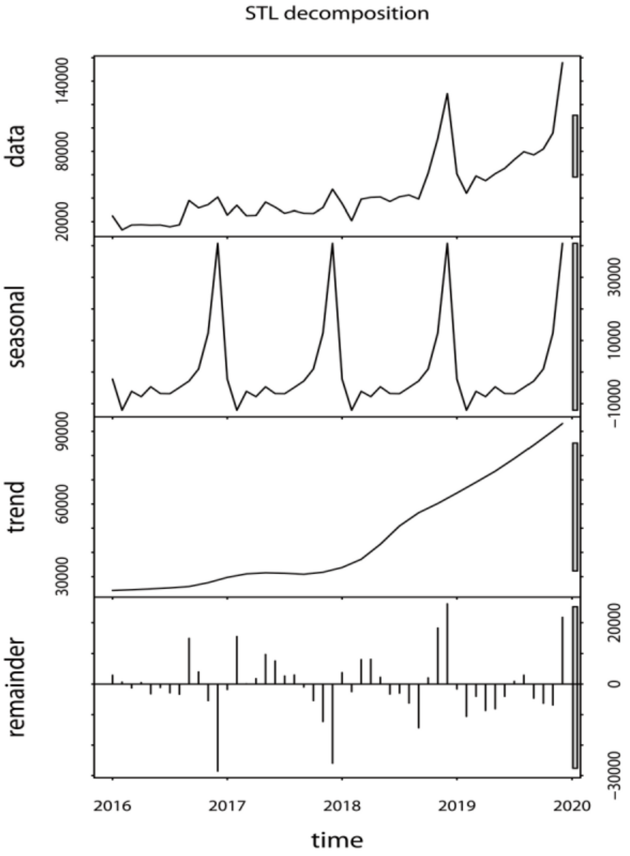


Figure 4. The monthly plots of the size of the HIV self-testing kit–purchasing population (HIVSTKPP) from January 1, 2016, to December 31, 2019, in mainland China.

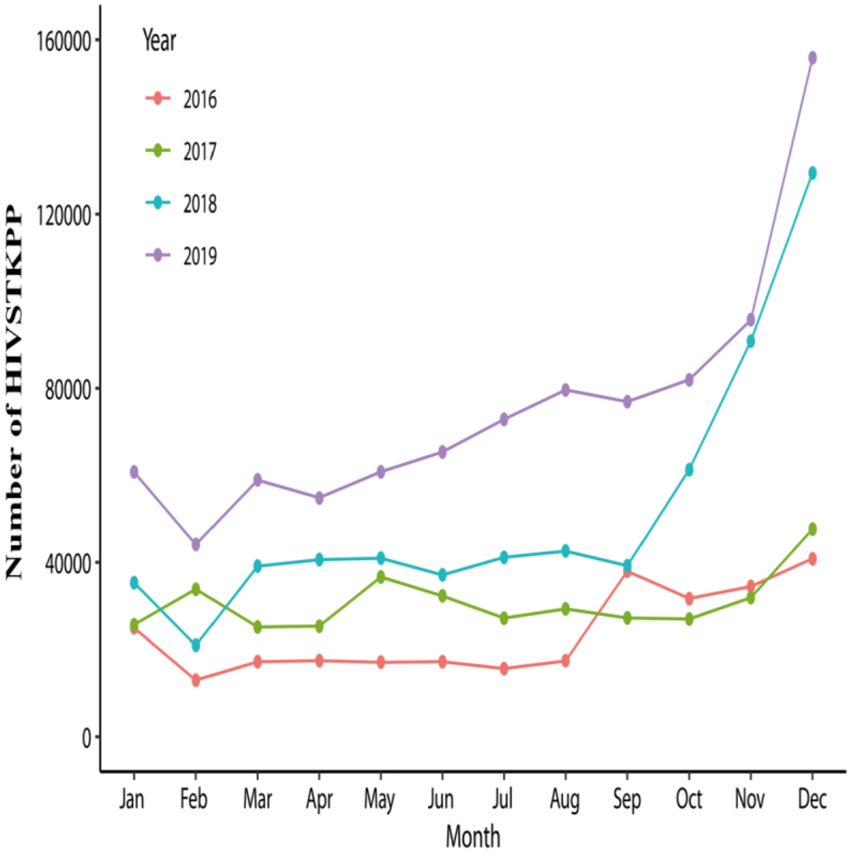


Figure 5. The seasonal plots of the size of the HIV self-testing kit–purchasing population (HIVSTKPP) from January 1, 2016, to December 31, 2019, in mainland China.

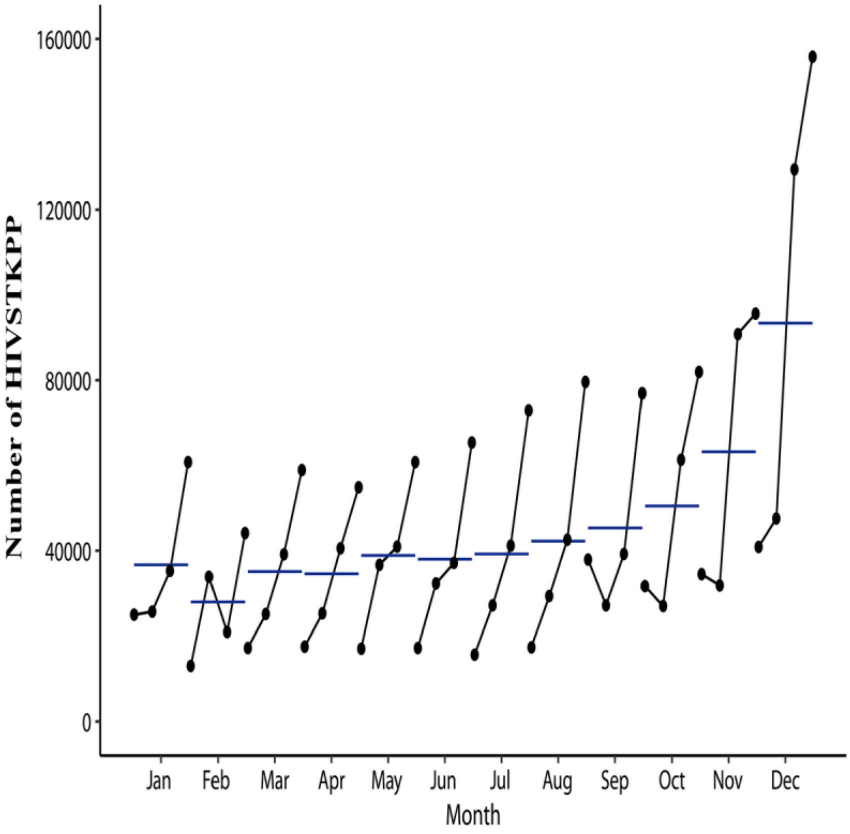
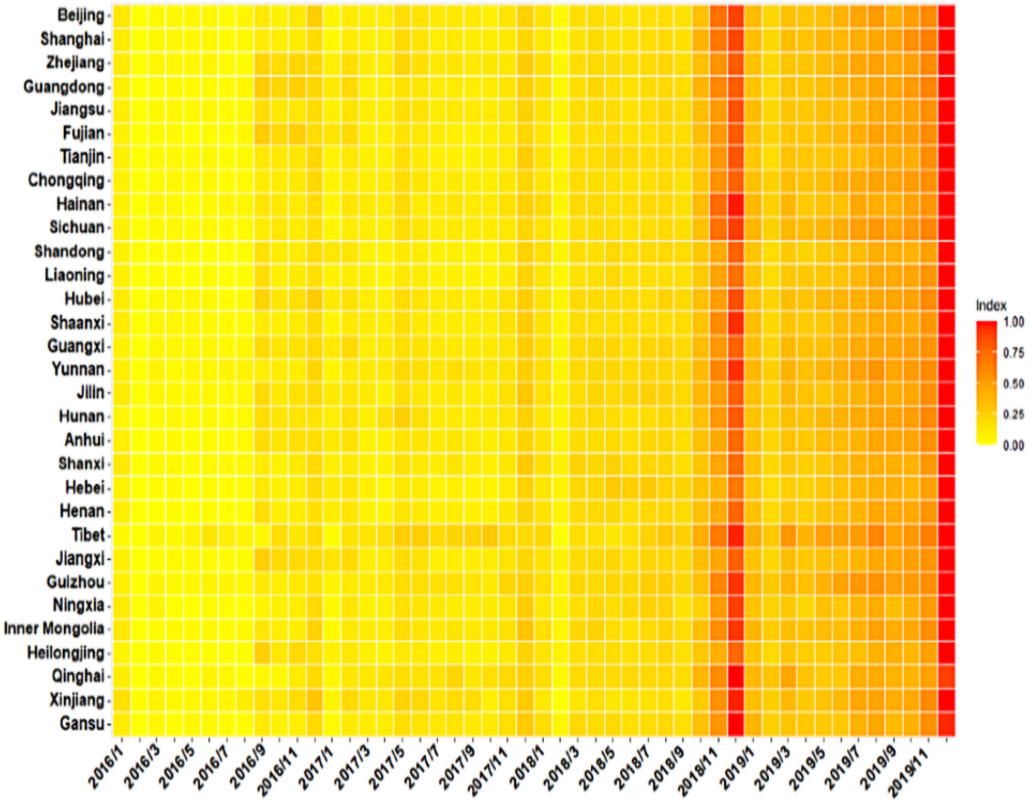


Figure 6. Heat map showing the size of the HIV self-testing kit–purchasing population by month after min-max normalization from January 1, 2016, to December 31, 2019, in 31 provinces in mainland China.



Temporal Trends and Spatial Distribution in the HIVSTKPP Rates per 100,000 Population

From January 1, 2016, to December 31, 2019, the HIVSTKPP rate increased by 2.14 times (from 20.62 per 100,000 to 64.82 per 100,000, average annual percentage change [AAPC]=48.2%; *P*<.001; Table 3). Among all 7 regions in mainland China, the highest and lowest average annual HIVSTKPP rates between January 1, 2016, and December 31, 2019, were seen in South China (50.85 per 100,000) and Northwest China (24.91 per 100,000), respectively (Table 3). Among the 31 provinces, the largest sizes of HIVSTKPP were observed in Guangdong (0.27 million), Jiangsu (0.18 million), Zhejiang (0.15 million), Shandong (0.14 million), and Sichuan (0.13 million; data not shown). The highest HIVSTKPP rates were observed in Beijing (106.20), Shanghai (103.32), Zhejiang (67.79), Guangdong (60.10), and Jiangsu (56.48; Figure 7 and Table 3).

From January 1, 2016, to December 31, 2019, the HIVSTKPP rates significantly increased among all 7 regions and 31 provinces (all *P*<.001; Figures 8-11, and Table 3). Southwest China, with a median annual HIVSTKPP rate of 35.25 per 100,000, showed the largest increase in HIVSTKPP rates (AAPC=53.3%; *P*<.001; Figure 8A and Figure 9). Most provinces had low annual HIVSTKPP rates but exhibited large increases in HIVSTKPP rates (Figure 8B and Figure 11). Beijing and Shanghai municipalities had both high average annual HIVSTKPP rates and large increases in HIVSTKPP rates.

The spatial distributions in HIVSTKPP rates at city and provincial-controlled–county levels were distinctly heterogeneous (Figure 12A and Figure 13). The top 10 cities with the highest average annual HIVSTKPP rates are shown in Textbox 3, and those with the largest sizes of HIVSTKPP are shown in Textbox 4.

Table 3. Average annual percentage change (AAPC) in HIV self-testing kit–purchasing population rates per 100,000 population between January 1, 2016, and December 31, 2019, among the 7 regions and 31 provinces in mainland China.

	Average annual HIVSTKPP[a] rates per 100,000 population					AAPC (%)[b]	*P* value
	2016 to 2019	2016	2017	2018	2019		
China	39.16	20.62	26.56	44.32	64.82	48.2	<.001
North China	38.73	19.75	25.92	45.58	63.43	50.1	<.001
Beijing	106.20	58.92	73.68	119.28	173.59	45.1	
Tianjin	50.27	26.08	33.13	59.15	82.68	49.8	
Hebei	27.23	12.67	17.23	33.90	44.83	56.3	
Shanxi	27.42	13.06	18.21	32.62	45.56	54.2	
Inner Mongolia	24.75	12.84	17.64	28.39	40.02	47.5	
Northeast China	30.23	15.95	19.98	34.36	50.84	49.5	<.001
Heilongjiang	24.69	13.57	16.15	28.27	40.98	47.3	
Jilin	29.14	14.79	19.86	33.87	48.32	50.5	
Liaoning	35.70	18.75	23.38	39.92	60.90	50.2	
East China	47.44	25.78	32.63	53.15	77.62	46.1	<.001
Shanghai	103.32	56.09	70.14	116.35	170.43	46.8	
Jiangsu	56.48	30.07	39.37	63.74	92.43	47.0	
Zhejiang	67.79	38.87	48.80	73.54	108.15	41.6	
Anhui	27.69	14.55	18.84	30.66	46.22	48.5	
Jiangxi	26.02	14.03	17.79	29.22	42.80	46.8	
Shandong	35.80	18.08	23.59	42.03	59.24	51.3	
Fujian	51.42	30.76	34.98	55.58	83.63	41.4	
Central China	29.71	14.97	20.37	33.5	49.77	50.7	<.001
Henan	27.07	13.23	17.87	31.55	45.40	53.2	
Hubei	35.28	19.34	24.28	39.18	58.17	46.0	
Hunan	28.60	13.63	20.49	31.35	48.64	52.8	
South China	50.85	28.45	34.04	56.75	82.97	45.1	<.001
Guangdong	60.10	34.28	39.62	66.73	98.07	44.4	
Guangxi	31.81	16.97	22.75	35.49	51.55	45.9	
Hainan	39.37	19.04	26.34	47.60	63.75	52.5	
Southwest China	35.25	17.23	23.45	39.84	60.05	53.3	<.001
Chongqing	44.75	22.05	29.40	49.10	77.67	53.6	
Sichuan	39.32	19.04	25.18	44.69	68.01	55.2	
Guizhou	25.04	11.66	17.25	28.77	42.17	54.8	
Yunnan	30.35	15.51	21.51	34.57	49.46	48.5	
Tibet	26.51	12.07	20.14	28.36	44.44	53.0	
Northwest China	24.91	13.15	17.9	28.51	39.71	46.0	<.001
Shaanxi	32.25	15.98	21.83	37.84	52.99	51.4	
Ningxia	24.94	12.40	17.75	29.57	39.59	49.1	
Qinghai	20.97	9.76	16.19	25.00	32.62	50.0	
Xinjiang	20.13	13.42	16.35	20.19	30.11	30.2	
Gansu	19.56	9.75	14.02	23.22	31.09	49.0	

[a] HIVSTKPP: HIV self-testing kit–purchasing population.

[b] The average annual percentage change from January 1, 2016, to December 31, 2019, was calculated by joinpoint regression model.

Figure 7. Average annual rate per 100,000 population of the HIV self-testing kit–purchasing population (HIVSTKPP) between January 1, 2016, and December 31, 2019, among the 31 provinces in mainland China.

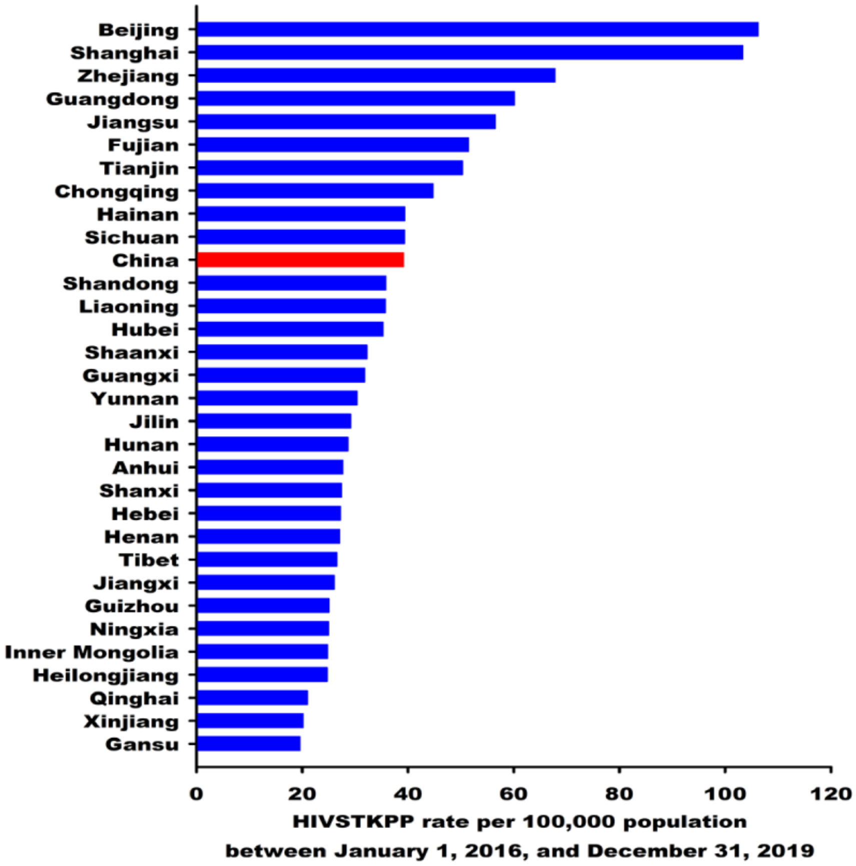


Figure 8. Average annual percentage change (AAPC) in the HIV self-testing kit–purchasing population (HIVSTKPP) rate per 100,000 population between January 1, 2016, and December 31, 2019, by average annual rate per 100,000 population of HIVSTKPP between January 1, 2016, and December 31, 2019, among the 7 regions (A) and 31 provinces (B) in mainland China.

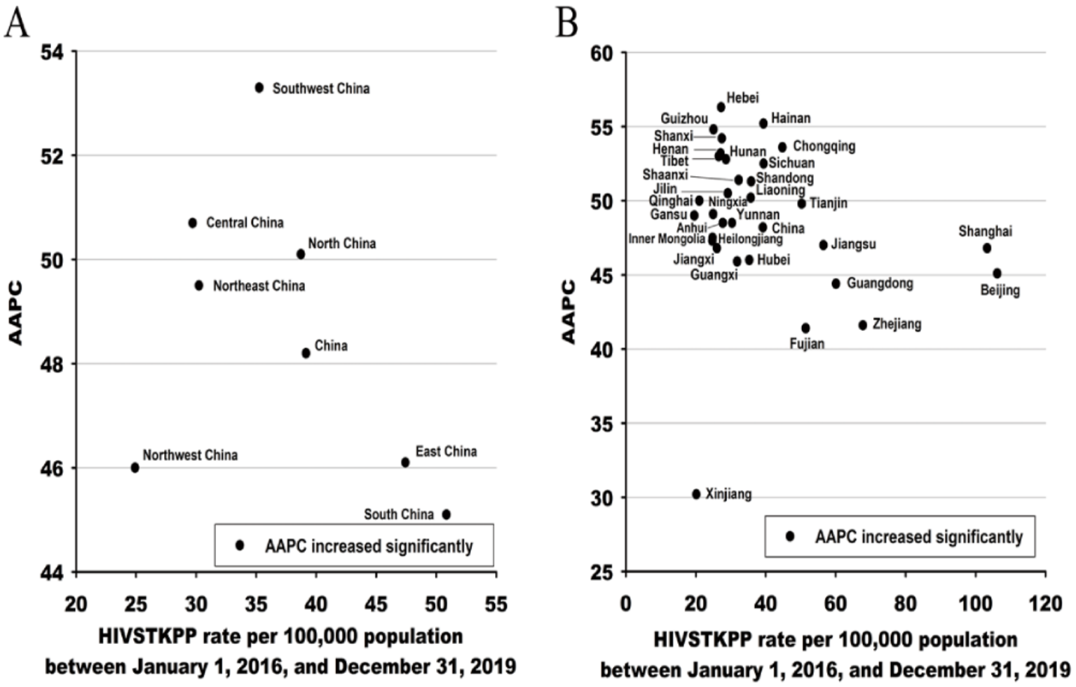


Figure 9. Temporal trend of the HIV self-testing kit–purchasing population (HIVSTKPP) rate per 100,000 population from January 1, 2016, to December 31, 2019, by region (refer to Textbox 1, which shows the number of regions and provinces).

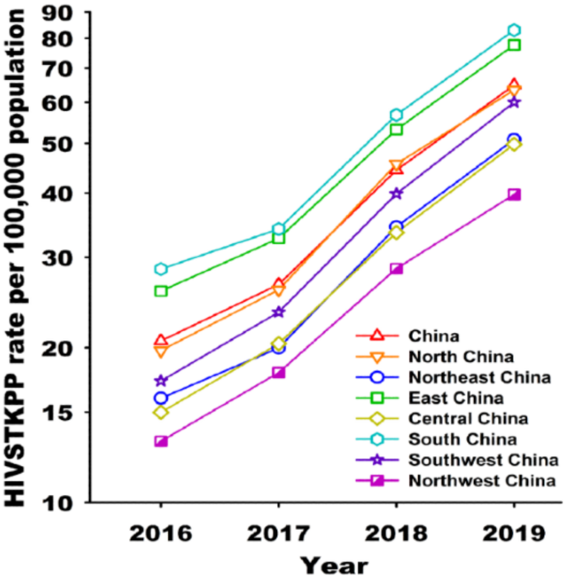


Figure 10. The HIV self-testing kit–purchasing population (HIVSTKPP) rate per 100,000 population from January 1, 2016, to December 31, 2019, for 31 provinces in mainland China.

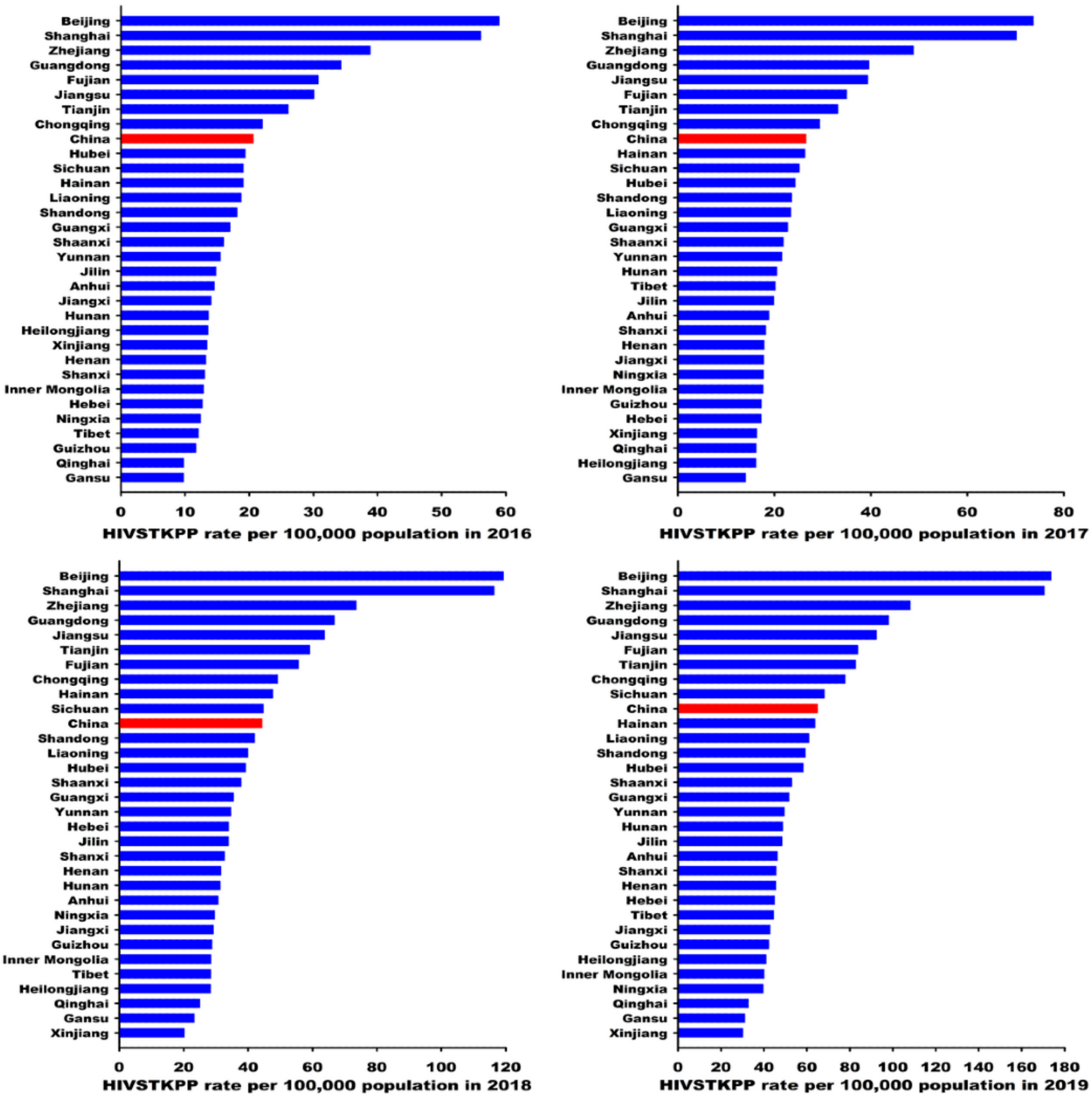


Figure 11. Temporal trend of the HIV self-testing kit–purchasing population (HIVSTKPP) rate per 100,000 population from January 1, 2016, to December 31, 2019, by province (there are 31 provinces in mainland China).

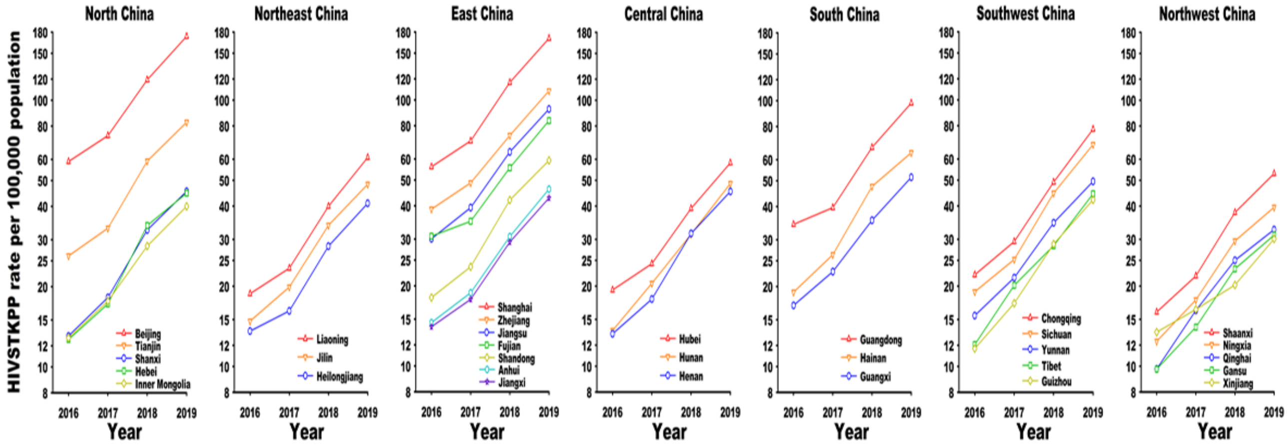


Figure 12. (A) Geographical distribution of the average annual rate per 100,000 population of the HIV self-testing kit–purchasing population (HIVSTKPP), (B) local clusters of the average annual rate of the HIVSTKPP identified by spatial autocorrelation analysis, (C) spatiotemporal clusters of the HIVSTKPP identified by temporal-spatial clustering analysis, and (D) hot spots and cold spots identified by the best-fitting Bayesian spatiotemporal model between January 1, 2016, and December 31, 2019, at city and provincial-controlled–county levels in mainland China. LISA: local indicators of spatial association; RR: relative risk.

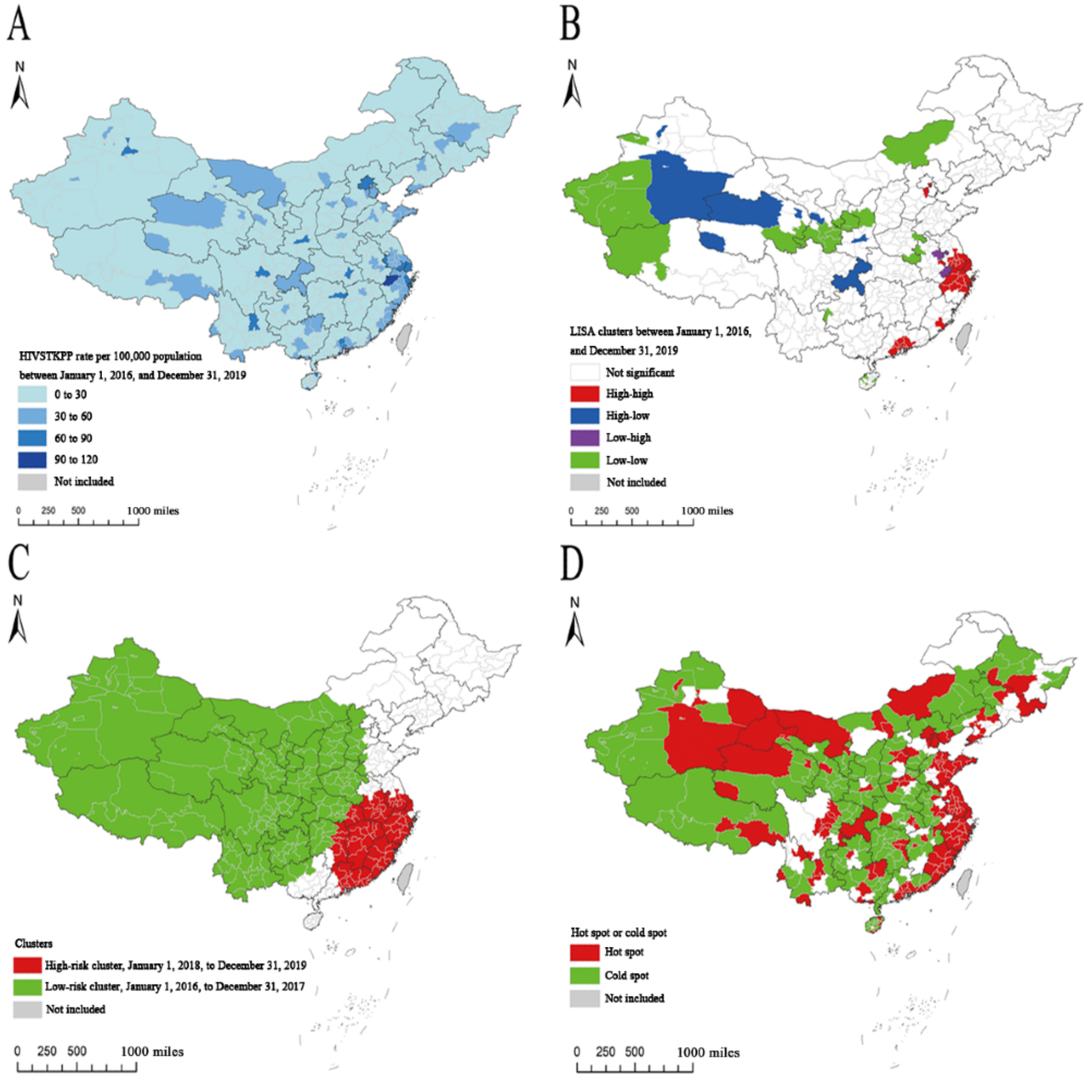
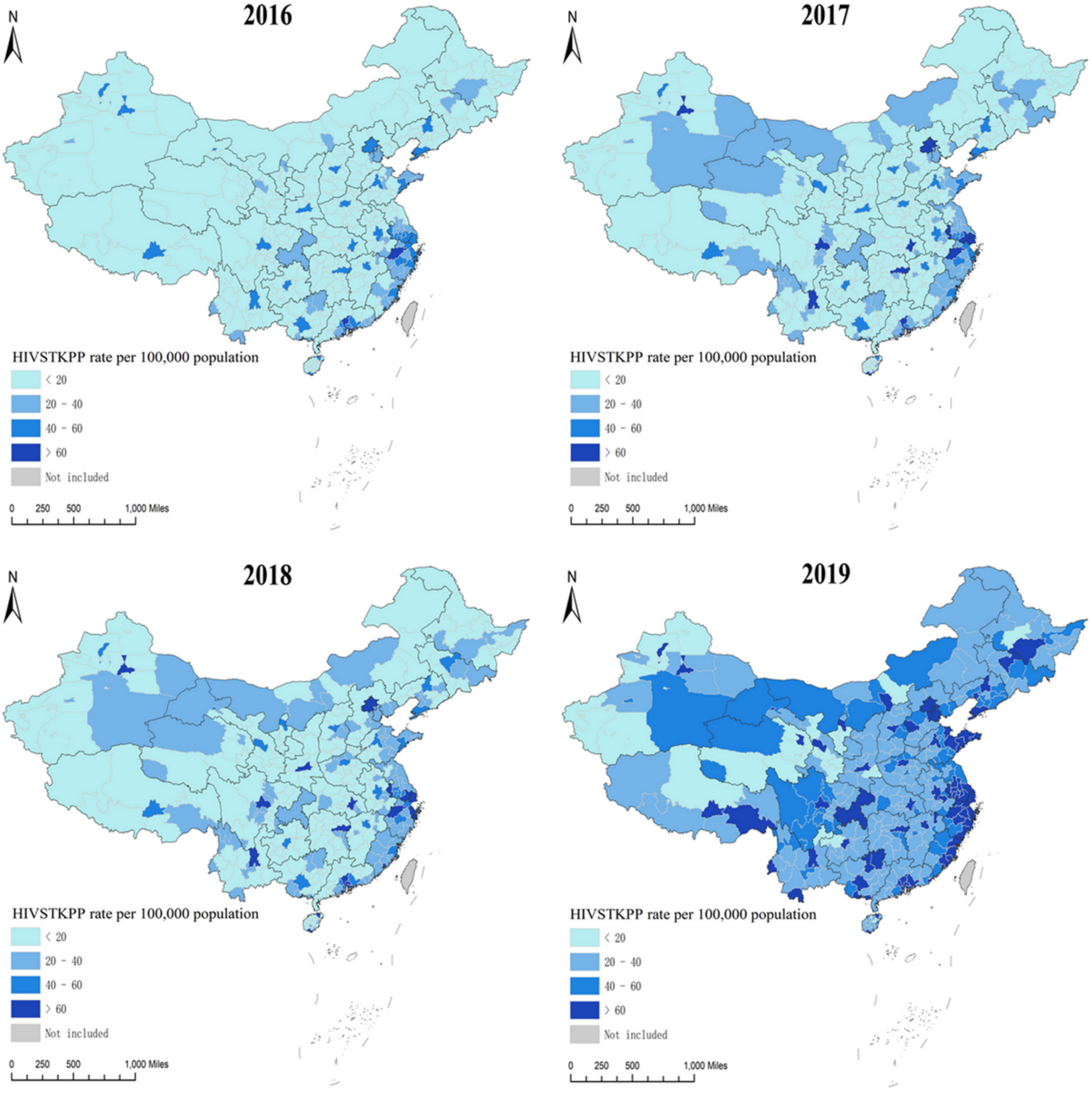


Figure 13. Geographical distribution of the HIV self-testing kit–purchasing population (HIVSTKPP) rate per 100,000 population from January 1, 2016, to December 31, 2019, at city and provincial-controlled–county levels in mainland China.



Textbox 3. The top 10 cities with the highest average annual HIV self-testing kit–purchasing population (HIVSTKPP) rates.

Top 10 cities with the highest average HIVSTKPP rates (per 100,000 population)

- Shenzhen in Guangdong province: 107.92
- Hangzhou in Zhejiang province: 97.17
- Zhuhai in Guangdong province: 93.98
- Nanjing in Jiangsu province: 86.75
- Guangzhou in Guangdong province: 85.74
- Beijing: 83.86
- Shanghai: 80.88
- Chengdu in Sichuan province: 80.62
- Xiamen in Fujian province: 80.49
- Wuhan in Hubei province: 79.37

Textbox 4. The top 10 cities with the largest sizes of HIV self-testing kit–purchasing population (HIVSTKPP).

Top 10 cities with the largest sizes of HIVSTKPP

- Shanghai: 0.10 million
- Beijing: 0.09 million
- Shenzhen in Guangdong province: 0.07 million
- Chengdu in Sichuan province: 0.07 million
- Guangzhou in Guangdong province: 0.07 million
- Chongqing: 0.06 million
- Hangzhou in Zhejiang province: 0.05 million
- Wuhan in Hubei province: 0.05 million
- Suzhou in Jiangsu province: 0.04 million
- Nanjing in Jiangsu province: 0.04 million

Spatial Autocorrelation Patterns

The global Moran I showed significant positive spatial clustering of average annual HIVSTKPP rates at the city and provincial-controlled–county levels during the entire study period (Moran I=0.252; *P*<.001; Table S1 in Multimedia Appendix 2). The global Moran I decreased from 0.317 in 2016 to 0.234 in 2019. Significant local indicators of spatial association were mainly detected in high-high and low-low clusters (Table 4).

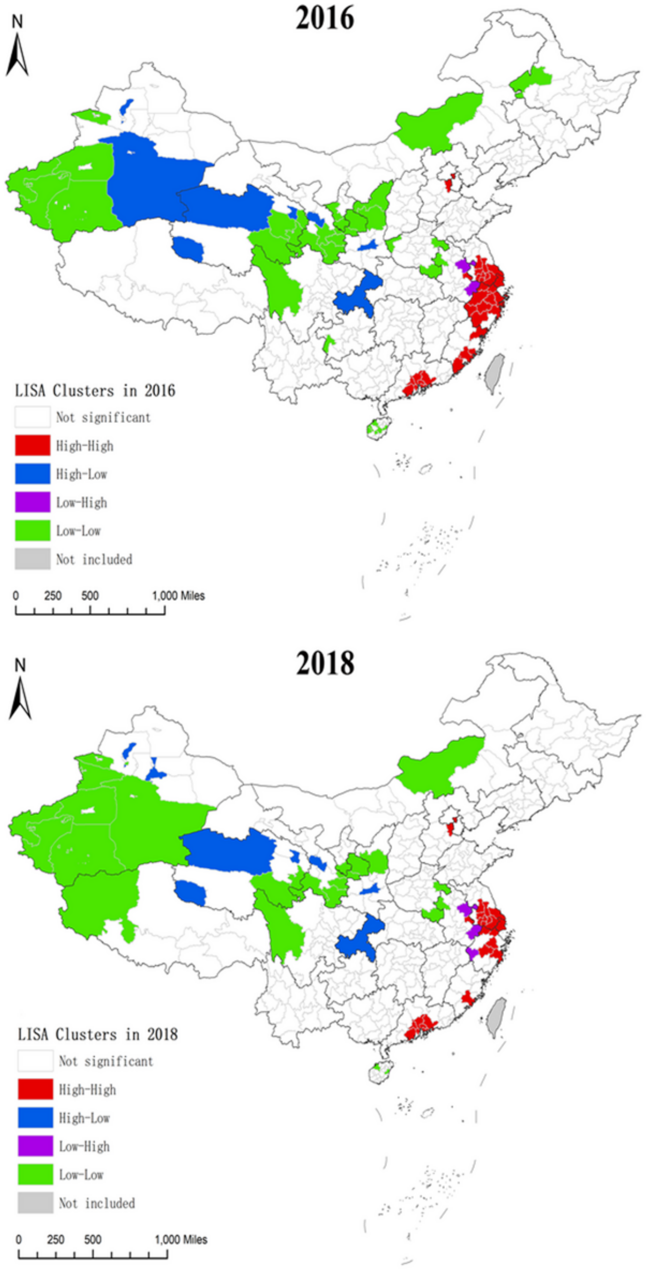
Between January 1, 2016, and December 31, 2019, of the 366 cities and provincial-controlled counties, 26 (7.1%) and 27 (7.4%) were identified as high-high and low-low clusters, respectively (Table 4). The average annual HIVSTKPP rate in high-high clusters (79.63 per 100,000) was 5.29-fold higher than that in low-low clusters (15.06 per 100,000). The high-high clusters, where the HIVSTKPP accounted for 26.16% (570,261/2,180,284) of all anonymous persons, were mainly located in East and South China, including Zhejiang, Guangdong, and Jiangsu provinces (Figure 12B and Table S2 in Multimedia Appendix 2). From January 1, 2016, to December 31, 2019, the local indicators of spatial association clusters remained relatively stable (Figure 14). The number of cities in high-high clusters decreased from 31 in 2016 to 24 in 2019, and the proportion of HIVSTKPP (high-high clusters vs all anonymous persons) decreased from 28.16% (80,297/285,107) in 2016 to 23.89% (216,848/907,539) in 2019, whereas the HIVSTKPP rates significantly increased from 41.61 per 100,000 in 2016 to 124.93 per 100,000 in 2019 (AAPC=45.6%; *P*<.001; Table 4).

Table 4. Descriptive statistics of 4 types of spatial clusters as defined by local indicators of spatial association analysis between January 1, 2016, and December 31, 2019, in mainland China.

Period and patterns	Rate[a]	HIV self-testing kit–purchasing population, n (%)	Cities (N=366), n (%)
January 1, 2016, to December 31, 2019 (N=2,180,284)			
High-high	79.63	570,261 (26.16)	26 (7.10)
High-low	52.01	100,477 (4.61)	7 (1.91)
Low-high	22.53	6062 (0.28)	2 (0.55)
Low-low	15.06	34,220 (1.57)	27 (7.38)
2016 (N=285,107)			
High-high	41.61	80,297 (28.16)	31 (8.47)
High-low	26.34	12,377 (4.34)	7 (1.91)
Low-high	13.00	864 (0.30)	2 (0.55)
Low-low	7.65	5522 (1.94)	34 (9.29)
2017 (N=369,140)			
High-high	54.38	95,153 (25.78)	27 (7.38)
High-low	34.94	16,744 (4.54)	7 (1.91)
Low-high	15.80	1057 (0.29)	2 (0.55)
Low-low	10.80	5396 (1.46)	22 (6.01)
2018 (N=618,498)			
High-high	86.16	140,666 (22.74)	23 (6.28)
High-low	60.35	30,046 (4.86)	7 (1.91)
Low-high	26.54	2381 (0.38)	3 (0.82)
Low-low	16.91	9840 (1.59)	27 (7.38)
2019 (N=907,539)			
High-high	124.93	216,848 (23.89)	24 (6.56)
High-low	89.98	45,060 (4.97)	7 (1.91)
Low-high	38.68	3491 (0.38)	3 (0.82)
Low-low	22.16	11,617 (1.28)	29 (7.92)

[a] The rate of HIV self-testing kit purchasing per 100,000 population was calculated by dividing the number of purchasers by the total population in an area.

Figure 14. Geographical distribution of local clusters of the population-level HIV self-testing kit–purchasing population rate per 100,000 population from January 1, 2016, to December 31, 2019, at city and provincial-controlled–county levels in mainland China by spatial autocorrelation analysis. LISA: local indicators of spatial association.



Spatiotemporal Clusters

Clusters with higher demand for HIVST kits available on the web were detected in 75 cities and provincial-controlled counties located in East China, South China, and Central China between January 1, 2018, and December 31, 2019, including 15 (20%) in Guangdong province, 11 (15%) in Zhejiang province, 11 (15%) in Jiangxi province, 10 (13%) in Anhui province, 9 (12%) in Fujian province, 7 (10%) in Jiangsu province, 6 (8%) in Hunan province, 5 (7%) in Hubei province, and 1 (1%) in Shanghai. Clusters with lower demand for HIVST kits available on the web were found in 181 cities and provincial-controlled counties between January 1, 2016, and December 31, 2017 (Figure 12C and Table 5). High-demand and low-demand clusters accounted for 42.2% (643,977/1,526,012) and 29.74% (194,571/654,240) of the total HIVSTKPP, respectively. The HIVSTKPP rate in high-demand clusters (165.79 per 100,000) was 5.03-fold higher than in low-demand clusters (32.94 per 100,000). Compared with neighboring cities and provincial-controlled counties, those identified in high-demand clusters had 2.55 times more HIVSTKPP (relative risk=2.55; *P*<.001).

Table 5. General description of the high-risk and low-risk clusters identified by temporal-spatial clustering analysis between January 1, 2016, and December 31, 2019, in mainland China.

Cluster type	Time interval	Cluster center (latitude, longitude)	Radius (km)	Cities (N=366), n (%)	Provinces included (number of cities)	Purchasers (N=2,180,284), n (%)	Rate[a]	Relative risk	Log likelihood ratio	*P* value
High-risk cluster	January 1, 2018, to December 31, 2019	26.049704 N, 119.180295 E	731.09	75 (20.49)	Guangdong (15), Zhejiang (11), Jiangxi (11), Anhui (10), Fujian (9), Jiangsu (7), Hunan (6), Hubei (5), and Shanghai	643,977 (42.20)	165.79	2.55	171422.12	<.001
Low-risk cluster	January 1, 2016, to December 31, 2017	36.712360 N, 94.531065 E	1931.67	181 (49.45)	Xinjiang (24), Sichuan (21), Henan (18), Yunnan (16), Gansu (14), Hubei (12), Shanxi (11), Shaanxi (10), Guizhou (9), Qinghai (8), Hunan (7), Inner Mongolia (7), Tibet (7), Hebei (6), Ningxia (5), Guangxi (3), Shandong (2), and Chongqing	194,571 (29.74)	32.94	0.36	119468.41	<.001

[a] The rate of HIV self-testing kit purchasing per 100,000 population was calculated by dividing the number of purchasers by the total population in an area.

Spatiotemporal Patterns

We found that the spatiotemporal model with type IV interaction had the lowest deviance information criterion valve. Therefore, this was the best-fit model and was applied in our analysis (Table S3 in Multimedia Appendix 2). During the study period, the highest spatial relative risk was noted in Shenzhen city of Guangdong province, Hangzhou city of Zhejiang province, and Zhuhai city of Guangdong province (Figure 15). Precisely 37.2% (136/366) and 48.1% (176/366) of the cities and provincial-controlled counties were classified as hot spots (higher demand for HIVST kits) and cold spots (lower demand for HIVST kits), respectively (Figure 12D and Table S4 in Multimedia Appendix 2).

Spatial variations in adjusted relative risk (ARR; relative demand for HIVST kits) of spatiotemporal interaction effect from January 1, 2016, to December 31, 2019, are presented in Figure 16. The ARRs in each region between January 1, 2016, and December 31, 2019, varied slightly, and the higher ARR (higher demand for HIVST kits) continued to be applicable in municipalities, provincial capitals, and large cities.

Figure 15. Geographical distribution of relative risk of the spatial effect at city and provincial-controlled–county levels from January 1, 2016, to December 31, 2019, in mainland China through the best-fitting Bayesian spatiotemporal model.

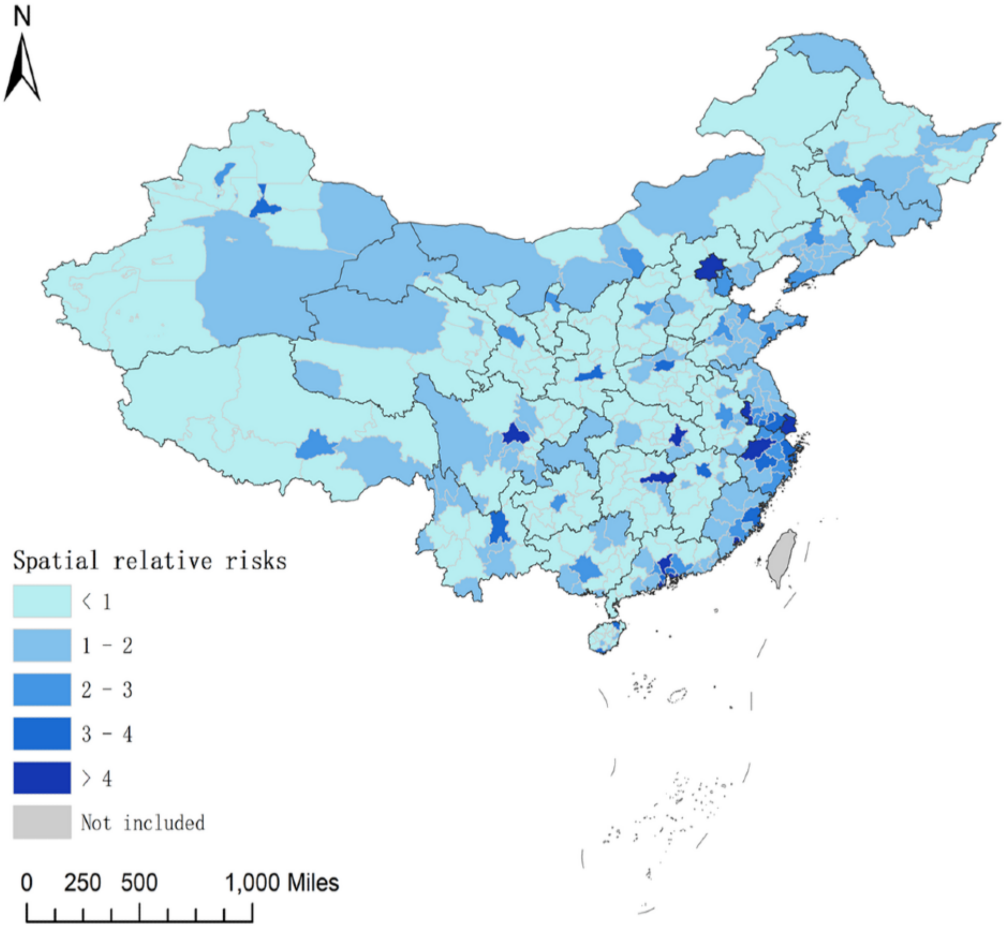
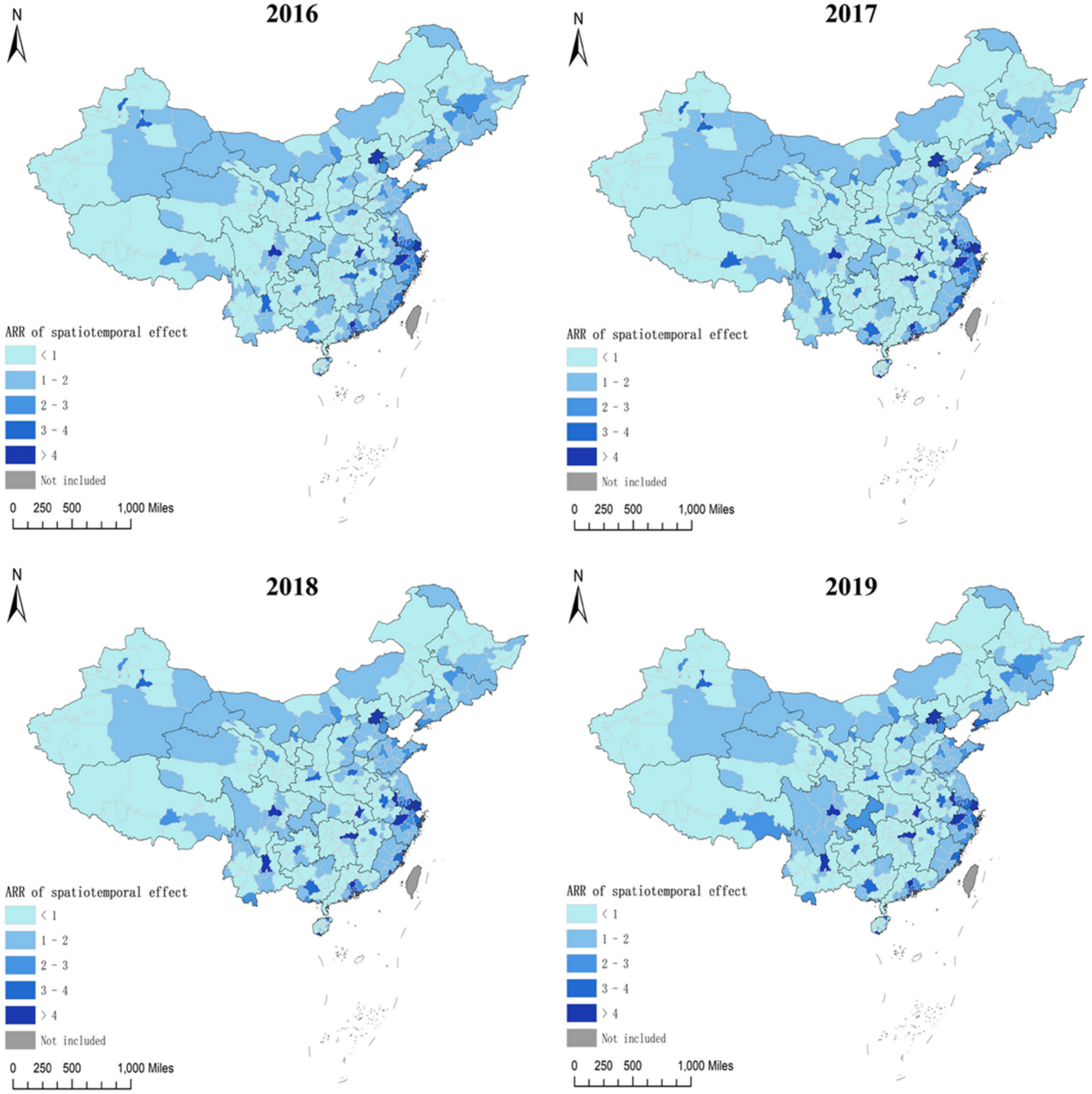


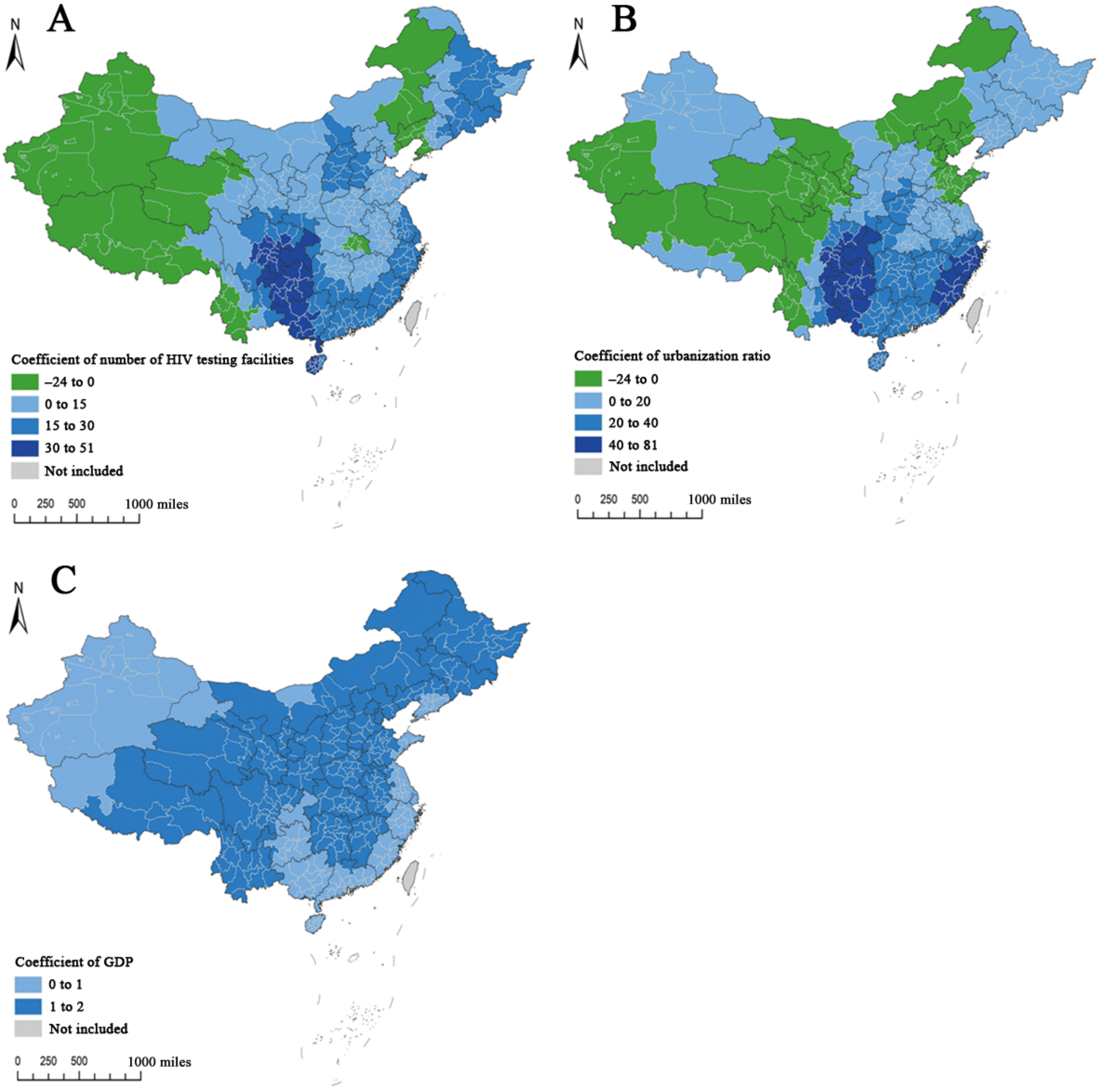
Figure 16. Geographical distribution of relative risk of the spatiotemporal interaction effect at city and provincial-controlled–county levels from January 1, 2016, to December 31, 2019, in mainland China through the best-fitting Bayesian spatiotemporal model. ARR: adjusted relative risk.



Correlates of HIVSTKPP

The SEM was found to be the most appropriate model for interpreting associations between city and provincial-controlled county–based factors and the HIVSTKPP (data not shown). The SEM results showed that the number of HIV testing facilities, urbanization ratio, and GDP per capita were positively associated with HIVSTKPP for the whole country, with the regression coefficients being 14.106, 11.236, and 1.057, respectively (all *P* values met the threshold for statistical significance; Table S5 in Multimedia Appendix 2). Notably, the geographically weighted regression model revealed a strong spatial heterogeneity in relationships between the HIVSTKPP and number of HIV testing facilities as well as urbanization ratio (Figure 17 and Table S6 in Multimedia Appendix 2). The number of HIV testing facilities and urbanization ratio were found to have a positive correlation with the HIVSTKPP in most cities (306/366, 83.6%, and 289/366, 79%, respectively). Cities with large positive correlations with the number of HIV testing facilities were concentrated in Sichuan and Guizhou provinces. In terms of urbanization ratio, cities with greater positive correlations were also predominantly in Sichuan and Guizhou provinces.

Figure 17. Geographical distribution of coefficients of the (A) number of HIV testing facilities, (B) urbanization ratio, and (C) gross domestic product (GDP) in the association with the number of the HIV self-testing kit–purchasing population at city and provincial-controlled–county levels in mainland China in 2019 through a geographically weighted regression model.



Discussion

Principal Findings

In this retrospective analysis of data involving 2.18 million anonymous persons in China who ordered 4.51 million HIVST kits on the web between January 1, 2016, and December 31, 2019, we identified key regions in which there was a larger demand for HIVST kits. Between January 1, 2016, and December 31, 2019, the size of the HIVSTKPP as well as HIVSTKPP rates increased across regions. High HIVSTKPP rates and hot spots identified by Bayesian spatiotemporal analysis were mainly located in large cities, provincial capitals, and municipalities. Spatial autocorrelation analysis identified high-high clusters and space-time cluster analysis identified higher-demand clusters that were predominantly in cities along China's southeast coast. The number of HIV testing facilities, urbanization ratio, and GDP per capita were correlated with larger HIVSTKPP for the whole country.

The Interpretation of the Temporal Distribution of the HIVSTKPP and Its Implication for HIV Prevention

We observed a steady increase in HIVST kit purchases over the 4-year study period. The growth in the size of the HIVSTKPP accelerated after 2017. This growth may have been prompted by the 13th Five-Year Plan for HIV Prevention and Control, which directed the CCDC and nongovernmental organizations to focus on promoting HIVST at the population level, including organizing a series of promotional activities for the *Nationwide HIV Testing and Consultation Month* program between November 20 and December 20 in both 2018 and 2019 to raise public awareness of HIV testing and promote active testing

[40,41]. Annual increases in the HIVSTKPP could also be explained by the fact that people are increasingly relying on web-based purchasing for their shopping generally, and HIVST kits are no different than other products. However, the numbers of HIV tests and of newly diagnosed people living with HIV in China did not show a similar rate of growth over the same period. The total number of HIV tests conducted in China was 169 million, 200.72 million, and 240.87 million in 2016, 2017, and 2018, respectively, which corresponded to annual growth rates of 18.77% in 2017 and 20% in 2018 [5]. The total number of newly diagnosed people living with HIV in China was 124,555, 134,512, and 148,589 in 2016, 2017, and 2018 respectively, which corresponded to annual growth rates of 7.99% in 2017 and 10.46% in 2018 [5]. Both were dwarfed by the increases in the HIVSTKPP in our study, with 0.64 million, 0.83 million, and 1.20 million in 2016, 2017 and 2018, respectively, which corresponded to annual growth rates of 29.80% in 2017 and 44.51% in 2018. The ranking of the size of the HIVSTKPP among 31 provinces was also different from those of HIV tests and newly diagnosed people living with HIV [5]. Although our study is not able to tease out whether the observed widespread and rapidly growing uptake of web-based purchase of HIVST kits is purely coming from a diffusion process of innovation or compounded with a worsening underlying epidemic, these phenomena confirm the potential existence of a previously unmet need in HIV prevention and control and highlight the urgent need for a novel strategy that links the HIVSTKPP to facility-based HIV testing and care.

The maximum monthly number of web-based purchases of HIVST kits occurs in December, which might indicate the effectiveness of public education campaigns that promote HIV testing on World AIDS Day (December 1). However, efforts to contain the epidemic should be in place throughout the year. Besides World AIDS Day, prevention campaigns may take place on a more frequent and regular basis.

The Interpretation of the Spatial Distribution of the HIVSTKPP and Its Implication for HIV Prevention

High HIVSTKPP rates and hot spots were identified in large cities, provincial capitals, and municipalities. The spatiotemporal distribution of the HIVSTKPP at local levels in our study provides policy makers with rare and valuable information about the number of people who are potentially in need of testing and treatment services. This may guide public health authorities to allocate resources, develop interventions, and deliver services.

Recent studies showed that HIV epidemic clusters among MSM spread from a few large cities in eastern China to most of the municipalities and provincial capitals countrywide between 2006 and 2015 [13]. HIV epidemic clusters among young people aged 15 to 24 years spread from southwestern China to central and northeastern China between 2005 and 2012 [14]. However, in our study, spatial clusters of the HIVSTKPP were mainly found in southeastern coastal cities between 2016 and 2019. Some studies showed that the majority of the HIVSTKPP reported that they had engaged in high-risk sexual behaviors in the last 6 months [12,42]. Thus, the web-based HIVST kit–purchasing behavior could largely indicate that recent high-risk sexual behavior may have been a factor in HIV acquisition, and the high-demand spatiotemporal cluster of the HIVSTKPP identified in our study could serve as an early warning sign for new HIV epidemics. Potential gaps in web-based HIVST kit–purchasing behavior and an HIV epidemic might exist and should be further identified by connecting and comparing our findings with these patterns of HIV epidemics in the same population and study period for a timely adjustment of the HIV prevention and control strategy.

The Interpretation of the Associations Between HIVST Kit Purchasing and Macroscopic Factors and Its Implication for HIV Prevention

Our SEM identified positive correlations between a region's number of HIV testing facilities, urbanization ratio, and GDP per capita and the HIVSTKPP. The number of HIV testing facilities was positively correlated with the size of the HIVSTKPP in 306 cities and provincial-controlled counties. Regions with larger numbers of HIV testing facilities may have higher levels of relevant health education, thus further promoting HIV testing. In addition, the urbanization ratio was positively associated with the size of the HIVSTKPP in 289 cities and provincial-controlled counties. The positive effect could be associated with the assumption that the increase in the proportion of the urban population may promote social networking and sexually risky behaviors (eg, multiple sexual partners, unprotected sex behaviors, and commercial sexual behaviors) [28], thus leading to an increase in the demand for HIVST kits. GDP per capita did not have an important role to play with regard to the size of the HIVSTKPP, and its effect varies slightly across regions. Thus, the spatial patterns of the HIVSTKPP could be largely explained by the spatial variation in the number of HIV testing facilities and urbanization ratio.

Our study shows more HIVST kit purchases in areas with greater access to HIV testing centers and more urbanization. For areas currently lacking adequate access to HIV testing, especially areas bearing heavy HIV burdens (eg, rural provinces such as Tibet, Sichuan, Guizhou, and Guangxi) [1,5,43], our study also found that there were few web-based HIVST kit purchases. Thus, public education campaigns that promote web-based HIVST kit purchases at the population level are urgently required to expand HIV testing as well as HIV prevention and control programs in these areas.

Comparison With Prior Work

To the best of our knowledge, this study is the first to evaluate the spatiotemporal patterns of the HIVSTKPP. Monitoring HIVST kit purchasing patterns could be a new tool for public health policy makers, researchers, and program implementers to reallocate resources, promote HIVST uptake, and optimize the HIV care continuum.

Limitations

Our study includes several limitations. First, although sales records from a leading e-commerce platform in China were included in our study, we did not include records from all e-commerce platforms, HIV clinics, hospitals, offline pharmacies, and CCDC offices. The sample in our study does not represent the entire HIVSTKPP in China, and HIVSTKPP rates are underestimated in our analysis. Our findings should be interpreted with caution, and further research that involves collecting data from all potential sources of HIVST kits is needed. Second, we could not quantitatively assess associations between the HIVSTKPP and HIV epidemiological data to identify potential gaps in current HIV-monitoring practices in China. In addition, we could not compare our findings with national CCDC data about new HIV diagnoses that were first screened using self-testing because these data were not publicly available, and we have no access to these data. Third, we could not evaluate the spatial patterns of the HIVSTKPP in finer geographic units (eg, street level). Finally, many sex workers, including male sex workers, could have purchased HIVST kits on the web in bulk at the end of the day. However, our study did not include the records of bulk purchases for analysis.

Conclusions

Our study provides an understanding of the spatiotemporal patterns of the HIVSTKPP in mainland China, which can inform the development of national and local HIVST guidelines in allocating resources and promoting HIV testing. The development of contextualized prevention and intervention strategies tailored to the HIVSTKPP in key regions identified from our study is urgently required for HIV prevention and control. Further research combining the spatiotemporal patterns of HIVST with HIV epidemiological data is needed to identify potential gaps in current HIV-monitoring practices and develop comprehensive HIV control strategies.

Acknowledgments

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Authors' Contributions

HZ and GL conceived the study design. GL participated in literature search, data cleaning, statistical analysis, creating the tables, plotting the graphics, interpreting the study findings, and manuscript writing. LS, GL, AF, and YFL participated in data collection. HZ and MH are responsible for the overall content. All authors critically reviewed and substantively revised the manuscript. All authors have approved the final version of the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Details of the statistical analysis.
[DOCX File , 46 KB - publichealth_v8i10e35272_app1.docx]

Multimedia Appendix 2
Detailed results (Tables S1-S6) of spatiotemporal analysis of the HIV self-testing kit–purchasing population (HIVSTKPP) from January 1, 2016, to December 31, 2019 in mainland China.
[DOCX File , 27 KB - publichealth_v8i10e35272_app2.docx]

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Abbreviations

AAPC: average annual percentage change
ARR: adjusted relative risk
CCDC: Chinese Center for Disease Control and Prevention
GDP: gross domestic product
HIVST: HIV self-testing
HIVSTKPP: HIV self-testing kit–purchasing population
MSM: men who have sex with men
SEM: spatial error model

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Original Paper

The Epidemiological Characteristics of Noncommunicable Diseases and Malignant Tumors in Guiyang, China: Cross-sectional Study

Qibing Zeng[1], PhD; Jingyuan Yang[1], PhD; Ziyun Wang[1], PhD; Haiyan Liu[1], MD; Junhua Wang[1], MD; Tingting Yang[1], MD; Jin Hu[1], MD; Han Guan[1], MD; Yun Lu[1], MD; Huijuan Liu[1], PhD; Feng Hong[1], PhD

The Key Laboratory of Environmental Pollution Monitoring and Disease Control, Ministry of Education & School of Public Health, Guizhou Medical University, Guiyang, China

Corresponding Author:
Feng Hong, PhD
The Key Laboratory of Environmental Pollution Monitoring and Disease Control
Ministry of Education & School of Public Health
Guizhou Medical University
Huayan Rd
Huaxi District
Guiyang, 550031
China
Phone: 86 851 8841 6175
Email: fhong@gmc.edu.cn

Abstract

Background: Studies that address the changing characteristics of diseases are of great importance for preventing and controlling the occurrence and development of diseases and for improving health. However, studies of the epidemiological characteristics of noncommunicable diseases (NCDs) and malignant tumors (MTs) of the residents in Guiyang, China, are lacking.

Objective: The aim of this study was to evaluate the prevalences of NCDs and MTs in residents of Guiyang, Guizhou Province, China, and analyze differences among ages, genders, and regions.

Methods: A multistage stratified cluster sampling method was used. Based on the inclusion and exclusion criteria, 81,517 individuals were selected for the study. Of these, 77,381 (94.9%) participants completed the study. Structured questionnaires were used to collect information on demographic characteristics, NCDs, and MTs. The chi-square test (with 95% confidence intervals) was used to analyze differences in disease prevalence among genders, ages, and geographical regions.

Results: The major chronic NCDs of Guiyang residents are obesity, hypertension, and diabetes. MTs in women are mostly breast cancer, cervical cancer, and endometrial cancer, whereas in men, MTs are mainly lung cancer, rectal cancer, and gastric cancer. The prevalences of hypertension and diabetes in women are higher than in men, but the prevalences of lung cancer and gastric cancer in men are higher than in women. The epidemiological characteristics of individuals in different life stages are dissimilar. In terms of regional distribution, the prevalences of the above diseases in the Baiyun and Yunyan districts of Guiyang are relatively high.

Conclusions: Several NCDs (obesity, hypertension, and diabetes) and MTs (women: breast cancer, cervical cancer, and endometrial cancer; men: lung cancer, rectal cancer, and gastric cancer) should be the focus for the prevention and control of chronic diseases in the future. In particular, the Baiyun and Yunyan districts of Guiyang are the important regions to emphasize.

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KEYWORDS

epidemiological characteristics; noncommunicable diseases; malignant tumors; cross-sectional study; Guiyang

Introduction

Noncommunicable diseases (NCDs) are a general term for a class of diseases with insidious onset, long course, and complex etiology—some of which have not been fully confirmed. NCDs are some of the main health challenges of the 21st century, posing a great threat to human survival and economic development [1,2]. Epidemiological studies have shown that

NCDs are on the rise in low-income countries and have led to higher mortality rates in these countries [3,4]. According to incomplete statistics, NCDs now account for more than one-half of the global burden of disease [5]. In 2020, NCDs were estimated to account for 80% of the global disease burden and 7 out of 10 deaths in low- and middle-income countries [6]. Therefore, the prevention and control of the pandemic of chronic NCDs has become a major scientific issue that needs urgent solutions to allow sustainable development while reducing disease burden in countries around the world [7-10].

Disease prevention is the most important means for promoting the health of the population, and although its purpose is to eliminate diseases, if diseases cannot be eliminated, disease prevention can still minimize the harm of diseases to the human body, thereby ensuring and improving the health of the population, social progress, and economic sustainability and continuous development [11]. However, in determining how to effectively implement disease prevention and control measures, the most critical issue is to grasp the epidemiology and characteristics of diseases in the population, among which disease spectrum investigation is one of the most important ways for exploring the prevalence of diseases [12].

Guiyang is one of the most distinctive regions in Southwest China, with highly heterogeneous genetic variation, cultural background, socioeconomic status, and geographical environment. With the continuous development of the economy and the increasing enrichment of lifestyle, the problem of resident disease burden has received continuous attention. However, studies of the epidemiological characteristics of NCDs and malignant tumors (MTs) of the residents in Guiyang, China, are lacking. The aim of this study was to evaluate the prevalences of NCDs and MTs in Guiyang, China, and analyze differences among ages, genders, and regions. To our knowledge, this is the first study of its kind. The study findings will aid the government in developing cost-effective and targeted local resource allocation and other preventive health policies that address NCDs, MTs, and related health inequities.

Methods

Study Participants

We conducted a cross-sectional study in Guiyang, China, from January 2017 to December 2017. We worked with the local centers for disease control and prevention, clinical centers, and local government to recruit volunteers. According to economic, geographical, population, and other factors in combination with the sample size requirement of the study design, a total of 81,517 individuals were selected as study participants by multistage stratified cluster sampling. Based on data from China's sixth census, the number of people in this study accounted for 3.52% of the population of the sampling area and 1.88% of the total population of Guiyang. The specific sampling method, the distribution of study participants, and the on-site investigation procedure are detailed in Multimedia Appendices 1-3, respectively.

Study selection criteria were as follows: (1) informed consent was received from the participant; and (2) the participant belonged to the permanent population of Guiyang, China (defined as either a member of the migrant population who lived in the city for 6 of the past 12 months or a member of the local population who has been away from the city for less than 12 months). Individuals in different stages of life were eligible, as there were no specific age requirements for study participation. Study exclusion criteria were (1) inability to provide a unique national identity card, (2) presence of a severe physical or mental illness (such as schizophrenia or bipolar disorder), and (3) refusal to comply with research requirements.

Ethics Approval

The content, protocol, informed consent, and recruitment materials of this study were approved by the ethics committee of the affiliated hospital of Guizhou Medical University (NO.2017ER67). Written informed consent was obtained from all participants before data collection.

Questionnaire Interview

A structured questionnaire was used to record information about demographic factors, health behavior, and the disease history of the participants (see more details in Multimedia Appendix 4). The information was collected during a face-to-face interview, conducted by well-trained interviewers recruited from students with a medical background at Guizhou Medical University. The specific procedure and methods of the questionnaire interview are detailed in Multimedia Appendices 1 and 4, respectively.

We also instituted a series of quality control measures including designing logical constraints into the questionnaire to avoid errors in logic, noting the time spent on each questionnaire, and randomly sampling questionnaire responses on the interview day to evaluate the data quality (ie, the sampling plan ensured that each interviewer had at least been sampled once). Questionnaires that were classified as unqualified were excluded from the final analysis.

Clinical Examination

We conducted medical examinations of the participants using mainly the resources and personnel at local clinical centers. To unify the data standards across different sites, we implemented a standardized training program for doctors and nurses before the study began.

Physicians at local clinical centers performed physical examinations (including measurements of height, weight, blood pressure, waist circumference, and hip circumference) and clinical examinations and determined diagnoses. The specific methods of the physical examinations are detailed in the Multimedia Appendix 1. Except for self-declaration by the participants, all disease information must have been recorded in the local health management system, or the participants could present a hospital diagnosis certificate to confirm the diagnosis.

According to the health industry standard of the People's Republic of China "criteria of weight for adults" (WS/*t* 428-2013) [13], all participants were stratified into 1 of 4 groups: underweight (BMI<18.5), normal weight (18.5≤BMI<24.0), overweight (24.0≤BMI<28.0), or obese (BMI≥28.0).

Statistical Analysis

EpiData software (version 3.0; EpiData Association) was used to input the data. Statistical analysis (including prevalence and chi-square test) was performed using SPSS statistical software (version 22.0; IBM Corp). Pearson chi-square test (T≥5), continuity-adjusted chi-square test (1≤T<5), and Fisher exact test (T<1) were used to analyze differences in the prevalences of chronic NCDs or MTs in different genders and various age groups. Choropleth maps were produced within a geographic information system to visually examine geographical variations in the prevalences of chronic NCDs and MTs across Guiyang. Data illustrated in the choropleth maps were median prevalence estimates with 95% confidence intervals calculated from unadjusted logistic regressions. A threshold of *P*<.05 was set to determine any significant differences between the averages.

Results

Characteristics of the Study Participants

At the end of the study, a total of 77,381 (94.9%) participants of the original 81,517 selectees had completed the standardized, full-course questionnaire interview and clinical examination. The characteristics of the study participants are presented in Table 1.

Table 1. Characteristics of the study participants (n=77,381).

Characteristic	Participant, n (%)
Area (n=77,381)	
Yunyan district	29,479 (38.1)
Baiyun district	11,262 (14.55)
Wudang district	12,808 (16.55)
Xiuwen county	10,243 (13.24)
Qingzhen city	13,589 (17.56)
Age (years; n=77,292)[a]	
0-19	18,263 (23.63)
20-29	10,330 (13.36)
30-39	11,139 (14.41)
40-49	11,951 (15.46)
50-59	10,000 (12.94)
60-69	8569 (11.09)
≥70	7045 (9.11)
Gender (n=77,369)[a]	
Male	37,492 (48.46)
Female	39,877 (51.54)
Ethnicity (n=77,334)[a]	
Han	65,205 (84.32)
Buyi	4108 (5.31)
Miao	2678 (3.46)
Dong	517 (0.67)
Yi	873 (1.13)
Chuanqing	1433 (1.85)
Other	2520 (3.26)
Education (n=77,338)[a]	
Illiterate or semiliterate	20,447 (26.44)
Primary school	14,577 (18.85)
Middle school	21,291 (27.53)
High school	6618 (8.56)
Technical secondary school or secondary vocational technical school	4270 (5.52)
Junior college	5008 (6.48)
Bachelor’s degree or above	5127 (6.63)
Occupation (n=77,261)[a]	
Unemployed	13,075 (16.92)
Farmer	16,095 (20.83)
Civil servant	1080 (1.4)
Medical staff	977 (1.26)
Teacher	1023 (1.32)
Active serviceman	74 (0.1)
Policemen	135 (0.17)

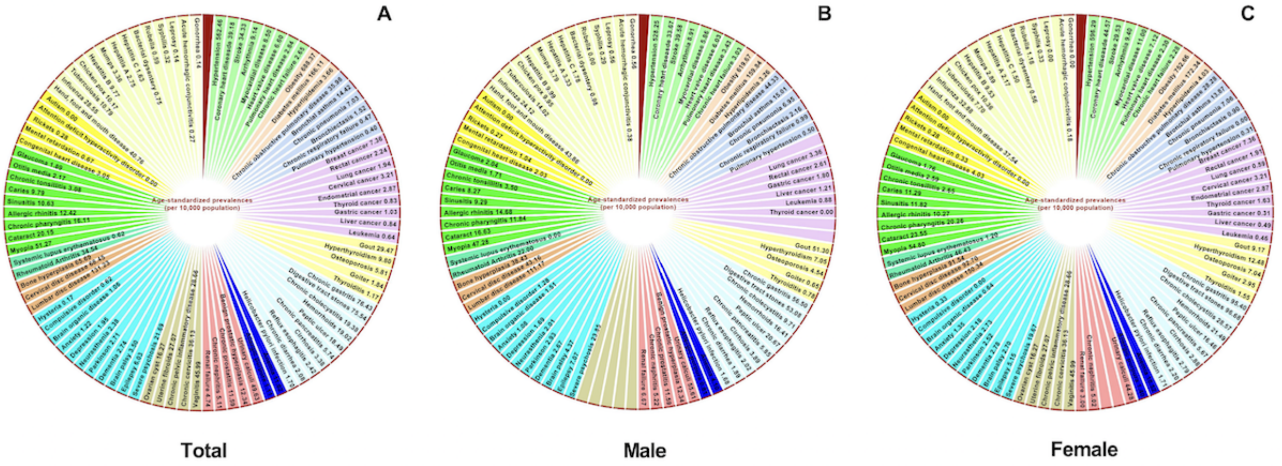
Characteristic	Participant, n (%)
Private or individual business operator	7823 (10.13)
Worker	2646 (3.42)
Driver	1003 (1.3)
Retired staff	7957 (10.3)
Student	9802 (12.69)
Child	8057 (10.43)
Other	7514 (9.73)
Marital status (n=77,271)[a]	
Unmarried	23,877 (30.9)
Married	47,343 (61.27)
Divorced	1662 (2.15)
Widowed	3652 (4.73)
Cohabitation	595 (0.77)
Other	142 (0.18)
Migrant worker (n=77,294)[a]	
Yes	8409 (10.88)
No	68,885 (89.12)

[a] The missing values for age, gender, ethnicity, education, occupation, marital status, and migrant worker are 89, 12, 47, 43, 120, 110, and 87, respectively.

Epidemiological Characteristics of Diseases

The epidemiological characteristics of diseases among residents in Guiyang, China, are shown in Figure 1 and Multimedia Appendices 5-6. The main diseases of residents are chronic NCDs, but there are still local epidemics of infectious diseases, such as hand, foot, and mouth disease. Based on our study findings in the natural population, the common NCDs in Guiyang residents are ranked from the most to least prevalent as follows: obesity, hypertension, diabetes mellitus, lumbar disc disease, chronic gastritis, digestive tract stones, cervical disc disease, bone hyperplasia, myopia, and urinary calculi. MTs in women are mostly breast cancer, cervical cancer, and endometrial cancer, whereas those in men are mainly lung cancer, rectal cancer, and gastric cancer.

Figure 1. Epidemiological characteristics of diseases in Guiyang, China. All data are presented as age-standardized prevalence with 95% CIs (per 10,000 people). (A) Epidemiological characteristics of diseases. (B) Epidemiological characteristics of diseases in men. (C) Epidemiological characteristics of diseases in women. Higher-resolution version of this figure is available in Multimedia Appendix 7.



Total

Male

Female

Gender Distribution Characteristics of NCDs and MTs

Table 2 shows the gender distribution characteristics of the top NCDs and MTs in Guiyang, China. Compared to women, the prevalences of obesity, hypertension, lumbar disc disease, chronic gastritis, digestive tract stones, cervical disc disease, and bone hyperplasia in men were significantly lower (all $P<.001$). However, the prevalence of urinary calculi in men was significantly higher than in women ($P=.03$). For MTs, the prevalence of thyroid cancer in women was higher than in men ($P=.049$), but prevalences of lung cancer and gastric cancer were lower in women than in men (*P*=.003 and *P*=.03, respectively). The disease rankings of NCDs and MTs in different genders are shown in Multimedia Appendices 8-9.

Table 2. Gender distribution characteristics of noncommunicable diseases and malignant tumors in residents of Guiyang, China. All data are presented as prevalence with 95% CIs (per 10,000 people).

Characteristic	Female, prevalence (95% CI)	Male, prevalence (95% CI)	*P* value
Noncommunicable disease			
Obesity	752.66 (726.55-778.77)	619.57 (595.00-644.34)	<.001
Hypertension	596.29 (573.04-619.53)	528.25 (505.61-550.90)	<.001
Diabetes mellitus	172.34 (159.57-185.11)	159.84 (147.15-172.54)	.17
Lumbar disc disease	150.34 (138.40-162.29)	111.17 (100.55-121.78)	<.001
Chronic gastritis	95.40 (85.86-104.94)	56.50 (48.91-64.08)	<.001
Digestive tract stones	96.68 (87.08-106.29)	53.08 (45.72-60.43)	<.001
Cervical disc disease	92.70 (83.29-102.11)	43.16 (36.20-48.56)	<.001
Bone hyperplasia	91.54 (82.19-100.89)	38.43 (30.70-46.13)	<.001
Myopia	54.80 (47.56-62.05)	47.28 (40.34-54.22)	.13
Urinary calculi	44.28 (39.31-54.04)	55.61 (48.08-63.14)	.03
Malignant tumor			
Lung cancer	0.59 (0.00-1.35)	3.36 (1.51-5.22)	.003
Gastric cancer	0.31 (0.00-0.86)	1.80 (0.44-3.16)	.03
Liver cancer	0.49 (0.00-1.18)	1.21 (0.10-2.32)	.22
Rectal cancer	1.91 (0.55-3.26)	2.61 (0.97-4.24)	.55
Thyroid cancer	1.63 (0.37-2.88)	0.00 (0.00-0.00)	.049
Leukemia	0.46 (0.00-1.12)	0.88 (0.00-1.82)	.61

Age Distribution Characteristics of NCDs and MTs

The age distribution characteristics of diseases in Guiyang, China, are shown in Multimedia Appendices 8-10. The results clearly show that the spectrum of disease varies widely across age groups. Obesity (prevalence per 10,00 people: 385.69, 0-19 years; 462.58, 20-29 years; and 719.76, 30-39 years) and myopia (prevalence per 10,000 people: 60.78, 0-19 years; 84.22, 20-29 years; and 102.34, 30-39 years) are more common in people aged <40 years. The prevalences (per 10,000 people) of obesity (872.88, 40-49 years; 966.21, 50-59 years; 893.25, 60-69 years; and 869.43, ≥70 years); hypertension (467.74, 40-49 years; 1375.00, 50-59 years; 2556.89, 60-69 years; and 3730.31, ≥70 years); diabetes (150.62, 40-49 years; 477.00, 50-59 years; 718.87, 60-69 years; and 905.61, ≥70 years); and lumbar disc herniation (200.82, 40-49 years; 343.00, 50-59 years; 418.95, 60-69 years; and 420.16, ≥70 years) were higher in the age groups ≥40 years, and the prevalences increased with age except obesity. In the older adult population, in addition to the above diseases, coronary heart disease (162.21, 60-69 years and 445.71, ≥70 years, per 10,000 people); lumbar disc herniation (418.95, 60-69 years and 445.71, ≥70 years, per 10,000 people); and bone hyperplasia (324.43, 60-69 years and 363.38, ≥70 years, per 10,000 people) have gradually become the main diseases that threaten health. Hand, foot, and mouth disease (161.53 per 10,000 people) mainly occurs in school-age children. The analysis of the age distribution characteristics of the top 10 MTs in the study results showed that the prevalence of MTs was significantly different with increasing age (all *P*<.001).

Regional Distribution Characteristics of NCDs and MTs

Figure 2 shows the regional distribution characteristics of the common NCDs in Guiyang, China. From the statistics for single diseases, obesity is the disease with the highest prevalence in each district and county, followed by hypertension. Diabetes is the third most common of the NCDs in the Yunyan district of Guiyang, and lumbar disc herniation is most common in other districts. The high prevalence areas of hypertension and diabetes are mainly concentrated in the Baiyun and Yunyan districts and in Qingzhen county-city. Wudang and Huaxi districts and the counties of Xifeng and Kaiyang have lower prevalences of the abovementioned NCDs. As illustrated in Figure 3, Baiyun and Yunyan districts were the main high-prevalence areas of MTs, whereas the 4 regions of Xifeng (county), Kaiyang (county), Huaxi (district), and Qingzhen (county-city) had lower prevalences of MTs. The prevalences of lung cancer and breast cancer in Baiyun district are higher than in other districts or in counties, and the prevalences of rectal cancer, liver cancer, and cervical cancer are also higher in this area. The highest prevalence of MTs in Yunyan district is rectal cancer, and the prevalence of endometrial cancer is higher than in other districts or counties.

Figure 2. Regional distribution characteristics of noncommunicable diseases in Guiyang, China. Data illustrated in the choropleth maps are median prevalence estimates calculated from unadjusted logistic regressions. Higher-resolution version of this figure is available in Multimedia Appendix 7.

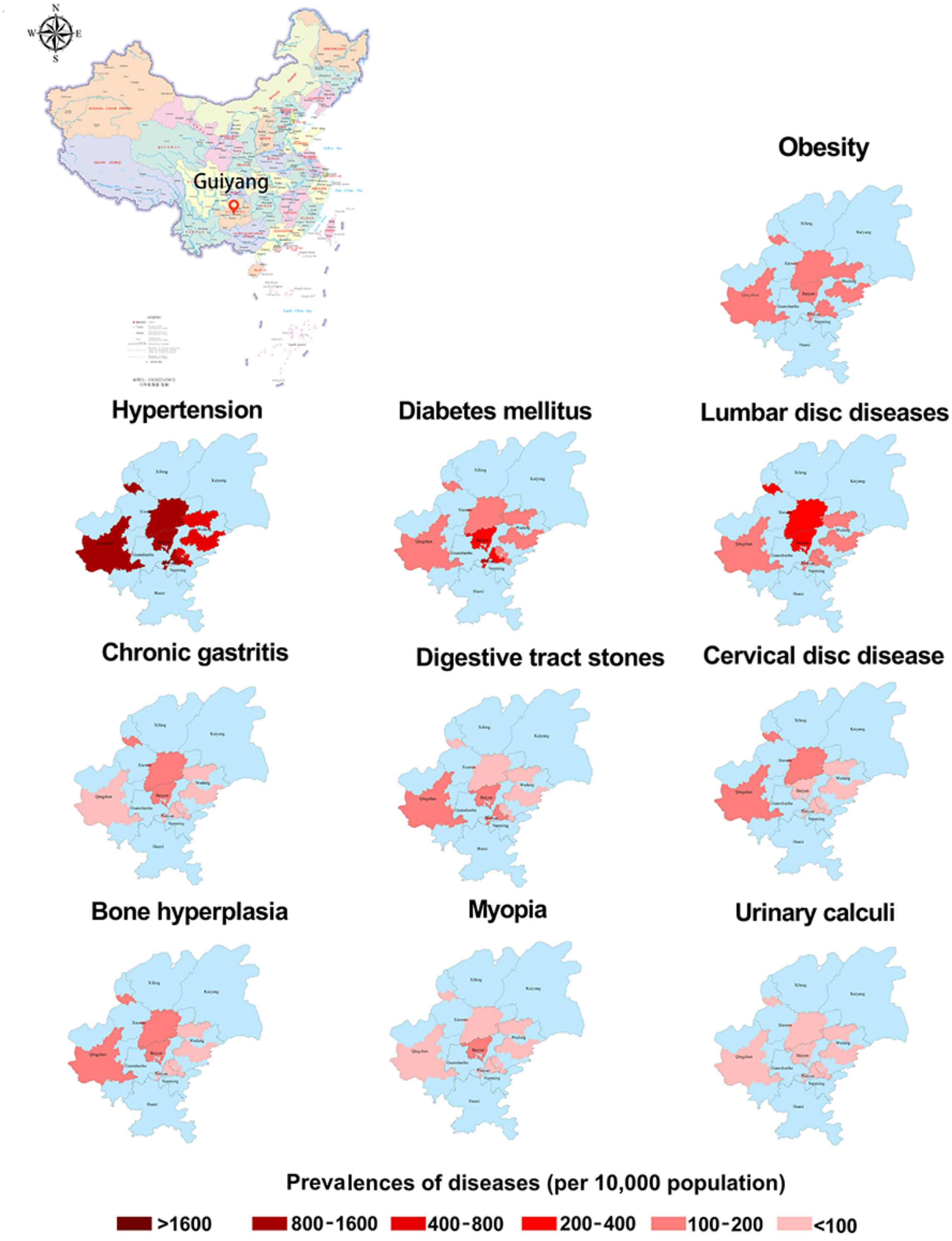
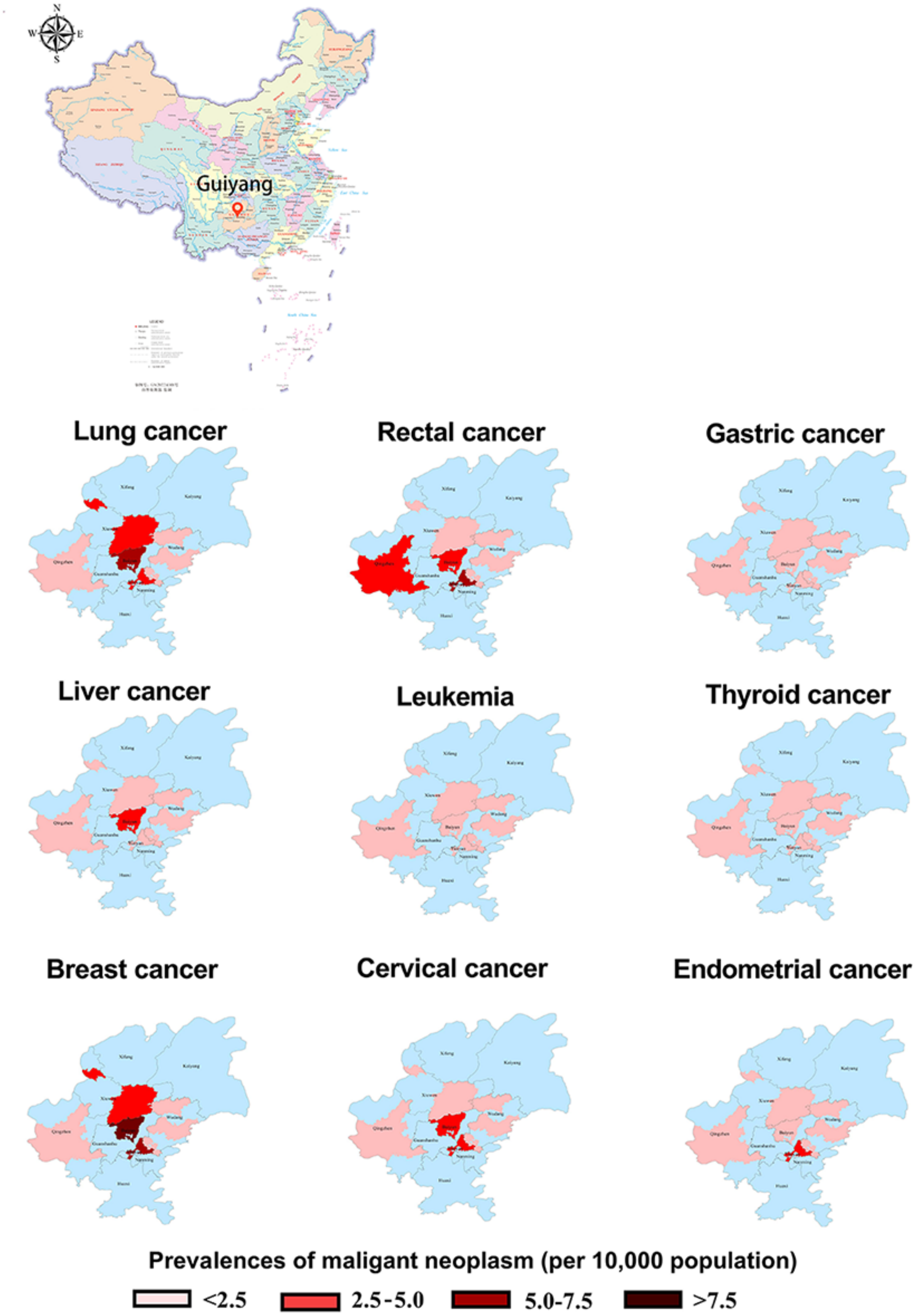


Figure 3. Regional distribution characteristics of malignant tumors in Guiyang, China. Data illustrated in the choropleth maps are median prevalence estimates calculated from unadjusted logistic regressions. Higher-resolution version of this figure is available in Multimedia Appendix 7.



Discussion

Principal Findings

According to the latest statistics from the World Health Organization, in 2019, among the top 10 causes of death, 7 were NCDs; the total number of deaths from the 4 major NCDs was 33.2 million, including cardiovascular disease (17.9 million), cancer (9.3 million), diabetes (2 million), and chronic respiratory diseases (2.1 million) [14]. NCDs pose the greatest threat to human health in the modern world. From the perspective of the overall disease epidemiological characteristics, our study results show that the main diseases of residents in Guiyang are chronic NCDs, but there are still local epidemics of infectious diseases. These results are similar to those reported in other parts of the world [15-17]. From the perspective of population distribution characteristics, the epidemiological characteristics of diseases vary for different genders, ages, and regions. To effectively improve the health of the population, especially for people in different life stages, our findings suggest that disease prevention work should be targeted to different groups of people and that measures should be adapted to local conditions.

To better elucidate the epidemiological characteristics of NCDs among residents in Guiyang, the ranking of different diseases was analyzed based on standardized prevalences. The results demonstrated that obesity, hypertension, and diabetes mellitus are the top 3 NCDs in Guiyang. According to the latest estimates, 6.8% of children and adolescents (aged 5-19 years) worldwide were obese in 2016 [18]. Among adults aged ≥18 years, the age-standardized prevalence of obesity ranged from 4.7% in the Southeast Asia region to 28.6% in the region of the Americas [19]. Our results indicate that the prevalence of obesity is 6.88% for the entire population and 3.86% for the 0-20–year-old population. Globally, 59% of women and 49% of men with hypertension reported a previous diagnosis of hypertension in 2019 [20]. Our results are much lower than the world average, with a prevalence of hypertension of 5.96% in men and 5.28% in women. Although the global adult diabetes prevalence increased from 4.7% in 1980 to 8.5% in 2014 [21], the prevalence of diabetes in Guiyang remains low at 1.66%.

These findings are relatively encouraging—that the prevalences of NCDs and MTs in Guiyang are low. We speculate that the possible reasons are closely related to the good ecological environment and good air quality in Guiyang. A recent study of air pollution in Southwest China showed that the 3-year averages of particulate matter $(PM)_1$, $PM_{2.5}$, PM_{10}, and NO_2 in Guizhou were 26.3, 34.9, 56.2, and 22.0 $\mu g \cdot m^{-3}$, respectively, which were significantly lower than those in the municipality of Chongqing and Sichuan province [22]. Air pollution is significantly associated with NCDs [5]. However, overweight and obesity are major risk factors for NCDs such as cardiovascular disease, diabetes, and some cancers [23]. Moreover, hypertension and diabetes are the leading causes of death worldwide [6]. Therefore, strengthening health management and reasonably controlling weight, blood pressure, and blood glucose are still effective measures for preventing NCDs in Guiyang.

Our results demonstrate that MTs in women are mostly breast cancer, cervical cancer, and endometrial cancer, whereas in men, they are mainly lung cancer, rectal cancer, and gastric cancer. It is exciting to note that the prevalences of these tumors are significantly lower than the average age-standardized prevalence in the world (222 per 100,000) and China (225.4 per 100,000) [2]. Moreover, our MT findings appear to be at odds with the latest research reports around the world, as the latest cancer statistics [2] show that there is no gastric cancer among the top 10 most common MTs in men and no cervical cancer among the top 10 most common MTs in women. Previous studies [24,25] have shown that diet is closely related to the occurrence of gastric cancer, and a low-sodium diet can significantly reduce the incidence of gastric cancer. Several studies [26,27] have also found that human papillomavirus (HPV) infection is significantly associated with cervical cancer, and a small number of studies [28,29] have also revealed a high HPV infection rate among women in Guizhou. These studies suggest that the high rankings of gastric cancer and cervical cancer in Guiyang may be related to high-sodium diet and high HPV infection rate, respectively, in Guizhou. Therefore, implementing targeted preventive measures, such as disease screening and health education, for the high-risk groups for these key diseases may effectively control and prevent the occurrence of these diseases.

From a regional perspective on the prevalences of NCDs and MTs in Guiyang, the results clearly show that the prevalences of NCDs and MTs are relatively high in Yunyan district, Baiyun district, and other areas in central and western Guiyang. High population density, as well as rapid industrial and economic development are typical features of the Baiyun and Yunyan regions. These booming conditions may inevitably increase pollution sources and pollution loads, which may be the main reason for the high incidences of NCDs and MTs in these regions. Taking air pollution as an example, although air pollution affects people in all regions, all ages, and all social groups, it is likely to cause greater disease for those with high exposure and high susceptibility [30]. A previous study showed that from 1990 to 2019, the age-standardized mortality rate of cancer caused by $PM_{2.5}$ had the highest increase [31], which may explain the high incidence of lung cancer in the Baiyun and Yunyan areas, because these areas are industrially developed areas in Guiyang, especially the nonferrous metal industry. Therefore, for the future in Guiyang, the management of populations in key areas should also be the focus of the prevention and control of NCDs and MTs. In addition, lifestyle choices, including smoking, drinking, sleeping, and eating habits, are related to the prevalence of many chronic diseases and MTs; regular physical exercise can reduce the occurrence of these diseases [32,33]. Therefore, actively advocating a healthy lifestyle, especially health education for high-risk groups, is an effective means for preventing disease.

Strengths, Limitations, and Policy Recommendations

A strength of our study is that this is the first time the epidemiological characteristics of NCDs and MTs in Guiyang, China, were evaluated. Another strength is that we used a large-sample cross-sectional study. Our study also has limitations. Although we obtained the epidemiological characteristics of NCDs and MTs in Guiyang, including age, gender, and region, this study lacks comparison with previous baseline study data. In addition, we did not analyze possible factors that may underlie the high prevalences of NCDs and MTs, such as climate, air pollution, diet, lifestyle, and behavior. In addition, our study design required that the diagnosis of a specific disease was based on a clear medical history or a hospital diagnosis certificate. Thus, our study may have missed some patients, resulting in a slight underestimation of the prevalence and actual situation of a particular disease. Nevertheless, our study findings still have guiding significance for the epidemiology of diseases in Guiyang. Based on the current research results, the following policy recommendations are proposed: (1) combining high-risk groups with whole-population strategies to promote disease prevention; (2) strengthening multidepartmental collaboration and whole-society participation in health promotion, such as reducing unhealthy lifestyles and encouraging exercise; (3) making disease screening of key high-risk groups the starting point for improving the ability and efficiency of secondary prevention of diseases; (4) strengthening health education and actively guiding residents to use health services rationally; and (5) innovating the management of chronic diseases and improving the registration management of cancer patients.

Conclusions

Overall, our study provides some evidence that several NCDs (obesity, hypertension, and diabetes) and MTs (women: breast cancer, cervical cancer, and endometrial cancer; men: lung cancer, rectal cancer, and gastric cancer) should be the focus for the prevention and control of chronic diseases in Guiyang in the future. In particular, the Baiyun and Yunyan districts of Guiyang, China, are the important regions to emphasize. The findings of this study may be of great value for preventing and controlling the occurrence and development of key chronic NCDs and MTs in Guiyang, as well as for improving the health of both urban and rural residents. Furthermore, our study results may aid decision makers in formulating more reasonable and effective resource allocation; preventive health policies; and solutions for NCDs, MTs, and related health inequalities.

Acknowledgments

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Data Availability

The data sets generated during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Authors' Contributions

JY, ZW, Haiyan Liu, JW, TY, JH, HG, and YL performed the epidemiological investigation and clinical examination. Huijuan Liu wrote the manuscript. QZ made major contributions to data acquisition and analysis and to the writing of the manuscript. FH made substantial contributions to the conception and design of the study. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary methods.
[PDF File (Adobe PDF File), 241 KB - publichealth_v8i10e36523_app1.pdf]

Multimedia Appendix 2
Distribution of the study participants.
[PDF File (Adobe PDF File), 125 KB - publichealth_v8i10e36523_app2.pdf]

Multimedia Appendix 3
The on-site investigation procedure.
[PDF File (Adobe PDF File), 255 KB - publichealth_v8i10e36523_app3.pdf]

Multimedia Appendix 4
Summary of measurements at the baseline survey.
[PDF File (Adobe PDF File), 96 KB - publichealth_v8i10e36523_app4.pdf]

Multimedia Appendix 5
The ranking of the top noncommunicable diseases (NCDs) in Guiyang, China.
[PDF File (Adobe PDF File), 2431 KB - publichealth_v8i10e36523_app5.pdf]

Multimedia Appendix 6
The ranking of the top malignant tumors (MTs) in Guiyang, China.
[PDF File (Adobe PDF File), 1980 KB - publichealth_v8i10e36523_app6.pdf]

Multimedia Appendix 7
Higher resolution versions of Figures 1-3.
[PDF File (Adobe PDF File), 3470 KB - publichealth_v8i10e36523_fig.pdf]

Multimedia Appendix 8
Age distribution characteristics of diseases in Guiyang, China.
[PDF File (Adobe PDF File), 1504 KB - publichealth_v8i10e36523_app8.pdf]

Multimedia Appendix 9
The prevalence of the top noncommunicable diseases (NCDs) in Guiyang, China, in different life cycles.
[PDF File (Adobe PDF File), 2912 KB - publichealth_v8i10e36523_app9.pdf]

Multimedia Appendix 10
The prevalence of the top malignant tumors (MTs) in Guiyang, China, in different life cycles.
[PDF File (Adobe PDF File), 1593 KB - publichealth_v8i10e36523_app10.pdf]

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Abbreviations

HPV: human papillomavirus
MT: malignant tumor
NCD: noncommunicable disease
PM: particulate matter

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Original Paper

Key Population Size Estimation to Guide HIV Epidemic Responses in Nigeria: Bayesian Analysis of 3-Source Capture-Recapture Data

Anne F McIntyre[1], MPH, PhD; Andrew Mitchell[2], BS; Kristen A Stafford[2,3,4], MPH, PhD; Samuel Uchenna Nwafor[5], MPH; Julia Lo[2,3], MSPH; Victor Sebastian[6], MBBS, MPH; Amee Schwitters[6], MPH, PhD; Mahesh Swaminathan[6], MD; Ibrahim Dalhatu[6], MBBS, MPA; Man Charurat[2,3], PhD

[1]Division of Global HIV and TB, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, United States
[2]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, United States
[3]Center for International Health, Education, and Biosecurity, University of Maryland School of Medicine, Baltimore, MD, United States
[4]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, United States
[5]Center for International Health, Education, and Biosecurity, University of Maryland School of Medicine, Abuja, Nigeria
[6]Division of Global HIV and TB, Center for Global Health, Centers for Disease Control and Prevention, Abuja, Nigeria

Corresponding Author:
Anne F McIntyre, MPH, PhD
Division of Global HIV and TB
Center for Global Health
Centers for Disease Control and Prevention
1600 Clifton Road NE MS E-30
Atlanta, GA, 30329
United States
Phone: 1 404 639 8284
Email: zat4@cdc.gov

Abstract

Background: Nigeria has the fourth largest burden of HIV globally. Key populations, including female sex workers, men who have sex with men, and people who inject drugs, are more vulnerable to HIV than the general population due to stigmatized and criminalized behaviors. Reliable key population size estimates are needed to guide HIV epidemic response efforts.

Objective: The objective of our study was to use empirical methods for sampling and analysis to improve the quality of population size estimates of female sex workers, men who have sex with men, and people who inject drugs in 7 states (Akwa Ibom, Benue, Cross River, Lagos, Nasarawa, Rivers, and the Federal Capital Territory) of Nigeria for program planning and to demonstrate improved statistical estimation methods.

Methods: From October to December 2018, we used 3-source capture-recapture to produce population size estimates in 7 states in Nigeria. Hotspots were mapped before 3-source capture-recapture started. We sampled female sex workers, men who have sex with men, and people who inject drugs during 3 independent captures about one week apart. During hotspot encounters, key population members were offered inexpensive, memorable objects unique to each capture round. In subsequent rounds, key population members were offered an object and asked to identify objects received during previous rounds (if any). Correct responses were tallied and recorded on tablets. Data were aggregated by key population and state for analysis. Median population size estimates were derived using Bayesian nonparametric latent-class models with 80% highest density intervals.

Results: Overall, we sampled approximately 310,000 persons at 9015 hotspots during 3 independent captures. Population size estimates for female sex workers ranged from 14,500 to 64,300; population size estimates for men who have sex with men ranged from 3200 to 41,400; and population size estimates for people who inject drugs ranged from 3400 to 30,400.

Conclusions: This was the first implementation of these 3-source capture-recapture methods in Nigeria. Our population size estimates were larger than previously documented for each key population in all states. The Bayesian models account for factors, such as social visibility, that influence heterogeneous capture probabilities, resulting in more reliable population size estimates. The larger population size estimates suggest a need for programmatic scale-up to reach these populations, which are at highest risk for HIV.

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KEYWORDS

sex workers; men who have sex with men; people who inject drugs; HIV; population size; population; data; female; men; drugs; drug injection; epidemic; Nigeria

Introduction

Key populations, including female sex workers, men who have sex with men, and people who inject drugs, are disproportionately vulnerable to HIV infection compared to the general population due to stigma, discrimination, and criminalization of key population–defining behaviors [1-5]. The poor social visibility and high mobility of these populations obscure understanding of the magnitude and distribution of their HIV burden. To guide focused and appropriately scaled HIV epidemic response efforts for these key populations, program and policy development requires reliable, empirical population size estimates [6-8].

Nigeria has the fourth-largest burden of HIV globally, with an estimated 1.9 million people living with HIV [9]. It is a mixed [10] epidemic, with a relatively low HIV prevalence of 1.4% among the adult general population [11] but higher estimated prevalence among key populations: 15.5% among female sex workers, 25% among men who have sex with men, and 10.9% among people who inject drugs [12]. The Government of the Federal Republic of Nigeria (GoN)'s National HIV and AIDS Strategic Framework 2017-2021 [13] outlines the plan to "fast-track the national response towards ending AIDS in Nigeria by 2030" and includes focused interventions to increase testing and treatment for key populations. Results of the 2018 Nigeria HIV/AIDS Indicator and Impact Survey (NAIIS) demonstrated a lower HIV prevalence in the general population than previously reported [11,14], suggesting that key populations are an important contributor to the epidemic. As a result, focus is shifting to key populations as an opportunity to have the greatest impact on HIV epidemic control. With that shift comes the need to have better data to inform HIV programming, including reliable population size estimates.

Previous efforts to estimate key population sizes in Nigeria [15-17] were largely based on programmatic mapping [18] with enumeration of female sex workers and people who inject drugs at specific venues. These approaches did not provide uncertainty bounds and likely resulted in underestimates, as only the members of each population who could be identified at specific venues were counted. During the 2015 effort, traditional (2-source) capture-recapture was used to estimate the population size of men who have sex with men in 8 states of Nigeria [15]. In 2009, 2-source capture-recapture was used to estimate the population size of men who have sex with men in 3 large Nigerian cities [19]. Since these efforts, improved methods like 3-source capture-recapture (3S-CRC) sampling have been used to estimate population sizes of female sex workers in sub-Saharan African countries, such as South Sudan [20], Uganda [21], and Rwanda [22]. Compared to programmatic mapping and enumeration, which incorporate only those populations present and visible at a venue, the 3S-CRC sampling approach is an improvement, because it accounts for lack of social visibility, thereby producing more realistic population size estimates to inform HIV prevention and treatment programs for key populations. These examples of successful population size estimates using 3S-CRC data were analyzed using Bayesian nonparametric latent-class models [23]. We expanded use of 3S-CRC sampling of key populations from female sex workers in East Africa [20-22] to female sex workers, men who have sex with men, and people who inject drugs in Nigeria.

The methods for sampling and analysis we present here have the potential for far broader use than just key population size estimation of those at high risk of HIV in Nigeria or other countries. These methods may be applied to estimate the prevalence or incidence of HIV diagnoses in specific age groups, such as children [24]; people with diabetes [25], ophthalmologic conditions [26], or spinal cord injuries [27]; people experiencing homelessness [28]; people exposed to environmental hazards, such as lead, in homes [29]; and people who have died from injuries [30]. The methods can also be used to determine the completeness of disease reporting, such as for tuberculosis notification [31].

The objective of our study was to use empirical methods for sampling and analysis to improve the quality of population size estimates of female sex workers, men who have sex with men, and people who inject drugs in 7 states (Akwa Ibom, Benue, Cross River, Lagos, Nasarawa, Rivers, and the Federal Capital Territory [FCT]) in Nigeria for program planning and to demonstrate improved statistical estimation methods. These 7 states represent the US President's Emergency Plan for AIDS Relief (PEPFAR) priority states in Nigeria based on unmet needs for HIV services in areas with high HIV prevalence.

Methods

Study Design

We sampled female sex workers, men who have sex with men, and people who inject drugs using 3S-CRC in the 7 states from October through December 2018. Traditional (ie, 2-source) capture-recapture methods for human population size estimates, where the term "capture" refers to the confirmed counting of a specific person, are described well elsewhere [19,32-35]. Accurate estimates generated from this method are challenged by violations of capture-recapture assumptions: that the study population is closed, the captures are independent, the probability of capture is similar across the entire population (ie, captured and not captured) for each source, and capture histories are accurate. The addition of one or more data sources strengthens the method, relaxing the independence assumption, as interaction can be accounted for in the statistical models.

A formative assessment that included focus group discussions and key informant interviews was used to engage key population communities in planning the implementation of this study, and was also used to identify acceptable unique objects for capture-recapture. Comprehensive measures were implemented to ensure the safety and security of the study teams and participants who were members of groups whose behavior is highly stigmatized and criminalized. The unique objects were distributed in hotspots, defined as venues where key population members congregate or engage in sexual or injecting behaviors. With the most recent lists (from 2013 and 2015) produced by efforts to map key population hotspots [15,16] as a foundation, we engaged 261 key population members from 36 key population–led, community-based organizations in the 7 states for a comprehensive review and update of hotspot information during August 2018 [36]. Local government areas were grouped into 3 zones per state to manage staff, equipment, and travel for the mapping activity, which facilitated better control over missing or duplicate hotspot visits. The mapping teams consisted of 2 to 3 key population community members who used updated lists and tablets with the REDCap survey tool (Research Electronic Data Capture; Vanderbilt University); they were assigned to visit several hotspots per day depending on their proximity and travel time. The mapping teams visited every local government area in every zone of every state and documented geographic coordinates, name (formal or informal), address, peak days and times of key population activity, and an estimate of the number of key population members present during the visit. There was at least one hotspot identified in every local government area in each of the 7 states; all hotspots were visited and documented during this activity. Most local government areas were a combination of urban and rural areas, although boundaries between the two were often difficult to distinguish, hindering our efforts to define each hotspot as urban or rural. Information collected during mapping was reconciled, deduplicated, and verified. The updated list of hotspots informed venue sampling, allocation of the 261 trained key population data collectors, and scheduling of hotspot visits to distribute the unique objects for each of the 3 sampling rounds of the 3S-CRC activity.

All hotspots identified during the mapping and validation exercise that were still active at the time of 3S-CRC were included in venue sampling for each capture round. During all sampling rounds, if a hotspot was inactive when the team arrived, this was documented, and the team moved to the next hotspot on the schedule. If new hotspots were discovered during any sampling round, the list was updated, but the hotspot was not sampled for 3S-CRC.

Study Subjects

We sampled key population members from hotspots based on the mapping and validation activity completed immediately prior to 3S-CRC sampling [36].

Female sex workers were defined as any woman (female sex at birth) aged 18 years or older who received money or goods in exchange for sexual services, either regularly or occasionally, in the 12 months preceding this activity. All 15- to 17-year-old girls who reported receiving money or goods in exchange for sexual services were defined as sexually exploited minors (referrals to support services were provided) and were counted as sex workers for the purposes of population size estimates. Men who have sex with men were defined as any man (male sex at birth) aged 15 years or older who had engaged in oral or anal (receptive or insertive) sex, or both, with another man at least once in the previous 12 months. People who inject drugs were defined as any person aged 15 years or older who injected drugs (ie, illicit, nonprescribed, or illegal substances) at least once in the preceding 12 months.

Individuals were excluded if they reported having already been captured during a given round; if they failed to meet their key population definition, did not consent to participate, or were aged less than 15 years; if the hotspot they had been captured in during a previous round was no longer active; or if the key population team was unable to return in subsequent rounds.

Sampling

To estimate the sample size for each capture round, we compared the recorded number of key population members present in each hotspot during mapping and validation with previous population size estimates [15,16] to produce reasonable approximations for each state and key population.

During the 3 capture rounds, we aimed to have 3 people per distribution team, with at least two being members of the same key population at the assigned hotspot to optimize acceptance of the unique objects. During encounters with key population peers in hotspots, team members described the population size estimate activity and asked the peers whether they had been approached during this sampling round. If not, the team members obtained verbal consent from those who agreed to participate and administered a brief survey to capture age, sex at birth, gender identity, education, primary source of income, local government area and state of residence, whether the individual traveled to the current or another local government area for work, and whether they currently injected drugs or engaged in sex work. Participants were offered an inexpensive and memorable object (a “gift”) unique to each of the 3 capture rounds and 3 key populations (ie, female sex workers, men who have sex with men, and people who inject drugs). This process was repeated by different unique-object distribution teams for each of 3 distinct capture rounds, performed approximately one week apart.

In subsequent rounds, participants were asked to show or describe the objects they had received during all previous rounds; affirmative responses were tallied upon correct identification of the object for each previous round.

Measures

A capture was defined as acceptance of the gift offered by the data collection team. Recaptures (ie, second and third captures) were defined as either showing distributors the gifts from previous capture rounds or correctly describing and identifying the gift from a set of 20 pictures of various unique objects (some with the same object in a different color and some with completely different objects).

Data Collection

Distributors recorded participant responses on tablets with REDCap software [37,38] and uploaded the data to a secure central server after each encounter. All encounters were documented with consent.

Data Analysis

Individual encounter data were exported to SAS (version 9.4; SAS Institute Inc). After reviewing the data for missing or nonsensical responses, individual encounters were subdivided by state, key population group (ie, female sex workers, men who have sex with men, and people who inject drugs), age group (15-24 years and ≥25 years), and, for people who inject drugs, sex. Aggregated data sets detailing counts of each capture and recapture combination were produced for each subset of data. For the 3 capture rounds, matrices with 4 columns (round 1, round 2, round 3, and total count) and 7 rows representing each potential combination of captures (with 1 representing "captured" and 0 "not captured") were produced. Aggregated data sets summarizing data counts in each capture round combination were produced for each subset.

Bayesian nonparametric latent-class models [23], which are able to account for capture heterogeneity, were used to produce key population size estimates from aggregated 3S-CRC data. State-specific models were generated for each key population and disaggregated by age group. The results presented here represent combined estimates for male and female people who inject drugs, as there were insufficient sample sizes for female people who inject drugs. The posterior distribution for latent-class models may produce wide 95% credible intervals with a long tail, so we calculated 80% highest density intervals (HDIs) to facilitate interpretation of population size estimates and improve ease of application to HIV programming.

All statistical analyses of aggregated data sets to generate median population size estimates with 80% HDIs were performed with R statistical software (version 3.4.4; R Foundation for Statistical Computing) using packages for latent-class models for capture-recapture [39] and HDI (HDInterval) [40].

Ethical Considerations

This study was approved by the National Health Research Ethics Committee Nigeria and the Institutional Review Board of the University of Maryland at Baltimore (HP00080293). The study was reviewed in accordance with the US Centers for Disease Control and Prevention (CDC) human research protection procedures and was determined to be research, but CDC investigators did not interact with the human subjects or have access to identifiable data for research purposes.

Results

Enrollment

Overall, 9015 hotspots identified during mapping were sampled and included in the analysis, including 5946 (66%) hotspots for female sex workers, 1256 (13.9%) hotspots for men who have sex with men, and 1813 (20.1%) hotspots for people who inject drugs. A total of 310,140 individual encounters from capture rounds 1, 2, and 3 were included in the analyses (Table 1). There were 88,805 individuals excluded from the analysis due to nonconsent, ineligibility, or captures and recaptures from hotspots that were not visited in all 3 rounds due to accessibility, security, or time constraints.

Table 1. Numbers of encounters and hotspots by state and key population.

State	FSWs[a], n	FSW hotspots, n	MSM[b], n	MSM hotspots, n	PWID[c], n	PWID hotspots, n	Total subjects, n	Total hotspots, n
Akwa Ibom	32,635	690	11,760	230	14,659	307	59,054	1227
Benue	35,284	845	9726	221	14,059	272	59,069	1338
Cross River	13,344	544	3670	195	10,142	291	27,156	1030
Federal Capital Territory	25,800	837	3427	100	3076	85	32,303	1022
Lagos	36,147	1171	2444	83	7363	149	45,954	1403
Nasarawa	25,609	929	4600	232	9790	283	39,999	1444
Rivers	30,447	930	7733	195	8425	426	46,605	1551
Total	199,266	5946	43,360	1256	67,514	1813	310,140	9015

[a] FSW: female sex worker.

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

[c] PWID: people who inject drugs.

Population Size Estimates

Modeled median population size estimates with 80% HDIs for each state are presented for female sex workers (Table 2), men who have sex with men (Table 3), and people who inject drugs (Table 4). The tables include general population census projections from 2018 for the relevant sex or sexes (ie, men only for men who have sex with men, women only for female sex workers, and both for people who inject drugs) and age groups (15-24 years or ≥25 years) to provide context for the population size estimates. Posterior densities generated from Bayesian nonparametric latent-class models are slightly different each time the models are run. For this reason, the population size estimates and HDIs presented in these 3 tables, as well as Table 5, are rounded to the nearest 100 and the 2 distinct models by age group (ie, 15-24 years and ≥25 years) run for each state will not sum to the overall model representing all ages (ie, ≥15 years).

Table 2. State-specific median population size estimates for female sex workers with 80% highest density intervals using Bayesian nonparametric latent-class models, compared with 2018 general population census projections for 7 states in Nigeria.

Age group by state	Median female sex worker PSE[a], (80% HDI[b])	General population 2018 census projection[c] (age ≥15 years)	Median female sex worker PSE/general population, % (80% HDI)
Akwa Ibom			
Total	64,300 (44,100, 84,900)	1,557,841	4.1 (2.8, 5.4)
15-24 years	18,200 (11,400, 23,000)	465,126	3.9 (2.5, 4.9)
≥25 years	45,200 (32,600, 61,400)	1,092,715	4.1 (3, 5.6)
Benue			
Total	46,700 (27,500, 113,900)	1,653,910	2.8 (1.7, 6.9)
15-24 years	11,000 (9500, 13,400)	624,617	1.8 (1.5, 2.1)
≥25years	28,900 (23,500, 35,500)	1,029,293	2.8 (2.3, 3.4)
Cross River			
Total	15,300 (11,900, 20,000)	1,070,063	1.4 (1.1, 1.9)
15-24 years	5500 (4100, 6900)	331,424	1.7 (1.2, 2.1)
≥25 years	9600 (7600, 12,200)	738,639	1.3 (1, 1.7)
Federal Capital Territory			
Total	45,700 (23,100, 56,700)	439,067	10.4 (5.3, 12.9)
15-24 years	15,800 (12,200, 21,800)	186,017	8.5 (6.6, 11.7)
≥25 years	31,100 (14,700, 38,600)	253,050	12.3 (5.8, 15.3)
Lagos			
Total	48,200 (30,900, 76,100)	3,858,772	1.2 (0.8, 2)
15-24 years	12,100 (7600, 19,600)	955,681	1.3 (0.8, 2.1)
≥25 years	32,700 (23,400, 46,800)	2,903,091	1.1 (0.8, 1.6)
Nasarawa			
Total	55,600 (26,000, 73,700)	569,223	9.8 (4.6, 12.9)
15-24 years	22,600 (7100, 29,400)	235,045	9.6 (3, 12.5)
≥25 years	42,800 (19,100, 52,000)	334,178	12.8 (5.7, 15.6)
Rivers			
Total	14,500 (14,100, 15,200)	2,128,841	0.7 (0.7, 0.7)
15-24 years	5400 (5200, 5600)	606,665	0.9 (0.9, 0.9)
≥25 years	9300 (8900, 10,100)	1,522,176	0.6 (0.6, 0.7)

[a] PSE: population size estimate.

[b] HDI: highest density interval.

[c] National Population Commission census projections for 2018 population are age- and sex-specific for each.

Table 3. State-specific median population size estimates for men who have sex with men with 80% highest density intervals using Bayesian nonparametric latent-class models, compared with 2018 general population census projections for 7 states in Nigeria.

Age group by state	Median men who have sex with men PSE[a], (80% HDI[b])	General population 2018 census projection[c] (age ≥15 years)	Median men who have sex with men PSE/general population, % (80% HDI)
Akwa Ibom			
All	34,600 (12,000, 72,400)	1,594,978	2.2 (0.8, 4.5)
15-24 years	38,900 (8200, 55,800)	499,067	7.8 (1.6, 11.2)
≥25 years	17,000 (8900, 31,200)	1,095,911	1.6 (0.8, 2.8)
Benue			
All	10,800 (8000, 13,100)	1,683,863	0.6 (0.5, 0.8)
15-24 years	2900 (2100, 3600)	650,662	0.4 (0.3, 0.6)
≥25 years	7500 (5700, 9000)	1,033,201	0.7 (0.6, 0.9)
Cross River			
All	3200 (2700, 3600)	1,046,104	0.3 (0.3, 0.3)
15-24 years	1400 (1200, 1600)	347,758	0.4 (0.3, 0.5)
≥25 years	1700 (1500, 1900)	698,346	0.2 (0.2, 0.3)
Federal Capital Territory			
All	8200 (6500, 10,700)	483,100	1.7 (1.3, 2.2)
15-24 years	3500 (1400, 14,500)	155,809	2.2 (0.9, 9.3)
≥25 years	6200 (2200, 18,500)	327,291	1.9 (0.7, 5.7)
Lagos			
All	6500 (4900, 8400)	4,746,577	0.1 (0.1, 0.2)
15-24 years	—[d]	938,061	—[d]
≥25 years	3800 (2900, 4700)	3,808,516	0.1 (0.1, 0.1)
Nasarawa			
All	5000 (3700, 6400)	477,029	1.0 (0.8, 1.3)
15-24 years	6500 (2500, 8800)	229,829	2.8 (1.1, 3.8)
≥25 years	2200 (1900, 2400)	247,200	0.9 (0.8, 1)
Rivers			
All	41,400 (8400, 61,800)	2,354,728	1.8 (0.4, 2.6)
15-24 years	8000 (2000, 11,300)	649,779	1.2 (0.3, 1.7)
≥25 years	43,200 (28,300, 63,700)	1,704,949	2.5 (1.7, 3.7)

[a] PSE: population size estimate.

[b] HDI: highest density interval.

[c] National Population Commission census projections for 2018 population are age- and sex-specific for each.

[d] Not available (effective sample size was too small to produce stable, reliable population size estimates).

Table 4. State-specific median population size estimates for people who inject drugs with 80% highest density intervals using Bayesian nonparametric latent-class models, compared with 2018 general population census projections for 7 states in Nigeria. People who inject drugs were not disaggregated by sex because the effective sample sizes for women were too small to produce stable, reliable population size estimates.

Age group by state	Median people who inject drugs PSE[a], (80% HDI[b])	General population 2018 census projection[c] (age ≥15 years)	Median people who inject drugs PSE/general population, % (80% HDI)
Akwa Ibom			
All	22,500 (15,100, 30,900)	3,152,819	0.7 (0.5, 1.0)
15-24 years	5100 (3500, 6000)	964,193	0.5 (0.4, 0.6)
≥25 years	17,600 (11,800, 23,600)	2,188,626	0.8 (0.5, 1.1)
Benue			
All	27,600 (22,900, 35,600)	3,337,773	0.8 (0.7, 1.1)
15-24 years	10,200 (7600, 13,900)	1,275,279	0.8 (0.6, 1.1)
≥25 years	17,900 (14,500, 22,500)	2,062,494	0.9 (0.7, 1.1)
Cross River			
All	20,100 (11,500, 25,500)	2,116,167	0.9 (0.5, 1.2)
15-24 years	6100 (4900, 7500)	679,182	0.9 (0.7, 1.1)
≥25 years	10,000 (6900, 15,400)	1,436,985	0.7 (0.5, 1.1)
Federal Capital Territory			
All	3400 (2800, 4100)	922,167	0.4 (0.3, 0.4)
15-24 years	1000 (800, 1300)	341,826	0.3 (0.2, 0.4)
≥25 years	2200 (1800, 2700)	580,341	0.4 (0.3, 0.5)
Lagos			
All	9400 (7100, 13,400)	8,605,349	0.1 (0.1, 0.2)
15-24 years	6200 (900, 11,100)	1,893,742	0.3 (0.0, 0.6)
≥25 years	16,900 (6100, 44,100)	6,711,607	0.3 (0.1, 0.7)
Nasarawa			
All	6900 (5800, 7600)	1,046,252	0.7 (0.6, 0.7)
15-24 years	1700 (1400, 1800)	464,874	0.4 (0.3, 0.4)
≥25 years	5200 (4300, 5700)	581,378	0.9 (0.7, 1.0)
Rivers			
All	30,400 (7600, 44,600)	4,483,569	0.7 (0.2, 1.0)
15-24 years	1700 (400, 2400)	1,256,444	0.1 (0.0, 0.2)
≥25 years	37,700 (26,200, 50,700)	3,227,125	1.2 (0.8, 1.6)

[a] PSE: population size estimate.

[b] HDI: highest density interval.

[c] National Population Commission census projections for 2018 population are age- and sex-specific for each.

Table 5. Comparison of states with 2013 and 2018 population size estimates. The source for the 2013 data is the National Agency for the Control of AIDS [16]. No population size estimates for 2013 were available for Akwa Ibom or Rivers.

Key population by state	2013 PSE[a], n	Hotspots, n	2018 PSE (80% HDI[b])	Hotspots, n
Benue				
FSW[c]	10,034	825	46,700 (27,500, 113,900)	1098
MSM[d]	1018	57	10,800 (8000, 13,100)	265
PWID[e]	221	32	27,600 (22,900, 35,600)	351
Cross River				
FSW	9858	692	15,300 (11,900, 20,000)	1782
MSM	276	15	3200 (2700, 3600)	268
PWID	54	8	20,100 (11,500, 25,500)	616
Federal Capital Territory				
FSW	24,376	1446	45,700 (23,100, 56,700)	977
MSM	1892	120	8200 (6500, 10,700)	116
PWID	205	22	3400 (2800, 4100)	111
Lagos				
FSW	46,691	4056	48,200 (30,900, 76,100)	2603
MSM	2946	191	6500 (4900, 8400)	131
PWID	1186	95	9400 (7100, 13,400)	240
Nasarawa				
FSW	19,953	1409	55,600 (26,000, 73,700)	990
MSM	440	19	5000 (3700, 6400)	246
PWID	414	12	6900 (5800, 7600)	314

[a] PSE: population size estimate.

[b] HDI: highest density interval.

[c] FSW: female sex worker.

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

[e] PWID: people who inject drugs.

The modeled estimates were compared with the 2013 population size estimates based on programmatic mapping and enumeration at key population venues, a method that was approved by the GoN [16] (Table 5). Hotspot coverage was broader in our 3S-CRC in 2018 for female sex workers and men who have sex with men in Benue and Cross River, broader for people who inject drugs in all 7 states, and broader in 2013 programmatic mapping for female sex workers and men who have sex with men in Lagos, Nasarawa, and the FCT. In every case, the modeled population size estimates were larger than those from programmatic mapping; only the 2013 population size estimates for female sex workers in Lagos and the FCT were within the 2018 80% HDI.

Discussion

Principal Findings

This study represents the first implementation of these sampling and analytic methods to produce large-scale population size estimates for female sex workers, men who have sex with men, and people who inject drugs in Nigeria. Several other applications of 3S-CRC and Bayesian nonparametric latent-class models to estimate female sex worker population sizes in sub-Saharan Africa have been published recently, in South Sudan [20], Kampala, Uganda [21], and Rwanda [22], but to our knowledge no other studies have used these sampling and analytic methods for men who have sex with men or people who inject drugs. Although we were unable to define each hotspot as either urban or rural, and all local government areas thus included urban and rural areas, our study included every local government area in each of the 7 states, and thus represents broad coverage. We demonstrated that these sampling and analytic methods were feasible to implement with appropriate resources and produced reasonable estimates for different key populations in both urban and rural areas. Given the success of our large-scale study with finite resources, these methods could be easily scaled down and applied in smaller settings (eg, cities or provinces).

Comparison With Prior Work

Of the few population size estimates from Nigeria published before our study, most employed different methods from those presented here. Previous estimates have been generated as a part of programmatic mapping with enumeration at key population venues [15,16]. Several studies used capture-recapture methods for men who have sex with men [16] and male sex workers [19] and were able to report precision, but were limited by geographic focus and probable violation of the independence assumption when only 2 sources were used. Our estimates were generated from 3S-CRC data, and our analysis accounted for dependence in the models, yielding more robust results with precision.

Our population size estimates were larger than previously documented in the 7 PEPFAR priority states in Nigeria. We compared our results with the last population size estimates published by the GoN in 2013 [16]. That study produced population size estimates for 5 of the 7 states in our study. Compared to the 5 states with 2013 estimates that overlap with our 2018 states, our median population size estimates for all men who have sex with men and people who inject drugs in each of the 5 states and female sex workers in 3 of the 5 states were considerably larger than those generated from programmatic mapping and enumeration at key population venues during 2013. In each of the 2 states—FCT and Lagos—where the 2013 female sex worker population size estimates were within the uncertainty bounds of our 2018 study, the number of hotspots contributing to the 2013 estimates was approximately 50% more than the number of hotspots included in our 2018 study. Counts and enumeration from programmatic mapping produce underestimates because only visible individuals who are present at a given venue or hotspot are included, whereas Bayesian statistical models use observed, captured data to estimate the unknown data with uncertainty. In addition, our study had overall broader coverage of hotspots than previous estimates. Extensive hotspot coverage and analysis using Bayesian models that account for heterogeneity in capture probabilities may reflect more accurate population size estimates than previous efforts.

Most of our results fall within expected ranges as a percentage of the general population for each state and key population. We might expect female sex workers in sub-Saharan Africa to comprise 0.4% to 4.3% of the adult female population in urban areas [41]. Our results for 5 of 7 states fall within that range. In the adjacent FCT and Nasarawa areas, where the population size estimates appear to be larger than expected, there is a considerable amount of female sex worker mobility within and between the 2 states, and potential violations of assumptions might provide some possible explanations. For men who have sex with men, Joint United Nations Programme on HIV/AIDS (UNAIDS) 2020 guidance is that the lower bound should be at least 1% of the adult male population [42], although earlier West and Central Africa estimates ranged from 0.05% to 2% in other reports [43]. The overall population size estimates for Akwa Ibom, the FCT, Nasarawa, and Rivers fall within UNAIDS guidance; Benue, Cross River, and Lagos population size estimates are more aligned with the lower bounds of the earlier reported ranges in West and Central African countries. It is possible that the participation of men who have sex with men in our 2018 study might have been impacted by the Same Sex Marriage (Prohibition) Act (SSMPA), signed into law in January 2017 [44]. The SSMPA built on existing laws against sodomy and same-sex marriage and included criminalizing participation in or support of men who have sex with men–friendly organizations and meetings and providing services to men who have sex with men. This might have resulted in fewer hotspots, and fewer men who have sex with men present in those hotspots who were willing to disclose their identity to the study teams composed of their peers. For people who inject drugs, we expected population size estimates to fall within 0.1% to 1.6% of the adult population [8,45], and all of our results met those expectations. Overall, most of our estimates appear reasonable as a percentage of the general population.

We used Bayesian nonparametric latent-class models to analyze the 3S-CRC data. We had several options to analyze our multiple-source capture-recapture data using empirical methods for robust estimates, such as log-linear modeling [24,35,46,47], Bayesian model averaging [48,49], and Bayesian nonparametric latent-class modeling [23,50,51]. Accounting for the heterogeneity of captures and accommodating sparse data are two of the advantages of Bayesian latent-class models over the more traditional log-linear models for analysis of multiple-source capture-recapture data. The Bayesian nonparametric latent-class models account for differences in heterogeneity from capture to capture and combine similar strata into latent classes [23,51]. This feature allows the models to directly estimate the joint distribution, unlike log-linear models that are based on strong assumptions about capture patterns that can result in potentially biased estimates and confidence intervals that display poor coverage. Model selection using the Akaike information criterion or the Bayesian information criterion poses the additional challenge of selecting consistent and correct models [51]. Bayesian model averaging fits all possible log-linear models, weights each model according to the posterior probability, and returns the model-probability–weighted average across many models with uncertainty [48-51]. The Bayesian models are similar in that they inform themselves during Markov chain Monte Carlo sampling, beginning with an infinite number of probability distributions and ending with a smaller, more representative subset of those that fit the data best to produce population size estimates [23,51]. In addition, the Bayesian models can accommodate sparse data (ie, when the total number of individuals with 1 of the 7 patterns of captures across 3 rounds is small or zero). One can chose a method accounting for the independence assumption or the homogeneity assumption, but not both. Bayesian model averaging is best when relaxing independence and the latent-class models are best when relaxing homogeneity. In the context of key populations, individuals have considerably different visibility levels; therefore, we prioritized the homogeneity assumption and opted for the Bayesian nonparametric latent-class models.

Limitations

The population size estimates presented here are subject to several limitations. First, capture probabilities across rounds might have been heterogeneous. Hotspots, by definition, are key population–friendly locations where members of these groups congregate, so study participants with higher social visibility captured in the first round might have been more likely to be captured again in the second and third rounds. One solution to the issue of capturing only those with strong social visibility might be to have the final capture be part of a respondent-driven sampling survey, with recruitment based on network connections and the ability to reach key population members with poor social visibility (ie, those who do not frequent hotspots). Another option might be to include other types of data sources, such as online social apps, which might have broadened the catchment area, particularly for key population members who do much of their social networking online. Second, unique object (ie, “gift”) acceptance may have influenced our results. A formative assessment with key population communities informed the selection of the unique objects, although it is possible that some objects were less desirable than others and were not accepted by key population members encountered in hotspots, resulting in smaller captures and specious estimates with impractically wide credible sets. Third, compared to other model approaches, Bayesian nonparametric latent-class models are more flexible, which may lead to less stable estimators. Although some may consider this a weakness, we consider it a strength, because there is fundamental uncertainty that is captured by the model in the form of a wider posterior distribution. Finally, although we asked respondents where they resided and whether they traveled to the encounter hotspot or elsewhere for work, the data were insufficient to use for any sort of mobility adjustment to the population size estimates. However, the data did provide some possible explanations for differences among the number of key population members sampled across capture rounds and states. These limitations would likely have resulted in underestimates of population sizes. However, the magnitude of those underestimates might have been mitigated by our broad hotspot coverage throughout the 7 states and stakeholder feedback that many of the key population members who meet sexual or injecting partners online are also found in hotspots. Despite these challenges, our population size estimates were based on 3 high-quality capture rounds analyzed with models that account for capture heterogeneity, and the estimates were endorsed by key stakeholders with local expertise.

Conclusions

The findings from this study are critical in supporting efforts to respond to the HIV epidemic, as outlined in Nigeria’s National Strategic Framework, as focus shifts from the general population to key populations, suggested by the results of the NAIIS 2018. These population denominator data are essential to align responses and resources from the HIV prevention and treatment programs. In most of West Africa, including Nigeria, most HIV epidemics are not generalized; they are rather mixed epidemics, such that they are focused and propagated within the highest-risk populations yet would be sustained if transmission in either population were interrupted. Indeed, a surge strategy in HIV prevention and treatment is being implemented in each of the 7 PEPFAR priority states. Hotspots identified in this study are also being utilized to map facility-based and community-based programs.

The empirical methods for population size estimates described here provide essential information for planning and implementing targeted HIV prevention, care, and treatment programs. The results of this study demonstrate that this is a method that can be employed in future population size estimate efforts among female sex workers, men who have sex with men, and people who inject drugs in Nigeria and elsewhere. Continuing developments in technology (eg, Shiny apps [50]) that support sampling and analyses of multiple-source capture-recapture by program implementers will increase the accessibility of these methods.

Conflicts of Interest

None declared.

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Abbreviations

3S-CRC: 3-source capture-recapture
CDC: US Centers for Disease Control and Prevention
FCT: Federal Capital Territory

GoN: Government of the Federal Republic of Nigeria
NAIIS: Nigeria HIV/AIDS Indicator and Impact Survey
PEPFAR: President’s Emergency Plan for AIDS Relief
SSMPA: Same Sex Marriage (Prohibition) Act

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Corrigenda and Addenda

Correction: Cost-Effectiveness of Lung Cancer Screening Using Low-Dose Computed Tomography Based on Start Age and Interval in China: Modeling Study

Zixuan Zhao[1*], PhD; Lingbin Du[2*], MPH, PhD; Yuanyuan Li[3], MD, PhD; Le Wang[2], PhD; Youqing Wang[2], MD; Yi Yang[1], PhD; Hengjin Dong[1], PhD

[1]Department of Science and Education of the Fourth Affiliated Hospital, Center for Health Policy Studies, School of Public Health, Zhejiang University School of Medicine, Hangzhou, China

[2]Department of Cancer Prevention, Cancer Hospital of the University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China

[3]Department for Science and Education, Hangzhou Ninth People's Hospital, Hangzhou, China

[*]these authors contributed equally

Corresponding Author:
Hengjin Dong, PhD
Department of Science and Education of the Fourth Affiliated Hospital, Center for Health Policy Studies
School of Public Health
Zhejiang University School of Medicine
No. 866 Yuhangtang Road, Xihu District
Hangzhou, 310058
China
Phone: 86 13221076129
Email: donghj@zju.edu.cn

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In “Cost-Effectiveness of Lung Cancer Screening Using Low-Dose Computed Tomography Based on Start Age and Interval in China: Modeling Study” (JMIR Public Health Surveill 2022;8(7):e36425), the authors noted an error:

In the originally published article, Affiliations 1 and 4 were inadvertently presented as two different affiliations due to erroneous presentation of organizational units within these affiliations.

In the corrected version, the two affiliations are merged into a single affiliation with the correct order of organizational units. With this update, the numbering and attribution of affiliations to the authors are updated as follows:

> *Zixuan Zhao[1]; Lingbin Du[2]; Yuanyuan Li[3]; Le Wang[2]; Youqing Wang[2]; Yi Yang[1]; Hengjin Dong[1]*
>
> *[1]Department of Science and Education of the Fourth Affiliated Hospital, Center for Health Policy Studies, School of Public Health, Zhejiang University School of Medicine, Hangzhou, China*
>
> *[2]Department of Cancer Prevention, Cancer Hospital of the University of Chinese Academy of Sciences, Zhejiang Cancer Hospital, Hangzhou, China*
>
> *[3]Department for Science and Education, Hangzhou Ninth People's Hospital, Hangzhou, China*

Affiliation noted in the corresponding author's contact information is also updated accordingly.

The correction will appear in the online version of the paper on the JMIR Publications website on October 17, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Google Trends on Human Papillomavirus Vaccine Searches in the United States From 2010 to 2021: Infodemiology Study

Akshaya Srikanth Bhagavathula[1*], PharmD, PhD; Philip M Massey[1*], MPH, PhD

Center for Public Health and Technology, Department of Health, Human Performance, and Recreation, College of Education and Health Professions, University of Arkansas, Fayetteville, AR, United States

[*]all authors contributed equally

Corresponding Author:
Philip M Massey, MPH, PhD
Center for Public Health and Technology
Department of Health, Human Performance, and Recreation, College of Education and Health Professions
University of Arkansas
346 West Ave.
West Avenue Annex Building, Suite 317
Fayetteville, AR, 72701
United States
Phone: 1 4795758491
Email: masseyp@uark.edu

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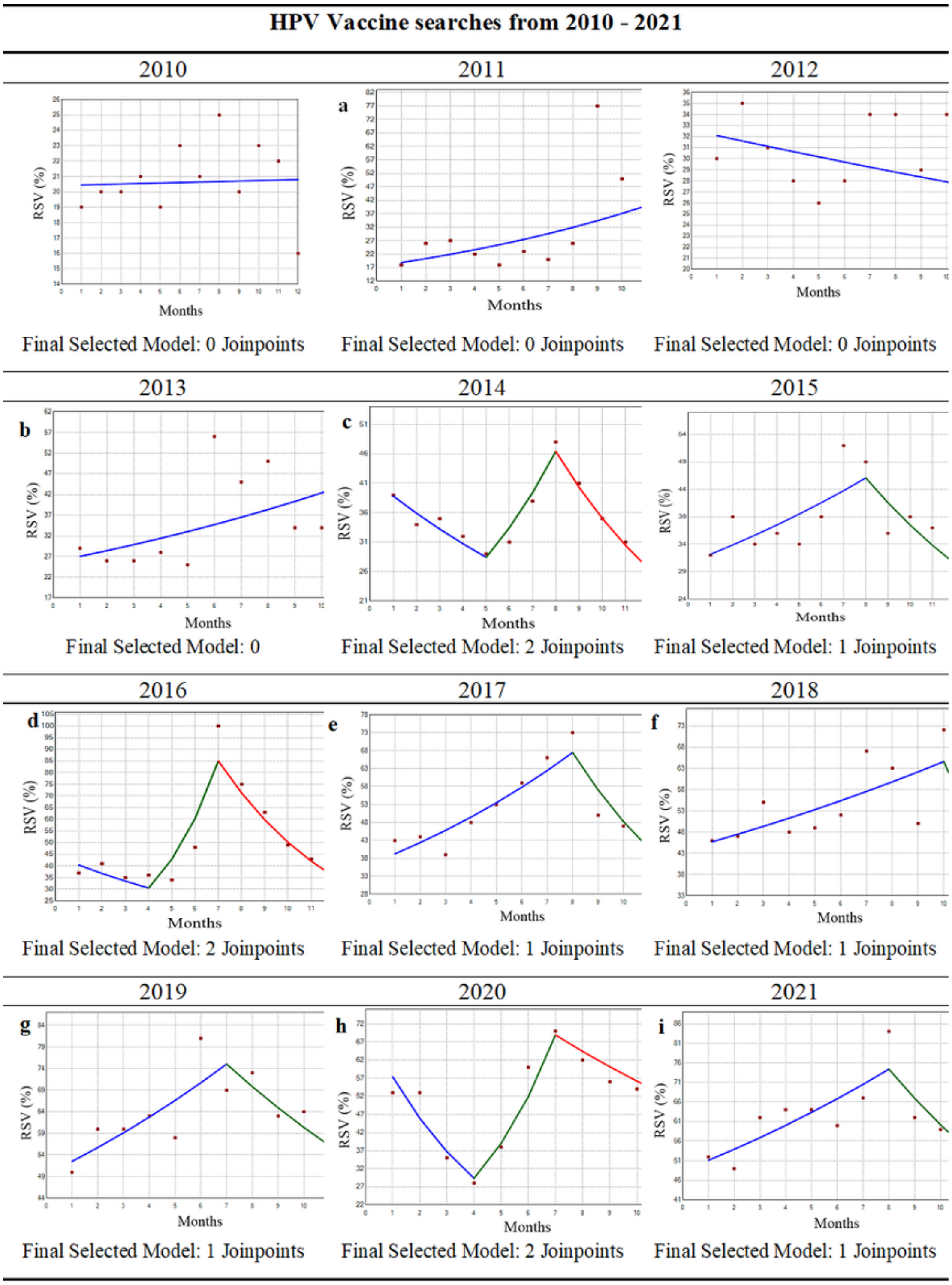
In “Google Trends on HPV vaccine searches in the U.S. from 2010 - 2021: An Infodemiology Study” (JMIR Public Health Surveill 2022;8(8):e37656) the authors noted one error.

In the originally published article, Figure 2 appeared incorrectly (as shown in Multimedia Appendix 1).

The correct Figure 2 is provided below.

The correction will appear in the online version of the paper on the JMIR Publications website on October 4, 2022, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Figure 2. Joinpoint regression analysis indicating trends in HPV vaccine Relative Search Volume (RSVs) on Google Trends from 2010 – 2021 in the U.S.



Multimedia Appendix 1
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Original Paper

Paracetamol Use in Patients With Osteoarthritis and Lower Back Pain: Infodemiology Study and Observational Analysis of Electronic Medical Record Data

Gisèle Pickering[1], MD, PhD; Linda Mezouar[2], MBA, MD; Hayet Kechemir[3], MD; Caty Ebel-Bitoun[4], MD

[1]Centre d'Investigation Clinique, Inserm 1405, CHU Clermont-Ferrand, Clermont-Ferrand, France
[2]Sanofi Specialty Care, Gentilly, France
[3]Sanofi Research and Development, Chilly-Mazarin, France
[4]Sanofi Consumer Healthcare, Gentilly, France

Corresponding Author:
Gisèle Pickering, MD, PhD
Centre d'Investigation Clinique
Inserm 1405
CHU Clermont-Ferrand
Rue Montalembert
CHU G Montpied
Clermont-Ferrand, 63000
France
Phone: 33 473178416
Fax: 33 473148412
Email: gisele.pickering@uca.fr

Abstract

Background: Lower back pain (LBP) and osteoarthritis (OA) are common musculoskeletal disorders and account for around 17.0% of years lived with disability worldwide; however, there is a lack of real-world data on these conditions. Paracetamol brands are frequently prescribed in France for musculoskeletal pain and include Doliprane, Dafalgan, and Ixprim (tramadol-paracetamol).

Objective: The objective of this retrospective study was to understand the journey of patients with LBP or OA when treated with paracetamol.

Methods: Three studies were undertaken. Two studies analyzed electronic medical records from general practitioners (GPs) and rheumatologists of patients with OA or LBP, who had received at least one paracetamol prescription between 2013 and 2018 in France. Data were extracted, anonymized, and stratified by gender, age, and provider specialty. The third study, an infodemiology study, analyzed associations between terms used on public medical forums and Twitter in France and the United States for OA only.

Results: In the first 2 studies, among patients with LBP (98,998), most (n=92,068, 93.0%) saw a GP, and Doliprane was a first-line therapy for 87.0% (n=86,128) of patients (71.0% [n=61,151] in combination with nonsteroidal anti-inflammatory drugs [NSAIDs] or opioids). Among patients with OA (99,997), most (n=84,997, 85.0%) saw a GP, and Doliprane was a first-line therapy for 83.0% (n=82,998) of patients (62.0% [n=51,459] in combination). Overall, paracetamol monotherapy prescriptions decreased as episodes increased. In the third study, in line with available literature, the data confirmed that the prevalence of OA increases with age (91.5% [212,875/232,650] above 41 years), OA is more predominant in females (46,530/232,650, 20.0%), and paracetamol use varies between GPs and rheumatologists.

Conclusions: This health surveillance analysis provides a better understanding of the journey for patients with LBP or OA. These data confirmed that although paracetamol remains the most common first-line analgesic for patients with LBP and OA, usage varies among patients and health care specialists, and there are concerns over efficacy.

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KEYWORDS

osteoarthritis; lower back pain; general practice; rheumatology; paracetamol; real-world evidence

Introduction

Background

Musculoskeletal disorders are associated with chronic and debilitating pain, account for 17% of all years lived with disability worldwide, and are particularly prevalent in higher income countries (Western Europe, 20.8%; United States, 25.8%; Japan, 26.2%) [1]. The recurrent pain experienced can have considerable consequences, causing anxiety and generally negatively impacting a patient's quality of life [2]. With the global population of individuals over 60 years of age expected to increase significantly by 2050 [3], management of these disorders, which often progress with age, is particularly important. Two of the most common conditions causing musculoskeletal pain are lower back pain (LBP) and osteoarthritis (OA) [4].

LBP

LBP, the most common musculoskeletal disorder, is experienced by approximately 38.0% of the general population, and is the leading cause of disability worldwide [5,6]. A previous study has shown that most patients experience mild LBP (25.0%), with severe LBP experienced by the least patients (5.0%) [7]. With rates increasing in the United States by 62.3% between 1992 and 2006, and more patients seeking assistance from health care professionals (HCPs), the prevalence appears to be increasing [8]. LBP can result from acute trauma, such as strenuous physical activities like lifting, pushing, or pulling a heavy load, with pain intensity ranging from sharp shooting pain, arising during sudden strenuous activity, to chronic pain that develops slowly over time as a result of degenerative changes within the spinal cord [9,10]. However, the vast majority of cases are classified as acute nonspecific, as no definitive cause can be identified, and this will be the focus of this study [11]. Frequently, nonspecific LBP is acute or subacute in nature and may resolve within days to a few weeks; however, LBP is considered chronic if the pain persists for more than 12 weeks [12].

For patients with acute nonspecific LBP, effective treatment remains a challenge [12,13]. Management is often patient centered and involves patient education and reassurance. Nonpharmacological options, such as physical exercise and manual techniques, are usually considered prior to pharmacological therapies. For chronic LBP, multidisciplinary care, involving a number of specialists, may also be considered. Paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the first-line pharmacological options. If ineffective, stronger medications, such as opioids, antidepressants, and gabapentinoids, can be used; however, the risk of an adverse reaction is higher, and regular patient re-evaluation is required. Invasive surgery is usually the last option and is considered on a case-by-case basis (Table 1) [12,14-19].

Table 1. Guideline recommendations for acute lower back pain.

Guideline	Disease management options in the guideline
High Authority of Health Recommendation of Good Practice Management of a patient with common low back pain [19]	First-line option: Patient information and self-management Second-line option: Physical activity, paracetamol, and nonsteroidal anti-inflammatory drugs Third-line option: Multidisciplinary approach Fourth-line option: Biopsychosocial
French Society of Rheumatology (Société Française de Rhumatologie) How is low back pain or common low back pain treated? [18]	First-line option: Reassurance Second-line option: Pharmacological and nonpharmacological pain treatment Third-line option: Physical activity and psychosocial therapy
National Institute for Health and Care Excellence (NICE) Guideline Low back pain and sciatica in over 16s: assessment and management [17]	First-line option: Patient information and physical activity Second-line option: Nonsteroidal anti-inflammatory drugs and paracetamol in combination with weak opioids Third-line option: Specialist referral
Noninvasive treatment for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians (ACP) [12]	First-line option: Nondrug therapies such as physical activity, acupuncture, relaxation, and biofeedback Second-line option: Nonsteroidal anti-inflammatory drugs Third-line option: Tramadol or duloxetine Fourth-line option: Opioids

OA

OA is characterized by the progressive destruction of articular cartilage associated with subchondral bone remodeling, formation of osteophytes, and secondary inflammation of synovial membranes [20,21]. Pain, mediated by a number of factors, including innervation and vascularization of the articular cartilage, is a principal symptom of OA [21,22]. Compressive forces, along with hypoxia, are believed to stimulate the development of nerves, causing pain even after inflammation has subsided [23]. OA-related pain includes both nociceptive and nonnociceptive components [24], and is associated with abnormally excitable pain pathways in the peripheral and central nervous systems [21].

Symptomatic knee OA is one of the more common forms of OA, experienced by approximately 22.9% of individuals over 40 years, and is a significant cause of disability [25,26]. In France, current OA management guidelines recognize the need for a combinational approach, using both pharmacological and nonpharmacological treatments tailored to each patient. First-line pharmacological options include paracetamol and NSAIDs, followed by opioids, symptomatic slow-acting drugs, and duloxetine (off-label use). Topical agents and intra-articular treatments have also been recommended (Table 2) [27]. Furthermore, these patients often have comorbidities, which may increase the risk of drug-drug interactions and limit the range of drugs that can be used. Age-associated differences in drug sensitivities should also be considered when treating older patients [28,29].

Table 2. Guideline recommendations for osteoarthritis.

Guideline	Disease management options in the guideline
French Society of Rheumatology (Société Française de Rhumatologie) Recommendations on the pharmacological treatment of knee osteoarthritis [27]	First-line option: Nonsteroidal anti-inflammatory drugs (paracetamol if nonsteroidal anti-inflammatory drugs are contraindicated) Second-line option: Weak/strong opioids Third-line option: Symptomatic slow-acting drugs Fourth-line option: Duloxetine
National Institute for Health and Care Excellence (NICE) Osteoarthritis: care and management [30]	First-line option: Patient information, self-management, and thermotherapy Second-line option: Exercise, manual therapy, weight loss, and electrotherapy Third-line option: Pharmaceutical management (eg, creams, paracetamol, nonsteroidal anti-inflammatory drugs, and opioids) Fourth-line option: Surgery
American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee [31]	First-line option: Topical or oral nonsteroidal anti-inflammatory drugs alongside physical, psychosocial, and mind-body approaches Second-line option: Intra-articular glucocorticoid injections, paracetamol, and duloxetine Third-line option: Tramadol

The Role of Paracetamol

Given the similarities in the initial treatment recommendations for both LBP and OA, paracetamol is the most commonly employed first-line analgesic for both conditions, used by over 94.4% of patients with LBP and over 96.0% of patients with OA [32-35]. There are a variety of paracetamol brands available in France, and Doliprane is the most prescribed paracetamol (Table 3) [36,37]. This is backed up by an infodemiology study analyzing 44,283 social media posts, in which Doliprane was the most mentioned paracetamol with 31.7% of posts, followed by Dafalgan with 10.9% of posts and Ixprim with 9.8% of posts [38].

The use of long-term analgesia for patients over 65 years remains challenging, and HCPs must weigh the benefits and risks given the potential increased risk of adverse effects in these patients [39,40]. A high proportion of patients discontinue prescription analgesics within the first few months due to inadequate pain relief or intolerable side effects [41,42]. With few clinical trials enrolling patients over 65 years and fewer incorporating diverse races and ethnicities, there is limited data available for patients over 65 years. Infodemiology, a relatively new method allowing real-word data collection, may help fill the knowledge gap [28]. In this project, infodemiology encompasses electronic medical records (EMRs), interactive online medical forums, and social media (Twitter), allowing analysis of this publicly available, previously unexplored, valuable source of data [43].

As the prevalence of these diseases is expected to increase with the aging population, having a thorough understanding of the requirements of patients who seek treatment is important and may assist in the development of gold-standard care. This retrospective project was designed to provide an insight into the journey of French patients with OA or LBP treated with paracetamol.

Table 3. Chemical and brand names of drugs evaluated for use in lower back pain and osteoarthritis.

Chemical name	Brand name
Betamethasone	Diprostene
Diclofenac	Unbranded Voltarene
Diclofenac epolamine	Flector
Gabapentin	Neurotonin
Ketoprofen	Bi-Profenid
Paracetamol	Dafalgan Doliprane Unbranded
Paracetamol-codeine	Klipal
Paracetamol- dextropropoxyphene	D-Antalvic
Paracetamol-opium	Lamaline
Tramadol-paracetamol	Ixprim

Methods

Project Design

Two retrospective noninterventional studies were performed in France, using EMRs, with a focus on patients with LBP and OA. These studies were distinct, and the data were analyzed separately, but the methods used to generate the results were the same.

The third study, an OA open-source study, used social listening. For this, publicly available data were analyzed, focusing on patients with OA, from both the United States and France.

For all 3 studies, the data collected were used to identify usage of analgesics in anonymized patients with either LBP or OA. This retrospective project analyzed data extracted from EMRs provided by doctors working in the community and discussions on social media. As such, no efficacy or safety data, or reasons for termination of medication were collected.

Population Characteristics and Patient Journey Data Sources

For the EMR studies, prescription data for approximately 3 million people were obtained from general practitioners (GPs) and rheumatologists in France. Comprehensive data on diagnoses, prescriptions, referrals, physician visits, and laboratory results allowed for analysis of pharmacological and nonpharmacological therapies. For patients with OA, data were collected between September 2013 and August 2018, and the following criteria were applied: (1) the patient must have visited a GP or rheumatologist between September 2013 and August 2018; (2) the patient must have at least one OA diagnosis, defined by International Classification of Diseases Version 10 (ICD-10) codes M15-M19; and (3) the patient must have at least one paracetamol prescription. For patients with subacute, acute, or chronic LBP, data were collected between October 2013 and September 2018, and the following criteria were applied: (1) the patient must have visited a GP or rheumatologist between October 2013 and September 2018; (2) the patient must have at least one LBP diagnosis, defined by ICD-10 code M54.5; and (3) the patient must have at least one paracetamol prescription. Distinguishing between different brands of paracetamol was not possible, so drugs were separated by brand name in order to understand usage patterns and distinguish preference.

Details on drugs prescribed in addition to paracetamol were extracted from the database. The drugs included in the analysis were the most frequently used and approved drugs for the treatment of either OA or LBP. For OA, this included ketoprofen, opioids, and NSAIDs in combination with opioids and some intra-articular steroidal injections. For LBP, this included ketoprofen, opioids, and NSAIDs in combination with opioids, intra-articular steroidal injections, antiepileptic drugs, and some antidepressants. In some cases, details of dose and the type of concomitant medication were not collected and therefore not reported in this analysis.

OA Open-Source Study

The OA open-source study, which focused on both French and United States populations, gathered data from only publicly available sources. Questions, comments, and posts related to back pain and OA from both English and French language public medical forums and Twitter were extracted into a text data set. For the United States only, data were extracted for the year 2016 from The Centers for Disease Control and Prevention National Health Interview Survey (CDC NHIS), which comprehensively captures major aspects of a respondent’s health and wellness condition; however, only relevant data, such as demographics, occupation, income bracket, and major medical conditions, were included.

Endpoints

The endpoint of this project was to define the demographics of patients with OA and LBP, and develop an understanding of the management of these conditions in France, including how prescribing methods differ between GPs and rheumatologists. In addition, this project aimed to evaluate the use of paracetamol in patients with OA and LBP within France.

Data Management and Transformation

For the EMR studies, anonymized patient data provided by the Decision Resources Group (DRG) [44] were loaded into the querying platform (Snowflake platform version 3.12.0), and analysis was performed using Structured Query Language. The following transformations and operations were applied to the data: demographics; comorbidities and clinical profiling; treatment persistence; and patient journey.

Patients were stratified by gender and age, as well as provider specialties. Comorbidities and clinical profiling were assessed by interrogating the medical history data that triggered an entry related to a prescription, procedure, or diagnosis in the physician's office. Medical history data were captured as part of a patient's anamnesis. Diagnostic data were captured on an ongoing basis, and medical history data and current diagnoses were consolidated to map a patient's comorbidity profile.

To take into account gender and age, medical history and diagnostic data were assessed to determine the frequency and distribution of diagnoses based on ICD-10 codes (either for OA [M15-M19] or LBP [M54.5]), and these data were then further segmented into gender and age groups (10-year increments).

Treatment persistence was assessed for patients who had received a paracetamol prescription. For this, the first paracetamol prescription was defined as the initiation of therapy, and longitudinal prescription data were then assessed to account for further paracetamol prescriptions over time. For patients with more than 60 days without a prescription, defined by the difference between the first prescription plus days of supply and the subsequent prescriptions, 2 separate pain therapies were reported. Prescription for another main medication, either a different brand or active compound, was considered termination of the preceding pain medication and considered a switch event; however, no distinction between concomitant and new agents was made. Treatment duration was assessed and visualized across the entire population and analyzed in smaller cohorts based on age, gender, and comorbidity profile.

Assessment of the patient journey involved analyzing pain medication dynamics for patients with either OA or LBP across the entire patient population, as well as subcohorts over time. Switching dynamics assessed the share for each pain medication brand by month. This also segmented the patient share for "new" patients, who had no preceding pain medication prescription over the observation period; "switch" patients, who received other pain medication brands and whose treatment was switched during the respective month; and "repeat" patients, who were prescribed the same brand as in the preceding month. Where the volume of data was sufficient for product brands, the patient share and uptake rate analyses were segmented across age, gender, and comorbidity subcohorts.

For the OA open-source study, Python's Natural Language Toolkit library was employed to extract nonrelevant discussions and responses from public medical forums and Twitter data, leaving only the key relevant "talking points," which were then broken down into key words and phrases for analysis. For the CDC NHIS data, all unanswered fields in a record were floored to zero, categorized features were label encoded and dummied to separate columns, and prevalence of OA was selected as the target variable.

Statistical Methods

All analyses conducted in this work were descriptive, and no other confirmatory statistical tests were applied. For the EMR studies, patient data were primarily summarized with percentages, which were calculated using Excel (Microsoft Corp). In some instances, the median for the duration in days was calculated. The data are reflective of what was presented within the EMRs, and no missing values were imputed. Internal DRG therapeutic area experts who specialized in OA and LBP reviewed the results of the analysis for the respective OA or LBP data. For this analysis, in some cases, absolute numbers were recalculated from percentages.

For the OA open-source study, graph/network analysis was applied to study pairwise relationships between the following: symptom-condition, condition-treatment, symptom-medicine, symptom-treatment, symptom-diet and supplements, and symptom-activities. The relationship between 2 terms was determined by their co-occurrence in the same comment or post.

Ethical Considerations

This noninterventional work was performed on fully deidentified and anonymized patient EMRs, and the methodology did not require any human interaction. Therefore, no notifications to the National Competent Authorities or Ethics Committee were required by national and local regulations and requirements.

Results

LBP

LBP Population Characteristics

In the first EMR study, 98,998 patients with LBP were included. The majority (n=69,299, 70.0%) of the patients were between 21 and 60 years, and 54.0% (n=53,459) were female (Table 4). Most (92,068/98,998, 93.0%) patients were treated by a GP, with acute and subacute LBP being the most common complaints. Many patients presented with comorbidities, including additional musculoskeletal system disorders, and respiratory system and digestive system disorders.

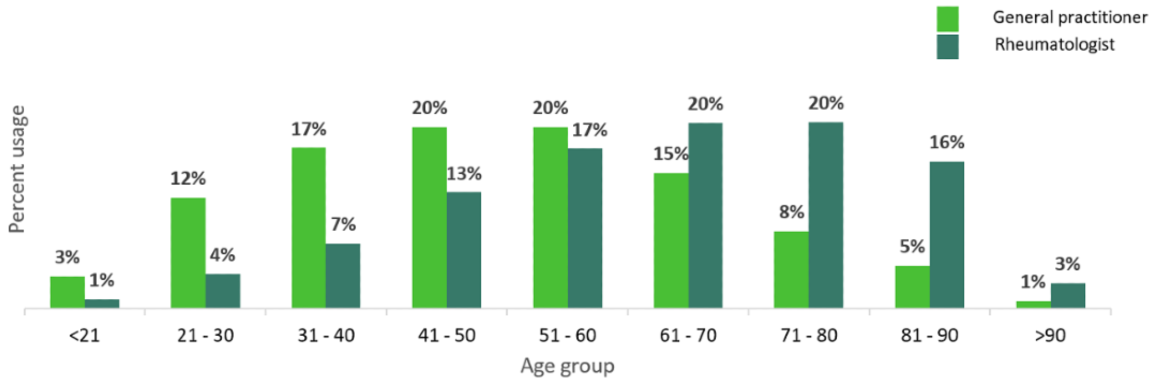
The distribution by age and specialty showed that the difference in distribution was highest in patients aged 21-40 years compared with those aged 61-90 years, who had a higher percentage of visits to the rheumatologist (Figure 1).

Table 4. Patient characteristics for the electronic medical record–based studies.

Baseline demographics	Lower back pain[a] (N=98,998)	Osteoarthritis[a] (N=99,997)
Age (years), n (%)		
<40	30,689 (31.0)	1000 (1.0)
41-50	18,810 (19.0)	3000 (3.0)
51-60	18,810 (19.0)	12,000 (12.0)
61-70	14,850 (15.0)	24,999 (25.0)
71-80	8910 (9.0)	27,999 (28.0)
81-90	4950 (5.0)	23,999 (24.0)
>90	990 (1.0)	6000 (6.0)
Gender, n (%)		
Female	53,459 (54.0)	67,998 (68.0)
Male	45,539 (46.0)	31,999 (32.0)
Care setting, n (%)		
General practitioner	92,068 (93.0)	84,997 (85.0)
Rheumatologist	6930 (7.0)	15,000 (15.0)

[a] Absolute numbers were recalculated from percentages.

Figure 1. Distribution of patients with lower back pain by age group and specialist setting.



Patient Therapeutic Journey

Paracetamol prescription was required for inclusion into the study. Among those included, 87.0% (86,128/98,998) received the Doliprane paracetamol brand as first-line therapy and 71.0% (61,151/86,128) were taking it in combination with other drugs, such as NSAIDs or opioids.

Of the 12.0% (10,335/86,128) of patients who switched from the Doliprane brand to a second-line therapy, 52.0% (5374/10,335) received an alternative paracetamol product, of which, Lamaline, Dafalgan, and Ixprim were equally prescribed (all n=215, 4.0%). Voltarene (397/4961, 8.0%) was the most popular option for the 48.0% (4961/10,335) of patients who switched to a nonparacetamol product as second-line therapy, followed by Bi-Profenid (198/4961, 4.0%).

Of the 13.0% (12,870/98,998) of patients who received a non-Doliprane brand paracetamol as first-line therapy, 57.0% (7336/12,870) switched to Doliprane as second-line therapy, and 43.0% (5534/12,870) of those taking a nonparacetamol product as first-line therapy switched to Doliprane as second-line therapy. Of those taking Doliprane as second-line therapy, 69.0% (5062/7336) were using it in combination with other drugs, such as NSAIDs or opioids.

Assessing the choice of treatment by episode and setting, the prescribing patterns of paracetamol as a monotherapy by GPs appeared consistent over multiple episodes; however, their use of paracetamol combination treatments decreased over time and the use of other drugs increased (Figure 2).

Reviewing the top 5 brand paracetamol agents used for the treatment of LBP, Doliprane was the most used (approximately 57.0% [52,440/92,000] and 64.0% [3840/6000] for GPs and rheumatologists, respectively), with GPs making more use of unbranded paracetamol and Bi-Profenid, compared with rheumatologists, who favored Flector and Diprostene (Table 5). For rheumatologist prescriptions, the use of Doliprane as monotherapy and combination therapy decreased over time.

Overall, 90.0% (89,098/98,998) of all paracetamol products prescribed were branded and 79.0% (57,670/73,000) of all nonparacetamol medications were branded.

Figure 2. Distribution of patients with lower back pain on Doliprane versus other medications by episode.

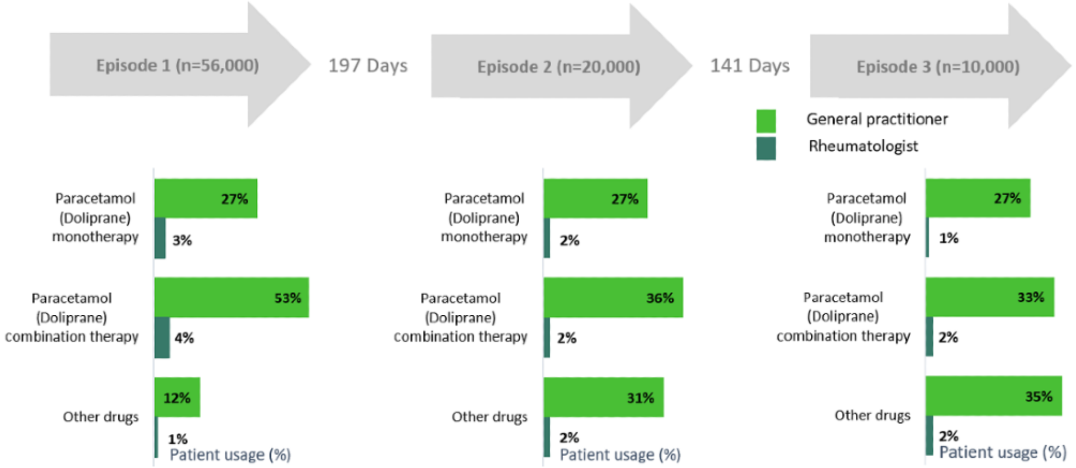


Table 5. The top 5 agents prescribed for patients with lower back pain by general practitioners and rheumatologists.

Drug used	General practitioner[a] (N=92,000), n (%)	Rheumatologist[a] (N=6,000), n (%)
Paracetamol (Doliprane)	52,440 (57.0)	3840 (64.0)
Paracetamol (Dafalgan)	26,680 (29.0)	1620 (27.0)
Paracetamol (Voltarene)	16,560 (18.0)	480 (8.0)
Paracetamol (unbranded)	12,880 (14.0)	N/A[b]
Ketoprofen (Bi-Profenid)	11,040 (12.0)	N/A
Diclofenac epolamine (Flector)	N/A	600 (10.0)
Betamethasone (Diprostene)	N/A	540 (9.0)

[a] Absolute numbers were recalculated from percentages.

[b] N/A: not applicable.

OA

OA Population Characteristics

In the second EMR study, 99,997 patients with OA were included, of which, 96.0% (n=95,997) were over 50 years, with most between 71 and 80 years (n=27,999, 28.0%), and 68.0% (n=67,998) were female (Table 4). The majority (84,997/99,997, 85.0%) of cases were seen by a GP, of which, approximately 60.0% (50,998/84,997) were for diffuse OA or unspecified OA; in comparison, 67.0% (10,050/15,000) of cases seen by a rheumatologist were for knee OA.

Patient Therapeutic Journey

Doliprane as a prescribed paracetamol brand was the most common analgesic of those analyzed among both GP and rheumatology specialties, being the first-line therapy for 83.0% (82,998/99,997) of patients. Among patients who received Doliprane as a prescribed paracetamol first-line therapy, 62.0% (51,459/82,998) used it in combination with another drug. Of the 13.0% (10,790/82,998) of patients who used Doliprane as a prescribed paracetamol first-line therapy and switched to an alternative therapy, 30.0% (3237/10,790) moved to an alternative paracetamol product, with the most common being Dafalgan (194/3237, 6.0%), followed by Lamaline (129/3237, 4.0%), while 70.0% (7553/10,790) moved to a nonparacetamol product, with the most common being diclofenac (Voltarene) (906/7553, 12.0%), followed by Flector (453/7553, 6.0%). Among the patients who switched from a non-Doliprane drug (n=16,999) as a prescribed first-line therapy, 30.0% (5100/16,999) of those taking paracetamol moved to Doliprane as second-line therapy, and 70.0% (11,899/16,999) of those taking a nonparacetamol product moved to Doliprane as second-line therapy. Among those for whom Doliprane was a prescribed paracetamol brand as a second-line therapy, 63.0% (10,709/16,999) were using it as a combination therapy.

GPs showed fairly consistent prescribing patterns, with Doliprane as monotherapy being the most common choice across episodes; however, rheumatologist prescribing patterns were comparatively less consistent (Figure 3).

Reviewing the top 5 paracetamol agents prescribed overall for OA, Doliprane as a prescribed brand was the most popular in both GP (48,999/99,997, 49.0%) and rheumatologist (11,000/99,997, 11.0%) settings, followed by Dafalgan (Figure 4). Regarding nonparacetamol agents, Voltarene was prescribed in 27.0% (15,120/56,000) of patients by GPs and 4.0% (2,240/56,000) by rheumatologists, followed by Flector (Figure 4). Of the paracetamol products prescribed, 92.0% (91,997/99,997) were branded, and of the nonparacetamol products prescribed, 86.0% (48,160/56,000) were branded. Overall, paracetamol was favored over NSAIDs for both LBP and OA; however, NSAID use was higher in patients with OA.

Figure 3. Distribution of patients with osteoarthritis on Doliprane versus other medications by episode.

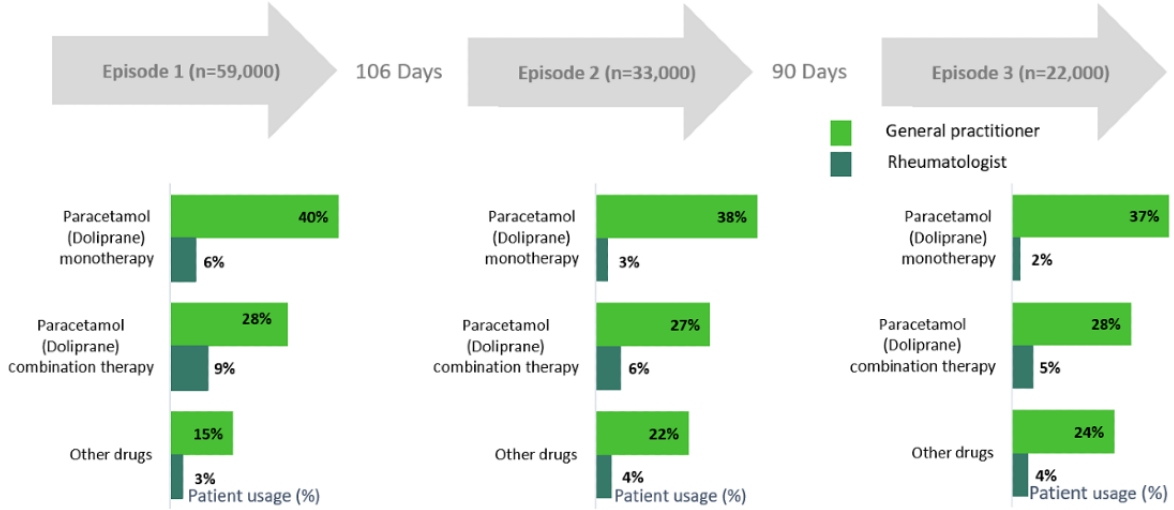
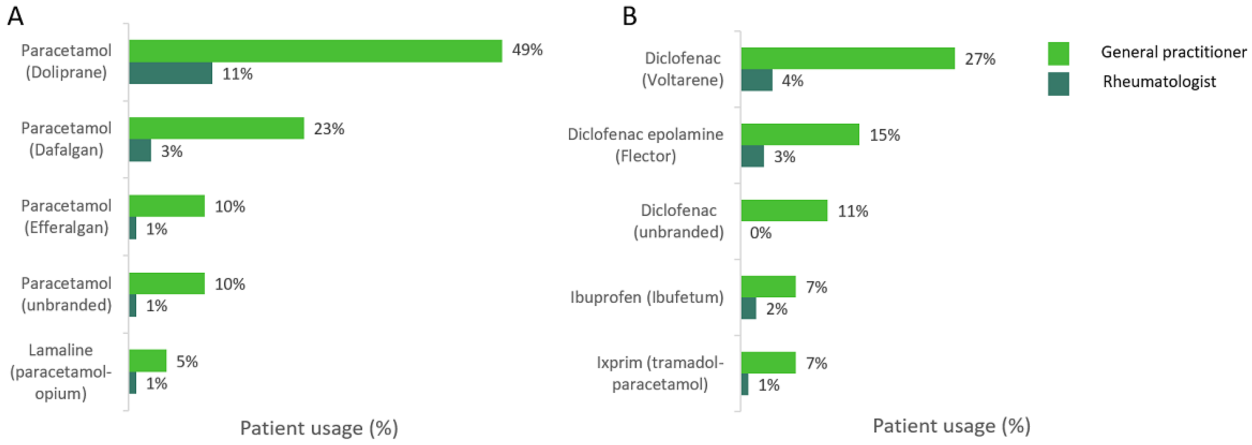


Figure 4. The top 5 agents among (A) paracetamol and (B) nonparacetamol treatments for patients with osteoarthritis.



OA Open-Source Study

Population Characteristics

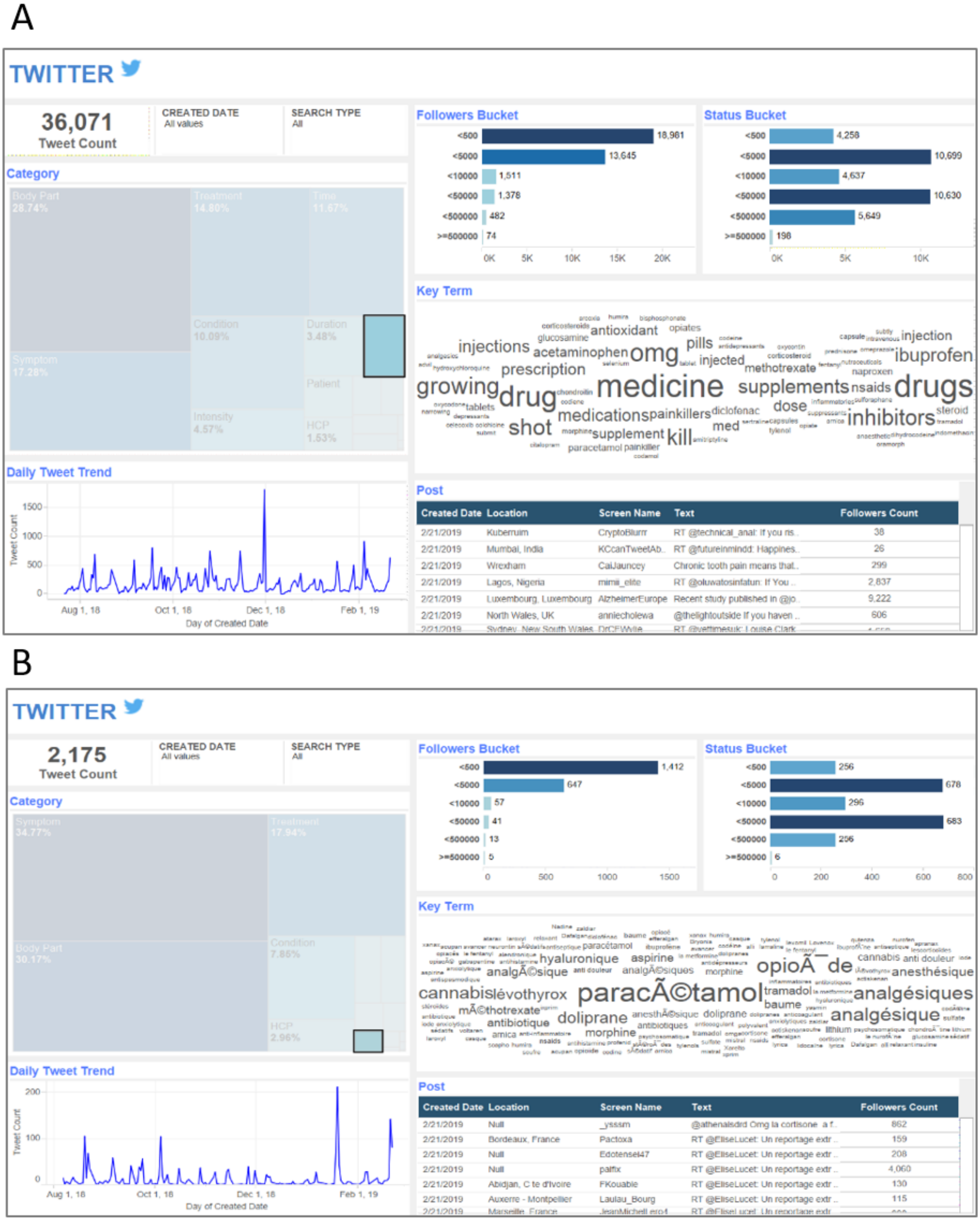
The OA open-source study, using data obtained by social listening, showed that OA occurrence increases with age, that is, approximately 91.5% (212,875/232,650) of patients were over 41 years. These data suggest that the overall incidence of OA is 17.3% (40,248/232,650) and that OA is more predominant in females (46,530/232,650, 20.0%) than males (32,571/232,650, 14.0%). Furnishing workers, communications equipment operators, and workers in military-specific occupations reported the highest incidence of OA, whereas life and physical scientists and computer specialists reported the lowest rates. There is an indication that both smoking and alcohol consumption may influence the overall risk of OA. The most common comorbidities reported, including circulatory and respiratory system disorders, are shown in Multimedia Appendix 1.

Patient Therapeutic Journey

According to the data obtained from medical forums, pain was the most commonly reported reason for using medication, with anti-inflammatory drugs and analgesics mentioned the most. Specific drugs, such as tramadol, Doliprane, Dafalgan, and Voltarene, were also mentioned. The discussion around pain medications shifted from analgesics and NSAIDs, to stronger medications, such as morphine, Lamaline, Di-Antalvic, Neurontin, and Klipal, as pain intensity increased.

From the 285,315 posts discussing when to seek medical advice on Twitter, the primary reasons identified were inflammation, pain, overweight, stiffness, and swelling. Evidence also suggested that noninvasive nonpharmacological options, such as massage therapy, are generally preferred by patients for the management of OA-related pain. Of the 36,071 posts discussing pain medications in the context of back pain and OA, 2175 posts revealed that paracetamol, analgesics, and opioids were the most frequently discussed (Figure 5). Furthermore, posts from France were more likely to mention specific drug names or classes, whereas posts from the United States contained general terms related to medicine.

Figure 5. The most commonly used medications for osteoarthritis-related pain according to Twitter in (A) English (United States) and (B) French (France). Information was collected through the automated metrics provided by each of the social media monitored during the study.



Daily Tweet Trend

Post

Created Date	Location	Screen Name	Text	Followers Count
2/21/2019	Kuberruim	CryptoBlurrr	RT @technical_anal: If you ris..	38
2/21/2019	Mumbai, India	KCcanTweetAb..	RT @futureinmindd: Happines..	26
2/21/2019	Wrexham	CaiJauncey	Chronic tooth pain means that..	299
2/21/2019	Lagos, Nigeria	mimii_elite	RT @oluwatosinfatun: If You ..	2,837
2/21/2019	Luxembourg, Luxembourg	AlzheimerEurope	Recent study published in @jo..	9,222
2/21/2019	North Wales, UK	anniecholewa	@thelightoutside If you haven ..	606

Daily Tweet Trend

Post

Created Date	Location	Screen Name	Text	Followers Count
2/21/2019	Null	_yssm	@athenaisdrd Omg la cortisone a f..	862
2/21/2019	Bordeaux, France	Pactoxa	RT @EliseLucet: Un reportage extr ..	159
2/21/2019	Null	Edotensei47	RT @EliseLucet: Un reportage extr ..	208
2/21/2019	Null	palfix	RT @EliseLucet: Un reportage extr ..	4,060
2/21/2019	Abidjan, C te d'Ivoire	FKouable	RT @EliseLucet: Un reportage extr ..	130
2/21/2019	Auxerre - Montpellier	Laulau_Bourg	RT @EliseLucet: Un reportage extr ..	115

Discussion

This overview of analgesic usage in France analyzed data obtained from GP and rheumatologist practice settings, along with information extracted from publicly available sources, such as medical forums and Twitter, in France and the United States. The data presented within this project provides several insights into the journey of patients with LBP and OA.

In this project, across all 3 studies, the proportion of women experiencing LBP or OA was higher than that in men. In line with this finding, a study in France assessing chronic musculoskeletal pain found a higher prevalence in women (41%, 95% CI 40.2-42.4) than in men (29%, 95% CI 28.0-30.3) [45]. We showed that the prevalence of OA increases with age, with the majority of patients being over 60 years. This was expected, owing to the degenerative nature of this disease that progresses with age [46,47].

With 70.0% of the patients with LBP aged between 21 and 60 years, lifestyle and physical workload have been considered factors associated with an increased risk of LBP [48]. Data obtained from patient records indicated that a higher percentage of patients with LBP and OA visited GPs as opposed to rheumatologists, likely due to the need for a referral in order to see a specialist. Additionally, older patients (>61 years) were more likely to visit a rheumatologist rather than a GP, possibly due to pre-existing comorbidities (eg, arthritis).

The top 5 treatments prescribed by GPs and rheumatologists differed between conditions, with diclofenac use more prevalent in patients with OA, possibly reflecting the differences in practice guidelines. However, these variations could also be attributed to the different underlying pain mechanisms involved (eg, chronic vs acute pain), with chronic inflammation predominant in patients with OA [49].

In both EMR studies, the majority of prescriptions, both for paracetamol and nonparacetamol, were branded, possibly due to the majority of patients in France using national insurance to cover medical costs [50]. In both cohorts, increasing episodes correlated with increased drug use over time and a shorter duration between episodes, indicating that patients who need repeat visits require stronger medication to manage disease progression.

In the OA open-source study, social listening, a relatively new approach, was used to gain better insights into OA prevalence and the treatment strategies employed by patients with OA across France and the United States. Due to instant accessibility and ease of use, many patients turn to online interactive medical forums or other social media platforms to discuss medical issues and treatment strategies. Social listening allows the exploration of this potentially valuable source of information [51,52]. Analysis of thousands of medical forums suggested that OA occurs in approximately 17.3% of the general population in the United States. These data also indicated that the majority of patients with OA are over 41 years, and that the incidence is higher in females (20.0%) than males (14.0%). Pain appeared to be the main reason prompting patients to seek medical care and for the initiation of pharmacological treatment, with both anti-inflammatory drugs and analgesics commonly discussed. With increasing pain, the discussion shifted to stronger medications, such as morphine, Lamaline, Di-Antalvic, Neurontin, and Klipal; however, social media posts suggested that patients prefer nonpharmacological options, such as massage.

Notably, patients in France were more likely to tweet about specific drug classes (eg, NSAIDs and opioids) and drug names (paracetamol), whereas patients in the United States were more likely to tweet general terms, such as medicine and medication. Paracetamol was well recognized as a first-line therapy for both OA and LBP [53-55], and a 2005 international study that reviewed the opinions of HCPs found that 82.0% of rheumatologists and 90.0% of French GPs recommended paracetamol as first-line therapy for OA. In this project, 76.0% of patients interviewed were taking paracetamol for OA and a further 39.0% of patients had switched from an NSAID due to side effects [56].

On the other hand, contrary evidence on the efficacy of paracetamol for musculoskeletal disorders has been published. A randomized double-blind study by Williams et al [32] compared paracetamol use with placebo for the treatment of acute back pain in 1643 participants and found no effect on recovery time. The median time to recovery was 17 days (95% CI 14-19) for those who took paracetamol regularly, 17 days (95% CI 15-20) for those who took paracetamol as needed, and 16 days (95% CI 14-20) for the placebo group [32]. Additionally, a meta-analysis review that included 1785 cases reported that paracetamol did not produce better outcomes than placebo for patients with LBP, including for scores of sleep, quality of life, or physical function [57]. Interestingly, a 2005 meta-analysis review found that paracetamol use was an effective pain management approach for patients with chronic pain, with a favorable safety profile compared with NSAIDs, recommending that paracetamol be used as an NSAID sparer [58]. Another meta-analysis review of 10 randomized controlled trials, including 1712 patients with OA, found that while NSAIDs were more effective than paracetamol for pain relief, paracetamol was still effective [59]. Conversely, paracetamol in combination with weak opioids (eg, tramadol) has been proven to be effective in managing pain symptoms associated with OA [60]. In addition to being clinically ineffective in the treatment of LBP and OA, use of paracetamol can result in abnormal liver function test results compared with placebo [61].

The conflicting evidence on the efficacy of paracetamol may, in part, be due to the different types of pain experienced by patients. Nociplastic pain, defined as pain occurring through altered nociception without nociceptor activation and nerve injury, is characterized by widespread pain through multiple body regions and often causes ongoing pain symptoms [60]. However, neuropathic pain is caused by nerve damage and often does not respond to certain medications. As such, it is important to identify the type of pain, as different therapies may be needed for appropriate management [62]. Given the conflicting evidence around the benefits of paracetamol for musculoskeletal disorders, current guidelines for the treatment of OA and LBP now vary on whether paracetamol is recommended as a first-line therapy.

Multiple guidelines, including the 2016 recommendations from the National Institute of Clinical Excellence (NICE) and the 2017 American College of Physicians clinical guidelines, advise against the use of paracetamol alone as a first-line therapy for acute LBP [17,55,63-65]; however, paracetamol is still recommended as an effective treatment in some guidelines, including the 2019 American College of Rheumatology guidelines for the management of OA and the 2019 Osteoarthritis Research Society International (OARSI) guidelines for the nonsurgical treatment of knee OA [66]. Nevertheless, it is clear from the data in this project that many physicians are still prescribing paracetamol both alone and in combination with other drugs as first- and second-line therapy.

Pain, a significant symptom for both OA and LBP, is complex and multifaceted, and is influenced by many aspects of a patient's body and environment. It is affected by, but not limited to, their mood, sleep patterns, and avoidance behavior [2,67,68]. The relationship between HCPs and the patients who experience musculoskeletal pain is important, with guidelines recommending that they engage in shared decision-making, taking into consideration the needs of the patients, as well as their comorbidities, preferences, and values [69], and ensuring that patients receive enough information related to their condition in a clear and concise manner [70]. Consequently, it is important to not only address pain medication needs, but also ensure that the patient's specific needs are addressed throughout the patient journey. It is hoped that the data in this project may provide insights into the patient journey, to assist physicians by highlighting prescribing patterns, so that they may make informed decisions when treating their patients.

The limitations associated with obtaining data through EMRs include the fact that only information recorded by the HCP is available for analysis, providing a possible information bias, as the EMR may not always contain accurate information because it relies on the patients to provide factual reports of their condition and medication consumption to the physician. Additionally, the data were not adjusted to account for disease severity. Furthermore, while treatment switches were recorded, details on the reasons for treatment switches were not available due to a lack of physician notes. It should also be noted that different patient identification methods are used within the EMRs, depending on the patient setting, which may mean that only part of a patient's journey is captured. Since these data did not record self-medication with over-the-counter drugs or the dose of paracetamol prescribed, the actual consumption of analgesics in these patients could be higher.

The use of EMRs within this project had advantages with the supply of data from multiple settings. The project period allowed review of the treatment journey over multiple years, and included recent data for visibility of current trends. The use of social listening also allowed access to extensive information, which could lead to better understanding of the real-world management of LBP and OA. Combining these methodologies provided a substantial overview of a patient's journey, allowing for the analysis of treatment selection and providing a better understanding of the health care system and its strengths and weaknesses overall.

Overall, this exploratory study used infodemiology, a new data collection approach, to confirm the currently available literature on the epidemiology of LBP and OA, and investigate commonly used treatment strategies. In France, LBP and OA are prevalent musculoskeletal conditions, with OA predominantly affecting patients over 60 years of age and LBP predominantly affecting patients between 21 and 60 years of age; in both groups, the majority of patients are female. Although the use of paracetamol as a first-line analgesic to treat patients with OA and LBP is quite common, its efficacy is debatable. Usage variability between GPs and rheumatologists suggests that OA severity differs among settings. These data will provide clinicians, pharmacists, and patients with a better understanding of the usage of analgesic medications within these settings, and aid in the understanding of prescriber behavior in the real-world setting when treating musculoskeletal disorders.

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Conflicts of Interest

LM, HK, and CEB are employees of Sanofi and may hold shares or stock options in the company. GP has received consultancy fees from Grunenthal, Mylan, MundiPharma, and Sanofi.

Multimedia Appendix 1
Comorbidity conditions recorded for patients.
[DOCX File , 14 KB - publichealth_v8i10e37790_app1.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
DRG: Decision Resources Group
EMR: electronic medical record
GP: general practitioner
HCP: health care professional
ICD-10: International Classification of Diseases Version 10
LBP: lower back pain
NHIS: National Health Interview Survey
NSAID: nonsteroidal anti-inflammatory drug
OA: osteoarthritis

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Original Paper

Excessive Drinking Among Men Who Have Sex With Men Recruited From Web-Based Resources: Cross-sectional Questionnaire Study

César Pérez-Romero[1*], MPH; Juan-Miguel Guerras[2,3*], PhD; Juan Hoyos[4*], PhD; Marta Donat[1,3*], MPH; Gregorio Barrio[1,3*], PhD; Luis de la Fuente[2,3*], PhD; David Palma[3,5*], MPH; Patricia García de Olalla[3,5*], MPH; María-José Belza[1,3*], PhD; Methysos Project Group[6*]

[1]Escuela Nacional de Sanidad, Instituto de Salud Carlos III, Madrid, Spain
[2]Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain
[3]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública, Madrid, Spain
[4]Departamento de Salud Pública y Materno-Infantil, Universidad Complutense de Madrid, Madrid, Spain
[5]Servicio de Epidemiología, Agència de Salut Pública de Barcelona, Barcelona, Spain
[6]see Acknowledgments
[*]all authors contributed equally

Corresponding Author:
Juan-Miguel Guerras, PhD
Centro Nacional de Epidemiología
Instituto de Salud Carlos III
Avenida Monforte de Lemos 5
Madrid, 28029
Spain
Phone: 34 918222699
Email: guerrasmoreira@hotmail.com

Abstract

Background: US and Northern European studies have found a higher prevalence of alcohol-related problems among men who have sex with men (MSM) than among the general population of men (GPM). However, most of them relied on traditional sampling methods, not profiting from MSM dating apps and websites for recruitment. Besides, analogous comparisons in Southern Europe are lacking.

Objective: This study aimed to compare several indicators of excessive drinking between MSM and GPM in Spain.

Methods: Overall, 5862 MSM were recruited through dating apps or websites for the Méthysos Project, and 10,349 GPM were recruited using probability sampling via the Household Survey on Alcohol and Drugs in Spain from 2018 to 2020. The outcomes were the prevalence of hazardous or harmful drinking (Alcohol Use Disorders Identification Test [AUDIT] ≥8), hazardous drinking (AUDIT-Consumption ≥4), harmful drinking (AUDIT-Problem ≥4), regular hazardous drinking (>14 standard drinks per week), and monthly binge drinking. The prevalence of excessive drinking indicators was calculated for MSM and GPM and compared using the adjusted prevalence ratio (aPR). Two different aPRs and their 95% CIs were estimated using Poisson regression models with robust variance. The first was adjusted for sociodemographic characteristics, and the second was adjusted for the aforementioned covariates plus other drug use.

Results: The prevalence of hazardous or harmful drinking was 15.6% (913/5862) among MSM versus 7.7% (902/10,349) among GPM. After adjusting for sociodemographic covariates, the risk was higher in MSM than in GPM for harmful or hazardous drinking (aPR 1.8, 95% CI 1.6-2.0), harmful drinking (aPR 2.3, 95% CI 2.0-2.7), and binge drinking (aPR 1.7, 95% CI 1.5-1.9); the same in both populations for hazardous drinking (aPR 0.9, 95% CI 0.9-1.0); and higher in GPM than in MSM for regular hazardous drinking (aPR 0.7, 95% CI 0.6-0.9). The relative excess risk of harmful drinking and binge drinking among MSM tended to increase with increasing education level and size of the place of residence, and the opposite was true for the deficit risk in regular hazardous drinking. Additional adjustment for other drug use greatly buffered the relative excess risk in harmful drinking and binge drinking in MSM, while it deepened its deficit risk in regular hazardous drinking.

Conclusions: The use of web-based resources allowed recruiting a large sample of MSM. The risk of hazardous or harmful drinking was 80% greater in MSM than in GPM, which was mainly because of the higher risk of harmful drinking and binge drinking among MSM. Nearly 1 in 6 MSM would benefit from early brief alcohol intervention procedures. The subgroup with harmful or binge drinking combined with other drug use is an important contributor to excess MSM risk in hazardous or harmful drinking and must be a priority target for harm reduction interventions.

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KEYWORDS

alcohol use; men who have sex with men; MSM; dating apps or websites; new recruitment methods; Alcohol Use Disorders Identification Test; AUDIT; hazardous drinking; harmful drinking; binge drinking; alcohol-related problems

Introduction

In recent years, concerns have been raised about health disparities due to sexual orientation [1-5]. Surveys in the United States have found a higher prevalence of alcohol-related problems among men who have sex with men (MSM) compared with general population of men (GPM) [6-9]. However, studies on the prevalence of excessive drinking and frequency of binge drinking have not found significant increases among MSM [1,2,7,10-13]. Here may be a disparity in alcohol indicators between MSM and GPM depending on what is measured: consumption levels or consequences of alcohol use. It should be noted that there are some exceptions: some studies describe higher consumption levels among certain subgroups of MSM [14-16].

To our knowledge, the only studies in Europe that compared alcohol use between MSM and GPM have been conducted in Northern or Central European countries [2,17-21]. One study in Sweden showed more alcohol-related problems, but not increased consumption, among MSM than among heterosexuals [17]. Another study in Sweden, found a higher prevalence of high-risk alcohol use among homosexuals (men and women jointly) but not among bisexual men [18]. Other studies in the United Kingdom [2,20] or The Netherlands [21] did not observe significant differences in consumption levels, while a recent study in Ireland [22] showed a 3-fold increase in the prevalence of alcohol use disorder in MSM compared with GPM, although 2 different instruments were used.

Knowledge of alcohol use among MSM living in southern European countries is important given that historical cultural norms regarding alcohol use differ between these countries and those where research has been conducted [23]. The Mediterranean consumption pattern, characterized by almost daily drinking (primarily wine accompanying meals), may be less followed by MSM living in Southern European countries compared with GPM, given their higher openness to the cultural habits of other countries. This could affect findings among MSM in terms of both alcohol consumption and related problems.

In contrast, most of the former studies comparing MSM and GPM are based on representative population samples [2,7,9,12,16]. This method, although ensuring probabilistic recruitment, entails as a substantial limitation the small sample of MSM frequently included. We consider that recruitment methods based on new technologies, such as apps and websites, may overcome this problem and increase the size of the MSM sample.

A common problem when comparing drinking indicators between MSM and GPM is the existence of important differences between both groups in sociodemographic characteristics (such as age, place of residence, immigration, or socioeconomic status) that can distort the comparison [24-28]. To avoid this, it is necessary to adjust the comparative measures for these covariates carefully. In addition, the evidence shows that the use of other psychoactive drugs is higher in MSM than in GPM [29], so the difference between comparative measures with and without adjustment for such covariates will allow us to estimate which part of the MSM-GPM differences in drinking indicators can be explained by differences in the use of other drugs.

The Alcohol Use Disorders Identification Test (AUDIT) is a 10-item scale that screens for alcohol use disorders to identify and assist individuals at high risk [30]. It includes several subscales, the most widespread of which is the AUDIT-Consumption (AUDIT-C) (consumption items, Q1-Q3) [31-34]. However, although AUDIT-C performs well as a proxy for hazardous drinking, it is less accurate in identifying alcohol-related problems [35-38], especially within the framework of general population surveys [39]. The complementary subscale AUDIT-Problem (AUDIT-P) (problems items, Q4-Q10) has been shown to screen for these issues as well as full-scale [35]. Some authors have suggested that this two-factor conceptualization (consumption and problems, AUDIT-C and AUDIT-P) is a better fit for scale content than the three-factor structure originally proposed [40].

To the best of our knowledge, only 2 published studies have compared AUDIT scores between MSM and GPM [19,41]. The results were not separated according to consumption or related problems. One of the two studies focused on the full-scale score, whereas the other focused only on AUDIT-C. In contrast, other studies that analyzed AUDIT among MSM did not include a comparative sample of GPM, and none analyzed AUDIT-P separately [42-48].

In this study, we took advantage of dating apps and websites commonly used by MSM to recruit a large sample of MSM and compare various indicators of excessive drinking, including hazardous and harmful drinking, between MSM and GPM in Spain. We used the AUDIT to assess MSM who would potentially benefit from early alcohol interventions. In addition, we aimed to discern the differences between the 2 dimensions of hazardous drinking (distinguishing regular hazardous drinking from binge drinking) and harmful drinking.

Methods

Study Design

We conducted a cross-sectional comparison of several measures of excessive drinking between MSM and GPM in Spain. Data were obtained from the results of the AUDIT questionnaire on 2 different samples for MSM and GPM.

Setting

The MSM sample included participants from the Méthysos Project, which aimed to investigate their health status. Participants were recruited through different web-based resources (see *Participants, MSM Sample*) between May and July 2020. The GPM sample was recruited between February and April 2018 within the framework of the Household Survey on Alcohol and Drugs in Spain (Encuesta Sobre Alcohol y Otras Drogas en España [EDADES], 2017 edition) [49].

Participants

MSM Sample

MSM were invited to participate through 3 types of web-based resources:

1. A total of 7 MSM dating apps using promotional banners (Scruff, Grindr), personal messages (GROWLr), or both (Wapo, Bakala, MachoBB, and Xtudr) contributed 70.5% (4655/6602) of the participants.
2. Furthermore, 3 influencers largely followed by the MSM community (Gabriel José Martin–with a video on YouTube available throughout the recruitment period–and @frewaskachannel and @tigrilloig–with 24-hours available stories launched twice (@frewaskachannel) or once (@tigrilloig) during the recruitment period), which contributed 26.3% (1741/6602) of the participants.
3. Finally, a message encouraging the diffusion of the study among friends and acquaintances, placed at the end of the questionnaire, and distribution lists from 3 organizations (Agència de Salut Pública de Barcelona, Pink Peace, and Chem-Safe), which contributed with 3.1% (206/6602) of the participants.

Individuals who decided to participate were addressed to an initial screen where they were informed about the aim and content of the survey. Before starting, they were obliged to check on the “I am of legal age for sexual intercourse and want to participate in the study.” All participants were required to meet the inclusion criteria of being male, at least 16 years old, and having ever had anal intercourse with a male. We provided unique links to each recruitment site to identify the recruitment site for each participant. To avoid multiple participation, the initial screen also included a request to complete the questionnaire only once if the invitation was received in various ways. In addition, to further limit the possibility of multiple responses from one individual, we used the option provided by the software that only allowed the completion of one questionnaire per electronic device. No incentive was offered for participation, limiting the chances of multiple participation. The questionnaire was self-administered, computer- or app-based, and treated for sexual behavior and drug and alcohol use (including AUDIT). The full questionnaire is available in the Multimedia Appendix 1.

In studies using this type of methodology, it is impossible to calculate or estimate the response rate. The apps identify the number of displayed banners and sometimes the number of clicks on the banner, but not the number of different people who see or click on them to obtain some information. Something similar happens with influencers. They may know the number of views on a promotion, but not the number of people, or whether those people meet the criteria to participate. Of the 6602 MSM who began the questionnaire, 740 abandoned it before completing the AUDIT questions; thus, the final sample comprised 5862 MSM.

GPM Sample

The GPM sample was obtained from the anonymous database of EDADES, 2017 edition provided by the National Plan on Drugs. The EDADES is a biennial national survey of a representative sample of the population aged 15-64 years living in Spain. It uses a 3-stage random sampling design (census tract, household, and individual sampling). Census tracts and subjects within households were selected using random probabilistic methods. The sample was stratified by age (15-34/35-64) and living region (19 categories). In this edition, people aged 15 to 34 years and living in small regions were oversampled, so analyses were weighted to account for strata imbalance compared with the universe. The global response rate was 50.6%, and the main causes of nonresponse were not opening the door, preventing interviews, and the absence of all household members or the selected person. Before classifying a household or person as absent and selecting another household, the fieldworker should visit the household that was initially selected at least three times on different days and times.

We selected all men aged 16-64 years who participated in the survey (women and men aged 15 years were excluded). EDADES does not have any variables to identify sexual identity or behavior; thus, we could not estimate the proportion of MSM among the group of men participating in the survey, nor excluding them in our analysis. Therefore, we refer to this group as GPM. However, we can infer that this sample is principally composed of heterosexual men, relying on the most recent estimation of the Spanish population on sexual orientation, in which 93.9% (2791/2972) of people declare themselves heterosexual [50]. The EDADES used a self-administered paper-and-pencil questionnaire. The interviewer was present in the household to support the participant if needed. The questions included the AUDIT. We provided the full questionnaire used in the 2017 edition (only in Spanish) in the Multimedia Appendix 2. More information about the survey methodology is available on web [49]. Of the 10,576 GPM who began the questionnaire, 227 (2.1%) abandoned it before completing the AUDIT questions; thus, the final sample comprised 10,349 GPM.

Variables

Only the participants who had consumed alcohol in the past 12 months answered the AUDIT questionnaire. For the remaining participants, the AUDIT score was imputed as 0. Questionnaire skips were automatically included in the resources used by the MSM sample but had to be manually included in the GPM sample. Textbox 1 presents the AUDIT questionnaire.

This study uses labels and concepts from the recently published 11th revision of the International Classification of Diseases [51] to refer to the different AUDIT measures analyzed. Hazardous alcohol use is defined as “a pattern of alcohol use that appreciably increases the risk of harmful physical or mental health consequences to the user or to others,” while a harmful pattern of use of alcohol is that which “has caused damage to a person’s physical or mental health or has resulted in behavior leading to harm to the health of others.” Even if the AUDIT tool considers the concept of alcohol dependence [30], we opted to include all harm-related questions (dependence and harm) in a single variable for harmful drinking. As explained above, this was done to accomplish the two-domain division of AUDIT (consumption and consequences). The results of the full-scale AUDIT (including questions for hazardous and harmful drinking) were categorized as hazardous or harmful drinking.

Regarding consumption levels, we differentiated a variable of regular hazardous drinking (cumulative weekly exposure to alcohol over a pre-established threshold) from binge drinking to identify differences in drinking patterns. Although weekly alcohol consumption above a certain threshold entails health-related consequences [52], these are expected to be more severe when engaging in binge drinking [53]. Regular hazardous drinking has been named “excessive” or “heavy” drinking elsewhere [15,54], while binge drinking (consumption of more than 5 drinks on one occasion, sometimes equated to 2 hours) is also referred to as “heavy episodic drinking” [12] or “risky single occasion drinking” [25].

Textbox 1. Alcohol Use Disorders Identification Test (AUDIT) questionnaire (English version) [30]. Full-scale AUDIT comprises all questions (score between 0 and 40; utilized threshold: 8), AUDIT-Consumption comprises questions Q1 to Q3 (score 0-12; utilized threshold: 4), and AUDIT-Problem questions Q4 to Q10 (score 0-28; utilized threshold: 4).

Q1. How often do you have a drink containing alcohol?

0. Never (skip to Qs 9-10)
1. Monthly or less
2. 2-4 times a month
3. 2-3 times a week
4. 4 or more times a week

Q2. How many drinks containing alcohol do you have on a typical day when you are drinking?

0. 1 or 2
1. 3 or 4
2. 5 or 6
3. 7, 8, or 9
4. 10 or more

Q3. How often do you have six or more drinks on one occasion?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily or almost daily

Skip to questions 9 and 10 if total score for questions 2 and 3=0

Q4. How often during the last year have you found that you were not able to stop drinking once you had started?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily or almost daily

Q5. How often during the last year have you failed to do what was normally expected from you because of drinking?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily or almost daily

Q6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

0. Never
1. Less than monthly
2. Monthly
3. Weekly
4. Daily or almost daily

Q7. How often during the last year have you had a feeling of guilt or remorse after drinking?

0. Never
1. Less than monthly
2. Monthly

3. Weekly

4. Daily or almost daily

Q8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

0. Never

1. Less than monthly

2. Monthly

3. Weekly

4. Daily or almost daily

Q9. Have you or someone else been injured because of your drinking?

0. No

2. Yes, but not in the last year

4. Yes, during the last year.

Q10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

0. No

2. Yes, but not in the last year

4. Yes, during the last year.

Quantitative Variables

Scores for the full-scale AUDIT (hazardous or harmful drinking), AUDIT-C (hazardous drinking), and AUDIT-P (harmful drinking or alcohol-related problems) instruments were calculated by adding the scores in Q1-10, Q1-Q3, and Q4-Q10, respectively. The weekly average number of standard drinks was used as an indicator of the intensity of regular alcohol consumption. It was estimated by multiplying the answers for questions on drinking frequency (Q1) and quantity (Q2). To this end, the median values of each response category of Q1 and Q2 were used, except for the extreme categories "monthly or less" in Q1, where 0.25 drinking days per week was assigned, and "ten or more were assigned to Q2, where 10 standard drinks per day were assigned. A similar method was used previously [11]. The occurrence of binge drinking at least monthly was obtained from the AUDIT Q3 on binge drinking frequency. This method has been used elsewhere [55,56].

Statistical Methods

For the GPM sample, to account for strata imbalance compared with the universe, data were weighted by region (19 categories), size of place of residence (7 categories), age (7 categories), and sex (2 categories), resulting in 619 different values for the ponderation factor (from 0.04 to 3.06). For the MSM sample, as the global universe of MSM residing in Spain was unknown, all participants were assigned a ponderation factor of 1. An initial descriptive analysis of the general characteristics of the MSM and GPM samples was performed, and the statistical significance of the differences was assessed using the Pearson χ^2 test. The main outcomes were the prevalence of harmful or hazardous drinking (AUDIT score≥8), hazardous drinking (AUDIT-C score≥4), harmful drinking or alcohol-related problems (AUDIT-P score≥4), regular hazardous drinking (>14 standard drinks per week or >20 g of pure alcohol per day in a year), and monthly binge drinking (occurrence of binge drinking at least monthly in a year). The AUDIT cutoff was originally established by the World Health Organization [24], and the AUDIT-C has been widely used [27,42]. As there are no well-established cutoffs for AUDIT-P, we adapted the cutoff used by Hansen et al [52] considering the recommendations of the lower thresholds [24,29]. We selected the threshold for regular hazardous drinking based on updated recommendations from national and international guidelines regarding limits on low-risk alcohol consumption [53-55].

The prevalence of the different drinking indicators was calculated in both MSM and GPM and compared between the groups using the adjusted prevalence ratio (aPR). aPR is a measure of relative inequality without units, which indicates the number of times the risk is higher or lower in MSM compared with GPM. Two different aPRs and their corresponding 95% CI were estimated using Poisson regression models with robust variance [57]. The first was adjusted for age, education level, size of place of residence, country of birth, and perceived economic status (Model I), and the second for the aforementioned covariates plus the use of other drugs in the past 12 months (Model II). Analyses were carried out globally and by age group (16-24, 25-34, and 35-64 years), education level (university or no university), and size of their place of residence (<10,000, 10,000-500,000, and >500,000 inhabitants). Categories were chosen following usual classifications and to obtain a differentiated profile in young men (16-24 years) versus other groups, or in rural areas (<10,000 inhabitants), and large cities (>500,000 inhabitants) as opposed to other living conditions. Differences and comparative measures were considered statistically significant if 2-tailed *P*-values were <.05. The analysis was not preregistered, and the results should be considered exploratory. Statistical analyses were performed using Stata version 15 (StataCorp).

Ethical Considerations

This study was approved by the Research Ethics Committee of the Instituto de Salud Carlos III (Comité de Ética de la Investigación [research ethics committee] Proyecto de Investigación [research project; principal investigator] 35_2020-v3). Concerning the MSM sample, individuals approved their conformity to participate by clicking on “On my age, I am legally authorized to have sexual relations and I want to participate in the study.” This message appeared before starting the questionnaire, as can be observed in the (Multimedia Appendix 3). Privacy was ensured by not asking for personal data, which led to possible identification. Regarding the GPM sample, individuals selected by randomized sampling had the possibility of denying participation. For those who wanted to participate, the interviewers provided informed consent before starting the study.

Results

Baseline Characteristics

Participants were more frequently aged 25-34 years (MSM) and 35-44 years (GPM). Compared with the GPM, they had a higher education level, lived more frequently in urban settings, and declared a better economic status. The prevalence of alcohol use in the past 12 months was similar between MSM and GPM, but that of other drugs was much higher among MSM (Table 1).

Table 1. Baseline characteristics of the sample: men who have sex with men (MSM) and general population men (GPM), Spain, 2018-2020.

Characteristics	MSM (N=5862), n (%[a])	GPM (N=10,349), n (%[a,b])	*P* value
Age group (years)			<.001
16-24	821 (14.0)	1955 (18.9)	
25-34	1650 (28.1)	2701 (26.1)	
35-44	1625 (27.7)	2665 (25.8)	
45-54	1265 (21.6)	1668 (16.1)	
55-64	501 (8.5)	1360 (13.1)	
Education level			.001
≤Lower secondary	586 (10.0)	5109 (49.6)	
Upper secondary	2104 (35.9)	3424 (33.2)	
University	3169 (54.1)	1767 (17.2)	
Place of birth			<.001
Spain	4827 (82.3)	9116 (93.0)	
Latin America	797 (13.6)	110 (1.1)	
Other	238 (4.1)	580 (5.9)	
Size of place of residence (inhabitants)			<.001
>1 million	1689 (31.6)	638 (6.2)	
500,000-1 million	617 (11.5)	770 (7.4)	
100,000-500,000	1155 (21.6)	2142 (20.7)	
50,000-100,000	528 (9.9)	1613 (15.6)	
10,000-50,000	734 (13.7)	2758 (26.6)	
<10,000	622 (11.6)	2428 (23.5)	
Perceived economic status			<.001
Good	3447 (64.4)	3379 (48.3)	
Regular	1462 (27.3)	2732 (39.0)	
Bad	443 (8.3)	886 (12.7)	
Alcohol use in past 12 months	4729 (80.7)	8129 (78.5)	.046
Other drug use in past 12 months	3529 (72.6)	2402 (23.6)	<.001

[a] Percentages were estimated over cases with valid data.

[b] Data were weighted by region, size of place of residence, age, and sex.

Hazardous Drinking and Harmful Drinking

The prevalence of hazardous or harmful drinking among MSM was 15.6% (913/5862) compared with 7.7% (902/10,349) in the GPM group, leading to an aPR of 1.8 (95% CI 1.6-2.0). Significant MSM-GPM disparities in prevalence in the same direction were observed in all subgroups, except for those who did not consume other drugs in the past 12 months (Table 2).

The prevalence of hazardous drinking was similar for MSM (1950/5862, 33.3%) and GPM (3472/10,349, 34.1%; aPR 0.9, 95% CI 0.9-1.0). A slight disparity favoring GPM was observed in several subgroups: those aged 35 to 64, with no university education level, and living in places with <10,000 inhabitants. Moreover, both MSM users and nonusers of other drugs were less frequent hazardous drinkers than their GPM counterparts (Table 2).

Table 2. Comparison of the prevalence of 3 Alcohol Use Disorders Identification Test (AUDIT) measures between men who have sex with men (MSM) and general population men (GPM), by age, education level, size of place of residence and other drug use, Spain, 2018-2020[a].

	MSM, n (%)	Sample size (n)	GPM, n (%[a])	Sample size (n)	aPR[b] (95% CI)[c]
Hazardous or harmful drinking (AUDIT score ≥8)					
All participants	913 (15.6)	5862	902 (7.7)	10,349	1.8 (1.6-2.0)
Age (years)					
16-24	184 (22.4)	821	216 (10.4)	1955	1.5 (1.2-2.0)
25-34	310 (18.8)	1650	275 (9.4)	2701	1.8 (1.5-2.3)
35-64	419 (12.4)	3391	411 (6.7)	5693	1.8 (1.5-2.2)
Education level					
No university	437 (16.2)	2690	773 (8.1)	8533	1.8 (1.5-2.1)
University	475 (15.0)	3169	125 (6.0)	1767	1.7 (1.3-2.3)
Size of place of residence (inhabitants)					
<10,000	73 (11.7)	622	213 (7.9)	2428	1.5 (1.1-2.0)
10,000-500,000	338 (14.0)	2417	566 (7.7)	6513	1.8 (1.5-2.1)
>500,000	385 (16.7)	2306	123 (7.5)	1408	2.2 (1.7-2.9)
Other drug use in past 12 months					
No	67 (5.0)	1332	443 (5.0)	7797	0.9 (0.7-1.3)
Yes	755 (21.4)	3529	450 (16.9)	2402	1.2 (1.0-1.5)[d]
Hazardous drinking (AUDIT-Consumption score ≥4)					
All participants	1950 (33.3)	5862	3472 (34.1)	10,349	0.9 (0.9-1.0)
Age					
16-24	316 (38.5)	821	595 (30.2)	1955	1.1 (0.9-1.3)
25-34	633 (38.4)	1650	923 (34.0)	2701	1.1 (1.0-1.3)
35-64	1001 (29.5)	3391	1954 (35.0)	5693	0.9 (0.8-0.9)
Education level					
No university	849 (31.6)	2690	2900 (34.9)	8533	0.9 (0.8-1.0)[d]
University	1100 (34.7)	3169	554 (30.4)	1767	1.0 (0.9-1.1)
Size of place of residence (inhabitants)					
<10,000	188 (30.2)	622	946 (39.2)	2428	0.8 (0.7-0.9)
10,000-500,000	764 (31.6)	2417	2064 (32.9)	6513	1.0 (0.9-1.0)
>500,000	815 (35.3)	2306	462 (32.4)	1408	1.0 (0.9-1.2)
Other drug use in past 12 months					
No	219 (16.4)	1332	2303 (30.5)	7797	0.6 (0.5-0.7)
Yes	1451 (41.1)	3529	1121 (46.3)	2402	0.9 (0-8-0.9)
Harmful drinking (AUDIT-Problem score ≥4)					
All participants	715 (12.2)	5862	604 (5.0)	10,349	2.3 (2.0-2.7)
Age (years)					
16-24	173 (21.1)	821	164 (7.6)	1955	2.3 (1.7-3.1)
25-34	231 (14.0)	1650	177 (6.1)	2701	2.1 (1.6-2.7)
35-64	311 (9.2)	3391	263 (4.2)	5693	2.4 (1.9-3.0)
Education level					
No university	366 (13.6)	2690	527 (5.4)	8533	2.2 (1.8-2.6)

	MSM, n (%)	Sample size (n)	GPM, n (%[a])	Sample size (n)	aPR[b] (95% CI)[c]
University	348 (11.0)	3169	74 (3.6)	1767	2.6 (1.7-3.8)
Size of place of residence (inhabitants)					
<10,000	60 (9.6)	622	129 (5.0)	2428	1.8 (1.2-2.6)
10,000-500,000	270 (11.2)	2417	403 (5.2)	6513	2.1 (1.7-2.6)
>500,000	296 (12.8)	2306	72 (4.3)	1408	3.4 (2.4-4.7)
Other drug use in past 12 months					
No	61 (4.6)	1332	260 (2.9)	7797	1.4 (1.0-2.0)[d]
Yes	583 (16.5)	3529	336 (12.3)	2402	1.5 (1.2-1.8)

[a] Crude prevalence. For the GPM sample, data were weighted by region, size of place of residence, age, and sex.

[b] aPR: adjusted prevalence ratio.

[c] aPR were obtained from Poisson regression with robust variance in the framework of generalized linear models and adjusted by age, education level, size of place of residence, country of birth and economic status. The reference group (aPR=1) was general population men.

[d] *P*<.05.

Regular Hazardous Drinking and Binge Drinking

The prevalence of regular hazardous drinking (>14 drinks per week) was lower among MSM (245/5862, 4.2%) than among GPM (524/10,349, 5.8%), with an aPR of 0.7 (95% CI 0.6-0.9). A statistically significant MSM-GPM disparity in such prevalence was not observed among individuals aged between 16 and 34 years, with university education level, or living in places with >500,000 inhabitants (Table 3).

The prevalence of monthly binge drinking was higher among MSM (798/5862, 13.6%) than among GPM (855/10,349, 7.6%), with an aPR of 1.7 (95% CI 1.5-1.9). Significant MSM-GPM disparities in prevalence in the same direction were observed in all subgroups, except for other drug users (Table 3).

Finally, the prevalence of harmful drinking was higher among MSM (715/5862, 12.2%) than among GPM (604/10,349, 5.0%), with an aPR of 2.3 (95% CI 2.0-2.7) Significant MSM-GPM disparities in such prevalence in the same direction were observed in all subgroups (Table 2).

The aPRs of Model II after further adjustment for the use of other drugs in the past 12 months are shown in Tables S1 and S2 in Multimedia Appendix 4. The considerable relative excess prevalence in MSM found in Model I for both harmful and binge drinking was greatly dampened in Model II. Thus, the aPR went from 2.3 (95% CI 2.0-2.7) in Model I to 1.5 (95% CI 1.3-1.7) in Model II for harmful drinking, and from 1.7 (95% CI 1.5-1.9) to 1.2 (95% CI 1.0-1.3) for binge drinking. Regarding regular hazardous drinking, the relative prevalence deficit in MSM found in Model I increased in Model II. Thus, aPR went from 0.7 (95% CI 0.6-0.9) in Model I to 0.5 (95% CI 0.4-0.6) in Model II. In contrast, the aPR for hazardous drinking went from 0.9 (95% CI 0.9-1.0) in Model I to 0.8 (95% CI 0.7-0.8) in Model II, and that of hazardous or harmful drinking, from 1.8 (95% CI 1.6-2.0) to 1.2 (95% CI 1.0-1.4).

Table 3. Comparison of the prevalence of regular hazardous drinking and monthly binge drinking between men who have sex with men (MSM) and general population men (GPM), by age, education level, size of place of residence, and other drug use, Spain, 2018-2020[a].

	MSM, n/N (%)	GPM, n/N (%)	aPR[b] (95% CI)[c]
Regular hazardous drinking (>14 drinks per week)			
All participants	245/5862 (4.2)	524/10,349 (5.8)	0.7 (0.6-0.9)
Age (years)			
16-24	25/821 (3.1)	43/1955 (2.2)	0.6 (0.3-1.2)
25-34	75/1650 (4.5)	103/2701 (4.2)	0.9 (0.6-1.4)
35-64	145/3391 (4.3)	378/5693 (7.0)	0.6 (0.5-0.8)
Education level			
No university	104/2690 (3.9)	470/8533 (6.4)	0.6 (0.5-0.8)
University	141/3169 (4.4)	53/1767 (3.5)	0.8 (0.5-1.2)
Size of place of residence (inhabitants)			
<10,000	13/622 (2.1)	173/2428 (7.2)	0.3 (0.2-0.6)
10,000-500,000	77/2417 (3.2)	286/6513 (5.6)	0.6 (0.5-0.9)
>500,000	106/2306 (4.6)	65/1408 (4.8)	1.1 (0.7-1.7)
Other drug use in past 12 months			
No	13/1332 (1.0)	297/7797 (4.4)	0.3 (0.2-0.6)
Yes	212/3529 (6.0)	221/2402 (10.6)	0.5 (0.4-0.6)
Binge drinking (at least monthly)			
All participants	798/5862 (13.6)	855/10,349 (7.6)	1.7 (1.5-1.9)
Age (years)			
16-24	144/821 (17.5)	200/1955 (10.2)	1.7 (1.2-2.3)
25-34	270/1650 (16.4)	266/2701 (9.3)	1.7 (1.3-2.1)
35-64	384/3391 (11.3)	389/5693 (6.7)	1.6 (1.3-2.0)
Education level			
No university	372/2690 (3.8)	740/8533 (8.1)	1.6 (1.4-1.9)
University	426/3169 (13.4)	111/1767 (5.5)	1.8 (1.3-2.4)
Size of the place of residence (inhabitants)			
<10,000	70/622 (11.3)	218/2428 (8.1)	1.4 (1.0-1.9)[d]
10,000-500,000	307/2417 (12.7)	527/6513 (7.5)	1.7 (1.4-2.1)
>500,000	314/2306 (13.6)	110/1408 (7.6)	1.8 (1.4-2.4)
Other drug use in the past 12 months			
No	70/1332 (5.3)	453/7797 (5.4)	1.0 (0.7-1.3)
Yes	645/3529 (18.3)	393/2402 (15.4)	1.2 (1.0-1.4)

[a] Crude prevalence. For the GPM sample, data were weighted by region, place of residence, age, and sex.

[b] aPR: adjusted prevalence ratio.

[c] aPR was obtained from Poisson regression with robust variance in the framework of generalized linear models and adjusted by age, education level, size of place of residence, country of birth, and economic status. The reference group (aPR=1) was general population men.

[d] *P*<.05.

Discussion

Principal Findings

Compared with GPM, we found a relative excess risk of hazardous or harmful drinking (full-scale AUDIT) among MSM living in Spain. Nearly 1 in 6 MSM had hazardous or harmful drinking and would benefit from early brief alcohol intervention procedures (the ultimate goal for which the AUDIT tool was designed) [30]. The MSM's excess risk was mainly because of harmful drinking and binge drinking. In contrast, both populations had similar risks for hazardous drinking

(AUDIT-C), resulting from the balance of a higher risk of regular hazardous drinking among GPM than MSM, and the opposite for binge drinking.

The relative excess risk in the GPM of hazardous drinking and regular hazardous drinking tended to increase among older, less educated, and rural-dwelling individuals. In contrast, the relative excess risk of harmful and binge drinking in MSM tended to be larger among individuals aged 16-24 years (only in the case of harmful drinking) or with university education level and living in big cities (in both cases).

Additional adjustment for other drug use greatly buffered the considerable relative excess risk in MSM compared to that in GPM for harmful drinking and binge drinking while deepening the risk deficit in MSM for regular hazardous drinking. This suggests that drinking behaviors and other drug use were strongly associated in the studied populations. Therefore, the considerable excess of risk in MSM compared with GPM for binge drinking and harmful drinking is mainly because of the subgroup having both these drinking patterns and the use of other drugs. This subgroup represents a much higher proportion of the total in MSM than in GPM, and must clearly be a priority target for harm reduction interventions.

Comparison With Previous Work

This is the first study to directly compare excessive drinking indicators (hazardous and harmful drinking) between MSM and GPM in a southern European country. Moreover, this is the first study ever published that differentiates between these 2 dimensions using a validated instrument (AUDIT). Moreover, because of the use of new technologies in the recruitment process, namely apps and websites, it includes a larger sample of MSM than that in most previous studies inside and outside Europe [1,2,6,7,9-18,41,58].

Only one study has compared hazardous or harmful drinking between these 2 populations using full-scale AUDIT [19], and the results showed a lower mean AUDIT score among MSM than among heterosexual men. In this study, both populations were recruited using snowball sampling and the study did not include a stratified analysis to distinguish between the 2 dimensions evaluated here. Other studies [42-48] have estimated the proportion of MSM who engage in hazardous or harmful drinking using AUDIT but did not compare it to that of GPM. The proportion of hazardous or harmful drinking (full-scale AUDIT) in nearly all these studies was higher than that in our study, and it is likely because of the fact that these studies included individuals with a higher risk of unhealthy behaviors. However, we believe that it does not make much sense to compare these prevalences, nor those of the 2 dimensions separately, because the levels and patterns of alcohol consumption are primarily determined by the social environment in which one lives. From our perspective, the most relevant measures to use are relative comparisons of MSM and their heterosexual counterparts, such as aPR.

There are 3 studies [7,12,17] that have used instruments or indicators other than AUDIT, which estimated both dimensions separately. Their results showed low or insignificant differences in hazardous drinking but higher and significant differences in harmful drinking among MSM compared with GPM. This study also found the same clear disparity between the two dimensions.

One study [41] compared only hazardous drinking using AUDIT-C and found a higher but not statistically significant prevalence in MSM compared with heterosexual men, which agrees with the results of various studies using other indicators [1,10,11]. However, the MSM sample size used in these studies tends to be limited, as is usually observed in studies derived from general population surveys. It was not possible to compare our results in terms of regular alcohol consumption with those of 2 other studies that also performed this analysis because their results were presented [2,15]. Our findings suggest that higher binge drinking among MSM contradicts the findings of most prior studies, which have reported no such differences between MSM and GPM [1,2,7,13], or an even lower prevalence among certain subgroups of MSM [10,12].

No other study has analyzed harmful drinking using AUDIT-P; however, our findings of a high aPR MSM or GPM are similar to those previously described in studies using Diagnostic and Statistical Manual of Mental Disorders criteria [6-8].

Considering these findings, we can affirm that there is a slight difference in hazardous drinking between MSM and GPM, but a remarkable increase in harmful drinking among MSM also exists in Mediterranean countries such as Spain. However, the reasons for this discrepancy are not well understood. In the case of Spain, it could be that MSM adopted Northern European drinking patterns more quickly, characterized by a higher frequency of binge drinking, which is more likely to produce harmful consequences [53]. As an indicator of more traditional habits, in our sample, the Mediterranean alcohol consumption pattern was predominant among older, lower-educated, and rural-dwelling GPM. The changes in consumption patterns among MSM may be related to their greater knowledge of habits in other countries because of their openness to cultural differences and the higher proportion of young, university-educated, large city dwellers in this group. Attributing differences between homosexuals and heterosexuals to differential consumption patterns was mentioned in one of the first studies on this issue, whose author suggested a higher frequency of “European and continental drinking patterns” among Swedish MSM [17]. Nevertheless, there were no differences in consumption patterns between MSM and GPM.

In contrast, minority stress theory has also been proposed to explain the increase in harmful and hazardous drinking among MSM [59,60]. According to this theory, alcohol and other drug use is a response to psychological discomfort derived from stigma or internalized homophobia among lesbian, gay, bisexual, transgender community [61]. As our study did not explore psychological variables or drinking motives, further studies are needed to interpret our findings in terms of this theory.

Other factors may have influenced the results. It is well known that certain potentially alcohol-linked phenomena, such as sex work [62], chemsex [63], or sex tourism [64] are more frequent among MSM. Even though only 13.0% (431/3319) of MSM in our sample (data not shown, nonrespondents excluded from the denominator) declared engaging regularly in binge drinking during chemsex sessions, and only 15.3% (898/5854) affirmed having received economic rewards for sex more than once in their life course, the influence of these variables warrants further investigation. Concerning sex tourism, 92.8% (596/642) of foreign MSM in our sample declared living in Spain for at least 1 year, so their consideration as tourists can be ruled out. Moreover, all analyses were adjusted for country of birth.

In summary, it could be that there are differences in consumption patterns between MSM and GPM that have not been properly analyzed, or, more probably, that MSM are more susceptible to the harmful effects of alcohol use or that they have a greater ability to identify or disclose them. Further research is needed to clarify this last point, which requires the use of large samples for both comparison groups. Studies based on general population surveys, which represent the majority to date, do not permit discerning of these particular issues and often include a small number of MSM.

Finally, although not an objective of this study, our findings suggest that AUDIT measures 2 different domains [40]. It also illustrates the inadequacy of using the AUDIT-C scale in isolation to assess differences in alcohol-related problems among MSM [35].

Limitations

The use of 2 different sampling methods for MSM and GPM is a limitation of this study. However, using dating apps and websites for the recruitment of MSM was a way to overcome 2 handicaps: the small sample of MSM frequently included in studies based on representative samples of the general population and the fact that the national drug survey in Spain does not include questions about sexual orientation. Although this sampling method may have overrepresented hazardous drinkers among MSM, it provided a significantly larger MSM sample than that in most studies with probabilistic sampling methods, in which the inclusion of a large number of MSM was hindered by the low percentage of men who reported having sex with other men. In our study, the MSM questionnaire was self-administered, which is not always guaranteed in general population surveys. This might have reduced the probability of reporting bias for nonnormative behaviors, such as homosexual behavior or alcohol use.

Another limitation related to recruitment is the different contexts in which alcohol was more frequently consumed in these 2 groups. Even though dating apps as well as other Internet-based resources were used to recruit MSM, a skew toward “party-goers” may have taken place. As some questions in AUDIT (notably in AUDIT-P, such as Q6 or Q8) are related to nightlife drinking, this point may have had an influence. Unfortunately, we did not have a variable to measure the context of consumption. On the contrary, we do not think that recruiting MSM, but not GPM, during the COVID-19 pandemic (between May and July 2020) may have increased the differences favoring MSM. It has been observed that hazardous drinking increased during lockdowns [65-68], but AUDIT questions refer to common habits in the last 12 months, so most times evaluated had occurred out of the general lockdown in March and April 2020.

Another limitation is related to AUDIT thresholds. Cutoffs are needed for screening; however, when different cutoff points are used, epidemiological research is hindered. We offset this limitation by estimating new results by applying different cutoffs used in other studies. In addition, problems related to thresholds were not exclusive to AUDIT; they also appeared when establishing the recommended levels of weekly alcohol consumption. The final limitation relates to the use of only 2 AUDIT questions (quantity and frequency) to estimate alcohol consumption. Although this was not the first study to measure this variable using these 2 questions (or similar questions) [11], a more complete module concerning consumption in the 2 surveys would have provided more detailed results.

Conclusions and Implications for Intervention and Research

This is the first study to compare indicators of hazardous and harmful drinking (problems or consequences) between MSM and GPM living in southern Europe. The use of different Internet-based resources in recruitment (mainly apps and influencers) allowed us to obtain information on alcohol use from a large and diverse sample of MSM. Using a validated brief screening tool (AUDIT), we found an 80% excess risk of hazardous or harmful drinking among MSM, which was mainly owing to the higher risk of harmful drinking and binge drinking among MSM.

From the perspective of the implications for clinical practice, it is important to emphasize that the periodic use of brief screening tools such as AUDIT would seem to be highly recommended in health consultations of MSM. This would result in a significant proportion of MSM benefiting from early brief alcohol harm reduction interventions and from referral to specialized services when needed. Harm reduction strategies should focus on binge drinking. Nursing professionals in primary care and sexual transmitted infections or HIV clinics (which take care of a large number of MSM) may provide appropriate services for the implementation of these screening instruments.

From the perspective of future research, it is desirable to enrich these findings by conducting studies based on a single population-based survey. To achieve this goal, surveys in Spain (and in other countries) should include a variable on sexual behavior or gender identity, as it has been common in the United States for a decade. Second, we want to highlight that there are currently no clear explanations for the disparity in the findings in the 2 domains of AUDIT. Neither the tendency toward incorporation of non-Mediterranean consumption patterns among MSM nor the minority stress theory satisfactorily explains these results. Therefore, further studies are needed to analyze whether differential consumption patterns exist or whether there are different levels of susceptibility to alcohol use and its harmful consequences.

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Authors' Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafted the article or revised it critically for important intellectual content, and granted final approval of the version to be published.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Men who have sex with men sample questionnaire.
[ZIP File (Zip Archive), 4357 KB - publichealth_v8i10e32888_app1.zip]

Multimedia Appendix 2
General population of men sample questionnaire Encuesta Sobre Alcohol y Otras Drogas en España (Spanish National Survey on Alcohol and Drugs).
[PDF File (Adobe PDF File), 768 KB - publichealth_v8i10e32888_app2.pdf]

Multimedia Appendix 3
Message appeared before starting the questionnaire Méthysos.
[PDF File (Adobe PDF File), 157 KB - publichealth_v8i10e32888_app3.pdf]

Multimedia Appendix 4
Supplementary tables.
[PDF File (Adobe PDF File), 86 KB - publichealth_v8i10e32888_app4.pdf]

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Abbreviations

aPR: adjusted prevalence ratio
AUDIT: Alcohol Use Disorders Identification Test
AUDIT-C: Alcohol Use Disorders Identification Test-Consumption
AUDIT-P: Alcohol Use Disorders Identification Test-Problem
EDADES: Encuesta Sobre Alcohol y Otras Drogas en España
GPM: general population of men
MSM: men who have sex with men

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Original Paper

COVID-19 Cases Among Congregate Care Facility Staff by Neighborhood of Residence and Social and Structural Determinants: Observational Study

Huiting Ma[1], BMath, MSc; Kristy C Y Yiu[1], BHSc, MSc; Stefan D Baral[2], MD, MPH; Christine Fahim[1], MSc, PhD; Gary Moloney[1], BASc, MSA; Dariya Darvin[1], BSc; David Landsman[1], BSc, MScAC; Adrienne K Chan[3,4,5,6], MD, MPH; Sharon Straus[1,7], MD, MSc; Sharmistha Mishra[1,3,4,6], MD, PhD

[1]St Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada
[2]Department of Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD, United States
[3]Division of Infectious Diseases, Department of Medicine, University of Toronto, Toronto, ON, Canada
[4]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[5]Division of Infectious Diseases, Sunnybrook Health Sciences, University of Toronto, Toronto, ON, Canada
[6]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada
[7]Department of Medicine, University of Toronto, Toronto, ON, Canada

Corresponding Author:
Sharmistha Mishra, MD, PhD
St Michael's Hospital
Unity Health Toronto
Room 315, 209 Victoria Street
Toronto, ON, M5B 1T8
Canada
Phone: 1 416 864 6060 ext 5568
Email: sharmistha.mishra@utoronto.ca

Abstract

Background: Disproportionate risks of COVID-19 in congregate care facilities including long-term care homes, retirement homes, and shelters both affect and are affected by SARS-CoV-2 infections among facility staff. In cities across Canada, there has been a consistent trend of geographic clustering of COVID-19 cases. However, there is limited information on how COVID-19 among facility staff reflects urban neighborhood disparities, particularly when stratified by the social and structural determinants of community-level transmission.

Objective: This study aimed to compare the concentration of cumulative cases by geography and social and structural determinants across 3 mutually exclusive subgroups in the Greater Toronto Area (population: 7.1 million): community, facility staff, and health care workers (HCWs) in other settings.

Methods: We conducted a retrospective, observational study using surveillance data on laboratory-confirmed COVID-19 cases (January 23 to December 13, 2020; prior to vaccination rollout). We derived neighborhood-level social and structural determinants from census data and generated Lorenz curves, Gini coefficients, and the Hoover index to visualize and quantify inequalities in cases.

Results: The hardest-hit neighborhoods (comprising 20% of the population) accounted for 53.87% (44,937/83,419) of community cases, 48.59% (2356/4849) of facility staff cases, and 42.34% (1669/3942) of other HCW cases. Compared with other HCWs, cases among facility staff reflected the distribution of community cases more closely. Cases among facility staff reflected greater social and structural inequalities (larger Gini coefficients) than those of other HCWs across all determinants. Facility staff cases were also more likely than community cases to be concentrated in lower-income neighborhoods (Gini 0.24, 95% CI 0.15-0.38 vs 0.14, 95% CI 0.08-0.21) with a higher household density (Gini 0.23, 95% CI 0.17-0.29 vs 0.17, 95% CI 0.12-0.22) and with a greater proportion working in other essential services (Gini 0.29, 95% CI 0.21-0.40 vs 0.22, 95% CI 0.17-0.28).

Conclusions: COVID-19 cases among facility staff largely reflect neighborhood-level heterogeneity and disparities, even more so than cases among other HCWs. The findings signal the importance of interventions prioritized and tailored to the home geographies of facility staff in addition to workplace measures, including prioritization and reach of vaccination at home (neighborhood level) and at work.

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KEYWORDS

long-term care; nursing home; staff; essential worker; retirement home; shelter; congregate living; COVID-19; observational; risk; transmission; elderly; older adults; retirement; nurse; health care worker; congregate; trend; geography; Canada; Toronto

Introduction

Across Canada, the COVID-19 epidemic has been marked by a conflation of microepidemics across settings, including congregate living facilities (eg, long-term care homes [LTCHs], retirement homes, and shelters), essential workplaces, or households [1-6]. Many congregate facilities experienced outbreaks, with residents experiencing a 3- to 5-fold higher test positivity rate than the community-dwelling population [1,3,4,7,8]. Meanwhile, data on the community-dwelling population suggested a consistent pattern of geographic clustering of cases with 50% of cases occurring in approximately 25% of the population and disproportionately affecting those residing in neighborhoods that are less affluent and with a higher proportion of essential workers [9,10].

What is less understood is how congregate facilities may be connected with neighborhood disparities. Emerging data on congregate facility outbreaks suggested that facility-level spread among staff, among residents, and between staff and residents may have been partially triggered by undiagnosed infections and lack of support for effective isolation among staff [3,7]. Reducing transmission in the wider community may reduce outbreaks in congregate settings. However, data on facility staff are limited with few studies that characterized the socioeconomic, living, and working conditions of staff [11] and, thus, the extent to which social and structural determinants of community-level transmission might influence outbreaks in congregate facilities. Surveillance data on COVID-19 cases offer an opportunity to examine the pattern of cases among facility staff and other health care workers (HCWs) against community cases and neighborhood disparities. Lorenz curves, Gini coefficients, and the Hoover index, traditionally used as measurements of economic inequality [12,13], have been used in a range of health care research to measure health inequality [14,15]; for example, these measurements of health inequality have been recently applied in the context of the COVID-19 pandemic [10,16]. We sought to adapt Lorenz curves, Gini coefficients, and the Hoover index to compare the concentration of cases using neighborhood-level rates and neighborhood-level social and structural determinants across 3 mutually exclusive subgroups: community, facility staff (LTCHs, retirement homes, shelters), and other HCWs not working in congregate settings (eg, only working in hospitals). Our overarching objective was to determine if and how the pattern and magnitude of inequality and concentration in COVID-19 cases among HCWs differed between facility staff and other HCWs.

Methods

Study Design, Setting, and Population

We conducted a retrospective, observational study using provincial surveillance data on laboratory-confirmed COVID-19 cases reported between January 23, 2020, and December 13, 2020, in the Greater Toronto Area (population: 7.1 million) [17] and in accordance with the RECORD (Reporting of Studies Conducted Using Observational Routinely-Collected Data) statement [18]. We restricted the study to the period before COVID-19 vaccination was available due to differential vaccine allocation and coverage over time by each subgroup after vaccine rollout [19].

Data Sources and Measures

We used person-level data from Ontario's centralized surveillance system [20], which includes information on laboratory-confirmed COVID-19 cases by reported date, demographic characteristics, exposure category, and setting-specific characteristics (eg, LTCHs), as well as data on social and structural determinant measures from the Statistics Canada 2016 Census [21]. The surveillance data classify cases as an HCW if a person works or volunteers in any health care setting (including LTCHs, retirement homes, shelters, hospitals, clinics, or homecare). We stratified HCWs into those associated with working or volunteering in an LTCH, retirement home, and/or shelter as facility staff, and all others as "other HCWs." If an HCW fell into both categories (facility staff and other HCWs), then they were categorized as facility staff.

We examined social and structural determinants at the level of the dissemination area (neighborhood) because it was the smallest geographic unit (population size ranging from 400 to 700) for which census data were available. Other geographic units include the forward sortation area and census tracts, but the dissemination area is most commonly used when examining social and structural determinants because it reflects the smallest geographic unit and is less prone to ecological fallacy than larger geographic units [22]. We conceptualized and defined the social and structural determinants as reported previously [9,10]. The variables are detailed in Multimedia Appendix 1 [21,23,24] and are related to socioeconomic status (per-person equivalent after tax income) and proxies for systemic racism (% visible minority, % recent immigration), or to the potential for increased contact rates (housing: % not living in high-density housing [25,26], % living in multigenerational households) and employment in other essential services (ie, excluding health care) [27] not amenable to remote work [28].

Analyses

We aggregated the number of confirmed COVID-19 cases at the neighborhood level during the study period into 3 mutually exclusive subgroups: community (excluding facility staff, other HCWs, congregate facility residents, and travel-related cases), facility staff (workers or volunteers in LTCHs, retirement homes, and shelters), and other HCWs. We generated Lorenz curves and Gini coefficients to quantify the magnitude of inequalities (ie, the concentration in cases), and the Hoover index was used as an alternate measure for validation [15,16,29]. With the Gini coefficient, a value closer to zero represents greater equality [30]. The Hoover index measures the percentage of cases that would need to be redistributed to achieve equality in how cases are distributed across neighborhoods. As with the Gini coefficient, a larger Hoover index represents greater inequality [31]. We generated 95% CIs for Gini coefficients using bootstrapping [29,32].

First, we compared the magnitude of geographic concentration of cases for each subgroup (y-axis) against the distribution of total cases (x-axis, community plus travel related) at the neighborhood level. To examine the extent to which facility staff and other HCW cases mirrored community cases, we generated a separate set of Lorenz curves and Gini coefficients using community cases on the x-axis. Second, to examine the magnitude of inequalities by each social or structural determinant, we ranked the cumulative proportion of the population by each determinant (eg, from lowest to highest income decile) on the x-axis. A detailed analytic plan can be found in Multimedia Appendix 2 [9,10,15,16,20-22,25-32]. We also generated spatial maps to describe and overlay cases among facility staff and among other HCWs using one social determinant as an example (neighborhood-level income).

Analyses were conducted in R (version 4.0.2; R Core Team), and spatial maps were generated using ArcGIS (version 10.7; Esri).

Ethics Approval

The University of Toronto Health Sciences Research Ethics Board approved the study (protocol #39253).

Results

Overview

Of the 92,210 cases (excluding congregate facility residents and travel-related cases) included during our study period, there were 83,419 cases in the community, 4849 cases among facility staff, and 3942 cases among other HCWs (Table 1). Among facility staff, there were 4241, 363, and 245 cases among LTCH staff, retirement home staff, and shelter staff, respectively.

Table 1. Number of COVID-19 cases in 3 mutually exclusive subgroups (community, facility staff, and other health care workers) in the Greater Toronto Area (January 23, 2020, to December 13, 2020).

Subgroup	COVID-19 cases, n	Dissemination areas[a] with zero cases, n (%)[b]
Community[c]	83,419	1058 (12.8)
Facility staff[d]	4849	5771 (69.7)
Other health care workers	3942	5879 (71.0)

[a] Dissemination area refers to the geographic unit of measurement for the social and structural determinants examined in this study generated from Statistics Canada [21]. In the Greater Toronto Area (population: 7.1 million), the median population size of a dissemination area is 561 (IQR 442-800) residents.

[b] A total of 8278 dissemination areas in the region.

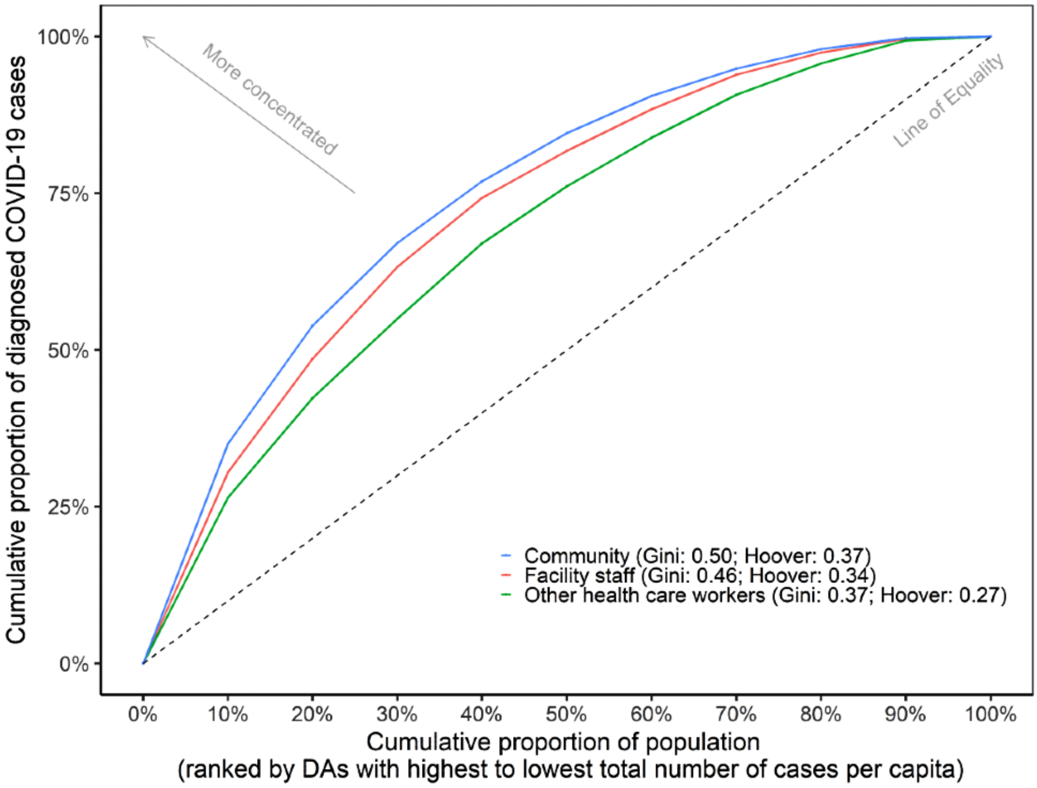
[c] Excludes residents of congregate settings and facility staff (long-term care homes, retirement homes, and shelters), other health care workers, and travel-related cases.

[d] Includes staff and volunteers who work in long-term care homes, retirement homes, and shelters, and excludes all other health care workers.

Geographic Concentration of Cases Across Subgroups

The most affected neighborhoods (x-axis) comprising 20% of the total population accounted for 53.87% (44,937/83,419) of community cases, 48.59% (2356/4849) of congregate setting worker cases, and 42.34% (1669/3942) of other HCW cases (Figure 1). Compared with other HCWs, cases among facility staff more closely reflected the geographic distribution of community cases (Gini 0.06 vs 0.16; Hoover 0.05 vs 0.12) (Multimedia Appendix 3).

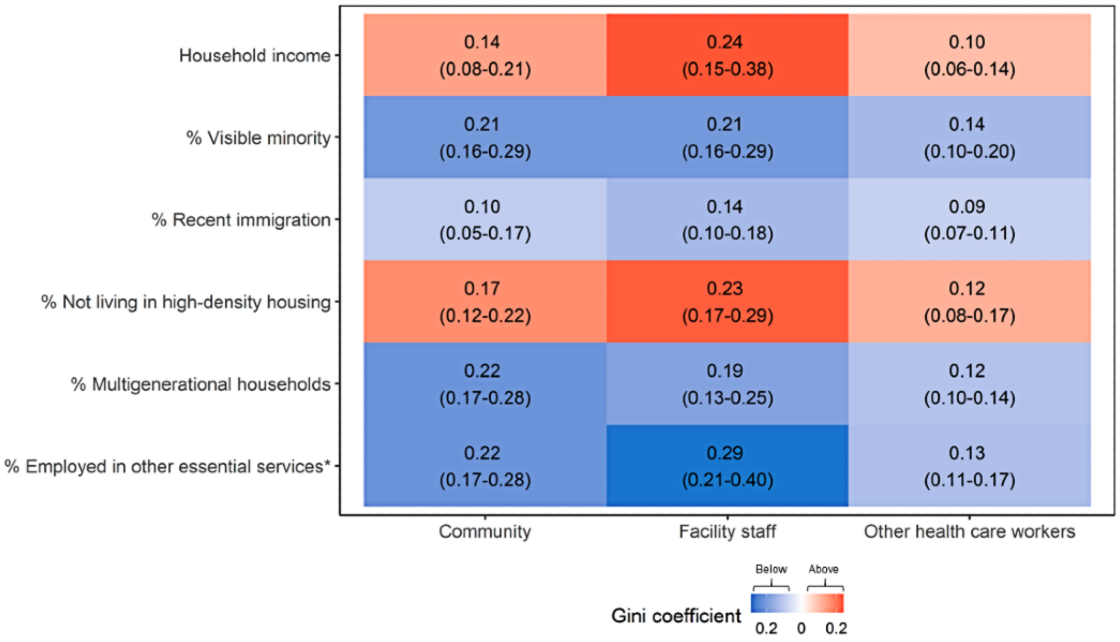
Figure 1. Geographic concentration of COVID-19 cases in the community population, among facility staff, and among other health care workers in the Greater Toronto Area (January 23, 2020, to December 13, 2020). The magnitude of concentration is depicted by Lorenz curves (the dashed line represents the line of equality) and the corresponding Gini coefficient for each subgroup. The x-axis represents the cumulative proportion of the population ranked by DAs from the highest to lowest number of cumulative cases per capita. "Community" excludes residents of congregate settings and facility staff (long-term care homes, retirement homes, and shelters), other health care workers, and travel-related cases. "Facility staff" includes staff and volunteers who work in long-term care homes, retirement homes, and shelters and excludes all other health care workers. DA: dissemination area.



Differences in the Concentration of Cases Across Subgroups by Social and Structural Determinants

Multimedia Appendix 4 depicts Lorenz curves and Gini coefficients by each social and structural determinant. Cases among facility staff reflected greater social and structural inequalities (larger Gini coefficients and a larger Hoover index) than other HCWs across all determinants (Figure 2, Multimedia Appendices 4 and 5). Multimedia Appendix 6 depicts how cases among facility staff and other HCWs were clustered along neighborhood-level income. Although facility-level cases mirrored that of community cases (Multimedia Appendix 3), there were greater inequalities in facility-level versus community cases with respect to income (Figure 2; Gini 0.24, 95% CI 0.15-0.38 vs 0.14, 95% CI 0.08-0.21), household density (Gini 0.23, 95% CI 0.17-0.29 vs 0.17, 95% CI 0.12-0.22), and other essential services (Gini 0.29, 95% CI 0.21-0.40 vs 0.22, 95% CI 0.17-0.28). Cases in the community, among facility staff, and among other HCWs were disproportionately concentrated in areas with lower household income and in areas with a higher proportion of visible minorities, recent immigration, high-density housing, multigenerational households, and employment in other essential services (Figure 2).

Figure 2. A heat map with estimated Gini coefficients showing the magnitude of concentration by social and structural determinants in COVID-19 cases in the community, among facility staff, and among other health care workers in the Greater Toronto Area (January 23, 2020, to December 13, 2020). Gini coefficients above and below the line of equality in the Lorenz curves (Multimedia Appendix 5) are depicted in red and blue, respectively. *Other essential services include trades, transport, and equipment operation; sales and services; manufacturing and utilities; and resources, agriculture, and production [32]. "Community" excludes residents of congregate settings and facility staff (long-term care homes, retirement homes, and shelters), other health care workers, and travel-related cases. "Facility staff" includes staff and volunteers who work in long-term care homes, retirement homes, and shelters and excludes all other health care workers.



Discussion

We found that the distribution of COVID-19 cases among facility workers mirrored neighborhood heterogeneity and social and structural disparities, a pattern that was less evident with other HCWs. Facility staff cases reflected greater inequalities by social and structural determinants than cases among other HCWs, and with some determinants (income and other essential workers), greater inequalities were seen with facility staff cases compared to community cases.

Cases among facility staff more closely reflected the geographic distribution of community cases than the distribution of cases among other HCWs and in the community. The similar distributions of facility staff and community cases could occur if there was an equal distribution of facility staff living across neighborhoods and the infection rate ratio between facility staff and the community was the same across neighborhoods. The implication of this potential mechanism is that most infections among facility staff would have been acquired outside the facility or workplace. The Lorenz curve patterns may also occur if facility staff were more likely than other HCWs to live in harder-hit neighborhoods with greater social and structural disparities, irrespective of workplace exposures in congregate facilities.

Although our study was centered on the Greater Toronto Area, the findings are likely to be generalizable to other large, urban cities and metropolitan areas with similar patterns of social and structural inequalities. In Canada, most congregate facilities are concentrated in large cities [34], and previous research comparing 16 cities demonstrated a similar neighborhood clustering of COVID-19 cases by social and structural determinants [10]. Data on the neighborhood characteristics of LTCH staff in the United States [11] suggest workers tend to live in lower-income neighborhoods, and individual-level data in Canada suggest that a high proportion of LTCH staff identify as racialized women with low household income [35]. In current LTCH staffing models across Canada and the United States, approximately 60% to 90% of workers who provide direct care to residents are providing services as unregulated staff (personal support workers, care aides, orderlies, and nurse assistants) [36-40] and receive the lowest wages in the health care sector at or just above minimum wage [36], often in the context of contract or casual work without benefits [36,37,41-45].

Our study suggests that cases among facility staff may disproportionately intersect with household exposures that are connected with other essential workplaces or amplified in the context of household density [21]. Our study was limited by a lack of confirmed denominators for setting-specific workers in the region, but data from England and Wales suggest a 2-fold increased rate of COVID-19 among LTCH workers versus other HCWs [46]. Based on government reports, just over 100,000 employees serve 78,000 LTCH residents in the province [36], such that the ratio of staff to LTCH residents in Ontario is approximately 1 staff for every 0.78 LTCH resident. If we extrapolate the provincial ratio to the Greater Toronto Area, where 28,316 LTCH residents reside, the city would have approximately 36,303 LTCH staff. With 4241 cases among LTCH staff in the Greater Toronto Area during our study period and a total population in the Greater Toronto Area of 7.1 million [17], the cumulative rate of COVID-19 cases among LTCH staff (at 11,682 per 100,000) would have been 10 folds higher than that of the community (1174 cases per 100,000).

This study has several limitations. First, we derived the dissemination area–level social determinants from the 2016 Census data, which may not be representative of the population during the COVID-19 pandemic. Second, the occupation status obtained from Ontario's centralized surveillance system could have been misclassified due to possible misinterpretation of the question in self-reporting; further, facility staff or HCWs may work in multiple settings. Third, we did not have data on the residence of all HCWs across the various congregate settings to compare neighborhood-level per-HCW rates of cases. Finally, data were not available to link cases among HCWs to specific facilities and to directly examine how cases in communities influenced outbreaks in congregate settings.

The findings have implications for COVID-19 modeling and interventions. The magnitude of inequalities can be used as calibration or validation targets for epidemic and prediction models to reproduce the observed pattern of cases in relation to the distribution of overall cases and by social and structural determinants. In doing so, detection systems (eg, neighborhood wastewater surveillance) designed to predict the potential for exposures in congregate facilities could leverage data on underlying vulnerabilities in the neighborhood of facility staff residence. A study in the United States found that neighborhood characteristics of LTCH staff's residences were the most important predictor of LTCH outbreaks [11]. These data could then be used to implement strategies to mitigate risks. For example, proximal strategies to reduce community-level transmission risks conferred through social and structural inequalities have the potential to reduce workplace exposure risks. Examples include systematically addressing the lived realties of workers that make physical distancing challenging (eg, household density) or that remain barriers to effective isolation and quarantine (eg, precarious job security and absence of benefits such as paid sick leave), with interventions such as wraparound care including access to food, medications, and child and senior care (especially in the context of multigenerational households) to facilitate staff quarantine and isolation. Prioritizing vaccination coverage in the hardest-hit neighborhoods is another example of indirectly reducing workplace exposures in LTCHs, retirement homes, and shelters. Finally, the findings highlight an urgent need for a long-term commitment and resources to comprehensively address social and structural barriers at a systems level (integration of health, education, social services, public health, and labor) given the long-standing history of infectious disease outbreaks in facilities and disparities experienced by its staff even before the COVID-19 pandemic [37].

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Data Availability

Reported COVID-19 cases were obtained from Case and Contact Management Solutions via the Ontario COVID-19 Modelling Consensus Table and with approval from the University of Toronto Health Sciences Research Ethics Board. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Authors' Contributions

HM and SM conceived and designed the study with input from KCYY. HM, DD, and SM conducted the literature review. HM developed the analysis plan with input from SM. HM led data management, data cleaning, data linkage, and variable creation, with support from DD and DL. GM sourced and generated the census-level data and wrote the appendix related to the census variables. HM executed the analysis plan and conducted the statistical analysis. HM wrote the first draft of the manuscript. All authors provided critical input on the study design, interpretation of results, and manuscript review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Social determinants of health: variables from the Statistics Canada 2016 Census of Population.
[DOCX File , 17 KB - publichealth_v8i10e34927_app1.docx]

Multimedia Appendix 2
Detailed analytic plan.
[DOCX File , 15 KB - publichealth_v8i10e34927_app2.docx]

Multimedia Appendix 3
Geographical concentration of COVID-19 cases among facility staff and other health care workers compared with community cases in the Greater Toronto Area, from January 23, 2020, to December 13, 2020.
[DOCX File , 651 KB - publichealth_v8i10e34927_app3.docx]

Multimedia Appendix 4
Lorenz curves and Gini coefficients of COVID-19 cases in the community, among facility staff, and among other health care workers by social determinants in the Greater Toronto Area, from January 23, 2020, to December 13, 2020.
[DOCX File , 967 KB - publichealth_v8i10e34927_app4.docx]

Multimedia Appendix 5
Magnitude of concentration of COVID-19 cases by social and structural determinants in the community, among facility staff, and among other health care workers in the Greater Toronto Area, from January 23, 2020, to December 13, 2020.
[DOCX File , 335 KB - publichealth_v8i10e34927_app5.docx]

Multimedia Appendix 6
Map overlay of household income deciles by dissemination area and distribution of (A) COVID-19 facility staff cases and (B) other health care worker cases in the Greater Toronto Area, from January 23, 2020, to December 13, 2020.
[DOCX File , 2870 KB - publichealth_v8i10e34927_app6.docx]

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Abbreviations

HCW: health care worker
LTCH: long-term care home
RECORD: Reporting of Studies Conducted Using Observational Routinely-Collected Data

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Original Paper

Effectiveness, Policy, and User Acceptance of COVID-19 Contact-Tracing Apps in the Post–COVID-19 Pandemic Era: Experience and Comparative Study

MingXin Liu[1]; SiYu Zhou[2], PhD; Qun Jin[3], PhD; Shoji Nishimura[3], PhD; Atsushi Ogihara[3], PhD

[1]Graduate School of Human Sciences, Waseda University, Tokorozawa, Japan
[2]School of Public Health, HangZhou Normal University, HangZhou, China
[3]Faculty of Human Sciences, Waseda University, Tokorozawa, Japan

Corresponding Author:
MingXin Liu
Graduate School of Human Sciences
Waseda University
2-579-15 Mikajima
Tokorozawa, 3591192
Japan
Phone: 81 04 2949 8111
Email: liumingxin98@akane.waseda.jp

Abstract

Background: In the post–COVID-19 pandemic era, many countries have launched apps to trace contacts of COVID-19 infections. Each contact-tracing app (CTA) faces a variety of issues owing to different national policies or technologies for tracing contacts.

Objective: In this study, we aimed to investigate all the CTAs used to trace contacts in various countries worldwide, including the technology used by each CTA, the availability of knowledge about the CTA from official websites, the interoperability of CTAs in various countries, and the infection detection rates and policies of the specific country that launched the CTA, and to summarize the current problems of the apps based on the information collected.

Methods: We investigated CTAs launched in all countries through Google, Google Scholar, and PubMed. We experimented with all apps that could be installed and compiled information about apps that could not be installed or used by consulting official websites and previous literature. We compared the information collected by us on CTAs with relevant previous literature to understand and analyze the data.

Results: After screening 166 COVID-19 apps developed in 197 countries worldwide, we selected 98 (59%) apps from 95 (48.2%) countries, of which 63 (66.3%) apps were usable. The methods of contact tracing are divided into 3 main categories: Bluetooth, geolocation, and QR codes. At the technical level, CTAs face 3 major problems. First, the distance and time for Bluetooth- and geolocation-based CTAs to record contact are generally set to 2 meters and 15 minutes; however, this distance should be lengthened, and the time should be shortened for more infectious variants. Second, Bluetooth- or geolocation-based CTAs also face the problem of lack of accuracy. For example, individuals in 2 adjacent vehicles during traffic jams may be at a distance of ≤2 meters to make the CTA trace contact, but the 2 users may actually be separated by car doors, which could prevent transmission and infection. In addition, we investigated infection detection rates in 33 countries, 16 (48.5%) of which had significantly low infection detection rates, wherein CTAs could have lacked effectiveness in reducing virus propagation. Regarding policy, CTAs in most countries can only be used in their own countries and lack interoperability among other countries. In addition, 7 countries have already discontinued CTAs, but we believe that it was too early to discontinue them. Regarding user acceptance, 28.6% (28/98) of CTAs had no official source of information that could reduce user acceptance.

Conclusions: We surveyed all CTAs worldwide, identified their technological policy and acceptance issues, and provided solutions for each of the issues we identified. This study aimed to provide useful guidance and suggestions for updating the existing CTAs and the subsequent development of new CTAs.

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KEYWORDS

COVID-19; contact-tracing app; digital contact tracing; mobile phone

Introduction

Background

COVID-19 was first identified in Wuhan, Hubei, China, in December 2019 [1,2]. In previous research, the mean reproductive number of COVID-19 was 3.28, which was higher than that of severe acute respiratory syndrome [3]. COVID-19 has a relatively high reproductive number and an initial estimated case fatality rate of 5.6% [4]. As of May 2022, a total of 525 million cases have been confirmed by government agencies worldwide, and more than 6.2 million deaths have been reported [5]. In addition, COVID-19 has considerably affected various service sectors such as tourism [6].

Transmission of COVID-19 is mainly because of airborne transmission of the virus; thus, surface disinfectants, hand hygiene, wearing a mask, ventilation, maintaining social distance, and rapid tracing and notification of potentially infected persons are crucial to prevent infection spread [7,8]. Contact tracing, followed by the prompt isolation of close contacts of an infected individual, is another strategy for preventing virus propagation. Therefore, for tracing infected persons, many countries have launched several digital contact tracing (DCT) methods to supplement manual contact tracing (MCT) [9]. As mobile phones are indispensable in today's society, several nations have implemented mobile phone–based contact-tracing apps (CTAs) to alert people who have been exposed to the SARS-CoV-2. Currently, despite widespread vaccination in some countries, many parts of the world remain unvaccinated. Even in highly vaccinated countries, COVID-19 continues to cause increased mortality and high levels of infections every 3 to 6 months. The widespread and effective use of CTAs may allow most people to return to their jobs, social events, and family life in capacities similar to those before the pandemic, implying less future morbidity and mortality from COVID-19. In addition, for diseases other than COVID-19 that are transmitted through close contact in the current (eg, monkeypox, Ebola, and COVID-19) and potential future outbreaks, CTA can be used to trace contacts. For example, CTAs have already been used to trace Ebola worldwide, serving as a precedent for mobile phone apps being used to trace contacts for diseases other than COVID-19.

Moreover, because some CTAs register personal information and collect user location data, the protection of personal privacy is an important issue facing CTAs. People worldwide have different attitudes regarding whether governments should protect personal privacy. A study showed that only 6% of people in the United States were very confident, and 25% were somewhat confident that the US government protected data privacy [10]. By contrast, a survey showed that in 2021, a total of 91% of Chinese respondents said that they trusted the Chinese government, the highest rate among the 28 countries surveyed, with a global average of only 52% of respondents saying that they trusted their governments [11]. Another study showed that 37.6% of the Chinese respondents investigated lacked privacy trust in the government [12]. In general, Chinese people have far more trust in their government's ability to protect their privacy than people in the United States do. This trust may lead to a higher acceptance of CTAs in China than in the United States. Additionally, people in countries with lower economic living standards tend to have lower web-based concerns about private personal information than those living in low-income countries [13]. Differences in people's privacy concerns and trust in the ability of governments to protect privacy in different countries can lead to large differences in the acceptance of CTAs.

Literature Review

Previous studies have assessed the effectiveness of CTAs in single countries, including Finland, Switzerland, and Australia [14-16]. Since our study was an international study, it was extremely difficult to assess the effectiveness of all CTAs using the same research method. Therefore, this study focuses on identifying the theoretical and technical issues that may affect the effectiveness of CTAs and offers suggestions for addressing them. A previous study showed that different countries have different data protection policies that prevent most CTAs from being used in other countries like they are used in their own country [17]. However, this study did not mention the extent of interoperability of CTAs or list specific interoperable CTAs. Previous studies in Europe, New Zealand, and Japan have investigated the public acceptance of CTAs and the factors that influence public acceptance using questionnaires [18-20]. Therefore, this study clarifies which CTAs have issues that may affect their public acceptance. Several previous studies have investigated dozens of CTAs. A study selected CTAs from the Google Play Store and Apple App Store, summarized the technology used in the CTAs, and analyzed the advantages and disadvantages of each technology (Bluetooth, GPS, and Wi-Fi) [21]. Another study categorized CTAs by underlying technology and investigated the number of CTA installations and the privacy design and public acceptance [22]. A third study analyzed the different technologies for implementing contact tracing using centralized, decentralized, and hybrid protocols and analyzed privacy issues at the technical level [23]. In addition, several previous studies have compared CTAs around the world [24-26]. However, no study has exhaustively investigated every CTA worldwide or the respective technologies used. CTAs in different countries or continents have various shortcomings, owing to differences in regional characteristics and national policies and the use of different technologies. In contrast to studies that have investigated several CTAs, this study investigated nearly every available CTA and identified common issues across CTAs.

Study Aims

In this study, we aimed to survey all the CTAs launched in the 197 countries recognized by the United Nations. To the best of our knowledge, this study has investigated the largest number of CTAs and countries to date; we have also categorized and evaluated the features and functions of each CTA by practically using of each CTA, read the description of each CTA, and combined this information with findings from previous research to summarize the known problems and challenges of the CTAs in terms of technical issues, effectiveness, user acceptance, policies, and privacy and given possible solutions for each of these issues. We aimed to provide information for future CTA development and make recommendations for improving CTAs. Governments, health authorities, and technical teams in countries that have already launched CTAs may update and improve the CTAs by following our recommendations, such as extending the tracing distance of Bluetooth-based CTAs and enhancing the cross-border interoperability of CTAs. Countries that have not yet launched CTAs may design them based on the findings of our research.

Methods

Overview

The methodology was divided into 2 parts: data collection and data analysis. The data collected in this study included the countries that launched their own CTAs, basic information about these CTAs, and the detection rates of COVID-19 in these countries. For data analysis, we used a literature study to compare our collected data with the results of previous studies; we aimed to determine the problems associated with CTAs and ways to improve them.

CTA Data Collection Method

To determine the countries that developed COVID-19 apps and collect information on these apps initially, we used Google, Google Scholar, and PubMed to search the keywords of the “country names” of the 197 countries recognized by the United Nations and “COVID-19 contact tracing app,” “digital contact tracing,” “COVID-19 app,” and “mobile applications” in combination. We searched the databases from December 9, 2019 (when COVID-19 was officially confirmed), to March 15, 2022. Only the first 5 pages of the search results were considered because information on the pages thereafter was not relevant to this research. After searching a combination of country names and keywords, we identified the following 3 inclusion criteria based on which the country that was searched for launched its own app. All COVID-19 apps that could be installed during initial data collection were installed and used on the Android system (Samsung Galaxy S20 Ultra) and iOS system (iPhone 11 Pro Max) mobile phones of the first author LMX. The initial collection of COVID-19 apps followed the exclusion criteria for secondary screening. The inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for contact-tracing apps (CTAs); search keywords: “country names,” “COVID-19 contact tracing app,” “digital contact tracing,” “COVID-19 app,” and “mobile apps.”

Inclusion criteria

- Google search results contained information from the government or the health department of the respective country about the COVID-19 app, such as an official website developed by the government.
- Google Scholar and PubMed search results showed published literature indicating that the country launched its own COVID-19 apps.
- Google search results did not contain information from the government or the health department, but there were news reports regarding COVID-19 app use in the country. We searched names of the COVID-19 apps mentioned in news reports on Google, Google Scholar, and PubMed, and the search results satisfied the first 2 criteria.

Exclusion criteria

- The app could not be installed with contact-tracing functionality for practical use.
- The app could not be installed or used, but a description of the contact-tracing function of the app could be found on the official website or in literature.
- Apps that were not CTAs, such as the official app launched by Timor-Leste for COVID-19 education.
- Regions that were not among the 197 United Nations–recognized countries were excluded from the study (eg, the British Gibraltar region, despite launching its own CTA, was excluded from this study because the region is not a sovereign state).
- CTAs that were not available in all parts of a country (eg, nonnational CTAs launched by each state government in the United States such as HMushrif, which was only used to trace isolated people and required a bracelet in Oman, and Msafari, which could only trace users in public transportation in Kenya).

Information in languages other than English, Chinese, and Japanese from government and health departments was translated using Google Translate for reading and comprehension. News reports in languages other than English, Chinese, and Japanese were not included in this study during the Google search. Although using each app, it was found that some did not support English, Chinese, or Japanese; for example, many apps from South American countries only supported Spanish. The relevant words or sentences were translated through screenshots using the translation software, DeepL Translate (DeepL SE) and Google Translate.

In this study, information on all CTAs was collected after secondary screening through practical use, consulting official websites, and literature. This information included the technology used by each CTA, whether there was an official website containing information on CTAs, whether they had interoperability with CTAs in other countries, and the COVID-19 detection rate in the country that launched the CTA. The information was first collected through the practical use of the installed CTAs. Regarding CTAs that were installed but could not be used for various reasons (such as the absence of a mobile phone number in the country they were launched) and those that could not be installed, relevant literature and information from the government or health departments was referred to supplement the information gathered by us on these CTAs. The information on CTAs may be outdated in previous literature; thus, even if our results are inconsistent with those of official government or health departments or previous literature, they can be used clinically.

Data Analysis Through Literature Study

In this research, the information obtained by the method described in the CTA Data Collection Method section was integrated with the findings of previous research and analyzed, and the problems and challenges of the investigated CTAs were summarized.

Results

Basic Information of CTAs

After searching keywords through Google, Google Scholar, and PubMed, 64.5 % (127/197) of the countries were found to have launched 166 COVID-19 apps. Excluding 34 nonnational apps, 9 of the remaining apps were not CTAs; 25 apps have been reported to have been used for contact tracing, but they could not be used practically or did not have sufficient evidence (official websites or research papers) regarding contact tracing. Finally, 98 apps developed by 95 countries with sufficient evidence of a contact-tracing function were identified (Multimedia Appendix 1 and Figure 1). China, Saudi Arabia, and Pakistan each had 2 CTAs that were used for contact tracing. A flow diagram depicting the screening procedure is shown in Figure 2.

Among the 95 countries with CTAs, Asian countries had the highest number of CTAs (35/95, 36.8%), whereas Oceania and South America each had the lowest number of CTAs (6/95, 6.3%). Regarding the number of countries with CTAs as a percentage of all countries on a continent, Asia had the highest percentage (35/48, 72.9%), and Africa had the lowest (9/54, 16.7%). The number of CTAs that could be practically used on either Android or iOS systems was 63, accounting for 64.3% (63/98) of all the CTAs. In the remaining CTAs (37/98, 37.8%), the app could not be used because it could not be installed, requiring mobile phone number in a specific country or personal ID, or it could be installed but could not be opened or crashed after opening. After testing all the available CTAs and investigating the introductory information from official websites or previous literature for the nonavailable CTAs, we found that the technologies used for contact tracing could be divided into 3 main categories: Bluetooth, geolocation, and QR code. Bluetooth was the most widely used technology, used in 71 (72.4%) of the 98 CTAs; 35 (35.7%) CTAs used geolocation, and 21 (21.4%) used QR codes (Multimedia Appendix 1). Of the 98 CTAs included in this study, 45 (45.9%) required the registration of personal information, 42 (42.8%) did not, and for 11 (11.2%) CTAs, this information was unknown. The personal information required most often included data such as name, mobile phone number, government identification number, date of birth, and address (Multimedia Appendix 1).

Regarding the interoperability of CTAs among different countries, 17 national CTAs could be operated in different countries. Table 1 shows specific information on the CTAs that had interoperability and the CTAs that could be operated. Of these, 16 were CTAs in EU countries; these CTAs are generally available and can be operated in >10 countries in the European Union. The only CTA other than the CTAs in EU countries that had interoperability was the careFIJI (CTA of Fiji), which can be used in New Zealand.

In addition to collecting information on CTAs, we investigated the estimated COVID-19 infection detection rate (percentage of positives detected to the number of true positives) based on the Institute for Health Metrics and Evaluation model in countries with CTAs; the data were available for 33 countries (Table 2). The highest detection rate was observed in Iceland (52%), and the lowest was observed in Myanmar, Pakistan, Niger, Uganda, and Bangladesh (close to 0%).

Detection rate means percentage of positives detected to the number of true positives. Of the 98 CTAs, 85 (87%) had official websites created by their respective governments, health departments, or developers (Multimedia Appendix 2). In the CTA information available in Multimedia Appendix 2, yes indicates that the official website includes a CTA guide, functions of the CTA, and other CTA-related information, with a total of 70 CTAs; no indicates CTAs with official websites, but without any introduction in official websites, with a total of 15 CTAs; unknown indicates CTAs without official websites, with a total of 13 CTAs. Investigating the download number data for 2022 for each CTA was difficult; only the 2020 download data were available for most CTAs. Of the countries for which download number data were available for 2022, WeChat (a Chinese CTA) had the highest percentage of downloads to the total population at approximately 88.8% (1.28 billion/1.45 billion). The reasons for this high percentage are as follows. (1) WeChat is not only a CTA but also a national chat app in China. (2) In China, it is impossible to enter large public places and move across provinces without the health codes contained in the app. Downloads as a percentage of the total population were, in descending order, Corona-Warn-App (45,820,000/84,324,494, 54.3%; Germany), NHS COVID-19 (31,044,213/68,605,590, 45.3%; United Kingdom), CoronaMelder (5,864,547/17,211,368, 34.1%; the Netherlands), COCOA (37,340,000/125,695,455, 29.7%; Japan), Koronavilkku (1,311,220/5,506,784, 23.8%; Finland), Radar COVID (8,568,514/46,791,314, 18.3%; Spain), and Aarogya Setu (216,800,000/1,407,993,700, 15.4%; India).

Figure 1. Countries that have released COVID-19 contact-tracing apps (CTAs) as of March 15, 2022 (created with mapchart.net [27]. *Created maps are licensed under a Creative Commons Attribution 4.0 International License [28]).

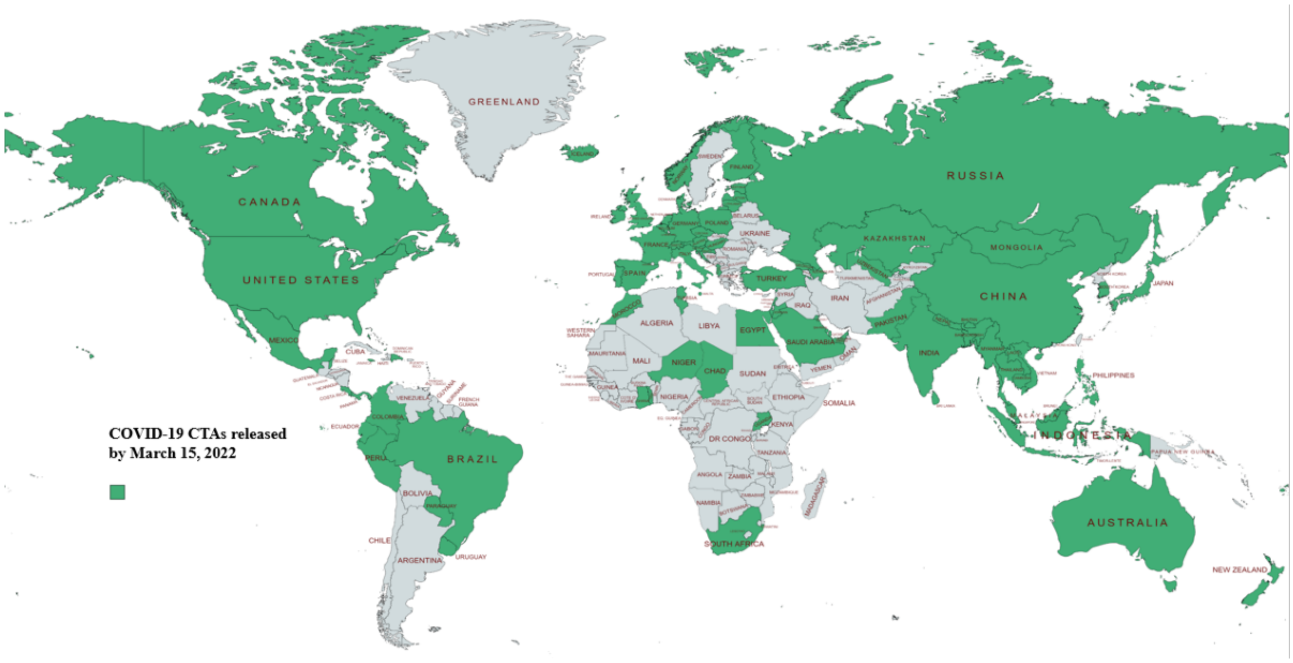


Figure 2. A flow diagram depicting the screening procedure. CTA: contact-tracing app.

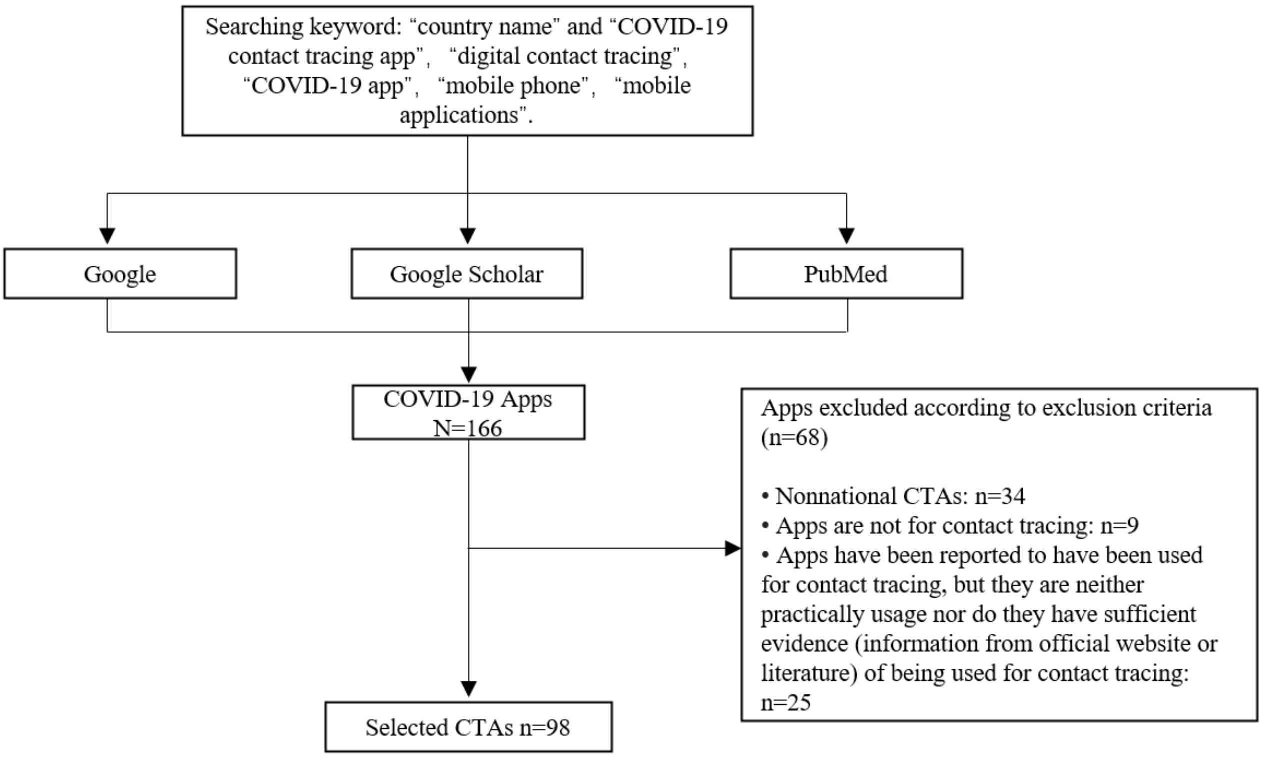


Table 1. Contact-tracing apps (CTAs) with interoperability and the countries where they can be used.

Country	App name	Countries or regions where apps can be used outside of their own country
Germany	Corona-Warn-App	Belgium, Croatia, Denmark, Estonia, Finland, Germany, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Slovenia, Spain, and Switzerland
Switzerland	SwissCovid	Switzerland, Liechtenstein, and Germany
Estonia	HOIA	Belgium, Croatia, Denmark, Estonia, Finland, Germany, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Slovenia, Spain, Switzerland, and Cyprus
Spain	Radar COVID	Belgium, Croatia, Denmark, Finland, Germany, Italy, Lithuania, Malta, the Netherlands, Norway, Poland, Slovenia, Ireland, and Latvia
Slovenia	#OstaniZdrav	Austria, Belgium, Croatia, Denmark, Finland, Germany, Ireland, Italy, Latvia, the Netherlands, Poland, and Spain
Croatia	Stop COVID-19	Other European countries
Fiji	careFIJI	New Zealand
Norway	Smittestopp	Denmark, Germany, Ireland, Spain, Latvia, Poland, Cyprus, Croatia, Austria, Finland, the Netherlands, and Belgium
Denmark	Smittestop	Germany, Italy, Ireland, Spain, and Latvia
Finland	Koronavilkku	Other European countries
Ireland	COVID Tracker	Northern Ireland and other European countries
Belgium	Coronalert BE	Germany, the Netherlands, Spain, Ireland, Italy, Denmark, Latvia, Croatia, Poland, and Cyprus
Austria	Stopp Corona	Other European countries
Latvia	Apturi Covid Latvia	Ireland, Italy, Germany, Spain, Denmark, Croatia, Poland, the Netherlands, Belgium, Finland, Austria, Norway, Slovenia, Cyprus, Malta, and Lithuania
Lithuania	Korona Stop LT	Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, Germany, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Slovenia, Spain, and Croatia
Malta	COVID Alert Malta	Other European countries

Table 2. Detection rate of countries that launched contact-tracing apps (CTAs).

Country	App names	Detection rate (%)	Date of detection rate data
China	WeChat and Alipay	42	March 14, 2022
Japan	COCOA	17	May 2, 2022
Korea	Corona 100m	26	March 14, 2022
Mongolia	ERSDEL	34	August 16, 2021
Vietnam	PC-Covid	32	May 2, 2022
Thailand	Mor Chana	6	May 2, 2022
Myanmar	SawSaw Shar	0	May 2, 2022
Malaysia	MySejahtera	14	May 2, 2022
Indonesia	PeduliLindungi	1	May 2, 2022
Pakistan	COVID-19 Gov PK and CoCare	0	May 2, 2022
India	Aarogya Setu	1	May 2, 2022
Bangladesh	Corona Tracer BD	0	May 2, 2022
Lebanon	Ma3an	9	May 2, 2022
Iceland	Rakning C-19	52	May 2, 2022
The United Kingdom	NHS COVID-19	35	April 4, 2022
Belgium	Coronalert BE	24	May 2, 2022
Switzerland	SwissCovid	34	May 2, 2022
Hungary	VirusRadar	7	May 2, 2022
Russia	Госуслуги.COVID трекер	6	May 2, 2022
Portugal	StayAway Covid	39	May 2, 2022
Spain	Radar COVID	13	May 2, 2022
Malta	COVID Alert Malta	33	May 2, 2022
Cyprus	CovTracer-EN	25	May 2, 2022
Niger	Niger Contact Tracer	0	May 2, 2022
Uganda	MoH CTC	0	May 2, 2022
South Africa	COVID Alert SA	3	September 27, 2021
New Zealand	NZ COVID Tracer	29	May 2, 2022
Canada	COVID Alert	9	May 2, 2022
The United States	NOVID	13	May 2, 2022
Colombia	CoronApp - Colombia	3	May 2, 2022
Peru	Perú en tus manos	3	May 2, 2022
Brazil	Coronavírus – SUS	5	May 2, 2022
Uruguay	Coronavirus UY	50	April 4, 2022

Discussion

Principal Findings

The principle of Bluetooth-based CTAs for contact tracing is that when 2 users with smartphones come into proximity, the CTA records the contact, and the contact record is retained for a certain number of days depending on the presettings of the CTA, usually 14 or 21 days. During this period, if one of the users tests positive for COVID-19, the user will either voluntarily or compulsorily be registered as positive in the CTA. The user who was in close contact with the COVID-19 positive user will be sent an alert notification on their smartphone. The protocols developed based on Bluetooth technology include BlueTrace, DP-3T, Google or Apple Exposure Notification, Pan-European Privacy-Preserving Proximity Tracing, and OpenCovidTrace [9], which differ in the centralization or decentralization in data collection.

Governments can develop their own CTAs based on any of these protocols and determine the specific time and distance for which that proximity will be recorded for the respective CTAs. In this study, 71 CTAs using Bluetooth to record the specific time and distance of contact were investigated; the time and distance data were available for 21 (29.6%) CTAs (Table 3). The shortest contact distance recorded was 1 meter for COCOA (CTA of Japan) and the longest contact distance recorded was 5 meters for Self Safety (CTA of Uzbekistan; Figure 3). The shortest contact time recorded was 1 minute for Self Safety and COVIDSafe (CTA of Australia) and the longest contact time recorded was 20 minutes for VirusRadar (CTA of Hungary). Of the 21 CTAs, 11 (52.4%) set the recorded contact time and distance at 2 meters and 15 minutes. In addition, some countries' CTAs, such as HaMagen (CTA of Israel), use Wi-Fi–assisted Bluetooth technology for contact tracing.

It should be noted that in Android systems, CTAs using the Google or Apple Exposure Notification protocol request permission to obtain a user's geolocation but do not use geolocation for contact tracing.

Geolocation-based CTAs trace contact in the following 2 ways. (1) Geolocation records the proximity between mobile phone users and alerts those who have contacted a user who tested positive for COVID-19 and was registered in the CTA, similar to Bluetooth contact tracing. Some CTAs such as Mor Chana (CTA of Thailand) and Aarogya Setu (CTA of India) trace the proximity of contact between 2 users through a combination of GPS and Bluetooth data. This approach can be centralized or decentralized for data collection. (2) WeChat and Alipay (CTAs of China) record the user's geographic location via a cell tower, and the user's health code turns red when an infection outbreak occurs in a city or region that the user visited in the past 14 days. This approach is typically centralized for data collection.

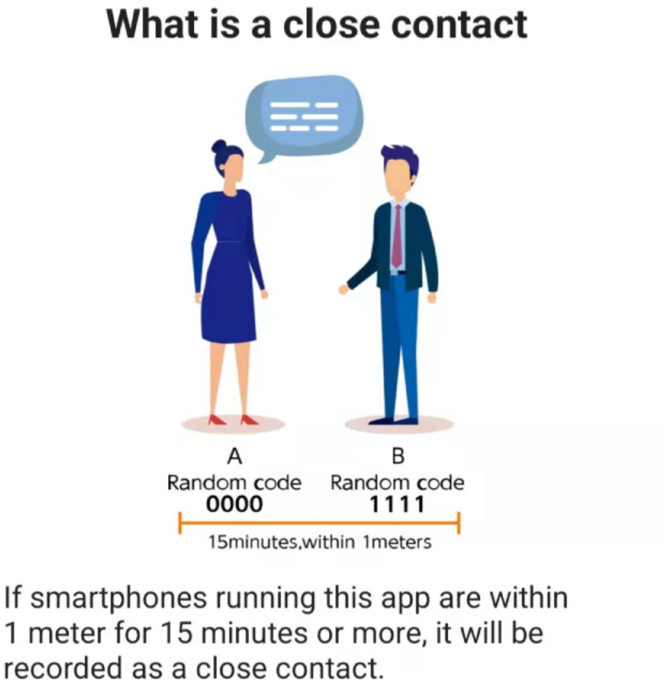
The principle of CTAs using QR codes to trace contacts is as follows: when a user wants to enter a public place (eg, supermarket, restaurant, or movie theater), the user will either volunteer or be instructed to scan the QR code set up in the public place to record check in and if the user tests positive for COVID-19, the public place that they visited will be classified as a high-risk area. Other users who visited the same area will be notified through an alarm or a red health code in their CTAs (Figure 4).

Table 3. Contact-tracing distance and time of contact-tracing apps (CTAs).

Country	App	Contact-tracing distance (m）	Contact-tracing time (min）
Japan	COCOA	1	15
Kazakhstan	Saqbol	2	15
Uzbekistan	Self Safety	5	1
Denmark	Smittestop	1	15
Ireland	COVID Tracker	2	15
France	TousAntiCovid	2	5
The Netherlands	CoronaMelder	1.5	15
Belgium	Coronalert BE	1.5	5
Switzerland	SwissCovid	1.5	15
The Czech Republic	eRouška	2	7
Hungary	VirusRadar	2	20
Latvia	Apturi Covid Latvia	2	15
Lithuania	Korona Stop LT	2	15
Portugal	StayAway Covid	2	15
Spain	Radar COVID	2	15
Tunisia	E7mi	3	N/A[a]
South Africa	COVID Alert SA	2	15
Australia	COVIDSafe	1.5	1
Canada	COVID Alert	2	15
The United States	NOVID	2.7	15
Georgia	Stop Covid	2	15

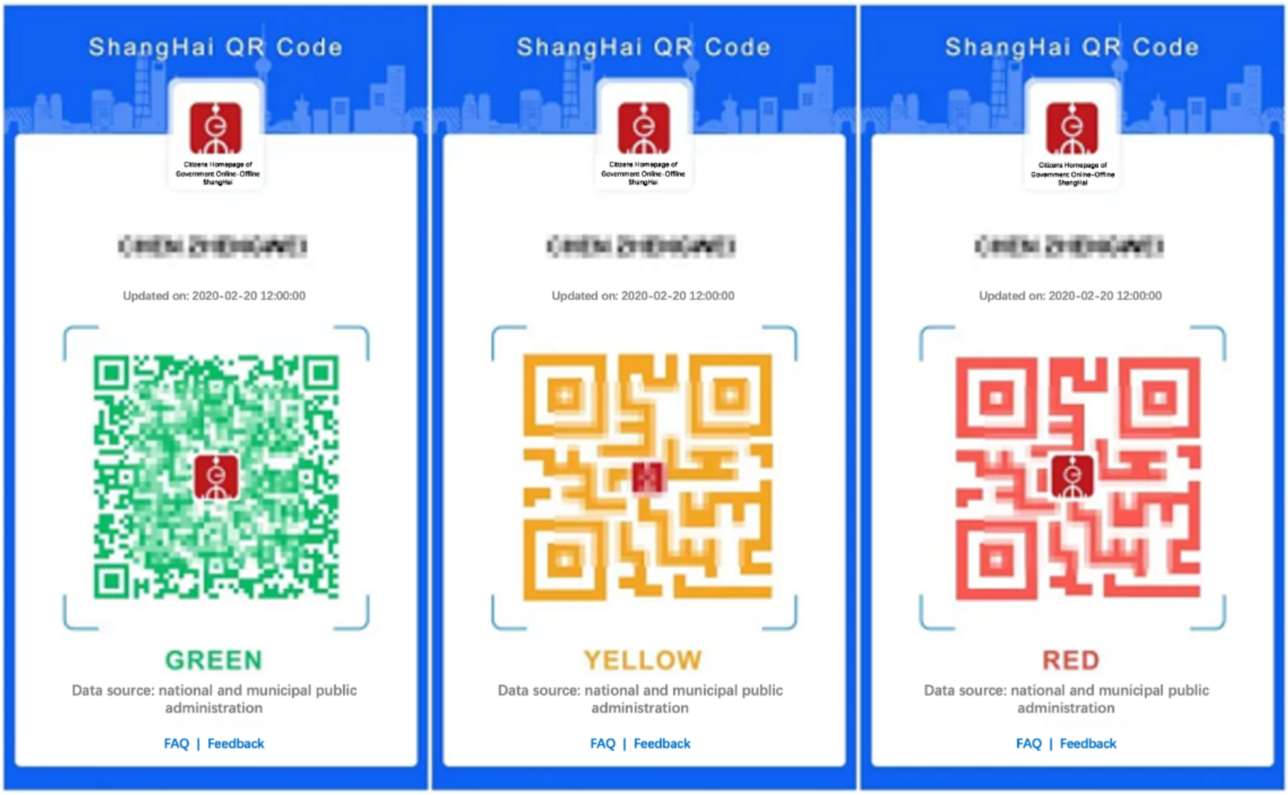
[a] N/A: not applicable.

Figure 3. A screenshot within the COCOA app (contact-tracing app of Japan).



If smartphones running this app are within 1 meter for 15 minutes or more, it will be recorded as a close contact.

Figure 4. A screenshot of health code used in China.



Data source: national and municipal public administration

Data source: national and municipal public administration

Data source: national and municipal public administration

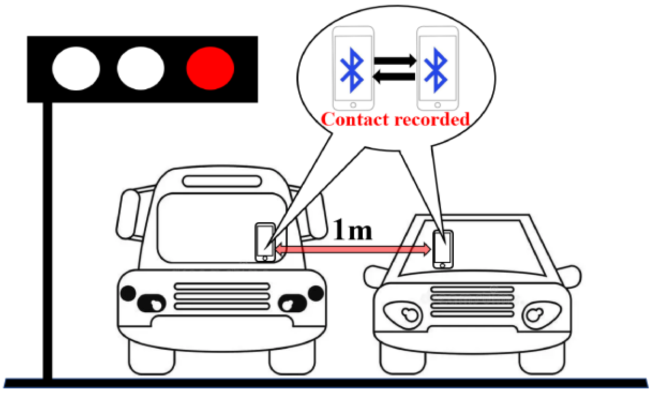
Comparison With Prior Work

Regarding contact-tracing distance and effectiveness, the criteria for the time and distance of proximity set by Bluetooth-based CTAs vary among countries. Regarding the safe social distance for preventing the spread of COVID-19, previous research has shown that 1.6 to 3.0 meters is a safe social distance for the airborne transmission of large droplets exhaled during speech, whereas the distance can reach 8.2 meters if all droplets are considered; furthermore, a social distance of 2 meters is not effective in preventing the spread of infection. [8,29]. Moreover, infectivity varies among different variants of viruses; earlier viruses are usually considered to be the least infectious, while the Alpha variants are considered to be 50% more infectious than the earlier strains, and the Delta variants are considered to be 60% more infectious than the Alpha variants [30]. By contrast, the Omicron variant, recognized by the World Health Organization on November 26, 2021, is considered to be the most infectious variant to date and is >10 times more infectious than earlier strains or 2.8 times more infectious than the Delta variants [31]. Omicron variant transmission was simulated by a Japanese research team in February 2022 using the supercomputer Fugaku. The results showed that while talking without a mask for 15 minutes, the maximum and average rates of infection were approximately 50% and 25%, respectively, for a distance of 2 meters between 2 people, and the rates of maximum and average rates of infection dropped to approximately 10% and 5%, respectively, when the distance was increased to 3 meters [32]. The study also simulated the infection rate of 2 people talking at different times, and the results showed that at a distance of 1 meter, 2 people talking without masks for 15 minutes showed a maximum infection rate of 95% and an average infection rate of 60%; for 6 minutes, they showed a maximum infection rate of 70% and an average infection rate of 30%; for 3 minutes, their maximum and average rates of infection dropped to 30% and 10%, respectively. Therefore, to maintain the infection rate of the Omicron variant at <10%, the tracing distance and time should be set to 1 meter and 3 minutes or 3 meters and 15 minutes. Among the 21 CTAs in Table 3, 14 (66.7%) had a tracing time of 15 minutes and 13 (92.8%) of these had a tracing distance of ≤2 meters. The contact-tracing distance and time settings for these CTAs were 2 meters and 15 minutes, as per the European Center for Disease Prevention and Control guidelines [33]. However, with the drastic reduction in face mask use in some countries, more infectious variants may be transmitted to others at a tracing distance and time much greater than 2 meters and much lesser than 15 minutes, respectively. Thus, current Bluetooth-based CTAs may not be able to trace many potentially infected individuals, because it may have tracing ranges that are too short to identify possible contact and spread. Importantly, in most countries, users who receive a CTA exposure notification are not mandated to quarantine or to undergo polymerase chain reaction (PCR) tests. Instead, with longer tracing distances and shorter tracing times, users can prepare for possible infections after receiving the exposure notification; for example, preparing food and sanitary products before the infection leads to fever and weakness. Thus, setting longer tracing distances and shorter tracing times for CTAs should be preferred.

Bluetooth- and geolocation-based contact tracing face many real-life problems that lead to decreased accuracy or false positives. For instance, in a public toilet, although 2 users with CTAs may be at a distance of ≤2 meters, making the CTAs trace contact, the 2 users may actually be separated by a thin wall or two, which could prevent infection [34]. Individuals in 2 adjacent vehicles may face a similar situation during traffic jams (Figure 5). In addition, signal absorption by the human body (when the mobile phone is in the pocket); interference of Wi-Fi signals; and absorption, interference, and diffraction caused by obstacles made of different materials in the signal propagation path can decrease the accuracy of Bluetooth tracing [35-37]. Moreover, different CTA detection rules in railways may lead to a 50% false-alarm rate [37]. Some countries have developed various countermeasures to cope with situations that may lead to decreased accuracy in CTAs. For example, the CTA in Singapore records contacts at a distance of ≥10 meters; therefore, there will often be signals being transmitted through walls, ceilings, and floors. In response, TraceTogether (CTA of Singapore) uploads contact-tracing data to the Ministry of Health, which processes and filters them based on their duration and signal strength to identify only close contacts [38]. HaMagen requests access to body movement data during initial use to avoid false alarm situations when individuals are separated by 2 adjacent vehicles during traffic jams. NOVID, developed at Carnegie Mellon University, uses a combination of ultrasound and Bluetooth. It is the only CTA that uses ultrasound to measure the distance for contact tracing. The NOVID research team experimentally found that at distances<1.82 meter, 103 out of 187 total experimental samples were correctly identified with an accuracy rate of 55.1%, whereas at distances >12 feet, 225 experimental samples were correctly identified 224 times, with an accuracy rate of 99.6%. Moreover, in real life, the tracing accuracy for a distance of <6 feet would be significantly >55.1% [39]. In addition, the ultrasonic method used by NOVID is effective in excluding false positives even in the presence of obstacles [39]. Therefore, ultrasonic technology has great potential for improving the accuracy of CTAs in contact tracing, particularly at long distances and in the presence of obstacles.

The detection rate of COVID-19 is one of the key factors affecting the effectiveness of CTAs. Low detection rates reduce the effectiveness of CTAs because contact tracing is impossible without a confirmed diagnosis, which is a serious challenge for both DCT and MCT. Previous research has shown that contact tracing barely reduces viral propagation when the detection rate is only 13%, and the effectiveness of contact tracing increases significantly when the detection rate increases to 26% or 37% [40]. In June 2020, the average detection rate worldwide was <10% and varied significantly among countries [41]. Therefore, the use of CTAs may not be effective in reducing viral propagation in most countries. Table 2 shows the data for the 33 countries that have developed CTAs wherein detection rates are available [42]. Even in the latter half of 2021 and 2022, only 11 (33.3%) of the 33 countries showed detection rates of >26%, and 3 (9.1%) countries showed detection rates of >37%. There are 16 (48.5%) countries that have not yet reached a detection rate of 13%; in these countries, CTAs can have an extremely limited effect. Currently, PCR testing is free and routine in some countries such as China and Japan. However, the cost of PCR testing varies greatly depending on factors such as the type of laboratory, country or region, and insurance provider [43]. Previous studies have shown that the cost of PCR testing, cost of commuting to a testing site, and time required for PCR testing can make it difficult for people who are willing to be tested [44,45]. Moreover, the convenience and comfort of the sample extraction method affected the willingness to test [45]. In many countries, PCR testing is expensive and difficult to access. This lack of access may lead to CTAs not being able to effectively trace potential infections and eventual getting discontinued. Therefore, making PCR testing free and routine may increase the willingness of users to undergo the test and improve the effectiveness of CTAs. In China, the following methods were used to increase the testing rates. Nationals who did not have a PCR testing certificate within the last 72 hours were not allowed to enter public places such as shopping malls, movie theaters, and public bathrooms and were not allowed to move across provinces by any means of transportation. To reduce costs and improve efficiency, China used a 10-in-1 or 20-in-1 mixed sample, in which samples from 10 or 20 people were tested together in a single sampling tube [46,47]. If the result was negative, it was assumed that all 10 or 20 participants were negative. If the test result was positive, the staff immediately individually isolated 10 or 20 samples in that mixed tube for a temporary period and recollected separate single-tube samples for testing. Furthermore, oropharyngeal swabs were used for routine testing in China and were less painful and more widely accepted than nasopharyngeal swabs [46,47]. These methods have allowed China to maintain a 42% detection rate based on the Institute for Health Metrics and Evaluation model even with a large population of 1.4 billion.

Figure 5. False tracing may happen in 2 adjacent vehicles during traffic jams.



According to our results, of the 197 sovereign countries around the world, 95 (48.2%) have developed 98 apps for contact tracing. However, different countries have different data protection policies that prevent most CTAs from being used in other countries as they are used in their own countries [17]. The CTA interoperability system, which was launched in October 2020 within the European Union, was the first CTA system to remove national operational barriers. The first countries to join this system were Germany, Italy, and Ireland [48]. We investigated CTAs that can be used in other countries as of May 2022; currently, only 17 CTAs can be used in other countries, 16 (94.1%) of which are in the European Union (Table 1). However, with the increasing liberalization of border measures of each country and international travel, the current interoperability of CTAs among countries other than those from Europe does not meet the status quo. International travelers may come into close contact with patients who tested positive for COVID-19 in other countries while traveling on international flights and while traveling in their destination country. However, because CTAs are not interoperable, travelers may not be able to detect transmission or infection resulting from close contact. Since the novel coronavirus has an incubation period of days to weeks, travelers may mistakenly believe that they are not infected until they have significant symptoms. Thus, tourists may spend time in public places for sightseeing, unaware that they have been infected. In this case, if tourists do not restrict their activities in public places, the virus may be further transmitted to more people. Increasing the interoperability of CTAs and removing national barriers among different countries is an important method to avoid cross-country transmission of COVID-19.

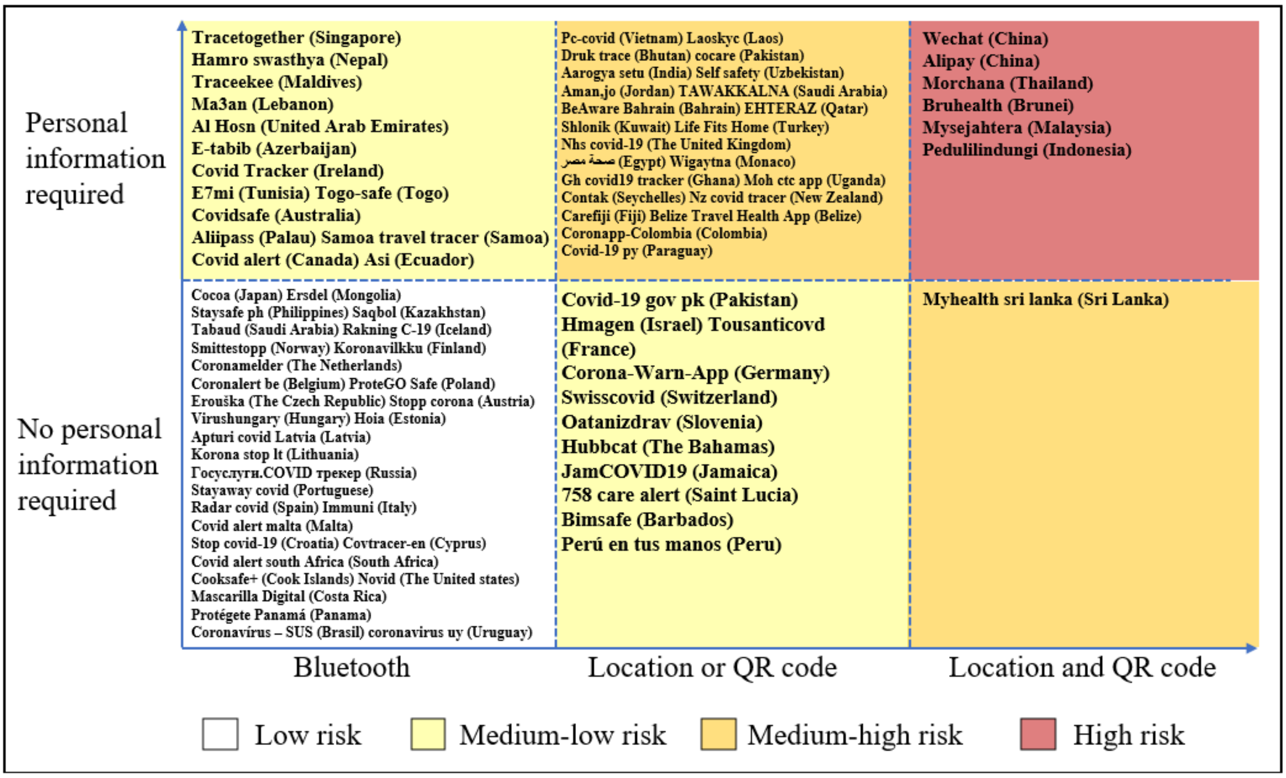
CTA policy is no longer stringent. With the increasing number of vaccinations, high asymptomatic rates, and low mortality presented by the Omicron variant compared with initial strains [49], many countries are easing their COVID-19 protection policies, with a trend of relaxation in rules regarding CTAs. For example, according to official information, the QR code–based "check-in" function was abolished in the United Kingdom from February 24, 2022 [50]. Meanwhile, we found through practical use, the QR code scanning function of the previous version of the NHS COVID-19 app (CTA of the United Kingdom) was removed. Moreover, Austria, Cyprus, the Czech Republic, Poland, Denmark, Finland, and Canada have discontinued their CTAs. This implies that CTAs no longer support contact tracing or notifications. However, we believe that this was a premature discontinuation of CTAs because of the following reasons. First, a study in South Africa investigated the asymptomatic rate of different variant infections in 577 health care patients who received a single dose of the Johnson & Johnson vaccine (2.6% for Beta and Delta and 16% for Omicron variants) [49], and another meta-analysis showed an asymptomatic rate of 40% for those infected with the Omicron virus [51]. According to the data, even with vaccination, more than half of the patients infected with Omicron developed symptoms. Therefore, as stated earlier in this section, users who receive notifications of exposure through CTAs can be well prepared for the possibility of symptoms. Especially in countries where medical resources are scarce, users can contact their physicians and reserve hospital beds earlier. Second, in the 2 years since the launch of CTAs, many countries have shown large CTA-using populations. Among the CTAs of countries that have discontinued CTAs, eRouška (CTA of the Czech Republic) has 1.7 million users, reaching 15.9% of the total population [52], and discontinuing CTAs may cause widespread uninstallation of the app. However, it is not possible to predict whether a more infectious variant of COVID-19 with a higher mortality rate or other new infectious diseases will emerge in future; the increase in the number of CTA-installed users is a slow process that may miss the best time for contact tracing. The official website of Smittestopp (CTA of Norway) shows that people in Norway no longer need to register COVID-19 positivity on their CTA. However, the Norwegian Institute of Public Health still supports the CTA and suggests that people keep Smittestopp on their mobile phones in case infection rates start to rise again [53].

We believe that even if the COVID-19 outbreak is contained, it is better to advise people to leave CTAs on their phones, as Norway has done, rather than to uninstall them.

Regarding user acceptance, a study based on a large-scale web-based survey in Japan showed an increase in the level of knowledge related to COCOA (CTA in Japan) to be associated with acceptance of the CTA. Therefore, sufficient knowledge about CTAs, such as the technology of the CTAs for contact tracing, privacy policy, and data storage time, can be effective in encouraging their use among people [20]. Official websites containing information on CTAs are one of the main sources of information for understanding CTAs. In this study, 98 official websites of CTAs were investigated, of which 70 (71.4%) had detailed information, and among the 28 CTAs that lacked sufficient information, 15 (53.6%) had official websites without relevant information, and 13 (46.4%) did not have official websites (Multimedia Appendix 2). Creating understandable information sources for CTAs has great potential for increasing their acceptance among users.

Multimedia Appendix 1 lists the 98 CTAs that required personal information to be entered at the time of registration. Compared with other continents, CTAs in Europe generally do not require personal information or require only a small amount of personal information. Of the 28 CTAs in Europe, only the United Kingdom and Ireland require personal information to be entered at the time of registration. It is important to note that the NHS COVID-19 CTA (CTA of the United Kingdom) requires information about the postal code and region of address, and the COVID TRACKER (CTA of Ireland) requires the selection of whether the person is aged >16 years. In contrast to CTAs that require detailed personal information, CTAs in the United Kingdom and Ireland do not require a user's name, exact address, mobile phone number, or any other detailed information. By contrast, 25 (65.8%) of the 38 CTAs in Asia require personal information; most of which require detailed information such as name and mobile phone number. CTAs that do not require personal information have a lower risk of violating privacy than those that require detailed information. However, as nationals from different countries have different levels of trust in their governments and previous literature shows that people in countries with lower economic living standards are less concerned about the privacy of personal information than people in developed countries [13], nationals of different countries may be differently receptive to CTAs that require personal information. In addition, at the technical level, CTAs based on decentralized Bluetooth technology do not require the user's location data and thus are most likely to protect the user's location data. By contrast, location-based CTAs access the user's location data and thus know where the user is in real time. With QR code–based CTAs, the user's location is not known when the user does not enter a public place; however, once the user enters a public place, the CTA records "check-ins" at specific locations. Therefore, location-based CTAs and QR code–based CTAs carry the risk of violating users' location privacy. Figure 6 classifies CTAs by technology and by whether personal information is required, indicating the risk of possible privacy violations. CTAs that use decentralized Bluetooth technology and do not require any personal information have the lowest risk of violating user privacy. Most European CTAs are classified under this category. CTAs that use both location and QR code technologies and require detailed personal information have the highest risk of privacy violation. CTAs in China, Thailand, Brunei, Malaysia, and Indonesia were classified in this category.

Figure 6. The risk of privacy violation among contact-tracing apps.



	Bluetooth	Location or QR code	Location and QR code
Personal information required	Tracetogether (Singapore) Hamro swasthya (Nepal) Traceekee (Maldives) Ma3an (Lebanon) Al Hosn (United Arab Emirates) E-tabib (Azerbaijan) Covid Tracker (Ireland) E7mi (Tunisia) Togo-safe (Togo) Covidsafe (Australia) Aliipass (Palau) Samoa travel tracer (Samoa) Covid alert (Canada) Asi (Ecuador)	Pc-covid (Vietnam) Laoskyc (Laos) Druk trace (Bhutan) cocare (Pakistan) Aarogya setu (India) Self safety (Uzbekistan) Aman.jo (Jordan) TAWAKKALNA (Saudi Arabia) BeAware Bahrain (Bahrain) EHTERAZ (Qatar) Shlonik (Kuwait) Life Fits Home (Turkey) Nhs covid-19 (The United Kingdom) صحة مصر (Egypt) Wigaytna (Monaco) Gh covid19 tracker (Ghana) Moh ctc app (Uganda) Contak (Seychelles) Nz covid tracer (New Zealand) Carefiji (Fiji) Belize Travel Health App (Belize) Coronapp-Colombia (Colombia) Covid-19 py (Paraguay)	Wechat (China) Alipay (China) Morchana (Thailand) Bruhealth (Brunei) Mysejahtera (Malaysia) Pedulilindungi (Indonesia)
No personal information required	Cocoa (Japan) Ersdel (Mongolia) Staysafe ph (Philippines) Saqbol (Kazakhstan) Tabaud (Saudi Arabia) Rakning C-19 (Iceland) Smittestopp (Norway) Koronavilkku (Finland) Coronamelder (The Netherlands) Coronalert be (Belgium) ProteGO Safe (Poland) Erouška (The Czech Republic) Stopp corona (Austria) Virushungary (Hungary) Hoia (Estonia) Apturi covid Latvia (Latvia) Korona stop lt (Lithuania) Госуслуги.COVID трекер (Russia) Stayaway covid (Portuguese) Radar covid (Spain) Immuni (Italy) Covid alert malta (Malta) Stop covid-19 (Croatia) Covtracer-en (Cyprus) Covid alert south Africa (South Africa) Cooksafe+ (Cook Islands) Novid (The United states) Mascarilla Digital (Costa Rica) Protégete Panamá (Panama) Coronavírus – SUS (Brasil) coronavirus uy (Uruguay)	Covid-19 gov pk (Pakistan) Hmagen (Israel) Tousanticovd (France) Corona-Warn-App (Germany) Swisscovid (Switzerland) Oatanizdrav (Slovenia) Hubbcat (The Bahamas) JamCOVID19 (Jamaica) 758 care alert (Saint Lucia) Bimsafe (Barbados) Perú en tus manos (Peru)	Myhealth sri lanka (Sri Lanka)

Limitations

We summarized the contact-tracing techniques used in 98 CTAs through practical use and through information on official websites and previous literature. The CTAs we used were the latest versions that could be downloaded; thus, our information on contact-tracing techniques was also up-to-date and reliable. However, after collecting information on the CTAs that could not be used practically through information on official websites and previous literature, we found that some information, especially in the literature, was more than a year old; this information could be inconsistent with the latest version of the CTA. The CTAs marked with letter a in the upper right corner in Multimedia Appendix 1 are those that cannot be used, and the sources of information about these CTAs can be found in Multimedia Appendix 3.

In addition, we used Google Translate and DeepL Translate to understand the content of the literature in languages other than Chinese, English, and Japanese and of CTAs that do not support Chinese, English, or Japanese. Google Translate and DeepL Translate were not always accurate. However, the literature in languages other than Chinese, English, and Japanese and the CTAs in these other languages only account for a very small portion of this study, so they do not have a significant impact on the study. In future studies, we invite researchers who can read other languages to help us.

Conclusions

For airborne infectious diseases, such as COVID-19, contact tracing is important to reduce viral propagation, and mobile app–based DCT is an effective tool to assist MCT. In this study, we investigated CTAs worldwide; to the best of our knowledge, this is the first study to investigate nearly all CTAs worldwide. We combined the results of this study with those of previous studies to identify common issues in the technology, policy, and user acceptance of CTAs. Most of the current Bluetooth-based CTAs have set the distance and time of tracing contact at 2 meters and 15 minutes; however, considering that several viral variants have stronger infectivity than the initial strains, 2 meters and 15 minutes is not sufficient. Contact-tracing distance and time set at 3 meters and 15 minutes or 1 meter and 3 minutes is preferred. Although some low-income countries with low infection detection rates have launched their own CTAs, the CTAs may not be effective in reducing viral propagation. Currently, only the European Union has developed an interoperable system that allows CTAs to be used in other countries, and outside the European Union, only careFIJI (CTA of Fiji) can be used in New Zealand. Other countries' CTAs do not have interoperability among different countries. Removing CTAs' national barriers and increasing interoperability worldwide are critical because countries are gradually opening their borders, and COVID-19 policies are being implemented less strictly. Creating official websites that include information on CTAs would increase their user acceptance and promote installation; 28 (28.6%) of 98 CTAs lacked access to comprehensive and reliable CTA information through official websites. We examined several practical situations that may affect the accuracy of GPS location; 3 CTAs were found to address this lack of accuracy. Among these, the ultrasonic technology used by NOVID was effective in improving the accuracy of the CTA after several rounds of experiments. We found that CTAs have been discontinued in 5 countries since February 2022. We believe that this was a premature discontinuation because COVID-19 has not been eliminated, and it is not possible to predict whether new variants will emerge in the future.

In addition, vaccination has been shown to reduce infection rates, alleviate infection symptoms, and reduce case fatality rates. Therefore, we believe that in countries with widespread vaccination, users do not need extremely stringent measures such as mandatory hospitalization or 14-day self-isolation after receiving notifications of CTA exposure. Overresponse to CTA exposure notifications disrupts both the daily lives of users and the national economy. However, we believe that the greatest benefit of CTAs is that users who receive exposure notifications can prepare for possible infections in advance. For example, users who receive exposure notifications can wear masks to avoid spreading the virus to more people, cancel unnecessary plans to visit public places, make appointments for PCR testing, and prepare medicines in advance to deal with fever and debilitation after infection. Currently, most countries do not mandate that nationals respond upon receiving CTA exposure notification, but the government or health departments should provide guidelines and suggestions on measures to be taken by users who receive an exposure notification. We created a recommendation list for future CTA updates and designs as well as for policy development (Textbox 2).

Textbox 2. Recommendation list for contact-tracing app (CTA) design and policy development.

Technical level

- Setting tracing distance and time to 1 meter and 3 minutes or 3 meters and 15 minutes in Bluetooth-based CTAs
- Improving contact-tracing accuracy by using ultrasonic technology, accessing body movement data, and uploading data to the Ministry of Health for processing and filtering

Policy level

- Removing CTAs' cross-border barriers and increasing their interoperability worldwide
- Continuing using and maintaining CTAs; encouraging people to use CTAs or at least leave the CTAs installed on their phones
- Providing guidelines and suggestions for users who receive exposure notifications from their CTAs
- Increasing infection detection rate for improving the effectiveness of CTAs by making polymerase chain reaction (PCR) testing free; encouraging people to participate in PCR testing; adopting 10-in-1 mixed samples to reduce costs and improve efficiency; adopting oropharyngeal swabs instead of nasopharyngeal swabs to reduce pain

Acceptance

- Creating an official website that includes information on CTAs to increase user acceptance and promote installation

Conflicts of Interest

None declared.

Multimedia Appendix 1
Basic information of all contact-tracing apps.
[XLSX File (Microsoft Excel File), 17 KB - publichealth_v8i10e40233_app1.xlsx]

Multimedia Appendix 2
Official website of all contact-tracing apps.
[XLSX File (Microsoft Excel File), 21 KB - publichealth_v8i10e40233_app2.xlsx]

Multimedia Appendix 3
Information sources of contact-tracing apps that cannot be actually used.
[XLSX File (Microsoft Excel File), 16 KB - publichealth_v8i10e40233_app3.xlsx]

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Abbreviations

CTA: contact-tracing app
DCT: digital contact tracing
MCT: manual contact tracing

PCR: polymerase chain reaction

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Original Paper

The #VaccinesWork Hashtag on Twitter in the Context of the COVID-19 Pandemic: Network Analysis

Aïna Fuster-Casanovas[1,2], MSc, RPh; Ronnie Das[3], PhD; Josep Vidal-Alaball[1,2,4], MD, MPH, PhD; Francesc Lopez Segui[5,6], PhD; Wasim Ahmed[7], BA, MSc, PhD

[1]Unitat de Suport a la Recerca de la Catalunya Central, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Sant Fruitós de Bages, Spain

[2]Health Promotion in Rural Areas Research Group, Gerència Territorial de la Catalunya Central, Institut Català de la Salut, Sant Fruitós de Bages, Spain

[3]Audencia Business School, Nantes, France

[4]Faculty of Medicine, University of Vic-Central University of Catalonia, Vic, Spain

[5]Germans Trias i Pujol Hospital, Institut Català de la Salut, Badalona, Spain

[6]Research Group on Innovation, Health Economics and Digital Transformation (Institut Germans Trias i Pujol), Badalona, Spain

[7]Management School, University of Stirling, Stirling, United Kingdom

Corresponding Author:
Josep Vidal-Alaball, MD, MPH, PhD
Unitat de Suport a la Recerca de la Catalunya Central
Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
Pica d'Estats 13-15
Sant Fruitós de Bages, 08272
Spain
Phone: 34 93 693 0040
Email: jvidal.cc.ics@gencat.cat

Abstract

Background: Vaccination is one of the most successful public health interventions for the prevention of COVID-19. Toward the end of April 2021, UNICEF (United Nations International Children's Emergency Fund), alongside other organizations, were promoting the hashtag #VaccinesWork.

Objective: The aim of this paper is to analyze the #VaccinesWork hashtag on Twitter in the context of the COVID-19 pandemic, analyzing the main messages shared and the organizations involved.

Methods: The data set used in this study consists of 11,085 tweets containing the #VaccinesWork hashtag from the 29th to the 30th of April 2021. The data set includes tweets that may not have the hashtag but were replies or mentions in those tweets. The data were retrieved using NodeXL, and the network graph was laid out using the Harel-Koren fast multiscale layout algorithm.

Results: The study found that organizations such as the World Health Organization, UNICEF, and Gavi were the key opinion leaders and had a big influence on the spread of information among users. Furthermore, the most shared URLs belonged to academic journals with a high impact factor. Provaccination users had other vaccination-promoting hashtags in common, not only in the COVID-19 scenario.

Conclusions: This study investigated the discussions surrounding the #VaccinesWork hashtag. Social media networks containing conspiracy theories tend to contain dubious accounts leading the discussions and are often linked to unverified information. This kind of analysis can be useful to detect the optimal moment for launching health campaigns on Twitter.

(JMIR Public Health Surveill 2022;8(10):e38153) doi:10.2196/38153

KEYWORDS

Twitter; social media; COVID-19; misinformation; vaccination; public health; vaccine hesitancy; infodemiology; health campaign; content analysis; social network; layout algorithm

Introduction

The outbreak of the COVID-19 pandemic in December 2020 in China and its rapid spread around the world has highlighted health and health care systems as one of the most important human vulnerabilities. To tackle a virus with a worldwide high transmission rate, institutions identified priorities for combating it; limiting the spread of the virus, providing medical equipment, research, and tackling the sociodemographic consequences were their main objectives [1]. On January 30, 2020, the World Health Organization (WHO) Emergency Committee declared a global health emergency because of rising case reporting rates [2].

In the absence of a vaccine or treatments, social distancing and handwashing were the first measures promoted to reduce the spread of the virus. Next, as a complementary measure, the mass lockdown of the population helped reduce the increase in cases and gave the scientific community time to develop other mechanisms to curb the contagion [3]. In parallel, the development of a vaccine was a key objective for all countries [4]. On December 23, 2020, the European Medicines Agency approved the first vaccine from the Pfizer-BioNTech Comirnaty laboratory [5]. This was followed by the approval of other vaccines, such as the Moderna/Lonza-Spikevax, the Oxford/AstraZeneca, and finally, the Johnson and Johnson/Janssen vaccines, to achieve group immunity as quickly as possible.

Vaccination is one of the most successful public health interventions for the prevention of communicable infectious diseases [6]. The increasing use of new technologies by the population has given an important role to social networks in obtaining information on health and health promotion. Although social media is a good channel for health organizations to disseminate verified and accurate information, there is also considerable potential for misinformation that is harmful to patients [7-9]. One of the best-known social networks, Twitter, is a platform that allows short messages to be shared in real time, accompanied by images, hashtags (it serves as an indication that a piece of content relates to a specific topic or category), or mentions (ie, when the short message contains another person's username) [10]. Twitter was created in 2006 and currently has 322.4 million monthly users around the world [11].

The increase in vaccine hesitancy, delay, and refusal despite the availability of vaccination services may be fueled, in part, by claims on the internet about the harmfulness of vaccinations [12-14]. In fact, the analysis carried out by Jamison et al [15] classifying the different topics of discussion about vaccines on Twitter suggests that there is a slightly higher proportion of antivaccine messages (22%) than provaccine messages (17%), and the remaining messages (61%) were neutral. It was identified that the main topics of antivaccine messages were security concerns and conspiracies. Conversely, provaccination users generated content promoting the vaccine, criticizing antivaccine beliefs about vaccine safety and efficacy.

Toward the end of April 2021, UNICEF and the WHO, alongside other accounts and organizations, were promoting the hashtag #VaccinesWork during World Immunization week, which took place between April 29th and 30th. Using this as a case study, the aim of this paper is to analyze the #VaccinesWork hashtag on Twitter in the context of the COVID-19 pandemic, analyzing the main messages shared and the organizations involved. To analyze the information, the study sought to address the following research questions (RQs):

- RQ1: Who were the key opinion leaders?
- RQ2: What were the most shared URLs?
- RQ3: What were the most used hashtags?

Methods

Data Retrieval

The data set used in this paper consists of 11,085 tweets containing the #VaccinesWork hashtag from the 29th to the 30th of April 2021. Our data set included tweet replies and mentions in tweets with the #VaccinesWork hashtag. The data were retrieved using NodeXL (Social Media Research Foundation), and the network graph was laid out using the Harel-Koren fast multiscale layout algorithm [16]. The #VaccinesWork hashtag and time period studied were selected because they corresponded to the final two days of World Immunization week. This study used the Academic Track application programming interface to retrieve tweets. The library 'academictwitteR' [17] was used to retrieve tweets. Finally, tweet IDs were entered into NodeXL. A computer running Microsoft Windows 8 was used to retrieve data in Microsoft Excel 2010 using the professional version of NodeXL (release code: +1.0.1.428+). NodeXL uses Twitter's search application programming interface. URLs were automatically expanded within NodeXL.

Ethics Approval

The study received ethical approval from Newcastle University, under the review number 14026/2020.

Data Analysis

The data analysis has identified 6 network shapes and structures that Twitter topics tend to follow, such as broadcast networks, polarized crowds, brand clusters, tight crowds, community clusters, and support networks [18]. This study analyzes influential users (ie, a user who is able to reach and create debate among other users), the keywords related to the main hashtag (ie, words related to the topic that appears in the tweets), the topics (ie, the subject of which there is a thread of conversations), and web sources (ie, the URLs that people have shared by a tweet). In this study, influential users were identified by drawing upon the betweenness centrality algorithm. In addition, social network analysis of the discussion was conducted with NodeXL, as in previous research, which provided an understanding of the shape of the conversation. The graph's vertices were grouped by cluster, using the Clauset-Newman-Moore algorithm [8,9]. Individual users have been anonymized in line with current best practices for research on Twitter [19].

Results

Social Network Visualization

Figure 1 provides an overview of the network and key groups of users who were tweeting using the hashtag or keyword 'VaccinesWork,' and Figure 2 provides a zoomed in view of the top 6 groups. It could be seen that groups 2, 4, 5, and 6 look like they are mentioning or retweeting each other. The circles are similar in size in these groups indicating that users in those groups were more influential. Red lines coming out of these groups indicate strong relationships with other users or groups and highlight how they have a strong influence. The graph shows various communities of users who shared and tweeted using this hashtag. The largest group in the network was of an isolated group (labelled group 1); it shows that users were tweeting without mentioning one another. They simply tweeted in support of the campaign by adding their message of support alongside ‘VaccinesWork.’ The tweet and hashtag would appear on their timeline, visible to all their followers. There were also many other smaller pockets of discussion indicating several communities that were tweeting using the hashtag.

Figure 1. Social network graph of #VaccinesWork.

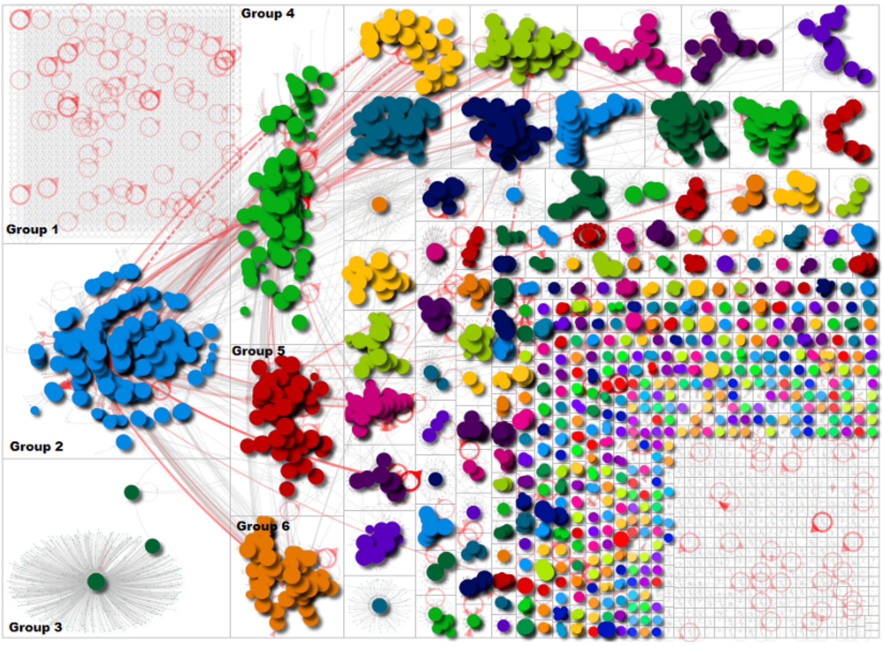

Figure 2. Zoomed-in social network graph of the top 6 groups.

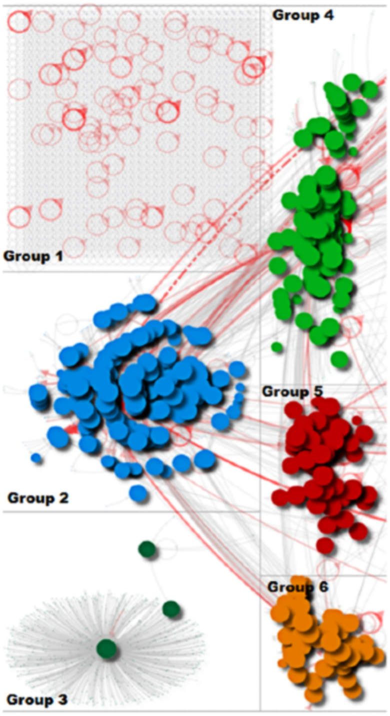

Table 1 shows the most used hashtags across the different groups within the network. These correspond to the group labels applied to Figure 1. It can be seen that group 2 has used the hashtag #VaccinesWork the most (1315 times), followed by group 1 (1161 times). The rest are placed far away from these. Furthermore, the shape of group 3 (a broadcast network where a single user is being retweeted) demonstrates that only one main hashtag was used in this group. Between other groups, there are relevant hashtags in common promoting vaccination. 'Covid19' appears in second position in group 1 and group 5; in group 2 and group 4, it appears in third position.

The hashtag #worldimmunizationweek also appears across groups 1, 2, 4, and 5. In addition, there are hashtags, such as #avw2021 or #eiw2021, promoting vaccination week in Africa and Europe, respectively. Other hashtags such as #protectedtogether, #vaccinesbringuscloser, and #vaccinessavelives are related to #VaccinesWork to promote group immunity.

Table 1. Top hashtags in tweets per group.

Group 1	Hashtag, n	Group 2	Hashtag, n	Group 3	Hashtag, n	Group 4	Hashtag, n	Group 5	Hashtag, n
VaccinesWork	1161	VaccinesWork	1315	VaccinesWork	793	VaccinesWork	982	VaccinesWork	539
Covid19	224	Worldimmunizationweek	245	Wearamask	1	Worldimmunizationweek	312	Covid19	205
Vaccinated	150	Covid19	206	Largestvaccinedrive	1	Covid19	225	Europeanimmunizationweek	169
Vaccine	100	Avw2021	167	Vaccinated	1	Vaccinequity	196	Worldimmunizationweek	128
Getvaccinated	76	Protectedtogether	48	Stayhome	1	Dayofimmunology	63	Eiw2021	68
Worldimmunizationweek	62	Wiw2021	46	Tomandjerry	1	Healthforall	53	Worldimmunisationweek	47
Covidvaccine	52	Worldimmunisationweek	41	Doctors	1	Primaryhealthcare	52	Vaccinessavelives	37
Vaccineregistration	42	Vaccinated	38	Weremask	1	Askwho	33	Vaccination	33
Covid19vaccine	41	Endpolio	38	Indiafightscovid19	1	Eiw2021	31	Vaccinesbringuscloser	31
Covid19india	41	Wcc	38	Covidemergency2021	1	Vaccines	28	Wewontrest	29

Most shared URLs

Table 2 provides an overview of the top 5 key URLs within tweets. The links used point to legitimate sources of information and high-quality information sources such as peer-reviewed papers.

The first most shared URL (N=136) is an article published by The Lancet. The article shared is a modelling study that estimates the health impact of vaccination against 10 pathogens in 98 low-income and middle-income countries from 2000 to 2030. The second most shared URL (N=87) is an article published by a web-based news service, available as a free-access website that provides daily and weekly newsletters to subscribers. The article is about Medicago, a pioneer company in developing plant-based vaccines and therapeutics in Canada. The company had started a rolling submission for its plant-derived adjuvanted COVID-19 vaccines candidate. The third most shared URL (N=62) belongs to the WHO. The article shows the issue of vaccine equity and the solution proposed by the organization. The fourth most shared URL (N=58) belongs to the European Vaccination Information Portal. The main purpose of this website is to provide evidence on vaccines and vaccination in general. The final most shared URL (N=45) is about the Campaign Vaccination Week in the Americas 2021 by the Pan American Health Organization.

Table 3 provides an overview of the influential users within the network. It has to be considered that betweenness centrality refers to the influence a user exerts on other users by his tweets. In addition, the concept of influence refers to the popularity or reputation of a user in the social network, calculated using the betweenness centrality metric [20]. The study identified the top 5 users who were influential based on their betweenness centrality score.

First, the betweenness centrality score ranks users among each other, such that users with higher scores have greater influence within the network; in this context, the user who has had the most influence on other users is the WHO. This is followed by UNICEF, one of the world's largest providers of vaccines and one of the organizations that started promoting the hashtag #VaccinesWork. In this instance, the Twitter account of the WHO has a betweenness centrality score that was 70.90% greater than that of UNICEF, which was in second place. This demonstrates that the WHO has considerably more influence compared to other users.

Third place belonged to Gavi, the Vaccine Alliance, which is a public-private global health partnership with the goal of increasing access to immunization worldwide. In the fourth place was the Centres for Disease Control and Prevention (CDC) of the US Department of Health and Human Services. CDC focuses on the development and application of disease prevention and control, environmental health, and health education activities. In the fifth place was UNICEF India, in line with UNICEF's general goal.

Table 2. Overview of the 5 most shared URLs.

Rank	Title	URLs	Count, n
1	Estimating the health impact of vaccination against 10 pathogens in 98 low-income and middle-income countries from 2000 to 2030: a modelling study	[21]	136
2	Plant-derived COVID-19 vaccine candidate starts rolling review with Health Canada	[22]	87
3	Call to action: vaccine equity	[23]	62
4	COVID-19 vaccines	[24]	58
5	Vaccination Week in the Americas 2021	[25]	45

Table 3. Overview of the top 5 influential users.

Rank	Top 5 users, ranked by betweenness centrality	User biography (date taken)	Betweenness centrality
1	WHO[a]	We are the #UnitedNations' health agency—#HealthForAll. Always check our latest tweets on #COVID19 for updated advice/information (20/07/2021)	15285431
2	UNICEF[b]	As conflict escalates in #Ukraine, UNICEF is on the ground reaching children with water, health and education services. Here's how you can help (20/07/2021)	8943804
3	Gavi	Gavi, the Vaccine Alliance, helps vaccinate half the world's children against deadly and debilitating diseases. #VaccinesWork #COVAX #OneWorldProtected (20/07/2021)	3513609
4	CDC[c]global	CDC works 24/7 to save lives, reduce disease, and improve #globalhealth around the world. Links, follows, and retweets do not constitute endorsement (20/07/2021)	2650617
5	UNICEFindia	Since 1949, UNICEF has worked side-by-side with India to save children's lives, defend their rights, and help them fulfill their potential. #ForEveryChild (20/07/2021)	2028529

[a] WHO: World Health Organization.

[b] UNICEF: United Nations International Children's Emergency Fund.

[c] CDC: Centres for Disease Control and Prevention.

Discussion

Principal Findings

Social networks are part of people's daily lives. Although Twitter is a relevant tool for obtaining verified information, conspiracy theories with incorrect information also emerge [8,9].

The hashtag #VaccinesWork was created by UNICEF in 2019 to promote immunization on social media. UNICEF ensures that every US $1 spent on childhood immunization returns up to US $44 in benefits [26]. In April 2019, the Bill & Melinda Gates Foundation contributed US $1 to UNICEF for every like or share of social media posts using the hashtag. This economic contribution to the promotion of the hashtag most probably boosted UNICEF's early campaign. Three years after this campaign, our study analyzed the status of this hashtag after the spread of COVID-19.

To respond to RQ1, this study identified influential users who were actively tweeting and spreading information in favor of vaccines. According to Figure 1, there are many groups of users who used the #VaccinesWork hashtag. The most influential user accounts were well-known organizations, such as the WHO, UNICEF, or Gavi, among others. In this context, the results suggest that the hashtag was linked to groups of users who were tweeting factual information. The betweenness centrality metric was useful in finding users with greater influence within the network. The results highlight how influential users were effective broadcasters in favor of vaccines, and how their reach extended beyond their own network of Twitter followers, according to the number of red lines (Figure 1 and 2) that were coming out of the groups and extending to other users. They show the reach of these users. In this context, these types of social network analyses can also be useful for detecting when the volume of health-related tweets increases among the population. When the popularity of a topic increases significantly on social media, it could be the optimal moment to launch a health campaign on social and traditional media to maximize the impact [27,28].

Regarding RQ2, the most shared URL is an article published by The Lancet. This indicates that users involved with the #VaccinesWork hashtag are more likely to share information with high levels of trust. According to the article, users find the evidence provided on mortality reduction from vaccines relevant, not only in the context of COVID-19 but also concerning the mortality reduction produced by vaccines against

10 different pathogens [21]. Furthermore, regarding the most shared URLs and comparing the results with other articles about misinformation in Twitter by authors, provaccine user groups tend to disseminate articles from indexed journals [8,9]. The results have shown that the first most shared URL is from the scientific Journal The Lancet, a peer-reviewed source with a high impact factor. The other URLs are from organizations related to health issues, such as the WHO, Pan American Health Organization ,or Biopharma. In contrast, other studies on conspiracies on Twitter have shown that the most shared URLs were those of YouTube videos and press articles attempting to disprove the conspiracy [8,9].

Regarding RQ3, it is remarkable that group 3 has only promoted the hashtag #VaccinesWork, and this could suggest that this group of users may have tried to amplify this hashtag. Users who used the hashtag #VaccinesWork have other hashtags in common. #Worldimmunizationweek is a clear example of the awareness of these groups about the importance of vaccination. Overall, the hashtags related to #VaccinesWork belonged to users who promote group immunity (with hashtags such as #protectedtogether, #vaccinesbringuscloser, and #vaccinessavelives) and vaccination for other diseases and not only COVID-19, such as poliomyelitis (with hashtags such as #endpolio). There are several studies evaluating the effectiveness of health-related campaigns on social media in relation to public health. Some examples are a campaign to increase awareness of cervical cancer, a campaign promoting food safety, or a campaign to improve autism awareness [29-31]. These studies show that the effectiveness of social media campaigns depends on their ability to involve its targets. However, in the actual context of COVID-19, observing hashtags promoted by the health organizations is relevant to making recommendations for more effective campaigns related to vaccination.

Conclusions

This study investigated the discussions surrounding the #VaccinesWork hashtag. It was found that organizations including the WHO, UNICEF, or Gavi were the key opinion leaders and had a big influence on the spread of positive and factual vaccine information among users. Social media networks containing conspiracies tend to contain dubious accounts leading the discussions and often link to unverified information. This kind of analysis can be useful to detect the optimal moment to launch health campaigns on Twitter.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centres for Disease Control and Prevention
RQ: research question
UNICEF: United Nations International Children’s Emergency Fund
WHO: World Health Organization

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Phone: (+1) 416-583-2040
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