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Impact of public health and social measures for COVID-19 control on infectious disease epidemiology

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Impact of public health and social measures for COVID-19 control on infectious disease epidemiology

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Editorial: Impact of public health and social measures for COVID-19 control on infectious disease epidemiology

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Editorial on the Research Topic
Impact of public health and social measures for COVID-19 control on infectious disease epidemiology

Introduction

The World Health Organization declared coronavirus disease 2019 (COVID-19) a public health emergency of global concern, which prevailed from January 2020 until May 2023. Various levels of stringency, scale, and temporal characteristics of the public health and social measures (PHSMs) were adopted to mitigate or control the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission globally, with possible disease outcomes for COVID-19 and other diseases. Therefore, this Research Topic aimed to explore the scientific outcomes of the impact of COVID-19 PHSMs on the control of infectious disease transmission and associated burdens.

This Research Topic reviewed articles under the following subtopics: surveillance, modeling of the impact assessment of public health interventions, population epidemiology and case management, mass gathering preparedness, and the impact of COVID-19 on other infectious diseases.

Surveillance

Screening and testing constitute the most critical and fundamental components of surveillance to establish case definition and confirm diagnosis. Screening strategies for COVID-19 using different testing methods such as nucleic acid and antigen testing were implemented during the COVID-19 pandemic. Cost-effectiveness analysis helped determine the optimal screening strategy that maximized societal benefit and minimized costs for the cumulative number of infections, and deaths during the pandemic (Li and Zhang).

Investigations into knowledge, attitudes, practices, and acceptance help to determine other reasons behind the effects of health interventions. Therefore, limited understanding of COVID-19 prevention and control and their impact could result in ineffective precautionary behaviors among college students living in minority areas in China, who also experienced depression and stress during the pandemic (Li et al.).

Monitoring population mobility is also a prerequisite for elucidating and predicting infectious disease transmission dynamics, since it provides insights into importation risks of infections and defines effective contacts in the community. However, mobility data do not truly reflect contacts and the probability of infection upon contact; moreover, they inadequately explain transmission dynamics compared with individual social contact data. Okada et al. conducted a time series linear regression analysis exploring the association between the 7-day moving average of the night-time population in the downtown areas of three megacities in Japan and COVID-19 incidence in 2020–2022. In the time-varying regression model, the night-time population level positively affected SARS-CoV-2 transmission over 2 years. Although further validation may be necessary, public health authorities may utilize such mobility surveillance data to infer SARS-CoV-2 disease transmission in future epidemics and their control.

Modeling the impact assessment of public health interventions

Modeling is essential in assessing the impact of PHSMs. Yi et al. used public health data released by the National Health Commission and the Shanghai Municipal Health Commission on the COVID-19 epidemic in Shanghai (January to May 2022) and the effective reproduction number to model the public health intervention's impact during the epidemic in Shanghai. The researchers found that the effective reproduction number of SARS-CoV-2 rapidly declined from 4.02 to below 0.99 after intervention adoption, and the implementation of PHSMs reduced the number of cases and epidemic wave duration compared to the counterfactual scenario of implementing 1–4 weeks later.

Population epidemiology and case management

Understanding the population epidemiology, stratifying its risk among individual patients, and optimizing referral at the appropriate time to mitigate case fatality is imperative.

Shao et al. investigated the epidemiology of the Omicron variant in Tibet in August 2022, using retrospective data on mild or asymptomatic patients admitted to a mobile cabin hospital. The researchers demonstrated that the Omicron variant generally resulted in fewer symptoms and shorter hospital stays than wild-type SARS-CoV-2.

Keller et al. employed a German nationwide inpatient sample to analyze predisposing factors for intensive care unit (ICU) admission among patients with COVID-19. They provided insights into the risk factors associated with a high mortality rate. Furthermore, they proposed parameters for estimating the number of patients requiring ICU admission, for which ICU capacities should be considered to ensure adequate healthcare and pandemic planning.

Kaur et al. described a manually curated and validated database of long-term care facilities in Canada. The reliability of an epidemiological study depends on data quality, and database curation and validation initiatives, which are requisites for understanding infectious disease dynamics among different subgroups and populations.

Mass gathering preparedness

Mass gatherings have become a significant public health concern owing to their super-spreading potential for SARS-CoV-2 transmission and pandemic progression. During the COVID-19 pandemic, the 2020 Olympic Games and annual Hajj were delayed and resumed step-wise, with various PHSMs implemented to control and prevent further SARS-CoV-2 transmission.

Alhussaini et al. systematically reviewed international sports mass gatherings in 2010–2022 and explored prevention strategies against COVID-19 and other infectious diseases in such events. The researchers identified risk factors for disease transmission and proposed general and specific recommendations for pre-, during-, and post-event control strategies. They presented a model representing the three stages of prevention to be embedded within community/public social responsibility, healthcare system preparedness, and public health authorities' policies/guidelines.

Impact of COVID-19 and PHSMs on other infectious diseases

The COVID-19 pandemic and the implementation of PHSMs modified the population behavior and contact patterns, altering the transmission dynamics of other infectious diseases. A plethora of research reveals the profound impact of COVID-19 PHSMs on mitigating other respiratory infections, such as influenza and respiratory syncytial virus. However, knowledge regarding changes in the incidence of sexually transmitted diseases, such as chlamydia, is relatively limited. Chiara et al. reported changes in the monthly and yearly incidence rates of *Chlamydia* infection in South Korea by comparing the pre-pandemic (2017–2019) and peri-pandemic (2020–2022) periods, stratified by sex, age group, and region. Overall, the researchers demonstrated the changes in the trends and absolute number of *Chlamydia* infections before and after PHSMs implementation.

Conclusions

This Research Topic discussed diverse aspects of interventions adopted during the COVID-19 pandemic, including understanding the epidemiological characteristics, the effectiveness of interventions, human behavioral factors interfering with their adherence, and suggestions for preparing and managing future health emergencies. Additionally, beyond the COVID-19, it highlights the indirect impacts of these interventions on other diseases in general. The pandemic was undeniably catastrophic, with immeasurable social and health impacts that should be adopted as a lesson for consistent public health preparation. Therefore, we anticipate that this Research Topic will contribute to this aim.

Author contributions

DK: Investigation, Writing – original draft, Writing – review & editing. HL: Writing – original draft, Writing – review & editing. SX: Writing – original draft, Writing – review & editing. STA: Writing – original draft, Writing – review & editing. SR: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. CV: Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

STA is affiliated with Laboratory of Data Discovery for Health Limited.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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COVID-19 epidemic and public health interventions in Shanghai, China: Statistical analysis of transmission, correlation and conversion

Dali Yi[1,2†], Xicheng Chen[1†], Haojia Wang[1†], Qiuyue Song[1†], Ling Zhang[2], Pengpeng Li[1], Wei Ye[1], Jia Chen[1], Fang Li[1], Dong Yi[1] and Yazhou Wu[1]*

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Background: The Shanghai COVID-19 epidemic is an important example of a local outbreak and of the implementation of normalized prevention and disease control strategies. The precise impact of public health interventions on epidemic prevention and control is unknown.

Methods: We collected information on COVID-19 patients reported in Shanghai, China, from January 30 to May 31, 2022. These newly added cases were classified as local confirmed cases, local asymptomatic infections, imported confirmed cases and imported asymptomatic infections. We used polynomial fitting correlation analysis and illustrated the time lag plot in the correlation analysis of local and imported cases. Analyzing the conversion of asymptomatic infections to confirmed cases, we proposed a new measure of the conversion rate (C_r). In the evolution of epidemic transmission and the analysis of intervention effects, we calculated the effective reproduction number (R_t). Additionally, we used simulated predictions of public health interventions in transmission, correlation, and conversion analyses.

Results: (1) The overall level of R_t in the first three stages was higher than the epidemic threshold. After the implementation of public health intervention measures in the third stage, R_t decreased rapidly, and the overall R_t level in the last three stages was lower than the epidemic threshold. The longer the public health interventions were delayed, the more cases that were expected and the later the epidemic was expected to end. (2) In the correlation analysis, the outbreak in Shanghai was characterized by double peaks. (3) In the conversion analysis, when the incubation period was short (3 or 7 days), the conversion rate fluctuated smoothly and did not reflect the effect of the intervention. When the incubation period was extended (10 and 14 days), the conversion rate fluctuated in each period, being higher in the first five stages and lower in the sixth stage.

Conclusion: Effective public health interventions helped slow the spread of COVID-19 in Shanghai, shorten the outbreak duration, and protect the healthcare system from stress. Our research can serve as a positive guideline for addressing infectious disease prevention and control in China and other countries and regions.

KEYWORDS

COVID-19, public health, interventions, dynamic prevention and control, effective regeneration number

Introduction

In December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in China and spread to all parts of the world (1–4). COVID-19 causes symptoms such as fever, cough, fatigue, shortness of breath, and pneumonia, which can lead to death in severe cases. COVID-19 had spread to the vast majority of countries by May 2022, with over 500 million confirmed cases and over 6 million deaths, having a profound impact on politics, economies, and societies around the world.

To effectively control the COVID-19 outbreak, China responded with a policy of "dynamic clearing and social clearing." However, with the continuous variation in the virus and the complex situation of the international environment, a small-scale outbreak and rebound of the epidemic were inevitable (5, 6). In late February 2022, a new round of local COVID-19 infections occurred in Shanghai. Shanghai is China's most important economic center, and if the outbreak were to spread to other parts of the country, the consequences would be incalculable. On March 28, 2022, the Shanghai government gradually implemented public health intervention measures in the city to curb the spread of the epidemic, including closed district management, paying attention to elderly individuals, establishing designated hospitals and carrying out double-antibody screening (7, 8). In late May, the epidemic situation in Shanghai was essentially controlled, and normal production and life were restored on June 1. The epidemiological characteristics of the Shanghai epidemic and the effect of public health interventions are still unclear, and there are few relevant studies (9). Thus, the association cannot be comprehensively and accurately described.

The Shanghai epidemic was quite different from that in Wuhan (December 8, 2019, to March 8, 2020) (10). Reviewing the progress of the epidemic in Shanghai, inadequate control of imported cases from abroad was an important cause of the outbreak. As a result of the epidemic in Hong Kong (December 31, 2021, to March 23, 2022) (11), Shanghai had taken on the responsibility of transporting some imported personnel to Shenzhen. The epidemic was sparked by an increase in the number of imported personnel and flaws in isolation management. In addition, the proportion of asymptomatic infections in Shanghai was significantly higher than that in Wuhan. Therefore, it is necessary to analyze the correlation between local cases and imported cases as well as the conversion between confirmed cases and asymptomatic infections (12, 13).

Many studies have calculated the basic regeneration index (R_0) of the COVID-19 epidemic, and its estimated value is generally in the range of 2–7, revealing the high infectiousness of COVID-19 (14–16). However, due to the small number of cases and regions, more research is needed to confirm this finding. The effective reproductive number (R_t) refers to the average number of new cases that can be caused by one case at time t. It can reflect the epidemic trend of infectious diseases in real time, and it is an important index to guide epidemic prevention and control and to evaluate intervention measures (17–19). However, there is a lack of relevant research evaluating the developmental trend of R_t and the effect of public health intervention measures in Shanghai in 2022. We use statistical methods to investigate and quantify changes in the epidemiological characteristics of the spread of COVID-19 in Shanghai as well as the effects of public health interventions, with the goal of developing a comprehensive assessment system for the disease process, disease transmission, and the impact of control measures that will serve as a foundation for future interventions. Policy formulation provides a scientific foundation for accuracy and operability as well as significant promotional value.

Therefore, we use Shanghai, China, as a case study to examine the epidemiological characteristics and the impact of public health interventions against the backdrop of normalized prevention and control to provide a positive guideline for the follow-up response to the 2022 Shanghai epidemic. The main work and contributions of this paper are as follows.

(1) We conducted extensive research on the main period of the epidemic in Shanghai (January 30 to May 31, 2022), taking into account cluster analysis and public health interventions to divide the development stages of the epidemic, with the goal of analyzing the epidemic situation in Shanghai. Changes in transmission characteristics and control measures as well as their correlations were investigated. (2) Because the Shanghai epidemic may have been caused by imported cases and there were many asymptomatic infections, we examined not only the correlation between local and imported cases but also the conversion of confirmed cases and asymptomatic infections.

The difference between the Shanghai epidemic analysis and previous epidemic analyses, as well as the innovation of this study compared to previous research, lies in the two types of analysis. (3) We used effective reproduction number (R_t) analysis to determine the impact of public health interventions on epidemic prevention and control, with the goal of evaluating the temporal correlation between public health interventions and Shanghai epidemic prevention and control and then analyzing the significance and correctness of public health interventions. (4) We simulated and predicted the evolution of the epidemic when the implementation of interventions was delayed, and we examined the number of cases that could have been avoided due to public health interventions. This study confirms the timeliness and effectiveness of the interventions and provides a new model and experience related to the global fight against the Omicron-based epidemic.

Materials and methods

Data sources

The data and public health interventions in this study were public data released by the National Health Commission and the Shanghai Municipal Health Commission. Newly added cases were classified as local confirmed cases, local asymptomatic infections, imported confirmed cases and imported asymptomatic infections. In this outbreak, a local case was first found on March 1. Since this round of the epidemic came from abroad, we collected case data starting from January 30. On June 1, Shanghai announced the restoration of normal production and everyday life. Therefore, the data that we collected covered the period from January 30 to May 31, 2022, totaling 121 days.

Statistical analysis

Transmission analysis

We used cluster analysis to aid segmentation and plotted dynamic time-series maps to improve the interpretability of the intervention phase. As feature vectors, we used the number of newly added cases of local confirmed cases, local asymptomatic infections, imported confirmed cases, and imported asymptomatic infections, and we grouped the samples using time as the label. The Manhattan distance method was used to create a hierarchical clustering of the closest dates. In the rectangular coordinate system, the date and the number of infected people are denoted by X and Y, respectively. Assuming that there are points i of coordinate (X_1, Y_1) and j of coordinate (X_1, Y_2) on the plane, the Manhattan distance $D(i,j)$ between them is expressed as follows:

$$D(i,j) = |X_1 - X_2| + |Y_1 - Y_2| \tag{1}$$

we used R_t analysis based on the Poisson distribution to determine the transmission capacity of each stage and the impact of public health interventions. R_t is defined as the average number of secondary cases of primary cases in the population at time t, representing the average number of second-generation cases that an infected person diagnosed at a certain time will infect during the infection period (20, 21). R_t can be used to measure the real-time transmissibility during an epidemic and to evaluate viral transmission before and after intervention measures. The R_t at the beginning can be defined as R_0, and the R_t at the end can be defined as R_{final}.

We used the EpiEstim package in R software (version 3.6.3) to fit R_t and the 95% confidence interval (CI) using the number of new cases reported daily. R_t can be expressed as follows:

$$R_t = \frac{I_t}{\sum_{s=1}^{t} I_{t-s} w_s} \tag{2}$$

Here, I_t represents the number of new cases generated at time t; $\sum_{s=1}^{t} I_{t-s} w_s$ represents the sum of the infection incidence up to time (t – 1); and w_s represents the probability function of the serial interval (SI). The infectious characteristics of infected individuals are the basic idea of R_t calculation, and the specific principle is shown in references (22, 23). In short, R_t can be calculated by dividing the proportion of new cases at time t by the cumulative cases at time (t – 1), and its weight isw_s. Assuming R_t has a gamma prior distribution, Bayesian statistical inference using the Poisson distribution can generate a posterior distribution of R_t. The steps in the calculation can be summarized as follows: (1) Determine the SI of the epidemic situation, including the mean and standard deviation. (2) Determine the sliding window time length, and estimate the SI using the previously studied SI distribution. That is, the infection time interval in two consecutive generations follows the Gamma distribution with a mean value of 4.87 and a standard deviation of 0.65 when a 1-day moving window is used. (3) The plot function is used to plot the change in R_t over time.

Correlation analysis

In the time-series correlation analysis of domestic and imported cases, we used polynomial fitting to obtain the fitting curve and performed time lag analysis. Here, x and y represent the number of local and imported cases at a given time. The overall sample with m time points can be written as follows:

$$\{(x_1, y_1)(x_2, y_2) \cdots (x_m, y_m)\} \tag{3}$$

Here, a sample time point can be expressed as follows:

$$(x_i, y_i), i = 1, 2, 3, \ldots, m \tag{4}$$

When the distribution of these points resembles the graph structure of a polynomial of degree n, the final fitting formula is as follows:

$$\hat{y} = a_0x^n + a_1x^{n-1} + a_2x^{n-2} + \cdots + a_{n-1}x + a_n \tag{5}$$

Here, X and Y represent the number of local and imported cases at a certain time and construct a polynomial fitting formula; a_0 – a_n represent the fitting coefficient; n in x^n represents the index of the fitting polynomial; and $\hat{y}$ represents the fitting value of the corresponding imported case when the local case is x.

We used interval geographic maps and nuclear density maps to describe the incidence distribution in each region and the time point in the spatial distribution. Kernel density estimation, which analyzes the density distribution of each element in the observed object's corresponding geospatial domain, was conducted based on ArcGIS 10.8.1.

Conversion analysis

Asymptomatic infections account for a relatively high proportion of the overall infections, which is not only an important feature of this epidemic but also an important basis for studying the impact of public health interventions. To better analyze the ratio of asymptomatic infections to confirmed cases and to analyze the changing characteristics of the epidemic as it developed, we innovatively propose the concept of the "conversion rate." If the incubation period is defined as t, the number of converted cases (i.e., the number of confirmed cases) on that day is N_1, and the number of untransformed cases (i.e., the number of asymptomatic infections) within t days before that day is N_2. Thus, the conversion rate C_r can be defined as follows:

$$C_r = \frac{N_1}{N_2} \tag{6}$$

Because the exact incubation period for transitioning from an asymptomatic infection to a confirmed case is currently unknown, we used a variety of settings, including 3, 7, 10, and 14 days, to better analyze the law of conversion. Next, we used simulation studies to validate the significance of public health interventions. Assuming that no public health intervention measures were implemented after March 28, the number of cases continued to rise in line with the C_r value (3.02%) on March 28, and the conversion number of asymptomatic infections can be calculated accordingly.

Results

Division of development stages

We conducted cluster analysis based on the total number of newly added cases per day. We comprehensively considered the optimal clustering results and the public health intervention time points and then divided the main epidemic period into six stages. Figure 1 illustrates the epidemic curve of the symptom occurrence date and key intervention events.

Regarding the first stage (1.30–3.11), sporadic infections began to appear and were mainly imported cases, and sporadic local cases began to appear. The imported cases were not controlled in a timely manner, and cryptic transmission likely began at this time, leading to the local transmission of COVID-19. Regarding the second stage (3.12–3.28), local asymptomatic cases and confirmed cases showed an upward trend. On March 24, thousands of new asymptomatic infections were reported every day for the first time.

Regarding the third stage (3.29–4.04), the epidemic rapidly worsened, and the government conducted nucleic acid screening and implemented personnel and traffic controls, further reducing the population's social mobility. The fourth stage (4.05–4.12) represented the high-risk period of the outbreak, with the number of newly local confirmed cases exceeding 1,000 per day and the number of asymptomatic infections exceeding 20,000 per day.

In the fifth stage (4.13–4.26), the epidemic was in the remission period. There was a delay in the effectiveness of public health intervention measures, and the incidence trend had been alleviated at this stage. The sixth stage (4.27–5.31) represented the epidemic control period. In local cases, newly confirmed cases and asymptomatic infections were gradually controlled to $<$100 cases every day.

Transmission analysis using the effective reproduction number

We combined the new case map and the R_t change map (the sum of both local and imported cases) in the six stages to analyze the epidemic transmission characteristics in each stage, as shown in Figure 2.

In the first stage, R_t rose sharply and reached a maximum value on February 17 ($R_t = 3.19$). At this stage, R_t was mainly distributed between 1 and 3. In the second stage, R_t continued to rise and reached an overall peak on March 16 ($R_t = 4.02$). At this stage, R_t was mainly distributed between 2 and 4.

In the third stage, asymptomatic infections began to appear, causing fluctuations in R_t. R_t showed a trend of first increasing and then decreasing. It reached a peak in this stage on April 1 ($R_t = 3.01$) and then gradually decreased, but R_t remained above 1.5. This stage is when the public health intervention measures

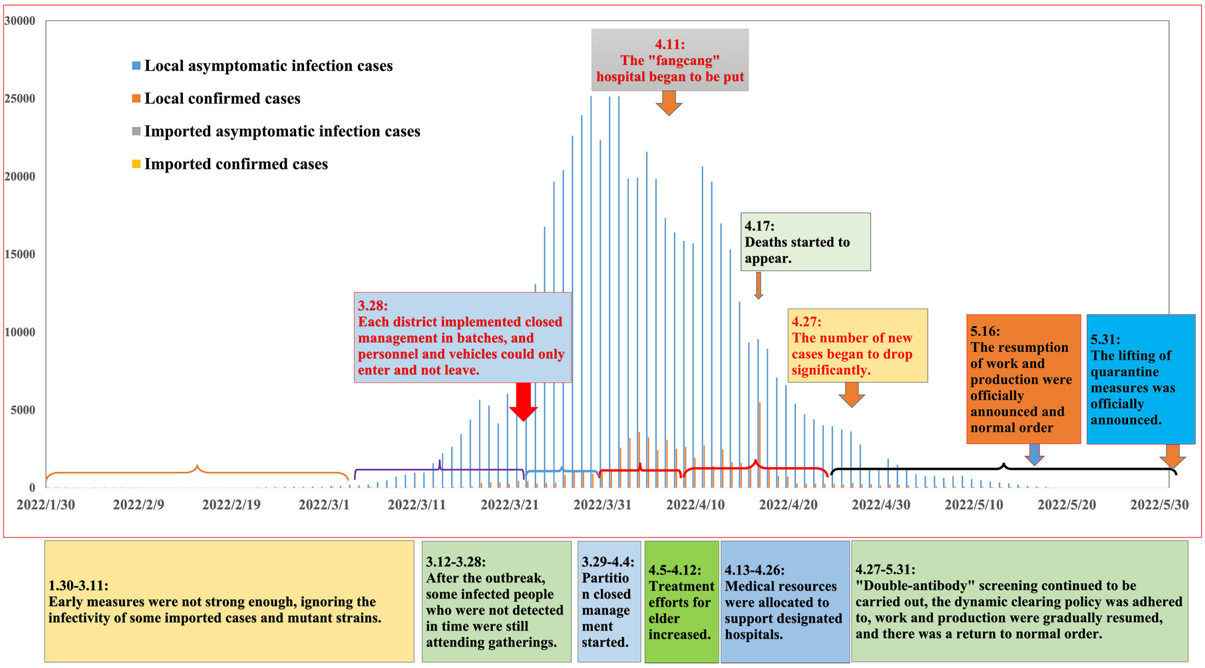

FIGURE 1
Correlation analysis between daily cases and public health intervention. Based on the date of symptoms, the epidemic curve shows the number of cases and events per day. We also further describe the key events, situation characteristics and details of public health interventions at each stage.

began to take effect. In the fourth stage, R_t continued to decline, and it fell below 1 on April 9 ($R_t = 0.99$), indicating that the spread of the epidemic had reached a controllable range.

In the fifth stage, R_t rebounded in a small range of cases, but it was controlled 2 days later. R_t increased to above 1 on April 18 ($R_t = 1.04$) and decreased to below 1 on April 20 ($R_t = 0.91$). In the sixth stage, the fluctuation trend of R_t was obvious, but R_t was below 1.

In general, from February 28 to April 10, affected by imported cases from abroad, the average R_t in Shanghai was higher than the epidemic threshold, lasting ∼5.5 weeks. Following the implementation of public health intervention measures in Shanghai (March 28), the estimated R_t generally decreased and fell below the epidemic threshold on April 10. The overall R_t level in the first three stages was higher than 1, and the overall level in the last three stages was lower than 1.

Furthermore, as shown in Figure 3, we examined the change in the number of predicted cases (compared to the actual value) and the end time of the epidemic under various simulation conditions. The predicted number of cases was reduced by 664 when the public health interventions were implemented 1 week earlier, and the epidemic was expected to end 9 days sooner. The number of predicted cases increased by 1,265, 2,450, 10,811, and 29,073 when the public health interventions were delayed by 1, 2, 3, and 4 weeks, respectively, and the epidemic was expected to end 18, 35, 56, and 63 days later, respectively.

Time-series correlation analysis of imported and local cases

We analyzed the time distribution characteristics of epidemic development in Shanghai, as shown in Figure 4. The epidemic curve shows the bimodal epidemic of local and imported cases. The earliest local confirmed cases occurred on March 1, and the largest number of cases (5,487) in a single day occurred on April 28. As Shanghai undertook the task of transporting imported cases, imported confirmed cases continued to exist, and more than 20 cases occurred in a single day on February 20, with the largest number of cases (59) on February 24. The 95% CIs of the four types of cases were calculated, and their main concentration dates were analyzed, as shown in Table 1. The results show that compared with imported cases, local cases had a certain time lag effect of approximately 1 month.

According to the above results, there were mainly imported cases in the first stage. Shanghai had not strictly controlled and managed imported infected persons, and the number of imported cases was higher than that of local cases. During the second stage, local cases continued to rise. Local cases occurred with the emergence of imported cases, and there was a certain time lag effect of approximately 31 days. We analyzed the correlation between the number of imported and the number of local cases (including both confirmed cases and asymptomatic infections) and drew time lag analysis charts and correlation analysis charts, as shown in Figure 5. In the time lag analysis chart, compared with imported cases, local cases had a greater lag and amplification, and the lag period was approximately 31 days, confirming the previous speculation. In the correlation analysis chart, the curves fitted by various methods revealed that there was a strong correlation between local cases and imported cases, with R^2 values above 0.8.

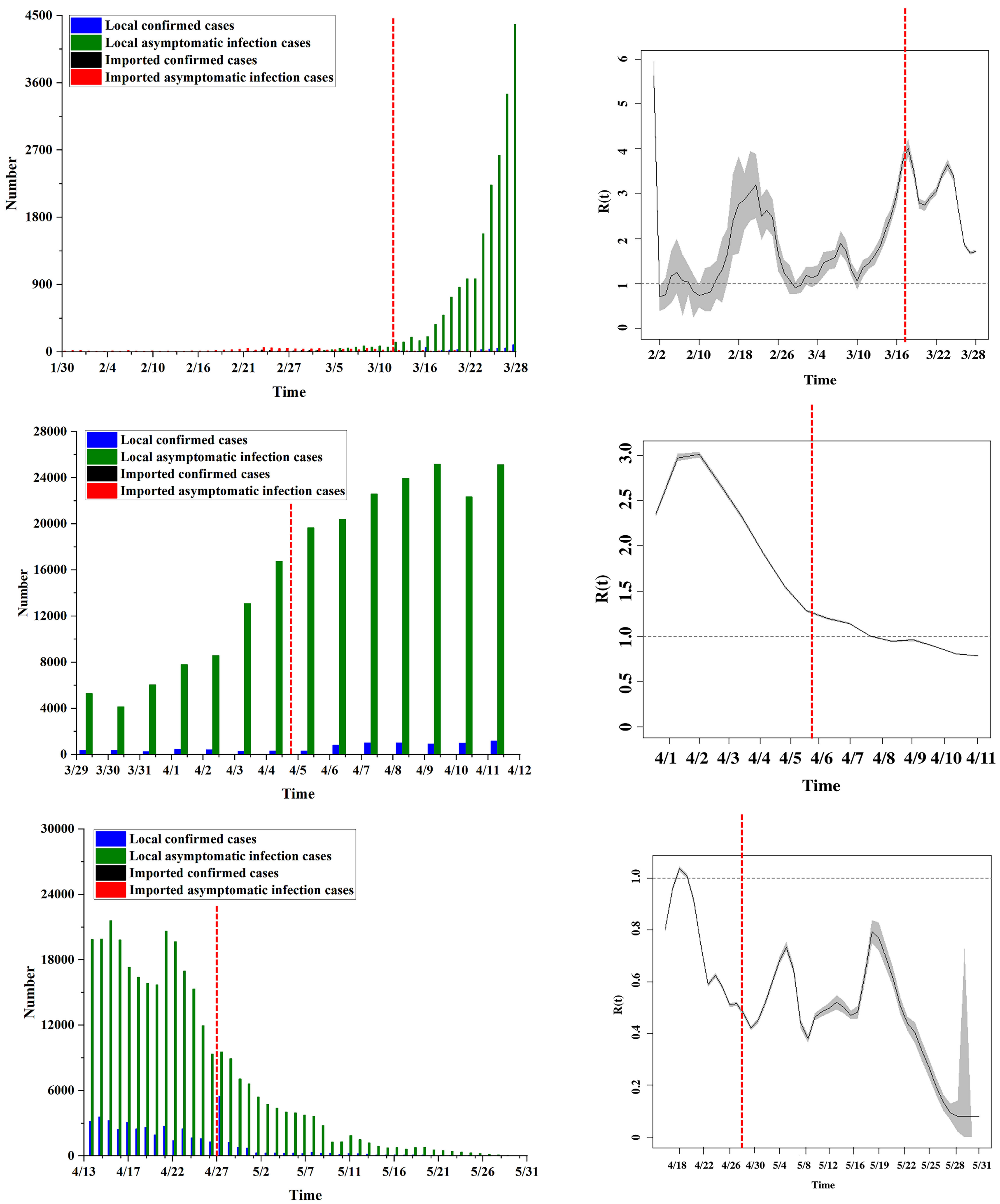

FIGURE 2
The shifting pattern of R_t. In the six stages, the daily new cases and the change trend of the R_t value are compared.

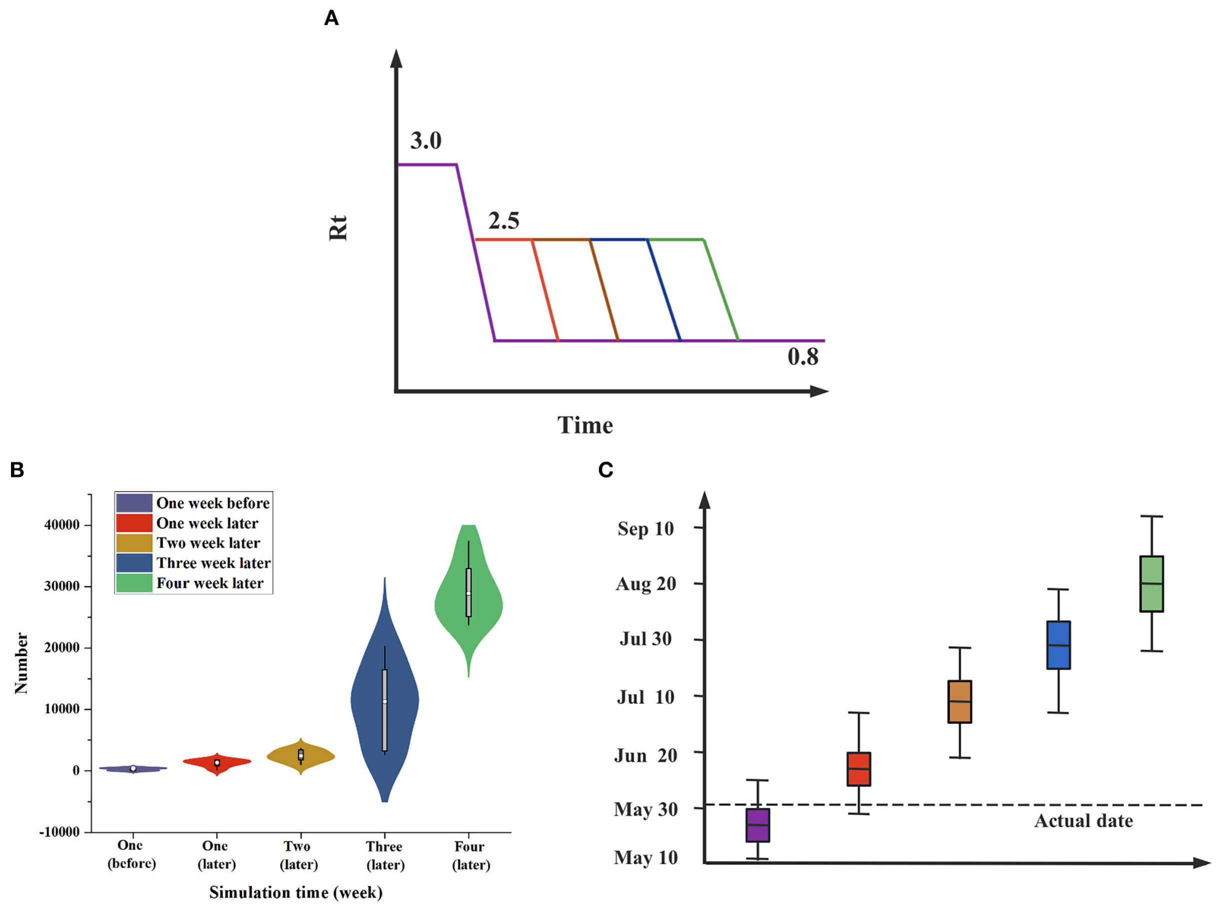

FIGURE 3
R_t-based simulation prediction. **(A)** R_t is assumed to decline linearly over a 1-week period from R_0 to R_{final}. Estimates in advance simulations are obtained by considering $R_0 = 3.0$ and $R_{\text{final}} = 0.8$; estimates in deferred simulations are obtained by considering $R_0 = 2.5$ and $R_{\text{final}} = 0.8$. **(B)** Differences in the number of cases (when compared to actual values) when public health interventions were implemented 1 week earlier or 1–4 weeks later. **(C)** The case end date if public health interventions began 1 week earlier or 1–4 weeks later.

The spatial distribution of local cases (including local confirmed and asymptomatic infections) in Shanghai is shown in Figure 6. In the first stage, the epidemic peak occurred in the Minhang District, the Jiading District, etc. From the second stage on, the epidemic peak gradually spread to the Pudong New Area, reaching a peak in the fifth stage and decreasing in the sixth stage. Therefore, there were case reports in 16 districts of Shanghai, but there were significant geographical differences in the distribution of confirmed cases. The highest incidence rate was mainly in the Pudong New Area, followed by the Minhang District.

Conversion analysis of asymptomatic infections to confirmed cases

At present, the accurate incubation period from asymptomatic infections to confirmed cases has not been determined. Therefore, we adopted a variety of settings, such as 3, 7, 10, and 14 days, to better analyze prognostic rules. In practice, because no asymptomatic infections were converted into confirmed cases in the first and second stages, the conversion rates for each incubation period for the third to sixth stages were calculated, as shown in Table 2 and Figure 7A.

When the incubation period was set to 3 and 7 days, the overall conversion rate of each period showed a stable trend, which was controlled between 10 and 20%. When the incubation period was set to 10 and 14 days, the change in the conversion rate in each period was more obvious, the conversion rate in the fifth stage and before was higher, and the conversion rate in the sixth stage was lower. The box chart shows the distribution of the recovery rate at each incubation period setting, and the results show that the distribution of the recovery rate was close at each incubation period setting.

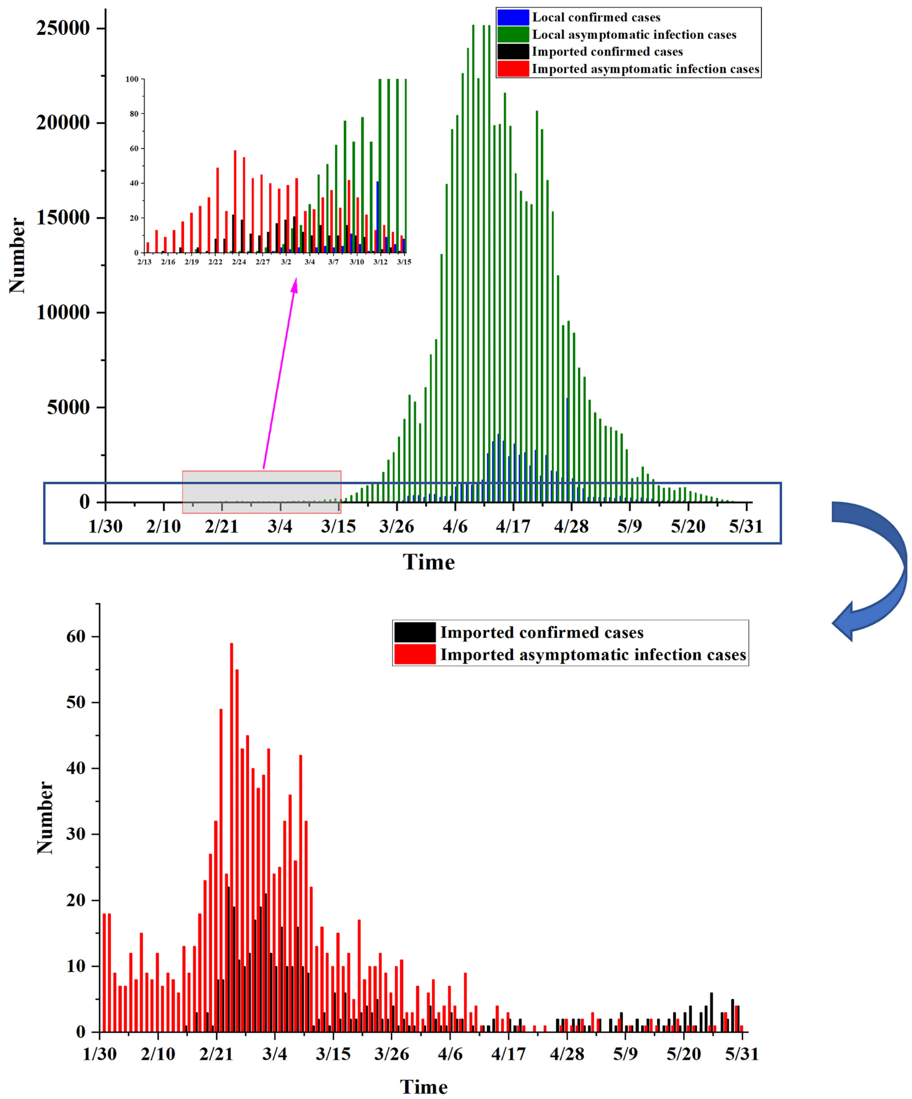

FIGURE 4
The temporal distribution of the epidemic. The time of onset and the epidemic curve of the Shanghai epidemic: Based on the daily number of new cases listed on the report date, the cases were divided into local confirmed cases, local asymptomatic infections, imported confirmed cases and imported asymptomatic infections.

TABLE 1 Distribution analysis of daily new incidences of four types of cases.

Type	Distribution date	Average value	95% CI	
			Lower bound	Upper bound
Local confirmed cases	3.29~5.1	475.41	305.97	644.85
Local asymptomatic infection cases	3.27~5.8	4,847.13	3,496.70	6,197.57
Imported confirmed cases	2.5~4.3	10.42	8.03	12.81
Imported asymptomatic infection cases	2.18~3.25	3.25	2.39	4.10

In addition, we simulated the change in the conversion rate under the condition of an uncontrolled epidemic, as shown in Figure 7B. Assuming that Shanghai had not taken public health intervention measures after March 28, the case growth thereafter was calculated based on the R_0 on March 28 and simulated based on a Poisson distribution.

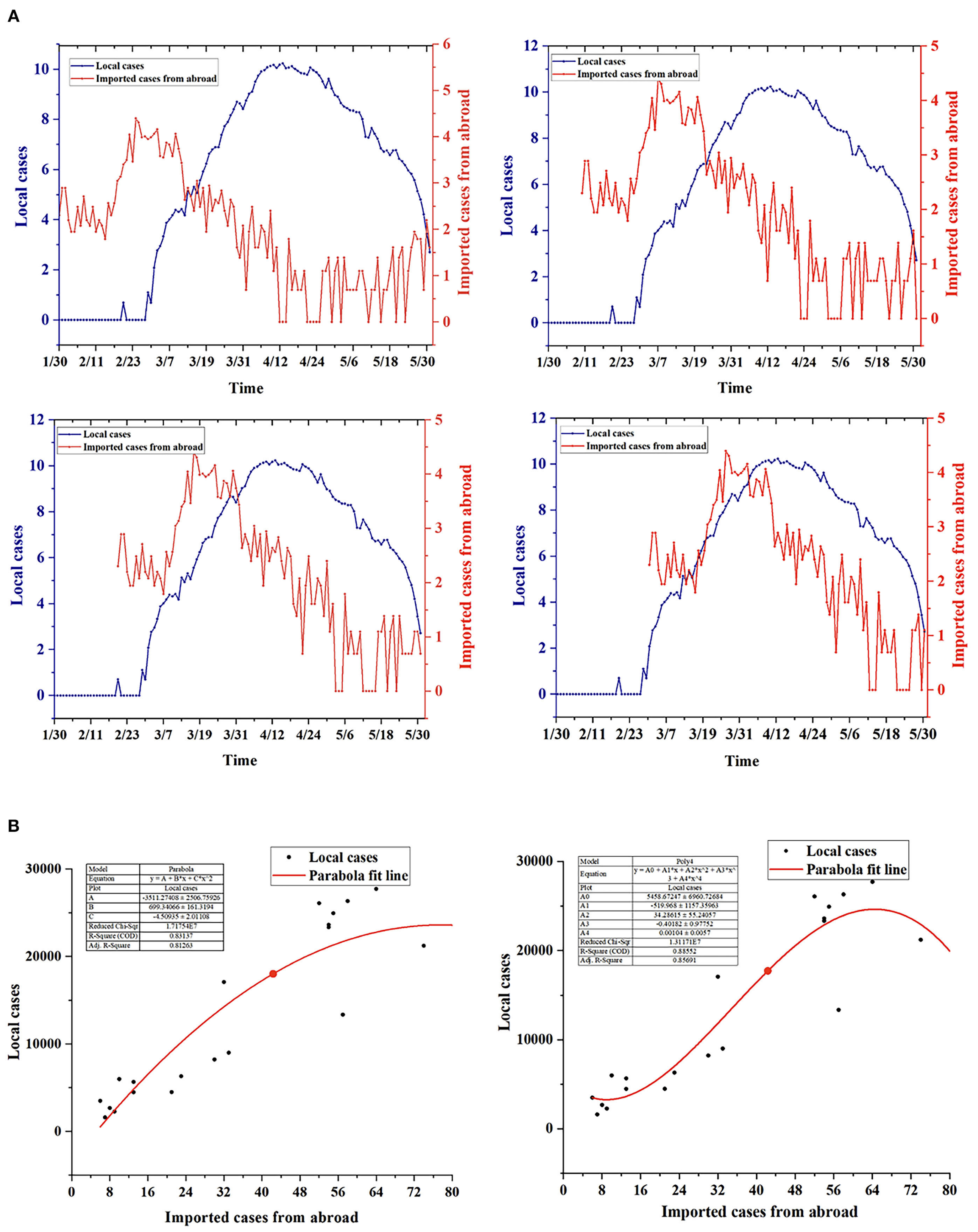

FIGURE 5
Correlation analysis between local cases and imported cases. **(A)** Time lag analysis of the change trend between local cases and imported cases: There was a large difference in the magnitude of factors. Natural logarithm processing was applied to local and imported cases. Based on the time of imported cases, the order was as follows: January 30, February 10, February 20 and March 2. **(B)** Correlation analysis between local cases and imported cases: The included local cases ranged from March 24 to April 13, and the imported cases ranged from February 11 to March 3.

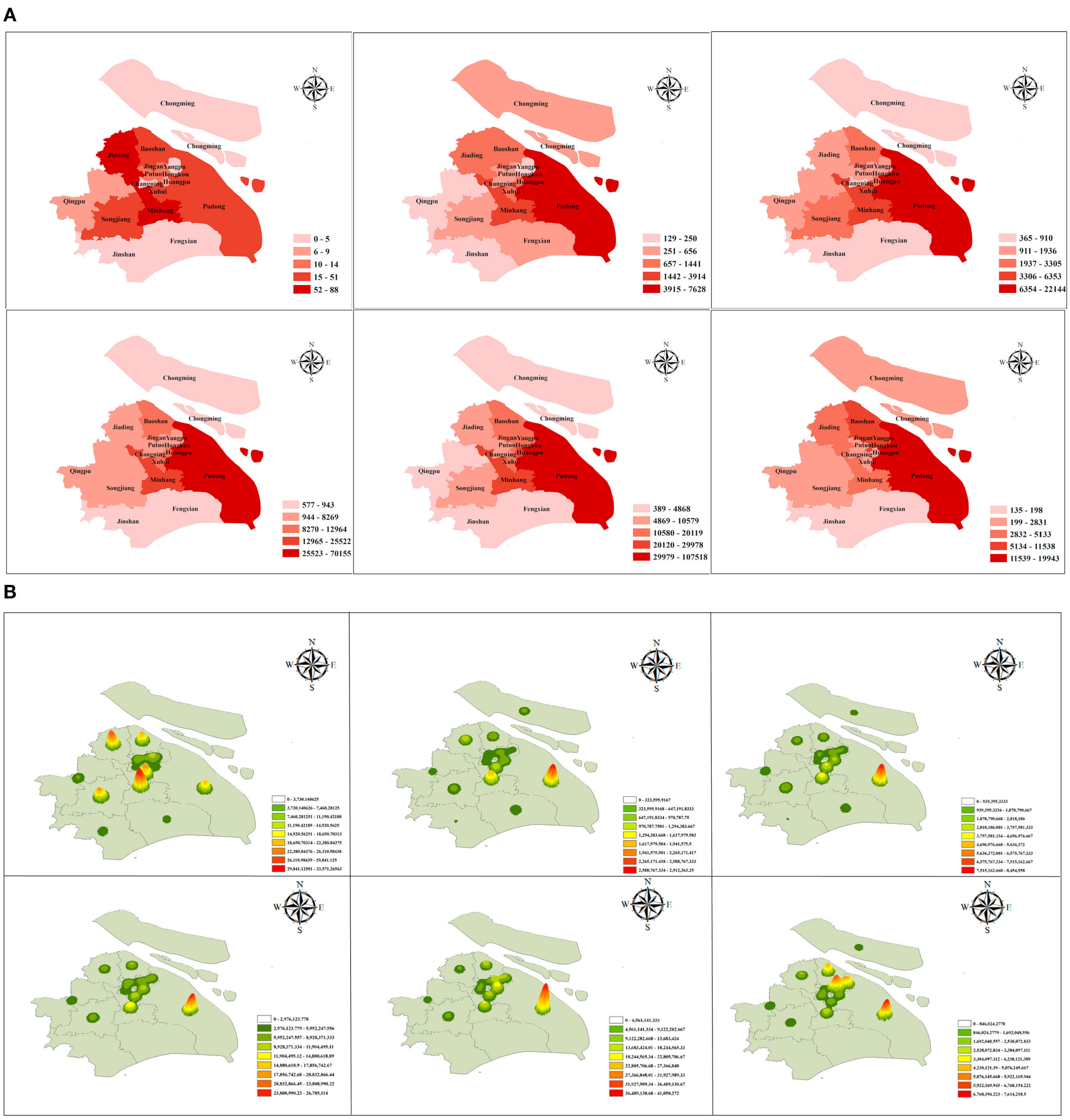

FIGURE 6
The spatial distribution of the epidemic. **(A)** A geographical map and **(B)** a nuclear density map showing the spatial distribution of local cases in Shanghai, divided into 16 districts. The six submaps represent the six stages of epidemic development. Limited by media reports, this article covers only the period from March 5 to May 31.

The results show that the recovery rate was higher when the incubation period was set to 10 and 14 days and gradually leveled off after May. It is speculated that public health intervention measures need ∼10 days to be effective. This simulation study also verifies the importance of public health interventions.

Discussion

Principal results

We investigated and quantified changes in the epidemiological characteristics of COVID-19 in Shanghai

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TABLE 2 Conversion rate (%) during each incubation period.

	3 days	7 days	10 days	14 days
Third stage	0.74 (0.04, 1.71)	1.14 (0.09, 2.77)	2.76 (0.18, 7.43)	5.90 (0.46, 14.78)
Fourth stage	1.09 (0.10, 2.50)	2.89 (0.14, 7.79)	3.53 (0.30, 7.42)	7.99 (0.41, 20.38)
Fifth stage	3.68 (0.45, 6.83)	3.50 (0.58, 7.64)	3.56 (0.64, 5.99)	5.95 (0.70, 15.24)
Sixth stage	4.82 (0.89, 11.11)	2.93 (0.29, 5.41)	2.26 (0.17, 6.00)	1.49 (0.13, 4.94)
Total	3.80 (0.04, 11.11)	2.91 (0.09, 7.79)	2.74 (0.17, 7.43)	3.62 (0.13, 20.38)

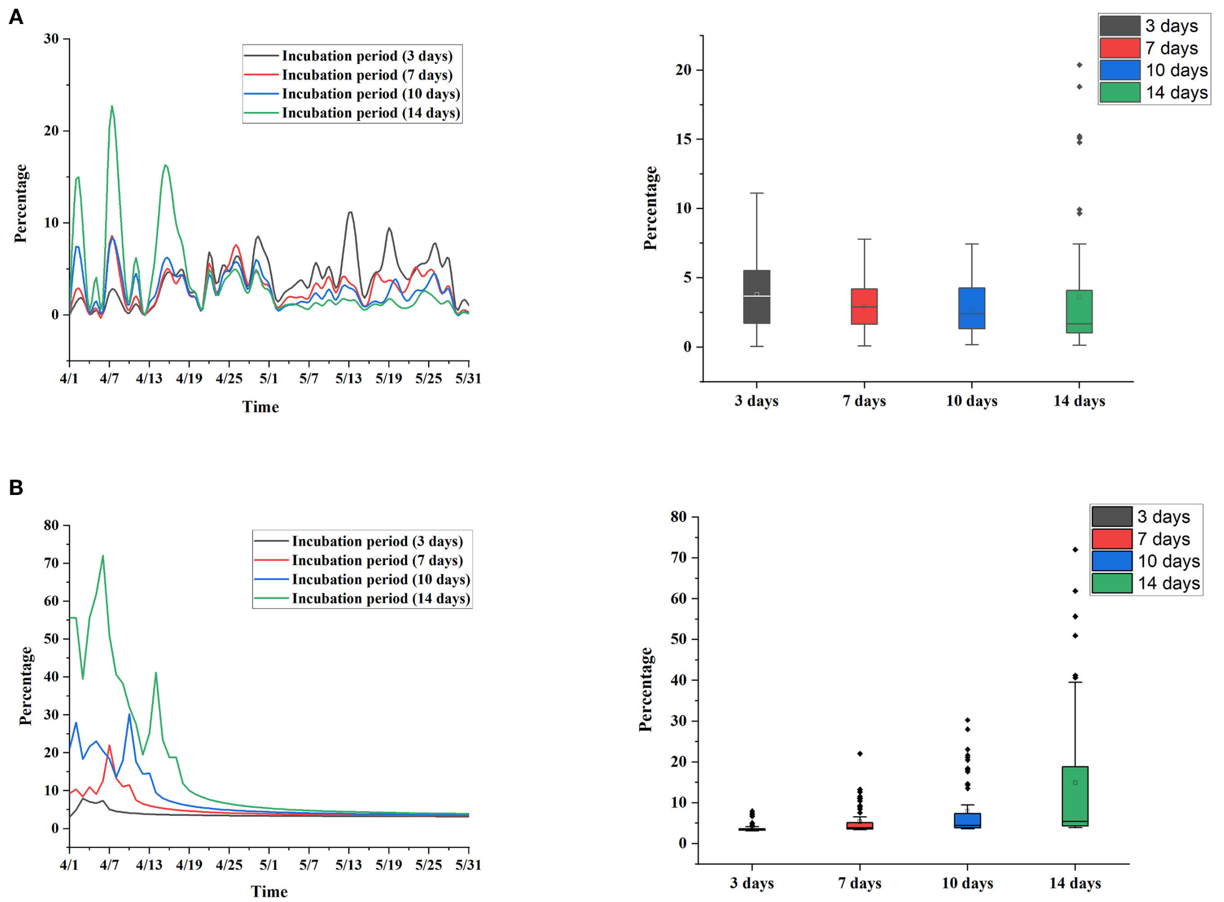

FIGURE 7
Conversion rate during each incubation period. **(A)** Actual situation. **(B)** Simulation without public health interventions.

as well as the effect of public health interventions. To divide the development stages for subsequent research, we used new feature vectors and dynamic time-series maps. We created a feature vector using the four indicators of local confirmed cases, local asymptomatic infections, imported confirmed cases, and imported asymptomatic infections and then drew a dynamic time-series map of interventions using the cluster analysis results and public health intervention measures. On this basis, we divided the epidemic into six stages and then dynamically and intuitively assessed the impact of public health interventions on the development of the epidemic. Compared with a subjective division (10), the stage division in this paper was scientific and objective. The subsequent R_t analysis also verified this conclusion. We then built a comprehensive assessment system for the process, transmission, and the impact of control measures in the analysis of COVID-19 transmission, correlation and conversion. The following points of innovation are described below.

First, we used R_t to perform transmission analysis and to review common public health interventions, with the goal of assessing the impact of public health interventions on the epidemic from an epidemiological standpoint. The first and second stages were defined as the "rapid rise period." Shanghai had not implemented targeted intervention measures for cases introduced from other countries. Mobility restrictions in some key areas were implemented only in the second stage, resulting in a rapid increase in the R_t value. The third and fourth stages were defined as the "preliminary prevention and control period." To control the spread of the disease and to promote the recovery of infected people, Shanghai implemented strong intervention measures, such as mobility restrictions in the city, the use of Fangcang shelter hospitals, and attention to elderly individuals, resulting in an increase in the R_t value. It gradually decreased after reaching its peak. The fifth and sixth stages were defined as the "control and remission period." Shanghai also implemented measures such as conducting zoning management, optimizing the efficiency of Fangcang shelter hospitals, and standardizing nucleic acid testing on the basis of the previous measures so that the R_t value continued to fall. The overall level of R_t in the first three stages was higher than the epidemic threshold (i.e., 1) but decreased rapidly after the implementation of strict public health intervention measures. Additionally, the overall level in the last three stages was lower than the epidemic threshold. Both the decrease in the R_t value and the gradual decrease in the number of new confirmed cases per day indicate that the Shanghai government's interventions had a positive impact on controlling the COVID-19 epidemic and were able to effectively block the spread of the epidemic and ease the disease burden. The simulation analysis results indicate that the implementation time of public health interventions is more important, and the longer the delay is, the longer the epidemic is expected to last.

Second, for the first time, we used temporal correlation analysis to reveal the relationship between local and imported cases, with the goal of determining whether the outbreak was caused by cases imported from other countries. The spatiotemporal distribution analysis revealed the characteristics of a bimodal epidemic of local and imported cases, with local cases emerging concurrently with the appearance of imported cases. The curves fitted by various methods in the correlation analysis revealed that there was a strong correlation between local and imported cases, and the R^2 value reached more than 0.8. According to the time lag analysis, there was some lag and amplification in local cases compared to imported cases, with a lag time of ~31 days. The epidemic in Shanghai was characterized by a combination of local transmission and imported cases. Therefore, it is speculated that this round of the epidemic came from imported cases. Analysis of the main causes of local infections revealed the following. (1) The spread of the epidemic was hidden and delayed. Insufficient attention was given to cryptic transmission in the early stage of imported cases. (2) The virus variant of this outbreak in Shanghai was the Omicron BA.2 mutant, which has a faster transmission speed and stronger transmission strength and can better break through the immune barrier conferred by vaccines (24–26).

Next, for the first time, we investigated how asymptomatic infections became confirmed cases. A significant feature of this round of the Shanghai epidemic was the high proportion of asymptomatic infections. The conversion of asymptomatic infections to confirmed cases is conducive to directly reflecting the impact of interventions, but previous studies on similar topics have focused less on asymptomatic infections (27–30). Therefore, our research evaluated asymptomatic patients and analyzed the relationship between asymptomatic infections and confirmed cases. When the incubation period was set to be short, the overall conversion rate of each period showed a stable trend. When the incubation period was set to be long, the volatility of the conversion rate in each period was more obvious. The conversion rate in the fifth stage and before was higher, while the conversion rate in the sixth stage was lower. The distribution of the conversion rate was similar with different incubation period settings. There are two possible causes. (1) The first is the role of public health interventions: When the incubation period is short, intervention measures may not yet come into effect. When the incubation period is long, intervention measures take effect, and then, the conversion rate gradually decreases. (2) The second is the constancy of the true conversion rate: As of May 31, the true conversion rate was ~10%. The conversion rate calculated at the setting of each incubation period was close to the true conversion rate. Furthermore, we conducted a simulation study on the change in the conversion rate under the assumption that the epidemic was not under control, i.e., the calculation was based on the R_0 value without public health intervention measures. Additionally, the simulation study was carried out using the Poisson distribution. The effect of public health interventions was verified.

Finally, we summarized and compared our findings with those of previous studies. The analysis of transmission, correlation and conversion presented above allowed us to confirm the role of public health interventions in COVID-19 prevention and control from a variety of perspectives. To better validate the findings of this paper, we compared them to previous studies on the impact of public health interventions on the epidemic (10, 31–34). The Shanghai epidemic differed from previous epidemics in terms of viral types, the proportion of asymptomatic infections, and the intervention times. In terms of viral strains, the Shanghai epidemic was primarily caused by the Omicron BA.2 strain, which has high infectivity and rapid transmission. In terms of the proportion of asymptomatic infections, the Shanghai epidemic had a relatively high proportion of asymptomatic infections, and there was a certain proportion of confirmed cases. In terms of the intervention times, the Wuhan epidemic was controlled in 76 days, the Sichuan epidemic in 42 days, and the Shanghai epidemic in 66 days. Despite the many differences in these outbreaks, studies have shown the role of public health interventions in COVID-19 prevention and control, demonstrating their effectiveness and generalizability. Our experience can help China and other countries and regions address the prevention and control of similar infectious diseases.

Limitations

This study still has some limitations. First, this paper describes the result of the joint action of multiple interventions. The effectiveness of a single measure cannot be assessed due to ethical requirements. Second, the corresponding clinical characteristics of confirmed cases could not be obtained. More baseline data will be collected in the future to carry out an analysis of population characteristics. Third, for other countries and regions, the outbreak and development stages of the epidemic do not necessarily show the same dynamic trajectory, and more regional and temporal analyses are needed to verify the robustness of the results.

Conclusion

In the foreseeable future, the epidemic process will still depend on the efficiency of the implementation of public health interventions. Timely and effective public health interventions can effectively and quickly curb the spread of an epidemic and protect the health care system from the overwhelming pressure caused by the epidemic. This study describes an effective Chinese experience and can be a positive guideline for global epidemic prevention and control.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://github.com/STUDWHJ/Shanghai.

Author contributions

DaY: conceptualization, data curation, resources, methodology, software, formal analysis, validation, investigation, and writing—original draft. XC: methodology, software, formal analysis, validation, investigation, writing—original draft, and editing and polishing. HW: data curation, resources, software, and formal analysis. QS: software, validation, investigation, and data curation. LZ and WY: validation, investigation, and writing—polishing. PL: software, validation, and investigation. JC: investigation, resources, and writing—polishing. FL: validation, resources, and formal analysis. DoY: conceptualization, investigation, validation, resources, and methodology. YW: funding acquisition, conceptualization, investigation, resources, methodology, software, writing—review and editing, project administration, and supervision. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A scoping review of the risk factors and strategies followed for the prevention of COVID-19 and other infectious diseases during sports mass gatherings: Recommendations for future FIFA World Cups

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Objective: Sports mass gatherings of people pose particular concerns and place an additional burden on the host countries and the countries of origin of the travelers. It is imperative to identify how countries dealt with various communicable diseases in the context of previous world cups and identify possible advice for protection from outbreaks.

Methods: A scoping review was employed in this study and a PRISMA extension for scoping reviews was employed to guide the reporting of this study. A systematic search was performed using PubMed, Embase, Web of Science, SCOPUS, SportDiscus, and Google scholar. The search strategy included two main strings viz "communicable disease" AND "sport" AND "setting" as keywords for each string. A total of 34 studies were included in this review.

Results: Information on risk factors for infectious diseases during FIFA, and recommendations for disease prevention in various stages of the event: pre-event, during, and post-event were charted. These strategies can be achieved with the empowerment of the public by enhancing their social responsibility and the coordination between the healthcare system, the ministry of public health, and other stakeholders.

Conclusion: The findings will support planning for protection strategies to prevent any outbreak while having the FIFA World Cup or any other sports gatherings. A model was constructed to present the findings and recommendations from this review.

KEYWORDS

world cup, COVID-19, infectious diseases, sports events, mass gatherings, prevention, Qatar

1. Introduction

Mass gatherings of people pose particular concerns and place an additional burden on the host countries and the countries of origin of the travelers (1). These mass gatherings could range from global sporting events to global religious occurrences (2–5). A number of health concerns can accompany mass gatherings, including increased human crowding and the spread of pathogens, which can raise the chance of infectious disease spread among attendees, specifically respiratory disease infections, causing pandemics (6, 7).

The World Cup is one of the world's biggest events bringing people and countries together in celebration and competition. The World Cup was hosted previously by several countries where different strategies to reduce the risk and the impact of acquiring communicable diseases during a mass gathering were implemented. Strategies have focused on pre-travel consultation (8, 9), the provision of standard operating procedures for epidemic response (10), and enhanced international multi-disciplinary surveillance to monitor and assess the risk of any infectious disease threats and promptly detect incidents (11–16). Medical facilities were established at the airport for the isolation of patients and extensive staff training was conducted in the use of infection control practices (14). Additionally, close Devi Priya rapid detection of infectious diseases (14).

1.1. FIFA World Cup 2022

Qatar served as the first Middle Eastern host of the FIFA World Cup in 2022 (17) located on the western coast of the Arabian Gulf (18). The Qatar FIFA World Cup 2022 welcomed 32 teams and was hosted across eight stadiums (19). Stadiums were constructed as some of the most eco-friendly and architecturally innovative stadiums with cooling technology capable of reducing temperatures within it by up to 20°C (36°F) (19). Qatar is home to around 3 million people (18) from around the world and approximately welcomed external fans equal to more than half of the country's total population. Certainly, hosting with such an enormous number of fans like the FIFA World Cup necessitate vigorous security measures to protect players, spectators, and residents.

The World Cup 2022 came with exceptional challenges being held against the background of Corona virus disease (COVID-19) pandemic. Qatar has one of the lowest COVID-19 mortality rates in the world. This could be due to the government's quick and comprehensive measures, which include adjusting public health measures based on the ongoing epidemiological surveillance system, strategic testing, COVID-19 awareness campaigns, and free vaccinations to the public (20). The government has also implemented strict travel regulations for individuals coming from abroad (21). However, other infectious diseases and resulting epidemics had become significant health threats around the time of this event, such as monkeypox (22) and Middle East respiratory syndrome coronavirus (MERS-CoV) (23). The risk of an outbreak of different infections would be even more significant in such events as the visitors were expected to be from more diverse backgrounds. In order to reduce the risk of communicable disease outbreaks during the World Cup, event planners in Qatar recommended conducting a thorough risk assessment prior to the event, and creating risk management/communication plans (24).

The literature reported that large sport events and other mass gatherings impose a risk in increasing the cases of COVID-19 and other infectious diseases (25, 26). No studies have reviewed the health risks and prevention of infectious diseases during sport mass gathering events; therefore, it needs to be thoroughly reviewed in order to be able to develop effective risk management/communication plans. This scoping review will map the available literature regarding the risk factors of infectious diseases including COVID-19 and strategies followed for prevention in previous world cups or sports events to provide recommendations for future FIFA World Cups and other sports mass gatherings.

2. Methods

This review was conducted by employing the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) (27). During the review, we followed these steps: Identifying the research question, identifying the relevant studies, selecting the studies, extracting the data, collating, summarizing, and synthesizing the results.

2.1. Identifying the research question

The overarching research question for our review is: what are the strategies followed for the prevention of infectious diseases in sports mass gatherings? To address the main question, we also identified the following specific questions:

1. What are the risk factors for infectious diseases from previous world cups or sports events with mass gatherings?
2. What are the recommended strategies to be followed for the prevention of infectious diseases before, during, and after the sports mass gatherings?

2.2. Identifying the relevant studies

A systemic search was performed using PubMed, Embase, Web of Science, SCOPUS, SportDiscus, and Google scholar. These databases were searched without restrictions to reclaim any publications related to our research question in the period between 2010 and 24 January 2022. The search strategy included three main strings viz "communicable disease" AND "sport" AND "setting" as keywords for each string were used when building the search strategy. The combination of keywords used were (world cup OR sport OR stadium) AND (infectious disease OR communicable disease OR virus) AND (mass gather OR crowd). Table 1 describes the search strategies used to gather the articles from the mentioned databases. To assure not missing any publications related to our purpose, google scholar was further searched, and the reference lists of the selected articles were also screened for articles that might have been not captured from the initial search of the databases.

TABLE 1 Search strategies.

Database	Search strategy	Number of studies
Pubmed	#1 ((“world cup”[Title/Abstract]) OR (stadium*[Title/Abstract])) OR (sport*[Title/Abstract]) #2 ((“infectious disease*”[Title/Abstract]) OR (“communicable disease*”[Title/Abstract])) OR (virus*[Title/Abstract]) #3 (“mass gather*”[Title/Abstract]) OR (crowd*[Title/Abstract]) ((#1) AND (#2)) AND (#3)	36
Embase	#1 “world cup:”ab,ti OR sport*:ab,ti OR stadium*:ab,ti #2 “infectious disease*:”ab,ti OR “communicable disease*:”ab,ti OR virus*:ab,ti #3 “mass gather*:”ab,ti OR crowd*:ab,ti #1 AND #2 AND #3	25
Web of science	#1 ((TS = (“world cup”)) OR TS = (sport*)) OR TS = (stadium*) #2 ((TS = (“infectious disease*”)) OR TS = (“communicable disease*”)) OR TS = (virus*) #3 (TS = (“mass gather*”)) OR TS = (crowd*) #1 AND #2 AND #3	47
SPORTDiscus	(“world cup” OR stadium* OR sport*) AND (“infectious disease*” OR “communicable disease*” OR virus*) AND (“mass gather*” OR crowd*)	6
SCOPUS	(TITLE-ABS (“world cup”) OR TITLE-ABS (sport*) OR TITLE-ABS (stadium*)) AND (TITLE-ABS (“infectious disease*”) OR TITLE-ABS (“communicable disease*”) OR TITLE-ABS (virus*)) AND (TITLE-ABS (“mass gather*”) OR TITLE-ABS (crowd*))	44

2.3. Selecting studies

Any study investigating infectious diseases in the previous FIFA World Cups and other sporting events with mass gatherings was eligible to be included. The first two authors and the corresponding author independently screened titles and abstracts of the citations retrieved from the search. Then, these articles were divided among the same three authors to assess full texts of the relevant records independently. During the study selection and assessment process, the three authors would meet to resolve any conflict and reach an agreement.

Inclusion criteria:

- Articles covering sports mass gatherings.
- Peer-reviewed articles published in the period between 2010 and 24 January 2022.
- Articles covering other mass gatherings, but/or with recommendations for infectious disease prevention in sports events.
- Articles addressing risk factors of viral infectious diseases and/or protection and prevention of infectious diseases.
- Review articles providing recommendations for infectious disease prevention in sports events and other mass gatherings.
- Articles on infections that are transmitted through air, direct contact, or droplets.
- Articles published in English.

Exclusion criteria:

- Small-scale sports events.
- Articles addressing risk factors irrelevant to viral infectious diseases.
- Articles addressing infectious diseases caused by pathogens other than viruses.
- Reports, book chapters, and conference papers.
- Articles on vector-borne disease.

2.4. Extracting the data

A priori identified spreadsheet was developed for data extraction. Data were reported in two tables: Table 1 reported the characteristics of the included studies and Table 2 reported the strategies and recommendations for infectious disease prevention pre, during, and post sports mass gatherings events. Specifically, the following information was included in Table 1: the first author of the study, publication year, country, article type, setting of the study, population description, type of sport, and type of infection. While the second table included the following information: risk factors of infectious diseases, strategies that are recommended to be followed before, during, and after the sports mass gatherings to prevent infectious diseases, and general recommendation for infectious disease prevention in sports mass gatherings.

2.5. Synthesizing the results

In our review, we clustered the infectious disease prevention strategies into three stages: pre-event, during the event, and post-sports event mass gatherings. Description of the scope of literature was presented in a model according to the various strategies and recommendations followed to prevent infectious diseases in various stages of the planning, implementation, and follow-up after the sports mass gatherings are finalized. The model also showed how these strategies of the three stages are impeded in different three contexts that would support their implementation, monitoring and evaluation. These contexts are community/ public social responsibility, preparedness of the health care system, and the regulations/policy/guidelines of public health authorities and other partners.

3. Results

Following the mentioned search strategy, 158 records were retrieved from the mentioned databases search. The remaining records, after removing the duplicates, amounted to 109 records.

TABLE 2 Characteristics of included studies.

References	Country	Article type	Setting of research study	Population description	Type of sport	Type of infection
Blumberg et al. (8)	South Africa	Editorial	2010 FIFA World Cup in South Africa	Populations in mass gatherings	Football	H1N1, H3N2, HIV, malaria, food borne illnesses
Gallego et al. (10)	Brazil	Scoping review	2014 FIFA World Cup in Brazil	Populations in mass gatherings	Football	Yellow fever, dengue, chikungunya fever, chagas disease, malaria, leishmaniasis, cutaneous larva migrans, rickettsiosis, tuberculosis, influenza, hantavirus, leptospirosis, schistosomiasis, HIV/AIDS, foodborne illnesses
Dove et al. (28)	NS	Scoping review	Sport events	Athletes	Multiple sports	COVID-19
Parnell et al. (29)	NS	Commentary	Mass gatherings in general	Populations in mass gatherings	NS	COVID-19
Mantero et al. (30)	South Africa	Scoping review	2010 FIFA World Cup in South Africa	Populations in mass gatherings	Football	Influenza, measles
Griffith et al. (11)	Japan	Summary of national surveillance data	• 2019 Rugby world cup • 2020 Tokyo summer olympic and paralympic games	Travelers	Multiple sports	Rubella, invasive pneumococcal disease, measles, non-A and non-E viral Hepatitis, hepatitis A, Invasive hemophilus influenzae disease, tetanus, typhoid fever, invasive meningococcal disease, Japanese encephalitis, influenza, varicella, mumps, pertussis
Annear et al. (31)	Japan	Scoping review	2020 Tokyo summer olympic and paralympic games	Athlete and spectator	Multiple sports	Mumps, measles, chicken pox, H1N1
Miles and Shipway (32)	N/A	Scoping review	Sport events	Tourists, travelers, athletes	Multiple sports	COVID-19
Alshahrani et al. (12)	Qatar	Scoping review	FIFA World Cup 2022	Populations in mass gatherings	Football	Influenza, COVID-19, hepatitis A
Pshenichnaya et al. (9)	Russia	Editorial	World cup Russia 2018	Attendees	Football	Influenza, tuberculosis, rabies, west nile fever, gastrointestinal infections, measles, mumps, tick-borne encephalitis (TBE), lyme disease
Ahmed and Memish (33)	NS	Scoping review	Hajj and sporting events (olympic games)	Populations in mass gatherings	Multiple sports	Biological agents (terrorism) hepatitis A
Abubakar et al. (34)	NS	Series (report)	Hajj and sporting events (olympic games, cricket worldwide, world cups)	Populations in mass gatherings	Multiple sports	Multiple infectious diseases (NS)
Gaines et al. (35)	Brazil	Special communication	• 2014 FIFA World Cup in Brazil • 2016 summer olympic and paralympic games in Brazil	Populations in mass gatherings	Multiple sports	Hepatitis A, hepatitis B, yellow fever, rabies, dengue
Wilson and Chen (13)	Brazil	Editorial	• 2014 FIFA World Cup in Brazil • 2016 summer olympic and paralympic games in Brazil	Travelers	Multiple sports	Influenza, measles, chikungunya

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TABLE 2 (Continued)

References	Country	Article type	Setting of research study	Population description	Type of sport	Type of infection
Blumberg et al. (36)	West Africa	NS	• African youth games, 2014 • Africa cup of nations, equatorial guinea, 2015 • All-Africa games, Republic of Congo, 2015	Populations in mass gatherings	Multiple sports	Ebola virus
Wilson et al. (14)	Brazil	Cross-sectional study	2014 FIFA World Cup and the 2016 summer olympics	Populations in mass gatherings	Multiple sports	Dermatologic problems, diarrhea, febrile systemic infections, dengue, and malaria
Wong et al. (15)	Hong Kong	Randomized controlled study	Hong Kong premier league (HKP)	Football players	Football	COVID-19
Duarte Muñoz and Meyer (37)	NS	Editorial	Mass gatherings in general	Populations in mass gatherings	Football	COVID-19
Hoang and Gautret (38)	NS	Scoping review	• The summer and winter olympics • FIFA World Cup and the EURO football cup from 1984 through 2015	Populations in mass gatherings	NS	Measles, Influenza, Gastrointestinal infections, and respiratory infections
Vyklyuk et al. (39)	NS	NS	Mass gatherings in general	Populations in mass gatherings	NS	COVID-19
Gautret et al. (40)	Brazil and Korea	Cross-sectional study	• The 2016 summer olympic and paralympic games in Brazil • The 2018 winter olympics in south Korea	Ill travelers	NS	NS
Al-Romaihi et al. (41)	Qatar	Cross-sectional study	Mass gatherings in general	Populations in mass gatherings	NS	NS
McCloskey et al. (16)	London	Series	London 2012 olympic and paralympic games	Populations in mass gatherings	Multiple sports	Multiple (NS)
McCloskey et al. (42)		Comment	Mass gatherings in general	Populations in mass gatherings	NS	COVID-19
Murray et al. (43)	United states	Report	Major league baseball	Team members	Baseball	COVID-19
Chan et al. (44)	Australia	Case study	Sport league	Populations in mass gatherings	Football	COVID-19
Aitsi-Selmi et al. (45)	NA	Scoping review	Mass gatherings in general	Populations in mass gatherings	NS	NS
Drury et al. (46)	UK	Scoping review	Live events: sports and music arena events	Populations in mass gatherings	NS	COVID-19
Al-Tawfiq et al. (47)	Saudi Arabia	Scoping review	Hajj pilgrimage	Pilgrims	NS	Influenza, Rhinovirus
Dénes et al. (48)	Ukraine	Epi study	2012 UEFA European football championship	Populations in mass gatherings	Football	Measles

(Continued)

TABLE 2 (Continued)

References	Country	Article type	Setting of research study	Population description	Type of sport	Type of infection
Leal Neto et al. (49)	Brazil	Participatory surveillance	2014 FIFA World Cup in Brazil	Healthy cup app users	NS	Influenza, measles, rubella, cholera, acute diarrhea, dengue fever
Chiampas and Ibiebele (50)	NS	Scoping review	Sports and mass gatherings in general	Athletes, travelers, audience	NS	COVID-19
Hassanzadeh-Rad and Farzin (51)	NS	Letter to editor	Sports	Populations in mass gatherings	NS	COVID-19
Eberhardt et al. (52)	Brazil	Prospective case-control survey	2014 FIFA World Cup in Brazil	Travelers	NS	NS

NS, Not specified; N/A, not applicable.

After screening the titles and abstracts, 23 were excluded; the remaining 86 full-text articles were assessed for eligibility, and 34 studies were reserved for this review. The PRISMA diagram demonstrates the selection process and clarifies the reasons for exclusion of other studies (Figure 1).

3.1. Characteristics of the included studies

The studies were divided by design into 11 scoping reviews (10, 12, 28, 30–33, 38, 45–47, 50), three cross-sectional studies (14, 40, 41), four editorials (8, 9, 13, 37), two series reports (16, 34), one randomized controlled study (15), one commentary (29), one summary of national surveillance data (11), one special communication (35), one comment (42), one report (43), one case study (44), one epidemiological study (48), one participatory surveillance (49), one letter to the editor (51), one prospective case-control survey (52), one epidemiological study (48), and two articles were not specified (36, 39). The majority of these studies reported their findings from one country, one study reported data from two countries, and 12 studies were not in specific countries. In 23 studies, the settings of the research were related to sports events, six studies looked at mass gatherings in general, four studies looked at two settings:

Hajj and sporting events or music arena events or mass gatherings in general and one study looked at the Hajj pilgrimage. The majority of studies have described populations in mass gatherings, and the rest of the studies have described athletes or/and travelers or/and the audience. In 11 studies, the types of sports that were described were multiple sports, in nine studies it was football, in one study it was baseball, while in 13 studies the type of sport was not specified. The type of infection that was addressed varied between studies. In 15 studies, they described more than one infection. The most common infection addressed in the majority of these studies was influenza and 12 studies were focused on COVID-19 solely. In six studies, there was no specific type of infection, while two studies described the Ebola virus or measles (see Table 2 for the characteristics of the included studies).

3.2. Risk factors of the infectious diseases' outbreaks in the included studies

In order to prevent the spread of infectious diseases through a specific event, several risk factors must be considered. In general, risks to travelers involve locally endemic infections that are unfamiliar to many travelers, or infections that are more likely to arise as a result of crowding related to mass events. In terms of risks to citizens, travelers carry pathogens that could initiate a local epidemic, such as the corona virus as well as influenza virus (13). Others included non-compliance with basic infection control and prevention standards such as poor hygiene, lack of sanitation, inadequate vaccination coverage, lack of immunity due to non-vaccination such as the fact that the majority of people who became ill with measles had not been vaccinated, close contact between the players, also the infection risky behaviors including touching the face and spitting (9, 12, 15, 28, 33, 38). Traveling is one of the most important factors in

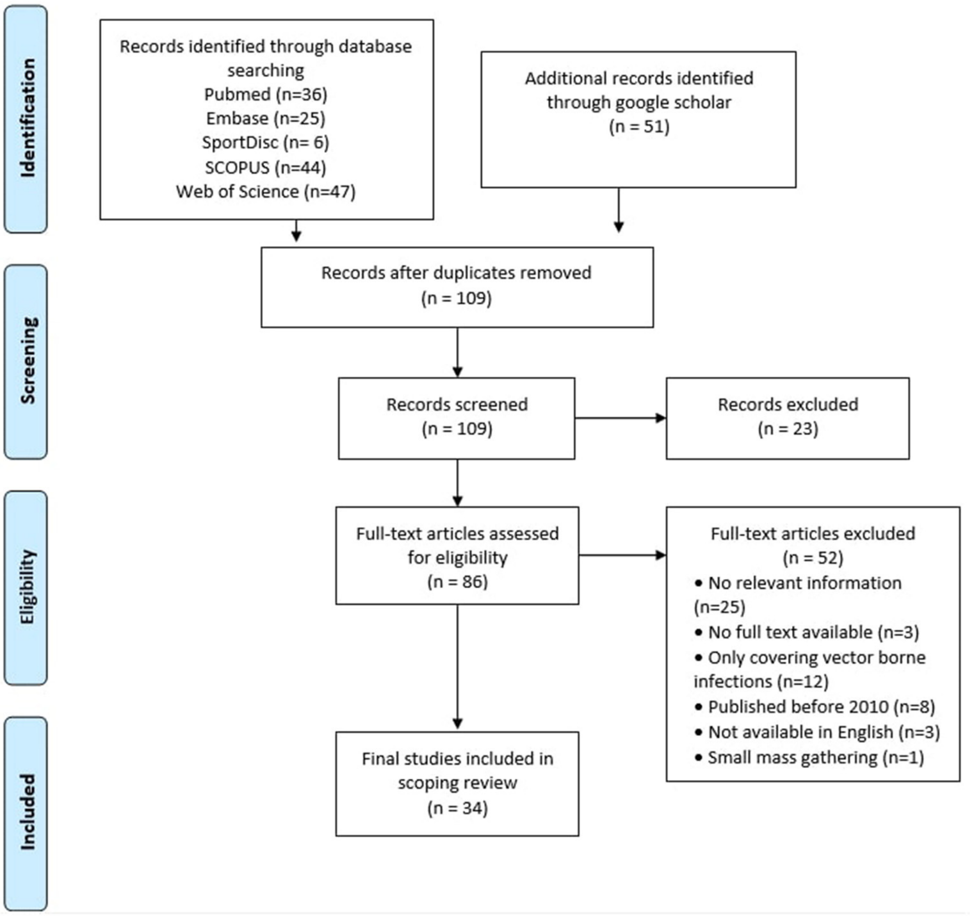

FIGURE 1
PRISMA flow chart for recording included studies.

disease transmission particularly when visiting high-risk areas (10–13, 28, 29, 40), because the risk of disease transmission is across communities due to overcrowding, localized high population density (9, 12, 30, 34) and challenges in contact tracing due to the mobility of attendees with communicable diseases (8, 30). In addition to group identity, physical setting, climate, population participating in the event, and potential infections, crowd behaviors at live events may be affected by behaviors before and during the pandemic (34, 46), a study has also shown that transmission is most intense from February to June, with influenza peaking in June and July (14). In addition, one of the most critical factors is the ability to respond effectively and quickly to outbreaks and other emergency situations (41).

3.3. Pre-event strategies

In our review, several studies documented the pre-event preparations in worldwide sports events during epidemics. The immunization and vaccination for hepatitis A&B, yellow fever, rabies, mumps, measles, rubella, and influenza were recommended strategies, in which travelers should be encouraged to visit a health-care provider 4–6 weeks before travel to manage any risk through vaccinations (8, 9, 11–14, 31, 34–38, 47, 48, 50). Other strategies included educational messaging through targeted media and communications prior to the matches (8, 44), infection control practices such as hand hygiene, cough etiquette (8, 31, 36, 38, 44), pre-travel consultation (8, 10, 12, 52), and advice on the correct timing and use of personal protection measures (10, 36), self-isolation and quarantine for new arrivals or symptomatic individuals (31), physical distancing measures and regular COVID-19 testing were proposed with strict adherence required from staff, players, coaches, and others (28, 44), as well as travel precautionary measures including COVID-19 test certificates, quarantine, digital apps (12, 44), and travel restrictions by reducing flights and public transport (29).

The recommendations for the athletes, staff, and others included testing all athletic activities including pre-events, training sessions in the recognition and management of communicable diseases (12, 28, 36, 41), informing the travelers about their role in transmitting or preventing the transmission of the disease (11), as well as providing health education psychology supporting materials for athletes. Another study recommended that employees could operate from home to avoid having direct contact with athletes (15). Some studies mentioned the contribution of efforts to create multidisciplinary surveillance (40), and public health risk assessment to follow the principles of risk analysis, surveillance, and reporting in order to enhance public awareness of public health concerns (16, 42, 52), and how to inform about the health situation and any relevant advice

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TABLE 3 Strategies pre, during, and post-events to prevent the spread of infectious diseases.

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Blumberg et al. (8)	Mobility of attendees with communicable disease	– Immunity (vaccines) – Pre-travel consultation – Educational messaging (cough etiquette and hand hygiene	Availability of tissues and facilities to cleanse hands in public areas, voluntary isolation of mild cases at home when showing symptoms		Enhanced epidemic intelligence
Gallego et al. (10)	Visiting elevated risk areas possibility of travelers bringing the virus with them	– Pre-travel consultation – Advice on the correct timing and use of personal protection measures			– Enhanced epidemic intelligence to promptly detect incidents – Provision of standard operating procedures for epidemic response
Dove et al. (28)	– Close contact between football and soccer players – Travel also increases the risk of viral spread	Testing all athletic activities including pre-events	– Daily self-health checks – Universal masking on all sidelines – Testing athletic activities during the events	Testing athletic activities post-events	
Parnell et al. (29)	Travel is one of the key contributors to disease transmission	Travel restrictions, including reduced flights and public transport and route restrictions without compromising essential services	Use of social distancing measures		Community mitigation strategies
Mantero et al. (30)	Localized high population density, risk of importation of non-endemic diseases, exportation of endemic diseases, challenges in contact tracing due to visitor mobility, and temporary structures such as mass catering and accommodation for visitors		Adapted routine epidemic intelligence activities by the ECDC and was further enhanced by using a targeted and systematic screening approach through tailored tools (MediSys)		
Griffith et al. (11)	Traveling	– Up-to-date vaccinations with additional preventive measures should be included in pre-travel advice – Prioritized rubella, mumps, and influenza for pre-travel advice – Travel advisers should also consider individual traveler behaviors and itineraries. Health professionals should also inform travelers about the role they could play in transmitting or preventing the transmission of disease to MG attendees from across the world			
Annear et al. (31)		Vaccination of attendees Ensuring self-isolation and quarantine for new arrivals or symptomatic individuals, distributing personal protective equipment (e.g., facemasks) and promoting rigorous hand and respiratory hygiene	Restricting spectator attendance (creating a so-called event bubble), imposing social distancing rules, conducting mandatory diagnostic testing		Impose significant control measures

(Continued)

TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Miles et al. (32)					Implementing protective measures, including staffing, physical protection systems, perimeter control, access control, risk management, emergency management, crowd management, and traffic control; all form an integral part of international sport event management
Alshahrani et al. (12)	International travel increases the risk of transmitting communicable diseases across communities overcrowding, poor hygiene, and malnutrition (influenza)	– Vaccination with doses adjusted based on age and presence of comorbidities of the individual – Providing appropriate education to traveler's Pre-travel consultation on health and safety measures, including vaccination – Any defects in the previous plans must be discovered and processed, and the capacity of Qatar's hospitals and stockpiles should be increased due to the mass casualties that may occur. In addition to this, having an adequate workforce, providing appropriate training for the medical staff, and having multilingual services to address the language barrier is also essential – Travel precautionary measures including COVID-19 test certificates, quarantine, and digital apps			– Implementing an appropriate health surveillance system – Maintaining hand hygiene (washing and disinfecting), wearing a protective mask, and social distancing as preventive measures against COVID-19
Pshenichnaya et al. (9)	– High crowd densities, non-compliance with hygiene rules or inadequate sanitation may lead to enhanced transmission of infectious disease agents among attendees with a potential for globalization given the international component of the event – Non-compliance with basic hygiene rules, inadequate sanitation, and insufficient vaccination coverage	– Up to date with the routine vaccination courses recommended in their home country – Additional vaccines for those who may be at increased risk of a vaccine preventable illness due to their lifestyle choice, or pre-existing illness visit their travel medicine advisors prior to travel		Clinicians seeing ill-returned travelers	

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Ahmed and Memish (33)	Lack of immunity due to non-vaccination		– Bio-surveillance to detect illnesses – Enact surveillance and disease reporting mechanisms during the mass gathering events themselves to be able to identify case clusters or even infectious disease outbreaks	– Countries must be ready with a public health surge capacity to respond to returning travelers – Control measures and means to prevent infections exported back by attendees to their countries of origin	– Collaborative approach – Sharing resources across sectors and agencies whether public or private entities is critical to mass gatherings being safe-guarded
Abubakar et al. (34)	– Existing influenza tests are inappropriate for prompt detection of all strains at mass gatherings – Risk factors for spread of infectious disease depend on setting, event, climate, likely mixing patterns, population attending the event, and possible infections	– Planning using a recognized framework depending on the nation involving a range of government and non-government agencies at local, regional, and national levels – All travelers to large events should be encouraged to visit a health-care provider 4–6 weeks before travel to manage any risk through vaccinations, drugs, and advice – Pre-event vaccination when appropriate, and vaccination of all individuals who are identified as not immunized previously	– Prompt isolation and treatment of detected infectious cases might have a role in preventing the spread of some infections – Continuous assessment of how the public health system, health-care system, and general community that are coping with increases in the number of cases of communicable diseases or disease risk related to the mass gathering. Risk assessment of communicable diseases should be both strategic and case based – Enhanced surveillance system during the event. Prompt recognition of emerging patterns of infectious diseases, using systems such as the WHO global alert and response system GeoSentinel and the EuroTravNet and other equivalents are functioning optimally rapid identification of an outbreak during an event		– Control measures, including vaccination adequate surveillance to identify the disease, appropriate respiratory hygiene – Prompt isolation and treatment of detected infectious cases might have a role in preventing the spread of some infections – Collaborative approach: all elements of planning (before, during, and after the event) require close liaison with international organizations, including recognition of the obligations of each nation state according – Robust routine surveillance system exists for likely pathogens – Adequate laboratory facilities are essential for the provision of accurate and timely confirmation or exclusion of individuals with the disease – Syndromic surveillance has been suggested as a composite approach to identification of disease syndromes, a process that usually needs to be complemented by appropriate laboratory surveillance – Required or recommended immunization and other health-care guidance

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Gaines et al. (35)		– Education of travelers on preventive measures vaccination for hepatitis A & B, yellow fever, rabies (3 doses) – Pre-travel consultation 4–6 weeks before departure – Refer patients to a travel medicine specialist when needed – Before departure, travelers should contact their health insurance company to determine whether their policy includes coverage overseas and for emergency expenses such as aeromedical evacuation. Travelers are advised to consider supplemental travel health insurance with specific overseas coverage, including 24-h access to assistance for health care and medical evacuation contingency plans	Travelers who become sick or injured while traveling should seek immediate health care		
Wilson and Chen (13)	– Risk on travelers: locally endemic infections that may be unfamiliar to many travelers and clinicians (e.g., dengue, cutaneous larva migrans, malaria, yellow fever). Infections that may be more likely to occur because of crowding and activities related to the mass events. Non-communicable diseases and problems that stem from the high density of people engaged in competitive events in an environment that may be hot, volatile, or otherwise unstable – Risk on citizens: visitors also pose risks to the host country. Visitors could carry pathogens that could spark a local epidemic, if the local population is susceptible or local conditions favor spread Examples include a new influenza virus, a new coronavirus, or a new, virulent serogroup or strain of Neisseria meningitides piddly to travelers with potential exposure – Concerns might include a new genotype of dengue virus – Visitors who are only attending the mass sporting events (and are in urban areas) face fewer risks than those who will have more extended stays that include the Amazon basin and rural areas	Vaccination to influenza and measles			Enhanced surveillance will be important to identify infections early (Chikungunya virus)

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Blumberg et al. (36)	With people coming to the country from many African countries, the risk of importing EVD existed, and required mitigation	– Vaccination of yellow fever as requirement for entry of travelers from endemic countries – Airport health staff screened incoming travelers for fever – A small medical facility was established at the airport for the isolation of patients – Extensive staff training was conducted using videos and demonstrations in the use of personal protective equipment (PPE) and infection control practices, as well as simulation exercises – Training sessions in the recognition and management of a range of communicable diseases were held for medical personnel	During the games, the Ministry of Health participated in daily all-hazard assessment with the National Organizing Committee and developed and shared daily situation reports		– While a strong national surveillance system supported by district outbreak response teams was already in place for epidemic-prone diseases, this was supplemented by a daily surveillance system for specific priority conditions pertinent to the event – A daily analysis attempted to establish trends. An emergency 24-h reporting system was established for persons with suspected meningitis or VHF, and for any outbreaks – An isolation facility was established in an existing health center outside of the major hospitals – The requisite export permits and transport arrangements were facilitated. The public health and hospital laboratories in Gaborone were able to test for malaria and meningitis and common pathogens – The Ministry of Health and Population of Congo was responsible for the overall coordination and delivery of health services, and worked in close collaboration with other ministries, the organizing committee, and the WHO, to ensure rapid detection and containment of infectious diseases, especially EVD – Enhanced surveillance for key notifiable diseases was implemented in all eleven stadia and other important locations like the airport

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Wilson et al. (14)	Gengue: urban areas, Transmission is most intense during February through June influenza showed clear seasonality, peaking in June and July	– All travelers should be up to date on their routine vaccines ● Hepatitis A ● Influenza – Measles-mumps-rubella – Influenza and yellow fever – Advise travelers on specific risks – Examined and aggregated top diagnoses reported during June through September – Travelers should check their entry requirement with Brazilian authorities in their own countries as well as the Brazil Ministry of Health		Post-travel surveillance is important for infections with long incubation times	– Used the The GeoSentinel Surveillance Network that is an international network of specialized travel and tropical medicine clinics located on six continents – All sites collect data by using a standard reporting form on ill travelers seen during or after international travel – Anonymized data on demographics, travel history, reason for travel, pre-travel advice, hospitalization, major clinical symptoms, and final diagnoses assigned by the GeoSentinel site clinician are electronically entered into a central database – Diagnoses are selected from a standard list of >500 diagnostic codes and involve syndromic groupings alone if no etiology is defined or syndromic groupings plus specific etiologies where possible – All sites use the best reference diagnostic tests available in their own country – Country of exposure is identified by the clinician based on the travelers' itinerary, known endemicity patterns of the destinations visited, and incubation period of the illness

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Wong et al. (15)	– Asymptomatic cases – As the virus was also found in stool samples, eight contaminated environments, such as soil, may pose a threat to outdoor sporting events infection-risky behaviors, such as spitting and touching the face, are common during football games	– Relevant health education and psychology supporting materials were provided for athletes – A work-from-home roster and flexible office hours have also been implemented for administrative staff, and they were instructed not to have direct contact with athletes – The HKSI strictly abided-by the government's policy on inbound travelers, all activities to Mainland China and mass activities in HKSI were suspended from February 8 onward	– To quantify these transmission-risky behaviors, we obtained video footage of four male professional football players with dedicated cameras for an entire match. We tracked their time of close body contact (defined as an inter-personal distance of <1.5 m) and frequency of infection-risky behaviors (touching the mouth, touching the eyes, touching the nose, and spitting) – Weekly updates to remind all personnel on personal and maintaining physical distance between individuals during and after training	– Upon the issuance of Government "Red Outbound Travel Alert," all personnel returning to Hong Kong after March 5 from overseas must report their temperature and symptoms (if any) electronically for 14 days and optional COVID-19 tests were provided – All personnel returning from COVID-19 affected areas (even if not included the governments' compulsory quarantine regions) were required to self-isolate at home or a hotel for 14 days before returning to HKSI. All travel to the affected areas were disallowed during the corresponding period	– Minimize the number of people congregated at one single place and time through closed competitions with no spectators and minimizing non-essential personnel present at the venue, such as by canceling press conferences and interviews – Sporting equipment should be cleaned as frequently as possible – All personnel were required to measure body temperature and declare FTOCC (Fever, Travel, Occupation, Contact and Clustering) status before entering the institute and the daily body temperature report of all athletes were obtained
Duarte Muñoz and Meyer (37)	– The likelihood of respiratory disease transmission among members of a football team is not particularly large – One must not forget all the situations around training and competition which happen in dressing rooms, during social activities or during medical care	Vaccination guidelines should be strictly met	– Basic preventive measures among football players, coaches and staff members and the general public – Adequate hand hygiene and "coughing etiquette," as well as abstaining from social gatherings, especially when symptomatic, are key – Among athletes it is also important to avoid sharing personal objects, such as towels and water bottles – Organizational measures to increase distance between dressing and showering athletes (e.g., use of more dressing rooms than usual) – Players should not be treated together in one room to avoid spread among medical personnel	Looking at ill travelers returned from Brazil who were subsequently seen at a GeoSentinel clinic	

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Hoang and Gautret (38)	Most ill individuals with measles had not been vaccinated	Individual preventive measures such as cough etiquette, the use of face mask and disposable handkerchiefs and hand hygiene vaccination of measles, mumps, meningococcal Influenza, and pneumococcal diseases			
Vyklyuk et al. (39)	–		– Identify disease through a mobile application by detecting the tone and strength of the cough. The accuracy of this method of identification is 70% – Another method involves identifying infected people by fever – Measure body temperature through tools: thermometer, Stationary thermal imaging systems, thermal sensors, and mobile thermal imagers		
Gautret et al. (40)	Most illnesses among travelers attending the Olympics were linked to trave	Contributing to efforts to create enhanced international multidisciplinary surveillance			
Al-Romaihi et al. (41)	Prompt and effective response to CD outbreaks during MG events requires that frontline HCWs have the correct knowledge, adequate training, and proper attitude about CDs and outbreaks and especially those working in EDs (7, 8). It is also necessary for EDs to have the necessary preparedness to effectively and promptly respond to such drastic situations	– Getting HCWs and staff in hospitals ready and prepared for disasters in MG events: – Increase HCWs understanding of relevant concepts such as disasters, pandemics, and influenza – Trained in disaster-related subject			

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
McCloskey et al. (16)	–	The approach taken to the public health risk assessment was to follow the principles of risk analysis, surveillance and reporting, and response. In response to this risk assessment, systems were enhanced to provide additional surveillance data, improve understanding of the public health effect of the 2012 Games, and raise public awareness and understanding of public health concerns Authorities began public health planning more than 7 years before the Games, following the principles laid out in the WHO Communicable Disease Alert and Response for Mass Gatherings Guidelines, and the experiences of previous host cities Important to address public health issues with the utmost urgency The systems and capacity need to be in place to rapidly receive and analyze information from surveillance, reporting, and intelligence systems, and to identify and respond to any potential health protection threat	The national Center for Infectious Disease Surveillance and Control routinely collates reports of incidents, outbreaks, and adverse trends from across the UK; during the Games, in addition to undertaking this daily, they collated enhanced systems Daily analyses of mortality data were also done, and a new system was introduced for sentinel intensive care units to report unexplained illness of probable infectious cause This system involved clinicians in pediatric and adult intensive care units rapidly reporting cases using a customized web-based method During the 2012 Games a national event-based surveillance team was the hub for reporting of incidents and outbreaks of an infectious disease from across the UK that might substantially affect the Games, by their effect on venues, Olympic staff, athletes, or visitors, or by the public's perception of the Games The team enhanced established systems by reviewing and collating daily incident and response reports submitted by all local health-protection teams. The team also reviewed the national public health case-management system (HPZone) for incidents and diseases of special interest Information from both these sources was collated, and a Games-specific risk assessment made according to agreed criteria seven information about any notable events identified was routinely reported daily to the national coordination center, or more frequently, if needed		These systems were the HPA/NHS Direct Syndromic Surveillance System, which provides so-called pre-primary care data using call information from the health advice telephone service for a range of syndromes, and the HPA/QSurveillance National General Practitioner (GP) Surveillance System, one of the largest GP surveillance systems in Europe, which monitors weekly consultation data from a network of more than 3,500 GP practices across the UK For the first time syndromic surveillance reporting was undertaken at the Games polyclinic. This polyclinic, in the Athletes' Village in the main OlympicParalympic park, was the principal point of access to medical services for athletes and others. Medical facilities were also located in every sporting venue, as well as in one of the main hotels housing the OlympicParalympic family Each time a medical service was used, the doctor, first aider, physiotherapist, dentist, or other health-care provider recorded details of the consultation and treatment using a medical encounter form The HPA worked with international partners-particularly the European Center for Disease Prevention and Control (ECDC) and WHO-to set up enhanced international surveillance for the 2012 Games (34, 37). This international surveillance monitored and assessed the risk, on a day-to-day basis throughout the surveillance period, of any infectious disease threats abroad that had the potential to affect health in the UK, and, in particular, at the Games. The team undertook joint risk assessments of incidents identified as relevant through an agreed set of criteria designed for the Games, using methods developed for this purpose Enhanced clinical, public health, and environmental microbiology laboratory capability and capacity are necessary to meet the increased demands of a mass gathering. As well as additional routine testing requirements, response teams need the ability to rapidly scale up the testing capability as part of the response to an infectious-disease outbreak

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References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
McCloskey et al. (42)		Risk assessments for COVID-19 (panel) need to consider the capacity of host countries to diagnose and treat severe respiratory illness Encompassed joint planning, enhancement of health infrastructures, and taking proper pre-emptive and preventive measures to control infectious diseases on an international scale 1)General considerations at the beginning of the planning phase: • Risk assessment must be coordinated and integrated with the host country's national risk assessment • Comprehensive risk assessment (with input from public health authorities) reviewed and updated regularly (2)COVID-19 specific considerations: • Consult WHO's updated technical guidance on COVID-19 (3)Specific action plan for COVID-19: action plans should be developed to mitigate all risks identified in the assessment. Action plans should include: • Integration with national emergency planning and response plans for infectious diseases • Command and control arrangements • Any appropriate screening requirements for event participants • Disease surveillance and detection • Treatment • Decision trigger points (4) If the decision is made to proceed with a MG, the planning should consider measures to: • Detect and monitor event-related COVID-19 • Reduce the spread of the virus • Manage and treat all ill persons • Disseminate public health messages specific to COVID-19 (5) Risk communication and community engagement: • Event organizers should agree with the public health authority on how participants and the local population will be kept informed about the health situation, key developments, and any relevant advice and recommended actions	(6)Risk mitigation strategies: • Reducing the number of participants or changing the venue to prevent crowding, or having a participant-only event without spectators • Staggering arrivals and departures • Providing packaged refreshments instead of a buffet • Increasing the number of, and access to, handwashing stations • Promoting personal protective practices (hand hygiene, respiratory etiquette, staying home if ill) • Offering virtual or live-streamed activities • Changing the event program to reduce high-risk activities such as those that require physical contact between participants		

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Murray et al. (43)		Developed new health and safety protocols before the July 24 start of the 2020 season. In addition, MLB made the decision that games would be played without spectators	– Mitigation strategies for COVID: 1. Minimize contact between players and staff members (tiers) 2. Symptom screening and testing 3. Isolation of persons testing positive and quarantine of close contacts 4. Face masks 5. Social distancing 6. Environmental cleaning and disinfection – Increasing cloth face mask use among players and staff members (i.e., at all times except on the field of play), limiting travel to essential staff members, and prohibiting visits to gatherings of large groups of persons Frequent diagnostic testing for rapid case identification, isolation of persons with positive test results, quarantine for close contacts, mask wearing, and social distancing		

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Chan et al. (44)		Sport leagues was planned with a collaborative approach among key stakeholders, including public health authorities, other governmental agencies, AOSMA, AFL, and SANFL A COVID-19 protocol including physical distancing measures and regular COVID-19 testing was proposed with strict adherence required of officials, staff, players, coaches, and where necessary, members of their household. Targeted media and communications prior to the matches contributed to the management of expectations and motivations of the attending spectators Key messages of physical distancing, hygiene, and infection prevention and control measures were communicated to attending spectators both in the time leading up to the matches (*via* targeted communications as well as traditional and social media) Spectators were also discouraged to attend if displaying COVID-19 symptoms, required to provide accurate personal information for contact tracing and encouraged to download the COVID Safe application	Specifying number of attendees and increasing it on stages Physical distance between seats Reminders on preventive measures during the matches (*via* broadcasting of health campaigns and visual reminders including clear signage, ground markings, and visual overlays)		Early collaborative planning among key stakeholders, both from government agencies and non-government agencies

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Aitsi-Selmi et al. (45)					For an evidence-based approach to the health impacts (including infectious disease control) of mass gatherings to be effective, it will be important to blend all-hazard risk management strategies across current global initiatives
Drury et al. (46)	Group identity, physical setting, norms, broader trends in public beliefs, and behaviors before and during the pandemic might affect crowd behaviors at live events (proximity behaviors)	A key objective of the communication strategy is to make the behaviors listed above into new norms: first, ensure that the venue is organized in such a way as to make desired behaviors (such as distancing) possible, second, draw on an understanding of the relevant group identity in order to promote the new norms (or rather, to promote new forms of behavioral expression for old social norms). Effective communication should stress the following messages about risk: unsafe behaviors put fellow group members at risk and not only within the venue; they also put everybody's families at risk and also the entire community at risk; this in turn would present a major risk to the standing of the group in the community. Third, it is important that messages address not only what group members should do (so-called "injunctive norms"), but also what they are typically doing ("descriptive norms"). Fourth, the source of information is as important as its content Designing pilot studies and evaluations of events to inform strategies for opening events with minimal risk of transmitting the virus	Preventive measures: physical distancing; wearing of face coverings; and regular handwashing or sanitizing Specific behaviors that are commonplace at live events-such as singing, shouting, chanting, hugging, jumping up and down-need to be limited or substituted. Many of the behaviors required, or that need to be limited, can be moderated by the environment in the venue: i) Limited access/density and effective management of the flow of people in and around the venue ii) Enforced wearing of face coverings (with special arrangements for those unable to wear them) iii) Hand-hygiene stations at multiple points in the venue iv) Minimal shared surfaces that require touching (e.g., contactless doors and lavatories).		

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TABLE 3 (Continued)

References	Risk factors	Recommendations			
		Pre-event	During event	After event	General recommendations
Al-Tawfiq et al. (47)		Utilizing the recommended vaccines	The use of masks, practice of social distancing, hand hygiene, and contact avoidance		
Dénes et al. (48)		To prevent imported epidemics, it should be emphasized that vaccinating travelers would most efficiently reduce the risk of epidemic, while requiring the minimum doses of vaccines as compared to other vaccination strategies			
Leal Neto et al. (49)					Participatory surveillance through community engagement is an innovative way to conduct epidemiological surveillance
Chiampas and Ibiebele (50)		Organizations need to have established scalable protocols for athletes who do contract the virus with symptom-based algorithms for length of time away from play and with screening for cardiac and pulmonary complications from COVID-19 encouraging our athletes to become immunized against the virus and educating our athletes about nutrition and the relation to immune health is important as we return to play			Hygiene and social distancing, use of masks, rigorous monitoring and screening of symptoms, widespread testing, comprehensive contact tracing, and considerations for travel and facilities
Hassanzadeh-Rad and Farzin (51)					Contact tracing: For audiences inside the stadiums, there should be obligatory rules for all federations in all countries to sell traceable electronic tickets for each seat. By doing this, if an infected patient with COVID-19 who has recently participated in a crowded sports match as a spectator is discovered in clinics or hospitals, it is feasible to track all seats in a certain distance from the infected patient's seat (e.g., seats located in a radius of 2 m from that seat) and by information provided with electronic ticket systems, targeted PCR testing (instead of blind testing or no testing) is performed for other at-risk audiences whose seats were in close vicinity of that of the infected patient
Eberhardt et al. (52)		The additional health risks of travelers to sporting events as the FIFA World Cup 2014 should be addressed in addition to addressing traditional health threats in pre-travel counseling			

and recommended actions (42). See Table 3 for summary of the pre-event strategies.

3.4. Strategies followed during the event

During the sports events, numerous studies identified particular recommendations as shown in Table 3. These recommendations were basic preventive measures among football players, coaches, staff members, and the general public (37, 44, 46) including the use of masks (46, 47) and the practice of social/ physical distancing (29, 31, 46, 47) with adequate hand hygiene (37, 46, 47), coughing etiquette (37), and contact avoidance (37, 47). In addition, a couple of studies were conducted among athletes to avoid sharing personal objects such as towels and water bottles (37), test athletics activities during the events (28), send weekly updates to remind all personnel on maintaining physical distance between individuals during and after training (15), and implement the organizational measures to increase the distance between dressing and showering athletes (37). Also imposing social distancing rules (31) through the physical distance between seats, specifying the number of attendees (44), limiting access and effective management of the flow of the people in and around the venue (46), and limiting some behaviors at live events such as singing, hugging, and jumping (46).

Murray and McCloskey both reported in 2020 about risk mitigation strategies such as staggering arrivals and departure, offering virtual or live–streamed activities, increasing the number of and access to handwashing stations, reducing the number of participants, or having a participant-only event without spectators, symptoms screening and testing, frequent diagnostic testing for rapid case identification, isolation of persons with positive test results and quarantine for close contacts, limiting travel to essential staff members, and prohibiting visits to gatherings of large groups of persons (42, 43). In addition, a study recommended identification of the disease through a mobile application by detecting the tone and strength of the cough, in which the accuracy of it is 70%, or by checking fever (39). Furthermore, the ministry of health's participation with the National Organizing Committee in daily all-hazards assessment report about the situation (36), enhancement of established systems by reviewing and collating daily incident, outbreak, and response reports (16), daily analysis of mortality data by all local health-protection teams (16), development of enact surveillance and disease reporting mechanism in order to identify infectious disease outbreaks during the event (33, 34) and assessing the frequency of infection-risky behaviors such as spitting, coughing (15) are recommended strategies during the event (see Table 3 for summary of the strategies recommended during the event).

3.5. Post-event strategies

In general, post-event recommendations include post-travel surveillance, particularly for infections with long incubation times (14), and testing athletics activities post-event (28). Countries must be prepared with a public health surge capacity and implement control measures to prevent infections from being exported back to their countries of origin by attendees (33), and in a study conducted in Hong Kong 2020, all personnel returning to their nation were obliged to electronically record their temperature and symptoms for 14 days, and any staff arriving from a COVID-19 impacted country was self-isolated at home for 14 days (15) (see Table 3 for summary of the post-event strategies).

3.6. General recommendations

Several general recommendations to prevent the spread of infectious diseases were suggested in some studies as shown in Table 3. Infection control measures recommendations include hand hygiene, using a protective mask, and social distancing (12, 34, 50), prompt isolation, and treatment of detected infectious cases which aims to prevent the spread of infections (34), adequate vaccination and recommended immunization (34), strict monitoring and screening of symptoms, widespread testing (15, 50), and minimizing the number of people congregated at one single location through closed competitions with no spectators, as well as unnecessary personnel present at a venue (15). Furthermore, a couple of studies considered enhancing epidemic intelligence to detect incidents efficiently (8, 10), implementing standard operating procedures for epidemic response (10), and developing community mitigation plans as general recommendations to consider (29). Implementation of protective and control measures such as risk, emergency, and crowd management, physical protective systems (31, 32, 45), and contact tracing for the audience (50, 51) all form an integral part of any sports event management. Moreover, other studies assessed the establishment of an appropriate routine health surveillance system in order to identify infections early (12–14, 16, 34, 36, 49) such as Syndromic Surveillance (16, 34), a collaborative approach between the ministry of health and other ministries, the committee and WHO to ensure rapid detection and containment of infectious diseases (33, 34, 36, 44), and enhancement of clinical, public health, and environmental microbiology laboratory capability and capacity (16, 34).

4. Discussion

To the best of our knowledge, this is the first systematic attempt to comprehend communicable disease risk in the context of previous mass gatherings sport. Several key findings were highlighted including the risk factors of different infectious diseases and prevention strategies that were clustered into three stages: pre-, during, and post-sport event mass gatherings.

Traveling continues to pose risks related to the prolonged close contact with people who may be carrying transmissible illnesses (53). Traveling results in increasing mobility, overcrowding and localized high population density, which impact the transmission of infectious diseases among communities. Another important risk factor is crowd behavior. In contrast to our findings, it's found that developing common identities between crowds can transform hazardous mass gatherings into a health-promoting event (54). This is explained by how behaviors are influenced by group identity, physical setting, climate, and individuals participating (46).

The majority of studies included has identified pre-event recommendations. This indicates that pre-event recommendations are the first line of defense and, if implemented correctly, can reduce the risk of COVID-19 transmission. Supporting our findings, pre-event vaccination and travel medicine measures were successful in preventing epidemics of influenza A H1N1 during the worldwide pandemic in 2009 at the Hajj and the Asian Youth Games in Singapore (55, 56). Immunization is a critical component of travel medicine, particularly for high-profile events such as the World Cup. Additionally, employing health communication by generating and spreading educational materials in the press for the public. Similarly, a study included all of FIFA's risk management published articles from 1994 to 2011 showed the effectiveness of risk communication in any risk management strategy (57). They provided the residual risk levels associated with certain risk factors to stakeholders in an appropriate and accessible manner, allowing informed critical discussions (57). Communication and collaboration are crucial among public health authorities within the host country as well as across participants' home countries to ensure the spread of health information among visitors.

During-event recommendations normally receives the most attention when events take place. According to the findings of this scoping review, adequate respiratory hygiene measures and practices, as well as rapid responses from public health authorities to detect infectious cases, was found to lower the likelihood of outbreaks. Similar to these findings, a study done to evaluate the effect of preventive measures, including face masks, stadium capacity, and capacity proportion on the infection risk has found that with the introduction of face masks and hand washing methods, the infection risk was decreased by 86–95 percent (58). This demonstrates that violations of COVID-19 recommendations, including not wearing masks, social distance, and self-isolation, will have a considerable influence on the total number of COVID-19 cases, and other respiratory diseases.

Only few studies considered taking actions after the end of sports events, which is considered as a limitation in the preparedness process. It was found that post-travel infections become apparent soon after, with 43–79% of travelers becoming ill with a travel-related illness (59). In addition, global surveillance after the event can be used as a guide to detailed travel history during every patient encounter (60). A study conducted in Brazil found that skin problems, diarrhea, and febrile systemic infections are most prevalent in returned travelers (14). Similar to our findings, a study reported that despite the success with mitigating spread of diseases, the returning Saudi pilgrims who visited pilgrimage sites in Iran and Iraq were early sources of COVID-19 spread, contributing to 150,000 cases (61). Thus, applying post-travel surveillance would contribute to COVID-19 mitigation.

In addition, some general recommendations were suggested. These recommendations include increasing the speed and accuracy of existing surveillance capabilities, developing active surveillance systems, conducting a detailed risk assessment to prioritize infections, and having the capability to receive and evaluate data quickly are all diverse ways to improve surveillance during sports mass gatherings (62). Even though the enhancement of the surveillance system might be relevant to the sports event itself, it should benefit the host country's public health infrastructure eventually (63).

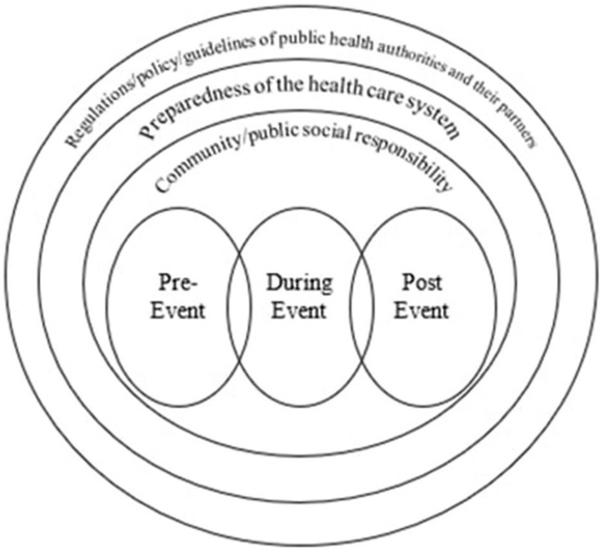

FIGURE 2
A model representing the three stages in which infectious disease prevention is followed during sport mass gatherings embedded in various contexts.

4.1. Implications and recommendations for practice represented in a model

Based on this review, a model was constructed to represent the strategies followed to prevent infectious diseases in various stages of the event: pre-event, during the event, and post-event, and to describe the scope of literature. The model also shows how these strategies are related, and are supporting each other to achieve the goal of preventing infectious diseases during the three stages of the event. In addition, the model reflects on how these strategies are impeded in different three contexts that would support their implementation, monitoring, and evaluation. These contexts are the public social responsibility, preparedness of the health care system, and the regulations/policy/guidelines of public health authorities and their partners (see Figure 2).

It is recommended that tourists have a pre-travel consultation before traveling to consider suitable health and safety precautions, including vaccination. Since COVID-19 is still not over and there is a concern of emergence of new strains of SARS-CoV-2 virus, it is recommended that athletes, visitors, and citizens get the full vaccinations; provide them with a passport containing information about previous infections, results, testing, and vaccination status; and provide free rapid test centers for fans near each stadium, as well as directly matching these results in the spectators' passport. Authorities need to have an agreed preparedness plan, strengthen health emergency preparedness, and ensure the maintenance of precautionary measures for containing infectious diseases including COVID-19. Hospitals should be assessed with adequate workforce, providing appropriate training for the medical staff, and having multilingual services to address the language barrier are also essential. Event organizers should agree with the public health authority on how participants and the local people will be kept informed about the health situation, key developments, and any relevant recommended actions. Following these strategies would enhance the effective implementation of the other precautions during and after the effect.

Public health authorities and their partners authorities are advised to follow critical proposed recommendations, including implementation of the syndromic surveillance systems, or enhancing surveillance systems, disseminating public health messages specific to infectious diseases, and educating participants on prevention measures of these diseases. The public plays a vital role in mitigating any pandemic. Hence, enhancing social responsibility is a key to prevent outbreaks or combat the virus during events with mass gatherings. Low et al. illustrates that individuals' social responsibility actions are a result of the interaction between perceived infection risk and societal role responsibility. Public perception is critical in improving health risk communication, fostering public trust, and collaborating with the government's outbreak prevention efforts. Members of society can be empowered through organizations emphasizing their roles during the epidemic and recommend certain actions.

4.2. Implications for future research

This study will serve as a roadmap for preparedness for mega sports events in order to prevent infectious disease outbreaks. Our review reflects on a clear gap in quantitative evidence and highlights the need to conduct the quantitative assessment during the different stages of the event. Further observational research on post-sports mass gatherings is needed to explore various prevention strategies that should be implemented for this stage. In addition, it would be remarkably interesting to conduct qualitative research to study the perception of the public the World Cup hosting countries on social responsibility toward the World Cup, which may help improve future prevention and control efforts.

4.3. Strengths and limitations

This scoping review is the first to explore COVID-19 recommendations in the setting of the FIFA World Cup. The review includes a comprehensive search strategy and the most recent compilation of relevant up-to-date data from 2010 to January 24, 2022. There were no restrictions put on the study design, allowing for a broad exploration of peer-reviewed articles. This scoping review, however, has some limitations. A major limitation of this review is that the majority of the included studies are reviews and qualitative research, which reduces the quality of the evidence provided. Evidence of quantitative assessment is lacking in this scoping review and the quantitative contributions of the proposed specific recommendations in the prevention and control of infectious diseases cannot be certified, thus this is an urgent call for conducting quantitative research to provide evidence for effective planning for these events.

The included articles were not checked for validity in line with the scoping analysis approach, which is a less relevant method in scoping reviews. Furthermore, by excluding gray literature and non-English language literature, some bias may have been introduced.

5. Conclusion

The current scoping review identified a variety of studies and review articles that emphasize key findings, in order to develop a mitigation strategy for dealing with COVID-19 and other infectious diseases within the context of the FIFA World Cup The risk of COVID-19 infection and other infections among spectators at mass gathering events was reported. This review provides fundamental pre, during post-event recommendations to narrow and ideally achieve a "virus-free" event. The constructed model is reflecting on the importance of the involvement and empowerment of the public by enhancing their social responsibility and the coordination between the healthcare system, the ministry of public health, and other stakeholders for infectious disease prevention during the FIFA World Cup.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

NA, GA-J, and UE participated in creating the research questions, conceptualizing the idea of the project, building the search strategy, selecting studies, extracting data, analyzing data, and drafting and editing the manuscript. NH, MN, and MA participated in the data analysis, drafting, and editing the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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COVID-19 in Ontario Long-term Care Facilities Project, a manually curated and validated database

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KEYWORDS

COVID-19, long-term care facilities, database, Ontario—Canada, manually curated and validated database

Background and summary

In late December 2019, a novel, emerging coronavirus, termed as "Severe Acute Respiratory Syndrome-related Coronavirus Type 2" (SARS-CoV-2) was identified as the infectious agent responsible for the generally mild, but sometimes life-threatening and even fatal "Coronavirus Disease 2019" (COVID-19).

As of December 7, 2021, COVID-19 has imposed a dramatic toll of infections (more than 265 million cases) and deaths (more than 2.5 million deaths).

Long-term care facilities, including nursing homes, residential aged care facilities, retirement homes, skilled nursing facilities and assisted living communities, among others, have represented and still represent healthcare settings particularly vulnerable to the COVID-19 spread (1). For instance, in Canada, residents living in these facilities, being elderly and particularly frail, often with many co-morbidities, have been disproportionately hit by the pandemic, contributing to approximately two thirds (67%) of the entire total toll of deaths (2).

As of December 5, 2021, 11.8% and 7.0% of COVID-19 outbreaks occurred in the Ontario region have affected long-term care facilities and retirement homes, respectively, according to Public Health Ontario (PHO).

A recently published systematic review (3) has identified an array of parameters, including bed size and location in a high SARS-CoV-2 prevalence and mortality area, and number of staff members, as variables predicting COVID-19 related outcomes.

However, in some cases, findings were contrasting, with a number of studies reporting that higher staffing was associated with a higher mortality rate and other investigations obtaining opposite results. Discrepancies in both the direction and magnitude of the effect could be found also for other parameters, such as quality indicators, like star rating, and ownership, or pandemic preparedness indicators, including implementation of public health interventions for controlling and managing prior infections and the number of previous outbreaks occurred in the facility.

Such conflicting findings may depend on the specific nature of the jurisdiction and the setting of each long-term care facility. As such, local data is of paramount importance to inform public health workers, policy- and decision-makers and relevant stakeholders in a data-driven and evidence-based fashion.

Several databases exist, mainly dedicated to (non-pharmaceutical and pharmaceutical) public health interventions (4, 5), underlying biological mechanisms, in terms of pathways and cascades (6), but, to the best of authors' knowledge, no one specifically on long-term care facilities. Specifically, there are websites that provide information for each long-term care home in Ontario such as the location of the home, type of facility, and general statistics pertaining to the care offered. However, the information is limited as the focus of this data is to provide guidance for people looking to send their loved ones to a long-term care home to assist with their daily needs. In contrast, British Columbia has one comprehensive resource curated by Seniors Advocate BC that is sponsored by the province of British Columbia called the Long-Term Care Facilities Quick Facts Directory (7). It contains detailed information regarding the facility, rooms, funding, care offered (e.g., direct care hours), licensing, incidents, resident profiles, and vaccine coverage that is specific to each long-term care home. Since this information is compiled into one reliable resource, it makes it possible for relevant information to be quickly accessed and analyzed. In Ontario, no such counterpart was found. Further, it was difficult to access relevant data that was directly available online. The only publicly available data pertaining to long-term care homes offered by the Ministry of Long-Term Care is data regarding the long-term care home location and data for publicly reported COVID-19 cases (MLTC datasets) (8). The present database was devised and implemented to fill in this gap.

Methods

The dataset consists of 74 variables collated from over 30 sources verified by the Ontario Ministry of Health. The data was collected and compiled using a ranked source approach where original documents pertaining to each long-term care home, such as accountability agreements, were prioritized. For long-term care homes where the individual documents could not be located, sources such as The Healthline (thehealthline.ca) (9), that include annual reviews, were used. This ensured that the relevant data for each long-term care home that was available in one database but not another could be compiled into one collective dataset. The major data sources used include Long-Term Care Home Service Accountability Agreements (L-SAA) found on the LHIN websites, Ministry of Long-Term Care Inspection Reports (10), CIHI Your Health System (11), HQ Ontario Long-Term Care Performance (12), The Healthline (9), AdvantAge Ontario (13), Ontario Health Coalition (14), and Toronto Star (15). After reviewing literature to determine the relevant variables and based on available systematic reviews and published evidence (2), data regarding resident demographics, facility characteristics, region classifications, and COVID-19 cases and deaths were collected.

Review of comparable datasets

Before beginning the collecting process, available data was reviewed and representatives of the Ministry of Long-Term Care and individual long-term care homes were contacted. The existing data publicly available online for Ontario was found to be limited in information, not as extensive as the data available in other provinces, or focusing on an overall region rather than being specific to each long-term care home.

After reaching out to the Ministry of Long-Term Care, it was found that in order to get more data, each long-term care home must be contacted. As a result, 364 homes were contacted with a response rate of 5.62% of homes that agreed to provide the necessary information for the research. Due to the low response rate, the focus of curating data shifted solely toward collecting and compiling data that was found online. It was found that different organizations, such as HQ Ontario, the Healthline, AdvantAge Ontario, and Ontario Health Coalition had collected data regarding a specific aspect of long-term care homes such as facility performance indicators, room classifications, case mix index (CMI), or bed classifications, respectively. Therefore, one of the aims of the dataset was to combine all the information into one complete dataset that can be accessed in one place.

All of the long-term care homes in Ontario are classified under the 14 Local Health Integrated Networks, or LHINs, that are responsible for overseeing the operation of the homes. After contacting the LHINs and examining their websites, it was found that they provided publicly available Long-Term Care Home Service Accountability Agreements (explained in Data Collection Process). By individually analyzing each accountability agreement for the 627 long-term care homes, it was possible to extract information such as number and type of classification beds, construction dates of the homes, and if the home was accredited. The variables are available in Schedule A of the agreement, under the heading "Description of Home and Beds." This information was not observed to be present in currently available datasets.

The Ministry of Health and Long-Term Care maintains a website containing all the reports conducted in long-term care homes (Reports on Long-Term Care Homes) (10). The website contains all of the inspections done in the home and the inspector's reports. This resource was looked at from the perspective of aiding research pertaining to the impact of COVID-19 on long-term care home residents. As a result, information for inspections related to Sufficient Staffing, Infection Prevention and Control, and Orientation and Training was extracted and compiled. By quantifying qualitative data, it became possible to utilize the data for research that requires observing and analyzing trends. The process required reading through over 2,000 inspection reports that were written for inspections conducted in 2019 and 2020 and were classified under Complaints or Critical Incident Inspections. An extraction of data from the long-term care home reports to advance research pertaining to the COVID-19 pandemic and long-term care homes in Ontario does not seem to have been completed before.

Data collection process

The process adopted to systematically identify, collate and compile data sources is pictorially shown in Figure 1. Data collected on resident demographics, long-term care facility characteristics and quality of care indicators was compiled from CIHI Your Health System (www.yourhealthsystem.cihi.ca) (11) and HQ Ontario Long-Term Care Performance (http://www.hqontario.ca) (12). AdvantAge Ontario and Ontario Health Coalition contained datasets pertaining to Case Mix Index (CMI) and classification of the long-term care home beds, respectively. For the CIHI Your Health data, explanation of the measures can be found in their Technical Notes for Contextual Measures (PDF) (16). Most notably, for the variable "Long-Term Care Facility Location," the designation as rural or urban is dependent on the facility's statistical area classification. Second, the facility size classification has three possibilities: small, medium, and large. Small is designated by facilities with 1–29 beds, medium as facilities with 30–99 beds and large facilities have 100 or more beds. This classification can also be adjusted and eventually be re-categorized by the researcher as the total

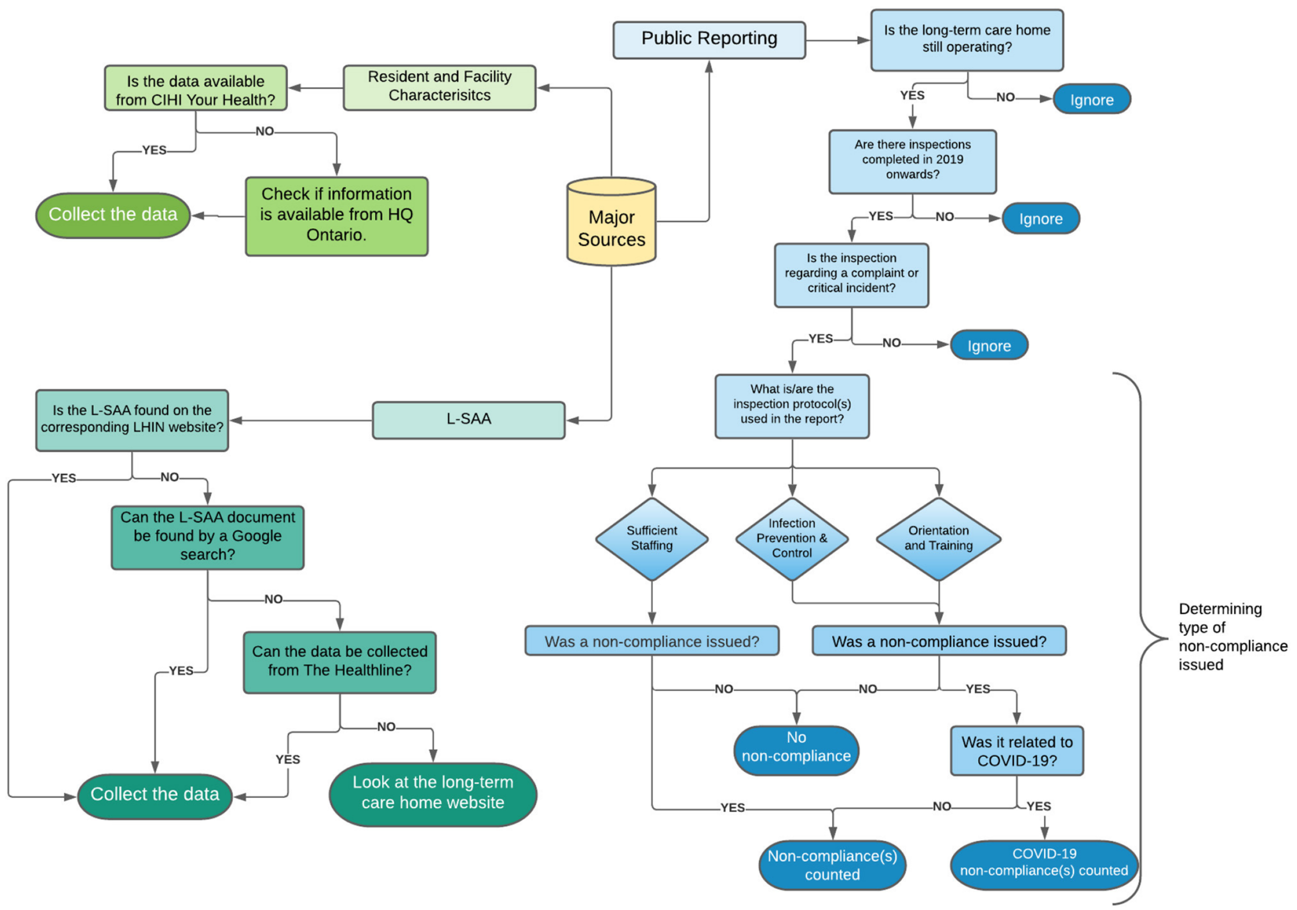

FIGURE 1
Overview of data collection process. The flow-chart pictorially represents the process by which data sources were identified, collated and compiled within a single, comprehensive manually curated and validated database. The Public Reporting steps correspond to the website titled "Reports on Long-Term Care Homes" which is maintained by the Ministry of Health and Long-Term Care. The process outlined describes the classification of each report as it pertains to sufficient staffing (SS), Infection Prevention and Control (IPAC), and Orientation and Training (OAT). Data from the Long-Term Care Home Service Accountability Agreements (L-SAA) was collected from the Local Health Integration Network (LHIN) website, by a Google search, The Healthline, or the individual website of the home. Data pertaining to resident and facility characteristics were collected through CIHI Your Health system and HQ Ontario.

number of beds in each long-term care home are provided in the dataset.

Long-Term Care Home Service Accountability Agreements (L-SAA) are service accountability agreements between the Local Health Integration Network (LHIN) and the Long-Term Care Home that falls within that region. It is a yearly agreement that outlines the operations of the long-term care home in order for the LHIN to continue to provide funding. Of particular interest was Schedule A of the agreement which outlined factors such as accreditation of the home, classification of licensed beds, and information regarding the home's construction. The agreement for the homes was found on their respective LHIN's website, analyzed, and the relevant information was extracted. Priority was given to the latest agreements, such as 2019–2020, to reflect and include contemporary data. Some accountability agreements were not found on the LHIN websites or were named under another long-term care home. In that case, a Google search was performed by searching the name of the long-term care home and typing "L-SAA filetype:pdf" to directly locate the agreement pdf from the internet. For the agreements that could not be located on the websites, an alternative source was used. The Healthline (thehealthline.ca) (9) provides information on local health services in Ontario, is reviewed annually, and contains service profiles created by the LHINs. Lastly, if specific information was not found through the agreements or the Healthline, then the long-term care home websites were analyzed for the data. By having a systematic approach of prioritizing agreements, then the Healthline, then the long-term care home websites, consistency and reliability of the data was ensured.

In 2018, the long-term care home sector underwent a transition from comprehensive, annual inspections to issue-specific inspections with a focus on complaints and critical incidents. Resident Quality Inspections (RQIs) are considered a comprehensive inspection of the home, and, after 2018, there were only nine conducted in Ontario (17). Of the different types of inspections, data for complaints, critical incidents, and resident quality inspections was collected. Further, the inspection reports for long-term care homes in Ontario, part of the Ministry of Long-Term Care, were screened to identify if an inspection was completed relating to "Sufficient Staffing," "Infection Prevention and Control (IPAC)," or "Orientation and Training (OAT)" and if the inspection resulted in a non-compliance issued for the long-term care home. IPAC and OAT inspections were further divided into general non-compliance(s) and COVID-19 related non-compliance(s).

Standards for inclusion

The sources deemed to be eligible were restricted to websites created or approved by the Ministry of Health and Long-Term Care. The aim was to collect reliable and validated data relevant to explaining the effects of COVID-19 on the number of long-term care home resident cases and deaths. As a result, some variables such as wait-times for the long-term care homes and avoidable emergency department visits, were omitted. However, since all the sources are provided within the dataset, it is possible to easily access them, saving time.

For the inspection reports, standards for inclusion consisted of keywords that determined if an inspection will count as a relevant non-compliance or not. First, all the reports were screened to determine if an inspection for "Sufficient Staffing," "Infection Prevention and Control," (IPAC) or "Orientation and Training" occurred. Since all inspections cite the Long-Term Care Homes Act of 2007, failure to comply by the standards falling under 2007 S.O. 2007, c.8, s. 8 (Nursing and personal support services) was recorded in order to have an objective criteria for the sufficient staffing category. For IPAC, a non-compliance was recorded if the home failed to comply with O.Reg 79/10, s. 229 of the Act. Further, it was identified as a COVID-19 related non-compliance if the report stated that the licensee failed to follow the directives, such as Directive #3, given by the government in 2020. For OAT, a non-compliance was recorded if the home failed to train their staff on infection prevention and control measures or if the licensee failed to keep their staff up-to-date with specific COVID-19 procedures. To help with the search process, relevant keywords such as "staffing mix," "fewer than the scheduled staffing complement," or "short-staffed" were searched for since this meant that the required number of staff, such as Personal Support Workers or Registered Nurses, were not present at all times. However, since not all reports included the keywords, all of the documents were manually screened for compliance or non-compliance to each of the policies to ensure accurate reporting. Additionally the source had inspection profiles for 653 homes. Since some of the homes were closed down or not operating in 2019 or later, they were excluded from the dataset. In the end, the data was collected for 627 homes.

Usage notes

The COVID-19 pandemic is still ongoing and is still disproportionately affecting long-term care facilities. Within the COVID-19 in Ontario Long-term Care Facilities Project, a manually curated and validated database with over 70 relevant variables from over 30 sources was devised and implemented. This verified database is shared for any data mining effort, to test hypotheses or generate new ones about the determinants and predictors of outbreaks occurred in long-term care facilities. The structure of the database has been designed for use by biomedical, biomathematical and social scientists, to ensure broad accessibility to public health workers, decision- and policy-makers and other relevant stakeholders, (re-)use of data and high methodological transparency and reproducibility.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author. The database can be accessed at https://tinyurl.com/27zke95t.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JDK designed the research. MK conducted literature search and data collection. All authors analyzed data and wrote the paper.

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Conflict of interest

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Predisposing factors for admission to intensive care units of patients with COVID-19 infection—Results of the German nationwide inpatient sample

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Background: Intensive care units (ICU) capacities are one of the most critical determinants in health-care management of the COVID-19 pandemic. Therefore, we aimed to analyze the ICU-admission and case-fatality rate as well as characteristics and outcomes of patient admitted to ICU in order to identify predictors and associated conditions for worsening and case-fatality in this critical ill patient-group.

Methods: We used the German nationwide inpatient sample to analyze all hospitalized patients with confirmed COVID-19 diagnosis in Germany between January and December 2020. All hospitalized patients with confirmed COVID-19 infection during the year 2020 were included in the present study and were stratified according ICU-admission.

Results: Overall, 176,137 hospitalizations of patients with COVID-19-infection (52.3% males; 53.6% aged ≥70 years) were reported in Germany during 2020. Among them, 27,053 (15.4%) were treated in ICU. COVID-19-patients treated on ICU were younger [70.0 (interquartile range (IQR) 59.0–79.0) vs. 72.0 (IQR 55.0–82.0) years, $P < 0.001$], more often males (66.3 vs. 48.8%, $P < 0.001$), had more frequently cardiovascular diseases (CVD) and cardiovascular risk-factors with increased in-hospital case-fatality (38.4 vs. 14.2%, $P < 0.001$). ICU-admission was independently associated with in-hospital death [OR 5.49 (95% CI 5.30–5.68), $P < 0.001$]. Male sex [OR 1.96 (95% CI 1.90–2.01), $P < 0.001$], obesity [OR 2.20 (95% CI 2.10–2.31), $P < 0.001$], diabetes mellitus [OR 1.48 (95% CI 1.44–1.53), $P < 0.001$], atrial fibrillation/flutter [OR 1.57 (95% CI 1.51–1.62), $P < 0.001$], and heart failure [OR 1.72 (95% CI 1.66–1.78), $P < 0.001$] were independently associated with ICU-admission.

Conclusion: During 2020, 15.4% of the hospitalized COVID-19-patients were treated on ICUs with high case-fatality. Male sex, CVD and cardiovascular risk-factors were independent risk-factors for ICU admission.

KEYWORDS

COVID-19, SARS-CoV-2, healthcare resources, intensive care unit (ICU), mortality, case-fatality

Introduction

During December 2019 first pneumonia cases of unknown origin were detected in China. The causative pathogen was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1, 2). Patients with SARS-CoV-2 infections, also shortly named as coronavirus disease 2019 (COVID-19), presented in in- and outpatient settings (1, 3). First COVID-19 cases in Germany were detected at the end of January 2020 in Bavaria (3, 4) and a strong and fast spread from this initial cluster in the German population was observed (3, 5). This spread of SARS-CoV-2 infections was accompanied by a previously unprecedented strain on healthcare systems worldwide (6).

In the first wave of the disease in 2020, the German healthcare system had the advantage that several European countries faced this strain some weeks before. Thus, German hospitals were in part able to benefit from experiences made in other healthcare systems in terms of risk stratification for outpatient care, hospital and ICU admissions. Nevertheless, in the early phase of the COVID-19-pandemic, decisions for risk stratification and ICU admission of COVID-19-patients were primarily based on physicians' experience regarding health care management of critical care and the unsorted reports of colleagues all over the world in the light of pending study results.

In previously published studies analyzing also the German nationwide inpatient sample, we have shown that the in-hospital case-fatality rate of hospitalized patients with confirmed COVID-19-infection was ~18% in Germany during the year 2020 (3, 7) and the case-fatality rate increased dramatically if treatment on intensive care units (ICU) and/or mechanical ventilation were needed (3, 7–9). Since a large number of patients with severe respiratory and cardiovascular complications of COVID-19-infection had to be treated on ICU, in some areas, ICUs were completely overloaded (3, 6, 7, 10, 11). Thus, ICU has to be considered as a bottleneck regarding health care planning and threatening critical overload of the national healthcare systems (3, 6–11). ICU availability, admission policy and health care structure vary across Europe as additionally the demographics and government-policies do (3, 6).

Beside the previously published results, it is of outstanding interest to understand determinants of ICU admission and outcome, which are both crucial factors for adequate health care planning, decision making and pandemic management (3, 6). Therefore, we aimed to analyze the ICU admission and case-fatality rate in Germany and to identify characteristics and outcomes of patient admitted to ICU in order to identify predictors and associated conditions for worsening and case-fatality for this critical ill patients' group.

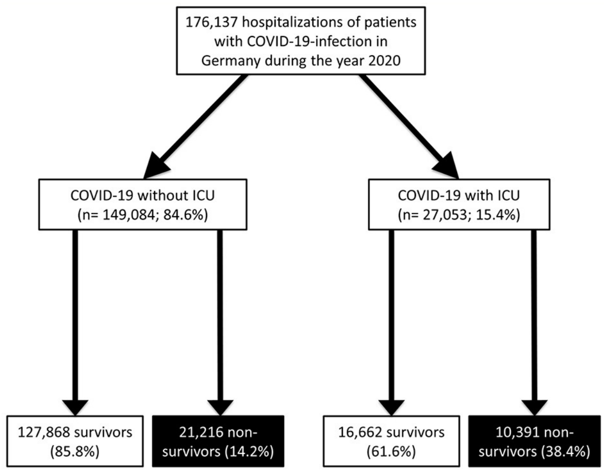

FIGURE 1
Flow-chart. COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Methods

Data source

The Research Data Center (RDC) of the Federal Bureau of Statistics (Wiesbaden, Germany) calculated the statistical analyses and provided aggregated statistic-results on the basis of our SPSS codes (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA), which were previously supplied by us to the RDC (source: RDC of the Federal Statistical Office and the Statistical Offices of the federal states, DRG Statistics 2020, own calculations) (12, 13).

With this computed analysis of the German nationwide inpatient sample, we aimed to analyze temporal trends of all hospitalized patients with a confirmed COVID-19 diagnosis. All patients, who were treated in German hospitals with a COVID-19 infection confirmed by a laboratory test (ICD-code U07.1) during the observational period between January 1st and December 31st of the year 2020 were included in the present study. The COVID-19 patients were stratified for ICU treatment and we identified independent predictors of ICU admission during hospitalization (Figure 1).

Study oversight and support

Since in the present study the investigators did not accessed directly individual patient data but only summarized results provided by the RDC, approval by an ethics committee as well as patients' informed consent were not required, in accordance with German law (12, 13).

Coding of diagnoses, procedures, and definitions

After introduction of a diagnosis- and procedure-related remuneration system in Germany in the year 2004, coding according the German Diagnosis Related Groups (G-DRG) system with coding of patient data on diagnoses, coexisting conditions, and on surgeries/procedures/interventions and transferring these data/codes to the Institute for the Hospital Remuneration System is mandatory for German hospitals to get their remuneration (10, 11). Therefore, patients' diagnoses are coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, with German modification (ICD-10-GM) (10, 11). In addition, surgical/diagnostic/interventional procedures are coded according to OPS-codes (Operationen- und Prozedurenschlüssel). In our present of the German nationwide inpatient sample, we were able to identify all hospitalized patients with a confirmed COVID-19 diagnosis (ICD-code U07.1) in Germany during the year 2020 (COVID-19 as main or secondary diagnosis).

Post-COVID-19 was defined as a status of previous survived COVID-19-infection before the patient's hospitalization with the actual COVID-19 infection.

Study outcomes

Primary study endpoint was admission on ICU. In addition, we analyzed occurrence of all-cause in-hospital death and the prevalence of major adverse cardiovascular and cerebrovascular events [MACCE, composite of all-cause in-hospital death, acute myocardial infarction (ICD-code I21), and/or ischemic stroke (ICD-code I63)].

Furthermore, we analyzed the occurrence of the aggravated respiratory manifestations pneumonia (ICD codes J12-J18) and acute respiratory distress syndrome (ARDS, ICD code J80) as well as other adverse events during hospitalization such as cardio-pulmonary resuscitation (OPS-code 8-77), venous thromboembolism (ICD codes I26, I80, I81, and I82), acute kidney failure (ICD-code N17), myocarditis (ICD code I40), myocardial infarction (acute and recurrent, ICD codes I21 and I22), stroke (ischemic or hemorrhagic, ICD codes I61-I64), intracerebral bleeding (ICD code I61), gastro-intestinal bleeding (ICD code K92.0, K92.1, and K92.2) and transfusion of blood constituents (OPS code 8-800). The outcomes were defined according current guidelines (14–23). The acute respiratory distress syndrome (ARDS) was defined in 1994 by the American-European Consensus Conference (AECC) and revised in 2011 with the Berlin Definition (15).

Statistical analysis

Differences in patient characteristics between the groups of hospitalized COVID-19-patients with ICU treatment vs. without ICU treatment were calculated with Wilcoxon-Whitney *U*-test for continuous variables and Fisher's exact or chi^2-test for categorical variables, as appropriate. Temporal trends regarding hospitalizations of COVID-19-patients with ICU treatment and in-hospital mortality over time and as well as trend-changes with increasing age were estimated by means of linear regression analyses. Results were presented as β-estimates and 95% confidence intervals (CI). Logistic regression models were calculated to investigate associations between (I) patients' characteristics and ICU-admission as well as (II) associations between adverse events and ICU-admission. Furthermore, we calculated logistic regression models to analyse (III) the associations of patients' characteristics and in-hospital death in ICU-patients as well as (IV) the associations of adverse events during in-hospital course and in-hospital death in ICU-patients. In order to warrant that the results of the mentioned logistic regressions are not substantially biased by other influencing factors and therefore, guarantying a widely independence of important different cofactors during hospitalization, the multivariable logistic regressions were adjusted for age, sex, diabetes mellitus, cancer, heart failure, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m^2), atrial fibrillation/flutter, hyperlipidemia, and obesity.

Results were presented as Odds Ratios (OR) and 95% CI. All statistical analyses were carried out with the use of SPSS software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. IBM Corp: Armonk, NY, USA). Only two-sided P-values $<$ 0.05 were considered to be statistically significant. No adjustment for multiple testing was applied.

Results

Baseline characteristics

During the year 2020, 176,137 hospitalizations (52.3% males; 53.6% aged 70 years or older) of patients with confirmed COVID-19-infection were reported in German hospitals. Of these inpatients, 27,053 (15.4%) were admitted to ICU, while overall, 31,607 (17.9%) died during hospitalization (Figure 1). ICU admission in COVID-19 patients was associated with increased case-fatality [univariate regression: OR 3.76 (95% CI 3.65–3.87), $P < 0.001$; multivariate regression: OR 5.49 (95% CI 5.30–5.68), $P < 0.001$].

The monthly percentage of COVID-19 patients admitted to ICUs of German hospitals decreased over time from 32.8% in January 2020 to a minimum of 14.8% in November 2020 [β −0.89 (95% CI −0.93 to −0.85), $P < 0.001$], while highest absolute numbers of total ICU admissions were observed in spring and winter of the year 2020 (Figure 2A). ICU admissions related to all COVID-19 hospitalizations increased with inclining age [β 0.11 (95% CI 0.09–0.14), $P < 0.001$] with a maximum in the 8th decade of life (27.8%; Figure 2B).

Comparison of COVID-19-patients admitted to ICU vs. those without ICU treatment

As aforementioned, ∼15% of the hospitalized patients with COVID-19 in Germany were admitted to ICUs who were in median 2 years younger [70.0 (Interquartile range (IQR) 59.0–79.0) vs. 72.0 (IQR 55.0–82.0) years, $P < 0.001$] and more often of male sex (66.3 vs. 48.8%, $P < 0.001$) compared to those hospitalized, but treated outside the ICU (Table 1). COVID-19 patients admitted to ICU had more frequently cardiovascular risk factors (CVRF) and cardiovascular diseases (CVD) as well as lung and kidney diseases than those without ICU-treatment resulting in higher Charlson comorbidity index in ICU treated patients [5.0 (IQR 3.0–7.0) vs. 4.0 (IQR 1.0–6.0), $P < 0.001$; Table 1]. As expected, the aggravated respiratory manifestations of COVID-19-infections such as pneumonia (89.2 vs. 55.5%, $P < 0.001$) and acute respiratory distress syndrome (ARDS, 35.4 vs. 1.4%, $P < 0.001$) were more frequently found in patients, who were in need of intensive care treatment (Table 1).

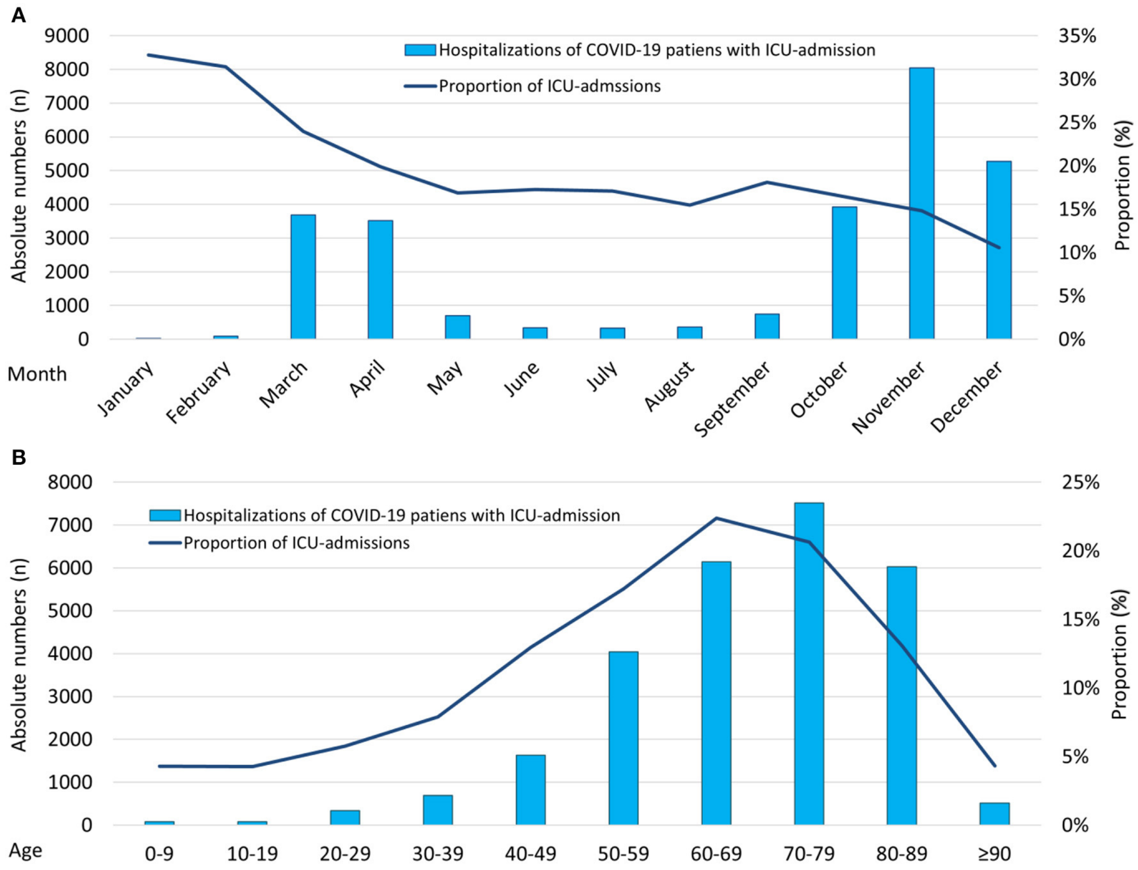

FIGURE 2
Temporal trends regarding total numbers of patients with COVID-19-infection admitted to ICU. **(A)** Temporal trends regarding total numbers of hospitalized patients with COVID-19-infection admitted to ICU (absolute numbers: blue bars; relative numbers: blue line) stratified for months. **(B)** Temporal trends regarding total numbers of hospitalized patients with COVID-19-infection admitted to ICU (absolute numbers: blue bars; relative numbers: blue line) stratified for age decades. COVID-19, coronavirus disease 2019; ICU, intensive care unit.

Outcomes of COVID-19-patients admitted to ICU vs. those without ICU treatment

MACCE (41.9 vs. 15.9%, $P < 0.001$) and in-hospital case-fatality (38.4 vs. 14.2%, $P < 0.001$) rates were substantially higher in patients with COVID-19-infection treated in ICU than in those without ICU treatment (Table 1). ICU treatment was independently associated with increased in-hospital case-fatality rate [OR 5.49 (95% CI 5.30–5.68), $P < 0.001$].

It has to be pointed out that the in-hospital case-fatality rate of COVID-19 patients on ICU was highest in months with high numbers of ICU admissions of COVID-19 patients (Figure 3A). In addition, the case-fatality rate of COVID-19 patients treated on German ICUs increased substantially with patients age (Figure 3C). Highest proportion of ARDS cases were observed in the initial phase of the pandemic during spring 2020 (March-April) and in the 6st to 8th decade of patients' life (Figures 3B, D).

The rates of the following acute organ failures were increased in ICU patients: the rate of myocardial infarction was nearby 4-fold, whereas the rate of myocarditis was 3-fold increased and the stroke rate more than doubled in patients treated on ICU. While the rate of sepsis was more than doubled, occurrence of encephalitis was 7-fold increased and that of severe liver disease was nearby 5-fold inclined. Additionally, all investigated bleeding events and need for transfusion of blood constituents occurred significantly more often in ICU admitted patients (Table 1). Beside the bleeding events, the rate of venous thromboembolism was also more than 3-fold higher in ICU patients. Furthermore, the risk for acute kidney injury was more than 4-fold higher and, consequentially, dialysis was 15-fold more often performed in patients with COVID-19-infection treated on ICU (Table 1).

Predictors of ICU admission of COVID-19-patients

Male sex [OR 1.96 (95% CI 1.90–2.01), $P < 0.001$] and age younger than 70 years [OR 1.47 (95% CI 1.43–1.52), $P < 0.001$] were independent risk factors of ICU admission (Table 2).

Regarding CVRF, obesity [OR 2.20 (95% CI 2.10–2.31), $P < 0.001$] as well as diabetes mellitus [OR 1.48 (95% CI 1.44–1.53), $P < 0.001$] were independent predictors of an increased need of ICU treatment (Table 2).

Interestingly, the association of atrial fibrillation/flutter as well as heart failure with ICU treatment were stronger than that of coronary artery disease and chronic obstructive pulmonary disease, which were also associated with ICU admission (Table 2).

TABLE 1 Patients' characteristics, medical history, presentation, and adverse in-hospital events of the 176,137 hospitalized patients with confirmed COVID-19 infection in Germany in the year 2020 stratified for ICU treatment.

Parameters	COVID-19 without ICU (n = 149,084; 84.6%)	COVID-19 with ICU (n = 27,053; 15.4%)	P-value
Age	72.0 (55.0 / 82.0)	70.0 (59.0 / 79.0)	**<0.001**
Age ≥70 years	80,277 (53.8%)	14,052 (51.9%)	**<0.001**
Female sex	74,834 (50.2%)	9,115 (33.7%)	**<0.001**
In-hospital stay (days)	7.0 (3.0 / 12.0)	16.0 (9.0 / 26.0)	**<0.001**
Cardiovascular risk factors			
Obesity	6,557 (4.4%)	2,826 (10.4%)	**<0.001**
Diabetes mellitus	35,581 (23.9%)	9,651 (35.7%)	**<0.001**
Essential arterial hypertension	68,080 (45.7%)	14,400 (53.2%)	**<0.001**
Hyperlipidemia	22,651 (15.2%)	4,922 (18.2%)	**<0.001**
Comorbidities			
Coronary artery disease	20,174 (13.5%)	5,400 (20.0%)	**<0.001**
Heart failure	20,521 (13.8%)	6,598 (24.4%)	**<0.001**
Peripheral artery disease	4,398 (3.0%)	1,242 (4.6%)	**<0.001**
Atrial fibrillation/flutter	26,478 (17.8%)	7,682 (28.4%)	**<0.001**
Chronic obstructive pulmonary disease	9,486 (6.4%)	2,668 (9.9%)	**<0.001**
Chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²)	22,494 (15.1%)	4,878 (18.0%)	**<0.001**
Cancer	7,416 (5.0%)	1,585 (5.9%)	**<0.001**
Vasculopathy	218 (0.1%)	112 (0.4%)	**<0.001**
Charlson comorbidity index	4.0 (1.0 / 6.0)	5.0 (3.0 / 7.0)	**<0.001**
Respiratory manifestations of COVID-19			
Pneumonia	82,784 (55.5%)	24,129 (89.2%)	**<0.001**
Acute respiratory distress syndrome	2,025 (1.4%)	9,569 (35.4%)	**<0.001**
Markers of acute organ failure			
Sepsis	9,423 (6.3%)	4,042 (14.9%)	**<0.001**
Encephalitis	14 (0.01%)	20 (0.07%)	**<0.001**
Mild liver disease	1,267 (0.8%)	378 (1.4%)	**<0.001**
Severe liver disease	2,216 (1.5%)	1,923 (7.1%)	**<0.001**
Mechanical ventilation	2,720 (1.8%)	9,422 (34.8%)	**<0.001**
Extracorporeal membrane oxygenation (ECMO)	65 (0.04%)	1,389 (5.1%)	**<0.001**
Proteinuria	93 (0.1%)	42 (0.2%)	**<0.001**
Dialysis	1,522 (1.0%)	4,053 (15.0%)	**<0.001**
Adverse events during hospitalization			
In-hospital case-fatality	21,216 (14.2%)	10,391 (38.4%)	**<0.001**
MACCE	23,696 (15.9%)	11,328 (41.9%)	**<0.001**
Cardio-pulmonary resuscitation	1,099 (0.7%)	1,760 (6.5%)	**<0.001**
Venous thromboembolism (VTE)	2,992 (2.0%)	1,995 (7.4%)	**<0.001**
Acute kidney failure	12,144 (8.1%)	9,931 (36.7%)	**<0.001**
Myocarditis	126 (0.1%)	100 (0.4%)	**<0.001**
Myocardial infarction	1,624 (1.1%)	1,129 (4.2%)	**<0.001**
Stroke (ischemic or hemorrhagic)	2,206 (1.5%)	990 (3.7%)	**<0.001**
Intracerebral bleeding	279 (0.2%)	297 (1.1%)	**<0.001**
Gastro-intestinal bleeding	2,133 (1.4%)	815 (3.0%)	**<0.001**
Transfusion of blood constituents	5,906 (4.0%)	7,968 (29.5%)	**<0.001**

COVID-19, coronavirus disease 2019; ICU, intensive care unit; VTE, venous thrombo-embolism; MACCE, major adverse cardiovascular and cerebrovascular events; ARDS, acute respiratory distress syndrome.
P-values < 0.05 were considered to be statistically significant.

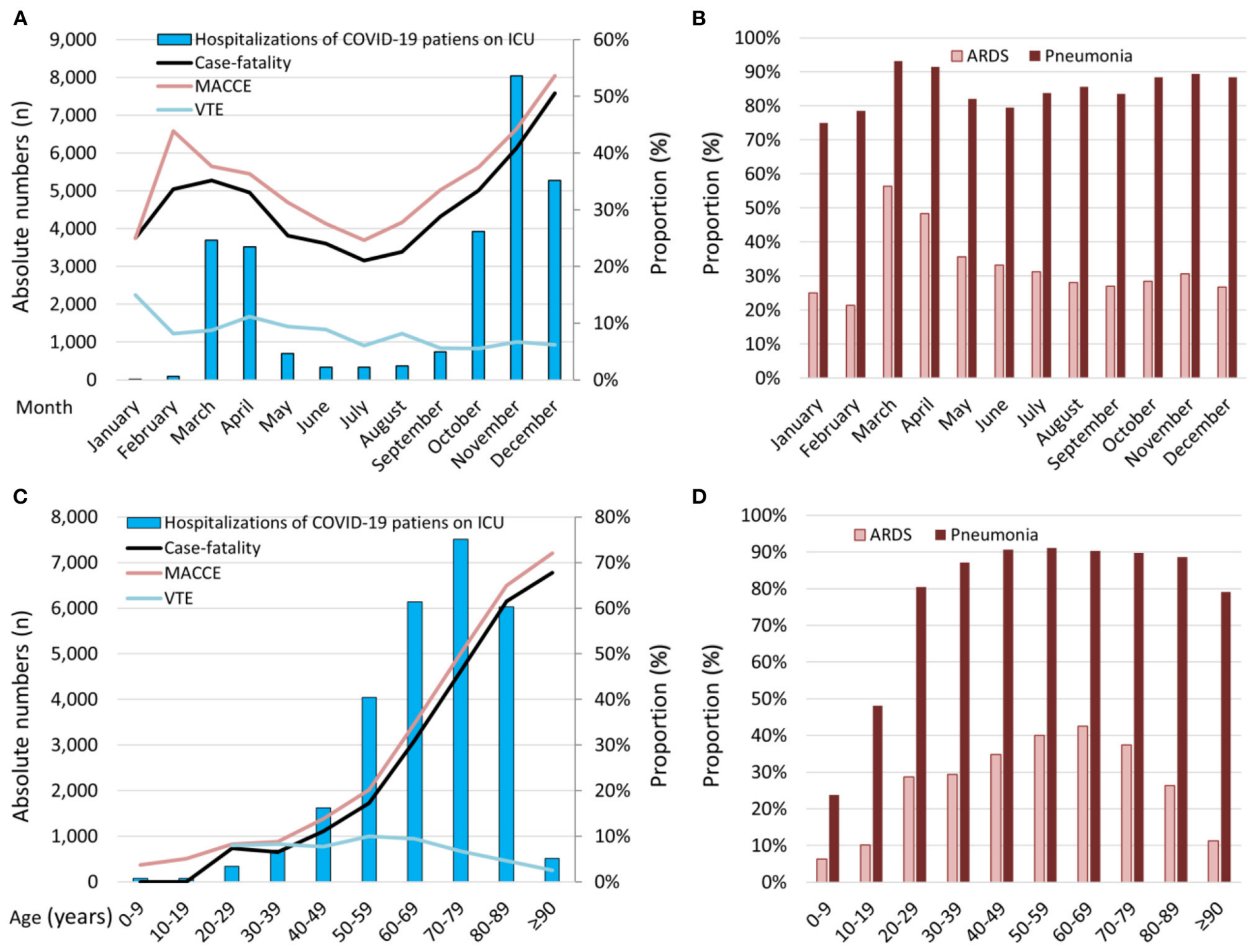

FIGURE 3
Temporal trends regarding total numbers of patients with COVID-19-infection admitted to ICU, in-hospital case-fatality, MACCE, and VTE rate. **(A)** Temporal trends regarding total numbers of patients with COVID-19-infection admitted to ICU (absolute numbers: blue bars) and rates of case-fatality, MACCE, and VTE stratified for months (lines). **(B)** Temporal trends regarding proportion of ARDS and pneumonia in patients with COVID-19-infection admitted to ICU stratified for months. **(C)** Temporal trends regarding total numbers of patients with COVID-19-infection admitted to ICU (absolute numbers: blue bars) and rates of case-fatality, MACCE, and VTE stratified for age decades (lines). **(D)** Temporal trends regarding proportion of ARDS and pneumonia in patients with COVID-19-infection admitted to ICU stratified for age decades. COVID-19, coronavirus disease 2019; ICU, intensive care unit; VTE, venous thromboembolism; MACCE, major adverse cardiovascular and cerebrovascular events; ARDS, acute respiratory distress syndrome.

The severe respiratory manifestations of COVID-19 pneumonia [OR 6.42 (95% CI 6.16–6.69), $P < 0.001$] and ARDS [OR 35.91 (95% CI 34.10–37.80), $P < 0.001$] were strongly and independently associated with ICU-admission. As expected, all adverse in-hospital events and acute organ failures were also associated with ICU-admission (Table 2).

Risk factors for in-hospital death in COVID-19-patients treated on ICU

Increasing age, male sex, obesity, diabetes mellitus and the CVD heart failure, atrial fibrillation/flutter as well as peripheral artery disease, but also chronic obstructive pulmonary disease, chronic renal insufficiency (glomerular filtration rate <60 ml/min/1.73 m^2) and cancer were independent risk factors for in-hospital death in COVID-19-patients treated on ICUs in Germany (Table 3). Aggravated respiratory manifestations of COVID-19-infection including pneumonia as well as ARDS were associated with more than 3-fold risk for in-hospital death in ICU-patients. In addition, as expected, adverse events during hospitalization were also accompanied by increased risk for in-hospital death (Table 3).

Discussion

One of the most critical determinants in the worldwide health care management of the COVID-19 pandemic are the local ICU capacities (3, 8, 9). This was impressively obvious in several epicenters of the COVID-19 pandemic with dramatic high case-fatality rates due to overloaded local health care and especially ICU capacities (3, 10, 11, 24–26).

Our study analyzing more than 175,000 hospitalizations of inpatients with COVID-19 infection revealed a substantially higher in-hospital case-fatality rate (24.2% higher) and MACCE rate (26.0% higher), if an ICU treatment was required in the not-vaccinated

TABLE 2 Association between different conditions and ICU-treatment in COVID-19-patients (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model*	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (per year)	1.003 (1.002–1.004)	**<0.001**	0.994 (0.993–0.995)	**<0.001**
Age ≥70 years	0.926 (0.903–0.951)	**<0.001**	0.681 (0.660–0.702)	**<0.001**
Female sex	0.504 (0.491–0.518)	**<0.001**	0.511 (0.497–0.526)	**<0.001**
Cardiovascular risk factors				
Obesity	2.536 (2.421–2.655)	**<0.001**	2.201 (2.097–2.310)	**<0.001**
Diabetes mellitus	1.769 (1.721–1.819)	**<0.001**	1.479 (1.436–1.524)	**<0.001**
Essential arterial hypertension	1.354 (1.319–1.390)	**<0.001**	1.276 (1.240–1.314)	**<0.001**
Hyperlipidemia	1.241 (1.200–1.284)	**<0.001**	0.908 (0.874–0.942)	**<0.001**
Comorbidities				
Coronary artery disease	1.594 (1.541–1.648)	**<0.001**	1.088 (1.048–1.130)	**<0.001**
Heart failure	2.021 (1.958–2.085)	**<0.001**	1.719 (1.658–1.783)	**<0.001**
Peripheral artery disease	1.583 (1.484–1.688)	**<0.001**	1.041 (0.972–1.114)	0.254
Atrial fibrillation/flutter	1.836 (1.783–1.891)	**<0.001**	1.566 (1.514–1.620)	**<0.001**
Chronic obstructive pulmonary disease	1.610 (1.539–1.684)	**<0.001**	1.263 (1.204–1.324)	**<0.001**
Chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²)	1.238 (1.196–1.281)	**<0.001**	0.872 (0.839–0.906)	**<0.001**
Cancer	1.189 (1.124–1.257)	**<0.001**	1.175 (1.110–1.245)	**<0.001**
Charlson comorbidity index	1.146 (1.141–1.152)	**<0.001**	–	
Respiratory manifestations of COVID-19				
Pneumonia	6.609 (6.352–6.877)	**<0.001**	6.421 (6.164–6.689)	**<0.001**
Acute respiratory distress syndrome	39.746 (37.791–41.802)	**<0.001**	35.906 (34.104–37.803)	**<0.001**
Adverse events during hospitalization				
Cardio-pulmonary resuscitation	9.370 (8.680–10.115)	**<0.001**	7.431 (6.862–8.047)	**<0.001**
Venous thromboembolism	3.887 (3.668–4.120)	**<0.001**	3.782 (3.560–4.018)	**<0.001**
Acute kidney failure	6.540 (6.341–6.746)	**<0.001**	5.987 (5.790–6.191)	**<0.001**
Myocarditis	4.386 (3.372–5.705)	**<0.001**	3.744 (2.848–4.922)	**<0.001**
Myocardial infarction	3.954 (3.661–4.271)	**<0.001**	3.158 (2.908–3.429)	**<0.001**
Stroke (ischemic or hemorrhagic)	2.529 (2.344–2.729)	**<0.001**	2.277 (2.104–2.465)	**<0.001**
Sepsis	2.603 (2.503–2.708)	**<0.001**	2.529 (2.427–2.634)	**<0.001**
Encephalitis	7.878 (3.979–15.598)	**<0.001**	7.384 (3.652–14.929)	**<0.001**
Mild liver disease	1.653 (1.473–1.856)	**<0.001**	1.326 (1.176–1.495)	**<0.001**
Severe liver disease	5.072 (4.764–5.399)	**<0.001**	4.129 (3.868–4.408)	**<0.001**
Intracerebral bleeding	5.920 (5.025–6.975)	**<0.001**	5.485 (4.626–6.504)	**<0.001**
Gastro-intestinal bleeding	2.140 (1.972–2.322)	**<0.001**	1.907 (1.751–2.076)	**<0.001**
Transfusion of blood constituents	10.121 (9.755–10.502)	**<0.001**	10.131 (9.735–10.542)	**<0.001**

*Adjusted for age, sex, diabetes mellitus, cancer, heart failure, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²), atrial fibrillation/flutter, hyperlipidemia, and obesity.
COVID-19, coronavirus disease 2019; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.
P-values < 0.05 were considered to be statistically significant.

German population. As the vaccination program started in Germany not before late December 2020, the wide majority of hospitalized patients with COVID-19 during the year 2020 were not vaccinated and vaccination has no influence on the outcomes of our present study. The need for ICU-treatment was independently associated with 5.4-fold elevated risk for in-hospital case-fatality rate. In accordance with our results, previously published studies have also revealed high case-fatality rates of COVID-19-patients admitted to ICUs and emphasized the importance of accessible ICU beds, ventilator capacities and trained staff to manage the COVID-19

TABLE 3 Impact factors for in-hospital case-fatality in COVID-19-patients treated on ICU (univariate and multivariate logistic regression model).

	Univariate regression model		Multivariate regression model*	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (per year)	1.069 (1.067–1.072)	**<0.001**	1.068 (1.065–1.070)	**<0.001**
Age ≥70 years	4.071 (3.861–4.293)	**<0.001**	3.553 (3.352–3.765)	**<0.001**
Female sex	0.964 (0.915–1.015)	0.161	0.763 (0.720–0.809)	**<0.001**
Cardiovascular risk factors				
Obesity	0.814 (0.750–0.884)	**<0.001**	1.127 (1.028–1.236)	**<0.001**
Diabetes mellitus	1.291 (1.227–1.358)	**<0.001**	1.107 (1.045–1.172)	**0.001**
Essential arterial hypertension	0.965 (0.919–1.014)	0.161	0.711 (0.672–0.752)	**<0.001**
Hyperlipidemia	1.040 (0.976–1.108)	0.225	0.725 (0.674–0.779)	**<0.001**
Comorbidities				
Coronary artery disease	1.649 (1.553–1.751)	**<0.001**	0.997 (0.929–1.070)	0.937
Heart failure	2.037 (1.926–2.155)	**<0.001**	1.267 (1.187–1.352)	**<0.001**
Peripheral artery disease	1.952 (1.741–2.189)	**<0.001**	1.293 (1.141–1.465)	**<0.001**
Atrial fibrillation/flutter	2.283 (2.163–2.409)	**<0.001**	1.295 (1.219–1.376)	**<0.001**
Chronic obstructive pulmonary disease	1.577 (1.456–1.709)	**<0.001**	1.195 (1.095–1.303)	**<0.001**
Chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²)	2.257 (2.119–2.403)	**<0.001**	1.337 (1.245–1.435)	**<0.001**
Cancer	1.738 (1.570–1.924)	**<0.001**	1.697 (1.520–1.895)	**<0.001**
Charlson comorbidity index	1.410 (1.394–1.425)	**<0.001**	–	
Respiratory manifestations of COVID-19				
Pneumonia	2.725 (2.480–2.994)	**<0.001**	3.441 (3.104–3.815)	**<0.001**
Acute respiratory distress syndrome	2.106 (2.001–2.217)	**<0.001**	3.049 (2.872–3.237)	**<0.001**
Adverse events during hospitalization				
Cardio-pulmonary resuscitation	6.164 (5.497–6.913)	**<0.001**	7.130 (6.291–8.082)	**<0.001**
Venous thromboembolism	1.075 (0.979–1.180)	0.129	1.367 (1.235–1.513)	**<0.001**
Acute kidney failure	4.305 (4.084–4.538)	**<0.001**	3.972 (3.747–4.211)	**<0.001**
Myocarditis	0.686 (0.447–1.053)	0.085	0.921 (0.562–1.507)	0.743
Myocardial infarction	1.383 (1.227–1.559)	**<0.001**	1.002 (0.876–1.145)	0.979
Stroke (ischemic or hemorrhagic)	1.755 (1.545–1.993)	**<0.001**	1.851 (1.611–2.127)	**<0.001**
Intracerebral bleeding	2.679 (2.116–3.391)	**<0.001**	4.676 (3.620–6.041)	**<0.001**
Gastro-intestinal bleeding	1.825 (1.587–2.099)	**<0.001**	1.543 (1.325–1.797)	**<0.001**
Transfusion of blood constituents	2.321 (2.201–2.449)	**<0.001**	2.339 (2.203–2.482)	**<0.001**

*Adjusted for age, sex, diabetes mellitus, cancer, heart failure, coronary artery disease, chronic obstructive pulmonary disease, essential arterial hypertension, chronic renal insufficiency (glomerular filtration rate <60 ml/min/1,73 m²), atrial fibrillation/flutter, hyperlipidemia, and obesity.
COVID-19, coronavirus disease 2019; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.
P-values < 0.05 were considered to be statistically significant.

pandemic adequately (3, 8, 27). This was underlined by data of the United States of America showing that 79% of the hospital beds at the ICUs were occupied by COVID-19-patients at the peak of the pandemic during January 2021 (28). The proportion of patients with COVID-19-infection, who were transferred to an ICU in Germany, was 15.4% and therefore, comparable to proportions in France (16.4%) (29), United Kingdom (17.0%) (30), and in the Unites States of America (10.2–19.6%) (31–33), but lower than in other countries such as Spain (26.3%) (34) or Iran (19.0%) (35). Pooled ICU admission rate among 17,639 hospitalized COVID-19 patients meta-analyzed from eight studies worldwide was reported as 21% (36). While the highest absolute numbers of total ICU admissions due to COVID-19-patients in the year 2020 were observed in spring and winter, the monthly percentage of COVID-19 patients treated at the ICU of German hospitals decreased over time from 32.8% in January 2020 to a minimum of 14.8% at November 2020 and revealed only small variations between May and December 2020.

In accordance with our finding of a high case-fatality rate of COVID-19-patients treated in German ICUs during spring and winter of the year 2020 when ICU demands were highest (Figure 3A), other studies have also shown that the ICU capacities and the ICU demand are important factors for COVID-19 patients' outcome (33, 37). COVID-19 patients who needed ICU-treatment during periods of increased COVID-19 ICU demand had an increased risk of mortality compared with patients treated during periods of low COVID-19 ICU demand, whereas no association between COVID-19 ICU demand and mortality was observed for patients with COVID-19 treated outside the ICUs (37). This finding is of outstanding interest for adequate pandemic management.

In addition, significant variations regarding in-hospital case-fatality rate across European countries were observed (38, 39). The in-hospital case-fatality rate of COVID-19 patients treated on ICU during the year 2020 in Germany identified by our study was 38.4% and therefore higher than the rates reported in studies from Spain, Andorra and Ireland (30.7%) (27), France (31.0%) (40), United Kingdom (32.0%) (30), Spain (16.7–34.0%) (41, 42), Netherlands (23.4–32.0%) (43), United States of America (21.0–29.7%) (32, 44), Sweden [17.4% (in-hospital mortality)−32.1% (60-day mortality after ICU discharge)] (45, 46), Iceland (14.8%) (47), was similar to rates in China (37.0%) (48) as well as in Denmark (37.0%) (49) and lower than in Iran (42.0%) (35), Russia (65.4%) (50), and Brazil (59.0%) (51). Two large review article including data of ICUs around the world reported summarized worldwide ICU mortality rates of 28.3% (36) and 35.5% (52), the second close to the value we calculated for Germany.

As aforementioned, inter-country differences regarding the COVID-19 patients' outcome are strongly impacted by ratio of ICU capacities and ICU demand (33, 37). In addition, patients' age, sex-distribution and comorbidities are important for these observed differences (27, 31, 43, 46, 53). In particular, the age-dependency of COVID-19 case-fatality is well-known and very important in this context (3). Therefore, variations in median age of the different COVID-19-cohorts in the different countries influence the case-fatality rates and might contribute to these variations. For example, in the Swedish COVID-19 intensive care cohort (46) as well as in cohort studies of the United States of America (31), the median age of the ICU patients was more than 10 years lower (31, 46) and in the cohort study in Spain, Andorra and Ireland the median age was 8 years lower than in Germany (27). In line with this age-comparison, age ≥70 years was a strong predictor of in-hospital death of COVID-19-patients admitted to ICUs in Germany. In addition, aggravated respiratory status such as pneumonia and ARDS as well as acute kidney injury were strongly and independently associated with increased in-hospital case-fatality. However, since not all COVID-19 patients without dyspnoea, who were treated on normal ward, will be and were examined with X-ray, the proportion of pneumonia in this patient group might be underestimated.

The prevalence rates of all investigated acute organ failures were substantially higher in ICU patients than in the COVID-19 patients treated on normal ward. Especially, rates of cardiac involvement, but also stroke, encephalitis and sepsis were substantially elevated. Sepsis is a common complication in COVID-19 patients and was detected in 7.6% of all hospitalized COVID-19 patients and in more than 14% of the COVID-19 patients treated on ICU in Germany in the year 2020. However, studies indicate that this number might be underestimated and the real rate of viral sepsis in hospitalized COVID-19 patients might be significantly higher (54). Cardiac involvement is a known phenomenon and complication in patients suffering from COVID-19-infection (3, 55–58) and comprises predominantly myocardial infarction as well as myocarditis. COVID-19 was identified as a risk factor for acute myocardial infarction and myocarditis (3, 55–60). In studies, SARS-CoV-2 was associated with an increased risk of both arterial and venous thrombotic complications and in particular the risk of myocardial infarction was approximately doubled in the first 7 days after COVID-19 diagnosis (60). Myocarditis incidence of hospitalized patients was reported ranging between 2.4 and 4.1 cases per 1,000 COVID-19 patients in a multi-center study of centers of different European countries and the United States of America (56, 58). Cerebral complications such as stroke and encephalitis were reported in studies (59, 61), but our data underlines the importance and impact of these widely overlooked complications. These different acute organ failures are key drivers of in-hospital mortality and therefore, the early detection of impending complications as well as prevention and treatment of these acute organ failures is of major interest for adequate management of COVID-19 patients. It is additionally of outstanding interest, that all investigated bleeding events occurred more often in COVID-19 patients admitted to ICUs. Bleeding events during hospitalization were in different studies strongly associated with increased in-hospital death (62, 63).

Although the COVID-19 pandemic was primarily managed by vaccination programme after the year 2020 (vaccination program started in Germany at late December 2020 and accelerated in the following years) (64), nevertheless, ∼1/4 of the German population has still no basic immunization by a COVID-19 vaccination at the beginning of the year 2023 (65). Therefore, risk factors for ICU admission in not-vaccinated patients are still important for health care management. While the understanding of impacting factors on ICU admission and outcome is crucial for adequate health care planning, decision making, and pandemic management (3, 6, 66), the understanding of these factors remains still unsatisfying (66). We identified male sex as well as obesity and diabetes mellitus as independent predictors for an increased probability of ICU treatment. These findings is consistent with previously published study results in which obesity and diabetes mellitus were associated with aggravated outcome in hospitalized patients with COVID-19 (3, 7, 67–70).

In accordance with contemporary literature (71), the prevalence of CVD is distinctly higher in COVID-19-patients requiring ICU care. Interestingly, the association of atrial fibrillation/flutter as well as heart failure with ICU-admission were stronger than the associations of coronary artery disease and chronic obstructive pulmonary disease with ICU-admission, respectively. Atrial fibrillation is the most common arrhythmia in patients with COVID-19-pneumonia affecting ∼20% of the patients with severe COVID-19 pneumonia during ICU stay (72). In patients with COVID-19, arrhythmias and chronic heart failure are key factors of the development of acute heart failure (73) and heart failure diagnosis is associated with aggravated mortality in COVID-19 patients (3, 73). COVID-19-infection is associated with increased risk of arterial und venous thrombosis with resulting ischemic events and patients with myocardial infarction infected by COVID-19 had an unfavorable outcome in comparison to those patients without COVID-19 infection (3, 60, 71, 74–77). Among COVID-19 patients, higher proportions of patients with COPD have to be admitted to ICU and treated with mechanical ventilation (78). Consequently, COPD is an independent risk factor for ICU admission and all-cause mortality in COVID-19 patients (78, 79).

In line with our results, other studies identified patients age, arterial hypertension, diabetes mellitus, chronic renal failure, bronchial asthma, obesity and immunosuppression as independently associated with ICU admission during COVID-19-infection (46, 80). Nevertheless, it has to be mentioned, that we were not able to distinguish whether the adverse in-hospital events occurred during, before or after ICU treatment during the hospitalization of the COVID-19 patients. However, the aim of the study was to emphasize and illustrate the stress and strain of the ICU in Germany.

Total number of patients necessitating ICU admission in relation to provided ICU capacities have to be taken into account for adequate health care and pandemic planning (3, 8, 9). Based on the knowledge regarding regional differences, epicenters of the COVID-19 pandemic with very high mortality rates, it is of outmost importance to identify trends and factors affecting ICU admission to avoid a critical overload of the healthcare system and particularly of the ICUs with increasing mortality rates (5, 8, 9).

Limitations

Certain limitations of the present study merit consideration: First, as our results are based on administrative data, we cannot exclude misclassification or inconsistencies. Additionally, our analysis of the German nationwide inpatient sample was not pre-specified and thus, findings of the study can only be considered to be hypothesis-generating. Second, patients with confirmed COVID-19 infection, who died out of hospital, were not included in the German nationwide inpatient sample. Third, the German nationwide inpatient sample does not report follow-up-outcomes after the discharge from hospital. Fourth, coding on medical treatments is only incompletely captured (especially regarding immunotherapy such as dexamethasone, tocilizumab, anakinra, and baricitinib).

Conclusion

During the year 2020, 15.4% of the hospitalized COVID-19-patients were admitted to ICUs in German hospitals. Important and independent risk factors for ICU admission are male sex, CVRF such as obesity and diabetes mellitus as well as several cardio-pulmonary diseases including atrial fibrillation/flutter, heart failure, coronary artery disease and chronic obstructive pulmonary disease. ICU-admission was accompanied by a case-fatality rate of 38.4% and for this substantially higher than the rate 14.2% on normal-ward treatment. COVID-19 patients who were treated in ICUs during periods of increased ICU demand had an increased risk of mortality compared to patients treated during periods of low COVID-19 ICU demand. These findings highlight to draw more attention to predictors for ICU admission in patients hospitalized with COVID-19 in order to optimize monitoring and prevention strategies, avoid critical overload of the healthcare system and particularly of the ICUs in order to prevent the subsequent increase in mortality rates.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

KK and LH conceived this study, led the writing of the paper, accessed and verified the data, and contributed to the study design. LH, IF, LV, SKoe, JW, SB, FS, CE-K, SKon, TM, and IS commented on the paper, oversaw the analysis, and edited the final manuscript. KK led the data analysis with support from LH. All authors had full access to all the data, contributed to drafting the paper, revised the manuscript for important intellectual content, and had final responsibility for the decision to submit for publication.

Conflict of interest

SB received lecture/consultant fees from Bayer HealthCare, Concept Medical, BTG Pharmaceuticals, INARI, Boston Scientific, and LeoPharma; institutional grants from Boston Scientific, Bentley, Bayer HealthCare, INARI, Medtronic, Concept Medical, Bard, and Sanofi; and economical support for travel/congress costs from Daiichi Sankyo, BTG Pharmaceuticals, and Bayer HealthCare, outside the submitted work. CE-K reports having from Amarin Germany, Amgen GmbH, Bayer Vital, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Leo Pharma, MSD Sharp & Dohme, Novartis Pharma, Pfizer Pharma GmbH, and Sanofi-Aventis GmbH. SKon reports institutional grants and personal lecture/advisory fees from Bayer AG, Daiichi Sankyo, and Boston Scientific; institutional grants from Inari Medical; and personal lecture/advisory fees from MSD and Bristol Myers Squibb/Pfizer. TM is PI of the DZHK (German Center for Cardiovascular Research), Partner Site Rhine-Main, Mainz, Germany. LH received lecture/consultant fees from MSD and Actelion, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Acceptability and perception of COVID-19 vaccines among foreign medical students in China: A cross-sectional study

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Background: Acceptability and perception of the COVID-19 vaccine among different social groups have been the subject of several studies. However, little is known about foreign medical students in Chinese universities.

Aim: This study, therefore, fills the literature gap using a focus group technique to assess the acceptance and perception of the COVID-19 vaccine among foreign medical students in China.

Methods: The study adopted an online cross-sectional survey method following the Chinese universities' lockdowns to collect the data between March and April 2022. A data collection questionnaire was developed, and then the link was shared with the respondents through key informants in different universities in China to obtain the data. The data collection process only included foreign medical students who were in China from May 2021 to April 2022. The authors received a total of 403 responses from the respondents. During data processing, we excluded 17 respondents since they were not in China while administering the questionnaire to enhance the data validity. The authors then coded the remaining 386 respondents for the estimation process. We finally applied the multilinear logistics regression technique to model the COVID-19 vaccine acceptance with the response or influencing factors, including the mediating factors among the foreign medical students in China.

Results: The data statistics show that 4.9% of the respondents were younger than 20 years, 91.5% were 20–40 years old, and 3.6% were older than 40 years; 36.3% of respondents were female subjects and 63.7% were male subjects. The results also show that the respondents are from six continents, including the African continent, 72.4%, Asia 17.4%, 3.1% from Europe, 2.8% from North America, 1.6% from Australia, and 2.3% from South America. The mediation analysis for the gender variable ($\beta = 0.235$, $p = 0.002$) suggests that gender is a significant channel in COVID-19 vaccine acceptance and perception among foreign medical students in China. Also, the main analysis shows that opinion on the safety of the vaccine ($\beta = 0.081$, $p = 0.043$), doses of the vaccine to receive ($\beta = 0.175$, $p = 0.001$), vaccine safety with some side effects ($\beta = 0.15$, $p = 0.000$), and the possibility of acquiring COVID-19 after vaccination ($\beta = 0.062$, $p = 0.040$) are all positive factors influencing vaccine acceptability and perception. Also, the home continent ($\beta = -0.062$, $p = 0.071$) is a negative factor influencing COVID-19 vaccine acceptance and perception. Furthermore, the finding shows that fear perceptions has affected 200 (51.81%) respondents. The medical students feared that the vaccines might result in future implications such as infertility, impotence, and systemic health conditions such as cardiovascular, respiratory, or deep vein thrombosis. In addition, 186 (48.19%) students feared that the vaccines were intended to shorten life expectancy.

Conclusion: COVID-19 vaccination acceptability and perception among medical students in China is high, most predominantly due to their knowledge of medicine composition formulation. Despite widespread acceptance by the general public and private stakeholders, we concluded that vaccination resistance remains a significant factor among medical students and trainees. The study further adds that in considering the COVID-19 vaccine, the factor of the home continent plays a significant role in vaccine hesitancy among foreign medical students. Also, knowledge, information, and education are important pillars confronting new medicine administered among medical trainees. Finally, there is a low rate of COVID-19 vaccine hesitancy among foreign medical students in China. The study, therefore, recommends targeted policy strategies, including sensitization, detailed public information, and education, especially for medical colleges and institutions on the COVID-19 vaccination, to achieve 100%. Furthermore, the study recommends that future researchers explore other factors influencing accurate information and education for successful COVID-19 vaccination implementation.

KEYWORDS

COVID-19, COVID-19 vaccine, international students, medical students, pandemic

Introduction

Coronavirus infectious disease 2019 (COVID-19) was declared a pandemic in March 2021 by the World Health Organization (WHO) (1, 2). The literature suggests that COVID-19 causes severe acute respiratory syndrome coronavirus (SARS-CoV-2) and continues to impact global public health significantly (3, 4). Many efforts by governments to combat the disease have led to implementing health prevention policies, including lockdowns, social distancing in public places, hand hygiene, using masks, and finally, the rollout of vaccines (2) as a last resort in health management protocols.

There are many COVID-19 vaccines available in the world market, specially manufactured by world high medical suppliers in countries like the United States of America, the United Kingdom, China, Russia, and India (5). Despite some of the challenges, usually encountered such as trust issues, the WHO has approved all COVID-19 vaccines after careful checks of the trial testing procedures, with special attention to ensuring human life safety (6). The approval process has led to a high level of trust, and not surprisingly, there has been a dependence on the COVID-19 vaccine, just like in previous epidemics management measures. Many developed countries depend on their vaccines while developing countries appear to have more trust in imported vaccines from developed countries because they cannot manufacture their own (6) due to limited medical resources and capacity. Because of mistrust in the sources of vaccines, the acceptance and perception of COVID-19 vaccines among people are affected due to religious beliefs and cultural and personal reasons (7). In some parts of the world, the vaccine has been received with high acceptability due to the system of governance and fear of the impact of COVID-19 (8). According to the literature, vaccine resistance was independently predicted as ignorance of vaccination eligibility, worry about vaccine side effects and effectiveness, and mistrust of the government (9). Greater awareness of the risk associated with COVID-19 appeared to lessen vaccine hesitancy (9). Several people have raised concerns about the scarcity of vaccination-related information as a prerequisite in vaccine introduction before the publication of safety and efficacy data (10, 11). Although vaccine reluctance has declined over time, health education programs designed to increase vaccination awareness and promote public confidence in government institutions would be beneficial (9). Enhancing health promotion and lowering obstacles to COVID-19 vaccination is crucial (10–12). Similarly, many participants (10–12) lacked knowledge of the COVID-19 vaccinations, although health authorities approved vaccine use in pregnant women and children over 12 years of age. Health knowledge updates, such as vaccinations for expectant mothers and children, should be provided as ongoing awareness campaigns that target all demographic groups (13). The COVID-19 mRNA vaccines are well known, but the confidence level of successful COVID-19 vaccine manufacturers differ significantly from one another (12). The pandemic may be a good opportunity to raise public understanding of vaccines, highlighting the importance of effective and ongoing scientific communication in the battle against the disease (13).

The literature studies show that the reluctance to vaccine acceptance is one of the biggest obstacles to conducting successful immunization programs (14) in many parts of the world. Studies show that adopting any vaccination among healthcare professionals is one important way to improve its acceptance efficacy and safety (15). Also, social media is yet another important key player in influencing the attitude toward the acceptance of COVID-19 vaccines (16). Furthermore, factors such as profession, alcohol intake, and knowledge and attitude toward the COVID-19 vaccination impact the intention to receive the vaccine (17). A study shows that Indian college students have a highly positive intention of receiving COVID-19 vaccines, although one-third were unsure or hesitant to receive vaccines (18). It is essential to relieve peoples' anxiety and improve their confidence through health education (19). Furthermore, studies suggest that gender (male) with higher educational status, urban housing, and using television or radio have COVID-19 information sources that are strongly associated with research participants' knowledge levels (20). The activities of the government, particularly through social distance measures, have favorably increased the feelings of safety and security among overseas students (21). The social media platform has significantly contributed to the spread of information and has praised Chinese institutions for its ongoing COVID-19 alerts that enabled students to have a complete understanding (22). Since the media and other related parties play a significant role in the acceptance or otherwise of the vaccine, the governments have advised them to spread accurate, reliable, and consistent COVID-19 vaccine information to foster public trust (23).

Studies show that the positive effects of COVID-19 vaccination are evident in many countries, but certain sectors still deny its impact (24). Governments have used various COVID-19 vaccination implementation strategies based on national policies (25). A large body of research exists about people's perceptions and attitudes toward COVID-19 vaccines among diverse social categories of society (10–12). Studies suggest that some social groupings still have a larger knowledge gap and unfavorable views on the subject (26). In line with the literature, it is important to examine the COVID-19 vaccine acceptance and perceptions among different groupings (27). According to studies, public health efforts have stressed the alleged advantages of vaccinations and the anticipated risks of skipping; however, the majority of students had weak knowledge and favorable perceptions (28). The WHO Strategic Advisory Group of Experts (29) described vaccine hesitancy as a delay in acceptance or refusal of immunization despite the availability of vaccination services. Studies including (30) COVID-19 vaccine hesitancy is substantially high, between 10% and 37% among medical students. As a result of the high hesitancy among medical students, it is an important subject, and currently, there needs to be more studies among foreign medical students in Chinese universities (31). The results could be instructive for decision-makers as they try to maximize the spread of vaccines (32). Therefore, this study seeks to contribute to the literature debate in the context of foreign medical students in Chinese universities. The relevance of the survey among foreign medical students' acceptance or otherwise of the COVID-19 vaccine may play a significant role in the general international students since they have adequate knowledge and information on the vaccine composition matrix in China. This may also be relevant to the WHO-SAGE method, which states that countries should use the Convenient, Complacency, and Confident (3-Cs) (33) model in the COVID-19 vaccine administration worldwide. The 3-Cs approach seeks to boost and break barriers to accepting the COVID-19 vaccine across all social groupings, such as foreign medical students (34, 35). So, the relevance of the study further seeks to assess the foreign medical students' trust in getting vaccinations in terms of no need to pay for vaccines, high vaccine availability, no language barriers, and availability of information on the vaccine to reduce any complacency among social categories such as students. In this regard, China is among the few countries to use the COVID-19 administering challenges to implement technological innovations to help build on their systems, particularly when students return to school after the lockdown periods. Therefore, this study has academic and policy relevance in broadening the understanding of the COVID-19 vaccine acceptance and assessing the efficacy of the 3-Cs model among foreign medical students on vaccine hesitancy in China (36). This study aims to model and evaluate the influencing factors (i.e., attitude, beliefs, experiences, reactions, and feelings) affecting COVID-19 vaccination acceptance among international medical students in Chinese universities and Colleges.

Materials and methods

The authors adopted the STROBE guideline in this study starting with the title (item 1) till funding (item 22) (34). In this section, we applied items 4–12 in guiding the cross-sectional study consistent with the STROBE checklist, see Appendix A. The authors adopted the focus group technique to draw upon the foreign medical students' attitudes, beliefs, experiences, reactions, and feelings through an online data-collecting survey which would not be feasible using other methods such as observational and one-on-one interviewing techniques because of COVID-19 lockdown protocols.

Population, sample size, and technique

In this study, we targeted all levels of international foreign medical students enrolled in Chinese universities, including undergraduate, graduate, and postgraduate. Therefore, we used a standard sampling technique to source the data from the students in different universities using an online survey technique. Consistent with the literature, we used a data sampling technique developed by Yamane [8/11] to generate the sample size. Consistent with [8/11], we used Yamane (1967:886)[32] to calculate a sample size

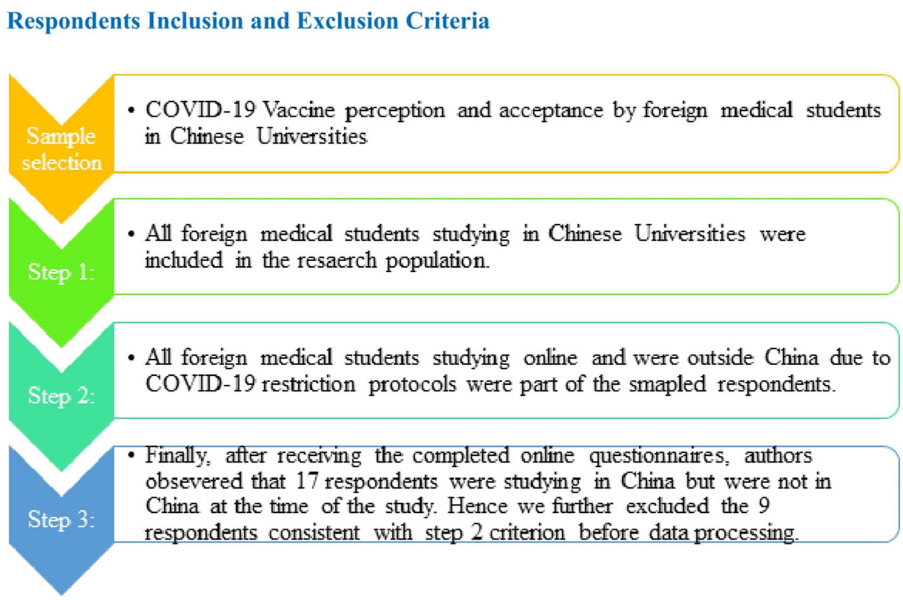

FIGURE 1
Respondents' inclusion and exclusion flowchart.

with a 95% confidence level and $P = 0.05^{32}$. That is, according to Yamane, the sample size is (n) $=N/(1+N(e)^2)$, where N is the population size and e is the level of precision. In applying this formula, the authors estimated the total number of foreign medical students in Chinese universities to be over 10,000[1] population. Therefore, the authors used the estimated 10,700 foreign medical students in China as a base using the Yamane formula to calculate the sample size of 386.

Study and questionnaire design

In this study, we used a qualitative research design using a one-time data collection technique involving a cross-sectional survey conducted from March to April 2022 to source data from international foreign medical students in Chinese universities. The authors designed the questionnaire in two sections. The first part of the questionnaire captures data on social demographic characteristics such as gender, age, program major, years in China, and religion. The second part of the questionnaire captured data on COVID-19 vaccination acceptability and perceptions formulated based on the literature (18).

Data collection and respondents recruitment procedures

First and foremost, the authors identified key informants (leaders) across the targeted Chinese universities in February 2022. So, the key informants or cadets connected us to foreign medical students. Furthermore, the authors sent the self-administrated online survey questionnaire link shared on the media, including WeChat and WhatsApp, and university groups in China through the identified key informants. The online questionnaire technique allowed the students to self-administer the online survey link shared, and responses were automatically generated after completing the questionnaire.

Respondents' inclusion and exclusion criteria

As shown in Figure 1, all the medical students studying medical-related majors in China, such as Clinical Medicine and Allied Health Sciences, in any year of study were included as potential respondents. Furthermore, as presented in Figure 1, all the students outside China at the time of the data collection period were not considered. That is, the authors included a respondent caveat (do not fill the questionnaire if you have not been in China since May 2021–April 2022) in the questionnaire. A total of 403 questionnaires were received through the online system. Therefore, to avoid bias and ensure validity in data collection, the authors screened the obtained data and observed that 17 students had completed the questionnaire while they were not in China. So, the authors then excluded 17 respondents, and the sample size remains at 386 for the final data processing.

Data processing

The obtained data were then processed into categorical and continuous variables. That is, the dependent acceptance is a dummy variable equal to one (1), and non-acceptance or otherwise

1 Foreign medical students in China: https://www.china-admissions.com/study-medicine-in-china/.

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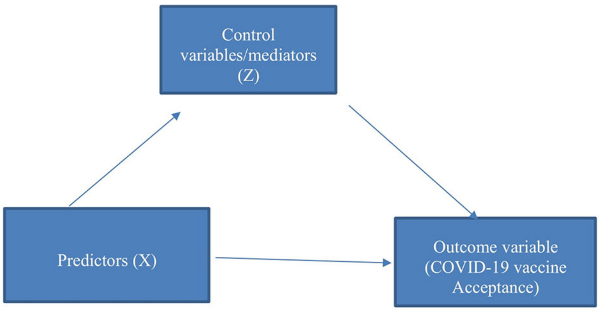

FIGURE 2
Conceptual framework of COVID-19 vaccine acceptance.

represents zero (0). The second part of the questionnaire captured data on COVID-19 vaccination acceptability and perceptions formulated based on the literature (18). Also, the authors processed other data into categorical, ordinal, and continuous variables. Finally, in complying with the literature and checking the data internal reliability test in the study, we used the SPSS technique to test the data reliability with Cronbach's alpha which is 0.8. The authors then applied the processed data with multilinear logistic regression techniques.

Multilinear logistic regression model design

The authors model logistic regression in equations (1–2) to capture the outcome variable, and qualitative term acceptance in a linear relationship with the independent variables (32). The independent variables or predictors are "is COVID-19 vaccine safe in your own opinion"; "how many doses do you think you can receive of COVID-19"; "home continent"; "think that the COVID-19 vaccine is safe with some side effects," and "think it not possible to get COVID-19 after taking the COVID-19 vaccine." Also, the authors included control variables (mediator variables) such as gender, age group, marital status, and religion since these may influence the respondents' behavior in different ways. That is, the inclusion of the control variables serves as the mediation channel and this is shown in the conceptual framework (Figure 2).

Furthermore, the authors designed the model, multilinear logistic regression, which is expressed as follows:

$$\ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 x \quad (1)$$

$$p = \frac{e\beta_0 + \beta_1 x}{1 + e\beta_0 + \beta_1 x} \quad (2)$$

Therefore, we code COVID-19 vaccine acceptance to be equal to one (1). From equation (2), the model can be expressed as follows:

$$p\left(COVID - 19 vaccine\ acceptance = 1\right) = \frac{1}{1 + e - (\beta_0 + \beta_1 x + \beta_2 z)} \quad (3)$$

Consequently, from equation (3), p is the probability, β_0 is the intercept, $\beta_1$and β_2 are the parameter coefficients of the predictors and control variables, x as explained above, and z is the control or mediator. The designed model shows the relationship that the probability of accepting the COVID-19 vaccine is related to the independent variables such as the safety of the vaccine, home continent, vaccine side effects, and the number of doses as also explained earlier.

TABLE 1 Social demographic characteristics of the respondents ($N = 386$).

Variable	Category	F	%
Gender	Female	140	36.3
	Male	246	63.7
Age-group	less than 20 Years	19	4.9
	Above 20 years less than 40	353	91.5
	Above 40	14	3.6
Marital status	Single	336	87
	Married	50	13
Level of program	Undergraduate	239	61.9
	Postgraduate	127	32.9
	Post Doctorate	20	5.2
Sources of information	Online-Internet	56	14.5
	Radio	6	1.6
	Hospital & School notifications	125	32.4
	Friends and Relatives	6	1.6
	Others	193	50

Results

The authors further followed the STROBE guideline in this section using items 13–17 for presenting the statistical analysis, outcome data, and the main results (34).

Statistical analysis

The authors used 386 responses after the data processing. Out of the 386 total respondents, 19 (4.9%) were younger than 20 years, 353 (91.5%) respondents were 20–40 years old, and 14 (3.6%) were older than 40 years. In the demographic analysis, there were 140 (36.3%) and 246 (63.7%) female and male students, respectively; please refer to Table 1. In terms of marital status, about 80% were not married because they were undergoing medical training. Furthermore, 239 (61.9%) of the participants were undergraduates, followed by 127 (32.9%) postgraduate and 20 (5.2%) post-doctoral respondents. The demographic statistics additionally show that 56 (14.5%) respondents had accessed COVID-19 vaccine information from the internet, 6 (1.6%) through radios, and 125 (32.4%) from the hospital and school notification prompts. Other means of obtaining COVID-19 information include friends and relatives, with 6 (1.6%) respondents, and 50% using various methods to access COVID-19 vaccine information; detailed information is

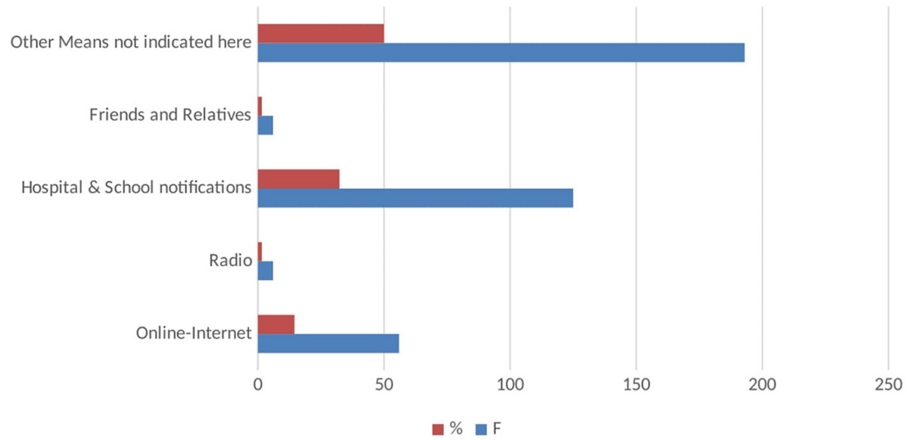

FIGURE 3
Sources of information regarding COVID-19.

TABLE 2 Regional location of the participants ($N = 386$).

Location	Region	F	%
Region in China	Central North Region	74	19.2
	Central Region	55	14.2
	Central West Region	14	3.6
	Eastern Region	41	10.6
	North West Region	20	5.2
	Northeast Region	88	22.8
	Southern Region	72	18.7
	Western Region	22	5.7
Continent	Africa	281	72.8
	Asia	67	17.4
	Australia	6	1.6
	Europe	12	3.1
	North America	11	2.8
	South America	9	2.3

found in Figure 3. Finally, most of the respondents 88 (22.8%), followed by 74 (19.2%) respondents resided in the North-Eastern and the Central-North regions of China, respectively, see Table 2. The data also reveal that about 324 (83%) respondents indicated that they had been vaccinated. However, about 48.96% agreed it was safe to get the vaccine, and the remaining 51.04% held a contrasting opinion, see Figure 4.

Main results and other analysis

Multilinear logistic regression results

The estimated model regression analysis revealed the following results. The findings show that six out of the 10 variables are statistically significant (Table 3). The relevant factors which influence the acceptance and perception of the COVID-19 vaccine include the following:

- Gender ($\beta = 0.235$, $p = 0.002$) is significant at a 99% confidence level.
- Opinion on the safety of the vaccine ($\beta = 0.081$, $p = 0.043$) is significant at 95% confidence.
- Doses of the vaccine to receive ($\beta = 0.175$, $p = 0.001$) are significant at a 99% confidence level.
- Vaccine safety with some side effects ($\beta = 0.15$, $p = 0.000$) is significant at 99% confidence.
- The possibility of getting coronavirus disease after vaccination ($\beta = 0.062$, $p = 0.040$) is significant at a 95% confidence level.
- Home continent ($\beta = -0.062$, $p = 0.071$) is significant at a 90% confidence level.

Furthermore, based on the results obtained in Table 3, the authors further selected three factors (gender, doses, and home continent) to determine which variable has the greatest influence on acceptance and perception as sensitivity analysis, and the results are presented in Table 4. Table 4 shows that gender is a more significant factor ($p = 0.000$) compared to the number of vaccine doses to be received ($p = 0.001$), with some significance that influences the level of vaccine acceptance among foreign medical students in China compared to the home continent with a significance of p = 0.090. Also, a single (1) vaccine dose was significant compared to triple (3) doses of vaccine based on the reference category (0a) used in Table 1. Moreover, the home continent variable has the least response significance of (0.090) compared to the number of doses ($p = 0.001$). The findings, therefore, suggest that the gender factor has a more powerful influence on vaccine acceptability than the number of doses indicated by the respondents and the home continent factors. The findings hereafter show that various factors influenced the COVID-19 vaccine's acceptance among foreign medical students in China. Also, the results suggest that fear perceptions has affected 200 (51.81%) of the respondent's decision. They feared the vaccines might result in future implications such as infertility, impotence, and systemic health conditions such as

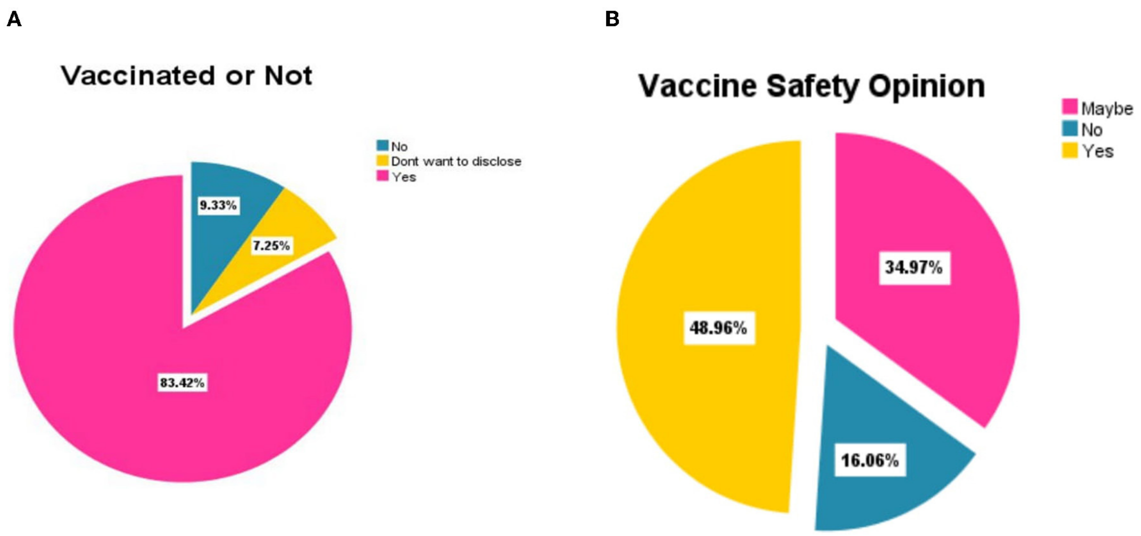

FIGURE 4
Results of vaccination and vaccine safety opinion of the respondents (*N* = 386). **(A)** Total respondents (*N* = 386) vaccinated or not. **(B)** Total respondents (*N* = 386) on vaccine safety opinion.

TABLE 3 Factors associated with COVID-19 vaccine acceptance among foreign medical students in China using a multilinear regression model.

Variables	β	*P*
(Constant)	0.433	0.232
Gender	0.235	0.002***
Your age group	−0.026	0.838
Your marital status	0.124	0.280
Study program level	0.022	0.745
Are you affiliated with any religion	0.125	0.227
Your home continent	−0.062	0.071*
Is COVID-19 Vaccine safe in your own opinion	0.081	0.043**
How many doses do you think you can receive of COVID-19	0.175	0.001***
Think that the COVID-19 vaccine is safe with some side effects	0.15	0.000***
Think it is not possible to get COVID-19 even after taking the COVID-19 vaccine	0.062	0.040**
R^2	0.86	
N	386	
Durban Watson	1.86	

*Significance at 10%; **Significance at 5%; ***Significance at 1%. The table further indicates the regression results obtained from the binary regression model.

cardiovascular, respiratory, or deep vein thrombosis. In addition, 186 (48.19%) respondents also feared that the vaccines were intended to shorten life expectancy.

Discussion

This section also applied the STROBE checklist, items 18–21 in presenting the key results, discussions, interpretation, generalization, and limitation of the study (34). This study was designed to examine foreign medical students' attitudes, beliefs, experiences, reactions, and feelings in Chinese universities regarding their willingness to receive the COVID-19 vaccine. That is, all the respondents were studying in medical institutions in China. Therefore, the study analysis is relevant to the general public, governments and policymakers, academic scholars, and private institutions in medicine production subject to foreign medical students. The medical students' acceptance and perception of COVID-19 vaccinations may significantly contribute to international students' population behavior on this subject in China. Accordingly, this study analysis may have policy relevance to foreign medical students worldwide on COVID-19 vaccination

TABLE 4 Selected variables in logistic regression.

Variables	Category	β	Sig.
Threshold	[HOW_LIKELY_SAFE = 1]	−3.199	0.000
	[HOW_LIKELY_SAFE = 2]	−1.599	0.028
Location	[GENDER = 1]	−0.988	0.000***
	[GENDER = 2]	0a	.
	[HOME_CONTINENT = 1]	−0.86	0.206
	[HOME_CONTINENT = 2]	0.497	0.503
	[HOME_CONTINENT = 3]	0.419	0.700
	[HOME_CONTINENT = 4]	−0.429	0.623
	[HOME_CONTINENT = 5]	2.116	0.090
	[HOME_CONTINENT = 6]	0a	.
	[DOSES = 1]	−1.115	0.001
	[DOSES = 2]	−0.232	0.370
	[DOSES = 3]	0a	.

*Significance at 10%; **Significance at 5%; ***Significance at 1%. (1): Reference Category using/based on Table 1.

protocol adoption. Furthermore, this study is an assessment case of foreign medical students in Chinese universities and should apply some caution in its generalization. That is, an extra note must further be taken into consideration in the application of this finding as there may be control factors that influenced the vaccine acceptance that was not included such as government and institutional pressures.

The study finds that the majority of the participants (83.4%) had already received the COVID-19 vaccine at different degrees of doses (some received single, double, or third), and the remaining 6.7% did not yet receive the vaccine at all. These findings are consistent with similar studies in Poland, where it was found that medical students were more than willing to get the vaccine (11, 12). These findings indicate that the impact of medical student's knowledge in their studies would help them have a positive attitude toward the vaccine. First of all, the gender factor in the study discovers that male students have a much higher acceptance level than female students. The finding reveals that the probability of being a male increases the possibility of accepting the COVID-19 vaccine by 23.5% among foreign medical students in Chinese universities, significant at a 99% confidence level. This finding agrees with another study conducted in Yemen, where male students had more level of acceptability and positive perception regarding COVID-19 (13). However, our study finds contrasting results with another study conducted in India which found that female students were more willing than male medical students (12); the differences would be the study design results, country policies' nature, and other external factors. This may be explained by another reason: the majority of male medical students actively participate in various hospital practices.

Furthermore, regarding COVID-19 vaccine safety, the study finds that the majority, about 45.1% of the study participants, had no concerns, while 37.3% had concerns about the vaccine's safety. The participants who recommended the vaccine were more likely and willing to receive the vaccine and 90% less likely to have vaccine hesitancy. Furthermore, the majority of the study participants, about 49%, gave a positive opinion that the vaccine is safe and can prevent COVID-19 disease. In contrast, only 16.1% stated that the vaccine was unsafe and 35% of the participants were not sure about the safety of the vaccine. That could explain why those who recommended the vaccine's safety had enough knowledge about the vaccine and its clinical trials, hence more likely to receive the vaccine than those who disagreed with its safety. The finding reveals that the probability of an increase in vaccine safety leads to more possibility of acceptance of COVID-19 by 8% among foreign medical students in Chinese universities, significant at a 95% confidence level. Our findings agree with another study among health workers, which found that among many factors, COVID-19 risks and safety were the main reasons why the workers took this vaccine (14, 15). The study achieved 49% and gave a positive opinion that the vaccine is safe and can prevent COVID-19 disease, despite being a new study conducted among medical students in China. Furthermore, our findings align with another study conducted elsewhere in India, which established a high positive intention of receiving COVID-19 vaccines (16–18).

In addition, regarding whether to accept or refuse the vaccine among foreign medical students, the study finds that among those who accepted to receive it and those willing to receive it also depends on the opinions of the vaccine's side effects on the human body. The finding reveals that about 37.8% agreed that the vaccine had side effects. Based on the regression estimation results, less probability of side effects would increase the possibility of acceptance of the COVID-19 vaccine by 15% among foreign medical students in Chinese universities, significant at a 99% confidence level. The finding in this study is consistent with a study conducted in the USA, where most people were willing to get vaccinated despite the side effects triggered by external pressure (16, 19). However, about 42.7% of the participants stated that the vaccine was safe without side effects. These findings also support the findings in another current study conducted in Egypt, where they found that many health workers did not get the vaccine because of the fear of side effects and other reasons such as inaccurate information which the media and other sources were using (17, 20). Much as it is found like this, the findings of this study disagree with another study that involved the vaccination of maternity care consumers and providers in Australia, where it was found that the majority of the medical practitioners did not recommend these groups to take vaccination (8, 17, 20). This can result from the fear of side effects for maternity care consumers, which can be associated with.

Easy access to quality information dissemination through radio reveals less response of 1.6%; however, this finding depicts a contrary result from a study that found higher access to information through the radio about COVID-19 (20, 21). The study discovers that current information *via* the internet is systematically becoming a major platform of information for public consumption and whether it is a credible subsequent study might be required to establish it. Being an educational institute affiliated with major hospitals, most (32.4%) students heard about COVID-19 *via* Hospital and school notifications. Such efforts are highly recommendable as they increase the knowledge and awareness of medical-related information (22–27). On the same note, this study also agrees with another recent study conducted in China on international students' safety and COVID-19, which found that the issue of school notices also helped during the combat of COVID-19 in China (21, 22, 28). Vaccination is more effective, even the first shot is good enough to reduce the spread of COVID-19 (25, 28–30). The result shows good acceptance and perception, but other studies had poor knowledge and positive perception among those respondents (26, 27, 30–33). Our study depicted that based on the adequate information provided to the students, it boosts confidence, ensuring convenience and reduced complacency for vaccine acceptance and hesitancy, and this is consistent with the WHO-SAGE 3-Cs model (32, 34).

Furthermore, the findings show that 72.8% of the respondents are from Africa, and the rest, 27.2% are from Asia, Australia, Europe, North America, and South America. The estimated regression statistic on the parameter home continent shows a negative impact on COVID-19 vaccine acceptance (-0.062) and is significant at a 90% confidence level. This suggests that people on different continents or countries may resist accepting the COVID-19 vaccine and this is consistent with (31, 34–36). That is, the probability increase of people in Africa (as the reference) continents among medical students reduce the acceptance of the COVID-19 vaccine by more than 6% in Chinese universities, and this is significant at a 90% confidence level. This may be due to language and information barriers. These results are supported by the data statistic of respondents (6.7%) who still need to receive the vaccine. This finding confirms the literature and, however, the hesitancy rate of 6% among foreign medical students in China is lesser compared to 10% (31), 30% (30) in India, and 37% in Uganda (32).

Limitations of the study

First and foremost, due to the COVID-19 lockdown protocols particularly on the Chinese University campuses, the authors applied the online (survey and questionnaire) data collection technique. Therefore, this study is not without responses and information biases, and difficulty in interpreting the respondent sentiments behind some answers received. However, it was the most effective means considering some lockdowns where the researchers could not go. Also, it is worth noting that the assessment of vaccination intention in this study did not account for other relevant factors influencing vaccination and the respondent's decisions, such as vaccine length of protection and the requirement for booster doses, which could impact participants' decisions. That is, the study did not also control for external factors (such as government and institutional pressure) on medical students, which may have some bias in the study.

Conclusion

This study examined foreign medical students' attitudes, beliefs, experiences, reactions, and feelings regarding the COVID-19 vaccine acceptance and perception. We found that the opinion on the vaccine's safety, doses of the vaccine to receive, vaccine safety with some side effects, and the possibility of getting coronavirus disease after vaccination are significant positive factors influencing the acceptability in China among foreign medical students. Also, the finding further showed that foreign medical students from different continents adversely affect COVID-19 vaccine acceptance and perception among foreign medical students. The implication is that vaccine hesitancy among medical students is primarily affected by continent factors. The study, therefore, concluded that the COVID-19 vaccine is crucial, mainly influenced by the continent consideration in which the medical students are originally from. This, therefore, has policy implications for government and public health administration. Even though there is evidence of COVID-19 vaccine hesitancy among foreign medical students, the rate is reasonably low (6%) compared to other countries such as India and Uganda. We conclude that there is 83% of COVID-19 acceptance among foreign medical students in Chinese universities. This may be mainly due to the safety and effectiveness of health systems, knowledge, and vaccine information availability.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of First Hospital of Shanxi Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CA: took part in drafting, revising, critically reviewing the article, and acquisition of data. ZD: study design and took part in drafting. HA: formal analysis, revising, modeling, and critically reviewing the article. ML: acquisition of data. GM: formal analysis, modeling and drafting, and revising. CZ: ethical consideration process and acquisition of data. SZ: analysis. RH: acquisition of data and ethical consideration process. SO: visualization and review. AD: acquisition of data. LJ: execution. DZ: interpretation. HZ: revising technical support. HH: conception and critically reviewing the article. All authors gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1112789/full#supplementary-material

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Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: what could have happened?

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Introduction

Canada's early response to COVID-19 primarily employed non-pharmaceutical interventions (NPIs)—school and business closures, physical distancing measures, stay at home orders, and mandatory public masking—despite little evidence supporting them (1, 2). These responses were not part of existing pandemic plans (3). Indeed, they ignored the basic principles of pandemic planning, which is to minimise serious illness and deaths, as well as limit societal disruptions (4). Canada and the world need detailed analyses of the effectiveness and the costs of the NPIs used to try to control COVID-19. Such analyses must be separated from politics and evidentially based on comprehensive data sets.

Unfortunately, a recent article entitled "Counterfactuals of effects of vaccination and public health measures on COVID-19 cases in Canada: What could have happened?" published in the Canadian Communicable Disease Report by Ogden et al. (5) contains questionable results that sully the evaluation of these important issues. Instead of performing a much-needed analysis of real-world data, Ogden et al. (5) focus on simulation to postulate how the COVID-19 pandemic would have affected Canada had certain public health measures not been implemented. Phrases like "This study illustrates what may have happened…", and "Canada could have experienced…" are repeatedly expressed by the authors.

While dynamical models can be useful policy simulators, the insights derived from them can all-too-often become the codified opinions of the modeller (6). In this case, the paper by Ogden et al. (5) is less likely an objective lens into the past than a loss of critical distance from an overly complicated model. In this commentary, we discuss selected authors' assumptions and conclude that they are problematic at-best. We first identify empirically antiquated and conceptually ambiguous justifications supporting the article; second, we critique the model used to substantiate the article's conclusions; and finally, we elaborate on the implications of the authors' position for effective public health policy and human wellbeing in times of crisis.

The justifications

In the "Introduction", the authors assert that at the start of the pandemic, humans had no known immunity to SARS-CoV-2 (5). However, if humans were truly immunologically naïve to SARS-CoV-2, then it becomes difficult to explain-away the existence of cross-reactive neutralising IgG antibody (7) or memory T-cells (8, 9) to conserved epitopes between endemic coronavirus and SARS-CoV-2 proteins. These latter T cells will activate, expand, and produce IL-2 and IFN-γ when stimulated (*in vitro*) with cognate antigen (8), which very possibly represents a larger central memory response capable of impacting COVID-19 severity (10). Thus, at the very least, exposure to other human coronaviruses, prior to March 2020, appears able to confer measurable levels of immunity that was not considered—even in sensitivity analyses—by Ogden et al. (5) Similar immune responses to the 1918 strain of influenza existed 90 years later (11), and SARS-CoV-2 is unlikely to be the exception.

The authors also state that, unless the public health measures had been adopted, the consequences for Canadians and for Canada's public health system would have been "dire" (5). This claim, which is predicated on other modelling output (12), assumed that because of no effective therapies, Canada experienced an infection fatality rate (IFR) "approaching" 1%—contrasting it with a much lower IFR of 0.4% for seasonal influenza. While the supporting references used by Ogden et al. (5) estimate the case fatality rate (see their main text references 10, 11, 35), other empirical evidence indicates that the IFR for COVID-19 could be much lower than 1%. For instance, Ioannidis (13) determined that the IFR was 0.15–0.20% globally, and 0.03–0.04% for those under 70 years of age. Canadian-specific estimates reported by Ioannidis were 0.59% (overall) and 0.08% (for people aged < 70 years). People aged >70 years only account for 12.9% of the population in Canada (14). Similarly, results from the COVID-19 Forecasting Team (15) were compatible with unadjusted global IFRs between 0.0054% and 0.43% for people aged < 50 years, while Canadian-specific, age-adjusted cumulative IFRs decreased from 0.54% (in April 2020) and 0.35% (in January 2021). As for the alleged lack of effective therapies, early in 2020 the international literature indicated that early outpatient treatment with multidrug therapy successfully reduced hospitalisation and death, even among populations considered at high risk because of occupation, underlying health conditions, or age (16–20).

The article's "Chronology of the Epidemic and Public Health Measures" justifies the adoption of public health measures based on the "unrestrained SARS-CoV-2 transmission in Italy." This implies the rampant spread of the infection throughout the entire population. However, Professor Walter Ricciardi, Italy's scientific advisor, corrected this assumption when he noted that "The median age of people infected with SARS-CoV-2 who [were] dying in Italy has been 80 years, and the average age of patients requiring critical care support [was] 67 years" (21). Ricciardi's point on risk-stratification provides an entirely different perspective on the epidemic's characteristics, and if true, nullifies a key justification for the author's model—a virus that if "unrestrained" would be an equal opportunity killer. As well, as shown in their Table 2, Ogden et al. (5) assume that the listed countries have agreed on what constitutes a COVID-19 death. However, they overlook that until recently, a COVID-19 death was anyone dying with, not necessarily from COVID-19 (this was corrected in Ontario March 11, 2022) (22). They also overlook the substantial differences, worldwide, in definitions of COVID-19 deaths (e.g., China likely counts them very differently than Canada).

Model structure

Ogden et al. (5) constructed an agent-based model (ABM) for understanding any benefits of Canada's pandemic response. ABMs are computational models for simulating the actions and interactions of autonomous agents (such as people) to understand the behaviour of a system and the processes that govern any outcomes of interest (23). Because ABMs maintain distinct information on every individual in a simulated population, their finer-grained nature allows them to represent certain types of activities, relationships, and interventions with greater precision and flexibility than with more traditional differential equation models used to study pathogen transmission (23, 24). However, the granularity of ABMs carries with it an obligation to understand the minutiae that links a model's structure with its behaviour (24). Ogden et al. (5) have circumvented this necessity by filling-in details of people's movements that are exogenous to the structure of the model, rather than being driven by factors or feedbacks that are internal to its current state. This expanded effort in deepening their model has inhibited a critical broadening of the model boundary that will surely limit its validity (6, 24).

For example, the behaviour of the model's agents has an all-or-none relationship with public health measures: when in-place, people changed their behaviour proportionately to the value Oxford Stringency Index; when not in-place, agents maintain their status quo. This forced dependence on government orders is contrary to other research demonstrating that people's inherent fear of infection, alone, will cause them to alter their behaviour rapidly (25), and often before strict rules are in-place (26).

One consequence of the exogeneous drivers of people's behaviour is that two model-derived metrics have diverged substantially from publicly available data. Cumulative case and death rates reported by April 2022 were approximately 9,000 cases and 98 deaths per 100,000 people, respectively (27). When compared to the estimated values in the "observed baseline" scenario in their Table 3, both these empirical values lie outside the 95th percentiles of their modelled counterparts. This directional bias in model output is indicative of structural errors (28) that could distort comparisons between the calibrated (baseline) model and its counterfactual scenarios.

Over-reliance on counterfactual scenarios

Like all simulation modelling, ABM approaches require that we depart from real-world environments (e.g., workplaces and schools) and create idealised agents and environmental conditions (29, 30). When Ogden et al. discuss Canada's experience with COVID-19 without restrictive measures or vaccination, they failed

TABLE 1 Per capita Canadian deaths (per 100,000 people) attributed to World War I, II, and the 1918 influenza pandemic compared to the counterfactual modelling scenario "*no public health measures or vaccination*" of Ogden et al. (5).

Event	Deaths (People)	Period	Population (mid-Period)	Death Rate (per 100,000)*	Refs.
World War I	60,000	1914–1918	8,001,000	750	39,40
1918 influenza pandemic	50,000	1918–1920	8,311,000	602	39,40
World War II	44,090	1939–1947	11,795,000	374	39,41
Ogden et al. (5) counterfactual	800,000†	2020–2022	N/A#	2,034 (1,938–2,115)‡	5

*Death Rate = (Deaths / Population) × 100,000; † Upper limit of mortality count for the "no public health measures or vaccination" scenario taken from Table 1 in Ogden et al. (5); # Ogden et al. do not provide an estimate of the Canadian population in their article; ‡ Median (95th percentiles) per capita death rate for 100 model realisations taken from Table 3 in Ogden et al. (5).

to note at least two problems. First, "up to 800,000" COVID-19 deaths are greater than any other historic event in Canada over the last 108 years, corresponding to higher per capita death rates than for all Canadian lives lost in World War I, the 1918 influenza pandemic, and World War II (see Table 1) (31–33). Second, the addition of 800,000 deaths would have large consequences for all-cause mortality over the pandemic period, more than doubling it from approximately 640,000 cumulative deaths (34) to 1.4 million. To us, it is an amazing coincidence that all the provincial pandemic responses, which were applied at different times in different sequences (35), could have produced such a large effect that all-cause mortality was reduced to nearly what can be predicted historically—before March 2020—when there was no pandemic and no public health measures, whatsoever [see Figure 5 in Rancourt et al. (36)].

Final comments

It is important that we try to assess the effectiveness and the costs of pandemic interventions dispassionately. The justifications and conclusions in the article by Ogden et al. (5) which are derived from a single model, with no sensitivity analyses around key assumptions, leads us to wonder: what was its point? Was it to showcase an evidence-based analysis of actual policies and their alternatives? Or was it an attempt to justify government action, despite other evidence of their limited benefit (37)?

As academic exercises, counterfactual analyses and what could have happened can possess epistemic benefits. These modes of thought and speech have been the subject of study in philosophy, politics, and history (38), as well as in medical decision making (39). In the analysis by Ogden et al. (5) counterfactuals represent an attractive means for "re-running" history. However, they represent a great disservice to public health in the way they have been used by Canadian public health officials. Just as counterfactual scenarios were used to justify "doing something" during the pandemic (e.g., (40)), the historical revisions of Ogden et al. (5) are used to vindicate that having "done something" was the right course of action. However, unlike modelling the future—which is testable—there is no way to demonstrate whether counterfactual scenarios are right or wrong about "what could have happened." The historical path, the one involving no interventions, was foreclosed the moment the pandemic responses began (29). Neither Ogden et al. (5) nor anyone else, can ever observe the simultaneous response and non-response of Canada's experience with SARS-CoV-2. Instead, all that remains are "what-if?" statements and modelling output akin to the simulated worlds found in online games; they might appear convincing, but their foundations are imaginary, and their walls are pixel thin (41).

That said, the article by Ogden et al. (5) has two redeeming features. The authors admit that: one, Canada's response to the pandemic was not perfect; and two, that the unintended consequences of the public health measures need to be investigated. It will be a measure of the honesty, courage, and integrity of the Public Health Agency of Canada, and their Provincial partners, if the latter is ever realised.

Author contributions

DV, SE, JH, CC, and SP contributed to the conception, writing, and editing of this opinion article. All authors contributed to the article and approved the submitted version.

Conflict of interest

SP is a Founder and Chief Scientific Officer at Kinexus Bioinformatics Corporation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The impact of the COVID-19 pandemic on chlamydia infection in South Korea: a comparison between the pre-pandemic and during-pandemic periods

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Background: Prior to COVID-19 pandemic, a yearly upward trajectory in the number of chlamydia infection cases was observed in South Korea. However, in response to the COVID-19 pandemic, Korea implemented several public health and social measures, which were shown to have an impact on the epidemiology of other infectious diseases. This study aimed to estimate the impact of the COVID-19 pandemic on the incidence and number of reported chlamydia infections in South Korea.

Methods: Using the monthly number of reported chlamydia infection data between 2017 and 2022, we compared the trends in the reported numbers, and the incidence rates (IR) of chlamydia infection stratified by demographic characteristics (sex, age group, and region) in the pre- and during COVID-19 pandemic period (January 2017–December 2019 and January 2020–December 2022).

Results: We observed an irregular downward trajectory in the number of chlamydia infection in the during-pandemic period. A 30% decrease in the total number of chlamydia infection was estimated in the during-pandemic compared to the pre-pandemic period, with the decrease greater among males (35%) than females (25%). In addition, there was a decrease in the cumulative incidence rate of the during COVID-19 pandemic period (IR: 0.43; 95% CI: 0.42–0.44) compared to the pre-pandemic period (IR: 0.60; 95% CI: 0.59–0.61).

Conclusions: We identified decrease in the number of chlamydia infection during COVID-19 pandemic which is likely due to underdiagnosis and underreporting for the infection. Therefore, strengthening surveillance for sexually transmitted infections including chlamydia is warranted for an effective and timely response in case of an unexpected rebound in the number of the infections.

KEYWORDS

chlamydia, surveillance, sexually transmitted infection (STI), sexually transmitted disease (STD), SARS-CoV-2, Korea

Introduction

Chlamydia infection caused by *Chlamydia trachomatis* is a common sexually transmitted infection (STI) worldwide. Globally, ∼50%−88% of chlamydia infection cases are asymptomatic (1). Due to the high rate of asymptomatic cases, systematic monitoring of chlamydia infections for high-risk populations, including sexually active young adults, has been recommended (2, 3). Furthermore, the monitoring of the infections provides us with a useful proxy for changes in sexual risk behaviors (4).

The first case of the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in South Korea was reported on 20 January 2020 (5). And in an attempt to control the SARS-CoV-2, South Korea, implemented several public health and social measures (PHSMs), including social distancing, and wearing of face masks from 22 March 2020, which were crucial in mitigating the burden of the COVID-19 pandemic (6). The implementation of these PHSMs had considerable effects on the incidence and prevalence rates of other bacterial and viral infectious diseases (7, 8). In addition, these PHSMs reduced person-to-person interactions as well as the access and use of clinical services such as screening, and treatment for sexually transmitted infections (STIs) (9). The reported shift in various screening services including STI screening services, toward only symptomatic patients, could reduce the ability to identify asymptomatic chlamydia infections, hence a reduction in the overall reported number of cases (10).

There have been several concerns among clinicians and researchers in different countries regarding the spread of STIs during the COVID-19 pandemic and the possible long-term consequences of their underdiagnosis (11).

In 2019 before the importation of SARS-CoV-2 in South Korea, a total of 48,756 outpatient screening for chlamydia infection was done compared to 40,640 screenings in 2020 and 37,632 in 2021, implying a 16% and 23% decrease in 2020 and 2022, respectively (12).

Previous empirical literature in Europe (13, 14) and the United States (15) have demonstrated a decrease in the number of new cases of sexually transmitted infections including chlamydia infection during the early stages of the COVID-19 pandemic, and during the period when the PHSMs were implemented. In South Korea, a study reported an apparent decrease in the incidence of chlamydia infections during the early stages of the COVID-19 pandemic (16). However, the impact of COVID-19 on the trends of the reported number of chlamydia infection and incidence in the pre- vs. during-COVID-19 pandemic period in Korea is yet to be compared. Here, we compared the monthly number of reported chlamydia infection cases in the pre-COVID-19 period (January 2017–December 2019) with the number of monthly cases reported in the same period during-COVID-19 (January 2020–December 2022) by age, sex and regions in South Korea.

Materials and methods

Study data and variables

In South Korea, sentinel-based surveillance for chlamydia infection has been conducted since 2000 by the Korea Disease Control and Prevention Agency (KDCA) (17), an electronic database that collects data reported from healthcare professionals and laboratories in South Korea. This surveillance includes data from 587 sentinel sites located throughout the country (18). We collected the monthly number of chlamydia infection cases between January 2017 and December 2022, with a focus on the month of confirmation of the first COVID-19 case in South Korea (serving as the cut-off point of the pre vs. during-COVID-19 pandemic periods) and the first period of implementation of PHSMs (22 March, 2020 to 01 November, 2020). We divided the study period into two; the pre-pandemic (January 2017–December 2019) and the during-pandemic (January 2020–December 2022) periods.

In July 2017, due to system maintenance schedules according to the KCDA reports, no data inputs were made into the database. Therefore, we assumed the number of cases for the period of maintenance to be the average number of cases for June and August 2017. The collected data were stratified by sex, age group, and region of residence.

Data analysis

We assessed the impact of the COVID-19 pandemic and the implementation of the PHSMs on the number of reported chlamydia infection cases using two approaches. First, we compared chlamydia infection reported case monthly and yearly trends for the pre-COVID-19 pandemic period compared with the during-COVID-19 pandemic period and for each subgroup (sex, age group, and region). Second, using the pre-pandemic values as the baseline, we estimated the percentage changes in the absolute number of cases during the pandemic period. We examined significant differences in the changes between the pre-pandemic and during-pandemic values using the Chi-squared test. Using the 2021 population of South Korea as the standard population, we estimated the cumulative incidence rates of chlamydia and 95% confidence intervals (CI) for the pre-pandemic and during-pandemic period per 1,000. Then, we conducted stratified analyses by age group in years (<20, 20–29, 30–39, 40–49, and ≥50), sex (male, and female), and region. We classified the regions into two categories; in the Seoul Capital Area (SCA) which was made up of Seoul, Incheon, and Gyeonggi; and out of SCA which included all other cities.

All analyses were performed using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria), and the level of statistical significance was set at $p < 0.05$.

Results

A total of 31, 238 new chlamydia infection cases were reported in the pre-pandemic period while 22,186 new cases were reported in the during-pandemic period. There was a 28.9% decrease in the total number of chlamydia infection cases in the during-pandemic period compared to the pre-pandemic period. Stratifying by sex, compared to females (−24.9%), there was a significantly greater decrease in the number of chlamydia infection cases in males (−34.9%, $P < 0.001$). By age group, we identified a significant decrease in the number of reported cases among all groups, with the

TABLE 1 Overall reported number of chlamydia infection cases during the pre-COVID-19 pandemic and during COVID-19 pandemic periods in South Korea.

Demographic characteristics	Pre-COVID-19 pandemic	During COVID-19 pandemic	Change in absolute value	Percentage Change (%)	*P-value
No. of cases	31,238	22,186	−9,052	−28.9	<0.001
Sex					
Male	12,582	8,181	−4,401	−34.9	<0.001
Female	18,656	14,005	−4,651	−24.9	<0.001
Age groups					
<20	2,259	1,808	−451	−19.9	0.004
20–29	15,080	11,702	−3,378	−22.4	0.0021
30–39	7,516	4,603	−2,913	−38.7	<0.001
40–49	3,847	2,232	−1,615	−41.9	<0.001
≥50	2,537	1,841	−696	−27.4	0.003
Region					
In SCA	18,430	13,159	−5,271	−28.6	<0.001
Out of SCA	12,628	9,027	−3,601	−28.5	<0.001

*p-values for the difference between the pre-pandemic and during-pandemic period for each demographic variable gotten by Chi-square test; SCA, seoul capital area.

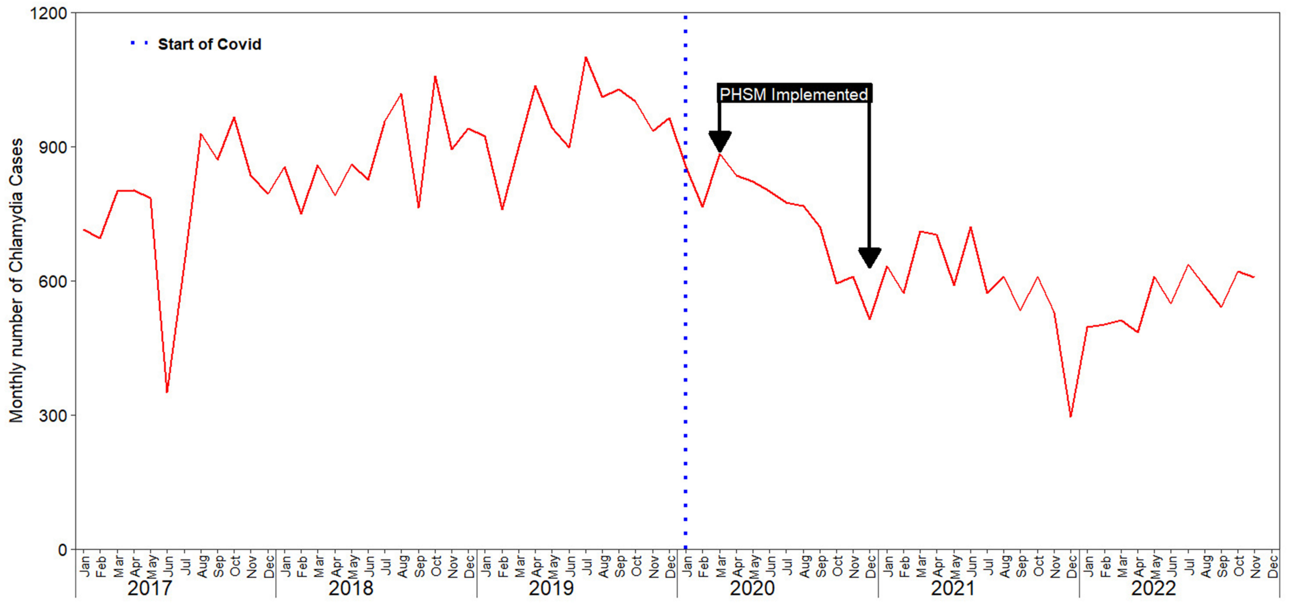

FIGURE 1
Impact of COVID-19 on chlamydia infection case reporting in South Korea: trends from 2017 to 2022.

highest decrease in the age group 40–49 years (−41.9%, $P < 0.001$). By region, an almost equal magnitude of decrease was observed in the number of chlamydia infection cases in both the Seoul capital area region and out of the Seoul capital area region (respectively, −28.6% and −28.5 %, $P < 0.001$) (Table 1).

We identified the monthly number of chlamydia infection cases reported had an irregular upward trajectory between 2017 and 2019, while, a downward trajectory was observed between 2020 and 2022 (Figure 1, Supplementary Figure S1).

Stratifying by sex, and age group an irregular downward trajectory was also observed in each subgroup, in the during-pandemic period (Figure 2). Similarly, we observed a downward trajectory in the during-pandemic period after stratification by region (Figure 3).

We also identified concurrent decreases in the during-pandemic chlamydia infection incidence rates in all subgroups in the during-pandemic period compared to the pre-pandemic period (Table 2).

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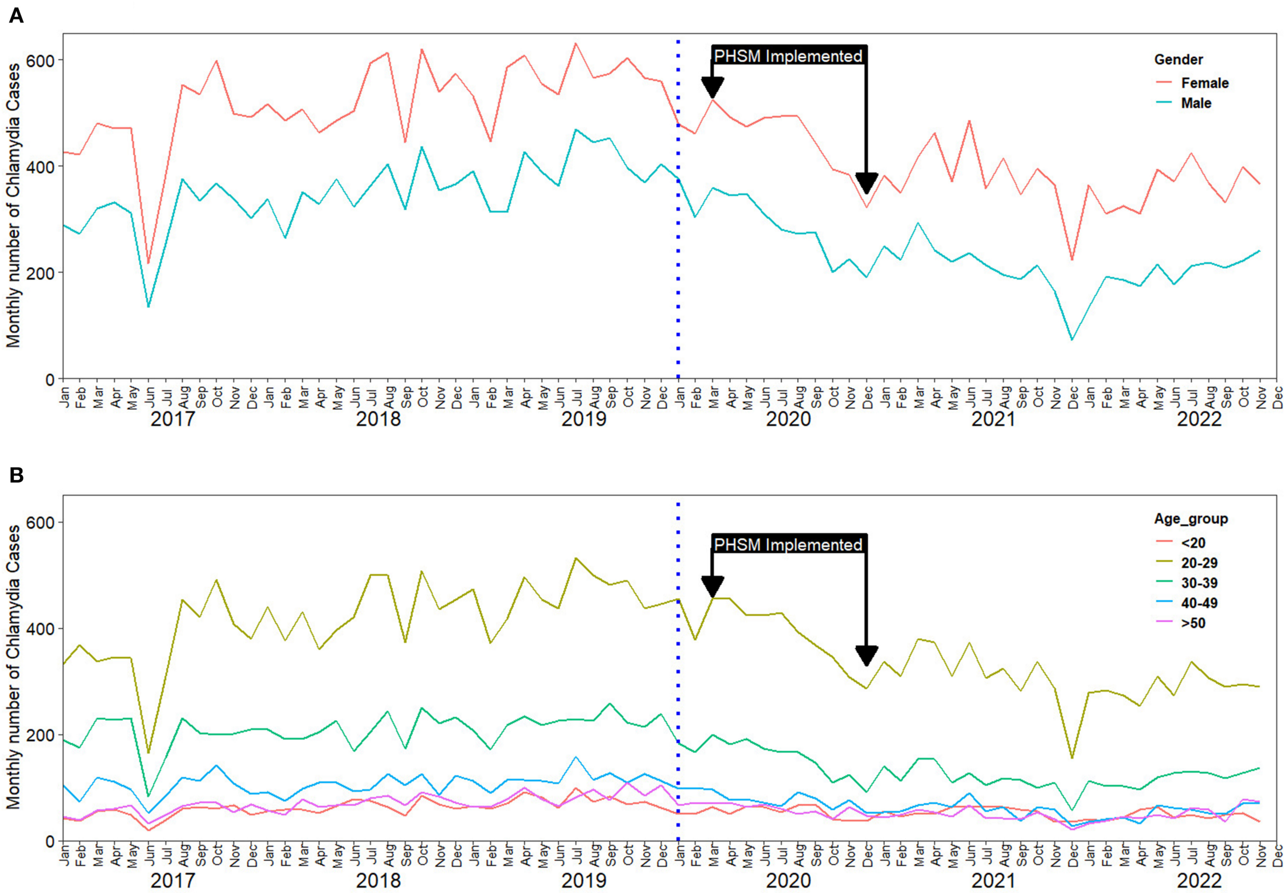

FIGURE 2
Impact of COVID-19 on chlamydia infection case reporting in South Korea: trends from 2017 to 2022; **(A)** Reported cases stratified by sex; **(B)** Reported cases stratified by age.

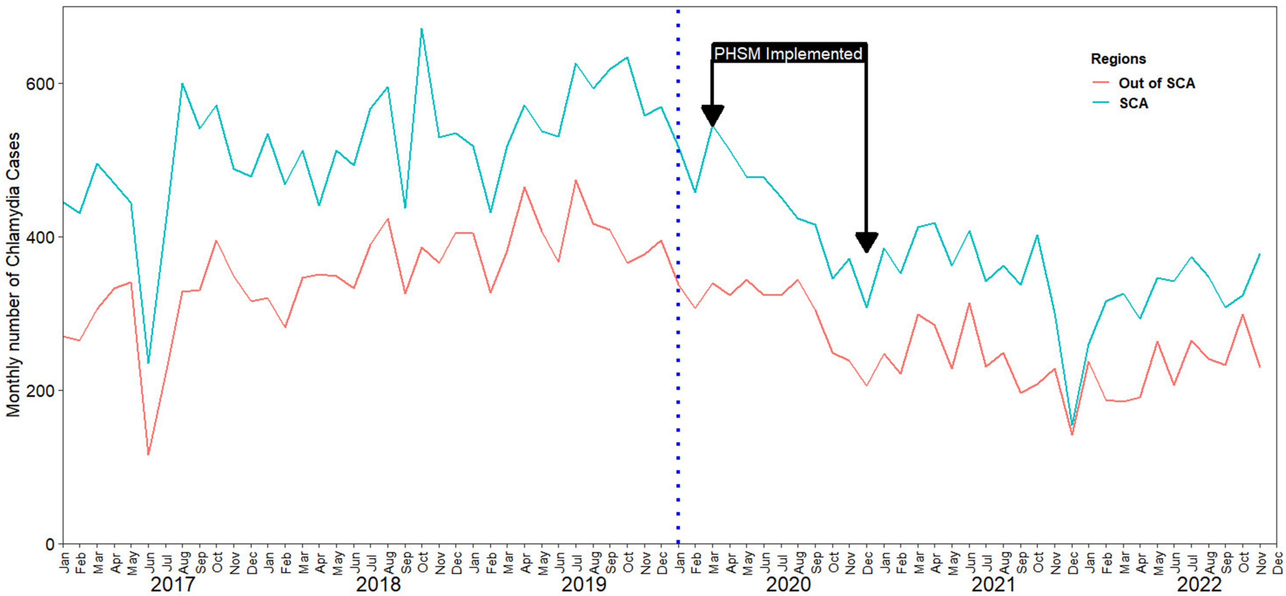

FIGURE 3
Impact of COVID-19 on chlamydia infection case reporting in South Korea by region.

TABLE 2 Changes in Chlamydia infection incidence rates (IR) per 1,000 population for the pre-COVID-19 pandemic and during COVID-19 pandemic periods in Korea.

		Pre-COVID-19 pandemic period IR (95% CI)								During COVID-19 pandemic period IR (95% CI)							
		Overall	Sex		Age group (years)					Overall	Sex		Age group (years)				
			Male	Female	<20	20–29	30–39	40–49	≥50		Male	Female	<20	20–29	30–39	40–49	≥50
Overall		0.60 (0.59–0.61)	0.49 (0.48–0.50)	0.72 (0.71–0.73)	0.27 (0.26–0.28)	2.34 (2.30–2.37)	1.08 (1.05–1.10)	0.47 (0.46–0.49)	0.12 (0.12–0.13)	0.43 (0.42–0.44)	0.32 (0.31–0.33)	0.54 (0.53–0.55)	0.21 (0.20–0.22)	1.81 (1.78–1.85)	0.66 (0.64–0.68)	0.27 (0.26–0.28)	0.09 (0.083–0.091)
Region	In SCA	0.71 (0.69–0.72)	0.55 (0.54–0.57)	0.88 (0.86–0.89)	0.31 (0.29 0.33)	2.61 (2.55–2.66)	1.17 (1.13–1.20)	0.51 (0.49–0.53)	0.13 (0.12–0.14)	0.51 (0.49–0.52)	0.37 (0.36–0.39)	0.63 (0.62–0.65)	0.24 (0.23–0.26)	1.98 (1.93–2.02)	0.73 (0.71–0.76)	0.29 (0.28–0.31)	0.10 (0.09–0.10)
	Out of SCA	0.49 (0.48–0.50)	0.43 (0.41–0.44)	0.56 (0.548–0.57)	0.22 (0.20–0.23)	1.99 (1.94–2.04)	0.97 (0.94–1.01)	0.43 (0.41–0.45)	0.11 (0.10–0.12)	0.35 (0.35 0.36)	0.26 (0.25–0.27)	0.45 (0.43–0.46)	0.18 (0.17–0.20)	1.60 (1.56–1.65)	0.57 (0.55–0.59)	0.25 (0.24–0.27)	0.08 (0.07–0.08)

SCA, seoul capital area.

Discussion

We assessed the impact of the COVID-19 pandemic on the number of reported chlamydia infection cases and the incidence of chlamydia infection in Korea using national surveillance data. This assessment demonstrates the substantial impact of the COVID-19 pandemic on the chlamydia prevention program.

We observed a continuous downward trajectory in the number of reported chlamydia infection cases across all the years in the during-pandemic period. Similarly, there was a decrease in the cumulative incidence rate in the during-pandemic period compared to the pre-pandemic period. A similar trend was observed with other STIs (Supplementary material). This observed decreases in the pandemic period could be a result of behavioral changes as part of the stay-at-home mandates and also as a result of some barriers to patient care and preventive services that were directly or indirectly introduced as a result of the COVID-19 pandemic. During the COVID-19 pandemic, individuals were very reluctant to visit the doctor's office for medical consultation for fear of SARS-CoV-2 infection (19, 20). These changes in health-seeking behaviors could have impacted the screening of asymptomatic individuals. Moreover, the constant surveillance of STIs done by the local public health centers as well as associated primary health clinics may have been interrupted by COVID-19 control activities, limiting doctor's appointments and screening of potential cases. Our findings are similar to other studies that have also reported a decrease in the incidence and number of reported cases of chlamydia infection and other STIs in the pandemic period compared to the pre-pandemic period (21–24). However, our results are contrary to a study that reported an increase in chlamydia infection cases and other STIs during the COVID-19 pandemic (25, 26).

In this study, a sharper decrease in the overall trend was observed after the implementation of the PHSMs. During this period, the activities of the adult entertainment sectors (including nightclubs, bars, and other nighttime activities) were shut down. This may have reduced the number of STI screenings, as workers in the adult entertainment sector in South Korea are mandatorily screened for STIs every 3 months according to Korean Infectious Disease Control and Prevention act. However, due to the limited public health resources during COVID-19 pandemic, many workers was not likely screened for STIs by public health authorities. Our results are contrary to previous research that showed that PHSMs implemented during the early pandemic did not affect STIs (15, 27). This is likely due to the different level of use for public health resources for COVID-19 pandemic in different countries.

Our study also showed a sex, age group, and regional decrease in the trend of incidence and number of reported cases of chlamydia infection in the during-pandemic compared to the pre-pandemic period. Specifically, a significantly greater decrease was observed in males (−34.9%) compared to females and among those between 40 and 49 years old (−41.9%) compared to other age groups. This is in line with other studies in the literature which have shown that males are less likely to seek health care, especially for preventive care visits (28, 29). Therefore, this could be explained by underdiagnosis and underreporting given that there are concerns that chlamydia infections may be underdiagnosed in males and in middle age individuals (30). Underdiagnosis and underreporting of chlamydia infections may be due to decreased screening during the pandemic. Appropriate screening and medical consultations are recommended and health education and promotion activities aimed at sensitizing the public and healthcare providers are also needed.

There are some limitations to the present study. First, this study does not take into account the number of chlamydia tests that were conducted. Although the number of reported chlamydia infection cases decreased in the during-pandemic period, it is highly likely that many screening tests for the infection were not conducted. Furthermore, it is possible that the decrease in reported cases was not only due to the COVID-19 pandemic, but potentially due to policy changes around the fear of exposure to SARS-CoV-2 infection in a clinical setting.

Secondly, although several cofactors may exist between the COVID-19 pandemic and the incidence and number of reported chlamydia cases, this study could not assess the magnitude of the effect of each mediator, such as social restrictions, physical distancing, and hygiene measures.

In conclusion, our results suggest that the incidence and number of chlamydia infection cases decreased during the COVID-19 pandemic in South Korea. In pandemic and epidemic emergencies that involve behavioral restrictions, the promotion of healthcare-seeking behaviors among high-risk individuals for the sexually transmitted infections including chlamydia is encouraged.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.kdca.go.kr/npt/biz/npp/ist/simple/simplePdStatsMain.do.

Ethics statement

Ethical review or informed consent was not required because all data used in this study were anonymous and publicly available.

Author contributions

S-MH and SR conceived the study and sought funding. SR, AC, and J-HJ did the data collection, assimilation, and data analysis. SR and AC wrote the first draft of the manuscript. S-MH and AC critically reviewed and edited the manuscript. All authors contributed to the interpretation of the results, critical revision of the manuscript, and have given final approval of the version to be published.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1167321/full#supplementary-material

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Cost-effectiveness analysis of COVID-19 screening strategy under China's dynamic zero-case policy

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This study aims to optimize the COVID-19 screening strategies under China's dynamic zero-case policy through cost-effectiveness analysis. A total of 9 screening strategies with different screening frequencies and combinations of detection methods were designed. A stochastic agent-based model was used to simulate the progress of the COVID-19 outbreak in scenario I (close contacts were promptly quarantined) and scenario II (close contacts were not promptly quarantined). The primary outcomes included the number of infections, number of close contacts, number of deaths, the duration of the epidemic, and duration of movement restriction. Net monetary benefit (NMB) and the incremental cost-benefit ratio were used to compare the cost-effectiveness of different screening strategies. The results indicated that under China's COVID-19 dynamic zero-case policy, high-frequency screening can help contain the spread of the epidemic, reduce the size and burden of the epidemic, and is cost-effective. Mass antigen testing is not cost-effective compared with mass nucleic acid testing in the same screening frequency. It would be more cost-effective to use AT as a supplemental screening tool when NAT capacity is insufficient or when outbreaks are spreading very rapidly.

KEYWORDS

COVID-19, cost-effectiveness, screening strategy, agent-based model, dynamic zero-case policy, China

1. Introduction

Coronavirus disease 2019 (COVID-19), is an infectious disease that causes fever, cough, shortness of breath, pneumonia, and lung infections. The pandemic poses a threat to the security of all humanity and has a huge negative effect on the economy, stability, and culture of countries around the world. A previous study estimated that the first wave of COVID-19 in China resulted in 2647 billion RMB losses (1). At present, China has effectively prevented large-scale outbreaks through the implementation of the strategy of "external prevention of importation and internal prevention of rebound" and the policy of "dynamic zero-case policy"(2). However, global COVID-19 is still in a pandemic state, Omicron is still sweeping across the world, and the sporadic cases and localized outbreaks in China are a reminder that the risk of large-scale outbreaks remains.

Dynamic Zero-Case Policy is to contain domestic virus flare-ups through timely actions. Once a localized outbreak has occurred, rapid and accurate epidemiological investigations are carried out to identify the source of infection, which is then combined with regional mass screening, contact tracing, quarantine, isolation, and movement restriction to break the chain of transmission and contain the spread of the outbreak (Figure 1).

Mass screening helps to detect asymptomatic infections promptly and reduces community transmission (3). In addition, it can help decision-makers make more scientific judgments about ongoing community transmission and flexibly adjust prevention and control measures accordingly. Due to the different epidemiological situations and prevention and control policies, there is currently no standardized screening strategy for COVID-19 that fits all countries. Moreover, the cost-effectiveness of different COVID-19 screening strategies under China's dynamic zero-case policy has not been fully explored and demonstrated. Therefore, this study aimed to assess the cost-effectiveness of different screening strategies for COVID-19 in different scenarios to optimize screening strategies and reduce losses from localized outbreaks.

2. Methods

2.1. Comparator strategies

The most commonly used testing methods for COVID-19 are nucleic acid testing (NAT) and antigen testing (AT) in China. Based on the latest COVID-19 disease prevention and control guidelines (2), nine competing strategies consisting of different screening frequencies and testing methods were designed and compared in this study (Table 1). Considering the enormous challenges posed by the highly infectious Omicron variant for outbreak control, and to better simulate the real situation and more comprehensively assess different screening strategies, two scenarios were set for this study: (1) Scenario I: the outbreak spreads slowly, epidemiological investigations were carried out accurately, and close contacts can be traced and isolated promptly; (2) Scenario II: the outbreak develops rapidly, the transmission chain was difficult to sort out, and a proportion of close contacts cannot be traced and isolated promptly.

2.2. Population and time Horizon

Community-based grid governance can be effective in helping to reduce or even stop outbreaks (4), hence the target population for this study was all community residents in China. All imported cases from abroad were excluded. The time horizon of the study was a localized outbreak, starting with the introduction of one infected case and ending with no un-isolated infected cases in the community.

2.3. Model

2.3.1. Model summary

Mathematical models based on the SEIR framework have proven to be excellent tools for simulating and predicting the spread of infectious diseases and for evaluating prevention and control measures (5–7). However, these models do not capture individual differences, individual-to-individual, and individual-to-group effects, and are not flexible enough to fully assess different prevention and control measures. To address the above shortcomings, a stochastic agent-based model (ABM) was used to simulate the COVID-19 outbreak in this study. ABM is a method of simulating the behavior and interactions of autonomous agents in a particular environment across time steps (8). NetLogo software (Wilensky, Northwestern University) was used for modeling and running.

2.3.2. Model description

Agents are generated at random coordinates and move randomly within a virtual community. Initially, all agents are at the state of susceptible (S) except for a preset latent (L) infection. Latent infections become infectious and detectable after progressing to pre-symptomatic (P). Pre-symptomatic agent progress to asymptomatic infection (Ia) or symptomatic infection (Is) in a proportion. Symptomatic infections will be hospitalized (H) as confirmed cases after routine testing. When the number of confirmed cases is >0, regional mass screening and close contact tracking procedures will be initiated. Close contacts will be quarantined (Q) after being tracked. Asymptomatic infections are still infecting other agents unless they are hospitalized after diagnosing by mass screening or recovered (R) after self-healing. When the number of confirmed cases is >50, a community lockdown procedure will be initiated, all agents are not allowed to move or contact other agents. Hospitalized agents will progress to recovered or deceased (D). When there are no unquarantined infected persons in the community means that the outbreak is contained, all intervention procedures such as community lockdown will be stopped and the simulation will be aborted (Figure 2).

2.3.3. Model parameters

Model parameters were mainly derived from previous studies, expert opinions, and fieldwork (Table 2). Population size was set to 6,000, which is approximately equal to the population of a small-scale community in China. Infectious capability of infections was based on the probability of infection in close contacts in previous studies (22) and adjusted for the basic regeneration number measured in this model. The time required for nucleic acid testing, including sampling, transfer, and laboratory testing, was based on expert opinion (9). Maximum mobility of agents and sizes of simulation space were adjusted for population density reasonably. Baseline values for epidemiological parameters were mainly taken from studies related to Omicron, as it is now the main prevalent strain worldwide (13–16, 18). In scenario I, maximum time needed for tracking close contacts was set to 72 h, and quarantined probability of close contact was set to 100%. In scenario II, these two values were set to 120 h and 75%.

Considering the huge impact of COVID-19 on productivity, societal perspective was adopted in this study. Both direct and indirect costs are included in the cost measurement. Indirect costs are calculated using the human capital approach (23). Cost parameters came from two studies of the disease burden of the first wave of COVID-19 in China (1, 7), and were calibrated according to the latest data and prevention and control policies (2). For example, the "14 + 14" quarantine policy was replaced by "7 + 3". The centralized quarantine period for close contacts was shortened to

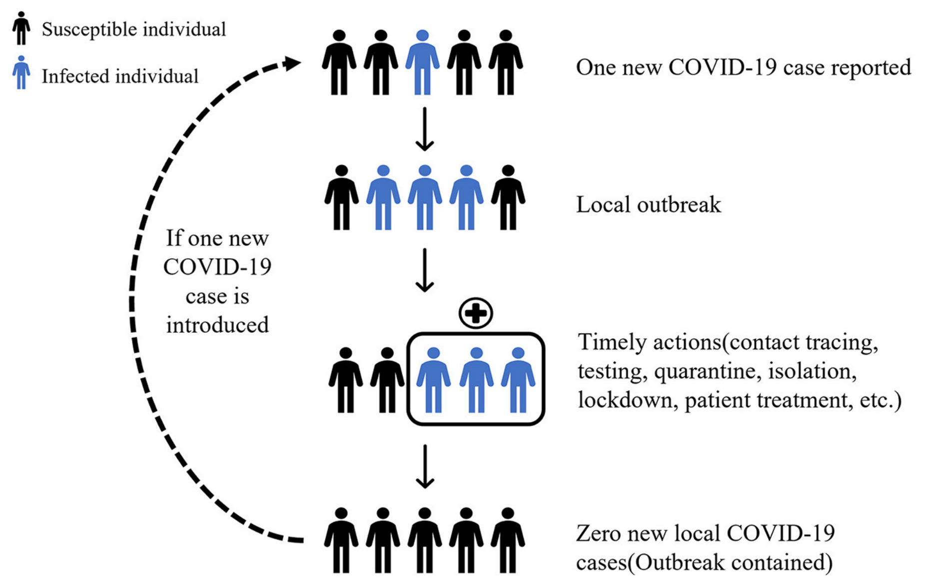

FIGURE 1
Schematic of dynamic zero-case policy.

TABLE 1 COVID-19 community screening strategies.

Screening strategies	Frequency of NAT	Additional AT
S1	Once a day	–
S2	Once every 2 days	–
S3	Once every 3 days	–
S4	Once every 4 days	–
S5	Once every 5 days	–
S6	Once every 6 days	–
S7	Once every 7 days	–
S8	Once a day	Once a day (12 h from the NAT)
S9	Once every 2 days	Once every 2 days (24 h from the NAT)

7 days, followed by 3 days of health monitoring, during which they could go to work with proper personal protective measures. Thus, working time lost of close contacts was calibrated to 7 days. The average medical costs and average work time lost per case were weighted by booster vaccination coverage and the proportion of clinical types. Due to the short time horizon of the study, costs were not discounted. All costs are converted to U.S. dollars (USD) at the exchange rate (1 USD = 7 RMB).

2.3.4. Key assumptions

Limited by the accessibility of some data and for the sake of model streamlining, the key assumptions of this study are mainly as follows:

(1) All infectious individuals have the same infectious capacity, and the infectious capacity does not change over time.
(2) Patients assumed to be non-infectious and not at risk of a second infection.
(3) Infections cannot infect other individuals during isolation.
(4) Individuals receive a NAT on days 1, 2, 3, 5, and 7 during quarantine according to China's COVID-19 disease prevention and control guidance.
(5) The time required for NAT or AT is ignored.
(6) Confirmed cases will be promptly isolated and treated.
(7) Deaths not due to COVID-19 infection (Background mortality) were not simulated.

2.4. Cost-effectiveness analysis

The outcome indicators of the outbreak simulation in this study were mainly the cumulative number of infections, close contacts, quarantined persons, deaths, duration of the outbreak, and length of community lockdown. The economic evaluation indicators for competing strategies were screening cost, total cost, and net monetary benefit (NMB). Based on the outcome indicators, the total cost calculation formula in the formula are as follows:

$$\begin{aligned}\text{Total cost} = {} & Cost_i * AI + Cost_{cc} * ACC + Cost_d * AD \\ & + Cost_{at} * TAT + Cost_{pnat} * TPNAT \\ & + Cost_{snat} * TSNAT + Cost_{cl} * LCL\end{aligned}$$

$Cost_i$ is the weighted average cost per case and contains both direct and indirect costs. Direct costs were based on costs of cases of different disease severities obtained from previous studies, weighted first by booster vaccination coverage and then by the proportion of cases of different disease severities with or without booster vaccination. After weighting in the same way to obtain the weighted average working time lost per case, the indirect costs were obtained by multiplying by the national daily average salary.

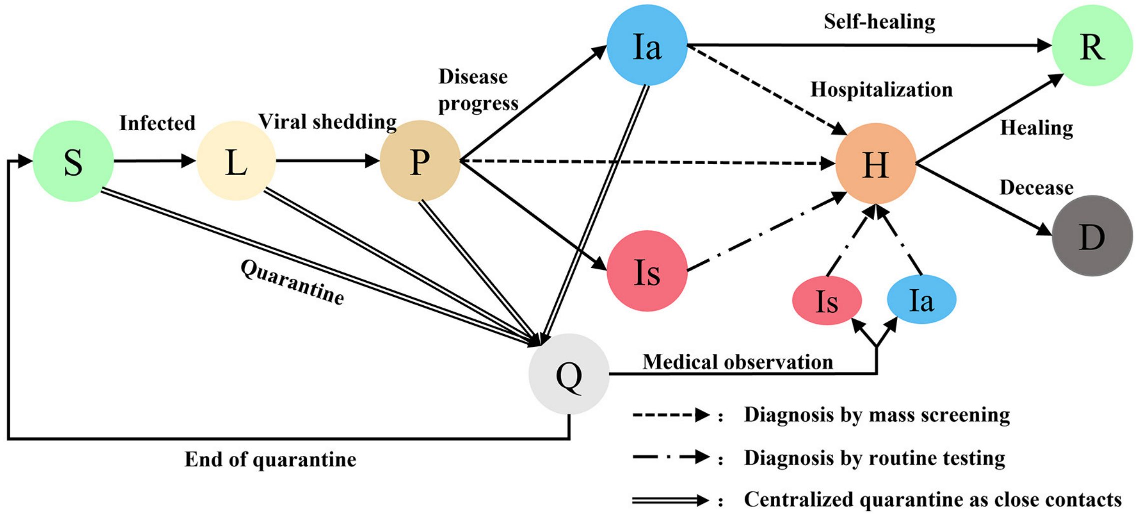

FIGURE 2
Different states of agents in COVID-19 transmission model. Susceptible S, Latent L, Pre-symptomatic P, Quarantined Q, Asymptomatic Ia, Symptomatic Is, Hospitalized H, Recovered R, Deceased D.

AI is accumulative infections. $Cost_{cc}$ is the total cost of each close contact including direct and indirect costs. Direct costs include staff allowances, accommodation for quarantine, meals, and NAT, were obtained from fieldwork. Indirect costs were derived by multiplying the number of days of quarantine by the national daily average salary. ACC is accumulative close contacts. $Cost_d$ is the total cost per death, obtained by multiplying lifetime working years lost for COVID-19 fatalities obtained from previous studies by per capital GDP, and only the labor loss due to death is considered here.AD is accumulative deaths. $Cost_{at}$ is the cost per sample for AT. TAT is the total number of antigen tests. $Cost_{pnat}$ is the cost per pooled sample NAT. TPNAT is the total number of pooled sample NATs. $Cost_{snat}$ is the cost per single sample NAT. TSNAT is the total number of single sample NATs. $Cost_{cl}$ is the cost of community lockdown per day. Due to the short time horizon of this study, only the labor loss due to the community lockdown is considered here. Its calculation formula is as follows:

$$Cost_{cl} = n*NDAS$$

Where n is the total number of agents who have not been quarantined, hospitalized, or died at the end of the simulation. NDAS is national daily average salary per person. LCL is the length of community lockdown. The detailed cost parameters are shown in Table 2.

To reflect the uncertainty of the outbreak and to reduce randomness, 1,000 simulations were performed for each competing strategy in each scenario. The mean and standard deviation of outcome indicators were reported. A one-way sensitivity analysis was performed to test the robustness of the results and to analyze the impact of variations in parameter values.

3. Results

3.1. Simulation results

In Scenario I, the duration of the outbreak, accumulative infections, accumulative close contacts, and the length of the community lockdown trended flatly upward as the frequency of community screening decreased (Figure 3). This upward trend is more evident in scenario II, where the accumulative infections increased from 18.32 to 97.20, accumulative close contacts increased from 378.79 to 1558.75, the duration of the outbreak increased from 156.36 to 336.54 h, and the length of community lockdown increased from 3.37 to 121.38 h. Due to the low infection fatality rate and the small population size simulated, there were no deaths under all screening strategies (Table 3).

3.2. Cost-effectiveness results

In both scenarios, as the frequency of community screening increased, the cost of screening increased, but the total cost decreased, and this downward trend was more evident in scenario II (Figure 4). In both scenarios, S8 had the highest community screening cost but the lowest total cost, and S7 had the lowest community screening cost but the highest total cost. Compared to S7, S8 avoided a total economic loss of $312,204 in Scenario I and $1,466,543 in Scenario II. Although the screening frequency was the same for S1 and S9, S9 had a higher screening cost and a higher total cost in both scenarios. In addition, the total cost of S9 is lower compared to S2, which has a lower frequency of screening (Table 3).

TABLE 2 Value and source of model parameters.

Parameter	Base-value	Source
Global Parameter		
Sizes of simulation space (patches)	60*60	Assumption
Population size	6,000	Assumption
Time unit (hour/tick)	1	Assumption
Random seed number	1–1,000	–
Time required to obtain routine NAT results after sampling (hours)	4	Expert opinion (9)
Time required to obtain mass NAT results after sampling (hours)	8	Expert opinion (9)
Time required to obtain AT results after sampling (hours)	0.25	Expert opinion (9)
Sensitivity of NAT (%)	100	Assumption
Sensitivity of AT (%)	70	(10–12)
Agent properties		
Maximum mobility (patches/ticks)	0.5	Assumption
Infectious capability (%)	10	Assumption
Epidemiological parameter		
Asymptomatic infection rate (%)	35	(13)
Incubation period (days)	3	(14)
Infectious period for symptomatic infections (days)	7	(15)
Infectious period for asymptomatic infections (days)	4	(15)
Basic reproductive number	6.33	(16)
Infection fatality rate (%)	0.09	(17)
Cost parameter		
Proportion of mild/moderate, severe, and critical case of non-booster-vaccinated individuals (%)	81.5;13.8;4.7	(1, 7)
Proportion of mild/moderate, severe, and critical case of booster-vaccinated individuals (%)	96.7;3.3;0.0	(18)
Booster vaccination coverage (%)	71.7	Previous studies
Average medical cost for a confirmed case of non-severe, severe, critical (US$)	800; 7,513; 21,620	(1, 7)
Weighted average medical cost per case (US$)	1,501.28	Calculated
Single sample nucleic acid test cost (US$)	2.29	(19)
Pooled sample nucleic acid tests cost (US$)	0.43	(19)
Antigen test cost (US$)	0.86	(20)
Per capital GDP (US$)	11,568	(21)
National daily average salary (US$)	31.69	Calculated
Daily quarantine costs for close contacts (US$)	57.14	Fieldwork
Other parameters		
Working time lost of close contacts (days)	7	(2)
Working time lost of mild/moderate, severe, and critical case (days)	29.71; 33.92; 35.35	Calibrated (1, 7)
Weighted average working time lost per case (days)	30.05	Calculated
Lifetime working years lost for COVID-19 fatalities (years)	10.23	(1, 7)

3.3. Sensitivity analysis

Detailed results of the sensitivity analyses are provided in Supplementary Tables 4, 5. Sensitivity analysis indicated that the base-case analysis was robust. The dominant strategy remained S8 when parameters were varied within the range. In both scenarios, the top 3 parameters that have the greatest impact on the total cost of S8 were basic reproductive number, national daily average salary and asymptomatic infection rate (Figure 5). Considering that S1 is the commonly used strategy in China during that period, we also provide the results of its one-way sensitivity analysis in Supplementary Tables 6, 7.

4. Discussion

This study evaluated different COVID-19 screening strategies under the current "dynamic zero-case policy" in China. The results showed that all indicators of outbreak size tended to decrease as the frequency of screening increased. This indicated that high frequency of screening could help contain the spread of the outbreak and reduce the size and burden of the outbreak, and this effect was more obvious in the case of a rapidly developing outbreak (Scenario II), which is consistent with the findings of previous studies (24–26). The most cost-effective screening strategy was daily NAT and an additional AT (S8). This suggested that such a high-frequency screening strategy is still cost-effective given the high transmissibility of the Omicron variant and the low cost of screening in China.

Meanwhile, the comparison of S1 with S9 revealed that mass AT is not cost-effective compared with mass NAT for the same screening frequency. This is probably because although AT has the advantage of convenience and speed, its sensitivity is lower compared to NAT, which may lead to missed and false detections, resulting in sequential transmission of outbreaks and increasing the total cost. Therefore, with the current low sensitivity of AT, it cannot completely replace NAT in community screening. However, additional AT in S9 would result in lower total costs compared to S2, which has a lower frequency of screening. The above suggested that using AT as a complementary screening tool would be more cost-effective in situations where NAT capacity is insufficient or the outbreak is spreading very rapidly.

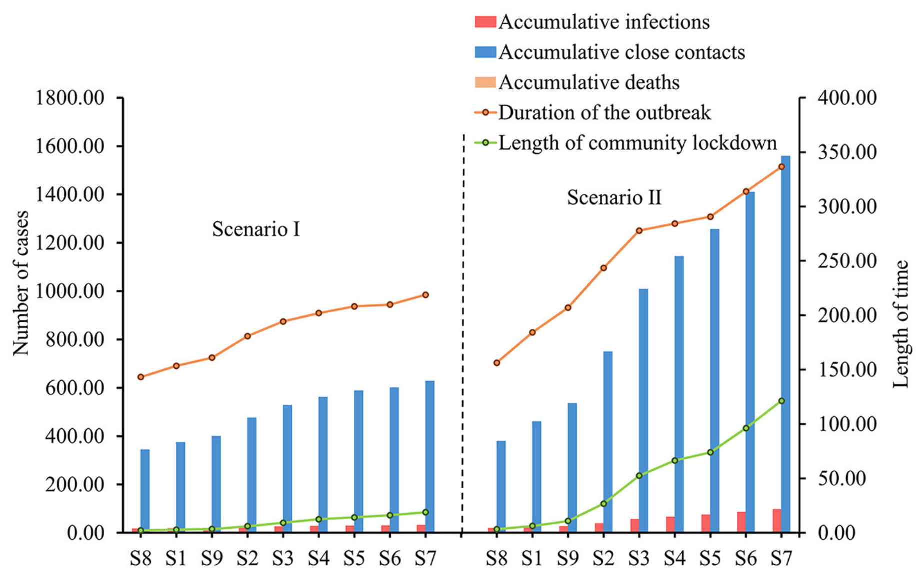

FIGURE 3
Simulation results of COVID-19 transmission under different strategies in two scenarios.

TABLE 3 COVID-19 transmission and cost effectiveness of different strategies.

Strategy	Duration of the outbreak	Accumulative infections	Accumulative deaths	Accumulative close contacts	Length of community lockdown	Community screening cost (1,000 USD)	Total cost (1,000 USD)	Net monetary benefit (1,000 USD)
Scenario I								
S1	153.48	17.95	0.00	374.11	2.89	9.83	275.79	297.45
S2	180.79	22.81	0.00	475.62	6.07	6.95	370.86	202.38
S3	194.25	25.52	0.00	527.19	9.27	5.48	431.04	142.20
S4	201.98	27.41	0.00	561.93	12.41	4.63	478.85	94.39
S5	208.15	28.75	0.00	587.50	14.25	4.09	510.33	62.91
S6	209.79	29.56	0.00	600.22	16.12	3.72	532.61	40.63
S7	218.78	31.10	0.00	628.46	18.87	3.51	573.24	-
S8	143.25	16.47	0.00	343.37	2.26	23.97	261.04	312.20
S9	160.99	19.17	0.00	399.27	3.48	15.43	304.15	269.09
Scenario II								
S1	184.17	22.36	0.00	460.11	6.26	13.13	283.38	1,409.32
S2	243.43	38.58	0.00	749.14	26.82	10.43	601.29	1,091.41
S3	277.87	55.87	0.00	1,007.94	52.48	8.67	930.70	762.01
S4	284.36	65.69	0.00	1,144.00	66.54	6.53	1,103.25	589.46
S5	290.63	74.30	0.00	1,256.22	73.96	5.90	1216.22	476.49
S6	313.77	85.58	0.00	1,408.91	96.28	5.64	1,452.28	240.43
S7	336.54	97.20	0.00	1,558.75	121.38	5.50	1,692.71	-
S8	156.36	18.32	0.00	378.79	3.37	28.66	226.16	1,466.54
S9	206.94	26.26	0.00	535.08	10.84	22.62	372.95	1,319.75

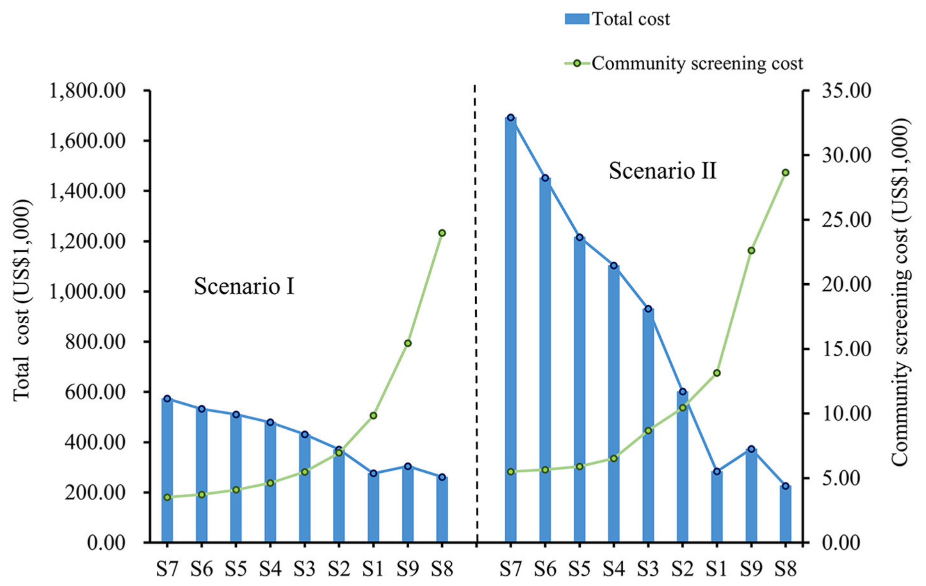

FIGURE 4
Total cost and community screening cost under different strategies in two scenarios.

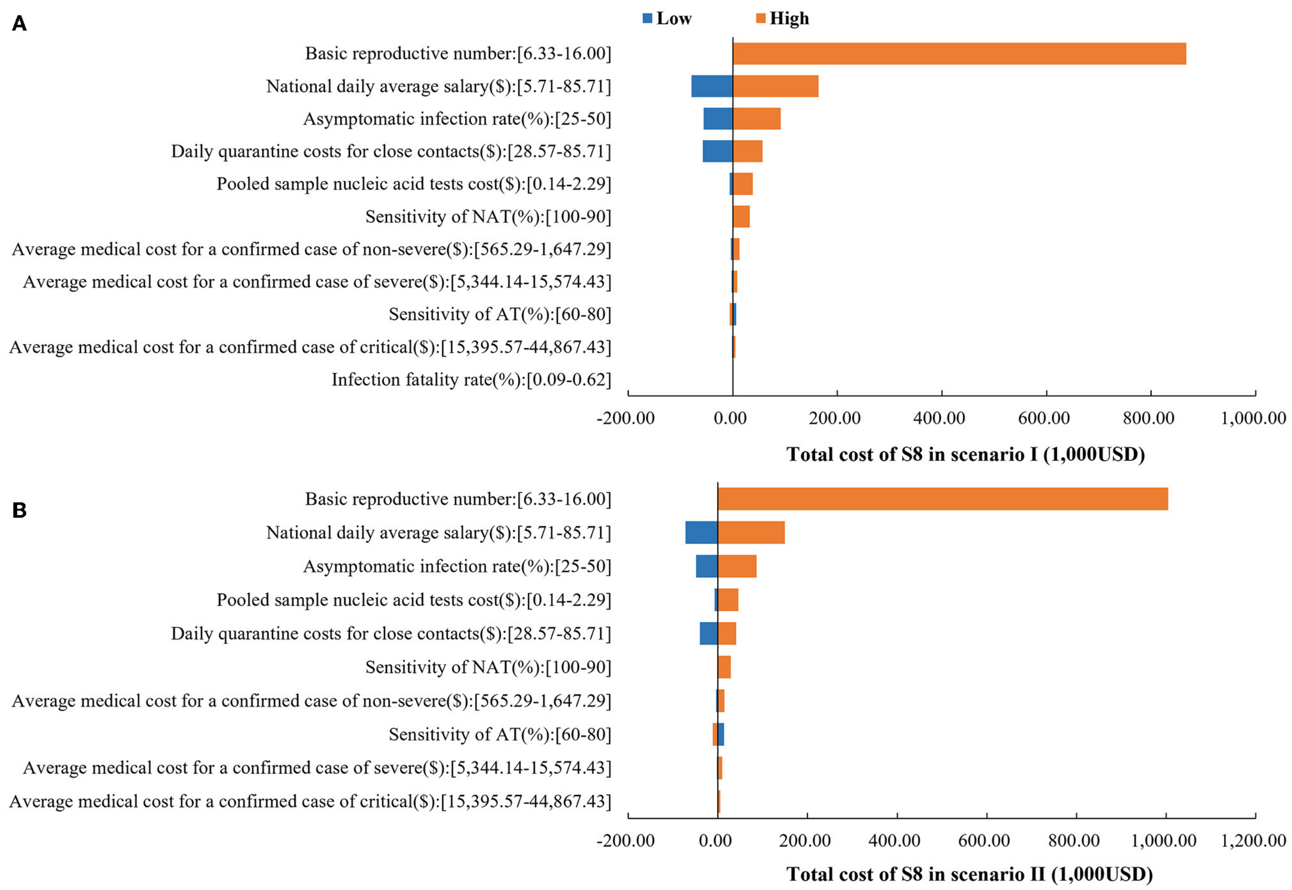

FIGURE 5
One-way sensitivity analysis results. **(A)** Impact of parameters on the total cost of S8 in scenario I. **(B)** Impact of parameters on the total cost of S8 in scenario II.

It is worth noting that when an outbreak occurs, screening alone cannot block the spread of the outbreak. In this study, it was found during model simulation that if preventive and control measures such as close contact tracing and quarantine and restriction of population movement were removed, it would lead to all individual infections. Thus, the significance of mass screening is the timely detection of cases, and its cost-effectiveness is predicated on the combination of other prevention and control measures. This is also in line with previous studies (27–29).

Sensitivity analysis showed that among the cost parameters, the results were more sensitive to the national daily average salary. With the current low rate of severe illness and mortality, the economic burden of COVID-19 is mainly attributed to the loss of productivity. As found in other studies, productivity loss accounted for 99.8% of the total cost in the first wave of COVID-19 outbreak in China. Therefore, further research is needed on how to continuously optimize prevention and control measures, reduce the impact of the epidemic on productivity, and integrate epidemic prevention and control with economic development.

There are several limitations of this study. First, due to the short time horizon of this study, the health and cost impacts of long-COVID were not taken into account. Second, the simulated population size is relatively small, so the extrapolation of the model may be affected. Third, due to the lack of data, age, gender, and behavioral differences may lead to bias between the model and the real world. Fourth, a human capital approach was adopted in the measurement of indirect costs. And since some workers can choose to work from home, the indirect costs may be overestimated. Finally, the transmission capacity of infected individuals may vary with viral load, which was not taken into consideration in this study due to model streamlining.

Since the outbreak of COVID-19, China has been adjusting and optimizing its prevention and control strategy accordingly to the evolving situation. In January 2023, China's management of COVID was downgraded to the less strict class B from the current top-level class A, as the disease has become less virulent. From then on, China has entered a new phase in coordinating economic and social development and epidemic prevention and control.

Through a brief review we found that during the period when China adopted a "dynamic zero-case" strategy, although some cities strictly implemented the "dynamic zero-case" policy, there were cases where the size of the outbreak was larger than the simulated results of this study. The reasons for this phenomenon may be as follows: First, considering that epidemic control in China is community-based and the fact that too many samples may lead to excessively long model runs, this study is based on a simulation of 6,000 individuals in a single community in China, not on an entire city or an entire province. In the real world, provinces consist of many cities, and cities consist of many communities and individuals, and the increased sample size may result in a larger real-world epidemic size than in this study. The population density and geographic characteristics of different cities in the real world may also affect the spread of the epidemic. Second, in reality, although there have been large epidemics, there have also been many successful cases of "dynamic zero". For example, the city of Shenzhen, with a population of 17.6 million and a highly mobile population, has implemented the "dynamic zero" policy well on more than one occasion, controlling the epidemic in a short period and keeping the prevalence rate at a low level. Third, some of the interventions in this model, such as close contact tracing and isolation, mass screening, and movement restrictions, are implemented according to set model parameter values. In contrast, in the real world, the effectiveness of interventions may be influenced by more factors such as affordability, civil compliance, country conditions, and government capacity, which may lead to higher data on the size of outbreaks in the real world than in this study. In light of the above, further research can be done in future studies to address the effects of affordability, civil compliance, national conditions, and government capacity on transmission in order to strengthen China's capacity for the prevention and control of infectious diseases, including COVID-19.

5. Conclusion

Under China's COVID-19 dynamic zero-case policy, high-frequency screening, such as daily NAT and an additional daily AT, can help contain the spread of the epidemic, reduce the size and burden of the epidemic, and is cost-effective. Mass AT is not cost-effective compared with mass NAT in the same screening frequency. It would be more cost-effective to use AT as a supplemental screening tool when NAT capacity is insufficient or when outbreaks are spreading very rapidly.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

HL: study design, model design, parameters colleting, and data analyses. HZ: resources, supervision, and funding acquisition. HL and HZ: the original draft preparation and writing—review and editing. Both authors contributed to the article and approved the submitted version.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1099116/full#supplementary-material

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There is a need for more precise models to assess the determinants of health crises like COVID-19

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The COVID-19 pandemic has had a significant impact on global mortality. While the causal relationship between SARS-CoV-2 and the anomalous increase in deaths is established, more precise and complex models are needed to determine the exact weight of epidemiological factors involved. Indeed, COVID-19 behavior is influenced by a wide range of variables, including demographic characteristics, population habits and behavior, healthcare performance, and environmental and seasonal risk factors. The bidirectional causality between impacted and impacting aspects, as well as confounding variables, complicates efforts to draw clear, generalizable conclusions regarding the effectiveness and cost-benefit ratio of non-pharmaceutical health countermeasures. Thus, it is imperative that the scientific community and health authorities worldwide develop comprehensive models not only for the current pandemic but also for future health crises. These models should be implemented locally to account for micro-differences in epidemiological characteristics that may have relevant effects. It is important to note that the lack of a universal model does not imply that local decisions have been unjustified, and the request to decrease scientific uncertainty does not mean denying the evidence of the effectiveness of the countermeasures adopted. Therefore, this paper must not be exploited to denigrate either the scientific community or the health authorities.

KEYWORDS

COVID-19, epidemiology - analytic (risk factors), public health, public health policies, epidemic determinants, confounding (epidemiology)

Introduction

The dramatic impact of COVID-19 on global mortality is a scientific fact (1–3). Indeed, the size and significance of the effect are so large and in agreement with the vast literature on the subject that bias analysis is not needed to ascertain the mere existence of this causal relationship (4). However, more precise and complex models are required to attribute the exact weight to all the epidemiological factors involved. Indeed, although it is true that the ability of a pathogen to compromise public health—in all its aspects—is part of its inherent hazard (e.g., overloading of health facilities due to high contagiousness and virulence), it is also true that such a threat is determined by the variables that it affects (e.g., the performance of health facilities). Moreover, COVID-19 behavior appears to be influenced by a wide range of risk factors and determinants, the assessment of which is undermined by known confounders and bidirectional relationships (Table 1). Specifically, in such a mathematically and scientifically complex system, constructing a global statistical cost function and ascertain primary causes of phenomena can be demanding. Since these elements are essential to draw up a prioritization scheme of interventions (i.e., which variables to tackle or influence

TABLE 1 COVID-19-related epidemiological variables.

Impacted/ing aspects	Determinants and risk factors	Confounders
- Availability of care beds - Availability of health personnel - Availability of medical equipment for treatments - Availability of drugs - Availability of protective equipment - Performance of healthcare personnel - Performance of healthcare systems	- Age (weaker immune system) - Gender - Pre - existing medical conditions - Population habits and behavior - Poor healthcare capacity and/or quality - Health infodemic - Pollution and other environmental factors - Seasonal risk factors	- Historical differences in determinants and risk factors - Historical differences in healthcare capacity and/or quality - Undesired NPC impact on healthcare system - Undesired NPC impact on people health - Undesired NPC impact on contagion - Asymptomatic cases - Testing capacity and/or quality

first to obtain the best benefit) as well as a methodology of intervention (i.e., how to tackle or influence a specific variable to obtain the best benefit), the whole public health decision-making process is potentially compromised and/or severely slowed down. To the best of the authors' knowledge, no current model satisfactorily incorporates all these variables. This also makes scientific conclusions, and therefore public health actions, varyingly exposed to authors' interpretations and biases (5).

Impacted and impacting aspects

A very contagious and aggressive virus like SARS-CoV-2 can impair the health system causing facilities overload (6), shortage of healthcare personnel (7, 8), shortage of medical-related supplies (6, 9), physical and mental exhaustion of healthcare workers (10), and other human errors in managing the emergency (10, 11) (impacted aspects). At the same time, poor healthcare can obviously increase COVID-19 (and other diseases) severity, fatality, and mortality. For this reason, causality between impacted and impacting aspects is bidirectional and subject to confounding.

Determinants and risk factors

The scientific literature on COVID-19 reports various risk factors related to the individual's health status, including age, gender, and a long list of specific pre-existing conditions (12–15), population habits, movements and adherence to anti-pandemic regulations (15, 16), insufficient or delayed healthcare, information overabundance and success of misleading and/or incorrect news (even among healthcare workers) (17), air pollution (18), environmental and meteorological factors including temperature, relative humidity, sunlight, and wind (19–22), and seasonal risks such as the arrival of cold weather (19, 20).

Confounders

Historical differences in risk factors and health service adequacy may create apparent differences in virus fatality and severity as intrinsic epidemiological characteristics. Furthermore, lockdowns and social distancing—considered by the majority of the scientific community as an essential tool for the containment of the infection (23–25)—have caused heterogeneous detrimental effects, varying in effect size and prevalence, both at the socio-psychological level (26–28) (which can have repercussions on physical health), in healthcare services, and even contagion dynamics (29). Alongside this, asymptomatic cases, insufficient testing capacity and quality can further bias the estimation of deaths possibly associated with COVID-19 (30–33).

Recommendations

In light of this evidence, I ask that the scientific community and health authorities worldwide begin to develop comprehensive models not only for the current pandemic emergency but also for future health crises. Considering a typical epidemiological study design, this means conducting a thorough literature search on all known or suspected variables that may potentially interact with the pathogen of interest. This also means developing multivariable models with parameters based on local empirical characteristics (from the availability of drugs to suspected evolutionary mutations) to determine the epidemiological role and weight of each variable by fitting the observed data. One possible approach to achieving this goal is to use mixed models with reciprocal effects, training established algorithms (e.g., hierarchical regression and extended SEIR) enhanced with artificial intelligence (e.g., machine learning and neural networks) on both historical and current data (34–38). Naturally, bias analysis and expertise play a crucial role in accurate implementation. This also calls for further research on mathematical-epidemiological modeling of human aspects in various contexts, including general (e.g., people behavior), professional (e.g., hospital assistance dynamics), psychological (e.g., psychological reactions), and infodemiological (e.g., the effects of infodemics on concrete actions). Although the inclusion of all relevant variables may be an unattainable objective, successful modeling of some additional single or even groups of factors would allow for a better estimation of the impact of the remaining (un-modeled). The sensitivity analysis should be utilized to assess the reliability and predictive power of the models, as well as to examine the intercorrelations among inputs and outputs (39). Besides, the mission should not solely be to ensure the short-term survival of as many people as possible, but rather to seek a solution that ensures a sustainable lifestyle (i.e., both socially and psychologically viable). For example, by establishing varying degrees of lockdown severity and quality of life, the aim should be to scientifically establish the minimum severity level at which the mere epidemiological risk and quality of life are deemed acceptable. Such a point is vital for the success of long-term policies since people's adherence is strongly affected by pandemic fatigue and similar phenomena (40–42). Thus, decisions should be made based on the related cost functions. Indeed, at present, it is challenging to draw clear, unequivocal, and generalizable conclusions not so much on the effectiveness as on the cost-benefit ratio of non-pharmaceutical health countermeasures. Likewise, comparisons between countries' policies are also often arbitrary. In this scope, such models should be implemented locally to account for micro-differences in epidemiological characteristics that may have relevant effects (e.g., evolutionary mutations and/or particularly polluted areas that increase the pathogen virulence in a certain region). By doing so, it would be possible to ensure and protect public health in a timely manner based on the best available scientific evidence, minimizing the epidemiological impact and uncertainty in decision-making thanks to more targeted and specific investigations and interventions. This could also lead to greater trust in institutions (which could plausibly translate into greater adherence to required health regulations) and a decrease in fallacious and misleading debates on counterfactual scenarios (e.g., what would have happened if...). Undoubtedly, such a strategy would necessitate increased investment in local resources, such as surveillance systems and appropriately trained personnel. However, comparing provincial, regional, and national models could yield valuable insights into their differences and similarities, allowing for a better understanding of which factors require local analysis versus those that can be effectively modeled at larger scales. Whether this paper is too ambitious or not, the above considerations highlight that it is paramount to establish a theoretical goal to strive for and to call for moderation among those scientists who express too much certainty on inherently dubious topics, risking fostering distrust toward institutions and science (43, 44). Finally, I conclude by saying that this perspective must not be exploited to denigrate either the scientific community or the health authorities since (i) the lack of a universal model does not in any way imply that local decisions have been unjustified, and (ii) the request to decrease scientific uncertainty does not mean denying the evidence on the effectiveness of the countermeasures adopted but only expecting greater precision in ascertaining the entity of costs and benefits for future implementations. In this regard, the author of this paper expresses their solidarity with the victims of the COVID-19 pandemic phenomenon and with those who made great responsibility decisions disposing only of limited and uncertain data during a period of extreme social tension.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Night-time population consistently explains the transmission dynamics of coronavirus disease 2019 in three megacities in Japan

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Background: Mobility data are crucial for understanding the dynamics of coronavirus disease 2019 (COVID-19), but the consistency of the usefulness of these data over time has been questioned. The present study aimed to reveal the relationship between the transmissibility of COVID-19 in Tokyo, Osaka, and Aichi prefectures and the daily night-time population in metropolitan areas belonging to each prefecture.

Methods: In Japan, the *de facto* population estimated from GPS-based location data from mobile phone users is regularly monitored by Ministry of Health, Labor, and Welfare and other health departments. Combined with this data, we conducted a time series linear regression analysis to explore the relationship between daily reported case counts of COVID-19 in Tokyo, Osaka, and Aichi, and night-time *de facto* population in downtown areas estimated from mobile phone location data, from February 2020 to May 2022. As an approximation of the effective reproduction number, the weekly ratio of cases was used. Models using night-time population with lags ranging from 7 to 14days were tested. In time-varying regression analysis, the night-time population level and the daily change in night-time population level were included as explanatory variables. In the fixed-effect regression analysis, the inclusion of either the night-time population level or daily change, or both, as explanatory variables was tested, and autocorrelation was adjusted by introducing first-order autoregressive error of residuals. In both regression analyses, the lag of night-time population used in best fit models was determined using the information criterion.

Results: In the time-varying regression analysis, night-time population level tended to show positive to neutral effects on COVID-19 transmission, whereas the daily change of night-time population showed neutral to negative effects. The fixed-effect regression analysis revealed that for Tokyo and Osaka, regression models with 8-day-lagged night-time population level and daily change were the best fit, whereas in Aichi, the model using only the 9-day-lagged night-time population level was the best fit using the widely applicable information criterion. For all regions, the best-fit model suggested a positive relationship between night-time population and transmissibility, which was maintained over time.

Conclusion: Our results revealed that, regardless of the period of interest, a positive relationship between night-time population levels and COVID-19 dynamics was observed. The introduction of vaccinations and major outbreaks of Omicron BA. Two subvariants in Japan did not dramatically change the relationship between night-time population and COVID-19 dynamics in three megacities in Japan. Monitoring the night-time population continues to be crucial for understanding and forecasting the short-term future of COVID-19 incidence.

KEYWORDS

severe acute respiratory syndrome virus 2 (SARS-CoV2), mobility, public health and social measures, *de facto* population, cluster

1. Introduction

Since the severe acute respiratory syndrome virus 2 (SARS-CoV-2) originated in Wuhan, China (1) and developed into a global pandemic that is still ongoing in many countries, closely monitoring the extent of human-to-human contact at a societal level has been a key issue in public health. Human mobility data in general are widely accepted as one of the most important sources of data for inferring the extent of human-to-human contact, because most contacts outside of households cannot be made without people traveling or staying outside. In fact, several studies have provided evidence on the explanatory power of mobility data and its effectiveness on controlling COVID-19 dynamics (2–5).

Among many data sources on human mobility, the usefulness of mobile phone location data for understanding and predicting coronavirus disease 2019 (COVID-19) dynamics has been revealed by studies in countries with high rates of mobile phone ownership (3, 6, 7). These data are also important for monitoring the effectiveness of non-pharmaceutical interventions by governments (8).

In Japan, several studies have examined the relationship between COVID-19 and mobility data. For example, two studies in Japan on COVID-19 dynamics in 2020 showed a positive relationship between COVID-19 spread and population volumes at several types of locations or time zones, particularly restaurant and bar usage (9, 10). This positive relationship was also observed in other empirical studies in Japan exploring different periods of time or using different sources of mobility data (11, 12).

Although a positive relationship between mobility and COVID-19 upsurge was observed for a specific period of time in Japan, it remains to be determined whether the effects of social contacts are relatively stable or are highly variable over time, because previous studies in Japan did not analyze data throughout the COVID-19 pandemic from 2020. This issue is particularly important because, if we know in advance about the periods during which the social contact level affects the dynamics of COVID-19, that knowledge could inform how we implement non-pharmaceutical interventions against COVID-19. Moreover, it is possible that the effect of mobility has changed because of vaccinations against COVID-19 or behavioral changes since the emergence of COVID-19. However, to the best of our knowledge, no previous study has tackled the predictive ability of mobility data over a long time-course. It is difficult to correctly estimate the effect throughout a long period of an epidemic, because in the early stages of the pandemic there is no way to know whether the effects are highly time-varying or not. Simply applying linear regressions to explain the dynamics of COVID-19 via mobility data may lead to erroneous results showing high time-dependent variability of the effect of mobility (Tokyo: right column of Figure 1; see Supplementary Figure S1 for Aichi and Osaka), and adequately considering serial correlation in statistical models may cause the results to differ.

One of the key public interests in Japan throughout the COVID-19 pandemic has been on eating and drinking activities that elevate the risk of COVID-19 transmission, and it is widely recognized that such activities are particularly intense in downtown areas at night. Motivated by the insufficiency of evidence on the relationship between night-time drinking or eating activity and COVID-19 dynamics, and the need for such evidence for future rises in COVID-19 caused by novel variants or the emergence of pandemics caused by other pathogens, the objective of the present study was to clarify the relationship between night-time population in the downtown area in three metropolitan areas in Japan and the transmission dynamics of COVID-19. Two linear regression models were employed to appropriately account for the time-dependent relationship between these two datasets.

2. Materials and methods

2.1. Epidemiological dataset of COVID-19

In Japan, COVID-19 has been designated as a notifiable disease according to The Infectious Disease Control Law, and all confirmed cases are mandatorily reported to the government via local health centers. Confirmatory diagnoses were made either by reverse transcription polymerase chain reaction or rapid diagnostic testing of nose or throat swabs. On the basis of this notification system, daily COVID-19 case count data are openly shared by Japan's Ministry of Health, Labor, and Welfare, as a function of the reporting date, and we used the open data for the following analyses (13). The dataset shows the daily number of reported COVID-19 cases in each prefecture, created by aggregating the reports from the local health departments in each prefecture. From this dataset, COVID-19 case counts from Tokyo, Osaka, and Aichi were extracted (shared as Supplementary Data).

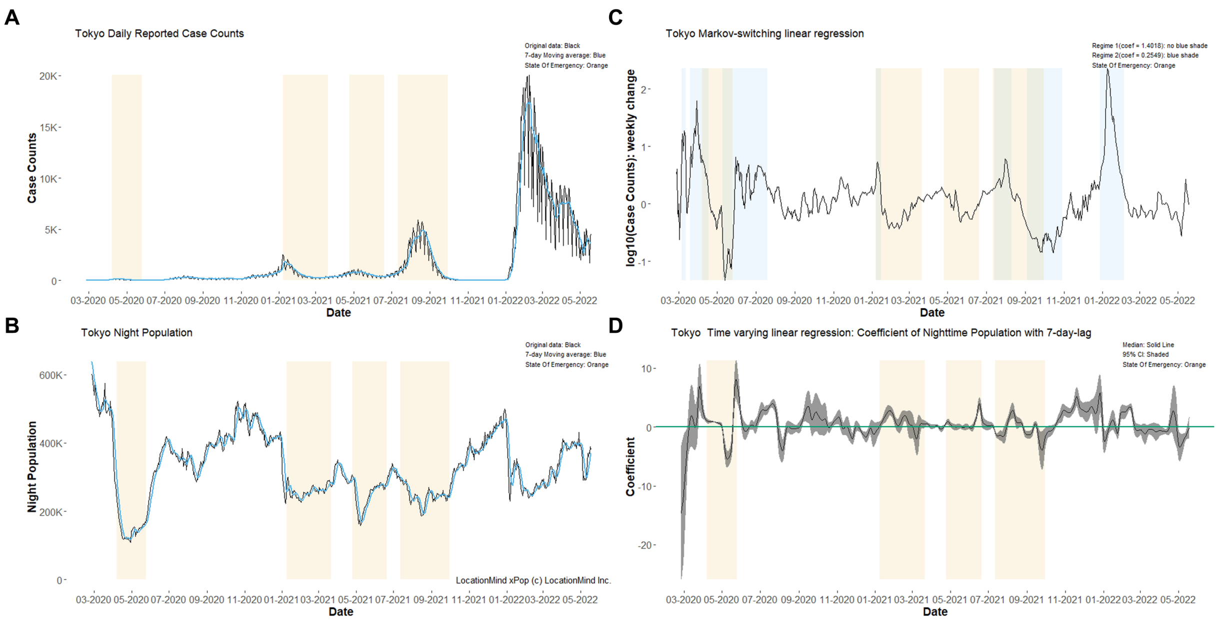

FIGURE 1
Time series plots showing the daily reported case counts of COVID-19 and daily downtown population from 10:00PM to 11:59PM in Tokyo, 2020–22. Tokyo's **(A)** daily reported COVID-19 case counts and **(B)** Night-time population in designated areas from 10:00PM to 11:59PM are shown in the left column (light blue lines show 7-day moving averages). The results of Markov switching linear regressions assuming two hidden states **(C)** and time-varying linear regression **(D)** are shown in the right column. In all figures, light orange shading corresponds to four publicly declared "State of Emergency" periods. For technical details of **(C,D)**, see Supplementary material. The same figures for Aichi and Osaka are shown in the Supplementary material.

The day-of-the week-effect observed in the original time series of case counts was intense. To exclude such an effect, as it makes the regression model too complex and less interpretable, for the subsequent analysis we used the 7-day moving average of case counts

$$C_a(t) = \frac{\sum_{i=0}^{6} I_a(t-i)}{7},$$

where $C_a(t)$ is the 7-day moving average of $I_a(t)$, which is the reported case counts on day t in prefecture a. Data from February 26th, 2020, to May 18th, 2022 were used in our study to match the span with the mobility data described below, and to exclude periods with very few COVID-19 case counts.

2.2. Mobile phone location data

In the present study, "LocationMind xPop" data on the hourly population volume estimates in selected areas in the Tokyo, Nagoya, and Osaka metropolitan areas were provided by LocationMind Inc. (14). These data were also used in a previous study on COVID-19 and night-time population in Japan (10).

"LocationMind xPop" data refers to people flow data collected by individual location data sent from mobile phones with users' consent through applications such as "docomo map navi" service (map navi, local guide) provided by NTT DOCOMO, INC. The data are processed collectively and statistically in order to conceal private information. Original location data come from GPS data (latitude, longitude) sent at a frequency of every 5 min at the shortest interval and do not include information that specifies individuals. NTT Docomo, Inc. accounts for about 36.3% of total mobile phone subscribers in Japan (12).

For each metropolitan area, mobile phone trajectories were used to selectively collect population volume that did not involve stay-at-work and stay-at-home behaviors. The areas of interest in this study were selected on the basis of designated areas for monitoring of people flow data by the Cabinet Office (15).

For subsequent analysis, for the same reason as for COVID-19 case counts, we calculated the 7-day moving average of *de facto* night-time population in downtown areas

$$NP_a(t) = \frac{\sum_{i=0}^{6} np_a(t-i)}{7},$$

where $NP_a(t)$ is the 7-day moving average of $np_a(t)$, which is the population staying in the areas of interest between 10:00 PM and 11:59 PM on day t in prefecture a. This particular time of night (i.e., 22:00–00:00) has been specifically used for routine monitoring purposes in Tokyo and for all of Japan on the basis of earlier successful improvements of predictive capability (10).

2.3. Variables used in regression analysis

We used the variables mentioned above in natural logarithmic form to ensure equivariance. Our analysis was performed using the 1-week change in $\log(C_a(t))$, i.e.,

$$\log\left(C_a(t)\right)-\log\left(C_a(t-7)\right)=\log\left[\frac{C_a(t)}{C_a(t-7)}\right],$$

as a response variable. For explanatory variables, we considered the $\log\left(NP_a(t)\right)$ as well as the daily difference of $\log\left(NP_a(t)\right)$, i.e.,

$$\Delta\log\left(NP_a(t)\right)=\log\left(NP_a(t)\right)-\log\left(NP_a(t-1)\right).$$

For all locations, all three variables tested negative for unit roots using the augmented Dickey–Fuller test using R package CADFtest, to ensure that the whole series of each dataset was valid for regression analysis.

2.4. Time-varying regression analysis

First, the following state space model with exogenous variables was applied to conduct time-varying regression analysis, where L was the lag to be determined by exploring the best-fit model:

$$\log\left[\frac{C_a(t)}{C_a(t-7)}\right]=S(t)+\varepsilon(t),\varepsilon(t)\sim N\left(0,\sigma_\varepsilon{}^2\right), \quad (1)$$

$$S(t)=\beta_0(t)+\beta_1(t)\log\left(NP_a(t-L)\right) +\beta_2(t)\Delta\log\left(NP_a(t-L)\right), \quad (2)$$

$$\begin{bmatrix}\beta_0(t)\\ \beta_1(t)\\ \beta_2(t)\end{bmatrix}=\begin{bmatrix}\beta_0(t-1)\\ \beta_1(t-1)\\ \beta_2(t-1)\end{bmatrix}+\begin{bmatrix}\xi_0(t)\\ \xi_1(t)\\ \xi_2(t)\end{bmatrix}, \quad (3)$$

$$\begin{bmatrix}\xi_0(t)\\ \xi_1(t)\\ \xi_2(t)\end{bmatrix}\sim MVN\left(\begin{bmatrix}0\\0\\0\end{bmatrix},\Sigma(t)\right), \quad (4)$$

$$\sigma=7,8,\ldots,14\left(days\right) \quad (5)$$

Eq. (1) is the observation process with state $S(t)$ and observation error $\varepsilon(t)$, which is assumed to follow a normal distribution with mean 0 and standard deviation σ_ε. Eq. (2) is the state equation consisting of time-varying level $\beta_0(t)$ and exogenous variables $\log\left(NP_a(t-L)\right)$ and $\Delta\log\left(NP_a(t-L)\right)$ with time-varying coefficients $\beta_1(t)$ and $\beta_2(t)$, respectively. Intercepts and coefficients $\beta_i(t), i=0,1,2$, are modeled to follow the time-varying process as described in (3) and (4), where £ is the variance–covariance matrix. The lag ranging from 7 to 14 days was specifically examined, because the mean time delay from infection to reporting was estimated at 13 days during the first wave of the pandemic from March to May 2020, and was then shortened to 11 days from June 2020 and 9 days when the Omicron variant (B.1.1.529) began to spread from January 2022 (16–18) [also see Supplementary material for symptom onset to reporting on the basis of publicly available data from the website managed by the Tokyo Metropolitan Government (18)]. Best-fit models (lag L) were selected on the basis of the Akaike information criterion (AIC).

2.5. Fixed-effect regression model

On the basis of the time-varying regression results, linear regression analysis by generalized least squares assuming fixed effects of $\log\left(NP_a(t-L)\right)$ and $\Delta\log\left(NP_a(t-L)\right)$ was also conducted throughout the study period. Below is the model description:

$$\log\left[\frac{C_a(t)}{C_a(t-7)}\right]=\beta_0+\beta_1\log\left(NP_a(t-L)\right) +\beta_2\Delta\log\left(NP_a(t-L)\right)+\varepsilon(t), \quad (6)$$

$$\varepsilon(t)=\rho\varepsilon(t-1)+\omega(t), \quad (7)$$

$$\omega(t)\sim N\left(0,\sigma_\omega^2\right), \quad (8)$$

$$L=7,8,\ldots,14\left(days\right), \quad (9)$$

where L is the lag to be determined by exploring the best fit model, $\varepsilon(t)$ is the autocorrelated error with coefficient ρ, and $\omega(t)$ is white noise following the normal distribution with mean 0 and standard deviation σ_ω. Models including either $\log\left(NP_a(t-L)\right)$ (fixing β_2 to zero) or $\Delta\log\left(NP_a(t-L)\right)$ (fixing β_1 to zero) or both were tested. The estimation of model parameters was performed via a Bayesian approach employing the Markov Chain Monte Carlo (MCMC) method. We used weakly informative priors (see Supplementary material) and ran five chains and 3,000 iterations with 1,000 warmups each. Convergence was confirmed with trace plots and the potential scale reduction factor (Gelman-Rubin statistics) Rhat as well as traceplots, and the widely applicable information criterion (WAIC) was used for selection of the best fit model.

2.6. Statistical analysis

All statistical and numerical analyses were performed using R version 4.1.2 (The R Project for Statistical Computing, Vienna, Austria) and Stan version 2.21.0. R package KFAS (19) was used in the time-varying regression analysis, and the R package brms version 2.18.0 (20) was used for fixed-effect regression analysis with CmdStan 2.30.1 (21).

3. Results

3.1. Time-varying regression analysis

For each lag $L=7,8,\ldots,14$ days, models described in Eqs (1)–(5) were estimated. The lag L of the best-fit model was 8 days in Tokyo,

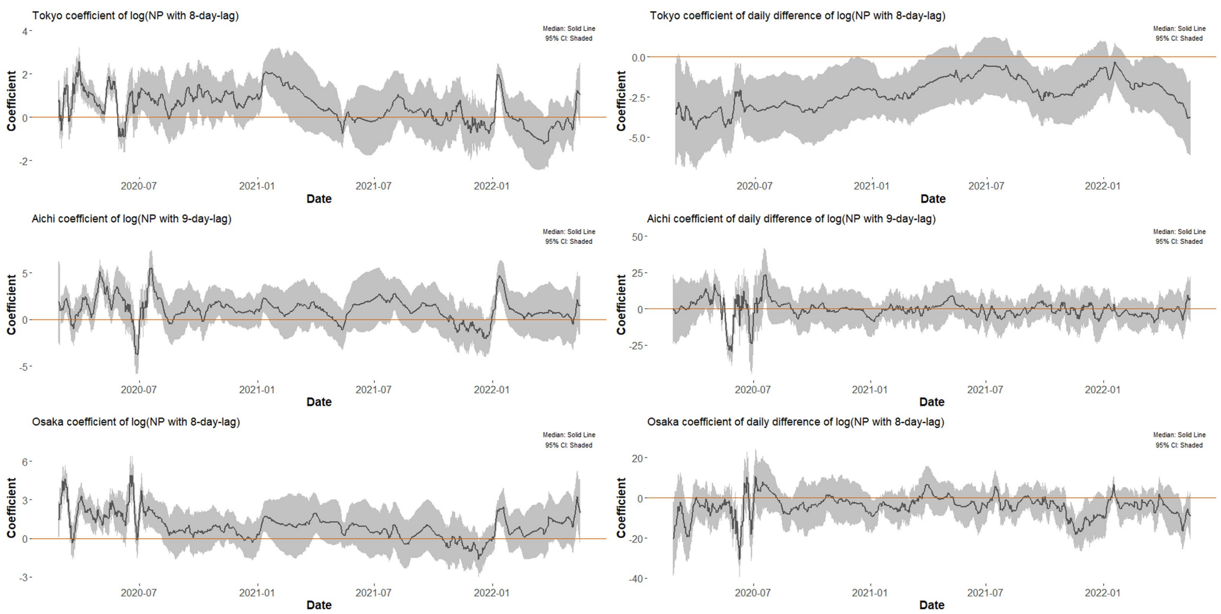

FIGURE 2
Time series of coefficients of night-time population and its daily change estimated by the time-varying regression models for Tokyo, Aichi, and Osaka, 2020–22. The change of $\beta_1(t)$ and $\beta_2(t)$ over time observed in time-varying regression analysis for Tokyo, Aichi, and Osaka. The shaded areas show the 95% confidence intervals for each estimated value.

9 days in Aichi, and 8 days in Osaka (see Supplementary materials for AIC used for best fit model choice). In all locations, the time series of $\beta_1(t)$ and $\beta_2(t)$ are shown in Figure 2. For all locations, the confidence interval of $\beta_1(t)$ stayed above or straddled zero, but in Tokyo and Aichi, there were short periods around mid-2020 when $\beta_1(t)$ turned negative. Regarding $\beta_2(t)$, the confidence interval stayed below zero most of the time throughout the pandemic period. However, the confidence interval of $\beta_2(t)$ in Aichi and Osaka straddled zero most of the time and was sometimes in negative territory. Both $\beta_1(t)$ and $\beta_2(t)$ stayed within a relatively narrow and confined range most of the time.

3.2. Fixed-effect regression analysis

For each lag $L = 7, 8, \ldots, 14$ days, models described in Eqs (6) to (9) are estimated. For each lag L, in addition to models including both $\log(NP_a(t-L))$ and $\Delta\log(NP_a(t-L))$, models including either one of these variables were also estimated (see Supplementary materials for WAIC used for best fit model choice).

In Table 1, the summary of estimates from best fit models for Tokyo, Aichi, and Osaka are shown.

For Tokyo and Osaka, models with 8-day-lagged night-time population including both $\log(NP_a(t-8))$ and $\Delta\log(NP_a(t-8))$ were chosen, whereas for Aichi, the model with 9-day-lagged night-time population including only $\log(NP_a(t-9))$ was chosen. For every location, the best-fit models suggested a positive correlation between weekly changes in COVID-19 case counts and night-time population with certain lags. For the daily difference in night-time population that was included in the best-fit models for both Tokyo and Osaka, a negative correlation was observed with the weekly change in case numbers. The residuals of fixed-effect models showed that the models were fitted well, but weak autocorrelation and heteroscedasticity in the earlier phases were observed (see Supplementary materials for residuals of these best fit models).

Using the fixed-effect model, the values of 1-week rate of changes in COVID-19 counts and the COVID-19 case counts of Tokyo, Aichi, and Osaka are shown in Figure 3, together with model predicted values with 95% prediction intervals. Because the models used in fixed-effect regression consider first-order autocorrelation of residuals, the prediction intervals for each time step are essentially a one-point-ahead forecast with errors.

4. Discussion

To the best of our knowledge, the current study is the first in Japan to reveal the long-term relationship between COVID-19 dynamics and night-time downtown populations in metropolitan urban areas where eating and drinking activity are intense. Although it is mechanistically obvious that activities such as drinking or eating indoors are positively linked to the transmission of COVID-19, the time-variability of this link has not been comprehensively explored. The current findings revealed that the effect of night-time population on COVID-19 dynamics was positive to neutral most of the time, and rarely negative over time. The lag considered for night-time population in the best-fit models also appeared to be reasonable, considering that, for major variants of SARS-CoV-2, the mean incubation period of COVID-19 was around 3–7 days (16), and the average lags between symptom onset and reporting in Japan have been estimated to be approximately 3–7 days (17, 18) (also see Supplementary materials). The minor heterogeneity of lags determined through the model fitting process among the three prefectures cannot be explained explicitly based

TABLE 1 Summary of results from best fit models for Tokyo, Aichi, and Osaka, 2020–2022.

	Covariate	Estimate	95% Confidence Interval	
			Lower	Upper
Tokyo	Intercept	−8.676	−12.089	−5.21
	log(NP with 8-day-lag)	0.692	0.427	0.955
	Daily change of log(NP with 8-day-lag)	−2.527	−3.345	−1.713
	First order autoregression coefficient	0.968	0.95	0.986
Aichi	Intercept	−20.165	−27.325	−13.172
	log(Night Population with 9-day-lag)	1.61	1.067	2.168
	First order autoregression coefficient	0.959	0.938	0.979
Osaka	Intercept	−17.167	−28.262	−8.663
	log(NP with 8-day-lag)	1.254	0.638	2.044
	Daily change of log(NP with 8-day-lag)	−3.398	−4.92	−1.843
	First order autoregression coefficient	0.976	0.949	0.997

For Tokyo and Osaka, models with 8-day-lagged night population as well as its daily change were the best fit model, whereas the best fit model for Aichi does not include daily change in night-time population. The estimates for intercept, coefficients of explanatory variables, and the first-order autocorrelation coefficients are shown with 95% confidence intervals.

on our result, but it is possible that they root in unknown behavioral differences or differences in the diagnosis-to reporting process of COVID-19 data by local healthcare institutions or governments.

The time-varying regression results revealed that, in addition to the level of night-time population, a neutral to negative correlation was observed between daily difference of night-time population level and COVID-19 transmission for most of the study period. The mechanism underlying this result is not entirely clear. One explanation might be the behavioral changes at the societal level based on expectations of COVID-19 case counts in the near future, or it might also be the reflection of changes in social contact patterns that is characteristic of specific seasons (such as the New Year holiday season). These are no more than guesses, but future research on this topic is of interest.

Fixed-effect regression also revealed that the night-time population level is the key driver of COVID-19 throughout the pandemic period. Although this result is consistent with previous studies in Japan on human mobility and COVID-19 (9–12), the current findings revealed that this positive link between night-time population and COVID-19 transmission was not only limited to a short period but was consistently maintained for a long time over the course of the epidemic. When overviewed as fixed effects, the daily difference in night-time population increased the explainability of best-fit models in Tokyo and Osaka with negative effects. Although this was not true for Aichi, it is possible that, in some locations, the change in night-time population level may account for behavioral changes linked to COVID-19 transmission to some extent, either directly or indirectly.

The current study involved several limitations. The two regression models revealed the correlation between COVID-19 dynamics and explanatory variables such as night-time population and its daily change. It might be possible that any spurious relationship exists between COVID-19 and the explanatory variables included in our models, and that there are other variables not included in our model that may also affect COVID-19 dynamics. About the former issue, generally it is difficult to deny any spurious relationship completely, but due to the definition of lags for variables in our model, there is little chance that the chronological order of possible effects is opposite compared with what we observed in the present study. About variables, several other types of variables are also suggested to affect COVID-19 dynamics. For example, populations staying in other type of locations, residential areas or workplaces, as considered by Nagata et al. (9), were not included in our study. The results of Nagata et al. (9) indicated that the night-time population was the best predictor of COVID-19 dynamics, suggesting that our results may not have been substantially changed by considering other types of locations. However, further analysis considering these locations is warranted if these data are available. The current study also did not include meteorological factors such as temperature and humidity as explanatory variables, which have been suggested to have negative impact on COVID-19 transmission (11, 22) Because these meteorological factors may also exhibit interactions with social contact patterns, we excluded them from consideration. Risk awareness was also considered in previous studies (11) but is difficult to quantify. It is likely that night-time population reflects risk awareness at a societal level to some extent.

The second limitation of the present study is that, in our models, the lags for night-time population were assumed as constants throughout the study period. Not only the substitution of major variants of SARS-CoV-2 but also factors such as the accessibility to hospitals (which might differ among periods or among different epidemic waves) may change the effective lag through which the night-time population affects COVID-19 transmission. It is difficult to adjust for these kinds of changes on the basis of available data when we consider not only known or observable factors but also unmeasured factors. However, the fact that the lag period chosen for best fit models matched that of the fixed-effect regression model in each location suggests that similar underlying correlation structures were maintained throughout the study period. Stepwise regression with sliding windows might also have been an option for our

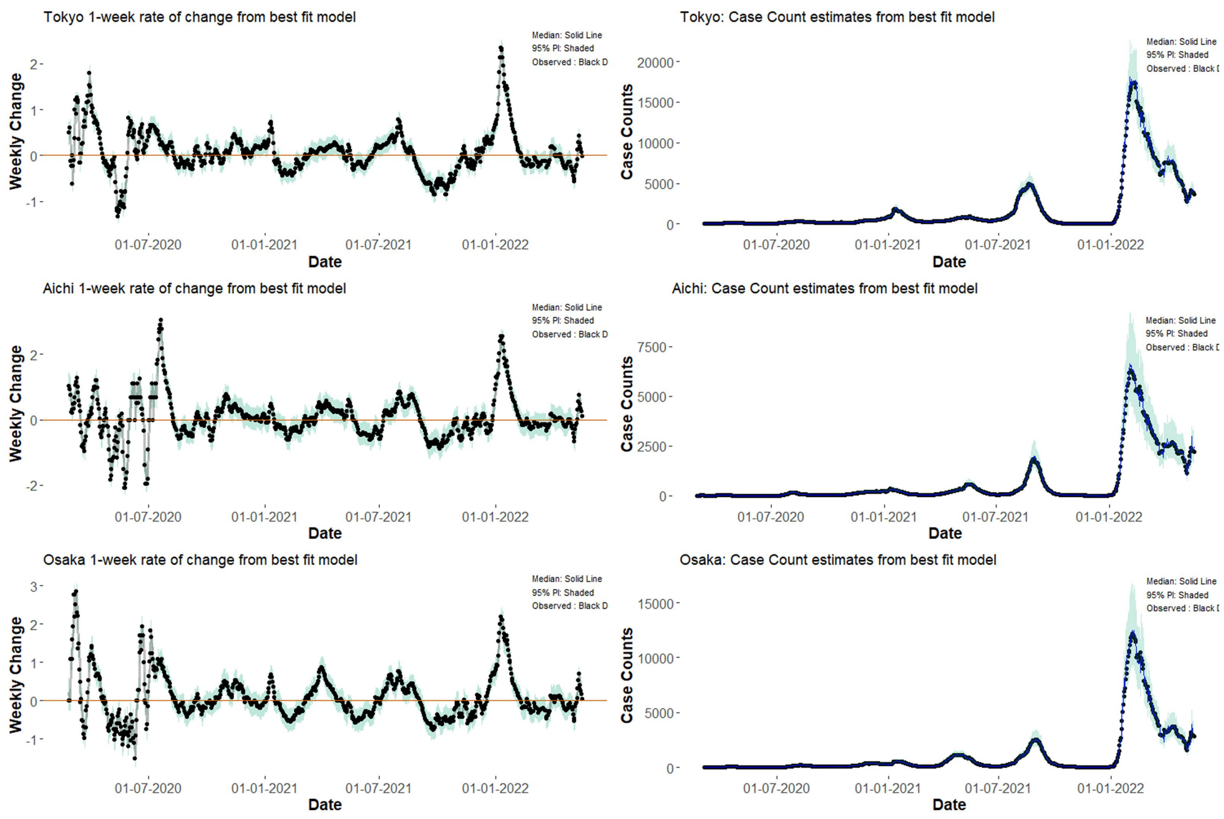

FIGURE 3
Model estimates of weekly case counts **(left column)** and case counts **(right column)** by the fixed effect regression models for Tokyo, Aichi, and Osaka. Dots represent observed case count by Ministry of Health, Labor, and Welfare, while lines represent the expected value from our fixed-effect regression model. Shaded areas represent the region of 95% prediction intervals computed from the posterior distribution.

analysis, but we believe that the choice of windows tends to be rather arbitrary, and that temporal dynamics are better elucidated by time-varying regression.

The third limitation is that we only considered three metropolitan areas in Japan using data that focus on social contacts in eating or drinking places. Because our results may not be valid in rural areas in Japan, further studies in other geographical locations are required. Also, unlike the openly accessible mobility data such as Google's COVID-19 Community Mobility Reports (23), our night-time population data are not open and widely accessible, which might limit validations by other research groups. Nevertheless, the accuracy of our mobility data enabled us to focus almost purely on social contacts at eating or drinking places while excluding residential populations from our scope, which is the key strength of our study. Based on these data, current findings provide important insight for understanding the dynamics of COVID-19 transmission in highly and densely populated areas that represent major parts of the Kanto, Chubu, and Kinki regions of Japan.

Another limitation is that weak autocorrelation was still observed in the residuals of the fixed-effect model even with the inclusion of 1st order autocorrelation structure for residuals. As for autocorrelation, we did not consider higher order autocorrelation considering the nature of COVID-19 transmission that usually occurs within the 1-week scope, but there is room to search candidate variables that might account for the remaining autocorrelation. In addition to autocorrelation, heteroscedasticity was observed mainly in the early phase, which is likely because weekly change rate in the early phase were volatile in all locations due to the relatively small number of COVID-19 cases. Even considering these issues, comparison with the result from time-varying regression suggests that the results from the fixed-effect regression model are also valid.

Despite the limitations mentioned above, we successfully quantified the positive effects of night-time population in downtown areas on COVID-19 transmission using two statistical methods. In addition, we also found that, in Tokyo and Osaka, the daily difference in night-time population may also be a predictor of COVID-19 transmission. Our results emphasize the importance of human mobility data related to eating and drinking activities in society and offer evidence for the effectiveness of public health and social measures targeting high-risk activities or locations for COVID-19 transmission. Specifically, our result shows that, if any dramatic change in population-level immune landscape may occur in the future due to the emergence of SARS-CoV-2 variants with significant immune evasiveness, public health policies should be designed so as to target social contacts that occur in eating or drinking settings including downtown areas. Moreover, this implication from our results can easily be expanded to other pandemics in the future that might be caused by other novel respiratory pathogens including highly pathogenic avian influenza with transmissibility among humans.

5. Conclusion

Our results elucidated that night-time population has consistently been a significant predictor of COVID-19 dynamics. The consistency of the effect of night-time population throughout the COVID-19 pandemic up to mid-2022 is especially of note, considering the behavioral changes as well as vaccination campaigns rigorously carried out in Japan.

Even under circumstances where a diminished effort to contain and track COVID-19 paid for by public health officials, our finding encourages close monitoring of mobility indicators particularly focused on places with high levels of eating and drinking activities as a key predictor of surge in COVID-19 cases. Also, from a policy point of view, this finding implicates the importance of targeted financial support for restaurants or pubs that cooperatively close when the endemic situations are bad.

Though our results showed consistent validity throughout the COVID-19 pandemic so far, the validity might change, for example, due to the change in immunity levels at high-risk populations. Thus, future follow-up studies on this topic are warranted.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: https://covid19.mhlw.go.jp/extensions/public/en/index.html.

Author contributions

HN conceived the research idea. YO and HN built the statistical models, reviewed the analyses, drafted the manuscript, and approved the final manuscript. YO conducted the statistical analyses on the datasets. All authors gave comments and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1163698/full#supplementary-material

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Knowledge, attitudes, and practices regarding COVID-19 and mental health status among college students in China: a cross-sectional study

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Background: During the prevalence of coronavirus disease 2019 (COVID-19), little was known about the knowledge, attitudes, practices (KAP) about COVID-19 and psychological status of college students in minority areas. This study aimed to evaluate the KAP of college students in minority areas of China toward COVID-19 and to provide a scientific basis for health education and policy formulation.

Methods: From October 28th to November 6th, 2021, a cross-sectional study was conducted with 5,272 college students to examine KAP and its effects on mental health.

Results: Regarding COVID-19 knowledge, the overall awareness rate was 24.11% (1,271). Regarding health attitudes, most students had positive attitudes about COVID-19 prevention and control (94.95%), and females had higher positive attitudes than males (OR: 1.920; CI: 1.494–2.469). Regarding preventive behaviors, more than half of the students took preventive measures (53.48%), and freshmen had the highest health behavior scores. In terms of psychological status, there were fewer females with depression and stress than males.

Conclusion: College students in minority areas have positive health attitudes; however, their knowledge of COVID-19 prevention and control is low. Moreover, their precautionary behaviors are insufficient, and they have many negative emotions.

KEYWORDS

knowledge, attitudes, practices, COVID-19, mental health

Introduction

An outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), occurred in Wuhan, China, in December 2019 and quickly spread worldwide. COVID-19 was listed as a public health emergency of international concern in January 2020 (1). The cumulative number of confirmed COVID-19 cases has reached 763.7 million, with the death toll exceeding 6.9 million, according to the WHO report on 19 April 2023 (2). As of April 19, 2023, a total of 99.2 million people have been diagnosed in China, and 120,912 have died from COVID-19. The strong infectivity, rapid spread, and wide infection range of COVID-19 seriously threatened people's safety and mental health; COVID-19 is one of the major public health emergencies experienced in China in the last hundred years, and its prevention and control present great challenges (3). Mass vaccination has become one of the most important public health policies for countries to prevent the spread of COVID-19. As of March 22, 2023, China has reported providing a total of 3.5 billion doses of COVID-19 vaccine. However, thus far, different variants of SARS-CoV-2, such as the Omicron variant, have been found to spread more widely and faster (4). Higher infection rates caused by mutation confirm that high vaccine coverage may not guarantee effective control of COVID-19 transmission. Therefore, the implementation of outbreak prevention and control measures cannot be ignored, which is closely related to public support (5).

The crisis caused by the COVID-19 pandemic is largely influenced by knowledge, attitudes and practices (KAP) (6). Knowledge, attitudes, and practices (KAP) are important cognitive components of health promotion in public health management, which greatly affects whether people follow preventive strategies and improve their behaviors as early as possible (7–9). Studies have found that knowledge of COVID-19 will affect people's attitudes and practices, while negative attitudes and practices will increase the risk of illness and death (10).

After the initial school closure and self-isolation period, universities reopened on September 7, 2020. However, due to the different severity of the COVID-19 pandemic in different provinces, the specific start time of the universities in different provinces is different (this study was conducted during the beginning of the third vaccination booster shot campaign in China). At present, the school has resumed classes and the order of teaching has been fully restored. The prevention and control of the COVID-19 pandemic on campus is facing new challenges. How to continue to do better in the prevention and control of campus pandemic and reduce the risk of students' physical and mental health affected by the pandemics has become an urgent public health problem (11). Despite daily prevention and control measures, such as maintaining social distance, frequent hand washing, and detecting suspected symptoms, universities were still at risk of outbreaks due to the large number of college students and their strong mobility. According to the statistics of education in 2021, the total number of students studying in higher education in China is 44.3 million. In addition, because it is unregulated, social media can provide misinformation, which can easily lead to ambiguity and misunderstandings regarding COVID-19 and even to panic and confusion (12). Studies have shown that college students' KAP level and mental health are affected by stressful events during the COVID-19 pandemic (13, 14), and the risk of anxiety, depression and other negative emotions among students increases, resulting in increased pressure (15–17). Therefore, good COVID-19-related knowledge, positive attitudes, healthy behaviors and good mental health are essential to effectively prevent and control pandemics and reduce the panic they cause (18–20).

The studied university is located in Yanbian ethnic Korean Autonomous Prefecture, a minority area in China, with 22,487 full-time college students. The time of questionnaire survey is in the normal prevention and control stage after the outbreak of COVID-19 in China. Yanbian University is a minority university and comprehensive university with strong ethnic regional characteristics. At the same time, it has the general characteristics of being a comprehensive university. Compared with universities in other regions, it has strong commonness and certain universality and representativeness. Investigating the knowledge, attitudes and practices of college students during the pandemic period is conducive to further understanding the weak points of pandemic prevention and control awareness in universities, so as to carry out accurate health education and prevention and control. From October 28th to November 6th, 2021, a questionnaire survey was conducted using the "Questionnaires" network platform to evaluate the KAP and mental health status of college students in China minority areas during the COVID-19 pandemic period and to analyze its influencing factors. This study provides a scientific basis for further health education and psychological intervention for college students' COVID-19 prevention and control and helps in the formulation of accurate prevention and control strategies to provide useful experience for curbing similar major public health emergencies in the future. The results are reported as follows.

Materials and methods

Study design

This cross-sectional survey was conducted from October 28th to November 6th, 2021 to evaluate the knowledge, attitudes, and practices about COVID-19 outbreak and psychological status of college students.

Population and data collection

The research subjects were college students from a minority area in China. Considering the limitation of actual status in the sampling design and investigation implementation stage, non-probability sampling (convenient sampling) was adopted to conduct the current survey. Convenient sampling, also known as accidental sampling or natural sampling, is that researchers choose those who are easy to find or obtain information as the investigation objects according to the actual status. Therefore, expanding the sample size as much as possible can reduce the difference between the sample and the population. Therefore, in the implementation stage, this survey included a total of 5,272 large sample data to improve the representativeness of the sample. The effective response rate was 100%.

Referring to the Guide to the Prevention and Control of COVID-19 in Colleges and Universities (21) and authoritative official reports, we created an electronic questionnaire through the online survey platform "Questionnaires" and conducted a presurvey (a total of 300 people). After improving the questionnaire, we conducted a formal online survey through social media platforms (e.g., WeChat) from October 28th to November 6th, 2021. Instructions of the questionnaire on the front page clearly informed the participants of the research purposes and their rights regarding joining or dropping out of this study at any time during participation. All participants were informed and assured that their participation was voluntary, anonymous, and strictly confidential.

Measures

The following tools were used in this study: (1) a general information questionnaire (sex, nationality, urban and rural areas, grade, major, etc.). (2) A self-made COVID-19 KAP questionnaire (COVID-19-related knowledge, attitudes and prevention practices), with 11 knowledge questions, receiving a total score of 11 points. And there are 10 health attitude questions. A 5-point Likert scale was used to measure and evaluate the support of COVID-19 prevention and control (1 = totally disagree to 5 = totally agree), with a total score of 50 points. Regarding health practice, five questions received scores of up to four points, and two questions received scores of up to three points, with a total possible score of 26 points. The study used a score of 80% as the cutoff. In terms of health knowledge, a score of ≥9 was considered high cognition, which was defined as awareness. In terms of health attitudes, a score of ≥40 was classified as positive health attitudes. In terms of health practice, a score of ≥21 was classified as good health behavior. (3) The Depression-Anxiety-Stress Scale (DASS-21) included 21 items divided into three dimensions: Depression, anxiety and stress. A stress scale score of >14 indicated psychological stress, an anxiety scale score of >7 indicated psychological anxiety, and a depression scale score of >9 indicated psychological depression. The scoring method of Bi et al. (22) was used. Those who had depression, anxiety and stress were classified as having negative emotions.

Data analysis

SPSS 26.0 statistical software was used for statistical analysis of the data. Descriptive statistical analysis was performed on the number distribution of college students according to demographic characteristics. The count data are expressed by the composition ratio. Percentage comparisons were tested by binary logistic regression analysis to evaluate the related influencing factors. The variables of influencing factors in the results of logistic analysis are to explain the risk factors that affect the knowledge, attitudes, practices of COVID-19 prevention and control and psychological status among college students. For measurement data comparisons, *T*-tests were used for two groups and ANOVA was used for three or more groups, as described by[[Inline Image]]. A two-sided test was adopted, with a test level of $\alpha = 0.05$, and the difference was considered statistically significant when $P < 0.05$.

Ethical considerations

Informed consent was obtained from all subjects involved in the study. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Yanbian University (Ethical Code: 2021576, October 26th, 2021).

Results

Basic information

A total of 5,272 college students were included in this study, and their general characteristics are shown in Table 1.

College students' awareness of COVID-19

The average COVID-19 prevention and control knowledge score of college students was 7.07 ± 2.01. Regarding college students' knowledge about COVID-19, college students had good knowledge about the attributes of COVID-19 virus pathogens (71.9%) but insufficient knowledge about the pathogens (51.9%). The awareness rate of survival conditions (41.5%) and preservation conditions of COVID-19 nucleic acid test specimens (39.3%) was low. College students (95.0%) had a high degree of knowledge of COVID-19 transmission channels. The awareness rate of symptoms such as fever and dyspnea after COVID-19 infection

TABLE 1 Respondents' demographic information.

Participants		No.	Cumulative percentage (%)
Gender	Male	1,824	34.6
	Female	3,448	65.4
Ethnic group	Han	3,590	68.1
	Korean	1,151	21.8
	Other nationality	531	10.1
Town and country	Town	4,218	80.0
	Country	1,054	20.0
Grade	Freshman	2,677	50.8
	Sophomore	1,474	28.0
	Junior	641	12.2
	Senior	394	7.5
	Five-grade	86	1.6
Major	Medical major	1,253	23.8
	Non-medical major	4,019	76.2
Knowledge score	<9	4,001	75.9
	≥9	1,271	24.1
Attitude score	<40	266	5.0
	≥40	5,006	95.0
Practice score	<21	2,454	46.5
	≥21	2,818	53.5
Psychological status	Bad	2,398	45.5
	Good	2,874	54.5

was good (86.5%); however, the awareness rate of whether diarrhea can be the first symptom of COVID-19 was low (56.3%). College students had poor knowledge of the correct way to cover their nose and mouth when coughing or sneezing (19.3%). The students had good knowledge of the medical observation period of close contact home isolation for COVID-19 (88.8%). The awareness rate of wearing (84.9%) and taking off (71.8%) disposable medical masks was good (see Table 2).

TABLE 2 Knowledge of COVID-19 among college students.

Item	Awareness rate (%)
COVID-19 transmission route	5,007 (95.0)
Medical observation period of close contact home isolation in COVID-19	4,684 (88.8)
Symptoms after COVID-19 infection (fever, dyspnea, etc.)	4,560 (86.5)
Wearing mode of disposable medical mask	4,476 (84.9)
What kind of virus does COVID-19 belong to?	3,791 (71.9)
Removing method of disposable medical mask	3,786 (71.8)
Can diarrhea be the first symptom of COVID-19?	2,968 (56.3)
COVID-19 pathogen	2,734 (51.9)
COVID-19 is more likely to spread where pathogens survive for a long time	2,189 (41.5)
Preservation conditions of COVID-19 nucleic acid samples that can be detected within 24 h	2,072 (39.3)
How do you cover your nose and mouth when coughing or sneezing?	1,019 (19.3)

The overall awareness rate of COVID-19 prevention and control knowledge was low, accounting for 24.11% of the sample (1,271 people). Univariate analysis showed that there were differences in the awareness rate of COVID-19 prevention and control knowledge among college students of different genders, grades and majors ($P < 0.05$), and the results are shown in Table 3. Specifically, females had higher awareness than males. Five-grade students had the highest awareness than students in other grades. Medical majors had significantly higher awareness than non-medical majors.

Logistic regression analysis was performed for the variables with statistical significance in the single factor analysis of the knowledge awareness rate, and the results were consistent with those of the single factor analysis. Multivariate regression analysis showed that females were the protective factors for the high awareness rate of prevention and control knowledge in COVID-19 (OR = 1.172, 95% CI = 1.024–1.341). Compared with freshmen, sophomores (OR = 0.787, 95% CI = 0.677–0.915) and juniors (OR = 0.793, 95% CI = 0.645–0.975) are the risk factors for high awareness (see Table 4).

College students' attitudes regarding the prevention and control of COVID-19

The average score of college students' attitudes toward COVID-19 prevention and control was 47.54 ± 5.70. More college students in minority areas have positive health attitudes (see Table 5). Univariate analysis showed that there were differences in the scores of COVID-19 prevention and control attitudes among college students of different sexes, nationalities, grades and majors ($P < 0.05$), and the results are shown in Table 6. Specifically, females had higher attitude scores than males. Students of Han nationality had higher attitude scores than students of other nationalities. Students in their first year had higher attitude scores than students

TABLE 3 Single factor analysis of the awareness rate of COVID-19 prevention and control knowledge among college students.

Participants		*n* (%)	χ^2	*P*-value
Gender	Male	410 (22.5)	4.052	0.044
	Female	861 (25.0)	–	–
Ethnic group	Han	887 (24.7)	2.363	0.307
	Korean	266 (23.1)	–	–
	Other nationality	118 (22.2)	–	–
Town and country	Town	1,041 (24.7)	3.766	0.052
	Country	230 (21.8)	–	–
Grade	Freshman	713 (26.6)	25.096	<0.001
	Sophomore	325 (22.0)	–	–
	Junior	141 (22.0)	–	–
	Senior	68 (17.3)	–	–
	Five-grade	24 (27.9)	–	–
Major	Medical major	366 (29.2)	23.379	<0.001
	Non-medical major	905 (22.5)	–	–

TABLE 4 Binary logistic regression analysis of influencing factors of COVID-19 prevention and control knowledge among participants (n = 5,272).

Participants		β	Wald χ^2	P-value	OR (95% CI)
Gender	Male*	–	–	–	–
	Female	0.158	5.278	0.022	1.172 (1.024, 1.341)
Grade	Freshman*	–	–	–	–
	Sophomore	−0.239	9.663	0.002	0.787 (0.677, 0.915)
	Junior	−0.232	4.842	0.028	0.793 (0.645, 0.975)
	Senior	−0.515	13.367	<0.001	0.597 (0.453, 0.787)
	Five-grade	0.030	0.014	0.904	1.030 (0.637, 1.665)
Major	Medical major*	–	–	–	–
	Non-medical major	−0.324	19.502	<0.001	0.724 (0.627, 0.835)

*as the control group.

TABLE 5 Attitudes of COVID-19 among college students.

Items	Negative perception (%)
In the last two months, if you have symptoms such as continuous fever, cough and runny nose, it is necessary to go to the hospital.	301 (5.7)
At this stage, do you think it is necessary to pay close attention to the news related to the COVID-19 epidemic?	255 (4.8)
At present, although the epidemic situation in China has been effectively controlled, it is still necessary to wear masks when going out to crowded places.	195 (3.7)
Prevention and control of the COVID-19 epidemic is not only a matter for the government, but also closely related to me personally.	229 (4.3)
Do you support quarantine measures for people who come into contact with suspected patients?	196 (3.7)
If the epidemic breaks out again, do you support stopping school and work in time?	320 (6.1)
Do you actively discourage friends and relatives from eating hunted meat now?	353 (6.7)
At present, the epidemic situation has been effectively controlled, and it is still necessary to inoculate COVID-19 vaccine.	177 (3.4)
COVID-19 vaccine is safe and effective.	349 (6.6)
Do you support the nucleic acid detection measures for the cross-regional flow of the public?	292 (5.5)

in other years, and those in their second year had the worst attitude scores. Medical majors had lower attitude scores than non-medical majors.

Most college students had positive health attitudes about COVID-19 prevention and control, accounting for 94.95% of the sample (5006). Logistic regression analysis was performed for the variables with statistical significance in single factor analysis of attitude scores, and the results were consistent with those of single factor analysis. Logistic regression analysis showed that females were the protective factors to keep positive perception on prevention and control of COVID-19 (OR = 1.920, 95% CI = 1.494–2.469). Compared with Han nationality, ethnic Korean nationality is a risk factor for maintaining a positive awareness of prevention and control in COVID-19 (OR = 0.633, 95% CI = 0.475–0.843). Compared with freshmen, other grades are risk factors for maintaining a positive attitude. Compared with medical majors, non-medical majors are the protective factors for maintaining a positive attitude (OR = 1.622, 95% CI = 1.268–2.177) (see Table 7).

College students' COVID-19 prevention and control practices

The average COVID-19 prevention and control practice score of college students was 20.48 ± 4.46. Most college students have taken the prevention and control measures in COVID-19. However, there are still many college students who have not taken preventive practice in using public chopsticks, exercising and keeping social distance (see Table 8).

The results of single factor analysis showed that there were significant differences in the scores of health practices for COVID-19 prevention and control among students with different urban and rural areas and grades ($P < 0.05$). More than half of the college students had good health behaviors, accounting for 53.48% of the sample (2818). Logistic regression analysis was further performed for the variables with statistical significance in the single factor analysis of practice scores. The results showed that, compared with freshmen, sophomores (OR = 0.601, 95% CI = 0.529–0.683), juniors (OR = 0.596, 95% CI = 0.501–0.709) and seniors (OR = 0.670, 95% CI = 0.542–0.828) were the risk factors for taken COVID-19 prevention and control behaviors. The results are shown in Tables 9, 10.

TABLE 6 Scores of college students' attitudes about COVID-19 prevention and control.

Participants		Mean score ± SD	t(F)	P-value
Gender	Male	46.92 ± 6.76	5.305	<0.001
	Female	47.87 ± 5.02	–	–
Ethnic group	Han	47.70 ± 5.67	5.919	0.003
	Korean	47.02 ± 5.95	–	–
	Other nationality	47.66 ± 5.23	–	–
Town and country	Town	47.59 ± 5.73	1.033	0.302
	Country	47.38 ± 5.57	–	–
Grade	Freshman	48.02 ± 4.62	9.766	<0.001
	Sophomore	46.88 ± 6.94	–	–
	Junior	47.22 ± 6.24	–	–
	Senior	47.35 ± 5.76	–	–
	Five-grade	47.33 ± 6.45	–	–
Major	Medical major	46.97 ± 6.58	3.707	<0.001
	Non-medical major	47.72 ± 5.38	–	–

TABLE 7 Binary logistic regression analysis of influencing factors of college students' attitudes toward COVID-19 prevention and control.

Participants		β	Wald χ^2	P-value	OR (95% CI)
Gender	Male*	–	–	–	–
	Female	0.653	25.909	<0.001	1.920 (1.494, 2.469)
Ethnic group	Han*	–	–	–	–
	Korean	−0.457	9.783	0.002	0.633 (0.475, 0.843)
	Other nationality	−0.384	3.613	0.057	0.681 (0.458, 1.012)
Grade	Freshman*	–	–	–	–
	Sophomore	−0.989	43.162	<0.001	0.372 (0.277, 0.500)
	Junior	−0.732	12.838	<0.001	0.481 (0.322, 0.718)
	Senior	−0.968	17.505	<0.001	0.380 (0.241, 0.598)
	Five-grade	−1.206	10.345	0.001	0.299 (0.144, 0.624)
Major	Medical major*				
	Non-medical major	0.508	13.577	<0.001	1.622 (1.268, 2.177)

*as the control group.

Mental health status of college students during the COVID-19 pandemic

During the pandemic period, there were 2,398 college students (45.50%) with negative emotions. The results of single factor analysis showed that there were significant differences in the proportion of depression among college students of different sexes and with different grades, knowledge, attitudes and practices ($P < 0.05$). There were significant differences in the proportion of anxiety symptoms among college students of different nationalities and with different grades, knowledge, attitudes and practices ($P < 0.05$). There were significant differences in the proportion of stress emotions among students of different sexes and nationalities and with different grades, attitudes and practices ($P < 0.05$). In the single factor analysis of negative emotions, the variables with statistical significance were further analyzed by logistic regression, and the results were consistent with those of the single factor analysis.

Logistic results showed that females were the protective factor for depression (OR = 0.799, 95% CI = 0.701–0.911). Compared with freshmen, sophomores (OR = 1.776, 95% CI = 1.534–2.056), juniors (OR = 1.506, 95% CI = 1.237–1.834) and seniors (OR = 1.763, 95% CI = 1.394) are risk factors for depression. Positive attitudes (OR = 0.497, 95% CI = 0.384–0.643) and healthy behaviors (OR = 0.570, 95% CI = 0.502, 0.648) are the protective factors for depression. In terms of anxiety, compared with freshmen, sophomores (OR = 1.790, 95% CI = 1.569–2.042), juniors (OR = 1.760, 95% CI = 1.474–2.100) and seniors (OR = 1.890, 95% CI = 1.521–2.348) are risk factors. Compared with Han nationality, ethnic Korean nationality (OR = 1.171, 95% CI

= 1.020–1.344) and other ethnic minorities (OR = 1.280, 95% CI = 1.061–1.544) are risk factors for anxiety. Positive cognition (OR = 0.737, 95% CI = 0.570–0.952) and adopting healthy behavior (OR = 0.567, 95% CI = 0.507–0.635) are protective factors. As for stress, females are the protective factors (OR = 0.688, 95% CI = 0.549–0.863). Compared with freshmen, sophomores (OR = 1.914, 95% CI = 1.471–2.489), juniors (OR = 1.599, 95% CI = 1.120–2.281) and seniors (OR = 2.535, 95% CI = 1.741) are risk factors. Compared with Han nationality, ethnic Korean nationality is a risk factor for stress (OR = 1.424, 95% CI = 1.098–1.848). Maintaining a positive attitude (OR = 0.312, 95% CI = 0.226–0.433) and healthy behavior (OR = 0.466, 95% CI = 0.369–0.590) are protective factors for stress (see Tables 11, 12 for details).

TABLE 8 Preventive practices of COVID-19 among college students.

Items	Untaken preventive practice
After returning to school, did you wear a mask in the place where many people studied (or worked) together?	1,561 (29.6)
In the last two months, did you wear a mask in crowded public places (such as supermarkets, shopping malls, buses, etc.)?	1,096 (20.8)
In the last two months, did you keep a distance when talking with others?	1,885 (35.8)
In the last two months, many people have eaten at the same table. Did you use public chopsticks?	2,060 (39.1)
Have you done any physical exercise in the last two months?	2,062 (39.1)
In the last two months, did you and your family buy or stock disinfection products or masks?	722 (13.7)
After the epidemic, if you have symptoms such as coughing or sneezing, will you consciously wear a mask?	527 (10.0)

Discussion

At present, the COVID-19 pandemic situation in China has been controlled, and it has entered the stage of normalized prevention and control (23). In addition to vaccines, strict preventive measures are the only other option to stop the rapid spread of diseases (24). Preventive measures play a vital role in reducing the infection rate of infectious diseases and controlling their spread, which suggests that it is necessary for the public to observe preventive measures, and the public's compliance with preventive measures is influenced by their KAP (25). Some studies have pointed out that people's KAP, as a part of public health emergency response capabilities, plays an important role in controlling the spread of COVID-19 (26). A large number of empirical studies have shown that health education can improve knowledge levels and change negative attitudes and behaviors, such as maintaining social distance, avoiding group gatherings and shaking hands, thus effectively curbing the spread of infectious diseases (27, 28). Empirical research on KAP can reveal basic information to determine the type of intervention to effectively control infectious diseases. Therefore, improving KAP is a potentially valuable strategy to gain better insight into misconceptions (29). Studies have found that in regard to health-related issues, college students can be a source of health awareness and health education because they are involved in spreading knowledge about the prevention and control of infectious diseases to the public for better tackling the ongoing pandemic (30, 31). In addition, a study found that social isolation and lockdowns due to the pandemic caused a series of mental health problems, such as stress, fear, anxiety, insomnia and emotional exhaustion (32). The evolution of the COVID-19 pandemic is uncertain and may have a long-term impact on mental health. College students with common mental health disorders are a vulnerable group. College students are in the delicate process of "transitioning" to adulthood and

TABLE 9 Scores for COVID-19 prevention and control practices.

Participants		Mean score ± SD	*t*(*F*)	*P*-value
Gender	Male	20.33 ± 4.69	1.711	0.087
	Female	20.56 ± 4.33	–	–
Ethnic group	Han	20.51 ± 4.51	0.366	0.694
	Korean	20.38 ± 4.32	–	–
	Other nationality	20.47 ± 4.40	–	–
Town and country	Town	20.54 ± 4.56	2.032	0.042
	Country	20.23 ± 4.45	–	–
Grade	Freshman	21.07 ± 4.21	26.524	<0.001
	Sophomore	19.77 ± 4.56	–	–
	Junior	19.71 ± 4.72	–	–
	Senior	20.26 ± 4.66	–	–
	Five-grade	21.06 ± 4.70	–	–
Major	Medical major	20.34 ± 4.39	1.302	0.193
	Non-medical major	20.52 ± 4.48	–	–

TABLE 10 Binary Logistic regression analysis of influencing factors for COVID-19 prevention and control practices.

Participants		β	Wald χ^2	*P*-value	OR (95% CI)
Town and country	Town*	–	–	–	–
	Country	−0.077	1.211	0.271	0.926 (0.808, 1.062)
Grade	Freshman*	–	–	–	–
	Sophomore	−0.510	60.728	<0.001	0.601 (0.529, 0.683)
	Junior	−0.517	34.123	<0.001	0.596 (0.501, 0.709)
	Senior	−0.401	13.724	<0.001	0.670 (0.542, 0.828)
	Five-grade	0.204	0.800	0.372	1.226 (0.784, 1.917)

*as the control group.

starting their careers, which makes them more prone to negative emotions (33). This study is helpful in bridging the gap in college students' knowledge, attitudes and behaviors regarding COVID-19 and improving their psychological states, which may reveal potential obstacles affecting changes in college students' social behavior.

Knowledge, attitudes and practices of college students regarding COVID-19

The results of this study showed that the COVID-19 knowledge awareness rate was low (24.11%). Most college students have poor knowledge of COVID-19 prevention and control and a poor understanding of COVID-19 infection. The reason for this phenomenon may be that pandemic information campaigns on the internet mainly focuses on personal protection and transmission, while less attention is given to related academic issues. As college students pay more attention to the prevention and control information and measures during the outbreak, they don't know enough about COVID-19's knowledge level, which leads to the poor awareness rate of COVID-19's related academic questions. The results show that most students are aware of the common symptoms of COVID-19, such as fever, cough and dyspnea, but they do not know enough about diarrhea and other symptoms. At present, most COVID-19 cases are asymptomatic infections. In Segen's medical dictionary, asymptomatic infections are defined as those lacking obvious clinical symptoms. An epidemiological investigation shows that the spread of asymptomatic infections of COVID-19, which means that the human body has almost no symptoms after infection, but it can be found that it has been infected through antibody testing, may lead to serious clinical diseases (34), suggesting that publicity and education regarding atypical symptoms should be strengthened through effective channels. It was found that college students have poor knowledge of the correct way to cover their noses and mouths when coughing and sneezing, which suggests that there are still some shortcomings regarding personal protection against COVID-19. With the continuous development of intelligent technology, network information is more and more concerned and relied on by people, and it is more and more deeply involved in people's daily life. While the Internet is becoming more and more prosperous, it is inevitable that the information is difficult to distinguish between true and false. It is found that one of the reasons for this phenomenon is that, driven by economic interests, some people who lack the awareness of public morality and the bottom line of laws and regulations, for their own interests (mainly economic interests), do not hesitate to create and spread false information and sensational news by online channels. There are also some online media participants who, with some bad motives, irresponsibly create rumors and attack and hurt today's society or individuals out of thin air. Therefore, the government official website, as the main channel for authoritative information sources, needs to expand its publicity to compensate for the lack of information validation for online social tools. In addition, the popularization of accurate COVID-19 knowledge should be strengthened in relevant school courses, and popular science of infectious disease prevention education should be provided. The research showed that the awareness rate of male students' health knowledge was lower than that of female students. The reason may be that female students pay more attention to social health problems, are more aware about preventive measures and have a higher knowledge acquisition ability than male students, which is consistent with related research results (35–39). Studies by Rana et al. (40) showed that there are significant differences in risk perception and coping mechanisms between the sexes. Compared with those of males, the risk perceptions of females increased by 2.26%, and their coping mechanisms increased by 3.41%. Therefore, accurate health education should be provided among college students, and attention should be given to boys. The results showed that the awareness rate of medical college students was higher than that of non-medical college students, which may be because medical students have corresponding medical professional knowledge, consistent with the results of other studies (41, 42). In addition, the knowledge awareness rate of fifth-year college students was high, which may be related to the fact that fifth-year college students are all medical students. It is suggested that health education should be strengthened for non-medical students.

The survey results showed that college students had a positive attitude and were supportive of the prevention and control of COVID-19, contributing to the prevention and control of COVID-19. An early set of studies on the attitudes and knowledge of COVID-19 found that people's attitudes toward the government's measures to curb the pandemic were highly correlated with

TABLE 11 Univariate analysis of depression, anxiety, and stress of college students with different characteristics.

Participants		Depression (%)	Anxiety (%)	Stress (%)
Gender	Male	529 (29.0)	760 (41.7)	156 (8.6)
	Female	846 (24.5)	1,507 (43.7)	196 (5.7)
	χ^2	12.343	2.025	15.750
	P-value	<0.001	0.155	<0.001
Ethnic group	Han	911 (25.4)	1,502 (41.8)	213 (5.9)
	Korean	324 (28.1)	512 (44.5)	97 (8.4)
	Other nationality	140 (26.4)	253 (47.6)	42 (7.9)
	χ^2	3.502	7.685	10.143
	P-value	0.174	0.021	0.006
Town and country	Town	1,083 (25.7)	1,798 (42.6)	293 (6.9)
	Country	292 (27.7)	469 (44.5)	59 (5.6)
	χ^2	1.800	1.204	2.462
	P-value	0.180	0.273	0.117
Grade	Freshman	548 (20.5)	953 (35.6)	118 (4.4)
	Sophomore	489 (33.2)	757 (51.4)	134 (9.1)
	Junior	190 (29.6)	325 (50.7)	48 (7.5)
	Senior	129 (32.7)	205 (52.0)	44 (11.2)
	Five-grade	19 (22.1)	27 (31.4)	8 (9.3)
	χ^2	96.172	135.163	50.284
	P-value	<0.001	<0.001	<0.001
Major	Medical major	330 (26.3)	546 (43.6)	78 (6.2)
	Non-medical major	1,045 (26.0)	1,721 (42.8)	274 (6.8)
	χ^2	0.056	0.221	0.538
	P-value	0.813	0.638	0.463
Knowledge score	<9	1,072 (26.8)	1,756 (43.9)	270 (6.7)
	≥9	303 (23.8)	511 (40.2)	82 (6.5)
	χ^2	4.365	5.342	0.136
	P-value	0.037	0.021	0.712
Attitude score	<40	123 (46.2)	149 (56.0)	59 (22.2)
	≥40	1,252 (25.0)	2,118 (42.3)	293 (5.9)
	χ^2	59.053	19.358	108.063
	P-value	<0.001	<0.001	<0.001
Practice score	<21	805 (32.8)	1,262 (51.4)	237 (9.7)
	≥21	579 (20.2)	1,005 (35.7)	115 (4.1)
	χ^2	107.616	132.970	65.471
	P-value	<0.001	<0.001	<0.001

their level of knowledge of COVID-19 (43). It was found that a higher level of information and education was related to a more positive attitude toward COVID-19 preventive measures. In this study, females had higher attitude scores than males. Studies have found that young men are more likely to express feelings of being invincible to COVID-19, so effective public health suggestions must be formulated for them (44). Non-medical majors had higher attitude scores than medical majors, suggesting that medical students may experience the phenomenon of separation of knowledge, attitudes and practice.

TABLE 12 Binary logistic regression analysis of influencing factors for college students' bad emotions.

Participants		Depression		Anxiety		Stress	
		P-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)
Gender	Male*	–	–	–	–	–	–
	Female	0.001	0.799 (0.701, 0.911)	–	–	0.001	0.688 (0.549, 0.863)
Grade	Freshman*	–	–	–	–	–	
	Sophomore	<0.001	1.776 (1.534, 2.056)	<0.001	1.790 (1.569, 2.042)	<0.001	1.914 (1.471, 2.489)
	Junior	<0.001	1.506 (1.237, 1.834)	<0.001	1.760 (1.474, 2.100)	0.010	1.599 (1.120, 2.281)
	Senior	<0.001	1.763 (1.394, 2.230)	<0.001	1.890 (1.521, 2.348)	<0.001	2.535 (1.741, 3.691)
	Five-grade	0.814	1.065 (0.629, 1.803)	0.419	0.824 (0.516, 1.316)	0.064	2.069 (0.959, 4.461)
Ethnic group	Han*	–	–	–	–	–	–
	Korean	–	–	0.025	1.171 (1.020, 1.344)	0.008	1.424 (1.098, 1.848)
	Other nationality	–	–	0.010	1.280 (1.061, 1.544)	0.099	1.345 (0.946, 1.913)
Knowledge score	<9*	–	–	–	–	–	–
	≥9	0.577	0.958 (0.824, 1.114)	0.444	0.950 (0.832, 1.084)	–	–
Attitude score	<40*	–	–	–	–	–	–
	≥40	<0.001	0.497 (0.384, 0.643)	0.020	0.737 (0.570, 0.952)	<0.001	0.312 (0.226, 0.433)
Practice score	<21*	–	–	–	–	–	–
	≥21	<0.001	0.570 (0.502, 0.648)	<0.001	0.567 (0.507, 0.635)	<0.001	0.466 (0.369, 0.590)

*as the control group.

The results showed that more than half of college students had high health behaviors (53.48%). Among them, urban college students had higher scores than rural college students. This may be because of the better implementation of protective measures in cities and towns, the lack of access to information in rural areas, and the limited access to information resources such as computers or social media that can help students understand the latest situation of the COVID-19 pandemic, suggesting that the education of relevant students should be strengthened (45). Medical students should continue to improve their cognition and attitude level, which play an important role in self-prevention measures and passing on knowledge to family, friends or relatives to help fight against epidemic diseases (46). The effective implementation of prevention and control measures is fundamental to curbing the spread of the pandemic. It was found that respondents had high execution ability in wearing masks, but the rate of good behaviors such as physical exercise was not high. At present, the COVID-19 pandemic is still spreading to different degrees. It is necessary to strengthen vaccination initiatives and continue to promote the existing guidelines for limiting the spread of the virus, including physical isolation, wearing masks, regular hand washing and indoor ventilation.

KAP theory emphasizes that knowledge is the foundation of behavioral change, attitude is the driving force of behavioral change, and knowledge improves attitudes, thus leading to a positive attitude toward change behaviors (47). Knowledge is a prerequisite for promoting healthy behaviors and developing a positive attitude to fight diseases (48). Providing training on COVID-19 prevention methods and publicizing correct information about the new coronavirus pneumonia will help to improve cognition and attitudes toward the prevention and control of COVID-19, which are essential to promote good COVID-19 prevention and control (49). Therefore, universities should plan to strengthen health education programs for COVID-19 prevention to educate students to take relevant preventive measures, such as maintaining social distance and avoiding gatherings in densely populated areas, and strengthen relevant publicity and education in a targeted manner; as a result, college students could develop a more comprehensive understanding of COVID-19, which is especially critical for enhancing their prevention and control behaviors.

Interventions for college students' mental health should be considered

The research results showed that there were more boys than girls who had negative emotions. This may be related to the better awareness and attitudes of female college students regarding COVID-19. It was found that senior students had more obvious stress, anxiety and depression, which is similar to the results of the 2020 Chinese College Students' Health Survey Report. Logistics analysis of psychological status shows that ethnic Korean college students' scores of COVID-19's attitudes toward prevention and control are lower than those of Han college students, and ethnic Korean college students have more negative emotions than Han college students. It is suggested that lower levels of trust of ethnic Korean college students is the influencing factor of ethnic Korean college students' bad emotional status. In addition, in China, Chinese is the mother tongue for Han college students, while Chinese is the non-mother tongue for ethnic Korean college students, and ethnic Korean college students have poor understanding of knowledge. Therefore, compared with Han college students, ethnic Korean college students have lower levels of trust in prevention and control of COVID-19, and there are more negative emotional situations. The results suggest that schools should pay attention to the health education and psychological counseling of students in ethnic minority groups. In addition, the study found that a low KAP level was a risk factor for negative mood. The research subjects had a certain psychological burden in understanding the pandemic situation. Studies have found that college students may suffer more psychological troubles, such as stress and anger, due to isolation, school suspension, the prohibition of private gatherings and the reduction in learning efficiency due to online education, which leads to an increase in dangerous behaviors such as online gambling (50). As a public health emergency, the COVID-19 pandemic easily leads to individual psychological stress reactions, and stressful events are an important influencing factor of individual anxiety (51). In the era of high internet use, college students have strong insights into social problems, and when faced with stressful events, their emotional responses are more intense, and they are more likely to have problems such as depression, anxiety and stress (52). These results show that the mental health of college students cannot be ignored during the COVID-19 pandemic. Schools should instill a sense of social responsibility and community support in students, which may improve poor mental health outcomes. Colleges and universities should provide psychological counseling hotlines, and well-trained counselors and psychologists should provide free psychological intervention and counseling services through the Internet (53). Relevant school departments should provide scientific and effective publicity and psychological counseling, plan long-term psychological services to control and reduce the burden of psychological problems, and advocate for college students to increase physical exercise, develop good habits, and enhance their own resistance to formulate corresponding strategies and measures for prevention and control. In addition, schools should cooperate with government agencies and medical staff to conduct health promotion and information literacy projects to effectively improve the mental health level of college students (54). Considering that college students' psychological problems were previously widespread, COVID-19 will aggravate students' psychological problems, and the existing academic pressure and occupational pressure cannot be ignored. The results of this study can supplement information regarding the mental health status of college students in the COVID-19 period. In addition, the results of this study can also help to identify college students with increased risk of psychological problems. Universities can consider developing long-term psychological services, such as implementing KAP intervention measures regarding COVID-19, for these students to reduce their risk of psychological problems (55).

This research has some limitations. First, this study was limited to students in public universities, and online questionnaires were used. Not all college students in the whole school participated in this study. Therefore, the representativeness of the research results to all students is controversial. In addition, the data provided in this study were self-reported, so there may be recall bias. Due to the cross-sectional study design, the viewpoint may change, and this study is also unable to establish causality.

Conclusion

College students in minority areas have good health attitudes, but the awareness rate of COVID-19 prevention and control is low, the proportion of healthy behaviors is low, and negative emotions easily occur. It is suggested that schools and other departments adopt relevant KAP intervention strategies, further strengthen targeted publicity and education measures, and provide relevant psychological counseling to reduce the harm of the COVID-19 pandemic to health.

Data availability statement

The datasets presented in this article are not readily available to avoid misuse of data and information, the datasets used or analyzed during the current study are available from the corresponding author Y-HL on reasonable request. Requests to access the datasets should be directed to Y-HL, liyihua@ybu.edu.cn.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Yanbian University (Ethical Code: 2021576, October 26th, 2021). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization and formal analysis: TW, Y-HL, and Y-QL. Data curation, methodology, and writing—original draft: TW and Y-HL. Investigation: Y-HL, Z-HH, Y-SC, and Y-QL. Supervision and validation: Y-HL, Y-SC, and Z-HH. Writing—review and editing: Y-HL and Y-QL. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Characterization of mild or asymptomatic patient admitted with Omicron variant of COVID-19 infection in Tibetan mobile cabin hospital China, August—October 2022

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Background: Prior to August 7, 2022, there had been no positive cases of novel coronavirus in Tibet for 920 consecutive days. However, with the first case of Omicron variant infection, the disease rapidly spread and was prevalent in Tibet for nearly 3 months, from August 7th to November 1st. With the spread of the epidemic, the local government responded quickly and established several mobile cabin hospitals to treat patients with mild and asymptomatic Omicron infection. However, the epidemiological and clinical characteristics of these patients are unknown.

Methods: This is a retrospective study including a total of 14,264 mild and asymptomatic cases with Omicron infection in Tibet between August to October, 2022. The clinical data and epidemiological characteristics of COVID-19 cases admitted to Tibet mobile cabin hospitals were collected by using standardized forms from mobile cabin hospital database system, including demographic characteristics, onset symptoms, medication use, past medical history, hospitalization time, and discharge time. In terms of statistical analysis, multivariate Cox regression model was used to analyze the relationship between case characteristics and the length of stay in hospital.

Results: Among 14,264 patients infected with Omicron, the average length of hospital stay was six (4–8, Interquartile range) days. Fifty percent of the patients were discharged by the 6th day, and 90% were discharged by the 10th day. Patients of all ages are generally susceptible to COVID-19, and there was no difference in discharge time, but the average length of hospital stay of Tibetan patients with COVID-19 was longer than that of Han patients. According to the statistics of clinical symptoms, sore throat (38.7%) and fever (19.4%) were the most common symptoms, while muscle pain (17.4%), cough (16.6%), and expectoration (13.2%) were also common. In addition, patients with chronic gastritis had significantly longer hospital stays.

Conclusion: Based on the experience of Tibet mobile cabin hospitals and data analysis, we believe that patients of all ages are generally susceptible to Omicron. Compared with other novel coronavirus strains, Omicron infected patients had a shorter hospital stay, and treatment of symptoms is expected to shorten the time of nucleic acid negative conversion.

KEYWORDS

COVID-19, Omicron, Tibetan mobile cabin hospitals, clinical observations, mild or asymptomatic patient

1. Introduction

Since the discovery of the coronavirus disease 2019 (COVID-19) at the end of 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been continuously mutating, with the Omicron variant strain globally dominant at present, whereas the previously prominent alpha, beta, gamma, and delta strains now account for a relatively smaller proportion of the circulating strains. As one of the important variants of COVID-19, Omicron is a strain that specializes in immune evasion, with discrete and rapid transmission processes, and a lower pathogenicity than that of previous strains; with a certain degree of acquired immunity in the population conferred by vaccination, the symptoms of patients infected with Omicron are generally relatively mild (1, 2), only a few patients with severe symptoms needed treatment in hospital. To date, Omicron mutant strains have evolved into various subtypes, with the virulence of some of these strain subtypes continuously increasing (3). From August 7th to November 1st, 2022, multiple clusters of Omicron outbreaks occurred in the Tibet Autonomous Region. Given that Tibet is located on a plateau and lacks substantial medical services and has low vaccination rates, the rapidly disseminating Omicron outbreak posed a huge challenge to the medical and health systems in the region. Under the strong support of the State Council's Joint Prevention and Control Mechanism Comprehensive Team, various provinces and cities assisted Tibet in conducting COVID-19 nucleic acid testing and provided outbreak treatment and rescue work.

Mobile cabin hospital originated from military warfare to ensure the medical needs of the frontline personnel. In 2020, in response to the sudden COVID-19 epidemic, China adopted mobile cabin hospitals for the first time. These mobile cabin hospitals can be quickly established on a large-scale at low construction costs, providing isolation, medical care monitoring, basic social life and other functions, which contribute to effectively curbing the spread of the virus (4). Since then, as the COVID-19 spread throughout China, shelter hospitals were adopted in a timely manner. Mobile cabin hospitals are generally large temporary hospitals that have been established in large public places and can centrally admit and treat patients with COVID-19, monitoring their condition, provide basic medical and health services, and effectively halting the spread of the virus. The construction of mobile cabin hospitals has laid an important foundation for the effective control of COVID-19 on multiple occasions in various parts of China and has become one of the core methods in China's fight against the epidemic for the past 3 years. Since the outbreak of the epidemic in Tibet, local government established a series of effective measures to ensure that people frequently carried out COVID-19 nucleic acid testing. Community staff, medical staff in shelter hospitals, and hospitals have established a standardized referral system to treat patients appropriately. Medical staff doing scientific research in the shelter hospital could better understand the characteristics of the prevalence of COVID-19 in the area. Numerous mobile cabin hospitals have been used in large public places, such as convention and exhibition centers and stadiums, with a focus on treating patients with mild, common, or no symptoms of COVID-19, through the integrated use of traditional Chinese and Western medicine providing a tailored fight against COVID-19 outbreak in China.

2. Methods

2.1. Study design and data collection

Here, we included a total of 14,264 cases of Omicron infections admitted in a Tibetan mobile cabin hospital from August to October 2022. All cases were diagnosed based on the diagnosis and treatment protocol of the National Health Commission of the People's Republic of China (9th edition). All data were collected by one of the largest mobile cabin hospitals in Tibet, and all cases were discharged from the cabin hospital following a COVID-19-negative nucleic acid test. All included cases were confirmed to be positive through evaluation by hospital emergency or fever clinic personnel, or community COVID-19 nucleic acid test screening. Patients were sent to the mobile cabin hospital for treatment within 2 days after diagnosis and were required to undergo daily COVID-19 testing and leave the cabin hospital following two consecutive days of COVID-19-negative nucleic acid test results. We collected the demographic, epidemiological, clinical data of cases using standardized forms.

2.2. Statistical analysis

Descriptive statistical methods were adopted to analyze the continuous variables and categorical variables for different ethnic cases (Tibetan, Han, and other), respectively. The statistical tests for the normal distribution of data included the Kolmogorov–Smirnov and Shapiro–Wilk tests. The differences between the groups were compared by chi-square test. Multivariate Cox regression model was used to analyze the relationship between case characteristics and the length of time in hospital. All statistical tests were two-sided with a significance level of <0.05. Statistical analysis was performed using GraphPad Prism (La Jolla, CA).

2.3. Ethical approval

The Ethics Review Committee of the Beijing hospital of Traditional Chinese Medicine, Capital Medical University provided approval for this study (No. 2022BL02-044-02). Additionally, patients' personal identifying information was anonymized to ensure privacy.

3. Results

Data showed that the average length of hospital stay for patients infected with the Omicron strain was 6 days (4–8, Interquartile range, IQR; Table 1), which was shorter than the length of hospital stay for patients infected with the Alpha strain at the Wuhan mobile cabin hospital (16.08 ± 5.13 days) in March 2020, or compared with that of patients infected with the Omicron strain at the Shanghai mobile cabin hospital (7.18 ± 3.05 days) in June 2022 (5, 6). Figure 1A shows the number of patients with COVID-19 according to the length of hospital stay, with patients being discharged from the hospital starting from the third day. Figure 1B shows that 50% of patients with COVID-19 were discharged by the sixth day, whereas 90% of them were discharged after 10 days of hospital stay, consistent with the results from the Shanghai mobile cabin hospital. Figure 1C shows the length of hospital stay of patients with COVID-19 according to their age group. In our study, the age range of patients ranged from 1 to 91 years old, and infected patients involved various age groups. In the Shanghai mobile cabin hospital, patients aged 20–29 years old had the fastest recovery. Likewise, in the Tibetan mobile cabin hospital, patients aged 20–29 years old also showed a relatively shorter length of hospital stay (6.36 ± 3.14 days); patients aged 70–79 had longer hospital stays. However, no statistical difference was seen in the discharge time of patients across all age groups. Interestingly, in the Tibet mobile cabin hospital, patients were mainly Tibetans, with Han individuals being only a small portion of patients. Figure 1D shows that the average length of hospital stay of Tibetan patients with COVID-19 was longer than that of Han patients with COVID-19, which might be attributed to the low vaccination rate of Tibetan patients, and/or differences based on ethnicity. Figure 1E shows the number of patients with COVID-19 in the Tibetan mobile cabin hospital with accompanying symptoms and underlying medical conditions, recorded as requiring treatment. Sore throat was one of the main symptoms among patients, with other main symptoms including fever, muscle pain, cough, expectoration, and abnormal bowel movements. Figure 1F shows average length of hospital stay with different symptoms and underlying medical conditions. Only a small proportion ($n < 600$) of patients were recorded to have common underlying medical conditions, such as diabetes, hypertension, and chronic gastritis. To analyze the influence of these factors on the mitigation of COVID-19, we incorporated them into a Cox regression analysis.

Table 2 shows the results of Cox regression analysis. The multivariate model showed that Tibetan people with COVID-19 had a longer length of hospital stay than Han individuals and that the presence of accompanying symptoms that required treatment, such as sore throat, fever, cough, expectoration, and worsening of abnormal

TABLE 1 Demographic characteristics and accompanying symptoms of patients with COVID-19.

Characteristics	All cases (n = 14,265)	Han (n = 10,641)	Tibetan (n = 3,228)	Other ethnicity (n = 396)	p-value
Gender (male)	7464 (52.3%)	5199 (48.9%)	2041 (63.2%)	224 (56.6%)	<0.001
Age (1QR)	32 (21–46)	31 (20–45)	34 (25–47.75)	32 (23–44)	<0.001
Age group (year)					
0–9	1294 (9.1%)	1136 (10.7%)	116 (3.6%)	42 (10.6%)	
10–19	2101 (14.7%)	309 (9.6%)	1756 (16.5%)	36 (9.1%)	
20–29	3118 (21.9%)	803 (24.9%)	2217 (20.8%)	98 (24.7%)	
30–39	3082 (21.6%)	813 (25.2%)	2170 (20.4%)	99 (25.0%)	
40–49	2122 (14.9%)	599 (18.6%)	1461 (13.7%)	62 (15.7%)	
50–59	1551 (10.9%)	513 (15.9%)	990 (9.3%)	48 (12.1%)	
60–69	665 (4.7%)	68 (2.1%)	591 (5.6%)	6 (1.5%)	
70–79	257 (1.8%)	7 (0.2%)	246 (2.3%)	4 (1.0%)	
80–	75 (0.5%)	0 (0.0%)	74 (0.7%)	1 (0.3%)	
Length of hospital stay (days)	6 (4–8)	6 (4–8)	6 (4–8)	5 (3–7)	
Accompanying symptoms					
Fever	2772 (19.4%)	2000 (18.8%)	671 (20.8%)	101 (25.5%)	<0.001
Cough	2372 (16.6%)	1636 (15.4%)	650 (20.1%)	86 (21.7%)	<0.001
Expectoration	1887 (13.2%)	1272 (12.0%)	541 (16.8%)	74 (18.7%)	<0.001
Sore throat	5518 (38.7%)	3954 (37.2%)	1403 (43.5%)	161 (40.7%)	<0.001
Muscle pain	2478 (17.4)	1760 (16.5%)	627 (19.4%)	91 (23.0%)	<0.001
Dyspnea	318 (2.2%)	247 (2.3%)	60 (1.9%)	11 (2.8%)	0.224
Abnormal defecation	465 (3.3%)	313 (2.9%)	136 (4.2%)	16 (4.0%)	0.001
Nausea and vomiting	69 (0.5%)	50 (0.5%)	17 (0.5%)	2 (0.5%)	0.919

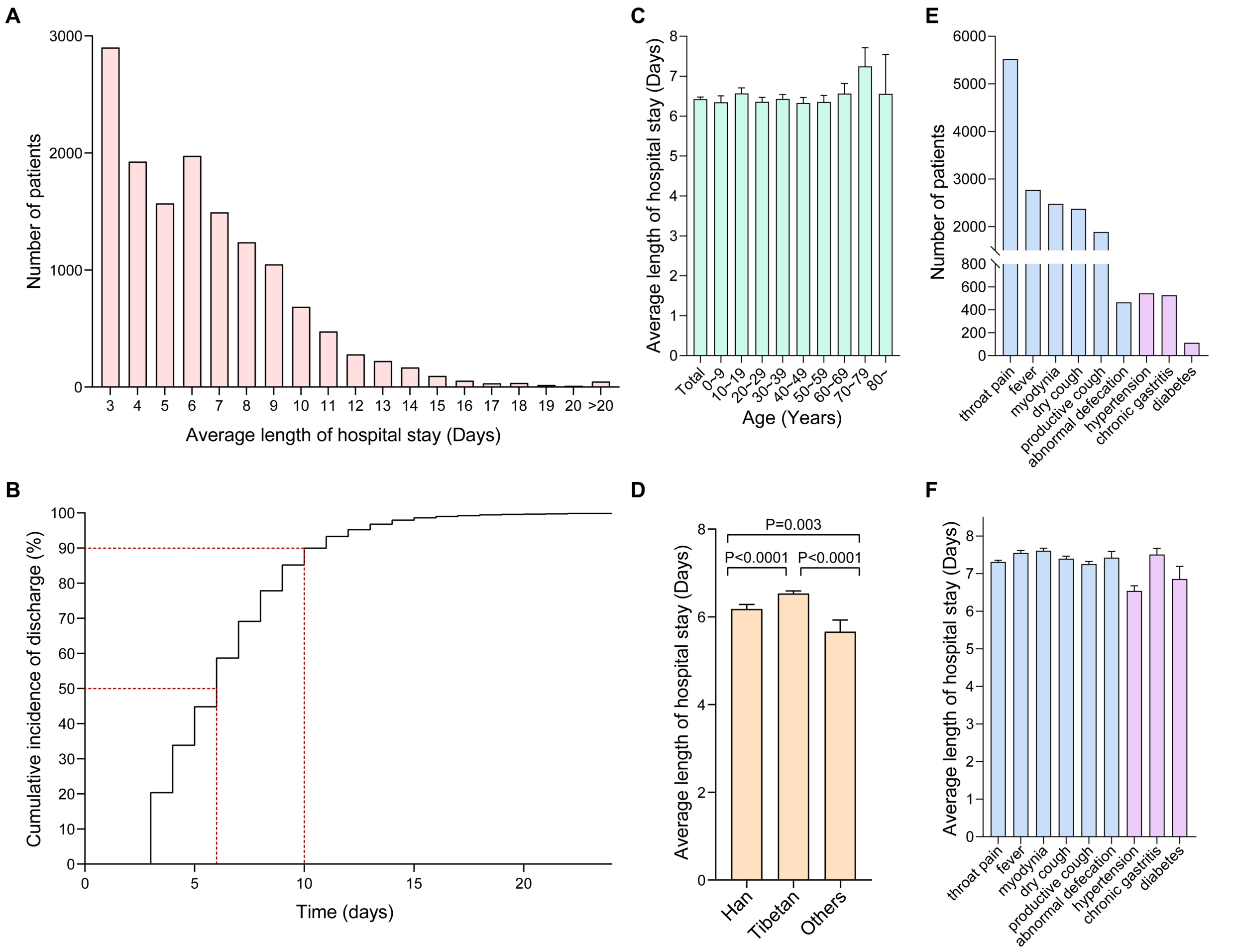

FIGURE 1
(A) The number of patients with COVID-19 with different lengths of hospital stay **(D)** in the Tibetan mobile cabin hospital. **(B)** Percentage of patients with COVID-19 who were discharged from the Tibetan mobile cabin hospital according to the length of hospital stay. Among them, 50% were discharged after 6 days, whereas 90% of them were discharged after 10 days of stay (dashed red lines). **(C)** The length of hospital stay of patients with COVID-19 of different age groups; the panel represents the average length of hospital stay of patients in each age group (the overall average length of hospital stay of patients was 6.43 ± 3.21 days). **(D)** Comparison of the length of hospital stay among Han, Tibetan, and other ethnic groups. **(E)** The number of people who required medication due to different symptoms and underlying medical conditions. **(F)** The average length of hospital stay for patients with different symptoms and underlying medical conditions.

bowel movements were unfavorable factors for the relief of COVID-19 among patients.

4. Discussion

During the epidemic of COVID-19 in Tibet, despite the rapid spread of the Omicron variant and the relative shortage of medical resources, medical staff in all parts of China provided rapid support and established several mobile cabin hospitals in a short time to ensure that COVID-19 cases were isolated and treated effectively in a timely manner.

In this study, most cases were mild or asymptomatic. We analyzed COVID-19 cases in the largest mobile cabin hospital in Tibet and found that all age groups were susceptible to Omicron variant infection. Infection with the Omicron strain is associated with a shorter length of hospital stay and relatively faster recovery from symptoms in general, which was also supported by a recent United Kingdom study showing that the risk of hospitalization and mortality from Omicron were approximately 41 and 31% that of Delta, respectively, in the same period (7). At the time of onset, Omicron mainly attacks the respiratory system of the host. While its S protein cannot be effectively cut by transmembrane serine protease 2 in the lungs, rendering its ability to invade the lower respiratory tract lower than that of other strains, Omicron is still able to invade the upper respiratory tract very effectively, leading to fever, sore throat, cough, expectoration, and other symptoms (8). Exacerbation of these symptoms also indicated that viral testing required a longer time to produce a negative result leading to an extended hospital stay. Hence, timely treatment according to symptoms not only helps improve physical discomfort, but also facilitates the yield of a negative result for the Omicron nucleic acid test, thereby reducing the length of hospital stay. Our data show that the proportion of patients who reported underlying medical conditions on their own accord was

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TABLE 2 Univariate/multivariate Cox analysis of the effect of demographics, symptoms, and underlying medical conditions on the length of hospital stay of patients with COVID-19.

Characteristic	Number of people entering and leaving the cabin (*n* = 14,264)					
	Univariate		Multivariate 1		Multivariate 2	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Gender (male vs. female) No. 7464 vs. *6801*	1.022 (0.989–1.056)	0.188	1.010 (0.977–1.044)	0.552	0.971 (0.939–1.004)	0.084
Age	0.999 (0.998–1.000)	0.094	0.999 (0.998–1.000)	0.065	1.001 (1.000–1.002)	0.095
Ethnicity						
Tibetan vs. Han No. 10641 vs. *3228*	0.904 (0.869–0.940)	<0.001	0.904 (0.869–0.940)	< 0.001	0.861 (0.828–0.896)	<0.001
Other ethnicity vs. Han No. 396 vs. *3228*	1.161 (1.046–1.289)	0.005	1.160 (1.045–1.288)	0.005	1.176 (1.059–1.306)	0.002
Accompanying symptoms						
Sore throat (with vs. without) No. 5518 vs. *8747*	0.687 (0.664–0.711)	<0.001			0.732 (0.707–0.758)	<0.001
Fever (with vs. without) No. 2772 vs. 11493	0.711 (0.682–0.741)	<0.001			0.828 (0.737–0.931)	<0.001
Muscle pain (with vs. without) No. 2478 vs. *11787*	0.707 (0.677–0.739)	<0.001			0.921 (0.815–1.041)	0.189
Cough (with vs. without) No. 2372 vs. *11893*	0.757 (0.724–0.791)	<0.001			0.846 (0.807–0.886)	<0.001
Expectoration (with vs. without) No. 1887 vs. *12378*	0.796 (0.758–0.835)	<0.001			0.906 (0.861–0.953)	<0.001
Abnormal bowel movements (with vs. without) No. 465 vs. 13800	0.777 (0.708–0.852)	<0.001			0.843 (0.768–0.926)	<0.001
Underlying condition						
Hypertension No. 544 vs. *13721*	0.972 (0.892–1.059)	0.510			0.989 (0.904–1.082)	0.404
Diabetes No. 112 vs. *14153*	0.898 (0.746–1.082)	0.257			0.923 (0.765–1.114)	0.809
Chronic gastritis No. 526 vs. *13739*	0.759 (0.695–0.828)	<0.001			0.824 (0.754–0.900)	< 0.001

relatively low, mostly consisting of patients with diabetes, hypertension, and chronic gastritis, potentially leading to data bias. Nevertheless, our analysis suggested that all three underlying medical conditions are potentially deleterious to the length of hospital stay of patients with COVID-19, although a statistical significance was only observed in patients with chronic gastritis. Research has shown that gastrointestinal dysfunction in patients with chronic gastritis or abnormal bowel movements can result in alterations to the gut microbiome and an increase in the levels of inflammatory cytokines, which might affect the prognosis of patients with COVID-19 (9). This suggested that attention should be given not only to the long-term treatment of patients with chronic diseases, but also to those with abnormal bowel movements. Although the variant strain of Omicron is different compared with the original strain used to produce the approved vaccine in China, our results suggest that the vaccine is still effective; thus, the low vaccination rate of Tibetan patients with COVID-19, may have contributed to their longer average hospital stay compared to Han patients.

As of November 1, 2022, the Omicron outbreak in Tibet was coming to an end; however, humanity will still has a long battle with such a cunning virus. Overall, the use of mobile cabin hospitals played a pivotal role in halting the spread of the outbreak and remains one of the key measures employed in various parts of China to overcome multiple rounds of outbreak over the years. As the virulence and pathogenicity of Omicron has gradually weakened, the various outbreak prevention policies of China are continuously optimized, with less large-scale COVID-19 nucleic acid screenings required, and with asymptomatic infections and mild cases being isolated at home, infected people are no longer restricted from purchasing the relevant therapeutic medications, rendering mobile cabin hospitals in China no longer a necessity in the fight against the outbreak. It is plausible that Omicron will continue to infect many people in the future, posing a challenge for China in view of its large population base, aging population, and notable disparity in the allocation of medical resources.

There are also some shortcomings in this study. First, most Omicron-infected individuals in the cabin hospital were mild or asymptomatic, and there is a lack of data support for severe or dying patients. Patients who are referred to the hospital for further treatment due to worsening conditions are also not included in the statistics, because the mobile cabin hospital's patient diversion strategy and referral system, and the mobile cabin hospital's statistical data do not include the relevant data of severe patients. Second, the information on Omicron infected individuals in the cabin hospital is not complete, such as vaccination status, nucleic acid CT values, and detailed disease history. But important information about patients was collected and statistically analyzed. It is hoped that this study will provide a basis for the epidemiology of the COVID-19 epidemic and a useful reference for the disease characteristics of mild or asymptomatic Omicron patients.

5. Conclusion

Based on the data from Tibetan mobile cabin hospital patients of all ages are susceptible to Omicron infection. Compared with other novel coronavirus strains, Omicron infected patients have a shorter hospital stay. In addition, symptomatic treatment with medications might shorten the time required to yield a COVID-19-negative nucleic acid test result from a previously positive patient. We believe that our report on patients with COVID-19 in Tibetan mobile cabin hospitals will facilitate understanding of the pathogenicity of Omicron and boost knowledge on its infection cycle and accompanying symptoms. As we continue to battle with the COVID-19 pandemic, we recommend that patients infected with the Omicron strain avoid exacerbation of symptoms caused by the infection as much as possible, through the provision of timely symptomatic treatment to eradicate the negative effects of Omicron more rapidly on the human body.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Committee of the Beijing hospital of Traditional Chinese Medicine, Capital Medical University provided approval for this study (No. 2022BL02-044-02). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

Q-qL and H-bW conceived and designed the project. FS and BL collected the data. J-jS and W-bL analyzed the data. FS prepared the manuscript. All authors read the manuscript, provided feedback, and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Molecular epidemiological characteristics of *Mycobacterium leprae* in highly endemic areas of China during the COVID-19 epidemic

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Objectives: The present study analyzed the impact of the COVID-19 pandemic on the prevalence and incidence of new leprosy cases, as well as the diversity, distribution, and temporal transmission of *Mycobacterium leprae* strains at the county level in leprae-endemic provinces in Southwest China.

Methods: A total of 219 new leprosy cases during two periods, 2018–2019 and 2020–2021, were compared. We genetically characterized 83 clinical isolates of *M. leprae* in Guizhou using variable number tandem repeats (VNTRs) and single nucleotide polymorphisms (SNPs). The obtained genetic profiles and cluster consequences of *M. leprae* were compared between the two periods.

Results: There was an 18.97% decrease in the number of counties and districts reporting cases. Considering the initial months (January–March) of virus emergence, the number of new cases in 2021 increased by 167% compared to 2020. The number of patients with a delay of >12months before COVID-19 (63.56%) was significantly higher than that during COVID-19 (48.51%). Eighty-one clinical isolates (97.60%) were positive for all 17 VNTR types, whereas two (2.40%) clinical isolates were positive for 16 VNTR types. The (GTA)9, (TA)18, (TTC)21 and (TA)10 loci showed higher polymorphism than the other loci. The VNTR profile of these clinical isolates generated five clusters, among which the counties where the patients were located were adjacent or relatively close to each other. SNP typing revealed that all clinical isolates possessed the single SNP3K.

Conclusion: COVID-19 may have a negative/imbalanced impact on the prevention and control measures of leprosy, which could be a considerable fact for official health departments. Isolates formed clusters among counties in

Guizhou, indicating that the transmission chain remained during the epidemic and was less influenced by COVID-19 preventative policies.

KEYWORDS

Leprosy, COVID-19, *Mycobacterium leprae*, Epidemiology, Genotype, strain typing and transmission

1 Introduction

Leprosy, caused by *Mycobacterium leprae* (*M. leprae*), remains a significant public health concern, with more than 200,000 new leprosy cases annually worldwide (1, 2). The number of reported cases per year has remained fairly constant over the past few years, emphasizing that leprosy continues to spread. The distribution and emergence of new leprosy cases are restricted to a small number of countries, with India, Brazil, and Indonesia accounting for more than 80% of cases worldwide, accounting for 59%, 14%, and 9% of cases, respectively (2, 3). This distribution of leprosy was found to be spatially unevenly distributed across countries. Due to the systematic and effective implementation of leprosy eradication programs, leprosy cases in China have declined rapidly over the last few years (4, 5). However, China still reported 422 newly diagnosed cases in 2021, mainly from the southwestern region, such as Sichuan, Hunan, Yunnan, and Guizhou (6–8).

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to the implementation of policy interventions such as social distancing, population density control, mask-wearing, and other general hygiene improvements. Existing studies suggest that leprosy transmission is primarily due to close contact with leprosy patients, most likely through infectious aerosols produced by coughing and sneezing but also through skin-to-skin contact. We speculate that these intervention strategies during coronavirus disease 2019 (COVID-19) could potentially impact the transmission and distribution of leprosy (1, 9–11). In addition, these policy interventions, as well as social, economic, and health systems, have a strong impact on other diseases, including leprosy, which has been a high prevalence area in Guizhou, China (12). Thus, 127,558 new leprosy cases were detected worldwide in 2020, a decrease of 37% compared to 2019, due to the implementation of the COVID-19 pandemic control programs (13). This is similar to what some authors have said that other public health priorities, such as the COVID-19 pandemic, pose a threat to the sustainability of surveillance and control efforts for diseases such as leprosy from a public health perspective (14, 15).

Recently, multiple-locus variable-number tandem-repeat (VNTR) analysis (MLVA) and single nucleotide polymorphism (SNP) typing have been used in epidemiological investigations to determine genotypic differences between different bacterial species (16–19). As *M. leprae* cannot be cultured on artificial medium, molecular techniques have been used to better characterize the organism (20, 21), including deciphering its genome sequence (22), to determine the exact origin and spread of *M. leprae* (23). Single nucleotide polymorphisms (SNPs) can be used in systematic geographical studies of leprosy (19), and identifying the source of the disease and trace transmission patterns has proven its importance as a valuable framework for global leprosy strain typing (16). Recent studies have reported 4 genotypes and 16 subtypes of *M. leprae* strains worldwide defined by SNPs (19, 23) In addition to SNPs, variable number tandem repeats (VNTRs) were used for genotyping. VNTR-based strain typing is sensitive, and its unique polymorphisms appear to be more suitable for monitoring the spread of *M. leprae* over shorter epidemiological distances (16–18, 24). It can distinguish different leprosy genotypes at the county level and predict the distribution and migration of leprosy (12, 25, 26). It was also observed that the number of some VNTR alleles was correlated with SNP type. Numerous studies have used large panels of VNTR loci and efficiently demonstrated the origin and transmission of leprosy (23, 27–30). Therefore, some scholars have proposed the combination method of VNTR multisite analysis and SNP typing to study leprosy and maximize the role of molecular epidemiology (15).

To better understand the impact of COVID-19 on the transmission of leprosy, we conducted an epidemiological study to assess the causes of measures and behavioral lifestyles associated with COVID-19 that may influence the transmission of leprosy in Guizhou, China. At the same time, we also investigated the genomic characteristics of *M. leprae* strains at the county level in Guizhou, China, at two periods to determine the temporal dynamic nature of leprosy before and during COVID-19.

2 Materials and methods

2.1 Study designs, enrollment, and data collection

The surveillance data of new leprosy cases in Guizhou from January 1, 2018, to December 31, 2021, were obtained from the Database of China Leprosy Management Information System (LEPMIS). Basic demographic data, including age, sex, source of infection, method of discovery, date of diagnosis, Ridley-Jopling, and WHO classification of patients, were extracted from LEPMIS. Microsoft Excel file (version 2016) was employed to compile data on newly identified leprosy cases and perform chi-square test analysis on their clinical characteristics, such as gender, age, delay, deformity, and disability.

2.2 Ethics statement

The present study was approved by the Institutional Review and Ethics Committees of the Institute of Dermatology, Chinese Academy of Medical Sciences, China (2014-KY-003). Tissue samples were collected from all patients after informed consent was obtained.

2.3 Sample collection and isolation of *Mycobacterium leprae* genomic DNA from skin biopsies

Skin biopsy samples were collected from all enrolled new leprosy patients at the Guizhou Provincial Center for Disease Control and Prevention from 2018 to 2021. As per the WHO guidelines, the confirmation of leprosy was accomplished by routine skin smear and histopathological examination (31). County-level registration and clinical information on cases in Guizhou are recorded in Supplementary Table S1. The biopsy samples were collected from all confirmed cases of leprosy in 70% ethanol and then transported into the central laboratory facility at the National Center for Leprosy Control, China CDC. The biopsy tissue samples were washed twice with phosphate-buffered saline (PBS) followed by grinding with a glass Dounce homogenizer. Total genomic DNA was isolated from ethanol-fixed biopsy samples by a DNeasy Blood & Tissue Kit (Qiagen, Germany, cat No. 69504) according to the manufacturer's instructions with minor modifications. The isolated genomic DNA was immediately used for genotyping analysis or stored at-70°C for further use.

2.4 Multiplex PCR amplification of VNTR loci

VNTR analysis of *M. leprae* was performed using 17 mini and microsatellite VNTR loci, such as (AC)8b, (GTA)9, (GGT)5, (AT)17, rpoT, 21–3, (AC)9, (AT)15, (AC)8a, 27–5, 6–7, (TA)18, (TTC)21, 18–8, 12–5, 23–3 and (TA)10. Primers for amplification of VNTR loci are listed in Supplementary Table S2 (3). Multiplex PCR was performed with four multiplex PCR combinations in a 20 µL reaction volume containing 12 µL Qiagen® Multiple PCR Mix, 2 µL (2 µM) each primer mix, 2 µL Q solution, and 2 µL DNA template. PCR amplification (Bio-RAD) was performed under the following cyclic conditions: initial denaturation at 95°C for 15 min; 40 cycles of final denaturation at 94°C for 30 s, annealing at 60°C for 90 s, and extension at 72°C for 90 s; and a final step of 72°C for 10 min. After verification by quality check on 2% agarose, the amplified multiplex PCR products were subjected to fragment length analysis (Applied Biosystems 3,130, United States), and the allelic copy number of each VNTR locus was calculated using Peak Scanner software (Applied Biosystems, ver. 1.0, United States).

2.5 SNP typing by PCR-RFLP

The SNP loci of *M. leprae* at positions 14,676 (L1), 164,275 (L2), and 2,935,685 (L3) were amplified using previously published primers that can be used to differentiate SNP types (1–4) by RFLP digestion (19, 22) (Supplementary Figure S1, Table S3).

These regions can be amplified with the following reaction ingredients in a final volume of 50 µL: 25 µL of GoTaq® Green Master Mix, 2 µL (10 pmol) of each primer mix, 5 µL of DNA template, and 16 µL of ddH2O. The thermocycling conditions were as follows: initial denaturation at 94°C for 5 min; 45 cycles of denaturation at 94°C for 60 s, annealing at 55°C for 60 s, and extension at 72°C for 2 min; and a final elongation step at 72°C for 10 min. Products that were not SNP typed by the RFLP method were subjected to direct DNA sequencing.

SNP subtyping of *M. leprae* was performed by amplification of the regions using previously published primer sequences as follows: SNP subtypes 1 A-D were identified by sequencing SNPs at positions 8,453, 313,361 and 61,425 (Supplementary Figure S2A, Table S3); SNP 3 K subtypes were determined by first sequencing SNPs at positions 2,312,059 and 413,902; and direct sequencing at positions 2,312,059, 413,902, 1,133,942 and 20,910 aided in the evaluation of other SNP 3 subtypes using information obtained from 3 K subtypes (Supplementary Figure S2B, Table S3) (16, 23).

2.6 VNTR copy number and clustering analysis

Clustering was defined based on a comparison of the copy number of VNTRs, considering VNTRs with the same copy number in all 13 alleles, excluding the four most variable loci (32). The unweighted pair group method using category similarity coefficients and arithmetic mean (UPGMA) was used to generate the similarity matrix for the clustering analysis, and then the minimum spanning tree (MST) was constructed using the ggnetwork and ggtree packages in R. The Microsatellite Tool kit (accessed on 27 March 2022[1]; University of the Basque Country, Spain) was used to calculate allele frequency (discriminatory power). The Hunter Gaston Discrimination Index (HGDI) was used for the interpretation of allelic variation (25).

3 Results

3.1 Epidemiological situation and sampling and data

From 2018 to 2021, 219 new leprosy cases were reported in Guizhou, among which 83 samples were collected from 9 prefectures and 50 counties, including 4, 40, 20 and 19 leprosy patients in 2018, 2019, 2020 and 2021, respectively. Details of registered cases and their clinical information at the county level are recorded in Supplementary Table S2. Although these counties are within the same geographical area, most of them are relatively distant from each other.

Of the 219 new leprosy cases, four were children aged 0 to 14 years, accounting for 1.83% of the total cases. The new leprosy cases were mainly male (66.66%), ethnic minorities (53.42%), farmers (67.12%), and 15–49 years old (77.17%; Table 1). The average annual detection rate was 0.1512/100000.43 cases of leprosy detected in 2020, accounting for 19.63% of the total cases. Considering only the COVID-19 epidemic period (January–March) in Guizhou, the number of new cases in 2021 increased by 167% compared to 2020 (24 confirmed cases in 2021 and 9 in 2020). This suggests that COVID-19 may have had an impact on the detection of leprosy cases (Figure 1).

1 http://insilico.ehu.es/mini_tools/discriminatory_power/index.php

TABLE 1 Characteristics of new leprosy cases before and during the epidemic of COVID-19.

Variable	Subgroup	2018–2019 [n (%)]	2020–2021 [n (%)]	χ^2	p
Age				4.222	0.123
	≤14 years	1 (0.85)	3 (2.97)		
	15 ~ 49 years	97 (82.20)	72 (71.29)		
	≥50 years	20 (16.95)	26 (25.74)		
Gender				1.112	0.292
	Male	75 (63.56)	71 (70.30)		
	Female	43 (36.44)	30 (29.70)		
Ethnic group				0.080	0.777
	Han Chinese	56 (47.46)	46 (45.54)		
	Minority group	62 (52.54)	55 (54.46)		
Occupation				1.622	0.197
	Farmer	84 (71.19)	63 (62.38)		
	Other	34 (28.81)	38 (37.62)		
Source of infection				3.232	0.199
	Unknown source of infection	66 (55.93)	46 (45.55)		
	Source of infection in the home	33 (27.97)	30 (29.70)		
	Source of infection out of home	19 (16.10)	25 (24.75)		
Detection method				10.716	0.013
	Suspect survey	33 (27.97)	12 (11.88)		
	Household examination	9 (7.63)	10 (9.90)		
	Spot survey	0 (0.00)	0 (0.00)		
	General skin clinic	53 (44.91)	63 (62.38)		
	self-reported	23 (19.49)	16 (15.84)		
Delay in diagnosis				5.015	0.025
	≤12 months	43 (36.44)	52 (51.49)		
	>12 months	75 (63.56)	49 (48.51)		
Type				2.537	0.111
	MB	99 (83.90)	76 (75.25)		
	PB	19 (16.10)	25 (24.75)		
Leprosy reaction				0.720	0.396
	Yes	12 (10.16)	7 (6.93)		
	No	106 (89.83)	94 (93.07)		
Disability grade				0.178	0.673
	G2D	20 (16.95)	15 (14.85)		
	0/1 grade	98 (83.05)	86 (85.15)		
Patient flow				13.754	<0.001
	From out of the province	15 (12.71)	34 (33.66)		
	Cases in the province	103 (87.29)	67 (66.34)		
Total		118	101		

3.2 Analysis of case characteristics

Comparing the two periods analyzed, we found a reduction in the number of counties reporting leprosy cases: 58 counties in 2018–2019 and 47 in 2020–2021, representing a reduction of 18.97%. Anshun and Qianxian in Guizhou were the regions with the most registered cases in 2018–2019 (23 and 22 cases, respectively), whereas there were 9 cases (−60.87%) and 20 cases (−9.09%), respectively, in 2020–2021 (Figure 2).

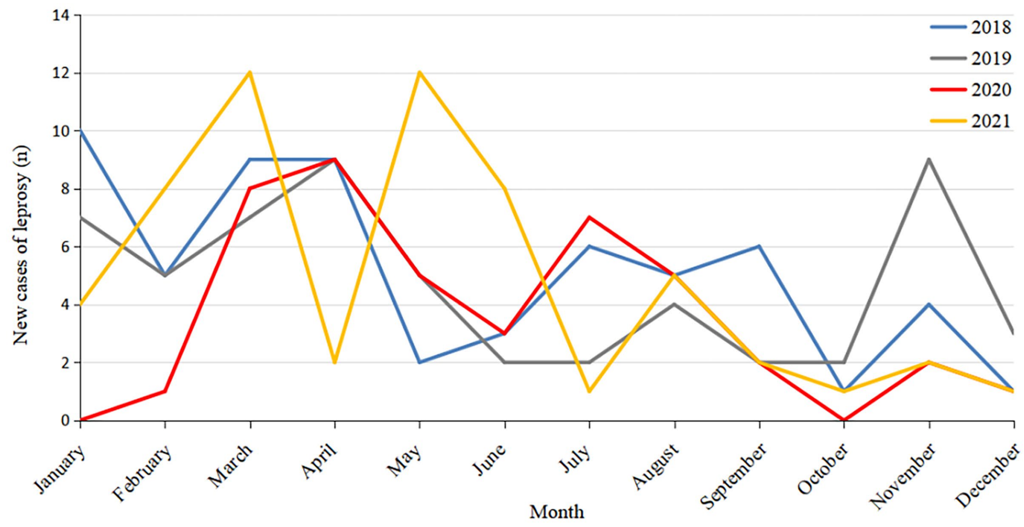

FIGURE 1
Temporal distribution of new leprosy cases in Guizhou from 2018 to 2021.

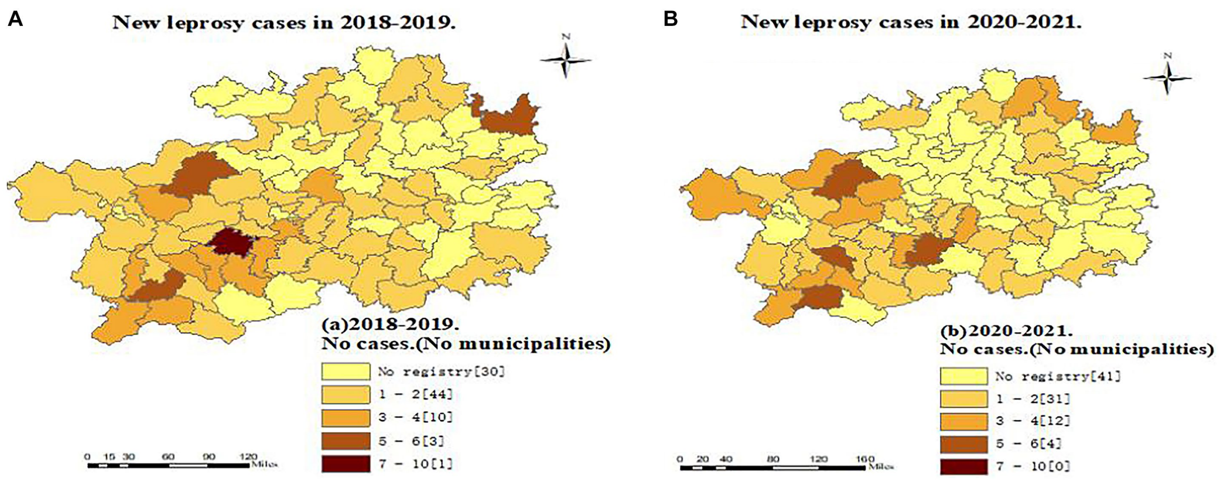

FIGURE 2
Regional distribution of new leprosy cases in Guizhou before and during the epidemic of the Covid-19.

The source of infection of 219 new leprosy cases was mostly unknown (51.14%), and the proportion of unknown sources of transmission during COVID-19 was less than that before. Dermatology screening was predominant (52.97%), and the number of new leprosy cases through dermatology clinics during COVID-19 was significantly higher than before ($\chi^2 = 12.70$, $p < 0.05$); the type of composition was dominated by multibacillary (MB; 79.91%), and the proportion of MB cases composition during COVID-19 was 75.25%, lower than before (83.90%). Of the 219 new leprosy cases, 8.68% had leprosy reactions, and 75.67% had nerve damage (Table 1).

The mean delay between onset and diagnosis was calculated in months. In 2018–2019, the longest delay was 156 months, and the shortest delay was 0.23 months. From 2020 to 2021, the longest delay was 139 months, and the shortest delay was 0.07 months. The number of cases in 2020–2021 with a delay of >12 months was significantly lower than that in 2018–2019 ($\chi^2 = 5.02$, $p < 0.05$), and 15.98% (35/219) of new leprosy cases had grade 2 deformity (G2D) at diagnosis. The rate of G2D deformity was the highest in 2018 (21.05%) and the lowest in 2020 (6.98%). G2D deformity decreased from 16.95% (2018–2019) to 14.85% (2020–2021). During the COVID-19 outbreak, the number of outflow cases was significantly higher than before ($\chi^2 = 13.75$, $p < 0.01$; Table 1).

3.3 VNTR analysis of *Mycobacterium leprae* strains

Eighty-one clinical isolates (97.6%) were characterized by 17 VNTRs, and two (2.40%) were characterized by 16 VNTRs (Supplementary Figure S3). Sixteen samples from Puding and Baiyun counties failed VNTR typing for the locus GTA9. Among all VNTRs, the (GTA)9, (AT)17, (TA)18, (AT)15, (AC)8a, 6–7, (TTC)21, and

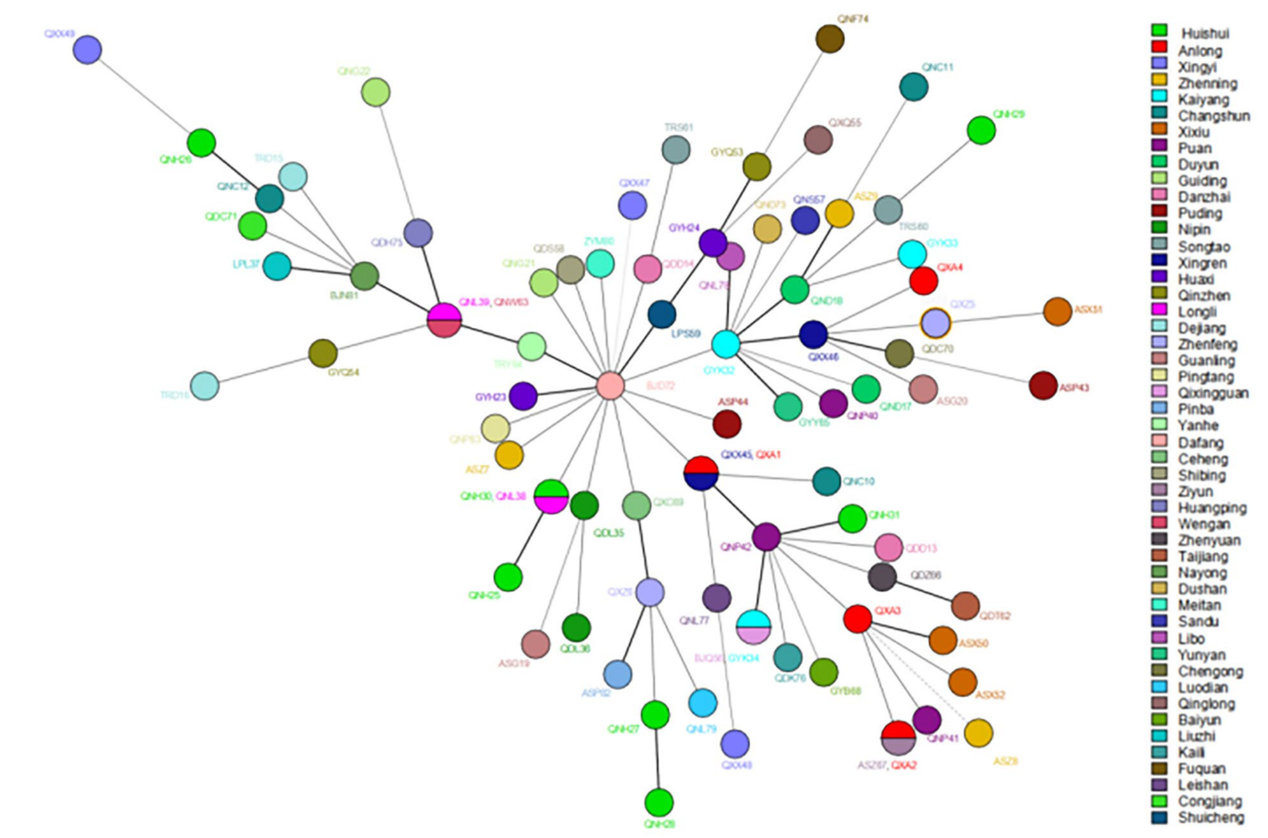

FIGURE 3
The MST of *Mycobacterium leprae* at the county levels. The circle with divisions designates strains having identical strain types and forming clusters at county levels. Different colors represent different country names.

(TA)10 loci were found to be highly variable, with an HGDI above 0.6; (AC)8b and (AC)9 were found to be moderately variable (HGDI 0.3–0.6); and the remaining (GGT)5, rpoT, 21–3, 23–3, 18–8, 12–5, and 27–5 loci were reported to be less variable (HGDI <0.3). The allelic copy number and HGDI for each locus are presented in Supplementary Table S4. In analyzing the VNTR profile within and between counties, we observed several distinct strain types with varied county-level geographic distributions. In addition to the common VNTR copy numbers observed in Guizhou, we also observed some specific copy numbers, including 10 and 11 for the loci (AC)8b from the isolates of Puan and Yunyan counties, respectively, and 11 for the loci 6–7 from the isolates of Xing County. The common VNTR copy number of the (GGT)5 loci was 4, and copy numbers 5, 3, and 3 of the (GGT)5 loci were observed in Xixiu, Baiyun, and Dushan counties, respectively. In addition, except for individual counties, the 3-copy number of rpoT, the 2-copy number of 21–3, the 3-copy number of 12–5, and the 2-copy number of 23–3 were predominant in Guizhou.

3.4 SNP distribution at the county level

The samples were amplified using primers at locus 3, and 180 bp amplicons were obtained. Restriction digestion of these samples was performed in locus-3, and we found a restriction digestion pattern with 148 bp and 32 bp fragments with nucleotide position C at site 3. These samples were then amplified for locus-1, which yielded a 194 bp amplicon. After restriction of the locus-1 amplicon, all samples remained undigested. All 83 new samples were SNP type-3. All samples were further subtyped. All samples from patients were observed to be subtype K (Supplementary Figure S3).

3.5 Population structure and clustering patterns

Regarding cluster analysis, when excluding the four markers with HGDI >0.80 [(GTA)9, (TA)18, (TTC)21, and (TA)10], 78 different genotypes were detected, 73 singletons and five clusters of two patients each, resulting in an overall cluster level of 12.80% (10/78). Three cluster cases are located in the same prefecture-level city in Figure 3; for example, Huishui and Longli counties are adjoined; Longli and Wengan counties are situated relatively close to each other; Xingren and Anlong counties are adjoined. The other two clusters were located in Anlong and Ziyun counties and Kaiyang and Qixingguan counties, which are geographically far apart. It is worth noting that all strains from these clusters reported similar SNP 3K types, further demonstrating the genetic similarity at the county level.

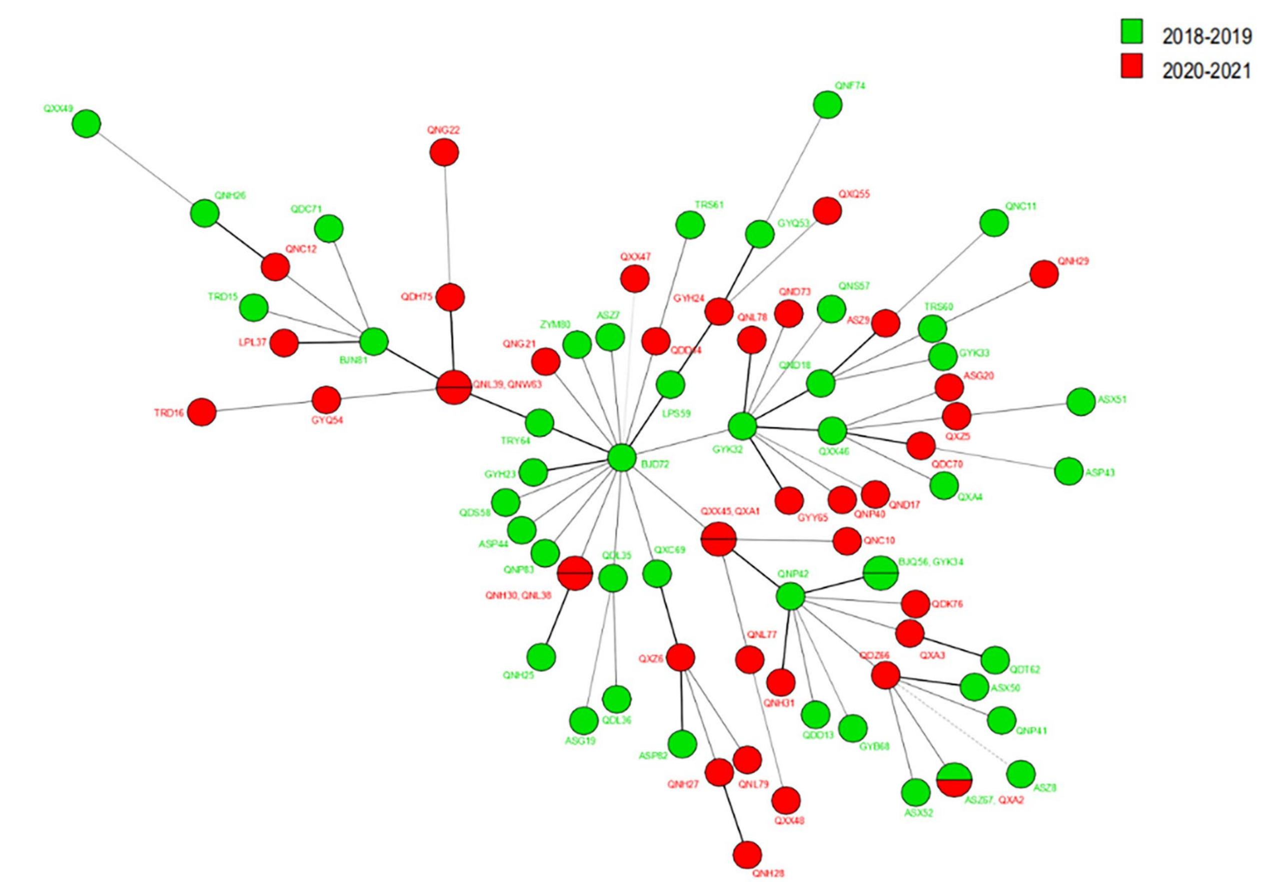

FIGURE 4
The MST of *M. leprae* isolates from Guizhou in 2018–2019 and 2020–2021.

3.6 Genotype comparison before and during the COVID-19 epidemic

The VNTR genotyping pattern of *M. leprae* isolates from Guizhou was analyzed before (2018–2019) and during the (2020–2021) epidemic of COVID-19. Regarding the cluster analysis, when the cluster analysis included 13 markers, we observed that the genotype remained relatively stable during these periods, as shown in Figure 4; however, some of the loci slightly varied from the others. As a stable VNTR pattern, the same SNP type (SNP 3 K) was found in all new cases, further supporting genome integrity during this period. Meanwhile, we observed less variation in branching patterns and less variation in strains of *M. leprae*, indicating that the transmission chain of leprosy still exists and that the transmission pattern is less affected by the prevention and control policy during the COVID-19 epidemic.

4 Discussion

The World Health Organization is effectively implementing leprosy control programs toward the elimination of leprosy across the globe, but the last stone has not been shaken (26, 33). China still has several provinces with leprosy epidemics that are unevenly distributed (7, 34). Meanwhile, COVID-19 and public health measures have taken place, such as lockdown measures and restrictions on the migration and travel of people, which have created barriers to access to leprosy services, such as difficulties in accessing care centers and reduced or closed service centers (9, 35). Therefore, we analyzed the distribution, transmission, and incidence of leprosy before and during COVID-19 through statistical analysis and molecular epidemiological approaches.

The survey report showed that the number of leprosy cases in Guizhou showed a downward trend from 2018 to 2021, and the number of leprosy cases in 2020 was much lower than that in the other 3 years. Meanwhile, in other years, new cases of leprosy began to be detected in January, but in the first few months of 2020, fewer cases were detected than in other years, with the peak of cases moving backward. Moreover, the number of leprosy cases in 2021 showed a rebound trend, especially when compared with the period of COVID-19 in early 2020 (1–3 months). These results suggest that due to the government's policies on COVID-19 prevention and control, some people's mobility is restricted by COVID-19-related factors, leading to difficulties in accessing medical services. At the same time, the Centers for Disease Control and Prevention and medical departments have focused on work related to COVID-19, reducing the proactive screening and skin examination of the public, which has affected the early detection and diagnosis of patients and resulted in a significant reduction in the number of reported cases.

The observed decrease in the number of counties registering new cases of leprosy in Guizhou may indicate that the COVID-19 pandemic has had a dramatic impact on the health care system in all counties in Guizhou, as well as a major setback in the prevention and control of leprosy. In the context of the COVID-19 pandemic, many national and international societies of Dermatology have proposed to discourage or postpone non-emergency consultations and hospitalizations (35, 36), resulting in a loss of business for leprosy surveillance programs and limiting access to hospital services for people with leprosy. At the same time, people living in some counties in Guizhou Province are at greater risk of COVID-19 infection due to the lack of proper sanitation facilities and limited medical infrastructure. Every year, a large number of the floating population from Guizhou go to economically developed eastern provinces such as Zhejiang to work as migrant workers (37, 38). The present study found that during COVID-19, the number of returning cases in the province was much higher than that before the outbreak and that mobile patients and most provincial hospitals had no experience in detecting leprosy. It can be assumed that they had time and opportunity to visit the local CDC or hospital for diagnosis because they were stranded in Guizhou due to the COVID-19 epidemic. It is necessary to strengthen the early detection and standardized management of leprosy cases in the floating population. Guizhou has one of the highest rates of leprosy in China (7, 8, 26), and local dermatologists and professionals from disease control and prevention agencies have been trained in leprosy diagnosis and treatment for many years. Greater vigilance in leprosy allows active and conscious identification and diagnosis of leprosy, leading to timely detection of patients, especially in low endemic areas, which is valuable for early detection and helps to reduce the rate of malformations.

This study showed that the highest number of dermatologic patients was seen before and during the COVID-19 epidemic, suggesting that enhanced training of dermatologists in healthcare facilities and increased capacity and vigilance in the province's dermatologic leprosy surveillance network for suspicious symptoms of leprosy could be an important tool for detecting leprosy cases in low endemic states (39). At the same time, close contact is an important means of transmission of leprosy (11). This study found close contact with pediatric cases in Guizhou in recent years by examination. Therefore, regular examination of close contact with patients should still be carried out in areas with a low prevalence of leprosy. Suspicious reports of leprosy were mainly provided by rural and village doctors. This survey showed that the number of patients found by clue investigation decreased significantly during the epidemic of COVID-19, which may be related to the impact on the work of township health centers and village doctors during the epidemic of COVID-19. Among the self-reported patients, 47.22% of the source of infection was unknown, suggesting that the public should strengthen the publicity of leprosy knowledge and improve self-awareness.

The main source of leprosy infection is MB cases. The proportion of MB cases among leprosy patients in Guizhou was 83.90% in 2018–2019 and 75.25% in 2020–2021, MB cases accounted for the largest proportion both before and during COVID-19, which reminds us to pay attention to the early detection and treatment of MB cases to prevent further spread of leprosy. According to available studies, the hidden prevalence of leprosy is high (40, 41). In this study, we observed that the G2D and delay period of leprosy cases during COVID-19 were lower than those before COVID-19, which may be related to the improvement in people's health awareness, and the specific reasons need further investigation.

According to existing genotyping studies of leprosy strains, the predominant SNP types in China are 3 K and 1D, especially SNP 3 K (16, 42), which is consistent with the results of the present study. However, SNP 1D was not found in our study, which was evidence that the transmission efficiency of leprosy in Guizhou was low, and the transmission power of other subtypes except SNP 3 K was in a state of attenuation. In addition, analysis of VNTR loci showed that the isolates in this study were similar to previously published data in China, with slight differences (12, 42, 43). The isolates formed clusters among counties in Guizhou, indicating that the transmission chain still exists and that the disease is still spreading. In addition to the county-level distribution, we found two clusters, both of which consisted of two distant counties. Additionally, we discovered that there was no migration of cases. Therefore, we believe that these cases may have been acquired through other transmission routes; for example, interprovincial transmission of leprosy was more common in the past (43).

Meanwhile, a comparison of the leprosy clustering patterns before and during COVID-19 shows that the leprosy transmission chain still exists and is less affected by policies during the COVID-19 epidemic.

This study has several limitations. First, fewer new cases were enrolled in 2020–2021, which may have masked transmission links caused by factors other than patient contact. Second, leprosy has a long incubation period, and the impact of the strategy may lag. Last, data on COVID-19 leprosy cases may not be accurately reported; for instance, there might be registration delays altering the diagnosis date. Therefore, it is necessary to include future new cases for comparison to further confirm whether the prevention and control strategies of COVID-19 have indirect effects on the distribution and migration of leprosy.

In conclusion, although there is a low prevalence of leprosy in Guizhou, effective public health information campaigns are still needed to consistently raise awareness of leprosy family health education and eliminate public fear of leprosy, especially to continue to strengthen the capacity of the provincial leprosy surveillance network. At the same time, relevant measures of leprosy prevention and control should be implemented, and screening work can be performed in key areas and populations to achieve early detection and treatment for leprosy patients to effectively eliminate the transmission of leprosy. The current molecular epidemiological study explicated the distribution and migration status of leprosy in Guizhou, China. The clustering pattern was lower at the county level in Guizhou. However, the isolates were distributed in small clusters among the counties, suggesting that leprosy transmission still exists. This suggests that there is demand for better approaches to further prevent the ongoing transmission of leprosy at the county level through close contact screening.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://www.ncbi.nlm.nih.gov/ PRJNA957589.

Ethics statement

The studies involving humans were approved by The Institutional Review and Ethics Committees of the Institute of Dermatology, Chinese Academy of Medical Sciences, China (2014-KY-003). The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from primarily isolated as part of your previous study for which ethical approval was obtained. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

JinL and HW were responsible for the experimental design and review of the manuscript. SC, JZ, and ZW performed the laboratory work, data analysis, and drafting of the manuscript. YT, JieL, DW, CW, TZ, KY, TL, LM, QY, and SW participated in data and sample collection. FH, WZ, YS, and HJ critically reviewed the manuscript. All authors have reviewed the manuscript, contributed to the article, and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1148705/full#supplementary-material

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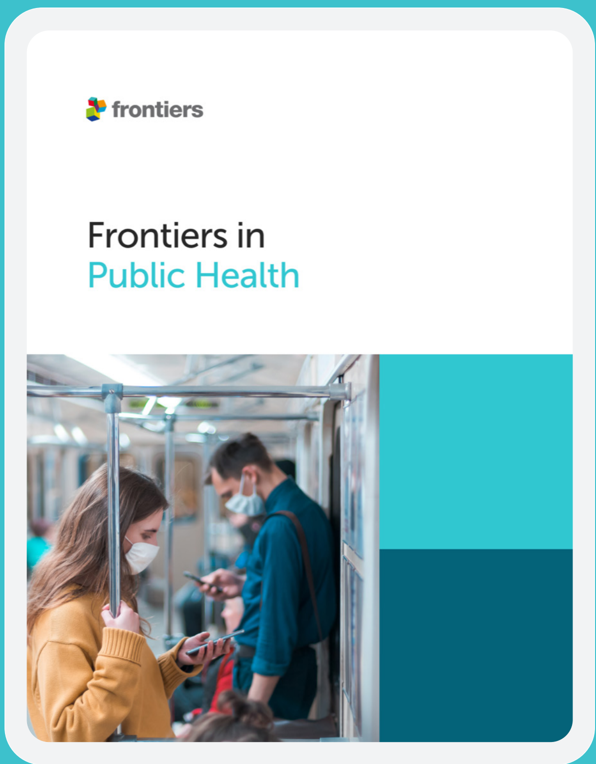

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