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ORIGINAL ARTICLE

Factors Associated with the Clinical Severity and Disease Burden of COVID-19 Caused by Omicron BA.2 in Shanghai and Hong Kong, China

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Abstract

Background: Shanghai and Hong Kong, China, experienced an outbreak of COVID-19 in early 2022. Both cities had similar dynamic prevention policies and population-level immunity, but showed differences in the numbers of cases and deaths.

Methods: We collected data from official websites to estimate and compare the infection rates, mortality rates, and infection fatality ratios (IFRs) between cities. We further performed univariable analysis and used two tree models to explore the factors affecting the differences.

Results: The infection rate in Hong Kong, China, was 42.45 (95% CI: 42.41–42.48) per 100 individuals (15.49 times higher than that in Shanghai). The mortality rate was 124.90 (95% CI: 122.33–127.46) per 100,000 individuals (51.61 times higher than that in Shanghai). The adjusted IFR was 0.29% (95% CI: 0.29–0.30%) (3.30 times higher than that in Shanghai). The infection rate was negatively correlated with the stringency of nonpharmaceutical interventions. The mortality rate and IFR negatively correlated with the vaccination rate. However, positive correlations were observed between the median age and both mortality and IFR, as well as between the proportion of people ≥65 and IFR.

Conclusions: Overall, a lack of medical resources, lower vaccination rates, and higher median age were associated with a higher infection rate, mortality rate, and IFR in Hong Kong.

Key words: COVID-19, Omicron, disease burden, clinical severity, factors

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INTRODUCTION

In the first two years of the COVID-19 pandemic, Hong Kong, China, was well positioned to contain the community transmission of COVID-19 by using strict nonpharmaceutical interventions (NPIs). By the end of 2021, fewer than 1.5 laboratory-confirmed cases per 1000 people were reported. However, from January to April 2022, the Omicron variant caused community transmission in Hong Kong. In a population of 7.4 million, more than 1 million cases were confirmed, thus resulting in more than 9,000 deaths [1]. The cumulative number of confirmed cases during the fifth epidemic period caused by the Omicron BA.2 variant was far higher than that during the four epidemic waves from 2020 to 2021. A study calculated that the COVID-19 confirmed case fatality ratio (CFR) for this wave was 0.53% (95% confidence interval [CI]: 0.36–0.70%), and that among adults 70 years of age or older was 4.46% [2]. The high mortality in the fifth wave was attributable primarily to low COVID-19 vaccination coverage among older individuals. Before the fifth Omicron epidemic wave, the primary vaccination rate among individuals older than 70 years was 47.88%, and only 24.61% had received booster vaccinations [3]. To effectively contain the Omicron outbreak, vaccination coverage was quickly increased during the Omicron epidemic [4].

Shanghai also experienced an Omicron BA.2 outbreak from March to June 2022, in which more than 626,811 cases and 588 deaths were reported. According to the official data, the unadjusted case fatality ratio of COVID-19 attributable primarily to Omicron BA.2 in Shanghai was only 0.092% [5]. Both Shanghai and Hong Kong are densely populated international metropolises with high economic development. Hong Kong did not experience COVID-19 outbreaks caused by the wild-type strain or previous variants of concern, because of consistent implementation of stringent prevention measures. The population immunity in both cities was based almost entirely on vaccine immunization rather than natural infection or mixed immunity. Nevertheless, considerable discrepancies were observed in the numbers of cases and deaths. Compared with Hong Kong, Shanghai controlled the disease burden and clinical severity more successfully [5]. The analysis and comparison of Shanghai and Hong Kong indicated that the disease burden and clinical severity associated with COVID-19 resulting from the same variant considerably differed, thus aiding in identification of critical factors for effective prevention policies. Moreover, the analysis of risk factors can provide a theoretical basis for policy measures to decrease clinical severity and disease burden during the next potential outbreak of a variant of SARS-CoV-2 in the future, and provide guidance for other cities to reformulate prevention strategies against new highly infectious mutant strains.

In this study, we collected key parameters from published articles and officially reported data to estimate the clinical severity and disease burden of COVID-19 attributable to Omicron BA.2 in Hong Kong, China. Furthermore, we aimed to explore factors affecting the differences between cities, and quantitatively analyze the correlation. The ultimate goal of our study was to help develop better prevention strategies for future pandemics caused by new variants.

MATERIALS AND METHODS

Data and parameter sources

We collected officially reported daily new COVID-19 case, vaccination coverage, NPI measures, and case surveillance information from the website of the Centre for Health Protection of the Department of Health of Hong Kong [6] (S1-S3 Tables). Data on medical resources, such as physicians/hospital beds per 1,000 population, were collected from the Hospital Authority of Hong Kong, and demographic and socioeconomic data were obtained from the Census and Statistics Department of Hong Kong [7] (S4 Table). Using predefined search terms (SARS-CoV-2, COVID-19, Omicron, infection rate, mortality, infection fatality risk, and infection fatality ratio [IFR]), we performed a literature review and extensively gathered studies reporting an IFR in other settings, to augment the sample size of the association analysis (S5 and S6 Tables). We additionally collected case data and demographic and socioeconomic data from Our World in Data [8] (including data from 20 countries/regions in which Omicron was the dominant variant, with Omicron variant proportions ≥90%) for sample expansion (S7 Table). Information on data sources, parameters, case definitions, case identification, and surveillance in Shanghai have been described in a previously published article [5].

Case definition

In Hong Kong, the definition of a confirmed COVID-19 case was a suspected case (with an epidemiological history and COVID-19-associated symptoms) with a positive nucleic acid test or antigen test; this definition was generally the same as the guidelines used in mainland China [9]. Severe cases were defined by breathing problems, low oxygen saturation/PaO_2/FiO_2, or worsening symptoms. Critical cases were defined by respiratory failure, shock, or organ failure necessitating admission to an intensive care unit. The criteria for hospitalization included only patients in moderate/severe/critical condition and high-risk groups (older people, children ≤5 years of age, pregnant women at >28 weeks of gestation, and people with underlying diseases or suppressed immunity). Deaths from COVID-19 were defined by a positive for SARS-CoV-2 test and death within 28 days after the date of the initial positive specimen collection (S1 Table).

Case identification, detection, and surveillance

The case surveillance system in Hong Kong is based on symptom-based surveillance within medical institutions, coupled with monitoring of specific occupational and high-risk groups [10]; this process was unable to achieve timely contact tracing or epidemiological investigation during the pandemic. People at high risk of developing severe/critical illness were hospitalized, whereas those with mild symptoms were sent to isolation facilities. Their close contacts and roommates were required to stay at home under medical surveillance. Nucleic acid tests were performed in key populations (residents of buildings with high infection risk, groups with high-risk occupational exposures), and nonmandatory antigen screening (distribution of rapid antigen test kits) was implemented for all individuals. Consequently, most confirmed cases counted by case surveillance were symptomatic patients, and most asymptomatic individuals were missed. On February 25, 2022, the government announced that a positive rapid antigen test (RAT) could also be considered the gold standard for confirmed cases (S1 Table).

Primary outcomes

In this study, the disease burden, including the infection rate (per 100 people), hospitalization rate (per 100,000 people), and mortality rate (per 100,000 people), was estimated for Hong Kong, China. Clinical severity, including the IFR, the infection hospitalization ratio (IHR), and hospitalization fatality ratio (HFR), was estimated. Detailed definitions are available in S8 Table. Because of the absence of official reporting of the total number of severe/critical illness cases in Hong Kong, we could not provide estimations for the severe/critical infection rate (per 100,000 people) or the infection severe/critical illness ratio. The definitions of COVID-19 cases and deaths in Hong Kong and Shanghai were mostly consistent, thus indicating that the infection rate, mortality rate, and IFR were generally comparable. However, because the hospital admission standards in Shanghai and Hong Kong differed, the numerators of hospitalization related indicators, such as the hospitalization rate and HFR, were not homogeneous and could not be compared.

STATISTICAL ANALYSIS

Estimation of disease burden and clinical severity

According to a population-based epidemiological study [11], the overall ascertainment ratio was 41% (38–45%) from RT-PCR testing augmented with RAT; age-specific ascertainment ratios were used to calculate the number of infection cases within each age group (S3 Table). The cumulative number of hospitalized individuals was calculated by addition of the cumulative number of discharged/recovered individuals and the current hospitalized individuals. The infection rate, hospitalization rate and mortality rate were estimated by division of the adjusted number of infected people, number of hospitalized people, and number of deaths by the total number of people, respectively. We applied Garkse's method [12] to adjust for the right censoring of data by weighting the denominators of the time interval distributions. The numerator represented the cumulative number of cases at the analysis cutoff date. The IFR, IHR, and HFR were estimated and stratified by age group, and 95% CIs were estimated with binomial distribution. Detailed parameters can be found in S3 Table.

Association analysis

Several studies have demonstrated that the clinical severity and disease burden of COVID-19 are associated with age structure, vaccination status, underlying disease status, accessibility of medical resources, and other factors [13-15]. Possible explanatory variables and their definitions are shown in S7 Table. We first explored possible factors by calculating Spearman correlation coefficients. Subsequently, we conducted random forest regression to explore the influence of multiple factors simultaneously [13]. Furthermore, we used the eXtreme Gradient Boosting (XGBoost) [16] model to explore the overall correlations for whole samples and the specific correlation between factors and indicators in Shanghai and Hong Kong, China. All statistical analyses and data visualization were conducted in R statistical programming language (R version 4.2.3).

RESULTS

Disease burden and clinical severity in Hong Kong, China

In Hong Kong, China, the overall infection rate was 42.45 (95% CI: 42.41–42.48) per 100 individuals (S1 Fig). The overall hospitalization and mortality rates were 578.53 (95% CI: 573.02–584.04) (S1 Fig) and 124.90 (95% CI: 122.33–127.46) per 100,000 individuals (S1 Fig), respectively. Both indicators increased with age. The overall adjusted IFR was 0.29% (95% CI: 0.29–0.30%) (S2 Fig), and the lowest IFR was recorded in the age group of 3–17 years. The IHR was 1.36% (95% CI: 1.35–1.38%), and also increased with age (S2 Fig). The IFR of the ≥80 year age group was significantly higher than that of the other age groups. In addition, the HFR was 21.59% (95% CI: 21.20–21.98%), and the highest HFR was observed among individuals 80 years of age or older (S2 Fig). The sensitivity analysis of disease burden and clinical severity, involving the adjustment of ascertainment rates to the upper and lower limit of the confidence interval, demonstrated consistent results and trends (S3 Fig).

Comparison of differences between Shanghai and Hong Kong, China

The overall infection rate in Hong Kong, China, was 15.49 times higher, the overall mortality rate was 51.61 times higher, and the overall adjusted IFR was 3.30 times higher, than that in Shanghai. The trend of IFR increasing with age was observed in both cities. The comparison of differences indicated that Hong Kong had a significantly higher infection rate, mortality rate, and IFR than Shanghai in each age group (Fig 1). In Hong Kong, compared with Shanghai, the most significant difference was in the lowest age group, a finding that cannot be ignored. The infection rate in Hong Kong in the 3–17 year age group was nearly 28 times higher than that in Shanghai. The mortality rate in the 3–17 year age group in Hong Kong reached 1.19% (0.45–1.93), a value was higher than that in the 40–59 age group in Shanghai (S9 Table).

Factors associated with disease burden and clinical severity

Spearman correlation analysis indicated that the infection rate was negatively associated with the stringency index of NPIs (ρ: −0.53; $p<0.05$) (Fig 2a). A significant correlation was observed between the mortality rate and the vaccination rate (ρ: −0.65; $p<0.005$), full vaccination rate

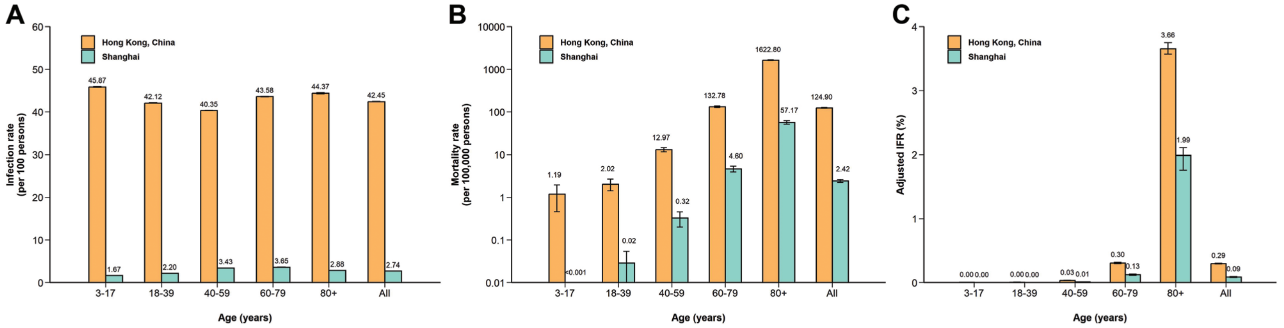

FIGURE 1 | Comparison of clinical severity and disease burden of COVID-19 caused by Omicron BA.2 in Shanghai and Hong Kong, China. (A) Infection rate (per 100 people) by age group. (B) Mortality rate (per 100,000 people) by age group. (C) Adjusted IFR (%) by age group. The number corresponds to the median estimations, and the error bars indicate the 95% CI.

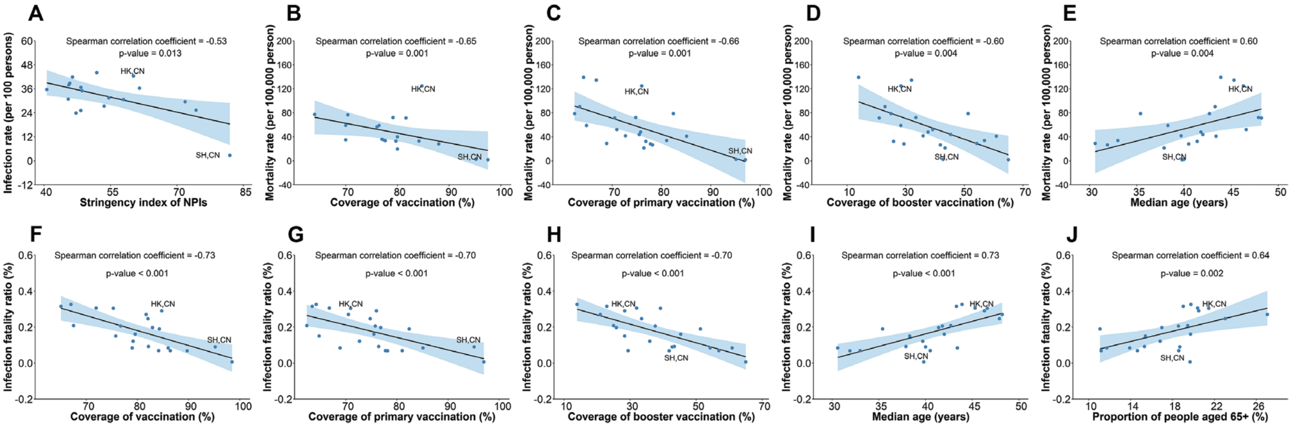

FIGURE 2 | (A) Correlation analysis between infection rate and various factors. (B–E) Correlation analysis between mortality rate and various factors. (F–J) Correlation analysis between IFR and various factors.

(ρ: −0.66; $p<0.005$), booster vaccination rate (ρ: −0.60; $p<0.005$), and median age (ρ: 0.60; $p<0.005$) (Fig 2b–2e). The IFR was correlated with the vaccination rate (ρ: −0.73; $p<0.001$), full vaccination rate (ρ: −0.70; $p<0.001$), and booster vaccination rate (ρ: −0.70; $p<0.001$). The results also revealed a higher IFR with increasing proportion of people ≥65 years of age (ρ: 0.73; $p<0.001$) and median age (ρ: 0.64; $p<0.005$) (Fig 2f–2j). However, other demographic or socioeconomic characteristics, such as life expectancy, per capita GDP, and HDI, showed no significant correlation in the univariate analysis.

The bar chart (Fig 3) shows all factors with an increase in MSE (%IncMSE) greater than 0, indicating that the factor affects the predictive accuracy of the model. In the ranking of importance of the variables regarding the infection rate, no factor was found to have significant importance (Fig 3a). The full vaccination rate (%IncMSE: 6.11; $p<0.01$) and median age (9.00; $p<0.01$) were the most significantly important variables for mortality. The vaccination rate (6.38; $p<0.05$), booster vaccination rate (4.76; $p<0.05$), and number of nurses per 1,000 population (4.79; $p<0.05$) had lower significant importance for mortality (Fig 3b). The booster vaccination rate (7.04; $p<0.05$) and median age (12.34; $p<0.01$) had the greatest effects on the IFR, whereas the full vaccination rate (6.07; $p<0.01$), vaccination rate (6.21; $p<0.05$), and proportion of people 65 years of age or older (5.56; $p<0.05$) had moderately important effects (Fig 3c). However, the effects of other variables were nonsignificant in the random forest regression model.

The protection or risk contributions of factors to the disease burden and clinical severity evaluated with the XGBoost model for each country/city are shown in the SHAP value plot (S5 and S6 Figs). The number of nurses per 1,000 people and the NPI index were protective factors with respect to the infection rate, whereas median age and vaccination rate negatively affected mortality and the IFR. However, for each sample, the main factors differed. In the bar chart, countries/cities are roughly ranked according to disease burden or clinical severity, with the value increasing from left to right (S6 Fig). The lower infection rate in Shanghai was due primarily to a greater number of hospital beds and more stringent governmental NPIs (S6a Fig). The main factors associated with the lower mortality in Shanghai were higher vaccination rates, a lower median age, and a greater number of health care workers (S6b Fig). Similarly, higher vaccination rates and lower median age were the main negative

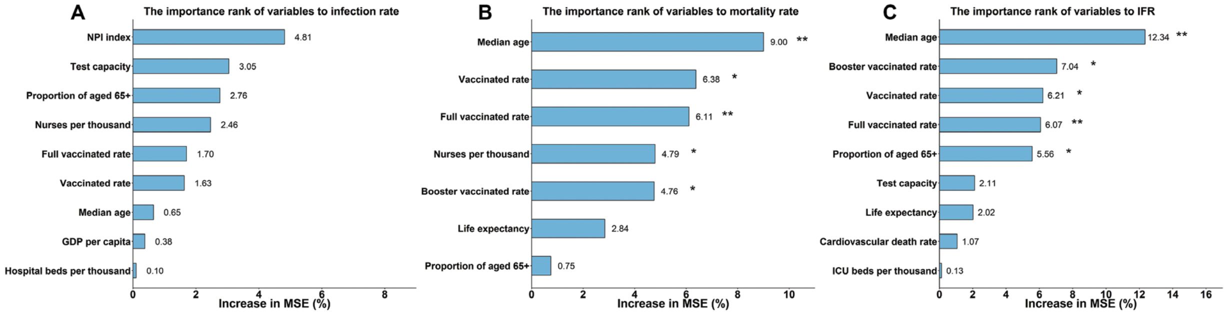

FIGURE 3 | Importance rank of factors associated with the clinical severity and disease burden, determined with a random forest (RF) regression model. The bar chart includes all factors with increase in MSE (%) (%IncMSE) greater than 0. The values of %IncMSE represent the importance of factors in clinical severity and disease burden. Significance of the importance score of the predictor variables: *p<0.05, **p<0.01.

factors influencing the lower IFR in Shanghai, whereas lower vaccination rates and a higher median age were the main positive factors influencing the high IFR (S6c Fig).

DISCUSSION

This study estimated the infection rate, hospitalization rate, mortality rate, IHR, IFR, and HFR in Hong Kong, and compared their differences between these cities during the Omicron wave of the COVID-19 pandemic. Association analysis was further conducted to explore the importance of factors influencing the infection rate, mortality rate, and IFR. The infection rate, mortality rate, and IFR of all age groups were significantly higher in Hong Kong than Shanghai, a finding attributed primarily to the limited vaccination coverage among the older population, the lack of medical resources, and the less strict NPI measures. We further collected data from 20 other countries to comprehensively explore the causes of the differences at the national level. Vaccination coverage and population age structure were the main factors affecting mortality and the IFR, whereas the number of health care workers and NPIs affected the infection rate to a greater extent.

The overall infection rate in Hong Kong, China, was higher than that in Shanghai, mainly because of the stricter NPIs in Shanghai. Measures such as social distancing, improving personal hygiene practices, and increasing self-testing can decrease the number of infections [17]. The two cities showed considerable differences in NPIs during the Omicron epidemic (S10 Table). Pre-Omicron, both Shanghai and Hong Kong maintained baseline NPIs, including stringent border controls, symptom-based surveillance, occupation-based screening, PCR screening for high-risk groups, and case isolation. Post-Omicron, Shanghai implemented additional measures, such as diverting international flights (mitigating external transmission risk), grid management (enhancing targeted control at subdistrict levels), contact tracing (with quarantine), and multiple rounds of population-wide nucleic acid screening (identifying and isolating cases promptly). High-risk areas underwent lockdowns with rapid screening, while the entire city was placed under lockdown (R_t began to decrease below the epidemic threshold). In contrast, Hong Kong could not provide sufficient isolation points or beds to isolate and accommodate people with mild symptoms. Home quarantine measures and RATs relied on the conscience of individuals. In addition, Hong Kong, unlike Shanghai, did not implement strict grid management or a health code system [18], and did not have sufficient nucleic acid testing capacity for the entire population [19], thus failing to detect infections in time to achieve early outbreak containment.

The overall mortality rate and IFR in Hong Kong, China, were also significantly higher than those in Shanghai, because Hong Kong has a rapidly aging population, with a higher proportion of people ≥60 years of age than Shanghai [20]. In addition, the vaccination rates among older people were higher in Shanghai than in Hong Kong before the Omicron epidemic [3], because many older adults with comorbidities in Hong Kong believed that vaccination might exacerbate their underlying diseases [21]. Moreover, large-scale multi-round nucleic acid screening of the entire population detected almost all infections in Shanghai, including many asymptomatic infections that could not be identified through usual symptom surveillance. In addition, timely intervention measures were performed for those in presymptomatic infection stages, thus decreasing the possibility of the development of severe/critical disease and death. As described above, the proportion of people with asymptomatic or mild infections among the denominators of the IFR was elevated.

We further included data from published articles and Our World in Data, and found that vaccination coverage and population age structure affected mortality and the IFR. An ecological study conducted among 110 countries during the Omicron epidemic has concluded that the IFR of COVID-19 is strongly associated with the vaccination rate [15]. This finding reinforces the importance of developing a cost-effective vaccine distribution campaign from a global perspective to decrease the risk of death for the largest population. The first dose of the vaccine still showed strong protection against Omicron-associated hospitalization, severe/critical illness, and death. Moreover, booster vaccination provided stronger and longer-lasting protection [22]. We found that some developing countries with younger age structures showed lower IFRs than developed countries with aging populations. In addition, medical resources and NPIs by governments were particularly important regarding infection rates. Government work efficiency has played an important role in integrating medical resources to control the epidemic. Higher levels of government trust are associated with adherence to public health remedies and vaccination rates [23]. Economically underdeveloped regions lack resources (including cold-chain vaccine storage facilities and health care workers) and are continually vulnerable to COVID-19.

Although this study explored only factors affecting the clinical severity and disease burden of COVID-19 mainly attributable to Omicron BA.2, the findings provide important guidance for the prevention and control of currently circulating and future variants with stronger immune escape and transmission abilities. The government should continue to strengthen the monitoring of new variants and the analysis of dynamic changes; consolidate the supplies of emergency medical resources; and increase vaccination coverage and the reserve of health care workers. To establish sustainable and effective NPIs, each country should tailor strategies according to its unique epidemiological and sociodemographic context. Considerations may include local variant prevalence, transmission dynamics, population density, health care infrastructure, and societal behaviors. Ongoing surveillance and data-driven decision-making are critical for adapting NPIs in response to real-time trends. Our study also provides valuable insights for policy-makers and public health officials in designing and implementing vaccination strategies tailored to different demographic profiles, thus ultimately influencing clinical outcomes. Specific considerations may involve prioritizing vaccination according to demographic characteristics, establishing targeted vaccination coverage goals, and conducting impactful communication campaigns. In addition, to effectively enhance emergency preparedness for potential future variants, key strategies include optimizing surge capacity in health care facilities, stockpiling essential medical supplies, investing in cutting-edge diagnostic technologies and therapeutic interventions, and advancing training programs for health care workers. Additionally, strengthening coordination and communication channels among public health authorities, health care institutions, and relevant stakeholders is crucial for seamless information exchange and resource mobilization.

This study has several limitations. First, in estimating the actual number of infections in Hong Kong, this study incorporated the ascertainment rate derived from serological research as the parameter. However, the inherent antibody decay might have led to a potential overestimation of the ascertainment rate, thereby resulting in an underestimation of the true number of infections. Moreover, the ascertainment rate exhibits temporal variability and cannot be represented by a single numerical value. In Shanghai, the definition of COVID-19 death excluded cases attributed to other diseases or underlying conditions. This exclusionary criterion might have resulted in an underestimation of mortality rates and IFRs in Shanghai. In contrast, in Hong Kong, the definition of COVID-19 death included all deaths within 28 days of confirmed infection. This inclusive criterion might have led to an overestimation of mortality rates and IFRs in Hong Kong, thereby potentially exaggerating the differences in the mortality rates and IFRs between Shanghai and Hong Kong. However, the primary and sensitivity analyses consistently showed that Hong Kong's lower bound significantly exceeded Shanghai's upper bound, and our conclusions were not affected. Second, constrained by a lack of data availability, our study was unable to account for the vaccination coverage by administration timing, vaccine types, and doses. Instead, we incorporated the overall vaccination rate of the population as a contributing factor. Third, owing to data constraints, obtaining detailed NPI data was challenging, thus limiting our ability to conduct a more in-depth quantitative analysis. Instead, we used a comprehensive scoring system with nine NPI indicators from the Oxford COVID-19 Government Response Tracker, offering a detailed assessment of various measures.

CONCLUSIONS

Further studies are necessary to estimate the clinical severity and disease burden in Hong Kong, China, and Shanghai, given the many limitations in evaluating these aspects by using only officially reported data. In addition, a lack of medical resources, lower vaccination rates, and higher median ages were associated with higher infection rates, mortality rates, and IFR in Hong Kong. Overall, continuing to increase the vaccination rate remains the most feasible measure.

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CONFLICTS OF INTEREST

All authors report no competing interests.

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