Report

Modeling the Prevalence of Asymptomatic COVID-19 Infections in the Chinese Mainland

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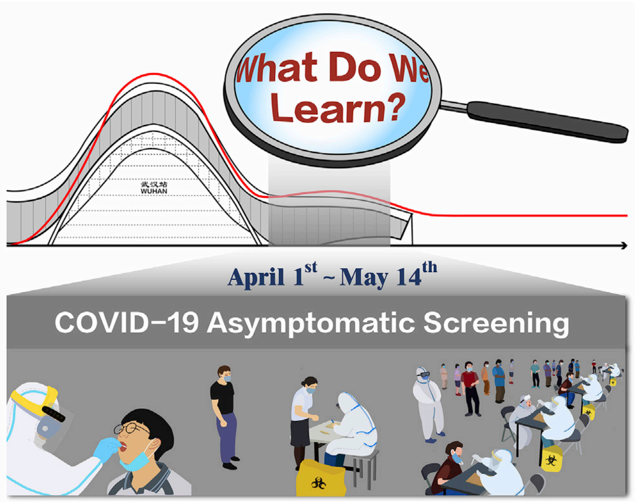
PUBLIC SUMMARY

- As entering a post-pandemic period, considerable efforts have been spent to intensify the screening of the asymptomatic COVID-19 infections by large-scale survey in the Chinese Mainland.
- However, only 0.8% and 3.3% asymptomatic cases in Wuhan City and Chinese Mainland developed into the symptomatic ones during this period, and the un-development ratios were up to 99.2% and 96.5% when assuming the developing lag = 5.2 days, respectively.
- A mathematical model based on the Bayes' formula was established to predict the prevalence of asymptomatic cases in Chinese Mainland, which revealed a very low prevalence of asymptomatic infections.
- When the basal prevalence became lower, some false positive results would appear. Therefore, another immediate confirmation test is suggested to perform for asymptomatic screening during the post-pandemic period.

GRAPHICAL ABSTRACT



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Recently, considerable efforts have been focused on intensifying the screening process for asymptomatic COVID-19 cases in the Chinese Mainland, especially for up to 10 million citizens living in Wuhan City by nucleic acid testing. However, a high percentage of domestic asymptomatic cases did not develop into symptomatic ones, which is abnormal and has drawn considerable public attention. Here, we aimed to investigate the prevalence of COVID-19 infections in the Chinese Mainland from a statistical perspective, as it is of referential significance for other regions. By conservatively assuming a development time lag from pre-symptomatic (i.e., referring to the infected cases that were screened before the COVID-19 symptom onset) to symptomatic as an incubation time of 5.2 days, our results indicated that 92.5% of those tested in Wuhan City, China, and 95.1% of those tested in the Chinese Mainland should have COVID-19 syndrome onset, which was extremely higher than their corresponding practical percentages of 0.8% and 3.3%, respectively. We propose that a certain false positive rate may exist if large-scale nucleic acid screening tests for asymptomatic cases are conducted in common communities with a low incidence rate. Despite adopting relatively high-sensitivity, high-specificity detection kits, we estimated a very low prevalence of COVID-19 infections, ranging from 10^{-6} to 10^{-4} in both Wuhan City and the Chinese Mainland. Thus, the prevalence rate of asymptomatic infections in China had been at a very low level. Furthermore, given the lower prevalence of the infection, close examination of the data for false positive results is necessary to minimize social and economic impacts.

KEYWORDS: COVID-19; ASYMPTOMATIC INFECTIONS; SUBCLINICAL INFECTION; BAYES' FORMULA; CHINA

INTRODUCTION

The sudden emergence and global rapid spreading of the novel coronavirus SARS-CoV-2 has created a severe public health challenge, resulting in ∼2.7 million confirmed infections of coronavirus disease 2019 (COVID-19) and ∼344,000 mortalities in about 220 countries and regions as of May 26, 2020.[1] By the end of March 2020, the COVID-19 infection appeared to be under control in the Chinese Mainland, and the epidemic situation entered a post-pandemic period. However, with the resumption of work and school, as well as the return of overseas populations to China, the risk of infection clusters remains. Controlling for asymptomatic infections is crucial for restraining COVID-19 transmission,[2] as researchers have found that COVID-19 cases are likely to begin shedding the virus before symptom onset.[3] Among the asymptomatic carriers, some subsequently did not have any COVID-19 symptoms during the communicable period (noted as "subclinical infection"), whereas others began to show signs of the illness (noted as "pre-symptomatic infection," i.e., referring to the infected cases screened before the COVID-19 symptom onset) in our study. From April 1, 2020, the National Health Commission of the People's Republic of China (NHC, P. R. China) began to officially report the daily increase in asymptomatic cases and their developing outcomes.[4] At the same time, the country stepped up large-scale routine screenings for asymptomatic cases, for those with a relatively high risk of being infected. According to the official reports, the accumulated asymptomatic cases increased rapidly to1303 domestic cases and 360 imported cases from April 1 to May 14, 2020. This has caused increasing concern among researchers, as COVID-19 transmission appeared to be well under control since mid-March in the Chinese Mainland.

Asymptomatic COVID-19 infection incidents have been widely documented in China, the United States, Iceland, Korea, Japan, and others (e.g., the Diamond Princess cruise ship) (Table S1, Supplemental Materials). The reported rate of asymptomatic infections among several representative studies varies with region, from 0.6% to 35.5%;[5–10] thus, the discrepancy in asymptomatic infection numbers greatly depends on the detection capabilities. In contrast, the rate of subclinical infections among asymptomatic cases has been less studied. In populations known to have been in close contact with confirmed COVID-19 cases, typical rates of 0% (0/55),[11] 20.8% (37/178),[12] 29.2% (7/24),[13] 16.7% (22/132),[14] and 11.1% (3/27)[5] were reported. For special populations, such as pregnant women, the percentage was about 5% (6/118).[15] Overall, the number of recruited participants in previous studies was not sufficient to establish the prevalence of subclinical COVID-19 infections. In China, large-scale screening surveys of asymptomatic infections in common communities have been conducted; symptomatic infections overall appeared to be under control in the Chinese Mainland, as of mid-March 2020. Notably, the positive predictive value (PPV) may decrease when the prevalence of infections is very low according to Bayes' formula.[16] Here, we aimed to investigate the prevalence of asymptomatic infections in the Chinese Mainland from a statistical perspective, to gain referential significance for other regions.

RESULTS AND DISCUSSION

High Predicted Non-development Percentage of the Asymptomatic Infections

From April 1 to May 14, 2020, a total of 897 domestic asymptomatic infections from Wuhan City and 1,303 from the Chinese Mainland were reported by official websites. When assuming a development lag time of 5.2 days[17] (i.e., the incubation time), higher ratios of the asymptomatic cases without developing to the symptomatic among the domestic residents (i.e., Wuhan City and the Chinese Mainland) than those among the imported travelers into Heilongjiang Province and the Chinese Mainland from abroad (see Figure 1). The detailed modeling results for various development lags are shown in Table 1. During the study period, only 7 cases (Wuhan City) and 43 cases (the Chinese Mainland) developed into the symptomatic illness, with crude development percentages (i.e., N_{act}/N_{asy}) of 0.8% and 3.3%, respectively. In contrast, the crude development percentages of imported asymptomatic infections in Heilongjiang Province and the Chinese Mainland were 77.8% and 58.9%, respectively. When development lag time is 5.2 days, the predicted development percentages were about 92.5%, 95.1%, 100%, and 98.6% for

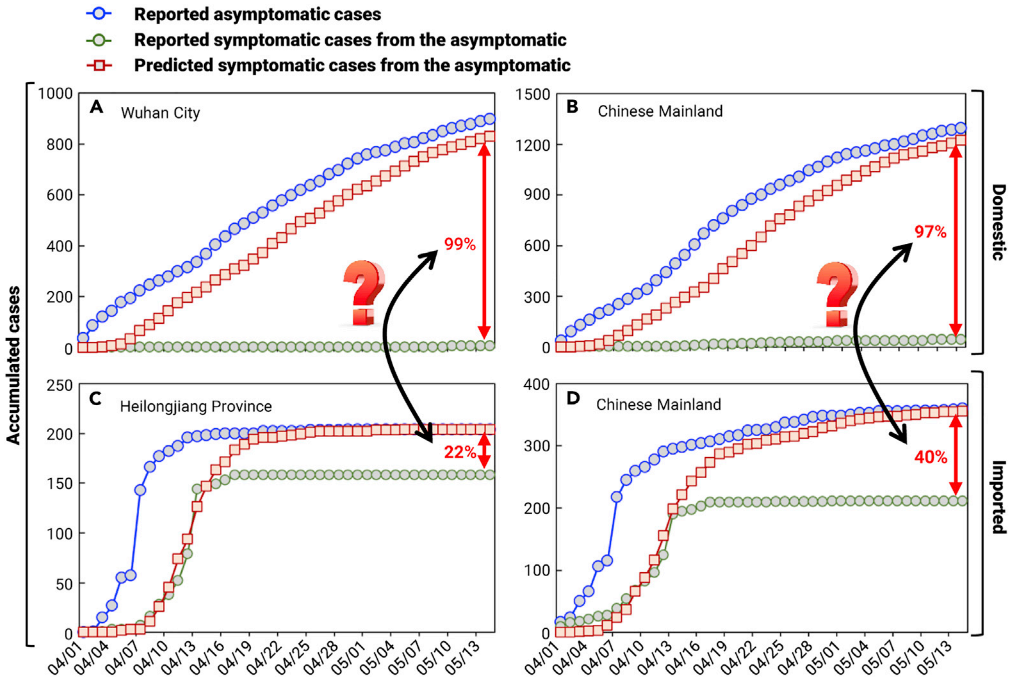

Figure 1. The accumulated asymptomatic cases. The officially reported data and modeling prediction for the domestic residents were provided in four scenarios of domestic residents in Wuhan City (A) and the Chinese Mainland (B), and the imported travelers into Heilongjiang Province (C) and the Chinese Mainland (D). The ratio of the undeveloped cases from asymptomatic to symptomatic during the period April 1 to May 14, 2020. The predicted ones are shown in red when the development lag is 5.2 days.

the domestic population living in Wuhan City, the domestic population of the Chinese Mainland, the population from abroad (imported) in Heilongjiang Province, and the imported population in the Chinese Mainland, respectively. The corresponding percentages would certainly increase to 96.1%, 97.5%, 100.0%, and 99.2% (lag time = 2.6 days), or slightly decrease to 86.6%, 89.1%, 100%, and 96.9% (lag time = 10.4 days), respectively. Therefore, the non-development percentages from asymptomatic to symptomatic given a lag time of 5.2 days were 99.2% and 96.5% for the domestic population living in Wuhan City and the Chinese Mainland, respectively, which were similar to those when lag time was 2.6 or 10.4 days. In contrast, the calculated non-development percentages in Heilongjiang (22.2%) and Chinese Mainland (40.3%) were much lower for imported travelers when the development lag was 5.2 days; similar values were obtained with a development lag time of 2.6 or 10.4 days, respectively.

In several previous studies, the percentage of asymptomatic cases that developed into symptomatic ones ranged from 70.8% to 100% (Table S4). For example, for the 55 subjects who were asymptomatic on admission to the Third People's Hospital of Shenzhen, China, from January 11, 2020, to February 29, 2020, up to 100% of them turned out to be symptomatic during hospitalization: 14 with mild symptoms, 39 with ordinary symptoms, and two with severe COVID-19.[11] Of the close contacts of COVID-19 cases (or suspected cases) in the cities of Nanjing, Chongqing, and Ningbo, 70.8%, 79.2%, and 83.3% developed into symptomatic cases, respectively.[6,12,13] A study with small population size conducted in the United States found that about 88.9% of those diagnosed with asymptomatic infection developed symptoms in subsequent observations.[5] Interestingly, from April 1 to May 14, 2020, only 0.8% and 3.3% of all asymptomatic cases in Wuhan and the Chinese Mainland converted to confirmed COVID-19-infected cases, much lower than the percentages cited in previous studies, and also lower than that of the imported asymptomatic population. If the pathogenic ability of the SARS-CoV-2 did not dramatically decrease in China, a possible explanation for this discrepancy is likely to be due to false positive asymptomatic results for the domestic population.

For the imported asymptomatic cases, we assumed that all travelers were tested with an RNA kit similar to the one used in domestic screening. Also, all of the operation protocols were consistent, as they followed the national regulation guidelines issued by The State Council of P. R. China.[18] The dramatic difference in the non-development percentages between domestic and imported populations may be due to a difference in the prevalence of COVID-19 infection. According to Bayes' formula, the false positive rate (i.e., 1 − PPV) was negatively correlated with prevalence. A similar outcome was also reported for HIV screening, specifically the false positive rate of volunteer blood donors (99.97%) with an infection rate of 0.001% was much higher than that of injection drug users (3.13%) with an infection rate of 50%.[19] For the COVID-19 diagnostics, a specificity of 100% cannot be absolutely reached due to nucleic acid contamination and other effects (Table 2). Moreover, the practical sensitivity and specificity may be lower than those cited in official reports, due to the virus load, inappropriate sampling, or cross-contamination.[20,21] Referring to the emergency project guidance of fast detection production research by the Ministry of Science and Technology, P. R. China,[22] the sensitivity and specificity must exceed 95% and 99%, respectively. When assuming a sensitivity of 95%, the median (interquartile range [IQR]) of the estimated minimum specificity was 99.958% (99.929%–99.972%) within the range from 99.626% to 99.992%, using officially reported data from the Wuhan population (see Table S2). However, even when the sensitivity and specificity of the test kit are very high, close to 100%, significantly overestimated asymptomatic infection rates will occur if the prevalence is very low, as mentioned in a previous study.[23]

Estimated Low Prevalence of Current COVID-19 Infections in the Chinese Mainland

Considering the improvement in COVID-19 detection techniques in China at the time of this study, we assumed that the practical sensitivity and specificity should be higher. A sensitivity of 99.9% and five specificities of 99.626% (Min), 99.929% (25% percentile), 99.958% (median), 99.972% (75% percentile), and 99.992% (Max) of the RNA kits was adopted for modeling prevalence (see Figure 2). The prevalence in Wuhan City was estimated as 3.4×10^{-6} (IQR = 2.3×10^{-6}–5.7×10^{-6}) when assuming PPV = $N_{\mathrm{act}}/N_{\mathrm{pred}}$ and using a development lag time of 5.2 days. There exists a certain ratio of subclinical infections in the total asymptomatic ones for various population, i.e., 0% (0/55),[11] 29.2% (7/24),[13] 16.7% (22/132),[14] 11.1% (3/27),[5] and 5.1%

Table 1. The Development Characteristics of the Asymptomatic Based on the Official Reports during April 1 and May 14, 2020, in the Chinese Mainland

	Domestic Residents		Imported Travelers from Abroad	
Statistics	**Wuhan City**	**Chinese Mainland**	**Heilongjiang Province**	**Chinese Mainland**
Official Reports				
N_{act}[a]	7	43	158	212
N_{asy}[b]	897	1,303	203	360
$N_{\text{act}}/N_{\text{asy}}$ (%)	0.8	3.3	77.8	58.9
Predicted Results				
Developing lag = 5.2 days				
N_{pred}[c]	830	1,239	203	355
$N_{\text{pred}}/N_{\text{asy}}$ (%)	92.5	95.1	100.0	98.6
$(N_{\text{pred}} - N_{\text{act}})/N_{\text{pred}}$ (%)	99.2	96.5	22.2	40.3
Developing lag = 2.6 days				
N_{pred}	862	1,271	203	357
$N_{\text{pred}}/N_{\text{asy}}$ (%)	96.1	97.5	100.0	99.2
$(N_{\text{pred}} - N_{\text{act}})/N_{\text{pred}}$ (%)	99.2	96.6	22.2	40.6
Developing lag = 10.4 days				
N_{pred}[c]	777	1,161	203	349
$N_{\text{pred}}/N_{\text{asy}}$ (%)	86.6	89.1	100.0	96.9
$(N_{\text{pred}} - N_{\text{act}})/N_{\text{pred}}$ (%)	99.1	96.3	22.2	39.2

[a] The officially reported number of asymptomatic cases who subsequently had any COVID-19 syndromes.

[b] The officially reported number of the total asymptomatic cases.

[c] The predicted number of the asymptomatic cases who subsequently had any COVID-19 syndromes during the concerned period using a gamma distribution of the development lag. The distributions of developing lags of 5.2, 2.6, and 10.4 days all follow a gamma distribution with the tuning parameters of (shape = 5.807, scale = 0.948),[17] (shape = 5.807/(2 × 0.948), scale = 0.948), and (shape = 11.31, scale = 0.948), respectively.

Table 2. The Information on the Sensitivity and Specificity from the Instruction Books and a Practical Application Study

Manufacturer	Data Sources	Approval No.[a]	Sensitivity (%)	Specificity (%)
BGI Biotechnology (Wuhan) Co., Ltd	instruction book	20203400060	91.2 (77.0–97.0)	100 (94.6–100)
Beijing Kinghawk Pharmaceutical Co., Ltd	instruction book	20203400322	91.34	100
BGI Biotechnology (Wuhan) Co., Ltd	practical application[20]	20203400060	82.5	81.25
Sansure Biotech	practical application[20]	20203400064	95	87.5
bioPerfectus Technologies	practical application[20]	20203400384	90	87.5

[a] The medical device registration certificate of P.R. China.

(6/118).[15] We thus assumed the percentage of truly subclinical cases among the total number of asymptomatic ones as 20%. Then, the prevalence rate increased to 1.1×10^{-4} (IQR = 7.4×10^{-5}–1.9×10^{-4}). Relatively higher prevalences of 1.5×10^{-5} (IQR = 1.0×10^{-5}–2.6×10^{-5}) and 1.3×10^{-4} (IQR = 8.6×10^{-5}–2.2×10^{-4}) were found without and with assuming a subclinical infection percentage of 20%, respectively. However, both estimation results tended to be higher than the realistic situation because the development lag time was less than 5.2 days, as discussed above. During 3 weeks in March 2020 (March 11–17, March 18–24, and March 25–31) the number of domestic confirmed COVID-19 cases were 27, 1, and 0 with testing of 97,720, 71,289, and 87,355 participants, respectively.[24] These data suggest that the COVID-19 spread had been well contained before the large-scale screening survey for asymptomatic infections in Wuhan City, as well as in the Chinese Mainland. However, although a certain percentage of false positives was present, the Chinese government continued with efforts to increase large-scale screening for infection, with the basic strategy of "early detection, early reporting, early isolation, early treatment," to provide medical care to as many domestic COVID-19 patients as possible.[25,26]

The State Council of P. R. China stipulated that hospitals and disease control departments nationwide take prompt action once asymptomatic carriers are detected in the "Management Standards for Asymptomatic Infection Cases of SARS-CoV-2" issued on April 8, 2020.[18] In these guidelines, when an asymptomatic case is detected by any medical institution, the information must be provided within 2 h using a direct web-based system, the case investigation completed within 24 h, and close contacts registered and documented. Based on the test results, asymptomatic infections must be quarantined for 14 days with medical care, with another 14 days of follow-up screening.[18] The problem arises because, after the first screening test, another confirmation test is supposed to be carried out after the 14-day period. Under these circumstances, false positive asymptomatic infections may not be accurately excluded because their RNA test results may also be negative after the 14 days of quarantine. To perfect the screening policy, we propose that another RNA test should be conducted to confirm the positive result and a third confirmation test performed immediately if there exists any contradiction between the first two tests. Following this suggestion, based on Bayes' formula, the false positive probability (i.e., 1 − PPV) would decrease to 0.04%, 0.35%, 3.41%, and 26.09% by assuming $Sens = 0.999$ and $Spec = 0.99958$ of a one-time test for a prevalence of 10^{-3}, 10^{-4}, 10^{-5}, and 10^{-6}, respectively. Therefore, at least two consecutive tests are standardly taken to give a conclusive infection case, which should considerably lower the false positive rate. Another way is to develop the detection kits with absolute 100% specificity, which can completely exclude false positive probability. However, it may certainly increase the expense on the research and development, as well as the corresponding detection operation. Hence, close attention should be paid to the false positive rate if large-scale screening is conducted in communities with a very low prevalence of COVID-19 infection of the current situation.

Indication for Other Countries or Regions

Due to the different stages of COVID-19 in various countries, the control and prevention measures for asymptomatic infections are highly dependent on location (Table S4). Besides China, asymptomatic infections have not been officially reported in most countries; however, there have been few epidemiological studies on this issue.[7,27,28] In addition, seroprevalence surveys have been conducted in China, Japan, Singapore, India, and the United States.[29,30] For asymptomatic or mild-syndrome infections, most governments recommend self-isolation at home if medical treatment is not immediately warranted. In China, all of the screened asymptomatic infections are quarantined immediately. Among the 48 countries in Asia, Europe, the Americas, Africa, and Oceania, the median (IQR) COVID-19 prevalence was 6.0/10,000 (0.03/10,000–50.6/10,000) (Table S3). If a false positive rate is a possibility, a confirmation test is immediately warranted in large-scale screening tests of affected communities.

Limitations and Strengths

The key limitation of our study was that the main findings were inferred by a modeling simulation based on certain assumptions, especially, that a one-time test was used to screen for asymptomatic infections during a large-

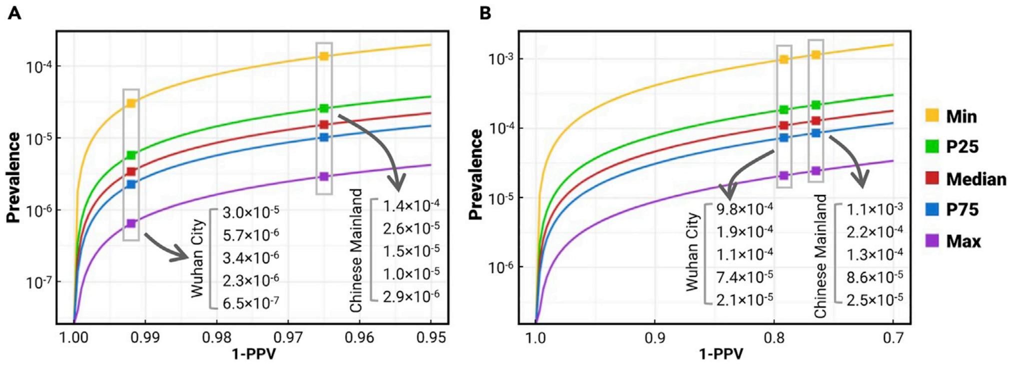

Figure 2. The estimated prevalence of the COVID-19 infections. Calculations were based on the un-development rates (i.e., 1-PPV) without (A) and with (B) subtracting the ratio of subclinical infections. The un-development rates in Wuhan City and the Chinese Mainland were 99.2% and 96.5%, respectively. The ratio of the subclinical infections in the asymptomatic ones was assumed as 20%, and sensitivity as 0.999; the minimum (Min), 25% percentile (P25), median, 75% percentile (P75), and maximum (Max) of specificity were 99.626%, 99.929%, 99.958%, 99.972%, and 99.992%, respectively; developing lag = 5.2 days.

scale survey. Also, we did not have sufficient data on the sensitivity and specificity for some of the serum antibody tests administered to reported asymptomatic cases. In addition, the ethnicity and clinical diagnostics of the included population were not obtained, thus we cannot assert that most of the screened asymptomatic cases definitely have a developing lag. Likewise, the reported number of asymptomatic cases may be derived based on different strategies, which were also not available. Overall, our study provides a snapshot for a given study period for policy reference, with two important advantages. First, we compared the predicted development rates between asymptomatic and symptomatic cases and between domestic and imported asymptomatic infections simultaneously to determine the possibility of getting a false positive result. Second, based on the large-scale survey in Wuhan City, with the highest prevalence of COVID-19 infections in China, we estimated the distribution of the minimum specificity of the detection kit. The prevalence of COVID-19 infection was subsequently calculated using a modified Bayes' formula. Our study results provide a reference for conducting large-scale screening surveys for asymptomatic infections in countries where the prevalence is very low.

Conclusions

With a significant decrease in the symptomatic COVID-19 infection rate in China, considerable efforts have focused on the best way to screen for asymptomatic infections using routine large-scale screening surveys in the Chinese Mainland. All positively tested infections had been quarantined with medical care, which can significantly reduce the likelihood of generation of secondary infection. However, false positive results should be confirmed when the prevalence in an area is very low to minimize the social and economic impacts. Our results indicate that asymptomatic infections can be controlled based on the current prevention and control measures being implemented in the Chinese Mainland. Related measures may be useful for other countries to mitigate secondary asymptomatic infections.

MATERIALS AND METHODS

Study Design

Our study comprised the following three steps. First, the percentage of pre-symptomatic and subclinical infection of the officially reported COVID-19 cases were modeled using an assumed "development lag," which is the time interval from an asymptomatic COVID-19 confirmation (before syndrome onset) to the confirmation of a symptomatic case based on guidelines set by the NHC. The PPV was an approximate estimation. Second, based on the sensitivity and specificity of commercially available RNA diagnostic kits, the prevalence of COVID-19 infection was calculated using Bayes' formula. Third, we compared the up-to-date related prevention and control measures on asymptomatic infections among the typical countries. The referential significance of our study is proposed.

Data Sources

In China, several large-scale surveillance studies of asymptomatic COVID-19 infections have been conducted; the results are reported on the official websites of Wuhan Municipal Health Commission, China,[24] and the NHC.[4] The reported results from April 1 to May 14, 2020, are summarized in Table S2. The number of reported COVID-19 cases in 48 countries around the world ranged from 288 to 1,340,098 as of May 14, 2020; notably, the populations of these countries range from 353,000 to 1.3 billion. Before April 25, 2020, a total of 30 detection kit products for SARS-CoV-2 from 26 manufacturers had been approved by the National Medical Products Administration, including 19 SARS-CoV-2 RNA detection agents and 11 SARS-CoV-2 antibody tests. Among them, only five kits provided documented sensitivity (*Sens*) and specificity (*Spec*) information, as summarized in Table 2.

Data Analysis

Assuming that the biological samples of all participants were detected by an RNA kit with one test, without an immediate second confirmation before reporting to the NHC, we can estimate the detection specificity, as described in "Estimation of the Specificity" (Supplemental Materials). The development lag time varies with the location, target population, medical conditions, and so forth; however, its median value should be less than the incubation period of COVID-19, e.g., 5.2 days.[17] For all asymptomatic cases, a set of random numbers from a gamma distribution were assigned as individual development lag times. If the lag time was less than the time interval between the date when diagnosed as an asymptomatic case and the end of the study period, i.e., May 14, 2020, the corresponding asymptomatic case would be supposed to be a pre-symptomatic infection. The total number of pre-symptomatic cases can be predicted during the period of concern, noted as N_{pred}. The officially reported actual number of pre-symptomatic cases on the NHC website is referred to as N_{act}. Thus, the non-development percentage of asymptomatic cases that did not develop into those with the COVID-19 syndromes can be characterized as $(N_{pred} - N_{act})/N_{pred}$. Also, the crude developing percentage of the officially reported asymptomatic infection (N_{asy}) can be calculated by N_{pred}/N_{asy}. Assuming that the *PPV* is approximately N_{act}/N_{pred}, the prevalence (*Prev*) of COVID-19 infection can be calculated by modifying Bayes' formula, $Prev = (1 - Spec)/[(1/PPV - 1) \times Sens + 1 - Spec]$. The median value (IQR) with minimum (Min) and maximum (Max) values is used here to describe the distributions. Statistical analysis was conducted using R software (version 3.6.1, NIH, Bethesda, MD, USA). Details of the calculation analysis are provided in Supplementary Materials in "R Code for Repeating the Analysis."

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AUTHOR CONTRIBUTIONS

B.W. and N.J. conceived the study. X.J., J.C., L.L., and T.X. curated the data. X.J., J.C., T.X., B.W., and N.J. performed the analysis. X.J., B.W., and N.J. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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