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Contrasting SARS-CoV-2 epidemics in Singapore: cohort studies in migrant workers and the general population

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ABSTRACT

Importance: Since January 2020, Singapore has implemented comprehensive measures to suppress SARS-CoV-2. Despite this, the country has experienced contrasting epidemics, with limited transmission in the community and explosive outbreaks in migrant worker dormitories.
Objective: To estimate SARS-CoV-2 infection incidence among migrant workers and the general population in Singapore.
Design: Prospective serological cohort studies.
Setting: Two cohort studies — in a migrant worker dormitory and in the general population in Singapore.
Participants: 478 residents of a SARS-CoV-2-affected migrant worker dormitory were followed up between May and July 2020, with blood samples collected on recruitment and after 2 and 6 weeks. In addition, 937 community-dwelling adult Singapore residents, for whom pre-pandemic sera were available, were recruited. These individuals also provided a serum sample on recruitment in November/December 2020.
Exposure: Exposure to SARS-CoV-2 in a densely populated migrant worker dormitory and in the general population.
Main outcomes and measures: The main outcome measures were the incidences of SARS-CoV-2 infection in migrant workers and in the general population, as determined by the detection of neutralizing antibodies against SARS-CoV-2, and adjusting for assay sensitivity and specificity using a Bayesian modeling framework.
Results: No evidence of community SARS-CoV-2 exposure was found in Singapore prior to September 2019. It was estimated that < 2 per 1000 adult residents in the community were infected with SARS-CoV-2 in 2020 (cumulative seroprevalence: 0.16%; 95% CrI: 0.008–0.72%). Comparison with comprehensive national case notification data suggested that around 1 in 4 infections in the general population were associated with symptoms. In contrast, in the migrant worker cohort, almost two-thirds had been infected by July 2020 (cumulative seroprevalence: 63.8%; 95% CrI: 57.9–70.3%); no symptoms were reported in almost all of these infections.
Conclusions and relevance: Our findings demonstrate that SARS-CoV-2 suppression is possible with strict and rapid implementation of border restrictions, case isolation, contact tracing, quarantining, and social-distancing measures. However, the risk of large-scale epidemics in densely populated environments requires specific consideration in preparedness planning. Prioritization of these settings in vaccination

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strategies should minimize the risk of future resurgences and potential spillover of transmission to the wider community.

Key points

Question: What was the incidence of SARS-CoV-2 infection in the general population and among migrant workers in Singapore in 2020?

Findings: Using serological evidence from two prospective cohorts, it was shown that < 0.2% of the Singapore general population had been infected with SARS-CoV-2 in 2020, but nearly two-thirds of residents in a SARS-CoV-2-affected dormitory were infected by July 2020, at the peak of an outbreak in migrant workers.

Meaning: Community transmission of SARS-CoV-2 can be effectively suppressed with prompt implementation of border restrictions, case identification, isolation and contact tracing, social distancing measures, and non-pharmaceutical interventions. However, high-risk, densely populated settings require special consideration in preparedness planning.

Introduction

Singapore reported its first imported case of coronavirus disease-2019 (COVID-19) on January 23, 2020. The first cases of local transmission were recorded on February 4, 2020. Subsequently, Singapore experienced three distinct COVID-19 epidemics, involving imported cases, clusters of community transmission linked mainly to workplaces, social gatherings and nursing homes, and outbreaks among migrant workers (Figure 1). The public health response involved a comprehensive set of control measures, including isolation of COVID-19 cases in hospitals or dedicated government facilities, extensive manual and digital contact tracing, and strict quarantining and testing of incoming travelers and exposed individuals. Gradual expansions of border restrictions were implemented from the end of January 2020, leading to border closures to all but essential services at the end of March 2020. Extensive restrictions on social gatherings and universal mask wearing have been in place since April 2020, when an 8-week national lockdown was initiated.

These measures have largely been effective at curtailing community transmission of SARS-CoV-2. However, from March 2020, Singapore experienced a series of large epidemics in densely populated migrant worker dormitories (Tan et al., 2021). There are over 320 000 migrant workers in Singapore, residing in around 50 dormitories nationwide. In response to the epidemic, workers were confined to dormitories during the lockdown period and movement within dormitories was restricted. Medical teams were deployed in all dormitories to provide testing and refer suspected COVID-19 cases to healthcare facilities, leading to the eventual interruption of transmission in September 2020. As of August 31, 2021, 67 459 confirmed COVID-19 cases had been reported nationally. Of these, > 80% had been among male foreign migrant workers living in dormitories. Our study reports on the contrasting SARS-CoV-2 epidemics found among migrant workers and in the community in Singapore, based on two longitudinal serological studies.

Methods

Migrant worker cohort

Between May and July 2020, a longitudinal serology study was conducted among 541 male residents of a migrant worker dormitory in Singapore. At the start of the epidemic, the dormitory housed over 4000 residents of primarily Indian, Bangladeshi, and Chinese origin, working mainly in the construction, shipping, manufacturing, and processing sectors. The dormitory consisted of 10 multistorey residential blocks, with rooms typically housing 10–14 residents. At the time of the study, clinical management and testing of suspected COVID-19 cases within the dormitory was performed by a mobile medical team. PCR-confirmed COVID-19 cases were referred to acute-care hospitals or community isolation facilities, depending on their medical needs.

Participants were recruited from randomly selected rooms within each residential block (~ five rooms per block — see Supplementary Information for sampling methodology). Consenting participants provided a 5 ml venous blood sample on enrollment and after 2 and 6 weeks. Information on participants' demographics, country of origin, work sector, pre-existing health conditions, and smoking history was collected on enrollment. Additionally, participants were asked whether they had experienced any symptoms associated with COVID-19 in the month prior to enrollment and in the intervening periods between follow-up visits. COVID-19-associated symptoms included fever, cough, shortness of breath, sore throat, runny nose, anosmia, muscle ache, fatigue, and diarrhea.

Community cohort

Participants were recruited from individuals taking part in the Singapore Population Health Studies (SPHS) initiative, which comprises 50 000 adult Singaporeans and long-term residents followed up over multiple waves to monitor risk factors for common health conditions. Individuals in the SPHS were eligible to take part in this study if they were Singapore citizens or permanent residents aged ≥ 21 years and had a stored serum sample collected prior to September 2019 available for serological testing. Participants were recruited between November and December 2020. Trained interviewers conducted an interview by telephone to collect demographic details and information on potential risk factors for SARS-CoV-2 infection, including occupation, travel history, contact with suspected or confirmed COVID-19 cases, and comorbidities. An in-person visit was subsequently arranged, at which participants provided a 5 ml venous blood sample for serological testing.

Serological testing

Tests were carried out for the presence of SARS-CoV-2-neutralizing antibodies in pre-pandemic sera and sera collected in November/December 2020 from all community cohort participants, and in sera collected at baseline, 2 weeks, and 6 weeks from the migrant worker cohort. Sera were extracted from fresh blood samples within 24 hours of collection. Tests for SARS-CoV-2-neutralizing antibodies (NAb) were performed using the cPass

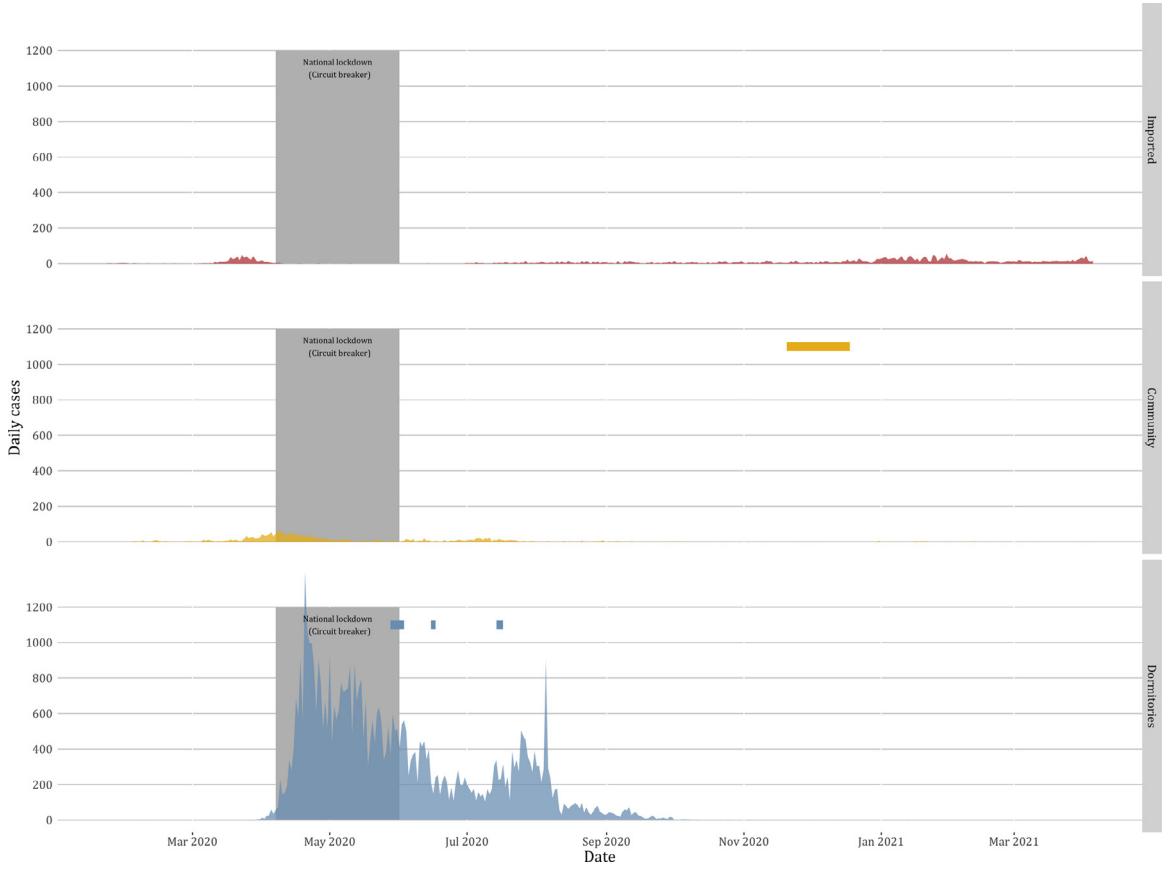

Figure 1. Epidemic patterns of imported (top panel), community (middle panel), and migrant worker dormitory (bottom panel) COVID-19 cases in Singapore, January 2020–March 2021. The shaded area represents the period of national lockdown (circuit breaker) between April 7 and June 1, 2020. Colored bars indicate the periods of sample collection for the community cohort (yellow) and the migrant worker cohort (blue).

SARS-CoV-2 Neutralization Antibody Detection Kit (GenScript). An inhibition threshold of 30% was used to define a positive result, as per the manufacturer's instructions.

Data analysis

Cumulative seroprevalence in the community cohort in November/December 2020 was estimated using a Bayesian approach, accounting for test sensitivity and specificity, as described by Larremore et al. (Larremore et al., 2021). Markov Chain Monte Carlo (MCMC) methods were used to obtain 5000 samples from the posterior parameter distribution, after a burn-in of 1000 iterations.

For the migrant worker cohort, cumulative seroprevalence was estimated at baseline, and after 2 and 6 weeks of follow-up, using a Bayesian random effects logistic model, as described by Stringhini et al. (Stringhini et al., 2020) (Supplementary Information), which additionally accounted for the clustering of observations from residents sampled from the same room. In addition, the risk of seroconversion during the follow-up period among individuals who were seronegative at baseline was estimated. 6000 samples were obtained from the posterior parameter distributions using four MCMC chains, each with a burn-in of 750 iterations. The R-hat statistic was used to check for model convergence, and visual inspection of trace plots to ensure good mixing of MCMC chains.

Information on false positivity and false negativity for the cPass assay was obtained from a validation study by Meyer et al. (Meyer et al., 2020), which estimated a sensitivity of 80.3% and a specificity of 99.3%.

Analyses were conducted using R software version 4.1 (R Core Team (2020), n.d.). Bayesian random effects models were fitted in Stan using the RStan package (Stan Development Team (2020), n.d.). The posterior parameter distributions were summarized using the median and central 95% of the posterior distribution.

Results

Participation

Of the 551 individuals approached, 541 (98.2%) participants were recruited in the male migrant worker cohort. Of these, 478 (88.4%) provided three blood samples on recruitment, and at 2 and 6 weeks, and were included in this analysis. The mean age was 35 years (range: 19–59 years). Among the participants, 51.4% originated from India, 34.9% from Bangladesh, and 9.4% from China. Nearly a third of participants were current smokers, but underlying medical conditions were uncommon (Table 1).

In the community cohort, 2608 individuals were approached, of whom 701 (26.9%) were not contactable after three attempts, and three (0.1%) were no longer in Singapore or had passed away. Of the remaining 1904 individuals, 937 (49.2%) agreed to participate and completed the baseline assessment. The participants had a mean age of 52 years (range: 23–83 years) and 480 (51.2%) were female. The most common underlying conditions were high blood pressure (23.2%), diabetes (15.0%), and chronic respiratory conditions (6.5%); 9.7% were current smokers (Table 1). In comparison with the census population, cohort participants were generally younger, with an over-representation of those of Indian ethnicity, married individuals, and those living in larger public housing apartments, and an under-representation of individuals of Malay

Table 1
Distribution of ages and underlying medical conditions in the community cohort and migrant worker cohort participants, Singapore 2020

Characteristic	Community cohort($N = 937$)	Migrant worker cohort($N = 478$)
Age (years)		
- Mean (SD)	52.3 (13.0)	35.2 (7.9)
- Range	23.0–83.0	19.0–59.0
Age category		
- < 30	45 (4.8%)	134 (28.0%)
- 30–39	114 (12.2%)	203 (42.5%)
- 40–49	232 (24.8%)	124 (25.9%)
- 50–59	270 (28.8%)	17 (3.6%)
- 60–69	169 (18.0%)	0 (0.0%)
- 70+	107 (11.4%)	0 (0.0%)
High blood pressure		
- No	718 (76.7%)	457 (95.6%)
- Yes	217 (23.2%)	21 (4.4%)
- Don't know	1 (0.1%)	0 (0.0%)
Heart disease		
- No	886 (94.6%)	478 (100.0%)
- Yes	48 (5.1%)	0 (0.0%)
- Don't know	3 (0.3%)	0 (0.0%)
Diabetes mellitus		
- No	794 (84.8%)	469 (98.1%)
- Yes	140 (15.0%)	9 (1.9%)
- Don't know	2 (0.2%)	0 (0.0%)
Chronic lung condition		
- No	873 (93.2%)	475 (99.4%)
- Yes	61 (6.5%)	3 (0.6%)
- Don't know	3 (0.3%)	0 (0.0%)
Smoking status		
- Non-smoker	792 (84.5%)	282 (59.0%)
- Ex-smoker	54 (5.8%)	46 (9.6%)
- Current smoker	91 (9.7%)	150 (31.4%)

ethnicity, unmarried individuals, and those living in private condominiums or landed property (Supplementary Information Table S1).

Recruitment summaries for the two cohorts are shown in Supplementary Information Figures S1 and S2.

Seroprevalence and infection risk

In the migrant worker cohort, 117 (24.5%) were positive for SARS-CoV-2 neutralizing antibodies at baseline. This rose to 178 (37.2%) after 2 weeks and to 245 (51.3%) after 6 weeks. After accounting for test characteristics, the cumulative seroprevalence was estimated to be 30.4% (95% credible interval, CrI: 26.1–35.9%) at baseline, 46.5% (95% CrI: 41.4–51.9%) after 2 weeks, and 63.8% (95% CrI: 57.9–70.3%) after 6 weeks. Among the initially seronegative migrant workers, the risk of seroconversion was 22.9% (95% CrI: 18.5–27.8%) after 2 weeks and 54.3% (95% CrI: 48.3–60.7%) after 6 weeks of follow-up (Figure 2).

There was statistical and epidemiological evidence that infections were clustered strongly by room (household random effect at baseline, $\sigma_h = 3.0$, 95% CrI: 1.93–5.27). This clustering effect decreased over time as seroprevalence increased over the 6-week follow-up period ($\sigma_h = 1.74$, 95% CrI: 1.11–2.86 at 6 weeks). Additionally, among 16 initially seronegative rooms, widely heterogeneous trajectories were observed (Multimedia File), with attack rates over the 6-week follow-up period ranging from 0% to 85% (Supplementary Information Figure S3).

The vast majority of migrant worker infections were asymptomatic. Among those seropositive at baseline, five (4.3%) reported experiencing any symptom associated with COVID-19 in the previous 4 weeks, while 3.8% (6/160) of seroconverters reported symptoms during the 6-week follow-up period. No association was found between seropositivity at baseline or seroconversion and age, country of origin, work sector, occurrence of symptoms, or smoking status.

In the community cohort, no pre-pandemic serum samples were positive for SARS-CoV-2 neutralizing antibodies. Among the samples collected in November/December 2020, 0.21% (2/937) tested positive. Both positive samples were non-reactive against SARS virus spike protein. After accounting for test characteristics, the cumulative seroprevalence in 2020 was estimated to be 0.16% (95% CrI: 0.008–0.72%).

In total, 2272 community cases of COVID-19 were reported in Singapore up to the end of December 2020, corresponding to a cumulative incidence of 0.042% (COVID-19 Situation Report, n.d.) This indicated a most likely value for the infection:case ratio of 3.8:1.

Discussion

Our findings highlighted the contrasting epidemics in the community and in migrant worker populations in Singapore, based on serological evidence from two longitudinal studies. Our results demonstrated the continuing effectiveness of nationally implemented, wide-ranging control measures for minimizing community transmission of SARS-CoV-2, while emphasizing the challenges to mitigating risk in densely populated settings. Our study also documented evidence of high rates of asymptomatic infection in migrant workers.

To our knowledge, this was the first study to report on SARS-CoV-2 cross-reactivity in pre-pandemic sera from a large, systematic, general population cohort. No evidence was found of population exposure to SARS-CoV-2 prior to September 2019. Since January 2020, Singapore has implemented a multi-pronged strategy for SARS-CoV-2 containment and suppression, including extensive testing and contact tracing, strictly enforced case isolation and quarantining, risk-based border restrictions, social-distancing measures, and mask-wearing policies. Early modeling work in Singapore emphasized the important role of case isolation, contact tracing, quarantining, and workplace distancing measures in controlling SARS-CoV-2 transmission (Koo et al., 2020), which is evi-

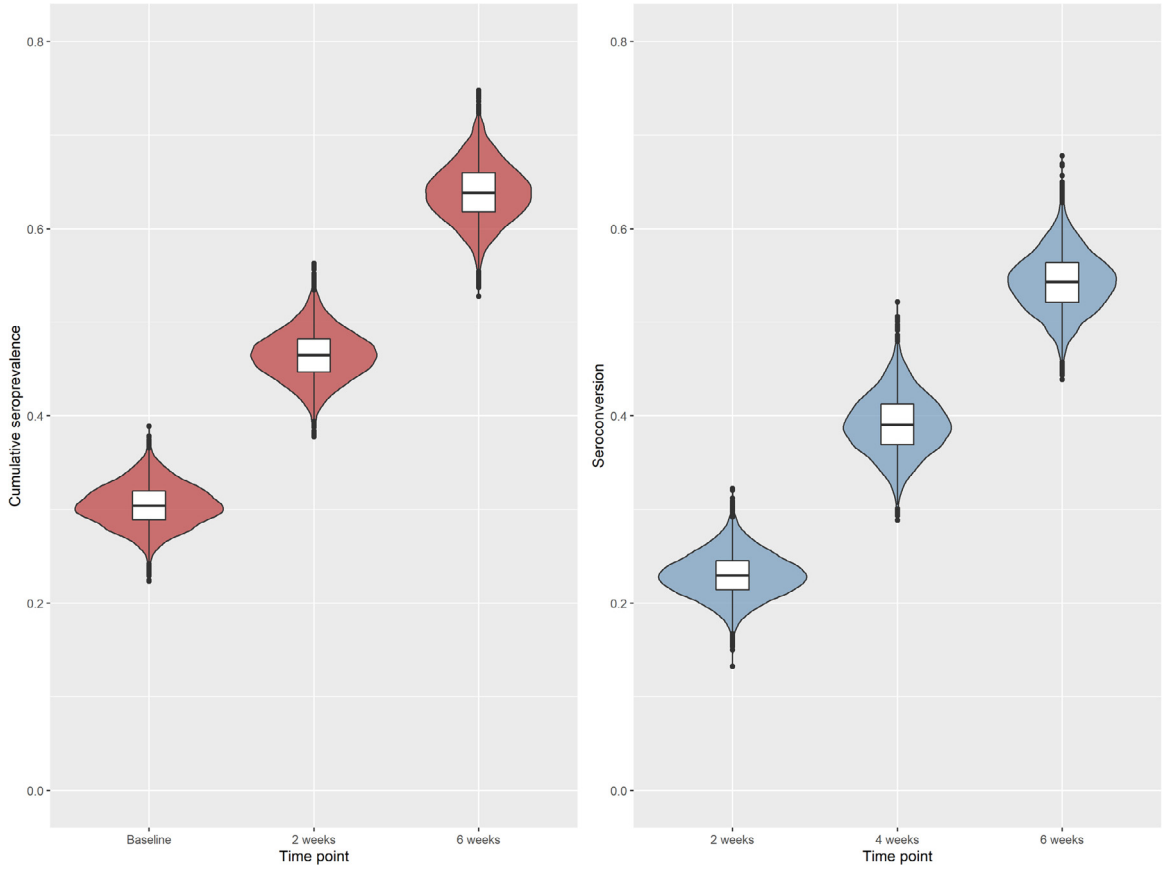

Figure 2. Cumulative seroprevalence (left panel) and seroconversion risk (right panel) over a 6-week period among migrant workers residing in a dormitory, Singapore 2020. The 2-week and 6-week seroconversion estimates are based on antibody test results at 2 and 6 weeks among individuals initially seronegative at baseline. The 4-week seroconversion estimates are based on antibody test results at the 6-week follow-up among individuals who were seronegative at the 2-week follow-up.
Multimedia file: Infections in a cohort of 541 migrant workers residing in a dormitory at baseline, and at 2 weeks and 6 weeks of follow-up. Circles represent individuals recruited from rooms within dormitory blocks. Grey circles represent individuals negative for SARS-CoV-2 neutralizing antibodies; red circles represent individuals positive for SARS-CoV-2 neutralizing antibodies. The animation shows the progression of infections by room. Some individuals were tested at baseline but did not complete the 6-week follow-up. These are denoted by lighter shading (see, for example, rooms in Block A, floor 5, extreme right, and Block B, floor 3, extreme left).

denced by the comparatively small number of community COVID-19 cases notified to date, and the extremely low seroprevalence observed in this study. In comparison, early seroprevalence studies in European settings indicated that between 5% and 10% of the population had evidence of SARS-CoV-2 exposure after the first epidemic wave (Pollán et al., 2020; Stringhini et al., 2020).

Initial measures in Singapore, however, were unable to prevent large epidemics in densely populated migrant worker dormitories. More than 49 000 COVID-19 cases were reported among dormitory residents between April and July 2020, corresponding to an incidence of 1526 cases per 10 000 residents. This compares with 1760 cases, or 3 per 10 000 population, in the community. Data from our study indicated that around two-thirds of dormitory residents had been infected between April and early July, in line with seroprevalence estimates reported from other migrant worker populations (Tan et al., 2021). Moreover, our data suggested extremely high infection risks in these settings, with more than half of initially immunologically naive individuals becoming infected over the 6-week follow-up period. Crowded, poorly ventilated indoor spaces are known to be high-risk environments for SARS-CoV-2 transmission, and have been associated with large outbreaks among processing plant workers (Günther et al., 2020; Middleton et al., 2020; Steinberg et al., 2020).

Nevertheless, the vast majority of infections were asymptomatic. This finding should be interpreted in the context of prevailing control measures in migrant worker dormitories. Individuals at higher risk of severe COVID-19, including older individuals and those with underlying medical conditions, were moved to alternative housing early on in the epidemic. Additionally, universal mask-wearing was mandatory during the study period, which is likely to have contributed to reducing droplet exposure from infectious individuals and, hence, viral inoculum (Spinelli et al., 2021). Although it is possible that participants may have under-reported symptoms, this is an unlikely explanation for the high fraction of asymptomatic infections. At the time of the study, dormitory residents were required to report their temperature every day and were asked to report to a medical post within the dormitory in the event of symptoms, for testing and referral to medical services where necessary. All but essential work had been suspended and residents were confined to the dormitory. The Singapore government set up a compensation scheme so that workers continued to be paid during this period. It is thus unlikely that there were strong disincentives to report symptoms.

Based on a comparison of cumulative seroprevalence in our community cohort with officially reported COVID-19 cases in the community up to the end of 2020, our estimate of a likely value for the infection:case ratio was around 4:1, although uncertainty was high because of the very small number of seroconversions. Importantly, Singapore has employed extensive testing, case identification, and contact tracing since the start of the pandemic, and ascertainment of community COVID-19 cases during the study period is likely to be near complete. Our estimate for the infection:case ra-

tio was in agreement with analyses of the *Diamond Princess* cruise ship outbreak, in which an estimated three-quarters of infections were asymptomatic (Emery et al., 2020). Data from extensive investigations of the wider outbreak in migrant workers also identified five times as many infections as symptomatic cases (Tan et al., 2021), although there may have been some under-ascertainment of symptomatic cases among migrant workers early in the epidemic.

A number of limitations should be considered when interpreting our findings. First, because of the extensive control measures and movement restrictions implemented within migrant worker dormitories, our study was limited to residents of a single dormitory. Within the dormitory, the sampling protocol had to be designed so as to minimize contact between residents on different floors and in different residential blocks; it was not possible to implement a sampling scheme that provided a truly representative sample. Our study accounted for this by using a model that incorporated the dependence of samples, and our infection rates were in line with other estimates from the broader migrant worker population in Singapore (Tan et al., 2021). Additionally, our study did not include virological detection of SARS-CoV-2 from respiratory samples. Combined use of polymerase chain reaction (PCR) tests and serological assays would have allowed for more precise determination of the timing of infection and more detailed investigation of transmission within the migrant worker dormitory. However, because of limitations on the availability of PCR test kits nationally early on in the pandemic, this was beyond the scope of this study. Due to the lag in the appearance of detectable neutralizing antibodies, our infection rate estimates therefore reflected levels of transmission 2–3 weeks earlier.

Conclusion

Within the broader context of the COVID-19 epidemic in Singapore, our findings demonstrated that suppression of SARS-CoV-2 transmission is possible with strict and rapid implementation of border restrictions, case isolation, contact tracing, quarantining, and social-distancing measures. However, the potential for large-scale epidemics in densely populated environments has proven to be a point of vulnerability in terms of virological containment, requiring special consideration in preparedness, mitigation, and control planning. Although the routes of transmission within the migrant worker dormitory were not specifically investigated, the strong clustering of infection within rooms highlights the role of crowding in transmission, and emphasizes the need to reduce density in dormitory settings in order to reduce vulnerability to outbreaks. Consideration and prioritization of these settings in vaccination strategies should help to minimize the risk of future resurgences and potential spillover of transmission to the wider community.

Author contributions

Drs Tam and Clapham had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Tam, Clapham.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: Tam, Clapham.

Critical revision of the manuscript for important intellectual content: all authors.

Statistical analysis: Tam, Clapham.

Administrative, technical, or material support: Tan, Lim, Shankar, Zahari, Kumar, Tun.

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Competing interests

L-FW and WNC are coinventors of the cPass test kit (patent pending). The remaining authors declare no competing interests in relation to this work.

Ethical statement

The community cohort study was approved by the National University of Singapore institutional review board (reference H-20-032). Participants in this study provided signed, informed consent. The migrant worker cohort study was approved by the Singapore Ministry of Health under the Infectious Diseases Act, and was exempt from institutional review board approval as it was conducted as part of the national public health response to the COVID-19 pandemic. Under the 2015 Singapore Infectious Diseases Act (Schedule 59A), the Ministry of Health can approve and require research to support the national public health response to an epidemic, as per schedule 59A. Participants provided verbal consent to take part. Prior to obtaining consent, the study team explained the purpose of the study to potential participants, and answered any questions about the study. Potential participants were also provided with written study information sheets, which were available in English, Chinese, Bengali, Tamil, and Burmese. It was made clear to individuals that participation was entirely voluntary, and that they could withdraw from the study at any time without providing a reason, and with no penalty or consequences for their access to health care, employment, or immigration status. Printed versions of the study questionnaire were also available in the five languages to make sure that participants understood the questions, and the study team included data collectors fluent in English, Chinese, Tamil, and Burmese. The study team also had access to a roster of interpreters, who could be contacted by telephone to aid communication with participants where necessary. Participants were informed of their serology results, and were provided with information sheets in their language of choice explaining the interpretation of the test results.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.11.043.

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