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Serial population-based serosurveys for COVID-19 in two neighbourhoods of Karachi, Pakistan

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Serial population-based serosurveys for COVID-19 in two neighbourhoods of Karachi, Pakistan

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ABSTRACT

Objective: To determine population-based estimates of coronavirus disease 2019 (COVID-19) in a densely populated urban community of Karachi, Pakistan.

Methods: Three cross-sectional surveys were conducted in April, June and August 2020 in low- and high-transmission neighbourhoods. Participants were selected at random to provide blood for Elecsys immunoassay for detection of anti-severe acute respiratory syndrome coronavirus-2 antibodies. A Bayesian regression model was used to estimate seroprevalence after adjusting for the demographic characteristics of each district.

Results: In total, 3005 participants from 623 households were enrolled in this study. In Phase 2, adjusted seroprevalence was estimated as 8.7% [95% confidence interval (CI) 5.1–13.1] and 15.1% (95% CI 9.4–21.7) in low- and high-transmission areas, respectively, compared with 0.2% (95% CI 0–0.7) and 0.4% (95% CI 0–1.3) in Phase 1. In Phase 3, it was 12.8% (95% CI 8.3–17.7) and 21.5% (95% CI 15.6–28) in low- and high-transmission areas, respectively. The conditional risk of infection was 0.31 (95% CI 0.16–0.47) and 0.41 (95% CI 0.28–0.52) in low- and high-transmission neighbourhoods, respectively, in Phase 2. Similar trends were observed in Phase 3. Only 5.4% of participants who tested positive for COVID-19 were symptomatic. The infection fatality rate was 1.66%, 0.37% and 0.26% in Phases 1, 2 and 3, respectively.

Conclusion: Continuing rounds of seroprevalence studies will help to improve understanding of secular trends and the extent of infection during the course of the pandemic.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in more than 62 million confirmed cases and over 1.4 million deaths globally, a case fatality rate (CFR) of approximately 5.4% and an infection fatality rate (IFR) of 0.9% (Johns Hopkins University, 2020; Rekatsina et al., 2020). As the world rushed to respond to the global health crisis, the pandemic revealed numerous cracks in healthcare systems (Armocida et al., 2020). Pakistan was one of the first low- and middle-income countries (LMICs) to be affected by the pandemic, and had reported 398,024 cases and 8025 deaths (CFR 2.51%) at the time of writing (Government of Pakistan, 2020; Johns Hopkins University, 2020). CFR has been variable, ranging from 5.11% in Khyber Pakhtunkhwa to 0.71% in Gilgit Baltistan, with rates of 1.82%, 1.80% and 1.28% reported for Punjab, Sindh and Baluchistan, respectively (Anser et al., 2020).

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The demographic characteristics of Pakistan are typical of most LMICs, with 41% of the population aged <15 years (Mahsud-Dornan, 2007). The societal construct in Pakistan boasts a patrilineal joint family system, intergenerational co-residence of family members, and an average household size of six or more (Rana, 2017). This is important because recent evidence indicates that households with individuals aged >60 years are at risk of life-threatening manifestations of the disease (Fenoll and Grossbard, 2020). Karachi is home to people from varying diasporas across Pakistan, and has been the epicentre of the epidemic since 26 February 2020, reporting the highest number of cases in Pakistan (84,232) and accounting for 28% of all cases in the country (Government of Sindh, 2021). Crowded neighbourhoods and urban slum dwellings, along with poor adherence to mitigation measures in the city, may have accelerated the transmission of infection (Wasdani and Prasad, 2020).

Surveillance systems form the basis for tracking cases of COVID-19, testing populations at risk and performing contact tracing, thereby representing the key components of the public health response (World Health Organization, 2020a). Facility-based surveillance efforts are likely to miss mild and asymptomatic cases, as bolstered by evidence from a WHO–China Joint Commission Report and several published studies which indicate that 5–80% of seropositive patients are asymptomatic. Therefore, household-targeted serological testing can decrease biases arising from selective testing, and generate concrete evidence on the role of asymptomatic transmission of infection in rapidly increasing infection rates (Kumar et al., 2020). Household transmission is of particular concern in congested neighbourhoods of metropolitan cities when lockdown measures are in place. Secondary transmission from index cases in households using prospective follow-up and active symptom monitoring with nasopharyngeal polymerase chain reaction (PCR) has indicated household attack rates as high as 32.4% [95% confidence interval (CI) 22.4–44.4%] (Wu et al., 2020). However, this exercise is resource intensive, and transmission may differ between symptomatic and asymptomatic households as symptomatic individuals are more likely to transmit the virus (Ferretti et al., 2020; Gudbjartsson et al., 2020; Lavezzo et al., 2020; Streeck et al., 2020).

Using seroprevalence data, the conditional risk of infection (CRI; i.e. the probability that an individual in a household is infected given that another household member is infected) can serve as a related index of infection within a household (Lavezzo et al., 2020). Additionally, true estimates of IFR can be calculated as it is possible to detect asymptomatic and mild cases who did not seek treatment.

This study estimated changes in seroprevalence in low- and high-transmission neighbourhoods of Karachi between April and August 2020 using serial cross-sectional surveys by adapting the World Health Organization (WHO) UNITY protocol. The estimates are presented by age and gender, and were used to compute CRI and IFR (World Health Organization, 2020b).

Methods

Study participants and sample collection

This study was conducted in two areas. Four sub-administrative units (union councils) of District East were selected as high-transmission areas based on the number of cases per million reported by the provincial government (Figure 1). One union council of District Malir was selected as a low-transmission area. This study was approved by Aga Khan University Ethical Review Committee.

Three cross-sectional surveys were performed sequentially at household level between 15–25 April, 25 June–11 July and 17–22 August 2020 (Phases 1, 2 and 3, respectively). Four research teams, each comprising one data collector and one phlebotomist, collected data and serology samples. A detailed line list of cases was available for District East, which enabled households to be selected using systematic random sampling as follows: a case was identified at random from the line list that served as a reference
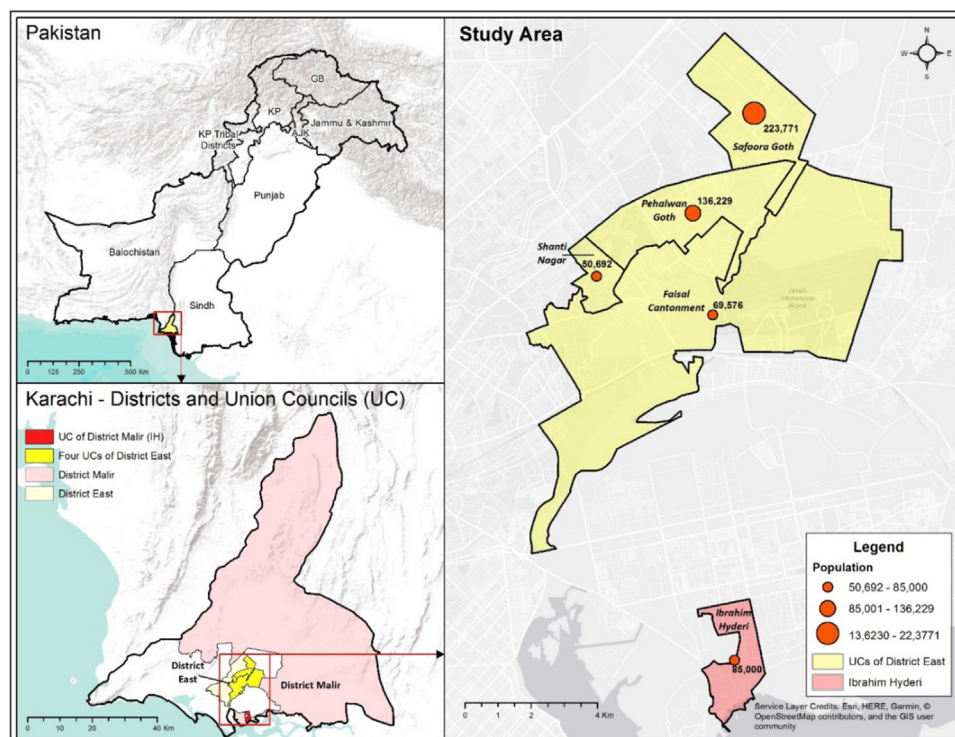

Figure 1. Study area and total population.

point. From here, the direction was determined by spinning a bottle or a pen, and the *n*th interval between structures was identified using the second last digit of a bank note. The reference household was not included in the survey. In the case of household refusal to participate, the next household was approached. Facilities such as hospitals, care homes, educational institutions and prison were excluded. However, healthcare workers within a household were not excluded. In District Malir, a line list of all residential households was available, and simple random sampling was used to select households. In both areas, all household members were eligible to participate regardless of their infectious status. Approval from the head of the household and written

informed consent or assent from individual participants was obtained.

All team members underwent training in the use of personal protective equipment, hand hygiene and safe transportation of biological samples. Blood samples (3 mL for infants, 5 mL for older participants) were collected by a trained phlebotomist and transported to the Infectious Diseases Research Laboratory for centrifugation, serum separation and storage at -20 °C. Information was collected from all participants on age, gender, occupation and household size, along with details of travel history and exposure to patients with COVID-19. Reported comorbidities, presence of symptoms and history of hospitalization were also
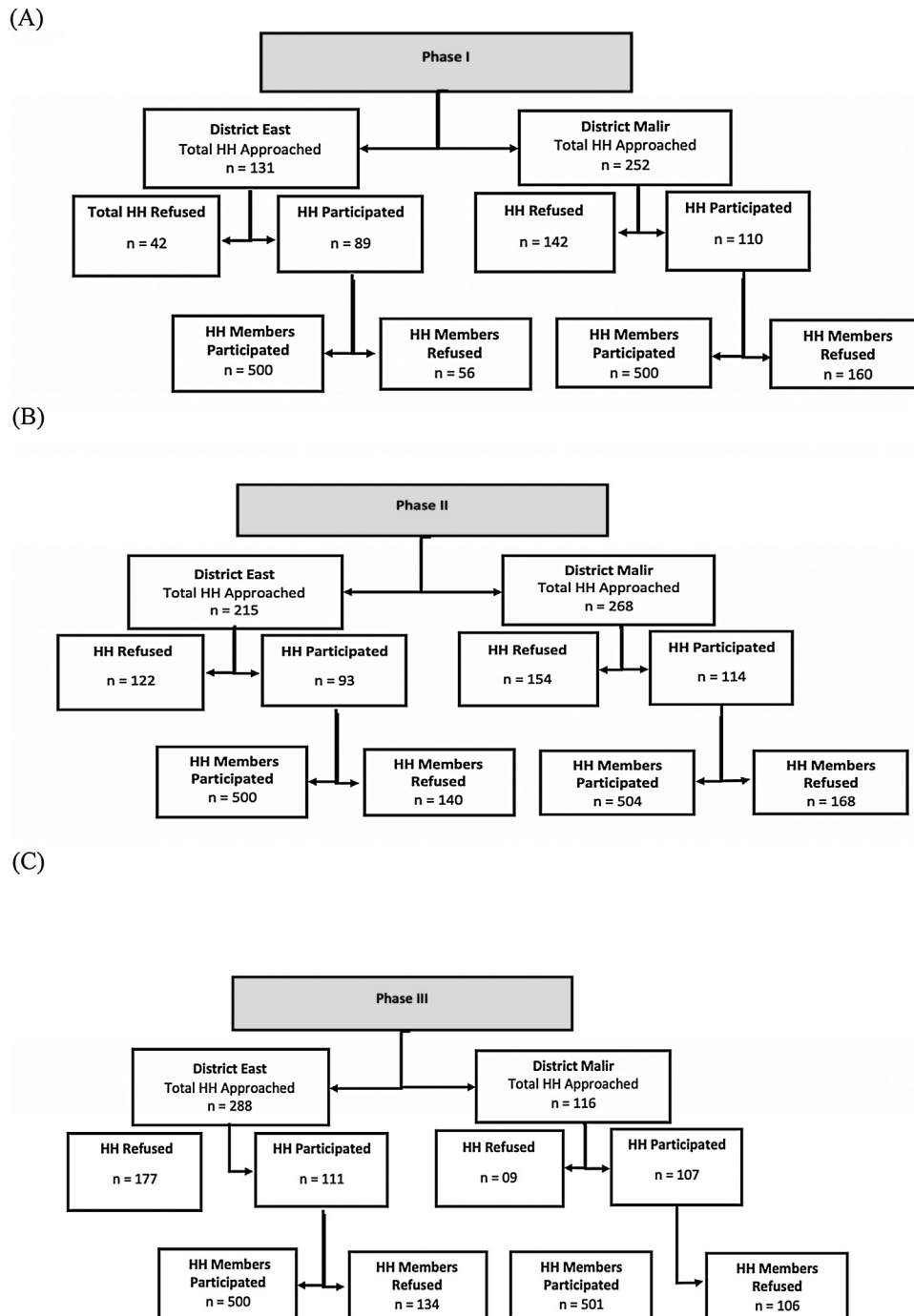
(A)

(B)

(C)

Figure 2. Flow chart of participants in (A) Phase 1, (B) Phase 2 and (C) Phase 3.

recorded. Participants were also asked about their occupational history in terms of working from home or otherwise. For symptoms, the clinical history recorded details of the presence of fever, respiratory symptoms (e.g. sore throat, shortness of breath) and chest pain in the preceding 2 months (Supplementary Table 1, see online Supplementary material).

Laboratory analysis

A commercial Elecsys Anti-SARS-CoV-2 immunoassay (Roche Diagnostics, Basel, Switzerland) targeting combined immunoglobulin (Ig) G and IgM against severe acute respiratory syndrome coronavirus-2 was performed at the Nutritional Research Laboratory at Aga Khan University. The manufacturer reported specificity >99.8% and sensitivity of 100% for individuals with a positive PCR test at least 2 weeks previously, and 88.1% sensitivity for individuals 7–13 days after a PCR-positive test (Roche Diagnostics, 2020).

Statistical analysis

Sample size

The sample size for each phase of the survey was calculated to be 500 participants for each site. This allowed for estimation of age-adjusted prevalence in the range of 20–30% with 95% CI, with precision of ±5% and a design effect of 1.5 for household-level clustering.

Data management

Data entry was performed in duplicate on a structured query language database (My SQL, 2021), and was checked thoroughly for completeness and consistency. Continuous variables such as age and household size were reported as mean and standard deviation (SD). Categorical variables such as gender, occupation and symptoms were reported as frequency and percentage. Participants reporting fever or respiratory symptoms in the preceding 2 months were categorized as symptomatic and presented as proportions. Age was also categorized.

Estimation of overall, age-stratified and gender-stratified seroprevalence

Age- and gender-stratified seroprevalence estimates were computed for each district and each phase independently using a Bayesian hierarchical regression model. This approach, described in detail in the online Supplementary material, accounts for uncertainty due to finite laboratory validation data (Larremore et al., 2020a), and produces estimates using typical choices of uninformative or weakly informative prior distributions (Gelman and Carpenter, 2021; Larremore et al., 2020b).

Given the correlation between household seropositivity values, the model also considered factors such as the total number of household members, and adjusted for test accuracy by modelling directly on the laboratory validation data reported by the test manufacturer (Roche Diagnostics, 2020). Seroprevalence estimates by age and gender were post-stratified to adjust for the demographic make-up of the respective districts.

Estimates are expressed as posterior means and 95% CI based on 20,000 samples from a Bayesian posterior distribution. All calculations were performed using R Software, and samples from posterior distributions were obtained using Stan (https://mc-stan.org).

Household conditional risk of infection and infection fatality rate analysis

CRI is the probability that an individual is infected, conditioned on a household member being infected (Curmei et al., 2020). CRI was calculated and presented as a fraction, where the numerator was the total number of ordered pairs among infected individuals in the same household, and the denominator was the total number of ordered pairs in the same household in which the first individual in the pair is infected. A 95% CI was estimated via bootstrap for each area by resampling households with replacements.

Age-specific IFR estimates the prevalence of infection (including both asymptomatic and mildly symptomatic cases). The cumulative number of deaths due to COVID-19 was calculated until 14 days after dissemination of the serosurvey. This number was divided by the figure obtained from multiplying the relevant

Table 1
General characteristics of the study participants.

Characteristics	District East			Districts	District Malir		
	Phase 1 (n = 500)	Phase 2 (n = 500)	Phase 3 (n = 500)	Phase 1 (n = 500)	Phase 2 (n = 504)	Phase 3 (n = 501)	
Gender, male, n (%)	256 (51.2%)	225 (45.0%)	211 (42.2%)	207 (41.4%)	199 (39.5%)	206 (41.1%)	
Age in years, mean (SD)	26.2 (17.9%)	25.9 (16.7%)	27.1 (17.7%)	28.5 (17.9%)	24.32 (16.7%)	26 (16.7%)	
Age group, years, n (%)							
0–4	35 (7.0%)	22 (4.4%)	31 (6.2%)	26 (5.2%)	33 (6.6%)	29 (5.8%)	
5–9	57 (11.4%)	54 (10.8%)	56 (11.2%)	52 (10.4%)	74 (14.7%)	75 (15.0%)	
10–18	107 (21.4%)	139 (27.8%)	91 (18.2%)	86 (17.2%)	120 (23.9%)	87 (17.4%)	
19–39	185 (37.0%)	170 (34.0%)	206 (41.2%)	203 (40.6%)	186 (37.0%)	195 (38.9%)	
40–59	83 (16.6%)	97 (19.4%)	84 (16.8%)	103 (20.6%)	65 (12.9%)	90 (18.0%)	
≥60	33 (6.6%)	18 (3.6%)	32 (6.4%)	30 (6.0%)	25 (5.0%)	25 (5.0%)	
Household size, mean (SD)	6.1 (4.17)	6.6 (3.6)	5.7 (2.3)	6 (2.8)	5.89 (3.2)	5.6 (2.6)	
Working outside home, n (%)	155 (31.0%)	145 (29.0%)	107 (21.4%)	143 (28.6%)	124 (24.6%)	116 (23.2)	
Comorbidities, n (%)							
None	453 (92.3%)	463 (93.0%)	471 (94.2%)	473 (94.6%)	479 (95.0%)	482 (96.2%)	
Diabetes	20 (4.0%)	14 (2.8%)	8 (1.6%)	6 (1.2%)	10 (2.0%)	5 (1.0%)	
Hypertension	14 (2.8%)	13 (2.6%)	16 (3.2%)	16 (3.2%)	11 (2.2%)	14 (2.8%)	
Asthma or allergy	3 (0.6%)	3 (0.6%)	3 (0.6%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	
Chronic hepatitis	2 (0.4%)	3 (0.6%)	1 (0.2%)	3 (0.6%)	3 (0.6%)	0 (0.0%)	
Chronic heart disease	0 (0.0%)	3 (0.6%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	
Asymptomatic	435 (87.0%)	453 (90.6%)	471 (94.2%)	472 (94.4%)	487 (96.6%)	473 (94.4%)	
Sought care	9 (1.8%)	9 (1.8%)	2 (0.4%)	3 (0.6%)	4 (0.8%)	0 (0.0%)	
Hospitalization	1 (0.2%)	5 (1.0%)	0 (0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	
History of travel	2 (0.4%)	11 (2.2%)	7 (1.4%)	8 (1.6%)	1 (0.2%)	4 (0.8%)	
Contact with suspected or confirmed cases of COVID-19	1 (0.2%)	1 (0.2%)	2 (0.4%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	

COVID-19, coronavirus disease 2019; SD, standard deviation.

population of an area with the adjusted estimate of seroprevalence (Ioannidis, 2021).

Results

Participant flow

In total, 3005 participants were enrolled across three phases from District East and District Malir (Figure 2). There were high refusal rates in both areas at household level: 68%, 43% and 61% in District East and 44%, 42% and 8% in District Malir in Phases 1, 2 and 3, respectively. Amongst the households who agreed to participate, the individual participation rate was 82.3% (1000 of 1215 eligible household members) in Phase 1, 76.5% (1004 of 1312 eligible household members) in Phase 2 and 80% (1001 of 1243 eligible household members) in Phase 3. Table 1 describes the baseline demographic and clinical characteristics of the enrolled participants.

Seropositivity

In Phase 1, only two of 500 samples tested positive in District East, while none of the 500 participants tested positive in District Malir. In Phase 2, 100 of 500 samples (20.0%) tested positive in District East and 64 of 504 samples (12.7%) tested positive in District Malir. In Phase 3, 119 of 500 samples (24%) tested positive in District East and 79 of 501 samples (16%) tested positive in District Malir.

Adjusted seroprevalence

In Phase 1, post-stratified seroprevalence was estimated to be 0.4% (95% CI 0–1.3%) in District East and 0.2% (95% CI 0–0.7%) in District Malir. In Phase 2, post-stratified seroprevalence was estimated to be 15.1% (95% CI 9.4–21.7%) in District East and 8.7% (95% CI 5.1–13.1%) in District Malir. In Phase 3, post-stratified seroprevalence was estimated to be 21.5% (95% CI 15.6–28%) in District East and 12.8 % (95% CI 8.3–17.7%) in District Malir.

Both districts showed a marked, significant increase in seroprevalence between sequential phases, with a sharp increase between Phases 1 and 2 and a smaller increase between Phases 2 and 3. Overall reporting of symptoms was documented to be 9.4%. Of the total 364 participants who tested positive, 27 (7.4 %) reported a history of fever, respiratory symptoms or both in the preceding 2 months (Table S1, see online Supplementary material).

Conditional risk of infection and infection fatality rates

To measure whether individuals in the same household were more likely to have similar serostatus, CRI was calculated for Phases 2 and 3. CRI estimates were 0.41 (95% CI 0.28–0.52) and 0.38 (95% CI 0.27–0.52) in District East and 0.31 (95% CI 0.16–0.4) and 0.33 (95% CI 0.12–0.47) in District Malir in Phases 2 and 3, respectively. In parallel, the age-specific IFR, calculated based on the cumulative total of infected persons (based on seroprevalence) and number of deaths (obtained from local government surveillance data), was calculated to be 1.66% in Phase 1, 0.37% in Phase 2 and 0.26%% in Phase 3.

The increase in seroprevalence in District East corresponded with the epidemiology as ascertained through daily case reporting in the district as well as the four study sampling sites (Figure 3). Seropositivity rates were indistinguishable between males and females within each district, as well as between age groups (Table 2, represented graphically in Figure S1, see online Supplementary material).
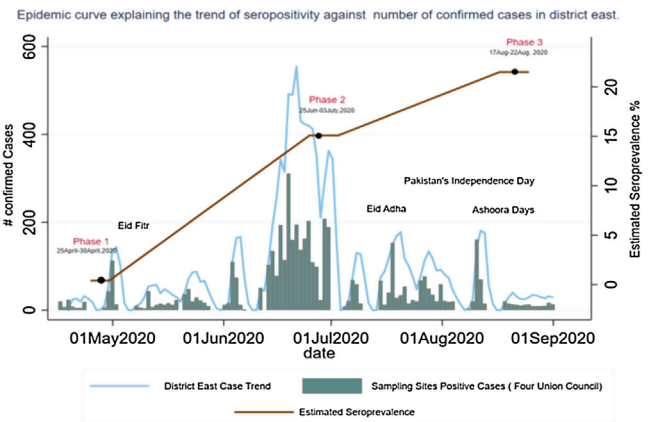

Figure 3. Comparison of trends in coronavirus-disease-2019-positive cases from District East and study sampling sites, and estimated seroprevalence in Phases 1, 2 and 3.

Discussion

This study used three serial cross-sectional surveys to summarize the seroprevalence rates in two neighbourhoods of Karachi, from the very early phase of the pandemic to the post-peak phase. Seroprevalence increased over time, with only a tiny fraction of seropositive individuals reporting any symptoms. A study from Karachi reported a seroprevalence rate of 17.5% among workers across various occupational sectors, while a study from Lahore reported a seroprevalence rate of 15.6% among police force personnel (Chughtai et al., 2020; Javed et al., 2020). The National Institute of Blood Disease in Karachi found an overall estimate of 36% among their participants that included industrial workers (50% positivity), healthcare workers (13% positivity), general public (15.6% positivity) and healthy blood donors (36% positivity) (Zaidi et al., 2020). Preliminary reports of seroprevalence studies from the international literature have highlighted high seroprevalence rates in large metropolitan areas. A study from Mumbai, India reported a seroprevalence rate of 55% (The Times of India, 2020), while a survey carried out in Guilan Province, Iran reported a seroprevalence rate of 33% at the peak of the pandemic (Bhattacharyya et al., 2020; Shakiba et al., 2020).

The three serial serosurveys conducted in the same populations in Karachi indicated an early increase in Phase 2 that continued over the next few months, as demonstrated by Figure 3. A number of reasons can explain this trend; Phase 1 of the study was undertaken early in the pandemic, 3 weeks after a provincial lockdown was declared, while Phase 2 was conducted after lockdown measures were eased in anticipation of the religious festivities observed during Eid in Pakistan. Although individual associations cannot be discerned, the effectiveness of social mitigation measures could explain the smaller increase in Phase 3.

The survey did not identify any difference in seroprevalence between males and females, or any age-specific trends in infection rates across different age categories. Prevalence appeared to increase with age and was documented to be consistently high between 19 and 39 years of age and 40 and 59 years of age in both males and females. This is consistent with age-related seropositivity patterns in the literature (Nickbakhsh et al., 2020). The survey found a large number of asymptomatic seropositive individuals. Only three of 10 reported any respiratory symptoms, with or without fever. In contrast to these findings, the proportion of asymptomatic infections was reported to be much lower (27.7%, 95% CI 16.4–42.7%) in a meta-analysis (He et al., 2021). However, higher rates of asymptomatic infection have been reported in some parts of the world such as India. According to WHO and the Indian

Table 2

Age- and gender-based prevalence of coronavirus disease 2019 in District East and District Malir for Phases 2 and 3.[a]

Variables		Phase 2		Phase 3	
Gender	Age (years)	District East	District Malir	District East	District Malir
Female	0–4	0.14 (0.04–0.25)	0.08 (0.02–0.14)	0.20 (0.09–0.30)	0.13 (0.07–0.21)
Female	5–9	0.13 (0.04–0.22)	0.09 (0.04–0.15)	0.20 (0.10–0.23)	0.13 (0.07–0.19)
Female	10–18	0.13 (0.05–0.21)	0.09 (0.04–0.14)	0.20 (0.12–0.23)	0.12 (0.07–0.19)
Female	19–39	0.15 (0.07–0.23)	0.10 (0.05–0.16)	0.24 (0.16–0.33)	0.13 (0.08–0.19)
Female	40–59	0.15 (0.07–0.26)	0.08 (0.03–0.14)	0.23 (0.15–0.33)	0.14 (0.08–0.21)
Female	≥60	0.15 (0.05–0.27)	0.01 (0.04–0.19)	0.21 (0.12–0.31)	0.13 (0.06–0.19)
Male	0–4	0.14 (0.04–0.25)	0.08 (0.02–0.14)	0.19 (0.09–0.29)	0.12 (0.06–0.19)
Male	5–9	0.13 (0.03–0.23)	0.08 (0.03–0.14)	0.19 (0.08–0.28)	0.12 (0.06–0.19)
Male	10–18	0.17 (0.09–0.28)	0.01 (0.04–0.17)	0.22 (0.14–0.32)	0.14 (0.08–0.22)
Male	19–39	0.15 (0.08–0.24)	0.08 (0.03–0.13)	0.22 (0.14–0.31)	0.12 (0.07–0.18)
Male	40–59	0.22 (0.10–0.40)	0.08 (0.03–0.14)	0.22 (0.14–0.35)	0.13 (0.08–0.22)
Male	≥60	0.14 (0.05–0.26)	0.09 (0.03–0.15)	0.21 (0.11–0.32)	0.13 (0.07–0.20)

[a] Numbers are probability estimates with 95% CI.

Council of Medical Research, India, the number of asymptomatic cases appears to be approximately 80% (Chatterjee et al., 2020). Lower reporting of symptoms in Pakistan may be attributable to innate fears of disclosure of disease positivity and lack of awareness about the high transmissibility of the disease in the general public in the early stages of the pandemic.

The increase in seroprevalence over time, even in an area of presumed low transmission, indicates that seroprevalence studies may serve as important tools to determine the spread of infection in populations where a large majority of the people are asymptomatic. Monitoring the general population through serial serosurveys can detect resurgence, especially when lockdown measures are eased, and enable policy makers to devise strategies for containment of the disease. Heterogeneity between low- and high-income neighbourhoods is likely and has been suggested previously (Hooper et al., 2020; de Souza et al., 2020; Rafael et al., 2020). In the present study, an alternate explanation for this could be the different sampling strategy for the two districts. However, it is difficult to discern the direction in which this may bias the results. Nevertheless, temporal trends within the districts can be established from the present study.

These results also confirm that close contact within households is linked to a high probability of being infected, and should be an important consideration in the transmission of SARS-CoV-2 (Pakistan Bureau of Statistics, 2021). This study indicated that the probability of an individual acquiring an infection in the presence of another infected household member, as measured by CRI, was between 35% and 40%. An unpublished review which used a secondary attack rate, which is a more reliable indicator of intrahousehold transmission, reported this to be lower (18.8%, 95% CI 15.4–22.2%) (Madewell et al., 2020). CRI can therefore function as a substitute in situations where comprehensive surveillance efforts and disease notification strategy are absent, and where secondary attack rates are difficult to estimate.

This study indicated that the age-specific IFR was higher in Phase 1 (1.66%), and decreased in Phases 2 and 3 to 0.37% and 0.26%, respectively. This may be attributed to early detection and improved management of symptomatic disease. A systematic review and meta-analysis conceded that overall IFR could be 0.68% (0.53–0.82%) due to heterogeneity from the studies contributing to the review, or due to various factors such as age and the presence of comorbidities in the population (Meyerowitz-Katz and Merone, 2020). Population demographics can affect estimates of population-weighted IFR, with the lowest IFRs recorded for countries with younger populations, such as Kenya (0.09%, 95% CI 0.08–0.10%) and Pakistan (0.16%, 95% CI 0.14–0.19%) (O'Driscoll et al., 2021).

Strengths of this study include the fact that it captured baseline seropositivity at population level at the beginning of the pandemic when transmission was low. Subsequent surveys at 2-monthly intervals enabled sequential evaluation of changes in seroprevalence. At least one-third of the sample consisted of children aged <18 years, thus focusing on an understudied age group in the pandemic. Adaptation of the standardized WHO UNITY protocol enables comparison of the results of this study with other studies that have used the same protocol.

However, this study also had certain limitations. The geographical area of the study was limited to two neighbourhoods of Karachi, Pakistan. Although Karachi is a large multi-ethnic, socio-economically diverse metropolitan city (population 16 million), it is definitely not representative of Pakistan as a whole. The sample size did not allow comparison between the two neighbourhoods. In addition, the rate of household-level refusal — which can result in underestimation or overestimation of prevalence rates — was high. Due to limited supply chain issues for test kits in Pakistan, in-house validation on local samples was not undertaken; however, this was compensated by modelling directly from the data reported by the manufacturer.

Conclusion

Seroprevalence increased in both neighbourhoods over time. Most seropositive cases were reported to be asymptomatic. The probability of an individual being infected following exposure within the same household was high. IFR decreased over time. Finally, serial cross-sectional surveys are valuable to monitor population-level immunity against COVID-19 during the pandemic and post-vaccine era.

Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.03.040.

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