FOREWORD

The prevalence of SARS-CoV-2 at the community level is an especially important indicator of the progression of the COVID-19 pandemic. The seroprevalence of SARS-CoV-2 in public sector patients in Cape Town Metropolitan sub-districts was recently assessed, showing high community positivity rates ranging between 31% and 46%. In light of projections based on the herd immunity effect, these high levels of community infection are likely the main contributor to the decline of the COVID-19 epidemic in the Cape Town Metro.

Given the value of these data, we trust our readers will find this special issue - the 5th in the series- interesting and useful.

Prof Basil Brooke, Editor

SARS-COV-2 SEROPREVALENCE IN THE CAPE TOWN METROPOLITAN SUB-DISTRICTS AFTER THE PEAK OF INFECTIONS

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Summary

In this sentinel surveillance study, residual diagnostic blood samples from women attending antenatal clinics and people living with HIV (PLWHIV) were used to determine the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) seroprevalence in public sector patients in Cape Town Metropolitan (Metro) sub-districts. Using the Roche Elecsys™ anti-SARS-CoV-2 assay on an automated platform, antibodies were present in 1123/2791 (40%) of individuals surveyed. The seroprevalence varied between subdistricts (range 31%-46%), males and females (33% and 42%, respectively), and source populations (42% in PLWHIV and 38% in antenatal women). Using linked reverse-transcription polymerase chain reaction (RT-PCR) data, the coronavirus disease 2019 (COVID-19) case detection rate by RT-PCR among antibody-positive individuals was 4%. The study findings suggest that high level of community infection is likely the main contributor to the observed decline in the epidemic curve in the Cape Town Metro.

Introduction

The global coronavirus disease (COVID-19) pandemic, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), has caused substantial morbidity and mortality, and has resulted in major disruption of economic activities, travel and healthcare systems across the world. In South Africa, the early implementation of a national lockdown and other non-pharmacological interventions (NPIs) slowed the initial spread of the virus,[1] but continued community transmission took root. Cape Town experienced its epidemic peak and subsequent decline in cases earlier than other regions in South Africa.[2] As Cape Town and the rest of the country emerges from the COVID-19 peak, a survey of the true extent of the epidemic may help to guide policy to mitigate against a second wave of infection.

Reverse-transcription polymerase chain reaction (RT-PCR) is the gold standard for acute COVID-19 diagnosis. This method is used to detect viral nucleic acid from upper respiratory tract samples in a relatively narrow infection window,[3,4] and cannot therefore be used to estimate SARS-CoV-2 prevalence at the community level. This limitation was compounded when, following the acceleration phase of the local

epidemic, the testing strategy in the Cape Town Metro limited virological diagnosis only of symptomatic patients at greatest risk of severe disease, further underestimating the true extent of infections.

Serological assays can detect evidence of SARS-CoV-2 infection from 2 weeks[5,6] to several months[7] after the onset of symptoms; a positive result indicates past infection even in the absence of symptoms. Therefore, if used at scale, serology can give better estimates of disease prevalence in a population. For example, population-based surveys conducted in Europe demonstrated a seroprevalence of 10.8% in Geneva, Switzerland, and up to 13.6% in urban 'hotspots' in Spain, with 5% across the whole country.[8,9].

By contrast, it has been anticipated that lower-income countries like South Africa may have experienced a more pervasive epidemic. This is evidenced by relatively high mortality attributed to COVID-19 even though South Africa has a much younger population[10,11] and the curtailment in cases at the height of epidemic occurred as lockdown regulations eased.

The aim of this study was to conduct a SARS-CoV-2 sero-survey of public sector healthcare clients in the Cape Town Metro after the peak of the local epidemic.

Methods

A sentinel surveillance approach was used. The sero-survey was conducted using residual serum and plasma from non-COVID-19 related, routine diagnostic samples over a 21-day period 3 weeks after the peak of lab-confirmed cases. The source of the residual samples was pregnant women who required blood grouping as part of standard antenatal care, and persons living with HIV (PLWHIV) who underwent routine annual viral load monitoring at public sector clinics. A pragmatic consecutive sampling approach was used to retrieve these samples from National Health Laboratory Service (NHLS) laboratories at Groote Schuur and Tygerberg hospitals. Available samples with sufficient residual volume for antibody testing were selected. The study was approved by the University of Cape Town Human Research Ethics Committee and adhered to South African Health Products Regulatory Authority (SAHPRA) section 21 regulations.

SARS-CoV-2 total antibody (IgG and IgM) testing was performed on the Roche Cobas e601 platform using the Elecsys™ anti-SARS-CoV-2 assay (Roche, Geneva, Switzerland) according to manufacturer's instructions. From a local assay validation prior to the study using local RT-PCR positive symptomatic individuals and stored negative sera taken prior to December 2019, we established a sensitivity of 91.2% and specificity of 99,7% (Dr M Naidoo, personal communication). This performance is similar to findings in independent evaluations in Germany[12], Iceland[7] and an evaluation by Public Health England that found a sensitivity of 86.1% (95% confidence interval (CI) 74.8-90.7%) and specificity of 100% (95% CI 99.1-100%) using the same assay.[13] Results were not reported to clinicians or patients, as this was a surveillance exercise and the assay was not approved for diagnostic use at the time of testing. Results were linked to relevant clinical, demographic and laboratory data provided by the Western Cape Provincial Health Data Centre (PHDC) and anonymized before analysis. Seroprevalence was calculated for the study population, stratified by age, sex, sample source and health facility sub-district. A subset of individuals with RT-PCR-confirmed COVID-19 was analyzed in order to infer the number of cases in the Cape Town Metro in the given sentinel population.

Results

The majority (>99%) of the study samples were collected between 15 July and 7 August 2020. The temporal relationship of sampling and epidemic peak is shown in Figure 1. During the study period, the number of average daily reported cases had declined to approximately 700/day, a decrease from 1700/day at the peak of the epidemic in the Western Cape Province. SARS-CoV-2 PCR positivity rate in the Cape Town Metro region was 20-25% among total tests performed during that period. Approximately 60,000 confirmed COVID-19 cases had been reported by the beginning of the sampling period in the Western Cape Province with an average daily mortality of 5 per million.

Antibodies to SARS-CoV-2 were detected in 1287 (39%) of the 3301 samples tested. Of 3301 samples, 510 (15%) were from hospitals and the remainder were from primary care facilities. The seroprevalence in the hospitalised patients was 32%. To limit possible bias introduced by potential clinical COVID-19-related admissions in the hospital samples, we restricted the analyses to the 2791 samples from primary care settings. The demographic and sample source breakdown is shown in Table 1. Notably, 81% were female and 84% were from individuals between the ages of 20-50 years. Despite the intention to include an equal number of antenatal women and PLWHIV, after excluding the hospital patients, the greater number of included samples were from PLWHIV (65%). In addition, some sub-districts (e.g. Khayelitsha, Western) were over-represented in the sample while others were under-represented (e.g. Tygerberg, Northern).

The seroprevalence was higher among PLWHIV than in antenatal women, (42% vs 38%; p<0.001) and higher in women vs men, (42% vs 33%; p<0.001). When stratified by sample source and sex, seroprevalence was still higher in women vs. men among PLWHIV (45% vs 33%; p<0.001) and in female PLWHIV vs. the attendees of antenatal clinics (45% vs 38%; p<0.001). The seroprevalence varied between subdistricts (e.g. ranging from Khayelitsha at 46% to Southern at 31%; Table 1). In general, the subdistricts with higher population densities and higher confirmed incidence of COVID-19 disease and mortality (e.g. Klipfontein and Khayelitsha sub-districts) had higher seroprevalences when compared to those with a lower population density and incidence (Southern and Eastern sub-districts), notwithstanding differences in PCR testing and case detection between sub-districts. Seroprevalence was similar across age strata with overall prevalence in the 20-50 years range of 41% (95% CI 39%-43%). Seroprevalence at the age extremes was slightly lower (36% and 35% for <20 years and >55 years, respectively).

Applying the sensitivity (91.2%) and specificity (99.7%) derived from the local assay validation, the corrected seroprevalence of the study population was estimated to be 44.6% (95% CI 42.6%-46.6%). It has been reported that the magnitude and longevity of the antibody response may be lower in patients with asymptomatic infection.[14] In addition, the assay sensitivity is substantially lower for individuals with recent (<14 days) infection. The impact of a possible further reduction in sensitivity on estimated population seroprevalence is illustrated in Figure 2.

The RT-PCR testing and case detection in the study cohort were also examined using the linked laboratory and clinical data. Overall, 154/3301 (5%) individuals in the sero-survey had documented RT-PCR testing in the public sector. Of the 60 study individuals who were confirmed COVID-19 cases (based on a positive RT-PCR in either the public or private sector), 54 were positive for serology

suggesting a sensitivity of 90%. Among individuals who tested antibody positive in the serosurvey in the primary care setting, only 51/1287 individuals had a linked positive PCR identified by PHDC at least 2 weeks prior to the survey (4% case ascertainment).

Discussion

This is the first SARS-CoV-2 serosurvey conducted in South Africa at time of writing. The high prevalence of SARS-CoV-2 antibodies in public sector patients is in keeping with some international seroprevalence data in settings where a high number of reported cases and/or deaths were reported, for example in Delhi (23.5%)[15] and parts of New York City.[16] The seroprevalence, in part, may explain the post-peak epidemic trajectory in the Cape Town Metro i.e. following the rapid growth of cases in May and early June in Cape Town, the increases slowed and then waned rapidly despite easing of lockdown regulations. We found the seroprevalence to be higher among PLWHIV and in poorer, more densely populated communities. This is likely due to the relative difficulty in observing social distancing in over-crowded areas and associated challenges with implementing NPI measures, leading to substantially higher exposure to SARS-CoV-2 during the epidemic. The higher seroprevalence among women is intriguing. The significant seroprevalence difference between genders recorded here has been observed in very few similar study settings, suggesting either a sampling bias or unique regional epidemiology. The difference in prevalence between women and men remained when analysing only the PLWHIV, suggesting this effect is not due to differential levels of exposure in pregnant women. One hypothesis is that in the Cape Town Metro, the early epidemic which occurred during strict level 5-4 lockdown was primarily driven by super-spreader events among essential workers in the retail and service sectors, the majority of whom, are female.[17] This, however, is unlikely to completely explain the difference and other factors such as increased inter-personal physical contact as a result of child caring or participation in social/religious gatherings need to be explored.[18]

In the subset of patients for whom RT-PCR and clinical data were available, the sensitivity of serology (90%) was similar to that reported in the general validation. However, owing to the restricted PCR testing criteria, these likely reflect only symptomatic cases and the sensitivity of serology testing among asymptomatic individuals remains unclear.

In terms of external validity, several factors can bias the prevalence estimate. The lower serology sensitivity in asymptomatic and recently-exposed individuals, if correct, would mean that the estimates derived in this study under-estimate the true prevalence in the sampled population. However, these two sampling groups, comprising persons from the most vulnerable communities that are at a substantially higher risk of SARS-CoV-2, may not be representative of the greater Cape Town population. The estimate derived from these groups thus likely represents the upper bound of the true population seroprevalence in the greater Cape Town region. Work is ongoing to statistically model these findings to adjust for potential bias and estimate the true underlying population seroprevalence and infection fatality ratio (IFR).

The relatively high seroprevalence in the most vulnerable urban communities ought to provide some reassurance that, in the short term and assuming the population antibody prevalence is a reasonable proxy for population immunity, future resurgences are unlikely to be as severe as the initial epidemic. There likely remain, however, many areas or groups where seroprevalence is much lower, and the risk

of resurgence is greater, underscoring the importance of continued NPIs and heightened COVID-19 surveillance.

Conclusion

These seroprevalence findings support the inference that high levels of community infection contributed to the observed decline in the epidemic curve in the Cape Town Metro at a time when lockdown restrictions were easing and travel, occupational and community interactions were increasing. They also help contextualise the relatively high mortality when compared to global settings, whereby much lower anticipated IFRs due to the younger average age of the local population were offset by more pervasive transmission and higher population attack rates than described in many settings with high mortality but low seroprevalence.

Acknowledgements

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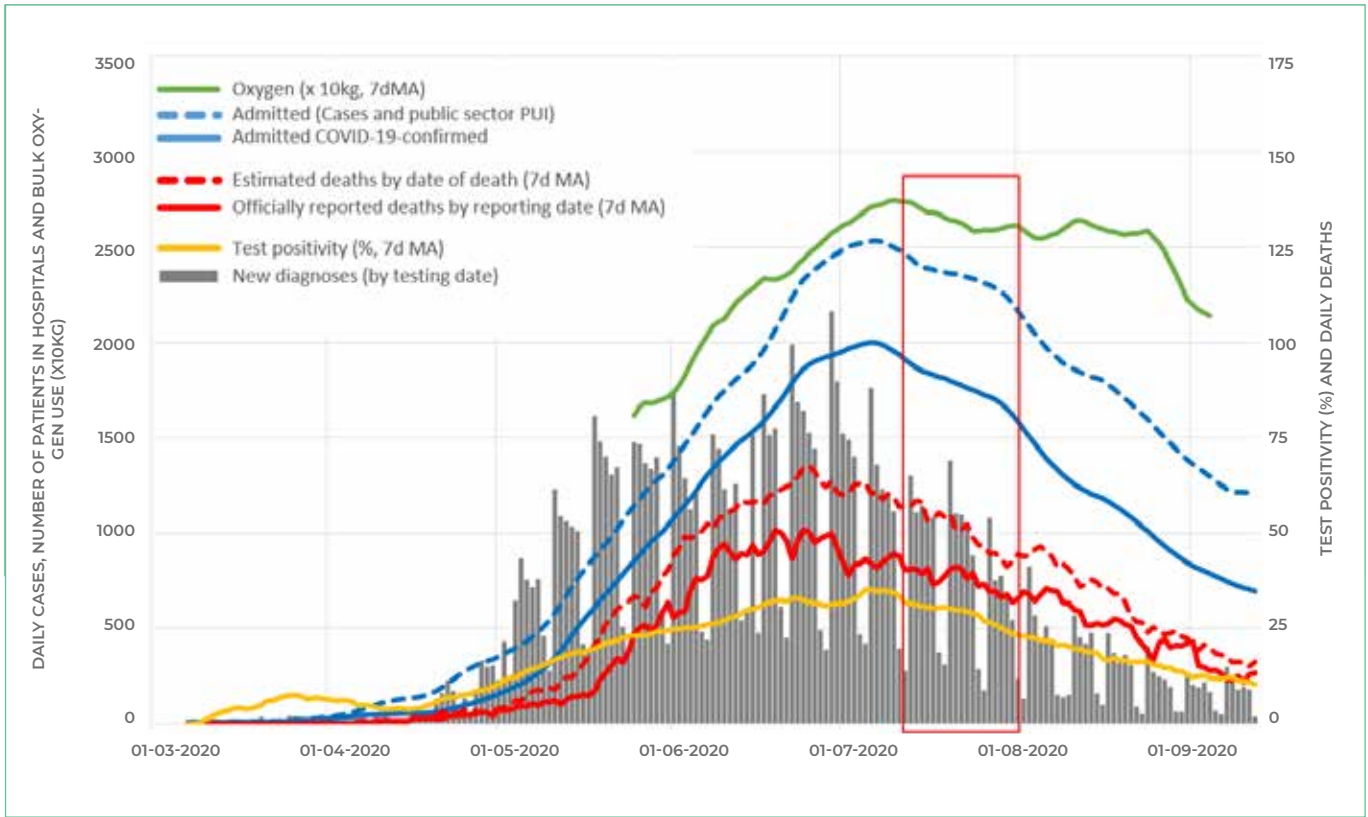
Figure 1. Dates (15 July-7 August 2020) of seroprevalence sampling (in red box) in relation to the various parameters of the COVID-19 epidemic in Cape Town Metro sub-districts. Epidemic curves for the City of Cape Town between March and September 2020 are indicated by new PCR confirmed cases (grey bar), RT-PCR positivity (yellow line), official reported COVID-19 related deaths (solid red line), estimated deaths (dotted red line), reported COVID-19 admission in public sector hospitals (dotted blue line), all COVID-19 admissions (dotted blue line) and bulk oxygen consumption (green line).

Table 1. Summary of the SARS-CoV-2 seroprevalence study sample sources (15 July–7 August 2020), demographic information of individuals and SARS-CoV-2 antibody (Ab) prevalence, Cape Town Metro, South Africa.

	n	SARS-CoV-2 Ab positive	SARS-CoV-2 Ab negative	% positive (95% CI)
All Metro clinics	2791	1123	1668	40.2 (38.4-42.1)
Sex				
Male	518	170	348	32.8 (28.8-36.9)
female	2240	944	1296	42.1 (40.1-44.2)
Source population				
Antenatal	956	359	597	37.6 (34.5-40.6)
PLWHIV	1794	749	1045	41.8 (39.5-44)
Subdistrict				
Khayelitsha	517	239	278	46.2 (41.9-50.5)
Klipfontein	437	196	241	44.9 (40.2-49.5)
Mitchell's Plain	531	224	307	42.2 (38.0-46.4)
Western	500	198	302	39.6 (35.3-43.9)
Northern	161	59	102	36.7 (29.1-44.2)
Tygerberg	161	54	107	33.5 (26.2-40.9)
Eastern	213	70	143	32.9 (26.5-39.2)
Southern	271	83	188	30.6 (25.1-36.2)
Age group				
<20 years	151	54	97	35.8 (28-43.5)
20-50 years	2349	966	1383	41.1 (39.1-43.1)
>50 years	291	103	188	35.4 (29.9-40.9)
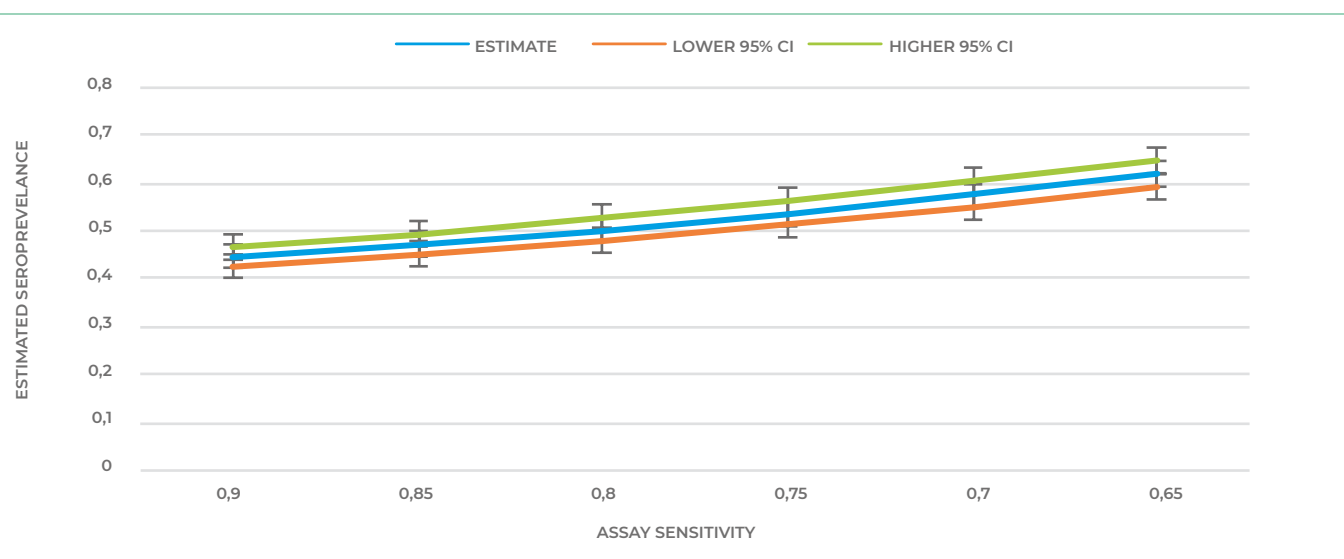
Figure 2. Impact of assay sensitivity reduction on estimated SARS-CoV-2 seroprevalence, Cape Town Metro, South Africa, 15 July-7 August 2020. The blue line represents the adjusted overall study seroprevalence based on the various theoretical sensitivities on the x axis. Estimated serology sensitivity ranged between 65% and 90%, and adjusted seroprevalence ranged between 43% and 62%. The grey and orange lines represent the upper and lower 95% confidence interval of the estimate respectively.