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Abstract

Background: Population-level estimates of the prevalence of anti-SARS-CoV-2 antibody positivity (seroprevalence) are crucial epidemiological indicators for tracking the Covid-19 epidemic. Such data are in short supply, both internationally and in South Africa. The South African blood services (the South African National Blood Service, SANBS and the Western Cape Blood Service, WCBS) are coordinating nationwide surveillance of blood donors.

Methods: Leveraging existing arrangements, SANBS human research ethics committee permission was obtained to test blood donations collected on predefined days (in January and May 2021) for anti-SARS-CoV-2 antibodies, using the Roche Elecsys Anti-SARS-CoV-2 assay on the cobas e411 and e801 platforms currently available in the blood services' donation testing laboratories. Using standard methods, prevalence analysis was done by province, age, time, sex and race.

Results: We report on data from 16762 donations. Prevalence varied substantially across race groups and between provinces, with seroprevalence among Black donors consistently several times higher than among White donors, with the other main population groups (Coloured and Asian) not well represented in all provinces. There is no clear evidence that seroprevalence among donors varies by age or sex. The weighted national estimate of prevalence (in the core age range 15-69 years) is 47.4% (95% CI 46.2-48.6). From January to May, we noted a slight but statistically insignificant increase in seroprevalence in those provinces (Gauteng and Free State) where sufficient data were available to make such an estimate.

Conclusions: Our study demonstrates substantial differences in dissemination of SARS-CoV-2 infection between different race groups and provinces, in patterns consistent with known differences in historically entrenched socio-economic status and housing conditions. As has been seen in other contexts, even such high seroprevalence does not guarantee population-level immunity against new outbreaks, as evidenced by a substantial third wave that has emerged almost contemporaneously with the end of sampling in this study. The relative importance of various contributions to this resurgence (notably viral evolution, waning of antibody neutralization efficacy, and infection control fatigue) are unclear. Despite its limitations, notably a 'healthy donor' effect and the possible waning of detectable antibodies over the time scale of the COVID-19 pandemic, it seems plausible that these estimates are reasonably generalisable to actual population level anti-SARS-CoV-2 seroprevalence. The interpretation of occasional seroprevalence surveys as a proxy for total attack rates, over the ever-lengthening pandemic time scale is likely to become ever more complex. More frequent sampling, including linked repeat observations of frequent donors, could substantially improve the utility of blood donor surveillance.

Introduction

Coronavirus disease 2019 (Covid-19) caused by the virus SARS-CoV-2, manifests in a plethora and range of symptoms, varying from asymptomatic to severe disease which may lead to death. It is this range of severity as well as limited access to health care that makes it difficult to determine how many people have been infected with the virus. After contracting SARS-CoV-2, the majority of people will develop antibodies as part of their immune response. These antibodies last from between 6 and 12 months and can therefore provide an indication of the number of people who have been infected during that time. Given the substantial uncertainties around the true counts of cases of SARS-CoV-2 infection, and prior studies indicating that in many settings the confirmed case count is only a small proportion of all laboratory confirmed infections, it is of ongoing importance to obtain credible estimates of *the prevalence of anti-SARS-CoV-2 antibody positivity* (seroprevalence), at the community level (1,2).

Methods

The South African National Blood Service (SANBS, serving 8 of 9 provinces in South Africa) and Western Cape Blood Service (WCBS, servicing the Western Cape) obtained ethics clearance from the SANBS Human Research Ethics Committee to perform a SARS-CoV-2 seroprevalence study among South African blood donors. The protocol allowed for the testing of routinely collected donor screening samples on predefined 'collection days' in January, March and May; which were internally communicated to blood centre staff at participating collection sites, but without prior notice to potential donors. All donors underwent routine screening through a self-administered questionnaire, one-on-one assessment and a mini-health screening by blood centre staff. Donors who did not meet the routine donor eligibility criteria were excluded from donation and therefore from the study. Contact with persons infected by COVID-19, unresolved COVID-19 infection or COVID-19-like symptoms in the preceding 14 days resulted in temporary deferral of potential donors

Samples collected at the time of donation were tested for anti-SARS-CoV-2 antibodies, using the Roche Elecsys Anti-SARS-CoV-2 total immunoglobulin nucleocapsid assay on the cobas e411 and e801 platforms already in use at the blood services. This assay, according to the package insert, has diagnostic specificity in excess of 99.5%, and near perfect sensitivity (point estimate of 100%) at 16 days post PCR positivity. It detects only anti-nucleocapsid antibodies, and so does not detect antibodies mounted in response to any of the vaccines in use, which only present (and stimulate production of antibodies against) viral spike proteins. We do not here explore various nuances of how to define and estimate test performance characteristics by distribution of cases (defined primarily by severity of infection and time since infection/symptoms/PCR detection), but we note:

- Sensitivity and specificity 'in our hands' was investigated by testing 618 samples from the pre-COVID-19 era (1 marginal false positive precisely at the diagnostic threshold) and 50 samples confirmed as positive in a COVID-19 convalescent plasma study protocol (with 1 false negative).
- For epidemiological interpretation, we take seroprevalence as a close proxy of the prevalence of having been infected with SARS-CoV-2 at some point. The Elecsys Anti-SARS-CoV-2 assay appears to have particularly good durability of antibody detection for months post PCR reversion and symptom resolution, with no evidence of antibody waning and seroreversion over more than four months in a US COVID-19 convalescent plasma cohort (9).

- We ignore, for now, the effects of 1) the donor deferral rule that people with confirmed SARS-CoV-2 infection, or COVID-19-like symptoms, are precluded from donation for a period of two weeks after PCR test and/or symptom resolution, and 2) deferral of regular donors who were in quarantine due to a positive contact, and who therefore skipped their routine donation. Given the high rate of asymptomatic infection, this is a relatively minor limitation.

We did not perform structured sampling in the sense of selecting a subset of donation sites or regions within a province. The study merely observed all consenting donors who happened to present themselves at any donation facility on collection days.

Prevalence was estimated by typical categorical and continuous predictors (age, sex, race and province) by standard methods, using the R platform for statistical computation. Although we are not aware of any biological basis for expecting racial differences – in South Africa, as elsewhere, race is, for historical reasons, a strong correlate of socio-economic status, living conditions, and social circumstances, and therefore a suspected predictor of prevalence. As freely downloadable data sets from Statistics South Africa do not disaggregate sufficiently for our purposes, our provincial weighted seroprevalence estimates are based on population size estimates from Machedze et al (3), interpolated to March 2021, and a racial breakdown of provinces as observed in the 2011 census (4). The level of (dis)aggregation for headline estimates was chosen based on the results of exploratory analysis, as reported below.

Each province was sampled primarily in either January or May, with only Gauteng (GP) and Free State (FS) having a statistically meaningful number of specimens from another month (GP – January, FS - May). To understand the time dimension in our data, we performed a regression in which the data for White and Black donors, from the FS and from GP, was fitted to a model that assigns each of the four subgroups their own prevalence, but with an exponential time dependence that is governed by a single universal rate shared by both provinces and race groups.

Results

The demographic breakdown of the sampled donors is displayed in figure 1 and tabulated in Table 1. There were slightly more male donors (51.2%). The large majority of donors in our study were White (51.4%) and Black (35.6%) with the remainder distributed mainly between donors self-identifying as Asian (4.2%) and 'Coloured' (8.1%) – a uniquely South African racial label indicating persons with a significant mix of ancestry from, amongst other lineages, South Asia, Indonesia, Southern Africa and Europe (5). Only 0.8% did not report a racial identification. Figure 1 shows the age distribution of donors included in the present analysis, further decomposed by race and province. The provincial totals are shown in Table 2.

After categorizing by either broad or narrow age bins in all provinces and the major race groups, there was no association between seroprevalence and age (see Figure 2a and 2b for broad age bins). There was no association between seroprevalence and sex. See Figure 3 for disaggregation by sex, race and province. Therefore, for the remaining analysis, we do not disaggregate by either age or sex. The regression of data from GP and FS against time provided an estimate of a (relative) 1.6% per month growth in prevalence, which, at a p value of 0.3, is not statistically significant, but is large enough (and in the right direction) to be consistent with the crude growth in case detections, in the absence of seroreversion.

Figure 4 shows the seroprevalence estimates by the remaining meaningful disaggregation – race and province. The large difference by both race and province are highly statistically significant as well as epidemiologically meaningful. Note also the race-weighted overall provincial prevalence estimates (which we interpret as provincial ‘attack rates’), and the official prevalence of having been diagnosed, based on reporting of positive PCR diagnostic test results, according to the National Institute for Communicable Diseases (NICD) (6) in the dominant month of sampling: January for the Eastern Cape (EC), Free State (FS), Northern Cape (NC), KwaZulu Natal (ZN); May for Gauteng (GP), Limpopo (LP), Mpumalanga (MP), Northwest (NW), Western Cape (WC). The NICD reports on testing performed both in the private and public sector.

Table 3 shows our provincial estimates of attack rates, as a percentage; the implied number of infections; the number of laboratory confirmed cases according to the NICD (6); and the (multiplicative) discrepancy between our estimate and the official count. Note that our estimated number of infections is conservatively based on our estimated prevalence being applied only to the age group 15-69, so these factors are not quite as large as implied by Figure 4. The estimated seroprevalence ranges from 31.8% in NC to 62.5% in the EC and ranges from 6 (WC) to 26 (LP) fold higher than the official case count.

Discussion

Our study confirms high seroprevalence rates, particularly among Black donors, with little sign of significant population level immunity among other race groups. These substantial differences most likely can be explained by historically based socio-economic factors which hinder the implementation of COVID-19 preventative measures at a community level. The generally high levels of seroprevalence across the whole country are consistent with expectations, given the high burdens experienced on the health care system, and generally low proportion of SARS-CoV-2 infections which present as serious illness.

Previous seroprevalence estimates from South Africa, specifically the WC already found, before the second wave: 1) a very high prevalence (30-40 percent) among pregnant women attending state sector antenatal care, and people living with HIV presenting for routine viral load assessment (7); and 2) higher prevalence among workers with lower socioeconomic status (8). A household cohort study performed in a rural setting in Mpumalanga and an urban setting in North West province found a seroprevalence of 7% (95%CrI 5-9%) and 27% (95%CrI 23-31%), after the first wave of infection, and 26% (95%CrI 22-29%) and 41% (95%CrI 37-45%) respectively after the second wave (10).

For an indication of the meaning of such high seroprevalence values, in a one year old epidemic, consider: a prevalence of 50%, accumulated over 50 weeks, of a condition with a duration of infectiousness of 1 week, implies an average ‘prevalence of infectiousness’ of 1% of the population, with inevitable significant elevations above this average value during peaks. For people reliant on public transport, or working in public spaces, it will be difficult to limit close encounters to fewer than 100 people on any given day – i.e. it will be difficult to encounter fewer than one infectious person per day.

We do not claim that blood donors are perfectly representative of the South African population. Firstly, Black and White donors each account for roughly half the total participants of this study, though South Africa’s population is about 80 percent Black African and only 8 percent White/European (4). Other population groups are generally insignificantly small except Asian in ZN

(about 20%) and Coloured in the WC (about 50%). Of course, our analysis explicitly weights for racial representativeness. The age weighting we adopted to estimate total infections also produces a face value underestimate for population totals, as it assigns no cases in the age range 0-14 years, which accounts for about 30 percent of the population. Furthermore, repeat blood donors (who supply the majority of donations) are pre-selected to have recently been negative for pathogens included in routine blood safety screening. In South Africa this selection for being HIV negative is certainly relevant, given the country's extraordinary HIV prevalence. Communities which are economically stressed, or without ease of access to blood donor centres, will be under-represented among the study population.

Survey dates represented in this analysis are either:

- barely past South Africa's 'second wave' in COVID-19 incidence - whence deferral rules based on confirmed infection or COVID-19-like symptoms should slightly depress seroprevalence estimates relative to 'true' prevalence; or
- shortly before the emergence of the 'third wave' – whence the interpretation of all these samples, as being from a fairly well-defined epidemiological stage, is not entirely unreasonable.

The Elecsys Anti-SARS-CoV-2 antibody assay appears to have particularly good detection sensitivity for months post PCR reversion (9), though there may be some seroreversion. Therefore, while further investigation of the issue of representativeness will clearly need to be done, our estimates are subject to downward bias by at least some obvious considerations.

With due consideration to both the patent and latent limitations of our study, the key observations we wish to make at this point are:

- The particularly high attack rates in majority Black communities points to the limitations, thus far, of non-pharmaceutical interventions in the context of economic deprivation and high population density, and the urgency of making vaccines available in all communities.
- The high seroprevalence (especially amongst Black donors) also raises interesting and important questions about the level of collective immunity thus far obtained through the two primary infection waves to date – but we caution against simplistic interpretations, given that substantial outbreaks have been seen in cities *after* the observation of very high seroprevalence (11), and more recent concerns about vaccine efficacy against new variants.
- The low seroprevalence amongst White donors suggests that predominantly White suburban communities lack meaningful collective immunity, and should take infection control measures very seriously for the foreseeable future, especially at the time of writing, when the third wave is presenting many communities with rapidly increasing incidence.
- Given the relatively low marginal cost of leveraging the infrastructure of the blood services, we are keen to further probe the representativeness of blood-donor-based seroprevalence surveys, and to see to what extent surveillance in the blood services can be a valuable and efficient ongoing activity during major infectious disease outbreaks.

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Conflicts of Interest

The Authors affirm they have no conflicts of interest with regard to this publication.

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Figures/Tables

Figure 1: Age and sex structure of surveyed donors, broken down by race and province (EC-Eastern Cape, FS-Free State, GP-Gauteng, LP-Limpopo, MP-Mpumalanga, NC-Northern Cape, NW-North West, WC-Western Cape, ZN-KwaZulu Natal)

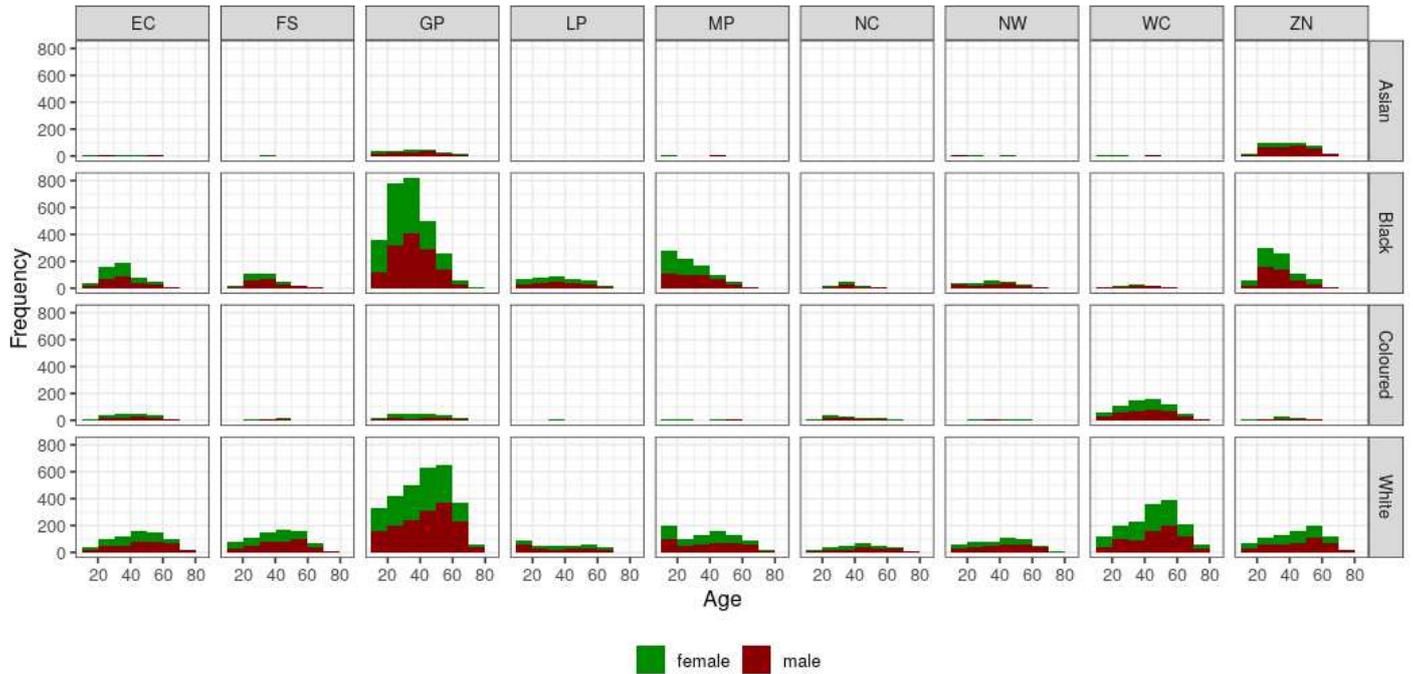


Table 1: The demographic breakdown of the blood donor population.

	Reactive	Non-Reactive	Total	Crude Estimates (%)
Province				
Eastern Cape	569	896	1465	38.8
Free State	289	793	1082	26.7
Gauteng	1988	4216	6204	32.0
KwaZulu Natal	663	1444	2107	31.5
Limpopo	217	494	711	30.5
Mpumalanga	563	1132	1695	33.2
Northern Cape	100	367	467	21.4
North West	202	530	732	27.6
Western Cape	503	1796	2299	21.9
Race				
Asian	156	539	695	22.4
Black	3155	2810	5965	52.9
Coloured	448	908	1356	33.0
Unreported	47	94	141	33.3
White	1288	7317	8605	15.0
Sex				
Female	2567	5611	8178	31.4
Male	2527	6057	8584	29.4
Totals	5094	11668	16762	30.4

Table 2: Total number of donors surveyed by province.

Province	Specimens	Proportion (%)
Eastern Cape	1,465	8.7
Free State	1,082	6.5
Gauteng	6,202	37.0
Limpopo	711	4.2
Mpumalanga	1,695	10.1
Northern Cape	467	2.8
Northwest	732	4.4
Western Cape	2,299	13.7
KwaZulu Natal	2,107	12.6
Total	16,762	100

Figure 2a: Prevalence by age group, broken down by province and race for four provinces (EC-Eastern Cape, FS-Free State, GP-Gauteng, LP-Limpopo)

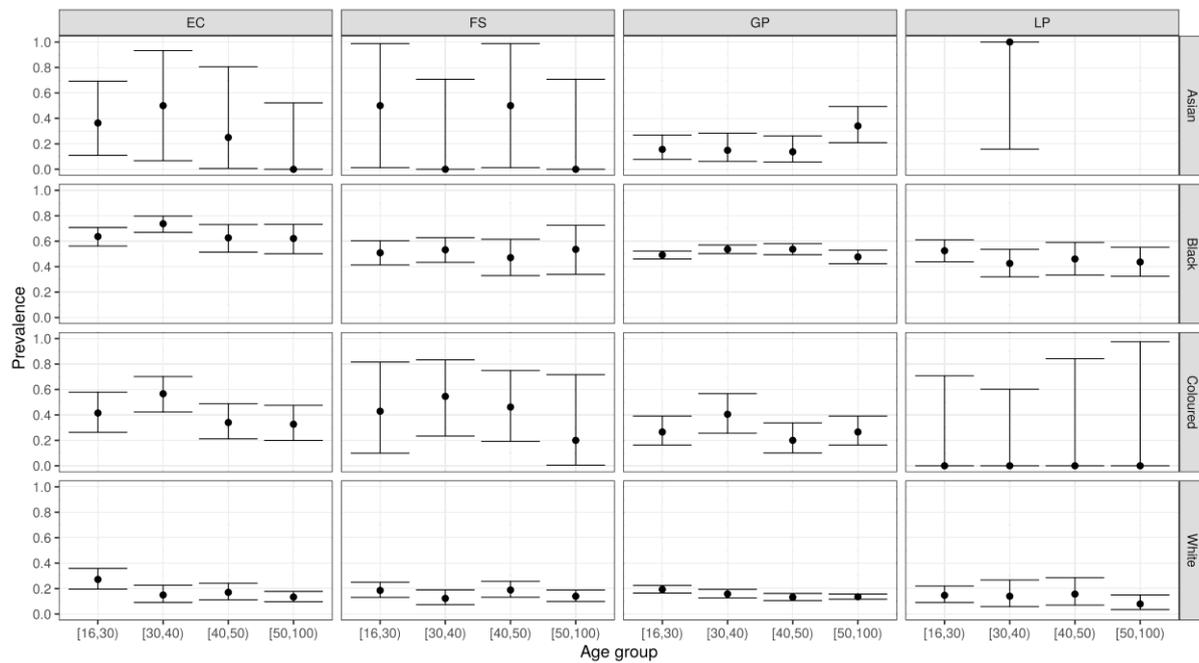


Figure 2b: Prevalence by age group, broken down by province and race for five provinces (MP-Mpumalanga, NC-Northern Cape, NW-North West, WC-Western Cape, ZN-KwaZulu-Natal)

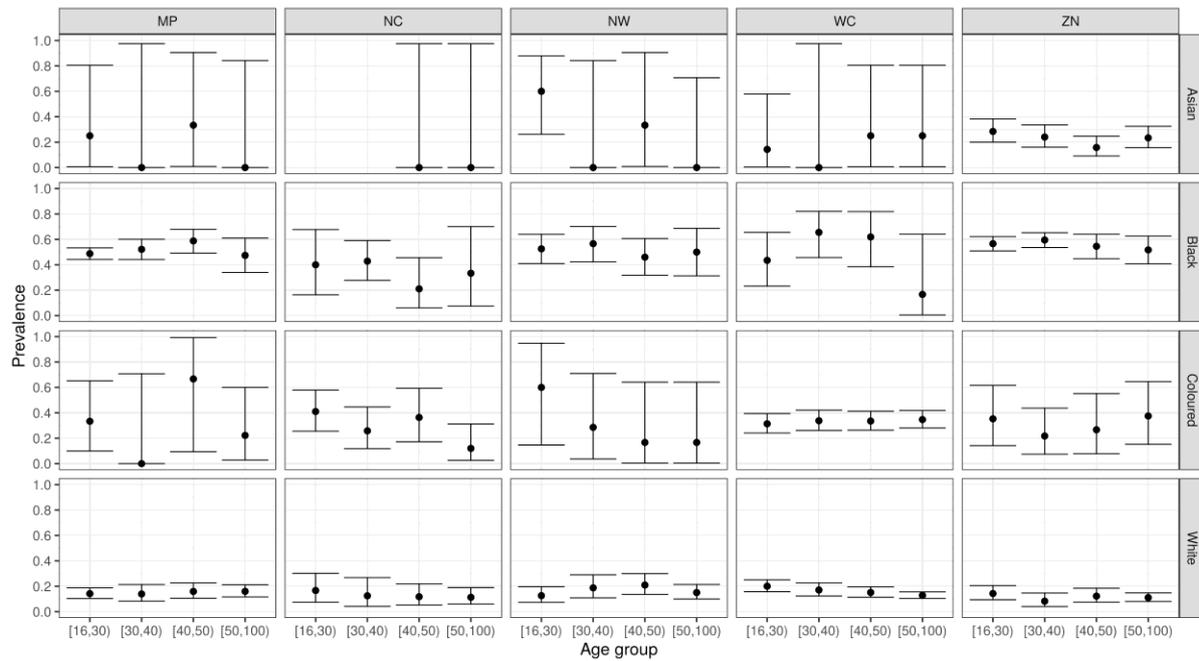


Figure 3: Prevalence comparison between sexes, by race and province (EC-Eastern Cape, FS-Free State, GP-Gauteng, LP-Limpopo, MP-Mpumalanga, NC-Northern Cape, NW-North West, WC-Western Cape, ZN-KwaZulu-Natal)

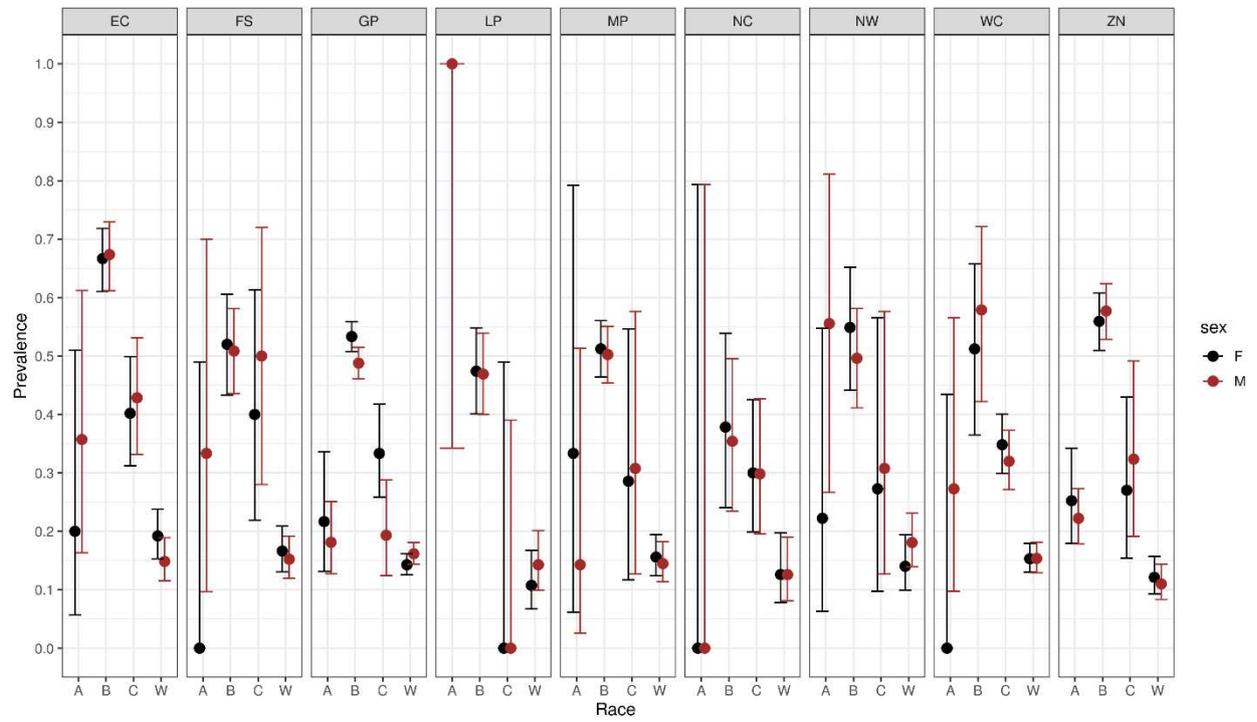


Figure 4: Prevalence by race (W-White, A-Asian, C-Coloured, B-Black) and province (EC-Eastern Cape, FS-Free State, GP-Gauteng, LP-Limpopo, MP-Mpumalanga, NC-Northern Cape, NW-North West, WC-Western Cape, ZN-KwaZulu-Natal), showing also the race weighted provincial estimates (Tot), and the prevalence implied by diagnosed cases reported to the National Institute for Communicable Diseases (Dx).

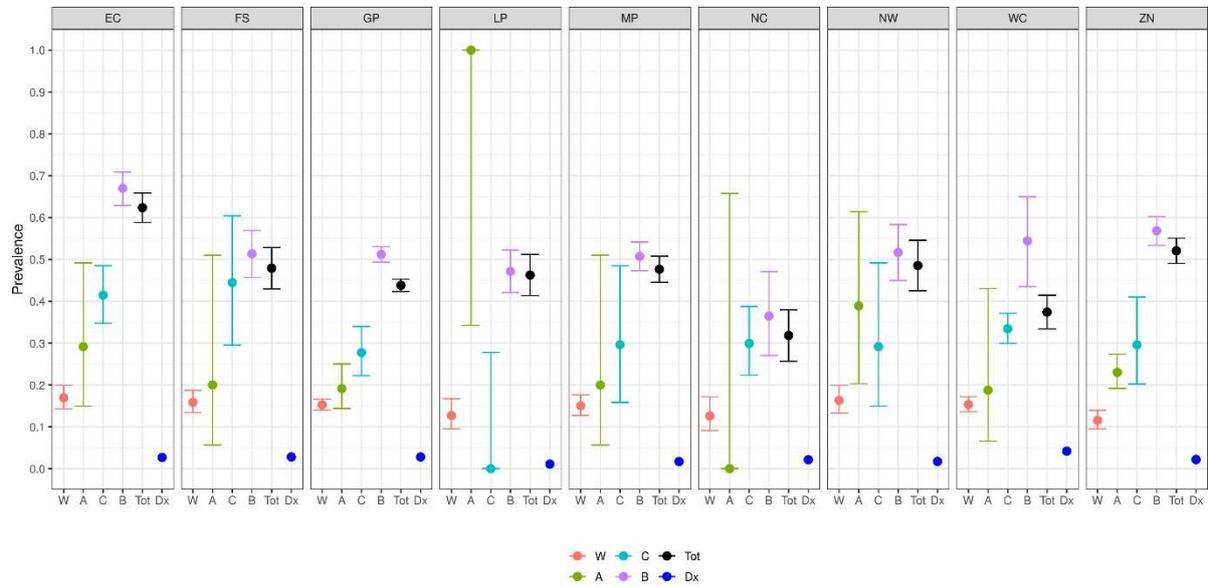


Table 3 Provincial estimates of prevalence; the implied number of infections; the number of laboratory confirmed cases; and the (multiplicative) discrepancy between our estimate and the official count.

Province	Estimated Prevalence (%)	Estimated Total Infections	Official Diagnosed Cases	Diagnostic Underestimate (Fold)
Eastern Cape	62.5 (58.8, 65.9)	2,724,350	176,902	15.4
Free State	47.8 (42.8, 53.0)	925,093	81,622	11.3
Gauteng	43.8 (42.3, 45.4)	4,926,044	434,495	11.3
Limpopo	46.3 (41.3, 51.2)	1,687,558	64,966	26.0
Mpumalanga	47.6 (44.5, 50.8)	1,523,296	81,758	18.6
Northern Cape	31.8 (25.7, 38.0)	235,156	25,007	9.4
Northwest	48.5 (42.5, 54.6)	1,302,318	69,328	18.8
Western Cape	37.4 (33.4, 41.4)	1,855,484	294,201	6.3
KwaZulu-Natal	52.1 (49.1, 55.1)	3,950,784	249,703	15.8