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## COVID-19 in pregnancy in South Africa: Tracking the epidemic and defining the natural history

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## COVID-19 in pregnancy in South Africa: Tracking the epidemic and defining the natural history

South Africa (SA) has seen a rapid increase in COVID-19 infections in recent weeks, with cases exceeding 40 000 in early June and anticipated to escalate rapidly as lockdown is eased. The country also has the largest HIV burden globally, and poor maternal and child health indices in many parts. Although early indications were that COVID-19 infection does not worsen pregnancy and birth outcomes,<sup>[1-4]</sup> recent reports have raised fresh concerns.<sup>[5]</sup> Preterm birth,<sup>[6-8]</sup> neonatal pneumonia<sup>[9-11]</sup> and cases of vertical transmission and postpartum infections have been reported, including in SA.<sup>[1,11-15]</sup> Some maternal deaths related to COVID-19 have occurred, possibly linked to haemodynamic changes immediately postpartum<sup>[2,16]</sup> and/or to the thrombogenic nature of both pregnancy and COVID-19.<sup>[17-19]</sup> Maternal wellbeing in pregnant women with COVID-19 infection is a major concern, as these women often have high anxiety about infecting their newborn child, and may experience challenging interactions with healthcare providers and community stigma.<sup>[2,18]</sup> Most evidence on COVID-19 and pregnancy to date is limited to case series, involves only symptomatic women without HIV, and is almost exclusively from high-income countries. Cohort data across a range of settings and population groups are the only means of fully understanding the natural history, clinical disease spectrum and risks of COVID-19 in pregnant women, fetuses and infants.<sup>[19,20]</sup>

Pregnant women have multiple interactions with the health system, with important implications for SARS-CoV-2 transmission to and from health workers and other patients and to newborns.<sup>[21-23]</sup> One study in New York, USA, for example, performed universal SARS-CoV-2 testing in all women in an obstetric ward. In total, 15% of the 221 women were SARS-CoV-2-positive, and 88% of those who were infected were asymptomatic.<sup>[24]</sup> In another study in Connecticut, USA, 2.9% of ~750 women tested at delivery were COVID-19-positive and asymptomatic.<sup>[25]</sup> It is clear that an infection control strategy and research agenda that includes asymptomatic pregnant women is necessary.<sup>[26]</sup> This editorial describes a set of surveillance and research activities among pregnant women that could provide key evidence to inform the response to COVID-19 in SA.

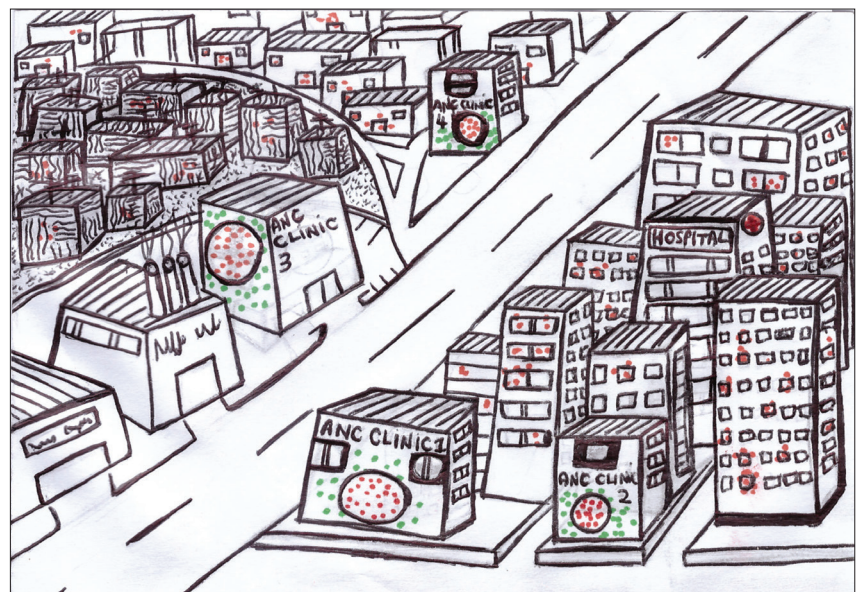
### Sentinel surveillance among pregnant women

Sentinel surveillance of infectious disease among pregnant women is commonly used as an indicator of disease burden at a population level. This approach was used during the height of the HIV epidemic in sub-Saharan Africa and elsewhere to track the epidemic and derive population-based HIV prevalence estimates.<sup>[27-29]</sup> With serial surveys in sentinel clinics one can track population-level incidence, quantify case detection rates and assess the relative effectiveness of different control measures. Identifying infections in pregnant women attending antenatal clinics may allow for timely identification and control of local clusters of infections<sup>[30]</sup> and for evidence-based decisions around lockdown deconfinement in different locales.<sup>[31-33]</sup> Alternative surveillance methods such as household surveys are logistically challenging, costly, often have high refusal rates, have a low yield, and are unable to give local estimates unless sample sizes are considerable.<sup>[34-36]</sup>

COVID-19 surveillance in antenatal clinics may be particularly important in heavily affected provinces and in areas that are densely populated. These include informal settlements and areas with predominantly high-rise apartment buildings, such as

Hillbrow in Johannesburg,<sup>[37]</sup> which may be vulnerable to the kind of outbreaks that occurred in New York City. Similarly, surveillance in SA should prioritise economic hubs with overcrowded informal densely populated settlements that may have poor access to health services and cover a range of geographical areas, including metropolitan hubs in all provinces. Surveillance could neatly be layered onto existing initiatives and collaborations, such as the recently launched hospital-focused Maternal and Perinatal Outcomes of Novel Coronavirus in Pregnancy Study and a national pregnancy exposure registry, planned for implementation in 19 facilities in Gauteng, KwaZulu-Natal and Western Cape provinces.<sup>[38]</sup> Establishing sentinel site pregnancy exposure registries, harmonised across sites and consolidating routine clinical data on pregnancy exposures and outcomes, provides a platform onto which additional surveillance activities such as with COVID-19 can be built as the need arises.

Surveillance activities would need to adopt innovative approaches to COVID-19 testing given the limited availability of testing at present. Pregnant women with symptoms suggestive of COVID-19 would be prioritised for individualised polymerase chain reaction (PCR) testing of nasopharyngeal swabs,



*Proposed sentinel site surveillance of COVID-19 in pregnant women. The figure represents diverse environments including high-rise buildings, informal settlements, RDP (government subsidy) housing and the potential for pregnant women to represent COVID-19 infection within the broader population. (Red dots = COVID-19 infection; green dots = COVID-19-uninfected; ANC clinic = antenatal clinic.)*

as per national guidelines. Pooled testing among asymptomatic pregnant women may be an efficient alternative for diagnosis of acute infection and is increasingly being used in SA and elsewhere.<sup>[39-41]</sup> This approach appears cost-effective up to a prevalence of SARS-CoV-2 of ~10%.<sup>[39]</sup> Nasopharyngeal or serological samples of ~10 women could be 'pooled' into one specimen. If that tests negative, it can be assumed that all 10 samples are negative. If the pooled test is positive, each sample in the pool would then be tested individually to detect the positive case(s). It is anticipated that serological testing will become available shortly and form the mainstay of active surveillance, and until then samples could be stored for later testing. In time, once barriers to COVID-19 testing have been addressed, 'universal testing' of pregnant women, a cornerstone of HIV programmes, may become a key element in COVID-19 control. Since antenatal cohorts represent diverse populations of women, testing of blood routinely collected may also provide opportunity for COVID-19 and other disease screening and testing.

Ideally, serological testing would be performed on serial maternal specimens, cord blood and infant blood to determine immune dynamics, which would have implications both for population seroprevalence and for informing the potential impact of future vaccination strategies. Although widespread sampling falls outside routine practice in public sector health services, practical approaches may be required, including limiting maternal sampling to certain time points, such as delivery, to optimally leverage routine blood tests such as maternal HIV testing and HIV viral load testing at delivery, infant birth HIV-PCR and stored dry blood spots.

## Cohorts of pregnant women with COVID-19

Surveillance in sentinel antenatal clinics offers a unique opportunity to establish population-based prospective cohorts of women and children, which would be the optimal means of defining key COVID-19 epidemiological parameters such as asymptomatic infection rates and case severity.<sup>[20]</sup> These cohorts can also identify signals of adverse maternal or infant outcomes following COVID-19 infection.<sup>[42]</sup> Natural history and birth outcomes could be disaggregated by HIV status, and between women living with HIV who initiate antiretroviral therapy in pregnancy and those on long-term treatment. In this cohort, ideally PCR sampling and serological sampling would be performed serially to determine immune dynamics and antibody kinetics. Here again, superimposing SARS-CoV-2-specific investigations on existing surveillance infrastructure that includes all pregnant women at a facility (such as the National Pregnancy Exposure Registry) could conserve resources and provide appropriate denominators for calculations. These platforms provide an opportunity for testing the performance of health interventions targeting COVID-19 such as therapeutics and vaccines in this important patient group. Then, once these modalities become more widely available, these systems serve to assess the safety of these products post-marketing in pregnant and postpartum women and their infants.

## Conclusions

In summary, surveillance and cohort studies among pregnant and postnatal women and their infants could provide critical information. This includes estimates of COVID-19 infection rates in pregnant women, which are likely to be reflective of the disease burden in the broader community; an understanding of the natural history of COVID-19 in pregnant and postnatal women and their infants; and an assessment of innovative testing strategies such as pooled PCR and serological testing. Additionally, such data could determine whether COVID-19 disease manifests differently in women living with and

without HIV infection. Lastly, this approach would provide a platform to evaluate whether or not pregnant women should be prioritised to be included in COVID-19 therapeutic and vaccine studies because of enhanced concerns about maternal and infant wellbeing. The considerable experience in SA of HIV research and prevalence surveys among pregnant women, together with the pregnancy registry infrastructure being developed, set the scene for a robust COVID-19 surveillance system and nested cohort studies in antenatal clinics.

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