Cross-sectional survey of healthcare utilization and seroprevalence during the COVID-19 pandemic in South Africa

1. Overview

In December 2019, a novel coronavirus (SARS-CoV-2) emerged in Wuhan, China. During the first few months of 2020, the virus rapidly spread throughout the world resulting in the WHO declaring a pandemic on 11th March 2020. In South Africa, the first case of Coronavirus disease 2019 (COVID-19), the respiratory disease caused by SARS-CoV-2, was detected on 5th March 2020. Factors prevalent in South Africa such as malnutrition, HIV, tuberculosis and limited access to healthcare, among others, may impact both transmission dynamics and disease progression associated with SARS-CoV-2 infection as well as the burden on the healthcare system and society.

We will conduct cross-sectional community surveys in three communities serviced by facilities where severe respiratory illness (SRI) and influenza-like illness (ILI) surveillance is conducted in South Africa (Mitchell's Plain, Pietermaritzburg and Klerksdorp) after the first wave of SARS-CoV-2 circulation in each location to explore the healthcare seeking behavior for and cost of respiratory illness during the pandemic and to estimate SARS-CoV-2 community seroprevalence and the COVID-19 knowledge, attitudes and practices (KAP) of the selected communities. This will be achieved through the implementation of a community healthcare utilization survey (HUS) coupled with a costing study, a KAP study and sero-survey study. The study will complement data from inpatient and outpatient syndromic surveillance conducted in the same target communities to document the clinical spectrum of illness, including the proportion of asymptomatic, mild, severe and fatal cases, both medically and non-medically attended.

Study participants will be identified using randomly selected GPS coordinates to identify households located in the catchment areas of the site hospitals. Field workers will administer structured questionnaires with the primary caregiver of the household ((i) household demographic information and the economic effect of COVID-19 mitigation measures on the household, (ii) knowledge, attitude and practices related to COVID-19 and (iii) symptoms of household members over a pre-defined period), and a healthcare utilization and costing questionnaire for each individual member of the household who reported a respiratory illness. The questionnaires will probe for mild or severe respiratory illness during a pre-established period (influenza-like illness in (i) previous 30 days and (ii) since March 2020, and severe respiratory illness since March 2020) and ask about their health-seeking behaviour and associated costs during any reported respiratory illness. For the sero-survey, blood will be collected from each individual in the household among a selected subset of households and tested for SARS-CoV-2 antibodies and HIV.

2. Investigators

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3. Background

On 31st December 2019, the World Health Organization (WHO) was alerted to a cluster of pneumonia cases of unknown etiology in patients in Wuhan City, Hubei Province of China. One week later, on 7th January 2020, Chinese authorities confirmed that they had identified a novel (new) coronavirus as the cause of this pneumonia[1]. The novel coronavirus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses due to its genetic similarity (different strain of the same species) to the severe acute respiratory syndrome coronavirus (SARS-CoV) that emerged in 2002[2]. The disease associated with SARS-CoV-2 has been named by WHO as COVID-19 (for coronavirus disease 2019)[3].

Initially person-to-person transmission was not apparent, and the majority of the cases were epidemiologically linked to a seafood, poultry and live wildlife market (Huanan Seafood Wholesale Market) in Jianghan District of Hubei Province. Available evidence, and experience from the SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) suggested that the novel coronavirus has a possible zoonotic origin[1,4]. However, the number of cases continued to increase rapidly, and evidence of person-to-person transmission mounted in travellers diagnosed with SARS-CoV-2 who had visited Wuhan[1]. Given its rapid spread globally, WHO declared that the outbreak of COVID-19 meets the criteria for a pandemic on 11th March 2020[5]. By 1st October 2020 more than 33 million cases and more than 1 million deaths have been reported globally. The body of evidence gained thus far suggests that older individuals and those with underlying medical conditions such as diabetes, hypertension, asthma, chronic heart disease are at increased risk of severe illness (i.e., hospitalization and death); whereas children and young adults appear to be less prone to develop severe illness following SARS-CoV-2 infection. However, rare cases of multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2 infection in children and adolescents have been reported [6,7].

The South Africa National Department of Health (NDoH) activated the Emergency Operation Centre (EOC) on 31st January 2020. The first positive case of SARS-CoV-2 infection in South Africa was reported on 5th March 2020 from a patient in KwaZulu-Natal. A state of disaster was declared in South Africa on 16th March 2020. As of 1 October 674,339 laboratory-confirmed cases have been identified. The pandemic and resulting mitigation measures are likely to have consequences on healthcare. Access to prevention, care or treatment during the pandemic may be affected by lockdown measures, closing of healthcare facilities as a result of staff infections, reluctance to visit a healthcare facility or economic circumstances of households. Results from wave 1 of the National Income Dynamics Study (NIDS) - Coronavirus Rapid Mobile Survey (CRAM), which surveyed approximately 7000 individuals nationally between May and June 2020, showed that 23% of respondents were unable to access medication, condoms or contraception in the past four weeks, 96% of those that needed to see a healthcare worker for a chronic condition were not able to, and of those that needed care for an acute condition only 78% visited a healthcare facility[8].

Healthcare utilization surveys (HUS) are useful to characterize the healthcare utilization patterns for diseases of interest. They have been used to complement sentinel surveillance by allowing assessment of the sensitivity of a surveillance system and adjustment of facility-based surveillance data to estimate disease burden within the community [9,10]. Understanding healthcare utilization in a community helps to

characterize healthcare seeking behavior, access to healthcare and improve the interpretation of surveillance data. In a HUS conducted in 2012 in Soweto and Klerksdorp communities in South Africa, for approximately one-third of all illnesses, the individual did not seek care[11]. In a HUS conducted in Pietermaritzburg in 2013, 35% of deaths in the previous year occurred at home, and were therefore missed by facility-based surveillance[12].

NICD has conducted sentinel syndromic surveillance for severe respiratory illness (SRI) and influenza-like illness (ILI) in five provinces of South Africa since 2009. In March 2020, surveillance samples have been additionally tested for SARS-CoV-2. However, in order to accurately interpret this data, it is important to understand the healthcare utilization patterns of the communities within the catchment populations of these sentinel sites and adjust the COVID-19 incidence obtained from facility-based surveillance to obtain a better measure of the burden of disease. In addition, the urgent need for community surveys combined with sero-epidemiological data in order to understand community-level incidence, the spectrum of disease and the degree of herd immunity has been highlighted[13].

Molecular diagnostic tests were rapidly developed in response to the novel virus. PCR-based tests, currently being used to diagnose SARS-CoV-2 infection worldwide, identify the presence of viral genomic material, and therefore are only able to identify individuals who are currently infected. Individuals who had asymptomatic infection[14], or mild illness without accessing healthcare, are not likely to have been tested resulting in an underestimation of the burden of the pandemic. Preliminary data has shown that 70-80% of individuals infected with SARS-CoV-2 may be asymptomatic[15,16]. Serological tests, which measure an individual's antibody response to infection, can therefore estimate the number of past infections, track the epidemic progression and have the potential to inform public health decisions such as the effectiveness of physical distancing measures during the COVID-19 pandemic. Current evidence indicates that antibodies to SARS-CoV-2 develop within 29 day's post-onset of symptoms, depending on the severity of disease[17–21]. Based on a serological study (using antibodies to SARS-CoV-2 nucleocapsid protein) of 342 sequential serum samples from 65 patients at different stages of disease progression, IgM appears at approximately 7 days after illness onset, increases until 28 days, after which the quantity declines rapidly. IgG appears at approximately 10 days after illness onset and persists for at least 49 days (at which time the study was concluded)[22]. The antibody response also appeared earlier and titers were higher in severe cases compared to non-severe cases. In another study of 258 patients with COVID-19, all patients tested positive for IgG within 19 days of symptom onset[19]. IgG antibodies from patients with Severe Acute Respiratory Syndrome (SARS) infection were found up to 2 years after recovery [23], however the duration of SARS-CoV-2 antibodies following infection in one study showed a decline after three months following onset of symptoms[19].

A seroprevalence study conducted in California early in the epidemic found that the SARS-CoV-2 seroprevalence was between 2.5% and 4.2%, and indicated that the number of infections was 50 to 85-fold greater than the reported number of cases for that area[24]. In a cross-sectional study for SARS-CoV-2 antibodies among 100 individuals in an outpatient setting in Kobe City, Japan, the seroprevalence was 3.3%, 396 to 858-fold higher than the number of PCR-confirmed cases[25]. In Gangelt, Germany among

500 individuals tested, the seroprevalence was found to be 14% while only 2% were found to have active viral infection by PCR[26].

Mitigation measures such as lockdown and social distancing are highly dependent on behavioral changes and the co-operation of the community. KAP studies are used to identify knowledge gaps, cultural beliefs, and behavioral patterns in order to guide the design and implementation of interventions. KAP surveys have been carried out previously in South Africa to understand factors associated with unwillingness to receive influenza vaccination in order to improve uptake[27]. COVID-19 KAP community surveys have been conducted in other countries such as the Phillipines[28], Malaysia[29] and United States[30] in order to guide preventative measures. In Malaysia, the KAP survey among 4850 individuals highlighted the need for consistent messaging from health authorities and tailored education programs. Costing studies are useful to understand the economic impact of illness and mitigation measures on households and the community. Understanding the knowledge, attitudes and practices, as well as the economic burden of COVID-19 in South African communities, is important to plan effective health messages and interventions for an effective response to future waves of COVID-19.

4. Justification and aim of the study

Understanding community healthcare utilization, KAP and economic burden on households associated with the COVID-19 pandemic is key to guide containment and mitigation measures in local settings and globally. In addition, understanding the disease burden of COVID-19 and groups at increased risk of severe COVID-19 is key to inform mitigation guidelines for ongoing and potential future epidemics. Factors prevalent in Africa such as malnutrition, HIV, tuberculosis and limited access to healthcare may impact both the transmission dynamics and disease progression associated with SARS-CoV-2 infection as well as the burden on an already stressed healthcare system and the society. In particular, HIV infection has been associated with >5-fold increased risk of severe illness (including death) associated with respiratory infections such as influenza and respiratory syncytial virus and this may also be true for SARS-CoV-2 infection. According to Statistics South Africa, in 2017 the overall national HIV prevalence in the general South African population was estimated to be 14.0%, translating to an estimated 7.9 million people living with HIV. There is limited information on COVID-19 in HIV-infected individuals, however preliminary data indicates that individuals with HIV infection may have an increased risk of severe outcomes [32,33].

The NICD conducts prospective syndromic sentinel surveillance for severe respiratory infection (SRI) and influenza-like illness (ILI) at six hospitals and three clinics in three provinces (Edendale Hospital and Edendale Gateway Clinic in KwaZulu-Natal, Klerksdorp Hospital, Tshepong Hospital and Jouberton Clinic in North West Province and Red Cross Children's Hospital, Groote Schuur Hospital, Mitchell's Plain hospital, Eastridge Clinic and Mitchell's Plain Clinic in Western Cape Province). Surveillance officers review the clinical details of all admitted patients to identify cases for inclusion in sentinel surveillance, and consenting patients complete a questionnaire about medical history and clinical data and provide a respiratory specimen which is tested for viruses including influenza and, since March 2020, SARS-CoV-2. However, facility-based surveillance programs only capture individuals presenting to the facilities and who had a test for SARS-CoV-2 and therefore will only represent a proportion of the disease and will not

include asymptomatic infection. In order to interpret the sentinel surveillance data and estimate the true burden of COVID-19 at the community level, it is important to understand patterns of healthcare utilization in the catchment areas for these healthcare facilities.

While PCR provides a highly sensitive and specific diagnostic tool, essential for case identification, contact tracing and patient management, reliance on this method alone is likely to under-estimate the true burden of the virus. Individuals with asymptomatic infection or mild illness are less likely to be tested, and PCR would not detect convalescent cases due to its reliance on detection of viral material. Understanding the under-ascertainment of infections is important to provide a better estimate of the prevalence of infection and the case-fatality ratio for COVID-19, in order to guide control measures.

Serology testing for SARS-CoV-2 is important in order to better quantify the number of COVID-19 cases, including those that may have been asymptomatic or recovered without having been tested. Public health action is guided by the incidence of infection, and therefore understanding the full burden of infection and potentially immunity, is important. As SARS-CoV-2 is a novel coronavirus, the initial seroprevalence in the population can be assumed to be negligible. Surveillance of antibody seropositivity in the South African population will therefore allow inferences to be made about the extent of infection in the community.

We aim to characterize healthcare utilization behaviors related to COVID-19 and estimate, by triangulation with facility-based surveillance data, the community burden of disease by conducting cross-sectional household surveys following the first wave of the pandemic in three communities served by the sentinel surveillance sites (Mitchell's Plain, Pietermaritzburg and Klerksdorp). We additionally aim to conduct a serological survey, nested within the HUS, to estimate the number of people previously infected with SARS-CoV-2, and thereby the community infection rate of disease. This study, coupled with data from facility-based surveillance, will provide information on the spectrum of disease including the fraction of mild or asymptomatic infections that did not require medical attention. The information obtained from the HUS, the sero-survey and estimates of medically attended illness will be triangulated to estimate the number of medically and non-medically attended, mild, severe-non-fatal and fatal illness and potentially the asymptomatic fraction by HIV-infection status. This will be done using approaches previously developed for influenza in South Africa[34].

5. Objectives

In three communities in South Africa, Klerksdorp North West Province, Pietermaritzburg KwaZulu-Natal and Mitchells Plain Western Cape, address the following:

Primary objectives:

1. Characterize healthcare seeking behavior for respiratory illness during the first wave of the COVID-19 pandemic
2. Determine the proportion of mild and severe respiratory illnesses that were not medically attended during the epidemic period

3. To estimate the household and community economic burden of respiratory illness during the first wave of the epidemic
4. To describe the economic impact of mitigation measures on households during the first wave of the epidemic
5. Describe knowledge, attitudes and practices related to COVID-19 in the community, including prevention
6. Determine the seroprevalence of antibodies to SARS-CoV-2 following the first wave of the pandemic, by age group and HIV-infection status.

Secondary objectives:

7. Provide a more accurate estimate of the burden of COVID-19 in the community by adjusting facility-based surveillance data for healthcare seeking behavior
8. Assess the sensitivity of sentinel surveillance for COVID-19 at each site
9. Identify risk factors for SARS-CoV-2 infection including age, HIV infection and underlying illnesses
10. To estimate the SARS-CoV-2 infection case-fatality ratio through triangulation with COVID sentinel surveillance and mortality data
11. Determine the seroprevalence of antibodies to other respiratory viruses such as influenza, respiratory syncytial virus and other human coronaviruses

6. Methods

6.1 Study definitions

- Household - individuals who live in the selected household at least one night every week, excluding guest and temporary visitors. A household may be located in a housing unit or in a set of collective quarters.
- Head of household – person self-identified or identified by other household members to be the head of the family and person in authority
- Primary caregiver – person that is self-identified or identified by members of the household as knowing the most about the health of members of the household and is most involved in the daily care of the household members.
- Influenza-like illness (ILI) - sudden onset of fever or worsening of fever (measured temperature ≥38C or subjective) with cough (i) within the last 30 days and (ii) since beginning March 2020
- Severe respiratory illness - diagnosis of pneumonia by a healthcare worker, or sudden onset or worsening fever (measured temperature≥38C or subjective) and cough and difficult breathing lasting 2–30 days, since beginning March 2020.
- Death – death from any cause since beginning March 2020

6.2 Study Design

Following the first epidemic wave of COVID-19, we will conduct cross-sectional surveys of randomly selected households in the catchment areas of three sentinel surveillance sites located in Mitchell's Plain (Mitchell's Plain Hospital), Pietermaritzburg (Edendale Hospital) and Klerksdorp (Klerksdorp-Tshepong Hospital Complex) using a one-stage cluster design. We will visit households to administer questionnaires to collect information on (i) household demographic information, symptoms of household members over a pre-defined period and the economic effect of social distancing measures and movement restrictions on the household, (ii) household knowledge, attitude and practices to COVID-19, and (iii) individual healthcare seeking behavior for any reported respiratory illness and associated costs.

Nested within the survey, we will conduct a sero-survey. One-third of households selected for the HUS will be randomly selected for inclusion in the sero-survey. Blood will be collected from all individuals in these households and testing for antibody response to SARS-CoV-2, as an indication of prior infection. Blood specimens will also be tested for HIV infection. Should funding be available, we plan to conduct repeat sero-surveys at later time points to monitor the evolution of the pandemic and SARS-CoV-2 antibody responses over time. This will include repeat HIV (for previously HIV-negative individuals) and viral load testing.

The end of the first epidemic wave in each community will be approximated through modelling projections and monitoring of COVID-19 surveillance data at each of the respective sentinel sites.

6.3 Study population and setting

Individuals from randomly selected households in the catchment areas for three SRI/ILI surveillance sites located in Mitchell's Plain (Mitchell's Plain Hospital, Mitchells Plain Clinic and Eastridge Clinic), Pietermaritzburg (Edendale Hospital and Edendale Gateway Clinic) and Klerksdorp (Klerksdorp Hospital, Tshepong Hospital and Jouberton Clinic).

Pietermaritzburg is the provincial capital of KwaZulu-Natal Province. The area is urban and situated approximately 80 km from the coastal city of Durban. SRI surveillance is conducted at Edendale Hospital, a large regional public hospital and outpatient ILI surveillance is conducted at Edendale Gateway Clinic. Klerksdorp is an urban site located in North West Province, in which SRI and ILI surveillance are conducted at Klerksdorp-Tshepong Hospital Complex and Jouberton Clinic, respectively. Cape Town is the second most populous city in South Africa, and the capital of the Western Cape Province. SRI surveillance in the province is conducted at Mitchell's Plain Hospital, and ILI surveillance at Eastridge and Mitchell's Plain clinics.

6.4 Eligibility criteria

Inclusion criteria: Individuals of all ages that lived in recruited households since 1st March 2020, irrespective of prior confirmed or suspected SARS-CoV-2 infection.

Exclusion criteria: A household will be excluded if the head of the household/primary caregiver is unavailable after three visits by the interview team on separate days or times, or declines participation in the study. All individuals with unknown residence or residence outside of the catchment area will be excluded.

6.5 Selection of households

Households will be identified by the NICD prior to the commencement of the study using randomly selected GPS coordinates in each community. Catchment areas for the surveillance sites in Klerksdorp and Pietermaritzburg have been defined in previous studies[11,12]. The catchment area for Mitchell's Plain will be obtained from the Western Cape Department of Health. The boundaries of each catchment area will be delineated on aerial maps available from Google Earth or the local municipality. Non-residential areas such as parks, industrial areas and sports complexes will be excluded. Geographic coordinates will be randomly selected within study area. In township areas, we will use aerial images of the townships, available from Google Earth or the local municipality, to create polygons corresponding to the townships. Within each township polygon, we will randomly sample geographic coordinates where the number of coordinates is proportional to the population of the township. The household closest (within 30 meters) to each random geographic coordinate will be selected for the survey. If there are multiple dwellings equidistant from the randomly selected coordinate, the survey team will systematically select one household. If no dwelling exists within 30 meters around the GPS point, the point will be considered invalid. In case a household needs to be replaced, an additional list of households will be prepared, and replacement households will be visited according to the order on the list (not by convenience).

Site teams will visit each selected household up to three times on separate days or times including evenings and Saturdays as needed to interview the primary caregiver in each household.

6.6 Sample size

The sample size for the HUS was calculated using a one-stage cluster sampling design, with a 95% confidence interval, 10% precision, a 50% (resulting in maximum sample size) expected healthcare seeking among individuals reporting a severe respiratory illness within a predefined period of time in the community and a 1.5 design (household cluster) effect. The total sample size for this study, using the above-mentioned assumptions will be 144 individuals reporting a severe respiratory illness in the selected households. Based on data obtained from population-based hospital surveillance and the use of healthcare utilisation surveys previously conducted in the target communities, the annual cumulative incidence of severe respiratory illness in these communities is estimated to be 2 per 100 population; hence 7,200 individuals (i.e., 144/0.02) will be interviewed in each community to obtain the desired number of individuals having experienced severe respiratory illness in the given community. Assuming an average household size of 3 members, 2,400 households will be enrolled in each community. We will account for a 20% household refusal during random selection of households[11]. Mild respiratory illness is more common than severe respiratory illness hence the sample size calculated for severe respiratory illness would be in excess of that needed for the estimation of the healthcare seeking behavior among individuals reporting severe respiratory illness with the same desired precision.

Nested within the HUS we will implement a sero-survey among randomly selected households visited within the HUS. The sample size is calculated for a one-stage cluster sampling design (i.e., households randomly selected within those selected for the HUS and sera collected from all household members). The sample size is calculated for a 95% confidence interval, a 5% desired absolute precision, a 30% expected SARS-CoV-2 seroprevalence and a 1.5 design (household cluster) effect within 3 age groups: 0-18, 19-39 and ≥40 years. Because of the cluster design of this study we applied the required sample size (484 individuals) obtained using the above-mentioned assumptions to the age strata least represented in the target communities. In the target communities the proportion of individuals in the three selected age strata is 55% for individuals aged 0-18 years, 24% for individuals aged 19-39 years and 21% in individuals aged ≥40 years. Hence, the total sample size will be 2,304 individuals (i.e., 484/0.21) in each community. Assuming an average household size of 3 members, 770 households in each community will be randomly selected for enrollment in the sero-survey. We will account for a 20% household refusal during random selection of households.

Table 1. Sample size for HUS and sero-survey

	Sample size for HUS		Sample size for serosurvey	
	Minimum required	**Total, including 20% refusal rate**	**Minimum required**	**Total, including 20% refusal rate**
Number of individuals per site	7,200	9,000	2,304	2,880
Number of households per site	2,400	3,000	768	960
Total number of individuals	**21,600**	**27,000**	**6,912**	**8,640**
Total number of households	**7,200**	**9,000**	**2,304**	**2,880**

6.7 Data collection

Structured questionnaires (Appendix 2) with closed-ended and open-ended questions will be translated, piloted and pre-tested prior to being administered to the respondent by the field team. The field team will consist of at least two fieldworkers including a trained nurse/phlebotomist and data capturers that are fluent in English and the local language (Tswana in Klerksdorp, isiZulu in Pietermaritzburg and Afrikaans and Xhosa in Mitchell's Plain). Fieldworkers that are appropriately skilled and experienced in surveys and sample collection will be recruited and trained on study-specific standard operating procedures. There will be ten fieldworker teams at each site, who will each aim to enroll 3-4 households per day. Each team will have a dedicated motor vehicle to transport the team members and supplies. The interview will be administered by the interviewer who will complete the responses on a tablet.

For each household, the primary caregiver will be interviewed to collect information on (i) household demographics, (ii) COVID-19 related KAP and (iii) symptoms experienced by household members. If the primary caregiver identifies a household member who incurred mild or severe respiratory illness during

a pre-established prior to the interview period (past 30 days and since March 2020 for ILI, or since March 2020 for SRI), the household member will be interviewed for individual-level healthcare seeking behavior and associated costs if she or he is available. If the household member is aged <18 years, information will be obtained from the child's parent/guardian. If the household member is not available, information about that household member's illness will be obtained from the primary caregiver. During the interview, participants will be asked to provide information on underlying illnesses including tuberculosis (current and previous), asthma, diabetes, chronic heart disease, chronic lung disease, hypertension and cancer, to be assessed as a risk factors for COVID-19 infection and disease severity. The height and weight of participants will be measured in order to calculate body mass index (BMI) and identify obesity. The table below provides the list of forms used for household enrollment and the HUS.

The KAP survey will be administered to the primary caregiver. The primary caregivers will be asked to complete a questionnaire to assess knowledge of prevention, transmission and practice of COVID-19, and where primary caregivers obtain their information on health-related matters.

In the case of an illiterate person, the information sheet will be read to the individual by a person selected by him/her that is independent of the study, such as a family member. We will confirm the individual's comprehension of the study with a standard set of questions. The person selected by the participant will sign consent on behalf of the individual. This process will be documented.

Table 2. Summary of study questionnaires

QUESTIONNAIRE	PURPOSE	RESPONDENT	LEVEL OF DATA COLLECTED	MINIMUM REQUIRED SAMPLE SIZE
Healthcare utilization survey				
Record of household visits		Enumerator	Household	7,200
Introduction and identifying the head of household/primary caregiver		Any member of the household (≥18 years)	Household	7,200
Record of consent for primary caregiver		Household head/primary caregiver	Individual	7,200
General household demographics and socioeconomic information	Understand demographic and socioeconomic characteristics, including risk factors including questions on how COVID-19 has affected the household.	Household head/primary caregiver	Household	7,200
Knowledge, attitudes, and practices relating to COVID-19	Explore the household's understanding, knowledge,	Household head/primary caregiver	Household	7,200

	attitudes and practices towards COVID-19			
Household screening form	Identify members of the household, underlying illness, and individuals that had a respiratory illness	Household head/primary caregiver	Household	7,200
Record of consent for household members who had a respiratory illness ● Consent for adults and children ● Assent for children		Individual who had respiratory illness as identified in screening form[1]	Individual	~432[2]
Healthcare utilization and costing	Explore health-seeking behaviour during any reported illness and estimate the out-of-pocket expenditure incurred by individuals, including direct expenditure for health services as well as indirect expenditure to access services, e.g. travel costs and lost income, for medically and non-medically attended, respiratory illness	Individual who had respiratory illness as identified in screening form[3].	Individual household members who had respiratory illness as identified in screening form	~432[4]
Mortality questionnaire	Identify medically and non-medically attended deaths as a result of respiratory illness	Household head/primary caregiver	Individual household members	~9[5]-
Sero-survey				
Record of consent for serosurvey blood draw • Consent for adults • Assent for children	Estimate the community attack rate of SARS-CoV-2 in communities of South Africa following the first wave of the epidemic.	All household members	Individual household members	6,912

[1] If the individual is less than 18 years of age, or unavailable, this questionnaire will be answered by the parent, guardian, household head, or primary caregiver on behalf of the household member who incurred mild or severe respiratory illness during a pre-established period prior to the interview period.

[2] Assumes prevalence of SARS-COV-2 is 2%. Does not account for prevalence of other respiratory illness.

[3] If the individual was less than 18 years of age, or unavailable, this questionnaire will be answered by the parent, guardian, household head, or primary caregiver on behalf of the household member who incurred mild or severe respiratory illness during a pre-established period prior to the interview period.

[4] Assumes cumulative incidence of SARS-COV-2 is 2% in community and does not account for other respiratory illness.

[5] Assumes mortality rate for SARS-COV-2 is 2%.

HIV Screening form	Identify HIV as a risk factor associated with SARS-COV-2 infection and offer HIV point of care (POC) test	All household members	Individual household members	6,912
Laboratory slip	Link blood sample to patient ID and track transportation	All household members	Individual household members	6,912

All attempts will be made to ensure that the research is a positive experience for all participants. Field workers will be trained to identify stress in the participants and will be trained in counselling techniques, dealing with distress and a referral procedure. We will put in a place a Distress Protocol (appendix 1) should a participant become distressed during the interview. This includes pausing the interview at the sign of early distress, asking the participant if s/he would like to continue, and following a specified referral mechanism should distress escalate.

6.8 Sample collection and transport

For households enrolled in the sero-survey, two blood samples will be collected by an experienced phlebotomist from each participant in the household including a serum sample (SST tube; 8.5 ml for adults and 2.5 ml for children) and plasma (PPT tube; 8.5 ml for adults and 2.5 ml for children). In the event that collection of venous blood is not possible or acceptable to parents for children aged <12 years, we will have the option of collecting blood by a finger prick in children 1-11 years and a heel stick in children under 1 year into microtainers. We will collect up to 5 ml of blood from children aged <15 years and up to 10 ml of blood from individuals aged ≥15 years. Detailed procedures will be described in the study SOP for sample collection.

Specimens for a participant will be labelled with the unique participant study identifier. Following specimen collection, specimens will be transported to the site laboratory. Serum specimens (SST tubes) will be centrifuged and the serum layer transferred to a separate tube at the site laboratory. Serum specimens will be transported in a cooler box with cooled ice packs to the NICD in Johannesburg daily, where they will be aliquoted, tested for SARS-CoV-2 antibodies and frozen at -70°C . Plasma specimens (PPT tube) will be centrifuged at the site laboratory and transported in a cooler box with cooled ice packs within 24 hours of collection to NICD for HIV and viral load testing.

6.9 Serological testing

Serum samples will be tested for SARS-CoV-2 antibodies using two different ELISAs to increase the positive predictive value given the expected relatively low prevalence of this virus[35]. The first assay, an in-house ELISA, will detect binding IgG responses to the SARS-CoV-2 spike protein. The second assay will be performed using either the commercial Roche Elecsys or the Abbott SARS-CoV-2 IgG, both of which detect binding IgG antibodies to the nucelocapsid protein. The nucelocapsid ELISAs are aimed at estimating sero-prevalence, while the spike ELISAs will contribute to our understanding of antibodies that may block infection. The in-house spike ELISA has been verified using convalescent serum from

individuals with PCR-confirmed SARS-CoV-2 infection, specimens from SARS-CoV-2 uninfected individuals as well as historic specimens from HIV-positive individuals. All the commercial kits have been approved for research use by the South African Health Products Regulatory Authority (SAHPRA) and as part of this process have passed a verification by the National Priorities Programme of the National Health Laboratory Service. Serum samples will also be tested in the laboratory using rapid Biosynex COVID-19 BSS antibody tests (Biosynex, France) to compare their performance with ELISA-based serology tests. Serum samples will also be tested for antibody responses to other respiratory pathogens including influenza, respiratory syncytial virus and other human coronaviruses. Participants will have the opportunity to receive their SARS-CoV-2 antibody results by text message after testing has been completed at the NICD (approximately 1-2 months after sample collection).

6.10 HIV testing

Plasma samples will be collected for all individuals enrolled in the sero-survey and tested for HIV infection at the NICD in Johannesburg using PCR for individuals aged <18 months (Roche Cobas Ampliprep/Cobas Taqman HIV-1 Qualitative Test, v2.0), and ELISA-based methods for individuals aged ≥18 months (Abbott Architect HIV Ag/Ab Combo Reagent kit for screening and Bio-Rad Genscreen Ultra HIV Ag-Ab for confirmation on positive screen results). If individuals choose to receive their result, HIV testing will additionally be performed and results provided using a rapid point-of-care HIV test during the household visit, with pre- and post-test counselling provided by trained fieldworkers. If individuals do not know and choose not to receive their HIV result, they will be counselled and be provided with details of the local clinic for private testing. Patients newly diagnosed with HIV will be referred to the local clinic for assessment for initiation of antiretroviral therapy. If the patient is not ready to be referred, we will provide them with a pre-printed referral letter for assessment for antiretroviral treatment including CD4+ T cell count testing and which will list local clinics in the areas. Viral load testing by quantitative PCR (Roche Cobas Ampliprep/Cobas Taqman HIV-1 test, version 2.0) will be performed on the same plasma samples for all individuals that test HIV positive.

6.11 Data management

All data gathered during the HUS and sero-survey will be collected electronically using tablets provided by the investigation team during the household visit and captured using an electronic REDCap data collection system, with regular data checks conducted by the data manager. Participants will be assigned a unique study identifier which will be used for all study information and specimen labelling. Data validation will be built into all fields of the electronic data collection tools to minimise errors while enumerators are inputting data. The database will be password protected to prevent access by outside parties. The database will be backed up daily. A data quality/data verification process will be developed and will be implemented by the database manager. This will include verification of completeness and accuracy of collected data. The data manager will access the database on a daily basis to check and follow up on progress and data quality. Laboratory results for SARS-CoV-2 serology and HIV will be entered into the same data system and linked to the individual using the study identifier.

The data management team will include a site coordinator/manager located each of the sites, as well as a dedicated project data manager and data analyst located in Johannesburg. Data analysis will be conducted by an experienced team at the NICD consisting of epidemiologists and scientists.

6.12 Data analysis

Main outcomes of interest:

- Prevalence of SARS-CoV-2-infection confirmed by serology
- Proportion of respiratory illness that were medically attended
- Financial cost associated with medically attended and non-medically attended respiratory illness

Supplemental data sources:

- Facility-based surveillance for ILI and SRI
- COVID-19 Sentinel hospital surveillance (DATCOV)
- National COVID-19 case master list

The following will be calculated:

- Seroprevalence (attack rate): proportion of individuals who show seropositivity for SARS-CoV-2 infection by age group and HIV status
- Risk factors for SARS-CoV-2 infection: multivariable logistic regression comparing exposures (age group, gender, HIV status and underlying conditions including TB, asthma, diabetes, chronic heart disease, chronic lung disease, obesity, hypertension and cancer) of infected and non-infected individuals
- Case fatality ratio: number of COVID-19 related deaths (obtained from surveillance and national COVID-19 case and hospitalization databases) as a proportion of infected individuals
- Estimate the burden of COVID-19 in the community by adjusting facility-based surveillance data for healthcare seeking behavior

In order to estimate the burden of COVID-19 in the community, we will use the healthcare seeking behavior data collected in this study to adjust the facility-based SRI and ILI surveillance data. We will describe the proportion of persons with (i) SARS-CoV-2 infection and (ii) symptomatic illness that accesses different healthcare services, including those that access care at one of the syndromic sentinel surveillance sites. The proportion of persons meeting the surveillance case definition for each syndrome who seek care at the sentinel site will be used to estimate the burden of disease in the community serviced by the sentinel site. Community burden of disease for SRI can be estimated as follows:

$$Burden_{SRI} = \frac{Cases_{Sentinel\ site}}{k}$$

The parameter *k* is the proportion of SRI/pneumonia cases in the community that seek care at the sentinel surveillance site.

COVID-19 mortality data will be obtained from the supplemental data sources and the mortality rate calculated as the number of COVID-19 related deaths during the first wave (first group of individual infected after which the infection rate decreases) of the pandemic as a proportion of the number of infected (seropositive) individuals in the study communities.

If other COVID-19 surveys are conducted in these same areas over time, relevant study findings will be compared to these surveys where feasible.

Continuous variables will be summarized using median and interquartile ranges, and compared using the Student's t-test or Wilcoxon Rank Sum test. Categorical variables will be summarized using frequency distributions and compared using Pearson's Chi-squared test. Factors associated with SARS-CoV-2 infection and symptomatic illness, such as age, gender, HIV and co-morbidities, will be assessed using multivariable conditional logistic regression, to account for cluster sampling.

6.13 Community partnership

The study team will establish strong community relationships in the study areas prior to starting the study. The study team will set up a study research group including stakeholders within each of the study areas. The study team, in partnership with the study research group, will inform the community about the study prior to starting the field work. Thus the research support group members play a key role in being the interface between the researchers and community members serving as advocates for the community's best interests and ensuring that the researchers are aware of any concerns within the community about the research being conducted. At the end of the study, we will disseminate the research findings to the communities through the research support group.

6.14 Ethics

Ethical approval for the study will be obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC). The protocol will be submitted for a reliance from the US CDC Institutional Review Board.

Informed consent: The purpose of the study will be explained to all household members in English or the local languages (Afrikaans and Xhosa in Mitchell's Plain, isiZulu in Pietermaritzburg and Tswana in Klerksdorp) as per the preference of the participant. Participants aged 18 years and older will be asked to give written consent. For participants younger than 18 years of age the parent/legal guardian/primary caregiver will provide written consent for the child. If an individual agrees to participate but is unable to sign, a thumbprint will serve in place of a signature, and an impartial household member will sign as a witness.

After obtaining permission from the head of the household (if different to the primary caregiver), the purpose of the study will be explained to the primary caregiver in English or the local language, and the primary caregiver will be asked to accept or decline participation in the study. The primary caregiver will be asked to provide written consent on behalf of all household members to provide household-level data. For each household member aged ≥18 years on whom individual-level data are collected, we will

obtain individual written consent from the individual. Written assent will additionally be obtained from children between 7 years and 17 years of age. If the household member is <7 years, the parent/guardian will be asked to provide the information. If the household member is 7-17 years the parent/guardian and, if available, the child will be asked to provide the information. If after three visits to an enrolled household on separate days or times the person is unavailable, we will ask the primary caregiver to respond on behalf of that individual. This is necessary because the survey requires information on all household members. Only recording data about individuals present at the time of the interview will result in a biased sample and threaten the validity of our findings.

Confidentiality: participant confidentiality will be maintained throughout the study. All participants will be assigned a study identification number. The link of the study identification number to identifying information will be maintained separately by the investigation team and will not be disclosed elsewhere. If data is shared, data shared will not include personally identifiable information.

Risks and benefits for participants: The study poses minimal risks to participants involving the collection of a small amount of blood in individuals enrolled in the sero-survey. In addition, HIV testing may cause psychological stress. HIV counselling will be provided to all participants by a trained and experienced counsellor. Direct benefits of this study include the opportunity for participants to be tested for HIV and SARS-CoV-2 antibodies. In addition, the indirect benefit of this study is that data collected will help improve and guide efforts to understand the extent of COVID-19 infection and may prevent further transmission of the virus. Pregnant women and children will be included in the study. Parents/legal guardians will answer questions about children, and children aged <7 years will not be interviewed directly. Following interviews in a household, the head of the household will be provided with a COVID-19 information leaflet (appendix 2) answering frequently asked questions related to COVID-19 and providing details of sources for additional information.

Prevention of COVID-19 infection in study personnel: All personnel involved in the study will be trained in infection prevention and control. These procedures will include proper hand hygiene and correct use of masks to minimize their own risk of infection when in close contact with study participants, and also to minimize the risk of spread to participants. In order to protect staff, in the working environment, study staff will be trained on and equipped with appropriate PPE. Random audits of field procedures will be conducted to ensure that procedures are followed. Study transport will be arranged to protect staff from exposure to public transport. Staff transport will be by vehicle with a maximum number of people in the vehicle (no more than 3 or 4 per car, depending of the type of car). Staff will wear cloth masks at all times while travelling. The interior of study cars will be sanitized at the end of every day. Staff will practice physical distancing at all times. All equipment needed for the day will be sanitized prior to leaving the offices for the field. Each team will be equipped with suitable portable sanitation daily. Symptom screening and temperature checks of staff members will be performed daily.

On arrival, and before entry at the study household all staff who will be interacting with study participants will replace the cloth mask with a surgical mask. Prior to any interaction with study staff each participant will be required to sanitize their hands and wear masks. These will be provided by the study team if the participant does not have them available. Interviews will be conducted from a distance of at least 2 meters from the interviewer with no physical contact between participants and study staff

member. Where possible, and acceptable to the participant, interviews will be conducted outdoors. Where not possible to meet outdoors or where the participant is concerned about privacy, field staff will wear appropriate PPE (masks, visors, gloves, aprons). Wearing of PPE will be monitored by random field visits and team support (nurse and field worker will know the PPE required and check on each other).

When all the samples and data have been collected all equipment used such as chairs, table, visors and electronic equipment will be sanitized. Prior to leaving the household all staff members will sanitize their hands.

All employees that develop COVID-19 symptoms (fever, cough, sore throat, shortness of breath, loss of sense of taste/smell, diarrhoea) will be tested with a nasopharyngeal swab and real-time PCR at the NICD. They will be asked to stay at home and self-quarantine until the test result is available. If they test positive for COVID-19, they will be asked to self-isolate at home for 10 days from the date of symptom onset, in line with Department of Health guidelines. The staff member will be contacted telephonically each day to check on them and referred to a healthcare facility if symptoms become more severe. Should an employee contract COVID-19 during the study medical expenses and leave will be covered by workman's compensation. Fellow employees who have been in close contact with the symptomatic person will be asked to quarantine at home until the suspected case's test result is available. Should the suspected case have been infected with COVID-19, all staff that were close contacts will also be tested at the NICD and monitored daily telephonically for the development of symptoms.

7. Study limitations

This study will be conducted in three selected sites, and therefore study findings may not be generalizable to other areas or settings. Limited recall of symptoms for the specified time period may lead to underestimates of symptomatic illness. Social desirability such as wearing of a mask and self-isolation may influence responses to questions with a perceived value judgment. Calculation of the case fatality ratio is dependent on full ascertainment of COVID-19 related deaths. Limitations to the sero-survey include the uncertainty regarding production and persistence of antibodies following SARS-CoV-2 infection. The sero-survey is planned as a cross-sectional survey at a single point in time however should additional funding become available, repeated cross-sectional surveys will be performed in the same geographical areas.

8. Dissemination and publication of results

Results will be used to interpret data from existing SRI and ILI surveillance in South Africa to provide estimates of COVID-19 burden and healthcare seeking behavior. Findings of the study will be communicated to relevant stakeholders, including study communities, the National and Provincial Departments of Health, policy, community and modelling groups. Study findings will be published in the peer-reviewed literature.

9. Study timelines

Activity	Date
Protocol development	June-July 2020
Ethics review and approvals	July-August 2020
Appoint staff and staff training	August-September 2020
Data and sample collection	Dependent on the epidemic trajectory at each site. Estimated to start from approximately September 2020. Survey will continue for a period of 4 months at each site, with end date of approximately December 2020
Laboratory testing	September 2020 – February 2021
Data finalization and cleaning	January - February 2021
First draft of manuscript	April 2021

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12. Appendices

Appendix 1:

HUSS Distress Protocol

The following is provided as a means of preparation for the site teams should a participant become distressed during the interview. Although it is unlikely that these interviews will be distressing for the participant, it is the interviewer's duty of care to the participant that these strategies are put in place prior to commencing the interviews.

Strategies to assist those distressed during an interview.

Should a participant become uncomfortable or distressed while being interviewed the following actions will be taken by the interviewer:

1. The interviewer should be kind and empathetic with the participant
2. The interviewer will ask if the participant would like a break and to continue the interview at a later stage, or to terminate the interview if they wish.
3. If the participant wishes this to happen, the interview will be paused and resumed at a later stage, or terminated.
4. Time will be spent with the participant and assistance provided, within the scope of interviewer's abilities, to discuss their concerns and support them, if appropriate.
5. If the participant continues to show signs of distress, the participant will be referred for counselling to a health professional at a local clinic or to contact The South African Depression and Anxiety Group (SADAG) to discuss their concerns.
6. A follow-up phone call will be made by the interviewer the following day to ensure that the participant is alright. During this time, the information previously provided regarding counselling services in the community and at SADAG will be, once again, provided.

SADAG - 24hr Helpline 0800 456 789

Lifeline - 24hr Helpline 0861 322 322

Appendix 2:

HUSS Information Leaflet for Households

What is the novel coronavirus disease (COVID-19)?

Coronaviruses are a large family of viruses found in both animals and humans. Some infect people and are known to cause illness ranging from a cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The new coronavirus (SARS-CoV-2) and its disease (COVID-19) is a new strain of coronavirus first found in Wuhan, China in December 2019. There are still some things we don't know about the virus, but researchers are working hard to find out how to prevent and cure it.

How dangerous is it?

For most people, coronavirus is mild and similar to a cold (runny nose, fever, sore throat, cough and shortness of breath). It can be more severe for some persons and can lead to pneumonia or breathing difficulties. For example, older people, and people with a weak immune system or existing illnesses (such as diabetes, high blood pressure, obesity and heart or lung disease) appear to be more vulnerable to becoming severely ill with the virus. The disease can lead to death, but this is rare.

How does someone get the virus?

A healthy person can get the virus from an infected person. The virus spreads through direct contact with 'drops' of saliva containing the virus. These fluids come out of the nose or mouth. For example, when an infected person coughs or sneezes, these droplets can enter the eyes, nose or mouth of another person or if an infected person sneezes and coughs into their hands and touches another person or a surface.

The new coronavirus is usually transmitted through close contact with an infected person, for example, when caring for them. "Close contact" means physically touching them, touching items they have used or coughed on, or spending a lot of time within 1 metre of them while they are sick.

What can I do to protect myself and my family?

Here are six precautions you and your family can take to avoid infection:

1. Wash your hands frequently using soap and water for at least 20 seconds. If soap is not available, alcohol-based hand sanitiser (at least 70% alcohol) may be used to wash away germs.

2. When coughing or sneezing, cover your mouth or nose with your bent elbow, or a tissue. Try to not sneeze and cough into your hands because then you will spread the virus with your hands. Throw the tissue into a bin. If you cough/sneeze into your hand, don't touch anything and immediately wash your hands with soap and water.

3. Avoid close contact with anyone who is coughing, sneezing, or sick. Keep at least 2 metres distance and encourage them to go to a nearby healthcare centre.

4. Avoid touching eyes, nose and mouth. Hands touch many things which can be contaminated with the virus.

5. Wear a mask covering your nose and mouth when you are around other people outside of your home.

6. Go to the doctor if you have a fever, cough or feel that it is difficult to breathe. This is the best way to look after yourself and stop the infection spreading to your family and others.

What should I do if a family member or I have symptoms?

If your symptoms are mild, you should isolate at home and if possible, in a separate room away from your loved ones. If your condition worsens, please seek medical help as soon as possible. You should tell your doctor if you have been in close contact with someone with who had COVID-19.

Are there any specific medicines to prevent or treat the new coronavirus?

The disease can be treated, and many people have already recovered from it. While there is no specific medicine recommended, those infected with the virus should receive care to relieve and treat symptoms. Those with severe illness should get care in a hospital.

Is there a vaccine?

There is no vaccine yet because this is a new virus. It takes time to develop a new vaccine that is efficient and safe. Researchers are working on it.

How can I keep my child safe?

It is important to teach your children to wash their hands regularly with soap and water or alcohol-based hand sanitiser. You should also teach them to cough/sneeze into their bent elbow or into a tissue and put the tissue directly into the bin and wash their hands right after. Keep windows open at home and on public transport so the air circulates and carries germs away!

You can find more information at www.nicd.ac.za and www.health.gov.za. You can also call the NICD General Public Hotline on 0800 029 999.