A **P**rospective **H**ousehold study of SARS-**C**oV-2, **I**nfluenza, and **R**espiratory **S**yncytial virus community burden, **T**ransmission dynamics and viral interaction in South Africa (the PHIRST-C Study)

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1. Summary

Title: A **P**rospective **H**ousehold study of SARS-**C**oV-2, **I**nfluenza, and **R**espiratory **S**yncytial virus community burden, **T**ransmission dynamics and viral interaction in South Africa (the PHIRST-C Study)

Partners: National Institute for Communicable Diseases (NICD), Johannesburg, South Africa; University of the Witwatersrand, School of Public Health, Johannesburg, South Africa; United States Centers for Disease Control and Prevention, Atlanta, United States of America (USA); Perinatal HIV Research Unit, Johannesburg, South Africa; MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), Bushbuckridge, South Africa; Institute for Scientific Interchange, Torino, Italy; Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States.

Background and justification: 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, which, one week later, was attributed to a novel coronavirus (severe acute respiratory syndrome coronavirus 2: SARS-CoV-2). Given its rapid spread globally, WHO declared that the outbreak of SARS-CoV-2 met pandemic criteria on 11th March 2020. By mid-April 2020 more than 2.5 million cases and more than 170,000 deaths have been laboratory-confirmed in 210 countries and territories.

Influenza virus is responsible for elevated morbidity and mortality globally every year. In South Africa annual seasonal influenza epidemics occur during the winter months (May-October, with peak transmission in June-July) and result in an estimated 19 million symptomatic infections, 128,000 severe cases and 11,000 deaths on average every year.

Human respiratory syncytial virus (RSV) is the commonest cause of childhood acute lower respiratory tract infection, especially among infants <3 months of age. In South Africa RSV circulates throughout the year with peak transmission occurring usually during February-April. Nonetheless, from systematic virologic surveillance data delayed RSV transmission is expected to occur in South Africa in 2020. This has the potential to result in concomitant SARS-CoV-2, influenza and RSV peak transmission in the country.

HIV incidence remains high in South Africa. Similarly, rates of pulmonary tuberculosis (PTB), with concomitant damage to lung tissue, remain persistently high despite concerted national efforts. HIV and PTB infections have been associated with an increased risk of severe illness (i.e., hospitalization and death) following infection with common respiratory pathogens, including influenza and RSV, even among individuals on antiretroviral therapy.

Understanding the community burden, transmissibility potential and clinical features of illness associated with SARS-CoV-2 infection is critical to inform the design and duration of containment and mitigation measures, both locally and globally. An accurate estimation of risk factors for community transmission, acquisition and duration of infectiousness is crucial to inform guidance for public health measures to limit transmission as well as models for epidemic forecasting for this and potential future epidemics. Moreover, factors specific to South and sub-Saharan Africa (SSA) such as HIV, tuberculosis, high proportion of the population who are children, malnutrition, and limited healthcare resources have the potential to impact

both the transmission dynamics, progression and prognosis of SARS-CoV-2 disease; as well as the burden on the healthcare system and society.

Whereas knowledge has been gained on the transmissibility and clinical features of SARS-CoV-2 since its emergence several key questions related to the natural history of the virus remain poorly answered, notably in African context. In particular, the community attack rate by age, the role of children in community and household transmission, the asymptomatic infected fraction, the role of asymptomatic individuals in transmission, the interaction of SARS-CoV-2 with other common respiratory pathogens such as influenza and RSV, the risk of reinfection with SARS-CoV-2 and the correlation between PCR-confirmed infection and serologic response among others, remain poorly understood. Critically, the effect of HIV infection on transmission and disease severity associated with SARS-CoV-2 infection is unknown. South Africa has an HIV prevalence of approximately 15% in the general population, representing over 7 million people of whom over 5 million are taking antiretroviral therapy.

Aim: In urban and rural South African environments, we aim to characterize the community burden (including the clinical features) and transmissibility of SARS-CoV-2 within the context of a functional antibody response. In addition, we will assess the effect of the interaction of SARS-CoV-2 with influenza virus and RSV on disease severity and transmission dynamics. This will be undertaken from an early stage throughout the epidemic in South Africa.

Primary objectives:

1. **To estimate the community burden of SARS-CoV-2, including:**
   - 1.1 the incidence of SARS-CoV-2 infection in the community as determined by polymerase chain reaction (PCR) and serologic assays;
   - 1.2 the correlation between individuals that seroconverted for SARS-CoV-2 and tested positive by PCR;
   - 1.3 the incubation period and the symptomatic fraction associated with SARS-CoV-2 infection;
   - 1.4 the spectrum of severity associated with symptomatic infections;
   - 1.5 the fraction of individuals with symptomatic infection seeking medical care; and
   - 1.6 the effect of the interaction of SARS-CoV-2 with influenza and RSV on disease severity.

2. **To assess the transmission dynamics of SARS-CoV-2 infections in the community, including:**
   - 2.1 the estimation of the SARS-CoV-2 household secondary infection risk (SIR), generation time and length of shedding;
   - 2.2 the estimation of the probability of transmission of SARS-CoV-2 infection between individuals (both symptomatic and asymptomatic/presymptomatic) within the household and potentially the community;
   - 2.3 the estimation of the SARS-CoV-2 effective reproduction number (Rt) and its variation over time in the community; and
   - 2.4 the effect of the interaction of SARS-CoV-2 with influenza and RSV on transmission dynamics.

Methods: We will conduct a household-level prospective cohort study in one rural and one urban community located in Mpumalanga Province (the Agincourt demographic surveillance site) and North West Province (Klerksdorp), respectively. The study will be conducted for 12 months of intensive follow up (July 2020 to June 2021) with a post-intensive follow-up continuing for a further 6 months (until December 2021).

Two hundred households; 100 per site with expected average number of household members of 5 resulting in 1,000 study participants of all ages; will be randomly selected from a list of 327 households that participated and successfully completed a 10-months follow-up period in a study similar to that currently proposed, but directed at community burden and transmission dynamics of influenza, respiratory syncytial virus and other respiratory pathogens (the PHIRST study conducted during 2016-2018 in the same two communities). The approached households will be re-assessed for study eligibility (i.e., a minimum of 3 household members and at least 80% of household members consenting to participate). The households in the 2016-2018 PHIRST study were identified by randomly selected geo-coordinates within the two communities. Baseline characteristics for this cohort are already available and will be re-ascertained after obtaining consent. Consenting household members that have entered the household since termination of the 2016-2018 PHIRST study will be also enrolled. Each household and household member will be enumerated and the HIV infection status and the level of immunosuppression of HIV-infected individuals will be assessed (if unknown) in consenting individuals.

Each household member will be followed twice per week during the intense follow-up period (12 months) of the study. During this period upper respiratory tract samples will be collected irrespective of presence of symptoms and data on key symptoms, healthcare seeking, hospitalization and death will be captured at each follow up visit on a REDCap tablet-based real-time database. Respiratory samples will be tested by reverse transcriptase real-time polymerase chain reaction (rRT-PCR) for SARS-CoV-2, influenza and RSV, and selected samples will be cultured and sequenced. An infection risk questionnaire will be administered to all study participants at enrollment and every month thereafter. Sera will be collected at enrollment and every 2 months during the 12-month intense follow-up period from all participants. In addition, sera will be collected every 2 months for a further 6 months following the 12-month intense follow-up period from study participants that tested positive for SARS-CoV-2 by rRT-PCR on respiratory specimens at 14, 16 and 18 months and from all study participants at 18 months. Sera will be tested for the presence of SARS-CoV-2, influenza and RSV antibodies. Wearable proximity sensors will be deployed for 8-12 days in each household over the 6-month intense follow-up period.

Impact: This study will provide essential information on the natural history of the virus that will impact decisions on optimal strategies for the containment and mitigation of the current and potential future epidemics of SARS-CoV-2 locally, regionally and globally.

2. Investigators

Name	Role	Contact	Contribution
National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa			

Cheryl Cohen, Centre for Respiratory Diseases and Meningitis	Principal Investigator	cherylc@nicd.ac.za	Study protocol design, supervision, data entry planning, field supervision, training, data analysis
Jocelyn Moyes, Centre for Respiratory Diseases and Meningitis	Co-Investigator	jocelynm@nicd.ac.za	Study protocol design, supervision, data entry planning, field supervision, training, data analysis
Thulisa Mkhencele, Centre for Respiratory Diseases and Meningitis	Co-investigator	thulisam@nicd.ac.za	Field supervision, database design training, data analysis
Jackie Kleynhans, Centre for Respiratory Diseases and Meningitis	Co-investigator	jackiel@nicd.ac.za	Field supervision, database design training, proximity sensor, data analysis
Anne von Gottberg, Centre for Respiratory Diseases and Meningitis	Co-Investigator	annev@nicd.ac.za	Laboratory design and testing
Jinal Bhiman, Centre for Respiratory Diseases and Meningitis	Co-Investigator	jinalb@nicd.ac.za	Supervision, lab design, testing, data analysis
Nicole Wolter, Centre for Respiratory Diseases and Meningitis	Co-Investigator	nicolew@nicd.ac.za	Lab design and testing, data analysis
Mignon du Plessis, Centre for Respiratory Diseases and Meningitis	Co-Investigator	mignond@nicd.ac.za	Lab management
MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt), Bushbuckridge, South Africa			
Kathleen Kahn	Co-Investigator	Kathleen.Kahn@wits.ac.za	Site-PI, field data collection, site coordination,

			analysis and write-up
Stephen Tollman	Co-Investigator	Stephen.Tollman@wits.ac.za	Centre Director, Field support, Health Service partnerships, analysis and write-up
Xavier Gómez-Olivé	Co-Investigator	F.Gomez-OliveCasas@wits.ac.za	Field methods & data collection, site management, analysis and write-up
Perinatal HIV Research Unit (PHRU), Johannesburg, South Africa			
Neil Martinson	Co-Investigator	martinson@phru.co.za	Site-PI, field data collection, site coordination, analysis and write-up
Limakatso Lebina	Co-Investigator	lebinal@phru.co.za	Field methods & data collection, site management, analysis and write-up
Influenza Division, Centers for Disease Control and Prevention (CDC), Atlanta, United States			
Meredith McMorrow, Influenza Division	Co- Investigator	bwe3@cdc.gov	Study protocol design, supervision, data entry planning, field supervision, training, data analysis
Stefano Tempia, Influenza Division	Co-Investigator	wlu4@cdc.gov or stefanot@nicd.ac.za	Study protocol design, supervision, data entry planning, field supervision, training, data analysis

Fatimah Dawood, Influenza Division	Co-Investigator	hgj0@cdc.gov	Study protocol design, data analysis
Institute for Scientific Interchange, Torino, Italy			
Ciro Cattuto, Institute for Scientific Interchange	Co-Investigator	ciro.cattuto@isi.it	Design an analysis of proximity sensors study
Michele Tizzoni	Co-Investigator	michele.tizzoni@isi.it	Design an analysis of proximity sensors study
Laura Ozella, Institute for Scientific Interchange	Co-Investigator	laura.ozella@isi.it	Design an analysis of proximity sensors study
Laetitia Gauvin, Institute for Scientific Interchange	Co-Investigator	laetitia.gauvin@isi.it	Design an analysis of proximity sensors study
Fogarty International Center, National Institutes of Health, Bethesda, Maryland, United States			
Cecile Viboud, Fogarty International Center	Co-Investigator	viboudc@mail.nih.gov	Study design, data analysis, modeling
Kaiyuan Sun, Fogarty International Center	Co-Investigator	Kaiyuan.sun@nih.gov	Study design, data analysis, modeling

3. Main centres

1. National Institute for Communicable Diseases (NICD)
   1 Modderfontein Rd, Sandringham
   Johannesburg 2193
   South Africa

2. MRC/Wits Rural Public Health and Health Transitions Research Unit (Agincourt)
   School of Public Health
   Faculty of Health Sciences
   University of the Witwatersrand
   New School of Public Health Building
   Education Campus
   27 St. Andrews Road
   Parktown
   2193
   South Africa
   Email address: Dawn.Dalby@wits.ac.za
   Tel: +27-11-717-2085

3. Perinatal HIV Research Unit (PHRU)
   WITS Health Consortium T/A Perinatal HIV Research Unit
   New Nurses Home
   Chris Hani Baragwanath Academic Hospital
   Chris Hani Road, Diepkloof, Soweto
   Johannesburg, 1864
   South Africa
   Tel: +27 11 989 9700
   Fax: +27 11 989 9762
   Email: info@phru.co.za

4. Centers for Disease Control and Prevention (CDC),
   Influenza Division
   1600 Clifton Rd NE, Mailstop A-32,
   Atlanta, GA 30329
   USA

5. Institute for Scientific Interchange (ISI),
   Via Chisola 5
   10126 Torino
   Italy

6. Fogarty International Center,
   at the National Institutes of Health
   31 Center Drive
   MSC 2220, Bethesda, MD
   USA

4. Contact details

Dr Cheryl Cohen
Centre Head: Epidemiology
Centre for Respiratory Diseases and Meningitis (CRDM)
National Institute for Communicable Diseases &
Associate Professor
Wits School of Public Health
University of the Witwatersrand
1 Modderfontein Rd, Sandringham
Johannesburg 2193
South Africa
Telephone: +27 11 386 6593
Fax:+27 11 882 9979
Mobile: +27 82 803 8093

E mail: cherylc@nicd.ac.za

5. List of abbreviations

ARI	Acute respiratory illness
ART	Antiretroviral treatment
CDC	United States Centers for Disease Control and Prevention
cDNA	Complementary deoxyribonucleic acid
C_t	Cycle threshold
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme linked immunosorbent assay
FTD	Fast Track Diagnostics
GPS	Global positioning system
HA	Haemaglutinin
HAI	Haemagglutination inhibition
HIV	Human immunodeficiency virus
HDSS	Health and socio-demographic surveillance system
ILI	Influenza-like illness
NAAT	Nucleic acid amplification test
NALC-NaOH	N-Acetyl L-Cysteine sodium hydroxide
NICD	National Institute for Communicable Diseases
NP	Nasopharyngeal
NYC	New York City
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
rRT-PCR	Reverse Transcriptase Real-Time Polymerase Chain Reaction
RSV	Respiratory syncytial virus
Rt	Effective reproduction number
SIR	Secondary infection risk
USA	United States of America
VA	Verbal autopsy
VCT	Voluntary counselling and testing

6. Background

6.1. Severe Acute Respiratory Syndrome Coronavirus 2

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 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019). One week later, on 7th January 2020, Chinese authorities confirmed that they had identified a novel (new) coronavirus as the cause of pneumonia [1]. This novel coronavirus has been named as 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 (https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1.full.pdf). The disease associated with SARS-CoV-2 has been named by WHO as COVID-19 (for **co**rona**vi**rus **d**isease 20**19**) (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it).

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) suggests that the novel coronavirus has a possible zoonotic origin [2,3]. 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 [4]. Given its rapid spread globally, WHO declared that the outbreak of COVID-19 meets the criteria for a pandemic on 11th March 2020 (https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020). By mid-April 2020 more than 2.5 million cases and more than 170,000 deaths have been laboratory-confirmed in 210 countries and territories. The body of evidence gained thus far suggest that older individuals and those with underlying medical conditions are at increased risk of severe illness (i.e., hospitalization and deaths); whereas children and young adults appear to be less prone to develop severe illness following SARS-CoV-2 infection.

The South Africa National Department of Health (NDoH) activated the Emergency Operation Centre (EOC) on 31st January 2020 and is currently actively screening persons under investigation (PUI) for COVID-19 using a standard case definition. The first positive case of SARS-CoV-2 infection in South Africa was reported on 5th March 2020 from a patient in KwaZulu-Natal.

6.2. Influenza

Influenza virus is responsible for elevated morbidity and mortality globally every year [5]. Similar to SARS-CoV-2, older individuals and those with underlying medical conditions (including HIV-infected persons) are at increased risk of severe influenza [6]. In addition, for influenza, young children are also at increased risk of severe illness [6]. In South Africa annual seasonal influenza epidemics occur during the winter months (May-October, with peak transmission in June-July) [7]and result in an estimated 19 million symptomatic infections, 128,000 severe cases and 11,000 deaths on average every year [8]. During 2016-2018 the National Institute for Communicable Diseases (NICD), Johannesburg, South Africa implemented a large community burden and transmission dynamics study for influenza, respiratory syncytial virus (RSV) and other respiratory pathogens (the PHIRST study) in two communities (the Jouberton township in Klerksdorp, North West Province and the Agincourt health and socio-demographic surveillance site, Bushbuckridge Municipality, Mpumalanga Province) using a methodology similar to those proposed for this study (PHIRST-C). The aim of the PHIRST study was to gain thorough understanding of key burden and transmissibility parameters for influenza, RSV and other respiratory pathogens to design and optimize prevention and containment measures during recurring seasonal epidemics and potential pandemics (the latter for influenza only). Key study outcomes were an influenza infection community attack rate of 41 per 100 person-season (of which 57% were symptomatic infections), the ability of asymptomatic individuals to transmit to exposed household members (even though at lower rates than symptomatic individuals) and an increased attack rate, symptomatic fraction and infectiousness among young children. HIV-infected individuals did not differ from HIV-uninfected individuals in their likelihood of acquiring or

transmitting influenza infection (unpublished results). It is expected that SARS-CoV-2 and influenza will co-circulate in South Africa in 2020, potentially experiencing almost synchronous peaks of community transmission and associated disease burden for the two pathogens. The interaction between SARS-CoV-2 and influenza virus in terms of potential increased disease severity and competition/synergism for transmission/acquisition remains poorly understood.

6.3. Respiratory syncytial virus

Human respiratory syncytial virus (RSV) is the commonest cause of childhood acute lower respiratory tract infection, especially among infants <3 months of age [9]. In South Africa, RSV circulates throughout the year with peak transmission occurring usually during February-April [10]. Nonetheless, systematic virologic surveillance conducted by NICD indicates that peak RSV transmission may occur later than expected in 2020 as few cases, but increasing in numbers, have been detected only from late March in 2020. This has the potential to result in concomitant RSV, influenza and SARS-CoV-2 peak transmission in the country. Similar to influenza, the interaction between SARS-CoV-2 and RSV in terms of potential increased disease severity and competition/synergism for transmission/acquisition remains poorly understood.

6.4. HIV

Although the public health antiretroviral therapy program which has initiated over 2.6 million people on antiretroviral treatment (ART) since 2004 has had immediate and dramatic beneficial impacts on survival, risk of opportunistic infection, quality of life and household wealth; HIV incidence remains high in South Africa. Recent reports of HIV incidence for the country [11], and in the non-intervention arms of clinical trials of prevention interventions show that HIV incidence overall remains high. Whereas, HIV prevention of mother to child transmission programs in South Africa have been effective in lowering the prevalence of HIV infection in children, the proportion of HIV exposed but uninfected children remains high. HIV infection has been associated with an increased risk of severe illness (i.e., hospitalization and death) following infection with common respiratory pathogens, including influenza and RSV, even among individuals on antiretroviral therapy. A similar pattern has been observed among HIV exposed infants aged <6 months.

6.5. Household contact patterns and disease transmission

Respiratory infections spread mainly through large droplets and self-inoculation from contaminated surfaces [12,13]. Measuring the quantity and duration of face-to-face interactions among people is important to understand this transmission [14]. Most of the contacts we make tend to be in limited social groupings such as households, school or work setting [15], and this has also been suggested to influence the spread of respiratory pathogens [16]. Despite the importance of empirical rates of contact in transmission models, data from developing countries are limited [17].

In infectious disease epidemiology, contact networks consist of individuals (nodes) with connections between individuals (edges) that represent interactions which can lead to infection transmission [18]. For respiratory and close contact infections, social contact networks can be used to highlight potential transmission routes [19]. Mathematical models to forecast the evolution of the epidemic and the impact on the healthcare system and the society have been widely used (including in South Africa) for SARS-CoV-2 with the aim to inform policy makers on needs and optimal containment and mitigation measures. Current SARS-CoV-2 models that omit important factors such as frequency, duration and location of

contacts do not capture the heterogeneity of transmission that has direct bearing on intervention measures [20].

Radio frequency (RF) proximity sensors (henceforth referred to as "tags") have been used in closed settings such as schools [21], hospitals [22], workplace [23]and conferences [24]to characterize close contact social networks relevant to the spread of respiratory infections and were used also in the PHIRST study. The sensor platform in these studies has been designed to collect proximity data only from individuals facing each other while wearing the tags, representing conversations or actual physical touch that can lead to infection transmission (http://www.sociopatterns.org). The majority of studies using this platform reported a high participation rate (≥75%) suggesting that an unobtrusive way of data collection requiring minimal participant intervention elicits better response rates compared to paper diaries, especially in settings with a high proportion of illiterate individuals, and has been shown to be feasible in a rural Kenyan and South African settings [25]. Tags provide a rich data source, even for partial networks, that can be used to investigate plausible characteristics of infection transmission on networks weighted by frequency and duration of contacts. In addition, statistical methods are available to impute missing data by generating synthetic networks based on the network properties supplemented by additional demographic assumptions [26]. The use of proximity sensors in this study will allow to obtain a framework to model the spread of SARS-CoV-2 and to assess the impact of social distancing measures on social contact networks.

7. Justification, impact and aim of the study

Understanding the community burden, transmissibility potential and clinical features of illness associated with SARS-CoV-2 infection is critical to inform the design and duration of containment and mitigation measures, both locally and globally. An accurate estimation of risk factors for community transmission, acquisition and duration of infectiousness is crucial to inform models for epidemic forecasting for this and potential future epidemics. Moreover, factors specific to sub-Saharan Africa (SSA) such as HIV, tuberculosis, high proportion of the population who are children, malnutrition, and limited healthcare resources has the potential to impact both the transmission dynamics, progression and prognosis of SARS-CoV-2 disease; as well as the burden on the healthcare system and society.

Whereas knowledge has been gained on the transmissibility and clinical features of SARS-CoV-2, several key questions related to the natural history of the virus remain poorly answered. In particular, the community attack rate by age, the role of children in community and household transmission, the asymptomatic infected fraction, the role of asymptomatic/pre-symptomatic individuals in transmission, the interaction of SARS-CoV-2 with other common respiratory pathogens such as influenza and RSV, the risk of reinfection with SARS-CoV-2 and the correlation between PCR-confirmed infection and serologic response among others, remain poorly understood. Critically, the effect of HIV infection on transmission and disease severity associated with SARS-CoV-2 infection is unknown. South Africa has an HIV prevalence of approximately 15% in the general population, representing over 7 million people of whom over 5 million are taking antiretroviral therapy.

The protocol amendment (version 1.1 November 2020) describes the extension of the intensive follow up period (6 months to 12 months). As of November 2020 we are observing ongoing high levels of COVID-19 transmission in communities under surveillance. There is concern that following the Christmas period there may be an increase or resurgence of COVID-19 transmission. In addition, we have not recorded an

influenza season in South Africa (https://www.nicd.ac.za/diseases-a-z-index/covid-19/surveillance-reports/weekly-respiratory-pathogens-surveillance-report-week/). RSV detection was substantially reduced during the typical RSV season but from November 2020 RSV circulation has begun to increase substantially. We propose to extend the follow up period of PHIRST-C to allow for the documentation of possible case increases following the Christmas period and possible associated reinfections and to include a longer follow-up period into winter of 2021 to track the co-circulation of influenza, RSV and SARS-CoV-2. With many countries experiencing a dramatic second wave of the pandemic the extension of the intensive follow-up period will also assist in tracking the start of a second wave and document the household transmission associated with this wave. Due to SARS-CoV-2 circulating prior to the start of the study, collecting blood for serology is important to accurately describe the secondary attack rate. Similarly, the objectives of attack rate on PCR and serology cannot be achieved without a blood sample. The inclusion and exclusion criteria for the study have been adjusted to make it a requirement that each participant over the age of 5 years give at least one blood during the study intensive period and at least 50% of children in a household under the age of 5 year participate in at least one blood draw.

This study will provide essential information on the natural history of the virus that will impact decisions on optimal strategies for the containment and mitigation of the current and potential future epidemics of SARS-CoV-2 locally, regionally and globally.

8. In urban and rural South African environments, we aim to characterize the community burden (including the clinical features) and transmissibility of SARS-CoV-2 within the context of a functional antibody response. In addition, we will assess the effect of the interaction of SARS-CoV-2 with influenza virus and RSV on disease severity and transmission dynamics. This will be undertaken from an early stage throughout the epidemic in South Africa Objectives

8.1. Primary

8.1.1. To estimate the community burden of SARS-CoV-2, including:

8.1.1.1. the incidence of SARS-CoV-2 infection in the community as determined by polymerase chain reaction (PCR) and serologic assays;

8.1.1.2. the correlation between individuals that seroconverted for SARS-CoV-2 and tested positive by PCR;

8.1.1.3. the incubation period and the symptomatic fraction associated with SARS-CoV-2 infection;

8.1.1.4. the spectrum of severity associated with symptomatic infections;

8.1.1.5. the fraction of individuals with symptomatic infection seeking medical care; and

8.1.1.6. the effect of the interaction of SARS-CoV-2 with influenza and RSV on disease severity.

8.1.2. To assess the transmission dynamics of SARS-CoV-2 infections in the community, including:

8.1.2.1. the estimation of the SARS-CoV-2 household secondary infection risk (SIR), generation time and length of shedding;

8.1.2.2. the estimation of the probability of transmission of SARS-CoV-2 infection between individuals (both symptomatic and asymptomatic/presymptomatic) within the household and potentially the community;

8.1.2.3. the estimation of the SARS-CoV-2 effective reproduction number (Rt) and its variation over time in the community; and

8.1.2.4. the effect of the interaction of SARS-CoV-2 with influenza and RSV on transmission dynamics.

8.2. Secondary

8.2.1. Objectives related to burden, health-seeking behavior and transmission dynamics of SARS-CoV-2, influenza and RSV

8.2.1.1. To estimate the incidence, the symptomatic fraction, the severity associated with symptomatic infections and the fraction of individuals with symptomatic infection seeking medical care among SARS-COV-2-, influenza- or RSV-positive cases by HIV serostatus and age;

8.2.1.2. To estimate the effect of age and HIV-infection status of household index case (first individual positive in the household) on the SIR and length of shedding of SARS-CoV-2, influenza and RSV and the effect of age and HIV-infection status of household members on the rates of acquisition of SARS-CoV-2, influenza and RSV infection;

8.2.1.3. To compare the incidence and the transmission dynamics of influenza and RSV in 2020 (when social distancing measures have been implemented for SARS-CoV-2) to that observed in the PHIRST study during 2016-2018 in the same communities.

8.2.2. Objectives related to SARS-CoV-2, influenza and RSV virus characterization and evolution and determination of the nasopharyngeal microbiota

8.2.2.1. Determine the heterogeneity of SARS-CoV-2, influenza and RSV virus strains within household clusters and describe viral evolution within and between households as well as the association between virus strains and the duration of virus shedding and HIV status;

8.2.2.2. Use molecular evolutionary analysis to better understand transmission networks associated with SARS-CoV-2, influenza virus and RSV spread within households and communities;

8.2.2.3. Determine the contribution of specific influenza A and B subtypes or lineages on the community burden of influenza;

8.2.2.4. Determine the contribution of RSV-A and -B strains on the community burden of RSV; and

8.2.2.5. Determine the antigenic relatedness of influenza virus strains circulating within the community to the vaccine strains.

8.2.2.6. Determine the composition of the nasopharyngeal microbiota.

8.2.3. Objectives related to household contact patterns

8.2.3.1. Estimate the proportion of time spent in the home and outside the home by age group, setting and location overall and, if feasible, in relation with potential different social distancing measures;

8.2.3.2. Describe and compare the contact patterns and location of contacts within the house between individuals living within households in a rural and peri-urban environment in South Africa overall and, if feasible, in relation with potential different social distancing measures;

8.2.3.3. Measure the number of contacts between individuals from the same household inside of the home overall and, if feasible, in relation with potential different social distancing measures;

8.2.3.4. Estimate the association between contact patterns and transmission events between individuals within households for SARS-CoV-2, influenza and RSV; and

8.2.3.5. Compare the contact patterns of individuals when they develop respiratory symptoms to the contact patterns of individuals not experiencing respiratory symptoms.

9. Methods and procedures

9.1. Definitions

Household: A group of three or more people who regularly share at least two meals in the same residence at least two days per week (residential institutions excluded).

Migrant household member: A person considered as a household member who resides elsewhere but regularly spends weekend or holiday periods within the household.

Laboratory-Confirmed SARS-CoV-2 Infection on PCR: An individual with a positive SARS-CoV-2 result on real-time reverse transcriptase polymerase chain reaction (rRT-PCR).

Laboratory-Confirmed SARS-CoV-2 Infection on Serology: An individual with a positive SARS-CoV-2 result on a SARS-CoV-2 receptor binding domain or spike enzyme-linked immunosorbent assay (ELISA) or neutralization assay.

Laboratory-Confirmed Influenza Infection on PCR: An individual with a positive influenza result on rRT-PCR.

Laboratory-Confirmed Influenza Infection on Serology: An individual (who did not receive influenza vaccine) with a four-fold rise in serum titres of antibodies to influenza on the haemagglutination-inhibition test between pre- and post-influenza season serum samples.

Laboratory-Confirmed RSV Infection on PCR: An individual with a positive RSV result on real-time reverse transcriptase PCR (rRT-PCR).

Laboratory-Confirmed RSV Infection on Serology: An individual with a four-fold rise in serum titres of antibodies to RSV between pre- and post-RSV season serum samples.

Asymptomatic individuals: Study participants with laboratory-confirmed SARS-CoV-2 infection by PCR that do not report or present with selected symptoms (Appendix 2) during the time of SARS-CoV-2 positivity by PCR.

Influenza-like illness (ILI) with documented fever: An acute respiratory infection with measured fever of ≥38 C° and cough, with onset since the last household visit or within the last ten days.

ILI with feeling feverish: An acute respiratory infection with self-reported fever (but not documented) and cough, with onset since the last household visit or within the last ten days.

Any acute respiratory illness (ARI) not meeting the ILI case definition: self-reported cough, cold, sore throat or other respiratory symptom with onset since the last household visit or within the last ten days that does not meet the ILI case definition.

Household SIR: The proportion of household contacts of an index case that subsequently become infected with SARS-CoV-2, influenza or RSV.

Generation time: The time interval between onset of confirmed infection by PCR in index case and confirmed infection in household contacts.

9.2. Study design overview

We will conduct a household-level prospective cohort study in one rural community located in Mpumalanga Province (the Agincourt health and socio-demographic surveillance site) and one urban community in North West Province (Klerksdorp). The characteristics of the study population are provided in Section 10.3. The study will comprise of a 12-month intense follow-up period with households visits twice per week (July 2020 to June 2021) followed by serological surveys until 18 months (total study period: 18 months).

Two hundred households; 100 per site with expected average number of household members of 5; will be randomly selected from a list of 327 households that participated and successfully completed a 10-months follow-up period in the PHIRST study conducted during 2016-2018 in the two communities. The approached household will be re-assessed for study eligibility (i.e., a minimum of 3 household members and at least 80% of household members consenting to participate). The households in the PHIRST study were identified by randomly selected geo-coordinates within the two communities. Baseline characteristics for this cohort are already available and will be re-ascertained after obtaining consents (Appendix 2 Form 2). Household members that have entered the household since termination of the 2016-2018 PHIRST study will be also enrolled. Each household and household member will be enumerated and the HIV infection status and the level of immunosuppression of HIV-infected individuals will be assessed (if unknown) in consenting individuals. The process of household selection is described in Section 10.5.

Each household member will be followed up twice per week during the intense follow-up period (12 months) of the study. During this period upper respiratory tract samples will be collected irrespective of presence of symptoms and data on key symptoms, healthcare seeking, hospitalization and death will be captured at each follow up visit on a REDCap tablet-based real-time database. Sera will be collected at enrollment and every 2 months during the 12-month intense follow-up period from all participants. In addition, sera will be collected every 2 months for a further 6 months following the end of the 12-month intense follow-up period from study participants that tested positive for SARS-CoV-2 by rRT-PCR on respiratory specimens at 14, 16 and 18 months and from all study participants at 18 months. Wearable proximity sensors will be deployed for 8-12 days with the aim of obtaining one week of complete data in each household over the 12-month intense follow-up period.

In Agincourt, there is a high rate of migrancy and therefore we expect that many households will have one or more household members who work and reside elsewhere but spend weekends or holiday periods within the household; however, migrancy may be limited under lock down measures. These individuals will be enumerated in the baseline survey (even if absent at baseline) and consented for study participation if they are present at any household visit. Thereafter, if they are present in the household at the time of a household visit, forms will be completed, and specimens will be collected from them as per other household members for that visit. When not present, they will be recorded as absent.

9.2.1. Estimation of the community burden and transmission dynamics of SARS-CoV-2, influenza, and RSV

Following enrollment, upper respiratory tract samples (nasopharyngeal or nasal swabs or saliva) will be collected twice a week from each household member irrespective of symptoms during the 6-month intense follow-up period. Samples will be tested by rRT-PCR (see Section 9.11.1) for SARS-CoV-2, influenza and RSV throughout the study period. During each visit a follow up questionnaire will be administered to household members to assess development of symptoms and oxygen saturation will be measured using a pulse oximetry instrument. Following the detection of the first SARS-CoV-2-positive member in a household daily symptoms collection will be instituted for all household members for a period of up to 6 weeks. Daily symptoms collection will be conducted using a daily symptom diary, daily phone calls or specifically designed mobile applications depending on feasibility and preference of the household members. Sera will be collected from all participants at enrollment and at 2, 4, 6, 12 and 18 months and tested for SARS-CoV-2, influenza and RSV using pathogen-specific serological tests as detailed in Section 9.11.3.

9.2.2. Assessment of household social contact associated with SARS-CoV-2, influenza and RSV transmission

Information on proximity data between household members will be collected from consenting household members. All participating household members will be asked to wear the proximity tag devices for a period of 8 – 12 days during the 6-month intense follow up period. All participating household members will be asked to complete a questionnaire twice during the follow-up period on their time use and social contacts (appendix 6) which will be used to validate and supplement the proximity tag data.

9.3. Study setting and population

The study will be conducted at two sites, one in the Mpumalanga Province and one in the North West Province.

9.3.1. Mpumalanga Province site

The study will be conducted within the Agincourt health and socio-demographic surveillance system site (HDSS) at the MRC/Wits Rural Public Health and Health Transitions Research Unit. The population is approximately 120,000 people living in 20,000 households and 31 villages covering 450km^2 and is set in the rural Bushbuckridge sub-district of Mpumalanga Province. While HIV prevalence is high, life expectancy is improving with marked epidemiological transition leading to rising prevalence of non-communicable disease including cardio-metabolic conditions and stroke.

9.3.2. North West Province Site

Klerksdorp is located in the local municipality of Matlosana in North West Province and has a population of over 385,000 people and is 115 km^2. The city of Klerksdorp is surrounded by the townships of Jouberton, Alabama, Kanana, Khuma, and Tigane. The townships are organized into extensions that include mostly single-family houses and shacks. Prevalence of HIV in Klerksdorp is approximately 12%. Annual incidence of tuberculosis is extremely high approaching 1200/100,000 with an HIV coinfection rate of over 80%.

9.4. Inclusion and exclusion criteria

Eligible households will be randomly selected from a list of 327 households that participated and successfully completed a 10-months follow-up period in the PHIRST study conducted during 2016-2018 in the two communities and that: (i) consent to participate to the study; and (ii) that are planning to reside in the selected community for the duration of the study. (iii) Provide at least one serum sample in the intensive follow up period, for individuals five years and older and (iv) Households should have at least 3 or more resident individuals in order to be eligible If the required sample size (section 9.5) cannot be reached because of high refusal rate of the 2016-2018 PHIRST cohort, households not forming part of the 2016-2018 PHIRST co-cohort will be randomly selected from the two communities.

Non-eligible households will be households that were not randomly selected, that were selected but did not consent to participate to the study or, that have >20% of household members who do not consent for inclusion in the study. A household in whom >20% of individuals decide to suspend study participation will be considered suspended. A household in which <50% children under the age of 5 years do not provide a blood sample. Each household's eligibility will be reviewed by investigators prior to withdrawing the household.

Households that do not fit the inclusion or meet the exclusion criteria will be withdrawn and replaced with new households on the randomization list.

9.5. Sampling and sample size

The selection process will be based on a one-stage cluster sampling design whereby 200 households (100 per study site) will be randomly selected from an available sampling frame in the two selected communities and all household members will be enrolled. Assuming an average number of household members per household of 5 we will enroll 1,000 study participants. The sampling frame will consist of a list of 327 households that participated and successfully completed a 10-months intense follow-up period

in the PHIRST study conducted during 2016-2018 in the two communities. The study procedures implemented in the 2016-2018 PHIRST study were similar to that proposed for this study (PHIRST-SARS-CoV-2). The households in the PHIRST study were identified by randomly selected geo-coordinates within the two communities. The decision to enroll households that formed part of the PHIRST cohort during 2016-2018 was dictated by the following considerations: (i) study participants already familiar with the study procedures, hence less likely to withdraw from the study and more likely to consent to the study (potentially reducing loss to follow-up and enrollment time); and (ii) cohort already well characterized (potentially reducing cohort characterization time following enrollment). One hundred additional geo-coordinates will be also generated in each study site. These geo-coordinates will be used to identify households not included in the 2016-2018 PHIRST cohort and used only in the event of a high refusal rate among households from the 2016-2018 PHIRST cohort. A maximum of 30 additional households in each community will be enrolled to cater for loss to follow-up. In addition, we will account for a 20% household refusal of enrollment during random selection of households.

We assumed an overall maximum cumulative attack rate (CAR) of SARS-CoV-2 in the two communities of ≤60% based on an estimated R_0 value of 2.5 [27]. To estimate this value for a 95% confidence interval, a 10% desired absolute precision and a 1.3 design (household cluster) effect, 120 individuals are needed.

The expected age distribution in the target cohort is 16% for individuals aged <5 years (160 expected individuals in the cohort), 41% for individuals aged 5-18 years (410 expected individuals in the cohort), 26% for individuals aged 19-44 years (260 expected individuals in the cohort), 12% for individuals aged 45-64 and 5% for individuals aged ≥65 years (120 expected individuals in the cohort). Assuming a constant CAR across age groups we will be powered to estimate an age-specific CAR of 60% with the above-mentioned precision among all age groups provided above. Assuming a constant CAR across age groups we will be powered to estimate an age-specific CAR of 50% with the above-mentioned precision among individuals aged <5, 5-18, 19-44 and 45-64 years, but not in elderly individuals. If the CAR will be ≤40% or ≥60% we will obtain increased precision in the CAR estimates.

We assumed 30% symptomatic fraction among individuals infected with SARS-CoV-2 [28]. We assumed 20% severe cases and a 2% mortality among all symptomatic individuals [28]. The sample sizes to estimate the above parameters for a 95% confidence interval and a 10% desired absolute precision are as follows: (i) 30% symptomatic fraction among infected individuals: 81 infected individuals; (ii) 20% severe cases among symptomatic individuals: 62 symptomatic individuals; (iii) 2% mortality among symptomatic individuals: 8 symptomatic individuals. At total of 270 individuals (i.e., 81 symptomatic individuals/0.3 symptomatic fraction; CAR: 27.0%) will be needed to estimate the above-mentioned parameters with the desired level of precision.

We assumed a household secondary infection risk (SIR) of 16% in household members exposed by an index case (the first individual with study diagnosed infection in the household). Preliminary estimates from China report a SIR of 3%-16% [28]. For this study we chose the higher value in order to have sufficient power (i.e., larger sample size) to precisely estimate SIR values ≤16%. In addition, in our setting crowding may result in higher transmission risk and hence higher SIR. To estimate a 16% SIR for a 95% confidence interval, a 5% desired absolute precision and a 1.5 design (household cluster) effect, 310 exposed household members are needed. It is difficult to predict how many households will have at least one individual infected during the epidemic in the household. In the PHIRST study 75% of households were

infected with influenza at the end of the influenza season. We assumed an average household size of 5 individuals as observed in the PHIRST study, which would result in 78 households in the entire cohort having to be infected to reach the required sample size (i.e., 310 needed exposed household members divided by 4 exposed household members on average per household, excluding the index case). This will equal to a CAR of 12.8% [i.e., 128/1,000 infected individuals in the cohort; 50 infected exposed household members (16% of 310) and 78 index cases).

9.6. Recruitment period and follow up visits

9.6.1. Recruitment

Household identification and recruitment will be implemented in mid-May 2020. Upon random selection of dwellings within the sampling frame (see Section 10.5), households will be visited by trained staff to verify inclusion criteria (i.e., ≥3 individuals in the household) and consenting. Written informed consent will be obtained from each household member as detailed in Section 10.6.1 and Appendix 4. Each enrolled household and household member will be enumerated, and the demographic characteristics of the household will be re-assessed. Household members that participated in the PHIRST study during 2016-2018 will be assigned the same study number. Household members that have entered the household since termination of the PHIRST study will be also enrolled and assigned a new unique study number comprised of the household number and a new household member number. If household not forming part of the 2016-2018 PHIRST cohort will be enrolled, a new household and associated household member number will be allocated. After enrollment and enumeration of the target number of households is completed, the number of enrolled household members will be evaluated to assess that the target sample size (i.e., at least 1,000 individuals) is met. If the number of enrolled household members is below the target number of household members then additional households will be recruited until the target sample size is met.

After recruitment is completed, a follow-up plan for each household will be developed. The intense 6-month follow-up period will start the first Monday after the day of enrollment of each household even if the enrollment of the whole cohort is not completed. This is to ensure that we capture as much as possible the full SARS-CoV-2 season in communities where the virus is already circulating. Any babies who are born into the study household or any individual that joins the study household (i.e., in-migrates) during the study period will be recruited.

- Detailed baseline questionnaires on household composition, demographics, regular sleeping and eating arrangements, occupation and underlying illnesses will be completed (Appendix 2)

9.6.2. First study visit

At the first study visit the household demographics on record will be verified and the follow-up schedule will be communicated and agreed upon with the head of the household and household members. A copy of the follow up visits calendar will be provided to the head of the household. During the first study visit the following specimens will be collected and assessments made for each household member or the whole household as appropriate:

- A serum sample will be collected for serological testing for SARS-CoV-2, influenza and RSV. If serum is insufficient SARS-CoV-2 testing will be prioritized, followed by influenza and RSV.

- HIV rapid testing will be offered as described under the section HIV testing below for patients of unknown/previously negative status (i.e., enrolled study participants that did not form part of the 2016-2018 PHIRST cohort, or individuals aged ≥12 years that were HIV-uninfected when enrolled in the PHIRST-study).
- Nasopharyngeal or nasal swabs or saliva (or similar as per Section 9.6.7 for determination of specimen type) will be collected for viral detection by rRT-PCR
- A copy of the vaccination card of all children aged <5 years and the verbal vaccination history for influenza vaccine and other vaccines outside of the routine infant immunization schedule of each household member will be collected.
- A structured questionnaire will be administered to assess presence, duration and severity of selected symptoms (including hospitalization and death) (Appendix 2)
- The presence of underlying chronic medical conditions, including current or previous tuberculosis infection.
- The date and time of the next visit will be communicated and agreed upon

9.6.3. Twice-weekly follow-up visits

After the first study visit, each household will be visited twice per week according to a pre-established schedule.

During each visit the following will take place:

- Nasopharyngeal or nasal swabs will be collected for viral detection by rRT-PCR (see Section 9.6.7. for determination of specimen type).
- Structured questionnaires will be administered to assess presence, duration and severity of symptoms (including hospitalization and death).
- For symptomatic individuals the following will be performed at each visit until symptoms resolve:
    - A digital temperature will be measured and documented
    - A detailed symptom history will be completed (Appendix 2)
    - Healthcare seeking behavior will be recorded
    - For any individuals who are admitted to hospital or die, a detailed form (Appendix 2) will be completed to collect information on clinical presentation, management and laboratory results.
    - Individuals who warrant admission to hospital with respiratory illness will be referred to Matikwana or Mapulaneng Hospital in Mpumalanga and Klerksdorp or Tshepong Hospital in Klerksdorp and enrolled into the ongoing NICD pneumonia surveillance programme (Wits HREC Protocol number M140824). Household members may also independently seek care at other healthcare facilities. If this occurs data will be obtained from the relevant facility.

9.6.4. End-of-study visit

At this visit a copy of the vaccination card and the vaccination history of each household member aged <5 years will be evaluated to ascertain if vaccination status has changed during the study period.

9.6.5. Bi-monthly follow-up visits during the intense 12-month follow-up period

Follow-up visits for the collection of additional blood specimens will be performed every two months counted from the first follow-up visit (i.e. the first follow-up visit of the intense 12-months follow up). The collection of blood specimens for each bi-monthly sero-survey will be completed for the entire cohort within 2 weeks of the serum-collection starting date. At these visits all specimens and information will be collected as per twice-weekly follow-up visits. In addition, a blood specimen will be collected from each household member.

9.6.6. Bi-monthly follow-up visits after the intense 12-month follow-up period

Sera will be collected every 2 months for a further 6 months following the end of the 12-month intense follow-up period from study participants that tested positive for SARS-CoV-2 by rRT-PCR on respiratory specimens at 14, 16 and 18 months and from all study participants at 12 and 18 months. These specimens will be tested for antibodies to SARS-CoV-2, influenza and RSV. This has the purpose to assess medium to long term immunity against SARS-CoV-2 infection and assess infection following the intense 12-month follow-up period for the 3 pathogens.

9.6.7. Collection of upper respiratory tract samples and use of personal protective equipment

The specimen of choice for detecting SARS-CoV-2 is a nasopharyngeal (NP) specimen. This sampling method requires a healthcare professional to take the sample and is considered an aerosolizing procedure requiring specific PPE (N95/P2 masks, goggles/visor, gown/apron and gloves), Table 1. During the study, we aim to collect NP swabs from participants at twice-weekly visits. However, should the ongoing validation of nasal mid-turbinate (NMT) and/or anterior nares (nasal swab; NS) swabs and/or saliva collected by a healthcare professional or self-administered with healthcare supervision, show to be comparable to NP, or should suitable PPE for NP specimen collection not be available, the study will modify sample collection methods to collect either NMT or NS or saliva. In the case of self-administered swabs/saliva collection, a healthcare worker will observe the specimen collection process from a distance of 2 meters or more.

Household visits will be performed by teams of an enrolled nurse who will be accompanied by a field worker. All specimen collection and medical investigations, specifically, nasopharyngeal/nasal swabs, saliva and blood specimens will be performed by enrolled nurses. All staff will be fully trained in collection of specimens and data, as well as donning and doffing of PPE and physical distancing. Details of procedures for specimen and data collection are described below.

Table 1 Personal protective equipment needed for each sample procedure.

Type of sample	N95 mask/surgical mask	Goggles or visor	Gloves (single use)	Gown/apron
Nasopharyngeal swab	N95 mask*	Goggles or visor**	Yes	Gown*** and apron

Nasal or mid-turbinate swab or saliva	Surgical mask	Goggles or visor	Yes	Apron
Observed (from 2 meters) self-administered swab or saliva collection	Surgical mask	No	No	No
Blood sample	Surgical mask	Goggles or visor	Yes	Yes

*N95 masks may be re-used up to 1 week by the same health care worker unless seal is compromised, or the integrity of the mask is compromised (https://www.nicd.ac.za/wp-content/uploads/2020/04/Covid-19-Infection-and-Prevention-Control-Guidelines-1-April-2020.pdf). For this study we will reuse for the day only.

**re-useable if cleaned appropriately (https://www.nicd.ac.za/wp-content/uploads/2020/04/Covid-19-Infection-and-Prevention-Control-Guidelines-1-April-2020.pdf)

*** Gowns are reusable if washed appropriately (https://www.nicd.ac.za/wp-content/uploads/2020/04/Covid-19-Infection-and-Prevention-Control-Guidelines-1-April-2020.pdf)

9.6.8. Verbal autopsy

Verbal autopsy (VA) will be implemented for every death occurring among study participants during the 18-month study period using the WHO 2016 VA form assessed by the InterVA software and a COVID-enhanced VA model.

9.7. Data collection

9.7.1. Questionnaires

The demographic characteristics of the households will be collected/re-assessed on enrollment by structured interview conducted by trained field workers. During each visit the development of symptoms and healthcare-seeking behavior of symptomatic cases will be recorded. Baseline and follow-up data will be collected in a REDCap tablet-based real-time database. The questionnaires are included in Appendix 2. This is due to the size and format of the download from the REDCap database.

9.7.2. Household contact data collection

All participating households will be approached to participate in the household contact study. All household members will be asked to wear the proximity device for 8 – 12 consecutive days (depending on the exact day the tag can be issued to each participant and recollected) during the intense 6-month follow-up period. To identify the location of contacts between household members within the home and the amount of time the study participants spend at home, tags will be placed in key locations within the houses (for example kitchen, living room, and bedrooms). During deployment, participants will be asked to complete a time sheet (Appendix 6) to indicate during what periods the tag was not worn. Household members will be eligible to participate in the main study even if they refuse to participate in the contact study.

9.7.2.1. Data collection infrastructure and type

The proximity tags detect dyadic close proximity interactions between individuals separated by ≤1.5 meters, suggestive of a conversation or skin-to-skin touch such as a handshake. The tags are considered to be in proximity when at least one data packet (device ID, timestamp, power level) was exchanged between them during a 20 second interval. A 20-second gap indicates a contact break. The tag will be

worn in a plastic pouch pinned to the chest or on a lanyard around the neck, on either the inside or outside of the clothing as preferred by the participant. Only face-to-face proximity relations will be detected since the radiofrequency used cannot propagate through the human body. For each deployment, field workers will issue each participating household member with a tag. Fieldworkers will ensure participants are properly trained on carriage and storage of devices. During the data collection with the devices, trouble-shooting and mitigation according to laid down SOPs will be conducted. The head of the household will also be asked to ensure that correct use of the devices is maintained throughout the study. At the end of each deployment period, fieldworkers will collect all the tags from participants and ship these to NICD where data retrieval will take place.

9.7.2.2. Community engagement and consent

A community engagement plan will be developed together with site partners, including relevant stakeholders (e.g., local health services). The household head will be requested to assent to engaging the rest of the household. Other residents will provide individual informed consent or assent as appropriate.

9.8. Specimen collection

Respiratory pathogen diagnosis depends on the collection of high-quality specimens, their rapid transport to the laboratory and appropriate storage before laboratory testing. Viruses are best detected in specimens containing infected cells and secretions. In addition, it is important for blood specimens for serology to be transported to the laboratory as soon as possible and cold chain maintained as delays in the transportation increase the number of contaminating bacteria, which secrete enzymes that can degrade antibodies within the sample. Specific procedures for the collection of specimens are described in Appendix 1.

The recommended specimen type for detecting SARS-CoV-2 is a nasopharyngeal (NP) specimen. This sampling method requires a healthcare professional to take the sample and is considered an aerosolizing procedure requiring specific PPE (N95 masks, goggles/visor, gown/apron and gloves) as detailed in section 9.6.7. Other specimen types such as nasal swabs or saliva have been proposed for the laboratory confirmation of SARS-CoV-2 infection and will be considered in this study based on validation of the specimen type, safety considerations for staff and availability of PPE. Standard operating procedures for the collection of specimens, use of appropriate PPE and the disposal of waste will be followed and monitored. Training at the start of the study will be intensive and documented. Also weekly training on safety and PPE will be done at each site. Audits of field procedures will be done on a regular basis and documented.

All human biological materials collected as part of this protocol will be used only for the study described in this protocol. A table summarizing the types of specimens to be collected and testing to be done is included below (Table 2).**Table 2: Specimens to be collected, timing, collection procedures and tests performed in the PHIRST study**

Specimen type	When collected	Collection container	Storage conditions	Tests performed

Blood	Seven times during the intense 12-month follow-up period (at enrollment and then every 2 months) from all study participants	Clotted tube	Refrigerate specimen, spin down within 8 hours and ship as soon as possible	Serology for SARS-CoV-2, influenza and RSV. HIV testing for consenting patients, when needed.
Blood	(i) Three times after the intense 12-month follow-up period (every 2 months for 6 months) from all study participants that tested positive for SARS-CoV-2 on rRT-PCR (14, 16 and 18 months); (ii) Once from all study participants (at 18 months)	Clotted tube	Refrigerate specimen, spin down within 8 hours and ship as soon as possible	Serology for SARS-CoV-2, influenza and RSV.
Blood	For confirmed HIV positive participants at the start of the study	EDTA and Heparin tube	Sample transported within 24 hours to reference laboratory	Viral load and CD4 count test
Nasopharyngeal or nasal flocked swabs or saliva	Twice weekly during the intense 12-month follow-up period	Universal Transport Medium (UTM)	Short term refrigerate at 2-8 ◦C, long-term freeze at -20◦C or -80◦C	PCR* for SARS-CoV-2, influenza and RSV

*PCR polymerase chain reaction

9.8.1. Blood samples for serologic testing

We will collect whole blood for serologic testing from each household member as described in sections 9.6.5 and 9.6.6. These specimens will be tested for anti-SARS-CoV-2, influenza and RSV antibodies. 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 at each blood draw. Detailed procedures are described in Appendix 1 - Section 3.

9.8.2. EDTA tube for CD4 testing and heparin tube for viral load testing,

We will collect a sample for CD4 count and viral load testing on individuals testing positive for HIV.

9.8.3. Nasopharyngeal or nasal swabs or saliva for identification of respiratory pathogens

Nasopharyngeal or nasal flocked swabs (Copan Diagnostics, Murrieta, CA or Media Mage) or saliva will be collected twice weekly and placed in universal transport medium. Procedures for collection are described in Appendix 1 Section 2.

9.9. Specimen labeling

The collection containers will be marked with:

- The unique identifier
- Visit number
- The specimen collection date
- The type of specimen in the tube (e.g. nasopharyngeal swab)

Note: The tube/universal container itself and not the cap should always be marked with identifying details. An indelible and alcohol resistant marker should be used as stick on labels can easily come off, especially when the specimens are chilled.

As soon as the specimens are collected, the relevant information should be recorded on the Laboratory Specimen Submission Form (Appendix 2).

9.10. Specimen transport and storage

9.10.1. Nasopharyngeal/nasal/saliva specimens

Specimens should be placed in universal transport medium and can be stored for up to 4 days at 2-8˚C. Specimens will be transported from the site laboratory to the NICD for testing on the day of collection or the following day. Specimen aliquots will be stored in a -70 deg C freezer until testing.

9.10.2. Blood samples

Clotted blood samples collected in vacutainer tubes should be kept refrigerated (2-8°C) and should be transported as soon as possible to the laboratory on ice along with the laboratory slip. Site laboratories will spin the blood at 1000g for 10 minutes, keep tubes upright after centrifugation and ship in that manner to NICD. ETDA/heparin samples will be collected for CD4 and viral load testing, these will be shipped immediately to Lancet laboratories in either Hazyview or Klerksdorp for testing.

9.10.3. Packaging and transport

Detailed information about packing/transporting specimens can be found in Appendix 4. Specimens will be transported in sealed plastic bags. Blood and respiratory specimens must be kept cold during transport and a cooler box filled with ice packs can be used for this purpose.

9.11. Laboratory methods

9.11.1. PCR testing for SARS-CoV-2, influenza and RSV

Nucleic acids will be extracted from UTM using automated extraction methods. Upper respiratory tract samples will be tested for SARS-CoV-2, RSV and influenza A and B viruses by real-time reverse transcriptase PCR (rRT-PCR) using commercial kits validated in the laboratory. Influenza A and B positive samples will be subtyped using the CDC influenza A (H1/H3/H1pdm09) subtyping and the CDC B/Yamagata- B/Victoria lineage typing kits respectively (available through Influenza Reagent Resource Program; www.influenzareagentresource.org) RSV A and B subtypes will also be determined using an in-house rRT-PCR.

9.11.2. Microbiome studies

A subset of specimens will be selected for in-depth analysis of the composition of the nasopharyngeal microbiota. The 16S gene is a conserved gene with variable regions amongst bacteria, and therefore sequencing of this gene enables the detection of all bacteria in the microbiota. Bacterial DNA will be extracted from nasopharyngeal specimens, quantified, and the 16S rRNA gene amplified and sequenced using next generation sequencing technology [29,30]. Sequences from the 16S rRNA V5-V7 variable regions will be compared to a database of known microbial sequences to identify the microbes present. There will be no direct or intentional sequencing of human DNA, any residual human reads will be informatically filtered and discarded prior to analysis.

9.11.3. Serologic testing for immunologic response to SARS-CoV-2, influenza and RSV

Blood samples will be tested for rise in SARS-CoV-2, influenza and RSV antibody titres. SARS-CoV-2 antibody titres will be determined using three different serological assays, as each may detect different antibody classes and may differ in sensitivity. We will characterize binding antibody kinetics to the SARS-CoV-2 spike trimer and receptor binding domain using in-house ELISAs. In addition, we will investigate neutralizing antibody titres and duration using an in-house pseudotyped neutralization assay.

Hemagglutination inhibition (HAI) assays will be performed to determine serological reactivity titres for serum samples against reference influenza virus antigens based on the selected vaccine strains and strains predominantly circulating in South Africa during each year. Turkey red blood cells will be used as indicator in the HAI assay. The protocol will be based on the method described by Rowe et al. (1999) [31].

RSV antibody titres will be determined using an enzyme-linked immunosorbent assay based microneutralization assays previously described [32,33].

9.11.4. HIV testing

All patients will be offered HIV testing at the baseline visit and then 6 monthly for individuals testing HIV-negative at the previous visit.

HIV status will be defined as follows:

- If the patient has a documented positive HIV result (or evidence of ART) available in the medical records they will be recorded as HIV positive.

- If the patient is not aware of their status or a previous result documents a negative result the patient will be offered voluntary counselling and testing (VCT) by rapid HIV-antibody detection tests or by PCR assay from dried blood spots (tested at NICD) for patient under the age of 18 months.
- From consenting patients who do not want to have a rapid HIV test as described above, blood samples already collected for serologic testing will be also tested for HIV infection. Patients will be offered the option to receive their result if they would like to.
- A documented HIV negative status for the mother would be confirmation of negative status for a child under the age of 10 years.
- In order to define HIV exposure in infants, the mother's HIV status at the time of pregnancy will need to be defined; this information will be gained verbally from the mother and confirmed by the clinic/hospital records or the child's road to health card. If mother's HIV status is unknown, she will be offered VCT and rapid HIV testing as described above.
- Patients not wanting to know their HIV status or unwilling to provide an anonymous sample may still be enrolled into the study.
- For HIV-positive patients, a specimen for CD4 count will be collected if there is no recent documented CD4 count results (within 6 months of household enrolment).
- Patients newly diagnosed with HIV will be referred to the local clinic for assessment for initiation of antiretroviral therapy
- All individuals who decline HIV testing, will be encouraged to test at follow up visits and the benefits of knowing your status emphasized.

9.11.5.Organism characterisation

SARS-CoV2, influenza virus and RSV viral diversity within or amongst households will be investigated using whole genome or cell entry gene sequencing .Sequencing of all three viruses will be performed following cDNA synthesis and either PCR of HA gene segments or complete genomes or probe selection of viral nucleic acids [34,35]. Cell entry gene amplicons will be multiplexed and run at low-cost on the PacBio Sequel platform, while genome sequencing will be performed on the Illumina MiSeq next generation sequencing platform. In-house and published pipelines will be employed to map whole genomes or gene-specific sequences to known references. Multiple sequence alignment of nucleotide and amino acid sequences in addition to subsequent phylogenetic analysis will be performed on codon aligned sequences with the Geneious software package employing a Hasegawa-Kishino-Yano (HKY) substitution and Gamma site heterogeneity models as inferred by the data. Tree topologies and robustness will be assessed by bootstrap analysis using 100-1,000 replicates depending on whether maximum likelihood or neighbour-joining tree drawing methods are used. Representative reference sequences of relevant viral strains will be retrieved from GenBank and GISAID. Influenza-positive samples may also be shared with the World Health Organization Collaborating Centres as part of the Global Influenza Surveillance and Response Network.

9.12. Patient compensation for household visits

Each participant will be compensated for the time commitment involved in this intensive study. Each participant will be compensated for each study visit with a voucher for the local supermarket to the value of R50 and R100 for the blood draws on COVID-19 positive cases that continue after the intensive follow

up. An additional voucher will be issued to each participant upon return of a proximity tag with no visible physical damage after each deployment.

9.13. Procedures for enrolment and consent

Study participants will be identified through random sampling as described in Section 10.5. The purpose of the study will be explained to all household members in English or the local languages (as per the preference of the participant). In addition, a printed study information sheet will be provided in English and appropriate local languages for participants to read. Participants aged 18 years and older will be asked to give written consent. For participants younger than 18 years of age the parent/guardian/primary caregiver will provide for written consent for the child. Assent will be obtained from children between 7 years and 17 years by a similar process. 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. Consent to continue in the study will be obtained verbally at all follow up visits. Consent and assent forms can be found in Appendix 5.

9.14. Ethical consideration and approval

Ethical approval for the study will be obtained from the University of the Witwatersrand Human Research Ethics Committee (HREC) making use of the COVID-19 fast-track ethics review. The protocol will be submitted for a reliance from the US CDC ethics committee.

9.15. Referral to health services

Study health care providers (nurses) will be trained in the symptoms of COVID-19, signs of severity and will do an initial assessment of any positive cases. As the household is visited twice a week the study nurse will review symptoms of severity as per standard operating procures at each of these visits. If the nurse has concerns over the wellbeing of a participant, she will be able to call any of the clinicians associated with the study and if necessary refer the participant to the nearest appropriate health facility (clinic or hospital) as per the provincial guidelines for COVID-19 cases. In principle, the following hospitals are the closest point of referral (Matikwana, Mapulaneng and Tintswalo hospitals for Agincourt sites and Klerksdorp/Tshepong hospitals in the Northwest Province). Matikwana, Mapulaneng, Klerksdorp and Tshepong hospitals form part of the NICD pneumonia surveillance programme and patients referred to these hospitals will be enrolled into the pneumonia surveillance programme (Wits HREC Protocol number M140824). Patients with newly-diagnosed HIV infection will be referred to the local clinic for assessment for antiretroviral treatment including CD4+ T cell count testing.

9.16. Prevention of SARS-CoV-2 and other infections in front line staff

The investigators acknowledge there is tangible risk to the study team and potentially to participants due to the circulation of SARS-CoV-2. This risk will be hard to quantify in the presence of community transmission. Front-line staff including study nurses will be trained in infection control procedures including proper hand hygiene and the correct use of surgical face masks, not only to minimize their own risk of infection when in close contact with patients during home visits and elsewhere, but also to minimize the risk of the nurses acting as a vector of infection between household members or between households. They will also be offered influenza vaccination prior to commencing the study, and again before the influenza season next year (we are in the process of acquiring stock of vaccine for 2020). Staff will be properly trained in collection of blood specimens and disposal of sharps. Staff will be requested to

stay home from work and practice good respiratory hygiene and handwashing if they have symptoms of any respiratory illness.

In order to protect staff, in the working environment, study staff will be trained on and equipped with appropriate PPE. Standard operating procedures will be written to cover all aspects of the study. Retraining on PPE will be conducted on a weekly basis. Random audits of field procedures will be conducted to ensure that procedures are followed. The following additional procedure will be applied to the working environment to protect staff and participants.

Study transport will be arranged to protect staff from exposure to public transport. Staff transport will be by vehicle with a minimum 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.

On arrival at work staff members will change into scrubs (and head cover) after handwashing procedures. Staff will practice physical distancing at all times. All equipment needed for the day will be washed down with soap and water prior to leaving the offices for the field. Electronic equipment will be cleaned with alcohol-based disinfectant. Each team will be equipped with a portable handwashing station (including a bucket of water and soap) and adequate hand sanitiser daily. Temperature will be checked 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 wash their hands and wear a cloth mask provided by the study (additional masks and washing instructions will be provided). Interviews will be conducted from a distance of at least 2 metres from the interviewer outside of the house and with no physical contact between participants and study staff member.

When all the samples and data have been collected all equipment such as chairs, table, visors and electronic equipment will be washed with soap and water or wiped down with alcohol solution. Prior to leaving the household all staff members will wash their hands.

At the end of each workday staff will remove their scrubs and shower. All cloth masks and scrubs used during the day will be removed and washed at the study office in a washing machine. Washing procedures will be done as per the Environmental Guideline (REF NICD webpage). The interior of study cars will be washed down with soap and water at the end of every day.

The study team will convene a safety advisory board (SAB) to advise investigators on the safety procedures in the study including the appropriate PPE, safety procedures for interaction with infected household members, other workplace safety concerns. The SAB members will be independent of the study and constitute clinical, microbiology and infection prevention and control experts. A community representative will be included from each site. The SAB will review and advise the investigators on the study design and procedures specifically with respect to securing the safety of study staff and participants. This is primarily due to the infectious nature of the SARS-CoV-2 virus and the potential severity of infection with the virus. The SAB will also make recommendations to modify safety and other procedures related to safety during the trial as these arise.

Individuals testing positive for SARS-CoV-2 will be notified through the NMC (Notifiable Medical Conditions) system and rapidly communicated to the provincial Departments of Health (Mpumalanga and North West provinces) and contact tracing handed over to the province. All relevant information will be shared on the NMC system as required, and a contact line list will be completed and shared with provincial colleagues. Positive participants and household members will be advised to isolate or quarantine at home or at designated facilities as per guidelines of the national Department of Health.

A nasopharyngeal swab will be collected from all field workers on a weekly basis and tested for SARS-CoV-2, influenza and RSV to document possible infection transmission to and by fieldworkers. Any positive test will be considered an adverse event and will be reported to the study SAB. This testing is for the safety of the staff member, other staff members in the research teams, and participants.

9.17. Study instruments

- The study forms will include: Study logs for each visit
- Forms for completion at the first study visit:
  .1. Identification form
  .2. Enrolment of household form
  .3. Case intake form
- Forms for completion at twice weekly visits:
  .1. Follow-up form
  .2. Lab slip
  .3. Hospitalization forms (if triggered)
  .4. Death form (if triggered)
- Once off forms for each cohort
  .1. HIV staging form
  .2. Proximity sensor time sheet

9.18. Data management

All data gathered during household enrollment, first study visit, follow-up visits and bi-monthly visits will be collected electronically during each household visit using the REDCap electronic data collection system and uploaded directly to the REDCap database at Wits University. This will include information on household demographics, signs and symptoms, contact patterns among household members, sample collection and selected laboratory results (e.g. HIV testing results). Unique identifiers including household, household members and follow-up visit identifiers will be used for each household visit. 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 on-site study manager and database manager. This will include verification of completeness and accuracy of collected data. A study log will be maintained by study staff and compared with a pre-established study calendar to assess concordance of study implementation with study procedures.

The data manager at NICD will access the database on a daily basis to check and follow up on progress and data quality. Data quality and completeness will be again evaluated at NICD by a dedicated data manager.

Laboratory results for SARS-CoV-2, influenza and RSV will be entered into the same data system (REDCap) which will be hosted on the server at Wits University. Each sample will be identified by the same unique identifier allocated to each individual household member (including the follow-up visit identifier) and, after data quality verification, linked monthly with the central database encompassing data collected at both sites.

Participant names and study identifiers will be captured in a separate database at the start of the study and will be concealed from data entry staff. All patients will be allocated a unique study number which will be used for all study information and specimen labelling. Patient identifier data may be accessed by laboratory staff for the purposes of laboratory reporting of diseases which require patient treatment or public health action.

To fulfil the requirements of anonymity, no personal identification will be displayed in any reports or communication regarding this investigation. All study data will be archived electronically on the REDCap server at Wits University, which has additional back-up capability.

9.18.1. Data management for the household contact study

9.18.1.1. Data Storage

Data collected by the wearable devices will be stored internally and downloaded from the sensors using a JLINK JEGGER nRF51 development kit and programmer connected to a Windows computer with Oracle VM installed and a Linux (Ubuntu) virtual machine created. Raw data will be downloaded in an encrypted format from the devices and stored together with log files in a secured folder on NICD servers.

9.18.1.2. Data analysis

Characterizing contacts: Patterns of contact will be described using several quantities that quantify the number of unique individuals contacted (degree), number of contacts between individuals (frequency), the duration of these contacts (weight) and the cumulative time spent in contact by each pair of individuals. The statistical distribution and variations will also be assessed. Heterogeneity of the contacts and their statistical distributions will be assessed across six key variables: demography, temporality, grade, role and setting. Analysis will be conducted using R and Python.

Characterizing networks: To describe the characteristics of networks, network data analysis and visualization will be aggregated at the household level. Temporal data will be aggregated hourly, daily and over the entire duration of study. Networks will be stratified by the covariates (demography, grade, role, setting). Nodes and edges will represent individuals within the stratum and the occurrence of a contact between the nodes, respectively. Results obtained from this descriptive analysis will be used to determine the appropriate statistical network model to be used to better understand the heterogeneities affecting the observed network structure. This will also provide household-based mixing parameters to be used in a transmission model.

Network and Transmission models: The transmission model will investigate the role of mixing between and within households and schools on the risk of the SARS-CoV-2 epidemic. The network model will investigate the impact on transmission dynamics of key features identified from the household and school socio-behavioural structure. This will be undertaken to establish which quantities appear to have dominant impact on transmission rates and patterns and intervention impact on SARS-CoV-2 infection.

9.19. Variables

9.19.1. Main outcomes of interest for the primary study objective

The main outcomes of interest, will be as follows:

- Laboratory-confirmed SARS-CoV-2-infection on PCR or serology
- Consultation with a primary care provider
- Proportion of laboratory-confirmed SARS-CoV-2 infections that are symptomatic

9.19.2. Main exposures of interest and secondary outcomes

9.19.2.1. Individual level exposures on questionnaire

- Age – in months for <1 year and in years thereafter
- Date of birth
- Sex
- Study site – Agincourt area of Bushbuckridge, Mpumalanga or Klerksdorp, North West Province
- Influenza/RSV co-infection
- HIV status – infected, uninfected, unknown
- Underlying conditions other than HIV – the presence of immunocompromising conditions other than HIV will be recorded: Such conditions include a) prematurity or ex-prem babies with a history of chronic lung disease; b) protein-energy malnutrition; c) primary immunodeficiency states involving the adaptive and innate arms of the immune system e.g. agammaglobulinaemia, common variable immunodeficiency, DiGeorge syndrome, severe combined immunodeficiency, chronic granulomatous disease, complement deficiencies, leukocyte adhesion deficiencies; d) conditions in which there is functional or anatomic asplenia e.g. sickle cell anaemia, situs inversus with polysplenia or asplenia, splenectomy following trauma or as part of the management of chronic immune thrombocytopenic purpura; e) chronic organ dysfunction with impaired production of immune mediator proteins, or enhanced excretion of such proteins, e.g. chronic liver disease and chronic renal disease (specifically nephrotic syndrome); f) chronic lung disease, e.g. poorly-controlled asthmatics on long-term systemic steroid therapy, bronchiectasis, bronchiolitis obliterans, cystic fibrosis, Kartagener syndrome; g) conditions in which respiratory secretions are poorly mobilised due to neuromuscular disease, e.g. cerebral palsy, congenital myopathies, muscular dystrophies; h) chronic cardiac disease predisposing to recurrent episodes of cardiac failure, and/or pneumonias, e.g. atrioseptal and/or ventriculoseptal defects, cardiomyopathy; i) children on immunosuppressive therapies, e.g. cancer chemotherapy, immunomodulatory therapy for connective tissue diseases, immuosuppressive therapy post organ transplantation; j) children with metabolic diseases, e.g. congenital adrenal hyperplasia, poorly-controlled diabetes mellitus, galactosaemia; k) intrinsic genetic defects predisposing to recurrent infections, e.g. Trisomy 21.
- Type of residential dwelling categories include: formal house/apartment, informal dwelling, traditional house (information available from 2016-2018 PHIRST study)
- Overcrowding in residences: this will be assessed by determining number of people residing in the household, as well as the number of rooms in the household (excluding bathrooms and kitchen). An index of number of people per room will be used to assess impact of crowding in the household. We will also assess the number of people sleeping in the same bedroom, as well as the number of children residing in the household.

- Cigarette smoke exposure: in children exposures to passive smoking on history will be analyzed. Passive smoking will be defined as a participant who resides in a household where there is active smoking indoors and/or where they are exposed to an indoor cigarette smoking environment (other than their residence) for more than three hours every week. For adults and teenagers a detailed smoking history will be taken.
- Exposure to smoke in the household from indoor fires.
- Education level: the highest level of education achieved by each participant will be determined. This will be analysed according to whether the caregiver achieved a primary, secondary or tertiary level of education.
- Socioeconomic status: various tools will be used and adapted to determine the socioeconomic status of participants. Items used by the World Bank in the Demographic and Health Survey Wealth Index as well as those used in the Agincourt Health and Demographic Surveillance System Asset status module57 will be included in the questionnaire. These items will be analysed and participants will be placed into one of five social classes (quintiles) ranging from wealthiest to poorest.
- Locality type: urban formal, urban informal, rural formal or rural informal.
- Race group: participants will be asked to classify which category would best describe their race. Options included in the questionnaire are: Asian, Black, Coloured or White.
- Vaccine history for individuals <18 years EPI vaccines will be assessed
- Influenza and pneumococcal vaccine in adults will be assessed in the questionnaire
- Breastfeeding: for children we will assess whether the child is currently being breastfed and breastfeeding in the first 6 months of life.
- Attendance at day care: attendance at a day-care facility with more than 5 other children for at least 3 days a week for 3 hours each day for children <7 years.
- Attendance at school: will be assessed for all individuals aged <21 years
- HIV exposure status (mothers HIV status) will be assessed for children aged <10 years
- Receipt of cotrimoxazole prophylaxis (this may be prescribed for HIV-exposed but uninfected children as well as HIV-infected patients) will be assessed in the baseline questionnaire,
- Variables for HIV infected individuals
    - HIV stage – the clinical stage of HIV infection in HIV infected individuals will be assessed in a questionnaire and CD4 count test
    - Use of antiretrovirals (ARVs)
        - Whether the patient is currently receiving ARVs (Y/N)
    - Duration of ARV therapy (current date minus date of initiation of therapy)
        - This will be categorised into groups: <3 months; 3 - 6 months; 6 - 12 months; 12 - 36 months; > 36 months
    - Current antiretroviral drugs taken
    - Attendance at dedicated HIV clinic: whether the patient reports regular attendance (more than 2 scheduled visits attended in the last year) at an HIV clinic

9.20. Statistical analysis

9.20.1. Estimation of the community burden of SARS-CoV-2, influenza and RSV infection

Incidence of SARS-CoV-2, influenza and RSV infection within age groups and HIV infection status will be estimated using serological and PCR data. Incidence obtained from the study subjects will be standardized to the demographic characteristic of the study sites to account for potential differences between the selected households and the population. The symptomatic fraction will be expressed as the proportion of SARS-CoV-2, influenza and RSV positive cases that developed symptoms. Severity of symptoms will be assessed over a pre-established scale and analyzed using ordinal regression (proportional odds model) to discriminate between severe and mild disease. In addition, the proportion of individuals that were hospitalized and/or died will be reported. The healthcare seeking behavior among the symptomatic patients will be assessed.

9.20.2. Estimation of the transmission dynamics of SARS-CoV-2, influenza and RSV in the community

The incidence of infection of PCR confirmed cases will be estimated for each of the selected pathogens. The SIR for each pathogen will be evaluated among all households in which at least one household member tested positive by PCR for one of the selected pathogens The SIR will be expressed as the proportion of infected individuals divided by the individuals at risk excluding the index case. The generation time in the transmission chain will be expressed as the time of infection of the index case to the time of infection of secondary cases within the household. The incubation period will be defines as the time of infection to the time of symptoms onset.

A metapopulation transmission model will be developed for each pathogen to assess the characteristics of the individuals serving as the most likely source of infection for the household as well as the transmission dynamics of infection when the pathogen is introduced in the household.

For each pathogen the intensity of the transmission will be assessed through the estimation of the effective reproduction number (R_t) and it's variation over time.

9.20.3. Estimation of determinant of transmission within household

For each pathogen factors associated with risk of infection will be assessed using unconditional logistic regression and survival analysis. Predictors will include individual and household level demographic characteristics, co-infection (or preceding infection) with other respiratory pathogens, co-morbidities (including HIV infection) as well as environmental and behavioral factors.

9.21. Personnel, training and supervision

Surveillance staff (registered nurses, enrolled nurses, and/or research assistants/counsellors) will be employed at each proposed study site to assist with patient enrolment, sampling and completing questionnaires. All nurses and research assistants/counsellors will be trained in obtaining consent, completing study forms and HIV pre-and post-test counseling. The nurses will be trained in taking adequate samples. In the context of COVID-19, additional weekly training on PPE for each procedure will be done. This will include the PPE needed for each specimen type, reuse of PPE (if appropriate), sample taking, waste disposal and repeated cleaning of surfaces/equipment. PPE is imperative for the protection of staff members and participants but is in short supply nationally, so conservation of PPE will be

considered, for example planning of blood draws at the same time as NP swabs to use the same PPE for two procedures on the same participant.

Each study site will have a study co-ordinator, accountable to the site-PI, who will be responsible for on-site supervision of day-to-day activities of the study team. The site co-ordinator and database manager/epidemiologist will monitor the forms submitted and review a subset of forms for completeness and consistency of data on a regular basis. Staff from NICD will conduct study calls weekly to evaluate overall site performance.

9.22. Monitoring and evaluation

Performance indicators will be developed for:

- Questionnaire completion e.g. number of fields completed, inconsistencies in data, visits with missing forms
- Completeness of visits – completeness of household visits including specimen collection and forms
- Specimen submission – numbers of cases with no specimens submitted, specimen labeling
- Data entry – consistency checks, lag in data entry etc.
- Laboratory indicators – time taken to transport specimens to laboratory, turn-around-time for results

9.23. Study limitations

The limitations of this study pertain mainly to the implementation of the study in two selected study settings, which may put limits on the generalisability of the study results to other areas or settings.

9.24. Risks potentially affecting the successful implementation of the study

The following are considered realistic threats to the study not being started/completed: The context of the study within the country in terms of Department of Health and National Government measures to control SARS-CoV-2 spread will need to be considered when implementing the study, for example movement of staff members during a lock-down situation. Lockdown restriction may impede supply chains and procurement of supplies. Rural communities, some distant from urban centres, may not experience the introduction of SARS-CoV-2 in the next few months delaying the start or lead to slow introduction and low incidence rate of infection and low community attack rate. Conversely, community transmission in the target community may occur before the study is fully operational. Lack of regular supply of sampling material, personal protective equipment, or reagent and consumables may cause stoppages in the study.

9.25. Dissemination and publication of results

Finding of the study will be summarized in monthly reports and study results will be communicated to relevant stakeholders, including the National and Provincial Departments of Health, policy community and modelling groups. Study findings will be published in the peer-reviewed literature.

9.26. Study timelines

Activity	Date	Details
Protocol development	April 2020	

Ethics review and approvals	Early May 2020	Approval finalized Mid-May 2020
Appoint staff and staff Training	April to early May	
Selection and enrolment of households	Mid-May 2020	
First household visits	As household enrolled (May 2020).	
Proximity tag pilot study	May- November 2020	
End of intense follow-up period	June 2021	
End of study (including blood sampling up to 12 months following the intense follow-up period	December 2021	
Data finalization and cleaning for publication (data will also be analyzed as they become available and outputs will be shared in real time with the relevant stakeholders)	January 2022	
First draft of main manuscripts	February 2022	
Other manuscripts	December 2021 to December 2022	

9.27. Budget and funding source

The main study is funded as a project under the Cooperative Agreement between the United States Centers for Disease Control and Prevention with the South Africa National Health Laboratory Service (NHLS) – Agreement # 5U19GH000622-03 Research Cooperative Agreement.

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Appendix 1 Specimen collection

1. Mid-turbinate self-swab nasal specimen collection

- **Open nasal swab:** remove the nasal swab from the wrapper by pulling the two ends of the wrapper apart. Be careful to only touch the handle, not the tip (Figure 1).

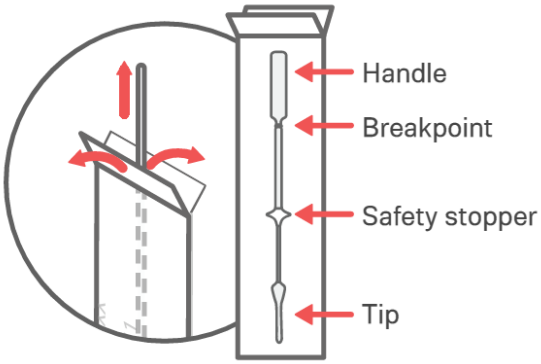

Figure 1: Nasal swab

- **Loosen cap on tube:** slightly loosen the cap from the tube so it's easier to open later. Place it in a safe location where it won't spill – there is liquid inside (you'll be putting your swab into this tube when finished) (Figure 2).

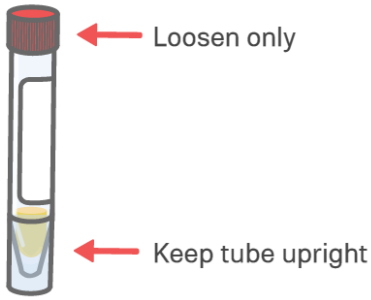

Figure 2: Specimen collection tube

- **Swab nose:** Tilt your head back, look up at the ceiling, and gently insert the soft tip of the swab into one nostril until the safety stopper touches the edge of your nostril. Gently twist the handle in a circular motion for 15 seconds. Next, gently insert the same swab into the other nostril and repeat the same 15-second procedure (Figure 3).

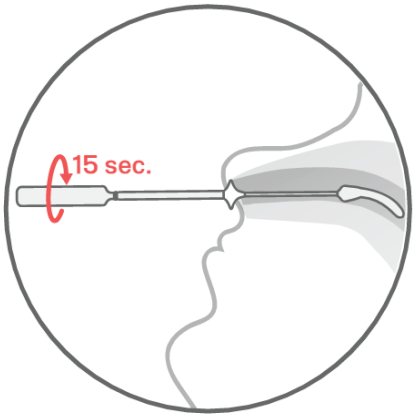

Figure 3: Sample collection

- **Put swab in tube:** Lower the swab, tip first, into the provided tube. Once the tip is at the bottom, break the swab handle at the swab breakpoint by bending back and forth. Screw the cap on tightly and hand it to the study staff (Figure 4).

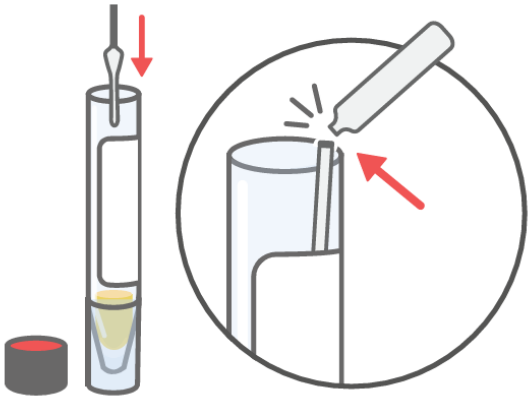

Figure 4: Putting swab in tube

2. Nasopharyngeal (NP) swab collection

- A flexible, fine-shafted flocked swab is inserted into the nostril and back to the nasopharynx until a slight resistance is met the swab is rotated two to three times and held in place for 5 seconds to ensure maximum absorbency (Figure 5).
- It is then slowly withdrawn with a rotating motion and placed in virus transport medium (VTM). The tip of the swab is put into a vial containing 2–3 ml of VTM and the plastic shaft is broken at the break point line so that it can fit in the VTM, taking care not to touch the tip.
- The NP swab can be put in the same container as the OP swab.
- Place the specimens on ice in laboratory cooler box.
- Complete the lab requisition forms/lab slip
- Note: Nasopharyngeal swabbing is an invasive process that can cause considerable distress to the patient.

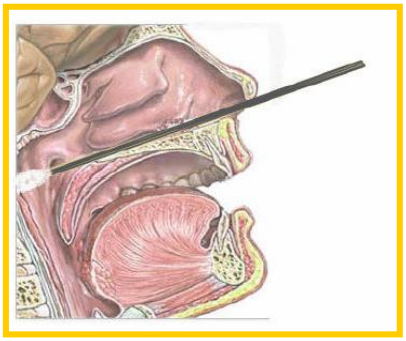

Figure 5: Nasopharyngeal (NP) swab

3. Blood specimens collection

- Specimens will be collected using the vacutainer collection system, as follows (Figure 6):
- By twisting, remove the bottom white cap (D) of the needle.
- Now, firmly screw the needle in the needle holder/barrel (B).
- Remove the top cap (C) to ready the needle (A) for use just before the sample is taken.

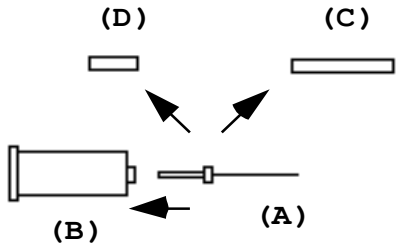

Figure 6: The Vacutainer Needle & Barrel System

- Apply the tourniquet to the patient's arm (a) and disinfect the site of venepuncture (Figure 7).
- Hold the needle holder between thumb and index finger of the right hand and insert into the vein (b).
- Now change the position of the hand i.e. fixes the needle holder on the patient's arm with the thumb and index finger of the left hand. The left hand now serves to keep the needle immobilized in the vein during the different actions.
- Position the first tube in the holder and press it onto the needle to allow the tube to fill (c).

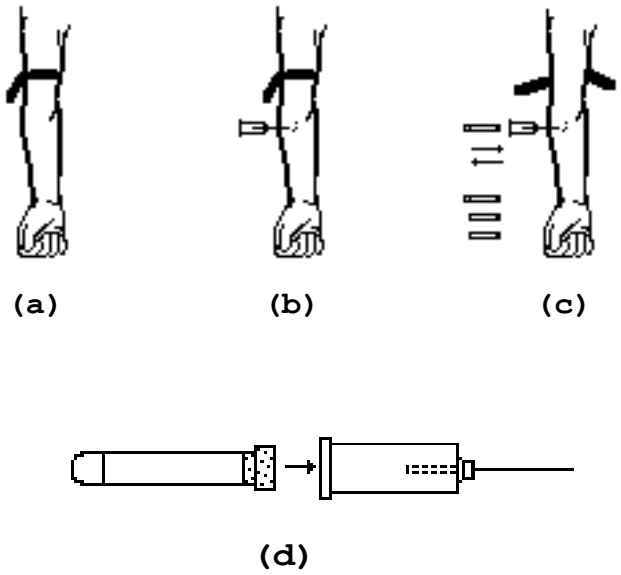

Figure 7: Collecting the Sample

- Fill the tube and remove once full.
- Release the tourniquet then remove the needle from the patients arm and immediately apply pressure to the venipuncture site. Firm pressure at this time will minimize bruising and therefore discomfort and distress to the patient.
- Ask the patient to take over applying pressure to the site.

If collecting blood in EDTA:

- Invert the ETDA, purple topped, tube gently 6 to 8 times (Figure 8)

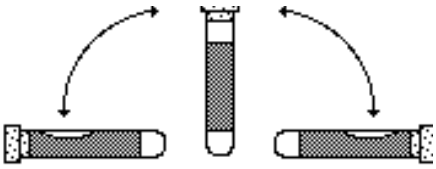

Figure 8: Inverting the EDTA

- Check that all the barcodes match and that you have marked the tube with the patient's unique bar coded study number.

Blood collection for infants and young children

- Use a winged 23 gauge needle, with a butterfly. Avoid gauge ≥25 gauge because these may cause haemolysis.
- Use a butterfly with either a syringe or an evacuated tube with an adaptor that has a barrel volume of 1-5 mls depending on collection needs.

Appendix 2 Forms and logs (Sample documents, updated version as per initial approval)

1. Study logs

Centre for Respiratory Diseases and Meningitis (CRDM), NICD
TEL: 011 386 6410 or 011 386 6434 **FAX:** 086 723 3569

Site: □ Klerksdorp □ Agincort

Household code: _____

Household visit: □ Household enrollment □ First study visit □ Follow up visit □ Last study visit

Thick all that apply

□ Household enrollment form (for household enrollment visit only)

Form/Event	Household member														
	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____	ID:____
Household member enrollment form*	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Follow up questionnaire	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Household member hospitalized	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Hospitalization Form	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Household member died	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Death Form	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Laboratory Slip	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Nasopharyngeal swabs	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Blood (clotted)	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
HIV rapid test	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□
Copy of vaccination card	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□

* For household enrollment visit only

2. Household enrollment form

PHIRST Study: Enrolment of household Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

Household Characteristics

To be administered at the household enrolment visit after verification that enrollment criteria are met and consenting of household members.

ID Code

Date __/__/____ Time __:__

Interviewer_____

Household Characteristics *(For the head of the household)*

1. Total number of household members: ____
   1a. Total number of household members enrolled: ____
   1b. Number of temporary/transient household members:____

2. Total number of rooms in the house:____

3. Number of rooms for sleeping in the house:____

4. Do you have place to wash your hands? □ Yes □ No
   If YES:
   7a. Can you show me where you typically wash your hands? *(Observed)*
   □ At a sink with running water
   □ From a water bottle reserved for that purpose
   □ At a faucet outside
   □ Other (specify):_____
   7b. Is water available at the hand washing area? *(Observed)* □ Yes □ No

5. What type of product is most available for family members to clean their hands in your household?
   □ Soap
   □ Hand gel
   □ Hand wipes
   □ Other (specify): _____
   □ Nothing

6. What type of hand dryer is most available in your household?
   □ Tissue/paper

□ Cloth towel
□ Other (specify)_____
□ None

7. Do you cook inside or outside of the home?
□ Inside
□ Outside
□ Don't know

3. Case intake form

PHIRST Study: Case Intake Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

Individual Member Information to be collected form each household member

Demographics

1. ID Code

2. Date Enrolled: ___/___/____

3. Relationship to head of household
   - □ Self
   - □ Caregiver/Parent/Guardian
   - □ Sibling
   - □ Child
   - □ Spouse
   - □ Relative

4. Date of birth: ___/___/____

5. Sex
   - □ Male
   - □ Female

Study/Work Environment

For students:

6. Are you currently a student/scholar? □ YES □ NO

(IF YES Q7-8)

(IF NO skip to Q9)

7. What type of school do you go to?
   - □ Nursery/Kindergarten
   - □ Primary school
   - □ Secondary school
   - □ Post-secondary education/University
   - □ Other (specify) _____

8. What is the average class size (persons/class)?_____

(Skip to Q14)

For non-student

9. What is the highest level of education you completed?

□ No schooling / kindergarten
□ Primary
□ Secondary
□ Matriculation
□ Post-secondary

10. What is your occupation?
□ Not working (Skip to 25)
□ Agriculture
□ Mining
□ Construction
□ Sales/retail
□ Health, medical, healing
□ Domestic helper
□ Other (Specify): _____

11. Do you work indoors or outdoors?
□ Indoors
□ Outdoors

12. What type of indoor environment do you work in?
□ Office buildings
□ Hotels & boarding houses
□ Shopping centre / plaza
□ Healthcare facility
□ Mine
□ School
□ Other (Specify):_____

13. How many work colleagues do you routinely meet daily? _____

Social Habits *(If ≤15 years old skip to Q16*)

14. Do you drink alcohol? □ YES □ NO

If **YES**

14a. How many units per week? _____ (a unit is a glass of wine, a bottle of beer, or a shot of liquor)

□ liquor
□ wine
□ beer

15. Do you currently smoke? □ YES □ NO

If **YES**

15a., how many cigarettes do you smoke per day? _____

Hand washing / social behaviors

16. When you do NOT wash your hands, why do you not wash them?

□ Inconvenient
□ Forget
□ Too busy to wash hands
□ No towel, tissue or blower to dry hands
□ No water
□ No soap
□ Unnecessary
□ Other, specify: _____

17. Do you avoid contact with the index case, the household member who first became sick?

□ Always
□ Often
□ Sometimes
□ Never

18. Do you slept in a separate bed from a person that become sick in the house?

□ Always
□ Often
□ Sometimes
□ Never

Past Medical History

19. Do you have any underlying illness or condition at the moment?

Asthma	□ YES	□ NO
Other chronic lung disease	□ YES	□ NO
CVA/Stroke	□ YES	□ NO
Cirrhosis/Liver failure	□ YES	□ NO
Chronic renal failure	□ YES	□ NO
Heart failure	□ YES	□ NO
Valvular heart disease	□ YES	□ NO
Coronary artery disease (except hypertension)	□ YES	□ NO
Pregnancy	□ YES	□ NO
Organ transplant	□ YES	□ NO
Any immunosuppressive therapy, cortisone, chemotherapy, radiation therapy	□ YES	□ NO
Sickle cell	□ YES	□ NO

Splenectomy	□ YES	□ NO
Diabetes	□ YES	□ NO
Burns	□ YES	□ NO
Immunoglobulin deficiency	□ YES	□ NO
Autoimmune disease, SLE	□ YES	□ NO
Kwashiorkor/Marasmus	□ YES	□ NO
Nephrotic syndrome	□ YES	□ NO
Spinal cord injury	□ YES	□ NO
Seizure disorder	□ YES	□ NO
Prematurity	□ YES	□ NO
Obesity / BMI >=30	□ YES	□ NO
COPD/Emphysema	□ YES	□ NO
Malignancy/Cancer	□ YES	□ NO

If yes, specify: _____

Other (Specify): _____

20. Are you currently being treated for tuberculosis? □ YES □ NO

<u>Current Medications</u>

21. Over the past 2 weeks, have you taken the following medications regularly?
    □ Antivirals
    □ Antibiotics
    □ Neither

22. If yes, what is the name of the medication?
(Record full name of any antibiotics or antivirals used) _____

AMO Amoxicillin; AMP Ampicillin; AUG Augmentin; CEF Cefuroxime, CIP Ciprofloxacin; CLI Clindamycin; CTX Ceftriaxone; DOX Doxycycline; ERY Erythromycin; PEN Penicillin; TMX/SMX Cotrimoxazole; VAN Vancomycin; TFR Tenofovir; EFA Efavirenz; LAM Lamivudine; FDC Fixed-Dose Combined ARV; U Unknown

23. Did you receive an influenza vaccine in the past 12 months? □ YES □ NO

If YES, dose given	□ 1 □ 2
Dose 1 Date given	___/___/____
Dose 2 Date given	___/___/____

<u>NB:ALL PATIENTS WHO DO NOT HAVE A CONFIRMED CURRENT HIV STATUS SHOULD BE OFFERED AN HIV TEST</u>

HIV Testing: Confidential

24. Have you ever been tested for HIV? □ YES □ NO
If YES, go to Q26
If NO: and ≤10 years, skip to Q27; if >10 years, skip to Q28

25. What was the result of your most recent HIV test? □ P □ N □ Unknown
If Pos or Neg:
Date of Result: ___/___/____
What was the source of the results?
□ Road to Health Card (RTHC)
□ Laboratory report
□ Medical records
□ Verbal
□ Other (Specify):_____
If HIV positive, skip to Q29;
If Unknown or Neg with results reported verbally or documented results older than 3 months and person ≥10 years of age skip to Q28

26. What was the HIV status of the mother during pregnancy (with the child being interviewed)? □ P □ N □ Unknown
If Pos or Neg:
What was the source of the results?
□ Road to Health Card (RTHC)
□ Laboratory report
□ Medical records
□ Verbal
□ Other (Specify):_____
If Positive or Unknown or verbally reported Negative go to Q35

27. Would you like to be tested for HIV today? □ YES □ NO
Which test was done today?
□ Finger-prick Rapid Test
What is the test result? □ P □ N
□ Blood sample

28. If HIV positive, are you on ARV treatment? □ YES □ NO

4. Follow-up form

PHIRST Study: Follow-Up Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

To be administered at every follow-up visit to each household member (presence of symptoms to be verified by study staff)

Date __/__/____ Time __:__

ID Code: _____

Interviewer_____ Place of Interview □ Home □ Other (specify): _____

Vital signs to be measured by nurse at the start of each visit:

Measured temperature: _____ °C
Heart rate: _____ beats per minute (from pulse oximeter)
Pulse oximeter reading: _____ % if measured pulse ox. Is <94% please refer to the nearest health facility immediately.

Symptoms questions for adults and children aged ≥5 years:

1.	Have you had a measured fever ≥38°C since the last visit?	□ Yes	□ No
2.	Have you felt feverish or had chills since the last visit?	□ Yes	□ No
3.	Have you had a cough since the last visit?	□ Yes	□ No
4.	Have you had shortness of breath or difficulty breathing since the last visit?	□ Yes	□ No
5.	Have you had a sore throat since the last visit?	□ Yes	□ No
6.	Have you had nasal congestion or runny nose since the last visit?	□ Yes	□ No
7.	Have you lost your sense of smell or taste since the last visit?	□ Yes	□ No
8.	Have you had vomiting since the last visit?	□ Yes	□ No
9.	Have you had diarrhea (≥3 loose stools in 24 hours) since the last visit?	□ Yes	□ No
10.	Have you had abdominal pain since the last visit?	□ Yes	□ No
11.	Have you had muscle aches since the last visit?	□ Yes	□ No
12.	Have you had fatigue for one or more days since the last visit?	□ Yes	□ No
13.	Have you had a headache since the last visit?	□ Yes	□ No
14.	Have you been confused or unable to respond to questions since the last visit?	□ Yes	□ No

If yes to any of the above, please record the date of symptom onset.

Symptoms questions for caregivers of children aged <5 years:

1. Has the child had a measured fever ≥38°C since the last visit? □ Yes □ No
2. Has the child felt feverish or had chills since the last visit? □ Yes □ No
3. Has the child had a cough since the last visit? □ Yes □ No
4. Has the child had difficulty breathing or chest indrawing since the last visit? □ Yes □ No
5. Has the child had nasal congestion or runny nose since the last visit? □ Yes □ No
6. Has the child been feeding poorly or had little appetite since the last visit? □ Yes □ No
7. Has the child been vomiting since the last visit? □ Yes □ No
8. Has the child had diarrhea (≥3 loose stools in 24 hours) since the last visit? □ Yes □ No
9. Has the child been irritable or inconsolable since the last visit? □ Yes □ No
10. Has the child been lethargic (unable to walk, sit, feed) since the last visit? □ Yes □ No

If yes to any of the above, please record the date of symptom onset.

For all participants who answer yes to one or more questions above:

1. Did you seek medical or traditional medicine help with your symptoms? □ Yes □ No
2. If yes, did you receive any medicine? □ Yes □ No
    a. If yes, what medicine: ___Drop down of common medications or Other, specify_____
3. Were you hospitalized? □ Yes □ No
    a. If yes, complete the hospitalization form.

5. Hospitalisation form

PHIRST Study: Hospitalization Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

To be administered to the hospitalized person when he/she returns from the hospital. If the person is not available for interview the information will be collected retrospectively form the caregiver or other household members. If the person died complete the death form.

ID Code of person admitted to hospital: _____

Relationship to hospitalized household member:
□ Self
□ Caregiver/Parent/Guardian
□ Sibling
□ Son/Daughter
□ Spouse
□ Relative

If relationship to hospitalized household member different than self, then:

ID code of respondent: _____

Date ___ /___ /____ Time ___:___

Interviewer_____ Place of Interview: □ Home □ Other (specify): _____

1. When were you/the person admitted to hospital? ___ /___ /____

2. Which hospital were you/the person admitted to?
   □ Klerksdorp
   □ Tshepong
   □ Matikwana
   □ Mapulaneng
   □ Tintswalo
   □ Other (specify): _____

3. What was the reason for hospitalization?
   □ Accident
   □ Illness
   □ Operation
   □ Childbirth
   □ Other (specify): _____
   If answer different that Illness, end.

4. If the hospitalization was for illness did you/the person have any of the following symptoms prior to the admission?
   - □ Fever
   - □ Sore throat
   - □ Cough
   - □ Runny nose
   - □ Headache
   - □ Night sweats
   - □ Difficulty breathing
   - □ Wheezing/noisy breathy

5. When did the symptoms start? ___ /___ /____

6. Did you/the person seek care before being admitted to the hospital? □ YES □ NO
   If No, skip to Q7

7. Where did you/the person seek care (tick all that apply)?

	Rank in chronological order
□ Clinic	_____
□ Private doctor	_____
□ Traditional healer	_____
□ Pharmacy	_____

8. Do you/the person have a diagnosis from the hospital? □ YES □ NO
   If No, skip to Q10.

9. What was the diagnosis?
   - □ Pneumonia
   - □ Bronchopneumonia
   - □ Bronchiolitis
   - □ Chest infection
   - □ TB
   - □ Fluid on the lungs/around the lungs
   - □ Pneumothorax
   - □ Other, (specify): _____

10. What was the outcome of the hospitalization?

□ Discharge	
□ Referred to step-down facility	Name of facility: _____
□ Transferred	Name of facility: _____

11. Date of hospital outcome: ___ /___ /____

6. Death form

PHIRST Study: Death Form

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

To be administered at any follow-up visit if any household member has died

ID Code of person who died: _____

ID code of respondent: _____

Relationship of respondent to household member who died:
□ Caregiver/Parent/Guardian
□ Sibling
□ Son/Daughter
□ Spouse
□ Relative
□ Other (specify): _____

Date ___ /___ /____ Time ___:___

Interviewer_____ Place of Interview: □ Home □ Other (specify): _____

If a death certificate is available, please record the cause of death as per the death certificate: _____

_____

_____

_____

1. When did the person die? ___ /___ /____
2. What was the cause of death
   □ Accident
   □ Illness
   □ Operation
   □ Childbirth
   □ Old age
   □ Other (specify): _____
   If the cause of death was different than illness, skip to Q11

3. If the cause of death was for illness did the person have any of the following symptoms prior to dying?
   - □ Fever
   - □ Sore throat
   - □ Cough
   - □ Runny nose
   - □ Headache
   - □ Night sweats
   - □ Difficulty breathing
   - □ Wheezing/noisy breathy
4. When did the symptoms (any) start? ___ /___ /____
5. Did the person seek care before dying? □ YES □ NO
   If No, skip to Q11
6. Where did the person seek care before dying (tick all that apply)?

	Rank in chronological order
□ Hospital	_____
□ Clinic	_____
□ Private doctor	_____
□ Traditional healer	_____
□ Pharmacy	_____

7. Was the person hospitalized before dying? □ YES □ NO
   If No, skip to Q11
8. In which hospital was the person hospitalized?
   - □ Klerksdorp
   - □ Tshepong
   - □ Matikwana
   - □ Mapulaneng
   - □ Tintswalo
   - □ Other (specify): _____
9. Do you have a diagnosis from the hospital? □ YES □ NO
   If No, skip to Q11
10. What was the diagnosis?
    - □ Pneumonia
    - □ Bronchopneumonia
    - □ Bronchiolitis
    - □ Chest infection
    - □ TB
    - □ Fluid on the lungs/around the lungs
    - □ Pneumothorax
    - □ Other, (specify): _____
11. Where did the person die?
    - □ Hospital
    - □ Home

□ Other (specify): _____

7. Laboratory slip

PHIRST Study: Laboratory Slip

Centre for Respiratory Diseases and Meningitis (CRDM)
TEL: 011 386 6410 or 011 386 6434
FAX: 086 723 3569

ID Code: _____

Date ___ /___ /____

Interviewer_____ Time ___:___

Specimen Type	**Number of specimens (indicate 0 if not collected)**
□ Nasal swab	_____
□ Nasoparyngeal swab	_____
□ Saliva	_____
□ Blood (clotted)	_____
□ Blood (EDTA)	_____

Appendix 4: Specimen packaging and transport protocol

Specimen for a patient will be placed in a sealed plastic Ziploc bag and transported in a cooler box with cooled ice packs. Samples should be transported upright as much as possible to prevent leaks. All samples will be accompanied by a shipping log.

Appendix 5 Informed consent and assent forms (sample documents, final approved version as per initial protocol approval) Form updated and attached for this amendment)

Information leaflet for household members in the household transmission study

Information leaflet 1: consent for adults

STUDY TITLE: A Prospective Household observational cohort study of COVID-19, influenza, respiratory syncytial virus (RSV) and other respiratory pathogens community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

Each participant must read this document and sign the attached informed consent before any study-related procedure is done.

Institution: National Institute for Communicable Diseases (NICD), South Africa; funded by a grant from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the MRC-Wits Rural Public Health and Health Transition Unit (Wits-Agincourt) and the Peri-Natal HIV Research Unit (PHRU).

Investigator: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, afterhours

Hello, my name is Prof Cheryl Cohen, I am the Head of the Centre for Respiratory Disease and Meningitis (CRDM) at the NICD) in Johannesburg. I would like to invite you to think about helping us with a research study called the PHIRST-C (household transmission study).

- Before you agree to take part in this study, we would like you to read this information sheet about the study.
- Please make sure you understand what you need to do.
- You should also make sure you understand the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time.
- This information leaflet is to help you to decide if you would like to participate. You need to understand what is involved before you agree to take part in this study.
- If you have any questions, do not hesitate to ask me or the study staff that are introducing the study to you.
- You should not agree to take part unless you are satisfied with all the procedures involved.

- Please be open with me regarding your health history, since you may otherwise harm yourself by participating in this study.
- If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

Background/Purpose

Infectious diseases are caused by different germs (virus, bacteria or parasites). By infectious we mean that the illness can be passed from one person to the next. It is important to understand the way these infections are passed between people. The household (home) is an important place for transmission (passing on) of these infections because people spend time together in close contact. It is also possible that someone is infected with a germ (virus) but do not become ill. It is important to understand the number of people who get infected and do not get ill. The information from the study will help to make guidelines for the use of vaccines and other interventions to help prevent these illnesses in people.

We are conducting a study to try and understand how infectious diseases are passed on in households. We are interested in viruses that cause respiratory illness (for example COVID-19 and influenza). Respiratory illness are illnesses of the airways, so nose, throat and lungs.

COVID-19 is the disease caused by the SARS-CoV-19 virus. This virus was first noticed in China and has quickly spread around the world, causing a pandemic (world-wide infections). This is a new virus and disease so we are still learning many things about the disease. There are still many questions that need to be answered about the virus. Answering these questions is really important so that we can find ways to decrease the spread of the virus or find medications or vaccines to prevent the virus. One of the ways to answer these questions is to study the way this virus spreads in households and communities. The virus is already infecting people in South Africa and the main spread of the virus is likely to happen during our winter months. This is also the time that other respiratory infection commonly occur. Two of these are influenza (Flu) and RSV. This study will also help us to define how the spread of COVID-19 is affected by or affects these two viruses.

We have some answers as to who gets severely ill from COVID-19 and this includes the elderly, people with other illnesses (like heart disease, diabetes and other lung conditions), and people who have weak immune systems. We are not sure how HIV infected people will react to infection with COVID-19.

For flu and RSV infection we know what some people are at risk of getting very severe forms of these illnesses, these groups include very young children, people with HIV, people with heart and lung diseases, people with diabetes and the elderly.

We would like to know how COVID-19 infection enter the household and then how they are passed on in the house. In the first part of the PHIRST study, we learnt that school-going children often brought the flu or RSV home and then passed it on to other household members. We still need to know if this will be the same when all three viruses are passing around together. There are important factors in households, including the compositions of the household (how many young children, children who go to school, people who work and people who stay in the household). There are also important factors like smoking and making of fires inside the house, which also play a role in the transmission of infections.

In order to help us explain all these things we are planning a study that will enroll 100 household in the Bushbuckridge district and 100 household in Klerksdorp in May/June 2020 and follow each household up for 6 months. Households that participated in PHIRST during 2017 and 2018 will be asked if they would like to participate in this new PHIRST-C. Each household will be asked to be part of the study for tsix months (we will visit you again at 1 year and 18 months after the start for a blood sample only). During this year we will do a number of things after the household members have signed consent to participate, details of each of these procedure are outlined later in this form.

All the following procedure apply to you as an adult and/or your child

1. Complete a detailed questionnaire for each person in the home including questions about your age, the kind of work you do, what illness you may have and some questions about your home (number of rooms, cooking etc).
2. We will ask about your HIV status and if necessary do testing for HIV (as explained in detail below).
3. We will take blood samples 10mls (two teaspoon) from adults and 5mls (one teaspoon) from children aged <15 years:
    a. 4 times in the 6 month follow up periods (enrollment and every 2 months)
    b. If you test positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months for 1 year.
4. These blood samples will be tested for your bodies' reaction to these viruses. Some people may have a reaction to a virus but not get sick.
5. If you test positive for HIV or are already HIV positive we will take additional blood samples for CD4 and viral load testing, this is an additional two 10ml (two teaspoon) samples
6. At the enrolment visit and following that at the twice weekly household visit we will take a swab (from the nose) or collect saliva from each member of the household. At the follow up visits we will ask a few simple questions about any respiratory symptoms you may have experienced. These swabs will be tested for the germs that cause respiratory illness. If you have experienced/are experiencing any respiratory symptoms we can refer you for treatment.
7. We will also ask if anyone has been in hospital or died. We will ask questions about why they went to hospital and what they died from.

8. For two weeks at one point of time in the study will ask you to wear a small device on your clothing, this device is called a proximity sensor and is designed to measure how close you come to other members of you household. We would like you to wear this device all day and at night. This device is not a camera.

   As HIV infection weakens the immune system. HIV-infected people react differently to infection, knowing the HIV status of people in this study is very important. There are a number of ways for us to do this. We can offer you a rapid test and you will get the result after about 15 minutes. We can take a blood sample and test it in the laboratory (you will get the result in about a month), or if you do not wish to know your results we can test the blood sample but not give you the results. Because HIV is a treatable infection it is important to know your status so that you can access treatment for the infection and live a healthy life. In this study we will offer you an HIV test. It may be difficult for you to receive your test results at home and so we can facilitate giving you the result at a nearby clinic or in a private location. In addition, we able to refer you for further counselling to deal with your HIV status should you need this assistance. Our teams are trained in HIV pre and posttest counselling and will provide this before and after testing. Some people may find it hard to disclose their HIV status to family members. Our trained counselors will help you through the process of disclosure should you need this assistance. You may change your mind at any stage of the study and we can arrange for you to receive the latest HIV test results. We will also be doing HIV testing later in the year and we will discuss the test with you prior to the time. If you would like to test for HIV at any time during the study we will be happy to assist you with testing and receiving your results.

Length of study and number of participants

- The study will be performed in South Africa only.
- Approximately 5 participants per household will participate in this study, 100 households at each site.
- Every household member, regardless of their age will be asked to participate.
- We will visit the household twice a week for the period of six months.
- After that we will visit the twice more, at one year from the start of the study and at 18 months from the start of the study.

Study procedures

1. Blood samples: Blood will be taken from your arm in a standard medical procedure; this will be done by a trained nurse.
2. HIV testing
   a. If you are HIV-positive and have some way of showing us this, either by a clinic record or your ARV treatment we will not need to test you for HIV.
   b. We can do a rapid HIV test at your house by doing a small prick on your finger and you will be able to receive the result immediately

   c. We can also test the blood sample that we have taken at the beginning of the study or at one of the follow up visit for HIV in the laboratory in Johannesburg. If you choose for us to do this we can still give you your results if you would like to know them, as per the details on HIV testing above.
3. Naso-pharyngeal swab (swabs are like a long cotton bud), the nurse will put a swab into your nose until it touches the back of your throat.
4. Saliva we may ask you to spit into a bottle, this will happen if we need to change the specimen type from nose swab to saliva.

Your rights as a participant

It is your right to choose if you want to take part in this study. If you chose not to participate this will not affect your right to health care, other services or your right to participate in future studies.

Expected duration of participation

The first visit will take about 2-3 hours; we will collect consent from each person. Followed by information on people in the household and information about the layout of the home.

At the second visit we will take all the samples this visit will take about an hour per person including taking the blood samples, sputum, skin test, urine sample and HIV test.

The follow-up visits will be about 15 minutes per person. We will try to arrange these visits when most people in the household are present and this may involve us visiting your household in the evening or over weekends. At the end of each visit the study team will tell you what will be happening at the next visit and how long they will need with each person. This will include the once of visits for the additional blood samples and the throat swabs.

Risks of this study

Because there is COVID-19 in your community there is risk of infection due to your interaction with the study team. It is possible that you will get the infection from study staff. In order to decrease the risk of this we will be taking every possible precaution to protect you and the study staff. At the beginning of the study visits the study staff will explain all these precautions to you. During the course of the study, the study team will keep reminding you of these procedures. They will ask you to wear masks (provided by the study), wash your hands or use sanitiser (provided by the study), practise physical distancing from study staff, sit at least 2 metres apart when answering question and other measures that are considered important to reduce the risk of

infection. The study staff will wear mask, goggles, gowns and gloves when taking samples. Study equipment will be cleaned using sanitising procedures.
There is minimal risk to you from the study procedures (NP swab and blood samples). We are only asking questions about your normal behaviour at home. You may find some of the questions uncomfortable. There may be minimal discomfort when we take the nasopharyngeal sample but the procedure only takes a few seconds. Some people may experience a short nose bleed.
Venipunctures (i.e. drawing blood) are normally done as part of routine medical care and present a slight risk of discomfort. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Your protection is that experienced personnel perform the procedures under sterile conditions.
Testing for HIV may be stressful, we will have a trained counsellor to explain all about the test and what the results will mean to you or your child. We will also refer you directly into the treatment programme if you do test positive for HIV.

Benefits of this study

By taking part in this study, you will help us learn more about how certain infectious diseases, specifically the pandemic of COVID-19. This will include information on how COVID-19 affects different people and who may benefit from vaccines.

You will have a chance to get the results of your HIV if you test positive for HIV you will get the benefit of early treatment.

Confidentiality

Every effort will be made to protect your confidentiality: study forms and blood samples will be marked with a number and not a name. Study staff will keep a log of household members and identifying details of household members, these will be kept in secure locked offices. No reference to personal detail will be made in any study report or in the final results of the study.

Withdrawal from the study

Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your access to other medical care.

- The investigators retain the right to withdraw you from the study if it is considered to be in your best interest.
- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study at any time.

Reimbursement for Participation

You will not be paid to participate in this study. However we will offer you some reimbursement for the time and inconvenience of participating in this study. We will offer you a voucher to be redeemed at a supermarket for items sold at that supermarket. Each member of the household will receive a voucher to the value of R50 for each of the visits. If you miss a visit you will not be reimbursed for the visit. For a household of 5 people counting the twice weekly visits this would be in the region of R2000 worth of vouchers for an average month.

The study will not pay for any care that you need for the any illness diagnosed during this study. We will share the results of the HIV and TB tests with you so that you will know if you have been infected with these illnesses. In addition, we are able to refer you for medical help to your nearest clinic if this is necessary.

Ethical approval

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has also been approved by the Mpumalanga Provincial Ethics Committee and the North West Provincial Ethics Committee
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.
- I do not have any financial or personal interests with this organisation that may bias my actions.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

STUDY TITLE: A Prospective Household observational cohort study of Influenza, Respiratory Syncytial virus and COVID-19 community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study team member, ... *(INSERT NAME OF STUDY TEAM MEMBER)*, about the nature, conduct, benefits and risks of the Household transmission study
- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.

- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by NICD or on their behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- By signing this form I agree to:
-

1. My blood being taken at the beginning of the study every 2 months for 6 months	Yes/No
2. If I test positive for COVID-19 my blood being taken every 2 months for 1 year	Yes/No
3. An HIV test and I wish to get my result	Yes/No
If yes to HIV test please indicate where you would like to receive your result	
I will receive my HIV results at home by rapid test on the day of testing	Yes/No
I would like my test done at NICD in the laboratory and will receive my results at a later date at home	Yes/No
I would like my test done at NICD in the laboratory and will receive my results at a later date at my local clinic	Yes/No
An HIV test and I do not wish to get my results	Yes/No
4. To wear a small device once off for 2 weeks to track the contact with other household members	Yes/No
5. A swab from through my nose to the back of my throat (or spit into a bottle), twice a week for six months	Yes/No

-

PARTICIPANT:

Printed Name Signature / Mark or Thumbprint Date and Time

I, ... *(INSERT NAME OF STUDY TEAM MEMBER)*, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY team member:

Printed Name	Signature	Date and Time

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT……**(DESIGNATION):**

Printed Name	**Signature**	**Date and Time**

WITNESS (If applicable)**:**

Printed Name	Signature	Date and Time

Information leaflet for household members in the household transmission study

Information leaflet 1: consent for children

STUDY TITLE: A Prospective Household observational cohort study of COVID-19, influenza, respiratory syncytial virus (RSV) and other respiratory pathogens community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

Each participant must read this document and sign the attached informed consent before any study-related procedure is done.

Institution: National Institute for Communicable Diseases (NICD), South Africa; funded by a grant from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the MRC-Wits Rural Public Health and Health Transition Unit (Wits-Agincourt) and the Peri-Natal HIV Research Unit (PHRU).

Investigator: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, afterhours

Hello, my name is Prof Cheryl Cohen, I am the Head of the Centre for Respiratory Disease and Meningitis (CRDM) at the NICD) in Johannesburg. I would like to invite you to think about helping us with a research study called the PHIRST-C (household transmission study).

- Before you agree for your child to take part in this study, we would like you to read this information sheet about the study.
- Please make sure you understand what your child need to do.
- You should also make sure you understand the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to your child, and your right to withdraw your child from the study at any time.
- This information leaflet is to help you to decide if you would like your child to participate. You need to understand what is involved before you agree to take part in this study.
- If you have any questions, do not hesitate to ask me or the study staff that are introducing the study to you.
- You should not agree for your child to take part unless you are satisfied with all the procedures involved.
- Please be open with me regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that child can take part in this study, you will be asked to sign this document to confirm that you understand what is required for your child to participate in the study. You will be given a copy to keep.

Background/Purpose

Infectious diseases are caused by different germs (virus, bacteria or parasites). By infectious we mean that the illness can be passed from one person to the next. It is important to understand the way these infections are passed between people. The household (home) is an important place for transmission (passing on) of these infections because people spend time together in close contact. It is also possible that someone is infected with a germ (virus) but do not become ill. It is important to understand the number of people who get infected and do not get ill. The information from the study will help to make guidelines for the use of vaccines and other interventions to help prevent these illnesses in people.

We are conducting a study to try and understand how infectious diseases are passed on in households. We are interested in viruses that cause respiratory illness (for example COVID-19 and influenza). Respiratory illness are illnesses of the airways, so nose, throat and lungs.

COVID-19 is the disease caused by the SARS-CoV-19 virus. This virus was first noticed in China and has quickly spread around the world, causing a pandemic (world-wide infections). This is a new virus and disease so we are still learning many things about the disease. There are still many questions that need to be answered about the virus. Answering these questions is really important so that we can find ways to decrease the spread of the virus or find medications or vaccines to prevent the virus. One of the ways to answer these questions is to study the way this virus spreads in households and communities. The virus is already infecting people in South Africa and the main spread of the virus is likely to happen during our winter months. This is also the time that other respiratory infection commonly occur. Two if these are influenza (Flu) and RSV. This study will also help us to define how the spread of COVID-19 is affected by or affects these two viruses.

We have some answers as to who gets severely ill from COVID-19 and this includes the elderly, people with other illnesses (like heart disease, diabetes and other lung conditions), and people who have weak immune systems. We are not sure how HIV infected people will react to infection with COVID-19.

For flu and RSV infection we know what some people are at risk of getting very severe forms of these illnesses, these groups include very young children, people with HIV, people with heart and lung diseases, people with diabetes and the elderly.

We would like to know how COVID-19 infection enter the household and then how they are passed on in the house. In the first part of the PHIRST study, we learnt that school-going children often brought the flu or RSV home and then passed it on to other household members. We still need to know if this will be the same when all three viruses are passing around together. There are important factors in households,

including the compositions of the household (how many young children, children who go to school, people who work and people who stay in the household). There are also important factors like smoking and making of fires inside the house, which also play a role in the transmission of infections.

In order to help us explain all these things we are planning a study that will enroll 100 household in the Bushbuckridge district and 100 households in Klerksdorp in May/June 2020 and follow each household up for 6 months. Households that participated in PHIRST during 2017 and 2018 will be asked if they would like to participate in this new PHIRST-C. Each household will be asked to be part of the study for six months (we will visit you again at 1 year and 18 months after the start for a blood sample only). During this year we will do a number of things after the household members have signed consent to participate, details of each of these procedure are outlined later in this form.

All the following procedures apply to your child

1. Complete a detailed questionnaire for each person in the home including questions about your child's age, what illness your child may have and some questions about your home (number of rooms, cooking etc).
2. We will ask about your child's HIV status and if necessary do testing for HIV (as explained in detail below).
3. We will 5mls (one teaspoon) from children aged <15 years, at the beginning of the study.
    a. 4 times in the 6 month follow up periods (enrollment and every 2 months)
    b. If you test positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months for 1 year.
4. These blood samples will be tested for your bodies' reaction to these viruses. Some people may have a reaction to a virus but not get sick.
5. If your child tests positive for HIV or is already HIV positive we will take additional blood samples for CD4 and viral load testing, this is an additional two 10ml (two teaspoon) samples
6. At the enrolment visit and following that at the twice weekly household visit we will take a swab (from the nose) from each member of the household. At the follow up visits we will ask a few simple questions about any respiratory symptoms you may have experienced. These swabs will be tested for the germs that cause respiratory illness. If you have experienced/are experiencing any respiratory symptoms we can refer you for treatment.
7. We will also ask if anyone has been in hospital or died. We will ask questions about why they went to hospital and what they died from.
8. For two weeks at one point in time we will ask your child to wear a small device on your clothing, this device is called a proximity sensor and is designed to measure how close you come to other members of you household. We would like your child to wear this device all day and at night. This device is not a camera.

As HIV infection weakens the immune system. HIV-infected people react differently to infection, knowing the HIV status of people in this study is very important. There are a number of ways for us to do this. We can offer your child a rapid test (if the child is >18 months of age) and you will get the result after about 15 minutes. We can take a blood sample and test it in the laboratory (you will get the result in about a month), or if you do not wish to know your results we can test the blood sample but not give you the results. Because HIV is a treatable infection it is important to know your child's status so that you can access treatment for the infection and live a healthy life. It is also important that you know the status of your children so that they can access treatment early. In this study we will offer you an HIV test, we will also offer this test to your children. It may be difficult for you to receive your test results at home and so we can facilitate giving you the result at a nearby clinic or in a private location. The study team can also assist you with giving an HIV result to your child/ren. In addition, we able to refer you for further counselling to deal with your HIV status should you need this assistance. Our teams are trained in HIV pre and posttest counselling and will provide this before and after testing. Some people may find it hard to disclose their HIV status to family members. It may also it be difficult to disclose the status of your child to your family. Our trained counselors will help you through the process of disclosure should you need this assistance. You may change your mind at any stage of the study and we can arrange for you to receive the latest HIV test results. We will also be doing HIV testing later in the year and we will discuss the test with you prior to the time. If you would like to test for HIV at any time during the study we will be happy to assist you with testing and receiving your results.

Length of study and number of participants

- The study will be performed in South Africa only.
- Approximately 5 participants per household will participate in this study, 100 households at each site.
- Every household member, regardless of their age will be asked to participate.
- We will visit the household twice a week for the period of six months.
- After that we will visit the twice more, at one year from the start of the study and at 18 months from the start of the study.

Study procedures

1. Blood samples: Blood will be taken from your arm in a standard medical procedure; this will be done by a trained nurse.
2. HIV testing
    a. If your child is HIV-positive and you have some way of showing us this, either by a clinic record or your child's ARV treatment we will not need to test you for HIV.
    b. We can do a rapid HIV test at your house for your child (if the child is older than18 months) by doing a small prick on your child'sfinger and you will be able to receive the result immediately.
    c. We can also test the blood sample that we have taken at the beginning of the study or at one of the follow up visit for HIV in the laboratory in Johannesburg. If you choose for us

to do this we can still give you your child's results if you would like to know them, as per the details on HIV testing above.

3. Naso-pharyngeal swab (swabs are like a long cotton bud), the nurse will put a swab into your child's nose until it touches the back of your throat.
4. Saliva we may ask your child to spit into a bottle, this will happen if we need to change the specimen type from nose swab to saliva.

Your rights as a participant

It is your right to choose if you want your child to take part in this study. If you chose for you child not to participate this will not affect your child's right to health care, other services or your child's right to participate in future studies.

Expected duration of participation

The first visit will take about 2-3 hours; we will collect consent from each person. Followed by information on people in the household and information about the layout of the home.

At the second visit we will take all the samples this visit will take about an hour per person including taking the blood samples, sputum, skin test, urine sample and HIV test.

The follow-up visits will be about 15 minutes per person. We will try to arrange these visits when most people in the household are present and this may involve us visiting your household in the evening or over weekends. At the end of each visit the study team will tell you what will be happening at the next visit and how long they will need with each person. This will include the once of visits for the additional blood samples and the throat swabs.

Risks of this study

Because there is COVID-19 in your community there is risk of infection due to your interaction with the study team. It is possible that you will get the infection from study staff. In order to decrease the risk of this we will be taking every possible precaution to protect you and the study staff. At the beginning of the study visits the study staff will explain all these precautions to you. During the course of the study, the study team will keep reminding you of these procedures. They will ask your child to wear masks (provided by the study), wash your hands or use sanitiser

(provided by the study), practise physical distancing from study staff, sit at least 2 metres apart when answering question and other measures that are considered important to reduce the risk of infection. The study staff will wear mask, goggles, gowns and gloves when taking samples. Study equipment will be cleaned using sanitising procedures.

There is minimal risk to your child from the study procedures (NP swab and blood samples). We are only asking questions about your child's normal behaviour at home. You may find some of the questions uncomfortable. There may be minimal discomfort when we take the nasopharyngeal sample but the procedure only takes a few seconds. Some people may experience a short nose bleed.

Venipunctures (i.e. drawing blood) are normally done as part of routine medical care and present a slight risk of discomfort. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Your protection is that experienced personnel perform the procedures under sterile conditions.

Testing for HIV may be stressful, we will have a trained counsellor to explain all about the test and what the results will mean to you or your child. We will also refer you directly into the treatment programme if you do test positive for HIV.

Benefits of this study

By taking part in this study, you will help us learn more about how certain infectious diseases, specifically the pandemic of COVID-19. This will include information on how COVID-19 affects different people and who may benefit from vaccines.

You will have a chance to get the results of your child's HIV if you test positive for HIV your child will get the benefit of early treatment.

Confidentiality

Every effort will be made to protect your confidentiality: study forms and blood samples will be marked with a number and not a name. Study staff will keep a log of household members and identifying details of household members, these will be kept in secure locked offices. No reference to personal detail will be made in any study report or in the final results of the study.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can decline your child's participation, or stop your child's participation at any time, without stating any reason. Your withdrawal will not affect your child's access to other medical care.

- The investigators retain the right to withdraw your child from the study if it is considered to be in your child's best interest.
- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you and your child may be withdrawn from the study at any time.

Reimbursement for Participation

You will not be paid to participate in this study. However we will offer you some reimbursement for the time and inconvenience of participating in this study. We will offer you a voucher to be redeemed at a supermarket for items sold at that supermarket. Each member of the household will receive a voucher to the value of R50 for each of the visits. If your child misses a visit you will not be reimbursed for the visit. For a household of 5 people counting the twice weekly visits this would be in the region of R2000 worth of vouchers for an average month.

The study will not pay for any care that your child needs for the any illness diagnosed during this study. In addition, we are able to refer your child for medical help to your nearest clinic if this is necessary.

Ethical approval

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has also been approved by the Mpumalanga Provincial Ethics Committee and the North West Provincial Ethics Committee
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.
- I do not have any financial or personal interests with this organisation that may bias my actions.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

SEPARATE INFORMED CONSENT FOR PARENTS/LEGAL GUARDIANS:

(On behalf of minors under 18 years old)

CONFIRM THAT IF THE PARTICIPANT IS 7-17 YEARS OF AGE THAT THEY HAVE READ THE ASSENT FORM Y/N

- ….. *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the household transmission study and has fully explained to me the nature, risks, benefits and purpose of the study.
- The study team has given me the opportunity to ask any questions concerning the study.
- It has been explained to me that I will be free to withdraw my child from the study at any time, without any disadvantage to future participation in studies.
- I am aware that the results of the study, including personal details regarding my child's sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by NICD or on their behalf.
- I have understood everything that has been explained to me and I consent for my child to participate in this clinical study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- By signing this form I agree to: please circle Yes/No for each statement

1. My child's blood being taken at the beginning of the study and every 2 months for 6 months.	Yes/No
2. If my child tests positive for COVID-19 blood to be taken every 2 months for one year	Yes/No
3. For my child to wear a small device on his/her clothing to measure contact with other family members	Yes/No
4. An HIV test for my child and I wish to get the result	Yes/No
If yes to HIV test please indicate where you would like to receive to receive your result	
I will receive my child's HIV results at home by rapid test on the day of testing (only if child older than 18 months)	Yes/No
I would like my child's test done at NICD in the laboratory and will receive my child's results at a later date at home	Yes/No
I would like my child's test done at NICD in the laboratory and will receive my child's results at a later date at my local clinic	Yes/No
An HIV test for my child and I do not wish to get my child's results	Yes/No
5. A swab from through my child's nose to the back of his/her throat (or spit into a bottle), twice a week for six months	Yes/No

-

PARENT/LEGAL GUARDIAN:

Printed Name	Signature / Mark or Thumbprint	Date and Time

PARTICIPANT ASSENT: * (7-17 years of age)

Printed Name	Signature / Mark or Thumbprint	Date and Time

(* Minors competent to understand must participate as fully as possible in the entire procedure)

Staff member:

Printed Name	Signature	Date and Time

For participant unable to read: OTHER PERSON EXPLAINING INFORMED CONSENT:……(DESIGNATION):

Printed Name	Signature	Date and Time

WITNESS (If applicable)**:**

Printed Name	Signature	Date and Time

Information leaflet for household members in the household transmission study

Form2: assent for children ages 7 to 17

STUDY TITLE: A Prospective Household observational cohort study of Influenza, Respiratory Syncytial virus and COVID-19 community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

Each participant aged between 7 and 17 should be offered the chance to read this information sheet must read this document and sign the attached informed consent before any study-related procedure is done.

Parental consent is require for each person younger than 18

Institution: National Institute for Communicable Diseases, South Africa; funded by a grant from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America.

Investigator: Prof Cheryl Cohen 011 3866593, day time and 082 803 8093, afterhours

Hello. My name is _____ and I would like to explain the surveillance that we are doing here that we'd like you to be part of. You can help by listening and then tell me whether you would like to be part of the study or not.

Why are we doing this study?

Infectious diseases are caused by different germs (virus, bacteria or parasites). By infectious we mean that the illness can be passed from one person to the next. It is important to understand the way these infections are passed on to other people. The home is an important place for passing on these infections because people spend time together in close contact. The information from the study will help to make guidelines for the use of vaccines (injections that prevent infections) and other ways that we can prevent these illnesses in people.

We are interested in viruses that cause respiratory illness (for example influenza and COVID-19).

COVID-19 is the disease caused by the SARS-CoV-19 virus. This virus was first noticed in China and has quickly spread around the world, causing a pandemic (world-wide infections). This is a new virus and disease so we are still learning many things about the disease. There are still many questions that need to

be answered about the virus. Answering these questions is really important so that we can find ways to help people who are sick and to find medicine or vaccine to stop people getting the virus.

One of the ways to answer these questions is to study the way this virus spreads in households and communities.

We would like to know how these infections come into the home, meaning who brings the infection into the house and then how the infections are passed to other people in the home.

There are important things about homes, including the how many young children, how children who go to school, how many people go to work and how many people stay at home that can help us understand how infections are passed from one person to the next.

In home there are also factors like people who smoke, the amount of fresh air that flows through the house and the making of fires inside the house which also play a part in passing infections from one person to the next.

We will also be testing people for HIV in this study. This is because people with HIV react differently to infections. If you are older than 12 and would like to know your HIV status please talk to your parents and the counsellor. We can give you the result at your home with your parents support or if you are older than 12 we can refer you to a clinic to receive your results.

We will also ask you to wear a small button on your clothes for one week; this device is able to measure how close you come to other household members. This device is not a camera.

In order to help us understand all these things we are planning a study that will ask people in 100 homes in the Bushbuckridge district and 100 in Klerksdorp to agree to be part of the study. Each person in the home will be asked to be part of the study for one year. During this year we will do a number of things after the people in the home members have signed consent to participate.

Here is a list of the things that we would like you to take part in.

What will happening to you during the study?

1. We will ask you a number of questions about your age, where you go to school, what illness you may have and some questions about your home (number of rooms, way of cooking etc).
2. Blood samples: Blood will be taken from your arm; this will be done by a trained nurse.
3. Nose swab, we will put a swab into your nose until it touches the back of your throat.
4. Saliva we may ask you to spit into a bottle, this will happen if we c need to change the specimen type from nose swab to saliva.

5. Wear a small device on your clothes that will track your contact with people in the house. This device is not a camera.
6. We will 5mls (one teaspoon) from children aged <15 years, at the beginning of the study.
    a. 4 times in the 6 month follow up periods (enrollment and every 2 months)
    b. If you test positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months for 1 year.

Your rights as a participant

- You do not have to be in this study if you do not want to. You won't get into any trouble with me, or your parent/guardian if you say no.
- You may stop being in the study at any time. If you want to be in the study now but change your mind later, that's okay. You can stop at any time.
- Your parent/s/guardian/s will be asked if it is okay for you to be in this study. Even if they say it's okay, it is still your choice whether or not to take part.
- You can ask any questions you have, now or later. If you think of a question later, you or your parent/guardian can contact us.

Expected duration of participation

The first visit will be quite short, we will ask you to sign on a piece of paper if you want to take part, and then we will ask you/your parent some questions about your health and will ask questions about the house.

The second visit will take about an hour for each person including taking the blood samples; the follow-up visits will be about 15 minutes per person. We will try to arrange these visits when most people in the household are present and this may involve us visiting your household in the evening or over weekends.

Risks of this study

There is a chance you get COVID-19 during the study either from people you see daily, household members and at school. Children do not usually get very sick from COVID-19 but you may feel sick like if you have flu. Because COVID-19 is easily passed on between people we will asking you to do some things to protect you and your household when you are talking to the study staff and when the samples are taken. We will provide you with a cloth mask, ask you to wash your hands/use sanitizer and practice physical distancing (stay at least 2 metres away from people). The study staff will help you and remind you about all these procedures.

We don't think that any big problems with the study procedures, but you may feel some pain when we prick you to collect blood and it may be uncomfortable when we collect samples from your nose and

throat but this will be quick and the discomfort will not last for long. The nurse/s that will be collecting the samples are all trained and they have been collecting similar type of samples from other children without any problems.

Benefits of this study

By taking part in this study, you will help us learn more about how certain infectious diseases affect different people and who may benefit from vaccines. You will also get the results of the tests if you have any infection that can be treated, like HIV.

Confidentiality

Every effort will be made to keep all your information a secret: study information and blood samples will be marked with a number and not a name. Your name will not be used when we report on the results to other people.

Withdrawal from the study

Your participation in this study is entirely voluntary and you can stop participating, stop at any time, without giving a reason. If you leave the study it will not affect your access to other medical care.

Ethical approval

All researchers have to explain the work they plan to do to a committee. This committee helps to protect your rights

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has also by approved by the ethics committees in the Mpumalanga Province and the North West Province.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

Appendix 6: Proximity study collection tools

Figure 1: Proximity sensor device

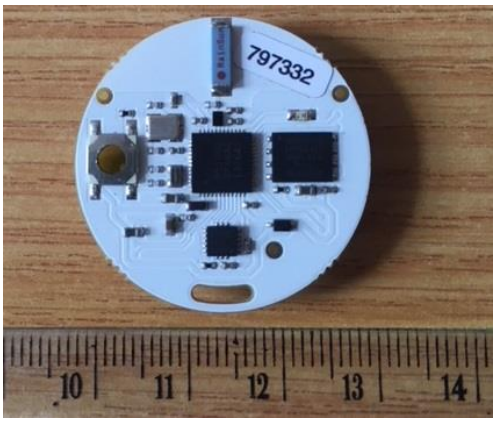

Figure 2: Packaging of proximity sensor

Please fill in the date and time when sensor put on in the morning and off in the evening.

Week 1:

Monday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Tuesday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Wednesday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Thursday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Friday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Saturday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Sunday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___

Week 2:

Monday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Tuesday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Wednesday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Thursday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Friday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Saturday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___
Sunday	D D / M M	Time tag put on in the morning	___ : ___	Time tag taken off in the evening	___ : ___

Information leaflet for household members in the household transmission study

Information leaflet 1: consent for adults

STUDY TITLE: A Prospective Household observational cohort study of COVID-19, influenza, respiratory syncytial virus (RSV) and other respiratory pathogens community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

Each participant must read this document and sign the attached informed consent before any study-related procedure is done.

This updated consent will apply to newly enrolled individuals after (insert approval date) date and for existing participants (all participants already enrolled in the study will be re-consented). New procedures have been highlighted in bold font to help the participants identify changes to the consent.

Institution: National Institute for Communicable Diseases (NICD), South Africa; funded by a grant from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the MRC-Wits Rural Public Health and Health Transition Unit (Wits-Agincourt) and the Peri-Natal HIV Research Unit (PHRU).

Investigator: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, afterhours

Hello, my name is Prof Cheryl Cohen, I am the Head of the Centre for Respiratory Disease and Meningitis (CRDM) at the NICD) in Johannesburg. I would like to invite you to think about helping us with a research study called the PHIRST-C (household transmission study).

- Before you agree to take part in this study, we would like you to read this information sheet about the study.
- Please make sure you understand what you need to do.
- You should also make sure you understand the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to you, and your right to withdraw from the study at any time.
- This information leaflet is to help you to decide if you would like to participate. You need to understand what is involved before you agree to take part in this study.
- If you have any questions, do not hesitate to ask me or the study staff that are introducing the study to you.
- You should not agree to take part unless you are satisfied with all the procedures involved.
- Please be open with me regarding your health history, since you may otherwise harm yourself by participating in this study.
- If you decide to take part in this study, you will be asked to sign this document to confirm that you understand the study. You will be given a copy to keep.

Background/Purpose

Infectious diseases are caused by different germs (virus, bacteria or parasites). By infectious we mean that the illness can be passed from one person to the next. It is important to understand the

way these infections are passed between people. The household (home) is an important place for transmission (passing on) of these infections because people spend time together in close contact. It is also possible that someone is infected with a germ (virus) but do not become ill. It is important to understand the number of people who get infected and do not get ill. The information from the study will help to make guidelines for the use of vaccines and other interventions to help prevent these illnesses in people.

We are conducting a study to try and understand how infectious diseases are passed on in households. We are interested in viruses that cause respiratory illness (for example COVID-19 and influenza). Respiratory illness are illnesses of the airways, so nose, throat and lungs.

COVID-19 is the disease caused by the SARS-CoV-19 virus. This virus was first noticed in China and has quickly spread around the world, causing a pandemic (world-wide infections). This is a new virus and disease so we are still learning many things about the disease. There are still many questions that need to be answered about the virus. Answering these questions is really important so that we can find ways to decrease the spread of the virus or find medications or vaccines to prevent the virus. One of the ways to answer these questions is to study the way this virus spreads in households and communities. The virus is already infecting people in South Africa and the main spread of the virus is likely to happen during our winter months. This is also the time that other respiratory infection commonly occur. Two if these are influenza (Flu) and RSV. This study will also help us to define how the spread of COVID-19 is affected by or affects these two viruses.

We have some answers as to who gets severely ill from COVID-19 and this includes the elderly, people with other illnesses (like heart disease, diabetes and other lung conditions), and people who have weak immune systems. We are not sure how HIV infected people will react to infection with COVID-19.
For flu and RSV infection we know what some people are at risk of getting very severe forms of these illnesses, these groups include very young children, people with HIV, people with heart and lung diseases, people with diabetes and the elderly.

We would like to know how COVID-19 infection enter the household and then how they are passed on in the house. In the first part of the PHIRST study, we learnt that school-going children often brought the flu or RSV home and then passed it on to other household members. We still need to know if this will be the same when all three viruses are passing around together. There are important factors in households, including the compositions of the household (how many young children, children who go to school, people who work and people who stay in the household). There are also important factors like smoking and making of fires inside the house, which also play a role in the transmission of infections.

In order to help us explain all these things we are planning a study that will enroll 100 households in the Bushbuckridge district and 100 households in Klerksdorp in **June/July 2020 and follow each**

household up twice a week for 12 months (July 2020-June 2021). Households that participated in PHIRST during 2017 and 2018 will be asked if they would like to participate in this new PHIRST-C. **Each household will be asked to be part of the study for a maximum of 18 months:**

- **12 months of twice weekly visits, July 2020 to June 2021 for all participants followed by:**
  - **either every 2 months until 18 months (if you test positive for COVID-19) or**
  - **once at the end of 18 months (if you do not test positive for COVID) for blood draws.**

During the 12 months of twice weekly follow up we will do a number of things after the household members have signed consent to participate, details of each of these procedure are outlined later in this form.

-

All the following procedure apply to you as an adult

1. Complete a detailed questionnaire for each person in the home including questions about your age, what illness you may have and some questions **about the structure of your home** (number of rooms etc).
2. We will ask about your HIV status and if necessary do testing for HIV (as explained in detail below).
3. We will 10mls (two teaspoon) of blood from you at the beginning of the study, then
   a. **6 times in the 12 month** follow-up period (every 2 months)
   b. If you test positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months after the initial 12 months until 18 months from the start of the study (July to November 2021)
   c. If you only test negative for COVID-19 during the study will only collect a final blood at 18 months from the start of the study (November 2021)
4. These blood samples will be tested for your bodies' reaction to these viruses. Some people may have a reaction to a virus but not get sick. **These blood samples are really important to the outcome of the study and your household may be withdrawn from the study if we are not able to get enough household members to give blood.** If you test positive for HIV or are already HIV positive we will take additional blood samples for CD4 and viral load testing, this is an additional two 10ml (two teaspoon) samples
5. At the enrolment visit and following that at the twice weekly household visit we will take a swab (from the nose) from each member of the household. At the follow up visits we will ask a few simple questions about any respiratory symptoms you may have experienced. These swabs will be tested for the germs that cause respiratory illness. If you have experienced/are experiencing any respiratory symptoms we can refer you for treatment.
6. We will also ask if anyone has been in hospital or died. We will ask questions about why they went to hospital and what they died from.
7. For two weeks at one point of time in the study will ask you to wear a small device on your clothing, this device is called a proximity sensor and is designed to measure how close you come to other members of your household. We would like you to wear this device all day and at night. This device is not a camera.

As HIV infection weakens the immune system. HIV-infected people react differently to infection, knowing the HIV status of people in this study is very important. There are a number of ways for us to do this. We can offer you a rapid test and you will get the result after about 15 minutes. We can take a blood sample and test it in the laboratory (you will get the result in about a month), or if you do not wish to know your results we can test the blood sample but not give you the results. Because HIV is a treatable infection it is important to know your status so that you can access treatment for the infection and live a healthy life. In this study we will offer you an HIV test. It may be difficult for you to receive your test results at home and so we can facilitate giving you the result at a nearby clinic or in a private location. In addition, we able to refer you for further counselling to deal with your HIV status should you need this assistance. Our teams are trained in HIV pre and posttest counselling and will provide this before and after testing. Some people may find it hard to disclose their HIV status to family members. Our trained counselors will help you through the process of disclosure should you need this assistance. You may change your mind at any stage of the study and we can arrange for you to receive the latest HIV test results. We will also be doing HIV testing later in the year and we will discuss the test with you prior to the time. If you would like to test for HIV at any time during the study we will be happy to assist you with testing and receiving your results.

COVID-19 is a notifiable medical condition, and by law we have to provide your name, surname, date of birth, identification/passport number, contact number and address to the National Department of Health if you test positive for COVID-19. This may lead to the district health officials contacting you and asking about your contact with other people in order to prevent further spread of the virus.

Length of study and number of participants

- The study will be performed in South Africa only.
- Approximately 5 participants per household will participate in this study, 100 households at each site.
- Every household member, regardless of their age will be asked to participate.
- We will visit the household twice a week for the period of six months.
- After that we will visit the twice more, at one year from the start of the study and at 18 months from the start of the study.

Study procedures

1. Blood samples: Blood will be taken from your arm in a standard medical procedure; this will be done by a trained nurse.
2. HIV testing
    a. If you are HIV-positive and have some way of showing us this, either by a clinic record or your ARV treatment we will not need to test you for HIV.

   b. We can do a rapid HIV test at your house by doing a small prick on your finger and you will be able to receive the result immediately
   c. We can also test the blood sample that we have taken at the beginning of the study or at one of the follow up visit for HIV in the laboratory in Johannesburg. If you choose for us to do this we can still give you your results if you would like to know them, as per the details on HIV testing above.
3. Naso-pharyngeal swab (swabs are like a long cotton bud), the nurse will put a swab into your nose until it touches the back of your throat.
4. Saliva we may ask you to spit into a bottle, this will happen if we need to change the specimen type from nose swab to saliva.

Your rights as a participant

It is your right to choose if you want to take part in this study. If you chose not to participate this will not affect your right to health care, other services or your right to participate in future studies.

Expected duration of participation

The first visit will take about 2-3 hours; we will collect consent from each person. Followed by information on people in the household and information about the layout of the home.

At the second visit we will take all the samples this visit will take about an hour per person including taking the blood samples, sputum, skin test, urine sample and HIV test.

The follow-up visits will be about 15 minutes per person. We will try to arrange these visits when most people in the household are present and this may involve us visiting your household in the evening or over weekends. At the end of each visit the study team will tell you what will be happening at the next visit and how long they will need with each person. This will include the once of visits for the additional blood samples and the throat swabs.

Risks of this study

Because there is COVID-19 in your community there is risk of infection due to your interaction with the study team. It is possible that you will get the infection from study staff. In order to decrease the risk of this we will be taking every possible precaution to protect you and the study staff. At the beginning of the study visits the study staff will explain all these precautions to you. During the course of the study, the study team will keep reminding you of these procedures. They will ask you to wear masks (provided by the study), wash your hands or use sanitiser (provided by the study), practise physical distancing from study staff, sit at least 2 metres apart when answering question and other measures that are considered important to reduce the risk of infection. The study staff will wear mask, goggles, gowns and gloves when taking samples. Study equipment will be cleaned using sanitising procedures.

There is minimal risk to you from the study procedures (NP swab and blood samples). We are only asking questions about your normal behaviour at home. You may find some of the questions uncomfortable. There may be minimal discomfort when we take the nasopharyngeal sample but the procedure only takes a few seconds. Some people may experience a short nose bleed.
Venipunctures (i.e. drawing blood) are normally done as part of routine medical care and present a slight risk of discomfort. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Your protection is that experienced personnel perform the procedures under sterile conditions.
Testing for HIV may be stressful, we will have a trained counsellor to explain all about the test and what the results will mean to you or your child. We will also refer you directly into the treatment programme if you do test positive for HIV.

Benefits of this study

By taking part in this study, you will help us learn more about how certain infectious diseases, specifically the pandemic of COVID-19. This will include information on how COVID-19 affects different people and who may benefit from vaccines.
You will have a chance to get the results of your HIV if you test positive for HIV you will get the benefit of early treatment.

Confidentiality

We will ensure your confidentiality: study forms and blood samples will be marked with a number and not a name. Study staff will keep a log of household members and identifying details of household members, these will be kept in secure locked offices. No reference to personal detail will be made in any study report or in the final results of the study.

Withdrawal from the study

Your participation in this study is entirely voluntary and you can decline to participate, or stop at any time, without stating any reason. Your withdrawal will not affect your access to other medical care.

- The investigators retain the right to withdraw you from the study if it is considered to be in your best interest.
- **We may withdraw you or your entire household if we are not able to get blood samples from household members**
- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you may be withdrawn from the study at any time.

Reimbursement for Participation

You will not be paid to participate in this study. However we will offer you some reimbursement for the time and inconvenience of participating in this study. We will offer you a voucher to be redeemed at a supermarket for items sold at that supermarket. Each member of the household will receive a voucher to the value of R50 for each of the visits. If you miss a visit you will not be

reimbursed for the visit. For a household of 5 people counting the twice weekly visits this would be in the region of R2000 worth of vouchers for an average month.

The study will not pay for any care that you need for any illness diagnosed during this study. We will share the results of the HIV and TB tests with you so that you will know if you have been infected with these illnesses. In addition, we are able to refer you for medical help to your nearest clinic if this is necessary.

Ethical approval

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has also been approved by the Mpumalanga Provincial Ethics Committee and the North West Provincial Ethics Committee
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.
- I do not have any financial or personal interests with this organisation that may bias my actions.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

STUDY TITLE: A Prospective Household observational cohort study of Influenza, Respiratory Syncytial virus and COVID-19 community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

INFORMED CONSENT:

- I hereby confirm that I have been informed by the study team member, ... *(INSERT NAME OF STUDY TEAM MEMBER),* about the nature, conduct, benefits and risks of the Household transmission study
- I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study.
- I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by NICD or on their behalf.
- I may, at any stage, without prejudice, withdraw my consent and participation in the study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- By signing this form I agree to:
-

1. My blood being taken at the beginning of the study and every 2 months for up to 12 months then again at 18 months (if you do not test positive for COVID) or 2. **My blood being taken at the beginning of the study and every 2 months for 18 months (if I do tests positive for COVID**	Yes/No
3. An HIV test	Yes/No
How would you like to receive your HIV result?	Yes/No
• **I will receive my HIV results at home by rapid test on the day of testing (only if child older than 18 months)**	Yes/No
• **I would like my test done at NICD in the laboratory and will receive my results at a later date at home**	Yes/No
• **I would like my test done at NICD in the laboratory and will receive my results at a later date at my local clinic**	Yes/No
4. An HIV test and I do not wish to get my results	Yes/No
5. To wear a small device once off for 2 weeks to track the contact with other household members	Yes/No
6. A swab from through my nose to the back of my throat (or spit into a bottle), twice a week for **up to 12 months**	Yes/No

▪

PARTICIPANT:

Printed Name Signature / Mark or Thumbprint Date and Time

I, ... *(INSERT NAME OF STUDY TEAM MEMBER)*, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY team member:

Printed Name Signature Date and Time

TRANSLATOR / OTHER PERSON EXPLAINING INFORMED CONSENT……**(DESIGNATION):**

Printed Name **Signature** **Date and Time**

WITNESS (If applicable)**:**

Printed Name	Signature	Date and Time

Information leaflet for household members in the household transmission study

Information leaflet 1: consent for children

STUDY TITLE: A Prospective Household observational cohort study of COVID-19, influenza, respiratory syncytial virus (RSV) and other respiratory pathogens community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

Each participant must read this document and sign the attached informed consent before any study-related procedure is done.

This updated consent will apply to newly enrolled individuals after (insert approval date) date and for existing participants (all participants already enrolled in the study will be re-consented). New procedures have been highlighted in bold font to help the participants identify changes to the consent.

Institution: National Institute for Communicable Diseases (NICD), South Africa; funded by a grant from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the MRC-Wits Rural Public Health and Health Transition Unit (Wits-Agincourt) and the Peri-Natal HIV Research Unit (PHRU).

Investigator: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, afterhours

Hello, my name is Prof Cheryl Cohen, I am the Head of the Centre for Respiratory Disease and Meningitis (CRDM) at the NICD) in Johannesburg. I would like to invite you to think about helping us with a research study called the PHIRST-C (household transmission study).

- Before you agree for your child to take part in this study, we would like you to read this information sheet about the study.
- Please make sure you understand what your child need to do.
- You should also make sure you understand the purpose of the study, the study procedures, benefits, risks, discomforts, and precautions as well as the alternative procedures that are available to your child, and your right to withdraw your child from the study at any time.
- This information leaflet is to help you to decide if you would like your child to participate. You need to understand what is involved before you agree to take part in this study.
- If you have any questions, do not hesitate to ask me or the study staff that are introducing the study to you.
- You should not agree for your child to take part unless you are satisfied with all the procedures involved.
- Please be open with me regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that child can take part in this study, you will be asked to sign this document to confirm that you understand what is required for your child to participate in the study. You will be given a copy to keep.

Background/Purpose

Infectious diseases are caused by different germs (virus, bacteria or parasites). By infectious we mean that the illness can be passed from one person to the next. It is important to understand the way these infections are passed between people. The household (home) is an important place for transmission (passing on) of these infections because people spend time together in close contact. It is also possible that someone is infected with a germ (virus) but do not become ill. It is important to understand the number of people who get infected and do not get ill. The information from the study will help to make guidelines for the use of vaccines and other interventions to help prevent these illnesses in people.

We are conducting a study to try and understand how infectious diseases are passed on in households. We are interested in viruses that cause respiratory illness (for example COVID-19 and influenza). Respiratory illness are illnesses of the airways, so nose, throat and lungs.

COVID-19 is the disease caused by the SARS-CoV-19 virus. This virus was first noticed in China and has quickly spread around the world, causing a pandemic (world-wide infections). This is a new virus and disease so we are still learning many things about the disease. There are still many questions that need to be answered about the virus. Answering these questions is really important so that we can find ways to decrease the spread of the virus or find medications or vaccines to prevent the virus. One of the ways to answer these questions is to study the way this virus spreads in households and communities. The virus is already infecting people in South Africa and the main spread of the virus is likely to happen during our winter months. This is also the time that other respiratory infection commonly occur. Two if these are influenza (Flu) and RSV. This study will also help us to define how the spread of COVID-19 is affected by or affects these two viruses.

We have some answers as to who gets severely ill from COVID-19 and this includes the elderly, people with other illnesses (like heart disease, diabetes and other lung conditions), and people who have weak immune systems. We are not sure how HIV infected people will react to infection with COVID-19.

For flu and RSV infection we know what some people are at risk of getting very severe forms of these illnesses, these groups include very young children, people with HIV, people with heart and lung diseases, people with diabetes and the elderly.

We would like to know how COVID-19 infection enter the household and then how they are passed on in the house. In the first part of the PHIRST study, we learnt that school-going children often brought the flu or RSV home and then passed it on to other household members. We still need to know if this will be the same when all three viruses are passing around together. There are important factors in households, including the compositions of the household (how many young children, children who go to school, people who work and people who stay in the household). There are also important factors like smoking and making of fires inside the house, which also play a role in the transmission of infections.

In order to help us explain all these things we are planning a study that will enroll 100 households in the Bushbuckridge district and 100 households in Klerksdorp in **June/July 2020 and follow each household up twice a week for 12 months (July 2020-June 2021).** Households that participated in PHIRST during 2017 and 2018 will be asked if they would like to participate in this new PHIRST-C. **Each household will be asked to be part of the study for a maximum of 18 months:**

- **12 months of twice weekly visits, July 2020 to June 2021 for all participants followed by:**
    - **either every 2 months until 18 months (if you test positive for COVID-19) or**
    - **once at the end of 18 months (if you do not test positive for COVID) for blood draws.**

During the 12 months of twice weekly follow up we will do a number of things after the household members have signed consent to participate, details of each of these procedure are outlined later in this form.

All the following procedures apply to your child

1. Complete a detailed questionnaire for each person in the home including questions about your child's age, what illness your child may have and some questions **about the structure of your home** (number of rooms etc).
2. We will ask about your child's HIV status and if necessary do testing for HIV (as explained in detail below).
3. We will 5mls (one teaspoon) from children aged <15 years, at the beginning of the study, then
    a. **6 times in the 12-month follow-up period (every 2 months)**
    b. **If your child tests positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months after the initial 12 months until 18 months from the start of the study (July 2020 to November 2021).**
    c. **If your child only tests negative for COVID-19 during the study will only collect a final blood at 18 months from the start of the study (November 2021)**
4. These blood samples will be tested for your bodies' reaction to these viruses. Some people may have a reaction to a virus but not get sick. **These blood samples are really important to the outcome of the study and your household may be withdrawn from the study if we are not able to get enough household members to give blood.**
5. If your child tests positive for HIV or is already HIV positive we will take additional blood samples for CD4 and viral load testing, this is an additional two 10ml (two teaspoon) samples
6. At the enrolment visit and following that at the twice weekly household visit we will take a swab (from the nose) from each member of the household. At the follow up visits we will ask a few simple questions about any respiratory symptoms you may have experienced. These swabs will be tested for the germs that cause respiratory illness. If you have experienced/are experiencing any respiratory symptoms we can refer you for treatment.
7. We will also ask if anyone has been in hospital or died. We will ask questions about why they went to hospital and what they died from.

8. For two weeks at one point in time we will ask your child to wear a small device on your clothing, this device is called a proximity sensor and is designed to measure how close you come to other members of you household. We would like your child to wear this device all day and at night. This device is not a camera.

   As HIV infection weakens the immune system. HIV-infected people react differently to infection, knowing the HIV status of people in this study is very important. There are a number of ways for us to do this. We can offer your child a rapid test (if the child is >18 months of age) and you will get the result after about 15 minutes. We can take a blood sample and test it in the laboratory (you will get the result in about a month), or if you do not wish to know your results we can test the blood sample but not give you the results. Because HIV is a treatable infection it is important to know your child's status so that you can access treatment for the infection and live a healthy life. It is also important that you know the status of your children so that they can access treatment early. In this study we will offer you an HIV test, we will also offer this test to your children. It may be difficult for you to receive your test results at home and so we can facilitate giving you the result at a nearby clinic or in a private location. The study team can also assist you with giving an HIV result to your child/ren. In addition, we able to refer you for further counselling to deal with your HIV status should you need this assistance. Our teams are trained in HIV pre and posttest counselling and will provide this before and after testing. Some people may find it hard to disclose their HIV status to family members. It may also it be difficult to disclose the status of your child to your family. Our trained counselors will help you through the process of disclosure should you need this assistance. You may change your mind at any stage of the study and we can arrange for you to receive the latest HIV test results. We will also be doing HIV testing later in the year and we will discuss the test with you prior to the time. If you would like to test for HIV at any time during the study we will be happy to assist you with testing and receiving your results.

COVID-19 is a notifiable medical condition, and by law we have to provide your name, surname, date of birth, identification/passport number, contact number and address to the National Department of Health if you test positive for COVID-19. This may lead to the district health officials contacting you and asking about your child's contact with other people in order to prevent further spread of the virus.

Length of study and number of participants

- The study will be performed in South Africa only.
- Approximately 5 participants per household will participate in this study, 100 households at each site.
- Every household member, regardless of their age will be asked to participate.
- We will visit the household twice a week for the period of six months.
- After that we will visit the twice more, at one year from the start of the study and at 18 months from the start of the study.

Study procedures

1. Blood samples: Blood will be taken from your arm in a standard medical procedure; this will be done by a trained nurse.
2. HIV testing
    a. If your child is HIV-positive and you have some way of showing us this, either by a clinic record or your child's ARV treatment we will not need to test you for HIV.
    b. We can do a rapid HIV test at your house for your child (if the child is older than18 months) by doing a small prick on your child's finger and you will be able to receive the result immediately.
    c. We can also test the blood sample that we have taken at the beginning of the study or at one of the follow up visit for HIV in the laboratory in Johannesburg. If you choose for us to do this we can still give you your child's results if you would like to know them, as per the details on HIV testing above.
3. Naso-pharyngeal swab (swabs are like a long cotton bud), the nurse will put a swab into your child's nose until it touches the back of your throat.
4. Saliva we may ask you to spit into a bottle, this will happen if we need to change the specimen type from nose swab to saliva.

Your rights as a participant

It is your right to choose if you want your child to take part in this study. If you chose for you child not to participate this will not affect your child's right to health care, other services or your child's right to participate in future studies.

Expected duration of participation

The first visit will take about 2-3 hours; we will collect consent from each person. Followed by information on people in the household and information about the layout of the home.

At the second visit we will take all the samples this visit will take about an hour per person including taking the blood samples, sputum, skin test, urine sample and HIV test.

The follow-up visits will be about 15 minutes per person. We will try to arrange these visits when most people in the household are present and this may involve us visiting your household in the evening or over weekends. At the end of each visit the study team will tell you what will be happening at the next visit and how long they will need with each person. This will include the once of visits for the additional blood samples and the throat swabs.

Risks of this study

Because there is COVID-19 in your community there is risk of infection due to your interaction with the study team. It is possible that you will get the infection from study staff. In order to decrease the risk of this we will be taking every possible precaution to protect you and the study staff. At the beginning of the study visits the study staff will explain all these precautions to you. During the course of the study, the study team will keep reminding you of these procedures. They will ask your child to wear masks (provided by the study), wash your hands or use sanitiser (provided by the

study), practise physical distancing from study staff, sit at least 2 metres apart when answering question and other measures that are considered important to reduce the risk of infection. The study staff will wear mask, goggles, gowns and gloves when taking samples. Study equipment will be cleaned using sanitising procedures.

There is minimal risk to your child from the study procedures (NP swab and blood samples). We are only asking questions about your child's normal behaviour at home. You may find some of the questions uncomfortable. There may be minimal discomfort when we take the nasopharyngeal sample but the procedure only takes a few seconds. Some people may experience a short nose bleed.

Venipunctures (i.e. drawing blood) are normally done as part of routine medical care and present a slight risk of discomfort. Drawing blood may result in faintness, inflammation of the vein, pain, bruising or bleeding at the puncture site. There is also a slight possibility of infection. Your protection is that experienced personnel perform the procedures under sterile conditions.

Testing for HIV may be stressful, we will have a trained counsellor to explain all about the test and what the results will mean to you or your child. We will also refer you directly into the treatment programme if you do test positive for HIV.

Benefits of this study

By taking part in this study, you will help us learn more about how certain infectious diseases, specifically the pandemic of COVID-19. This will include information on how COVID-19 affects different people and who may benefit from vaccines.

You will have a chance to get the results of your child's HIV if you test positive for HIV your child will get the benefit of early treatment.

Confidentiality

We will your confidentiality: study forms and blood samples will be marked with a number and not a name. Study staff will keep a log of household members and identifying details of household members, these will be kept in secure locked offices. No reference to personal detail will be made in any study report or in the final results of the study.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can decline your child's participation, or stop your child's participation at any time, without stating any reason. Your withdrawal will not affect your child's access to other medical care.

- The investigators retain the right to withdraw your child from the study if it is considered to be in your child's best interest.
- **We may withdraw you or your entire household if we are not able to get blood samples from household members**
- If you did not give an accurate history or did not follow the guidelines of the study and the regulations of the study facility, you and your child may be withdrawn from the study at any time.

Reimbursement for Participation

You will not be paid to participate in this study. However we will offer you some reimbursement for the time and inconvenience of participating in this study. We will offer you a voucher to be redeemed at a supermarket for items sold at that supermarket. Each member of the household will receive a voucher to the value of R50 for each of the visits. If your child misses a visit you will not be reimbursed for the visit. For a household of 5 people counting the twice weekly visits this would be in the region of R2000 worth of vouchers for an average month.

The study will not pay for any care that your child needs for the any illness diagnosed during this study. In addition, we are able to refer your child for medical help to your nearest clinic if this is necessary.

Ethical approval

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has also been approved by the Mpumalanga Provincial Ethics Committee and the North West Provincial Ethics Committee
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2013), which deals with the recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.
- I do not have any financial or personal interests with this organisation that may bias my actions.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

SEPARATE INFORMED CONSENT FOR PARENTS/LEGAL GUARDIANS:

(On behalf of minors under 18 years old)

CONFIRM THAT IF THE PARTICIPANT IS 7-17 YEARS OF AGE THAT THEY HAVE READ THE ASSENT FORM Y/N

- ..... *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the household transmission study and has fully explained to me the nature, risks, benefits and purpose of the study.
- The study team has given me the opportunity to ask any questions concerning the study.
- It has been explained to me that I will be free to withdraw my child from the study at any time, without any disadvantage to future participation in studies.
- I am aware that the results of the study, including personal details regarding my child's sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report.
- In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by NICD or on their behalf.

- I have understood everything that has been explained to me and I consent for my child to participate in this clinical study.
- I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.
- By signing this form I agree to: please circle Yes/No for each statement

1. My child's blood being taken at the beginning of the study and every 2 months for up to 12 months then again at 18 months (if the child does not test positive for COVID) or My child's blood being taken at the beginning of the study and every 2 months for 18 months (if the child does tests positive for COVID	Yes/No
2. For my child to wear a small device on his/her clothing to measure contact with other family members	Yes/No
3. An HIV test for my child	Yes/No
How would you like to receive your child's HIV result?	
• **I will receive my child's HIV results at home by rapid test on the day of testing (only if child older than 18 months)**	Yes/No
• **I would like my child's test done at NICD in the laboratory and will receive my child's results at a later date at home**	Yes/No
• **I would like my child's test done at NICD in the laboratory and will receive my child's results at a later date at my local clinic**	Yes/No
4. An HIV test for my child and I do not wish to get my child's results	Yes/No
5. A swab from your child's nose to the back of his/her throat (or spit into a bottle), twice a week for **up to 12 months**	Yes/No

•

PARENT/LEGAL GUARDIAN:

Printed Name **Signature / Mark or Thumbprint** **Date and Time**

PARTICIPANT ASSENT: * (7-17 years of age)

Printed Name **Signature / Mark or Thumbprint** **Date and Time**

(* Minors competent to understand must participate as fully as possible in the entire procedure)

Staff member:

Printed Name **Signature** **Date and Time**

For participant unable to read: OTHER PERSON EXPLAINING INFORMED CONSENT:……..…**(DESIGNATION):**

Printed Name	**Signature**	**Date and Time**

WITNESS (If applicable)**:**

Printed Name	**Signature**	**Date and Time**

Information leaflet for household members in the household transmission study

Form2: assent for children ages 7 to 17

STUDY TITLE: A Prospective Household observational cohort study of Influenza, Respiratory Syncytial virus and COVID-19 community burden and Transmission dynamics in South Africa (The PHIRST-C Study)

Each participant aged between 7 and 17 should be offered the chance to read this information sheet must read this document and sign the attached informed consent before any study-related procedure is done.

Parental consent is required for each person younger than 18

Institution: National Institute for Communicable Diseases, South Africa; funded by a grant from the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America.

Investigator: Prof Cheryl Cohen 011 3866593, day time and 082 803 8093, afterhours

Hello. My name is _____ and I would like to explain the surveillance that we are doing here that we'd like you to be part of. You can help by listening and then tell me whether you would like to be part of the study or not.

We are changing a few things about the study, so we are asking all participants (those already in the study and new participants joining the study) to sign this form.

To help participants who are already in the study we have marked the changes in bold font so you can quickly see the changes.

Why are we doing this study?

Infectious diseases are caused by different germs (virus, bacteria or parasites). By infectious we mean that the illness can be passed from one person to the next. It is important to understand the way these infections are passed on to other people. The home is an important place for passing on these infections because people spend time together in close contact. The information from the study will help to make guidelines for the use of vaccines (injections that prevent infections) and other ways that we can prevent these illnesses in people.

We are interested in viruses that cause respiratory illness (for example influenza and COVID-19).

COVID-19 is the disease caused by the SARS-CoV-19 virus. This virus was first noticed in China and has quickly spread around the world, causing a pandemic (world-wide infections). This is a new virus and disease so we are still learning many things about the disease. There are still many questions that need to be answered about the virus. Answering these questions is really important so that we can find ways to help people who are sick and to find medicine or vaccine to stop people getting the virus.

One of the ways to answer these questions is to study the way this virus spreads in households and communities.
We would like to know how these infections come into the home, meaning who brings the infection into the house and then how the infections are passed to other people in the home.
There are important things about homes, including the how many young children, how children who go to school, how many people go to work and how many people stay at home that can help us understand how infections are passed from one person to the next.
In home there are also factors like people who smoke, the amount of fresh air that flows through the house and the making of fires inside the house which also play a part in passing infections from one person to the next.

We will also be testing people for HIV in this study. This is because people with HIV react differently to infections. If you are older than 12 and would like to know your HIV status please talk to your parents and the counsellor. We can give you the result at your home with your parent's support or if you are older than 12 we can refer you to a clinic to receive your results.

We will also ask you to wear a small button on your clothes for one week; this device is able to measure how close you come to other household members. This device is not a camera.

In order to help us understand all these things we are planning a study that will ask people in 100 homes in the Bushbuckridge district and 100 in Klerksdorp to agree to be part of the study. Each person in the home will be asked to be part of the study for one year. During this year we will do a number of things after the people in the home members have signed consent to participate.
Here is a list of the things that we would like you to take part in.

What will happening to you during the study?

1. We will ask you a number of questions about your age, where you go to school, what illness you may have and some questions about your home (number of rooms, way of cooking etc).
2. Blood samples: Blood will be taken from your arm; this will be done by a trained nurse.
3. Nose swab, we will put a swab into your nose until it touches the back of your throat.
4. Saliva we may ask you to spit into a bottle, this will happen if we need to change the specimen type from nose swab to saliva.
5. Wear a small device on your clothes that will track your contact with people in the house. This device is not a camera.
6. **We will 5mls (one teaspoon) from children aged <15 years and 8mls (about one and a half teaspoons) from people older than 15v year, at the beginning of the study.**
    a. **06times in the 12 month follow up period (enrollment and every 2 months) and once at the end of 18 months (total of 7 blood samples)**
    b. **If you test positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months for 6 months after the one year of follow up a total of 10 samples**.

Your rights as a participant

- You do not have to be in this study if you do not want to. You won't get into any trouble with me, or your parent/guardian if you say no.
- You may stop being in the study at any time. If you want to be in the study now but change your mind later, that's okay. You can stop at any time.
- Your parent/s/guardian/s will be asked if it is okay for you to be in this study. Even if they say it's okay, it is still your choice whether or not to take part.
- You can ask any questions you have, now or later. If you think of a question later, you or your parent/guardian can contact us.

Expected duration of participation

The first part of the study will be 12 months (from July 2020 to June 2021), in this time we will visit you twice a week every week and every 2 months we will take a blood sample

After that one of the following will happen:

a. **If you test positive for COVID-19 during the study will would like to continue to visit you to take blood every 2 months after the first 12 months until 18 months from the start of the study (July 2020 to November 2021).**
b. **If you only tests negative for COVID-19 during the study will only collect a final blood at 18 months from the start of the study (November 2021)**

The first visit will be quite short, we will ask you to sign on a piece of paper if you want to take part, and then we will ask you/your parent some questions about your health and will ask questions about the house.

The second visit will take about an hour for each person including taking the blood samples; the follow-up visits will be about 15 minutes per person. We will try to arrange these visits when most people in the household are present and this may involve us visiting your household in the evening or over weekends.

Risks of this study

There is a chance you get COVID-19 during the study either from people you see daily, household members and at school. Children do not usually get very sick from COVID-19 but you may feel sick like if you have flu. Because COVID-19 is easily passed on between people we will asking you to do some things to protect you and your household when you are talking to the study staff and when the samples are taken. We will provide you with a cloth mask, ask you to wash your hands/use sanitizer and practice physical distancing (stay at least 2 metres away from people). The study staff will help you and remind you about all these procedures.

We don't think that any big problems with the study procedures, but you may feel some pain when we prick you to collect blood and it may be uncomfortable when we collect samples from your nose and throat but this will be quick and the discomfort will not last for long. The nurse/s that will be collecting the samples are all trained and they have been collecting similar type of samples from other children without any problems.

Benefits of this study

By taking part in this study, you will help us learn more about how certain infectious diseases affect different people and who may benefit from vaccines. You will also get the results of the tests if you have any infection that can be treated, like HIV.

Confidentiality

Every effort will be made to keep all your information a secret: study information and blood samples will be marked with a number and not a name. Your name will not be used when we report on the results to other people.

Withdrawal from the study

Your participation in this study is entirely voluntary and you can stop participating, stop at any time, without giving a reason. If you leave the study it will not affect your access to other medical care.

Ethical approval

All researchers have to explain the work they plan to do to a committee. This committee helps to protect your rights

- This clinical study protocol has been submitted to the University of the Witwatersrand, **Human Research Ethics Committee (HREC)** and written approval has been granted by that committee.
- The study has also by approved by the ethics committees in the Mpumalanga Province and the North West Province.
- If you want any information regarding your **rights as a research participant, or complaints regarding this research study**, you may contact Prof. Clement Penny, Chairperson of the University of the Witwatersrand, Human Research Ethics Committee (HREC), which is an independent committee established to help protect the rights of research participants at (011) 717 2301.

PARTICIPANT ASSENT: * (7-17 years of age)

Printed Name	**Signature / Mark or Thumbprint**	**Date and Time**

(* Minors competent to understand must participate as fully as possible in the entire procedure)

Staff member:

Printed Name	**Signature**	**Date and Time**