

Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

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The roles of all investigators and collaborators are detailed in section 15, along with an organogram in Figure 2.

4. STUDY SYNOPSIS

Title: Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

Background and justification:

Annual influenza epidemics cause an estimated 290 000–650 000 deaths globally, with a disproportionately high burden in sub-Saharan Africa. In South Africa, approximately 20% of the population develops influenza-associated illness annually, with the highest rates of severe illness and mortality among infants and the elderly. Children under five years of age show particularly high infection rates (up to 67 per 100 person-seasons) and play a key role in transmission. Paediatric vaccination programmes in high-income countries have shown indirect protection to vulnerable populations, but such strategies are not implemented in sub-Saharan Africa in part because the mechanism for the indirect effects are not well understood and because influenza vaccination is only moderately effective. To elucidate the mechanism through which the indirect effects are acting, such as through reducing transmission, and to develop more effective vaccines, further studies and trials are needed.

Correlates of protection are immune markers that predict if an individual will be protected from infection or illness. For vaccine trials, it is a useful tool to allow for the estimation of immune responses without doing large efficacy trials. For influenza, the commonly accepted correlate of protection, especially for inactivated vaccines, is antibodies against the haemagglutinin surface protein, measured as HAI titres. However, limitations exist with HAI titre as a correlate of protection, particularly in children where higher titres are needed for protection compared to adults.

More recent research has suggested promise that mucosal immune markers may better correlate with influenza infection and illness, as this is where the infection begins, but these markers have not yet been fully identified or described. In this study we aim to identify additional correlates of protection/infection, including mucosal correlates, to provide essential evidence to inform vaccine development, regulatory pathways, and implementation strategies aimed at reducing influenza transmission and disease burden in South Africa and other similar settings.

Aim:

To describe and compare humoral and cellular immune responses to natural influenza virus infection in the mucosa and blood to identify possible correlates of protection against influenza infection, illness and duration of virus shedding.

Primary objectives:

In children aged 2-5 years:

1. Characterise mucosal and systemic immune markers profiles among children with and without PCR- and/or serologically-confirmed naturally acquired influenza infection
2. Characterise mucosal and systemic immune marker profiles among children with and without PCR-confirmed naturally acquired influenza-associated illness
3. Characterise how natural infection-induced mucosal and systemic immune markers may correlate with reduction in viral load and duration of shedding during influenza infection

Secondary objectives

1. Determine whether immune markers that correlate with protection against infection also correlate with protection against illness and with reduction in viral load/duration of shedding
2. Assess the impact of respiratory viral co-infection between influenza virus and RSV or SARS-CoV-2 on influenza presentation, viral load, duration of shedding, and on the magnitude/direction of mucosal/systemic immune responses

3. Quantify the waning of naturally-induced mucosal and systemic immunity over time and estimate the half-life of immune markers
4. Evaluate seroconversion and boosting rates following PCR-confirmed infection and correlate these with mucosal markers
5. Utilise mathematical modelling to define the optimal target product profiles for paediatric transmission-reducing vaccines capable of significantly lowering influenza burden in all ages
6. In a subset of participants:
 - 6.1. Describe how cellular immunity markers (CD4+, CD8+ T cells) from mucosa and periphery correlate with
 - 6.1.1. Protection against PCR- and/or serologically-confirmed influenza infection
 - 6.1.2. Protection against PCR-confirmed influenza illness
 - 6.1.3. Duration of shedding and viral load during PCR-confirmed influenza infection
 - 6.2. Describe the kinetics of cellular immunity (CD4+ and CD8+ T cells)

Methods:

Study design: Prospective, non-interventional, cohort study.

Study site and population: The study will be conducted in Jouberton in the North West Province of South Africa, which was the site of previous studies of community influenza and SARS-CoV-2 transmission (PHIRST and PHIRST-C) and an intensive cohort study among toddlers that estimated the incidence of influenza infection (ISiT). Enrolled participants will be healthy children aged 2-5 years, resident in Jouberton and available for follow up for the duration of the study.

Sample size: We will enrol a maximum of 150 children, which even if loss to follow-up reaches close to 30% and the final sample size is 100, will provide 80% power to detect a 50% protection with an influenza attack rate of 45%.

Enrolment and follow up: We will enrol healthy children at clinics in Jouberton, attending for Expanded Programme of Immunization (EPI) vaccination or other well-child visits. Children aged 2-5 years will be pre-screened and those meeting enrolment criteria will be formally enrolled at the clinic following written informed consent from a parent.

Potential participants will be evaluated for study eligibility and eligible children with caregiver consent will be enrolled and baseline data collected from March through April 2026.

Children will be followed from April through October 2026 during the influenza season. Follow-up includes collection of thrice weekly mid-turbinate nasal swabs to be tested by reverse transcription polymerase chain reaction (RT-PCR) for influenza and other respiratory viruses. One swab per week will be collected by study nurses during a household visit, and two additional swabs per week will be collected by the caregiver. Data on symptoms and tympanic temperature will be collected by nurses at weekly visits and daily by caregivers using an electronic symptom diary. Serum will be collected before and after the season, and at two additional time points during the follow-up period. Peripheral blood mononuclear cells (PBMCs) will be collected before and after the season, and nasal mucosal fluid, oral fluid and nasopharyngeal swabs will be collected monthly to test for immunological markers, including antibodies, cytokines and T- and B-cells.

Analysis: To explore how mucosal and systemic immune markers correlate with protection against influenza infection, illness and virus shedding, we will summarise and compare marker levels between groups with and without influenza infection using geometric means and regression modelling.

Duration of study: 8 months (March – October 2026)

Funding Mechanism: Research cooperative agreement with US Centers for Disease Control and Prevention (CDC) (6U01IP001269-02L001).

5. BACKGROUND AND INTRODUCTION

5.1. Influenza Burden of Disease

Influenza virus infections cause substantial annual morbidity and mortality worldwide including in South Africa [1-3]. Annual influenza epidemics result in an estimated three to five million cases of severe illness, and about 290 000-650 000 deaths globally.

The burden of influenza in sub-Saharan Africa (and specifically in South Africa) is substantial, with some studies suggesting elevated influenza-associated mortality rates compared to other regions [4, 5]. During the influenza season (usually between May and September) in South African hospitals, approximately 14% of inpatients with lower respiratory tract infection and 25% of patients with influenza-like illness test positive for influenza by polymerase chain reaction (PCR) [6]. A modelling study from South Africa, using case-based and ecological data, estimated that during 2013-2015, on average 19.8% (10 737 847 individuals) of the South African population were affected by influenza-associated illness annually [6]. Of these episodes, 10 598 138 were mild, 128 173 were severe episodes and 11 536 (0.1%) were fatal [7]. Rates of influenza-associated severe non-fatal illness were higher among individuals aged <1 year (1550.9 per 100 000 individuals in the population) and ≥65 years (761.3 per 100 000 individuals in the population), and rates of influenza-associated deaths were higher among infants <1 year (80.3 per 100 000 individuals in the population) and persons aged ≥65 years (137.9 per 100 000 individuals in the population)[6].

In South Africa, extremes of age (<6 months [adjusted odds ratio (aOR), 37.6], 6–11 months [aOR, 31.9], 12-23 months [aOR, 22.1], 24–59 months [aOR, 7.1], and ≥65 years [aOR, 40.7] compared to those aged 5-24 years) are significantly associated with increased risk of influenza-associated hospitalisation [8]. The burden of hospitalisation and deaths due to influenza can vary substantially from year to year depending on the transmission and virulence characteristics of the circulating strain(s) [1].

A recent study in South Africa assessed the mean annual national burden of medically and non-medically attended influenza-associated illness among potential target groups for influenza immunisation during 2013-2015. This study reported that rates of mild influenza-associated illness were highest in children aged 6-59 months (23,983 per 100,000 population), and rates of fatal illness were highest in individuals aged ≥65 years (138 per 100,000 population) [9].

A recent population-based study from South Africa found an extremely high incidence of influenza infection (67.4 per 100 person seasons) among children aged <5 years in a rural and urban community; 74% of these infections were associated with one or more influenza symptoms [10]. The proportion with a repeat infection in the same season was 23% in this age group. Household transmission was highest from index case patients aged 1-4 years (16%). Symptomatic individuals were more likely to transmit influenza compared to asymptomatic individuals, but asymptomatic individuals were still able to transmit influenza [10]. In a study focusing on South African children aged 6-23 months, the influenza attack rate was 65%, with 14% of the 93 participants experiencing more than one influenza infection during the influenza season [11].

The high burden of influenza in young children and their important role in household transmission, suggests that increased influenza vaccine coverage in this age group could potentially be associated with substantial reductions in disease burden in the targeted age group as well as potentially in other age groups through reductions in disease transmission.

5.2. Vaccination to reduce the burden of influenza

To reduce influenza-related severe disease and mortality, the World Health Organization (WHO) recommends the vaccination of individuals at risk for severe disease, including older adults, pregnant women, those with underlying conditions and children <59 months [12]. In line with this, the South African public influenza vaccination programme follows a risk-based approach and prioritises vaccinating those most vulnerable to severe disease (including the WHO-specified risk groups but not children <59 months), but vaccine coverage is only 4.6% among these target groups [13]. Current influenza vaccines are also suboptimal: vaccination is needed seasonally due to the change in circulating strains and waning immunity. Vaccine and circulating strain mismatches due to viral evolution can lead to low effectiveness, and effectiveness is lower in certain groups like the elderly [14]. These challenges are amplified in sub-Saharan Africa, where influenza-related mortality is 30-50% higher than other regions [3], and influenza vaccination rates are lowest [15]. Low vaccination rates are in part driven by large numbers of individuals in risk groups as well as the difficulty of targeting these groups for annual vaccination [16].

An alternative to the risk-based approach would be to target age groups that drive transmission in the community, specifically younger children, to interrupt transmission and provide indirect protection to vulnerable populations. By leveraging this indirect protection, a greater public health impact could be achieved.

Paediatric vaccination programmes have been implemented in high-income countries such as the UK, where a paediatric live-attenuated influenza vaccine (LAIV) programme was implemented in 2013 [17]. England and Wales reported a 59% reduction in general practitioner influenza-like disease consultations in the 2014/15 season in pilot regions [17]. Paediatric vaccination has not been implemented in low to middle income countries (LMIC) and specifically sub-Saharan Africa, where indirect effects may be greater due to the younger population and high influenza incidence [18].

This approach has become more attractive with transmission-reducing vaccines being identified as a key priority area by the influenza vaccine roadmap (IVR) [14]. Vaccines that induce mucosal immunity in the upper respiratory tract have been proposed as promising candidates to reduce transmission by generating immunity directly at the site of infection. Such vaccines could potentially inhibit or block viral replication, thereby reducing both infection and subsequent transmission [19]. In light of this, it is important to better understand mucosal immunity that correlates with protection against influenza infection to guide the development and evaluation of novel vaccines aiming to reduce or even block infection and transmission [20].

5.3. Correlates of protection

Correlates of protection are immune markers that predict if an individual will be protected from infection or illness. For vaccine trials it is a useful tool to allow for the estimation of immune responses without doing large efficacy trials. For influenza, the commonly accepted correlate of protection, especially for inactivated vaccines, is antibodies against the haemagglutinin surface protein, measured as HAI titres. However, limitations exist with HAI titre as a correlate of protection, particularly in children where higher titres are needed for protection compared to adults [21, 22]. Recent data showed that HAI titres may only mediate 20-37% of protection against influenza disease [23], and a 35-70% reduction in risk of infection acquisition [24].

There are other potential mucosal and systemic (circulating in blood) correlates of protection against influenza infection, illness and duration of shedding. Mucosal correlates of protection are of special interest as these may be a better indication of protection against infection, compared to systemic immunological markers. By preventing infection, higher indirect effects might be possible due to the interruption of transmission chains. The identification of novel correlates of protection, especially mucosal correlates, to assess influenza vaccines has also been identified as a high priority by the IVR [14]. Other potential correlates of protection that are currently being investigated for influenza, includes antibody effector functions, anti-HA stalk antibodies, anti-NA antibodies, and mucosal IgA antibodies, cytokines, cross reactive CD4+ and CD8+ cells [25-27].

5.4. Respiratory syncytial virus and SARS-CoV-2 in children

Respiratory infections in children often present with overlapping symptoms, making clinical distinction challenging. Detecting multiple viruses can reveal important co-infections associated with illness severity and immunological responses. Thus, although influenza is the primary research target for this study, employing a multi-pathogen assay provides richer epidemiologic data and clinical understanding. This approach aligns with current clinical guidelines and emerging evidence supporting multiplex testing for more accurate and timely diagnosis of respiratory infections.

Respiratory syncytial virus (RSV) is a major cause of acute respiratory illness in children under five globally and in South Africa, with an estimated mean annual number of approximately 96 220 RSV-associated severe illness cases in children under five years in South Africa [28]. The highest incidence and mortality occur in infants under two months old [28], with RSV having a high attributable fraction in children younger than 5 years presenting with influenza-like illness (>75%) and severe acute respiratory infection (>83%) [29]. The Drakenstein cohort study found RSV to be strongly associated with pneumonia (OR 8.05, 4.21-15.38) in healthy children [30].

SARS-CoV-2 infection in children under five, including in South Africa, tends to present with milder clinical symptoms compared to adults, although SARS-CoV-2 still accounted for 5–15% of paediatric severe acute respiratory illness hospitalisations in South Africa during pandemic waves, with higher rates observed during the Omicron variant surge [31]. Surveillance from South Africa show SARS-CoV-2 positivity rates of 4% in out-patient influenza-like illness and 3.5% in in-patient pneumonia surveillance [32]. Data on the attributable fraction of SARS-CoV-2 in respiratory illness in children, especially post-pandemic, is still lacking.

6. JUSTIFICATION

Despite the substantial burden of influenza among young children in South Africa, particularly those under five years of age, current vaccination strategies remain limited in both coverage and impact. This age group experiences the highest incidence of infection and plays a critical role in household and community transmission, making them an ideal target for interventions that could yield both direct and indirect protection through prevention of transmission to individuals at high risk of severe illness. However, the development and evaluation of next-generation transmission-reducing influenza vaccines, such as mucosal or broadly protective vaccines, are constrained by incomplete understanding of immune correlates of protection, particularly at the mucosal level where infection is initiated. Current correlates, such as serum HAI titres, are insufficient to fully explain protection against infection, illness, or shedding, especially in children. Identifying mucosal and systemic immune markers associated with protection against influenza infection and illness will be essential to guide vaccine development and evaluation, support regulatory pathways, and inform immunisation strategies aimed at reducing transmission. Furthermore, co-circulating respiratory viruses such as RSV and SARS-CoV-2 can influence clinical presentation, viral and transmission dynamics, and immune responses. By characterising natural infection-induced immune responses and their relationship to influenza outcomes, this study will generate critical evidence to inform the design and implementation of more effective paediatric vaccination strategies with the potential for broader population-level impact. In addition, establishing baseline data on mucosal and systemic correlates of protection will strengthen pandemic preparedness by improving our ability to rapidly evaluate candidate influenza vaccines and immune responses to emerging strains in future outbreaks.

7. STUDY AIM AND OBJECTIVES

7.1. Aim

To identify possible correlates of protection against influenza infection, illness and duration of virus shedding and to describe and compare humoral and cellular immune responses to natural influenza virus infection in the mucosa and blood.

7.2. Objectives

7.2.1. Primary objectives

In children aged 2-5 years:

1. Characterise mucosal and systemic immune markers profiles among children with and without PCR- and/or serologically-confirmed naturally acquired influenza infection
2. Characterise mucosal and systemic immune marker profiles among children with and without PCR-confirmed naturally acquired influenza-associated illness
3. Characterise how natural infection-induced mucosal and systemic immune markers may correlate with reduction in viral load and duration of shedding during influenza infection

7.2.2. Secondary objectives

1. Determine whether immune markers that correlate with protection against infection also correlate with protection against illness and with reduction in viral load/duration of shedding
2. Assess the impact of respiratory viral co-infection between influenza virus and RSV or SARS-CoV-2 on influenza presentation, viral load, duration of shedding, and on the magnitude/direction of mucosal/systemic immune responses
3. Quantify the waning of naturally-induced mucosal and systemic immunity over time and estimate the half-life of immune markers
4. Evaluate seroconversion and boosting rates following PCR-confirmed infection and correlate these with mucosal markers
5. Utilise mathematical modelling to define the optimal target product profiles for paediatric transmission-reducing vaccines capable of significantly lowering influenza burden in all ages
6. In a subset of participants:
 - 6.1. Describe how cellular immunity markers (CD4+, CD8+ T cells) from mucosa and periphery correlate with
 - 6.1.1. Protection against PCR- and/or serologically-confirmed influenza infection
 - 6.1.2. Protection against PCR-confirmed influenza illness
 - 6.1.3. Duration of shedding and viral load during PCR-confirmed influenza infection
 - 6.2. Describe the kinetics of cellular immunity (CD4+ and CD8+ T cells)

8. METHODS

8.1. Study site and population

The study will be conducted in Jouberton township, where a previous study of influenza community transmission was also performed (PHIRST) [10, 33]. Jouberton is one of five townships surrounding the city of Klerksdorp which is located in the City of Matlosana municipality in the North West Province of South Africa. The City of Matlosana municipality has a population of 431 231, spanning 115 km [34].

8.2. Study design

A prospective, non-interventional, observational cohort study of healthy children aged 2-5 years with intensive follow-up during the influenza season (April – October 2026) at one site, for one influenza season (2026).

8.3. Inclusion criteria

1. Children aged 2-5 years of age (i.e. from the second birthday until 5 years and 11 months of age) at the time of enrolment.
2. Healthy children as established by medical history and clinical examination before entering the study.

3. Caregiver availability and willingness to provide written informed consent to all study procedures.
4. Child planning to reside in the selected community for the duration of the study.

8.4. Exclusion criteria

1. Presence of malnutrition (defined as z score for age <-2 based on WHO child grown standard at time of screening for eligibility).
2. Presence of any serious systemic disorder determined by medical history and/or physical examination that would compromise the participant's health or is likely to result in non-conformance to the protocol or a child who is on treatment for any chronic medical condition.
3. Prior history of receiving influenza vaccination.
4. Not providing consent for storage and shipment of samples for immunological testing.
5. Parent of participating child not able, available or willing to accept active weekly follow-up by the study staff, performing a twice-weekly caregiver swab and completing symptom diary on an electronic device or any medical condition in the parents that, in the judgment of the investigator, would interfere with or serves as a contraindication to protocol adherence or a parent's ability to give informed consent. History of chronic administration (defined as more than 14 days) of immunosuppressant medications, including corticosteroids, in the last 6 months (those on inhaled or topical steroids may be permitted to participate in the study).
6. Child is HIV-infected as identified by self-report or if screening of study eligibility identifies that the child is HIV-infected.

8.5. Sample size

We aim to enrol a maximum of 150 children. As this is an exploratory, hypothesis-generating study, sample size is based on available funding. We will aim to enrol approximately equal numbers of children in each 1 year age band (2, 3, 4 and 5 years). Table 3 summarizes power calculations for three sample size scenarios to detect a hazard of 0.50 (50% protection) or 0.25 (75% protection) using closed-form approximation for an unadjusted Cox proportional hazards model [35]. Power is shown across assumed attack rate ranging from 25% to 65% and using assumptions of moderate-to-high and high heterogeneity of the immune marker titres [36]. Based on these scenarios, even if loss to follow-up reaches close to 30% and the final sample size is 100, we would have 80% power to detect a 50% protection under the assumption of moderate-to-high heterogeneity in the immune marker with an influenza attack rate of 45%, and 90% power if the heterogeneity is high. For a higher protection level of 75% power will be 100% for all scenarios.

Table 3. Power calculation for ranging sample size, influenza incidence and immune marker heterogeneity and protection levels.

High heterogeneity (0.7 standard deviation)										
	50% protection					75% protection				
Attack rate	25%	35%	45%	55%	65%	25%	35%	45%	55%	65%
N=100	0.68	0.82	0.90	0.95	0.97	1.00	1.00	1.00	1.00	1.00
N=138	0.81	0.92	0.97	0.99	1.00	1.00	1.00	1.00	1.00	1.00
N=150	0.84	0.94	0.98	0.99	1.00	1.00	1.00	1.00	1.00	1.00
Moderate-to-high heterogeneity (0.6 standard deviation)										
	50% protection					75% protection				
Attack rate	25%	35%	45%	55%	65%	25%	35%	45%	55%	65%
N=100	0.55	0.69	0.80	0.87	0.92	1.00	1.00	1.00	1.00	1.00
N=138	0.69	0.82	0.91	0.95	0.95	1.00	1.00	1.00	1.00	1.00
N=150	0.75	0.85	0.93	0.97	0.98	1.00	1.00	1.00	1.00	1.00

9. STUDY PROCEDURES

9.1. Screening

We will identify potentially eligible children by pre-screening at healthcare facilities within the study community in areas where well children are presenting for consultation. For example, children attending the clinic for Expanded Programme on Immunisation, vitamin A, deworming or whose mothers are attending clinics for other purposes. Parents of children visiting the clinic with children outside of the desired age bracket will also be approached to enquire if there are any children in their household aged 2-5 years, and invited to visit the clinic with these children for screening. Study pamphlets and posters will also be distributed and displayed in these clinics.

Children will be screened for study eligibility using a simple questionnaire to ascertain if they are likely to be eligible for the study (willingness to participate, RTHC available for HIV assessment, baseline medical history). Parents of children that do appear to meet eligibility criteria will be approached and invited to consider providing informed consent for their child to participate in the study. Inclusion and exclusion criteria are described in section 8.3 and 8.4 of this protocol.

9.2. Informed consent and enrolment visit

Informed consent is the process of ensuring that study participants, or, in the case of children aged 2-5 years, their parents, fully understand the purpose of the study and what will and may happen to their children while participating in a research study and what is expected from them during the course of the study. Initial written informed consent is required before performance of any study-related procedures. The informed consent process continues throughout the study. Written informed consent will be obtained from the parent of the participating child as detailed in appendix A. Separate consents for enrolment (ICF1), HIV testing (ICF2), storage and shipment of specimens outside of South Africa to collaborators for immunological testing (ICF3), HLA typing and transcriptomics (ICF4) and PBMC isolation (ICF5) will be obtained, however PBMC isolation will only be done on a subset of children as described in 9.3.

9.3. Enrolment visit procedures

Following consent:

1. A structured interview of the child's medical history will be conducted following which the child will have a directed clinical examination by a study nurse to assess for signs and symptom of serious illness. If any conditions requiring clinical care are identified the child will be referred for further management and the child will be withdrawn from the study.
2. HIV status will be assessed based on:
 - a. Informed consent will be obtained before assessment is done
 - b. If the child's mother had a negative test during pregnancy which is documented in the Road to Health Card (RTHC), child will be considered negative
 - c. If the child had a PCR blood test at 6 weeks of age and the negative result was documented in the RTHC, the child will be considered negative
 - d. If the biological mother agrees to a rapid HIV test and this test is negative, the child will be considered negative
 - e. If the rapid test done on the biological mother is positive for HIV, or the mother tested positive during pregnancy, or the biological mother do not agree to a rapid HIV test, the child will be tested for HIV:
 - i. Pre-test counselling will be done with the parent to explain what HIV is and why testing is important, what a positive or negative result means, available support and confirming understanding and agreement to test

- ii. A trained healthcare worker will perform a rapid HIV test using a finger-prick blood sample
 - 1. If the test is negative, enrolment will continue
 - 2. If the test is positive the child will be referred to the nearest clinic for serum collection and confirmatory testing
 - iii. Post-test counselling will be done with the parent based on the test result
- 3. Once the child is confirmed as healthy the following procedures will occur if not already done by study staff during the screening process:
 - a. Assign participant study number
 - b. Obtain vaccination history
 - c. Measure height/length & weight
 - d. Collect immunological samples (blood in serum-separating tube (SST), nasal mucosal fluid and oral fluid, detailed in Table 4)*
 - e. Set up a schedule for home visits
 - f. Arrange SIM card to be RICA'ed for use in study-issued digital symptom diary. Although devices are provided, a caregiver must be present when we register (RICA) the SIM card because South African law requires the person responsible for the device to show their ID and proof of address to link the SIM card to their name.

* In children selected for PBMCs, blood collection will be deferred to a visit scheduled later in the week.

Due to the resources required for PBMC isolation, this procedure will only be performed on 25% of participants. Every fourth child enrolled will be selected for PBMC isolation, and the date and time to return to the clinic for the blood draw for PBMC isolation will be arranged with the caregiver/parent of the child. The number of PBMC isolations performed per day will be based on laboratory capacity to ensure high yield and viability of cells. If the caregiver/parent does not consent to PBMC isolation, the next enrolled child will be selected. Blood collection volumes are detailed in 9.8.

9.4. Follow-up visits

Details and timing of specimens collected are summarised in Table 4.

9.4.1. First follow-up visit:

The first follow-up visit will take place at the child's home within 3 weeks of the enrolment visit.

At the first follow-up visit the nurse will complete the following with the parent:

- 1. Mid-turbinate nasal swabs will be collected by the nurse for real-time reverse transcription polymerase chain reaction (PCR) detection of influenza, RSV, and SARS-CoV-2. Swab collection procedures are detailed in the manual of operations (MOP).
- 2. Structured questionnaires will be administered to assess presence, duration and severity of symptoms and health-seeking behaviour (Appendix B)
- 3. Provide the parent/caregiver with the following:
 - a. A digital tympanic thermometer and digital symptom diary.
 - b. Two swab collection kits consisting of a nasal swab with transport medium in appropriate packaging and all marked with a barcode for the next parent/caregiver administered nasal swabs.
 - c. Detailed written instructions and a link to video instructions on:
 - i. How to complete the symptom diary
 - ii. How to measure and record temperature
 - iii. How to collect a nasal swab
 - iv. How to package the swab

- v. Contact details for collection
4. The parent/caregiver will be trained in temperature measurement and nasal swab collection by the study nurse. The nurse will ask the parent to demonstrate competency and repeat if necessary.
5. Parents/caregivers will be informed about the danger signs of respiratory illness and that they should take their child to the clinic immediately if they develop any danger signs (written materials will be made available to parents).

9.4.2. Weekly follow-up visits at home

These visits will commence in April 2026 (prior to the anticipated start of the influenza season). Each participant will be visited in their home once per week according to a pre-established schedule. There is a visit window of 1 day on either side of the scheduled visit. If a visit occurs out of schedule the next scheduled visit will occur as arranged. The same will apply to a missed visit.

During each visit the following will occur:

1. Nasal swabs for PCR testing will be collected for influenza, RSV and SARS-CoV-2 detection by a study nurse
2. Parent/caregiver will be provided with two swab collection kits for the next parent/caregiver administered nasal swabs
3. Structured questionnaires will be administered to assess presence, duration and severity of symptoms and health-seeking behaviour (Appendix B)
4. Tympanic temperature will be measured
5. The nurse will review daily symptom data collected by parent/caregiver
6. Date and time of the next visit will be confirmed with the parent/caregiver
7. Once a month the nurse will review the swab-taking procedures with the parent/caregiver

9.4.3. Collection of parent/caregiver administered swab

Twice a week on set days the parent/caregiver will collect a nasal swab from their child:

1. Swab test kits with swab, viral transport medium, zip lock bags and barcoded sticker will be provided weekly to the parent.
2. Detailed discussions about the requirements for specimen collection will be had with the parent prior to the swab collection (detailed in the MOP).
3. Once the swab has been collected and packaged as per instructions the parent will telephonically message the driver who will collect the sample, store it on ice packs in a cooler box and deliver it to the laboratory.
4. The parent will complete the electronic swab submission form. If the parent is unable to collect the swab for any reason a missed swab form will be completed and the nurse will discuss the reasons with the parent at the next scheduled visit and attempt to resolve any problems.

9.4.4. Daily data collected by caregiver

1. Once a day, in the morning, the parent will complete a symptom questionnaire on a device that will be provided with air time to the parent.
2. At the same time the parent will measure the child's temperature and capture this on the daily symptom form.

9.4.5. Second and third blood draw clinic visit

Two months after enrolment (second blood draw), and at a second time point during the intensive follow-up period (third blood draw) a clinic visit will be scheduled for blood collection in all participants. The timing of the third blood draw will be based on syndromic sentinel surveillance performed by CRDM in Matlosana district. The

draw will be timed to be no less than two weeks after the peak of the influenza season, and no more than one month after the peak of the influenza season.

9.4.6. End-of-season clinic visit

During the final two weeks of follow-up, or within two weeks of the end of the follow-up period or withdrawal from the study, a clinic visit will be scheduled for end-of-season blood collection (all participants) and PBMC collection (25% of participants, as selected during enrolment visit).

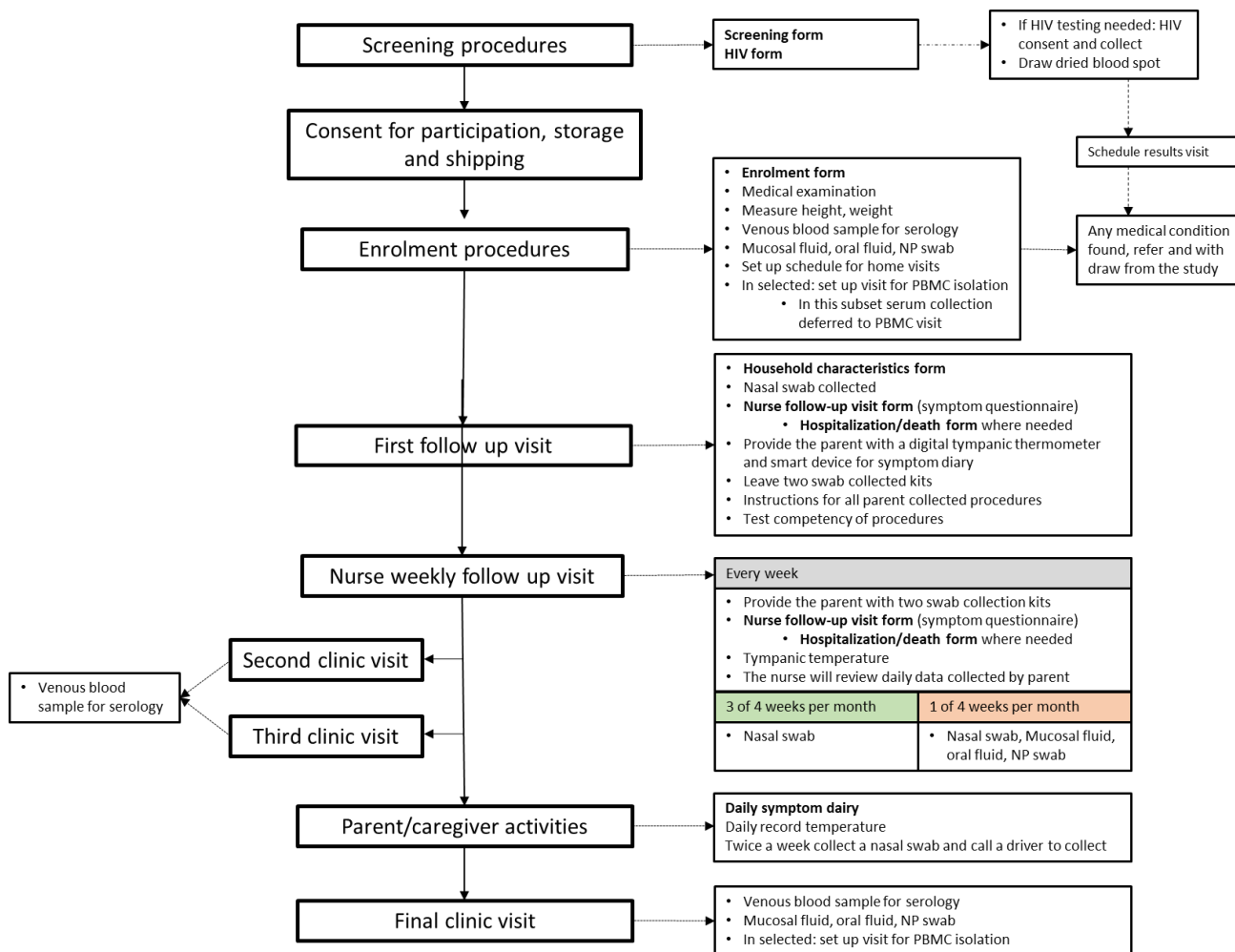


Figure 1. Flow diagram of study visits and procedures for MUSIC-Flu

NP: Nasopharyngeal swab

9.5. Referral to health services

If any participant has symptoms or signs that may need medical attention, they will be assessed by the study team and, if required, they will be referred to the relevant facility for further treatment. Parent/caregivers will be informed that if they are concerned about wellbeing of the child, he/she should firstly take the child to a healthcare practitioner or clinic, and then inform the study PI/site clinician of the outcome of the visit. For any individuals who are admitted to hospital or die, a detailed form (Appendix B) will be completed to collect

information on clinical presentation, management and laboratory results. Any admissions or deaths will be documented and reported to the HREC in the six monthly reports.

Any participant who is admitted to Klerksdorp Hospital will be assessed by the NICD pneumonia surveillance staff at the hospital and, if eligible, will be co-enrolled into the NICD pneumonia surveillance programme (Wits HREC Protocol number M210259).

9.6. Procedure methods

Study procedures are performed and recorded in source documents as outlined in the study specific MOP. All study staff will be trained and tested on these procedures. Follow-up training will be conducted by the study investigators and site coordinators.

9.6.1. Vital signs

1. Temperature in degrees Celsius (recorded to the nearest 0.1 degree) will be measured by a digital thermometer provided by the study, which records the temperature in the external ear canal. Body temperature will be measured daily by caregivers and during the weekly nurse home visit by the study nurse.
2. Database ranges will assist with recording appropriate numbers.

9.6.2. Height/length and weight

1. Height/length is measured in cm and recorded to the nearest 0.1 cm, this procedure will be done by a trained nurse in the clinic setting at the enrolment visit.
2. Weight is measured in kg and recorded to the nearest 0.1 kg this will be done by a trained nurse in the clinic setting at the enrolment visit.

9.6.3. Physical examination

A directed physical examination will be conducted by a trained nurse to assess the presence of any physical sign of chronic medical conditions. Data will be completed onto a standard form. Any concerning findings will trigger a referral to appropriate medical care prior to enrolling the child.

9.6.4. Medical history

A comprehensive medical history will be collected including details of any previous vaccinations and reaction to vaccinations, birth, participation in clinical trials, surgery, previous hospitalisation, allergy to food/drugs, current medication and history of any chronic or recurrent medical conditions. These will be collected on a standardised questionnaire.

9.7. Withdrawal from the study

An enrolled participant may be terminated from the study for any of these reasons.

1. Participant or parent withdraws consent for any reason.
2. The site PI decides that termination is in the best interest of the participant.
3. The site PI decides that termination is necessary to protect the integrity of the study or achieve the objectives of the study.
4. Interruption of study schedule makes the participant's data unusable according to protocol requirements, missing more than 4 consecutive study visits, more than 50% of symptom diaries not submitted, or as assessed by the principal investigator.

Withdrawals will be captured on the nurse follow-up form to collect date and reason for withdrawal.

9.8. Specimen collection and storage

Standard operating procedures for the collection of specimens, use of appropriate PPE and the disposal of waste will be detailed in the MOP. The study nurse will wear protective PPE when taking the nasal swab (surgical mask, gloves, gown/apron) as described in the MOP. Sanitiser will be available for use during the household visits. Training at the start of the study will be intensive and documented. Also, weekly training on safety and PPE will be done at the field site. Monitoring of field procedures will be done on a regular basis and documented. A table summarising the types of specimens to be collected and testing to be done is included below (Table 4).

Table 4. Specimen collection, timing and testing summary for MUSIC-Flu

Sample type	Time points	Specimens / participant	Collection device/ container/ transport medium	Storage conditions	Assays to be performed [Primary testing lab]
Serum	<ul style="list-style-type: none"> Enrolment visit (Feb/Mar) Two months post enrolment Two/three months after second draw¹ End-of-season clinic visit (Oct/Nov) 	4	Serum separator tube (5 mL)	Refrigerate upright, centrifuge within 8 hours, aliquot serum, freeze at -70°C at site lab, shipment to NICD on dry ice at end of study	<ul style="list-style-type: none"> HAI [NICD] Microneutralisation assays [NICD] Binding assay IgG [ICL, CDC] Binding assay IgM [CDC] Fc receptor binding assays [ICL]
Nasal mucosal fluid	<ul style="list-style-type: none"> Enrolment visit (Feb/Mar) End-of-season clinic visit (Oct/Nov) Monthly during nurse home visit (Apr-Sep) 	8	Nasosorption synthetic absorptive matrix (SAM) in cryopreservation buffer	Transport on dry ice to site lab, freeze at -70°C, shipment to NICD on dry ice, store at -70°C	<ul style="list-style-type: none"> Binding assay IgA [ICL, CDC] Binding assay IgG [ICL, CDC] Binding assay IgM [CDC] Fc receptor binding assay [ICL]
Oral fluid	<ul style="list-style-type: none"> Enrolment visit (Feb/Mar) End-of-season clinic visit (Oct/Nov) Monthly during nurse home visit (Apr-Sep) 	8	Oral specimen collection device in storage buffer	Transport on dry ice to site lab, freeze at -70°C, shipment to NICD on dry ice, store at -70°C	<ul style="list-style-type: none"> Binding assay IgA [ICL, CDC] Binding assay IgG [ICL, CDC] Binding assay IgM [CDC] Fc receptor binding assay [ICL]
Nasopharyngeal swab	<ul style="list-style-type: none"> Enrolment visit (Feb/Mar) End-of-season clinic visit (Oct/Nov) Monthly during nurse home visit (Apr-Sep) 	8	Flocked swab in cryopreservation buffer	Transport on dry ice to site lab, freeze at -70°C, shipment to NICD on dry ice, store at -70°C	<ul style="list-style-type: none"> T-cell phenotyping² [ICL] B-cell phenotyping² [ICL]
PBMCs	<ul style="list-style-type: none"> Enrolment visit (Feb/Mar) 	2	EDTA anticoagulant tube (2x 5mL) ³	Process within 6 hours, temperature controlled freezing overnight, stage at -70°C, shipment to	<ul style="list-style-type: none"> T-cell phenotyping⁴ [ICL] B-cell phenotyping⁴ [ICL]

	<ul style="list-style-type: none"> • End-of-season clinic visit (Oct/Nov) 			NHLS biobank on dry ice, long-term storage in liquid nitrogen	
Mid-turbinate nasal swab	<ul style="list-style-type: none"> • Nurse home visit (weekly, Apr-Oct) • Twice weekly by caregiver during follow-up (Apr-Oct) 	87	Flocked swab in universal/viral transport medium	Transport on ice packs to site lab, refrigerate short term at 2-8°C, shipment to NICD ice packs, long-term storage at -70°C	<ul style="list-style-type: none"> • rRT-PCR for influenza [NICD] • Digital rRT-PCR for influenza viral load (positives only) [NICD] • Whole genome sequencing (at least one positive per episode, with Ct<30) [NICD] • Influenza virus culture (positives with Ct<30) [NICD]
Finger prick	<ul style="list-style-type: none"> • Enrolment visit (Feb/Mar) If necessary to confirm HIV status 	1	Finger prick	None	<ul style="list-style-type: none"> • Rapid HIV ELISA [PHRU, study site]

¹ Dependant on peak of influenza season as determined by syndromic surveillance done by CRDM as detailed in section 9.4.5. ² Collected and stored for all participants, phenotyping will be completed in a selection of participants that also have PBMCs available, or had infections during the follow-up period. ³ Total volume of blood collected will be assessed based on weight of child, with no more than 3% of total blood volume collected. Please see section 9.8.1 for details. ⁴ Collected in a random selection of participants (25%).

HAI: hemagglutination inhibition assay. PBMC: Peripheral Blood Mononuclear Cells. rRT-PCR: real-time reverse transcription polymerase chain reaction to test for influenza, RSV, SARS-CoV-2. Ct: Cycle threshold, ELISA: Enzyme-linked immunosorbent assay. NICD: National institute for communicable diseases, ICL: Imperial College London. NHLS biobank: National Health Laboratory Services National Biobank in Braamfontein, Johannesburg.

9.8.1. Serum

Serum specimens will be tested for anti-SARS-CoV-2, influenza and RSV antibodies. We will collect up to 5ml in serum separating tube (SST) vacutainers. Detailed collection procedures are described in MOP. Specimens will be refrigerated after collection, centrifuged at the study site lab within 8 hours, serum aliquoted and frozen at -70°C until batched shipment to NICD on dry ice. HAI and micro neutralisation assays will be performed at NICD. Aliquots of all specimens will be shipped to Imperial College London (ICL) and Centers for Disease Control and Prevention in the United States (CDC) for further antibody testing.

9.8.2. Peripheral Blood Mononuclear Cells (PBMCs)

In a subset of children (every fourth enrolled child), we will collect up to 10ml of blood in Ethylenediaminetetraacetic acid (EDTA) vacutainers for PBMC isolation. Total volume of blood collected will be assessed based on weight of child, with no more than 3% of total blood volume collected, including the 5 mL collected in SST vacutainer. Considering the lowest acceptable weight for a child to be included in the study based on exclusion criteria is 9kg (Z-score of -2 for 2-year old girl child), the maximum allowable blood to be collected is 21.6 mL, which is above the total required volume of 15 mL.

PBMCs will be stored in liquid nitrogen and shipped to Imperial College London for T-cell and B cell phenotyping.

9.8.3. Nasal mucosal fluid, oral fluid and nasopharyngeal swabs for immune marker testing

Nasal mucosal fluid will be collected using Nasosorption™ FX-i synthetic absorptive matrix (SAM) devices (Hunt Developments, West Sussex, United Kingdom). Oral fluid will be collected using oral specimen collection devices. Flocked nasopharyngeal (NP) swabs will be collected and stored in cryopreservation buffer. Procedures for collection are described in the MOP. Oral fluid and NP swabs will be stored at -70°C, and SAM devices will be stored in liquid nitrogen at the National Health Laboratory Services (NHLS) National Biobank Braamfontein, Johannesburg, South Africa until shipment to the United Kingdom for immunological testing (oral and nasal mucosal fluid: binding anti-influenza IgG, IgA, IgM; NP swabs: T-cell and B cell phenotyping) at ICL. After elution is completed at ICL aliquots of all nasal mucosal and oral fluid specimens with sufficient volume will be shipped to the CDC for additional testing, inter-laboratory comparison and validation of results.

9.8.4. Mid-turbinate nasal swabs

Nasal flocked swabs will be collected thrice weekly and placed in universal transport medium. Procedures for collection are described in the MOP. Specimens will be transported on ice packs to site lab, refrigerated at 2-8°C, and then shipped to NICD on ice packs. Samples will be tested at NICD by RT-PCR for the presence of influenza, RSV and SARS-CoV-2 nucleic acids. Whole genome sequencing for further characterisation of identified viruses will be performed for influenza, RSV and SARS-CoV-2 positive samples at NICD. Specimens will be stored at -70°C for long-term storage. Once primary RT-PCR testing is completed, samples may be transferred to the National Health Laboratory Services (NHLS) National Biobank Braamfontein, Johannesburg, South Africa.

9.8.5. Finger prick blood sample

For children without a documented HIV status, a finger prick blood sample will be collected for rapid HIV testing using a point of care rapid test. Collection and testing procedures are detailed on the MOP. Any patients identified testing HIV positive will be referred to the nearest local healthcare facility for serum collection and confirmatory HIV-testing and referral into care if needed.

9.9. Specimen labelling

Collection containers will be marked with:

1. Barcoded unique identifier and visit number.
2. The specimen collection date.

Detailed procedure for specimen labelling are described in the MOP.

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

9.10. Packaging and transport

Detailed information about packing/transporting specimens are described in the MOP. Specimens will be transported in sealed plastic bags. Blood and respiratory specimens must be kept cold (2-8°C) during transport and a cooler box filled with ice packs will be used for this purpose. Nasal mucosal fluid, oral fluid, nasopharyngeal swabs, PBMCs and one serum aliquot will be shipped to Imperial College London, United Kingdom for immunologic testing. A subset of these samples will be shipped to the Centers for Disease Control and Prevention in the United States for inter-laboratory comparison and validation of results. Specimens will only be shipped once material transfer agreements (MTA) have been signed by both parties.

9.11. Laboratory methods

Detailed laboratory methods are provided in the MOP. A short description of each assay is provided below.

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

Nucleic acids will be extracted from 200µl of UTM using automated extraction methods. Extracts will be tested for SARS-CoV-2, RSV, influenza A and B viruses by RT-PCR using the Allplex™ SARS-CoV-2/FluA/FluB/RSV multiplex commercial kit (Seegene, Seoul, South Korea). A specimen will be considered positive for any of the detected pathogens if the respective targets are detected with Ct values ≤40 according to manufacturer instructions. Influenza A, influenza B, and RSV positive samples will be further subtyped using the CDC influenza and RSV subtyping kits, respectively, available through the International Reagent Resource (IRR: www.influenzareagentresource.org).

9.11.1. Digital rRT-PCR for viral load estimation

The viral load for samples PCR-positive for influenza A or influenza B will be further quantified using digital PCR. The positive RNA extracts will be analysed using the QIAcuity OneStep Advanced Probe Kit (Qiagen, Hilden, Germany) and the QIAcuity digital PCR system (QIAGEN, Hilden, Germany) using standard reverse transcription and amplification cycling conditions as per the manufacturer's protocol. Data acquisition and analysis will be performed using the QIAcuity Software Suite (Qiagen, Germany) in accordance with the manufacturer's guidelines.

9.11.2. Organism characterization

Influenza, RSV and SARS-CoV2 viral diversity within or amongst study participants will be investigated using whole genome sequencing. RNA for all three viruses will be extracted using the Chemagic360 automated extractor and the CMG-1049 kit (Revitii, Massachusetts, USA) and eluted in 60 µL elution buffer. PCR and library preparation for SARS-CoV-2 will be conducted using the Illumina COVIDSeq Kit (Illumina Inc., CA, USA) with nCoV-2019 ARTIC network tiling primers v5.4.3 (<https://artic.network/ncov-2019>). Amplicons will be indexed using the Illumina UDI indexes (Illumina) according to the manufacturer's instructions. For influenza, cDNA synthesis will be performed using Invitrogen™ SuperScript™ III One-Step RT-PCR System with Platinum™ Taq High Fidelity DNA Polymerase (ThermoFischer Scientific, Massachusetts, USA) and three universal primer sets namely; Uni13/Inf-1, Uni12/Inf-1 and MBTuni-12.4 for influenza A (Zhou et al., 2009), and eight universal primer sets for influenza B viruses (Zhou et al., 2014). Libraries will be sequenced using the Illumina DNA Library prep kit as per manufacturer's instructions. Viral sequencing for RSV viruses will be performed using LunaScript® RT SuperMix (New England Biolabs, Massachusetts, USA) according to the manufacturer's instructions, followed by amplification with Q5® Hot Start High-Fidelity 2X Master Mix (New England Biolabs, Massachusetts, USA) and eight pooled primer sets targeting RSV-A and RSV-B genome regions (Talts et al., 2024). Libraries for all three pathogens will be sequenced at 0.65pM using the NextSeq1000/2000 instruments with the P1 reagent cartridge (300 cycles) and the P1 Flow Cell (Illumina). Published pipelines will be employed to assemble whole genomes to known references. Phylogenetic analysis (maximum likelihood) will be performed on aligned sequences with IQtree/NextStrain and visualised using Figtree/Auspice. Tree topologies and robustness will be assessed by bootstrap analysis using 100-1,000 replicates. Representative reference sequences of relevant viral strains will be retrieved from GISAID to further support the phylogenetic inference. Influenza-positive samples may also be shared with the WHO Collaborating Centres as part of the Global Influenza Surveillance and Response System (GISRS).

9.11.3. Influenza virus culture

Samples PCR-positive for influenza and RSV with a Ct <30 will be selected for virus isolation. Influenza A and B viruses will be cultured in flasks containing Madin-Darby Canine Kidney (MDCK) cells, while RSV will be cultured using Hep-2 cell lines. The selected samples will be inoculated into the respective cell culture flasks and incubated at 33°C or 37°C for a maximum period of seven days, or until cytopathic effect (CPE) is evident. Once CPE is detected, an immunofluorescent assay (IFA) will be performed on the infected cells to confirm the presence of the target virus.

9.11.4. Serologic testing for immunologic response influenza

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 the 2026 influenza season for A(H1N1)pdm09, A(H3N2) and B/Victoria. Turkey red blood cells will be used as indicator in the HAI assay. The protocol will be based on the method described by the WHO [37].

9.11.5. Microneutralisation assay

Samples will be tested by the microneutralisation assay. The microneutralisation assay will be adapted from the WHO protocol [38]. Madine Darby Canine Kidney (MDCK) SIAT1 cells and all influenza viruses will be handled in BSL-2 laboratories and biosafety cabinets. The cells will be used to propagate relevant influenza viruses, representative of viruses circulating in the 2026 influenza season, and the infectious viral titre will be calculated using the TCID50 methodology. RDE-treated sera will be serially diluted in a 96-well plate, followed by the addition of 100 TCID50/well of influenza virus. Next, the MDCK-SIAT1 cells will be added to each well followed by an incubation of 18-20 hours at 37°C in 5% CO₂. After the overnight incubation, cells will be fixed with acetone followed by an enzyme-linked immunosorbent assay (ELISA). Briefly, an anti-influenza monoclonal primary antibody will be added followed by a secondary antibody conjugated to horseradish peroxidase (HRP). The substrate 3,3',5,5'-Tetramethylbenzidine (TMB) will then be added to each well followed by the stop solution which allows OD readings to be measured at 450nm using a microplate spectrophotometer. The neutralising antibody titre for each sample will be calculated whereby the reciprocal serum dilution that corresponds to the highest dilution with OD₄₅₀ less than 50% of the cut-off is the neutralisation antibody titre.

9.11.6. IgA, IgG and IgM binding assays

IgA, IgG and IgM are important potential correlates of protection against influenza infection. Custom MSD or other multiplex assays will be produced to include haemagglutinin antigens matched to the seasons influenza vaccine components, and the circulating influenza strain(s) from the study season. In addition, unmatched antigens will be included to study cross-binding potential, alongside positive and negative control antigens (RSV-F and HIV gp120, respectively). These will be incubated with serum/SAM eluates and titres determined using anti-IgA, IgG, or IgM detection antibody. WHO serum standards will be used to enable relative quantitation and standardisation between plates.

9.11.7. Fc receptor binding arrays

Antibody titre provides only a partial measure of antibody function, which is dependent on both the variable region (Fv) to bind the antigen target, and the constant region (Fc) to elicit an effector response from the innate arm of the immune system. Antibody effector function has been shown to be an important driver of protection against viral infections. Fifty µl of a microsphere mixture coupled with HA and NA proteins of subtype(s)/lineage(s) included in the respective year's vaccine will be incubated with 25 ul of a 1:100 serum or SAM dilution. After addition of beads and antibody sample, the plate will be covered and incubated for two hours at room temperature on an orbital plate shaker, then washed three times using a plate washing system. Antigen-specific antibody binding FcRs will be detected using 50 µL of 0.65ug/ml to biotinylated dimeric FcRs (FcγR2a and 3A) stained with Streptavidin-PE for 15 min with inverting the tube every 3 min. This mixture will be incubated with the beads for one hour and washed. A Bio-plex array reader will detect the beads and PE fluorescence was measured to calculate a Median Fluorescence Intensity (MFI) for each bead type.

9.11.8. T-cell and B-cell phenotyping

Cells from PBMCs and nasopharyngeal swabs will be stained with a multicolor antibody panel to characterize T and B cell subsets. Samples will be acquired on a flow cytometer and analyzed using established gating strategies. Full antibody panels, staining procedures, and analysis methods will be outlined in the MOP.

9.11.9. HLA typing

High-resolution HLA typing will also be performed as part of cellular phenotyping to determine participants' HLA class I and II alleles and explore associations with immune response patterns. Laboratory methods and analysis procedures will be described in the MOP.

9.11.10. HIV testing

For children with an unknown HIV status, HIV testing will be done from finger prick bloods using two different validated commercially available rapid ELISA assays, for screening and confirmatory testing, respectively.

9.12. Study instruments

A list of study instruments is provided below. Instruments are detailed in the appendices.

1. Screening form
2. HIV form
3. Enrolment form (medical history, clinical examination)
4. Household characteristics
5. Nurse follow-up visit form
6. Specimen collection form
7. Hospitalization form
8. Death form
9. Symptom diary enrolment form
10. Symptom diary form

9.13. Data collection tools

All data will be collected electronically with no identifiers in the database, in real time. Nurse-completed forms (screening, enrolment, nurse visit, specimen collection, hospitalization, death) will be collected using REDCap (Research Electronic Data Capture) hosted at the University of the Witwatersrand [39, 40]. Forms will be accessed by the study staff through their password-secured REDCap account on a tablet.

A custom-built mobile data collection system will be used to capture daily symptom information reported by caregivers of participating children. The system will be developed as a lightweight mobile application designed to run on low-cost smart devices. The application will allow caregivers to submit a short daily symptom form for their child. Each submission will include a date and time stamp and will be linked to the participant's unique study ID to ensure accurate data attribution.

The application will support offline data capture, with automatic synchronisation to a secure central server once internet connectivity is available. Data transmission will be configured to occur without requiring mobile data (zero-rated platform), thereby removing cost for participants.

To optimise compliance, the system will include automated reminder notifications if a daily symptom submission has not been received. Reminders will be sent at predefined intervals (10:00, 14:00, 16:00, and 18:00) until a submission is completed. Only one submission per participant per day will be permitted.

In the rare event that a caregiver loses their device or is unable to use the application temporarily, data may be captured manually on a paper form supplied by the study team. Data will then be entered through a secure web-based platform by study staff once connection to the database is restored.

The data management interface will include functionality for real-time monitoring of form submissions to track adherence and identify missing data. Submission logs will be used to determine caregiver eligibility for reimbursement based on predefined submission thresholds.

9.14. Data management

A unique individual identifier including visit number will be used for each visit. Separate database front ends will be used for collection of parent caregiver data for the electronic symptom diary and field worker data from home visits and other procedures. The database will be password protected to ensure that outside parties will not have access to the database. A data quality/data verification process will be developed and will be implemented by a study manager and a database manager at site. 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. Built in checks will be used for completeness of electronic symptom diaries and missing data will be followed up by an electronic message sent to the caregiver. Data quality and validity checks will also be performed on symptom diaries. Field teams will discuss out of range or incomplete data with caregivers at twice weekly visits. The MOP will describe in detail the regular data quality assurance and quality control activities in the Data Quality Management Plan.

NICD will access the database on a daily basis or as needed to check on follow up progress and data quality. Data quality and completeness will be evaluated at NICD by a dedicated data manager. Laboratory results will be entered into the same data system (REDCap). Each sample will be identified by the same identifier allocated to each individual participant and visit and, after data quality verification, linked monthly with the central database.

Participant names and study identifiers will be captured in a separate REDCap database at the start of the study. All patients will be allocated a unique study number which will be used for all study information and specimen labelling.

The database will be backed up daily. All study data will be archived electronically on the REDCap server at the University of the Witwatersrand, which has real-time, daily and twice weekly backups.

9.15. Data sharing

Demographic, virological, and immunological data will be shared with collaborating laboratories and investigators involved in testing study specimens. All data will be shared in an anonymised format, identified only by study and sample identification numbers. No personal identifying information, such as participant or caregiver names, surnames, contact details, or any other identifiers, will be shared. The child's date of birth will not be shared; instead, only age in months at enrolment will be provided for analytical purposes.

Data will be shared with collaborators via the NICD secure data transmission platform (Nextcloud). Access to data will be provided through password-protected secure links. Datasets will be shared in CSV or Excel formats, depending on data complexity. In line with the data-sharing policies of many peer-reviewed journals and to promote transparency and collaboration, anonymised study data will be made publicly available through an online repository (GitHub) at the time of manuscript publication. The shared dataset will include only de-identified demographic, virological and immunological variables, using study and sample identifiers without any personal information such as names, surnames, caregiver details, contact information, or unique database numbers. Only age in months at enrolment will be provided and not data of birth.

9.16. Analysis plan

To explore how mucosal and systemic immune markers may correlate with protection against influenza, an infection episode will be defined as ≥ 1 influenza positive swab on RT-PCR or a four-fold rise in HAI titre between enrolment and the end of the season. We will summarise all immune marker levels measured for the infected and uninfected group (individuals experiencing no infection with the pathogen of interest during follow up) at each time point using geometric means with 95% confidence intervals. To assess the association of an immune marker with protection, we will use Cox proportional hazard regression with influenza infection as the outcome (0/1) and an immune marker (continuous) measured at baseline as a predictor variable. We will also adjust for potential confounders (e.g. age and HIV exposure). Depending on the marker, values may be log-transformed or

normalised. A separate model will be done for each marker. Due to the limited sample size, significance will not be based on the traditional $p < 0.05$, but based on effect sizes, where any hazard ratios lower than 0.5 will be considered a potential correlate. To assess potential thresholds of protection, we will model each immune marker identified as a potential correlate as restricted cubic splines. Models will be adjusted for potential confounders. Predicted probabilities of infection will be plotted across the observed range of marker levels with 95% confidence intervals. Candidate protective thresholds will be identified by inspecting where the risk curve began to flatten and by examining cut-points with good sensitivity and specificity in receiver operator curve (ROC) analysis. All analyses will be subtype-specific.

Amongst all children with ≥ 1 influenza positive swab on RT-PCR, we will compare 1) the median viral load, 2) duration of positivity (days) and 3) the area under the curve when modelling the duration of positivity and viral load for the infection episode based on immune marker levels using linear or Poisson regression. We will also compare the culture success (yes/no) based on viral load and Ct values as a marker for viable virus shedding using mixed-effects logistic regression, controlling for multiple specimens for each child.

Changes in immune markers from baseline to the end of season will be compared between children with PCR- and/or serologically-confirmed infection and those without evidence of infection to describe immunological responses to natural infection.

9.17. Community engagement and consent

A community engagement plan will be developed in consultation with site partners, including relevant stakeholders. Joint feedback meetings with study participants and other stakeholders will be organized per site in consultation with the site teams. General results of the study and experiences will be presented and discussed. The study progress and findings will also be discussed at local and international scientific meetings, and published in peer-reviewed journals as appropriate.

9.18. Reimbursement

Participants/parents of participants will be compensated for their time and effort in this study, and be reimbursed for travel to study visits. Table 5 describes the reimbursement structure for the study.

Table 5. Reimbursement for time, travel and inconvenience, MUSIC-Flu

Procedure	Venue	Frequency	Total reimbursement per event/sample to parent and child ¹
Blood collection	Clinic	4 (start, twice during follow-up, and end)	T: $R250 \times 2 = R500$ I: $(R100 \times 2) + R100 = R300$ E: $R50 \times 2 = R100$ Total: R900 per visit
PBMC collection (subset of children)	Clinic	2 (start and end)	T: $R250 \times 2 = R500$ I: $(R100 \times 2) + R100 = R300$ E: $R50 \times 2 = R100$ Total: R900 per visit
Nurse-collected nasal swab	Home	21 (weekly, except for one week per month)	T: 0 I: $(R50 \times 3) + R50 = R150$ E: 0 Total: R200 per visit
Nurse-collected nasal swab, oral fluid, nasal mucosal fluid, nasopharyngeal swab	Home	8 (monthly)	T: 0 I: $(R50 \times 3) + (R50 \times 4) = R350$ E: 0 Total: R350 per visit

Caregiver-collected nasal swab	Home	58 (twice weekly)	T: 0 I: R50 + R50 = R100 E: 0 Total: R100 per visit
Symptom diary ²	Home	203 (10 minutes daily)	T: 0 I: R50 E: 0 Total: R50 per week for at least 6 diaries

¹ Reimbursement values are multiplied by two to account for parent/caregiver and child dyads. Travel (T) is based on a maximum of 30 km travelled from home to clinic (R4 x 30 km x 2[return]), and rounded to closest 50. Inconvenience (I) is based on R50 per hour, with an additional R100 for inconvenience of vaccination/blood draw or R50 for a specimen collection. Expense (E) is based on R50 per meal and refreshment. ² Reimbursement for daily symptom diaries will only be done if ≥ 6 of 7 diaries for the week are completed.

The daily recording of symptoms electronically will allow real-time data cleaning and review. The parent will be provided with a device for collection of symptoms data valued at approximately R1000. The parent will be able to keep the device at the end of the study; this is to encourage the safe keeping of device. The application used for submission of symptom diaries will be data free with no data costs for the caregiver.

10. ETHICAL CONSIDERATION AND APPROVAL

Ethical approval for the study will be obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) (HREC). Approval will also be obtained from the North West Province Department of Health and the primary health care facilities where enrolment will be taking place.

The study protocol will be submitted to the U.S. Centers for Disease Control and Prevention Human Research Protection Office (CDC HRPO) for review. CDC HRPO will confirm the roles, qualifications, and required human subject's protection training of all CDC collaborators and co-investigators, and will determine the appropriate mechanism for ethical oversight. This will include either reliance on the University of the Witwatersrand HREC through a formal reliance agreement, or review and approval by a convened CDC Institutional Review Board (IRB). In all cases, CDC will approve the roles of CDC investigators and collaborators as described in the protocol.

The study protocol will also be submitted to the Imperial College Research Ethics Committee (ICREC) for ethical clearance on specimen testing that will be performed at Imperial College London, and the involvement of the collaborator from the College.

10.1. Reporting

The following incidents will be reported within seven days of the site investigator being informed to Wits HREC and the CDC HRPO:

- Unanticipated problems (including an increased risk of physical, psychological, economic, or social harm), and adverse events involving risks to human subjects or others that have been found to be related or possibly related to the research study
- Serious or continuing non-compliance

Hospitalisations and deaths will be reported to Wits HREC every six months.

10.2. Study risks

Participation in this study carries minimal risk to the child. There is a theoretical risk of exposure to infectious agents, such as influenza or SARS-CoV-2, through contact with study personnel; all reasonable precautions will be taken to minimize this risk. Study procedures, including nasal, nasopharyngeal, oral, and nasal fluid sampling,

may cause transient discomfort, sneezing, coughing, or minor nosebleeds. Blood draws may result in slight pain, bruising, bleeding, inflammation at the puncture site, faintness, or a small risk of infection. All procedures will be performed by trained personnel using sterile or clean techniques to ensure participant safety. For HIV testing, appropriate counselling will be provided, and participants will be referred for care and treatment if a positive result is detected.

10.3. Study benefits

Participation in this study may not provide direct medical benefit to the child; however, it contributes to a broader understanding of infectious diseases, particularly influenza, and host immune responses. Any medical conditions identified during study assessments will be referred to appropriate healthcare facilities for further evaluation and management. Parents will also have access to the results of their child’s HIV test, and, if positive, the child will benefit from early linkage to treatment and care.

11. DISSEMINATION AND PUBLICATION OF RESULTS

Study findings will be published as peer-reviewed literature.

12. STUDY TIMELINES

Table 6. Study timelines, MUSIC-Flu

Activity	Date
Protocol development	Jul – Oct 2025
Ethics review and approvals	Oct 2025 – Feb 2026
Field implementation	Mar – Oct 2026
Specimen testing	Apr 2026 – Apr 2027
Data analysis	Jul 2026 – Jul 2027
Report	Aug 2027
First draft of manuscript	Oct 2027

13. BUDGET AND FUNDING SOURCE

The main study is funded through a cooperative agreement from the US Centers for Disease Control and Prevention (Cooperative Agreement: 6U01IP001269-02L001) as well as National Institute for Communicable Diseases, a division of the South Africa National Health Laboratory Service (NHLS).

This project will work with the Mucosal Vaccine Evaluation (MOVE) consortium, including partners at Imperial College London, AstraZeneca, and the United Kingdom Health Security Agency (UKHSA) on immunology assessments of samples arising from the study. Immunological testing (including phenotyping of immune cells, mucosal antibody and local gene-expression profiling) will be funded by the MOVE consortium. The MOVE consortium aims to understand the immune responses induced by LAIV and how these relate to efficacy. This will include shipping samples internationally to these partners. The analysis of these samples will include genetic testing where specific consent for this has been provided.

14. POTENTIAL STUDY IMPACT

The study will provide essential information on accurate measurement of infection and symptoms due to respiratory viral infection to inform future studies aiming to assess disease attenuation by vaccination.

15. ROLES OF THE INVESTIGATORS AND COLLABORATORS

Co-Principle (National) Investigators, Prof Cheryl Cohen and Dr Jackie Kleynhans (NICD and University of the Witwatersrand) will be responsible for the overall design, coordination, and conduct of the study, including supervision of data collection, data analysis, and interpretation of results, as well as the preparation of study reports and manuscripts. They have reviewed and approved the study protocol and all supporting documents, and will ensure that the research is conducted according to the approved protocol, ethical guidelines, and regulatory requirements. They will oversee the study team, ensure participant safety and data integrity, report any social harms arising from the study or protocol deviations as required, maintain accurate records, and ensure that all participants are treated with dignity and respect.

Site Principle Investigator, Dr Tumelo Moloantoa (PHRU), will be responsible for providing clinical oversight and leadership at the study site. This includes ensuring that the study is conducted according to the approved protocol, ethical and regulatory requirements, and Good Clinical Practice (GCP) guidelines. Dr Moloantoa will supervise all on-site study activities, including participant recruitment, informed consent, sample and data collection, and clinical assessments, ensuring participant safety and data integrity. They will provide clinical guidance to the study team, oversee the accuracy and completeness of source documentation and case report forms, and ensure timely reporting of social harms arising from the study and protocol deviations. Dr will also contribute to interpretation of results, and review of manuscripts, in collaboration with the other study investigators.

NICD sub-investigators, Dr Sibongile Walaza and Dr Jocelyn Moyes will contribute to the study design, ensuring that the research questions, sampling strategy, and analytic framework are scientifically sound and aligned with the study objectives. They will provide technical and analytical support for data management, data analysis, and interpretation of findings, with a focus on epidemiological, clinical, and implementation aspects. They will also review the study manuscripts and related outputs to ensure the accuracy and quality of the data interpretation and its relevance to public health practice.

Additional NICD sub-investigators, Prof Anne von Gottberg, Dr Nicole Wolter, Dr Mignon du Plessis, Dr Fahima Moosa will contribute to the study design, specifically in developing and refining the laboratory components of the protocol. They will provide scientific oversight of laboratory testing, including assay selection, implementation, quality assurance, and interpretation of laboratory results. These investigators will ensure that laboratory methods meet scientific and ethical standards and will review and contribute to the interpretation of results and preparation of manuscripts arising from the study.

Sub-investigator, Prof Neil Martinson (PHRU) will provide high-level oversight and guidance for the study at the site, ensuring that the research is conducted according to the approved protocol, ethical standards, and Good Clinical Practice. They will support study design and review study manuscripts and reports, providing strategic input on site implementation and overall study conduct.

Dr Aaron Samuels, sub-investigator from the US CDC, will provide technical assistance in the development of the study protocol, methodologies, data analysis, interpretation, and report and manuscript preparation. As an engaged investigator, Dr. Samuels will have access to identifiable information including coded data.

Julia Petras, sub-investigator from the US CDC, will provide technical assistance in the development of the study protocol, methodologies, data management, data analysis, interpretation, and report and manuscript preparation. As an engaged investigator, Julia Petras will have access to identifiable information including coded data. She will be performing site visits to observe study procedures, but will have no clinical oversight or perform any clinical procedures on or interviews with participants.

Collaborators Eduardo Azziz-Baumgartner, Min Levine, Brendan Flannery, Daniel Yoo, and Patrick Dawson (US Centers for Disease Control and Prevention) will not be involved with hands-on research or have any participant contact. They will however assist with analysis and scientific interpretation of results. These collaborators will have access to anonymised participant data.

Dr Ryan Thwaites (Imperial College London) will be responsible for testing of immunological specimens, data analysis and scientific interpretation, therefore having access to anonymised data, but will not have any direct participant contact.

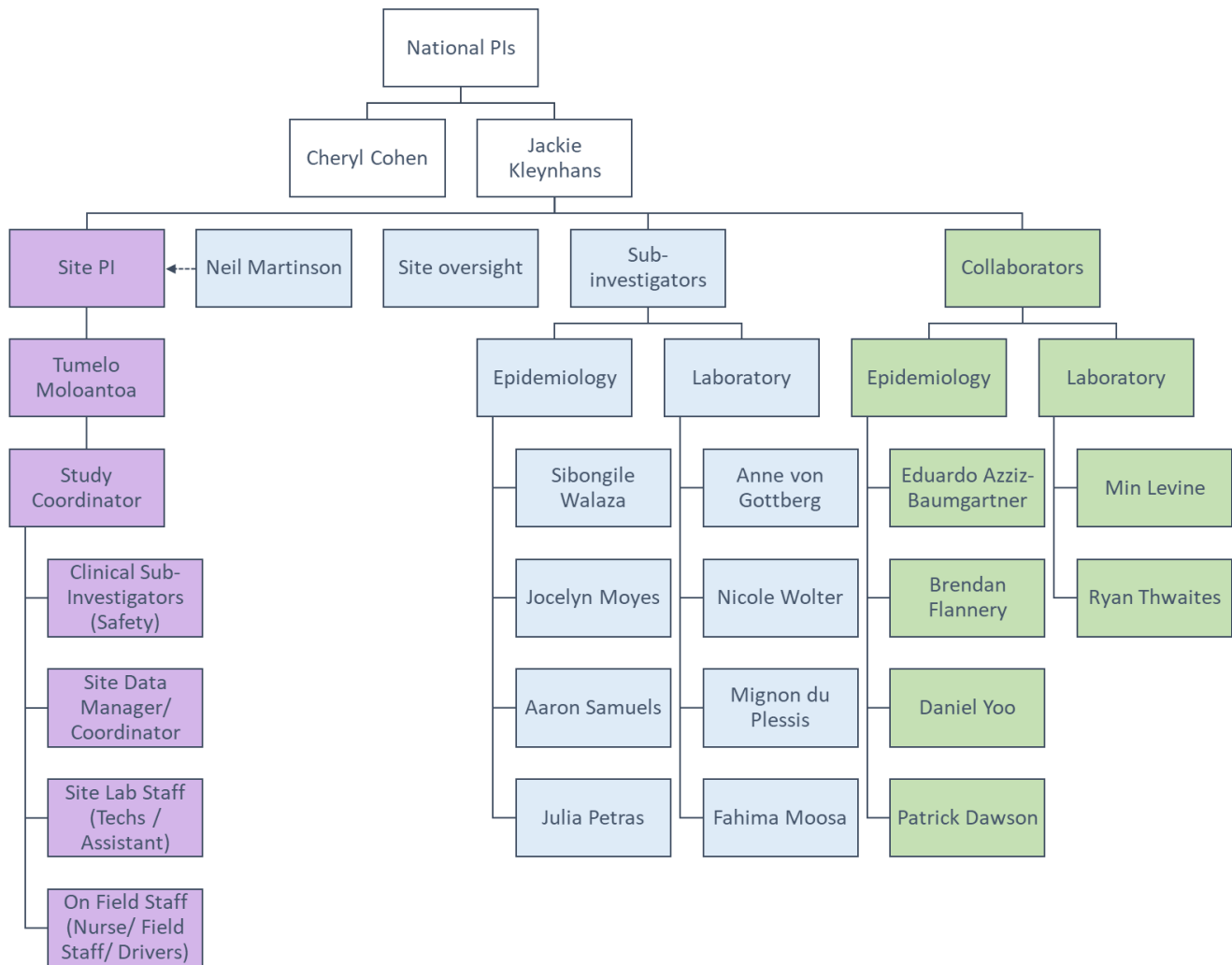


Figure 2. Organogram of study investigators and collaborators

16. LIST OF APPENDICES

16.1. Appendix A: Information sheets and Informed consent forms

- Information leaflet and consent 1: Consent for parent to enrol child in study
- Information leaflet and consent 2: Consent for parent to test child for HIV
- Information leaflet and consent 3: Consent for parent for the storage and shipment of child’s specimens
- Information leaflet and consent 4: Consent for parent for HLA testing for child
- Information leaflet and consent 5: Consent for parent for PBMC isolation from child

16.2. Appendix B: Data collection tools

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Information leaflet and consent 1: Consent for parent to enrol child in study

STUDY TITLE: Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

Each parent 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 cooperative agreement with the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the Perinatal HIV Research Unit (PHRU), University of the Witwatersrand.

Investigators: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, after hours.
Dr Jackie Kleynhans 011 555 0383

Site investigator: Dr Tumelo Moloantoa 018 011 3830

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 help us with a research study called the "MUSIC-Flu" that we will be doing in Matlosana, North West Province.

- 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 you need to do and what procedures your child needs 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 study staff regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that your 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 (viruses, 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 from one person to the next. This will help us to find or improve ways to stop these infections from making people sick. We are interested in how the body reacts to infections. Some people may get symptoms from respiratory illness (like a cough, sore throat or runny nose) and others may get the infection and have no symptoms. We are doing a study to try and understand how the body's defenses can prevent children from becoming infected or sick with respiratory viruses.

Influenza (flu) is a virus that causes respiratory illness (sore throat, cough, fever, muscle aches and headache). Usually flu circulates in the winter months. After having flu, our bodies usually respond by making immune cells (soldiers) and antibodies (weapons) that will protect us when flu tries to infect us again. We would like to understand which type of soldiers and weapons are needed to protect children from flu infection. We are also interested in how these soldiers and weapons may make some people have fewer symptoms. Another question is how long children stay sick for if they are infected. Knowing this will help us create better vaccines in the future.

In this study (which we are asking your child to take part in) we will collect different types of samples at different times from your child:

- We will collect four blood samples (15 ml or 1 tablespoon) from your child to test for the immune soldiers and weapons:
 - At the beginning of the study
 - Twice during the follow-up:
 - Two months after the first blood draw
 - Two-to-three months after the second blood draw
 - At the end of the study
- At the beginning and the end of the study, as well as once a month, we will collect three samples to also test for the soldiers and weapons:
 - A special swab that looks like a small cotton swab that goes in through the nose and reaches to the back of the nose (nasopharyngeal swab)
 - A small strip that goes into the nose called a SAM to collect fluid from the nose
 - A small sponge that goes into the mouth to collect fluid from the mouth
- Three times a week from the beginning to the end of the study we will also collect swabs (like small cotton swabs) from the middle of the nose to test for influenza, COVID-19 and respiratory syncytial virus (RSV). RSV is a very common virus that causes respiratory symptoms, mainly in children.
 - Two of these swabs will be collected by you. We will provide the swab in the tube it goes into, and a nurse will show you how to do this. We have done this in a study before and mostly parents found it very easy. After you collected the swab you can let a driver know to come and pick up the swab from your home.
 - One of the weekly swabs will be collected by the nurse when they visit your home.

When the nurse visits your home, she will also measure your child's temperature, and ask you about any symptoms (like cough, fever, sore throat) your child had in the previous week. Every day we will ask you to record your child's symptoms on a cell phone and to measure their temperature (we will provide the thermometer and cell phone).

We are only able to enroll HIV-uninfected (negative) children in the study. So at the first visit we will ask for your child's HIV status. We can do this by looking at the Road to Health Card (RTHC) or other proof of your/your child's status. We can offer testing (by taking a blood sample using a needle to prick your child's finger) if you are not sure and would like to know your child's status.

The study will continue until the flu season stops, which may be for up to 9 months, depending on when your child started the study. We are planning on enrolling about 150 children aged 2 – 5 years in the Jouberton area.

All the following procedures apply to your child (this is a summary to make it easier)

1. Proof of HIV status for your child (Road to Health Card (RTHC), a negative test from the child's mother or if necessary a PCR (blood test on your child).
2. A detailed medical history, we will ask you about any illness your child may have, if your child has a serious medical illness we will not be able to enroll them in this study.
3. A nurse or doctor will examine your child, this is a routine health check and will include this like taking a temperature, listening to the lungs and heart. Feeling your child's tummy, measuring height and weight.
4. We will also record any vaccines your child may have had from the Road to Health Card (RTHC).
5. The nurse or doctor will measure and record your child's weight and height recorded at the beginning of the study and again at the end of the study
6. We will take up to 15ml of blood from your child's arm (one tablespoon of blood) at the start of the study, at two points during the study, and at the end of the study
7. At the beginning, end, and once a month during the study, a nurse will collect three additional samples from your child:
 - a. Fluid from the nose, using a small strip (SAM) that will be placed in your child's nose for up to two (2) minutes
 - b. Fluid from the mouth using a sponge-like device that will stay in your child's mouth for up to three (3) minutes
 - c. A swab from the back of the nose using a small cotton bud which only takes a few seconds
8. Once weekly the study nurse will visit to your home to take a nose swab from your child and ask some questions about symptoms. The nurse can help you if you have questions about the symptom recording or taking swabs from your child.
9. Twice a week you will be required to take a nose swab from your child (the cotton bud one in the middle of the nose)
 - a. We will provide everything you need and show you how to do this procedure

- b. We will send a driver to pick up the sample from your home
- 10. We will require that you record any symptoms (or no if there are not symptoms) daily symptoms recorded on a phone
- 11. You will be required to take your child's temperature once a day and record the temperature on a phone
 - a. We will provide the thermometer and the phone, and show you how to use it

Length of study and number of participants

- The study will be performed in one place (Matlosana) South Africa only.
- Approximately 150 participants will participate in this study.
- The first visit will take place in a clinic, this is when we see if your child is well and you consent to join.
- We will visit your home once a week for the period of up to nine months.
- Twice a week after you have taken a swab from your child, someone will come to the house to pick up the sample.
- We will ask you to bring your child to the clinic for three additional blood draws (twice during the study, and once at the end of the study)

Study procedures

Because there are quite a few procedures to remember, we have made a simple list to help you:

1. HIV testing

- a. We will try to confirm your child's HIV status by using the RTHC and other information, like your negative test.
- b. We will only test your child if necessary or you would like to confirm your child's status, this will be done by taking a small blood sample from your child's finger.

- 2. **Fluid from the nose:** At the beginning, end and once a month during the study using a small strip that will be placed in your child's nose for up to two minutes. This is not painful but your child will be required to sit still.
- 3. **Fluid from the mouth:** At the beginning, end and once a month during the study using a sponge-like device that will stay in your child's mouth for up to three minutes. This is not painful but your child will be required to sit still.
- 4. **A swab from the back of the nose:** At the beginning, end and once a month during the study. The nurse will put a swab into your child's nose until it touches the back of their throat.
- 5. **Blood samples:** Blood will be taken from your child's arm in a standard medical procedure; this will be done by a trained nurse or doctor.
- 6. **Nose swab by the nurse:** The nurse will put a swab into your child's nose, these swabs only go 1.5 cm into the nose once a week. This only lasts a few seconds.
- 7. **Nose swab taken by yourself:** You will collect a swab from the middle of your child's nose twice a week, which only lasts a few seconds.
- 8. **Daily temperature.**

After all your child's samples have been collected, we will ship (send) your child's samples to other laboratories outside of South Africa (Imperial College London in the United Kingdom and the Centers for Disease Control and Prevention in the United States) for additional special testing that we cannot do in South Africa. We will ask you to complete a separate informed consent form to agree to shipping the samples. Because the special tests are important to complete the study, your child will not be able to participate in the study if you do not agree to sending the samples to these laboratories.

The study team will not provide clinical care for your child. If your child has a fever or other symptoms during a study visit, they will be referred to an appropriate health facility for further assessment and management. With the exception of HIV results, individual results from other study tests (including influenza, RSV, and SARS-CoV-2 detection or antibody testing) will not be returned to participants.

Your rights as the parent of a participant

It is your right to choose if you want your child to take part in this study. If you chose for your 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 at the study clinic will take about 1 hour
- The two additional visits at the clinic to collect blood will take about 1 hour
- Nurse visits to your home once a week will take about 30 minutes to 1 hour
- The monthly visit to collect the SAM sample and the mouth sample will take about 45 minutes to 1 hour
- Collecting the swab twice a week from your child will take your 5-10 minutes
- Capturing your child's symptoms each day will take about 5-10 minutes
- The final visit at the clinic will take about 1 hour

Risks of this study

Because there is flu, COVID-19 and other germs in your community there is risk of infection due to your interaction with the study team. In order to decrease the risk of this we will be taking every possible precaution to protect you and your child.

There is minimal risk to your child from the study procedures. There may be discomfort when we take the nasal, nasopharyngeal swab, oral or nasal fluid samples your child may sneeze or cough after the sample has been taken. Some people may experience a short nosebleed. Drawing blood is normally done as part of routine medical care and presents 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 child's protection is that experienced personnel perform the procedures under sterile/clean conditions.

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

Benefits of this study

By taking part in this study, you will help us learn more about certain infectious diseases and how our bodies respond to them, specifically influenza. If we find any medical conditions that need treatment during our examination of your child, we will assist you with a referral to the appropriate in or outpatient facility.

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

Confidentiality

We will keep all your and your child's information confidential: study forms and samples will be marked with a number and not a name. Study staff will keep a log of you and your child's identifying details, 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. Selected people working on the study, as well as representatives of government regulatory authorities and ethics committees will also have access to the results. These persons are required to maintain the confidentiality of your child's information, and will only access the data in connection with carrying out their obligations relating to this study. By signing this document, you are authorizing such access. When we share samples with other laboratories, we will not share any identifying information from you or your child. Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can say no to your child taking part in the study, 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. If your child misses a visit/swab you will not be reimbursed for the visit. We will also give you a voucher after we have received the

sample taken by you from your child. Because we are asking you to complete a daily diary of your child's symptoms we will provide you with an electronic device (phone) for this purpose. This device will have an application installed that will allow you to enter your child's symptoms without any cost to you. We would like you to take care of the device during the study period as entering the daily diary of symptoms is very important. You may keep this device at the end of the study period. The device will be given to you at the first follow-up visit.

The value of the vouchers depends on the type of visit:

- Clinic visit 1 (enrolment and collecting blood): R900. This is a once off visit
- Nurse visit to your home:
 - R200 per visit when collecting only the nasal swab (3 of the 4 weeks in a month)
 - R350 per visit when collecting the nasal swab, oral fluid, nasal fluid and nasopharyngeal swab (once a month)
- Collecting the nasal swab from your child (twice a week): R100 per swab collected
- Completing daily symptom diaries: R50 if completing at least 6 symptom diaries in a week
- Clinic visit 2 (blood draw 2), clinic visit 3 (blood draw 3) and clinic visit 4 (final blood draw and study end visit): R900.
- The study will not pay for any care that your child needs for any illness diagnosed during this study. But 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 North West Provincial Ethics Committee
- The study has been submitted to the United States Centers for Disease Control and Prevention Human Research Protection Office which relied on the local HREC
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2024), 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 Paul Ruff, 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.

INFORMED CONSENT FOR PARENTS:

(On behalf of minors under 18 years old)

- _____ *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the 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.
- 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 my child is prepared to participate in the study.
- I acknowledge that the National Institute for Communicable Diseases will have access to my personal information and will process my child’s personal information as required for purposes of this study, and / or national regulations, and in accordance with the South African Protection of Personal Information (POPI) Act of 2013.
- By signing this form, I agree to: please circle Yes/No for each statement

1. My child’s blood being taken at four time points: the beginning of the study, twice during follow-up, and at the end of the study	Yes/No
2. Weekly nasal swabs	Yes/No
3. Monthly oral fluid	Yes/No
4. Monthly nasal mucosal fluid	Yes/No
5. Monthly nasopharyngeal swab	Yes/No
6. Daily recording of symptoms and temperature	Yes/No
7. I will do a nasal swab on my child twice a week and be at home for the sample to be picked up	Yes/No
8. To be contacted telephonically for matters regarding the study, for example visit appointments, or to verify data collected	Yes/No
9. In accordance with the provisions of the Protection of Personal Information Act 4 of 2013 (as amended), I hereby consent	
a. For my and my child’s personal information (hereinafter 'data') being collected, processed, shared and stored on an electronic device (laptop or tablet) in accordance with the study protocol as approved by the Wits HREC (Medical)	Yes/No
b. To my and my child’s anonymized data being shared, processed, and transferred by third parties and between third parties, and where relevant beyond the jurisdictional borders of South Africa	Yes/No
c. To all findings and results flowing from my anonymized data being broadly shared and published at the conclusion of the research	Yes/No
10. The other adult(s) with whom I share parental rights and	Yes/No

responsibilities in respect of the identified child in terms of the Children's Act (for example, biological parent, adoptive parent, or legal guardian or representative) is (1) aware of and agrees with my granting permission for this child to participate in the study OR (2) deceased, unknown, incompetent, or not reasonably available (someone is "not reasonably available" when he/she cannot be reached by phone/mail/email/text because, for example, he/she is on active military duty or is incarcerated).	Date:
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Child's name _____ Child's DOB _____

PARENT:

Printed Name	Signature / Mark or Thumbprint	Date and Time
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STAFF MEMBER:

Printed Name	Signature	Date and Time
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For parent unable to read:

DETAILS OF OTHER PERSON EXPLAINING INFORMED CONSENT:

NAME AND SURNAME: _____

DESIGNATION: _____

Printed Name	Signature	Date and Time
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WITNESS (If applicable):

Printed Name	Signature	Date and Time
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Information leaflet and consent 2: Consent for parent to test child for HIV

STUDY TITLE: Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

Each parent 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 cooperative agreement with the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the Perinatal HIV Research Unit (PHRU), University of the Witwatersrand.

Investigators: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, after hours.
Dr Jackie Kleynhans 011 555 0383

Site investigator: Dr Tumelo Moloantoa 018 011 3830

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 help us with a research study called the "MUSIC-Flu" that we will be doing in Matlosana, North West Province. By now you will have read the study information. This sheet is specifically for HIV testing of your child.

- Before you agree for your child to have an HIV test, we would like you to read this information sheet about HIV testing in children.
- Please make sure you understand what you need to do and what procedures your child needs to do.
- You should also make sure you understand the reasons for HIV testing, how the test will be done, 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 be tested for HIV. 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 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 study staff regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that your child can have a HIV test, you will be asked to sign this document to confirm that you understand what is required for your child to be tested for HIV. You will be given a copy to keep.

Background/Purpose

You will have read the information sheet for the MUSIC-Flu study and by now will know that we need to know your child's HIV status. Because we were not able to confirm your child's HIV status from a Road to Health Card (RTHC) or other test result, we are offering you HIV testing. I would like to remind you of what HIV is and the ways we are able to determine your child's HIV status. We will reconfirm these ways with you.

The human immunodeficiency virus (HIV) is a virus that causes acquired immunodeficiency syndrome (AIDS). The HIV virus causes the immune system, the system the body uses to fight disease, to fail.

Infection with HIV occurs by the transfer of blood, semen or other similar fluid, vaginal fluid, or breast milk in which HIV is present. The three major ways of getting HIV are unprotected sex (having sex without a condom), transmission from an infected mother to her baby at birth, or through breast milk and people share needles when using drugs.

HIV mainly infects cells in the immune system such as CD4 cells and causes the number of CD4 cells to drop. When the number of CD4 cells drops below a certain amount, the body's ability to fight infection is lost, and opportunistic infections may increase. If untreated, eventually most HIV patients develop AIDS (Acquired Immunodeficiency Syndrome) and die.

There is a very effective treatment for HIV, known as antiretroviral or ART. People who take ART are able to live very healthy and productive lives. ART is available to all people (including children) who are infected with HIV. This treatment is free and available at all clinics in your area.

The reason for HIV testing in the MUSIC-Flu study

This study has nothing to do with HIV/AIDS or its treatment, but we can only enroll children who are NOT infected with HIV. Knowing your child's HIV status is important because early treatment with anti-retroviral treatment (ART) is important and can help your child to live a healthy life.

How we can know your child's HIV status

I will remind you of the ways we can help define your child's HIV status, please double check which of these apply to you and your child:

- If the child's mother had a negative test during pregnancy (and the result is written in the Road to Health Card), then we will say the child is HIV negative and we will not need to test
- If your child had a PCR blood test at 6 weeks of age and the negative result is written in the Road to Health Card, we will say your child is HIV negative and we will not need to test
- If you, as the biological mother, are happy to do a rapid HIV test (this test is done in about 15 minutes by a small prick on a finger) and this test is negative we will say your child is HIV negative and we will not need to test your child
- If the rapid test done on the biological mother is positive for HIV or the mother tested positive during pregnancy, we will have to do an HIV test on your child

How we will test for HIV

Your child's HIV status will be confirmed at the screening visit (first visit) at the clinic. We will speak to (counsel) you before and after your child has taken the test, to make sure that you understand what we are doing, what HIV is, and how to understand your child's HIV test.

To test for HIV, we will do a rapid HIV test by doing a small prick on your child's finger with a small needle and you will be able to receive the result immediately. If your child tests positive for HIV, they will be referred to for medical care. Another HIV test may have to be done at the clinic to confirm the results

Your rights as the parent of the participant

It is your right to choose if you want your child tested for HIV. If you chose for your child not to be tested for HIV, this will not affect your child's right to health care, other services or your child's right to participate in future studies. However, your child will not be able to be included in the current study.

Expected duration of HIV testing

HIV testing will take about 15 minutes.

Risks of this study

There is minimal risk to your child when testing for HIV. The finger prick to collect the drop of blood for the test might be a little painful. Your child's protection is that experienced personnel perform the procedures under sterile/clean conditions.

There may be a risk of rejection and discrimination by friends, family and colleagues following a positive test. It may also result in, emotional problems, increased stress levels and an uncertainty about the future. Our study staff (trained counsellors or nurses) will help you consider how to disclose results and arrange follow-up counselling at the clinic if you need further help with understanding or coping with a positive result.

We will also refer you directly into the treatment programme if your child does test positive for HIV.

Benefits of this study

There are advantages of knowing your child HIV status. If the test is negative, you may feel less anxious or less worried after knowing your child HIV status, and take preventative steps to keep it that way. If you know your child is HIV positive, it may reduce the stress that comes with the uncertainty of not knowing. You can take advantage of treating your child's HIV early, monitoring the health, eating well and healthily. You will also know whether or not your child can infect others and what to do to prevent this happening.

Confidentiality

We will keep all your and your child's information confidential: study forms and samples will be marked with a number and not a name. Study staff will keep a log of you and your child's identifying details, 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. Selected people working on the study, as well as representatives of government regulatory authorities and ethics committees will also have access to the results. These persons are required to maintain the confidentiality of your child's information, and will only access the data in connection with carrying out their obligations relating to this study. By signing this document, you are authorizing such access. When we share samples with other laboratories, we will not share any identifying information from you or your child. Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can say no to your child taking part in the study, 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. If you are enrolled into the main study you will be reimbursed for the follow-up visits.

Both before and after your child will be tested for HIV, you and/or your child will receive HIV counselling. The study will pay for the costs of HIV testing.

The study will not pay for any care that your child needs for the any illness diagnosed during this study. But 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 North West Provincial Ethics Committee
- The study has been submitted to the United States Centers for Disease Control and Prevention Human Research Protection Office which relied on the local HREC

- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2024), 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 Paul Ruff, 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.

INFORMED CONSENT FOR PARENTS:

(On behalf of minors under 18 years old)

- _____ *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the 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.
- 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 my child is prepared to participate in the study.
- I acknowledge that the National Institute for Communicable Diseases will have access to my personal information and will process my child’s personal information as required for purposes of this study, and / or national regulations, and in accordance with the South African Protection of Personal Information (POPI) Act of 2013.
- By signing this form, I agree to: please circle Yes/No for each statement

1. An HIV test for my child if no other verification is available	Yes/No
2. In accordance with the provisions of the Protection of Personal Information Act 4 of 2013 (as amended), I hereby consent	
a. For my and my child’s personal information (hereinafter 'data') being collected, processed, shared and stored on an electronic device (laptop or tablet) in accordance with the study protocol as approved by the Wits HREC (Medical)	Yes/No
b. To my and my child’s anonymized data being shared, processed, and transferred by third parties and between third parties, and where relevant beyond the jurisdictional borders of South Africa	Yes/No

c. To all findings and results flowing from my anonymized data being broadly shared and published at the conclusion of the research	Yes/No
3. The other adult(s) with whom I share parental rights and responsibilities in respect of the identified child in terms of the Children's Act (for example, biological parent, adoptive parent, or legal guardian or representative) is (1) aware of and agrees with my granting permission for this child to participate in the study OR (2) deceased, unknown, incompetent, or not reasonably available (someone is "not reasonably available" when he/she cannot be reached by phone/mail/email/text because, for example, he/she is on active military duty or is incarcerated).	Yes/No Date:

Child's name _____ **Child's DOB** _____

PARENT:

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

STAFF MEMBER:

Printed Name _____ Signature _____ Date and Time _____

For parent unable to read:

DETAILS OF OTHER PERSON EXPLAINING INFORMED CONSENT:

NAME AND SURNAME: _____

DESIGNATION: _____

Printed Name _____ Signature _____ Date and Time _____

WITNESS (If applicable):

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

Information leaflet and consent 3: Consent for parent for the storage and shipment of child's specimens

STUDY TITLE: Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

Each parent 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 cooperative agreement with the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the Perinatal HIV Research Unit (PHRU), University of the Witwatersrand.

Investigators: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, after hours.

Dr Jackie Kleynhans 011 555 0383

Site investigator: Dr Tumelo Moloantoa 018 011 3830

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 help us with a research study called the "MUSIC-Flu" that we will be doing in Matlosana, North West Province.

- Before you agree for your child's samples to be stored for future testing or shipping to another facility, we would like you to read this information sheet.
- Please make sure you understand what you need to do and what procedures your child needs to do.
- You should also make sure you understand the reasons for storage and shipment, and your right to withdraw your child from the study at any time.
- 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 the study staff regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that your 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.
- If you do not agree to the storage and shipment (sending) or your child's samples to laboratories outside of South Africa, your child will not be allowed to participate in this study.

Background/Purpose

You will have read the information sheet for the MUSIC-Flu study and signed consent for the study by now.

We are now asking you for additional consent to store your child's samples at NICD or the National Health Laboratory Services (NHLS) biobank in Johannesburg, and to ship (send) your child's samples to another laboratory (either in South Africa or outside of South Africa) for additional testing.

The reason for storing samples is that in the future we may develop new laboratory tests that will help us to describe the viruses we are interested in (influenza, RSV and COVID-19 viruses) better or your child's body's reaction to these viruses. These sample will only be tested once we have asked the Human Research Ethics Committee (HREC) at the University of the Witwatersrand for approval. To do this we will have to explain to the HREC what tests we are doing.

For this study we are also working with additional researchers who are already able to do more detailed tests to better understand your child's responses to these viruses. We may also find another institution in future that can run even more detailed test, so after approval from the Human Research Ethics Committee (HREC) at the University of the Witwatersrand, we may work with that institution to run these tests. This may involve moving all or part your child's sample to that institute.

All samples will be stored and shipped with only a study number, no names or location will be shared with the testing institution.

As part of this study will are working with laboratories in the following institutions, and with your consent we would like to send part of your child's sample to:

- Imperial College London in the United Kingdom for testing of how your child's body responds to the infections
- The Centers for Disease Control and Prevention in the United States to redo some of our tests to make sure that the tests are working properly. This is part of making sure that laboratories are quality controlled. This is a standard practice across the world.

We may also send the samples to other laboratories in the future if new tests become available, but we will first ask permission from the Human Research Ethics Committee (HREC).

How long samples will be stored

At the moment we are not sure how long your child's samples will be stored. Prior to shipping your child's sample, we will apply to the Human Research Ethics Committee (HREC) for approval of shipment.

Your rights as the parent of a participant

It is your right to choose if you want your child samples stored or shipped. If you chose not to have your child's sample stored, you may still participate in the study. You will also be able to participate in future tests.

Confidentiality

We will keep all your and your child's information confidential: study forms and samples will be marked with a number and not a name. Study staff will keep a log of you and your child's identifying details, 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. Selected people working on the study, as well as representatives of government regulatory authorities and ethics committees will also have access to the results. These persons are required to maintain the confidentiality of your child's information, and will only access the data in connection with carrying out their obligations relating to this study. By signing this document, you are authorizing such access. When we share samples with other laboratories, we will not share any identifying information from you or your child. Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can say no to your child taking part in the study, 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

There is no additional reimbursement associated with storage or shipment of samples.

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 North West Provincial Ethics Committee
- The study has been submitted to the United States Centers for Disease Control and Prevention Human Research Protection Office which relied on the local HREC
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2024), 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 Paul Ruff, 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.

INFORMED CONSENT FOR PARENTS:

(On behalf of minors under 18 years old)

- _____ *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the 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.
- 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 my child is prepared to participate in the study.
- I acknowledge that the National Institute for Communicable Diseases will have access to my personal information and will process my child’s personal information as required for purposes of this study, and / or national regulations, and in accordance with the South African Protection of Personal Information (POPI) Act of 2013.
- By signing this form, I agree to: please circle Yes/No for each statement

1. I agree to my child’s samples to be stored in a secure storage at the NICD and/or NHLS for further testing related to the study.	Yes/No
2. I agree for my child’s sample being sent to another facility for specialized testing as outlined in this information sheet, or additional testing once the testing procedure has been approved by the HREC of the University of the Witwatersrand	Yes/No
3. In accordance with the provisions of the Protection of Personal Information Act 4 of 2013 (as amended), I hereby consent	
a. For my and my child’s personal information (hereinafter 'data') being collected, processed, shared and stored on an electronic device (laptop or tablet) in accordance with the study protocol as approved by the Wits HREC (Medical)	Yes/No
b. To my and my child’s anonymized data being shared, processed, and transferred by third parties and between third parties, and where relevant beyond the jurisdictional borders of South	Yes/No

Africa	
c. To all findings and results flowing from my anonymized data being broadly shared and published at the conclusion of the research	Yes/No
4. The other adult(s) with whom I share parental rights and responsibilities in respect of the identified child in terms of the Children's Act (for example, biological parent, adoptive parent, or legal guardian or representative) is (1) aware of and agrees with my granting permission for this child to participate in the study OR (2) deceased, unknown, incompetent, or not reasonably available (someone is "not reasonably available" when he/she cannot be reached by phone/mail/email/text because, for example, he/she is on active military duty or is incarcerated).	Yes/No Date:

Child's name _____ **Child's DOB** _____

PARENT:

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

STAFF MEMBER:

Printed Name _____ Signature _____ Date and Time _____

For parent unable to read:

DETAILS OF OTHER PERSON EXPLAINING INFORMED CONSENT:

NAME AND SURNAME: _____

DESIGNATION: _____

Printed Name _____ Signature _____ Date and Time _____

WITNESS (If applicable):

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

Information leaflet and consent 4: Consent for parent for HLA testing for child

STUDY TITLE: Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

Each parent 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 cooperative agreement with the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the Perinatal HIV Research Unit (PHRU), University of the Witwatersrand.

Investigators: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, after hours.
Dr Jackie Kleynhans 011 555 0383

Site investigator: Dr Tumelo Moloantoa 018 011 3830

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 help us with a research study called the "MUSIC-Flu" that we will be doing in Matlosana, North West Province.

- 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 you need to do and what procedures your child needs 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 study staff regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that your 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

MUSIC-Flu Protocol

ICF4: HLA and Transcriptomics Version 2 20260206

Pls Prof Cheryl Cohen, Dr Jackie Kleynhans & Dr Tumelo Moloantoa

HREC approval date 25 February 2026

Infectious diseases are caused by different germs (viruses, 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 from one person to the next. This will help us to find or improve ways to stop these infections from making people sick. We are interested in how the body reacts to infections. Some people may get symptoms from respiratory illness (like a cough, sore throat or runny nose) and other may get the infection and have no symptoms. We are doing a study to try and understand how the body's defenses can prevent children from becoming infected or sick with respiratory viruses.

Influenza (flu) is a virus that causes respiratory illness (sore throat, cough, fever, muscle aches and headache). After having flu, our bodies usually respond by making immune cells (soldiers) and antibodies (weapons) that will protect us when flu tries to infect us again. We would like to understand which types of soldiers protect children from flu infection and how these soldiers do their job. To do this, we have to look closely at children's genes and how their bodies respond to the flu virus. A gene is a small piece of our DNA that gives the body instructions, like a recipe, for making proteins that help us grow and stay healthy. We will also look at each child's human leukocyte antigen (HLA) type, a special group of genes that help the body tell the difference between its own cells and germs like viruses. By studying these genes and HLA types, we can understand why some children's immune systems recognize and fight off the flu more effectively than others, and learn how to make vaccines that work better for everyone.

We are asking you to provide permission for us to test your child's cells for these genes. We will do this testing on the samples you already gave permission for us to collect.

We will not take any additional blood sample for this test. The samples collected for the main study will be divided up and used for all the tests

Your rights as the parent of a participant

It is your right to choose if you want your child samples to be tested for these genes. If you chose not to have your child's samples tested, they may still participate in the study. They will also be able to participate in future studies.

Risks of this study

There is no added risk involved for your child's samples to be tested for these genes. Testing will be done on the samples already collected as part of the main study.

Benefits of this study

By taking part in this study, you will help us learn more about certain infectious diseases and how our bodies respond to them, specifically influenza. If we find any medical conditions that need treatment during our examination of your child, we will assist you with a referral to the appropriate in or outpatient facility.

Confidentiality

We will keep all your and your child's information confidential: study forms and samples will be marked with a number and not a name. Study staff will keep a log of you and your child's identifying details, 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. Selected people working on the study, as well as representatives of government regulatory authorities and ethics committees will also have access to the results. These persons are required to maintain the confidentiality of your child's information, and will only access the data in connection with carrying out their obligations relating to this study. By signing this document, you are authorizing such access. When we share samples with other laboratories, we will not share any identifying information from you or your child. Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can say no to your child taking part in the study, 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

There is no additional reimbursement associated with genetic testing (HLA typing).

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 North West Provincial Ethics Committee
- The study has been submitted to the United States Centers for Disease Control and Prevention Human Research Protection Office which relied on the local HREC
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2024), 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 Paul Ruff, 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.

INFORMED CONSENT FOR PARENTS:

(On behalf of minors under 18 years old)

- _____ *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the 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 my child is prepared to participate in the study.
- I acknowledge that the National Institute for Communicable Diseases will have access to my personal information and will process my child’s personal information as required for purposes of this study, and / or national regulations, and in accordance with the South African Protection of Personal Information (POPI) Act of 2013.
- By signing this form, I agree to: please circle Yes/No for each statement

1. My child’s samples to undergo human leukocyte antigen (HLA) typing	Yes/No
2. In accordance with the provisions of the Protection of Personal Information Act 4 of 2013 (as amended), I hereby consent	
a. For my and my child’s personal information (hereinafter 'data') being collected, processed, shared and stored on an electronic device (laptop or tablet) in accordance with the study protocol as approved by the Wits HREC (Medical)	Yes/No
b. To my and my child’s anonymized data being shared, processed, and transferred by third parties and between third parties, and where relevant beyond the jurisdictional borders of South Africa	Yes/No
c. To all findings and results flowing from my anonymized data being broadly shared and published at the conclusion of the	Yes/No

research	
3. The other adult(s) with whom I share parental rights and responsibilities in respect of the identified child in terms of the Children's Act (for example, biological parent, adoptive parent, or legal guardian or representative) is (1) aware of and agrees with my granting permission for this child to participate in the study OR (2) deceased, unknown, incompetent, or not reasonably available (someone is "not reasonably available" when he/she cannot be reached by phone/mail/email/text because, for example, he/she is on active military duty or is incarcerated).	Yes/No Date:

Child's name _____ Child's DOB _____

PARENT:

Printed Name	Signature / Mark or Thumbprint	Date and Time

STAFF MEMBER:

Printed Name	Signature	Date and Time

For parent unable to read:

DETAILS OF OTHER PERSON EXPLAINING INFORMED CONSENT:

NAME AND SURNAME: _____

DESIGNATION: _____

Printed Name	Signature	Date and Time

WITNESS (If applicable):

Printed Name	Signature	Date and Time

Information leaflet and consent 5: Consent for parent for PBMC isolation from child

STUDY TITLE: Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)

Each parent 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 cooperative agreement with the Centers for Disease Control and Prevention (CDC), Atlanta, United States of America. In partnership with the Perinatal HIV Research Unit (PHRU), University of the Witwatersrand.

Investigators: Prof Cheryl Cohen 011 386 6593, daytime and 082 803 8093, after hours.
Dr Jackie Kleynhans 011 555 0383

Site investigator: Dr Tumelo Moloantoa 018 011 3830

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 help us with a research study called the "MUSIC-Flu" that we will be doing in Matlosana, North West Province.

- 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 you need to do and what procedures your child needs 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 study staff regarding your child's health history, since you may otherwise harm your child by participating in this study.
- If you decide that your 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

As part of the MUSIC-Flu study, we are asking some parents for permission to collect an additional sample from their child. We would like to collect this additional blood from children selected by

asking every 4th child's parents if they are willing to consent for their child to give the additional sample. You would have already consented to the main study, and have read that information sheet for the main study.

Our bodies usually respond to having flu by making immune cells (soldiers) and antibodies (weapons) that will protect us when flu tries to infect us again. To learn more about the immune "soldiers" that fight flu, we will take an additional blood sample from 25-38 children in total. In the laboratory we are able to separate out the soldiers called PBMCs (peripheral blood mononuclear cells). These are the white blood cells that help the body fight infections. We will look at the different types of these cells, such as T cells and B cells, and look at what each type is doing. This process is called cell phenotyping, and it helps us understand which immune cells are most active and important in protecting children from getting the flu.

To do this we will collect an additional tube of blood at the beginning and the end of the study. This will be done on a set day, after the enrolment visit. For this we will need you to bring your child back to the clinic. We will do the main study blood sample at the same time to avoid taking blood twice from your child. We will not collect more blood than what is safe based on your child's weight. We will collect no more than 15ml (one tablespoon). The study nurse can help you the amount that is safe for your child, once she/he has weighted your child.

Your rights as the parent of a participant

It is your right to choose if you want your child's blood to be collected for this test. If you chose not to have your child's blood collected for this test, they may still participate in the study. They will also be able to participate in future studies.

Risks of this study

There is minimal risk to your child from the study procedures. 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 child's protection is that experienced personnel perform the procedures under sterile/clean conditions.

Benefits of this study

By taking part in this study, you will help us learn more about certain infectious diseases and how our bodies respond to them, specifically influenza. If we find any medical conditions that need treatment during our examination of your child, we will assist you with a referral to the appropriate in or outpatient facility.

Confidentiality

We will keep all your and your child's information confidential: study forms and samples will be marked with a number and not a name. Study staff will keep a log of you and your child's identifying details, 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. Selected people working on the study, as well as representatives of government regulatory authorities and ethics committees will also have access to the results. These persons are required to maintain the confidentiality of your child's information, and will only access the data in connection with carrying out their obligations relating to this study. By signing this document, you are authorizing such access. When we share samples with other laboratories, we will not share any identifying information from you or your child. Your data will be collected, processed and stored according to the South African Protection of Personal Information (POPI) Act of 2013.

Withdrawal from the study

Your child's participation in this study is entirely voluntary and you can say no to your child taking part in the study, 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 an additional voucher of R900 (in addition to the enrolment visit R900) for these additional samples collected at the beginning and the end of the study. The voucher can be redeemed at a supermarket for items sold at that supermarket.

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 North West Provincial Ethics Committee
- The study has been submitted to the United States Centers for Disease Control and Prevention Human Research Protection Office which relied on the local HREC
- The study has been structured in accordance with the **Declaration of Helsinki** (last updated: October 2024), 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 Paul Ruff, 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.

INFORMED CONSENT FOR PARENTS:

(On behalf of minors under 18 years old)

- _____ *(INSERT NAME OF STUDY TEAM MEMBER)* has provided me with a copy of the Participant Information Leaflet and Consent regarding the 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 my child is prepared to participate in the study.
- I acknowledge that the National Institute for Communicable Diseases will have access to my personal information and will process my child’s personal information as required for purposes of this study, and / or national regulations, and in accordance with the South African Protection of Personal Information (POPI) Act of 2013.
- By signing this form, I agree to: please circle Yes/No for each statement

1. For my child to provide an additional blood sample at the beginning and the end of the study	Yes/No
2. In accordance with the provisions of the Protection of Personal Information Act 4 of 2013 (as amended), I hereby consent	
a. For my and my child’s personal information (hereinafter 'data') being collected, processed, shared and stored on an electronic device (laptop or tablet) in accordance with the study protocol as approved by the Wits HREC (Medical)	Yes/No
b. To my and my child’s anonymized data being shared, processed, and transferred by third parties and between third parties, and where relevant beyond the jurisdictional borders of South Africa	Yes/No
c. To all findings and results flowing from my anonymized data being broadly shared and published at the conclusion of the research	Yes/No
3. The other adult(s) with whom I share parental rights and responsibilities in respect of the identified child in terms of the Children's Act (for example, biological parent, adoptive parent, or	Yes/No Date:

<p>legal guardian or representative) is (1) aware of and agrees with my granting permission for this child to participate in the study OR (2) deceased, unknown, incompetent, or not reasonably available (someone is “not reasonably available” when he/she cannot be reached by phone/mail/email/text because, for example, he/she is on active military duty or is incarcerated).</p>	
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Child’s name _____ **Child’s DOB** _____

PARENT:

Printed Name	Signature / Mark or Thumbprint	Date and Time
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STAFF MEMBER:

Printed Name	Signature	Date and Time
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For parent unable to read:

DETAILS OF OTHER PERSON EXPLAINING INFORMED CONSENT:

NAME AND SURNAME: _____

DESIGNATION: _____

Printed Name	Signature	Date and Time
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WITNESS (If applicable):

Printed Name	Signature	Date and Time
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Mucosal and systemic immunity correlates of protection against influenza in young children (MUSIC-Flu)
Appendix B Data Collection Tools

Form Name	Variable	Field Label	Choices/ Calculations	Field Note	Show field only if
form_1_screening	record_id	Record ID			
form_1_screening	descrform1info1	This form is collected at the first contact with the caregiver, prior to doing informed consent. Introduce the study and then get verbal consent to ask some questions related to eligibility.			
form_1_screening	interviewer_username1	Interviewer			[screendate1]"
form_1_screening	screendate1	Date of screening			
form_1_screening	clinicscreen4	Clinic where screened	1, Jouberton clinic 2, Tshepong clinic		
form_1_screening	childwell1	Is the child visibly well?			
form_1_screening	descrnnotwellstop1	The child is not visibly well. Stop interview here.			[childwell1]=0 and [childwell1]"
form_1_screening	dobchild1	Child date of birth			[childwell1]=1
form_1_screening	agechildmonths1	Child age	rounddown(datediff([screendate1], [dobchild1], 'd')/30.25)	in months	[childwell1]=1
form_1_screening	descrousidagestop1	The child is outside of the age window and cannot be enrolled in this study. Stop interview here.			[agechildmonths1]=24
form_1_screening	sibling1	Is this child a sibling/twin of a child already enrolled?	0, No 1, Twin 2, Sibling		[agechildmonths1]>='6' and [agechildmonths1]<'24'
form_1_screening	descrsiblings1stop1	The child is a twin/sibling of an existing participant. Stop interview here.			[sibling1]='1' or [sibling1]='2'
form_1_screening	sexchild1	Child sex	1, Male 2, Female		[sibling1]='0'
form_1_screening	parguarparent1	Is there a parent accompanying the child that can provide consent to be enrolled in the study?			[sibling1]='0'
form_1_screening	descrnoparguarstop2	A parent is needed to provide consent for the child to be enrolled in this study. Stop interview here.			[parguarparent1]='0'
form_1_screening	dobpargar1	Parent or legal guardian date of birth		Person currently accompanying child. Only a parent/leg	[parguarparent1]='1'

				al guardian can provide consent.	
form_1_screening	parguarageyears1	Parent or legal guardian age	rounddown(datediff([screen date1], [dobpargar1], 'y'))	in years	[dobpargar1]'
form_1_screening	descrcaregiverminor1	The parent/legal guardian is younger than 18 years and therefore the child cannot be enrolled in this study. Stop interview here.			[parguarageyears1]=0
form_1_screening	livejouberton1	Do you live in the Jouberton township?			[parguarageyears1]>=18
form_1_screening	descroutjbrtstop1	The child does not live in Jouberton and cannot be enrolled in this study. Stop interview here.			[livejouberton1] = '0'
form_1_screening	descriinteressteddetails1	Are you interested in participating in a study that will run over 6 months? We will visit your house once a week for 6-8 months to collect information about respiratory illness. At each visit a nurse will to collect a swab from your child's nose. We will also ask you to take two swabs a week from your child, and to complete questions every day about any symptoms your child might have experienced. We will teach you how to do the swab, take your child's temperature and how to complete your child's symptom diary. At the beginning and end of the study we will collect blood from your child, and every month we will also collect an extra nose swab, oral fluid and nasal fluid.			[livejouberton1] = '1'
form_1_screening	interestparticipate1	Are you interested in participating?			[livejouberton1] = '1'
form_1_screening	nointerestreason1	Why are you not interested in participating in the study?	1, I'm worried it will be uncomfortable for my child 2, One visit a week is too many 3, I don't want to collect a swab from my child 4, I don't want to answer questions about by child's symptoms every day 5, Six months are too long 7, No one in my household can use a smart device to	SELECT ALL THAT APPLY	[interestparticipate1] = '0'

			complete the symptom questions 6, Other		
form_1_screening	nointerreas otherspec1	Specify other reason why not interested in the study			[nointerreas on1(6)] = '1'
form_1_screening	descrnoint ereststop1	The caregiver is not interested in the study and the child cannot be enrolled in this study. Stop interview here.			[interestpartici pate1] = '0'
form_1_screening	rthcwith1	Do you have your child's road to health card (RTHC) with you?			[interestpartici pate1] = '1'
form_1_screening	descrrthcno tavail1	The RTHC is not currently available. Pause interview and continue when available.			[rthcwith1] = '0'
form_1_screening	resumeinter view1	Will the interview be resumed?	1, Yes - the parent will still return with the RTHC 0, No - the parent never returned with the RTHC	Once the RTHC is available, update the question 'Do you have your child's RTHC with you?'. REDCap will prompt you to hide this question and its response. You can select OK.	[rthcwith1] = '0'
form_1_screening	childlivhiv1	Is your child living with HIV/AIDS?	0, No 1, Yes		[rthcwith1] = '1'
form_1_screening	descrlivhivst op1	The child is HIV positive and cannot be enrolled in this study. Stop interview here.			[childlivhiv1] = '1'
form_1_screening	asthma1	Does your child have Asthma?	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	chroniclung disease1	Does your child have Other chronic lung disease	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	liverdisease 1	Does your child have Liver disease	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	kidneydisea se1	Does your child have Kidney disease	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'

form_1_screening	heartcondition1	Does your child have Any heart condition	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	cancer1	Does your child have Any cancer	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	diabetes1	Does your child have Diabetes	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	autoimmunedisesele1	Does your child have Autoimmune disease	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	kwashiorkor marasmus1	Does your child have Kwashiorkor/Marasmus	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	nephroticsyndrome1	Does your child have Nephrotic syndrome	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	spinalabnormal1	Does your child have Spinal abnormalities e.g. Spine bifida	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	seizure disorder1	Does your child have Seizure disorder	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	cerebralpalsy1	Does your child have Cerebral palsy	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	prematurity1	Does your child have Prematurity	0, No 1, Yes	Born at less than 37 week gestation, confirmed on RTHC	[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	otherunderlyingcondition1	Does your child have Other underlying condition	0, No 1, Yes		[childlivhiv1] = '0' or [childlivhiv1] = '2'
form_1_screening	underlyingillnessspecify1	Specify other underlying illness			[otherunderlyingcondition1] = '1'
form_1_screening	descrunderlyingconditionstop1	The child has an underlying condition and cannot be enrolled in this study. Stop interview here.			[asthma1] = '1' or [chroniclungdisease1] = '1' or [liverdisease1] = '1' or [kidneydisease1] = '1' or [heartcondition1] = '1'

					n1] = '1' or [cancer1] = '1' or [diabetes1] = '1' or [autoimmuned iseasesle1] = '1' or [nephroticsynd rome1] = '1' or [spinalabnrm1] = '1' or [seizuredisorde r1] = '1' or [otherunderlyi ngcondition1] = '1' or [kwashiorkorm arasmus1] = '1' or [prematurity1] = '1' or [cerebralpalsy1]='1'
form_1_scre ening	chronicmed 1	Is your child receiving any long term medication?		Long term medicatio n is medicines that are taken every day for more than 2 weeks.	[asthma1] = '0' and [chroniclungdis ease1] = '0' and [liverdisease1] = '0' and [kidneydisease 1] = '0' and [heartconditio n1] = '0' and [cancer1] = '0' and [diabetes1] = '0' and [autoimmuned iseasesle1] = '0' and [nephroticsynd rome1] = '0' and [spinalabnrm1] = '0' and [seizuredisorde r1] = '0' and [otherunderlyi ngcondition1] = '0' and [kwashiorkorm arasmus1] = '0' and [prematurity1] = '0' and [cerebralpalsy1]='0'

form_1_screening	chronicmedspecify1	Specify the medication name(s)			[chronicmed1]='1'
form_1_screening	descrchronicmedstop1	The child is taking long term medication cannot be enrolled in this study. Stop interview here.			[chronicmed1]='1'
form_1_screening	descrdconsent1	Prior to continuing, please conduct study consent and the consent for sample storage, shipment and additional testing with parent/guardian explaining that you will still do an assessment of HIV status and if the child is positive they will be withdrawn from the study. HIV consent will only be done if you need to test for HIV. Update all the consent questions below to reflect exactly what is on the paper-based form. Two copies of the ICFs should be completed, in addition to updating the answers below. Then proceed to the HIV form.			[chronicmed1]='0'
form_1_screening	pbmcselect1	Was the child selected for PBMC collection?	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstsst1	I consent to My child's blood being taken at the beginning of the study and end of the study	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstns1	I consent to weekly nasal swabs	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstsympdiar1	I consent to Daily recording of symptoms and temperature	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstcaregivns1	I will do a swab on my child twice a week	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstoralf1	I consent to Monthly collection of oral fluid	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstmucf1	I consent to Monthly collection of nasal mucosal fluid	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstnp1	I consent to Monthly collection of a nasopharyngeal swab	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	cnstpmmc1	I consent to PBMC collection at the start and end of the study	1, Yes 0, No		pbmcselect1='1' AND [chronicmed1]='0'
form_1_screening	cnstdatastore1	I consent For my and my child's data to be stored, processed and analysed on an electronic device (laptop or tablet)	1, Yes 0, No		[chronicmed1]='0'

form_1_screening	cnstcontact1	I consent to be contacted telephonically for matters regarding the study, for example visit appointments, or to verify data collected	1, Yes 0, No		[chronicmed1]='0'
form_1_screening	descrchronimedstop2	The caregiver did not consent to all study procedures. Stop interview here.			[cnstsst1]='0' or [cnstns1]='0' or [cnstsympdiar1]='0' or [cnstcaregivns1]='0' or [cnstoralf1]='0' or [cnstmucf1]='0' or [cnstnp1]='0' or [cnstpbmc1]='0' or [cnstdatastore1]='0' or [cnstcontact1]='0'
form_1_screening	cnststorage1	I consent to my child's sample to be stored in a secure storage at the NICD for further testing related to the study.			[cnstsst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstoralf1]='1' and [cnstmucf1]='1' and [cnstnp1]='1' and [cnstdatastore1] = '1' and [cnstcontact1] = '1'
form_1_screening	cnstshipping1	I consent for my child's sample being sent to another facility for specialized testing, once the testing procedure has been approved by the HREC of the University of the Witwatersrand			[cnstsst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstoralf1]='1' and [cnstmucf1]='1' and [cnstnp1]='1' and [cnstdatastore1] = '1' and

					[cnstcontact1] = '1'
form_1_screening	initeligibilitystatus1	Initial eligibility status			
form_2_hiv	descnotelig1	The child is not eligible for enrolment. Close form.			[initeligibilitystatus1] 'Eligible'
form_2_hiv	interviewerusernamef2	Interviewer			(([cnstsst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstdatastore1] = '1' and [cnstcontact1] = '1') and [screenhivdate2] "
form_2_hiv	screenhivdate2	Date HIV interview completed			[cnstsst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstdatastore1] = '1' and [cnstcontact1] = '1'
form_2_hiv	descreviewhiv2	Ask to see the RTHC to confirm that the HIV data are completed. Please confirm the following HIV related data on the RTHC.			[cnstsst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstdatastore1] = '1' and [cnstcontact1] = '1'
form_2_hiv	momhivstatuspreg2	What was the mother's HIV status during pregnancy?	0, HIV negative 1, HIV positive 2, Mother was not tested for HIV during pregnancy 3, Mother's status is not recorded on RTHC		[cnstsst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstdatastore1] = '1' and [cnstcontact1] = '1'

form_2_hiv	descrnohiv thc2	If there is no HIV result documented for the mother on the RTHC, offer the mother a rapid HIV test.			[momhivstatus preg2] = '3' or [momhivstatus preg2] = '4'
form_2_hiv	child6wpcrh ivpcres2	What was the child's 6-week HIV PCR result?	0, HIV Negative 1, HIV Positive 2, 6-week HIV PCR test not done 3, No results documented		[momhivstatus preg2] = '1'
form_2_hiv	deschrivpos childstop2	The child is HIV positive and cannot be enrolled in this study. Stop interview here.			[child6wpcrhiv pcres2] = '1'
form_2_hiv	hivtestcons entmom2	Did the mother agree and consent to be tested for HIV?	1, Yes 0, No 2, Mother is not accompanying the child		[momhivstatus preg2] = '3' or [momhivstatus preg2] = '4'
form_2_hiv	momhivrapi dresult2	Mother's rapid HIV test result	0, Negative 1, Positive 3, Result pending	Select result pending if sent for ELISA	[hivtestconsen tmom2] = '1'
form_2_hiv	descrmomh ivpos2	The mother could not be tested OR is living with HIV and the child needs to be tested. Please conduct the HIV consent process for the child and proceed to collect a heel prick dried blood spot from the child. Capture the collection of the DBS sample here. Please pause the enrolment until the result is available.			[momhivrapidr esult2] = '1' OR [hivtestconsen tmom2]='2' or [hivtestconsen tmom2]='0'
form_2_hiv	hivtestcons entchild2	Did the mother agree and consent for her child to be tested for HIV? (As per ICF2)			(([momhivstatu spreg2] = '1' and ([child6wpcrh ivpcres2] = '2' or [child6wpcrhiv pcres2] = '3') or [momhivrapidr esult2] = '1' or [hivtestconsen tmom2] = '0' or [hivtestconsen tmom2]='2')
form_2_hiv	dbscollecte d2	Was a dried blood spot collected for HIV testing?			[hivtestconsen tchild2] = '1'
form_2_hiv	childhivpcrd bs2	What was the HIV test result?	3, Result pending 0, Negative 1, Positive 2, Inconclusive		[dbscollected2] = '1'
form_2_hiv	descrpause hivres2	Pause enrolment while HIV test result is pending			[dbscollected2] = '1' and [childhivpcrdbs 2] = '3'

form_2_hiv	deschrivchil dunkstop2	The child's HIV status cannot be confirmed and cannot be enrolled in this study. Stop interview here.			[hivtestconsentchild2] = '0' or [childhivpcrdb2] = '2' or [dbscollected2] = '0'
form_2_hiv	deschrivdbposstop2	The child is HIV positive and cannot be enrolled in this study. Stop interview here.			[childhivpcrdb2] = '1'
form_2_hiv	descproceedenrolment2	The child is HIV negative and enrolment can continue. Proceed to the enrolment form.			[momhivstatuspreg2] = '0' or [child6wpcr HIVpcrres2] = '0' or [momhivrapidresult2] = '0' or [childhivpcrdb2] = '0'
form_2_hiv	initeligibilitystatus2	Initial eligibility status			[cnstst1] = '1' and [cnstns1] = '1' and [cnstsympdiar1] = '1' and [cnstcaregivns1] = '1' and [cnstdatastore1] = '1' and [cnstcontact1] = '1'
form_3_enrolment	interviewerusernamef3	Interviewer			[enrolmentdate3]"
form_3_enrolment	descnotelig3	The child is not eligible for enrolment. Close form.			[initeligibilitystatus2]"Eligible"
form_3_enrolment	enrolmentdate3	Date enrolment interview completed			[initeligibilitystatus2]"Eligible"
form_3_enrolment	caregivername3	Parent/Caregiver Name			[initeligibilitystatus2]"Eligible"
form_3_enrolment	caregiversurname3	Parent/Caregiver Surname			[initeligibilitystatus2]"Eligible"
form_3_enrolment	caregivercontactnomain3	Parent/Caregiver main contact number			[initeligibilitystatus2]"Eligible"
form_3_enrolment	caregivercontactnoalt3	Parent/Caregiver alternative number			[initeligibilitystatus2]"Eligible"
form_3_enrolment	mobprov3	Which mobile provider has the best connectivity at your home?	1, CellC 2, MTN 3, Telkom 4, Vodacom 5, I don't know		[initeligibilitystatus2]"Eligible"
form_3_enrolment	childname3	Child name			[initeligibilitystatus2]"Eligible"
form_3_enrolment	childsurname3	Child surname			[initeligibilitystatus2]"Eligible"

form_3_enrolment	childidpassportno3	Child ID or passport number		If available	[initeligibilitystatus2]="Eligible"
form_3_enrolment	addresshome3	Child home living address			[initeligibilitystatus2]="Eligible"
form_3_enrolment	addresshomedirections3	Directions to child home living address		e.g. near X shop/school	[initeligibilitystatus2]="Eligible"
form_3_enrolment	daycare3	Does the child attend day-care or a play group?	0, No 1, Yes		[initeligibilitystatus2]="Eligible"
form_3_enrolment	height3	Measure the child's height/length		in cm (one decimal place, e.g. 80.0)	[initeligibilitystatus2]="Eligible"
form_3_enrolment	outrangeheight3	The height is out of range for age. Remeasure.	1, I remeasured and confirm the measurement for height is correct.		[height3]" AND (([agechildmonths1]>='6' AND [agechildmonths1]'85')) OR ([agechildmonths1]>='7' AND [agechildmonths1]'85')) OR ([agechildmonths1]>='8' AND [agechildmonths1]'85')) OR ([agechildmonths1]>='9' AND [agechildmonths1]'85')) OR ([agechildmonths1]>='10' AND [agechildmonths1]'90')) OR ([agechildmonths1]>='11' AND [agechildmonths1]'90')) OR ([agechildmonths1]>='12' AND [agechildmonths1]'100')) OR ([agechildmonths1]>='19' AND [agechildmonths1]'105'))
form_3_enrolment	weight3	Measure the child's weight		in kg	[initeligibilitystatus2]="Eligible"

form_3_enrolment	outrangeweight3	The weight is out of range for age. Remeasure.	1, I remeasured and confirm the measurement for weight is correct.		[weight3]" and ((([agechildmonths1]>='6' AND [agechildmonths1]'11')) OR ([agechildmonths1]>='7' AND [agechildmonths1]'11')) OR ([agechildmonths1]>='8' AND [agechildmonths1]'12')) OR ([agechildmonths1]>='9' AND [agechildmonths1]'12')) OR ([agechildmonths1]>='10' AND [agechildmonths1]'13')) OR ([agechildmonths1]>='11' AND [agechildmonths1]'13')) OR ([agechildmonths1]>='12' AND [agechildmonths1]'15')) OR ([agechildmonths1]>='19' AND [agechildmonths1]'17'))))
form_3_enrolment	descrplotheightweight3	Please plot weight and height on the RTHC, if the child is on or below the 25% percentile for either height or weight, please refer the child for further assessment at the well-baby clinic.			[initeligibilitystatus2]="Eligible"
form_3_enrolment	heightweightbelow253	Is the child is on or below the 25% percentile for either height or weight?			[initeligibilitystatus2]="Eligible"
form_3_enrolment	descrbelow25thstop3	The child is below the 25th percentile for height and/or weight and can not be enrolled in this study. Stop interview here.			[heightweightbelow253] = '1'
form_3_enrolment	headcircumference3	Measure the child's head circumference		in cm (one decimal place, e.g. 40.0)	[heightweightbelow253] = '0'

form_3_enrolment	outrangeheadcircum3	The head circumference is out of range for age. Remeasure.	1, I remeasured and confirm the measurement for head circumference is correct.		[headcircumference3]" AND (([agechildmonths1]>='6' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='7' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='8' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='9' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='10' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='11' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='12' AND [agechildmonths1]'50')) OR ([agechildmonths1]>='19' AND [agechildmonths1]'55'))
form_3_enrolment	muac3	Measure the child's mid-upper arm circumference (MUAC)		in cm (one decimal place, e.g. 9.5)	[heightweightbelow253] = '0'
form_3_enrolment	outrangermuac3	The MUAC is out of range for age. Remeasure.	1, I remeasured and confirm the measurement for MUAC is correct.		[muac3]" AND (([agechildmonths1]>='0' AND [agechildmonths1]'17')) OR ([agechildmonths1]>='12' AND [agechildmonths1]'18'))
form_3_enrolment	lungsclear3	Are both lungs clear?			[heightweightbelow253] = '0'

form_3_enrolment	abnormalitieslungs3	Describe abnormalities found during lung investigation			[lungsclear3] = '0'
form_3_enrolment	descrabnlungsstop3	Due to the abnormal lung sounds the child should be referred to care and cannot be enrolled in this study. Stop interview here.			[lungsclear3] = '0'
form_3_enrolment	heartsounds3	Are there any abnormal sounds when listening to the heart?			[lungsclear3] = '1'
form_3_enrolment	abnormalitiesheart3	Describe abnormalities found during heart investigation			[heartsounds3] = '1'
form_3_enrolment	descrabnheartstop3	Due to the abnormal heart sounds the child should be referred to care and cannot be enrolled in this study. Stop interview here.			[heartsounds3] = '1'
form_3_enrolment	lymphnodes3	Did you find any enlarged nodes?	0, No enlarged nodes 1, A single enlarged node 2, Multiple enlarged nodes		[heartsounds3] = '0'
form_3_enrolment	singlenodesdescription3	Describe the single node	1, Small mobile node 2, Tender node or attached to underlying tissue		[lymphnodes3] = '1'
form_3_enrolment	nodelocation3	Where is the single mobile node located?			[lymphnodes3] = '1'
form_3_enrolment	multinodelocations3	Describe where the multiple nodes are located?			[lymphnodes3] = '2'
form_3_enrolment	descrnodesfoundstop3	Due to the enlarged lymph nodes observed the child should be referred for care and cannot be enrolled in this study. Stop interview here.			[lymphnodes3] = '2' or [singlenodesdescription3] = '2'
form_3_enrolment	rashenrol3	Does the child have a rash?			[lymphnodes3] = '0' or ([lymphnodes3] = '1' and [singlenodesdescription3] = '1')
form_3_enrolment	rashenroldescription3	Describe the location and appearance of the rash			[rashenrol3] = '1'
form_3_enrolment	descrrashstop3	Due to the rash the child cannot be enrolled in this study. Stop interview here.			[rashenrol3] = '1'
form_3_enrolment	oedemaankle3	Is there oedema of the ankle?			[rashenrol3] = '0'
form_3_enrolment	descroedemastop3	Due to the oedema the child should be referred to care and cannot be enrolled in this study. Stop interview here.			[oedemaankle3] = '1'

form_3_enrolment	descrcontent3	The child is eligible for enrolment. Assign a unique study ID and continue to sample collection form to collect serum sample and arrange the first household visit.			[oedemaankle3] = '0'
form_3_enrolment	studyid3	Study ID		Allocate a unique study ID to the child, e.g. Mxxx	[oedemaankle3] = '0'
form_3_enrolment	rthcpic3	Upload a clear photograph of the vaccination page of the RTHC			[oedemaankle3] = '0'
form_3_enrolment	breastfed	Was the child ever breastfed?	0, No 1, Currently being breastfed 2, Was breastfed, but stopped		
form_3_enrolment	breastfed_top_year	What year was breastfeeding stopped?	2024 2024 2025 2025 2026 2026		[breastfed] = '2'
form_3_enrolment	breastfed_top_month	What month was breastfeeding stopped?	1, January 2, February 3, March 4, April 5, May 6, June 7, July 8, August 9, September 10, October 11, November 12, December		[breastfed] = '2'
form_3_enrolment	finaleligibilitystatus3	Final eligibility status			[finaleligibilitystatus2]="Eligible"
form_4_household_characteristics	studyid4	Study ID			
form_4_household_characteristics	firstvisitdone4	Was the first visit to the household done?			[visit_000a_arm_1][finaleligibilitystatus3]="Eligible"
form_4_household_characteristics	firstvisitnotreasons4	Why was the first visit never completed?	1, Caretaker no longer interested in study 2, Could not reach caretaker 3, Moved away permanently		[firstvisitdone4]='0'
form_4_household_characteristics	visitdate4	Visit date			[firstvisitdone4]='1'
form_4_household_characteristics	interviewerusername4	Interviewer			[firstvisitdone4]='1'
form_4_household_characteristics	hhsizes4	What is the number of people residing (staying) in this household currently?		The number of people in the household that shares four meals a week together.	[firstvisitdone4]='1'

				This excludes migrant workers.	
form_4_household_characteristics	childrenhh4	How many children (not including the child enrolled in the study) aged younger than 18 years live in the household?			[firstvisitdone4]='1'
form_4_household_characteristics	child1hhage4	Age child 1			[childrenhh4]>0
form_4_household_characteristics	child2hhage4	Age child 2			[childrenhh4]>0 and [childrenhh4]>1
form_4_household_characteristics	child3hhage4	Age child 3			[childrenhh4]>0 and [childrenhh4]>2
form_4_household_characteristics	child4hhage4	Age child 4			[childrenhh4]>0 and [childrenhh4]>3
form_4_household_characteristics	child5hhage4	Age child 5			[childrenhh4]>0 and [childrenhh4]>4
form_4_household_characteristics	child6hhage4	Age child 6			[childrenhh4]>0 and [childrenhh4]>5
form_4_household_characteristics	child7hhage4	Age child 7			[childrenhh4]>0 and [childrenhh4]>6
form_4_household_characteristics	child8hhage4	Age child 8			[childrenhh4]>0 and [childrenhh4]>7
form_4_household_characteristics	child9hhage4	Age child 9			[childrenhh4]>0 and [childrenhh4]>8
form_4_household_characteristics	child10hhage4	Age child 10			[childrenhh4]>0 and [childrenhh4]>9
form_4_household_characteristics	child11hhage4	Age child 11			[childrenhh4]>0 and [childrenhh4]>10
form_4_household_characteristics	child12hhage4	Age child 12			[childrenhh4]>0 and [childrenhh4]>11

form_4_household_characteristics	child13hhage4	Age child 13			[childrenhh4]>0 and [childrenhh4]>12
form_4_household_characteristics	child14hhage4	Age child 14			[childrenhh4]>0 and [childrenhh4]>13
form_4_household_characteristics	child15hhage4	Age child 15			[childrenhh4]>0 and [childrenhh4]>14
form_4_household_characteristics	roomtotal4	How many rooms are in the home (completed and in use)?			[firstvisitdone4]='1'
form_4_household_characteristics	roomsleeping4	How many rooms are used for sleeping in the home?			[firstvisitdone4]='1'
form_4_household_characteristics	totalhouseholdincome4	Which income category best describes your household gross (before tax) monthly income?	1, R51 201 10, Don't know 11, Refused to disclose 1, < R400 2, R401 to R800 3, R801 to R1 600 4, R1 601 to R3 200 5, R3 201 to R6 400 6, R6 401 to R12 800 7, R12 801 to R25 600 8, R25 601 to R51 200 9, > R51 201 10, Don't know 11, Refused to disclose	This is for all the people in the household earning money, added together and will include salaries and an average income in business and a private pension/medical boarding pay out and grants.	[firstvisitdone4]='1'
form_4_household_characteristics	smokeinside4	If allowed or allowed with exceptions, how often does anyone smoke inside your home?	1, Daily 2, Less than every day, but at least once a week 4, Less than every week, but at least once a month 5, Less than once a month 6, No one smokes in my home		[firstvisitdone4]='1'
form_4_household_characteristics	homewateravail4	What is the main source of water usually available for your household?	1, Water taps inside home 2, Water tap outside Home/tanker 3, Water from river/canal 4, Rain water 5, Other (specify):		[firstvisitdone4]='1'
form_4_household_characteristics	otherhomewater4	Specify other source of water			[homewateravail4]='5'

form_4_household_characteristics	handwashplace4	Do you have place to wash your hands?	0, No 1, Yes		[firstvisitdone4]='1'
form_4_household_characteristics	checkhandwash4	Can you show me where you typically wash your hands? Select the source of the water used to wash hands	1, At a sink with running water 2, From a water bottle reserved for that purpose - clean water used each time 3, At a tap outside 5, A bucket/container with used water - same water used each time 4, Other (specify)	(Observed)	[handwashplace4] = '1'
form_4_household_characteristics	otherhandwash4	Specify other place where hands washed			[checkhandwash4] = '4'
form_4_household_characteristics	handwateravail4	Is water available at the hand washing area?		(Observed)	[handwashplace4] = '1'
form_4_household_characteristics	handwashproduct4	What type of product is mostly available for family members to clean their hands in your household?	1, Soap 2, Hand gel 3, Hand wipes 4, Nothing 5, Other (specify):		[handwashplace4] = '1'
form_4_household_characteristics	otherproducts4	Specify other product to wash hands			[handwashproduct4] = '5'
form_4_household_characteristics	availhanddryer4	What type of hand dryer is most available in your household?	1, Tissue/paper 2, Cloth towel 3, None 5, Clothes they are wearing 4, Other (specify)		[handwashplace4] = '1'
form_4_household_characteristics	otherhanddryer4	Specify other hand dryer			[availhanddryer4] = '4'
form_4_household_characteristics	mainfuelsource4	What is the main source of cooking fuel used?	1, Electricity 2, Wood 3, Gas/Paraffin 4, Other		[firstvisitdone4]='1'
form_4_household_characteristics	otherfuelsource4	Specify other source of fuel used for cooking			[mainfuelsource4] = '4'
form_4_household_characteristics	majoritychildcare4	Who does the majority of the childcare?	1, Mother 2, Father 3, Guardian		[firstvisitdone4]='1'
form_4_household_characteristics	guardiansex4	Guardian sex	1, Male 2, Female		[majoritychildcare4]='3'
form_4_household_characteristics	maincaregiverdob4	Date of birth of person who does the majority of childcare			[firstvisitdone4]='1'
form_4_household_characteristics	caregiveducationlevel4	What is the highest level of education of the main caregiver?	1, No schooling / kindergarten 2, Primary 3, Secondary 4, Matriculation 5, Post-secondary		[firstvisitdone4]='1'
form_4_household_characteristics	caregiveroccupation4	What is the occupation of the main caregiver?	1, Not working/unemployed 11, Pensioner 2, Student 3, Agriculture 4, Mining 5, Construction 6, Sales/retail 9, Street		[firstvisitdone4]='1'

			vendor 10, Health medical/healing 7, Domestic helper 8, Other (Specify):		
form_4_household_characteristics	caregivothe roccup4	Specify other occupation of the main caregiver			[caregivoccupa tion4]='8'
form_4_household_characteristics	caregivsmo kecignow4	Does the main caregiver currently smoke cigarettes?		Including hand-rolled cigarettes, e.g. zol	[firstvisitdone4]='1'
form_4_household_characteristics	caregivsmo kecighist4	Did the main caregiver smoke cigarettes in the past?		Including hand-rolled cigarettes, e.g. zol	[caregivsmoke cignow4]='0'
form_4_household_characteristics	caregivwhe nstopsmoking4	When did the main caregiver stop smoking?	1, 0-3 months ago 2, 4 to 6 months ago 3, 7 to 12 months ago 4, > 12 months ago	Including hand-rolled cigarettes, e.g. zol	[caregivsmoke cighist4]='1'
form_4_household_characteristics	caregivcurre ntlytbtreat4	Is the main caregiver currently being treated for TB?			[firstvisitdone4]='1'
form_4_household_characteristics	tabletsn4	Serial number of phone issued to main caregiver		Update if tablet is replaced	[firstvisitdone4]='1'
form_4_household_characteristics	tabletno4	Mobile number of phone issued to main caregiver		Update if tablet is replaced	[firstvisitdone4]='1'
form_5_followup_visits	visitid5	Visit day ID		e.g. Mxxx-xxx	[visit_000a_arm_1][fineligibilitystatus3]="Eligible"
form_5_followup_visits	visitnr5	Visit number	right ([visitid5], 3)		[visitid5]"
form_5_followup_visits	attemptnr5	This is attempt number?	1, 1 2, 2 3,3 4,4	The number of times you tried to reach the participant. Update after each attempt	[visit_000a_arm_1][fineligibilitystatus3]="Eligible"
form_5_followup_visits	participantreached5	Did you manage to reach the participant and complete the visit?	1, Yes 2, No, unable to locate a family member, but reported to be around 3, No, child is travelling temporarily 4, No, child is currently hospitalized 5, No, child was withdrawn from study	Select correct reason if not reached	[attemptnr5]"
form_5_followup_visits	interviewerusernamef5	Interviewer			[participantreached5]"
form_5_followup_visits	visitdate5	Date of visit			[participantreached5] = '1' or

					[participantreasonwithdrew5] = '5'
form_5_followup_visits	reasonwithdrew5	Why was the participant withdrawn?	1, Child died 2, Death of a family member 3, Moved away permanently 4, My child is being swabbed too often 5, My child is uncomfortable with the swabs 6, You visit me too often 7, The study is too long 8, I don't like completing the daily symptom questions 9, I don't like to take a swab from my child 10, Study staff withdrew child due to non-compliance to study procedures 11, Other (specify)	Read all options to caregiver and select the most applicable	[participantreasonwithdrew5]='5'
form_5_followup_visits	reasonwithdrewother5	Specify other reason for withdrawal			[reasonwithdrew5]='11'
form_5_followup_visits	specifycaregiver5	Who was interviewed?	1, Mother 2, Father 3, Guardian		[participantreasonwithdrew5]='1'
form_5_followup_visits	wastempmeasuredurinvist5	Was the body temperature measured during the interview?			[participantreasonwithdrew5]='1'
form_5_followup_visits	temperaturemeasure5	Temperature measurement			[participantreasonwithdrew5] = '1' and [wastempmeasuredurinvist5] = '1'
form_5_followup_visits	tempnotmeasured5	Why was the body temperature not measured?	1, Thermometer not working 2, Thermometer not present 3, Participant not available 4, Participant refused		[wastempmeasuredurinvist5] = '0'
form_5_followup_visits	measfever5	Has your child had a measured fever higher than 38C since the last visit?			[participantreasonwithdrew5]='1'
form_5_followup_visits	feverish5	Has your child felt feverish or had chills since the last visit?			[participantreasonwithdrew5]='1'
form_5_followup_visits	cough5	Has your child had a cough since the last visit?			[participantreasonwithdrew5]='1'
form_5_followup_visits	shortbreath5	Has your child appeared to be short of breath or had difficulty breathing (chest moving in when he/she breaths) since the last visit?			[participantreasonwithdrew5]='1'
form_5_followup_visits	sorethroat5	Has your child appeared to have a sore throat i.e. indicated or appeared to have reluctance to swallow since the last visit?			[participantreasonwithdrew5]='1'
form_5_followup_visits	nasalcongest5	Has your child had a blocked or runny nose since the last visit?			[participantreasonwithdrew5]='1'

form_5_follo wup_visits	vomiting5	Has the child been vomiting since the last visit?			[participantrea ched5]='1'
form_5_follo wup_visits	diarrhea5	Has your child had diarrhoea (3 or more loose stools in 24 hours) since the last visit?			[participantrea ched5]='1'
form_5_follo wup_visits	lethargic5	Has your child been lethargic (no energy, reluctant to move, lying rather than sitting/walking, lazy or not sucking) since the last visit?			[participantrea ched5]='1'
form_5_follo wup_visits	poorfeed5	Has your child refused to eat since the last visit?			[participantrea ched5]='1'
form_5_follo wup_visits	irritable5	Has your child been unusually irritable or restless since the last visit?			[participantrea ched5]='1'
form_5_follo wup_visits	othersympt oms5	Has your child had other symptoms since the last visit?			[participantrea ched5]='1'
form_5_follo wup_visits	othersympt spec5	Specify other symptoms		List all of other symptoms	[othersympto ms5] = '1'
form_5_follo wup_visits	symptomon set5	On what date did the first symptom start?		Assist caretaker with calendar to identify the date.	sum([measfeve r5], [feverish5] , [cough5], [shortbreath5] , [nasalcongest5] , [poorfeed5] , [vomiting5], [diarrhea5], [irritable5], [lethargic5],[ot hersymptoms5] , [sorethroat5]) >0
form_5_follo wup_visits	symptomon going5	Is your child still experiencing these symptoms?			sum([measfeve r5], [feverish5] , [cough5], [shortbreath5] , [nasalcongest5] , [poorfeed5] , [vomiting5], [diarrhea5], [irritable5], [lethargic5],[ot hersymptoms5] , [sorethroat5]) >0
form_5_follo wup_visits	symptomst op5	On what date did the symptoms stop?		Assist caretaker with calendar to identify the date.	[symptomongo ing5]='0'

form_5_follo wup_visits	symptomdu ration5	Symptom duration	if([symptomonset5]="" and [symptomongoing5]='0',datediff([visitdate5],[symptomonset5],"d"),if([symptomonset5]="" and [symptomongoing5]='0',datediff([symptomstop5],[symptomonset5],"d"),""))		
form_5_follo wup_visits	selfmed5	Did you give your child any medication in the last 4 hours that you had at home?			[participantreached5]='1'
form_5_follo wup_visits	panadoself med5	Panado (Panadol, calpol etc.)	0, No 1, Yes		[selfmed5]='1'
form_5_follo wup_visits	coughmixse lfmed5	Cough mixture	0, No 1, Yes		[selfmed5]='1'
form_5_follo wup_visits	brufenselfm ed5	Brufen	0, No 1, Yes		[selfmed5]='1'
form_5_follo wup_visits	otherselfme d5	Other (specify)	0, No 1, Yes		[selfmed5]='1'
form_5_follo wup_visits	otherselfme dspec5	Please specify the other medication name			[otherselfmed5]='1'
form_5_follo wup_visits	saughthealt hcare5	Did you seek medical or traditional medicine help for your child since the previous visit for these symptoms?			sum([measfever5], [feverish5], [cough5], [shortbreath5], [nasalcongest5], [poorfeed5], [vomiting5], [diarrhea5], [irritable5], [lethargic5],[othersymptoms5], [sorethroat5]) >0
form_5_follo wup_visits	traditionalh ealer5	Traditional Healer	0, No 1, Yes		[saughthealthcare5]='1'
form_5_follo wup_visits	pharmacy5	Pharmacy	0, No 1, Yes		[saughthealthcare5]='1'
form_5_follo wup_visits	privatedoct or5	Private Doctor	0, No 1, Yes		[saughthealthcare5]='1'
form_5_follo wup_visits	publicclinic5	Public Clinic	0, No 1, Yes		[saughthealthcare5]='1'
form_5_follo wup_visits	hospitalout patient5	Hospital Outpatient	0, No 1, Yes		[saughthealthcare5]='1'
form_5_follo wup_visits	otherhealth prov5	Other healthcare provider	0, No 1, Yes		[saughthealthcare5]='1'
form_5_follo wup_visits	otherhealth provisited5	Specify other healthcare provider			[otherhealthprov5] = '1'
form_5_follo wup_visits	outptmedic prescribed5	Did you receive any medicine for your child?			[saughthealthcare5]='1'
form_5_follo wup_visits	amoxycillin 5	Amoxicillin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_follo wup_visits	augumentin 5	Augmentin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_follo wup_visits	contrimoxaz ole5	Cotrimoxazole (Bactrim)	0, No 1, Yes		[outptmedicprescribed5] = '1'

form_5_followup_visits	erythromycin5	Erythromycin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	penicillin5	Penicillin G	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	ampiclox5	Ampiclox	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	ampicillin5	Ampicillin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	cefuroxime5	Cefuroxime (Zinnat)	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	metronidazole5	Metronidazole	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	clarithromycin5	Clarithromycin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	azithromycin5	Azithromycin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	panado5	Panado	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	allergex5	Allergex	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	multivit5	Multivitamin	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	coughmix5	Cough mixture	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	otherprescribed5	Other	0, No 1, Yes		[outptmedicprescribed5] = '1'
form_5_followup_visits	specifyotherprescribed5	Specify other prescribed medication		List ALL not listed above - get medication name from the containers .	[otherprescribed5] = '1'
form_5_followup_visits	hospitalsincelastvisit5	Has your child been hospitalized since the last visit?			[participantreached5]='1' or [reasonwithdrew5] = '1'
form_5_followup_visits	hospitalformcompleted5	Has Form 12 (Hospital form) been completed for this hospital stay?			[participantreached5] = '4' or [hospitalsincelastvisit5] = '1' or [hospitalizedbydying8]='1'
form_5_followup_visits	anysymptoms5	Any symptoms follow-up form	if([measfever5],"if(sum([measfever5] , [feverish5] , [cough5] , [shortbreath5] , [nasalcongest5] , [poorfeed5] , [vomiting5] , [diarrhea5] , [irritable5] , [lethargic5],[othersymptoms5] , [sorethroat5]) >0 or ([temperaturemeasure5] '44.444' and [temperaturemeasure5] >='38'),1,0),"		[participantreached5] = '1'

form_5_follo wup_visits	completefor m65	You need to complete Form 6 Specimen collection			[participantrea ched5]='1'
form_5_follo wup_visits	completefor m75	You need to complete Form 7 Hospitalization			[participantrea ched5] = '4' or [hospitalsinca stvisit5] = '1' or [hospitalizedb4 dying8]='1'
form_5_follo wup_visits	completefor m85	You need to complete Form 8 Death			[reasonwithdr ew5] = '1' or [hospitalizatio noutcome7] = '5'
form_6_speci men_collectio n	visitid6	Visit day ID		e.g. Mxxx- xxx	
form_6_speci men_collectio n	visitnr6	Visit number	right ([visitid6], 3)		[visitid6]"
form_6_speci men_collectio n	collectornas alswab6	Who is scheduled to collect the nasal swab?			[visitid6]"
form_6_speci men_collectio n	interviewer usernamef6	Interviewer			[visitid6]"
form_6_speci men_collectio n	samplecolle ctiondate6	Date of sample collection			[participantrea ched5]='1' or [fineligibilitysta tus3]="Eligible " or [collectornasal swab6]="Caret aker"
form_6_speci men_collectio n	nasalswab6	Nasal swab collected?			[participantrea ched5] = '1' or [collectornasal swab6]="Caret aker"
form_6_speci men_collectio n	nasalswabre asonnotdone6	Nasal Swab: Reason Not Collected?	1, Child or caregiver refused 2, Child left before sample could be collected 3, Nurse unable to collect specimen 4, Collected but lost before reaching NICD 5, Collected but mislabeled and discarded		[nasalswab6] = '0' and [collectornasal swab6]='Nurse '
form_6_speci men_collectio n	cgnasalswa breasonnot done6	Nasal Swab: Reason Not Collected by caregiver?	1, Child or caregiver refused 2, Collected but lost before team did the visit 3, Caregiver unable to collect specimen 4, Collected but lost before reaching NICD 5, Collected but mislabeled and discarded		[nasalswab6] = '0' and [collectornasal swab6]='Caret aker'
form_6_speci men_collectio n	clottedbloo d6	Clotted blood (SST, yellow top) collected?	0, No 1, Yes 2, Not Scheduled		[participantrea ched5]='1' or [fineligibilitysta

					tus3]="Eligible"
form_6_specimen_collection	clotbloodreasonnotdone6	Clotted Blood: Reason Not Collected?	1, Child or caregiver refused 2, Child left before sample could be collected 3, Nurse unable to collect specimen 4, Collected but lost before reaching NICD 5, Collected but mislabeled and discarded		[clottedblood6] = '0'
form_6_specimen_collection	oralfluid6	Oral Fluid collected?			[participantreached5] = '1'
form_6_specimen_collection	oralfluidreasonnotdone6	Oral Fluid: Reason Not Collected?	1, Child or caregiver refused 2, Child left before sample could be collected 3, Nurse unable to collect specimen 4, Collected but lost before reaching NICD 5, Collected but mislabeled and discarded		[oralfluid6] = '0'
form_6_specimen_collection	nasmucfluid6	Nasal mucosal fluid collected?			[participantreached5] = '1'
form_6_specimen_collection	nasmucfluidreasonnotdone6	Nasal mucosal fluid: Reason Not Collected?	1, Child or caregiver refused 2, Child left before sample could be collected 3, Nurse unable to collect specimen 4, Collected but lost before reaching NICD 5, Collected but mislabeled and discarded		[nasmucfluid6] = '0'
form_6_specimen_collection	npswab6	Nasopharyngeal swab collected?			[participantreached5] = '1'
form_6_specimen_collection	npswabreasonnotdone6	Nasopharyngeal swab: Reason Not Collected?	1, Child or caregiver refused 2, Child left before sample could be collected 3, Nurse unable to collect specimen 4, Collected but lost before reaching NICD 5, Collected but mislabeled and discarded		[npswab6] = '0'
form_6_specimen_collection	completeform76	You need to complete Form 7 Hospitalization			[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_6_specimen_collection	completeform86	You need to complete Form 8 Death			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_7_hospitalization	interviewerusernamef7	Interviewer			[admissiondate7]"

form_7_hospitalization	admissiondate7	When was your child admitted to hospital?		Review medical records to confirm date	[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	hospitaladmittedto7	Which hospital are/were your child admitted to?	1, Klerksdorp 2, Tshepong 3, Other (specify)	Choose one	[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	otheradmittedinhosp7	Specify other hospital admitted to			[hospitaladmittedto7] = '3'
form_7_hospitalization	hospitalnr7	Provide hospital number		Review medical records to obtain/verify. Capture as 'pending' if review still needs to be done, and 'unknown' if not available.	[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	admissionreason7	What was the reason for hospitalization?	1, Accident (or injury or accidental ingestion of poison) 2, Illness (any symptoms that are not an injury e.g. fever, cough, sore throat, difficulty breathing, stomach problems, headaches, stiff neck) 3, Operation 4, Other (specify)	Review medical records to obtain/verify	[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	otherspecifyadmission7	Specify the other reason for admission			[admissionreason7] = '4'
form_7_hospitalization	diagnosis7	What was the diagnosis from the hospital for your child's illness?	1, Pneumonia 2, Bronchopneumonia 3, Pleural effusion 4, Bronchiolitis 5, LRTI 6, Chest Infection 7, TB 8, Diarrhea 9, Seizures 10, Sepsis 11, Apnoea 12, UTI 13, Otitis Media 14, Tonsillitis 15, STI 16, Fluid on/around the lungs 17, Pneumothorax 18, Unknown 19, Other (specify)	Review medical records to obtain/verify	[admissionreason7] = '2'

form_7_hospitalization	otherdiagnosis7	Specify other diagnosis			[diagnosis7] = '19'
form_7_hospitalization	supoxygen7	Did your child receive supplemental oxygen while hospitalized?			[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	icu7	Was your child admitted to the intensive care unit (ICU)?			[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	hosptmedicprescribed7	Did your child receive any medicine while they were hospitalized?	1, Yes 0, No 2, Unknown		[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedb4dying8]='1'
form_7_hospitalization	hosptamoxicillin7	Amoxicillin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptaugmentin7	Augmentin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptcotrimoxazole7	Cotrimoxazole (Bactrim)	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hospterythromycin7	Erythromycin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptpenicillin7	Penicillin G	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptampiclox7	Ampiclox	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptampicillin7	Ampicillin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptcefuroxime7	Cefuroxime (Zinnat)	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptmetronidazole7	Metronidazole	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptclarithromycin7	Clarithromycin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptazithromycin7	Azithromycin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptpanado7	Panado	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptallergex7	Allergex	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptmultivit7	Multivitamin	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptcoughmix7	Cough mixture	0, No 1, Yes		[hosptmedicprescribed7] = '1'
form_7_hospitalization	hosptotherprescribed7	Other	0, No 1, Yes		[hosptmedicprescribed7] = '1'

form_7_hospitalization	hospspecificotherpresmed7	Specify other prescribed medication		List ALL not listed above - get medication name from the containers	[hosptotherprescrbmedic7] = '1'
form_7_hospitalization	measfever7	Did your child have a measured fever higher than 38C before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	feverish7	Did your child feel feverish or have chills before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	cough7	Did your child have a cough before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	shortbreath7	Did your child appear to be short of breath or have difficulty breathing (chest moving in when he/she breaths) before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	sorethroat7	Did your child appear to have a sore throat i.e. indicated or appeared to have reluctance to swallow before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	nasalcongest7	Did your child have a blocked or runny nose before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	vomiting7	Had your child been vomiting before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	diarrhea7	Did your child have diarrhoea (3 or more loose stools in 24 hours) before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	lethargic7	Were your child lethargic (no energy, reluctant to move, lying rather than sitting/walking, lazy or not sucking) before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	poorfeed7	Did your child refuse to eat before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	irritable7	Were your child unusually irritable or restless before or during hospitalization?			[admissionreason7] = '2'
form_7_hospitalization	othersymptoms7	Did your child have other symptoms before or during hospitalization?			[admissionreason7] = '2'

form_7_hospitalization	othersymptspec7	Specify other symptoms		List all of other symptoms	[othersymptoms7] = '1'
form_7_hospitalization	symptomonset7	On what date did the first symptom start?		Assist participant with calendar to identify the date. If exact date not known, ask how many weeks ago, and select the Monday of that week	sum([measfever7], [feverish7], [cough7], [shortbreath7], [nasalcongest7], [poorfeed7], [vomiting7], [diarrhea7], [irritable7], [lethargic7],[othersymptoms7], [sorethroat7]) >0
form_7_hospitalization	symptomongoing7	Is your child still experiencing these symptoms?			sum([measfever7], [feverish7], [cough7], [shortbreath7], [nasalcongest7], [poorfeed7], [vomiting7], [diarrhea7], [irritable7], [lethargic7],[othersymptoms7], [sorethroat7]) >0
form_7_hospitalization	symptomstop7	On what date did the symptoms stop?		Assist participant with calendar to identify the date. If exact date not known, ask how many weeks ago, and select the Monday of that week	[symptomongoing7]='0'
form_7_hospitalization	symptomduration7	Symptom duration	if([symptomonset7]="" and [symptomongoing7]='0',datediff([visitdate5],[symptomonset7],"d"),if([symptomonset7]="" and [symptomongoing7]='0',dat		[symptomongoing7]='0'

			ediff([symptomstop7],[symp tomonset7,"d"],"")		
form_7_hospi talization	saughthealth hcare7	Did you seek medical or traditional medicine help for your child before they were hospitalized?			sum([measfeve r7] , [feverish7] , [cough7] , [shortbreath7] , [nasalcongest7] , [poorfeed7] , [vomiting7] , [diarrhea7] , [irritable7] , [lethargic7],[ot hersymptoms7], [sorethroat7]) >0
form_7_hospi talization	traditionalh ealer7	Traditional Healer	0, No 1, Yes		[saughthealthc are7]='1'
form_7_hospi talization	pharmacy7	Pharmacy	0, No 1, Yes		[saughthealthc are7]='1'
form_7_hospi talization	privatedoct or7	Private Doctor	0, No 1, Yes		[saughthealthc are7]='1'
form_7_hospi talization	publicclinic7	Public Clinic	0, No 1, Yes		[saughthealthc are7]='1'
form_7_hospi talization	hospitalout patient7	Hospital Outpatient	0, No 1, Yes		[saughthealthc are7]='1'
form_7_hospi talization	otherhealth prov7	Other healthcare provider	0, No 1, Yes		[saughthealthc are7]='1'
form_7_hospi talization	otherhealth provvisited7	Specify other healthcare provider			[otherhealthpr ov7] = '1'
form_7_hospi talization	outptmedic prescribed7	Did you receive any medicine for your child?			[saughthealthc are7] = '1'
form_7_hospi talization	amoxicillin 7	Amoxicillin	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	augmentin 7	Augmentin	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	contrimoxaz ole7	Cotrimoxazole (Bactrim)	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	erythromyci n7	Erythromycin	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	penicillin7	Penicillin G	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	ampiclox7	Ampiclox	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	ampicillin7	Ampicillin	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	cefuroxime 7	Cefuroxime (Zinnat)	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	metronidaz ole7	Metronidazole	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	clarithromy cin7	Clarithromycin	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	azithromyci n7	Azithromycin	0, No 1, Yes		[outptmedicpr escribed7] = '1'
form_7_hospi talization	panado7	Panado	0, No 1, Yes		[outptmedicpr escribed7] = '1'

form_7_hospitalization	allergex7	Allergex	0, No 1, Yes		[outptmedicprescribed7] = '1'
form_7_hospitalization	multivit7	Multivitamin	0, No 1, Yes		[outptmedicprescribed7] = '1'
form_7_hospitalization	coughmix7	Cough mixture	0, No 1, Yes		[outptmedicprescribed7] = '1'
form_7_hospitalization	otherprescribed7	Other	0, No 1, Yes		[outptmedicprescribed7] = '1'
form_7_hospitalization	specifyotherprescribed7	Specify other prescribed medication		List ALL not listed above - get medication name from the containers	[otherprescribed7] = '1'
form_7_hospitalization	hospitalizationoutcome7	What was the outcome of the hospitalization?	1, Discharge 2, Referred to step-down facility 3, Transferred to other facility 4, Still admitted in the same hospital 5, Died		[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedbydying8]='1'
form_7_hospitalization	datehospitaloutcome7	Date of hospital outcome		Review medical records to obtain date. If still admitted, select date form completed.	[participantreached5] = '4' or [hospitalsinceastvisit5] = '1' or [hospitalizedbydying8]='1'
form_7_hospitalization	transferfacility7	Name of step-down/transfer facility			[hospitalizationoutcome7]='2' or [hospitalizationoutcome7]='3'
form_7_hospitalization	anysymptoms7	Any symptoms hospitalization form	if([measfever7],"if(sum([measfever7], [feverish7], [cough7], [shortbreath7], [nasalcongest7], [poorfeed7], [vomiting7], [diarrhea7], [irritable7], [lethargic7],[othersymptoms7], [sorethroat7]) >0,1,0),"")		[admissiondate7] "
form_7_hospitalization	hospfinaldiagnosis7	Final diagnosis			
form_7_hospitalization	hospsaereceived7	Was SAE form received?		Severe adverse events	
form_7_hospitalization	hosprespill7	Was this related to respiratory illness			
form_7_hospitalization	hosprelpcrpos7	Related to PCR positive for study pathogen?			

form_7_hospitalization	completeform87	You need to complete Form 8 Death			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	interviewerusernamef8	Interviewer			[deathdate8]"
form_8_death	deathdate8	When did the child die?			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	causeofdeath8	What was the cause of death?	1, Accident (or injury or accidental ingestion of poison) 2, Illness (any symptoms that are not an injury e.g. fever, cough, sore throat, difficulty breathing, stomach problems, headaches, stiff neck) 3, Operation 4, Other (specify)		[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	otherspecifydeath8	Specify the other cause of death			[causeofdeath8] = '6'
form_8_death	deathplace8	Where did the child die?	1, Hospital 2, Home 3, Other(specify)		[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	otherdeathplace8	Specify the other place of death			[deathplace8] = '3'
form_8_death	measfever8	Did your child have a measured fever higher than 38C before they died?			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	feverish8	Did your child feel feverish or have chills before they died?			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	cough8	Did your child have a cough before they died?			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	shortbreath8	Did your child appear to be short of breath or have difficulty breathing (chest moving in when he/she breaths) before they died?			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	sorethroat8	Did your child appear to have a sore throat i.e. indicated or appeared to have reluctance to swallow before they died?			[reasonwithdraw5] = '1' or [hospitalizationoutcome7] = '5'

form_8_death	nasalcongest8	Did your child have a blocked or runny nose before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	vomiting8	Had your child been vomiting before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	diarrhea8	Did your child have diarrhoea (3 or more loose stools in 24 hours) before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	lethargic8	Were your child lethargic (no energy, reluctant to move, lying rather than sitting/walking, lazy or not sucking) before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	poorfeed8	Did your child refuse to eat before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	irritable8	Were your child unusually irritable or restless before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	othersymptoms8	Did your child have other symptoms before they died?			[reasonwithdrew5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	othersymptspec8	Specify other symptoms		List all of other symptoms	[othersymptoms8] = '1'
form_8_death	symptomonset8	On what date did the first symptom start?		Assist participant with calendar to identify the date. If exact date not known, ask how many weeks ago, and select the Monday of that week	sum([measfever8], [feverish8], [cough8], [shortbreath8], [nasalcongest8], [poorfeed8], [vomiting8], [diarrhea8], [irritable8], [lethargic8],[othersymptoms8], [sorethroat8]) >0
form_8_death	saughthealthcare8	Did you seek medical or traditional medicine help for your child before they died?			sum([measfever8], [feverish8], [cough8],

					[shortbreath8], [nasalcongest8], [poorfeed8], [vomiting8], [diarrhea8], [irritable8], [lethargic8],[othersymptoms8], [sorethroat8]) >0
form_8_death	traditionalhealer8	Traditional Healer	0, No 1, Yes		[saughthealthcare8]='1'
form_8_death	pharmacy8	Pharmacy	0, No 1, Yes		[saughthealthcare8]='1'
form_8_death	privatedoctor8	Private Doctor	0, No 1, Yes		[saughthealthcare8]='1'
form_8_death	publicclinic8	Public Clinic	0, No 1, Yes		[saughthealthcare8]='1'
form_8_death	hospitaloutpatient8	Hospital Outpatient	0, No 1, Yes		[saughthealthcare8]='1'
form_8_death	otherhealthprov8	Other healthcare provider	0, No 1, Yes		[saughthealthcare8]='1'
form_8_death	otherhealthprovvisited8	Specify other healthcare provider			[otherhealthprov8] = '1'
form_8_death	outptmedicprescribed8	Did you receive any medicine for your child?			[saughthealthcare8] = '1'
form_8_death	amoxicillin8	Amoxicillin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	augmentin8	Augmentin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	cotrimoxazole8	Cotrimoxazole (Bactrim)	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	erythromycin8	Erythromycin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	penicillin8	Penicillin G	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	ampiclox8	Ampiclox	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	ampicillin8	Ampicillin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	cefuroxime8	Cefuroxime (Zinnat)	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	metronidazole8	Metronidazole	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	clarithromycin8	Clarithromycin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	azithromycin8	Azithromycin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	panado8	Panado	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	allergex8	Allergex	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	multivit8	Multivitamin	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	coughmix8	Cough mixture	0, No 1, Yes		[outptmedicprescribed8] = '1'

form_8_death	otherprescribedmedic8	Other	0, No 1, Yes		[outptmedicprescribed8] = '1'
form_8_death	specifyotherprescribedmed8	Specify other prescribed medication		List ALL not listed above - get medication name from the containers .	[otherprescribedmedic8] = '1'
form_8_death	hospitalizedbefore4dying8	Was your child hospitalized before dying?			[reasonwithdrawn5] = '1' or [hospitalizationoutcome7] = '5'
form_8_death	anysymptoms8	Any symptoms death form	if([measfever8],if(sum([measfever8], [feverish8], [cough8], [shortbreath8], [nasalcongest8], [poorfeed8], [vomiting8], [diarrhea8], [irritable8], [lethargic8],[othersymptoms8], [sorethroat8]) >0 ,1,0),"")		[deathdate8] "
form_8_death	completeform78	You need to complete Form 12: Hospitalization form			[participantreached5] = '4' or [hospitalsincelastvisit5] = '1' or [hospitalizedbefore4dying8]='1'
form_9_sd_participant_details	record_id	Record ID			
form_9_sd_participant_details	enrolled	Enrolled			
form_9_sd_participant_details	withdrawn	Withdrawn			
form_9_sd_participant_details	first_visit_date	Date of first follow-up visit			
form_9_sd_participant_details	studyid	Study ID			
form_9_sd_participant_details	email	Email address			
form_10_symptom_diary	studyidsd	Study ID			
form_10_symptom_diary	datecompleted	Date and time completed			
form_10_symptom_diary	measured_temperature	Measure your child's body temperature		In degrees Celsius	
form_10_symptom_diary	fever	Has your child felt feverish or had chills in the last 24 hours?			

from_10_symptom_diary	cough	Has your child had a cough in the last 24 hours?			
from_10_symptom_diary	short_diff_breath	Has your child appeared to be short of breath or difficulty breathing (chest moving in when he/she breaths) in the last 24 hours?			
from_10_symptom_diary	sore_throat	Has your child appeared to have a sore throat in the last 24 hours i.e. indicated or appeared to have reluctance to swallow?			
from_10_symptom_diary	block_run_nose	Has your child had a blocked or runny nose in the last 24 hours?			
from_10_symptom_diary	vomit	Has your child vomited in the last 24 hours?			
from_10_symptom_diary	diarrhea	Has your child had diarrhoea (three or more loose stools in 24 hours) in the last 24 hours?			
from_10_symptom_diary	lethargic	Has your child been lethargic (no energy, reluctant to move, lying rather than sitting/walking, lazy sucking or not sucking) in the last 24 hours?			
from_10_symptom_diary	refuse_eat	Has your child refused to eat in the last 24 hours?			
from_10_symptom_diary	irritable	Has your child been unusually irritable or restless in the last 24 hours?			
from_10_symptom_diary	med_4h	Did you give your child any medication that you had at home in the last 4 hours?			
from_10_symptom_diary	med_4h_specify	What medication did you give your child? Select all that apply	1, Panado (Panadol, calpol etc) 2, Cough mixture 3, Brufen 99, Other		[med_4h] = '1'
from_10_symptom_diary	med_4h_specify_other	Please specify the other medication provided			[med_4h_specify(99)] = '1'
from_10_symptom_diary	nscollected	Did you collected a nasal swab from your child today?		Only one swab collected on Saturday OR Sunday	
from_10_symptom_diary	nsstudyid	Please enter the sample ID		(label on the sample e.g. M001-001)	[nscollected] = '1'
from_10_symptom_diary	comments	Is there anything else you would like to say about your child's health in the last 24 hours?			

from_10_symptom_diary	manual_capture	Manual capture			
from_10_symptom_diary	reason_manual_capture	Reason for manual capture	1, No device or device issues 2, System Down		
from_10_symptom_diary	manual_capture_form	Diary submitted via	1, Paper 2, E-mail		