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Survival and health of children who are HIV-exposed uninfected: study protocol for the CHERISH (Children HIV-Exposed Uninfected - Research to Inform Survival and Health) dynamic, prospective, maternal-child cohort study

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ABSTRACT

Introduction CHERISH is designed to establish a long-term sustainable system for measurement of in utero and postnatal exposures and outcomes in children who are HIV-exposed uninfected (HEU) and HIV-unexposed to compare survival, hospitalisation, growth and neurodevelopment in the Western Cape, South Africa.

Methods and analysis During 2022–2025, the CHERISH dynamic cohort is prospectively enrolling pregnant people with and without HIV at 24–36 weeks gestation from one urban and one rural community, following mother–child pairs, including children who are HEU (target N=1200) and HIV-unexposed (target N=600) for 3 years from the child’s birth. In-person visits occur at enrolment, delivery, 12 months, 24 months and 36 months with intervening 3-monthly telephone data collection. Children and mothers without HIV are tested for HIV at all in-person visits. Data on exposures and outcomes are collected from routine standardised healthcare documentation, maternal interview, measurement (growth and neurodevelopment) at in-person visits and linkage to the Western Cape Provincial Health Data Centre (survival and hospitalisation). A priori adverse birth outcomes, advanced maternal HIV and maternal mental health are considered potential mediators of outcome disparities in children who are HEU and will be evaluated as such in multivariable models appropriate for each outcome.

Ethics and dissemination Mothers interested in joining the study are taken through a visual informed consent document for their and their child’s participation, with the option to consent to anonymised de-identified data being contributed to a public data repository. All data is captured directly into an electronic database using alphanumeric identifiers devoid of identifying information. The cohort study is approved by Human Research Ethics Committees of Stellenbosch University (N20/08/084), University of Cape Town (723/2021) and Western Cape Government (WC_2021_09_007). Findings will be shared with participants, participating communities, local and provincial stakeholders, child health clinicians, researchers and policymakers at local, national and international forums and submitted for publication in peer-reviewed journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a contemporary prospective maternal-child cohort study with antenatal enrolment of mothers with and without HIV and follow-up of mother–child pairs, including children who are HIV-exposed (n=1200) and HIV-unexposed (n=600) to age 3 years.⇒ This study is set in two geographical locations, one urban and one rural, in a high HIV prevalence, resource-restricted setting providing good generalisability to many high HIV prevalence contexts.⇒ The large sample of children who are HIV-exposed uninfected allows for examination of subgroups at risk of adverse child outcomes according to the maternal HIV characteristics or birth outcomes.⇒ Linkage with the Western Cape Provincial Health Data Centre facilitates ascertainment of comprehensive maternal HIV status longitudinally and other comorbidity history as well as resource-efficient longitudinal follow-up of survival and hospitalisation outcomes in mothers and children.⇒ A limitation of the cohort is that, besides maternal and child HIV-testing, no study-specific biological or other diagnostic procedures are performed; however, clinically meaningful outcomes are being measured (survival, hospitalisation, growth and neurodevelopment) with good power to assess differences by HIV exposure status.


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INTRODUCTION

Annually, global UNAIDS (Joint United Nations Programme on HIV and AIDS) estimates report the population of pregnant people with HIV (PPHIV) to be 1.3 million, of which 1.1 million receive antiretroviral drugs for their own health and for prevention of vertical (perinatal and postnatal) HIV transmission. Worldwide in 2021 there were 15.9 million children (0–14 years) who were born to a mother with HIV, but had not acquired HIV themselves, that is, HIV-exposed but HIV-uninfected (HEU). In South Africa, with a public sector antenatal HIV prevalence of 29% since 2009, at least 25% of all children are HEU and South Africa is also home to 25% of the global population of children who are HEU.1 2

Maternal antiretroviral therapy (ART), essential for maternal health, has driven a remarkable reduction in vertical HIV transmission in South Africa, now occurring in less than 3% of the children born to PPHIV. By 2021, 96% of the South African PPHIV received ART.3 As a result, most of the 300,000 South African infants born annually to PPHIV are exposed in utero to both HIV, a chronic viral infection, and multiple antiretroviral drugs.4 4 No other condition has this extent of in utero exposure to either a pathogen or its treatment either in southern Africa or globally.5

Children who are HEU, despite avoiding vertical HIV acquisition, experience higher risk of suboptimal health outcomes including higher rates and more severe infant infectious morbidity, poorer early childhood survival and more frequent occurrence of stunted growth and neurodevelopment compared with children born without HIV exposure.6–8 Systematic reviews and meta-analyses of studies prior to the universal ART era demonstrated a 70%–90% increased risk for infant mortality in children who are HEU compared with those HIV-unexposed and HIV-uninfected (HUU).7,10 Recent studies in the context of universal ART and safer sustained breastfeeding have reported a similar size increase in mortality risk, particularly in the first 2–3 months of life, for children who are HEU compared with HUU.11 12 Infants who are HEU are also susceptible to starting life preterm or small-for-gestational-age (SGA) and children who are HEU born preterm or SGA are a subgroup with greater vulnerability for poor postnatal growth and neurodevelopment, even compared with their SGA or preterm HUU peers.13–17

Considering the size of the population of children who are HEU in southern Africa, it is essential to understand at a population level whether these children are surviving and thriving as well as children who are HUU. Small laboratory-based studies have identified several immunological and metabolic changes among children who are HEU, however in the absence of correlation with clinical outcomes the clinical significance of these findings is uncertain.18–20 The multifactorial aetiology driving potential outcome disparities in children who are HEU has been challenging to disentangle in studies to date, seldom adequately powered to allow for identification of potential causal pathways or subgroups of children at higher risk of adverse outcomes to inform prioritisation of groups or mechanisms for future study and intervention.8 21

Despite one in four South African children being HEU, there are no sustainable systems to evaluate the long-term outcomes of children exposed in utero to HIV and antiretrovirals. The CHERISH study aims to establish and optimise sustainable measurement of key in utero and postnatal exposures and outcomes in children who are HEU and HUU to compare their survival, hospitalisation, growth, and neurodevelopment in the Western Cape province of South Africa. This will be done at a population level leveraging province-wide routinely collected data curated by the Western Cape Provincial Health Data Centre (WCPHDC), the general cohort profile of which is described by Boulle et al22 and will not be described here, and at an individual level in the newly enrolled CHERISH dynamic cohort, which is the focus of this manuscript.

METHODS AND ANALYSIS

Objectives and hypotheses

This prospective cohort study is designed primarily to compare infant (under-1 year) and under-3 year survival (objective 1), all-cause and infectious-cause hospitalisation (objective 2) and growth and neurodevelopment (objective 3), in children who are HEU compared with HUU. Secondarily, we aim to identify factors that mediate the effects of HIV and antiretroviral exposure on these outcomes. We hypothesise that children who are HEU compared with HUU have lower infant and under-3-year survival, higher prevalence of >1 all-cause and >1 infectious-cause hospitalisation and poorer linear growth and neurodevelopmental outcomes in the first 3 years of life. Furthermore, we hypothesise that identifiable factors amenable to intervention will mediate a substantial proportion of the effects of HIV and antiretroviral exposure on these outcomes.

Study sites and populations

Western Cape is one of nine provinces in South Africa, with a population of ±6.8 million. Western Cape Government Health serves ±75% of the population including ±110,000 pregnant people annually, accounting for ±90,000 births. The Western Cape antenatal HIV prevalence is 19% and vertical HIV transmission in the province is ±2%–3% at 18 months of age.23 The first-line adult ART regimen, including for PPHIV, changed in 2021 from efavirenz/emtricitabine/tenofovir disoproxil fumarate, to dolutegravir/emtricitabine/tenofovir disoproxil fumarate, following WHO and South African National guideline updates.24 The CHERISH dynamic cohort is located in two communities, Gugulethu, an urban community in the City of Cape Town, and the Breede Valley, a rural agricultural community approximately 120 km from Cape Town. Gugulethu has an antenatal HIV prevalence of 29% and is served by the Gugulethu Midwife Obstetric Unit (MOU), providing primary level care.
Antenatal care (ANC) and delivery services to ±5500 pregnant people annually, with secondary and tertiary level care provided by Mowbray Maternity and Groote Schuur Hospitals in Cape Town, respectively. The Breede Valley has an antenatal HIV prevalence of 15% with ±3700 pregnant people annually receiving ANC services at seven primary healthcare clinics. Labour and delivery services are provided at the Worcester MOU (primary), Worcester Hospital (secondary) and Tygerberg Hospital (tertiary, in Cape Town) (figure 1).

Eligibility criteria
All pregnant people, with or without HIV, presenting at Gugulethu and Breede Valley antenatal clinics are eligible for inclusion if between 24 and 36 weeks gestation, as estimated by routine care ultrasounds or last menstrual period. Pregnant adolescents under age 18 years are eligible if (1) accompanied by a parent or legal guardian who can provide consent for their participation and (2) if the adolescent provides assent to participate. Pregnant people without known HIV status are not eligible.

Recruitment and retention
The cohort commenced enrolment of pregnant people, between 24 and 36 weeks gestation, with and without HIV, from the Gugulethu and Breede Valley antenatal clinics in the first quarter of 2022. Due to the heterogeneity of PPHIV, including type of ART regimens used, timing of initiation (preconception or during pregnancy) and duration on ART, we aim to enrol twice as many PPHIV than pregnant people without HIV (2:1), but no less than equal numbers in each group, to provide sufficient power for subgroup analyses within the group of PPHIV. By the end of 2025 we aim to enrol a total of 1200 children who HEU and 600 children who are HUU, with equal numbers from each site. Participants are consented for 3-monthly telephonic follow-up, child hospitalisation record review and in-person visits at 12, 24 and 36 months.

Pregnant people attending routine antenatal clinic visits are approached in the clinic waiting areas by research assistants supported by a senior research nurse. Should someone show interest in enrolling, further discussion, review of documented HIV status and informed consent takes place in a private setting at the clinical research sites.
near the antenatal clinics. Study retention is facilitated by collecting detailed contact information including telephone numbers, home addresses (with longitude/latitude coordinates) and additional contact details of close family and friends. Explicit consent is requested to contact participants on the provided telephone numbers and at the home address if not reached by telephone. A grocery voucher valued at ZAR30 (±US$2) is transmitted to the participant’s cell phone after completion of the telephonic data collection. For in-person visits, participants are remunerated for time lost on income-generating activities (ZAR300 (±US$20)/visit) and transportation is either provided or costs remunerated to attend study visits.

Study procedures

Data sources

In-person visits and telephonic interviews

Figure 2 summarises the schedule of data collection. At antenatal enrolment, research assistants conduct in-person interviews, collecting general, obstetrical and mental health data from the participant, as well as HIV-specific information from PPHIV. As soon as possible after birth, a telephonic visit (Gugulethu) or home-visit (Breede Valley) is conducted to confirm each mother’s informed-consent for participation of the infant and collection of birth information from the standardised Road to Health Booklet (RTHB). Following birth, 3-monthly telephonic interviews are conducted with maternal data collection staggered 6-monthly (at 3, 9, 15, 21, 27, 33 months) on general and mental health, and child data collected on general health (3-monthly), infant feeding and developmental milestones (6-monthly). Hospitalisation or mortality is ascertained through 3-monthly telephonic interviews and linkage to the WCPHDC (see paragraph “Linkage to provincial health data”). Care is taken by the research assistants conducting telephonic interviews to ensure that the participant is in a suitable environment where they feel comfortable to answer the interview questions particularly related to sensitive personal information. In-person visits at 12, 24 and 36 months collect all child data as for the 3-monthly telephone interviews, but also include measurement of growth parameters, the Developmental Screening Questionnaire, RTHB immunisation record review and HIV rapid testing on all children and all mothers not known to have HIV. At 36 months, detailed neurodevelopmental assessments will be conducted. All telephonic and in-person data collection is completed in one of the dominant local languages (Afrikaans, isiXhosa or English) of the mother’s choice. There are no study specific laboratory or other diagnostic procedures performed, nor storage of biological samples.
Linkage to provincial health data

The WCPHDC is a province-wide patient-level health information exchange that integrates data from electronic laboratory, pharmacy, administrative, community and disease-specific (e.g., HIV and tuberculosis registers) sources, daily. Individual-level data are linked using a unique numeric identifier and maternal and child unique identifiers are linked at child’s birth. Multiple types of evidence are used to define common health episodes such as pregnancy or HIV, which are available in the form of care cascades used to support service delivery, as well as for health system intelligence. The relevant provincial databases contributing to the WCPHDC are shown in the supplementary material of the WCPHDC. The scope and scale of the WCPHDC makes this a powerful clinical, management and epidemiological tool and is integral to achieving the CHERISH objectives. A dedicated CHERISH analyst is provided to the WCPHDC to optimise the algorithms identifying the occurrence of pregnancy, maternal and child HIV, mortality and hospitalisations. In addition to data collected in-person and by telephone, the study routinely links electronic data collected in the WCPHDC to the CHERISH dynamic cohort participants via their unique identifier, particularly maternal and child HIV testing results, maternal antiretrovirals and other medications dispensed, occurrences of maternal or child mortality and hospitalisations.

Variables

Exposure variables

The primary exposure variable for all objectives is in utero HIV exposure, with children classified as HEU or HUU according to maternal HIV testing to identify HIV exposure and child HIV testing to exclude HIV acquisition. Children HIV-exposed or HIV-unexposed, without evidence of HIV, are classified as HEU and HUU respectively according to DECIPHER levels of certainty of in utero HIV exposure. As part of standard care in the Western Cape, those not known to have HIV are tested for HIV at the first antenatal care visit, 36 weeks gestation and delivery. Infants known to be HIV-exposed have routine birth, 10-week and 6-month HIV PCR testing with additional testing 6 weeks after cessation of breast feeding and universal HIV serological testing at 18 months. Maternal report of HIV diagnosis date, ART history and ART adherence are supplemented by HIV and ART data collected from multiple sources within the WCPHDC including HIV diagnosis date, repeated CD4 and HIV viral load measurements, ART start with longitudinal data on regimens and dates dispensed. This allows for further classification of in utero antiretroviral exposure according to DECIPHER levels of certainty for children who are HEU.

Similarly, maternal report of tuberculosis and syphilis diagnosis and treatment, as well as non-communicable diseases (chronic hypertension, hypertensive disorders of pregnancy, diabetes, gestational diabetes, epilepsy and mental health conditions) is supplemented by International Classification of Diseases (ICD)-10/11 and pharmacy dispensing data from the WCPHDC. Tobacco dependence (Fagerström questionnaire), alcohol use (Alcohol Use Disorders Identification Test, or AUDIT), drug use (Drug Use Disorders Identification Test, or DUDIT), socioeconomic factors, food security and maternal mental health screening (Self-Reporting Questionnaire ~ 20 Item (SRQ-20) and Edinburgh Postnatal Depression Scale (EPDS)) are administered at antenatal enrolment and during follow-up telephonic interviews. The AUDIT, DUDIT, SRQ-20 and EPDS have all been validated in South Africa.

Outcome variables

Maternal and child mortality data (date and ICD-10/11 code for cause of death) are available from the WCPHDC. For any out-of-hospital mortality reported to the study team, and for which there was no forensic evaluation, the WHO 2016 Verbal Autopsy is performed with software to interpret cause of death. Hospitalisation events including admission and discharge date and ICD-10/11 discharge codes are available province-wide from the WCPHDC for all hospitalisation events. The primary growth variable of interest is WHO height-for-age Z-score (HAZ) at age 3 years as a continuous measure as well as categorised for stunting (HAZ<-2). Weight-for-age, weight-for-length and head-circumference for age Z-scores will also be evaluated. The neurodevelopmental assessment battery to be conducted at age 3 years is currently being finalised and will include the WHO Global Scales on Early Development (GSED).

Data storage

Study data are collected and managed using REDCap electronic data capture tools hosted at Stellenbosch University. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support
data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources. Back-up copies of data sets are extracted every 3 months from REDCap and stored on Stellenbosch University OneDrive. The Data Coordinator manages REDCap data access. Research staff entering data into REDCap during interviews are granted permission only for data entry. Only the Data Coordinator and Principal Investigator have permission to view or edit data after data entry and to extract data sets for analysis. The study Statistician has permission to view the database during development to advise on database structure and will only receive anonymised de-identified data sets at the time of analysis. Informed consent forms are the only paper data records and are securely filed in a lockable cabinet in locked storage rooms at both sites.

**Analytic approach**

**Analytic frameworks to evaluate multiple causal pathways**

Measures such as adverse pregnancy outcomes (including preterm birth or SGA), measures of maternal disease (CD4 count and HIV viral load) and maternal mental health have traditionally been considered confounders to the relationship between HIV exposure and child outcomes and have been adjusted for in multivariable analyses. A priori we consider preterm birth, SGA, advanced maternal HIV and maternal mental health vulnerability as important pathways to survival, hospitalisation, growth and neuro-developmental disparities in children who are HEU and will evaluate these as potential mediators and not confounders (figure 3).

**Analyses**

**Objective 1—survival outcomes**

Mortality is a rare outcome and will primarily be evaluated in the CHERISH province-wide cohort in the population of 500,000 children born in 2018–2024 using a non-inferiority approach. The CHERISH dynamic cohort, described here, is underpowered to evaluate survival differences but will be used to evaluate consistency with or differences in survival trends seen in the province-wide cohort in two different communities, as well as to interrogate potential associations with variables not universally measured in the province-wide cohort including preterm birth, SGA, maternal mental health, maternal smoking, alcohol and drug use.

**Objective 2—hospitalisation outcomes**

For hospitalisation outcomes, we will calculate prevalence ratios and their 95% CIs for >1 hospitalisation (all-cause and infectious cause separately) for two intervals, infancy (up to 12 months of life) and again up to 3 years of life. These prevalence ratios will be calculated using log-binomial regression, or alternatively with Poisson regression models with robust variance if the log-binomial regression models do not converge.37 A priori confounders of the relationship between HIV exposure and hospitalisation will be adjusted for in analyses (figure 3). Secondarily, we will explore causal effects of HIV exposure on all-cause hospitalisation and infectious-cause hospitalisation in infancy and under-3 years using the doubly-robust Targeted Maximum Likelihood Estimation method.38 Mediators of the relationship between HIV-exposure and hospitalisation to be considered include preterm birth, SGA and maternal pregnancy HIV viraemia (where data available). We will quantify, through mediation analysis, the proportion of the HIV exposure effect on these outcomes mediated by the factors listed above and whether there is a clinically meaningful hospitalisation difference between children who are HEU and HUU.39 We will...
compare the distributions of time to first hospitalisation for infant and under-3 years of age hospitalisations using Kaplan-Meier survival probability estimates and adjusted Cox proportional hazards models. Similar approaches will be employed to evaluate antiretroviral exposure and hospitalisation among children who are HEU.

Objective 3—growth and neurodevelopmental outcomes
For the primary growth outcome of HAZ at age 3 years, the mean difference and 95% CI between children who are HEU and HUU will be calculated and multivariable linear regression models will be used to adjust for confounders. To compare the prevalence of stunting, log-binomial regression with adjusted analyses considering important a priori confounders (figure 3) will be used to calculate prevalence ratios and their 95% CIs. Secondarily, we will explore causal effects of HIV exposure on growth and neurodevelopment as described for hospitalisation. In addition to the potential mediating factors described for the hospitalisation outcomes, antenatal and postnatal maternal mental health measures will be considered as additional potential mediators to the relationship between HIV-exposure and growth or neurodevelopment. Similar approaches will be employed to evaluate antiretroviral exposure in relation to growth and neurodevelopment among children who are HEU.

Study power
The effect sizes that can be measured at a power of 80% (beta=0.2) and significance level alpha=0.05 for the primary outcomes of mortality, hospitalisation and growth at the anticipated sample sizes with a ratio of 2:1 children who are HEU:HUU are indicated in table 1.

Participant and public involvement
Through a regular forum of the Worcester Community Advisory Board and researchers in the Breede Valley, the Worcester Community Advisory Board gave input on implementation of the study prior to commencement. Prior to commencing enrolment, community antenatal group leaders were engaged with to understand maternal wishes for study participation and information dissemination. Two focus groups were held with 20 of the first mothers enrolled to understand their experience with the visual informed consent process, their satisfaction in engaging with the study staff, as well as the burden of the study visits. Their suggestions were solicited relative to approaches to support study retention and preferences for dissemination of study findings to participants.

ETHICS AND DISSEMINATION

Ethics board approvals
The CHERISH dynamic cohorts are approved by the Human Research Ethics Committees (HREC) of Stellenbosch University for the Breede Valley site (N20/08/084) and University of Cape Town (UCT) for the Gugulethu site (723/2021). The CHERISH dynamic cohorts have approval from the Western Cape Government Health Research Committee to access participants at the Gugulethu and Breede Valley antenatal clinics and to receive anonymised de-identified data on cohort participants from the WCPHDC (WC_2021_09_007).

Informed consent
Pregnant people sign a visual informed consent document in the language of their choice (Afrikaans, isiXhosa or English) for their and their child’s participation. The novel visual informed consent document has been developed from the originally HREC approved full-text informed consent form and includes all the same elements as the text form but in a visual format with simplified language. The contents of the informed consent are verbally reviewed with the participant by a study team member. Participants are given the option to consent or decline to their and their child’s anonymised and de-identified data being contributed to a public data repository.

Potential risks
Breach of confidentiality is a risk for participants, as study staff have access to maternal and child HIV status and other sensitive maternal mental health and substance use

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Detectable effect sizes for primary outcomes at anticipated analytical sample sizes, 2:1 children who are HEU:HUU, a power of 80% (beta=0.2) and alpha=0.05 (calculated using OpenEpi software)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td><strong>Detectable effect size HEU:HUU</strong></td>
</tr>
<tr>
<td>Infant</td>
<td>1800</td>
</tr>
<tr>
<td>Under-3 years</td>
<td>900</td>
</tr>
<tr>
<td><strong>Hospitalisation</strong></td>
<td><strong>Detectable effect size HEU:HUU</strong></td>
</tr>
<tr>
<td>Infant all-cause</td>
<td>1800</td>
</tr>
<tr>
<td>Under-3 years all-cause</td>
<td>900</td>
</tr>
<tr>
<td>Infant infectious-cause</td>
<td>1800</td>
</tr>
<tr>
<td>Under-3 years infectious-cause</td>
<td>900</td>
</tr>
<tr>
<td><strong>Growth</strong></td>
<td><strong>Detectable effect size HEU:HUU</strong></td>
</tr>
<tr>
<td>Height-for-age Z-score at 3 years</td>
<td>900</td>
</tr>
<tr>
<td>Stunting at 3 years</td>
<td>900</td>
</tr>
</tbody>
</table>

HEU, HIV-exposed uninfected; HUU, HIV-exposed and HIV-uninfected.
information. All participants are given unique identification numbers used in all databases and all study documentation without any other personal identifying information. Identifying information for contact purposes is kept separate from other documentation in locked filing cabinets in a dedicated confidential research records room at each site that is only accessible to the Study Coordinators and Principal Investigators. All data is collected directly into the REDCap database and identified by the unique participant identifier only without the need for paper case report forms. These procedures are compliant with the South African Protection of Personal Information Act 4 of 2013. REDCap at Stellenbosch University resides on firewall protected servers, with registration and dual authentication procedures via University log-in and Google Authenticator required for access. All study staff who work with human subjects undergo human subjects’ protection training, training in maintaining confidentiality with standard operating procedures specific to this topic and sign confidentiality agreements as part of their conditions of employment. The risk of HIV-associated stigma is minor as people with and without HIV are included and the study sites are neutral locations not linked to any specific HIV care services.

Benefits
There are no immediate direct benefits to the subjects involved. However, study findings have the potential to influence policies or practices both locally and more broadly for mothers with and without HIV and their children in the future. The knowledge to be gained in this study is aligned with the Sustainable Development Goals and the South African National Governments priority to reduce maternal and child mortality and improve health of all mothers and children.

Dissemination
Two knowledge translation events will be held to share and discuss the implications of the findings with study families and communities in Gugulethu and Breede Valley. Study results will be shared with stakeholders at the Provincial Child Health meetings, Cape Winelands District Child Health Forum and Paediatric and Public Health academic departmental meetings at Stellenbosch University and the University of Cape Town. The investigators will share study findings at local South African meetings and international conferences and workshops, and manuscripts detailing study findings will be submitted for publication in peer-reviewed journals.

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