Protocol

SARS-CoV-2 Infections in a Triad of Primary School Learners (Grades 1-7), Their Parents, and Teachers in KwaZulu-Natal, South Africa: Protocol for a Cross-Sectional and Nested Case-Cohort Study

Reshmi Dassaye[1], MMedSci, PhD; Terusha Chetty[1,2], MBChB, PhD; Brodie Daniels[1], PhD; Zakir Gaffoor[1], MSc; Elizabeth Spooner[1], MBChB, PhD; Trisha Ramraj[1], MSc; Ncengani Mthethwa[1], BA, PGCE, PGDP, MPhil; Duduzile Faith Nsibande[1], MPH; Saresha Pillay[1], MBChB; Arvin Bhana[3,4], PhD; Vuyolwethu Magasana[1], MPH; Tarylee Reddy[5], MSc, PhD; Khanya Mohlabi[1], BHSc (Hons); Penelope Linda Moore[6,7,8], PhD; Wendy A Burgers[9,10,11], PhD; Tulio de Oliveira[11,12,13,14], PhD; Nokukhanya Msomi[15,16], MBChB, PhD; Ameena Goga[1,17], MBChB, MSc, PhD

[1]HIV and Other Infectious Diseases Research Unit, South African Medical Research Council, Cape Town, South Africa

[2]Discipline of Public Health Medicine, University of KwaZulu-Natal, Durban, South Africa

[3]Center for Rural Health, School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa

[4]Health Systems Research Unit, South African Medical Research Council, Durban, South Africa

[5]Biostatistics Research Unit, South African Medical Research Council, Durban, South Africa

[6]Centre for the AIDS Programme of Research in South Africa, Durban, South Africa

[7]National Institute for Communicable Diseases of the National Health Laboratory Service, Johannesburg, South Africa

[8]South African Medical Research Council Antibody Immunity Research Unit, School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[9]Wellcome Centre for Infectious Diseases Research in Africa, University of Cape Town, Cape Town, South Africa

[10]Division of Medical Virology, Department of Pathology, University of Cape Town, Cape Town, South Africa

[11]Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa

[12]Centre for Epidemic Response and Innovation, School of Data Science and Computational Thinking, Stellenbosch University, Stellenbosch, South Africa

[13]KwaZulu-Natal Research Innovation and Sequencing Platform, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

[14]Department of Global Health, University of Washington, Seattle, WA, United States

[15]Discipline of Virology, School of Laboratory Medicine and Medical Sciences, University of KwaZulu Natal, Durban, South Africa

[16]National Health Laboratory Service, Durban, South Africa

[17]Department of Paediatrics and Child Health, University of Pretoria, Pretoria, South Africa

Corresponding Author:
Reshmi Dassaye, MMedSci, PhD
HIV and Other Infectious Diseases Research Unit
South African Medical Research Council
Francie van Zijl Drive
Parowvallei
Cape Town, 7505
South Africa
Phone: 27 312604486
Email: Reshmi.Dassaye@mrc.ac.za

Abstract

Background: In low- and middle-income countries (LMICs) such as South Africa, there is paucity of data on SARS-CoV-2 infections among children attending school, including seroprevalence and transmission dynamics.

Objective: This pilot study aims to assess (1) the prevalence of self-reported or confirmed SARS-CoV-2 prior infections, COVID-19 symptoms (including long COVID), seroprevalence of SARS-CoV-2 antibodies, and general/mental health, (2)

longitudinal changes in SARS-CoV-2 seroprevalence, and (3) SARS-CoV-2 acute infections, immune responses, transmission dynamics, and symptomatic versus asymptomatic contacts in a unique cohort of unvaccinated primary school learners, their parents, teachers, and close contacts in semirural primary school settings.

Methods: Learners (grades 1-7) from primary schools in KwaZulu-Natal, South Africa, their parents, and teachers will be invited to enroll into the COVID kids school study (CoKiDSS). CoKiDSS comprises 3 parts: a cross-sectional survey (N=640), a follow-up survey (n=300), and a nested case-cohort substudy. Finger-prick blood and saliva samples will be collected for serological and future testing, respectively, in the cross-sectional (451 learners:147 parents:42 teachers) and follow-up (210 learners:70 parents:20 teachers) surveys. The nested case-cohort substudy will include cases from the cross-sectional survey with confirmed current SARS-CoV-2 infection (n=30) and their close contacts (n=up to 10 per infected participant). Finger-prick blood (from all substudy participants), venous blood (from cases), and nasal swabs (from cases and contacts) will be collected for serological testing, immunological testing, and viral genome sequencing, respectively. Questionnaires covering sociodemographic and general and mental health information, prior and current SARS-CoV-2 symptoms and testing information, vaccination status, preventative behavior, and lifestyle will be administered. Statistical methods will include generalized linear mixed models, intracluster correlation, descriptive analysis, and graphical techniques.

Results: A total of 645 participants were enrolled into the cross-sectional survey between May and August 2023. A subset of 300 participants were followed up in the follow-up survey in October 2023. Screening of the participants into the nested case-cohort substudy is planned between November 2023 and September 2024. Data cleanup and analysis for the cross-sectional survey is complete, while those for the follow-up survey and nested case substudy will be completed by the third quarter of 2024. The dissemination and publication of results is anticipated for the fourth quarter of 2024.

Conclusions: This study provides data from an LMIC setting on the impact of SARS-CoV-2 on school-attending learners, their parents, and teachers 3 years after the SARS-CoV-2 pandemic was declared and 21-24 months after resumption of normal school attendance. In particular, this study will provide data on the prevalence of self-reported or confirmed SARS-CoV-2 prior infection, prior and current symptoms, seroprevalence, changes in seroprevalence, SARS-CoV-2 transmission, SARS-CoV-2 adaptive immune responses, and symptoms of long COVID and mental health among a triad of learners, their parents, and teachers.

International Registered Report Identifier (IRRID): DERR1-10.2196/52713

(JMIR Res Protoc 2024;13:e52713) doi: 10.2196/52713

KEYWORDS

COVID-19; SARS-CoV-2; learners; seroprevalence; long COVID; transmission dynamics

Introduction

Since the onset of the COVID-19 pandemic, an estimated 75.3 million (21%) children and adolescents <20 years of age have tested positive globally [1]. In South Africa, like many low- and middle-income countries (LMICs), there is a significant population youth bulge: children aged <20 years and children attending primary school make up almost 37% and 28% of the populations, respectively [2]. In their last publicly available report, the National Institute of Communicable Diseases, South Africa, reported that as of December 4, 2021, individuals aged ≤19 years comprised 14.8% of the SARS-CoV-2 tests, 12.5% of laboratory-confirmed COVID-19 cases, 5% of all COVID-19–associated admissions, and 0.7% of COVID-19–associated in-hospital deaths [3]. In most LMICs, children aged <12 years were not offered SARS-CoV-2 vaccines and not prioritized for SARS-CoV-2 testing. In this context, the long-term impact of the COVID-19 pandemic on children requires investigation.

SARS-CoV-2 seroprevalence studies provide an estimate of SARS-CoV-2 antibodies and thus better insight into overall infections, given that access to viral diagnostic testing and testing among mild and asymptomatic cases may be low [4]. In South Africa, during the COVID-19 pandemic, 3 cardinal community studies have reported SARS-CoV-2 seroprevalence among adults and children (Table 1), with an overall increase in the seroprevalence with each successive wave [5-7]. Further, all studies reported that the seroprevalence in adolescents is analogous to that reported in adults, while young children had lower seroprevalence compared to adolescents and adults. Noteworthily, children constituted only a fraction of the sample size in all 3 seroprevalence community surveys (ie, ~55%, 10%, and 20%, respectively) [5-7]. To our knowledge, there is paucity of data reporting the seroprevalence of SARS-CoV-2 among primary school-age children in school settings in South Africa.

Table 1. Summary of SARS-CoV-2 seroprevalence studies in South Africa.

Study	Period	Variant of concern	Study setting	Participants (n)	Children and adolescents (n)	Age groups	SARS-CoV-2 infection/seroprevalence among children	SARS-CoV-2 infection/seroprevalence among adults
Cohen et al [5], 2022	July 2020 to August 2021	Beta and Delta variants	Mpumalanga and North West (2 provinces)	1200	664	<5 years of age (n=154, 12.8%) 5-12 years of age (n=340, 28.3%) 13-18 years of age (n=170, 14.2%) 19-39 years of age (n=265, 22.1%) 40-59 years of age (n=168, 14%) ≥50 years of age (n=103, 8.6%)	49% (75/154) in <5 years of age[a] 60% (205/340) in 5-12 years of age[a] 78% (132/170) in 13-18 years of age[a]	62.3% (165/265) among 19-39 years of age[b] 68.5% (115/168) among 40-59 years of age[b] 55.3% (57/103) among ≥50 years of age[b]
National household-based population seroprevalence survey of SARS-CoV-2 antibodies report [6]	November 2020 to February 2021 and April 2021 to June 2021	Beta and Delta variants	Western Cape, Eastern Cape, Northern Cape, Free State, Kwazulu-Natal, Northwest, Gauteng, Mpumalanga, and Limpopo (9 provinces in South Africa)	13,212	1363	Children<12 years not included 12-17 years of age (n=1363, 10.3%) 18-35 years of age (n=4494, 34%) 36-49 years of age (n=3060, 23.2%) >50 years of age (n=4294, 32.5%)	23.2%, (95% CI 19.2-27.8), 12-17 years of age[c]	17.3% (95% CI 15.0-19.9) among 18-35 years of age[d] 20.1% (95% CI 17.6-22.8) among 36-49 years of age[d] 21.3% (95% CI 19.1-23.7) among >50 years of age[d]
Madhi et al [7], 2022	October 2021 to December 9, 2021	Omicron	Gauteng (1 province)	7010	1375	<12 years of age (n=753, 10.7%) 12-17 years of age (n=622, 8.9%) 18-50 years of age (n=4047, 57.7%) >50 years of age (n=1588, 22.7%)	56.2% (95% CI 52.5-59.7) among <12 years of age[c] 73.8% (95% CI 70.2-77.1) among 12-17 years of age[c]	73.6% (95% CI 72.2-74.9) among 18-50 years of age[d] 79.7% (95% CI 77.6-81.5) among >50 years of age[d]

[a]SARS-CoV-2 infection among children.

[b]SARS-CoV-2 infection among adults.

[c]SARS-CoV-2 seroprevalence among children.

[d]SARS-CoV-2 seroprevalence among adults.

Initial evidence suggested that children and adolescents are susceptible to infections with ancestral SARS-CoV-2 but at a reduced risk of severe illness or death relative to adults [8]. However, the subsequent Delta and Omicron variants have been more infectious in children than previous variants [9]. A retrospective study in China (n=2135) demonstrated that up to 90% of the pediatric cases were asymptomatic, mild, or moderate [10]. The majority of children hospitalized with severe COVID-19 were unvaccinated or had additional comorbidities such as type 2 diabetes or obesity [11]. A study in the United Kingdom reported that children with underlying neurodisabilities or multiple comorbidities are vulnerable to hospital admission or death [12]. Similar to adults, children and adolescents can also experience long COVID, the frequency and characteristics of which are still under investigation [13].

Studies have focused on differentiating the SARS-CoV-2 immune response between adults and children. In response to SARS-CoV-2 exposure or infection, children elicit a stronger mucosal innate immune response, which facilitates viral clearance [14-22], a lower level of neutrophilia that has previously been associated with microangiopathy and thrombosis [18,20], and a difference in cytokine profiling with a reduced tendency to trigger a cytokine storm [18,19,21-24]. With reference to adaptive immunity, higher lymphocyte counts with a higher proportion of naïve T cells, T regulatory cells, and T follicular helper cells have been reported [24-27]. Additionally, there are conflicting data on mucosal and serum antibody levels reported in children [18-20,24,28-32], and there are discordant reports on the durability and sustainability of the nucleocapsid antibody response in children after infection [33-35]. The Texas Coronavirus Antibody Response ongoing survey reported that 95% of the previously infected children of 5-19 years of age tested positive for nucleocapsid antibodies at the onset of the study and continued to have nucleocapsid antibodies up to 6 months later [36]. SARS-CoV-2 variants have evolving mechanisms to evade host immune defenses; intermittent testing to understand immune response in children exposed to or infected with SARS-CoV-2 infection may contribute to providing key insights into the pathogenesis of severe COVID-19.

During the COVID-19 pandemic, decisions on school closures varied widely between and within countries [37]. Children play a critical role in the transmission of respiratory viruses such as influenza, and school closures were partly guided by such evidence [38,39]. However, the epidemiological benefits of school closures on the transmission of SARS-CoV-2 remain elusive. There are conflicting data on the transmission of SARS-CoV-2 from children to children and from children to adults [40-45], with a lower prevalence of infection reported in younger children [46-48], with studies focusing primarily on household transmissions, while the role of schools remains unclear [47,49]. Young children infected with SARS-CoV-2 have viral loads in their respiratory tract similar to those of adolescents and adults [50,51]. School infection control measures played a role in decreasing outbreaks in some countries [52-54], but cluster outbreaks were reported among children in several provinces of South Africa when schools fully opened in 2022. Hence, further evaluation is needed to determine whether children (and the school setting) play a more substantive role in the community spread of SARS-CoV-2, especially in LMICs.

The overall aim of the COVID kids school study (CoKiDSS) is to assess SARS-CoV-2 prior infection, prior and current COVID-19 symptoms, seroprevalence, acute infection, transmission, immune responses, and symptoms of long COVID among a unique cohort of learners in grades 1-7, their parents/guardians, and teachers in the KwaZulu-Natal province of South Africa. The objectives of this study are shown in Table 2. Here, we describe the research study, its implementation processes, methodology, and expected results.

Table 2. COVID kids school study objectives.

Objective	Description
Primary objective	• Objective 1: To assess the prevalence of self-reported confirmed SARS-CoV-2 prior infections, prior and current COVID-19 symptoms, and seroprevalence of SARS-CoV-2 antibodies in the overall triad of learners (grades 1-7), their parents/guardians, and teachers.
Secondary objectives	• Objective 2: To determine the prevalence of long COVID-19 symptoms, general health and mental health in participants overall, and by SARS-CoV-2 antibody status. • Objective 3: To determine the longitudinal changes in SARS-CoV-2 seroprevalence and symptoms in a subset of participants who are followed up.
Exploratory objectives	• Objective 4: To conduct viral genome sequencing and describe transmission dynamics in a subgroup of 30 consenting SARS-CoV-2–positive individuals from the learner-parent-teacher triad and up to 10 of their close contacts. • Objective 5: To determine the proportion of previously asymptomatic contacts who test SARS-CoV-2–positive above. • Objective 6: To investigate B-cell and T-cell responses in the subgroup of 30 SARS-CoV-2–positive individuals enrolled and correlate these with symptoms.

Methods

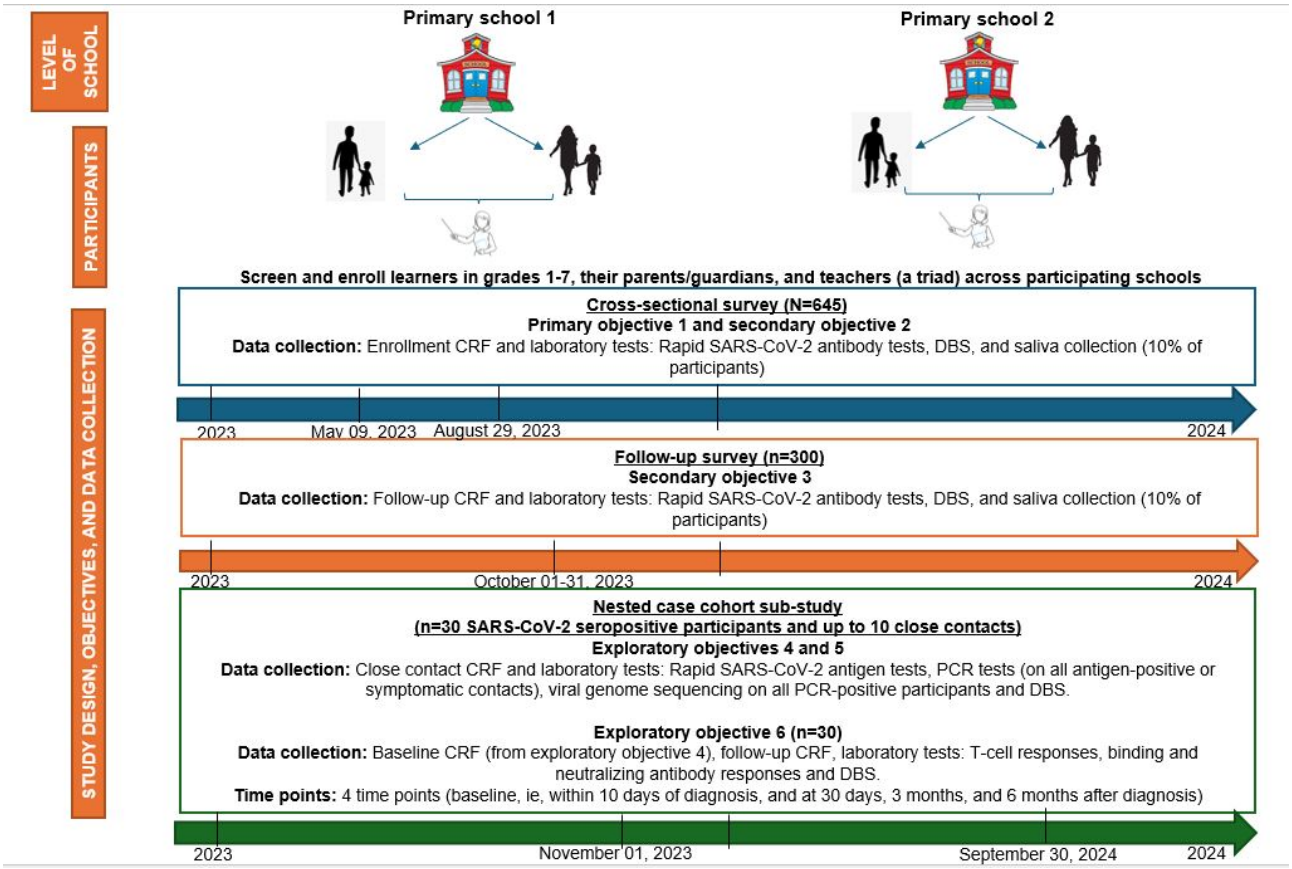
Study Setting

This study will be conducted within the catchment areas of the South African Medical Research Council (SAMRC)'s Verulam Clinical Research Site (CRS) based in the Verulam suburb of the eThekwini district in KwaZulu-Natal. The KwaZulu-Natal province has the second largest population in South Africa, with an estimated 11.3 million people; 43% of the population are younger than 18 years [2]. The province is divided into 1 metropolitan municipality (eThekwini Metropolitan Municipality; Durban) and 11 district municipalities. Verulam is an urban area in the northern part of eThekwini Municipality in close proximity to the iLembe district municipality. Approximately 94% of the school-age children between 5 and 17 years are in school in this municipality [3]. The catchment areas of the Verulam CRS comprise urban, periurban, and rural localities. In South Africa, the COVID-19 pandemic evolved against a backdrop of longstanding tuberculosis and HIV epidemics. KwaZulu-Natal has the largest burden of HIV and tuberculosis infections [55], and of the 9 provinces in South Africa, KwaZulu-Natal had the third highest cumulative number of COVID-19 cases recorded as of June 29, 2022 [56].

Study Design

This pilot study will implement a cross-sectional survey, follow up a subsample of survey participants, and conduct a nested case-cohort substudy in a preselect number of primary schools within the catchment area of the Verulam CRS in KwaZulu-Natal. Participating learners from primary schools (grades 1-7), their parents/guardians, and teachers will be invited to enroll in the CoKiDSS cross-sectional survey from May to August 2023 (primary objective 1; Figure 1). The cross-sectional survey will be conducted over 6 consecutive school weeks (window ±3 weeks; Figure 1). A subset of participants from the cross-sectional survey will be invited to participate in the follow-up survey (secondary objectives 2 and 3), with repeat SARS-CoV-2 antibody testing (3-4 months later from October 2023) until the desired sample is achieved (Figure 1). Saliva samples will be collected and stored from the first 10% (65/645 and 30/300, respectively) of the participants enrolled across the cross-sectional survey and in the follow-up survey for future testing. The nested case-cohort substudy (exploratory objectives 4-6) aims to enroll 30 cross-sectional survey participants with confirmed current SARS-CoV-2 infection—preferably all or at least 20 children (Figure 1) from November 2023 to September 2024. The follow-up survey will allow us to monitor the dynamics of SARS-CoV-2 seroprevalence. Long COVID will also be assessed in the cross-sectional and follow-up surveys as well as in the nested case-cohort substudy. Participants in the cross-sectional survey will have 1 study visit, while participants in the follow-up survey will have 2 study visits (Figure 1). During the follow-up survey, participants lost to follow-up will not be replaced.

Figure 1. Study design, objectives, and data collection. CRF: case report form; DBS: dried blood spot; PCR: polymerase chain reaction.



For objectives 4-6, the first 30 participants in the cross-sectional surveys (learner/parent/teacher) who test SARS-CoV-2 polymerase chain reaction (PCR)–positive (30 children or at least 20 children) identified through the school or existing

linkages with the National Institute of Communicable Diseases/National Health Laboratory Services will be invited to enroll into the exploratory substudy (nested case-cohort substudy; Figure 1). These participants are referred to as the primary positives. To assess transmission dynamics (objective 4) and proportion of asymptomatic cases (objective 5), all close contacts of the 30 primary positives (30 SARS-CoV-2 PCR-positive participants) up to a maximum of 10 contacts will be tested with a South African Health Products Regulatory Authority–approved SARS-CoV-2 point-of-care antigen test, and a swab will be sent to the National Health Laboratory Services for a SARS-CoV-2 PCR test. Only 1 swab will be collected from children who are primary positives or close contacts. For the primary positives and their PCR-positive contacts, remnant swabs will be sent for viral genome sequencing (objective 4; Figure 1). To assess B-cell and T-cell immune responses (objective 6), the primary positives (30 SARS-CoV-2 PCR-positive participants) will also provide venous blood at baseline (ie, within 10 days of a positive SARS-CoV-2 test), 30 days, 3 months, and 6 months post diagnosis (nested case-cohort substudy; Figure 1). Dried blood spot samples will be collected from all participants enrolled in the cross-sectional and follow-up surveys as well as the nested case-cohort substudy for future antibody testing.

Study Populations

The inclusion and exclusion criteria for the school, school-age learners, their parents or guardians, and teachers are summarized in Table 3.

Table 3. Inclusion and exclusion criteria for the school, learners in grades 1-7, their parents/guardians, and teachers.

Participant and part of the study	Inclusion criteria	Exclusion criteria
School		
Cross-sectional and follow-up surveys and nested case-cohort substudy	• Primary schools within the catchment areas of the Verulam South African Medical Research Council clinical research site in eThekwini, KwaZulu-Natal, South Africa.	• Special schools, learner referral units, and education colleges. • Schools where other school-based COVID-19 studies are already being conducted. • Small school size with <40 learners per grade in grades 1-7.
Learners, parents/guardians, and teachers		
Cross-sectional survey	• Learner must be attending school in person. • A parent/guardian is only eligible if his/her child is eligible and participating in the study. • A teacher is only eligible if the teacher teaches at a participating school. • For learners <18 years of age, a parent/guardian is able to provide consent. • For learners 8 to <18 years of age, the learner can provide assent. • For learners 7 years of age, only parental/guardian consent is required. • Willing for study staff to obtain routine SARS-CoV-2 results from National Institute of Communicable Diseases/National Health Laboratory Services.	• Learners 8 to <18 years of age who are unable to provide appropriate informed assent. • Parent excluded if learner already has 1 parent enrolled in the study. • Learner does not anticipate completing the school year in the selected school. • Learners with physical or intellectual challenges. • Learners who, in the opinion of the principal investigators or designees, will be at risk if they participate in this study.
Follow-up survey	• Same criteria as for cross-sectional survey • Learner must be attending school in person during the 2023 academic year. • Willing to be followed up once and to give blood during follow-up.	• Same criteria as for cross-sectional survey.

Ethics Approval

This study has been approved by the SAMRC Human Research Ethics Committee (EC018-9/2022) and the South African Department of Basic Education (national and provincial) and the South African Department of Health (provincial). Written informed consent will be obtained from parents or guardians of participating learners and from all participating parents/guardians and teachers. Additionally, assent will be obtained from children aged 8 to <18 years. All participants will be reimbursed with a voucher valued at R 300 (US $16), in accordance with local ethics guidance to cover the cost of time, inconvenience, and expenses.

Schools: Sampling and Sample Size

For objectives 1-6, a convenience sample of schools will be selected. In the first stage, a sampling frame of all public primary schools within the Verulam CRS catchment areas will be developed. Attempts will be made to obtain the head counts in these schools and number of classes. Only large schools (≥40 learners per grade in grades 1-7) able to contribute to the sample size will be shortlisted (short list 1) and their principals approached to ascertain interest. From short list 1, schools whose

principals are agreeable to study participation will be identified (short list 2), and a sample of 2 primary schools will be selected from short list 2. We will expand to additional selected primary schools if needed, until the enrolment target is reached.

Madhi et al [7] demonstrated a seroprevalence of 56.2% (95% CI 52.6%-59.7%) among children younger than 12 years in a seroepidemiological study conducted from October to December 2021 [7]. We opted to be more conservative due to the waning immunity anticipated in unvaccinated children or those who did not receive the booster dose almost 2 years after the pandemic. The sample size calculations for this study were based on estimating seroprevalence rates with a specific degree of precision. Specifically, the $n_{min} = DE \times \frac{z^2_{1-\alpha/2} \times p \times (1-p)}{d^2}$ was used, where DE refers to the design effect, p refers to the estimated prevalence, and d to the margin of error. A sample size of 640 will allow us to estimate seroprevalence rates in the combined group of 40% and greater with a margin of error of 6%, accounting for a design effect of 2.5 and assuming a 5% α. The survey is designed to be stratified by school, with class defining the cluster. We expect a minimum of 40 clusters in total across the 2 schools with an average cluster size of 16. In Figure 2, we have illustrated the margin of error for estimation under various sample sizes assuming all the other aforementioned parameters are fixed. As depicted in Figure 2, a reduction in the sample size below 600 will result in a greater margin of error (lower precision) larger than 7%.

A review of 14 studies indicated that long COVID symptoms varied from 4% to 66% among children and adolescents [57]. A cohort of 300 individuals will enable us to estimate the prevalence rates of long COVID at follow-up, 45% or greater with a 7% margin of error, accounting for a 20% loss to follow-up rate, and a maximum design effect of 1.2. Tables 4-5 summarize the sample size allocation for the respective surveys. The nested case-cohort substudy sample size is described in Table 6.

Figure 2. Margin of error for various sample sizes assuming a fixed prevalence of 40% and design effect of 2.5. MOE: margin of error.

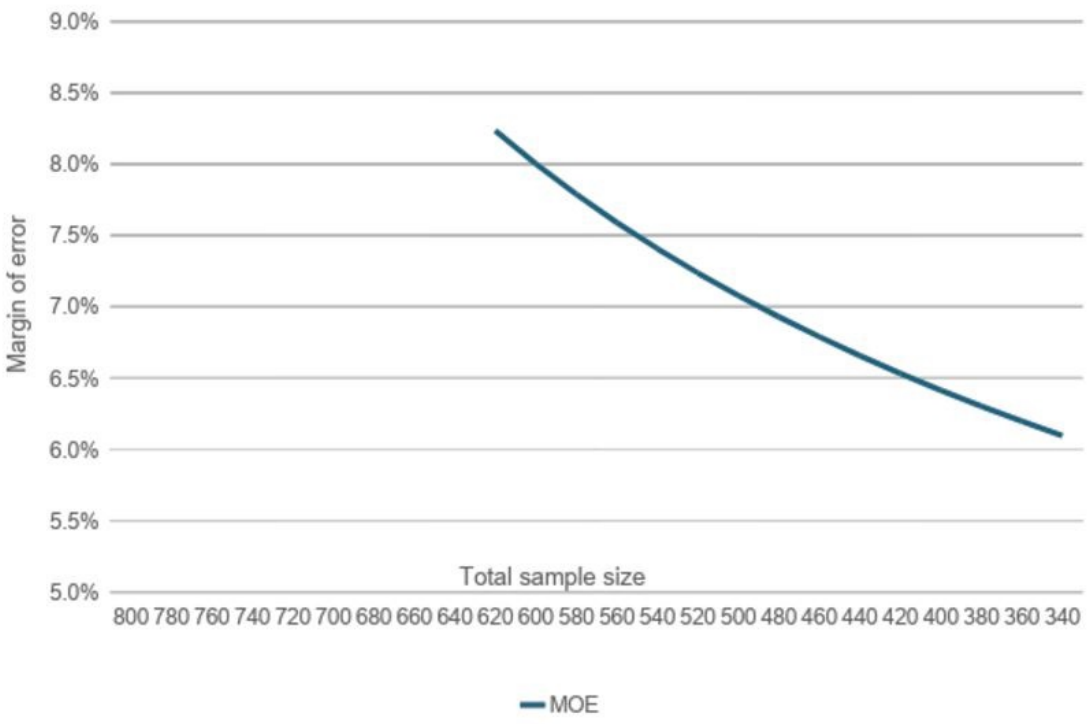


Table 4. Sample size allocation of primary school learners, parents, and teachers for the cross-sectional survey (N=640).[a]

Sample	Grade						
	1 (n=91)	2 (n=91)	3 (n=91)	4 (n=91)	5 (n=92)	6 (n=92)	7 (n=92)
Learners (n=451)	64	64	64	64	65	65	65
Parents (learner: parent, 3:1) (n=147)	21	21	21	21	21	21	21
Teachers (learner: teacher, 11:1) (n=42)	6	6	6	6	6	6	6

[a]The sample size might vary by ±10 people per group (learner, parent, teacher).

Table 5. Sample size allocation of primary school learners, parents, and teachers for the follow-up survey (n=300).[a]

Sample	Grade						
	1 (n=43)	2 (n=43)	3 (n=43)	4 (n=43)	5 (n=43)	6 (n=43)	7 (n=43)
Learners (% of cross-sectional survey ~50%) (n=210)	30	30	30	30	30	30	30
Parents (% of cross-sectional survey ~50%) (n=70)	10	10	10	10	10	10	10
Teachers (% of cross-sectional survey ~50%) (n=20)	3	3	3	3	3	3	2

[a]The sample size might vary by ±5 people per group (learner, parent, teacher).

Table 6. Sample size allocation for the nested case-cohort substudy.

Participants	Value, n
SARS-CoV-2–positive learners across grades 1-7	20-30
SARS-CoV-2–positive parents/teachers	0-10
Close contacts	10 per positive participant

Study Procedures

Stakeholder Engagement

A strong community engagement program is underway to assist with buy-in and recruitment for the study among the Department of Basic Education, school principals, school governing boards, teachers, and parents/guardians of learners in grades 1-7. Schools that agree to participate will be asked to register and complete a short questionnaire.

Participant Recruitment and Follow-Up

Informed consent will be sought from teachers and from parents/guardians for their own/their children's participation. Simplified informed consent forms were piloted to evaluate their understanding of the study and implications of the study. Assent will also be obtained from children aged 8 to <18 years, and participation will be contingent on obtaining both assent and parental consent. Only parental consent will be required for 7-year-old children. Flexible systems will be used to engage with parents, including weekend meetings and interviewer-administered or self-administered parental questionnaires. Multiple learners from one family can participate, but separate consent will be sought for each learner. Recruitment for the cross-sectional survey commenced on May 9, 2023, and was completed before the end of August 2023. The follow-up survey will follow up the first 210 learners, 70 parents, and 20 teachers who consent to follow-up at least 6 weeks after the first interview and after a school holiday. SARS-CoV-2–positive participants enrolled in the immunological substudy will be followed up for 6 months.

Data Collection

Questionnaire data will be gathered from school principals or a substitute member of the school senior leadership team, teachers, and parents/guardians of the primary school learners (in grades 1-7) (Table 7 and Multimedia Appendices 1-7).

Information will be collected on sociodemographic and basic health information; use of nonpharmacological measures; COVID-19 vaccination status of learner, parent/guardian, and teacher; household structure and COVID-19 history; symptoms of long COVID; household exposures; lifestyle; and preventive behavior related to the pandemic since January 2020 (see Multimedia Appendices 1-6). Parents/guardians will complete all the study case report forms on the children's behalf (Multimedia Appendices 3 and 4).

Additionally, information will be collected on the learner's lifestyle, mental health, and well-being. The Revised Children' Anxiety and Depression Scale will be used to determine the internalizing symptoms of anxiety and depression among children and young adolescents enrolled in this study (see Multimedia Appendix 7) [58]. If the tool triggers negative memories in participants, these participants will be referred to a counsellor at the nearest health care facility. Samples will be collected from participants as outlined in Table 7 and described in Multimedia Appendix 8.

Table 7. Summary of data collection.

Participant	Cross-sectional and follow-up survey	Nested case-cohort substudy	
		Immunology	Transmission dynamics
School principal or senior school leadership	Questionnaire about number of learners, number of staff, and nonpharmaceutical interventions	N/A[a]	N/A
Learner/parent/teacher triad	Questionnaire at baseline and follow-up (if applicable) about contacts/nonpharmaceutical interventions/symptoms of long COVID. Blood draw to determine seroprevalence (rapid antibody test), dried blood spot for anti-S IgA/IgG, anti-N IgG, neutralizing antibody and antibody titers. Saliva samples will be collected in 10% of participants and stored if applicable.	N/A	N/A
Primary positives identification and follow-up within 10 days, 30 days, 3 months, and 6 months of a positive SARS-CoV-2–positive test	N/A	Questionnaire at baseline and follow-up (if applicable) about contacts/nonpharmaceutical interventions/symptoms of long COVID. Blood draw to determine seroprevalence (rapid antibody test), dried blood spot for anti-S IgA/IgG, anti-N IgG, neutralizing antibody and antibody titers. Saliva samples will be collected in 10% of participants and stored if applicable.	Telephonic questionnaire to identify contacts. Initial swab sent for viral genome sequencing.
Contacts of the primary positives	May or may not be included in the cross-sectional and follow-up surveys.	N/A	Questionnaire + rapid antigen test + polymerase chain reaction + dried blood spot

[a]N/A: not applicable.

Data Management

Data will be collected in research electronic data capture, a secure web-based application hosted by the SAMRC. More information on this platform can be found elsewhere [59,60]. Research electronic data capture access will be restricted to CoKiDSS personnel. A lookup function will be created in research electronic data capture to link/track participants enrolled in the cross-sectional survey, follow-up survey, and nested case-cohort substudy. This will be useful if the close contact is already a participant in the study.

Biospecimen Management

Samples will be stored at the HIV and other Infectious Diseases Research Unit, SAMRC, biorepository. The Laboratory Data Management System program developed by Frontier Science is used by the HIV and other Infectious Diseases Research Unit biorepository and is a storage module that conforms to US Food and Drug Administration, 21 Code of Federal Regulations part 58 and 11 [61]. The program is utilized to manage specimen tracking, inventory storage, and specimen shipment.

Data Analysis

We will perform descriptive analysis of participant sociodemographic, lifestyle, and behavior information. Total seroprevalence and cumulative incidence (ie, total number of reverse transcription-PCR–confirmed infections in official statistics per population) will be calculated and compared as well as age-specific and time-specific estimates. The total numbers of learners in the respective grades per school will be used for poststratification so that the estimates are representative of the demographics in KwaZulu-Natal, which will be incorporated via weights. The prevalence prior and current COVID-19 symptoms and seroprevalence will be presented with 95% CIs, where standard errors will be computed via jackknife methods. Within the cohort, changes in seroprevalence, symptoms, mental health, and physical health will be assessed using generalized linear mixed models, considering the within-individual correlation of responses as well as the hierarchical structure of the data. The clustering of seropositivity within classes and school will be quantified using the intracluster correlation. To analyze the exploratory objectives, the following statistical methods will be employed: (1) means with standard deviations or medians with interquartile ranges (as appropriate depending on the distribution) will be presented for continuous data, (2) the graphical presentation of continuous outcomes will be undertaken using box plots, (3) bar charts will be used to represent categorical data across groups of interest, and (4) the correlation between variables will be addressed using 2-way scatterplots with the presentation of Spearman correlation coefficient.

Patient and Public Involvement

Several school principals were consulted during the development of the protocol to ensure the feasibility of the planned study procedures. Early feedback was collected from learners and parents invited to participate to adapt the communication strategies and channels. Further feedback will also be collected

from enrolled learners and school principals during the cross-sectional survey to adapt the follow-up survey. Results of individual tests will be communicated to the participants, and overall study results disseminated to participating schools. Findings will be disseminated to the South African Department of Basic Education and Department of Health.

Results

Recruitment for the cross-sectional survey occurred between May and August 2023, and a total of 645 participants were enrolled. Three hundred participants were followed up in the follow-up survey implemented in October 2023. Screening of the participants into the nested case-cohort substudy is planned between November 2023 and September 2024. Data cleanup and analysis for the cross-sectional survey is complete. Data cleanup and analysis for the follow-up survey and nested case substudy will be completed in the third quarter of 2024. The dissemination and publication of study findings is anticipated for the fourth quarter of 2024. The abovementioned activities and timelines are outlined in Multimedia Appendix 9.

Discussion

Anticipated Main Findings of This Study

We anticipate that this study will find high SARS-CoV-2 seroprevalence, especially among teachers and parents, despite low reported SARS-CoV-2 infections and low prevalence of long COVID-19 and that transmission dynamics will favor parent-child transmission.

Contextualization of the Anticipated Results

The direct impact of COVID-19 on child and adolescent mortality is limited, with these age groups accounting for a meagre 0.4% (over 17,400) of COVID-19 deaths worldwide as of March 2023 [1]. However, according to UNICEF (United Nations Children's Fund), children and adolescents bear the brunt of the indirect effects of the COVID-19 pandemic, including more households plummeting into multidimensional poverty, exacerbating the hardships of children living in the poorest countries, augmenting the learning crisis, threatening child survival and death, increasing child malnutrition, and deprivation and disruptions in health services [62]. Hence, the harms associated with school closures were profound. CoKiDSS is centered around the school rather than community settings, as schools play a critical role in a child's learning and development, and in many countries, schools also provide access to immunizations, health care, and nutritional services.

In LMICs, among children aged 5-13 years, there is a paucity of data on SARS-CoV-2 infections, including seroprevalence and transmission dynamics. In South Africa, 3 cardinal community studies have been published to date, reporting SARS-CoV-2 seroprevalence among adults and children [5-7]. However, the last serosurvey was conducted in December 2021 during the Omicron wave, and children constituted a small proportion of the study population [7].

CoKiDSS will provide data on the impact of COVID-19 on school-attending children ~36 months after the pandemic was declared and 21-24 months after the resumption of normal school attendance. In particular, data will be provided on the prevalence of confirmed prior SARS-CoV-2 infections, prior and current COVID-19 symptoms, seroprevalence of SARS-CoV-2 antibodies, prevalence of long COVID symptoms, and general and mental health in a triad of learners, their parents/guardians, and teachers in the current COVID-19 endemic. The longitudinal design will allow a description of the temporal trends of immunity to SARS-CoV-2. Presently, in South Africa, children aged 5-11 years are only eligible to receive SARS-CoV-2 vaccination if they are at risk of developing severe COVID-19. The CoKiDSS data will provide a better understanding on the natural protection within this population and could potentially guide local vaccination strategies.

Strengths and Limitations

This study is the first study of SARS-CoV-2 infections in a school setting within a high HIV/tuberculosis prevalence LMIC. Thus, it will provide information on the impact of COVID-19 on schools, learners, teachers, and parents in these settings, and could guide future responses to pandemics within these settings. However, this study is not without challenges and limitations. Given the limited geographic area and number of schools, the findings may not be representative of all South African schools. In order to recruit a triad of learners in grades 1-7, their parents, and teachers, several rounds of engagement may be needed, resulting in oversampling or undersampling at schools. This study will assess SARS-CoV-2 seroprevalence by using a qualitative SARS-CoV-2 point-of-care antibody test. It is possible that the qualitative antibody assessment is below the threshold of conferring immunity. We would, however, prefer to use a minimally invasive test in this vulnerable population. Notwithstanding these, this study will contribute to the limited body of knowledge on the effect of the COVID-19 pandemic on school-attending children 21-24 months after resumption of normal school attendance.

Dissemination Plan

The study objectives and outcomes will be disseminated to participants, community, and other stakeholders, including the South African Department of Health and South African Department of Basic Education (district, provincial, and national levels), regulatory bodies, research organizations, community members, and participants. Additionally, the information linked to this study will be shared by the community staff with the participating school principals and members of the school governing board as well as the community advisory board/community working group members. The results of this study will be disseminated via virtual methods and face-to-face meetings. Communication methods will include the use of SMS text messaging to mobiles, monthly telephone calls with community advisory board members, hand delivery of relevant written material, email, Microsoft Teams, and social media platforms (WhatsApp). These methods will contribute to ongoing community acceptance of the study and trust in the research team and the program.

Acknowledgments

We are grateful to the South African Medical Research Council (grant SAMRC-RFA-GIPD-03-2021) and the European Union Horizon Europe program under the project “EU-Africa Concerted Action on SARS-CoV-2 Virus Variant and Immunological Surveillance” (grant 101046041) for funding this pilot study. Views and opinions expressed are, however, those of the author(s) only and do not necessarily reflect those of the European Union or the Health and Digital Executive Agency. Neither the European Union nor the granting authority can be held responsible for them. Additionally, we would like to extend a huge thank you to the study participants and the communities that participated.

Data Availability

Data availability will need to be requested from the corresponding author. The request will be considered a concept note, and the reason for data access will be required. Data will only be shared after the minimum papers have been written by the authors. Data will be made publicly available on the South African Medical Research Council website after all the main papers have been published.

Authors' Contributions

RD and AG conceived, designed, and wrote the manuscript. TC, BD, ZG, ES, TR, NM, DFN, SP, AB, VM, PLM, WAB, TdO, and NM contributed to reviewing and critiquing the manuscript. TR and KM were responsible for the statistical design and data management plan for the study, respectively. All authors read and approved the final manuscript. There were no conflicts of interest. No artificial intelligence was used in developing this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Principal enrollment and follow-up case report form.
[PDF File (Adobe PDF File), 168 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Teacher enrollment and follow-up case report form.
[PDF File (Adobe PDF File), 401 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Parent of learner enrollment and follow-up e-case report form.
[PDF File (Adobe PDF File), 745 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Parent of learner enrollment and follow-up case report form.
[PDF File (Adobe PDF File), 460 KB-Multimedia Appendix 4]

Multimedia Appendix 5

Close contact case report form.
[PDF File (Adobe PDF File), 149 KB-Multimedia Appendix 5]

Multimedia Appendix 6

Nested case-cohort substudy case report form.
[PDF File (Adobe PDF File), 253 KB-Multimedia Appendix 6]

Multimedia Appendix 7

Learner mental health case report form.
[PDF File (Adobe PDF File), 439 KB-Multimedia Appendix 7]

Multimedia Appendix 8

Detailed data collection.
[DOCX File , 20 KB-Multimedia Appendix 8]

Multimedia Appendix 9

Study timeline.
[DOCX File , 16 KB-Multimedia Appendix 9]

References

1. Child mortality and COVID-19. UNICEF. URL: https://data.unicef.org/topic/child-survival/covid-19/ [accessed 2023-04-30]
2. Mid-year population estimates. Statistics South Africa, Statistical release P0302. Jun 23, 2019. URL: https://www.statssa.gov.za/publications/P0302/MidYear2022.pdf [accessed 2023-06-23]
3. Monthly COVID-19 in children. National Institute of Communicable Diseases. URL: https://www.nicd.ac.za/diseases-a-z-index/disease-index-covid-19/surveillance-reports/monthly-covid-19-in-children/ [accessed 2023-04-30]
4. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal screening for SARS-CoV-2 in women admitted for delivery. N Engl J Med. May 28, 2020;382(22):2163-2164. [FREE Full text] [doi: 10.1056/NEJMc2009316]
5. Cohen C, Kleynhans J, von Gottberg A, McMorrow M, Wolter N, Bhiman J, et al. PHIRST-C Group. SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020-21. Lancet Infect Dis. Jun 2022;22(6):821-834. [doi: 10.1016/S1473-3099(22)00069-X] [Medline: 35298900]
6. Moyo S, Simbayi LC, Zuma K, Zungu N, Marinda E, Jooste S, et al. Seroprevalence survey of anti-SARS-CoV-2 antibody and associated factors in South Africa: Findings of the 2020-2021 population-based household survey. PLOS Glob Public Health. 2023;3(9):e0002358. [FREE Full text] [doi: 10.1371/journal.pgph.0002358] [Medline: 37747851]
7. Madhi S, Kwatra G, Myers J, Jassat W, Dhar N, Mukendi C, et al. Population immunity and COVID-19 severity with Omicron variant in South Africa. N Engl J Med. Apr 07, 2022;386(14):1314-1326. [doi: 10.1056/NEJMoa2119658] [Medline: 35196424]
8. Novel coronavirus (2019-nCoV). WHO. URL: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200121-sitrep-1-2019-ncov.pdf [accessed 2024-11-26]
9. Cox D. What do we know about COVID-19 and children? British Medical Journal. 2023;380:21. [FREE Full text] [doi: 10.1136/bmj.p21]
10. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702. [FREE Full text] [doi: 10.1542/peds.2020-0702]
11. Smith C, Odd D, Harwood R, Ward J, Linney M, Clark M, et al. Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. Nat Med. Nov 11, 2021;28(1):185-192. [FREE Full text] [doi: 10.1038/s41591-021-01578-1]
12. Ward J, Harwood R, Smith C, Kenny S, Clark M, Davis P. Risk factors for PICU admission and death among children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year. Nature Medicine. 2022;28:193-200. [FREE Full text] [doi: 10.1038/s41591-021-01627-9]
13. Buonsenso D, Munblit D, De RC, Sinatti D, Ricchiuto A, Carfi A, et al. Preliminary evidence on long COVID in children. Acta Paediatics. 2021;110(7):2208-2211. [FREE Full text] [doi: 10.1111/apa.15870]
14. Loske J, Röhmel J, Lukassen S, Stricker S, Magalhães VG, Liebig J, et al. Pre-activated antiviral innate immunity in the upper airways controls early SARS-CoV-2 infection in children. Nat Biotechnol. Mar 2022;40(3):319-324. [doi: 10.1038/s41587-021-01037-9] [Medline: 34408314]
15. Pierce C, Sy S, Galen B, Goldstein D, Orner E, Keller M, et al. Natural mucosal barriers and COVID-19 in children. JCI Insight. May 10, 2021;6(9):e148694. [FREE Full text] [doi: 10.1172/jci.insight.148694] [Medline: 33822777]
16. Winkley K, Banerjee D, Bradley T, Koseva B, Cheung W, Selvarangan R, et al. Immune cell residency in the nasal mucosa may partially explain respiratory disease severity across the age range. Sci Rep. Aug 05, 2021;11(1):15927. [FREE Full text] [doi: 10.1038/s41598-021-95532-3] [Medline: 34354210]
17. Zhu Y, Chew K, Karawita A, Yamamoto A, Labzin L, Yarlagadds T. Pediatric nasal epithelial cells are less permissive to SARS-CoV-2 replication compared to adult cells. BioRxiv. Preprint posted online on April 1, 2022. [doi: 10.1101/2021.03.08.434300]
18. Carsetti R, Zaffina S, Piano Mortari E, Terreri S, Corrente F, Capponi C, et al. Different innate and adaptive immune responses to SARS-CoV-2 infection of asymptomatic, mild, and severe cases. Front. Immunol. Dec 16, 2020;11:610300. [FREE Full text] [doi: 10.3389/fimmu.2020.610300]
19. Bordallo B, Bellas M, Cortez AF, Vieira M, Pinheiro M. Severe COVID-19: what have we learned with the immunopathogenesis? Adv Rheumatol. Sep 22, 2020;60(1):50. [FREE Full text] [doi: 10.1186/s42358-020-00151-7] [Medline: 32962761]

20. Bartsch Y, Wang C, Zohar T, Fischinger S, Atyeo C, Burke J, et al. Humoral signatures of protective and pathological SARS-CoV-2 infection in children. Nat Med. Mar 2021;27(3):454-462. [FREE Full text] [doi: 10.1038/s41591-021-01263-3] [Medline: 33589825]
21. Neeland M, Bannister S, Clifford V, Dohle K, Mulholland K, Sutton P, et al. Innate cell profiles during the acute and convalescent phase of SARS-CoV-2 infection in children. Nat Commun. Feb 17, 2021;12(1):1084. [FREE Full text] [doi: 10.1038/s41467-021-21414-x] [Medline: 33597531]
22. Bordoni V, Sacchi A, Cimini E, Notari S, Grassi G, Tartaglia E, et al. An inflammatory profile correlates with decreased frequency of cytotoxic cells in coronavirus disease 2019. Clin Infect Dis. Nov 19, 2020;71(16):2272-2275. [FREE Full text] [doi: 10.1093/cid/ciaa577] [Medline: 32407466]
23. Li H, Chen K, Liu M, Xu H, Xu Q. The profile of peripheral blood lymphocyte subsets and serum cytokines in children with 2019 novel coronavirus pneumonia. J Infect. Jul 2020;81(1):115-120. [FREE Full text] [doi: 10.1016/j.jinf.2020.04.001] [Medline: 32325129]
24. Pierce C, Preston-Hurlburt P, Dai Y, Aschner CB, Cheshenko N, Galen B, et al. Immune responses to SARS-CoV-2 infection in hospitalized pediatric and adult patients. Sci Transl Med. Oct 07, 2020;12(564):eabd5487. [FREE Full text] [doi: 10.1126/scitranslmed.abd5487] [Medline: 32958614]
25. Yoshida M, Worlock K, Huang N, Lindeboom R, Butler C, Kumasaka N, NU SCRIPT Study Investigators, et al. Local and systemic responses to SARS-CoV-2 infection in children and adults. Nature. Feb 2022;602(7896):321-327. [FREE Full text] [doi: 10.1038/s41586-021-04345-x] [Medline: 34937051]
26. Fazolo T, Lima K, Fontoura J, de Souza PO, Hilario G, Zorzetto R, et al. Pediatric COVID-19 patients in South Brazil show abundant viral mRNA and strong specific anti-viral responses. Nat Commun. Nov 25, 2021;12(1):6844. [FREE Full text] [doi: 10.1038/s41467-021-27120-y] [Medline: 34824230]
27. Cohen CA, Li APY, Hachim A, Hui DSC, Kwan MYW, Tsang OTY, et al. SARS-CoV-2 specific T cell responses are lower in children and increase with age and time after infection. Nat Commun. Jul 29, 2021;12(1):4678. [FREE Full text] [doi: 10.1038/s41467-021-24938-4] [Medline: 34326343]
28. Goenka A, Halliday A, Gregorova M, Milodowski E, Thomas A, Williamson M, et al. Young infants exhibit robust functional antibody responses and restrained IFN-γ production to SARS-CoV-2. Cell Rep Med. Jul 20, 2021;2(7):100327. [FREE Full text] [doi: 10.1016/j.xcrm.2021.100327] [Medline: 34124701]
29. Ji S, Zhang M, Zhang Y, Xia K, Chen Y, Chu Q, et al. Characteristics of immune and inflammatory responses among different age groups of pediatric patients with COVID-19 in China. World J Pediatr. Aug 2021;17(4):375-384. [FREE Full text] [doi: 10.1007/s12519-021-00440-1] [Medline: 34341947]
30. Cervia C, Nilsson J, Zurbuchen Y, Valaperti A, Schreiner J, Wolfensberger A, et al. Systemic and mucosal antibody responses specific to SARS-CoV-2 during mild versus severe COVID-19. J Allergy Clin Immunol. Feb 2021;147(2):545-557.e9. [FREE Full text] [doi: 10.1016/j.jaci.2020.10.040] [Medline: 33221383]
31. Renk H, Dulovic A, Seidel A, Becker M, Fabricius D, Zernickel M, et al. Robust and durable serological response following pediatric SARS-CoV-2 infection. Nat Commun. Jan 10, 2022;13(1):128. [FREE Full text] [doi: 10.1038/s41467-021-27595-9] [Medline: 35013206]
32. Hachim A, Gu H, Kavian O, Kwan M, Wai-hung C, Yau Y. The SARS-CoV-2 antibody landscape is lower in magnitude for structural proteins, diversified for accessory proteins and stable long-term in children. MedRxiv. Preprint posted online on January 4, 2021. [doi: 10.1101/2021.01.03.21249180]
33. Weisberg S, Connors T, Zhu Y, Baldwin M, Lin W, Wontakal S, et al. Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum. Nat Immunol. Jan 2021;22(1):25-31. [FREE Full text] [doi: 10.1038/s41590-020-00826-9] [Medline: 33154590]
34. Dowell AC, Butler MS, Jinks E, Tut G, Lancaster T, Sylla P, et al. Children develop robust and sustained cross-reactive spike-specific immune responses to SARS-CoV-2 infection. Nat Immunol. Jan 2022;23(1):40-49. [FREE Full text] [doi: 10.1038/s41590-021-01089-8] [Medline: 34937928]
35. Renk H, Dulovic A, Seidel A, Becker M, Fabricius D, Zernickel M, et al. Robust and durable serological response following pediatric SARS-CoV-2 infection. Nat Commun. Jan 10, 2022;13(1):128. [FREE Full text] [doi: 10.1038/s41467-021-27595-9] [Medline: 35013206]
36. Messiah S, DeSantis S, Leon-Novelo L, Talebi Y, Brito F, Kohl H, et al. Durability of SARS-CoV-2 antibodies from natural infection in children and adolescents. Pediatrics. Jun 01, 2022;149(6):e2021055505. [doi: 10.1542/peds.2021-055505] [Medline: 35301530]
37. Ulyte A, Radtke T, Abela I, Haile S, Braun J, Jung R, et al. Seroprevalence and immunity of SARS-CoV-2 infection in children and adolescents in schools in Switzerland: design for a longitudinal, school-based prospective cohort study. Int J Public Health. Dec 2020;65(9):1549-1557. [FREE Full text] [doi: 10.1007/s00038-020-01495-z] [Medline: 33063141]
38. Litvinova M, Liu QH, Kulikov ES, Ajelli M. Reactive school closure weakens the network of social interactions and reduces the spread of influenza. Proc Natl Acad Sci U S A. Jul 02, 2019;116(27):13174-13181. [FREE Full text] [doi: 10.1073/pnas.1821298116] [Medline: 31209042]

39. Cauchemez S, Ferguson N, Wachtel C, Tegnell A, Saour G, Duncan B, et al. Closure of schools during an influenza pandemic. Lancet Infect Dis. Aug 2009;9(8):473-481. [FREE Full text] [doi: 10.1016/S1473-3099(09)70176-8] [Medline: 19628172]
40. Bai Y, Yao L, Wei T, Tian F, Jin D, Chen L, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. Apr 14, 2020;323(14):1406-1407. [FREE Full text] [doi: 10.1001/jama.2020.2565] [Medline: 32083643]
41. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic transmission of SARS-CoV-2 — Singapore, January 23-March 16, 2020. MMWR Morb Mortal Wkly Rep. Apr 10, 2020;69(14):411-415. [doi: 10.15585/mmwr.mm6914e1]
42. Kam K, Yung C, Cui L, Tzer Pin Lin R, Mak T, Maiwald M, et al. A well infant with coronavirus disease 2019 with high viral load. Clin Infect Dis. Jul 28, 2020;71(15):847-849. [FREE Full text] [doi: 10.1093/cid/ciaa201] [Medline: 32112082]
43. Huff H, Singh A. Asymptomatic transmission during the coronavirus disease 2019 pandemic and implications for public health strategies. Clin Infect Dis. Dec 17, 2020;71(10):2752-2756. [FREE Full text] [doi: 10.1093/cid/ciaa654] [Medline: 32463076]
44. Jiehao C, Jin X, Daojiong L, Zhi U, Lei X, Zhenghai Q, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. Clin Infect Dis. Sep 12, 2020;71(6):1547-1551. [FREE Full text] [doi: 10.1093/cid/ciaa198] [Medline: 32112072]
45. Teherani M, Kao C, Camacho-Gonzalez A, Banskota S, Shane A, Linam W, et al. Burden of illness in households with severe acute respiratory syndrome coronavirus 2-infected children. J Pediatric Infect Dis Soc. Nov 10, 2020;9(5):613-616. [FREE Full text] [doi: 10.1093/jpids/piaa097] [Medline: 32780809]
46. Viner R, Russell S, Croker H, Packer J, Ward J, Stansfield C, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. Lancet Child Adolesc Health. May 2020;4(5):397-404. [FREE Full text] [doi: 10.1016/S2352-4642(20)30095-X] [Medline: 32272089]
47. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer S, Baysson H, et al. Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. Lancet. Aug 01, 2020;396(10247):313-319. [FREE Full text] [doi: 10.1016/S0140-6736(20)31304-0] [Medline: 32534626]
48. Gudbjartsson D, Helgason A, Jonsson H, Magnusson O, Melsted P, Norddahl G, et al. Spread of SARS-CoV-2 in the Icelandic Population. N Engl J Med. Jun 11, 2020;382(24):2302-2315. [FREE Full text] [doi: 10.1056/NEJMoa2006100] [Medline: 32289214]
49. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. ENE-COVID Study Group. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet. Aug 22, 2020;396(10250):535-544. [FREE Full text] [doi: 10.1016/S0140-6736(20)31483-5] [Medline: 32645347]
50. Heald-Sargent T, Muller W, Zheng X, Rippe J, Patel A, Kociolek L. Age-related differences in nasopharyngeal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) levels in patients with mild to moderate coronavirus disease 2019 (COVID-19). JAMA Pediatr. Sep 01, 2020;174(9):902-903. [FREE Full text] [doi: 10.1001/jamapediatrics.2020.3651] [Medline: 32745201]
51. Jones T, Biele G, Mühlemann B, Veith T, Schneider J, Beheim-Schwarzbach J, et al. Estimating infectiousness throughout SARS-CoV-2 infection course. Science. Jul 09, 2021;373(6551):eabi5273. [FREE Full text] [doi: 10.1126/science.abi5273] [Medline: 34035154]
52. Larosa E, Djuric O, Cassinadri M, Cilloni S, Bisaccia E, Vicentini M, et al. Reggio Emilia Covid-19 Working Group. Secondary transmission of COVID-19 in preschool and school settings in northern Italy after their reopening in September 2020: a population-based study. Euro Surveill. Dec 2020;25(49):2001911. [FREE Full text] [doi: 10.2807/1560-7917.ES.2020.25.49.2001911] [Medline: 33303065]
53. Zimmerman K, Akinboyo I, Brookhart M, Boutzoukas AE, McGann KA, Smith MJ, et al. Incidence and secondary transmission of SARS-CoV-2 infections in schools. Pediatrics. Apr 2021;147(4):e2020048090. [FREE Full text] [doi: 10.1542/peds.2020-048090] [Medline: 33419869]
54. Brandal L, Ofitserova T, Meijerink H, Rykkvin R, Lund H, Hungnes O, et al. Minimal transmission of SARS-CoV-2 from paediatric COVID-19 cases in primary schools, Norway, August to November 2020. Euro Surveill. Jan 2021;26(1):2002011. [FREE Full text] [doi: 10.2807/1560-7917.ES.2020.26.1.2002011] [Medline: 33413743]
55. Strategic plan 2020/2021-2024/2025. KwaZulu-Natal DOH. Mar 19, 2020. URL: https://www.kznhealth.gov.za/Strategic-plan-2020-2025.pdf [accessed 2024-11-26]
56. COVID-19 online resource and portal. National Department of Health, Republic of South Africa. URL: https://www.health.gov.za/covid19/ [accessed 2020-06-29]
57. Zimmermann P, Pittet LF, Curtis N. How common is long COVID in children and adolescents? Pediatr Infect Dis J. Dec 01, 2021;40(12):e482-e487. [FREE Full text] [doi: 10.1097/INF.0000000000003328] [Medline: 34870392]
58. The Revised Children's Anxiety and Depression Scale (RCADS). UCLA. URL: https://www.childfirst.ucla.edu/wp-content/uploads/sites/163/2022/01/RCADSUsersGuide20220125.pdf [accessed 2022-07-20]
59. Laboratory data management system. Frontier Science Foundation. URL: http://www.fstrf.org/ldms/ [accessed 2024-09-08]
60. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. Apr 2009;42(2):377-381. [FREE Full text] [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]

61. Harris P, Taylor R, Minor B, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. Journal of Biomedical Informatics. Jul 2019;95:103208. [FREE Full text] [doi: 10.1016/j.jbi.2019.103208]
62. COVID-19 and children. UNICEF. URL: https://data.unicef.org/covid-19-and-children/ [accessed 2023-03-01]

Abbreviations

CoKiDSS: COVID kids school study
CRS: clinical research site
LMIC: low- and middle-income country
PCR: polymerase chain reaction
SAMRC: South African Medical Research Council
UNICEF: United Nations Children's Fund

Edited by T Leung; submitted 13.09.23; peer-reviewed by D Gornyk; comments to author 21.07.24; revised version received 29.07.24; accepted 16.09.24; published 19.12.24

Please cite as:
Dassaye R, Chetty T, Daniels B, Gaffoor Z, Spooner E, Ramraj T, Mthethwa N, Nsibande DF, Pillay S, Bhana A, Magasana V, Reddy T, Mohlabi K, Moore PL, Burgers WA, de Oliveira T, Msomi N, Goga A
SARS-CoV-2 Infections in a Triad of Primary School Learners (Grades 1-7), Their Parents, and Teachers in KwaZulu-Natal, South Africa: Protocol for a Cross-Sectional and Nested Case-Cohort Study
JMIR Res Protoc 2024;13:e52713
URL: https://www.researchprotocols.org/2024/1/e52713
doi: 10.2196/52713
PMID: