Collision of Three Global Pandemics: The Effect of Tuberculosis and HIV on the Epidemiological, Clinical, Virological, and Immunological Trajectory of COVID-19 in Botswana and Namibia – a Protocol for a Prospective Case-ascertained and Surveillance Study

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Abstract

In December 2019, the emergence of Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to a global pandemic, impacting over 620 million people, including approximately nine million in Africa. The COVID-19 pandemic introduced uncertainties, especially regarding co-infections, such as tuberculosis (TB) and human immunodeficiency virus (HIV). TB and HIV, both global pandemics, disproportionately affect low and middle-income countries. Namibia and Botswana reported high mortality rates due to TB and HIV which highlights ongoing challenges. This paper outlines the protocol for a comprehensive research study addressing the gaps, focusing on Botswana and Namibia, to enhance disease management.

The collision of three global pandemics: the effect of TB and HIV on the epidemiological, clinical, virological, and immunological trajectory of COVID-19 in Botswana and Namibia (Core-NB), is a clinical and epidemiological study of (i) individuals presenting to sentinel health facilities irrespective of any symptoms are tested for Covid-19, TB and HIV/AIDS , and (ii) identified confirmed COVID-19 patients and their household contacts. For (i), attendees of primary healthcare facilities independent of the reason for attending were enrolled. For (ii) participants were identified based on laboratory RT-PCR confirmation of their COVID-19 infection at Ministry of Health designated laboratories in each country. Primary health care participants and their household contacts who agreed to participate in the study had home visits, including an initial enrollment visit at Day 1 and three follow-up visits occurring within 28 days of enrollment. Additionally, there were telephonic follow-ups three months after enrollment. Researchers collected specimens and gathered information regarding risk factors and symptoms from COVID-19 cases as well as from all individuals living in the same households.

Ethics approval was obtained from the University of Namibia Research Ethics Committee (HREC-H) and permission to conduct the study was granted by the Ministry of Health and Social Services (MoHSS) in Namibia and the Ministry of Health in Botswana (MoH). Participants gave informed consent. The consent forms were designed using plain language. The study was registered on Clinicaltrials.gov with number NCT05268380. Dissemination will be through scientific peer-reviewed papers and presentations at international meetings, and to study communities.

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ABSTRACT

In December 2019, the emergence of Coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led to a global pandemic, impacting over 620 million people, including approximately nine million in Africa. The COVID-19 pandemic introduced uncertainties, especially regarding co-infections, such as tuberculosis (TB) and human immunodeficiency virus (HIV). TB and HIV, both global pandemics, disproportionately affect low and middle-income countries. Namibia and Botswana reported high mortality rates due to TB and HIV which highlights ongoing challenges. This paper outlines the protocol for a comprehensive research study addressing the gaps, focusing on Botswana and Namibia, to enhance disease management.

The collision of three global pandemics: the effect of TB and HIV on the epidemiological, clinical, virological, and immunological trajectory of COVID-19 in Botswana and Namibia (Core-NB), is a clinical and epidemiological study of (i) individuals presenting to sentinel health facilities irrespective of any symptoms are tested for Covid-19, TB and HIV/AIDS , and (ii) identified confirmed COVID-19 patients and their household contacts. For (i), attendees of primary healthcare facilities independent of the reason for attending were enrolled. For (ii) participants were identified based on laboratory RT-PCR confirmation of their COVID-19 infection at Ministry of Health designated laboratories in each country. Primary health care participants and their household contacts who agreed to participate in the study had home visits, including an initial enrollment visit at Day 1 and three follow-up visits occurring within 28 days of enrollment. Additionally, there were telephonic follow-ups three months after enrollment. Researchers collected specimens and gathered information regarding risk factors and symptoms from COVID-19 cases as well as from all individuals living in the same households.

Ethics approval was obtained from the University of Namibia Research Ethics Committee (HREC-H) and permission to conduct the study was granted by the Ministry of Health and Social Services (MoHSS) in Namibia and the Ministry of Health in Botswana (MoH). Participants gave informed consent. The consent forms were designed using plain language. The study was registered on Clinicaltrials.gov with number NCT05268380. Dissemination will be through scientific peer-reviewed papers and presentations at international meetings, and to study communities.

INTRODUCTION

In December 2019, an emerging respiratory illness known as coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in China and spread worldwide [1]. Recognizing its rapid worldwide transmission and impact, the World Health Organization (WHO) officially designated it as a pandemic on March 11, 2020 [1]. This pandemic affected over 620 million individuals across the globe, with an estimated nine million cases reported on the African continent [1].

Emerging respiratory pathogens pose a significant challenge to public health systems worldwide, often characterized by initial uncertainty regarding their epidemiological, clinical, and virological characteristics. The COVID-19 pandemic exemplified this phenomenon, with many key parameters remaining uncertain during its early stages [2]. Since its initial detection, COVID-19 had an unprecedented global impact, manifesting with a spectrum of clinical outcomes ranging from asymptomatic and mild cases to severe illness and death, particularly among older adults and individuals with underlying health conditions, including tuberculosis (TB) and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) [3,4]. However, a critical knowledge gap persisted concerning the influence of co-infections, notably HIV and TB, on both the susceptibility to acquiring COVID-19 and the outcomes of COVID-19 [5,6].

TB and HIV, two co-existing global pandemics, disproportionately affect low and middle-income countries with fragile healthcare systems [7]. TB, caused by *Mycobacterium tuberculosis complex* (Mtbc) strains, affects approximately 25% of the world's population, resulting in more than 10 million new TB cases and 1.5 million deaths annually [7]. HIV continues to infect about 1.7 million individuals each year causing an estimated 770,000 deaths with particularly devastating effects in regions with high TB burdens [7] highlighting the ongoing challenges posed by the pandemic [8]. Given the overlapping epidemics of TB, HIV, and COVID-19 in countries like Botswana and Namibia, where high prevalence rates of both TB and HIV exist [9,10], understanding the interplay between these diseases was crucial for effective pandemic management.

To address critical research gaps, studies investigating the impact of TB and HIV co-infections on COVID-19 outcomes were urgently needed. While some preliminary research explored the relationship between TB co-infection and COVID-19 severity, such as a case-control study of 36 patients in China [11], larger, high-quality studies were necessary to provide comprehensive insights, and to develop evidence-based interventions to treat and prevent COVID-19 in countries with high TB and HIV burdens.

This paper presents the protocol for a comprehensive research project designed to address these knowledge gaps, including household contact tracing and clinical studies within healthcare facilities. This initiative, focused on Botswana and Namibia, aimed to shed light on the complex dynamics of COVID-19, TB, and HIV co-infections and ultimately improve the management and prevention of these diseases in resource-constrained settings.

METHODS AND ANALYSIS

Study setting

The study was conducted in Namibia’s Omaheke region and in Gaborone, Botswana from November 2021 to August 2024.

Figure 1.

Primary health care (PHC) and household contact (HHC) participants were identified and taken

through the informed consent process (see **Figure 1**). Questionnaires were captured directly onto tablets and samples from each participant were collected. Participants with an unknown HIV status received a rapid test and if positive a viral load and CD4 test were done. Respiratory samples for reverse transcription (RT)-PCR for SARS-CoV-2 identification and GeneXpert Ultra (Cepheid, Sunnyvale, CA) for TB identification were collected; when positive, whole genome sequencing for *MTBC* and TB culture were done. Venous blood samples were collected for COVID-19 serology, interferon gamma release assay (IGRA, QIAreach QuantiFERON-TB, Qiagen GmbH, Germany) for TB infection and a PaxGene tube (BD Biosciences, Franklin Lakes, New Jersey) for the biorepository.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. However, the National TB programmes and the National and Regional directorates of Health were informed about the study and collaborated with the study teams on implementation. Community leaders and healthcare personnel were informed about the study.

Component 1: Household contact tracing

Aim

To characterize the COVID-19 epidemic in conjunction with TB and HIV, in terms of clinical, epidemiological, virological, and immunological data, by conducting a household transmission study.

Design and population

This was a prospective case-ascertained study of all identified confirmed COVID-19 patients and their household contacts. The participants were identified based on laboratory RT-PCR confirmation of their COVID-19 infection by the MOH's designated laboratories in the respective countries. Household contacts who agreed to participate in the study had four home visits, including an initial enrollment visit (Day 1) and three follow-up visits which occurred within 28 days of enrollment. Additionally, there were telephonic follow-ups three months after enrollment. During the visits, researchers collected specimens and gathered information regarding risk factors and symptoms from the primary COVID-19 case and from all individuals living in the same household.

Sample Size

The expected number of household contacts in Namibia and Botswana is three [12,13]. Based on a study involving influenza as a proxy (due to the limited availability of COVID-19 household transmission studies at the time of study design), a minimum sample size of 309 participants, including both index cases and contacts, was required to investigate household transmission of influenza-like illness [14,15]. Our goal was to include 360 participants to account for missing information, with an equal distribution between Namibia and Botswana. In the general adult population, the expected latent TB infection prevalence exceeds 30% [16], and the HIV prevalence ranged from 11.5% [17] to 20.7% [18]. Consequently, we assumed that we would have included enough participants with latent TB and HIV infection to enable a meaningful comparison.

Data collection methods

This study involved several steps once a COVID-19 case was identified. A home visit was conducted to identify eligible household contacts, collect socio-demographic and clinical information, confirm secondary infections through molecular testing, and establish baseline antibody status. Data were captured directly into a REDcap web-based database using tablets and specimens were collected from both the case and household contacts during home visits on Day 1 (recruitment day), Day 7,

Day 14, and Day 28. Household contacts completed a baseline questionnaire to monitor relevant symptoms and assess vaccine hesitancy. The final outcome data were collected 90 days after the initial visit.

Laboratory evaluation

Upper respiratory tract specimens (nasopharyngeal/oropharyngeal swabs) and venous blood were collected from confirmed cases and their household contacts after the laboratory confirmation of the index case. Collection took place during the initial home visit. Respiratory specimens were taken from all household members, irrespective of symptoms, along with the administration of the baseline questionnaire. Blood samples were taken, stored in serum tubes, and subjected to the QIAreach QuantiFERON-TB (Qiagen GmbH, Germany) assay testing for the detection of *MTBC* infection. Additionally, for individuals with an unknown HIV status, a HIV rapid test was conducted, with a confirmatory additional rapid test, if it yielded a positive result. HIV-infected individuals had viral load and CD4+ cell count testing. Participants were asked to provide a sputum sample to detect active TB disease by GeneXpert Ultra (Cepheid, Sunnyvale, CA)). Follow-up specimens were collected as outlined in **Figure 2**. On Day 7 and Day 14 visits, respiratory specimens were collected from household members for virological testing, regardless of symptoms. On Day 14 and Day 28 visits, a serum sample for Wantai SARS-CoV-Ab assay (Beijing, China) and Platelia SARS-CoV-2 (Biorad, Hercules, CA) total antibody assay testing was obtained from household contacts. Extracted viral RNA and bacterial DNA were stored for subsequent viral targeted next generation sequencing (t-NGS) and bacterial whole genome sequencing (WGS) analysis respectively. WGS was carried out at Research Center Borstel (RCB). A lung ultrasound was conducted on symptomatic index cases and household contacts and a PAXgene (BD Biosciences, Franklin Lakes, New Jersey) tube collected for the sample repository on Day 7**.**

Figure 2.

Confirmed primary health care (PHC) cases were followed up on day 7,14 and 28. The household contacts (HHC) were identified, and specimens collected for laboratory testing on day 1. If results were negative the HHC was followed up with specimen collections on Day 7, 14 and 28. If the HHC tested positive for COVID-19 s/he became a confirmed case.

Component 2: Surveillance within healthcare facilities

Aim

To carry out targeted COVID-19 screening and testing in conjunction with TB and HIV case finding, by conducting a primary healthcare facility (PHC) surveillance study.

Study design

Sentinel surveillance sites for COVID-19, TB and HIV, were established, in two primary healthcare facilities in each country. All attendees at the primary healthcare facilities were approached consecutively, informed about the study, and invited to participate. Collection of specimens occurred at baseline.

Sample Size

The determination of the sample size was based on a comparative analysis of prior studies conducted in Burkina Faso and South Africa [19,20]. Our assumption was rooted in the expectation that a

proportion of primary healthcare (PHC) attendees would test positive for SARS-CoV-2, ranging from 5% to 20%. Given the uncertainty regarding the trajectory of the epidemic when the study was designed, we adopted conservative estimates.

To achieve a 5% confidence interval width when measuring seroprevalence in the PHC study, we calculated that we would need to test 118 participants if the estimated seroprevalence was 1%, 337 participants for an estimated seroprevalence of 5%, and 595 participants for an estimated seroprevalence of 10%. Due to the uncertainty surrounding prevalence estimates, our target enrollment was set at 1190 participants, with an allowance for a 9% non-response rate. This resulted in a final sample size of N=1120.

Data collection methods

Questionnaires: During the enrollment process, participants were interviewed by research assistants in a private area within the facility. Interviews were conducted in English or a local language, based on the participant's preference, and typically lasted approximately 15 minutes. Participants were requested to provide consent for accessing their medical records, including national HIV and TB databases, to capture their clinical history and the clinical course of COVID-19 if relevant. Additionally, questions addressing vaccine hesitancy were included in the questionnaire. HIV testing was conducted on individuals whose HIV status was unknown. HIV-infected patients who were not on treatment or newly diagnosed were referred to the facility for HIV counselling and care.

Specimens: Participants were directed to the study area for the collection of appropriate samples, including sputum or equivalent samples in children, nasopharyngeal or other respiratory samples, and blood specimens. Each specimen was labeled with a barcode and transported to the research laboratories for SARS-CoV-2 RT-PCR and Xpert Ultra testing for TB. Acknowledging the significance of asymptomatic and mild infections in propagating COVID-19 transmission, we implemented a policy of testing all consenting PHC attendees with RT-PCR, irrespective of their presenting symptoms.

Laboratory evaluation

During the enrollment process, each participant had the collection of three respiratory specimens:

1. Nasopharyngeal swab: This specimen was obtained for SARS-CoV-2 RNA extraction and subsequent SARS-CoV-2 PCR testing.
2. Xpert Ultra testing for TB: A specimen was collected for TB testing using Xpert Ultra.
3. Extra sputum sample: An additional sputum sample was collected for in case the Xpert Ultra was positive, to use for culture and drug susceptibility testing (DST).

Additionally, venous blood was drawn using standard phlebotomy techniques for immunological testing with the Wantai SARS-CoV-Ab and Platelia SARS-CoV-2 total antibody assays, interferon-gamma release assay (IGRA) to assess *Mtbc* infection, and for HIV CD4+ and viral load in participants with HIV-infection.

Laboratory methodology

The study involved several key laboratory procedures:

1. Detection of SARS-CoV-2: The presence of SARS-CoV-2 identification in respiratory samples using the qRT-PCR protocol established by the WHO [21].
2. Serological testing: Assessment of immunological memory carried out by measuring SARS-CoV-2-specific antibody levels through enzyme-linked immunosorbent assays (ELISA). Plasma samples were used to determine the presence of IgM and IgG antibodies, which indicated recent

(approximately 3-10 days) and past (>7 days) infection, respectively.

3. Sequencing: SARS-CoV-2 RNA was isolated from oro-/nasopharyngeal or gargled fluid specimens at the in-country laboratory. Positive samples had t-NGS to document the diversity of circulating SARS-CoV-2 genomes. Xpert Ultra positive sputum samples had a Mycobacterium Growth Indicator Tube (MGIT, BD, Maryland) culture and whole genome sequencing (WGS) analysis respectively. WGS was carried out at Research Center Borstel (RCB), Borstel, Germany.

Analysis

The primary healthcare facility (PHC) surveillance study and the household transmission study focused on the temporal, spatial, and demographic aspects of Covid-19 in conjunction with TB and HIV infection. It will provide insights into the clinical presentation and progression of COVID-19. Genomic analysis of SARS-CoV-2 specimens will provide a comprehensive understanding of the pandemic's origins, the potential emergence of antiviral resistance mutations, and the identification of transmission chains. This analysis will involve comparison of the relatedness of virus isolates, which will aid in estimating the basic reproduction number. Serological testing will enable the quantification of events leading to immunological responses, while the analysis of PAXgene samples will yield insights into the nature of the host response. Additionally, lung ultrasound assessments will allow for the quantification of respiratory impairment attributable to COVID-19, stratified by severity, patient characteristics, and comorbidities.

Ethical considerations

Ethics approvals and consent

Ethics approval was obtained from the University of Namibia Health Research Ethics Committee (HREC-H) and permission to conduct the study by the Ministry of Health and Social Services (MoHSS) in Namibia and the Ministry of Health in Botswana. Well-trained staff experienced in the conduct of clinical research informed participants about the study. Written information was provided to potential participants, allowing them enough time to consider participation and discuss it with their family or friends, if desired. The consent forms were designed using plain language. For minors (individuals under the age of 18), consent was required to be signed by their parent or legal guardian prior to their inclusion. Additionally, assent forms were developed for adolescents aged 8 to under 18 who were deemed competent to provide their assent. All consent and assent forms contained detailed information regarding HIV testing and the potential secondary use of biological samples for future research purposes.

Data collection concerning individuals under 18 years of age was divided into two categories: (1) those who were of an appropriate age and possessed sufficient conceptual understanding to provide assent (typically around 8 years old or older), and (2) those who were either too young or lacked the necessary conceptual understanding to assent. For the first category, we upheld their autonomy by requiring both written consent from their *de facto* caregiver (determined on the day of enrollment) and written assent from the child. In the case of the second category, only consent from their caregiver was required; however, field staff made appropriate efforts to verbally engage with the child and explain the purpose of data collection in the home. The field staff underwent specific training to assess the capacity of children to provide assent. It was emphasized that individuals had the right to decline participation in the study without providing a reason, and once enrolled, they retained the freedom to withdraw at any time without the obligation to provide an explanation. Potential participants were assured that their decision to participate or not would not impact the

clinical care they will receive.

Minimizing the risk of study participation

Given that the study was observational in design, there were no anticipated risks to participants in addition to routine investigations conducted at the facility. Patients with co-morbidities, particularly those with HIV or TB, were referred and followed-up to receive appropriate care through routine health services. Rapid HIV tests were conducted, and the results promptly made available to participants. In the case of a confirmed positive result, participants were referred to the nearest healthcare facility for initiation of HIV care.

Respiratory sampling, both for TB and COVID-19, is a simple, well-tolerated, and risk-free procedure. These procedures are routinely conducted in public health systems, known to be safe, and generally well-tolerated. The total blood volumes and blood volumes per visit were minimal and within the limits allowed for research. Lung ultrasound testing is a straightforward and risk-free procedure.

Privacy and Data Security

Case report forms (CRFs), clinical notes, and administrative documentation were stored in a secure location, specifically locked filing cabinets within a restricted-access room. These records will be retained for a period of five years following the conclusion of the study. Throughout this duration, the data will remain accessible to competent or equivalent authorities and the funding entity, provided suitable notice is given. Electronic data are securely stored in password-protected files on computers with password protection measures in place. All personally identifiable information is kept separate from clinical data and is solely linked through a personal identifier number. No personally identifiable information is transferred to any analytical database used for data analysis. To ensure effective data management, the expertise of a skilled data officer was enlisted.

DISCUSSION

Our study was developed in response to the COVID-19 global pandemic to answer critical questions concerning how this disease manifests itself in the context of low resource countries with a high burden of poverty, and in the presence of high rates of TB and HIV. The study will document how the virus spread within susceptible populations. The development of this proposal was highly collaborative, with investigators from Namibia and Botswana working closely with colleagues in Europe.

The study was conducted in two components. The first followed the World Health Organization protocol for household transmission investigations in the context of COVID-19 [22], explored how commonly household transmission occurs and described the spectrum of disease seen. We collected respiratory samples and blood to analyse viral molecular epidemiology and host immunological responses. The second component evaluated the presentation, diagnosis and clinical characteristics of individuals presenting to sentinel health facilities in both countries, for Covid-19, TB and HIV.

Furthermore, the study assisted in guiding the national response to COVID-19 in both countries as well as assisting with our understanding of the pathogenesis of the virus in the context of TB and HIV, in turn providing vital information in how to deliver clinical care and how to design therapeutics and vaccines.

The scientific advisory committee (SAC) consisted of independent internationally renowned scientific experts. The SAC was invited to attend the kickoff meeting, as well as the progress and

final meetings. They provided critical feedback after the scientific sessions. The EDCTP project officer was an observer on the SAC. After the meetings, the SAC submitted a feedback report to the consortium including a concise SWOT analysis.

In summary, the study worked towards establishing a regional clinical and research hub. This will provide training and capacity building for public health, laboratory techniques and epidemiology. It developed a consortium of researchers who working together and developing research infrastructure and training, data and laboratory systems and to help train the next generation of African researchers. The collaborators are currently working on final reports and analyses.

LIST OF ABBREVIATIONS

RT-PCR – Reverse transcription polymerase chain reaction

CRF - Case Report Forms

DNA - Deoxyribonucleic Acid

EDCTP - European and Developing Countries Clinical Trials Partnership

HIV - Human Immunodeficiency Virus

MOHSS - Ministry of Health and Social Services

MTB - Mycobacterium tuberculosis

NGS - Next Generation Sequencing

TB - Tuberculosis

UNAM - University of Namibia

HREC - University of Namibia Health Research Ethics Committee

WGS - Whole genomic sequencing

WHO - World Health Organization

DECLARATIONS

Author contributions

MC, CM, SN, TK conceptualized and designed the study. MC, CM and SN wrote the grant applications. AD drafted the protocol manuscript. MC gave detailed input into the manuscript. All authors contributed to the final version of the manuscript and agreed to submission. MC is the guarantor.

Consent for publication

Not applicable.

Availability of data and materials

The stakeholders are involved in the preparation of manuscripts for international peer reviewed journals under the leadership of the PIs. Papers will be submitted after the approval of all stakeholders and submission of a final report to MOH. The data have been presented at international conferences. Data will be made available for further analyses after the primary outcome paper has been published.

Competing interests

The authors declare that they have no competing interests.

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Figure legends
Figure 1: Core-NB study flow
Figure 2: Case investigation algorithm and summary of data-collection tools (household transmission study)

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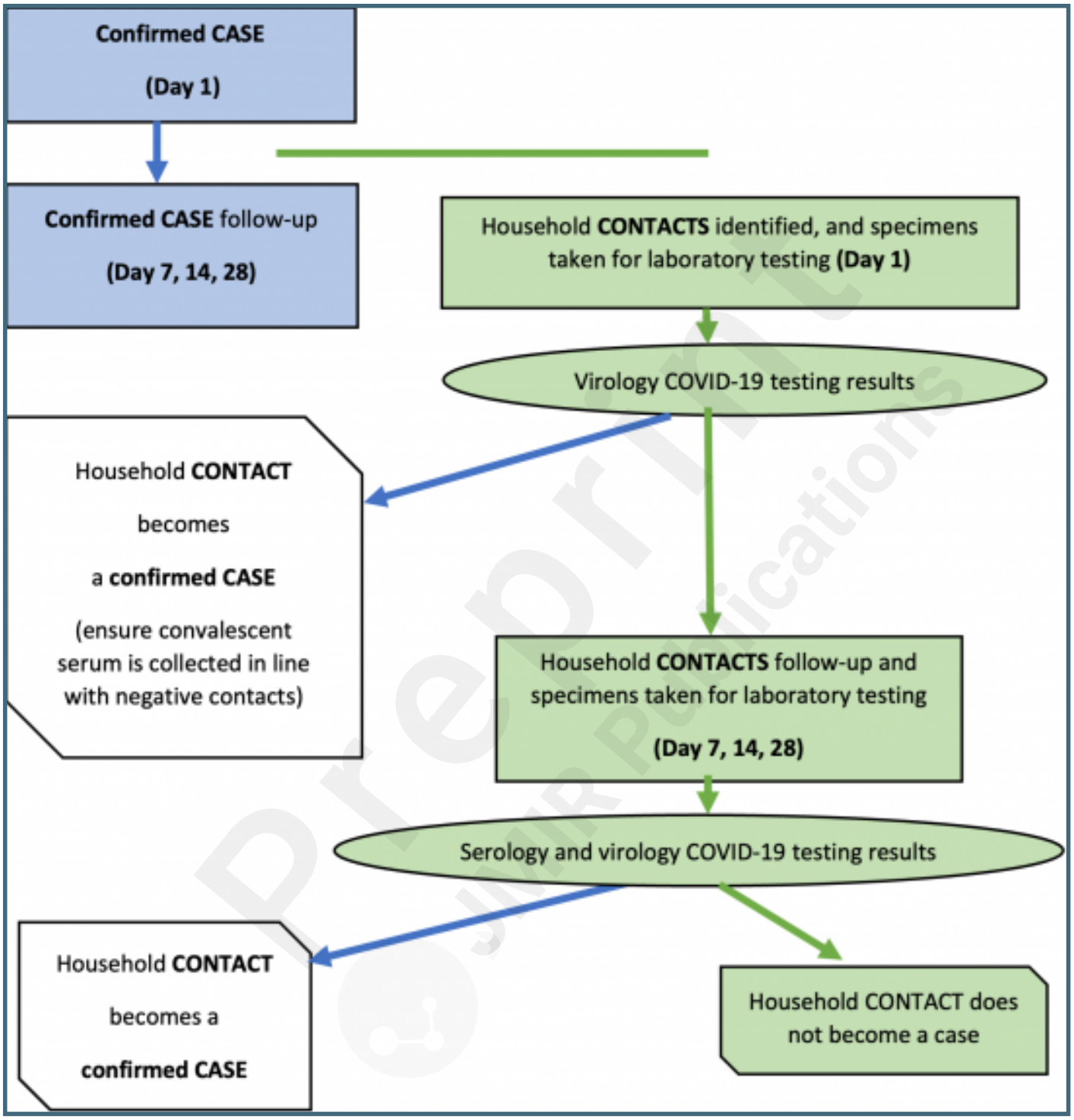
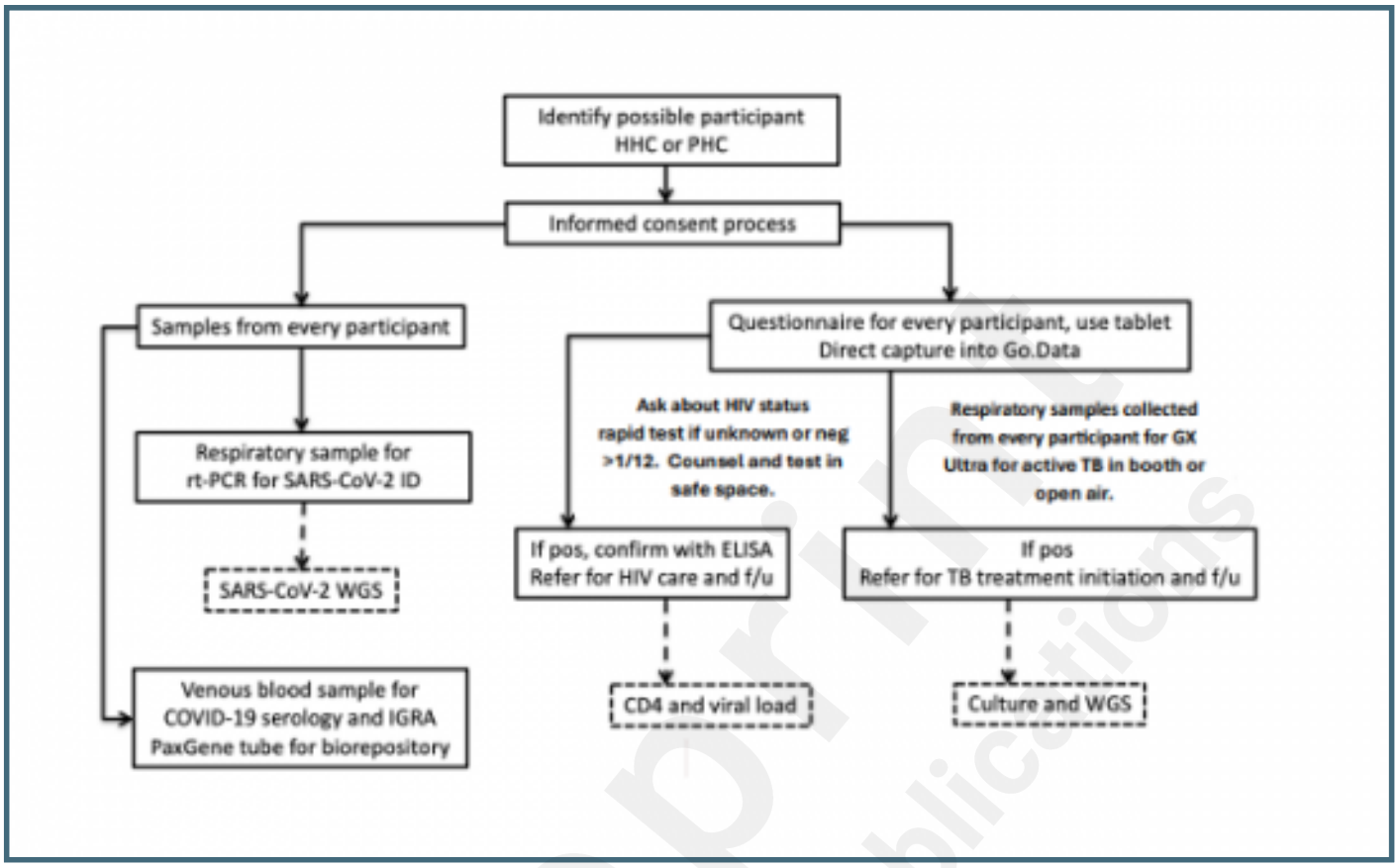
Supplementary Files

Untitled.


Confirmed CASE
(Day 1)
Confirmed CASE follow-up
(Day 7, 14, 28)
Household CONTACTS identified, and specimens taken for laboratory testing (Day 1)
Virology COVID-19 testing results
Household CONTACT becomes a confirmed CASE (ensure convalescent serum is collected in line with negative contacts)
Household CONTACTS follow-up and specimens taken for laboratory testing (Day 7, 14, 28)
Serology and virology COVID-19 testing results
Household CONTACT becomes a confirmed CASE
Household CONTACT does not become a case

Figures

Core-NB study flow.



Multimedia Appendixes

Funding review by EDCTP.
URL: http://asset.jmir.pub/assets/cd74107cdb9ba319c9b21c8db6e12da3.pdf

Ethics review by EDCTP.
URL: http://asset.jmir.pub/assets/715284fb560be4aed66809dd4a776107.pdf