

ANCILLARY RESEARCH STUDY PROTOCOL

**Factors affecting transmission of SARS-CoV-2 in Households
of SARS-CoV-2 patients in Sub-Saharan Africa**

**ANTICOV-EPI
Version 8.0 19/02/2021**

In

Principal investigator	<i>Please complete</i>
Scientific leads	Institute of Tropical Medicine

SIGNATURE PAGES

Sponsor Signatures

I have read and approved this protocol. My signature, in conjunction with the signatures of the Investigators, confirms the agreement of the Sponsor and Investigator that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

Signature of the Sponsor’s Medically Responsible Person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: _____ Role: _____
Date: _____ Signature: _____

Signature of the Scientific lead

The signatory agrees to the content of the final clinical study protocol as presented.

Name: _____ Role: _____
Date: _____ Signature: _____

Research study protocol: Ancillary epidemiologic study to AntiCOV study

Signature of Site Principal Investigator

I have read this protocol and agree that it contains all information necessary to carry out the study. I will conduct the study as described herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the study. I will discuss this material with them to ensure they are fully informed regarding the drug and the conduct of the study.

I will use only the Informed Consent Form approved by the Sponsor or its representative and will fulfil all responsibilities for submitting pertinent information to the Ethics Committee (EC) responsible for the study if required by national law.

I agree that the Sponsor or its representatives shall have access to any source documents from which case report form information may have been generated.

I agree that the study will be conducted in accordance with all applicable laws and regulations, including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Name:

Affiliation:

Date:

Signature:

.....

.....

TABLE OF CONTENTS

SIGNATURE PAGES	2
TABLE OF CONTENTS	4
LIST OF ABBREVIATIONS	6
1. INTRODUCTION	7
1.1 Background and Rationale	7
2. STUDY OBJECTIVES AND ENDPOINTS	8
2.1 Study Objectives.....	8
2.1.1 Primary objectives	8
2.1.2 Secondary objectives	9
2.1.3 Exploratory objectives	9
2.2 Study Endpoints	9
2.2.1 Primary Endpoints	9
2.2.2 Additional secondary endpoints.....	9
2.2.3 Additional exploratory endpoints.....	10
3. STUDY DESIGN	10
4. PARTICIPANTS, POPULATION & SELECTION	12
4.1 Study Setting, Population and Sampling Strategy.....	12
4.2 Inclusion and Exclusion Criteria	13
4.3 Sample size.....	13
4.4 Discontinuation/Withdrawal Criteria.....	14
4.6 End of study	14
5. PROCEDURES	14
5.1 Obtaining informed consent	14
5.2 Specific procedures and activities.....	16
5.3 Data collected (see Figure 1 and Figure 2 for summary)	18
5.4 Laboratory procedures (see Figure 1 and 2).....	19
5.5 Safety assessments	20
6. STATISTICAL METHODS	20
6.1 Statistical analysis	20
6.1.1 Analysis populations	21
6.1.2 Baseline characteristics	21

Research study protocol: Ancillary epidemiologic study to AntiCOV study

- 6.1.3 Primary Analysis..... 21
- 6.1.4 Secondary and exploratory analysis 21
- 6.1.5 Subgroup analyses 21
- 6.1.6 Multiplicity and Missing Data 21
- 7. DATA MANAGEMENT/ETHICS AND LEGAL ASPECTS 21**
 - 7.1 Data and sample management 22
 - 7.2 Costs for Patients 23
 - 7.3 Risks and benefits 23
 - 7.4 Community engagement..... 23
- 8. REFERENCES 25**
- ANNEX 1 27**
 - Symptom diary 27

LIST OF ABBREVIATIONS

BP	blood pressure
COVID-19	coronavirus disease 2019
eCRF	electronic case report form
HCQ	hydroxychloroquine
HIV	human immunodeficiency virus
RR	respiratory rate
SARS-CoV-2	severe acquired respiratory syndrome - coronavirus 2
SpO2	blood oxygen saturation level
WHO	World Health Organisation
HHC	Household contacts
HH	Households
RT -PCR	Reverse Transcription Polymerase Chain Reaction
Ag-RDT	Antigen Rapid Diagnostic Test
NP	Nasopharyngeal

1. INTRODUCTION

1.1 Background and Rationale

Control measures against COVID-19 in higher income countries have focused on physical distancing and lockdowns which have had success in reducing population transmission [1, 2]. However, in lower resourced countries with populations that live day by day, lockdown is unsustainable. Other measures to reduce transmission will need to be considered.

Several therapies improve individual patient clinical outcomes through a variety of effects including inhibiting viral replication. By doing so, therapies may also reduce transmission. SARS-CoV-2 binds to ACE2 receptors in the upper and lower respiratory tract [3] and cases can be very infectious. The basic reproduction number (R_0) of SARS-CoV-2 has been estimated as between 2-5 in data from high intensity outbreak zones [4, 5], higher than influenza for instance (R_0 1.3) [6] possibly because of pre-symptomatic transmission, high viral load in upper respiratory tract and possibly prolonged shedding [4, 7, 8], as well as an immunologically naive population. To date, COVID-19 has not been reported as frequently as feared in Africa, suggesting that the R_0 may be currently lower than reported in outbreak zones. Reasons for this are not clear since other respiratory viruses such as influenza seem to have as high burden in the African region as elsewhere [9]. Drug therapy of COVID-19 patients with mild/moderate disease, may prevent progression to severe disease, but may also reduce the viral load in the upper respiratory tract, the duration of symptoms and the duration of virus shedding. In turn, this would be expected to reduce transmission to contacts. In vitro studies show that hydroxychloroquine and lopinavir/ritonavir have antiviral effects on SARS-CoV-2 or Middle East Respiratory Syndrome (MERS) [10, 11]. Some evidence suggests that lopinavir/ritonavir may lower viral loads in respiratory swabs in SARS patients [12], and hydroxychloroquine may reduce viral load and shedding in COVID-19 patients [13]. Therefore it is plausible that these drugs, or other drugs with antiviral activity, may reduce transmission through the reduction in level and duration of viral shedding.

Any effect on transmission may be independent of the clinical effectiveness of the therapy; transmission may be reduced with no significant effect of therapy on clinical progression, for instance if pathology is immune modulated, or conversely, successful clinical treatment may have no practical effect on transmission if there is a threshold effect of viral load for transmission.

It remains unclear, however, how much of transmission is within households and how much is from outside the household. Reported secondary attack rates in households have varied from 11 to 75% [14-17], and this rate will vary with setting and interactions within the household. Also studies have been inconsistent with the use of seroconversion or clinical illness as an endpoint to calculate the attack rate- use of clinical illness only will underestimate attack rate because approximately 80% of SARS-CoV-2 infection may be asymptomatic [18], yet infected individuals still shed virus and contribute to transmission [7].

As yet, there are few data from Africa on the clinical presentation and risk factors for infection and illness. Households studies also allow a full and unbiased characterization of the clinical presentation, risk factors for infection and illness. Moreover, prospective household studies allow for understanding basic parameters of transmission in households, such as the secondary attack rate (probability that infection occurs among susceptible household contacts within a reasonable

Research study protocol: Ancillary epidemiologic study to AntiCOV study

incubation period following known contact with an index case), risk factors for transmission and disease, and the potential impact of drug treatment and preventive measures, such as mask-wearing and physical distancing on the transmission of SARS-CoV-2.

Understanding risks for household transmission and role of drugs with antiviral activity -in reducing this burden will be very important in the near future, since if case numbers rise, mild/moderate cases may no longer be isolated in facilities, and these data therefore will feed directly into policy on how best to control COVID-19 in different settings. This protocol is informed by the WHO UNITY Study protocol for household transmission [19] and aims primarily to look at household transmission in four sites in Africa.

Implementing measures for protecting populations not only requires better understanding of risk factors and timing for household transmission, but it also requires the proper testing tools for contact tracing. Assays should provide rapid results at point of sampling while remaining cheap and sensitive, allowing effective, targeted and fast public health measures. In September 2020, the WHO started recommending Antigen Rapid Diagnostic Tests (Ag-RDT) to be used on nasopharyngeal swabs for contact tracing [20]. These tests have varying sensitivity but consistently high specificity (> 97%).

Although nasopharyngeal (NP) swabbing has been shown to be the most sensitive method for detection of SARS-CoV-2 via PCR, collection of NP swabs can cause discomfort and therefore acceptability is low. Swabbing of both anterior nares (nasal swab) and subsequent testing by PCR however, has a better acceptability and has been progressively rolled out and recommended [21] as a method with acceptable sensitivity. Similarly, the current recommended specimen for testing by Ag-RDTs is a NP swab [20] but data is lacking on accuracy of Ag-RDT on nasal swabs, especially in heterogenous populations representative of contacts of known cases (with symptomatic and asymptomatic adults and children). Data on the accuracy of Ag-RDT with nasal swabs collected and tested in a household are key to understand if Ag-RDT can play a role in rapid contact tracing in a community.

This study thus additionally aims to validate the use of Ag-RDT on nasal swabs in a population of mildly symptomatic cases and their close contacts, regardless of age and symptoms.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary objectives

- 1) To estimate the effect of treatment on the secondary attack rate of SARS-CoV-2 infection and illness in household contacts.
- 2) To understand the overall extent of transmission of SARS-CoV-2 within a household, irrespective of treatment.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

2.1.2 Secondary objectives

- 1) To understand the extent of transmission of SARS-CoV-2 within a household, before isolation of index case.
- 2) To characterize the clinical presentation of COVID-19 secondary cases including the range of symptoms and the fraction of asymptomatic infections.
- 3) To determine risk factors for household infection and illness of SARS-CoV-2, including viral load and symptoms of index case, household and individual characteristics and behaviours to prevent infection.
- 4) Duration and level of shedding of SARS-CoV-2 among patients with SARS-CoV-2 infection.
- 5) Evaluate the sensitivity and specificity of Ag-RDT compared to PCR in persons with symptomatic (mild/moderate) and asymptomatic COVID-19 illness

2.1.3 Exploratory objectives

- 1) Baseline seroprevalence of anti-SARS-CoV-2 antibodies in households of populations served by sites.
- 2) To estimate the effect of treatment on hospitalisation and death for COVID-19 among household contacts.
- 3) Determine sequences of infecting SARS-CoV-2 strains and association with transmission and symptoms and clinical outcomes.
- 4) Seroprevalence and seroincidence of other respiratory pathogens in the study population.
- 5) Prevalence and incidence of other respiratory pathogens in the study population.
- 6) Description of the kinetics of Ag-RDT positivity compared to PCR over a period of 2 weeks in persons with symptomatic (mild/moderate) and asymptomatic COVID-19 illness.

2.2 Study Endpoints

2.2.1 Primary Endpoints

- 1) Seroconversion for SARS-CoV-2 IgM, IgA and IgG among household contacts and index case.
- 2) RT-PCR SARS-CoV-2 positive results at Day 1 (index case)/D2(household contacts), 7, 14, 21, and Month 1 in household contacts and index case.
- 3) Secondary attack rate of infection and illness for household contacts from index cases

2.2.2 Additional secondary endpoints

- 1) Mild, moderate and severe COVID-19 disease individual outcomes in household contacts
- 2) Sequence of SARS-CoV-2 in RT-PCR positive samples
- 3) Quantitative measure of viral load as measured by Ct values in RT-PCR
- 4) Quantitative levels of antibodies (IgM, IgG, IgA) against SARS-CoV-2.
- 5) Quantitative levels of antibodies (IgM, IgG, IgA) against other coronaviruses circulating in participating countries.
- 6) Results classified as positive, negative and inconclusive of Ag-RDT at D0/D1, D2, D7, D14 in nasal swab among mild symptomatic SARS-CoV-2 cases and their household contacts.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

2.2.3 Additional exploratory endpoints

- 1) RT-PCR positive results at Day 0/1,2, 7, 14, 21, and Month 1 in household contacts and index case for other respiratory pathogens circulating in participating countries.
- 2) Quantitative levels of antibodies (IgM, IgG, IgA) against other respiratory pathogens circulating in participating countries.
- 3) 3. Study Design

The study (ANTICOV-EPI) will be an ancillary study of the “An open-label, multicentre, randomised, adaptive platform trial of the safety and efficacy of several therapies, including antiviral therapies, versus control in mild/moderate cases of COVID-19” study. ANTICOV-EPI is a prospective study of household contacts (HHC - defined as sharing same cooking area) of COVID-19 patients enrolled in ANTICOV. Index cases (defined here as the first patients of a household enrolled in the Master Protocol) and their HHC will be followed up for 1 month with day 1 (D1) being the start of the index case treatment, to assess rate and characteristics of infection and illness in that period, and correlate with viral shedding in index case, risk factors for infection and protective measures taken. Based on the master protocol, baseline screening, enrolment and randomisation can be the same day - either on D0 or D1, and as such they can also be the same day in the ANTICOV-EPI study. Respiratory samples will be collected for RT-PCR and Ag-RDT for SARS-CoV-2 to assess presence of virus and viral load. Blood will be collected for serology. Risk factors for infection and illness will also be gathered. Some asymptotically infected household contacts will be approached for inclusion into the ANTICOV-IMMUNO study (See ANTICOV-IMMUNO ancillary protocol and flowchart).

Mild/moderate patients who are recruited by ANTICOV will be asked if their household contacts (HHC) can be contacted by the study team for recruitment into ANTICOV-EPI. The index will be consented into ANTICOV-EPI as will the HHC.

Master clinical trial

For the index cases enrolled in ANTICOV-EPI, in addition to the master protocol (ANTICOV), the following adjustments will be made and additional data are to be collected (see Figure 1):

- Patients will have the option to separately consent for this ancillary study.
- Patients will be asked for contact details of their household.
- Patients will only be recruited in a limited number of sites fully equipped for the planned analyses and participating in ANTICOV-EPI (outlined in 4.1)
- Initial demographic data, medical history, clinical information of index patient will be captured from the Master protocol.
- Additional data from index patients will be gathered as outlined in Figure 1.
- All additional ancillary patient data will be collected on eCRFs similar to those of the master protocol.

Assessments for index cases and HHC are noted in the study schedule and design (see Figures 1 and 2)

Research study protocol: Ancillary epidemiologic study to AntiCOV study

	Index					
	D0/D1*	D2	D7*	D14*	D21*	M1
Household visit		X	X	X	X	X
Additional ICF	X					
Clinical assessment and exam	FROM MASTER PROTOCOL (D1-D21)					X
Respiratory Swab for PCR	X		X	X	X	X
Respiratory swab for Ag-RDT	X		X	X		
Blood collection	X			X		X
Data on measures taken by index to reduce transmission	X		X	X	X	X

****Clinical assessments of the master protocol will be conducted at investigational site***

Figure 1: Additional study schedule for mild/moderate COVID-19 patients included in the master study.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

	HHC					
	D2	D7*	D14*	D21*	M1*	D2-M1
Household visits	X	X	X	X	X	
ICF	X					
Respiratory swab for PCR	X	X	X	X	X	
Respiratory swab for Ag-RDT	X	X	X			
Blood collection	X		X		X	
Data on measures taken by HHC to reduce transmission	X	X	X	X	X	
Patient screen and if positive physical exam	X	X	X	X	X	
Daily symptom diary						X
Data on Household characteristics	X					

**Clinical assessments of the master protocol will be conducted at investigational site in case the HHC is also enrolled in the master trial*

Figure 2: Study schedule for Household Contacts of Index case.

If a HHC becomes positive, he/she stays in the epidemiological study while being offered to be screened for the master study.

4. PARTICIPANTS, POPULATION & SELECTION

4.1 Study Setting, Population and Sampling Strategy

Patients and household will be planned to be recruited in several sites participating in the master protocol. Site selection will depend on patient load and capacity at start of the ANTICOV trial. ANTICOV-EPI will preferably be conducted in sites where ambulatory care is provided, where the paracetamol arm is included, and that are also conducting the ANTICOV-IMMUNO study. The total sample size of up to 700 index cases and their households will be distributed across several sites for an average of 175 households per site. The number of households enrolled by each site, and into which arm, will vary according to the epidemic rollout and arms implemented as per the Master protocol. Sites will be allowed to enrol index cases and their household contacts even if the index is isolated in a facility. The balance and total number of recruitments into each arm will vary by sites according to reality and intervention arm implemented.

4.2 Inclusion and Exclusion Criteria

In order to be eligible, study participants must meet all inclusion criteria and none of the exclusion ones as outlined below:

Inclusion criteria of index case

1. Able and willing to provide consent
2. Comes from household in accessible area
3. At least 1 HHC currently residing at household with index
4. Contact details of HH provided by index case
5. Majority (over 50%) of HHC provide consent and enrol in the ANTICOV-EPI study
6. Randomised to ANTICOV

Exclusion criteria of index case

1. a. For index cases belonging to households of 6 or more: More than 3 household members (including the index case) are known to have tested positive for SARS-CoV-2 in the past 7 days

b. For index cases belonging to households of 5 or fewer: More than 50% of the household members (including the index case) are known to have tested positive for SARS-CoV-2 in the past 7 days

Inclusion criteria of household contacts

1. Able and willing to provide consent
2. Index case enrolled in the epidemiological study
3. Member of same household as index case (household defined as sharing same cooking area) during the conduct of the study
4. Resides in household with index case before index case illness onset.
5. Majority (over 50%) of HHC provide consent and enrol in the ANTICOV-EPI study

4.3 Sample size

One study from China of 77 cases with 155 household contacts found a secondary household attack rate of 30% only using PCR on symptomatic cases and the number of contacts in households was low (<2)[16]. A second study from China with 105 cases and 392 HHC found a secondary attack rate of 16.3% with systematic testing, but no serology [15]. A third study in China found a household clinical attack rate of 11.2% [14] and a fourth study in Germany found a household clinical attack rate of 75%[17]

We assumed an attack rate of 25% in this study and we propose to include asymptomatic HHCs with seroconversions which will be higher than the clinical attack rate. We wish to detect a reduction of public health significance of at least 35% in transmission from index to HHC, therefore to establish a mean household attack rate of 16.25% in households with index cases treated with an antiviral

Research study protocol: Ancillary epidemiologic study to AntiCOV study

intervention compared with an attack rate of 25% in household with an index treated with paracetamol.

To obtain a power of 80% at 5% significance level to detect a difference of 35% in attack rate between one active drug arm (e.g. hydroxychloroquine) or lopinavir/ritonavir (LPR)) and paracetamol we need 217 households with a mean of 4 persons per household. In order to compare up to two additional other antiviral arms with paracetamol we need an additional 50% for each arm for a total of 434 HH. Since some index cases may not return to households once randomised and remain quarantined in a facility, we increase the total number of households by 100. This is in order to understand transmission before treatment. The number of households enrolled is then 534 households. To adjust for some presymptomatic shedding which will reduce power to detect a difference between treatment arms (10%)[22-24] and for loss to follow-up (15%) we plan to enroll up to 700 households in this study. The number of persons enrolled will vary depending on average household size which depends on size of household. **Assuming a mean household of 4 (index plus 3 HHC), we will enroll up to 700 index cases with up to 2100 household contacts.**

4.4 Discontinuation/Withdrawal Criteria

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time for the following reasons:

- At the request of the Investigator if s/he thinks that study participation is no longer in the best interest of the patient
- At the request of the Investigator if s/he thinks that the patient is at significant risk of failing to comply with the provisions of the protocol so as to cause harm to her/himself or seriously interfere with the validity of the study results
- At the request of the ethics committee or regulatory authorities in the exercise of their duties, or of the Sponsor.

If a patient withdraws his/her consent for future collection of information, the Sponsor may retain and continue to use any data collected before consent was withdrawn, unless the participant or legal guardian explicitly requests to withdraw his/her data.

If a patient withdraws from the study, s/he may request destruction of any samples collected and not tested, and this must be documented in the Investigator Site File.

4.6 End of study

The end of the study is considered the date of completion of all study objectives and analysis. The Competent Authority (CA), the applicable EC and the Institutional Review Boards (IRBs) will be informed within 90 days of the end of trial.

5. PROCEDURES

5.1 Obtaining informed consent

We will first obtain informed consent from the index case at D1 and obtain contact details for the household. We will then visit the household within 24 hours.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

At this baseline visit, called D2 (day after enrollment of the index case), household contacts (HHC) of the index case, (defined as persons using the same cooking area) will be approached for consent to be enrolled in the study.

The informed consent procedure will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, etc. Participants will be informed that participation in the study is completely voluntary. They will also be informed that they may withdraw from the study at any time without any negative consequences. Patients will have the option to separately consent for and withdraw from this ancillary study.

No participant may be enrolled in the study and no data nor study sample collection will take place until the study investigator or designee has obtained his/her informed consent. All informed consent procedures will be conducted by qualified staff members identified by the principal investigator and done in the language chosen by the participant. Participant Information Sheets and Consent Forms will be provided to the study participants for review. The participants will be given enough time to consider whether or not to participate in the study.

If a participant wishes to not be further swabbed for Ag-RDT at any time in the study, he/she can still continue participating in the EPI study with swabbing for PCR testing only.

Participants will be asked in writing on the informed consent form to consent, as an optional tick box in the ICF, for long term storage of samples pertaining to the study (max 25 years after final study report), in some countries depending on the country/institutional legislation or guidelines it may be for a shorter duration and this will be specified in Country Specific ICFs) for future testing, with the exception of genetic testing. Future testing may include repeat and confirmatory testing to arrive at a proper diagnosis, or additional research within the scope of infectious diseases' research. Before samples will be used or shared for secondary research, approval from the sponsor and the ethics committee will need to be obtained. For future studies not in line with infectious disease research, the participants may be re-contacted and asked for IC as per IRB/EC advice. If a participant refused long-term storage, his/her samples will be destroyed after the submission of the final study report (end of the study).

The link between biological specimens and personal identifiers of the donors will at all times be secured by data management and will not be shared/used in future pseudo-anonymized analyses unless patient safety is compromised.

For participants under 18 years of age, parental/legal guardian consent will be provided in writing after explanation of the study, its risks and benefits to both the parent/legal guardian and the child. For adolescents, oral assent will be asked for. When appropriate and for children below age of assent, the participation and procedures of the study will be explained in lay language to the child and the study team will ensure comprehension by the child.

5.2 Specific procedures and activities

For the index, relevant D0 to D21 patient data will be collected as part of the eCRF of the main protocol with the adjustments mentioned below and collected in the additional epidemiology study in the same eCRF.

The index will be informed of this study at Day 0 to check with him/her how many of his/her household contacts were tested positive in the past 7 days, and to allow him/her to discuss it with his /her household contacts. On the same day or at Day 1 the index will consent for this study at the health facility. At the Day 2 household visit (at least 24h after enrollment of the index case), household characteristics such as size/type/location of house, composition of household members and metrics of socioeconomic status will be gathered. The majority of HHC should be enrolled into study and all should provide informed consent. For each enrolled HHC, demographic and medical history will be obtained, including known HIV status and diagnosis of other comorbidities such as tuberculosis. Also information on contact with index patient in the week before illness and since illness, including mask use will be asked, as well as baseline data on hand washing, and daily contact with index. A baseline respiratory swab and blood sample will be collected from all HHC. HHC will be asked to keep a symptom diary on paper. (see Annex 1) Symptoms of the index case will be monitored via the master protocol, and at the household visit at Month 1 for the last week of the epidemiological follow-up. One thermometer will be given per household with the appropriate number of probe covers, so that the participants can measure their temperature when feeling unwell and check that their fever is over 38°C.

Household visits will be made at D2, 7, 14, 21, Month 1 . At each visit timepoint, a questionnaire will be administered to screen for COVID clinical symptoms (Section 6.3.1.4 of Master Protocol), contact with index case and protective measures implemented by index and contacts.

If a visit cannot be made on the ascribed day, the next nearest alternative day will be scheduled as long as it is not within 2 days of next scheduled household visit.

Visits will be made in Personal Protective Equipment (PPE) for study staff, with appropriate training and fit testing for N95 masks or equivalent. If study staff run short of PPE or teams are not allowed to enter households, the number of visits will be reduced and/or self-sampling approaches such as self-swabbing with appropriate training will be considered. In order to remain most relevant in the context of continuously fast-moving knowledge and scientific literature, self-sampling (as opposed to health care worker sampling) might also be implemented as the standard study sampling method for Ag-RDT testing.

During household visits, the presence of COVID-19 symptoms in HHC will be assessed, and if present and with an SpO2 \leq 93%, the HHC will be referred to care. In between study visits, the HHC will be asked to fill in a daily symptoms' diary. If any study participant is presenting with any symptoms related to COVID-19 outside of study visits and feels the need to get medical advice, a phone number will be available for them to ring. This phone number will be written on the ICF. Organisation of referral to care will be done locally, based on the severity of symptoms and distance of the HH to the nearest health facility.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

In the case of identification of a positive HH member during the study visit, the national guidelines in terms of management of case and contacts will be followed. The SARS-CoV-2 positive HH member will be offered to enter the master study. If in turn the HH member enters the master study, they will be instructed on not sharing treatments with the index case.

5.3 Data collected (see Figure 1 and Figure 2 for summary)

Data on household characteristics - collected at D2, first HH visit.

- Location (such as urban/rural, population density of neighborhood, nearest health care facility)
- Household size
- Number of rooms in house
- Number of bedrooms
- Age and sex of each household member (participating and non-participating)
- Participation in the master trial and/or epidemiological study for each household member (participating and non-participating)
- Positivity for SARS-CoV-2 and date of start of symptoms for each household member (participating and non-participating)
- Relationship of participating household members to the index case
- Type of house construction
- Setting
- Indicators of SES such as ownership of certain goods.
- Availability of soap, water source
- Exposure to indoor smoke.

Demographic and clinical data with medical history collected at baseline of all HHC

- Same as collected for Index in Master in section 6.2.1
- One additional element is vaccination data for all age groups from vaccination cards if available.
- Baseline data on hygienic practices such as hand washing and mask-wearing

Clinical data gathered during followup

- Daily symptom diary - gathered by all HHC (D2-M1) - See Annex 1
- During M1 index visit:
 - o A screening test will be applied– See Section 6.3.1.4 of Master Protocol, adjusted to ask for symptoms since D21 visit.
 - o For those with any symptoms consistent with COVID-19 then oxygen saturation will be measured and all those with at least one symptom consistent with COVID-19 and an SpO2 \leq 93% will be referred to care.
 - o Medications taken and health care sought
 - o Outcomes of any illness episodes – such as hospitalization, outpatient visits
 - o Medical events not related to the master study treatment but related to the participation to the epidemiological ancillary study
- During household visits:
 - o A screening test will be applied to HHC– See Section 6.3.1.4 of Master Protocol
 - o For those with any symptoms consistent with COVID-19 then oxygen saturation will be measured and all those with at least one symptom consistent with COVID-19 and an SpO2 \leq 93% will be referred to care.
 - o Medications taken and health care sought
 - o Outcomes of any illness episodes – such as hospitalization, outpatient visits

Research study protocol: Ancillary epidemiologic study to AntiCOV study

Other data collected at baseline and follow-up visit from index and HHC – based off WHO UNITY protocol

- Data on contact with index case before and after symptom onset
 - o Days and approximate number of hours in house together and within 1.5m
 - o Number of times and hours outside of house and for which activities, including number and intensity of contacts and mask use.
 - o Use of masks, hand washing and other hygiene measures by index and by HHC
- Data on potential exposure(s) outside the household
 - o Times, reasons and locations spent outside household
 - o Details on potential contacts (relationship, duration, intensity, symptoms)

Relevant patient data for the epidemiologic ancillary study (e.g. virologic, serological, clinical, behaviour data) not captured in the eCRF of the main protocol, will be captured on an additional eCRF that will be incorporated in a database.

Since procedures are all minimal risk, no reportable adverse events are expected from finger prick and respiratory swabs.

5.4 Laboratory procedures (see Figure 1 and 2)

In study sites or at timepoints requiring virus detection, respiratory nasal swabs will be collected and managed according to local procedures ~~and~~. If close direct contact with the patient is limited because of lack of personal protective equipment (PPE), then self-collected nasal swabs in the presence of a field-worker respecting at least a 2 meters distance or if not possible, self-collected saliva samples into a 2ml sterile vial with buffer added may be considered [25]. Saliva specimens will be managed and tested as for respiratory swabs.

In study sites or at timepoints requiring antibody evaluations, 200 µL of finger-prick blood samples will be collected with heparin microtainer, following by centrifugation within 6 hours of collection. Plasma will be aliquoted and stored at -80°C or at a minimum of -20°C.

All assays outlined below are planned to be performed in-country unless otherwise stated, but if the assay proves not possible in-country or for quality monitoring purposes, the specimens may be shipped out of country as described in Section 9.

Sample collection and serological procedures will be standardized with Standard Operating Procedures (SOPs) for all sites.

Samples will be biobanked at each respective site according to the local biobanking laws, unless requested by the site to be centrally biobanked at ISGlobal or ITM, in which case biobanking will adhere to Belgian or Spanish biobanking laws.

Antibody responses:

- Primary objectives: Levels (Median Fluorescence Intensity, MFI) of IgM, IgG and IgA against 5 or more SARS-CoV-2 antigens, including Receptor Binding Domain (RBD), will be measured by a multiplex Luminex assay. Seropositivity will be determined using a threshold of antibody

Research study protocol: Ancillary epidemiologic study to AntiCOV study

levels estimated with negative controls (pre-pandemic if possible) and/or using finite mixture models. Levels (MFI) of IgM, IgG and IgA against other coronaviruses (229E, HKU1, NL63 and OC43) will be measured by Luminex in a separate (secondary objectives) or the same SARS-CoV-2 Luminex panel.

Detection of SARS-CoV-2:

- Direct detection of SARS-CoV-2 will be performed by PCR in nasal swabs (HHC and index) in a quantitative or qualitative assay. It will be performed by PCR in saliva when nasal swabbing was not possible.

Sequencing of SARS-CoV-2:

Whole genome sequencing of a select number of positive samples will be undertaken in sites that have capacity or that do not but will allow specimens to be shipped to site that does.

Antigen testing:

Antigen testing for SARS-CoV-2 will be performed using Antigen Rapid Diagnostic Testing in respiratory swabs (HHC and index) that can either be sampled by the study health care worker, or self-sampled by the participant in a qualitative assay with a second independent reading to assess inter-operator agreement. Results will be further semi-quantitatively assessed via a scoring system (negative, faint, medium or strong). We specifically plan to evaluate the Panbio COVID-19 Ag Test from Abbott Rapid Diagnostics. This test has been performing well in a symptomatic and mostly adult population with a sensitivity of 91.4% and specificity of 99.8% on NP swabs compared to PCR on NP swabs; a sensitivity of 98.1% and specificity of 99.8% on nasal swabs compared to PCR on nasal swabs; a sensitivity of 91.1% and specificity of 99.7% on nasal swabs compared to PCR on NP swabs [26].

5.5 Safety assessments

Since specific study procedures are all minimal risk and no drugs will be administered as part of this ancillary study, no reportable adverse events are expected from finger prick, and respiratory/saliva sample collection, and no pharmacovigilance will be performed.

6. STATISTICAL METHODS

6.1 Statistical analysis

The secondary infection rate will be described and compared between arms using mixed effects logistic regression.

Characteristics of secondary cases will be estimated as proportions or means with 95% confidence interval, based on mixed effects models. The association of risk factors with secondary infection will be estimated using mixed effects logistic regression. Mixed effects models will be used to compare the evolution over time of viral load of SARS-CoV-2 of index cases between interventions. The mean number of baseline anti-SARS-CoV-2 antibodies will be estimated together with 95% confidence interval, based on a mixed effects model.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

6.1.1 Analysis populations

We will analyze the efficacy data both using Intention-to-Treat and Per-Protocol approaches, with Intention-to-Treat as primary approach. In the Intention-to-Treat analysis, all patients will be analyzed according to their randomized allocation, even in case they receive another treatment regimen, show protocol violations prior to or during the study, or are lost-to follow. In the per-protocol analysis only patients who receive study drug as planned, have complete follow-up and follow the protocol as planned are included.

6.1.2 Baseline characteristics

Patients in each treatment group, pooled and by site, will be described with respect to baseline characteristics. The clinical importance of any imbalance will be noted though statistical tests of significance will not be undertaken.

6.1.3 Primary Analysis

The secondary infection rate of infection (serologic endpoint PCR endpoint) will be compared between interventions using mixed effects logistic regression. Characteristics of secondary cases will be estimated as proportions or means with 95% confidence interval, based on mixed effects models.

The mean titers of baseline anti-SARS-CoV-2 antibodies will be estimated together with 95% confidence interval, based on mixed effects model.

6.1.4 Secondary and exploratory analysis

The association of risk factors and behaviours with secondary infection will be estimated using mixed effects logistic regression. Mixed effects models will be used to compare the evolution over time of viral load and SARS-CoV-2 positivity of index cases between interventions. Association of infection with preventive measures. The secondary infection rate will be compared between groups using non-pharmaceutical interventions or not using mixed effects logistic regression. Age-specific attack rates will be calculated for restricted to households where the index case has not returned home, also using using mixed effects logistic regression to understand risk factors for presymptomatic transmission.

Overall sensitivity and specificity of Ag-RDT will be calculated.6.1.5 Subgroup analyses

Stratification for calculation of sensitivity and specificity will be considered by index/HHC, age group, HIV status, PCR Ct group, symptoms and time from symptom onset.

6.1.6 Multiplicity and Missing Data

No multiplicity adjustments are needed. For each question, proportion and potential bias in missing information will be assessed. Sensitivity analyses will be conducted to assess the impact of missing information on the results.

7. DATA MANAGEMENT/ETHICS AND LEGAL ASPECTS

The ancillary study will adhere to the data management procedures (section 9 in master protocol) and legal/ethical aspects (section 10 to 12 in master protocol). In addition, the following procedures will be followed.

7.1 Data and sample management

- Separate patient logs will also be kept of all patients randomized/recruited in this ancillary study. Patient numbers from the main protocol and epidemiological ancillary study will be kept ensuring easy patient identification across studies.
- In addition to the Sponsor monitoring visits, regular laboratory monitoring activities will be conducted. For Luminex antibody assays, a control positive sample (pool of samples) will be used for all plates in all sites for QA/QC and to ensure comparability. Weekly assay reports will be evaluated for QA/QC purposes. Data cleaning will be performed on an ongoing basis.
- The collected respiratory and blood samples are planned to be stored for a maximum of 25 years after end of study to be used for future scientific research with objectives not covered in this protocol, but in some countries depending on the country/institutional legislation or guidelines it may be for a shorter duration. This duration and use for future scientific research will be updated in the country specific ICF, conditional on notification and approval by the national ethics committee. Such future research will be separately approved by the Ethics Committee in advance, according to local legislation. Participants will have the option to separately consent for the long-term storage of their samples by means of a tick box in the ICFs. If participants do not agree, their biological samples will be discarded at the end of the study.
- Samples will be biobanked at the respective sites and monitored by detailed inventory lists and temperature logs at site, unless central biobanking at ISGlobal/ITM is requested by the site by which relevant biobanking laws will be stipulated in the respective Material Transfer Agreement. Besides local measurements, some samples will be sent to ITM and ISGlobal to perform centralized assays as stipulated in the protocol. In this case, left-over materials can be biobanked for delayed QC at those institutions and will adhere to local biobanking legislation. All sample shipments will be preceded by a Material Transfer Agreement (aligned with country regulatory requirements) that will describe the sharing of data and derived results.
- Biological samples can be sent for analysis and storage to overseas to ITM and ISGlobal and other specialized organisations and institutions as indicated above, for analyses related to objectives if local capacity does not permit an assay to be performed, or for quality assurance and quality control purposes. In no case, personal identification data will be shared, and local regulations will be followed with regard to shipment and biobanking. The transfer of research materials will be stipulated in 'Material Transfer Agreements' and approved upfront by all involved organizations. The latter includes that all data and results and all intellectual property rights in the data and results derived from the study will be the property of the Sponsor who may utilize them in various ways, such as for submission to regulatory authorities or shared with research institutions through IDDO in the first instance and other mechanisms as needed. The Sponsor grants Recipient and Provider of materials a royalty-free non-exclusive license to use the data and results, including any resulting Intellectual Property, for further non-commercial research and education. We do not expect unsolicited findings that require to be disclosed. Samples will remain under the stewardship of the sites.
- Any party from the consortium may request access to the materials for future research. Access to materials will be regulated by the general access principles and after agreement of Consortium JSC and approval by the scientific leads of both ancillary studies. Future studies on biobanked samples will be separately approved by the Ethics Committee, according to local legislation.
-

Research study protocol: Ancillary epidemiologic study to AntiCOV study

-

7.2 Costs for Patients

The ancillary study will adhere to the compensation procedures mentioned in section 12 in the master protocol.

7.3 Risks and benefits

RISKS AND INCONVENIENCES

The minimal risks related to participating in this study are those of routine blood donation for laboratory testing: the discomfort of a needle prick. The volume of blood removed will be too small to affect health. The risk of breaches of privacy and confidentiality breach will be kept at an ultimate minimum by not mentioning the participants name from processed blood samples and data sheets (see privacy and data protection). The study team will be trained on how to best keep the participants privacy and healthcare workers and communities will be involved as per local procedure to avoid stigmatization. During household visits, each participating household member will be interviewed separately, at a distance preventing overhearing from other HH members. No data will be shared between HH members except for COVID-19 positivity: in case a HH member tests positive for COVID-19, the national guidelines on contact tracing and information of contacts will be applied. Teams will not be obviously identifiable as COVID teams and PPE use will be as discreet as possible.

BENEFITS

This study will not have direct influence on clinical outcome nor treatment. The ultimate goal and future benefits are the understanding of transmission in households in order to guide deconfinement, community and vaccine strategies.

All results (positive and negative) from SARS-CoV-2 PCR testing will be communicated to the study participants by the study team either during study visits in case of negative results or immediately by telephone if positive.

Results from SARS-CoV-2 serological testing will not be automatically communicated to the participants because 1) serological testing will be batched therefore often delayed, possibly for several months, therefore of no clinical relevance 2) it remains unclear if a negative or positive individual result equates to presence or absence of protection. The information could potentially be misinterpreted and lead to harmful behavior (e.g. asked to care for COVID-19 cases because they are thought immune). We will communicate serologic results to all participants that request the results at the end of the study or at the end of the sample analysis as per ICF or according to National Guidelines.

Results from antigen testing will be communicated to the participant. If the assay is approved for diagnostic use in the country, a positive result will be used for clinical purposes according to national guidelines. If the assay is not approved, it will be explained that this diagnostic method has not been evaluated yet and that all results need to be confirmed by PCR testing, or as per national guidelines, COVID-19 precautions nonetheless will be reemphasised.

7.4 Community engagement

Research study protocol: Ancillary epidemiologic study to AntiCOV study

Heads of health care facilities (who will in turn inform HCW) and communities will be informed of the ongoing study on COVID-19 to ensure proper care of the participants when needed and to avoid stigmatization of both the patients and HCW. The exact nature of that information to affected communities will be site specific. The study team and study HCW will be trained on the goals of the study and any concern from them will be addressed.

8. REFERENCES

1. Salje, H., et al., *Estimating the burden of SARS-CoV-2 in France*. Science, 2020.
2. Lau, H., et al., *The positive impact of lockdown in Wuhan on containing the COVID-19 outbreak in China*. J Travel Med, 2020. **27**(3).
3. Lan, J., et al., *Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor*. Nature, 2020. **581**(7807): p. 215-220.
4. Ferretti, L., et al., *Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing*. Science, 2020. **368**(6491).
5. Li, Q., et al., *Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia*. N Engl J Med, 2020. **382**(13): p. 1199-1207.
6. Biggerstaff, M., et al., *Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature*. BMC Infect Dis, 2014. **14**: p. 480.
7. Kimball, A., et al., *Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-Term Care Skilled Nursing Facility - King County, Washington, March 2020*. MMWR Morb Mortal Wkly Rep, 2020. **69**(13): p. 377-381.
8. Zhou, F., et al., *Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study*. Lancet, 2020. **395**(10229): p. 1054-1062.
9. Iuliano, A.D., et al., *Estimates of global seasonal influenza-associated respiratory mortality: a modelling study*. Lancet, 2018. **391**(10127): p. 1285-1300.
10. Yao, X., et al., *In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)*. Clin Infect Dis, 2020.
11. de Wilde, A.H., et al., *Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture*. Antimicrob Agents Chemother, 2014. **58**(8): p. 4875-84.
12. Chu, C.M., et al., *Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings*. Thorax, 2004. **59**(3): p. 252-6.
13. Colson, P., et al., *Chloroquine and hydroxychloroquine as available weapons to fight COVID-19*. Int J Antimicrob Agents, 2020. **55**(4): p. 105932.
14. Bi, Q., et al., *Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study*. Lancet Infect Dis, 2020.
15. Li, W., et al., *The characteristics of household transmission of COVID-19*. Clin Infect Dis, 2020.
16. Wang, Z., et al., *Household transmission of SARS-CoV-2*. J Infect, 2020.
17. Bohmer, M.M., et al., *Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series*. Lancet Infect Dis, 2020.
18. Team, T.N.C.P.E.R.E., *The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020*. China CDC Weekly, 2020.

Research study protocol: Ancillary epidemiologic study to AntiCOV study

- <http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51> (2(8)): p. 113-122.
19. Organisation, W.H., *Household Transmission Investigation Protocol for Coronavirus Disease 2019 (COVID-19)*. Available at [https://www.who.int/publications/i/item/HOUSEHOLD-TRANSMISSION-INVESTIGATION-PROTOCOL-FOR-2019-NOVEL-CORONAVIRUS-\(2019-NCOV\)-INFECTION](https://www.who.int/publications/i/item/HOUSEHOLD-TRANSMISSION-INVESTIGATION-PROTOCOL-FOR-2019-NOVEL-CORONAVIRUS-(2019-NCOV)-INFECTION), 2020.
 20. World Health Organization, *Antigen detection in the diagnosis of SARS-CoV-2 infection using rapid immunoassays*. Available at <https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays>
 21. Center for Disease Control and Prevention, *Interim Guidelines for Clinical Specimens for COVID-19*. Available at <https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html>
 22. Ganyani, T., et al., *Estimating the generation interval for coronavirus disease (COVID-19) based on symptom onset data, March 2020*. Euro Surveill, 2020. **25**(17).
 23. Wei, W.E., et al., *Presymptomatic Transmission of SARS-CoV-2 - Singapore, January 23-March 16, 2020*. MMWR Morb Mortal Wkly Rep, 2020. **69**(14): p. 411-415.
 24. He, X., et al., *Temporal dynamics in viral shedding and transmissibility of COVID-19*. Nat Med, 2020. **26**(5): p. 672-675.
 25. To, K.K., et al., *Additional molecular testing of saliva specimens improves the detection of respiratory viruses*. Emerg Microbes Infect, 2017. **6**(6): p. e49.
 26. Abbott, PANBIO™ COVID-19 Ag RAPID TEST DEVICE. Available at <https://www.globalpointofcare.abbott/en/product-details/panbio-covid-19-ag-antigen-test.html>

ANNEX 1

Symptom diary

Date of first entry: (please write the date of Day 1 of this diary).

Symptoms*	Day				
	1	2	3	...	28
No symptoms (check if none experienced)	<input type="checkbox"/> None	<input type="checkbox"/> None	<input type="checkbox"/> None		<input type="checkbox"/> None
Fever $\geq 38^{\circ}\text{C}$	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Chills	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Runny nose	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Cough	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Sore throat	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Shortness of breath	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Loss of sense of smell	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Distorted sense of taste	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Muscle pain	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Diarrhoea	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Vomiting/Nausea	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Headache	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Tiredness or malaise	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Skin rash or skin ulcer	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Pink eye	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No		<input type="checkbox"/> Yes <input type="checkbox"/> No
Other symptoms (specify)					

*Please select None for No symptoms. If no symptoms are experienced, then consider the entry complete.