RESEARCH STUDY PROTOCOL

Incorrect antibiotic use at community-level in the Kisantu and Kimpese districts in the Democratic Republic of the Congo

Community AntiBiotic Use – CABU–DRC

V1.1-04/10/2019

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Funder	Bacterial Infections in the Tropics (Inbev Baillet-Latour)

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STATEMENT OF COMPLIANCE

This protocol contains the necessary information for conducting this research study. By signing this document, the Investigator commits to carry out the study in compliance with the protocol, the applicable ethical guidelines like the Declaration of Helsinki, the European General Data Protection Regulation (GDPR), the ESF/ALLEA Code of Conduct for Research Integrity, and consistent with international scientific standards as well as all applicable regulatory requirements. The Investigator will also make every reasonable effort to complete the study within the timelines designated.

Once the final protocol has been issued and signed by the Investigator(s) and the authorized signatories, it cannot be informally altered. Protocol amendments have the same legal status and must pass through the mandatory steps of review and approval before being implemented.

Principal Investigator (INRB):

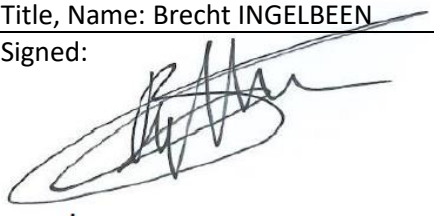
Title, Name: Placide MBALA-KINGEBENI Date: 02 September 2019

Signed:

Principal Investigator (ITM):

Title, Name: Brecht INGELBEEN Date: 02/09/2019

Signed:



Coordinating Investigator:

Title, Name: Marianne van der Sande Date:

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SYNOPSIS

The emergence and spread of antibiotic resistance are fuelled by the (incorrect) use of antibiotics in humans and animals, including wrong treatment choice, dose or duration, poor adherence and poor-quality antibiotics. Limited access to official healthcare facilities in low-resource countries results in widespread, potentially incorrect antibiotic use through self-medication, pharmacies or informal healthcare providers. Our objective is to quantify (i) community-level antibiotic use and (ii) its level of (in)correct use in several communities in the DRC and other low-resource countries, in order to evaluate the relationship between incorrect community-level antibiotic use and the development and spread of antibiotic resistance. We will develop, test and validate a cross-sectional study method to quantify antibiotic use at community-level in low-resource settings, for which currently no validated method exists. The current protocol concerns the DRC. The study will be repeated in three more low-resource countries, when additional funding is secured. After an initial exploratory qualitative study to identify the (range of) health providers and how to appropriately sample them, we will conduct patient healthcare visit exit interviews in 4 neighbourhoods of two health districts in the DRC, while relying on an ongoing population health seeking survey to weigh antibiotic use by healthcare provider. We will procure a representative sample of antibiotic treatment courses to assess the share of *suspected poor-quality* antibiotics, through visual inspection using an existing medicine quality checklist. We will quantify (in)formal antibiotic use, determine the proportion incorrectly used, the proportion of suspected poor-quality antibiotics used, and explore reasons to seek medication from informal providers. Subsequent similar assessments/measurements of community-level antibiotic use in multiple low-income neighbourhoods in three more countries will allow carrying out a multi-country ecologic analysis to assess to what extent (incorrect) community-level antibiotic use is associated with increased antibiotic resistance. From the findings, interventions to improve community-level antibiotic use can be developed.

1 INTRODUCTION

1.1 Background

Use of antibiotic medicines in humans and animals is *per se* a key driver of resistance to antibiotics (ABR), both at community (1–7), and individual level (7–9). Inappropriate use of antibiotics increases this risk even further (10), while at the same time resulting in poor control of infectious diseases. Inappropriate use includes (i) the prescription of antibiotics for patients who do not need them (wrong indication), (ii) the wrong choice of antibiotics, (iii) incorrect antibiotic use: a) the wrong dose, administration route or duration (too short, too long), b) lack of timely/early downscaling of treatment (intravenous to oral administration, broad to small spectrum), c) poor adherence to treatment, and (iv) the use of poor-quality medicines, in particular substandard underdosed or degraded antibiotics (11). Incorrect antibiotic use and the use of poor-quality antibiotics can result in under- or overdosed treatment in terms of dosage or duration. Suboptimal dosage is known to put almost any organism at increased risk of developing resistance to antibiotics (10). Overdosing antibiotics increases the exposure to antibiotics of commensal bacteria in the gut and, through urinary and faecal excretion of antibiotics, of bacteria in the environment or sewage, while out selecting resistant bacteria to prevail and adding selection pressure so that more ABR can develop.

Optimizing the use of antimicrobial agents is a key objective of World Health Organization (WHO)'s Global Action Plan on Antimicrobial Resistance, which also recommends more investments for research on the use of antibiotics (12). In high-income countries, human and animal antibiotic use are monitored through estimations from either sales data or hospital point prevalence surveys (13–16). Conversely, in low-resource countries a significant part of antibiotic use happens outside official health care facilities, through informal health seeking or self-medication (17–19). In the Democratic Republic of the Congo (DRC), access to quality health care is very limited both through the public and private sectors (20), and there is little opportunity to invest in formal monitoring and evaluation of healthcare services. As a result, in DRC, as in other low-resource countries, antibiotic use is not or inaccurately estimated, and the rare interventions to optimize antibiotic use overlook antibiotic use outside official health care facilities. For DRC in particular, we found no studies quantifying antibiotic use. ABR has been monitored in DRC since 2008, through a program for blood stream infection surveillance in St. Luc Hospital in Kisantu (2018 estimated population 66,400), supported by the Institut National de Recherche Biomedical (INRB, Kinshasa) and the Institute of Tropical Medicine (ITM, Antwerp, Belgium). During 2008-2017, of 23 134 patients with suspected bloodstream infections, in 2 987 (15%) a pathogen was identified: 53% nontyphoidal *Salmonella*, 11% *Salmonella* Typhi, 7% *Escherichia coli,* 7% *Klebsiella pneumoniae*, and 6% *S. aureus.* 5% and 29% of respectively nontyphoidal *Salmonella* and *Salmonella* Typhi infections had decreased ciprofloxacin susceptibility. 25% of *E.coli* and 62% of *K. pneumoniae* were ciprofloxacin-resistant. 14% of nontyphoidal *Salmonella*, 1% of *Salmonella* Typhi, 49% of *E.coli*, and 92% of *K. pneumoniae* infections were ceftriaxone resistant. Because of the persisting high ABR prevalence to first-line antibiotics (ampicillin, co-trimoxazole, chloramphenicol) observed in this sample (21,22), ceftriaxone (or other third- or fourth-generation cephalosporins) and ciprofloxacin (or other fluoroquinolones) are essential in the treatment of bacterial bloodstream infections at referral hospitals. The observed increases in ABR against ceftriaxone and ciprofloxacin may render treating bacterial bloodstream infections (BSI) impossible. Clearly these high prevalence of ABR necessitate research to reduce this risk, in particular to identify strategies to optimises (correct) use of antibiotics, known to be key drivers of ABR.

To inform the development and implementation of interventions to address incorrect antibiotic use at community-level, the following knowledge gaps need to be addressed first: (i) where, by whom and how much antibiotics are prescribed, dispensed and used; (ii) why and how these antibiotics are used by their recipients; (iii) to what extent this use can be considered (in)appropriate or (in)correct; (iv) to

what extent is such informal community-level and/or incorrect antibiotic use associated with a higher proportion of ABR among bacterial infections; and (v) to what extent can interregional differences in ABR prevalence be explained by local variations in the quantity of antibiotics used and in the proportion of correct antibiotic use?

In this work, we used the term '*antibiotic use'*, rather than *antibiotic consumption* (which is mostly utilized in studies of antibiotic sales data), or than *antibiotic prescription* (because we are also including antibiotics dispensed over-the counter, i.e. without prescription, and self-medication with antibiotics). Moreover we will collect data on the (quantity of) antibiotics that are eventually used by the patient. We will consistently use the term '*informal community-level antibiotic use*' to indicate human antibiotic use outside official health care facilities. *Official healthcare facilities* are hospitals, health centres and health posts which are recognised (licensed) at the health zone level, and can be either public or private (e.g. NGO or faith-based). With '*all-sectors community antibiotic use'* we indicate the human antibiotic use by the community, combining use in and outside official health care facilities. Measuring '*inappropriate antibiotic use'* would entail evaluating whether the choice to use an antibiotic and of which antibiotic to use, was appropriate. This necessitates evaluating the diagnosis and whether the antibiotic used fits the diagnosis, while taking the patients' contra-indications into account, which can be challenging or nearly impossible to assess at some community-level healthcare providers. Therefore, this study focuses on '*incorrect antibiotic use'* (in terms of dose, administration route, duration, and treatment adherence), on proportions of the groups of antibiotics used (Access, Watch or Reserve classification of antibiotics (AWaRe (28)), and on the use of *suspected poor-quality* antibiotics.

1.2 Rationale

In many low-resource settings, including DRC, no interventions currently address informal community-level antibiotic use, and informal community-level antibiotic use has not been reliably recorded. An association between community-level antibiotic use and antibiotic resistance in that same community has been established recently in a high-income setting (7), but the specific role of incorrect antibiotic use has never been studied.

This study will measure community-level antibiotic use (total use and the proportion of incorrect use) across all types of healthcare providers (formal and informal) in peri-urban and rural areas in low-resource settings. Doing so, the study will provide data to inform the development of interventions to optimize community-level antibiotic use in low-resource settings, in order to limit the development and spread of ABR, as well as to generate additional benefits for the population.

If further funding will be secured, the community-level antibiotic use measurement now planned in the DRC will be extended to several other low-income countries, to investigate the potential association between incorrect antibiotic use at community-level and the emergence of, or increase in, ABR community-acquired bacterial bloodstream infections.

2 Study Objectives

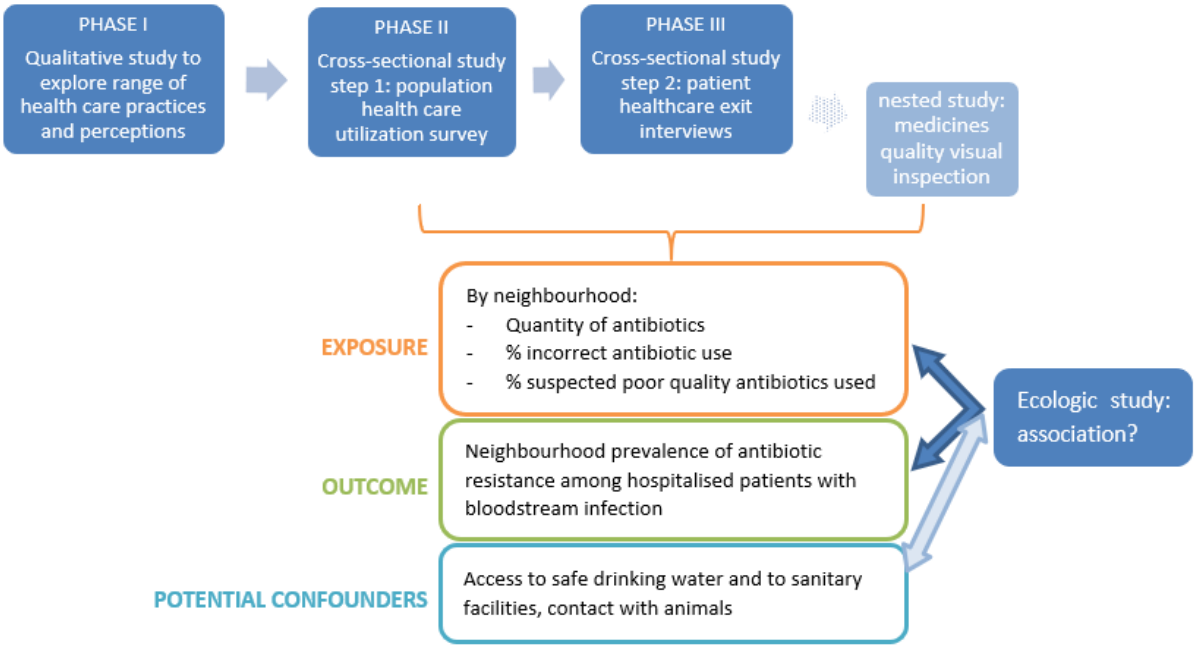
Our primary study objective is to determine to what extent incorrect antibiotic use and the use of suspected poor-quality antibiotics, at community-level, are associated with the emergence or increase of ABR community-acquired BSI.

Secondary objectives are:

- to develop, test and validate a point-prevalence study method to quantify all-sectors community antibiotic use and the proportion of incorrect antibiotic use by type of healthcare provider (proof-of-concept);

- to quantify informal community-level antibiotic use (in defined daily doses by group of antibiotics) and the percentage of incorrect antibiotic use by type of healthcare provider;
- to estimate the prevalence of *suspected poor-quality* antibiotics by means of a visual inspection checklist;
- to compare the performance of the quality visual inspection checklist, when used by staff with different qualifications.

3 STUDY DESIGN



3.1 Sequential mixed methods study (phase I to III)

A sequential exploratory mixed methods research design (noted as qual -> QUAN -> QUAN -> qual) will be used to develop the tool to cross-sectionally measure (point-prevalence) antibiotic use in a community and subsequently measure antibiotic use in several communities (23).

In an **initial exploratory qualitative research phase (phase I)**, using semi-structured interviews and participant observation through informal conversations and group discussions, we will identify the (range of) providers where patients seek healthcare, reasons to seek provider-specific care, reasons of incorrect antibiotic use, and patients' and providers' perceptions related to antibiotics. Findings of phase I will guide the cross-sectional study design (phase II and III) on how questions can be framed in a locally understandable and culturally acceptable way.

To estimate in a well-defined neighbourhood (i) the quantity of antibiotics used in the community by type of healthcare provider, and (ii) the proportion of incorrect antibiotic treatment courses, the **subsequent cross-sectional study** consists of **two steps**:

A) A population (healthy individuals) healthcare utilization survey to determine the relative weight of each type of healthcare provider **(phase II)**;
B) Patient healthcare-visit exit interviews to quantify (incorrect) antibiotic use per healthcare visit **(phase III)**.

3.2 Antibiotic medicines quality study, through visual inspection

A sample of the antibiotic-containing medicines used at community-level will be obtained by mystery shoppers, from the same facilities where they were dispensed to interviewed patients. The quality of these antibiotics will be evaluated using an existing standardized medicine quality checklist for visual inspection (24).

3.3 Multi-country ecologic analysis: the association between community-level incorrect antibiotic use and the emergence or increase of ABR

Next, the same study is planned to be implemented in twelve more neighbourhoods in three other countries (Burkina Faso, Mozambique, Cambodia). In an ecologic analysis comparing the neighbourhoods where community-level antibiotic use was estimated, we will explore the relationship between informal community-level antibiotic use (by neighbourhood) and the prevalence of antibiotic resistance of BSI in patients from those neighbourhoods.

In this protocol, a neighbourhood corresponds to an *aire de santé (AS)*, that is an administrative division of the healthcare system in DRC, delineating a geographical area with an estimated 5 to 10 000 residents, typically including at least one health centre. An AS can be either a (peri-)urban neighbourhood, or can be a few villages grouped together. A health district or *zone de santé* consists of multiple AS, and typically has one referral hospital. In an AS, patients with severe febrile illnesses should be referred by health providers to the same referral hospital, not necessarily located in the same AS.

4 METHODS

4.1 Study Setting and Population

4.1.1 Sequential mixed methods study (phase I to III)

While we intend to carry out this study to measure antibiotic use in sixteen neighbourhoods in four countries (DRC, Burkina Faso, Mozambique, Cambodia), we provide details here below for DRC only, as first study site. The selection of neighbourhoods in other countries will follow the same principles stated below.

In DRC, we will carry out the study in four AS in the Kisantu and Kimpese health districts: one peri-urban and one rural AS in each district. Kisantu and Kimpese are two towns and health districts in Kongo-Central province, South West of Kinshasa. Both health districts consist of several AS. Each includes a neighbourhood or village(s) with a primary healthcare centre, referring severe febrile illnesses to the Hôpital St. Luc in Kisantu (HSLK) or the Hôpital Général de Référence in Kimpese. The four selected study AS are relatively accessible, allowing patients with suspected bloodstream infection to be referred to the referral hospital of the health zone. In Kisantu, Nkandu (peri-urban; 2019 estimated pop. 26 876) and Kavuaya (rural; 2019 estimated pop. 7617) were selected as study AS. In Kimpese, the selected AS were Viaza (peri-urban; 2019 estimated pop. 4065) and Vundansole (rural; 2019 estimated pop. 3181).

In Phase I, several health providers, patients and additional key informants (e.g. health district staff) in the two study aires de santé of Kisantu, DRC, will be approached. Findings will be triangulated in the study AS in Kimpese. For Phase II, household heads have been surveyed on their household members' healthcare utilization in Kisantu, and will be surveyed in Kimpese. In Phase III, patients exiting a healthcare facility, having completed a healthcare visit or obtained medicines, will be interviewed. Phase II and III will be carried out in all four study AS. Following preliminary analysis of the results of the Phase III patient exit interviews in the two AS in Kisantu, and, if necessary, changes in the sample size, sampling strategy and/or exit interview forms, the interviews will be repeated in the two AS of Kimpese (validation).

For Phase II we will rely on existing data (Kisantu) or rely on an existing surveillance system (Kimpese) to study healthcare utilization of each AS' population. In Kisantu, in the context of a typhoid fever incidence study (Severe Typhoid in Africa, SETA (25); conducted by INRB, ITM and sponsored by the International Vaccine Institute), a population healthcare utilization survey has been done in two AS in February 2019 (dry season) and will be repeated in September 2019 (rainy season). We obtained approval to re-use these pseudonymised data, from the International Vaccine Institute and INRB, sponsor and coordinating investigators of the SETA study, for Phase II of this study. De-identified data sharing, on the condition of (i) a request and approval of the International Vaccine Institute and INRB, and (ii) at least one user of the data being a local member of the SETA study personnel, was permitted in the SETA study protocol in DRC (protocol approved by the University of Kinshasa School of Public Health Ethics Committee). In Kimpese, quarterly population surveys are routinely carried out as part of a health demographic surveillance system (HDSS), surveying a random sample of the population of 11 of 20 aires de santé in the health district (zone de santé de Kimpese). The proposed healthcare utilisation survey will be added to the quarterly HDSS surveys

The Phase III patient healthcare exit interviews will be carried out at health providers identified in Phase I and II. Patients of all ages will be included in Phase III, which is essential for the estimated antibiotic use to be representative of the AS. If children or adolescents have completed the healthcare visit, their caretakers will be proposed to answer for them. For adolescents to be included in the study, assent that a caretaker can respond for them, is required.

4.1.2. Antibiotic medicines quality study, through visual inspection

The antibiotic medicines quality study is a nested exploratory study, linked to the phase III patient healthcare exit interviews. The same four AS will be included again.

During the phase III patient healthcare exit interviews, patients will be asked whether (a) they have obtained the antibiotic course at the health facility and, if not, (b) where they plan to do it. After completing phase III , a random sample of antibiotic-containing medicines will be selected from the phase III data, and a course dispensing unit (box, blister, plastic bag,…) will be either (a) obtained at the healthcare facility, or (b) purchased by trained mystery shoppers at the formal or informal selling point indicated by the patient (see section Sampling strategy). It is important that these will be purchased from the same facilities where the interviewed patients indicate that they have obtained (or will obtain) the antibiotics.

4.1.3. Multi-country ecologic analysis: the association between community-level incorrect antibiotic use and the emergence or increase of ABR

The unit of analysis will be the neighbourhood, i.e. 16 in total, in four countries. In DRC that is the AS. The AS' exposures and outcome to study will be respectively the estimated all-sectors community antibiotic use (from the cross sectional study) and the prevalence of antibiotic resistance among bloodstream infections in that AS (from surveillance).

Bloodstream infection surveillance, including antibiotic susceptibility testing, is carried out on suspected bloodstream infections (of all ages) among admitted patients at HSLK in Kisantu since 2009, and will be started at the Hôpital Général de Référence de Kimpese in 2020. The surveillance is coordinated by the Institut National de Recherche Biomédicale (INRB) with support by ITM. The blood cultures are free of charge to the patients and hospital. Both hospitals are the referral structures for patients with suspected bloodstream infections from the four AS included in the study.

We selected the four sites in DRC, Cambodia, Burkina Faso and Mozambique because these countries represent four regions with large differences in ABR and presumably differences in community-level

antibiotic use. To be able to explore whether population ABR prevalence is related to community-level (incorrect) antibiotic use, the ABR prevalence and the antibiotic use of populations we are comparing should be sufficiently different. ABR prevalence in all four study countries is available as part of existing routine BSI hospital surveillance at the referral hospitals of the field sites. Due to each sites' link with ITM, the criteria to take a sample for blood culture, i.e. patients with suspected BSI, the laboratory set-up, standard operating procedures, reporting, quality assurance and control are nearly harmonized in all four sites. Only one blood culture per patient, within a day after admission, will be included. Hospital-acquired BSI will be excluded.

4.2 Sampling Strategy

4.2.1 Sequential mixed methods study

Phase I: Qualitative exploratory study

Sampling for the qualitative study will be theoretical (always including new participants based on emerging results following a flexible and iterative approach), while making use of snowball sampling techniques (the researcher is introduced to new potential participants by previous participants). Participants are chosen on purpose and not randomly (purposiveness). Participants will be selected in accordance with emerging findings (gradual selection) and cannot be specified already. An example: if drug vendors tell that male plantation workers go to one specific vendor who sells one specific antibiotic, then we need to go talk to male plantation workers, the vendor, but also to other patients visiting that provider, to possibly identify other exceptional providers. Critical cases, i.e. informants providing controversial or contradictory information, will be systematically included (Maximum variation). The sample will likely include patients and their households, members of targeted neighbourhoods, health staff and other key informants (e.g. drug vendors). Only adult participants will be interviewed. Sampling will start from the healthcare workers, health district staff and admitted patients at the study sites (HSLK in Kisantu and Hôpital Général de Référence in Kimpese).

In terms of sample size, we will aim for saturation of information rather than pre-determining the amount of interviews we will need to fully map out the health care landscape in the community. The flexible sampling process requires constant redefinition of inclusion/exclusion criteria and therefore doesn't allow for a fixed/pre-determined sample size. We expect, however, to sample a minimum of 20 informants, including traditional healers, health staff and other key informants that are able to provide in-depth information on health-seeking behaviour and the use of antibiotics.

Phase II: Population healthcare utilization survey

In the DRC Kisantu site, in the ongoing population healthcare utilization surveys (carried out in Feb 2019 and planned for Sep 2019), households are randomly picked and healthcare seeking of all members of the household is recorded. All household members, 645 households per AS are surveyed (can be adjusted up to 1000 households for the September survey, based on the outcome of the first survey). These sample sizes were based on the estimated proportion of the study population expected to visit the study healthcare facilities (HSLK and Nkandu and Kavuaya health centres) for fever (set at 0.2). In the DRC Kimpese site, a healthcare utilisation questionnaire will be included twice in the quarterly-held HDSS survey in two AS (Oct 2019 and Apr 2019). In the HDSS, the full population of the AS is surveyed, through surveys with the head of the household. An additional questionnaire with the health care utilisation survey will be added to the regular, routine HDSS survey. The HDSS procedures are followed: The household head is asked to consent to study inclusion and answer to the survey for minor household members, with assent of the household member if he/she is between 14 and 18 years of age.

In Burkina Faso, similarly as in Kimpese, the HDSS system in the Nanoro health district will be used. In Cambodia and Mozambique, healthcare utilization surveys will be undertaken similar as is Kisantu.

A household member is defined as any person living under the same roof in the same housing unit (unité d'habitation), who recognises the authority or legitimacy of a household head (parental link or not; male or female), who shares the same household facilities as other household members, belongs to a group of people who provide for their needs in terms of food and other essentials for living.

Phase III: Patient healthcare exit interviews

The health care providers of the AS were identified in phase I and II. Their relative frequency (number of visits) was measured in the first survey round of phase II. In phase III, for each of the four most frequently visited types of community-level health care providers in the AS, three providers will be randomly selected. The patients completing a healthcare visit at these providers will be approached and requested to participate in a healthcare exit interview. Patients of any age (or caretakers if aged below 18 years of age) and with any indication, will be asked to be interviewed. A convenience sample of patients will be taken, by picking the next patient exiting the healthcare provider when the interview of the previous participant is finished. Initially, we will interview 10 patients per provider, thus 30 per type of provider. If less than three providers of a provider type exist or agree to participate (e.g. Health centres), the 30 patients to be interviewed will be equally distributed between the available providers. In the referral hospital, 50 patients (25 of each study AS) will be interviewed and these will be distributed between the different services of the healthcare facility, according to the frequency of admissions/consultations in each service. The same rule will be applied to other facilities with multiple services.

Following the patient healthcare exit interviews in one AS of Kisantu, precision of the estimated quantity of key antibiotics used and of the percentage of incorrect use will be calculated. The sample size, the number of patients to interview and/or health providers to include, can be adapted before the interviews start in the other AS of Kisantu and in Kimpese, if the precision of the proportions of key antibiotic groups used, and of incorrect antibiotic use, surpass +/- 5%.

4.2.2. Antibiotic medicines quality study, through visual inspection

Being a nested study, the sampling frame will be that of the cross-sectional study, so that the same weighting and adjusting can be applied to estimate the proportion of suspected poor-quality antibiotics.

The antibiotic courses recorded in phase III were either (i) dispensed during the healthcare visit just before the patient exit interview, or (ii) only prescribed during the visit, to be procured after the interview, and confirmed to the interviewers during a follow-up phone call (see section data collection 4.3.2). From a list of all treatment courses recorded during phase III, a sample of 50 different antibiotic treatment courses, frequency-matched for the type of healthcare provider, will be procured by trained mystery shoppers (trained local research staff).

The samples will be stored at the end of the day at respectively the CLSK hospital pharmacy in Kisantu and the Centre de Recherche Sanitaire (CRSK) research office in Kimpese, where they will be classified and kept under in a dedicated and secure place under the responsibility of the site study coordinator at controlled temperature conditions below 25°C. The temperature should be recorded twice per day and written down in a registry. Any deviations from the appropriate range will be documented.

4.3 Data collection

4.3.1 Sequential mixed methods study

Phase I: Qualitative exploratory study

An anthropologist from ITM jointly with a social scientist from DRC will collect data carrying out (i) semi-structured interviews, (ii) participant observation techniques, which include observations, informal conversations and informal group discussions. During the first week, a social scientist from DRC will be trained and coached on the qualitative and mixed-methods data collection techniques described below. The iterative nature of qualitative data collection requires for data collection tools to be continuously adapted by intermittent analysis of raw data (interview and observation transcripts), which will – beyond the first week of data collection, be done by the DRC social scientist, with support of the ITM anthropologist. Which of the below described data collection techniques will be used, depends on the context: what would be acceptable for the participant, availability, confidentiality, etc.

In-depth semi-structured interviewing. In-depth interviews, mainly with different (formal and informal) healthcare providers, following continuously evolving semi-structured topic guides, will be conducted and will be held in a place where the respondents feel at ease to talk privately. Interviews will be recorded and transcribed.

Participant observation including informal conversations or group discussions. As per definition of the term "informal", the informal degree of conversations held with participants in public settings in everyday life settings allows for the discussion of sensitive topics and/or reduced stress for participants as compared to a formal interview, hence a higher quality of data collection. This will involve having conversations with various participants in their own "natural" setting that will not be recorded but documented in notes immediately after the conversation. Informal group discussions entail informal conversations in public spaces, for example in a pharmacy, where likely several people are present and it is not feasible to have a 'private' conversation with clients or providers. People around listen to the informal conversation, and often try to contribute to the discussion. This fosters informal debates about a topic, although not in any organized or structured way.

Informal conversations and interviews will follow topic guides, which will be continuously adapted.

Interviewees' verbal informed consent will be obtained before starting the interview or notetaking. Informed consent is verbal for interviewed healthcare providers due to the sensitive nature of selecting informal/non legal prescribers or vendors of medicines, and for interviewed patients because the sensitive nature of the information/data provided, i.e. contact details of informal/non legal vendors of medicines. As further described, verbal consent will be documented by the signature of the person who obtains the consent.

Through these methods, the local health care providers will be identified and local terminology for medicines and antibiotics in particular will be explored, as well as community members' knowledge of different medicines and pathogens. This in order to prevent a non-sensical patient healthcare visit exit interview questionnaire (phase III) or population healthcare utilization survey (phase II) from the patient's or healthy individuals' viewpoint, and thus optimize data quality throughout the rest of the study. As part of the phase III data collection training, the DRC or ITM anthropologist will use phase I findings to train/raise awareness among phase III interviewers about how to approach healthcare providers and their patients, how to formulate the interview questions, e.g. on vocabulary used when talking about antibiotic treatment, and possibly more relevant findings from the phase I study.

Phase II: Population healthcare utilization survey

In the two Kisantu study AS, within the SETA study, households are surveyed 2 times over a one year period (rainy and dry season) about disease episodes and healthcare utilization of each household member (including all ages) during the past three months. An adult member of the household is asked

to respond for the household. Also the structure of the household (age and sex of all household members) and geographical position of the household is recorded. For our study, we will retrieve the following health care utilisation results from the SETA database: for all surveyed household members (i) the frequency they sought healthcare and used antibiotics during the past three months, and (ii) the type of healthcare provider visited (including traditional healers, dispenser at market, store or private pharmacy, self-employed provider, first line health centre, referral hospital) or whether the person self-medicated with antibiotics stored at home. Household structure (number of household members by age group) will be retrieved to allow weighting and adjusting (design effect and standardisation), if needed. No direct identifiers will be retrieved. Data collection in the SETA study was done with paper-based collection tools, using a structured questionnaire which also contained the informed consent. Forms are double entered into the electronic database of the SETA study. We will extract the above pseudonymised data in a password locked csv file, onto the study laptop.

In the Kimpese AS, a healthcare utilization questionnaire will be added twice (rainy and dry season) to the three-monthly HDSS rounds in the two study AS. The questionnaire will be administered to the household head, who has participated in the HDSS survey, and to the selected individual household member (if adult, the latter should consent; if minor, the household head should consent, with assent of the minor household member if he/she is between 14 and 18 years old). As in Kisantu, we will survey the (i) the frequency they sought healthcare and used antibiotics during the past three months, and (ii) the type of healthcare provider visited (including traditional healers, dispenser at market, store or private pharmacy, self-employed provider, first line health centre, referral hospital) or whether the person self-medicated with antibiotics stored at home. On top of that, we will also survey participants on (iii) healthcare seeking frequency and antibiotic use during the past month (to allow for sensitivity analyses on potential recall bias or seasonal changes), (iv) which healthcare providers they would seek care (to identify all healthcare providers in the AS, for phase III), (v) access to a drinking water source protected from outside contamination, (vi) access to improved sanitation services that are not shared with other households (26), (vii) contact with animals and antibiotics used for animals in the household, (viii) consumption of industrially produced meat (potential confounders in an ecologic study; see data analysis), and (ix) ask individuals who report self-medication additional questions on their antibiotic use: quantity of antibiotics for systemic used by group of antibiotics, dose and duration, number of antibiotics and antimalarials used concomitantly. Photos of the boxes, blisters and tablets of the antibiotics, antimalarials and antipyretics most frequently sold in the community will be shown to the individuals to ensure accuracy of the reported antibiotic and its dosage. If the self-medication antibiotics are still present in the house, participants will be asked to verify, to avoid misclassification. The additional structured questionnaire will be added to the regular HDSS electronic questionnaire, on a mobile device. On a weekly basis the data recorded on the mobile device is synchronised from the mobile devices of the HDSS teams to the HDSS database (at CRSK). After completion of the HDSS in both AS, the healthcare utilization data will be extracted from the HDSS database, without direct identifiers (pseudonymised) and without HDSS data not included in the healthcare utilization questionnaire. This database will be saved on a password locked csv file on the study laptop.

Phase III: Patient healthcare exit interviews

After completing a healthcare visit (provider or outlet), patients and caretakers of paediatric patients who consent to the interview (section 4.1.1) will be asked about the following aspects, using a structured questionnaire: symptoms, the antibiotics for systemic use dispensed/purchased (generic name), number of units (tablet, cap, vial, bottle) per treatment course, dose, route of administration, intake frequency, duration of treatment (including potential up/downscaling), number of antibiotics and antimalarials used concomitantly, reasons for using antibiotics and for health seeking choices (options developed following phase I), and whether the choice, number, dose of dispensed/purchased

antibiotics differed from the prescribed antibiotics. If the antibiotics have already been purchased at the facility itself, also the following information can be obtained at this step, about the purchased product: price per unit, brand name, stated manufacturer, expiry date. A photo of the antibiotic and of its packaging (box, blister, bag or a combination of these) will be taken using the data collection mobile devices (stored as part of the data collection form).

In a follow-up phone call by the same interviewer, self-reported treatment uptake until day 7 will be assessed (number of days until treatment interruption; missed doses). If the prescription had not yet been dispensed/purchased at the time of the interview, the (incomplete) data from the interview will be updated by collecting missing information, such as the quantity actually purchased; if applicable, reasons for buying a different quantity than prescribed; where the product was purchased; price per unit, generic name brand name, stated manufacturer, expiry date.

Questionnaires will be immediately entered on a mobile device, which is uploaded on a daily basis to the study database. Six data collection teams, consisting of one medical doctor and one relais communautaire previously involved in the health care utilization survey of the SETA study, will carry out the patient healthcare exit interviews (phase III) in Kisantu; six data collection teams, involved in the HDSS, will carry out the health care utilization survey (phase II) and the patient healthcare exit interviews (phase III) in Kimpese.

A two-day data collection training will be organised once in each site, for 12 data collectors each.

4.3.2. Antibiotic medicines quality study, through visual inspection

For each antibiotic treatment course, either obtained at the prescribing facility (hospital or formal health centre stock), or purchased by the mystery shoppers at the place/area indicated by participants, we will record the type of healthcare providers where it was prescribed and/or dispensed (they may be the same or not); the kind of packaging (e.g. blisters with secondary packaging, blister without secondary packaging , bottle with secondary packaging, bottle without secondary packaging, plastic bag, paper bag, loose tablets etc.); the number of units (tablet, cap, vial, bottle) actually purchased; the generic and brand name; the stated manufacturer; the batch number; the expiry date; the price per unit.

We will determine whether each treatment course is *suspected poor-quality*, by means of a recently-developed standardised Checklist for Visual Inspection (24). It is important to consider that visual inspection cannot reveal all the potential quality problems, but it has been observed by various researchers that visual problems can be a good predictor of problems further identified through chemical testing. Therefore, the checklist can be used by frontline workers to screen products for those quality problems that can be visually detected. The visual inspection will assess compliance with specifications related to packaging, identification, traceability, physical appearance and shelf life. Antibiotic samples with significant out-of-specifications will be classified as *suspected poor-quality*. This assessment will be carried out twice for each treatment course by a trained pharmacist or dispenser from DRC, and once by the medicine quality lead or PI (to explore inter-personal differences in the assessment). Borderline cases and situations with discrepant opinions will be re-discussed with a third expert to come to a consensus decision.

Major suspected cases of poor-quality with a potential for harm will be reported to the National Regulatory Authority or Pharmacovigilance Program, in line with local regulations.

4.3.3. Multi-country ecologic analysis: the association between community-level incorrect antibiotic use and the emergence or increase of ABR

The data of the cross-sectional study (phase II and III) and of BSI surveillance of the sixteen study neighbourhoods in four study countries will be used in the ecologic analyses. No additional data need to be collected.

For each study AS/neighbourhood in the four study countries we will retrieve:

- As exposure of interest variables: the overall amount of antibiotics used and the amount of key antibiotics used (fluoroquinolones and 3rd or 4th generation cephalosporins), the percentage of incorrect use, the percentage of suspected poor-quality antibiotics (phase III and medicine quality study results, adjusted for healthcare utilization; see subsection 4.4 data analysis);
- As outcome: the proportion of a) multidrug-resistant (MDR) *E. coli*, b) ceftriaxone-resistant *E. coli*, c) MDR *Salmonella* Typhi and Typhimurium, d) ciprofloxacin-resistant *Salmonella* Typhi and Typhimurium, identified among BSI of patients of the AS;
- As potential confounders: percentage of households with access to a drinking water source protected from outside contamination, percentage of households with access to improved sanitation services that are not shared with other households, percentage of residents reporting contact with animals and antibiotics used for animals in the household, or consumption of industrially produced meat (phase II survey).

The BSI surveillance data from DRC are collected as part of routine patient care. Data collection, analysis and sharing follow procedures of the research protocol entitled "Surveillance of antimicrobial resistance among consecutive blood culture isolates in tropical settings, Version 6.0, 06 May 2019", approved by the ITM IRB and the ethics committee of the University of Kinshasa School of Public Health. According to this research protocol, identifying information will be removed in subsequent databases for activities beyond hospital care. In this studies' ecologic analysis we will rely on proportions of resistant pathogens (see above) and thus only aggregated data, the antibiotic resistance prevalence, without identifiers, will be used. Although estimating ABR among all community-acquired infections is not feasible, the proportion of BSI with ABR obtained from hospital surveillance is a reliable outcome measure to compare ABR between communities. Pathogen identification and antibiotic susceptibility testing are done at the hospital, repeated at the national reference laboratory, and again at ITM, so that results are validated twice. As outcome we selected several 'drug-bug' combinations (i) that were clinically relevant; (ii) underlying most confirmed BSI in Africa and Asia; (iii) that are supposedly community-acquired; and (iv) part of the WHO priority list of antibiotic-resistant bacteria (30). *Salmonella* Typhimurium is not often reported in Cambodia, but its ABR will also be explored comparing the African sites.

4.4 Data Analysis

4.4.1 Sequential mixed methods study

Phase I: Qualitative exploratory study

Qualitative data analysis will be a retroductive process, combining an emergent theory process with concurrent data collection. Preliminary data -collected through different techniques and at different moments in the process- will intermittently be analysed in the field (sequential analysis) after which further research, with question guides adapted to temporary findings, will be conducted confirming or refuting temporary results through constant validity checks until saturation is reached and the data could be theoretically supported. Raw data will be processed in their textual form and coded to generate and/or identify analytical categories or themes for further analysis.

Based on the preliminary qualitative data analysis, the survey/interview instruments for phase II and III will be finalized. After data collection has finished, the final analysis of all qualitative data (interviews transcripts and observation notes) will be done jointly by the ITM anthropologist and DRC social scientist, in Nvivo 12 software for qualitative data analysis.

Phase II and III: Quantifying (incorrect) antibiotic use in the community

We will assess patients' antibiotic treatment dose, dosage, duration, mode of administration and uptake courses to determine whether an antibiotic treatment course is incorrect: (i) too low, (ii) too high, (iii) interrupted, as (iv) a composite indicator of over- and underuse (dosage, quantity, duration, adherence based on the available local standardized treatment guidelines, the WHO Recommendations for management of common childhood conditions, 2012 (update Pocket book of hospital care for children), and the WHO IMAI First-level facility and Hospital Care Manuals for Adolescents and Adults, 2009 and 2011).

For each study AS, we will determine the proportion of the study population visiting each type of healthcare provider. This proportion will be used to adjust the percentage of incorrect antibiotic treatment courses and the quantity of antibiotics used for healthcare seeking behaviour in each AS. Because health care utilisation surveys will each be carried out twice (dry and rainy season), we can compare healthcare seeking between seasons variation, related to disease seasonality and season-related access to healthcare (17).

Antibiotic dosage, doses and duration will be recalculated to Defined Daily Doses (DDD) by Anatomical Therapeutic Chemical (ATC) group of antibiotics (27). For each ATC antibiotic group, we will calculate DDD per 1000 patients provided by each type of healthcare provider. By adjusting for the health utilization weight of each type of health provider, we will calculate DDD per 1000 inhabitants per day in each study AS.

We will undertake the same estimation of the quantity (DDD) of antibiotics used by Access, Watch or Reserve classification of antibiotics (AWaRe (28)), and relate this to available community antibiotic use estimates from high- and middle-income countries (29).

We will calculate the proportion under-dosed, over-dosed, interrupted, combined over-and-under-use, and suspected poor quality antibiotic treatment courses (see subsection 4.3.2) by type of health provider and by neighbourhood (again after adjusting for health utilization).

Phase II and III: Patients' health seeking choices and reasons for using antibiotics

We will determine frequencies of patients' provider-specific reasons to seek healthcare, choose a specific provider, barriers to seek healthcare through official health facilities, financial or other barriers to access antibiotics, and to use antibiotics.

4.4.2. Antibiotic medicines quality study, through visual inspection

Before and after adjusting for the health utilization weight of each health provider where the purchased antibiotics were prescribed, we will calculate the proportion of suspected poor-quality antibiotics purchased: overall, by ATC antibiotic group, by AWaRe category, by type of seller (e.g., health facility's pharmacy, private licensed retail, informal market etc.), by patient category (i.e. adult or pediatric formulation), and by AS (the latter to be used in the ecologic analysis). An important limitation of this nested study is that, when the information on purchase is obtained by phone, there is not 100% certainty that the information on the selling point is accurate. Also, we will not assess the quality of the product purchased by the patient, but of a product obtained at the same selling point, which we consider to be an acceptable surrogate for this exploratory assessment.

We will also evaluate differences in the visual inspection results between the two assessors using the checklist, to determine conditions where discrepancies exist, and if needed, consult expert opinion to conclude whether a condition is met or not.

4.4.3. Multi-country ecologic analysis: the association between community-level incorrect antibiotic use and the emergence or increase of ABR

When the (incorrect) antibiotic use in multiple AS in several countries has been quantified, we plan to assess the association between community antibiotic use and the prevalence of antibiotic resistance in an ecologic analysis, by comparing the two parameters between AS.

We will analyse the correlation between

1) The percentage of incorrect antibiotic use (under-dosed, over-dosed, interrupted, combined over-and-under-use, and poor quality antibiotics) in an AS, and the proportion of a) MDR *E. coli*, b) ceftriaxone-resistant *E. coli,* c) MDR *Salmonella* Typhi and Typhimurium, d) ciprofloxacin-resistant *Salmonella* Typhi and Typhimurium BSI in patients from that AS;
2) The quantity of fluoroquinolones or cephalosporins used in the AS, and the proportion of ceftriaxone-resistant *E. coli* BSI or ciprofloxacin-resistant *S. enterica* serotype Typhi BSI, respectively.

The unit of analysis will be an AS. Exposure (the percentage of incorrect antibiotic use and the quantity of antibiotics used and) and outcome (proportion of resistant BSI) will be measured by AS, and compared between AS.

Selecting in four countries four neighbourhoods each, will result in 16 neighbourhoods to include in the analysis. The ecologic association between types of community (incorrect) antibiotic use and the ABR prevalence of *E. coli*, *S. enterica* Typhi and *S. enterica* Typhimurium BSI (population outcome) will be analysed by plotting the proportions of incorrect use against ABR prevalence and calculating two-tailed Spearman's coefficient (r) for non-parametric correlations. We will repeat this analysis for each type of incorrect use (underdosing, substandard quality, and a composite indicator), and for each of the selected ABR prevalences. We will also explore other factors potentially associated with ABR. Through stratification, we will adjust the potential association between incorrect antibiotic use and ABR for potential confounders and effect modifiers (collected during phase I and II: exposure to animals or antibiotics for animal use, access to safe drinking water, access to improved sanitation).

5 ETHICAL ISSUES

5.1 Ethical Review

This study protocol and annexes has been submitted for formal review and approval to the Institutional Review Board of the ITM and local Ethics Committees. For DRC this is the Ethics Committee of the Université Protestante au RD Congo. No participants will be enrolled or participant related activities performed before written approval from the appropriate bodies in each country is obtained, and the same will apply to any further substantial amendments.

The collection and sharing of existing data that will be re-used in this study are specified in research protocols which have undergone ethics review by the competent bodies: the healthcare utilization data in Kisantu from the SETA study (approved by the University of Kinshasa School of Public Health Ethics Committee, review n° ESP/CE/011/2017; and review of an amendment to the protocol n°ESP/CE/037/2018) and the antibiotic resistance prevalence from the BSI surveillance (Surveillance of antimicrobial resistance among consecutive blood culture isolates in tropical settings, Version 6.0, 06 May 2019" protocol, approved by ITM IRB ref. 613/08 and the the University of Kinshasa School of

Public Health). Furthermore, a protocol HDSS in Kimpese, of which sampling frame will be used for the healthcare utilization survey in Kimpese, has been approved by the ethics committee of the Université Protestante au RD Congo.The study will be carried out according to the principles stated in the Declaration of Helsinki (2013, and any further updates), all applicable international regulations and regulations in force in DRC, and according to established international scientific standards. The study will be compliant with the EU GDPR.

5.2 Obtaining Informed Consent

Informed consent will be in place for phase I and for phase III.

For phase II:

- *a waiver of consent* is required for the secondary use of the retrospective data from the SETA study in Kisantu, considering that various conditions are simultaneously present: (a) data will be pseudo-anonymized, and will be treated confidentially, so that any risks related to privacy and confidentiality are acknowledged and minimized; (b) the SETA study, including sharing of study data under well defined conditions, has been approved by the relevant EC in DRC; (c) written informed consent has been obtained for the healthcare utilization survey (part of the ongoing SETA study), stating that data could also be used for other studies outside SETA; and (d) the study has a potential important social value for the concerned communities.

- a *waiver of written consent* is required for the use of data from the HDSS in Kimpese, considering that various conditions are simultaneously present: (a) the survey questions are part of the larger and regular HDSS survey, and the households in the HDDS have previously verbally consented to the periodical HDSS home visits; (b) data will be pseudo-anonymized, and will be treated confidentially, so that any risks related to privacy and confidentiality are acknowledged and minimized; (c) the study has a potential important social value for the concerned communities. The interviewers will inform the participants that a few more questions than usual will be requested for use in the study; he/she will inform them about the goal, topic, risk and benefit of the (additional) survey questions, provide an information sheet (Annex 12.4), and, if willing to participate, the interviewer will document a consent form (Annex 12.2) that the participants have verbally consented to these additional questions. Participants providing oral consent will be offered a copy of the participants' information leaflet. Information of household members of all ages will be included in this part of the study. For individuals under 18 years of age, the responding parent or caretaker will be asked verbal consent, and adolescents >14 years of age will be asked verbal assent.

For phases I and III:

Participants in phase I interviews or informal conversations or discussions will be identified by the anthropology researcher, starting with the healthcare workers and health district staff at the study sites (HSLK in Kisantu and Hôpital Général de Référence in Kimpese). Potential participants will be approached during working hours and proposed to participate to the semi-structured interviews and/or group discussions after working hours. Participants in phase III will be approached by the researchers in the health facility compound, when they are leaving it after a consultation.

All prospective interviewees will be informed before the start of the interview about project goals, the time requested for it, the topic and type of questions as well as their right to decline participation or to interrupt the conversation at any time, and that (non) participation or declining to participate will have no consequence for the access or quality of further healthcare. For health staff in licensed health facilities, it will be important to clearly state that this is not an evaluation, and that the contents of interviews will not be shared with their hierarchy/supervisors.

The informed consent interview will be conducted by an interviewer, who will have been trained in ethics requirements for informed consent, in a space allowing privacy of the interviewee and chosen or approved by them. Participants providing oral consent will be offered a copy of the participants' information leaflet.

The prospective participants information leaflets (Annexes 12.1, 12.4, 12.5 and 12.6) are adapted to each study phase and will be available both in the local language Kikongo and in French. The informed consent interview will be conducted in the language chosen by each prospective participant. The informed consent documents have been adapted to the study phase the person is participating in, and whether the interview concerns a child/adolescent or an adult. They will be paper-based, will be read to the patient or can be read by the patient.

For phase I, documented verbal consent (Annex 12.2) is proposed, because most interviewees will be informal healthcare providers, and requesting the subject's signature can have the potential of creating mistrust, leaving a trail for authorities to identify informal (sometimes not legal) vendors. If the prospective participant is willing to participate, the interviewer will declare and sign that the participant verbally consented. All participants will be above 18 years of age. The participant information leaflet (Annex 12.1) should be kept by the participant. The documented verbal consent form signed by the data collector should be kept at a secure location, under the responsibility of the DRC PI.

For phase III, written informed consent will be obtained (Annex 12.5). For individuals under 18 years of age, the parent or caretaker will be asked to give the written consent (Annex 12.6), while adolescents >14 years of age will be asked a verbal assent (and their willingness not to participate should be respected). The participant information leaflet should be kept by the participant. The consent forms will on a daily basis be added to the investigator file, kept at a secure location, under the responsibility of the DRC PI.

5.3 Insurance

The Coordinator of this study, the Institute of Tropical Medicine has obtained an umbrella insurance to cover any injury, damage or loss to study participants and which is caused directly or indirectly by participation in low-risk studies (Annex 12.7).

5.4 Risk-benefit assessment

There is no direct health-related risk to this study. However, during the survey, interview or group discussion, it is possible that questions are asked about personal experiences, which might bring up bad memories, or that informal health providers might feel stigmatised, or that formal health providers may fear that their opinion could be shared with their superiors/used for evaluating them. In addition, there are risks related to privacy and confidentiality, and these are especially important for informal health providers. Last but not least, full confidentiality can never be assured in group discussions, because it depends also on other participants, and not only on the researchers; and if a follow-up call is needed (phase III), there might be risks related to the habit of sharing telephones. These risks will be mitigated in different ways. First, by de-identifying quantitative data and by protecting the confidentiality of qualitative data, as described in the section on Data Management; second, by choosing private locations for interviews (the questions and setting where these interviews are held, will be prepared in a way that makes the interviewee feel comfortable and secure, thus keeping this risk to a minimum); third, by explaining to participants in group discussion that they should commit to protect each other confidentiality, and by "segregating" group discussion by category of participants (as an example, no group discussion will be held involving at the same time informal healthcare providers and the official health authorities); forth, by discussing upfront in the informed consent

interview the details of the follow-up phone call, to ensure that participants understand the possible risks before consenting to participate. How to deal with patients' personal bad experiences, will be part of the interviewers' skills and expertise, as documented by training and experience records. Interviewees will be offered a refreshment. When health providers need to move to participate in a group discussion, a transport reimbursement will be offered. Interviewees with a follow-up phone call scheduled will be given a phone recharge card.

There are no direct benefits for interviewees participating in the study. However, interviewers will be trained on the subject, and additional pharmacological and medical support will be provided to them if needed, to answer questions related to antibiotic use, brought up during focus group discussions or interviews. This will benefit the health providers' practices, leading to improved use of antibiotics. The study should allow setting up potential antibiotic stewardship interventions, which should benefit both the community's health, and provide support to healthcare providers.

It is possible that the qualitative interviews reveal bad medical practices, or even legally borderline behaviours. The qualitative researchers will be trained to identify major medical mistakes or bad medical practices. If such mistakes are identified, a feedback session with a medical doctor involved in the study will be proposed, to counsel the health provider on good medical practice and educate on correct, evidence-based treatment.

The patient healthcare exit interviews could reveal individual medical mistakes, such as prescription errors, e.g. contra-indicated antibiotics such as use of tetracyclines in children, wrong doses. The interviewer teams consist of one medical staff, and will be trained to detect severe and common treatment mistakes. If such mistakes are identified, after the interview of the patients they will be addressed/discussed a.s.a.p. with the health provider, to allow the provider to rectify the treatment. If not (possible to) address the error with the concerned healthcare provider, the patient will be referred to the referral hospital, HSLK or the Hôpital Général de Kimpese. A clinician in the hospital will be informed when a patient is referred by one of the study teams' medical doctors, and will follow up these referred patients, while ensuring discretion about the healthcare provider where the patient was referred from. The hospital direction will be informed on the possibility of such referrals from other healthcare facilities during the study..

The medicines quality study presents specific risks and mitigation measures. First, the use of mystery shoppers is important to avoid bias (if sellers know that they are dealing with a researcher, they will most likely select their "best" product, or in any case modify their usual behaviours), but if they were "discovered", this could result in suspicions and tensions in the community. Therefore, it is important that they are accurately trained and prepared for this task. Second, the study could reveal major non-compliances, with potential effects for the community: such instances will be promptly communicated to the Regulatory Authority or Pharmacovigilance Programme, in line with local regulations, and if needed reported to the WHO Alert system. Other quality problems, such as degradation of tablets because of poor storage conditions, will be discussed with the concerned healthcare providers, including sensitisation on good storage and dispensing practices. Third, when data are published, care must be taken in protecting the security of all those involved and avoiding stigmatization, therefore no identifiers of the surveyors and surveyed should be revealed either in the study reports or subsequent publications.

6 MONITORING AND QUALITY CONTROL

During phase I data collection, constant qualitative process evaluation will complement comparative analysis of intermittent quantitative indicators, to identify areas to focus on which could not be foreseen at the study design and protocol development stage. This is an on-going research process

focused on detecting emerging issues and providing an immediate response in close interaction with the stakeholders (i.e. healthcare providers, patients, researchers involved in phase II or III).

Phase II data collection, being part of the ongoing SETA study in Kisantu and the HDSS in Kimpese, will follow the procedures of those respective studies. Before data analysis, the completeness and accuracy of the data will be verified (the number of non-responders, missing data, compare the survey population's demographics with those of the source population, compare results from different interviewer teams). If the data quality of specific variables or observations cannot be guaranteed, the PIs with the support of a statistician could jointly decide to exclude specific observations and/or variables, with a justification for each exclusion (to be kept in the investigator's file and to be described and justified in the study report).

During phase III data collection, both in person and by phone, the ITM or INRB PI, or a researcher designated by the ITM or INRB PI, will be present on-site and generate on a daily basis quality reports, which he/she will follow up on. A potential-error-report will be generated (using a R-script) to identify inconsistencies (including keypunching errors, ranges, antibiotic-related inconsistency checks) in the recorded data that day. The report should allow rectification the following study day whenever still possible. Simultaneously, a summary report will be generated on the progress of the interviews carried out, as well as of the follow-up telephone call.

7 TIMELINE

Activity	2019			2020			
	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Finalize protocol							
Ethical review							
Qualitative phase healthcare practices							
Data collection training			Kis	Kim			
Population healthcare utilization survey		Kis	Kim		Kim		
Patient healthcare exit questionnaires			Kis	Kim			
Data analysis/writing							
Visual inspection of antibiotics			Kis	Kim			
Country + sites feedback session							
Manuscript preparation							

Kis = Kisantu site; Kim = Kimpese site

The protocol will be submitted for ethics review by 3 September 2019 to the Institutional Review Board of the ITM and the Ethics Committee of the Université Protestante au RD Congo. Outcome is expected by September 20 from ITM and within 3 weeks from Université Protestante au RD Congo.

The study in DRC should start on October 7, 2019 in the Kisantu site, with the phase I qualitative study, immediately followed by the phase III patients interviews, provided that the relevant ethical approvals have been obtained. Healthcare utilization (phase II) weights of the SETA study will be available by October 2019.

In the Kimpese site, healthcare utilization (phase II) will be surveyed as part of the health demographic surveys planned for Q4 2019 and Q2 2020. Triangulation of the phase I exploratory study results from Kisantu and the phase III patient exit interviews are planned to be held in January 2020.

The DRC pilot (development, test and validation of the 2-step cross-sectional study design) should be completed by April 2020, with findings submitted for publication by July 2020. The subsequent surveys

in other countries will be carried out following the study in DRC and final output of the multi-country ecologic study is expected by the end of 2023.

The medicines quality nested study is planned to be carried out in December 2019 in Kisantu and in January/February 2020 in Kimpese.

8 DATA MANAGEMENT AND ARCHIVING

8.1 Data Management

Following transcription, translation, processing and coding of the phase I interviews and observations, the recordings of interviews, kept in password-locked files on a password-locked laptop and encrypted USB key of the anthropology researchers (ITM and INRB), will be deleted within one year from the end of the study (planned for May 2021). No names will be recorded during transcription of recorded interviews. All original recordings, transcripts and notes will be pseudo-anonymized (not carrying a name or direct identifying information), but they will contain narrative information and data that easily allows indirect identification, especially with a small sample size. Therefore, the access to the social science database is restricted to the concerned members of the research team. A list of identified health care providers in the community, by type, will be stored in a separate paper based file, securely held with the Investigator's File.

All phase II and III data (health utilisation survey and patient healthcare exit interview) will be recorded without personal direct identifying information but with a unique identifier which will be noted on the informed consent form. Data collection happens electronically on mobile devices using ODK (Open Data Kit; https://opendatakit.org/). Upon completion of the interview, the database will be exported to a .csv file and stored on 2 password-locked encrypted USB keys, for both the DRC and ITM PI, who will not copy the data elsewhere, and run the data analyses while stored on the USB keys. Subsequent to the extraction, the data will be deleted from the Open Data Kit database.

For phase III, there will be follow-up phone conversation. Phone numbers will be noted, together with names and study ID code, on a dedicated "Identification Log", which will only be kept by the concerned research staff. Patient's data (names and telephone numbers) will be erased after completion of the follow-up telephone call and/or any other needed medical follow-up (if a patient had to be referred, if a potentially harmful prescribing error was found).

For the medicines' quality survey, data collected on the paper visual checklist will be copied into Excel for analyses by the ITM PI or a delegated person; no direct identifiers of the outlets will be recorded in this database. The source paper forms will be photocopied. The original copy will be brought and kept at the ITM, after deleting any direct identifiers, and the photocopy will be kept in the local study investigator's file, under secure conditions.

The signed Informed consent forms will be kept secured in folders at the local sites (HSLK and CRSK), under the responsibility of the DRC PI, separated from the study database, and held with the Investigator's File.

Daily data collection error-reports, fully documented follow-up of corrections made following the error-report and summary reports (see section 6. monitoring and quality assurance) will be kept in the Investigator's File.

Data security for the above stated data management will be augmented by automatic computer virus scanning at start-up of each data analysis session, and password protection for accessing data. Access to the electronic database and Informed consent forms will be restricted to the local and ITM PIs and coordinating investigators.

8.2 Data sharing

The study database will be the joint property of the INRB, CRSK (for Kimpese data), and ITM. Access to (viewing or extracting) the database will be jointly restricted to the INRB and ITM PIs in order to safeguard the privacy of the study participants and to protect confidential and proprietary data. Special considerations for shared access to deidentified study databases (i.e. with Ministry of Health and World Health Organization) may be made upon request. The data of the supplementary questionnaire to the HDSS in Kimpese can be shared with the HDSS researchers at CRSK, providing there is a research protocol with ethics approval from the competent body to re-use these additional data.

After reporting the primary objectives of the study, aggregated antibiotic use data will be made available through an open data repository (see section open access to research data). Other study data may be shared with other interested users under restricted conditions, provided that patient data is de-identified (in which patient identity cannot be determined, neither directly nor indirectly). Any subsequent reporting of the shared data will require approval from the local sites, INRB and ITM.

8.3 Archiving

As required by international guidelines and national regulations, the electronic database with the pseudonymized source data will be stored on an encrypted and pass-word locked USB key by the DRC and ITM PI for 5 years. The informed consent forms will be kept in the archives of the local sites (HSLK and CRSK) for 5 years. This is beyond the study completion, to allow for audits and inspections even after the study completion.

The DRC and ITM PI are responsible for ensuring a secure and appropriate location for storage of the Investigator's File and any other study related documentation, as well as for ensuring that only site staff that is competent and delegated to work for the study has got access to the files.

8.4 Open access to research data

At the time of publishing the related manuscript, aggregated antibiotic use data (quantity of each antibiotic group in DDD; % incorrectly used AB), by type of health provider, by study site (Kisantu, Kimpese), will be made available through Open Science Framework (https://osf.io/).

9 DISSEMINATION OF RESULTS

We plan to write manuscripts for submission to peer-reviewed journals on the following subjects and findings:

1) Description of the cross-sectional study method to measure community-antibiotic use, with validation results;
2) Healthcare and antibiotic utilization in DRC: a mixed-method study;
3) Types of incorrect antibiotic use associated with ABR BSI: an ecologic study;
4) Estimating the quality of antibiotics in DRC using a visual inspection checklist, in a context characterized by important levels of ABR.

Following the analysis of the results of the cross-sectional study, with a detailed overview of antibiotics used by healthcare provider in relation to the ABR prevalence reported in the surveillance system, we plan an on-site feed-back sessions in each site, involving Ministry of Health staff of the health zone, clinical staff of the referral hospitals, the involved healthcare providers (including non-official providers). Another session will be held with MoH staff at national level, involving the WHO regional office for Africa. These feedback sessions with a detailed report of antibiotic use should guide the set-up of potential antibiotic stewardship interventions and policies or regulations related to the community-use of antibiotics.

The articles will provide researchers in other countries and DRC regions with the methods to replicate the cross-sectional study and obtain community-level antibiotic use data. Setting up surveillance of antibiotic use, in order to guide interventions to optimize antibiotic use , are two among the five strategic objectives of WHO's global action plan on AMR.

When the community-level antibiotic use has been measured in 12 more neighbourhoods in three more countries, the ecologic study will be to provide insight in how incorrect antibiotic use is related to resistance, in order to guide priority setting when addressing incorrect use: which providers to focus on, patient behaviour to address, how use can best be optimized.

Apart from the peer-reviewed journal articles, findings will be communicated with the scientific community through conferences, and with ITM and INRB's global network through the ITM colloquia and newsletters.

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11 List Of Abbreviations

ABR	Antibiotic resistance
AS	Aire de santé
BSI	Bloodstream infection
CRSK	Centre de Recherche Sanitaire, Institut Médical Evangélique, Kimpese
DRC	The Democratic republic of the Congo
EC	Ethics Committee

GDPR	General Data Protection Regulation
HDSS	Health demographic survey system
HSLK	Hôpital Saint Luc de Kisantu
INRB	Institut National de Recherche Biomédical
IRB	Institutional Review Board
ITM	Institute of Tropical Medicine
PI	Principal Investigator
SETA	Severe Typhoid fever in Africa
WHO	World Health Organization

12 ANNEXES

12.1 Participant information form for in-depth interviews (phase I)

INFORMATION POUR LE PARTICIPANT – ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES stade I

Vous êtes invités à participer volontairement à une étude de l'Institut national de recherche biomédicale (INRB, Kinshasa) et de l'Institut de médecine tropicale (ITM, Anvers). L'étude est décrite dans cette fiche d'information. Si vous avez des questions au cours de l'étude, n'hésitez pas à les poser. De plus, vous êtes bien entendu libre d'interrompre votre participation à l'étude à tout moment.

But et description de l'étude

L'augmentation de la résistance aux antibiotiques rend des médicaments actuellement utilisés pour des infections bactérielles inefficaces. L'usage d'antibiotiques donne une exposition des pathogènes aux antibiotiques, ainsi permettant le développement de résistance chez ces pathogènes. Afin de développer et introduire des interventions qui permettraient un meilleur usage des antibiotiques dans la communauté, nous devrions d'abord comprendre où, quand, comment et quels antibiotiques sont utilisés. C'est pourquoi cette étude est proposée. Nous voudrions d'abord identifier l'ensemble des acteurs de soins où les antibiotiques sont utilisés dans une communauté (deux aires de santé à Kisantu et à Kimpese). Cette première étape sera suivie par des entretiens avec des patients pour étudier quels antibiotiques sont utilisés e plus fréquemment, et comment.

Temps requis pour la participation

On vous demandera de réserver environ une heure pour un entretien.

Participation volontaire

Votre participation à cette étude est entièrement volontaire et ce choix n'est pas documenté ou rapporté dans les documents de l'étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment.

Si vous souhaitez participer, indiquez verbalement que vous acceptez de participer à l'étude.

Confidentialité

Toutes les informations recueillies à votre sujet au cours de l'étude resteront strictement confidentielles. Votre nom n'est pas enregistré et toutes les informations que vous fournissez resteront confidentielles. Seuls deux chercheurs de l'équipe de recherche auront accès aux données

et informations collectées. Il est possible qu'un extrait de l'entretien ou discussion serve de «citation» pour appuyer notre étude / notre travail. Cependant, toute information qui vous identifie restera confidentiel.

Si vous êtes d'accord d'y participer, l'entretien ou discussion restera confidentiel. Votre identité ou contact ne sera dans aucun cas partagé avec les autorités, ou les autorités sanitaires. Nous garantissons que toutes les informations seront traitées de manière strictement confidentielle, et votre nom sera remplacé par un code dans tous les documents officiels de l'étude.

En cas de discussion en groupe, nous vous demandons de respecter les autres participants et de préserver la confidentialité des autres. Si vous êtes mal à l'aise de participer à une discussion, nous expliquerons / discuterons jusqu'à ce que tous les participants comprennent et se sentent à l'aise pour participer ou, si vous le souhaitez, vous pouvez retirer votre participation.

Une fois votre participation confirmée, nous aimerions enregistrer notre conversation uniquement à des fins de recherche. Vous êtes libre de le refuser, cependant, cela aidera notre analyse et notre travail. Toutes les informations enregistrées seront détruites après l'étude.

Avantages

Votre acceptation de participer à cet étude ne présente aucun avantage personnel direct. Néanmoins, en participant, vous pouvez nous fournir des informations précieuses qui pourraient le développement de futurs activités d'éducation ou support scientifique, et qui pourraient être utiles pour votre communauté.

Il n'y a pas de compensation pour participer à cette étude. Si vous avez dû vous déplacer, les frais de transport seront pris en compte (une somme forfaitaire).

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le comité d'éthique de l'Université Protestante au Congo et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

Ou le comité d'éthique de l'Université Protestante en RD Congo.

Nom: XX; Telephone: XX; Email: XX

(le consentement verbal du participant sera documenté par l'interviewer – voir annexe 12.2)

12.2 Documentation of consent form for in depth interviews (phase I) and health utilization surveys (phase II)

(En italique des points spécifiques à l'étude stade II. Nous préparerons deux différentes fiches)

CONSENTEMENT VERBAL à remplir par l'interviewer – ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES stade I et II

Je confirme que la fiche d'information a été lue et expliquée au répondant interviewé*, et aux personnes (>14 ans) dont la fréquence l'utilisation des soins de santé va être documenté.*

Je me suis assuré que le répondant a bien compris qu'il/elle peut choisir librement de participer à l'étude, qu'il/elle n'a pas à répondre à une question dont il/elle préfère pas répondre, et qu'il/elle peut à tout moment mettre fin à l'entretien.

Le répondant a eu l'occasion de poser des questions sur l'étude et ses objectifs. Si le répondant avait des questions, moi ou un collègue de l'équipe de recherche a répondu correctement et clairement aux questions.

Le répondant a été expliqué que son nom n'est pas enregistré*, ni le nom des personnes dont la fréquence l'utilisation des soins de santé va être documenté*, que les informations fournies resteraient pseudonymisés (pas d'identification directe), et que les enregistrements de l'entretien seront détruit au plus tard un an après la fin de l'étude.

L'âge du répondant est 18 ans ou plus.

Le répondant a consenti de participer à l'étude/ *L'adulte (>18 ans) dont la fréquence l'utilisation des soins de santé va être documenté a consenti de participer à l'étude*. *Pour les personnes entre 14 et 18 ans dont la fréquence l'utilisation des soins de santé va être documenté, on a vérifié qu'il/elle est d'accord que son gardien (adulte) ou chef de ménage va répondre pour lui/elle, et le gardien (adulte) ou chef de ménage devra consentir de participer à l'étude.*

Nom du chercheur Date (dd/mm/yy)

Signature du chercheur

N° de participant: ___

12.3 (Draft) guides for in-depth interviews

- Neighbourhood/village:

Who lives in this neighbourhood/village?
Are services (including healthcare) sought within the neighbourhood/village? Or are people of this neighbourhood working/going to school/seeking healthcare/buying medicine elsewhere?
Are there any particular patterns related to mobility of people in this neighbourhood (eg. Seasonal work, transportation)?
Who are the healthcare providers, agents/acteurs de santé? What are their roles?

- Household healthcare seeking in the neighbourhood

What do people do when they have fever? What do they do to treat fever?
Which household member usually decides on whether and where to seek healthcare?
Are household members, adult and minors, usually accompanied by anyone? What is their role in care?
Is healthcare seeking different depending on the household? Reasons? Socio-economic? Other?

- Healthcare trajectories

At what point in their disease episode do people usually seek healthcare with you (the interviewed healthcare provider)?
Is any healthcare sought before coming here?
Which diseases do you treat?
Why do patients come to you as a healthcare provider?
Do you/Where do you refer patients? Reasons for referral?

Does the decision to seek healthcare depend on other factors that could change, eg. Season? Mobility?
What is the role of distance and mobility in the choice (where) to seek healthcare?

- Personal qualifications

What diploma/training do you have? Where were you trained?
Do you prescribe/dispense medication? Specific classes of medication?
Are different profiles of health agents working in this facility/outlet? Which?

- Medical decision making

What type of patient visits do you offer? (eg. Consultations, observation, hospitalisation, only delivery/selling)
How do you diagnose? What tools do you have available (eg. Rapid diagnostic tests, clinical algorithms, guidelines)
Do you use a guideline for medical decision making? Which?

- Medication prescribed/dispensed

What medication do you prescribe/dispense? Large families (e.g. antibiotics, antimalarials, antihypertensive, diabetes, antituberculosis, ART,…) and modes of administration (oral: tablets, caps or suspensions/syrups, injectables)
Do you prescribe/dispense antibiotic or antibacterial medication? Which? Classes, mode of administration, most frequent?
How do you decide which antibiotic to prescribe/dispense (specific symptoms, first exclude other infections?)? Indications to prescribe/dispense antibiotics?
If not dispensed, where do patients obtain prescribed antibiotics?
If dispensed, prescribed antibiotics only? For specific antibiotic classes/groups? Prescribed where?
Do patients obtain full antibiotic courses? For how many days? Duration is indication specific? If not obtaining full antibiotic courses, how is the antibiotic course completed, if so?

- Patient perceptions

Are patients aware they might be suffering from a bacterial infection?
Is taking medicines/drugs common? What kind of medicines?
Are patients aware they receive an antibiotic to treat a bacterial infection?
Do patients ask for antibiotics/expect to receive antibiotics?
What are patients' possible reasons to search for antibiotics?
What is the role of traditional medicine?

- Infection prevention and control

If patients are kept in observation or hospitalised in the facility, are the observed/hospitalised patients separated from other patients?
Gloves used/handwashing by agent? (when, frequency, between different patient consultations?, for specific interventions such as injections or fingerpricks?)
Frequency of cleaning/washing? With soap/disinfectant? Which?
Water/tap available? From? If not, where is water obtained from?
Latrines? Type of latrine? Shared between staff and patients? Shared between patients?
Food/drinks of patients and staff? Where? Who prepares?

12.4 Participant information form for additional questions during the quarterly survey of the HDSS in Kimpese (phase II)

INFORMATION POUR LE PARTICIPANT - ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES stade II

Aujourd'hui, en plus des questions que vous sont normalement posés dans le cadre du système d'information sanitaire et démographique, on voudrait vous demander de répondre aissi à quelques autres questions ; et ceci, pour nous aider à comprendre où vous, votre famille et vos voisins cherchez des soins de santé en cas de maladie. Cettes questions sont posées dans le cadre d'une recherche de

l'Institut National de Recherche Biomédicale (INRB, Kinshasa) et de l'Institut de Médecine Tropicale en Belgique.

L'étude est décrite dans cette fiche d'information. Si vous avez des questions maintenant, ou plus tard , n'hésitez pas à les poser, y compris des questions sur les risques potentiels, les avantages et les inconvénients de la recherche.

But et description de l'étude

Le but de cette étude est de comprendre l'utilisation des soins de santé et l'usage de médicaments, en particulier les antibiotiques, dans votre communauté (Zone de santé de Kimpese). Les résultats de l'étude permettront de comprendre où et comment les médicaments sont utilisés, et où se trouvent des barrières pour accéder aux soins ou pour utiliser les médicaments. Cela, pourra permettre d'améliorer l'usage des médicaments, et en particuler des antibiotiques, dans votre communauté.

Temps requis pour la participation

Ces questions supplémentaires devraient prendre entre 5 et 20 minutes. En outre, on vous demande la permission de visiter votre ménage une deuxième fois pendant la saison sèche.

Participation volontaire

Votre participation à cette étude est entièrement volontaire, c'est-à-dire que vous avez le droit de refuser de participer, maintenant ou plus tard (au moment des visites à la maison), sans aucune conséquence. Ce choix ne sera pas documenté ou rapporté dans les documents de l'étude.

Vous, en tant que responsable principal pour la santé quotidienne et l'utilisation des soins de santé pour les membres de ce ménage, êtes invités à participer parce que vous vivez dans la localité où nous effectuons cette étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment. Vous êtes aussi libre de choisir les questions à répondre.

Si vous souhaitez participer, indiquez verbalement que vous acceptez de participer à l'étude.

Confidentialité

Toutes les informations recueillies sur vous ou votre ménage au cours de l'étude resteront strictement confidentielles. Votre nom n'est pas enregistré et toutes les informations que vous fournissez resteront confidentielles. Seulement l'équipe de recherche aura accès aux données et informations collectées.

Risques et avantages

Si des questions vous mettraient mal à l'aise, n'hésitez pas à tout moment de pas répondre à la question, de faire une pause, ou d'arrêter de participer à cette étude.

Il n'y a pas d'avantages directs à votre participation. Au cours des visites de votre ménage, notre équipe de recherche peut identifier les membres de votre ménage qui devraient chercher des soins de santé pour les maladies causant de la fièvre et autres. Par conséquent, l'équipe peut aider à fournir de l'information sur l'offre de soins établie dans votre communauté. Les avantages indirects sont que toutes les informations collectées contribueront à fournir des données importantes sur les problèmes de santé dans votre communauté. Ceci conduira à une meilleure compréhension du traitement de

nombreux maladies, en particulier celles à traiter avec les antibiotiques, et de la façon d'améliorer l'accès aux soins de santé. Il n'y a pas de compensation pour participer à cette étude.

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le comité d'éthique de l'Université Protestante au Congo et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

(le consentement verbal du participant sera documenté par l'interviewer – voir annexe 12.2)

12.5 Participant information + Informed consent form for the patient healthcare visit exit interview (adult participant)

INFORMATION POUR LE PARTICIPANT ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES stade III

Vous êtes invités à participer volontairement à une étude de l'Institut national de recherche biomédicale (INRB, Kinshasa) et de l'Institut de médecine tropicale (ITM, Anvers), en répondant à quelques questions, principalement sur les traitements utilisés dans votre communauté. L'étude est décrite dans cette fiche d'information. Si vous avez des questions, maintenant ou plus tard, n'hésitez pas à les poser, incluant sur les avantages et les inconvénients de l'étude. De plus, vous êtes bien entendu libre d'interrompre votre participation à l'étude à tout moment.

But et description de l'étude

Le but de notre étude est de comprendre l'usage des certains médicaments pour traiter certaines maladies dans votre communauté, et en particulier de ce que les médecins appellent des *antibiotiques*: où ils sont prescrits ou distribués, et comment ces médicaments sont utilisés. Les résultats aideront à améliorer l'offre de santé, par exemple en développant d'outils adaptés pour les agents de santé, pour mieux utiliser ces médicaments. Ainsi, l'étude veut contribuer à l'usage correcte des antibiotiques, afin de garder ces traitements efficaces quand un malade en a besoin.

Nous allons vous poser quelques questions sur les médicaments qui vous ont été prescrits, donné, ou que vous avez acheté, par exemple le dosage, la fréquence avec laquelle vous allez prendre ces médicaments. On vous posera aussi quelques questions sur les raisons pour lesquelles vous avez cherché ces médicaments ici, chez cet agent de santé ou fournisseur de médicaments ; et on vous demandera de regarder les médicaments que vous venez d'obtenir. Finalement, nous vous demandons aussi la permission de vous appeler dans une semaine, pour une suivie sur l'achat et l'usage de ces médicaments.

Après la fin de l'étude, les données peuvent être partagés avec des autres chercheurs pour être utilisées dans des études ultérieures sur l'usage de médicaments. Avant de les partager, les donner seront « pseudo-anonymisées », ce qui veut dire que toute information qui permettrait de vous identifier, comme votre nom et numéro de téléphone, ne sera pas partagée.

Temps requis pour la participation

Répondre aux questions devrait prendre un maximum de 20 minutes. Le suivi après une semaine, par un appel téléphonique, ne devrait prendre que quelques minutes.

Participation volontaire

Votre participation à cette étude est entièrement volontaire, c'est-à-dire que vous avez le droit de refuser de participer, maintenant ou plus tard (au moment des visites à la maison), sans aucune conséquence. Le choix de ne pas participer ne sera pas documenté ou rapporté dans les documents de l'étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment. Vous êtes aussi libre de choisir les questions à répondre.

Si vous souhaitez participer, nous allons vous demander de confirmer par écrit que vous acceptez de participer à l'étude, et vous garderez une copie de ce document de « consentement », signé par nous deux.

Confidentialité

Toutes les informations recueillies au cours de l'étude resteront strictement confidentielles. Votre nom n'est pas enregistré et toutes les informations que vous fournissez resteront confidentielles. Seulement l'équipe de recherche aura accès aux données et informations collectées. Votre contact (n° de téléphone) sera gardé jusqu'à l'appel de suivi, et ne sera pas gardé après. Nous garantissons que toutes les informations seront traitées de manière strictement confidentielle, et votre nom sera remplacé par un code dans tous les documents de l'étude.

Risques et avantages

Il n'y a pas de risque direct associé à cette étude. Si des questions vous mettraient mal à l'aise, n'hésitez pas à tout moment de pas répondre à la question, de faire une pause, ou d'arrêter de participer à cette étude. Après avoir terminé les questions, l'équipe de recherche pourra fournir des informations sur les soins de santé communautaire, ou l'usage d'un médicament.

Au cours de l'entretien, notre équipe de recherche pourrait identifier des contre-indications ou des erreurs dans l'usage des médicaments, et ensemble avec le fournisseur de soins rectifier le traitement et vous aider à assurer une prise correcte du médicament. L'avantage indirect est que toutes les informations collectées contribueront à fournir des données exactes sur les traitements utilisés dans votre communauté, et peut ainsi conduire à une meilleure compréhension du traitement de nombreux maladies, et de la façon d'améliorer l'accès aux soins de santé. Il n'y a pas de compensation pour participer à cette étude.

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le comité d'éthique de l'Université Protestante au Congo et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

PARTICIPANT

Nom du répondant (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

Empreinte du pouce

Si le répondant un témoin indépendant de l'équipe de recherche (par exemple membre du même ménage ou un voisin), doit être présente pendant l'entretien pour le consentement éclairé. Si à la fin de l'entretien, la personne accepte de participer, le témoin signera ce formulaire de consentement, et le/la participant/e enregistrera l'empreinte du pouce dans la boîte ci-dessus

TEMOIN

Nom du témoin (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

INTERVIEWER

Je confirme que la fiche d'information a été lue et expliquée au participant nommé ci-dessus dans une langue que le répondant comprend bien.

Je me suis assuré que le participant a bien compris qu'il/elle peut choisir librement de participer à l'étude, qu'il/elle n'a pas à répondre à une question dont il/elle préfère pas répondre, et qu'il/elle peut à tout moment mettre fin à l'entretien.

Le participant a eu l'occasion de poser des questions sur l'étude et ses objectifs. Si le répondant avait des questions, moi ou un collègue de l'équipe de recherche a répondu correctement et clairement aux questions.

Le participant a été expliqué que son nom n'est pas enregistré sauf sur le formulaire présent, qui sera gardé sécurisé, uniquement utilisé si le participant préfèrerait annuler sa participation à l'étude, et détruit un an après la fin de l'étude. Les informations fournies resteraient pseudo-anonymisés, c'est à dire que les identifiants directes tels que le nom seront remplacés par un code dans tous les documents officiels de l'étude .

Nom de l'interviewer (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

12.6 Participant information + Informed consent form for the patient healthcare visit exit interview (child or adolescent with caretaker)

INFORMATION POUR LE PARTICIPANT ETUDE D'USAGE COMMUNAUTAIRE D'ANTIBIOTIQUES stade III

Vous êtes invités à participer volontairement à une étude de l'Institut national de recherche biomédicale (INRB, Kinshasa) et de l'Institut de médecine tropicale (ITM, Anvers), en répondant pour l'enfant pour lequel vous êtes parent ou gardien à quelques questions, principalement sur les traitements utilisés dans votre communauté. L'étude est décrite dans cette fiche d'information. Si vous, comme parent/gardien ou comme patient adolescent, avez des questions, maintenant ou plus

tard, n'hésitez pas à les poser, incluant sur les avantages et les inconvénients de l'étude. De plus, vous êtes bien entendu libre d'interrompre votre participation à l'étude à tout moment.

But et description de l'étude

Le but de notre étude est de comprendre l'usage de certains médicaments pour traiter certaines maladies dans votre communauté, et en particulier de ce que les médecins appellent des *antibiotiques*: où ils sont prescrits ou distribués, et comment ces médicaments sont utilisés. Les résultats aideront à améliorer l'offre de santé, par exemple en développant d'outils adaptés pour les agents de santé, pour mieux utiliser ces médicaments. Ainsi, l'étude veut contribuer à l'usage correcte des antibiotiques, afin de garder ces traitements efficaces quand un malade en a besoin.

Nous allons vous poser quelques questions sur les médicaments que votre enfant (ou l'enfant pour lequel vous êtes gardien) ont été prescrits, donnés, ou que vous avez acheté pour votre enfant, par exemple le dosage, la fréquence avec laquelle l'enfant va prendre ces médicaments. On vous posera aussi quelques questions sur les raisons pour lesquelles vous avez cherché ces médicaments ici, chez cet agent de santé ou fournisseur de médicaments; et on vous demandera de regarder les médicaments que vous venez d'obtenir. Finalement, nous vous demandons aussi la permission de vous appeler dans une semaine, pour une suivie sur l'achat et l'usage de ces médicaments.

Après la fin de l'étude, les données peuvent être partagés avec des autres chercheurs pour être utilisées dans des études ultérieures sur l'usage de médicaments. Avant de les partager, les donner seront « pseudo-anonymisées », ce qui veut dire que toute information qui permettrait de vous identifier, comme votre nom et numéro de téléphone, ne sera pas partagée.

Temps requis pour la participation

Répondre aux questions devrait prendre un maximum de 20 minutes. Le suivi après une semaine, par un appel téléphonique, ne devrait prendre que quelques minutes.

Participation volontaire

Votre participation à cette étude est entièrement volontaire, c'est-à-dire que vous avez le droit de refuser de participer, maintenant ou plus tard (au moment des visites à la maison), sans aucune conséquence. Le choix de ne pas participer ne sera pas documenté ou rapporté dans les documents de l'étude.

N'hésitez pas à demander s'il y a quelque chose que vous ne comprenez pas ou demander des explications jusqu'à ce que vous soyez satisfait. Vous êtes libre de retirer ou d'arrêter votre participation à tout moment. Vous êtes aussi libre de choisir les questions à répondre.

Si vous souhaitez participer, nous allons vous demander de confirmer par écrit que vous acceptez de participer à l'étude, et vous garderez une copie de ce document de « consentement », signé par nous deux. Si l'enfant malade (la patient) a plus de 14 ans, nous demanderons s'il/elle est d'accord que son parent ou gardien répond pour lui/elle.

Confidentialité

Toutes les informations recueillies au cours de l'étude resteront strictement confidentielles. Votre nom et le nom de votre enfant ne sont pas enregistrés et toutes les informations que vous fournissez resteront confidentielles. Seulement l'équipe de recherche aura accès aux données et informations collectées. Votre contact (n° de téléphone) sera gardé jusqu'à l'appel de suivi, et pas gardé après. Nous garantissons que toutes les informations seront traitées de manière strictement confidentielle, et votre nom sera remplacé par un code dans tous les documents de l'étude.

Risques et avantages

Il n'y a pas de risque direct associé à cette étude. Si des questions vous mettraient mal à l'aise, n'hésitez pas à tout moment de pas répondre à la question, de faire une pause, ou d'arrêter de participer à cette étude. Après avoir terminé les questions, l'équipe de recherche pourra fournir des informations sur les soins de santé communautaire, ou l'usage d'un médicament.

Au cours de l'entretien, notre équipe de recherche pourrait identifier des contre-indications ou des erreurs dans l'usage des médicaments, et ensemble avec le fournisseur de soins rectifier le traitement et vous aider à assurer une prise correcte du médicament. L'avantage indirect est que toutes les informations collectées contribueront à fournir des données exactes sur les traitements utilisés dans votre communauté, et peut ainsi conduire à une meilleure compréhension du traitement de nombreux maladies, et de la façon d'améliorer l'accès aux soins de santé. Il n'y a pas de compensation pour participer à cette étude.

Comité d'éthique

Cette étude a été examinée par le comité de revue institutionnel de l'Institut de Médecine Tropicale en Belgique et le comité d'éthique de l'Université Protestante au Congo et a reçu une recommandation favorable.

Si vous avez des questions ou des commentaires au sujet de l'étude, maintenant, pendant ou après votre participation, vous pouvez contacter l'un des chercheurs:

Nom: XX; Telephone: XX; Email: XX

REPONDANT

Nom du répondant (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

Si le répondant un témoin indépendant de l'équipe de recherche (par exemple membre du même ménage ou un voisin), doit être présente pendant l'entretien pour le consentement éclairé. Si à la fin de l'entretien, la personne accepte de participer, le témoin signera ce formulaire de consentement, et le/la participant/e enregistrera l'empreinte du pouce dans la boîte ci-dessus

Empreinte du pouce

TEMOIN

Nom du témoin (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

INTERVIEWER

Je confirme que la fiche d'information a été lue et expliquée au répondant nommé ci-dessus et (si le patient concerné est adolescent) au patient concerné dans une langue qu'ils comprennent bien.

Je me suis assuré que le répondant et (si le patient concerné est adolescent) l'enfant ont bien compris qu'il/elle/ils peut/peuvent choisir librement de participer à l'étude, que le répondant n'a pas à répondre à une question dont il/elle préfère pas répondre, et qu'il/elle peut à tout moment mettre fin à l'entretien.

Le répondant a eu l'occasion de poser des questions sur l'étude et ses objectifs. Si le répondant avait des questions, moi ou un collègue de l'équipe de recherche a répondu correctement et clairement aux questions.

Le répondant a été expliqué que son nom n'est pas enregistré sauf sur le formulaire présent, qui sera gardé sécurisé, uniquement utilisé si le répondant préfèrerait annuler sa participation à l'étude, et détruit un an après la fin de l'étude. Les informations fournies resteraient pseudo-anonymisés, c'est à dire que les identifiants directes tels que le nom seront remplacés par un code dans tous les documents officiels de l'étude.

Nom de l'interviewer (prénom + deuxième prénom (si disponible) + nom de famille) :

_____

Date (jj/mm/aa) : __ / __ / __

Signature : _____

12.7 Proof of insurance for low-risk studies involving human participants

INSTITUTE OF TROPICAL MEDICINE ANTWERP

Commissie Medische Ethiek
Prof. Dr. Patrick Cras
Universitair Ziekenhuis Antwerpen
Wilrijkstraat 10
2650 Edegem

Concerns - No-fault liability insurance for the submitted protocol- Amlin Corporate public liability insurance agreement N° 99-002-067

Dear Chairperson

By means of this letter, I wish to inform you about the insurance agreement pertaining to this research study.

As required by the Belgian law on experiments involving human subjects of May 7th 2004, a no-fault liability insurance must be in place for this research study. As a research institute, we have negotiated an umbrella agreement with *Amlin Corporate Insurance* in which our minimal risk studies, in Belgium or abroad, are automatically no-fault insured. This umbrella agreement requires neither preceding notification to our insurer, nor a separate, study specific insurance agreement.

Since the herewith submitted study is a low-risk study which falls under this umbrella agreement, no separate insurance agreement has been drawn up.

Limits of indemnity are as follows:

Bodily injury: € 5.000.000,- per occurrence and per insured year
Material damage: € 1.000.000,- per occurrence and per insured year

I hope this arrangement and clarification is satisfying to you. In case of any additional questions, please do not hesitate to contact me.

Lastly, I wish to thank you for your genuine review and evaluation of the submitted study.

Sincerely,

Prof. Dr. Bruno Gryseels
Director

T. 03 247 07 62 00
E. bgryseels@itg.be