STUDY PROTOCOL

REVISED A pilot protocol for surveillance of infection and antibiotic prescribing in primary healthcare across the globe: Antibiotic Prescribing in Primary Healthcare Point Prevalence Survey (APC-PPS)

[version 2; peer review: 2 approved, 1 approved with reservations]

Aislinn Cook[1,2], Jan Goelen[1], Catrin E. Moore[1], Jennifer Martin[1], Koen B. Pouwels[2], Michael Sharland[1]

[1]Centre for Neonatal and Paediatric Infection, Institute of Infection and Immunity, School of Health & Medical Sciences, City St George's, University of London, London, England, UK
[2]Health Economics Research Centre, University of Oxford Nuffield Department of Population Health, Oxford, England, UK

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Abstract

Little data is available from the primary healthcare setting in low- and middle-income countries to describe the burden of clinical infections and antibiotic prescribing proportions for those infections. The AWaRe Antibiotic Book provides a framework for assessing antibiotic prescribing in primary healthcare but requires understanding both frequency of clinical infections and their antibiotic prescribing proportions. The Antibiotic Prescribing in Primary Healthcare Point Prevalence Survey (APC-PPS) project is a series of point prevalence surveys conducted at primary healthcare facilities in LMICs to capture the frequency of consultation for different clinical infections and diagnoses and the frequency and type of antibiotic prescribing associated with these infections in primary healthcare facilities. This study aims to assess the feasibility of using a PPS methodology to collect data on clinical presentation and antibiotic prescribing in primary healthcare settings. The data collected are necessary to be able to summarise relative frequencies of presentation of different clinical infections and antibiotic prescribing practices to inform global estimates of antibiotic use and inform the development of surveillance methods and representative sampling frames. Each site will conduct 6–8 point prevalence surveys over the course of 12 months. Completely anonymous data on age, sex, relevant comorbidities, infection symptoms and diagnoses and antibiotic

Open Peer Review

Approval Status ✓ ? ✓

	1	2	3
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1. **Lars Småbrekke**, UiT Arctic University of Norway, Tromsø, Norway
Robert Nuifondieng Foncha, UiT The Arctic University of Norway Faculty of Health Sciences (Ringgold ID: 60482), Tromsø, Norway
2. **Margaret Lubwama**, Makerere University College of Health Sciences (Ringgold ID: 58589), Kampala, Uganda
3. **Kevin L Schwartz**, University of Toronto, Toronto, Ontario, Canada

prescription are collected for patients of all ages with acute infection symptoms (up to 14 days of symptoms) who present to the facility on the day of the survey. No identifiable data will be collected from individuals. Data is collected via ODK Collect and stored in a secure ODK Cloud server hosted by City St. George's, University of London. Sites will be active between early 2023- mid 2025, with regular interim data analysis scheduled and final data analysis planned by mid 2026. All required local and national ethical and regulatory approvals will be obtained prior to sites starting.

Plain Language Summary

The Antibiotic Prescribing in Primary Healthcare Point Prevalence Survey (APC-PPS) study aims to fill a data gap in low and middle income countries to better understand the frequency that patients present to primary healthcare facilities with different types of infections and to understand which patients receive an antibiotic prescription and which antibiotic. Antibiotic prescribing patterns will be compared against antibiotic prescribing guidelines such as the AWaRe Antibiotic Book to understand how prescribing patterns follow recommended guidelines. The data are captured using an easy-to-use mobile app (ODK) with offline capabilities. The data from this study will also be used to understand the feasibility of using this type of methodology and data collection app in different primary healthcare settings and different countries to inform the development of a standard representative methodology for capturing these types of data. The study has been implemented in 66 sites in 9 countries (6 in Africa and 3 in Asia) between April 2023 - November 2024. There are a diverse types of primary healthcare facilities participating in the study including outpatient departments, community dispensaries, community health centres, polyclinics and more.

Keywords

Primary Care, Antibiotic prescribing, Infections, AWaRe system, Point prevalence survey (PPS), Antibiotic use, Low and middle income countries (LMIC)

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Aislinn Cook (aicook@sgul.ac.uk)

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REVISED **Amendments from Version 1**

We have updated the dates of data collection to reflect that some sites were delayed starting and did not finish data collection until part way through 2025 and data analysis is currently ongoing. We also updated references to the word "rate" for infection or prescribing to proportion to appropriately reflect our aims of quantifying frequency among consulting patients.

We have responded to reviewer comments.

Any further responses from the reviewers can be found at the end of the article

5.1 Introduction

The Antibiotic Data to Inform Local Action (ADILA) project is a Wellcome Trust funded study that aims to use data on antimicrobial consumption, resistance, and clinical outcomes to derive novel frameworks that can inform the development of national and local policies to improve antibiotic prescribing. One of the key objectives focuses on developing a primary care clinical antibiotic prescribing framework that integrates clinical infection presentation/diagnoses with antibiotic prescribing.

The World Health Organization (WHO) released the WHO Essential Medicines List (EML) AWaRe Antibiotic Book in 2022,[1,2] providing detailed guidance on the choice of antibiotic drug, dose and duration for 35 common infections in adults and children in primary care and hospital settings. The AWaRe Book is built around the AWaRe system (Access, Watch, Reserve), a classification for antibiotics related to their potential for selecting for resistance. Access antibiotics are the first choice for the most common infections and should be widely available and generally have a lower potential for selecting resistance; Watch antibiotics are broader spectrum antibiotics with higher potential for resistance so should be used only for specific indications; and Reserve antibiotics are important last line antibiotics, reserved for the management of multidrug-resistant pathogens.

The AWaRe Antibiotic Book recommends that 9 out of the 10 most common infections in primary care should be treated with Access antibiotics. The book also highlights that low-risk patients with mild infections may not need antibiotic treatment. There is very little data from the low and middle income (LMIC) setting describing the variation in the relative incidence of clinical infections presenting to different types of primary care/ambulatory care facilities.

Point prevalence surveys (PPS) are a simple method to measure antibiotic use (or other medicines use). They are generally implemented on a single day and capture anonymous data on patients receiving an antimicrobial on the given day including demographics, specific antibiotic and indication. These types of surveys have been used successfully globally to measure antibiotic use and indication for prescription in hospitals[3–14] and the WHO has a published methodology[3] for conducting these types of surveys in the hospital setting (Global Antimicrobial Resistance and Use Surveillance System, GLASS). These types of point prevalence surveys have not been widely adapted to capture antibiotic use in the primary healthcare setting[15] despite majority of antibiotic prescribing occurring in these settings compared to hospitals.

To inform and monitor local and national antibiotic use targets and quality indicators, understand the feasibility of collecting basic clinical and prescribing data in the primary healthcare settings using basic tools such as point prevalence surveys is necessary. This includes the sampling frame, costs and the minimum data required to provide reasonable levels of precision of estimates of antibiotic use accounting for variable clinical burden to allow comparison of actual use compared to local and global guidelines.

Very little data is available from the primary healthcare setting in LMICs to describe the burden of clinical infections and antibiotic prescribing proportions for those infections. The few datasets available include data on (estimates of) infection and incidence by country alone (e.g. Global Burden of Disease (GBD); https://www.healthdata.org/), antibiotic prescriptions sometimes linked to diagnosis[16] or sales data without information on linked diagnoses (e.g. IQVIA MIDAS database, WHO GLASS Antimicrobial Consumption (AMC) module). However, there is currently insufficient data to compare observed prescribing patterns for common infections compared to local, national or WHO guidance.

This project aims to understand the feasibility of using PPS methodology to collect data on patterns of clinical presentation and antibiotic prescribing/dispensing in primary healthcare.

The project also aims to determine the frequency of consultation for different clinical infection presentations/diagnoses together with the frequency of those prescribed and not prescribed and type of antibiotic prescribing (if prescribed) for these infections in primary healthcare facilities.

5.2 Objectives

- Quantify the frequency of people presenting to primary healthcare facilities with an infection and the relative frequency of presentation of different clinical infections.
- Quantify the proportion of those presenting with clinical infections that receive an antibiotic prescription
- Of those who receive an antibiotic prescription, quantify the proportion of each AWaRe antibiotic prescribed
- Inform the design of a future optimal sampling strategy to obtain a representative sample of sites within a region or country.

5.3 Outcome

To determine the feasibility of using PPS methodology for surveillance of antibiotic use and to inform the sampling strategy of future surveillance surveys.

To understand the relative presentation proportions of clinical infections covered in the WHO EML AWaRe Antibiotic Book in different settings and to understand antibiotic prescribing proportions for these infections.

Local data summaries and graphics will be shared with sites to inform local initiatives.

5.4 Study design

5.4.1 Study design and setting

The Antibiotics in Primary Care-Point Prevalence Survey (APC-PPS) is a multi-centre, multi-country series of point prevalence surveys (PPS) conducted in a range of primary healthcare settings that prescribe or dispense antibiotics (e.g., primary care facilities, community health centres, hospital outpatients/ambulatory care, pharmacies, etc.). Sites participating are from Tanzania, Ghana, Malawi, Kenya, South Africa, Namibia, Pakistan, Bangladesh and Thailand. Participating countries were identified through stakeholder engagements through existing networks.

Study set up commenced in Autumn 2022 with outreach to country and site partners together with any required local ethical approvals. The first site opened in early 2023 with additional sites opening throughout 2023 and 2024 (dependent

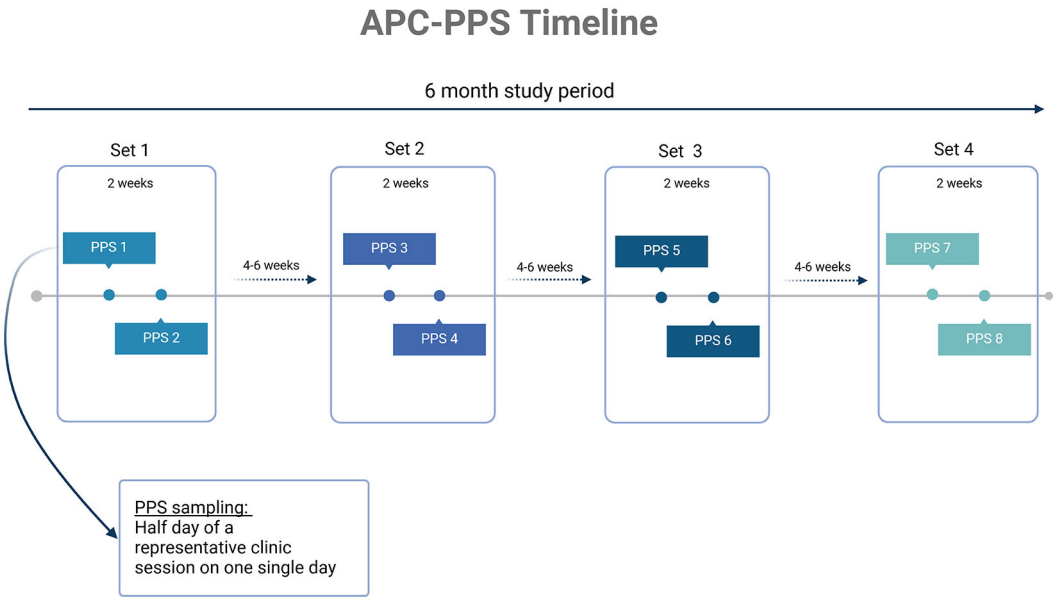

Figure 1. Study schematic timeline of APC-PPS for each site. Created with BioRender.com.

on local ethics timelines). Each site will conduct multiple PPS over 6 months from the first survey. The latest any site will be able to open in this phase is end of 2024 to allow for all data collection to be completed by mid 2025. Full analyses will be completed 6 months after the last site finishes data collection. Interim analyses have been conducted at the end of 2023 and in 2024.

Each site will collect data over the course of an approximate 6-month period to capture any seasonal differences in infection burden or antibiotic prescribing. Sites will conduct two half-day surveys in a two-week period (a "set" of surveys) and repeat these sets every 4–6 weeks conducting where possible a total of six to eight surveys in 6 months (Figure 1). All clinical decisions are determined by local staff at the point of care; this observational project is only collecting information on the prescribing decisions made.

5.4.2 Sample recruitment

5.4.2.1 Country eligibility

Any country is eligible to participate in the point prevalence survey provided a country coordinator has been identified and the appropriate regulatory and ethical obligations are met.

5.4.2.2 Facility/site eligibility

Any facility within a country providing primary healthcare with staff (e.g. physician/doctor, medical officer, nurse, pharmacist, pharmacy technician, etc.) who can evaluate patient symptoms and then prescribe or dispense antibiotics are eligible to participate provided the site has identified a site point-of-contact and has met any regulatory and ethical obligations required. Sites will also need to ensure teams collecting data have access to Android phones or tablets to use the Open Data Kit (ODK) Collect mobile app.

5.4.2.3 Patient eligibility criteria

This study will collect anonymous data on all eligible patients presenting to participating facilities on the day of the survey with acute infection symptoms. Data from each site will be grouped by a facility identifier to allow stratification by facility factors within a single country in order to assess heterogeneity.

Inclusion criteria

All children and adults presenting with acute infection symptoms on the day of the survey should be included. Acute is defined as symptom(s) occurring for less than 14 days.

Eligibility of patients presenting to the facility meeting these criteria will be determined by the local site team using the infection symptoms/diagnoses of interest outlined in Table 1 as a guide. Local clinical discretion will be used to determine patients with acute infection symptoms. Patients with underlying chronic conditions presenting because they have acute infection symptoms should be included.

Table 1. List of presenting infection symptoms/diagnosis and additional symptoms questions for each infection presentation.

Presenting infection symptoms/diagnosis	Additional symptoms queried
• Does the patient have/report having a fever?	• Persistent fever lasting 7 days or longer • Suspected enteric fever • Patient received anti-malarial prescription for this fever episode
• Acute cough	• Cough >5 days • Shortness of breath/difficulty breathing • Chest pain
• Sore throat/pharyngitis/tonsillitis	
• Facial pain or pressure/sinusitis	

Table 1. *Continued*

Presenting infection symptoms/diagnosis	Additional symptoms queried
• Runny nose/nasal congestion/coryza	
• Ear pain/acute otitis media	• Uni-lateral ear pain • Bi-lateral ear pain • Otorrhoea/ear discharge
• Toothache/tooth abscess	
• Acute diarrhoea/gastroenteritis	• Bloody diarrhoea
• Increased urgency or frequency of urination/urinary tract infection (UTI)	• Blood in urine
• Painful urination	
• Genital discharge/sexually transmitted infection (STI)	
• Wound/ burn/bite infection	
• Skin rash/spots – without swelling	
• Skin swelling/redness/warmth/pain	• Swollen lymph nodes
• Other primary presentation/diagnosis	Please specify other symptoms/diagnosis:

Exclusion criteria

Patients presenting to the facility seeking care for underlying chronic conditions as their primary reason for consultation will be excluded. Patients meeting the exclusion criteria will be determined by local clinical teams. Patients with chronic conditions (eg chronic obstructive pulmonary disease) who present with acute signs of infections should **not** be excluded.

5.4.3 Sampling strategies

5.4.3.1 Sampling strategy for site selection

Sites will be selected as a convenience sample based on the availability of a site team able to conduct data collection activities and for which they have met any local and/or national regulatory and ethics requirements.

As this study aims to determine the variability of clinical presentation and associated antibiotic prescribing proportions there is no minimum number of sites per country defined. We aim to include a mix of private and public facilities and a mix of different types of outpatient and primary healthcare facilities and urban and rural facilities.

5.4.3.2 Sampling strategy for point prevalence surveys

Each primary care facility will conduct 2 single-day point prevalence surveys in a two-week period (a "set") and repeat this every 4–6 weeks for 6 months in total. Each survey will be conducted for a half a day or approximately 4 hours of a ***representative*** standard clinic session on a single day. Surveys will be conducted over 6 months to capture any seasonal variation in clinical infections presenting to primary care (Figure 1). Sites were advised to avoid conducting the surveys on days of any specialist clinic sessions that may influence frequency of infection presentation.

Number of patients per facility:

As this is a point prevalence survey conducted within a specific period of time at different facilities, it is not possible to identify the specific size of the sample needed for each facility. The size of the facility and local population will influence the number of patients attending.

As presentation rates of different clinical infections will likely vary by country or facility it is difficult to determine the specific sample size of each type of infection at each facility. Some conditions are rarer than others and may not be captured on the specific day of the survey at each facility. In order to try to capture some of this variability in presentation we will conduct surveys in two half-days across different days in a two-week period.

This study will provide data on the number of patients with each diagnosis per time unit which will help to determine future sample size calculation for subsequent study designs aiming to define regional or country-level representativeness.

5.4.4 Consent

Data collected for this study will be fully anonymised at the time of data capture and will not contain any personal or identifiable information and clinics are only identified by a facility ID code in the data. In many settings, these types of data would be routinely collected as part of a clinical audit to assess adherence to local guidelines so we will not be obtaining individual informed consent from the patients for the purposes of this study. This is also to ensure feasibility by reducing the disruption to clinics and routine practice as formal written consent is more time burdensome and disruptive to routine practice. To understand prescribing practices in primary care, it is essential to capture as many patients presenting as possible to understand the true frequency of different infections and true prescribing proportion for each type of infection; therefore reducing burden on sites and disruption to patient visits was essential to ensure representative sampling.

5.5 Data collection

5.5.1 Data collection platform

Data will be collected and managed using Open Data Kit (ODK; https://getodk.org/). ODK allows for offline data collection through a mobile app, ODK Collect, which improves the ease of implementation in global sites.

Data will be hosted using ODK Cloud, the hosting service provided by ODK. Data will be hosted on a private server, and only authorised project users will have access to the database. ODK Cloud is based in a secure GDPR-compliant EU data centre, all data is encrypted in transit and at rest in the ODK Cloud, and the database and data are backed up continuously.

Site data collectors will collect data using the ODK Collect app, an open-source Android application that supports offline data collection. Users will be allocated to country-specific forms using a site-specific QR code. If QR scanning does not work at a site, users can connect to the project on their computers or mobile phones using a URL and username/password. Data is synced automatically from the app to the central server when the device is connected to the internet/mobile network. Users can also submit records when they are not connected to the internet/mobile network, all data will be synced with the central server when the device is next connected to the internet/mobile network.

ODK Collect allows for an anonymous device-ID to be collected to distinguish users at each site assuming each data collector uses a unique device. In cases where one device may be used by multiple data collectors, data collectors were able to login with their unique QR code to distinguish user data collection when needed. To understand the feasibility of data collection of this type, the amount of time it takes for each record to be collected will be captured using ODK Collect app's metadata features. This will capture the elapsed time from when the data collector started data entry for that record to when they submitted that record.

Data in the ODK Cloud server will only be accessible to the core project team based at City St George's University of London (CSG). Sites will not have access to view or edit their data or data from other sites after it has been submitted to the central server from the mobile app (ODK Collect). At the end of the data collection, each site will receive a copy of their raw data in CSV format. This will be sent from the core project team at CSG via CSG iDrop, a secure, encrypted, file transfer system. Sites will also receive summaries of their data which is outlined further in the data sharing and publication policy (available in extended data repository).

5.5.1.1 Training

Country coordinators will be trained in the protocol and data collection processes by the central Project Team at CSG. Site leaders will be trained by both the country coordinators and through online videos and documents. Data collectors at each site will be trained in ODK Collect and to understand the inclusion criteria by site leaders and online videos produced by the central Project Team. We utilised a cascading training model where country and site leadswere trained during live video training by the central Project Team at CSG and they were responsible for providing appropriate training of site data collection teams to adequately implement the project. Site leads were provided training slides and additional training documents and all teams had access to the study-specific online training platform hosted on The Global Health Network (APC-PPS • Antimicrobial Resistance (AMR) (tghn.org)). Training materials are available in the extended data repository.

5.5.2 Data collection workflow

5.5.2.1 Facility-level data

On the day of each PPS, data collectors will complete a form about the facility and the PPS time slot including information on total presenting patients, data collection methods and antibiotic availability (if applicable) on site on the day of the survey. Once over the time period, the site will complete an overall facility information form providing information on facility characteristics and an depth antibiotic availability and pricing form. The data collected in these forms is described in Table 2. The full data collection forms are available in the extended data repository.

Table 2. Data collected in the facility form and PPS time slot.

Overall facility information	PPS-specific information

• Facility name
• Facility location (city, country)
• Type of primary healthcare facility
• Public (e.g. government) or private
• How patients pay for visits and medications
• If there is a pharmacy onsite
  ○ List of antibiotics available at the facility
  ○ Cost of antibiotics available
	• Date of survey
	• Time slot for the PPS (e.g. start and end time indicating morning, afternoon or evening)
	• Total number of attenders (for all conditions) on the day of the PPS – split by number of adults (≥18 years) and children/babies (<18 years)
	• Qualification(s) of prescribers/dispensers on day of survey (e.g. nurse, doctor, pharmacist, medical officer, etc)
	• Number of prescribers/dispensers during the survey time period
	• Antibiotics in stock on day of survey (if pharmacy is onsite)

5.5.2.2 Patient-level data

Fully anonymous data will be collected on the day of the PPS for all patients who present with acute (present for <14 days) infection symptoms. Each record (patient encounter) collected is linked with a site/facility identifier based on the QR code/login used by each user at that facility which will enable analysis to account for facility differences in prescribing. The data collector will record the necessary clinical data about the patient's presentation (including patient/parent (or guardian) reported symptoms) and whether they were prescribed an antibiotic at this visit (as described in section 5.5.2.3).

Once data have been entered on the form in the ODK Collect app, the data collector will save/submit the finalised form at which point ODK will generate a unique ID number for that record. If the mobile device has internet access at the time, the data will be automatically uploaded to the server. If the mobile device is not connected to the internet, all data will be uploaded to the server when the device is next connected. Figure 2 illustrates the data collection flow.

5.5.2.3 Consultation data collected

No personal or identifiable data about patients will be collected on the case report forms (CRFs). Age (years for patients ≥2 years; months for <2 years) and sex of the patient will be collected to allow for reporting clinical presentation and prescribing proportions adjusted for different patient populations. Certain diagnoses are more common in children (e.g. ear infections) or in women (e.g. urinary tract infection, UTI) so these data are necessary to appropriately adjust to wider populations. These data are essential to interpret the presentation of clinical infections and associated prescribing proportions correctly. Time (in minutes) of travel from the patient's home to the facility will be collected for each patient to understand if there are any prescribing differences based on how far the patient had to travel to the facility. Information will also be collected as to whether the patient had previously sought medical care/medication for this infection episode.

Any relevant comorbidities that may influence antibiotic prescribing practices or clinical severity of infections will be collected as below with additional free text provision to specify any not included in this list:

- HIV
- Malnutrition
- Diabetes
- Chronic obstructive pulmonary disease (COPD)
- Asthma
- Other chronic lung problems
- Chronic heart problems

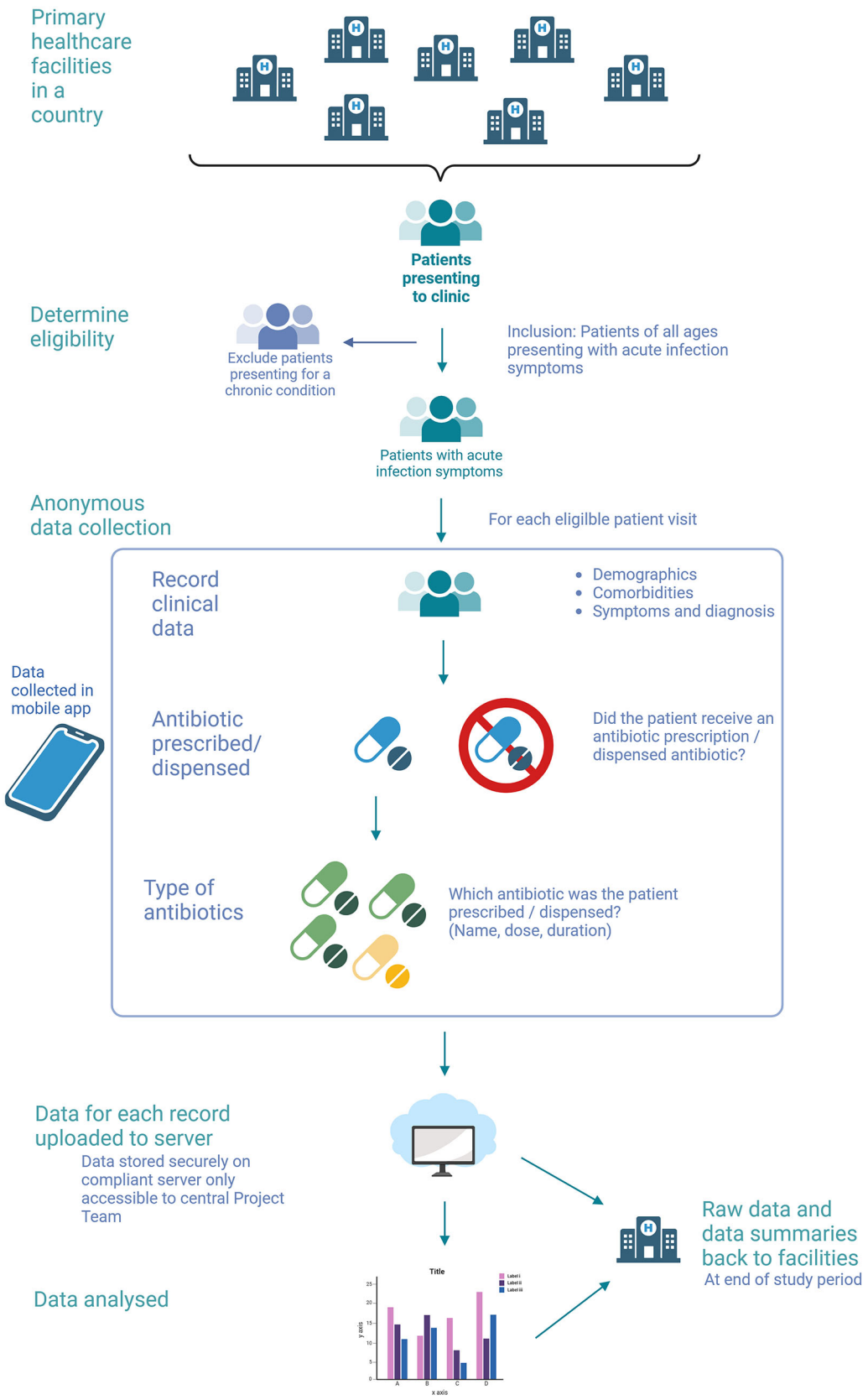

Figure 2. Data collection workflow diagram for the APC-PPS study. (created with BioRender.com).

Common infection symptoms and linked clinical diagnoses

Key infections symptoms/diagnoses are based around clinical presentations described in the WHO EML Antibiotic Book. As this book provides model global guidance on prescribing for 35 common infections in adults and children, including the choice of drug, dose and duration, collecting infections and symptoms that can be mapped back to the Antibiotic Book and other guidelines is important to standardise data collection and allow for observed prescribing to be compared to guidelines.

For all primary presentations, additional symptoms are also identified including the presence of fever to assess severity of infection based around indications for antibiotic prescribing. The full list of primary infection symptoms/clinical diagnoses and additional symptom questions for each infection presentation can be found in Table 1.

Antibiotics of interest

We are interested in capturing all systemic antibiotics (e.g oral, intramuscular, intravenous) and topical antibiotics prescribed in primary healthcare for a given infection episode after consultation. All antivirals, antifungals, anthelminthics, antimalarials, medicines for HIV, and any antibiotics eye drops are excluded. Generic name of antibiotic, prescribed dose and prescribed duration will be collected.

Case report forms (CRFs) for consultation data are available in extended data online repository.

5.5.3 Pragmatic approach to data collection

Given the different structures of primary healthcare facilities participating in our study and the structures of the study teams, we allowed for pragmatic approaches to data collection to ensure the study was feasible in different settings. Data was collected electronically in ODK Collect (see below); however sites were given the option to collect data directly into ODK or to use paper CRFs if they preferred and then enter the data in ODK Collect at a later time. Sites were encouraged to enter data directly into ODK as much as possible to reduce the time burden on data collection teams. Sites were also given flexibility in who collected the data. Data could be collected directly by the prescriber/dispenser on paper CRFs or in ODK, or by having an observer record the consultation data during the consultation or between the consultations. Sites were given an option to collect data from the medical notes as a last option; however, this was only allowed where symptoms were routinely and comprehensively enough recorded in the medical notes to allow for retrieval. The study team at CSG worked with site teams before and during the study to find the best approach for each team. Data were collected on the day of each survey regarding the methods of data collection used which can be used in analysis and to assess feasibility of the methodology.

5.5.4 Data management, protection and security

Data will be collected on devices using the ODK Collect app. Only users at sites authorised by the central Project Team at CSG, who have been allocated a QR code for the study and will be able to use the application and collect data. All patient data collected will be completely anonymous and there will be no unique identifiable patient data captured for any participant. Codebooks for electronic data capture in ODK (XLS forms) are available in the APC-PPS online repository.

Data is encrypted in ODK Collect app and is sent encrypted to the ODK Cloud server. Data collected by sites will be stored centrally on ODK Cloud server based in an EU data centre, hosted by ODK. The server will be private to the central Project Team members based at CSG and University of Oxford, and no unauthorised users will have access to the central server. The server is GDPR compliant and ISO27K, CSA STAR and SOC 2 certified. The server is backed up continuously and each back up is stored for 30 days. Data are encrypted on the ODK Central server at rest.

The data will also be downloaded from ODK Cloud monthly to a secure server based at City St. George's, University of London, and there will be encrypted back up tapes, with 24-hour security. CSG servers which are backed up overnight, every night, to hard disk and then cloned to tape storage. Full backups of all the data are carried out monthly. The cloned tapes are stored separately in a fireproof and bombproof safe off-site.

5.5.5 Data analysis

Data will be analysed descriptively in the first instance. Presentation proportions for each clinical infection will be calculated. Overall antibiotic prescribing proportion and overall proportions by AWaRe categories will be summarised. The antibiotic prescribing proportion and AWaRe categories will be summarised for each clinical infection and be compared with the new WHO AWaRe Antibiotic Book prescribing guidelines, peers, and ideal prescribing proportions.

Factors including demographics (e.g. sex, age, time to health facility), comorbidities and infection severity will be explored to understand how they relate to an antibiotic prescription for an encounter, where sufficient data exists.

These data will also be used in simulations to explore the ideal sample size and sampling frame that would be needed for surveillance of antibiotic use in primary healthcare including the number and type of sites in a country, number of patients per site and frequency of sampling to inform future surveillance using PPS. We will aim to use these data to inform sample size calculations, understand co-efficients of variation and how to extrapolate from the number of patients per PPS time unit.

5.6 Ethical and regulatory considerations

5.6.1 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, ethical approval was obtained for this study protocol from City St George's University of London ethics committee (REC 2022.0170). Individual sites are responsible for ensuring relevant local and national ethics and regulatory approvals are in place prior to starting the study. The Project Team at CSG supported sites in preparation of documents required to meet these obligations. No site started the study without having the appropriate approvals in place.

5.6.2 Amendments

For any amendment to the study, the Chief Investigator or delegated personnel, in agreement with the sponsor will submit information to the appropriate body to issue approval for the amendment. The Chief Investigator or delegated personnel will work with sites so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

5.6.3 Protocol compliance

Protocol deviations, or data breaches are departures from the approved protocol. Any protocol deviations and data breaches must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor in a timely manner. However, overall risk of deviations and data breaches are low given the study design and risk to participants is negligible as there is no identifiable or personal data collected.

5.6.4 Archiving arrangements

The full dataset will be downloaded from ODK Cloud at the end of data collection and the final dataset will be deposited on the City St. George's Research Data Repository upon study completion. Analysis code and reports will also be archived on the APC-PPS Project space on the City St. George's Research Data Repository. Access to the raw, unaggregated data on the repository will be restricted to only the central Project Team members at CSG and University of Oxford. Sites will not be able to view/access raw data on the repository; but will be returned their raw data separately. Data will not be used for any purposes beyond the current described APC-PPS project and the ADILA project, without explicit permission and data sharing agreements in place with each individual site. Any aggregate datasets, code used for summary analyses and data visualisations/dashboards will be available to view on the repository Project space by collaborators at site teams 6–12 months after study completion after summary data has been returned to sites and the main paper(s) submitted for publication.

Datasets will be retained on the repository for the duration of the data retention period of 5 years. Any aggregated datasets that have been made publicly available will be published with a DOI and retained in perpetuity. All datasets archived on the repository will be accompanied by corresponding metadata in the study's documentation and cataloguing standards.

The project coordinator as CSG will be responsible for uploading the final datasets, reports and code to the repository. The project coordinator will also be responsible for maintaining accuracy, completeness, relevance and timelines of all data archived on the repository. The City St George's Research Data Service will support the project coordinator where required and ensure the data is preserved to the highest available standards. The Chief Investigator will have overall responsibility for the data archived in the repository. For corporate information governance purposes, the PI will be considered the data owner and will be the main contact for the data for the duration of the retention period. If the PI leaves City St George's his/her institute manager will be responsible for the archived data.

5.7 Dissemination and publication policy

5.7.1 Guiding principles

The results of this study will be published in scientific and academic peer-reviewed journals and submitted as abstracts and presentations to relevant international conferences. The site and country collaborators will be involved in developing

and reviewing drafts of manuscripts, abstracts and other publications and presentations arising from the results of this project.

The dissemination and publication policy for the APC-PPS project is guided by two overarching principles:

1. Transparency – All sites contributing data to the project will be informed as to the use of their data. We will ensure a process is in place for sites and collaborators to access data from the APC-PPS project for the purpose of generating local abstracts, reports, presentations and publications and the process of project approval for subsequent work are clear and agreed by all participating members of the project.

2. Quality – We will maintain a centralised publication and abstract discussion and approval process within the APC-PPS project to maintain a high quality of overall scientific output.

5.7.2 Site data at the end of study

Individual sites will receive access to a summary report of their data and their raw data within 6–12 months of the end of the project (defined as end of data collection activities for all sites). Per individual agreements with each site, summary data will be shared separated by (anonymised) site, country and overall which will be published on the APC-PPS Project space of the City St. George's Research Data Repository at the end of the project and included in the analyses for the wider ADILA project. Access to raw individual site data by the country coordinator(s) will only be with explicit permission from each site in that country. Publications and other outputs from the wider ADILA project that use data contributed by collaborators from the APC-PPS will be governed by the ADILA project publication policy (separate attachment). Sites will have an opportunity to opt out of their data being used in the wider ADILA project for analyses beyond those described in the APC-PPS protocol.

5.7.3 Abstracts and papers authorship

In general, all authors publishing abstracts and papers using data from the APC-PPS project are expected to adhere to the ICMJE authorship guidelines which includes:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

- Drafting the work or revising it critically for important intellectual content; AND

- Final approval of the version to be published; AND

- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The full dissemination and publication policy for APC-PPS is available in the extended data.

Ethics and consent

Before the start of the study, ethical approval was obtained for this study protocol from City St George's University of London ethics committee (REC 2022.0170, 07/11/2022). Individual sites are responsible for ensuring relevant local and national ethics and regulatory approvals are in place prior to starting the study. The Project Team at CSG supported sites in preparation of documents required to meet these obligations. No site started the study without having the required approvals in place.

Data collected for this study will be fully anonymised at the time of data capture and will not contain any personal or identifiable information and clinics are only identified by a facility ID code in the data. In many settings, these types of data would be routinely collected as part of a clinical audit to assess adherence to local guidelines so we will not be obtaining individual informed consent from the patients for the purposes of this study. This is also to ensure feasibility by reducing the disruption to clinics and routine practice as formal written consent is more time burdensome and disruptive to routine practice. To understand prescribing practices in primary care, it is essential to capture as many patients presenting as possible to understand the true frequency of different infections and true prescribing proportions for each type of infection; therefore reducing burden on sites and disruption to patient visits was essential to ensure representative sampling.

All ethics committees approved the protocol as described without requiring formal written consent.

Data availability

Underlying data

No data are associated with this article.

Extended data

The following supplementary materials are available in the St George's University of London FigShare Research Data Repository.

St George's, University of London FigShare Research Data Repository: APC-PPS Protocol and Protocol Synopsis https://doi.org/10.24376/rd.sgul.27325758.[17]

This project contains the following extended data:

- pps_synopsis_v2.0_28Oct22.pdf
- adila_apc_protocol_v2.0_28Oct22_signed.pdf

This is the protocol and protocol synopsis for the Antibiotics in Primary Care Point Prevalence Survey (APC-PPS).

St George's, University of London FigShare Research Data Repository: Data collection forms for the APC-PPS. https://doi.org/10.24376/rd.sgul.27325332.[18]

This project contains the following extended data:

- Consultation Level Data CRF v2.0 01.05.2023 2 pages.pdf
- Facility Information antibiotic availability v1.0 20.04.2023.xlsx
- Facility Information CRF v1.0 26.04.2023.pdf
- Survey Data CRF v1.0 11.04.2023.pdf

These are the data collection forms (CRFs) for the Antibiotics in Primary Care Point Prevalence Survey (APC-PPS). There are three levels:

1. Facility form (to be completed once in the study period);
2. Survey level form (to be completed on every day the survey is conducted);
3. Consultation-level form (to be completed for every eligible consultation).

Additionally, the Antibiotic Availability form (excel) is completed once in the study period.

St George's, University of London FigShare Research Data Repository: Data Codebook for ODK electronic data capture. https://doi.org/10.24376/rd.sgul.27325695.[19]

This project contains the following extended data:

- ODK XLSForm APC PPS Consultation Level Data v1.3 30.08.2023.xlsx
- ODK XLSForm APC PPS Facility Information v1.0 12.04.2023.xlsx
- ODK XLSForm APC PPS Survey Data v1.0 12.04.2023.xlsx

These are the XLS forms used for electronic data capture via ODK (Open Data Kit) for the Antibiotics in Primary Care Point Prevalence Survey (APC-PPS). There are codebooks for each of the three CRFs to be completed in the study:

1. Facility form (to be completed once in the study period);

2. Survey level form (to be completed on every day the survey is conducted);

3. Consultation-level form (to be completed for every eligible consultation).

St George's, University of London FigShare Research Data Repository: E-Learning Platform on The Global Health Network. https://doi.org/10.24376/rd.sgul.27325728.[20]

This is the link to the e-learning platform of the Antibiotics in Primary Care Point Prevalence Survey (APC-PPS) e-Learning Platform on The Global Health Network (TGHN). The materials were designed by the APC-PPS Project Team at SGUL and the web platform and module design by the team at TGHN.

St George's, University of London FigShare Research Data Repository: Additional training materials for the APC-PPS. https://doi.org/10.24376/rd.sgul.27325707.[21]

This project contains the following extended data:

- APC-PPS Training Manual - Eligibility v0.3 231110.pdf

- APC-PPS Training Manual - How to do web-based data entry 19.04.2023.pdf

- APC-PPS Training Manual - How to set up ODK Collect for data collection 17.02.2023.pdf

- APC-PPS Training Manual - How to submit a form in ODK 17.02.2023 (1).pdf

- APC-PPS Training Manual - Study Design v0.2 231110.pdf

These are the training materials used for the Antibiotics in Primary Care Point Prevalence Survey (APC-PPS). They contain guidance on using ODK via the app and via the web, how to submit a form on ODK, and refresher guides on Eligibility and Study Design.

St George's, University of London FigShare Research Data Repository: Publication policy for APC-PPS. https://doi.org/10.24376/rd.sgul.27325725.[22]

This project contains the following extended data:

- apc_pps_pubpolicy_v1.1_15May23 - Master.pdf

The Master Publication Policy of the Antibiotics in Primary Care Point Prevalence Survey (APC-PPS).

Acknowledgments

We'd like to thank all of the collaborators who have participated in the study for their interest in the study and its outcomes and their subsequent hard work adapting the study to different complex settings and study team structures.

We'd also like to thank Faran Dhaliwal, William Cuningham and Baboucarr Njie for all of their work on developing the data management structures for the APC-PPS. The work developing the ODK codebooks, data cleaning and reporting to sites would not be possible without all of their hard work on the study.

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Open Peer Review

Current Peer Review Status: ✔ ? ✔

Version 2

Reviewer Report 24 April 2026

https://doi.org/10.21956/wellcomeopenres.28872.r152255

✔ **Lars Småbrekke**
Clinical Pharmacy and Pharmacoepidemiology, Department of Pharmacy, Faculty of Health Sciences, UiT Arctic University of Norway, Tromsø, Norway

The author response is clear and comprehensive, and I approve the revision of the manuscript.

However, I have one additional comment regarding the patient level data collected. The author could consider including information on whether the visit is a revisit due to treatment failure, and if so, also collect data on the choice of initial treatment.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacoepidemiology; Clinical Pharmacy;

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 29 August 2025

https://doi.org/10.21956/wellcomeopenres.25830.r127051

✔ **Kevin L Schwartz**
University of Toronto, Toronto, Ontario, Canada

This is a protocol for a point prevalence survey of antibiotic prescribing in primary care clinics from LMICs. According to this protocol, which appears published online, the actual study was conducted and completed in November 2024.

The study's primary objective is feasibility. The authors have not outlined the primary feasibility outcomes to be collected. Specifically, they have not defined the actual measures of feasibility, expected numbers or metrics that will measure/define as feasible.

Otherwise I have no concerns with the protocol. Aside from being reviewed after study completion it is clearly written and an important study.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious Diseases, Antimicrobial Stewardship, Epidemiology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 10 Mar 2026

Aislinn Cook

Thank you for your comments. I have responded to them below. This is a protocol for a point prevalence survey of antibiotic prescribing in primary care clinics from LMICs. According to this protocol, which appears published online, the actual study was conducted and completed in November 2024. The study was delayed in some facilities and data collection was not completed until partway through 2025. Analysis is currently underway.

The study's primary objective is feasibility. The authors have not outlined the primary feasibility outcomes to be collected. Specifically, they have not defined the actual measures of feasibility, expected numbers or metrics that will measure/define as feasible. Thank you for this comment. This is helpful. As this is a pilot, feasibility will be assessed in several ways. One will be the broad participation in the study – how many facilities participate and complete all 8 surveys in different settings. From a data collection perspective we will use the number of eligible patients compared to the number of patients for which data was collected as metric of data collection feasibility. We will also use the method and person

doing data collection which was collected as part of each survey to assess personnel required and ability to collect these data during consultations. We will also use the time taken to do data entry for each record from the metadata from ODK. We will send a feasibility survey at the end of the study to better capture self-reported measures of how easy it was to find data, do data entry, whether there was any disruption to clinics. During the study, we had regular contact with participating sites and recorded meeting notes of challenges discussed and solutions found. We allowed for unknown to be selected for all fields and we will use percentage of missingness for key fields as an assessment of data availability triangulated with method of data collection.

Competing Interests: No competing interests were disclosed.

Author Response 30 Mar 2026

Aislinn Cook

Thank you for you comments. I have responded below in bold

This is a protocol for a point prevalence survey of antibiotic prescribing in primary care clinics from LMICs. According to this protocol, which appears published online, the actual study was conducted and completed in November 2024.
The study was delayed in some facilities and data collection was not completed until partway through 2025. Analysis is currently underway.

The study's primary objective is feasibility. The authors have not outlined the primary feasibility outcomes to be collected. Specifically, they have not defined the actual measures of feasibility, expected numbers or metrics that will measure/define as feasible.
Thank you for this comment. This is helpful. As this is a pilot, feasibility will be assessed in several ways. One will be the broad participation in the study – how many facilities participate and complete all 8 surveys in different settings. From a data collection perspective we will use the number of eligible patients compared to the number of patients for which data was collected as metric of data collection feasibility. We will also use the method and person doing data collection which was collected as part of each survey to assess personnel required and ability to collect these data during consultations. We will also use the time taken to do data entry for each record from the metadata from ODK. We will send a feasibility survey at the end of the study to better capture self-reported measures of how easy it was to find data, do data entry, whether there was any disruption to clinics. During the study, we had regular contact with participating sites and recorded meeting notes of challenges discussed and solutions found. We allowed for unknown to be selected for all fields and we will use percentage of missingness for key fields as an assessment of data availability triangulated with method of data collection.

Competing Interests: None

Reviewer Report 12 August 2025

https://doi.org/10.21956/wellcomeopenres.25830.r127054

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Margaret Lubwama
Medical Microbiology, Makerere University College of Health Sciences (Ringgold ID: 58589), Kampala, Central Region, Uganda

Thank you for the invitation to review this study protocol.

This is an important study in this era of antimicrobial resistance (AMR). Given that the highest burden of AMR is in low- and middle-income countries (LMICs), and antibiotic overuse and misuse are among the drivers of AMR, it is of utmost importance that we understand the antibiotic prescribing practices and antibiotic use in primary healthcare in LMICs.

General comments

How does the WHO AWaRe guidelines affect the national clinical guidelines of the different countries? Are there any similarities or differences that may affect the prescribing practices of the different health facilities in the different countries? How well do the national clinical guidelines match the WHO AWaRe guidelines. This can guide in policy decisions. How is this study taking this into account?

Section 5.4

Is this study a cross-sectional study collecting data at different points in time. Can the authors clarify this?

What proportions of private and public facilities will be included for the different countries? Will it be representative of the facilities in the different countries?

The team has clearly outlined infection symptoms/diagnoses of interest which will be used for the eligibility criteria. It might be that the list provided by the study collects much more data than what the healthcare centers are used to collecting. This may require more time. How many patients are estimated per healthcare center? Will all the data on the list be collected in 4 hours? While the authors have mentioned that it may not be possible to know the sample size per clinic, including the number of patients estimated per healthcare center, and the amount of time it will take to complete screening for each patient will provide insight into the feasibility of 4 hours. Is it possible to get these estimates from the records in the different healthcare facilities?

While the authors mention that they will not be obtaining individual informed consent from the patients for the purposes of this study, they may need a waiver of consent from the respective IRBs. Was this obtained if the IRBs require it?

Section 5.5.4

How will the data collected in the CRFs be managed? Where will the CRFs be stored? Who will be responsible for the CRFs?

If phones go missing what is the risk of data leaking. What precautions have been taken to address this? This can be included in a risk analysis plan.

Section 5.5.5

How will infection severity be determined and measured in this study?

I agree with the authors that it is important to understand how the different factors are associated with antibiotic prescribing practices. However, it is not very clear which statistical method will be used to address this. A more detailed statistical analysis plan is needed to show how the associations will be measured in this study.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical microbiology, antimicrobial resistance (antibacterial)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Mar 2026

Aislinn Cook

Thank you for your thorough review and comments. I have answered your comments below.

How does the WHO AWaRe guidelines affect the national clinical guidelines of the different countries? Are there any similarities or differences that may affect the prescribing practices

of the different health facilities in the different countries? How well do the national clinical guidelines match the WHO AWaRe guidelines. This can guide in policy decisions. How is this study taking this into account?
Thank you for this important question. The WHO AWaRe book is an official WHO guideline which can fill gaps where national treatment guidelines aren't available or up to date in countries. Countries and clinics that have their own guidelines will be expected to be following those as part of routine practice. The AWaRe Book provides a global framework to compare to across diverse settings, however, we are aware that any comparison to global guidelines may not account for differences in local treatment guidelines. A recent analysis did find quite high agreement in first line antibiotic choices in the AWaRe Book and local treatment guidelines for paediatric infections (Donà D, et al. eClinicalMedicine. DOI: 10.1016/j.eclinm.2025.103437) across 80 countries for primary care infections. We acknowledge that expected antibiotic prescribing patterns may be different than we estimate using AWaRe Book guidance compared to national treatment guidelines if they differ but given the broad number of countries and facilities included, we won't be able to adapt this for the global analysis. However, we will look to provide guidance to our country partners for their analysis to compare prescribing patterns to their own treatment guidelines using the same framework as will be used for the AWaRe Book comparison. Is this study a cross-sectional study collecting data at different points in time. Can the authors clarify this? This study is a cross-sectional study collecting data at half-day intervals for 8 repeated time points in sets of two surveys as shown in Figure 1.

What proportions of private and public facilities will be included for the different countries? Will it be representative of the facilities in the different countries? This is a convenience sample as this is a pilot study and the participation of public and private facilities will depend on the country involved. Generally, it is more difficult to engage private facilities as there are less incentives to provide these types of data and concerns that it will be used by authorities for enforcement of practices. We tried to engage both types of facilities but expect it will be more public facilities that participate in the study. As this is a pilot of the methodology, it will likely not be representative of the facilities and broad care seeking behaviours in the different countries. The level to which it is or is not representative will depend on the structure of the primary healthcare system in each country and healthcare seeking behaviours.
 The team has clearly outlined infection symptoms/diagnoses of interest which will be used for the eligibility criteria. It might be that the list provided by the study collects much more data than what the healthcare centers are used to collecting. This may require more time. How many patients are estimated per healthcare center? Will all the data on the list be collected in 4 hours? While the authors have mentioned that it may not be possible to know the sample size per clinic, including the number of patients estimated per healthcare center, and the amount of time it will take to complete screening for each patient will provide insight into the feasibility of 4 hours. Is it possible to get these estimates from the records in the different healthcare facilities?
Thank you for your important questions. As this was a pilot study of a novel methodology, we did not limit participation to clinics based on the size of the clinic or the number of patients estimated to visit. We collected this information as part of the pilot study – total patient visiting, total with infections and the number included – to enable exploration of

minimum sample sizes needed for future studies. The data collected was data routinely needed during a consultation and the expectation was that this would be available during the study data collection period. For fields that were not available, data collectors were able to use medical notes/records where possible to fill in data such as age, etc or record unknown for fields that were not available. By including a diverse range of primary care facilities, the structure and flow of patients through clinics was different so we work closely with clinics to overcome any challenges with data collection and to minimise disruption to routine care. In some instances, not all data was available in the four hour period – i.e. if patients were triaged with symptoms collected, then sent for labs and returned later to have a prescribing decision made – in these instances, data on antibiotic prescribing was captured after the four hour period but still related to only consultations from the initial four hour period. We did not require any data collection to happen beyond the single day of the survey (e.g. if patients returned the next day for a prescribing decision). How will the data collected in the CRFs be managed? Where will the CRFs be stored? Who will be responsible for the CRFs?

Thank you for your comment. The data collection procedures are outlined in section 6.5.3 and 6.5.4. The data in the electronic CRF was managed by a data manager at City St George's of London using ODK Cloud. Data was backed up regularly by ODK Cloud and downloaded monthly to a secure server at City St George's. If data collectors used paper CRFs to collect data during the consultation, the site PI or country lead (depending on the structure of the team) was responsible for the storage of these CRFs and their destruction at the end of the study. No identifiable information was collected and all data was collected anonymously therefore it was not possible to link any paper CRFs directly to entries in ODK after data entry. Countries had separate data entry platforms to keep their data separate and each user had a unique QR code. If phones go missing what is the risk of data leaking. What precautions have been taken to address this? This can be included in a risk analysis plan. Country partners used dedicated study tablets or phones. Tablets and devices were password protected with the code known only to the data collector. All data was anonymously collected and clinics themselves were identified using a random identifier with the key kept separately to the clinical data collected. It was not possible for study teams to identify individuals in the data once the data had been sent to ODK and only the data collectors and the central study team knew which facility identifier related to which facility further reducing the risk if phones were to be missing or logged into. How will infection severity be determined and measured in this study?

Infection severity will be determined using a combination of fields such as presence of fever, presence of the follow up symptoms, age and comorbidities. The follow up symptoms such as presence of shortness of breath, chest pain, long cough for patients presenting with acute cough will be used to guide severity. It is of course not possible to fully determine severity beyond the fields available and that we don't have direct assessment of the clinicians who saw each patient. We will use presence of comorbidities, age, sex and pregnancy as well to determine severity and necessity of antibiotic prescription using the WHO AWaRe Book risk guidance. However, it is not very clear which statistical method will be used to address this. A more detailed statistical analysis plan is needed to show how the associations will be measured in this study.

Thank you for this comment. At the time of protocol development given this is a pilot study, we did not know whether there would be sufficient data to assess these factors and sufficient data from within countries and similar types of clinics to assess factors. We will be looking at guideline compliance with the WHO AWaRe Book in the first instance and incorporate data on antibiotic availability and pricing to compare observed vs. expected prescribing patterns within each clinic. Observed vs expected prescribing proportions, AWaRe proportions and specific antibiotic proportions will be summarised as proportions with binomial confidence intervals. Beyond that, where there is sufficient variability in case-mix and number of clinics in a country, we will explore the influence of case-mix on differences in prescribing choices between facilities within a country using causal variance decomposition. Additionally, where data allows, we will use a within-between model to look at patient and facility level factors that explain prescribing propensity.

Competing Interests: No competing interests were disclosed.

Author Response 30 Mar 2026

Aislinn Cook

Thank you for your comments and review. I have responded below in black to your comments (in bold).

General comments

How does the WHO AWaRe guidelines affect the national clinical guidelines of the different countries? Are there any similarities or differences that may affect the prescribing practices of the different health facilities in the different countries? How well do the national clinical guidelines match the WHO AWaRe guidelines. This can guide in policy decisions. How is this study taking this into account?
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Section 5.4

Is this study a cross-sectional study collecting data at different points in time. Can the authors clarify this? This study is a cross-sectional study collecting data at half-day intervals for 8 repeated time points in sets of two surveys as shown in Figure 1.

What proportions of private and public facilities will be included for the different countries? Will it be representative of the facilities in the different countries? This is a convenience sample as this is a pilot study and the participation of public and private facilities will depend on the country involved. Generally, it is more difficult to engage private facilities as there are less incentives to provide these types of data and concerns that it will be used by authorities for enforcement of practices. We tried to engage both types of facilities but expect it will be more public facilities that participate in the study. As this is a pilot of the methodology, it will likely not be representative of the facilities and broad care seeking behaviours in the different countries. The level to which it is or is not representative will depend on the structure of the primary healthcare system in each country and healthcare seeking behaviours.

The team has clearly outlined infection symptoms/diagnoses of interest which will be used for the eligibility criteria. It might be that the list provided by the study collects much more data than what the healthcare centers are used to collecting. This may require more time. How many patients are estimated per healthcare center? Will all the data on the list be collected in 4 hours? While the authors have mentioned that it may not be possible to know the sample size per clinic, including the number of patients estimated per healthcare center, and the amount of time it will take to complete screening for each patient will provide insight into the feasibility of 4 hours. Is it possible to get these estimates from the records in the different healthcare facilities? Thank you for your important questions. As this was a pilot study of a novel methodology, we did not limit participation to clinics based on the size of the clinic or the number of patients estimated to visit. We collected this information as part of the pilot study – total patient visiting, total with infections and the number included – to enable exploration of minimum sample sizes needed for future studies. The data collected was data routinely needed during a consultation and the expectation was that this would be available during the study data collection period. For fields that were not available, data collectors were able to use medical notes/records where possible to fill in data such as age, etc or record unknown for fields that were not available. By including a diverse range of primary care facilities, the structure and flow of patients through clinics was different so we work closely with clinics to overcome any challenges with data collection and to minimise disruption to routine care. In some instances, not all data was available in the four hour period – i.e. if patients were triaged with symptoms collected, then sent for labs and returned later to have a prescribing decision made – in these instances, data on antibiotic prescribing was captured after the four hour period but still related to only consultations from the initial four hour period. We did not require any data collection to happen beyond the single day of the survey (e.g. if patients returned the next day for a prescribing decision).

Section 5.5.4

How will the data collected in the CRFs be managed? Where will the CRFs be stored?

Who will be responsible for the CRFs? Thank you for your comment. The data collection procedures are outlined in section 6.5.3 and 6.5.4. The data in the electronic CRF was managed by a data manager at City St George's of London using ODK Cloud. Data was backed up regularly by ODK Cloud and downloaded monthly to a secure server at City St George's. If data collectors used paper CRFs to collect data during the consultation, the site PI or country lead (depending on the structure of the team) was responsible for the storage of these CRFs and their destruction at the end of the study. No identifiable information was collected and all data was collected anonymously therefore it was not possible to link any paper CRFs directly to entries in ODK after data entry. Countries had separate data entry platforms to keep their data separate and each user had a unique QR code.

If phones go missing what is the risk of data leaking. What precautions have been taken to address this? This can be included in a risk analysis plan. Country partners used dedicated study tablets or phones. Tablets and devices were password protected with the code known only to the data collector. All data was anonymously collected, and clinics themselves were identified using a random identifier with the key kept separately to the clinical data collected. It was not possible for study teams to identify individuals in the data once the data had been sent to ODK and only the data collectors and the central study team knew which facility identifier related to which facility further reducing the risk if phones were to be missing or logged into.

Section 5.5.5

How will infection severity be determined and measured in this study?
Infection severity will be determined using a combination of fields such as presence of fever, presence of the follow up symptoms, age and comorbidities. The follow up symptoms such as presence of shortness of breath, chest pain, long cough for patients presenting with acute cough will be used to guide severity. It is of course not possible to fully determine severity beyond the fields available and that we don't have direct assessment of the clinicians who saw each patient. We will use presence of comorbidities, age, sex and pregnancy as well to determine severity and necessity of antibiotic prescription using the WHO AWaRe Book risk guidance.
I agree with the authors that it is important to understand how the different factors are associated with antibiotic prescribing practices. However, it is not very clear which statistical method will be used to address this. A more detailed statistical analysis plan is needed to show how the associations will be measured in this study. Thank you for this comment. At the time of protocol development given this is a pilot study, we did not know whether there would be sufficient data to assess these factors and sufficient data from within countries and similar types of clinics to assess factors. We will be looking at guideline compliance with the WHO AWaRe Book in the first instance and incorporate data on antibiotic availability and pricing to compare observed vs. expected prescribing patterns within each clinic. Observed vs expected prescribing proportions, AWaRe proportions and specific antibiotic proportions will be summarised as proportions with binomial confidence intervals. Beyond that, where there is sufficient variability in case-mix and number of clinics in a country, we will explore the influence of case-mix on differences in prescribing choices between facilities within a country using causal variance decomposition. Additionally, where data allows, we will use a within-between model to look at patient and facility level factors

that explain prescribing propensity.

Competing Interests: None

Reviewer Report 12 February 2025

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Lars Småbrekke
Clinical Pharmacy and Pharmacoepidemiology, Department of Pharmacy, Faculty of Health Sciences, UiT Arctic University of Norway, Tromsø, Norway

Robert Nuifondieng Foncha
Department of Pharmacy, UiT The Arctic University of Norway Faculty of Health Sciences (Ringgold ID: 60482), Tromsø, Troms, Norway

Thank you for the invitation to review this paper on surveillance of infections and antibiotic prescribing in primary health care in LMIC countries in Africa and Asia. This project will significantly contribute to our understanding of infection presentation and antibiotic prescribing across diverse settings.

General Comments:

The sections on ethics, data collection platform, personnel training, data management, and consultation data are well-described. The volume of data collected is impressive.
While we agree that point prevalence surveys (PPS) based on a convenience sample can provide insights into local diagnostic quality, therapy choices, and antibiotic prescriptions, it is unclear whether these results would be representative beyond the local or regional level. Additionally, there is a risk that participants may alter their behavior when they know they are being observed (Hawthorne effect). What measures are in place to mitigate these challenges?

Chronological Comments:

In sections 5.1 and 5.2, you aim to quantify the frequency of different infection presentations and the proportion of patients receiving antibiotic prescriptions. We agree that this is a reasonable approach. However, in section 5.3, you state that the goal is to understand the relative presentation rate of clinical infections and antibiotic prescribing rates for these infections. Typically, a "rate" describes the occurrence of an event within a specific population over a defined period. It is usually expressed as a ratio where the numerator is the number of events (e.g., cases of a disease or patient encounters) and the denominator is the population at risk during that period. From the protocol, it is unclear how you define the population at risk and the risk period

based on these point prevalence data. The concept of "rate" is repeated in sections 5.4.3.2 and 5.4.4.

The sampling strategy aims to capture half a day of a standard clinic session using the ODK. Given the extensive data collection per patient encounter, it seems reasonable to restrict data collection to a four-hour period. However, it is unclear what the expected average time for completing data collection is and how this will be measured if data is not electronically collected during the consultation. Conducting all data collection during working hours will impact both employees and patients, potentially reducing the number of daily consultations. This will incur costs for the clinic and the patients (the "cost" for those who will not receive a consultation that day). How will these financial and ethical challenges be addressed?

In section 5.5.2.3 (Consultation data collected), you state that age will be recorded in months for those ≤2 years and in years for those older. However, in Table 2 on PPS-specific information, you differentiate between adults (≥18 years) and children (<18 years). We commend the high resolution on age in the data and believe this should be explored further by investigating age groups <2 years, 2-5 years, 6-15 years, and >15 years(1). The periodic prevalence of treatment for young children is high in some areas, and aggregating into one group <18 years will result in a significant loss of information. In the list of relevant comorbidities, we suggest including TB.
Consider recoding all generic names to ATC codes. This will facilitate analysis, allowing comparisons between regions with different prescribing patterns. It will also enable a comparison between the Defined Daily Dose (DDD) and the prescribed dose.

In section 5.5.5 (Data analysis), it is clearly stated in the first sentence that the data will be analyzed descriptively. However, you also mention that with sufficient data, you will explore factors related to antibiotic prescriptions for an encounter, which will necessarily involve analytical statistics. We believe the protocol would benefit from a more detailed statistical analysis plan.
A substantial amount of data is collected, and in our opinion, this resource will be underutilized if relying solely on descriptive measures. It is unclear whether representatives from the participating clinics are invited to participate in the project's evaluation.

References

1. Blix HS, Engeland A, Litleskare I, Rønning M: Age- and gender-specific antibacterial prescribing in Norway.*J Antimicrob Chemother*. 2007; **59** (5): 971-6 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Pharmacoepidemiology; Clinical Pharmacy;

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 10 Mar 2026

Aislinn Cook

Thank you for your comprehensive comments. I have split up your comment and my responses are below.

The sections on ethics, data collection platform, personnel training, data management, and consultation data are well-described. The volume of data collected is impressive.
While we agree that point prevalence surveys (PPS) based on a convenience sample can provide insights into local diagnostic quality, therapy choices, and antibiotic prescriptions, it is unclear whether these results would be representative beyond the local or regional level.
Thank you for your comment. The main findings from the study that will be applicable and representative beyond the local and regional level is the feasibility of the data collection tool. By working with partners in numerous clinics and at different levels of primary care (clinics, outpatients, community pharmacies) we will be able to provide a tool that works to collect basic clinical and prescribing data in diverse settings. By including a range of facilities and several facilities per country we think the study will demonstrate the applicability of this methodology to different settings. The findings will allow to us to compare similarities between countries and facility types within a country and to use a tool such as this for identifying conditions where interventions may provide the most improvement in inappropriate prescribing. Additionally, there is a risk that participants may alter their behavior when they know they are being observed (Hawthorne effect). What measures are in place to mitigate these challenges?
Thank you for your comments, we agree that this can be cause for concern. We collect survey-level data on how the data were collected at each survey – from the notes, during consultation and by whom (observer, prescriber) for each survey so we can examine descriptively whether we see differences in the same facility when using different methods across different surveys and include this as a covariate in any modelling. We also did not collect any data on the prescriber themselves and ensured that this was clearly communicated to prescribers at all clinics where observation or prescriber-led data collection was conducted. However, given that many medical notes are not routinely completed in these settings or available after the consultation, direct observation/data collection during consultation is one of the few ways to get comprehensive data so it is not entirely possible to mitigate this bias.

From the protocol, it is unclear how you define the population at risk and the risk period based on these point prevalence data. The concept of "rate" is repeated in sections 5.4.3.2 and 5.4.4.

Thank you for this important comment. You are correct that we are focused on frequency rather than true rates. While we collect start and end time of the consultation period and the total number of patients that consult for any reason and total that consult for infection presentations, we do not have the full underlying population. We have updated the word rate to proportion to align with the data we have. However, it is unclear what the expected average time for completing data collection is and how this will be measured if data is not electronically collected during the consultation. We expected the average data collection to take 2-5 minutes depending on the flow of the consultation and when the data were collected within the consultation. Teams were given options for who and how the data could be collected, to better understand what was feasible and to enable broadest participation. Methodology for data capture was recorded for each survey. The data collectors, if not the prescriber, was able to capture data during the consultation itself, or from the medical notes where available (i.e. for age, etc). We asked partners at the end of the study the average time it took to complete the data collection when not recorded electronically and we are able to capture the time it took to complete data entry through metadata in ODK.

Conducting all data collection during working hours will impact both employees and patients, potentially reducing the number of daily consultations. This will incur costs for the clinic and the patients (the "cost" for those who will not receive a consultation that day). How will these financial and ethical challenges be addressed?
We worked closely with country partners to address any concerns about length of data collection to find methods that were the least disruptive. Partners were able to collect data in several ways depending on how the flow of the clinic worked, given the myriad ways primary healthcare clinics are structured in different countries and different levels of primary care. Partners could choose to collect data using observers so as to minimise disruption to the consultation (by not having the prescriber collect the data). Patients provided consent for an observer to be in the consultation. Where that was not possible, data was able to be collected from clinical notes between and after consultations provided there was enough clinical information recorded. We allowed for unknown to be entered for majority of fields to facilitate ease of data collection and to understand which fields are not routinely available in these settings. Where partners expressed concerns about impact on consultations during the study, we worked with them to find different solutions to data collection to prioritise minimising disruption to routine consultations.

In section 5.5.2.3 (Consultation data collected), you state that age will be recorded in months for those ≤2 years and in years for those older. However, in Table 2 on PPS-specific information, you differentiate between adults (≥18 years) and children (<18 years). We commend the high resolution on age in the data and believe this should be explored further by investigating age groups <2 years, 2-5 years, 6-15 years, and >15 years(1). The periodic prevalence of treatment for young children is high in some areas, and aggregating into one group <18 years will result in a significant loss of information. In the list of relevant comorbidities, we suggest including TB.
Consider recoding all generic names to ATC codes. This will facilitate analysis, allowing comparisons between regions with different prescribing patterns. It will also enable a

comparison between the Defined Daily Dose (DDD) and the prescribed dose.
Thank you for this comment. We agree and we have collected data at the granular level (in months for children <2 years) and in years for everyone ≥2 years. We will explore age as a continuous variable in the first instance and consider grouping if needed based on granularity. Thank you for the suggestion regarding TB. We have included a space for "Other underlying conditions" for data collection and will consider explicitly adding TB in future versions. We will be mapping all generic names to ATC codes and AWaRe categories for comparison across groups and describing prescribed dosages. We believe the protocol would benefit from a more detailed statistical analysis plan. A substantial amount of data is collected, and in our opinion, this resource will be underutilized if relying solely on descriptive measures. Thank you for your comments. As this was a pilot of a new methodology in different types of clinics with a set time period, it was not clear how many encounters we would get in similar types of settings and similar conditions. In order to compare prescribing practices between facilities, we will also need to ensure there is enough variability in patient case-mix in enough similar facility types in the same country which could not be defined prior to developing the protocol. If there is sufficient data for this analysis, we will analyse the clinic and patient-level factors related to the choice to prescribe and the choice of antibiotic, or AWaRe category using mixed-effect regression analysis. As outlined in the protocol we will also be evaluating guideline compliance with the WHO AWaRe Book guidance to compare observed prescribing patterns (the decision to prescribe and the choice of antibiotic, dose, duration when an antibiotic is prescribed). Data collected at the facility level on antibiotic availability and price will be incorporated into this analysis. Provided there is suitable variation in case-mix between facilities, further analyses comparing prescribing practices between clinics will be undertaken using causal variance decomposition. A more detailed statistical analysis plan will be developed prior to starting analysis. As part of a future master protocol building on this work, we will include this analysis plan and guidance defining minimum sample sizes. It is unclear whether representatives from the participating clinics are invited to participate in the project's evaluation. Representatives from the countries and clinics participating in the research are invited to be part of the analysis and to use their own data for their own research questions. The results from each clinic will be fed back to country leads and clinic leads in the form of PDF reports of their common presentations, antibiotic prescribing practices as well as in the form of an interactive analytical dashboard that allows partners to explore their own datasets and use it for publications, reports and more to inform local research and policy interventions. We will also conduct a feasibility survey at the end of the study with participating data collectors at clinics and country leads to gain feedback on the challenges of implementation of this study.

Competing Interests: No competing interests were disclosed.

Author Response 30 Mar 2026

Aislinn Cook

Thank you for your comments. For ease I have responded below to your comments (in bold) with my responses in black.

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Representatives from the countries and clinics participating in the research are invited to be part of the analysis and to use their own data for their own research questions. The results from each clinic will be fed back to country leads and clinic leads in the form of PDF reports of their common presentations, antibiotic prescribing practices as well as in the form of an interactive analytical dashboard that allows partners to explore their own datasets and use it for publications, reports and more to inform local research and policy interventions. We will also conduct a feasibility survey at the end of the study with participating data collectors at clinics and country leads to gain feedback on the challenges of implementation of this study.

Competing Interests: None