

Henry Ford Health

Henry Ford Health Scholarly Commons

Global Health Initiative Articles

Global Health Initiative

8-1-2023

Protocol for a randomized controlled trial on community education and surveillance on antibiotics use among young children in Nepal

Prajwol Nepal

Anup Subedee

Henish Shakya

Sanjaya Poudel

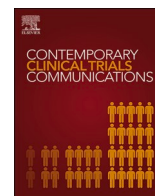
Supriya Joshi

See next page for additional authors

Follow this and additional works at: https://scholarlycommons.henryford.com/globalhealth_articles

Authors

Prajwol Nepal, Anup Subedee, Henish Shakya, Sanjaya Poudel, Supriya Joshi, Kshitij Karki, Deepak Bajracharya, Tyler Prentiss, Linda M. Kaljee, and Yubraj Acharya



Protocol for a randomized controlled trial on community education and surveillance on antibiotics use among young children in Nepal

Prajwol Nepal^a, Anup Subedee^b, Henish Shakya^c, Sanjaya Poudel^d, Supriya Joshi^e, Kshitij Karki^f, Deepak Bajracharya^f, Tyler Prentiss^g, Linda Kaljee^g, Yubraj Acharya^{e,*}

^a University of North Carolina-Chapel Hill, Chapel Hill, USA

^b Public Health Concern Trust, Nepal & Kirtipur Hospital, Nepal

^c KIST Medical College Hospital, Kathmandu, Nepal

^d SunyaEk, Kathmandu, Nepal

^e The Pennsylvania State University, University Park, USA

^f Group for Technical Assistance (G.T.A.) Foundation, Kathmandu, Nepal

^g Global Health Initiative, Henry Ford Health, Detroit, USA

ARTICLE INFO

Keywords:

Antimicrobial resistance
Randomized controlled trials
Nepal

ABSTRACT

Background: Antimicrobial resistance (AMR) is one of the top ten threats to global health. There exists limited empirical evidence on effective approaches to address this threat. In low- and middle-income countries (LMICs), one of the primary drivers of AMR is easy access to antibiotics without prescriptions, in particular from community pharmacies. Interventions to reduce non-prescribed use of antibiotics and surveillance systems to track such usage are critically needed. This protocol describes a study that aims to test the effect of an educational intervention targeted to parents of young children on non-prescribed antibiotics consumption in Nepal and to track such consumption using a phone-based application.

Methods: The study is a clustered randomized controlled trial, in which we randomly assign 40 urban wards of Kathmandu Valley to either treatment group or control group, and randomly select 24 households in each ward. Households in the treatment group will receive an education intervention consisting of an "AMR pitch" (an in-person interaction that lasts up to an hour) by community nurses, videos and text messages on AMR every two weeks, and a brochure. We will conduct a survey at baseline with the parents of children ages 6 months to 10 years and track consumption of antibiotics and health care use among these children for a period of 6 months using a phone-based application.

Conclusion: While the study will primarily inform future policy and programmatic efforts to reduce AMR in Nepal, the study—both the education intervention and the surveillance system—can serve as a prototype for tackling AMR in other similar settings.

1. Introduction

Antimicrobial resistance (AMR) is one of the top ten threats to global health, with antibacterial resistance associated with an estimated 4.95 million deaths in 2019 [1,2]. UNICEF has called AMR the "greatest threat to child survival and health of this generation." [3] Children in low- and middle-income countries (LMICs) are exposed to antibiotics at an early age, and most antibiotics administered are clinically unnecessary [4]. Overuse of antibiotics leads to adverse events including harm to gut microbiota and immune system, and contributes to AMR [5–9]. Approximately 253,000 children die in LMICs from AMR each year [10].

AMR is also rising rapidly in Nepal, the site for this study [11–13].

A growing body of literature suggests that pressure from patients plays a significant role in antibiotics use [14–16]. Therefore, the Government of Nepal's Antimicrobial Resistance Containment Action Plan 2016 identifies community education as one of its priorities to tackle AMR [17]. However, population-based interventions that discourage patients from obtaining antibiotics without prescription in LMICs are scant.

At the same time, surveillance of antibiotic use through users is lacking in LMICs. In settings where AMR surveillance exists, the data are often fragmented and lack representativeness [18], and are collected

* Corresponding author. Department of Health Policy & Administration, 601L Ford Building, University Park, PA, 16802, USA.

E-mail address: yua36@psu.edu (Y. Acharya).

<https://doi.org/10.1016/j.conctc.2023.101177>

Received 7 March 2023; Received in revised form 18 June 2023; Accepted 19 June 2023

Available online 21 June 2023

2451-8654/© 2023 Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

primarily through tertiary hospitals. Not surprisingly, most of the effort on optimizing antibiotic use is currently focused on physicians and other facility based providers [19,20]. There is a need to test innovative approaches to collect usage data directly from consumers, including on the type of antibiotics used; adherence to prescribed dosage, frequency, and duration; and implications on medical costs. Digital solutions, in particular smartphone-based applications, have the potential to help build such surveillance systems [21,22]. In Nepal, smartphone ownership and usage has risen rapidly in the last decade, with 73% Nepalese households using a smartphone in 2021 [23]. Nearly 91% of Nepal's population has access to Internet, 66% of whom access Internet on their mobile phones [24].

Against this background, the objective of the current randomized controlled trial (RCT) is to test the effect of an educational intervention targeted to parents of young children on non-prescribed antibiotics consumption in Nepal, and track antibiotic use for 6 months using a smartphone-based application. To our knowledge, this is the first study in Nepal attempting to change individuals' attitudes and behavior on non-prescribed antibiotics consumption in community settings and among the first in LMICs to track such consumption using a smartphone-based application.

2. Research design & methods

Study design. The proposed study is a clustered RCT whereby the treatment is randomized at the ward level (the lowest administrative unit in Nepal) and outcomes are assessed at the individual level. All participants within a ward will be in the same arm (treatment or control), thus reducing potential contamination across arms.

Target population. The target population consists of parents of children ages 6 months to 10 years in Kathmandu, Bhaktapur and Lalitpur districts of the Kathmandu Valley. In the federal structure adapted after the new constitution of 2015, these districts are divided into 2 metropolitan cities, 14 urban municipalities, and 3 rural municipalities. The 2 metropolitan cities and the 14 urban municipalities are divided into a total of 224 wards. High penetration of smartphones is a pre-requisite for our intervention as it requires households to download a phone-based application and submit information using it. Therefore, we focus on these 99 urban wards within or adjacent to Kathmandu and Lalitpur Metropolitan Cities.

Selection of wards, and treatment assignment. From this target population, we have identified the wards for the study in two stages. In the first stage, we randomly selected 40 wards from the 99 wards using a random number generator in the Stata software. In the second stage, we randomly assigned the wards into treatment and control (20 wards each), again using a random number generator in Stata. The Stata codes used to select and assign the wards to arms are available on request.

Sample size and statistical power. We will enroll 480 households in each arm (i.e., 24 children per ward from 20 wards in each arm) for a total sample size of 960 children. In our previous study involving standardized patients in Nepal, community pharmacies provided antibiotics without a physician's prescription for pediatric diarrhea and URTI in 60% of the cases (average of diarrhea and URTI). We assume that this proportion reflects consumption of non-prescribed antibiotics. A 20-percentage point reduction in this proportion would be meaningful for policy. Our sample size allows us to detect this difference at the 5% significance level with at least 80% power. There is no reason to believe that the intervention would have a negative effect—i.e., raise antibiotic consumption—so we base our calculation on a one-tail test. Our intervention will vary at the ward level to avoid contamination. We assume a conservative intra-cluster correlation of 0.2. Our prior experience suggests that non-response and attrition are very low in this setting (in the vicinity of 10%). Nonetheless, we plan on a 20% attrition rate (resulting in final sample of 760 children) as the study requires participants to use a smartphone-based application and access to Internet in order to submit information.

Note that the denominator in our primary outcome is the number of episodes in which antibiotics were given. We have made the following additional assumptions when estimating power. According to 2022 Nepal Demography and Health Survey, 34% children below age 5 are reported to have ARI, fever or diarrhea during the two weeks before the survey [25]. During the 6-month study period, we anticipate that at least 80% children will have an illness episode. Based on recent study in Nepal, we estimate that 80% will be given antibiotics (total of prescribed and non-prescribed) [26]. Under these assumptions, for the final analysis, we will have at least 12 children in each cluster who will be given antibiotics ($=0.8 \times 0.8 \times 760/40$), for a total of 480.

Selection of households. We will recruit 24 households in each ward ($=960/40$). In absence of clear addresses for buildings and recent census data (the 2021 census information is not available at the time of writing this protocol), we will identify households using a method appropriate for this setting. Specifically, in each ward, enumerators will first visit the ward's main administrative office (each ward has one) and walk in the direction in which the border of the ward is the furthest. Starting with the first residential building in that direction, they will visit and recruit participants in every 20th building until 24 households are reached. We will adjust for the size of the ward—thus, probability of a household being selected in the study—at the time of data analysis.

Recruitment and enrollment process. Recruitment and enrolment will take place during the same visit to the household by the research team. In each building, the study team—consisting of a community nurse and an enumerator—will ring the bell or knock on the door, as appropriate, and talk to the first adult who responds. They will ask how many families live in the building and select a household. If there are multiple floors, they will pick one floor and, if there are more than one family on that floor, they will pick one family. During pre-testing, we learned that selecting households randomly, such as by using a lottery, would not be practical, as it would raise suspicion, take time, and potentially turn into a fun activity, thus undercutting the seriousness of the subsequent conversation on AMR. Therefore, the enumerators will be asked to try to not pick the same floor in multiple adjacent households. The survey collects information on the floor of the household, which we will control for during analysis. The survey team will explain the study and administer baseline survey to households that consent to participate. If the selected household does not meet the eligibility criteria (see below) or declines to participate, adjacent household or building will be visited and respondents identified following the same procedures.

Inclusion criteria. If a household has more than one child ages 6 months to 10 years, the youngest child above 6 months of age will be used as the index child. Only one child per household is recruited in order to reduce burden on the household, as we would have to collect baseline information and households would have to upload health utilization information for each child—both of which can be time consuming. A household is eligible to participate if: (1) the household has a child ages 6 months to 10 years, (2) the respondent is at least 18 years of age and is one of the parents of the child, and (3) one of the available parents has a smartphone suitable for installing the phone-based application.

Exclusion criterion. A household will be ineligible to participate if the youngest child above 6 months of age is taking medicine for a chronic health condition. These conditions include chronic prophylactic antibiotic therapy, immunocompromising conditions (ongoing chemotherapy or primary immunodeficiency syndrome such as severe combined immunodeficiency, chronic granulomatous disease, and common variable immunodeficiency), organ transplant, HIV/AIDS, cystic fibrosis, and malignancy.

The intervention. Our main intervention is the education of the parents of children ages 6 months to 10 years to raise the parents' understanding of antibiotics and AMR, and change any misconceptions about antibiotics (e.g., "it is OK to stop antibiotics after illness becomes better even if the dosage is not complete", or "antibiotics are better for the child than other medicines because the former help heal quickly").

Recognizing the difficulty in changing individual attitudes and behaviors on health, we have designed an intensive intervention consisting of three components. The components are as follows.

- (1) *The “AMR Pitch”*. At the time of enrollment, trained nurses will visit selected households and conduct interactive sessions with one or both parents of the child for up to an hour. They will share prepared material—including a video consisting of a story and factual information on AMR—allowing the parents to ask questions as they arise.
- (2) *Periodic reinforcement*. We will send information about antibiotics and AMR through videos pushed in the phone-based application every two weeks during the 6-month study period. A previous study has found that two-week reminders are effective in changing health behavior by retaining engagement and avoiding habituation [27]. The topics of the videos, including the time and the order in which we will send them, are shown in Table 1.
- (3) *Brochure*. We have prepared a brochure containing information about antibiotics use and AMR in local language. We will give this brochure to all participating households at the time of the study team’s visit. The brochure is intended to trigger discussion among household members on AMR and antibiotic use, at least during the first few days of the study team’s visit.

To ensure that the study participants understand the materials provided to them, we have kept the Nepali version of the scripts at a grade-10 reading level; all but two members of our research team are native speakers of Nepali. To ensure simplicity without compromising technical correctness, we refined the script through multiple iteration.

Table 1
Timeline and Material to be Sent During the 6-Month Period.

	Treatment households	Control households
At the time of recruitment	CH 1 + AMR pitch, AMR video 1, ASA video	CH video 1, ASA video
End of week 2	AMR video 2 + text reminder	Text reminder
End of month 1 ^a	CH video 2	CH video 2
End of week 6	AMR video 3 + text reminder	Text reminder
End of month 2 ^a	CH video 3	CH video 3
End of week 10	AMR video 4 + text reminder	Text reminder
End of month 3 ^a	CH video 4	CH video 4
End of week 14	AMR video 5 + text reminder	Text reminder
End of month 4 ^a	CH video 5	CH video 5
End of week 18	AMR video 6 + text reminder	Text reminder
End of month 5 ^a	CH video 6	CH video 6
End of week 22	AMR video 7 + text reminder	Text reminder

Notes.

ASA video: Information on how to use ASA, including guidelines on how to access videos sent by the research team and upload information on episodes of child illness.

AMR video 1: General information about AMR, antibiotic use, encouraging parents to give antibiotics to their children only if prescribed by a doctor and emphasizing dose and duration.

AMR video 2: Information focused on diarrhea.

AMR video 3: Information focused on upper respiratory tract infection.

AMR video 4: Information focused on fever.

AMR video 5: Information focused on COVID-19 and dengue.

AMR video 6: Information focused on microbiome.

AMR video 7: General information about AMR, reinforcing key messages from videos 1-6.

CH video 1: Information on junk food.

CH video 2: Information on screen time.

CH video 3: Information on mental wellbeing.

CH video 4: Information on encouraging reading behavior.

CH video 5: Information on developing grit.

CH video 6: Information on personal hygiene.

^a Phone recharge amount of NRs 100 sent.

Acharya and Subedee drafted the first versions of the scripts in English, which Nepal and Joshi translated and reviewed. Shakya reviewed the material next (who also provided voice in the videos) followed by further refinement by the community health nurses at the training. In the videos, we use illustrative digital content. The videos, including the illustrations, have been developed by a professional developer with extensive prior experience preparing videos with health messages. The videos were further tested for clarity among 10 households near the office premises of the Group for Technical Assistance Foundation, the local collaborating organization, before the main field work commenced.

Surveillance and data collection. We have developed a smartphone-based application, called Antibiotic Surveillance Application (ASA), to support the implementation of education intervention in the treatment group and to track antibiotics, healthcare use, and expenses on antibiotics and other medicine across both groups. The application can be installed on android phones and access to internet (either through wireless or data) is required in order to submit information. However, videos and messages can be viewed offline after they have been downloaded on the phone.

ASA will serve the following functions.

- (1) **Enroll and collect baseline data (both groups):** At enrollment, households will be assigned a unique ID. After enrollment, community health nurses and trained enumerators (all with a bachelor’s degree) will use ASA to conduct the baseline survey.
- (2) **Assist nurses in the providing the ‘AMR Pitch’ (treatment group):** Nurses will use education module in ASA to deliver ‘AMR Pitch’ using illustrative digital content to explain the risks of AMR, in addition to face-to-face interactions.
- (3) **Enable households to record data in real time on antibiotics and healthcare use (both groups):** The data enumerators will demonstrate and train households on features and user interface of ASA. Households will send information required to assess the outcomes (see below) via ASA.
- (4) **Send periodic reminders on rational antibiotic use using illustrative digital content (treatment group):** Research team members from the Group for Technical Assistance Foundation will use the push notification system in ASA to send periodic reinforcement videos and reminders over the six-month period.
- (5) **Provide information on childhood development (both groups):** In order to ensure that households in the control group continue to provide data even though they do not receive AMR-specific education, we provide information about early childhood development. This information will be provided to both treatment and control households and in the same frequency to ensure comparability between the two groups. The topics covered in the child development modules include: 1) reducing screen time, 2) ensuring mental wellbeing, 3) encouraging reading behavior, 4) developing grit, and 5) personal hygiene (see Table 1). These topics were selected because they are unlikely to alter the key outcomes we evaluate as part of the study, while keeping the parents engaged with the phone-based application throughout the study period.

Measures and hypotheses. We will collect data on one primary and four secondary outcomes for 6 months using ASA. The primary outcome is non-prescribed antibiotic use (i.e., the proportion of times antibiotics are used without a prescription divided by the total number of times antibiotics are used). The secondary outcomes are: (a) overall antibiotic use (i.e., proportion of reported illness episodes on which antibiotics were given to the child), (b) provider type (e.g., hospital, clinic, pharmacy; public vs private), (c) expenditure on medicines and antibiotics, (d) dose, frequency and duration of the antibiotic usage. Additionally, at baseline, we will collect demographic information and 6-month health history of index child. Table 2 shows how information on these measures

Table 2
Measures.

Measure	Timing and procedure of data collection
Antibiotic use	Households will be requested to take a picture of the bottle(s), along with the expiration date(s), and upload it through ASA for each episode of their child's illness during the 6-month period. They will also be requested to take a picture of the prescription note and upload it, if any, for all episodes of illness. The information obtained will be used to calculate the primary outcome—non-prescribed antibiotic use (i.e., number of episodes in which antibiotics were non-prescribed/total episodes in which antibiotics were given) and overall antibiotic use (i.e., number of episodes in which antibiotics were given/total number of episodes).
Provider type	Households will be requested to specify the type of provider (e.g., hospital, clinic, pharmacy; and public vs private) they visited for each episode of their child's illness during the 6-month period using a drop-down menu in ASA.
Expenditure on medicine and antibiotics	Households will be requested to specify the amount of money they paid on medicine for each episode of their child's illness during the 6-month period through ASA.
Dose, frequency, and duration	When a household submit information on an episode of care, the research team members from the Group for Technical Assistance Foundation will call the household approximately 10 days later and ask information on dose, frequency, and duration of the antibiotics given to the child. In order to clarify which of the medications given to the children are antibiotics, we will check the names of the medication in the pictures of the prescription or on the pictures of the medication containers against the lists of all brand names or generic names of medications approved for use in Nepal by the Department of Drug Administration, Ministry of Health and Population.
Demographic information and health history	We will collect demographic information, such as age and gender of the index child, parental and household characteristics, and 6-month health history of the index child at baseline.
Engagement with educational materials	Participants' engagement with the smartphone-based application is central to the study. Therefore, we will track the number of households which view the videos sent through the application, including the frequency at which they do so and whether they watch the entire video (versus a part of it). This information can be obtained directly through the application.

will be collected. To ensure that households upload necessary information through ASA (for the primary and the secondary outcomes), households will receive a short reminder every two weeks requesting them to upload information. In treatment households, this reminder will be sent with the videos on AMR, while in the control households, only the reminder will be sent (see Table 1).

We have kept the procedure for uploading information through ASA simple. Households upload five pieces of information for every episode of care received by the index child. They are asked questions on condition for which the child sought care, whether the child was taken to a hospital or a pharmacy, the amount of money spent on medicine, and whether they had a prescription from a doctor. They are then asked to upload pictures of the prescription (if any) and of the medicine(s) they gave their child, showing the name of the medicine and the expiration date.

With these data, we will test the following hypotheses.

Hypothesis 1. Non-prescription antibiotic usage among children ages 6 months-10 years will be lower in households in the treatment group than in the control group.

Hypothesis 2. Antibiotics usage among usage among children ages 6

months-10 years will be lower in households in the treatment group than in the control group.

Hypothesis 3. The proportion of children ages 6 months-10 years who receive consultation from clinics and hospitals (i.e., through visits to a doctor, not a stand-alone pharmacy) during an illness episode will be higher in households in the treatment group than in the control group.

Hypothesis 4. Health care expenditures on antibiotics and other medicines among children ages 6 month-10 years will be lower in households in the treatment group than in the control group.

Hypothesis 5. Among children who use antibiotics, children in treatment group are more likely to complete the correct dosage, frequency, and duration than those in the control group. Note that for episodes with prescription note uploaded, we will compare whether the dose, frequency and duration are correct against what is prescribed.

Data and safety monitoring. We have formed a Data Safety Monitoring Board (DSMB), which will review and approve the study procedures, as well as procedures for reporting and tracking adverse events, and study progress. The DSMB will receive a progress report on a weekly basis during enrollment summarizing the number of households enrolled that week and any issues encountered, and on a monthly basis after that. If needed, meetings will be convened to discuss significant concerns. There are no planned interim analyses or stopping rules given the low risk nature of the interventions.

Analysis plan. Following standard practice, we will first screen the numerical data for missing cases and outliers, and generate descriptive characteristics. We will use student t-test or χ^2 analysis to compare means, proportions and distributions, across the two groups. To assess the effect of the education intervention on the outcomes, we will conduct regressions of the form $Y_i = \beta_1 + \beta_2 \text{Treat}_i + \delta M_i + \varepsilon_i$ to test the five hypotheses above. In this equation, Y_i is the outcome for child i , Treat_i is a binary variable indicating whether the child's household belonged to the treatment group, M represents a vector of potential child-, parental-, and household-level confounders collected at baseline, and ε is the usual error term.

We will address any missing values of baseline covariates using three approaches and include results from all three approaches in the manuscript: 1. replace them with the mean values from the sample, 2. include a separate binary indicator (=1 if missing, 0 if not missing), and 3. Conduct the analysis discarding the missing values.

The type of regression will depend on the outcome. For binary outcomes, we will use logistic regression and report marginal effects. For medical expenditure, we will use linear regression and consider a two-part model if there is clustering at zero [28]. We will cluster the standard errors at the ward level—the level at which treatment assignment varies—to account for potential dependence between observations within that level—for example, children within a Ward may have similar outcomes—and conduct Bonferroni correction to account for multiple hypotheses testing, as appropriate. Although the study is sufficiently powered, we will further ascertain our main findings using randomization inference test and report p-values from this test—as we have done in previous clustered trial [29].

Current implementation status. Fig. 1 shows the key steps involved in implementing the study. As of April 29, 2023, all preparatory work—including the selection and randomization of wards, development of ASA, training of nurses and enumerators, and pre-testing of the study materials—as well as recruitment and baseline have been completed. The study will conclude by October 2023.

2.1. Additional procedures

Training of nurses and enumerators. The fidelity of the study relies heavily on the quality of the interaction that nurses and enumerators visiting the households have—both on AMR and on the use of ASA. Eight nurses and eight enumerators were recruited and trained for 10 days at

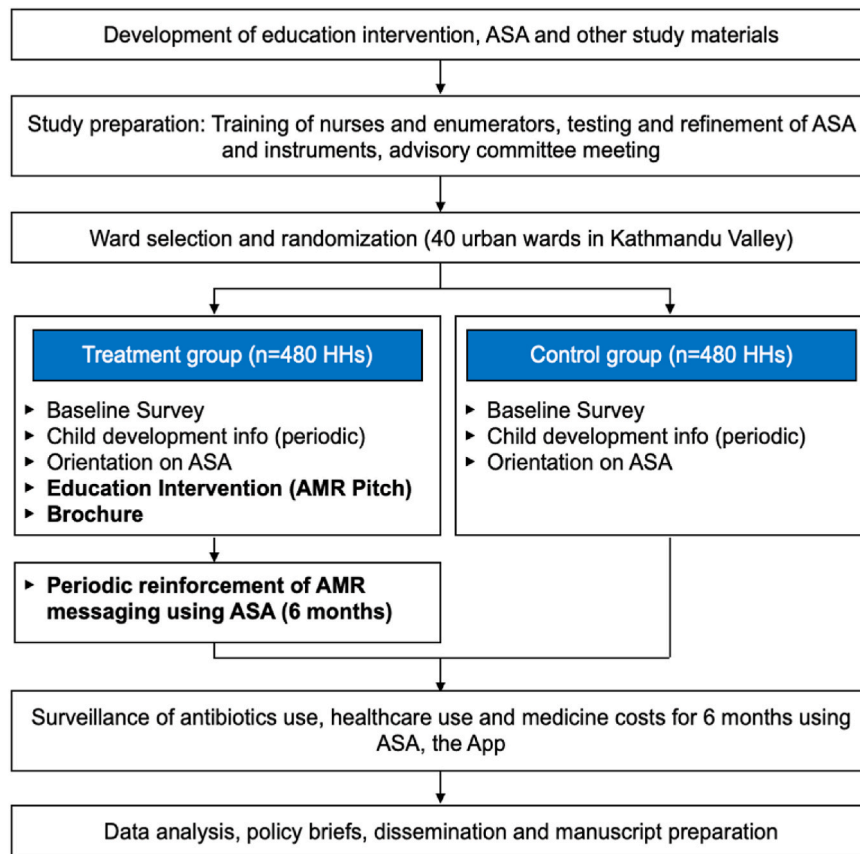


Fig. 1. Study procedures.

the premises of the Group for Technical Assistance Foundation, the local collaborating organization. The training for the nurses consisted of substantive material on AMR as well as effective communication. The key substantive topics covered were: 1) what are antibiotics and how they are different from other medications, 2) what are the common mistakes in the use of antibiotics, 3) what is AMR and how it affects personal health, 4) what are the key drivers of the rising threat of AMR, especially with regard to how antibiotics are used, 5) what are the most common misbeliefs in Nepal about antibiotics (based on our previous studies), 6) what is microbiome, how it relates to a One Health approach, and how it affects human health and illnesses, and 7) how antibiotics affect microbiome in the short and the long term. The training consisted of lectures and simulations. The nurses were also trained on various aspects of effective communication, including how to gain the study participants' trust and respect, how to listen (e.g., eye contact, body language), how to answer questions (e.g., the use of effective examples), and how to ensure that the participant understood the material shared (e.g., triggering the respondent to repeat the material by asking questions), among others. Likewise, the enumerators have been trained on data collection, including ethical considerations, consent process, and baseline survey administration through ASA. In addition, they have been trained on showing study participants how to send information through ASA during the 6-month period.

3. Conclusions

This is among the first studies in LMICs to test the effect of an education intervention and to track antibiotics consumption in a community setting using a phone-based application. While our study will primarily inform future policy and programmatic efforts to reduce AMR in Nepal, the study—both the education intervention and the surveillance system—can serve as a prototype for tackling AMR in other similar settings.

Unlike many antimicrobial stewardship programs to date, which focus on changing prescriber behavior, this study focuses on the demand side—specifically, the pressure that patients may exert on the provider. Recognizing that the deeply held misconceptions are difficult to change through one-off or remote interactions (such as through public and social media), we are testing an intensive intervention that combines one-on-one interaction with a community nurse, regular reinforcement of the messages through a phone-based application, and traditional modes of communication (a brochure).

Community based mobile tools are increasingly being used and have been highly successful in care coordination and delivery in South Asia and Sub-Saharan Africa [30–33], although not in AMR. In Nepal, Community Health Tools (CHT) is currently being implemented in four districts by our collaborating institution, SunyaEk, to conduct household health surveillance, as well as delivery of interventions relating to reproductive, maternal and child health, as well as mental health and common mental disorders [34,35]. CHT in Nepal has not yet been adapted for use at the household level or for rational antibiotic use. This study provides a unique opportunity to develop applications for household educational campaigns and surveillance using the core framework of CHT that has earned recognition as a digital public good [36].

Several limitations of the study warrant discussion. First, our data will be representative of the population in Kathmandu and Lalitpur Metropolitan cities and their surrounding areas. The population in this part of the country is richer and more educated, on average, than the rest of the country. We have chosen Kathmandu Valley for the study given the high penetration of smartphones and the relatively higher education level of the population—important requirements for ASA to work. We will compare the demographic characteristics of the analytic sample with that of 2021 census to gauge the external validity of our findings to the rest of the population in the country. We will also conduct

heterogeneity analysis to identify population groups for which the intervention works (or does not work) and probe deeper on these aspects during qualitative interviews with participants, so that adjustments can be made in the study when it is scaled up. Second, the outcome measures are self-reported by parents using ASA. Differential engagement with ASA across study arms can bias the results, although the net direction of the bias is unclear. To alleviate this concern and keep households in the control arm engaged with ASA during the study period, we will send periodic content on child development to both arms (thus having an “active control group”) [37]. Nonetheless, there is a risk of the intervention group under-reporting non-prescription antibiotic use if they perceive this to be the desired behavior. Additionally, text reminders to input health data for child illness episode will be sent on a regular basis. Participants in both arms will be sent phone credits (equivalent to Rs 500, or \$5) on a monthly basis to improve salience and engagement with ASA. A final limitation is that we are unable to assess the appropriateness of the antibiotics given, as assessment is not possible without seeing the patient at the time of care. This is an area for further research.

Ethical clearance

The study has been approved by the Institutional Review Boards of Nepal Health Research Council (ref: 555/2022) and the Pennsylvania State University (STUDY00021106). Since we collect individual health use data, we have taken caution to ensure that privacy is protected. Specifically, we collect the name and contact information of each participant on a separate sheet of paper. This form is used exclusively for the purpose of contacting the participants later, if needed. ASA generates a 6-digit household ID at baseline. The information households send through ASA as well as the baseline information collected (also through ASA) will contain this ID. Therefore, no information collected from the household after the initial interaction to seek consent and enroll the household will contain any identifying information. ASA’s development follows NIST SP800-53 and OWASP framework and guidelines. We will use data center certified by Ministry of Information Communication and Technology (MoICT) to host the application within the country. Data collected through ASA are stored in a secure server at the Group for Technical Assistance to which only designated staff at GTA and Co-investigator Nepal have access. The dataset that we will make available for replication after the conclusion of the study will not have any identifying information. Nonetheless, the consent form includes a statement that there is a risk of potential loss of confidential information; thus, the participating households are aware of the risks.

Funding statement

This study is funded by the Merck Investigator Support Program (MISP #101075).

Registration

This study has been registered in the Social Science Registry (AEARCTR-0010505): <https://www.socialscienceregistry.org/trials/10505>.

Statement on diversity and inclusion

We recognize the privilege that men and individuals from advantaged ethnic groups have had in Nepal as well as the existing gender-, ethnicity-, caste-, and class-based power imbalances. We have taken and will continue to take steps to consider these power imbalances. Specific steps include the following. 1) Our team includes an expert on gender and social inclusion in Nepal. The expert has reviewed all education materials (training resources, videos, content of the AMR pitch, etc.) as well as the questionnaire to ensure that language used is gender, caste, ethnicity and disability inclusive, and to ensure that the materials do not

help perpetuate—but counter—historical prejudices in relation to gender, caste, ethnicity and disability. 2) In the baseline survey, we collect information on gender of the respondent (using non-binary categorization) and education (as a proxy for economic status, appropriate to this setting). We will conduct heterogeneity analysis along these dimensions so that future efforts can be directed specifically to groups that need extra support. For example, if we find that less educated parents experience lower effect of the education intervention than educated parents, this would be an important consideration for future interventions. 3) As mothers tend to be the primary caretakers of young children—and thus the respondents in the baseline survey as well as the ones to submit information on antibiotics usage through ASA—we have designed ASA in a manner that it minimizes the burden to mothers. Specifically, we request households to submit on the information that is required to test the study’s hypotheses directly. 4) All staff recruited for the study (8 nurses, 8 enumerators, 2 supervisors, and 2 tech trainers) are women.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

- [1] World Health Organization. Global Action Plan on Antimicrobial Resistance. Published 2015. Available from <https://www.who.int/publications/i/item/9789241509763>.
- [2] C.J.L. Murray, et al., Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis, *Lancet* (2022), [https://doi.org/10.1016/s0140-6736\(21\)02724-0](https://doi.org/10.1016/s0140-6736(21)02724-0).
- [3] Time Is Running Out | UNICEF. <https://www.unicef.org/documents/time-running-out>.
- [4] G. Fink, V. D’Acremont, H.H. Leslie, J.L. Cohen, Antibiotic exposure among children younger than 5 years in low-income and middle-income countries: a cross-sectional study of nationally representative facility-based and household-based surveys, *Lancet Infect. Dis.* (2020), [https://doi.org/10.1016/s1473-3099\(19\)30572-9](https://doi.org/10.1016/s1473-3099(19)30572-9).
- [5] L. Dethlefsen, S.M. Huse, M.L. Sogin, D.A. Relman, The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing, *PLoS Biol.* (2008), <https://doi.org/10.1371/journal.pbio.0060280>.
- [6] C.L. Johnson, J. Versalovic, The human microbiome and its potential importance to pediatrics, *Pediatrics* (2012), <https://doi.org/10.1542/peds.2011-2736>.
- [7] S. Hashemi, A. Nasrollah, M. Rajabi, Original article: irrational antibiotic prescribing: a local issue or global concern? *EXCLI J* (2013) <https://doi.org/10.17877/de290r-10752>.
- [8] E.Y. Klein, et al., Global increase and geographic convergence in antibiotic consumption between 2000 and 2015, *Proc. Natl. Acad. Sci. U.S.A.* (2018), <https://doi.org/10.1073/pnas.1717295115>.
- [9] L. Shallcross, D.S.C. Davies, Antibiotic overuse: a key driver of antimicrobial resistance, *Br. J. Gen. Pract.* (2014), <https://doi.org/10.3399/bjgp14x682561>.
- [10] A. McDonnell, K. Klemperer, Drug-resistant Infections Are One of the World’s Biggest Killers, Especially for Children in Poorer Countries. We Need to Act Now, Center for Global Development blog, 22 January 2022. <https://www.cgdev.org/blog/drug-resistant-infections-are-one-worlds-biggest-killers-especially-children-poorer-countries>.
- [11] B. Basnyat, et al., Antibiotic use, its resistance in Nepal and recommendations for action: a situation analysis, *J. Nepal Health Res. Counc.* 13 (2015) 102–111.
- [12] S. Kakchapati, A. Rijal, S. Kc, Antimicrobial Resistance in Nepal: the Next Invisible Pandemic, *Health Prospect*, 2021, <https://doi.org/10.3126/hprospect.v20i1.41210>.
- [13] K.P. Acharya, R.T. Wilson, Antimicrobial resistance in Nepal, *Front. Med.* (2019), <https://doi.org/10.3389/fmed.2019.00105>.
- [14] Woohyeon Kim, E. Han, Antibiotic prescription for acute upper respiratory tract infections: understanding patient and physician contributions via patients’ migration, *Soc. Sci. Med.* 314 (2022), 115466–115466.
- [15] J. Currie, W. Lin, W. Lin, W. Zhang, Patient knowledge and antibiotic abuse: evidence from an audit study in China, *J. Health Econ.* (2011), <https://doi.org/10.1016/j.jhealeco.2011.05.009>.
- [16] Jessica King, Timothy Powell-Jackson, James Hargreaves, Christina Makungu, & Catherine Goodman. Pushy patients or pushy providers? Effect of patient

- knowledge on antibiotic prescribing in Tanzania. *Health Aff.* doi:10.1377/hlthaff.2021.01782.
- [17] Nepal: National antimicrobial resistance containment action plan. <https://www.who.int/publications/m/item/nepal-national-antimicrobial-resistance-containm-ent-action-plan>.
- [18] D.J. Morgan, I.N. Okeke, R. Laxminarayan, E.N. Perencevich, S.A. Weisenberg, Non-prescription antimicrobial use worldwide: a systematic review, *Lancet Infect. Dis.* (2011), [https://doi.org/10.1016/s1473-3099\(11\)70054-8](https://doi.org/10.1016/s1473-3099(11)70054-8).
- [19] A. Wilkinson, A. Ebata, H. MacGregor, Interventions to reduce antibiotic prescribing in LMICs: a scoping review of evidence from human and animal health systems, *J. Antibiot. (Tokyo)* 8 (2018) 2.
- [20] C. Cuevas, et al., Improving antibiotic use through behaviour change: a systematic review of interventions evaluated in low- and middle-income countries, *Health Pol. Plann.* 36 (2021) 594–605.
- [21] S. Miyano, T.T. Htoon, I. Nozaki, E.H. Pe, H.H. Tin, Public knowledge, practices, and awareness of antibiotics and antibiotic resistance in Myanmar: the first national mobile phone panel survey, *PLoS One* 17 (2022), e0273380.
- [22] Z. Akhtar, et al., Antibiotics use and its knowledge in the community: a mobile phone survey during the COVID-19 pandemic in Bangladesh, *Antibiotics* 10 (2021) 1052.
- [23] National Report | National Population and and Housing Census 2021 Results. <https://censusnepal.cbs.gov.np/results/downloads/national>.
- [24] Nepal's 91% of the population have access to the internet: regulator - OnlineKhabar English News. <https://english.onlinekhabar.com/nepals-91-of-the-population-have-access-to-the-internet-regulator.html>, 2021.
- [25] Nepal Demographic and Health Survey 2022 - Key Indicators (English). <https://dhsprogram.com/publications/publication-PR142-Preliminary-Reports-Key-Indicators-Reports.cfm>.
- [26] A. Nepal, D. Hendrie, S. Robinson, L.A. Selvey, Survey of the pattern of antibiotic dispensing in private pharmacies in Nepal, *BMJ Open* 9 (2019), e032422.
- [27] C. Pop-Eleches, et al., Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders, *AIDS Lond. Engl.* 25 (2011) 825–834.
- [28] F. Belotti, P. Deb, W.G. Manning, E.C. Norton, Twopm: two-Part Models, *Stata J. Promot. Commun. Stat. Stata* 15 (2015) 3–20.
- [29] Y. Acharya, J. Kim, Targeting using differential incentives: evidence from a field experiment, *Econ. Dev. Cult. Change* 70 (2022) 763–790.
- [30] J.E. Yang, et al., Effect of mobile application user interface improvements on minimum expected home visit coverage by community health workers in Mali: a randomised controlled trial, *BMJ Glob. Health* (2021), <https://doi.org/10.1136/bmjgh-2021-007205>.
- [31] Muthu Kioko, S., Balirwa, P. & Mutuma, S. Digital Health Tools for Community Health Worker Programs: Maturity Model and Toolkit.
- [32] N. Mahmud, N. Mahmud, N. Mahmud, J. Rodriguez, J. Nesbit, A text message-based intervention to bridge the healthcare communication gap in the rural developing world, *Technol. Health Care* (2010), <https://doi.org/10.3233/thc-2010-0576>.
- [33] R. Braun, R. Braun, C. Catalani, J. Wimbush, D. Israelski, Community health workers and mobile Technology: a systematic review of the literature, *PLoS One* (2013), <https://doi.org/10.1371/journal.pone.0065772>.
- [34] D. Citrin, et al., Developing and deploying a community healthcare worker-driven, digitally-enabled integrated care system for municipalities in rural Nepal, *Healthcare* 6 (2018) 197–204.
- [35] A.H. Bangura, et al., Practical issues in the measurement of child survival in health systems trials: experience developing a digital community-based mortality surveillance programme in rural Nepal, *BMJ Glob. Health* 1 (2016).
- [36] Digital Square. Mature Digital Public Goods for Health. <https://digitalsquare.org/digital-health-global-goods>.
- [37] I. Haaland, C. Roth, J. Wohlfart, Designing information provision experiments, *J. Econ. Lit.* 61 (2023) 3–40.