



BMJ Open Implementation of an antibiotic resistance surveillance tool in Madagascar, the TSARA project: a prospective, observational, multicentre, hospital-based study protocol

Christelle Elias ^{1,2}, Mathieu Raad,³ Saida Rasoanandrasana,⁴ Antso Hasina Raherinandrasana,⁵ Volatiana Andriananja,⁶ Mihaja Raberahona ⁶, Catrin E Moore,⁷ Mamy Randria,⁴ Laurent Raskine,³ Philippe Vanhems,^{1,2} François-Xavier Babin³

To cite: Elias C, Raad M, Rasoanandrasana S, *et al*. Implementation of an antibiotic resistance surveillance tool in Madagascar, the TSARA project: a prospective, observational, multicentre, hospital-based study protocol. *BMJ Open* 2024;**14**:e078504. doi:10.1136/bmjopen-2023-078504

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2023-078504>).

Received 03 August 2023
Accepted 08 March 2024



© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Dr Christelle Elias;
christelle.elias@chu-lyon.fr

ABSTRACT

Introduction Antimicrobial resistance (AMR) has become a significant public health threat. Without any interventions, it has been modelled that AMR will account for an estimated 10 million deaths annually by 2050, this mainly affects low/middle-income countries. AMR has a systemic negative perspective affecting the overall healthcare system down to the patient's personal outcome. In response to this issue, the WHO urged countries to provide antimicrobial stewardship programmes (ASPs). ASPs in hospitals are a vital component of national action plans for AMR, and have been shown to significantly reduce AMR, in particular in low-income countries such as Madagascar.

As part of an ASP, AMR surveillance provides essential information needed to guide medical practice. We developed an AMR surveillance tool—Technique de Surveillance Actualisée de la Résistance aux Antimicrobiens (TSARA)—with the support of the Mérieux Foundation. TSARA combines bacteriological and clinical information to provide a better understanding of the scope and the effects of AMR in Madagascar, where no such surveillance tool exists.

Methods and analysis A prospective, observational, hospital-based study was carried out for data collection using a standardised data collection tool, called TSARA deployed in 2023 in 10 hospitals in Madagascar participating in the national Malagasy laboratory network (Réseau des Laboratoires à Madagascar (RESAMAD)). Any hospitalised patient where the clinician decided to take a bacterial sample is included. As a prospective study, individual isolate-level data and antimicrobial susceptibility information on pathogens were collected routinely from the bacteriology laboratory and compiled with clinical information retrieved from face-to-face interviews with the patient and completed using medical records where necessary. Analysis of the local ecology, resistance rates and antibiotic prescription patterns were collected.

Ethics and dissemination This protocol obtained ethical approval from the Malagasy Ethical Committee n°07-MSANP/SG/AGMED/CNPV/CERBM on 24 January 2023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Technique de Surveillance Actualisée de la Résistance aux Antimicrobiens (TSARA) is a prospective, observational and multicentre protocol capturing data from hospitalised patients.
- ⇒ TSARA is an antimicrobial resistance surveillance tool that compiles microbiological and clinical data, including information on antibiotic prescriptions implemented in Malagasy hospitals belonging to the Réseau des Laboratoires à Madagascar network.
- ⇒ The data collection is performed on an electronic tablet which limits data entry bias.
- ⇒ The TSARA project is highly dependent on the infrastructure and the available resources in Malagasy laboratories.

Findings generated were shared with national health stakeholders, microbiologists, members of the RESAMAD network and the Malagasy academic society of infectious diseases.

INTRODUCTION

Antimicrobial resistance (AMR) is a global health threat associated with a poor prognosis and an increased mortality in the population infected with resistant bacteria. In the coming decades, deaths attributable to AMR will overcome the mortality due to non-communicable diseases through the lack of treatment options.¹ Recent data from the Global Burden of Disease² suggested that the impact of AMR on health is even more important than previous estimations.¹ To address the increasing problem, the WHO published the Global Action Plan on AMR in 2015³ and urged countries to build national action plans aiming to prioritise



interventions to combat AMR rapidly. One of the objectives was to implement and strengthen surveillance systems to monitor AMR as a first step of an antimicrobial stewardship programme (ASP),⁴ in particular in hospital settings where high levels of resistance occur. In addition to these measures, the WHO also advocates for the implementation of antibiotic management policies adapted to local resistance patterns in hospitals.^{5–8} Setting up an ASP is challenging, especially in low/middle-income countries (LMICs) due to the lack of infrastructure, good quality data and governance.^{7,9} For a country like Madagascar, where robust healthcare facilities, infrastructures and laboratories are very scarce, collecting resistance data remains a challenge.

Madagascar is the fifth largest island in the world, but is considered a low-income country according to the World Bank.¹⁰ Health coverage in Madagascar is extremely limited and the patient has to directly pay for the majority of healthcare (ie, diagnostics, treatment, consumables, surgery). Most drugs—especially antibiotics—are dispensed only with a medical prescription. However, in Madagascar, it is very common to deliver such medicines ‘Over The Counter’ and antibiotics can be sold easily outside hospital settings, for those who can afford them, without any medical prescription. Lack or substandard infection control practices contribute significantly to the spread of bacterial resistance, both in the community (through AMR/antibiotics in wastewater) and in hospitals (hospital hygiene and nosocomial transmission). The culture of systematic treatment against an infectious agent encourages the misuse and the overconsumption of antibiotics, prescribed or not. At the hospital level, AMR has a greater effect, as patients are in hospital for several days, receive more care, have invasive procedures performed and thus are more at risk of transmission of bacteria and healthcare-associated infections. Appropriate hygiene measures

and standard precautions are difficult to implement in low-resource settings, where there is for instance an average of five hospital beds per room in a Malagasy university hospital.

Outside of the Réseau des Laboratoires à Madagascar (RESAMAD) laboratories, there are very few laboratories that can perform microbiology cultures and antimicrobial susceptibility testing (AST) in Madagascar and the burdened cost remains prohibitive for many patients. Targeted antibiotic therapy is therefore rarely prescribed and antibiotic treatment often remains empirical without any de-escalation. In this context of low access to microbiology laboratory combined with high rates of bacterial resistance at the national level, practitioners use broad-spectrum therapies, increasing the selection pressure on the bacteria and creating emerging resistances. Knowledge of the local resistance patterns is essential to adapt the clinical decision-making and have locally adapted recommendations.⁸ Table 1 provides a Strengths, Weaknesses, Opportunities and Threats analysis as an overview of what is currently in place and the starting points of the implementation of an AMR surveillance tool in Madagascar.

In Madagascar as well as in multiple developing countries, the Mérieux Foundation has been strengthening clinical laboratories in the fight against infectious diseases for decades to enhance the quality and access to clinical laboratories aiming at preventing infections and improving patient care.¹¹ The Mérieux Foundation has been investing on the fight against AMR supporting countries to develop infrastructures, laboratories, personnel training and building a laboratory network to strengthen laboratory-based surveillance of infectious diseases. As a result, in 2022, 14 Malagasy laboratories were in the RESAMAD laboratory network, they were all able to perform bacteriology diagnosis, this was created in 2007 and has risen to 27 laboratories across the country to date

Table 1 SWOT analysis of the implementation of an AMR surveillance tool in hospitals in Madagascar

<p>Strengths</p> <ul style="list-style-type: none"> ▶ Laboratory network RESAMAD¹⁶ currently in place, already transferring data to the WHO through the GLASS-AMR module ▶ Active support of international stakeholders ▶ Identification of highly motivated Malagasy practitioners willing to work on AMR and ASP ▶ Existence of several scientific societies (infectious diseases, paediatrics, medical biology) 	<p>Weaknesses</p> <ul style="list-style-type: none"> ▶ Little knowledge on the local epidemiology of AMR ▶ Collection of antibiograms not performed on a daily basis ▶ Lack of visibility on antibiotic prescriptions in hospitals and their efficiency ▶ Implementation only doable where good laboratories exist ▶ Bacteriology results sometimes delivered to the prescriber in a paper format
<p>Opportunities</p> <ul style="list-style-type: none"> ▶ Capture high-level antibiotic use in hospitals ▶ Existing antibiotic recommendations in place, but they are not adapted to local resistance patterns²¹ ▶ Existing AMR protocols including the surveillance of antimicrobial use 	<p>Threats</p> <ul style="list-style-type: none"> ▶ Challenging implementation ▶ Substantial missing data ▶ Personnel require training ▶ Lack of funding ▶ Political instability ▶ Climate disorders
<p>AMR, antimicrobial resistance; RESAMAD, Réseau des Laboratoires à Madagascar; SWOT, Strengths, Weaknesses, Opportunities and Threats.</p>	

(RESAMAD—Fondation Mérieux (fondation-merieux.org)).

Given this context, and the challenge to combat AMR in healthcare settings, ASP in hospitals are a vital component of national action plans for AMR, and have been shown to significantly reduce AMR, in particular in low-income country such as Madagascar.^{9 12} As part of an ASP, AMR surveillance provides essential information needed to guide medical practice. An AMR surveillance tool called TSARA (Technique de Surveillance Actualisée de la Résistance aux Antimicrobiens) was developed thanks to the support of the Mérieux Foundation, with the objective of combining patient data with laboratory and epidemiological surveillance data to provide a better understanding of the scope and the effects of AMR in Madagascar, where no such surveillance tool was available, in order to treat patients more effectively. It will allow monitoring and follow-up compared with the scarce existing prescribing data.¹³ The TSARA project also aligns with the antimicrobial surveillance programme led by the direction of epidemiological surveillance and response of the Ministry of Health in the context of One Health and in collaboration with other Ministries to tackle AMR in Madagascar. TSARA also answers one of the objectives of the Malagasy national action plan on AMR.¹⁴

OBJECTIVES

One of the most important benefits of AMR surveillance at the pathogen level is to achieve a standardised, comparable and easily validated data collection method for quality data that is used to implement better patient treatment and hospital/national guidelines.¹⁵ The data allows an optimisation of the patient care by adapting treatment guidelines according to the patient demographics and type of infection, taking into consideration of the circulating pathogens and local resistance patterns. The primary objective is:

1. To institute a systematic approach towards microbiological data and clinical data collection and analysis of antimicrobial susceptibility information to optimise antimicrobial therapy in Malagasy hospitals. The secondary objectives are:
 2. To establish timely reporting of information on pathogens of interest and their antimicrobial susceptibility profiles to medical doctors.
 3. To allow monitoring of the hospital antibiotic prescription (quantity, quality and spectrum, concordance with bacteriological results).
 4. To provide data to the laboratory quality assessment and identify areas for improvement.

METHODS AND ANALYSIS

Study design and setting

Study design

TSARA is a prospective, observational, multicentre, hospital-based study based on a standardised data

collection tool deployed in 10 facilities with both adult and paediatric patients in Madagascar (figure 1), collecting microbiological, demographic, prescription and clinical data in one place.

Outcome measures

The outcomes of interest will be categorised into behavioural, clinical and microbiological outcomes. Behavioural outcomes include changes in prescribing practices among prescribers and compliance with AMS protocols. In the TSARA project, we consider an adapted antibiotic prescription as a behavioural outcome, defined as:

1. A prescription of an antibiotic therapy consistent with the national antibiotic guidelines, or
2. A prescription of an antibiotic therapy considering the laboratory results including antibiotic susceptibility testing results.

Then, a metric will be used to describe the number and the proportion of the adapted antibiotic prescriptions.

Microbiological outcomes include a description of the bacteria isolated by culture, bacterial resistance rates as well as the delay between the sample being collected and the laboratory results communicated to the prescriber (in days and hours, online supplemental materials 1 and 2).

Clinical outcomes include mortality defined as death occurring during the patient's hospital stay or the length of stay defined as the duration between the admission date and discharge date from the hospital (online supplemental materials 1 and 3).

Setting and laboratory capacity

All laboratories participating in the TSARA project are part of the nationwide RESAMAD network in Madagascar.¹⁶ Description of the infrastructure in each hospital included in the TSARA project is presented in online supplemental material 4.

These laboratories perform diagnostics and AST for infectious diseases, and have the capacity to perform phenotypic confirmation of the presence of resistance. To participate in TSARA, laboratories have to meet minimal quality standards requirements defined by the RESAMAD network and participate in an external quality assessment programme. The laboratories also have the required infrastructure, equipment, supplies and resources to perform AST following EUCAST standards. The reporting of results to clinicians is made by qualified and trained technicians supervised by clinical microbiologists. The Mérieux Foundation performs regular training to laboratory staff and support the purchase of consumables (ie, Petri dishes, antibiotic disks) and reagents.

Study population

The population of the study includes all patients (adults and children) arriving at the hospital who are inpatients and have bacterial samples taken by the physician and sent to the laboratory.

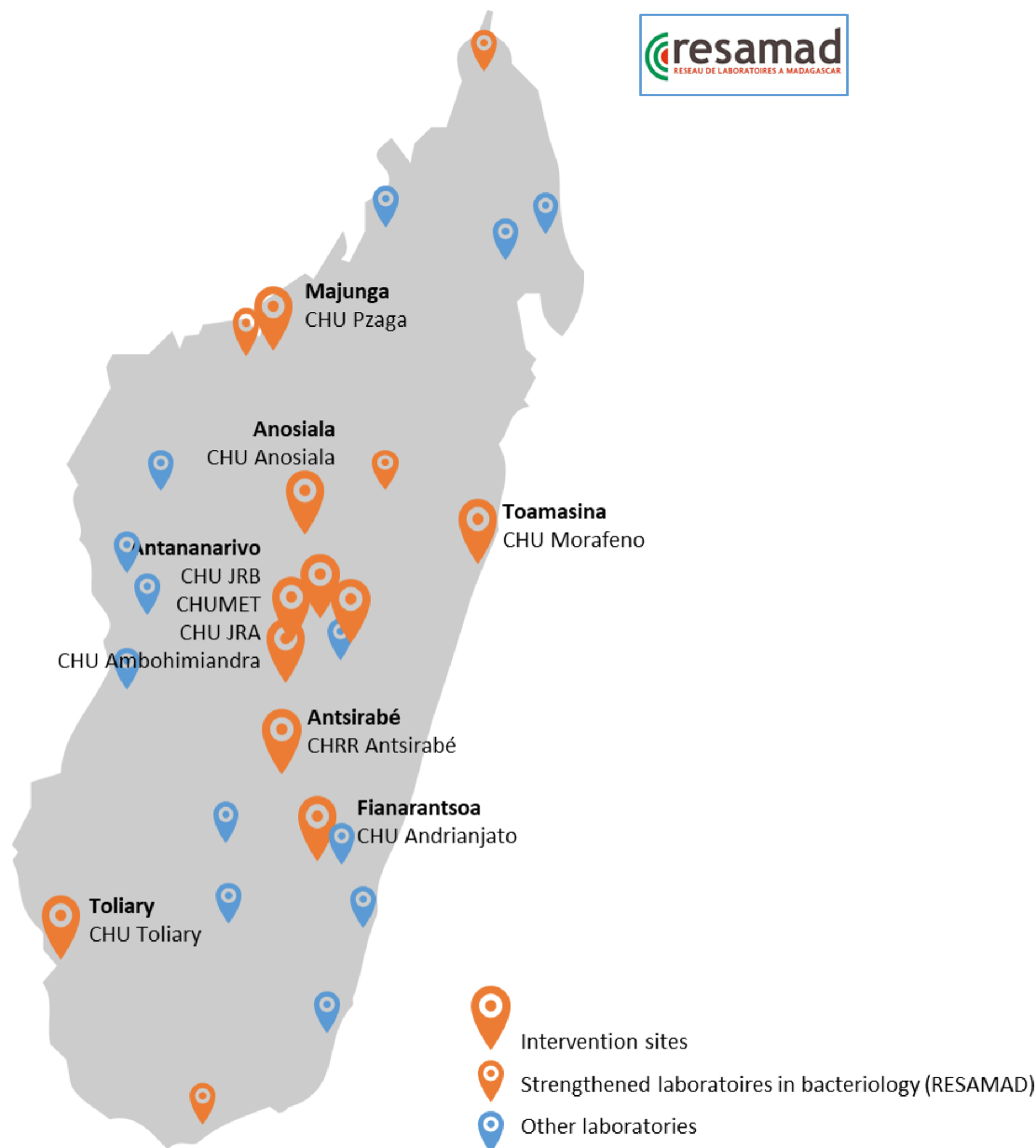


Figure 1 Map of the laboratories and implementation sites of Technique de Surveillance Actualisée de la Résistance aux Antimicrobiens in Madagascar. RESAMAD, Réseau des Laboratoires à Madagascar.

Inclusion criteria

All patients arriving at each hospital, who have a bacterial culture performed are included in the study. All positive and negative bacteriological samples from hospitalised patients in one of the participating institutions from January 2023 onwards will be included.

Exclusion criteria

The following criteria will be excluded from the TSARA project:

1. All non-bacteriological specimens (virological, fungal, parasitic).
2. All samples from patients not hospitalised >24 hours (emergency, consultation, outpatient hospitalisation).
3. All environmental samples (water, air, surfaces, medical devices).

4. All postmortem samples.
5. All samples reported as contaminated are defined as results that do not contribute to clinical decision-making.
6. All specimens for which culture was not possible.
7. All specimens with laboratory non-compliance.
8. All the patients or legal guardians who object to be included in the TSARA project.
9. All patients with severe cognitive impairment.
10. All patients who do not have a full understanding of the French or Malagasy language.

Participant timeline

Enrolled patients will be followed up during their hospital stay until discharge or death. Information on the vital status (alive, deceased, discharged or transferred to another hospital) will be collected.

Patient and public involvement

Patients and the public were not involved in the design of this study.

Data collection

Individual isolate-level data and AST on pathogens were collected routinely from the bacteriology laboratory using a first questionnaire (online supplemental material 1). These data were compiled using a second questionnaire with basic clinical, demographic and epidemiological information (including current antibiotic prescription) retrieved daily through face-to-face interviews with the patient and completed by medical records where necessary (online supplemental material 2). A third questionnaire was then filled in regarding follow-up data (online supplemental material 3). The data retrieved from TSARA meet the criteria and are linked to the GRAM project that seeks to estimate the burden of AMR worldwide.^{15 17}

To enhance data collection and limit data entry bias, data were directly captured on a tablet connected to the Epicollect5 platform (<https://five.epicollect.net>). Data were collected by Malagasy investigators (medical interns, biologists or clinical research associates) using tablets dedicated to this project, each of whom received specific training on the TSARA methodology prior to the start of the study. The investigator will examine the bacteriological samples daily, or as frequently as possible. A new eligible sample corresponds to a new inclusion in the TSARA project.

Statistical methods

Sample size

TSARA is a surveillance project, as such there is no calculation on the number of subjects needed a priori. Statistical analyses will be adapted a posteriori according to the total number of inclusions during the project period and the power needed to obtain valid results.

Description of the statistical methods

Any anomalies in the data will be checked with medical records during data cleaning. Data will be validated by quality control to identify outliers and inconsistencies by means of consistency tests (eg, filling in the inclusion criteria, date of admission to hospital later than the date of admission to the department, date of death later than the date of onset of symptoms).

Descriptive summary tables with numbers and frequencies will be drawn up. Similarly, visual representations of the variables may be made to detect irregular or missing values. Any changes to the data will be documented and recorded separately from the raw database. Recoded variables will also be filled in (eg, age categories).

A flow chart will be developed to describe the number of eligible, included and excluded patients and samples in our study. A descriptive analysis of the entire baseline population will be undertaken to identify the baseline characteristics of the study population (the specimen, bacterial, clinical and patient levels).

Categorical variables will be reported as frequencies and percentages of the total population. Quantitative variables will be described using the mean and SD if the distribution is normal, or the median and IQR if the distribution does not follow the normal distribution. The range with the minimum and maximum values will be filled in. For each variable, the proportion of missing values will be indicated.

Stratified analyses will also be provided to present results by facility, department, type of sample, and bacteria of interest (including species, and antibiotic resistance of interest) as well as by type of antibiotics prescribed. In addition, given the fact that data are collected for the adult and paediatric population, a stratified analysis will be performed for both populations.

A two-group comparison using univariate and then multivariate analysis and a logistic regression will be performed to estimate the associations between an adapted antibiotic therapy and the other variables. The OR and p value of each test will be reported. Only the variables with a p value lower than 0.2 will be retained to perform the multivariate analyses. In addition to the presentation of the multivariate analyses, the most efficient multivariate model will be presented after a top-down selection of only those variables with a p value less than 0.05. Stratified analyses will be conducted to identify potential confounders (comparison of crude and adjusted ORs) and interaction factors (Wald's test of homogeneity).

These analyses will be performed using the χ^2 test or Fisher's exact test for qualitative variables, and the Student's t-test or the Mann-Whitney test (depending on the nature of the variable or the size of the sample) for quantitative variables. A significance level of less than 0.05 is considered associated.

Patient survival will be calculated from the date of enrolment until in-hospital death, based on the Kaplan-Meier method. Follow-up will be censored at 14 days and 28 days. Survival distributions will be compared by the log-rank test. Variables independently associated with survival will be identified with a Cox regression model based on relative hazard with a 95% CI.

Missing data and outliers

Missing data will be documented individually. In the case of multiple missing data or if there is evidence of bias in the missing data on the variables of interest, multiple imputation methods may be used at the study level to substitute missing values. Imputation will be performed if the proportion of missing data does not exceed 20%. If this is the case, the variable will be removed from the statistical analysis.

A sensitivity analysis will be performed to compare the raw database (including missing data) with the imputed data.

Outliers were prevented by a blocking input mask, alert messages and an input guide. However, if new outliers are discovered after the quality checks and during the

analyses, they will be corrected as missing data. The scripts allowing these corrections will be communicated.

Data management and archiving

Case report form

The case report form only includes data necessary for participation in the TSARA project. All information required by the protocol is recorded in the anonymised case report forms. Data are collected as they are obtained in the laboratory and then at the patient's bedside, and recorded in these case report forms explicitly.

These case report forms are set up in each of the facilities using the electronic tablets equipped with Epicollect applications, including the TSARA project questionnaires. An instruction book to help the investigators use this tool was provided. The investigators are responsible for the accuracy, quality and relevance of all data entered, under the responsibility of the lead investigator.

These case report forms are associated with de-anonymised forms, in paper format, containing the first and last names of the patients enrolled, as well as an identification number shared between the paper and online forms. These second de-anonymised forms stay within the hospital and should allow possible corrections or deletions of data on request of the patients enrolled.

Data management

Collected data are computerised by the epidemiologist in charge of the project. Electronic databases are anonymous and locked with a password known only by the scientific staff. These data will be kept for a minimum of 15 years after the end of the study.

Archiving

The sponsor will keep the study documents (protocol and annexes, possible amendments, information forms, case report form, statistical analysis plan and output and the final study report) for a minimum of 15 years. After this period, the sponsor will be consulted before any data are destroyed. Study-related documents and reports may be subject to audit or inspection by the sponsor and/or other authorised bodies. No relocation or destruction will be made without the consent of the sponsor. At the end of the 15 years, the sponsor will be consulted for destruction. All data, documents and reports will be subject to audit or inspection.

Confidentiality

All personal data on the study participants will remain strictly confidential. To respect their privacy and for confidentiality, all participant details will be anonymous for the purpose of database preparation. Study subjects are coded with four numerical numbers.

Ethics and dissemination

Ethics

The TSARA study was approved by the National Ethics Committee in Madagascar on 24 January 2023 (n°07-MSANP/SG/AGMED/CNPV/CERBM).

Informed consent

Patients are fully and fairly informed, in understandable terms, of the objectives, their rights to refuse to participate in the study, or the opportunity to withdraw at any time.

All of this information is included on an information form given to the patient, and the patient's agreement will be collected by the investigator and will be recorded in the patient's source file.

The information will be communicated orally in French or in Malagasy by the investigators. An information form is also available in paper format in French and in Malagasy. When conditions permit, if the eligible patient does not speak French or Malagasy, the investigators will seek to volunteer a third party to provide a translation (a relative of the patient, or available hospital personnel).

Regulatory compliance

The study will be conducted in accordance with applicable laws and regulations currently in place in Madagascar.

Withdrawal criteria

Subjects may request to withdraw from the study at any time, without explanation, for any reason. In the event of premature exit, the investigator should document the reasons as completely as possible.

Stopping the research study

The Mériex Foundation reserves the right to discontinue the study at any time, if it is determined that the inclusion objectives are not met, or if the protocol is not respected in one or more participating institutions, or subject to other circumstances beyond the control of the Mériex Foundation (eg, political instability). In case of premature termination of the study in one of the institutions, the information will be transmitted by the sponsor to the Malagasy interlocutors.

Protocol amendments

In the eventuality of changes in the existing protocol that significantly affect the scope or the scientific quality of the investigation, an amendment containing a verbatim description of the changes and reference (date and number) to the submission that contained the original protocol will be submitted to the ethical committee for their approval.

Dissemination

Results and scientific reports that emerge from this study will be made publically available. This is under the responsibility of the principal investigator in agreement with the associated investigators. Results will be reported following the guidelines from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) consortium (www.strobe-statement.org) and STROBE-AMS.¹⁸ Publication rules will follow international recommendations. The findings will also be shared with national health and sports authorities.

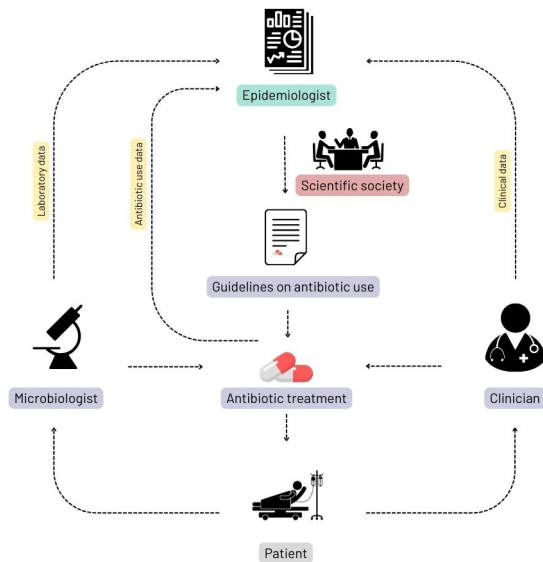


Figure 2 Data flow between the different stakeholders.

Authorship will follow the guidelines established by the International Committee of Medical Journal Editors (<https://www.icmje.org>), which require substantive contributions to the design, conduct and interpretation and reporting of an epidemiological study.

These data will help the Malagasy scientific societies of infectious diseases (SPIM), paediatrics (SMP) and microbiology (SOMABIO) to tailor antibiotic recommendations according to the resistance patterns as presented in [figure 2](#).

DISCUSSION

The TSARA project will provide original results that could (i) allow a more precise epidemiological knowledge of bacterial infections, prescribed antibiotic therapies and local resistance levels; (ii) inspire, correct and tailor local practices, including recommendations and guidelines for empiric antibiotic therapy according to local resistance patterns; (iii) encourage communication and use of AST results with and between clinicians; (iv) allow monitoring of hospital antibiotic prescription (quantity, quality and spectrum, concordance with bacteriological results) and (v) provide evidence to improve laboratory services and interactions with clinicians.

Surveillance is the primary strategy for tracking emerging drug resistance in the population, and thus provides a tool to pick up any unusual organisms early and perform appropriate action. Regular dissemination of AMR data is key to elaborate local, evidence-based recommendations and revise the AMR national policy.

Shortcomings

Implementing TSARA as an AMR laboratory and patient-based surveillance system presents some challenges. First, all the patients included in the study were hospitalised, and are self-paying for the majority of healthcare costs which induces a selection bias and may hamper the

representativeness of the data. Mainly tertiary care hospitals belonging to the RESAMAD laboratory network were included due to their laboratory capacities, secondary and primary care centres were under-represented in TSARA. Consequently, results from the AMR data generated might be inflated as these facilities harbour more vulnerable and sick patients, who may have previously taken antibiotics and been in hospital and therefore be subject to higher antibiotic exposure. Additionally, clinicians may prescribe antibiotics in the absence of microbiological documentation or for the treatment of non-bacterial infections, even though such practices could contribute to elevated rates of antibiotic resistance. This tool, although innovative, is highly dependent on the capacity and the willingness of staff, on laboratory capacity, which can sometimes be heterogeneous within the hospitals and over the time, depending on the turnover of the staff and the availability of consumables in country. The TSARA project can be implemented only in a facility where laboratory services are functional, robust and where bacterial cultures and AST are performed routinely. In addition, patient treatment could be influenced by a delay in obtaining the culture results. In Madagascar, as well as many LMICs, it is common to use diagnostic microbiology testing after treatment failure to improve on broad-spectrum antibiotics,¹⁹ which also overestimates local AMR rates. Negative perception of the laboratory capacity and associated costs could explain the unwillingness to perform microbiology testing by the clinicians.

No clear standard definition of multidrug-resistant bacteria has been set up by Malagasy health authorities, which results in difficulties in the data interpretation and comparison. Data collection currently relies on paper-based data capture, where no electronic medical records currently exist in the facilities. The quality of data may be another obstacle to getting validated results and there might be exposed to intersite variability. Clinical data and follow-up data could also be subject to a substantial proportion of missing data, as these are harder to retrieve than microbiological data. Finally, the investigator may have a lack of motivation to collect the data as it could be perceived as added work with a limited incentive or reward.

Opportunities

The culture to collect of laboratory and clinical data is a serious challenge in LMICs. In 2021, the Mériex Foundation implemented the Lab Book 3.0,²⁰ a Laboratory Information System which helps to computerise clinical laboratory data, in all the RESAMAD laboratories. This has both improved data collection and ensures data quality.

Additionally, the use of information and technology through a digital tool could be the next step for TSARA. It would encourage a timely reporting of AMR and clinical data ensuring the correct patient treatment. Thus, it may incentivise scientific societies to adjust national antibiotic guidelines according to the local resistance patterns and

hence support prescribers to make better, more informed clinical decisions and antibiotic prescriptions. Given the expansion of e-Health and connected devices, we imagine this tool to be integrated in a prescription assistance device on a mobile application as a future solution to combat AMR. Presenting the clinician with the antibiotic therapy recommendation associated with the WHO AWaRe classification has already shown its deployment in the fight against AMR.⁶

Furthermore, starting from January 2022, a change in the patient payment has occurred where any patient admitted to a Malagasy hospital with a life-threatening disease has received all the initial hospital care at no cost. Leadership and financial commitment from local health authorities has been invaluable (ie, direction of epidemiological surveillance and response of the Ministry of Health), and is key to the sustainability of the project and its expansion across the country.

Thanks to TSARA, significant progress should be made in AMR surveillance and antimicrobial stewardship in Madagascar. This project will also participate in supporting the implementation of the national action plan on AMR in Madagascar. Assessing the impact and the efficiency of this project that is, monitoring antibiotic prescriptions and checking their compliance with recommendations still need to be explored as clinicians' behaviours also drive AMR. Despite some challenges, future opportunities are encouraging for TSARA but rely on financial investment and strong leadership from health authorities to warrant the added value, the sustainability and the potential expansion of this project.

Author affiliations

- ¹Service Hygiène et Epidémiologie, Hospices Civils de Lyon, Lyon, France
²Public Health, Epidemiology & Evolutionary Ecology of Infectious Diseases (PHE3ID) team, Centre International de Recherche en Infectiologie (CIRI), Inserm U1111, CNRS UMR5308, ENS de Lyon, Université Claude Bernard Lyon 1, Lyon, France
³Direction des Opérations Internationales, Fondation Mérieux, Lyon, France
⁴Service de Biologie, Hôpital Befelatanana, Antananarivo, Madagascar
⁵Département de Santé Publique, Faculté de Médecine de l'Université d'Antananarivo, Antananarivo, Madagascar
⁶Service des Maladies Infectieuses, Hôpital Befelatanana, Antananarivo, Madagascar
⁷Centre for Neonatal and Paediatric Infection, St. George's, University of London, London, UK

Twitter Catrin E Moore @catmoore_1

Acknowledgements The authors thank all the biologists, namely Dr Christian Rafalimanana, Dr Lalaina Rahajamanana, Dr Zakasoa Ravaoaraisaina, Dr Tiana Andry Razafinikasa, Dr Lalaina Raelina, Dr Ainamalala Catherine Razafindrakoto, Dr Solotiana Rivo Rakotomalala, Dr Jocia Fenomanana, Dr Emile Ravelomandranto, Dr Irène Rakotoniaina and the local investigators of the RESAMAD network for their participation in the TSARA project. The authors are very thankful for Luciana Rakotoarisoa and Johannine Rakotoniaina for their support in the implementation of the project locally.

Contributors CE, M Raad, F-XB, LR, MRaberahona, SR, MRandria designed the study. CE and M Raad drafted the manuscript. CE, SR, AHR, VA and LR participated in the acquisition of data. CE, M Raad, SR, AHR, VA, MRaberahona, CEM, MRandria, LR, PV, F-XB have revised and approved the final version of the manuscript.

Funding The TSARA project has received funding from: Fondation Mérieux. PFIZER ISID Research Grant n°63019455.

Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the expression of any opinion whatsoever on the part of BMJ concerning the legal status of any country, territory, jurisdiction or area or of its authorities. Any such expression remains solely that of the relevant source and is not endorsed by BMJ. Maps are provided without any warranty of any kind, either express or implied.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Christelle Elias <http://orcid.org/0000-0002-6962-161X>
 Mihaja Raberahona <http://orcid.org/0000-0001-8857-5834>

REFERENCES

- O'Neill J, Davies S, Rex J, *et al*. *Review on Antimicrobial Resistance, Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*. London, UK: Wellcome Trust and UK Government, 2016.
- Murray CJL, Ikuta KS, Sharara F, *et al*. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022;399:629–55.
- WHO global action plan for AMR. World Health Organization; 2015.
- Pulcini C, Binda F, Lamkang AS, *et al*. Developing core elements and checklist items for global hospital antimicrobial stewardship programmes: a consensus approach. *Clin Microbiol Infect* 2019;25:20–5.
- Tebano G, Li G, Beovic B, *et al*. Essential and forgotten antibiotics: an inventory in Low- and middle-income countries. *Int J Antimicrob Agents* 2019;54:273–82.
- Budd E, Cramp E, Sharland M, *et al*. Adaptation of the WHO essential medicines list for national antibiotic stewardship policy in England: being aware. *J Antimicrob Chemother* 2019;74:3384–9.
- Mendelson M, Morris AM, Thursky K, *et al*. How to start an antimicrobial stewardship programme in a hospital. *Clin Microbiol Infect*; 2019. Available: <https://linkinghub.elsevier.com/retrieve/pii/S1198743X19304483>
- Elias C, Moja L, Mertz D, *et al*. Guideline recommendations and antimicrobial resistance: the need for a change. *BMJ Open* 2017;7:e016264.
- Cox JA, Vlieghe E, Mendelson M, *et al*. Antibiotic stewardship in Low- and middle-income countries: the same but different. *Clin Microbiol Infect* 2017;23:812–8.
- World Bank country classification. n.d. Available: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>
- Fondation Mérieux. n.d. Available: <https://www.fondation-merieux.org/en/who-we-are/>
- Morency-Potvin P, Schwartz DN, Weinstein RA. Antimicrobial stewardship: how the Microbiology laboratory can right the ship. *Clin Microbiol Rev* 2017;30:381–407.
- Protocol for enhanced isolate-level antimicrobial resistance surveillance in the Americas. primary phase: bloodstream infections. Pan American Health Organization; 2021. Available: <https://iris.paho.org/handle/10665.2/53275>

- 14 Plan D'Action national pour Combattre La Résistance aux Antimicrobiens 2019-2023. n.d. Available: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-npm/nap-library/madagascar_2019_2023.pdf?sfvrsn=cf290d1c_1&download=true
- 15 GRAM protocol. n.d. Available: <https://www.tropicalmedicine.ox.ac.uk/gram/research/global-burden-of-bacterial-antimicrobial-resistance/>
- 16 Resamad. 2023. Available: <https://www.fondation-merieux.org/projets/resamad/>
- 17 Schnall J, Rajkhowa A, Ikuta K, *et al.* Surveillance and monitoring of antimicrobial resistance: limitations and lessons from the GRAM project. *BMC Med* 2019;17.
- 18 Tacconelli E, Cataldo MA, Paul M, *et al.* STROBE-AMS: recommendations to Optimise reporting of Epidemiological studies on antimicrobial resistance and informing improvement in antimicrobial stewardship. *BMJ Open* 2016;6:e010134.
- 19 Krockow EM, Colman AM, Chattoe-Brown E, *et al.* Balancing the risks to individual and society: a systematic review and synthesis of qualitative research on antibiotic prescribing behaviour in hospitals. *J Hosp Infect* 2019;101:428–39.
- 20 Lab book. n.d. Available: <https://www.lab-book.org/>
- 21 Randriatsarafara FM, Ralamboson J, Rakotoarivelo R, *et al.* Consommation D'Antibiotiques au centre Hospitalier Universitaire D'Antananarivo: Prévalence et Défis Stratégiques. *Santé Publique* 2015;Vol. 27:249–55.

Supplementary material 1. TSARA microbiological questionnaire

Question	Name of the variable	Type of data	Format	Description
Hospital where the sample was taken	id_hosp	Single choice list	CHUJRB, CHUJRA, CHUMET, CHRR ANTSIRABE, CHU ANOSIALA, CHU MORAFENO , CHU PZAGA , CHU FIANARANTSOA, CHRR AMBOHIMIANDRA, CHU TULEAR	Hospital where the bacteriological sample was taken (hospital of inclusion)
Patient identification number	id_pat	Numeric	-----	Patient's inclusion number
Date of collection	dt_pvt	Date	DD/MM/YYYY HH:MM	Date of collection
Date of receipt of the sample in the laboratory	dt_rec_pvt	Date	DD/MM/YYYY HH:MM	Date of receipt of the sample in the laboratory
Date of bacteriological CR	dt_cr_pvt	Date	DD/MM/YYYY HH:MM	Date of delivery of the result to the patient or prescribing physician
Type of sampling	pvt_type	Single choice list	Blood culture, Intravascular device, Ascites fluid, Cerebrospinal fluid, Joint fluid, Respiratory specimen, Deep tissue specimen, Genital specimen, Urine, Neonatal specimen and placenta, Superficial pus, Deep tissue specimen, Stool culture (not screening), Other specimen, Unknown	Type of sampling performed
Positive culture	culture	Single choice list	Yes/No	Identification of a microorganism on the culture
If yes, identified pathogen	bact	Single choice list	List of bacteria	Identification of the micro-organism on the sample
Nalidixic acid	nalidixic_acid	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Fusidic acid	fusidic_acid	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Amikacin	amikacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Amoxicillin	amoxicillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Amoxicillin-clavulanic acid	amoxicillin_clav	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ampicillin	ampicillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ampicillin-Sulbactam	ampicillin_sulbactam	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Azithromycin	azithromycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Aztreonam	aztreonam	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested

Cefadroxil	cefadroxil	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefalexin	cefalexin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefalotin	cefalotin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefamandole	cefamandole	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefazolin	cefazolin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefepime	cefepime	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefixime	cefixime	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefotaxime	cefotaxime	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefoxitin	cefoxitin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefpodoxime	cefpodoxime	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ceftazidime	ceftazidime	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ceftriaxone	ceftriaxone	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cefuroxime	cefuroxime	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Chloramphenicol	chloramphenicol	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Chlortetracycline	chlortetracycline	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ciprofloxacin	ciprofloxacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Clarithromycin	clarithromycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Clindamycin	clindamycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Cloxacillin	cloxacillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Colistin	colistin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Daptomycin	daptomycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Doxycycline	doxycycline	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ertapeneme	ertapeneme	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Erythromycin	erythromycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Fosfomicin	fosfomicin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Gentamicin	gentamicin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Imipeneme	imipeneme	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Josamycin	josamycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Levofloxacin	levofloxacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested

Lincomycin	lincomycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Linezolid	linezolid	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Meropenem	meropenem	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Metronidazole	metronidazole	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Midecamycin	midecamycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Minocycline	minocycline	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Moxifloxacin	moxifloxacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Neomycin	neomycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Netilmycin	netilmycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Nifuroxazide	nifuroxazide	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Nitrofurantoin	nitrofurantoin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Norfloxacin	norfloxacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ofloxacin	ofloxacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Oxacillin	oxacillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Pefloxacin	pefloxacin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Piperacillin	piperacillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Piperacillin-Tazobactam	piperacillin_tazo	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Pivmecillinam	pivmecillinam	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Polymyxin	polymyxin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Pristinamycin	pristinamycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Rifampicin	rifampin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Spectinomycin	spectinomycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Streptomycin	streptomycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Sulfamethoxazole	sulfamethoxazole	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Tedizolid	tedizolid	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Teicoplanin	teicoplanin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Telithromycin	telithromycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Temocillin	temocillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Ticarcillin	ticarcillin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested

Ticarcillin-clavulanic acid	ticarcillin_clav	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Tigecycline	tigecycline	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Tobramycin	tobramycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested
Vancomycin	vancomycin	Single choice list	S, I, R, NOT TESTED	Sensitivity or resistance of the antibiotic tested

Supplementary material 2. TSARA Clinical Questionnaire

Question	Name of the variable	Type of data	Format	Description
Date of visit in the room	dt_visit	Date	DD/MM/YYYY	Date of patient/clinician visit to clinical service
Gender	gender	Unique choice	Male, Female	Sex of the patient
Date of birth	dt_naiss	Date	DD/MM/YYYY	Patient's date of birth
Age	age	Numeric	---	Age of patient at hospital admission in years
Size	size	Numeric	---	Patient height (cm) at admission
Weight	weight	Numeric	---	Patient weight (kg) at admission
Status at birth	status_naiss	Single choice list	Premature, Born at term	Premature status at the birth of the child
Patient's residence	place_resid	Single choice list	Urban, Rural	Patient's primary place of residence on admission
Patient's region of residence	reg_resid	Text	-----	Patient's primary area of residence on admission
Date of admission to hospital	dt_adm_hosp	Date	DD/MM/YYYY	Date of hospital entry (TSARA participant)
Patient's origin	from	Single choice list	Home, Transfer to another hospital, Unknown	Patient's origin before admission to hospital
Diagnosis at admission	diag_adm	Single choice list	Infectious, Non-infectious, Unknown	Patient diagnosis on admission to hospital
Type of service	type_service	Single choice list	Medicine, Surgery, Intensive Care, Gyneco-Obstetrics, Pediatrics, Other	Type of service where the sample was taken
Respiratory rate (beats per minute)	freq_resp	Numeric	---	Patient's respiratory rate on admission
Heart rate (beats per minute)	freq_card	Numeric	---	Patient's heart rate on admission
Systolic blood pressure (mmHg)	pa_sys	Numeric	---	Systolic blood pressure on admission
Disorder of consciousness	awareness	Single choice list	Yes/No	Presence of disturbed consciousness at admission
Peripheral venous access	vvp	Single choice list	Yes/No	Placement of a PVV between admission and collection
Central venous access	vvc	Single choice list	Yes/No	Placement of a CVC between admission and

				collection
Urinary catheterization	probe_uro	Single choice list	Yes/No	Placement of a urinary catheter between admission and sampling
Oro-tracheal intubation	intubation	Single choice list	Yes/No	Intubation performed between admission and collection
Reason for collection	motif_pvt	Multiple choice list	List of reason for samples	Reason for collection
Date of onset of symptoms	dt_sympt	Date	DD/MM/YYYY	Date of onset of the first symptoms for which the sample was taken
Antibiotic history within 3 months prior to admission	atcd_atb	Single choice list	Yes/No	Use of ATB within 3 months of hospital admission
If yes, specify ATBs	type_atcd_atb	Multiple choice list	List of antibiotics	If yes, specify the type of ATB
Antibiotic therapy during the stay before sampling	atb_hosp	Single choice list	Yes/No	Antibiotic treatment prescribed between admission to hospital and sampling
If yes, specify ATBs	type_atb_hosp	Multiple choice list	List of antibiotics	If yes, specify the type of ATB
Antibiotic therapy after receiving the antibiogram	atb_post_atbg	Single choice list	Yes/No	Antibiotic treatment prescribed after receiving the antibiogram
If yes, specify ATBs	type_atb_post_atbg	Multiple choice list	List of antibiotics	If yes, specify the type of ATB
History of hospitalization in the 6 months preceding the hospitalization	atcd_hosp	Single choice list	Yes/No	History of hospitalization in the 6 months preceding the hospitalization
History of surgery in the 6 months preceding hospitalization	atcd_chir	Single choice list	Yes/No	History of surgery in the 6 months preceding hospitalization
Comorbidities	comorbidities	Multiple choice list	List of comorbidities	Presence of clinical comorbidities at admission
Other comorbidities	other_comorbidity	Free text		Other comorbidities

Supplementary material 3. TSARA III follow-up questionnaire

Question	Name of the variable	Type of data	Format	Description
Date of discharge from hospital	dt_end_hosp	Date	DD/MM/YYYY	End date of hospital stay or date of death if the patient has deceased.
Exit diagnosis	diag_hosp	Single choice list	List of diagnosis	
Patient status at discharge	hosp_output	Single choice list	Return home, Deceased, Transfer to another hospital	Patient status at the end of the hospital stay

Supplementary material 4. Description of facilities included in the TSARA project

	CHU ^a Joseph Ravoahangy Andrianavalona (JRA)	CHU Joseph Raseta Befalatanana (JRB)	CHU Mère-Enfant Tsaralalana (MET)	CHU Ambohimandra	CHU Anosiala	CHRR ^b Antsirabe	CHU Andrianjato	CHU Pzaga	CHU Morafeno	CHU Toliary
City	Antananarivo	Antananarivo	Antananarivo	Antananarivo	Anosiala	Antsirabe	Fianarantsoa	Mahajanga	Toamasina	Toliary
Type of hospital^c	Tertiary	Tertiary	Tertiary	Tertiary	Tertiary	Secondary	Tertiary	Tertiary	Tertiary	Tertiary
University/Regional hospital	Teaching	Teaching	Teaching	Teaching	Teaching	Regional	Teaching	Teaching	Teaching	Teaching
Hospital size (number of beds)	595 beds	450 beds	200 beds	44 beds	180 beds	70 beds	120 beds	303 beds	120 beds	40 beds
Hospital ownership	Public	Public	Public	Public	Public	Public	Public	Public	Public	Public
Type of population	Adult	Adult	Pediatrics	Adult & Pediatrics	Adult	Adult	Adult	Adult	Adult	Adult
Presence of ICU^d	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Strengthened bacteriology laboratory	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Diagnostic AST^e method	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)	Disk diffusion (EUCAST v. 2021)
Local guidelines on the use of antibiotics in place	None	None	None	None	None	None	None	None	None	None

^aCHU : Centre hospitalier Universitaire (Teaching hospital)

^bCHRR : Centre Hospitalier de Référence régionale (Regional hospital)

^c<https://www.who.int/publications/i/item/WHO-EMP-IAU-2018.01>

^dICU: Intensive Care Unit

^eAST: Antibiotic susceptibility testing

RESEARCH

Open Access



Antibiotic prescribing practices and antibiotic use quality indicators in Luang Prabang, Lao PDR: a point prevalence survey in a tertiary care hospital

Christelle Elias^{1,2,11*}, Nay Thi Ha^{3*}, Onanong Sengvilaipaserth³, Athip Phaychith³, Vilada Chansamouth^{4,5,6}, Valy Phongsavath⁷, Bounxou Keohavong⁸, Khamsay Detleuxay⁹, Phaylinh Maniphonh⁷, Thongphout Soukhaseum⁷, Philippe Vanhems^{1,2} and François-Xavier Babin¹⁰

Abstract

Context The increase and global dissemination of antibiotic resistance limit the use of antibiotics to prevent and treat infections. Implementing antibiotic stewardship programs guided by local data on prescription profiles is a useful strategy to reduce the burden of antibiotic resistance. The aim was to determine the prevalence of antibiotic use and guideline compliance at Luang Prabang provincial hospital, Lao PDR.

Methods A point prevalence survey of antibiotics was conducted among hospitalized patients admitted to Luang Prabang hospital (204 beds) in Lao PDR on May 25, 2023. All patients presenting at 8:00 AM were eligible. Sociodemographic data, indications for antibiotic use, and antibiotic prescriptions were collected from medical records using a paper-based questionnaire and entered into an electronic platform following WHO methodology. The prevalence of antibiotic use was determined.

Results Out of the 102 patients included, 60(58.8%) were undergoing antibiotic treatment, of which 33(55.0%) received combination therapy, and 7(10.5%) had two indications for antibiotic use. The highest prevalence was in the surgical ward (14/15, 93%) followed by general paediatrics (18/27, 67%). Out of the 100 antibiotic prescriptions, 47(47%) were for community-acquired infections, 26(26%) for surgical prophylaxis, 13(13%) for hospital-acquired infections and 5(5%) for medical prophylaxis. Twenty(20%) antibiotics were prescribed for obstetrics and gynaecology prophylaxis, 17(17%) for intra-abdominal infections, and 10(10.0%) for pneumonia treatment as well as bone, and joint infections. The main antibiotics prescribed were ceftriaxone 36(34.6%), metronidazole 18(17.3%), ampicillin 8(7.7%), and gentamicin 8(7.7%). Only 2(3%) samples were sent to the laboratory, one of which showed a positive culture for *Escherichia coli* Extended Spectrum β -Lactamase. According to the WHO Access Watch and Reserve classification,

*Correspondence:

Christelle Elias
christelle.elias@chu-lyon.fr
Nay Thi Ha
nay.thiha@fondation-merieux.org

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

55(52.9%) molecules belonged to the Access category, 47(49.1%) to the Watch category, and none to the Reserve category. Only 14.9% of antibiotic prescriptions were fully compliant with current guidelines.

Conclusion This study indicated a significant prevalence of antibiotic use and a very low compliance with guidelines at Luang Prabang provincial hospital, Lao PDR. This highlights an urgent need for comprehensive strategies at all levels to optimize antibiotic use in hospitals, emphasizing diagnostic improvements, and continued research to address the factors driving this excessive antibiotic usage and improve adherence to guidelines.

Keywords Antibiotic, Antibiotic stewardship, Guidelines, LMICs, Antibiotic resistance

Introduction

Antimicrobial resistance (AMR) stands as one of the most pressing global health concerns of our time. This phenomenon occurs when bacteria, parasites, viruses, or fungi are exposed to antimicrobial substances but remain resilient, rendering these medicines ineffective. It is a natural adaptive process for organisms, allowing them to change and evolve. However, the alarming reality is that existing resistance patterns are not only persisting but also proliferating, while new patterns continue to emerge worldwide [1]. The menace of multidrug-resistant infections intensifies the challenges. Patients affected by these resistant bacteria face poorer clinical outcomes and an elevated risk of death [1]. Moreover, they consume a disproportionate share of healthcare resources compared to patients battling non-resistant strains of the same bacteria. Beyond the immediate health implications, AMR carries significant economic burdens [2]. In cases where infections resist first-line drugs, costlier therapies become necessary, often involving extended hospital stays and prolonged treatments. This not only escalates healthcare expenses but also contributes substantially to the economic strain caused by diseases. Understanding the complexity of AMR reveals a web of interconnected causes. Over-prescribing and over-dispensing of antimicrobial drugs by healthcare professionals, non-compliance with treatment regimens, the prevalence of low-quality medicines, incorrect prescriptions, and poor infection prevention and control practices in healthcare facilities are all contributing factors. AMR is not a challenge with a single root cause; rather, it thrives due to a combination of inappropriate antimicrobial use, lack of effective surveillance systems, insufficient infection prevention and control measures, and a paucity of accessible, affordable, and rapid diagnostic tests. In response to this growing crisis, the World Health Organization (WHO) took a pivotal step by formulating the Global Action Plan (GAP) in 2015 [3]. The primary objective of the GAP is to ensure the prolonged efficacy of infectious disease treatment and prevention through the responsible use of quality-assured medicines. A critical facet of combating AMR lies in optimizing the use of antimicrobial agents, particularly antibiotics. Antibiotics encompass a wide array of subclasses and substances, each with its spectrum of

activity. They often target a range of pathogens, and bacteria can develop diverse resistance mechanisms against them. In essence, the inappropriate use of antibiotics is widespread, especially in low and middle-income countries (LMICs) where data on antibiotic consumption and use are scant. To address this information gap and inform effective policies, the WHO advocates for harmonized data collection and robust monitoring systems. Hospitals, with their diverse patient populations and high antibiotic usage, serve as invaluable settings for understanding antibiotic prescribing patterns. The concentration of patients needing antibiotics not only provides insights into prescription trends but also facilitates the implementation of targeted interventions to optimize antibiotic use. However, continuous data collection is a resource-intensive task, leading to the exploration of complementary surveillance methods such as point prevalence surveys (PPS) [4]. PPS, successfully employed in hospitals across the world, offer a snapshot of antibiotic use at a specific point in time [4]. The European Union and the United States have conducted regional surveys using this methodology. The WHO has endeavoured to develop a similar methodology tailored to the resources available in low and middle-income countries while ensuring comparability with data from high-income countries (HICs) [4]. This approach encourages standardization, allowing for meaningful comparisons of antibiotic use across various parameters, including time, hospitals, districts, countries, and regions. Research conducted in Western Pacific countries by the WHO, including Malaysia, Japan, China, and Vietnam, has revealed varying levels of antimicrobial usage in hospitals, ranging from 28.5 to 67.4% [5–8]. Encouraging appropriate antibiotic use across human, animal, and environmental sectors through coordinated activities within a One-health approach includes the initiation of antibiotic stewardship programs (ASPs) in healthcare settings [9, 10], with ASPs described as a coherent set of activities promoting the responsible use of antimicrobials [11]. Evaluating the quality of antibiotic prescribing patterns using PPS is a starting point for further improvements within ASPs.

The implementation of these PPS aligns seamlessly with national strategies, exemplified by the Lao People's Democratic Republic (PDR) National Action Plan for

AMR 2019–2023 and fits into the strategic objective 4, Action 4.2 [12]. By conducting these surveys, countries not only gather essential baseline data but also lay the foundation for tailored interventions and therefore improve local antibiotic prescription practices. These surveys can be periodically repeated, enabling countries to track progress, assess the impact of interventions, and ensure the effectiveness of their strategies. Indeed, Chansamouth et al. conducted repeated surveys over a 4-year period in Lao PDR, indicating a high prevalence of antibiotic use exceeding in majority 65% and proportions of compliance with guidelines below 30% [13].

In comparison with other healthcare facilities in Lao PDR [13], no estimation of the use of antibiotics has been done in Luang Prabang provincial hospitals. This study extends upon the previous survey rounds by performing a PPS at Luang Prabang provincial hospital, a tertiary care hospital located in the northern region of Lao PDR, as a component of a broader ASP, with the aim of establishing foundational data on all core variables outlined in the WHO PPS methodology [4]. The goal was to inform potential quality improvement initiatives that could be implemented in Luang Prabang and other hospitals across Lao PDR to improve antibiotic prescription practices. This dataset can be used as a foundation for developing and refining facility-specific antibiotic policies and provide basis for progress.

Methods

Study design and setting

A cross-sectional study using the WHO PPS protocol [4] on antibiotic use was conducted on May 25, 2023 in the provincial hospital of Luang Prabang, Lao PDR, a 204-bed tertiary teaching hospital. This hospital is an acute care hospital located in the suburban area of the city of Luang Prabang (population 70,000 inhabitants), fourth city in Lao PDR in the Luang Prabang province (467 000 population in 2020). The provincial hospital of Luang Prabang encompasses an adult hospital (150 beds), as well as a 54-bed paediatric hospital (age limit 15 years old) and is equipped with one Intensive Care Unit, one infectious diseases ward, one surgical ward, one gynaecology and obstetrics ward, one internal medicine, one paediatrics and one neonatal unit with a pharmacy and a laboratory. In 2023, 10 232 patients were admitted amounting to 40 011 patient bed days. As described in the WHO protocol, we only included inpatient wards in this survey and we excluded emergency departments and day surgery wards. Data were collected for inpatients admitted to all hospital wards and present at 8.00 a.m. on the day of the survey (denominator). Detailed patient and antibiotic information was collected for patients who received an antibiotic at 8:00 a.m. on the day of the PPS (numerator).

Data collection

Six auditors (three local physicians, two epidemiologists, one microbiologist) conducted this one-day survey, during which all included wards had to be audited once. The auditors were trained on the methodology and data collection prior to the start of the survey. Three forms were completed where the first one gathered hospital-level data, the second collected ward-level data such as the total number of inpatients and the last collected patient-level data. Data for the hospital-level characteristics and hospital questionnaire were obtained from the hospital management department. Ward-level data were obtained from each visited ward. For each patient who was prescribed and received at least one antibiotic at 8:00 a.m. on the day of the PPS, we gathered data including baseline patient characteristics (age, gender, date of admission, surgery since admission and presence of invasive devices), the prescribed antibiotics, their diagnosis according to a predefined list, and whether it concerned treatment for a community-acquired infection (CAI) or healthcare-associated infection (HAI) or prophylactic prescribing (for both medical or surgical prophylaxis). Medical prophylaxis included prevention of opportunistic infections in immunocompromised patients (e.g. HIV/AIDS patients), prevention of bacterial infections in patients with late-stage cirrhosis, upper gastrointestinal bleeding, and acute necrotizing pancreatitis. The nature and duration of antibiotic prophylaxis and curative antibiotic therapy were also collected. A microbiology form was also completed in case a sample was sent to the laboratory for bacterial confirmation and Antimicrobial Susceptibility Testing (AST) results. The WHO Anatomical Therapeutic Chemical (ATC) classification system (2022 version) [14] was used to classify the antibiotics as well as the Access, Watch and Reserve (AWaRe) classification developed by WHO [15, 16]. The survey team collected from the medical records. Data were recorded in a paper-based worksheet prior to entering them into an online-based application provided by WHO (<https://amc-survey.voozahoo.net/amcsrv/>) for anonymised data entry.

Antibiotic use quality indicators

Quality indicators for antibiotic use encompass adherence to guidelines. In this study, Lao antimicrobial prescribing guidelines were used to assess guideline compliance in both adult and children [17, 18]. The definition of compliance was adapted from Willemsen et al. [19] and was evaluated based on: (i) the diagnosis of an infection, (ii) whether prophylaxis was indicated, (iii) whether an antibiotic was warranted based on the diagnosis (iv) the type of population (adult vs. paediatrics). Multiple antibiotics started on the same day for the same indication were considered combination therapy. Compliance

to guidelines was categorized into three levels: full compliance, indicating the appropriate selection of antibiotics for an infection or prophylaxis; partial compliance, signifying at least one appropriate antibiotic choice in cases of combination therapy; and non-compliance, encompassing the administration of unnecessary antibiotics or deviations from national guidelines.

Data analysis

This study served as a baseline exploratory analysis, aiming to generate hypotheses for future quality improvement initiatives on antibiotic use, given the limited number of patients included in the dataset. The prevalence rate of antibiotic use was defined as the proportion of total inpatients who were receiving antibiotics on the survey date divided by the total number of patient hospitalized at 8.00 a.m. We analysed the most commonly prescribed antibiotics and the reasons for use, categorized by ward type, indication for antibiotic use and diagnosis. Categorical variables were displayed as proportions. Descriptive and univariate statistical analyses were performed using Stata version 18.0 (StataCorp LLC, College Station, TX, USA). Univariate analyses were performed using the Chi-squared test or Fisher's exact test for qualitative variables, and the Student's *t* test or the Mann-Whitney test (depending on the nature of the variable or the size of the sample) for quantitative variables. Odds-ratio with 95% confidence intervals were estimated. No multivariate analysis was performed due to the exploratory nature of this survey and the small sample size. A significance level of less than 0.05 is considered associated.

Results

On May 25, 2023, a total of 102 patients were included in the survey with 58 (56.9%) at Luang Prabang adult hospital and 44 (43.1%) at Luang Prabang children's hospital. Antibiotics were prescribed in 60 (58.8%) of the patients with 67 indications for antibiotic treatment. Twenty seven (45.0%) inpatients received one antibiotic, 25 (41.7%) received two antibiotics and 8 (13.3%) received three antibiotics. The highest prevalence of antibiotic use was in the general surgery ward (14/15, 93.3%) followed by the general pediatric ward (18/25, 66.7%). Only two (3%) samples were sent to the bacteriology laboratory, of which one showed a positive bacterial culture for *Escherichia coli* Extended Spectrum β -Lactamase (ESBL). Figure 1 shows the flow chart of the survey. Table 1 provides baseline characteristics of the data collected in the survey. The sex ratio was equal to 1.08 with a median age of 32.5 years old, Interquartile range (IQR)[27.5–52] in the adult population and 10 years old, IQR [0–15] in the pediatric population. The prevalence of antibiotic use did not differ by gender but differed significantly with

patients who underwent surgery since hospital admission ($p < 0.001$) and by type of ward ($p = 0.001$).

Antibiotic use and prescriptions patterns

Table 2 offers insight into the classification of antibiotics prescribed by ATC therapeutic subgroup and chemical subgroup. In total, 100 antibiotics were prescribed of these, third-generation cephalosporins accounted for 41 (41.0%) of all antibiotic prescriptions. The four main antibiotics prescribed at the hospital were respectively ceftriaxone (36, 36.0%), metronidazole (18, 18.0%), ampicillin (8, 8.0%), and gentamicin (8, 8.0%). The prevalence of vancomycin and meropenem use was 4 (4.0%) and 3 (3.0%), respectively. Eighty two (82%) antibiotic prescriptions were administered parenterally. Also, more than one fifth of the molecules were broad-spectrum antibiotics (81, 81.0%). Ceftriaxone was the most prevalent antibiotic prescribed in the gynecology ward, ICU, general medicine and surgery ward. Sulfamethoxazole-trimethoprim was the most prevalent antibiotic prescribed in the infectious diseases ward, as a prophylactic treatment against pneumocystosis and toxoplasmosis for HIV patients. Ampicillin was the most prevalent antibiotic prescribed in neonatology ward. According to the WHO AWaRe classification, 55 (55.0%) molecules belonged to the Access category, 47 (47.0%) to the Watch category, and none to the Reserve category. Out of the 100 prescriptions, 47 (47.0%) were for community-acquired infections, 26 (26.0%) for surgical prophylaxis, 13 (13.0%) for hospital-acquired infections involving mainly clinical sepsis, 5 (38.5%) and 5 (5.0%) for medical prophylaxis. Furthermore, among the total antibiotic prescriptions, 20 (20.0%) were for obstetrics and gynaecology prophylaxis, 17 (17.0%) were for intra-abdominal infections, of which 12 (70.6%) were community-acquired and 10 (10.0%) were for pneumonia treatment as well as bone, and joint infections (Table 3). More than half of the antibiotics (58, 58.0%) were prescribed for the adult population (Supplementary material 1).

Table 4 demonstrates the distribution of antibiotic by ATC Code and duration of antibiotic use in surgical prophylaxis. Cefazolin (ATC Code: J01DB04) was prescribed once, exclusively in septic arthritis. Ceftriaxone (ATC Code: J01DD04) together with Metronidazole (ATC Code: J01XD01) and Gentamicin (ATC Code: J01GB03) were the most commonly prescribed antibiotics in obstetrics and gynaecology surgical prophylaxis with multiple doses administered in more than one day.

Antibiotic prescribing quality indicator

Table 5 presents compliance rates with antibiotic prescribing guidelines for different diagnoses in pediatric and adult patients. Sixty one (91.0%) antibiotic prescriptions were assessed and 6 (8.9%) were not due to missing

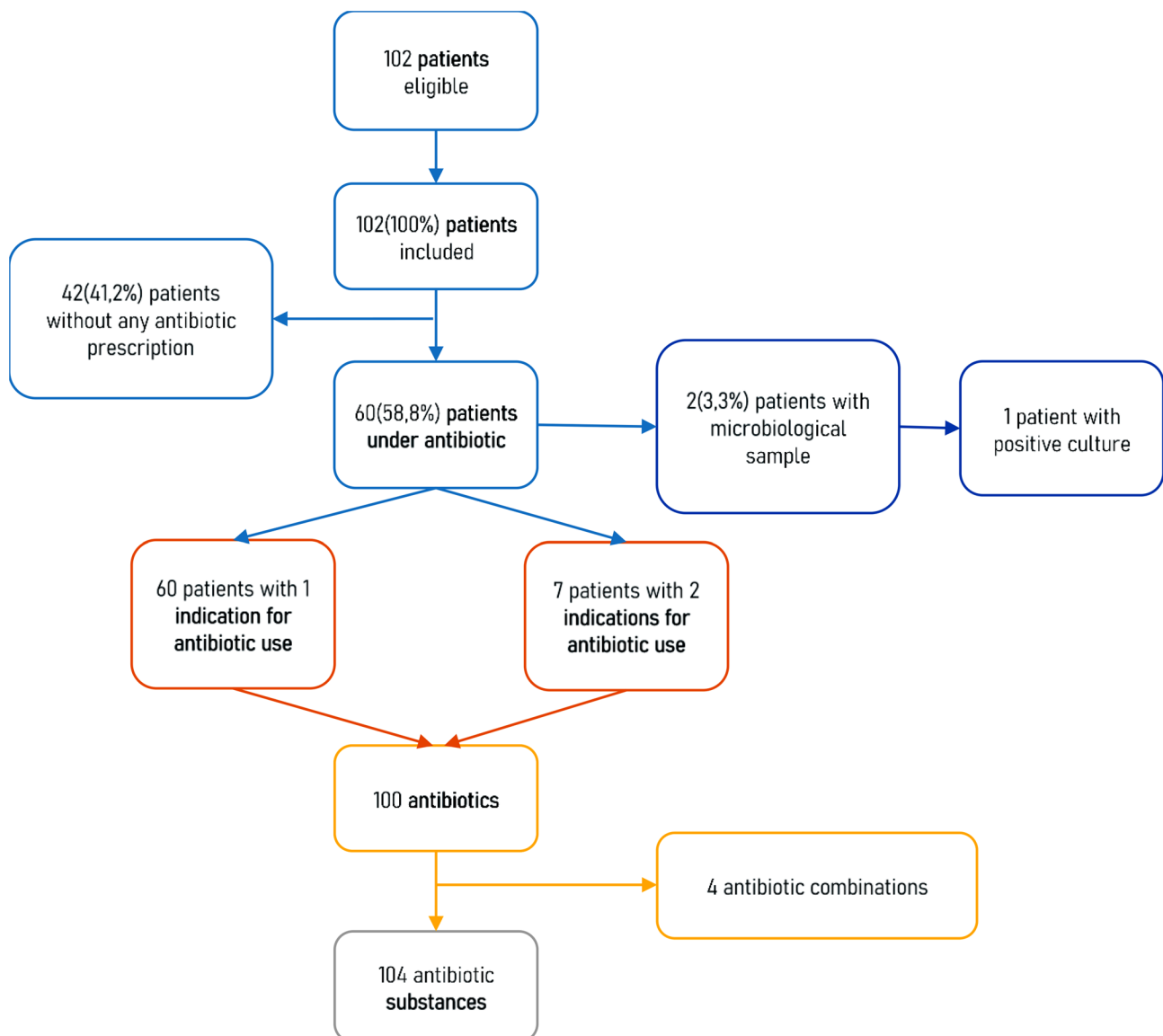


Fig. 1 Flow chart of the data collected, Point Prevalence Survey on antibiotic use, Luang Prabang provincial hospital, Lao PDR, 2023

or undefined diagnosis. Overall, 9 (14.8%) antibiotic prescriptions were fully compliant, 10 (16.4%) were partially compliant with guidelines and 42 (68.8%) antibiotic prescriptions were not compliant. Compliance (partial and full) with guidelines had a higher proportion in pediatric wards (36.6%) than in adults wards (25.8%). Antibiotic treatments for central nervous system infections and clinical sepsis were the most compliant antibiotic prescriptions. However, none of antibiotic prescription were compliant in obstetric infections, febrile neutropenia, wound surgical site infections, surgical site infection of bone and joint or Systemic Inflammatory Response Syndrome. The multiple correspondence analysis plot in Fig. 2 illustrated that antibiotic prescriptions for healthcare-associated clinical sepsis in neonatology were the most compliant with guidelines whereas surgical

prophylaxis in the prevention of surgical site infection in the gynecology and obstetrics ward appeared to be no compliant with guidelines. A prescription of ceftriaxone (OR=0.22, IC95%[0.07–0.73], $p < 0.039$) and the Watch group of the AWaRe classification (ref : Access group, OR=0.23, IC95%[0.07–0.74], $p = 0.049$) were significantly associated with a low compliance with guidelines, compared to an ampicillin prescription which was associated with a significantly higher compliance (OR=9.23, IC95% [1.66–51.46], $p = 0.011$) with guidelines.

Discussion

This study, the first using the WHO PPS methodology in Lao PDR indicated a prevalence of antibiotic use at Luang Prabang provincial hospital of 58.8%, which demonstrated lower results to surveys conducted in other

Table 1 Description of the data, Point Prevalence Survey on antibiotic use, Luang Prabang provincial hospital, Lao PDR, 2023

Variables	n	%
Number of screened hospital charts	102	(100)
Number of patients with antibiotics	60	(58.8)
Type of ward		
Pediatrics	27	(26.5)
Internal medicine	24	(23.5)
Obstetrics and Gynaecology	21	(20.6)
Surgery	15	(14.7)
Neonatology	11	(10.8)
Intensive Care Unit	2	(2)
Infectious diseases ward	2	(2)
Gender		
Men	53	(52.0)
Women	49	(48.0)
Median age [IQR] in years	28	[15–43]
In the adult population	33	[28–52]
In the pediatric population	10	[0–15]
Age category		
≤ 1 year	15	(14.7)
> 1–5 years	3	(2.9)
> 5–15 years	20	(19.6)
> 15 years	64	(62.7)
Median delay between date of admission and date of survey [IQR] in days	2	[1–5]
History of surgery since hospital admission	21	(20.6)
Invasive devices		
Peripheral vascular catheter	68	(66.7)
Urinary catheter	2	(2.0)
Intubation	1	(1.0)
Central vascular catheter	0	

IQR : Interquartile range

hospitals in Lao PDR where the prevalence was equal to 69.7%, 74.3% and 72.9% in 2020, 2021 and 2022, respectively [20]. However, it's worth noting that the overall prevalence of antibiotic use estimated at Luang Prabang provincial hospital exceeded the one reported in hospitals in high income countries where the prevalence does not reach 50% [21]. The proportion of antibiotic use varied from 37% in East and South Asian countries (29 hospitals) to 42% in nine west and central Asian countries (27 hospitals) [21]. The higher prevalence of antibiotic prescribing observed in this survey, as well as in surveys conducted in other hospitals in LMICs, in comparison to HICs, may be indicative of a greater burden of infectious diseases, more severe illnesses, or less stringent antibiotic prescribing policies.

Less than 15% of antibiotic prescriptions were fully compliant with current recommendations [17, 18], which was half as low as previous estimations in other

healthcare facilities in Lao PDR [13], or to other South-east Asian countries [6, 8]. Such low estimations might be explained by a lack of information about the guidelines, and by limited access to antibiotics in Luang Prabang hospital or by shortages which occurred at the time of the survey of ciprofloxacin, cephalexin and doxycycline which may have hampered the prescription of these drugs, recommended in the guidelines. There is clear evidence that adherence to guideline improves antibiotic use [22]. Better dissemination of the guidelines together with increased awareness, education and policy engagement might also assist prescribers in their clinical decision-making and therefore optimize the use of antibiotics.

Interestingly, this study revealed a higher proportion of antibiotic prescriptions for both medical and surgical prophylaxis compared to several other studies outside Lao PDR [23, 24]. However, this study did not delve into the reasons for antibiotic use for prophylactic purposes, warranting further investigation to determine whether the current proportion of antibiotic use allocated to prophylaxis is appropriate or necessitates intervention. Notably, prescriptions for treating hospital-acquired infections were lower in this study compared to other settings but associated with a better compliance with guidelines. Surprisingly, the majority of antibiotics at Luang Prabang hospitals were administered via the parenteral route. This pattern is consistent with previous estimations [13] and with a 2017 study conducted in Belgian acute care hospitals, where antibiotics were administered parenterally to 64.6% of patients [25]. It is likely that the high proportion of parenteral antibiotic administration at is partly attributed to the frequent use of ceftriaxone, metronidazole, and other parenteral antibiotics for which no equivalent oral formulations are available [26]. This prescribing pattern may also be attributed to the population's belief in the superior efficacy of parenterally administered medicines. However, studies have shown that oral treatments can reduce the risk of hospital-acquired infections and offer both clinical and economic benefits [27]. Nonetheless, regular clinician review of the necessity for parenteral therapy could promote the increased use of oral treatment when appropriate and therefore reduce the burden of AMR.

The widespread use broad-spectrum antibiotics under the Watch category of the WHO AWaRe classification [16] – mainly third-generation cephalosporins –aligns with findings from other antibiotics use surveys conducted in Asian and African countries but contrasts with the higher use of narrow-spectrum penicillins and penicillin-enzyme inhibitor combinations observed in the 2015 Global-PPS [21]. High levels of use of third-generation cephalosporins meaningfully drive the increase in ESBL-producing Enterobacteriaceae, also in Lao PDR [28]. Chansamouth et al. showed that the proportion of

Table 2 Classification of antibiotics prescribed by Anatomical Therapeutic Chemical classification system therapeutic subgroup and chemical subgroup, Point Prevalence Survey on antibiotic use, Luang Prabang hospital, Lao PDR, 2023

Antibacterial for systemic use	Spectrum	ATC code	AWaRe	Total		GynObs		ICUMix		Med-Gen		MedId		PedGen		PedNeo		Surgery	
				n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Ceftriaxone	Broad	J01DD04	Watch	36	(36.0)	10	(43.5)	1	(100)	5	(71.4)	1	(25.0)	7	(25.0)	1	(7.1)	11	(47.8)
Metronidazole (IV)	Broad	J01XD01	Access	17	(17.0)	6	(26.1)	0		1	(14.3)	0		1	(3.6)	2	(14.3)	7	(30.4)
Ampicillin	Narrow	J01CA01	Access	8	(8.0)	0		0		0		0		2	(7.1)	6	(42.9)	0	
Gentamicin	Broad	J01GB03	Access	8	(8.0)	5	(21.7)	0		0		0		0		1	(7.1)	2	(8.7)
Cloxacillin	Narrow	J01CF02	Access	6	(6.0)	0		0		0		0		6	(21.4)	0		0	
Cefotaxime	Broad	J01DD01	Watch	5	(5.0)	0		0		0		0		1	(3.6)	4	(28.6)	0	
Sulfamethoxazole/Trimethoprim	Broad	J01EE01	Access	4	(4.0)	0		0		0		2	(50.0)	2	(7.1)	0		0	
Vancomycin (IV)	Broad	J01XA01	Watch	4	(4.0)	0		0		0		0		4	(14.3)	0		0	
Meropenem	Broad	J01DH02	Watch	3	(3.0)	0		0		0		0		1	(3.6)	0		2	(8.7)
Doxycycline	Broad	J01AA02	Access	2	(2.0)	1	(4.3)	0		0		1	(25.0)	0		0		0	
Cefalexin	Narrow	J01DB01	Access	2	(2.0)	1	(4.3)	0		0		0		1	(3.6)	0		0	
Amoxicillin	Narrow	J01CA04	Access	1	(1.0)	0		0		0		0		0		0		1	(4.3)
Phenoxyethylpenicillin	Narrow	J01CE02	Access	1	(1.0)	0		0		0		0		1	(3.6)	0		0	
Cefazolin	Narrow	J01DB04	Access	1	(1.0)	0		0		0		0		1	(3.6)	0		0	
Azithromycin	Broad	J01FA10	Watch	1	(1.0)	0		0		1	(14.3)	0		0		0		0	
Metronidazole (O)	Broad	P01AB01	Access	1	(1.0)	0		0		0		0		1	(3.6)	0		0	
Total				100	(100)	23	(100)	1	(100)	7	(100)	4	(100)	28	(100)	14	(100)	23	(100)

ATC code: Anatomical Therapeutic Chemical classification code; GynObs: Obstetrics and Gynecology ward; ICUMix: Intensive Care Unit; MedGen: Internal Medicine ward; MedId: Infectious Disease ward; PedGen: Paediatrics ward; PedNeo: Neonatology ward; IV: Intravenous route; O: Oral route

Table 3 Most prevalent diagnoses for antibiotic prescription by hospital, Point Prevalence Survey on antibiotic use, Luang Prabang hospital, Lao PDR, 2023

Diagnosis	Antibiotics		Therapeutic use				Prophylactic use				Other indication for antibiotic use	
	Total		CAI		HAI		MP		SP			
	n	%	n	%	n	%	n	%	n	%	n	%
OBGY	20	(20.0)	0		0		0		20	(76.9)	0	
IA	17	(17.0)	12	(25.5)	3	(23.1)	0		2	(7.7)	0	
CSEP	13	(13.0)	7	(14.9)	5	(38.5)	0		0		1	(11.1)
PNEU	10	(10.0)	8	(17.0)	0		2	(40.0)	0		0	
BJ-O	10	(10.0)	9	(19.1)	0		1	(20.0)	0		0	
SST-O	6	(6.0)	2	(4.3)	2	(15.4)	2	(40.0)	0		0	
CNS	4	(4.0)	4	(8.5)	0		0		0		0	
SST-SSI	4	(4.0)	0		2	(15.4)	0		2	(7.7)	0	
UND	4	(4.0)	0		0		0		0		4	(44.4)
GI	3	(3.0)	1	(2.1)	0		0		0		2	(22.2)
ENT	2	(2.0)	0		1	(7.7)	0		1	(3.8)	0	
FN	2	(2.0)	2	(4.3)	0		0		0		0	
BJ-SSI	1	(1.0)	0		0		0		1	(3.8)	0	
PYE	1	(1.0)	1	(2.1)	0		0		0		0	
SIRS	1	(1.0)	1	(2.1)	0		0		0		0	
Missing	2	(2.0)	0		0		0		0		2	(22.2)
Total	100		47		13		5		26		9	

CAI: Community-acquired infection; HAI: Hospital-acquired infection; MP: Medical prophylaxis; SP: Surgical prophylaxis; OBGY: Obstetric or gynaecological infections; IA: Intra-abdominal sepsis, including hepatobiliary; CSEP: Clinical sepsis (suspected bloodstream infection without lab confirmation/results are not available, no blood cultures collected or negative blood culture), excluding febrile neutropenia; PNEU: Pneumonia; BJ-O: Septic arthritis, osteomyelitis, not related to surgery; SST-O: Cellulitis, wound, deep soft tissue not involving bone, not related to surgery; CNS: Infections of the central nervous system; SST-SSI: Surgical site infection involving skin or soft tissue but not bone; UND: Completely undefined; site with no systemic inflammation; GI: Gastrointestinal infections (e.g. salmonellosis, antibiotic-associated diarrhoea); ENT: Infections of ear, nose, throat, larynx and mouth; FN: Febrile neutropenia or other form of manifestation of infection in immunocompromised host (e.g. HIV, chemotherapy, etc.) with no clear anatomical site; BJ-SSI: Septic arthritis, osteomyelitis of surgical site; PYE: Symptomatic upper urinary tract infection (e.g. pyelonephritis); SIRS: Systemic inflammatory response with no clear anatomical site

Table 4 Distribution of antibiotic by ATC code and duration of antibiotic use in surgical prophylaxis, Point Prevalence Survey on antibiotic use, Luang Prabang hospital, Lao PDR, 2023

Antibacterial for systemic use	ATC Code	Total		BJ-SSI		ENT		IA		OBGY		SST-SSI	
		n	%	One dose		Multiple doses on more than one day		Multiple doses on more than one day		Multiple doses on more than one day		Multiple doses on more than one day	
				n	%	n	%	n	%	n	%	n	%
Cefazolin	J01DB04	1	(3.8)	1	(100)								
Ceftriaxone	J01DD04	12	(46.2)			1	(100)	1	(50.0)	9	(45.0)	1	(50.0)
Gentamicine	J01GB03	6	(23.1)							5	(25.0)	1	(50.0)
Metronidazole	J01XD01	7	(26.9)					1	(50.0)	6	(30.0)		
Total		26	(100)	1	(100)	1	(100)	2	(100)	20	(100)	2	(100)

ATC code: Anatomical Therapeutic Chemical classification code; BJ-SSI: Septic arthritis, osteomyelitis of surgical site; ENT: Infections of ear, nose, throat, larynx and mouth; IA: Intra-abdominal sepsis, including hepatobiliary; OBGY: Obstetric or gynaecological infections; SST-SSI: Surgical site infection involving skin or soft tissue but not bone

ESBL-producing *Escherichia coli* among cultured isolates of *E.coli* in blood culture is increasing year on year, going from 7% in 2004 to 35% in 2016 [13]. One reason for the frequent prescription of broad-spectrum antibiotics in this study may be the high prevalence of antibiotic resistance among several key pathogens as well as the availability of these drugs in hospitals. The judicious use of broad-spectrum antibiotics may be supported by an increased utilization of high-quality clinical microbiology laboratory services [29]. These results can be employed collectively to inform empiric therapy guidelines within the hospital and to rationalize the treatment of individual patients [30]. Such guidelines ought to align with the recommendations provided by the WHO essential medicines list, which advocates for the use of antibiotics categorized under the Access group which typically exhibit a narrow spectrum of activity [16, 31].

The 2015 Global-PPS demonstrated that across 53 countries, 37.9% of therapeutic antimicrobial prescribing was based on microbiology results [21]. In contrast, in this survey, we found that less than 5% of prescriptions at Luang Prabang hospital were based on microbiology results highlighting how neglected laboratory services are in this setting. The high prevalence of broad-spectrum therapies may be linked to the limited use of diagnostic services at the hospitals. Therefore, we suggest strengthening clinical microbiology services, encouraging clinicians to utilize them, and preparing, disseminating, and regularly updating guidelines on antibiotic use to inform empiric treatment decisions at each hospital. Clinical practice guidelines have the potential to improve quality of care through improving decision making and antibiotic prescription. These guidelines are particularly important in areas with limited laboratory and specialist capacity [22].

International and national guidelines for surgical prophylaxis recommend the administration of a single dose

of narrow-spectrum antibiotics within the 24-hour pre-operative period [17, 32]. However, surgical prophylaxis at Luang Prabang hospital was often prescribed for durations exceeding one day and frequently involved the use of broad-spectrum antibiotics such as ceftriaxone and metronidazole. Prolonged surgical prophylaxis does not benefit the patient but increases the risk of antibiotic resistance and adverse events, including acute kidney injury and *Clostridioides difficile* infection [33]. We suggest that adopting and implementing surgical prophylaxis guidelines at Luang Prabang provincial hospital represents a vital opportunity to enhance patient safety and control AMR.

As many LMICs, Lao PDR struggles with implementing strategies to combat AMR, in particular in hospital settings. Antibiotic stewardship activities to promote the rational use of antimicrobials in hospitals remain scarce and to our knowledge no such activity was in place over this survey period in Luang Prabang provincial hospital. Strengthening and empowering hospital drug and therapeutics committees, along with pharmacists, to oversee antibiotic use and propose interventions for adherence to guidelines, would represent a significant step forward.

This study has several limitations. Firstly, due to the cross-sectional design, we collected only antibiotic prescribing data on each ward for a single day, making it difficult to ascertain whether the observed prescribing practices were representative of typical practices. Secondly, we did not measure the severity and acuity of infection, the duration of antibiotic use, or whether clinical staff altered the route of antimicrobial administration over time or adjusted antibiotic prescriptions based on microbiology test results after the ward surveys. Thirdly, guideline compliance was assessed in comparison with national guidelines, as hospital-specific treatment guidelines were not available. Also resistance patterns in Luang Prabang might differ from other healthcare facilities in

Table 5 Guidelines compliance assessment of antibiotic prescriptions (n=61)

Diagnosis	Pediatrics						Adults						Total							
	None		Partial		Full		None		Partial		Full		None		Partial		Full		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
BJ-O	5	(83.3)	0		1	(16.7)	1	(100)	0		0		6	(85.7)	0		1	(14.3)	7	
BJ-SSI	1	(100)	0		0		0		0		0		1	(100)	0		0		1	
CNS	1	(50.0)	0		1	(50.0)	0		1	(100)	0		1	(33.3)	1	(33.3)	1	(33.3)	3	
CSEP	4	(44.4)	5	(55.6)	0		0		0		0		4	(44.4)	5	(55.6)	0		9	
ENT	1	(100)	0		0		0		0		1	(100)	1	(50.0)	0		1	(50.0)	2	
FN	1	(100)	0		0		0		0		0		1	(100)	0		0		1	
GI	0		1	(100)	0		1	(100)	0		0		1	(50.0)	1	(50.0)	0		2	
IA	0		1	(100)	0		6	(75.0)	2	(25.0)	0		6	(66.7)	3	(33.3)	0		9	
OBGY	0		0		0		9	(100)	0		0		9	(100)	0		0		9	
PNEU	3	(75.0)	0		1	(25.0)	2	(40.0)	0		3	(60.0)	5	(55.6)	0		4	(44.4)	9	
PYE	0		0		0		0		0		1	(100)	0		0		1	(100)	1	
SIRS	1	(100)	0		0		0		0		0		1	(100)	0		0		1	
SST-O	2	(66.7)	0		1	(33.3)	2	(100)	0		0		4	(80.0)	0		1	(20.0)	5	
SST-SSI	0		0		0		2	(100)	0		0		2	(100)	0		0		2	
Total	19	(63.3)	7	(23.3)	4	(13.3)	23	(74.2)	3	(9.7)	5	(16.1)	42	(68.9)	10	(16.4)	9	(14.8)	61	

OBGY: Obstetric or gynaecological infections; IA: Intra-abdominal sepsis, including hepatobiliary; CSEP: Clinical sepsis (suspected bloodstream infection without lab confirmation/results are not available, no blood cultures collected or negative blood culture), excluding febrile neutropenia; PNEU: Pneumonia; BJ-O: Septic arthritis, osteomyelitis, not related to surgery; SST-O: Cellulitis, wound, deep soft tissue not involving bone, not related to surgery; CNS: Infections of the central nervous system; SST-SSI: Surgical site infection involving skin or soft tissue but not bone; UND: Completely undefined; site with no systemic inflammation; GI: Gastrointestinal infections (e.g. salmonellosis, antibiotic-associated diarrhoea); ENT: Infections of ear, nose, throat, larynx and mouth; FN: Febrile neutropenia or other form of manifestation of infection in immunocompromised host (e.g. HIV, chemotherapy, etc.) with no clear anatomical site; BJ-SSI: Septic arthritis, osteomyelitis of surgical site; PYE: Symptomatic upper urinary tract infection (e.g. pyelonephritis); SIRS: Systemic inflammatory response with no clear anatomical site

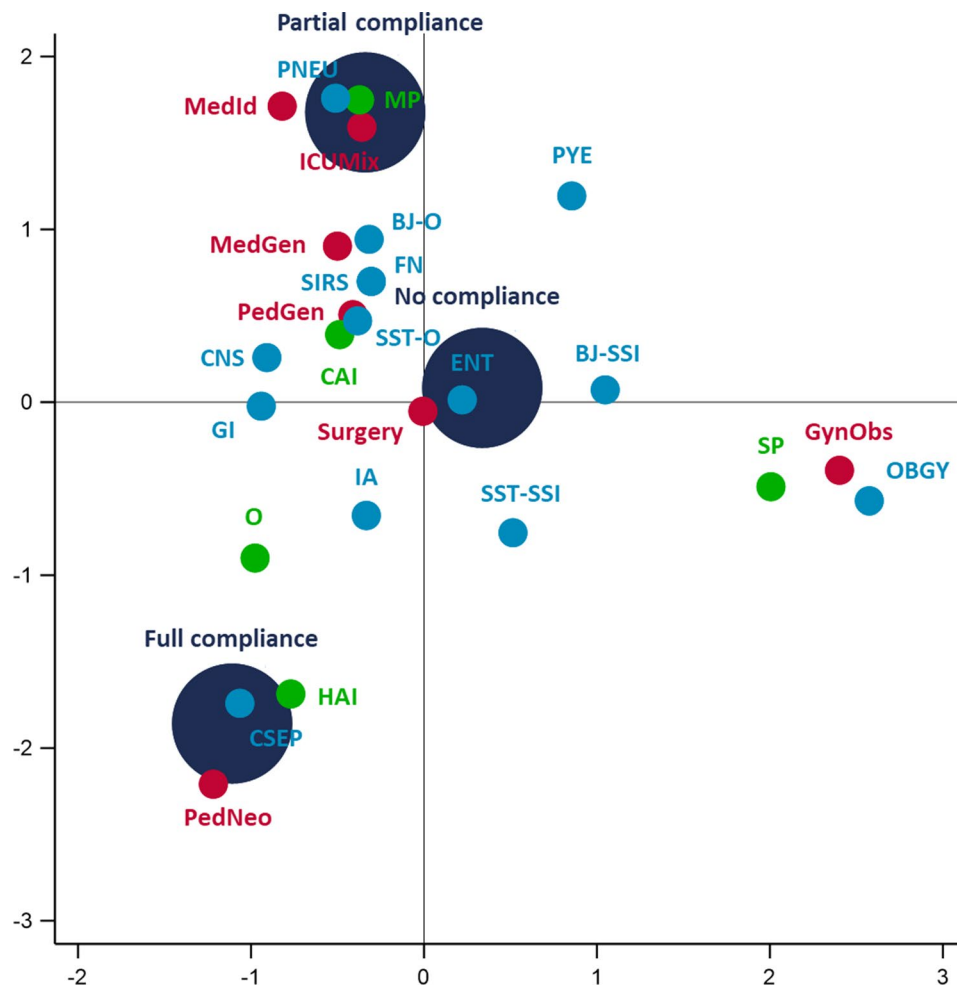


Fig. 2 Multiple correspondence analysis coordinate plot of guidelines compliance by indication, diagnosis and type of ward. Obs: Obstetrics and Gynecology ward; ICUMix: Intensive Care Unit; MedGen: Internal Medicine ward; MedId: Infectious Disease ward; PedGen: Paediatrics ward; PedNeo: Neonatology ward; CAI: Community-acquired infection; HAI: Hospital-acquired infection; MP: Medical prophylaxis; SP: Surgical prophylaxis; OBGY: Obstetric or gynaecological infections; IA: Intra-abdominal sepsis, including hepatobiliary; CSEP: Clinical sepsis (suspected bloodstream infection without lab confirmation/results are not available, no blood cultures collected or negative blood culture), excluding febrile neutropenia; PNEU: Pneumonia; BJ-O: Septic arthritis, osteomyelitis, not related to surgery; SST-O: Cellulitis, wound, deep soft tissue not involving bone, not related to surgery; CNS: Infections of the central nervous system; SST-SSI: Surgical site infection involving skin or soft tissue but not bone; GI: Gastrointestinal infections (e.g. salmonellosis, antibiotic-associated diarrhoea); ENT: Infections of ear, nose, throat, larynx and mouth; FN: Febrile neutropenia or other form of manifestation of infection in immunocompromised host (e.g. HIV, chemotherapy, etc.) with no clear anatomical site; BJ-SSI: Septic arthritis, osteomyelitis of surgical site; PYE: Symptomatic upper urinary tract infection (e.g. pyelonephritis); SIRS: Systemic inflammatory response with no clear anatomical site

Lao PDR. Adherence to guidelines for antibiotic use was determined solely by the selection of antibiotics, without considering dosage or duration, potentially leading to an overestimation of the appropriateness of antibiotic use. Finally, only mandatory variables of the WHO protocol were collected in this survey.

Conclusion

This study revealed a prevalent use of antibiotics, particularly broad-spectrum ones with low adherence to guidelines. These findings underscore the importance of raising awareness and providing support for antibiotic stewardship program interventions in the hospital setting. The data collected in our survey can serve as a

foundational reference point for a series of PPSs to track antibiotic prescribing patterns and gauge the impact of ASP interventions over time in Lao PDR. To ensure the effectiveness of ASPs, it is imperative to allocate resources for the review and development of evidence-based antibiotic prescribing guidelines adapted to local resistance patterns. Making standard guidelines available, endorsed by national health authorities, may instill confidence in clinicians regarding best practices, thereby enhancing the accuracy of diagnoses and antibiotic treatments. Additionally, there should be efforts to improve the documentation of antibiotic prescriptions, boost the utilization of microbiology testing, and provide support for microbiological laboratory services. Finally, the

implementation and success of ASP interventions need to be thoroughly evaluated.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12879-024-09614-4>.

Supplementary Material 1

Acknowledgements

The authors thank Dr Arno Muller and Dr Martina Escher from the WHO HQ and Dr Yu Lee Park from the WHO Lao office for their support in implementing this survey in Lao PDR. The authors thank Pr Elisabeth Ashley and Dr Tamalee Roberts from Lao-Oxford-Mahosot Hospital Wellcome Trust Research Unit for their input related to this survey. The authors thank Dr Phonevixay Vilaylangsy from the Department of Communicable Diseases and Control of the Ministry of Health of Lao PDR. The authors thank Dr Elodie Dorangeon for her help in the data collection.

Author contributions

Christelle Elias designed the study, analysed the data and drafted the first version of the manuscript. Christelle Elias, Vilada Chansamouth, Onanong Sengvilaipaserth, Valy Phongsavath and Phaylinh Maniphonh participated in the data collection. Christelle Elias, Nay Thi Ha, Onanong Sengvilaipaserth, Athip Phaychith, Vilada Chansamouth, Valy Phongsavath, Bounxou Keohavong, Khamsay Detleuxay, Phaylinh Maniphone, Thongphout Soukhaseum, Philippe Vanhems and François-Xavier Babin read and approved the final version of the manuscript.

Funding

This work was funded by the Laos Country Grant 2 of the Fleming Fund FF86-492. The funders of this study had no role in the study design, data collection, analysis, interpretation or writing the manuscript.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request. The datasets were also shared with WHO Headquarters for global analysis.

Declarations

Ethics approval and consent to participate

Ethics approval and informed consent by individual patient were not required for monitoring antibiotic use in Lao PDR, as it was implemented as a routine surveillance activity. No patient identifiable data were collected during the survey, which was conducted with approval from Luang Prabang hospital, the National Ethical Committee for Health Research and the Lao Ministry of Health. In addition, according to the WHO Methodology for Point Prevalence Survey on Antibiotic Use in Hospitals 2018 [4], ethical clearance depends on local and national requirements and is not mandatory because the PPS was designed for public health surveillance purposes. According to the International Ethical Guidelines for Health-related Research Involving Humans [34], neither an ethical review nor a waiver of consent is needed when study is mandated by national authorities. According to the National Action Plan of Lao PDR 2019–2023 [12], AMR activities were covered by one national policy on surveillance and control of infectious diseases (May 2014) and one law on prevention and control of infectious diseases (November 2017). Therefore, this survey was not subjected to ethical review or informed consent requirements as per international, national, and local regulations governing ethics and consent to participate.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

- ¹Service d'Hygiène, Epidémiologie, Infectiovigilance et Prévention, Hospices Civils de Lyon, Lyon, France
- ²Équipe Santé Publique, Epidémiologie et Eco-évolution des Maladies Infectieuses (PHE 3 ID), Centre International de Recherche en Infectiologie (CIRI), Université de Lyon, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, ENS de Lyon, Lyon, France
- ³Fondation Mérieux, South-East Asia Regional Office, Vientiane, Laos
- ⁴Microbiology Laboratory, Mahosot Hospital, Vientiane, Laos
- ⁵Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU), Mahosot Hospital, Vientiane, Laos
- ⁶Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK
- ⁷Luang Prabang Hospital, Luang Prabang, Laos
- ⁸Food and Drug Administration, Vientiane, Laos
- ⁹Department of Healthcare and Rehabilitation, Ministry of Health, Vientiane, Laos
- ¹⁰Fondation Mérieux, Lyon, France
- ¹¹Groupement Hospitalier Sud, Unité d'Hygiène, Epidémiologie, Prévention - Bâtiment 1 165 Chemin du Grand Revoyet, Pierre Bénite Cedex 69 495, France

Received: 18 March 2024 / Accepted: 15 July 2024

Published online: 13 August 2024

References

1. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet Lond Engl*. 2022;399(10325):629–55.
2. Hofer U. The cost of antimicrobial resistance. *Nat Rev Microbiol*. 2019;17(1):3.
3. World Health Organization. Global action plan on antimicrobial resistance [Internet]. Geneva: World Health Organization. 2015 [cited 2023 Oct 31]. 28 p. <https://iris.who.int/handle/10665/193736>.
4. WHO Methodology for point prevalence survey on Antibiotic Use in Hospitals [Internet]. [cited 2023 Oct 31]. <https://www.who.int/publications-detail-redirect/WHO-EMP-IAU-2018.01>.
5. Limato R, Nelwan EJ, Mudia M, de Brabander J, Guterres H, Enty E, et al. A multicentre point prevalence survey of patterns and quality of antibiotic prescribing in Indonesian hospitals. *JAC-Antimicrob Resist*. 2021;3(2):dlab047.
6. Thu TA, Rahman M, Coffin S, Harun-Or-Rashid M, Sakamoto J, Hung NV. Antibiotic use in Vietnamese hospitals: a multicenter point-prevalence study. *Am J Infect Control*. 2012;40(9):840–4.
7. Xie Dshuang, Xiang L, Li, Li R, Hu Q, Luo Qqin, Xiong W. A multicenter point-prevalence survey of antibiotic use in 13 Chinese hospitals. *J Infect Public Health*. 2015;8(1):55–61.
8. Jamaluddin NAH, Periyasamy P, Lau CL, Ponnampalavanar S, Lai PSM, Ramli R, et al. Point Prevalence Survey of Antimicrobial Use in a Malaysian Tertiary Care University Hospital. *Antibiot Basel Switz*. 2021;10(5):531.
9. Godman B, Ekwuenu A, Haque M, Malande OO, Schellack N, Kumar S, et al. Strategies to improve Antimicrobial utilization with a special focus on developing countries. *Life*. 2021;11(6):528.
10. Nathwani D, Varghese D, Stephens J, Ansari W, Martin S, Charbonneau C. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. *Antimicrob Resist Infect Control*. 2019;8(1):35.
11. Mendelson M, Morris AM, Thursky K, Pulcini C. How to start an antimicrobial stewardship programme in a hospital. *Clin Microbiol Infect*. 2020;26(4):447–53.
12. Lao PDR. National strategic plan on antimicrobial resistance in Lao PDR 2019–2023 (Laotian & English) [Internet]. [cited 2023 Oct 31]. <https://www.who.int/publications/m/item/lao-pdr-national-strategic-plan-on-antimicrobial-resistance-in-lao-pdr-2019-2023>.
13. Chansamouth V, Chommanam D, Roberts T, Keomany S, Paphasiri V, Phamisith C, et al. Evaluation of trends in hospital antimicrobial use in the Lao PDR using repeated point-prevalence surveys-evidence to improve treatment guideline use. *Lancet Reg Health West Pac*. 2022;27:100531.
14. WHOCC - ATC/DDD Index [Internet]. [cited 2023 Oct 31]. https://www.whooc.no/atc_ddd_index/.
15. WHO Antibiotics Portal [Internet]. [cited 2023 Oct 31]. <https://aware.essentialmeds.org/groups>.

16. Moja L, Zanichelli V, Mertz D, Gandra S, Cappello B, Cooke GS et al. WHO's essential medicines and AWaRe: recommendations on first- and second-choice antibiotics for empiric treatment of clinical infections. *Clin Microbiol Infect off Publ Eur Soc Clin Microbiol Infect Dis*. 2024;51198-743X(24)00059–4.
17. Department of Healthcare and Rehabilitation. Lao Adult Antimicrobial Prescribing Guidelines. 1st ed. 2020.
18. Department of Healthcare and Rehabilitation. Lao Pediatric Antimicrobial Prescribing Guidelines. 1st ed. 2020.
19. Willemsen I, Groenhuijzen A, Bogaers D, Stuurman A, van Keulen P, Kluytmans J. Appropriateness of Antimicrobial Therapy measured by repeated prevalence surveys. *Antimicrob Agents Chemother*. 2007;51(3):864–7.
20. AMR in Lao PDR [Internet]. [cited 2023 Oct 31]. <https://laoamr.net/>.
21. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Glob Health*. 2018;6(6):e619–29.
22. Maina M, McKnight J, Tosas-Auguet O, Schultz C, English M. Using treatment guidelines to improve antibiotic use: insights from an antibiotic point prevalence survey in Kenya. *BMJ Glob Health*. 2021;6(1):e003836.
23. Okoth C, Opanga S, Okalebo F, Oluka M, Baker Kurdi A, Godman B. Point prevalence survey of antibiotic use and resistance at a referral hospital in Kenya: findings and implications. *Hosp Pract* 1995. 2018;46(3):128–36.
24. Anand Paramadhas BD, Tiroyakgosi C, Mpinda-Joseph P, Morokotso M, Matome M, Sinkala F, et al. Point prevalence study of antimicrobial use among hospitals across Botswana; findings and implications. *Expert Rev Anti Infect Ther*. 2019;17(7):535–46.
25. Vandael E, Latour K, Goossens H, Magerman K, Drapier N, Catry B, et al. Point prevalence survey of antimicrobial use and healthcare-associated infections in Belgian acute care hospitals: results of the Global-PPS and ECDC-PPS 2017. *Antimicrob Resist Infect Control*. 2020;9(1):13.
26. Versporten A, Bielicki J, Drapier N, Sharland M, Goossens H, ARPEC project group. The Worldwide Antibiotic Resistance and Prescribing in European Children (ARPEC) point prevalence survey: developing hospital-quality indicators of antibiotic prescribing for children. *J Antimicrob Chemother*. 2016;71(4):1106–17.
27. Singh SK, Sengupta S, Antony R, Bhattacharya S, Mukhopadhyay C, Ramasubramanian V, et al. Variations in antibiotic use across India: multi-centre study through Global Point Prevalence survey. *J Hosp Infect*. 2019;103(3):280–3.
28. Chansamouth V, Mayxay M, Dance DA, Roberts T, Phetsouvanh R, Vanachone B, et al. Antimicrobial use and resistance data in human and animal sectors in the Lao PDR: evidence to inform policy. *BMJ Glob Health*. 2021;6(12):e007009.
29. Seale AC, Gordon NC, Islam J, Peacock SJ, Scott JAG. AMR Surveillance in low and middle-income settings - a roadmap for participation in the global Antimicrobial Surveillance System (GLASS). *Wellcome Open Res*. 2017;2:92.
30. Elias C, Moja L, Mertz D, Loeb M, Forte G, Magrini N. Guideline recommendations and antimicrobial resistance: the need for a change. *BMJ Open*. 2017;7(7):e016264.
31. Sharland M, Gandra S, Huttner B, Moja L, Pulcini C, Zeng M, et al. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use—the new 2019 essential Medicines List becomes a global antibiotic stewardship tool. *Lancet Infect Dis*. 2019;19(12):1278–80.
32. Leaper DJ, Edmiston CE. World Health Organization: global guidelines for the prevention of surgical site infection. *J Hosp Infect*. 2017;95(2):135–6.
33. Branch-Elliman W, O'Brien W, Strymish J, Itani K, Wyatt C, Gupta K. Association of Duration and Type of Surgical Prophylaxis with Antimicrobial-Associated adverse events. *JAMA Surg*. 2019;154(7):590–8.
34. Council for International Organizations of Medical Sciences (CIOMS). International Ethical Guidelines for Health-related Research involving Humans [Internet]. Council for International Organizations of Medical Sciences (CIOMS); 2016 [cited 2024 May 8]. <https://cioms.ch/publications/product/international-ethical-guidelines-for-health-related-research-involving-humans/>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.