**Implementation of an antibiotic resistance surveillance tool in Madagascar, the TSARA project: a prospective, observational, multicenter, hospital-based study protocol.**

C.Elias1,2, M. Raad3, S. Rasoanandrasana4, AH. Raherinandrasana5,, V. Andriananja6, M. Raberahona6, C.E. Moore7, M. Randria4, L. Raskine3, P Vanhems1,2, FX. Babin3

1. Service Hygiène et Epidémiologie, Hospices Civils de Lyon, Lyon, France
2. Public 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
3. Direction des Opérations Internationales, Fondation Mérieux, Lyon, France
4. Service de Biologie, Hôpital Befelatanana, Antananarivo, Madagascar
5. Département de Santé Publique, Faculté de Médecine de l’Université d’Antananarivo, Madagascar
6. Service des Maladies Infectieuses, Hôpital Befelatanana, Antananarivo, Madagascar
7. Centre for Neonatal and Paediatric Infection, St. George’s, University of London, London

Corresponding Author:

Dr Christelle ELIAS

Service Hygiène et Epidémiologie, Hospices Civils de Lyon, Lyon

165 Chemin du Grand Revoyet, 69645 PIERRE-BENITE Cedex

christelle.elias@chu-lyon.fr

Phone: +33 4 78 86 12 73

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**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- and- 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 programs (ASP). 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 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 - 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 standardized data collection tool, called TSARA deployed in 2023 in 10 hospitals in Madagascar participating to the national Malagasy laboratory network (RESAMAD). Any hospitalized 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 January 24, 2023. Findings generated were shared to national health stakeholders, microbiologists, members of the RESAMAD Network and the Malagasy academic society of Infectious diseases.

**Strengths and limitations of this study**

* TSARA is a prospective, observational and multicentre protocol capturing data from hospitalized patients.
* TSARA is an AMR surveillance tool that compiles microbiological and clinical data, including information on antibiotic prescriptions implemented in Malagasy hospitals belonging to the RESAMAD 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.

**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 Disease (2) suggested that the impact of AMR on health is even more important than previous estimations (1). To address the increasing problem, the World Health Organization (WHO) published the Global Action Plan on AMR in 2015 (3) 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 program (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- and- 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 health care (i.e. 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-resources settings, where there is for instance an average of five hospital beds per room in a Malagasy university hospital.

Outside of the RESAMAD laboratories, there are very few laboratories than 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 SWOT (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.

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

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| --- | --- |
| **Strengths**   * Laboratory network RESAMAD (11) 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, pediatrics, medical biology[[1]](#footnote-1)) | **Weaknesses**   * 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 |
| **Opportunities**   * Capture high level antibiotic use in hospitals * Existing antibiotic recommendations in place, but they are not adapted to local resistance patterns (12) * Existing AMR protocols including the surveillance of antimicrobial use | **Threats**   * Challenging implementation * Substantial missing data * Personnel require training * Lack of funding * Political instability * Climate disorders |

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 (13). 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 (Réseau des Laboratoires à Madagascar) 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 (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 (9,14). 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 to the scarce existing prescribing data (15). The TSARA project also aligns with the antimicrobial surveillance program 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 objective of the Malagasy national action plan on AMR (16).

Objectives

One of the most important benefits of AMR surveillance at the pathogen level is to achieve a standardized, comparable, and easily validated data collection method for quality data that is used to implement better patient treatment and hospital/national guidelines (17). The data allows an optimization of the patient care by adapting treatment guidelines according 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 optimize antimicrobial therapy in Malagasy hospitals.

The secondary objectives are:

1. To establish timely reporting of information on pathogens of interest and their antimicrobial susceptibility profiles to medical doctors;
2. To allow monitoring of the hospital antibiotic prescription (quantity, quality and spectrum, concordance with bacteriological results);
3. 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, multicenter, hospital-based study based on a standardized data collection tool deployed in ten facilities with both adult and pediatric patients in Madagascar (Figure 1), collecting microbiological, demographic, prescription and clinical data in one place.

Figure 1. Map of the laboratories and implementation sites of TSARA in Madagascar

*Outcome measures*

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

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 (Supplemental material 2 and 4).

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).

*Setting and laboratory capacity*

All laboratories participating in the TSARA project are part of the nationwide RESAMAD network in Madagascar (11). Description of the infrastructure in each hospital included in the TSARA project is presented in Supplmentary material 1.

These laboratories perform diagnostics and antimicrobial susceptibility testing 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 program. The laboratories also have the required infrastructure, equipment, supplies and resources to perform AST following EUCAST standards. The reporting of results to clinicians are 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 (i.e. Petri dish, 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.

*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 hospitalized 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:

* All non-bacteriological specimens (virological, fungal, parasitic)
* All samples from patients not hospitalized >24 hours (emergency, consultation, outpatient hospitalization)
* All environmental samples (water, air, surfaces, medical devices)
* All post-mortem samples
* All samples reported as contaminated defined as results that do not contribute to clinical decision-making
* All specimens for which culture was not possible
* All specimens with laboratory non-compliance
* All the patients or legal guardians who object to be included in the TSARA project
* All patients with severe cognitive impairment
* 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 (Supplementary material 2). 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 (Supplementary material 3). A third questionnaire was then filled in regarding follow-up data (Supplementary material 4). The data retrieved from TSARA meet the criteria and are linked to the GRAM project that seeks to estimate the burden of AMR worldwide (17, 18).

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 (e.g. 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 (e.g. 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 standard deviation if the distribution is normal, or the median and interquartile range 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 pediatric 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 Odds-Ratio 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 Odds-Ratios) and interaction factors (Wald's test of homogeneity).

These analyses will be 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. A significance level of less than 0.05 is considered associated.

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

*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 be 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 anonymized 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-anonymized 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-anonymized forms stay within the hospital and should allow possible corrections or deletions of data upon request of the patients enrolled.

*Data management*

Collected data are computerized 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 authorized 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 4 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 being included 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 Mérieux 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 Mérieux Foundation (e.g. 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 consortium (www.strobe-statement.org) and STROBE-AMS (19). Publication rules will follow international recommendations. The findings will also be shared with national health and sport authorities.

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), pediatrics (SMP) and microbiology (SOMABIO) to tailor antibiotic recommendations according to the resistance patterns as presented in the Figure 2.

Figure 2: Data flow between the different stakeholders

**Discussion**

The TSARA project will provide original results that could 1) allow a more precise epidemiological knowledge of bacterial infections, prescribed antibiotic therapies and local resistance levels ; 2) Inspire, correct and tailor local practices, including recommendations and guidelines for empiric antibiotic therapy according to local resistance patterns ; 3) encourage communication and use of AST results with and between clinicians ; 4) allow monitoring of hospital antibiotic prescription (quantity, quality and spectrum, concordance with bacteriological results) and 5) 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 hospitalized, 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 centers 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 (20), 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. Lastly, 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 Mérieux Foundation implemented the Lab Book 3.0 (21), a Laboratory Information System (LIS) which helps to computerize 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 incentivize 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 prescription. 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 (i.e. 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 i.e. monitoring antibiotic prescriptions and checking their compliance with recommendations still need to be explored as clinicians’ behaviors 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.

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**Authors’ contributions**

C. Elias, M. Raad, FX. Babin, L. Raskine, M. Raberahona, S. Rasoanandrasana, C. E. Moore and M. Randria designed the study.

C. Elias and M. Raad drafted the manuscript.

C.Elias, S. Rasoanandrasana, AH. Raherinandrasana, V. Andriananja, and L Raskine participated in the acquisition of data.

C.Elias, M. Raad, S. Rasoanandrasana, AH. Raherinandrasana, V. Andriananja, M. Raberahona, C.E. Moore M. Randria, L. Raskine, P Vanhems and FX. Babin have revised and approved the final version of the manuscript.

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**Competing interests**

None declared.

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1. Société de Pathologie Infectieuse de Madagascar, Société Malgache de Pédiatrie, SOMABIO [↑](#footnote-ref-1)