ADDRESSING AMR IN MADAGASCAR: THE EXPERIENCE OF ESTABLISHING A MEDICAL BACTERIOLOGY LABORATORY AT THE BEFELATANANA UNIVERSITY HOSPITAL IN ANTANANARIVO

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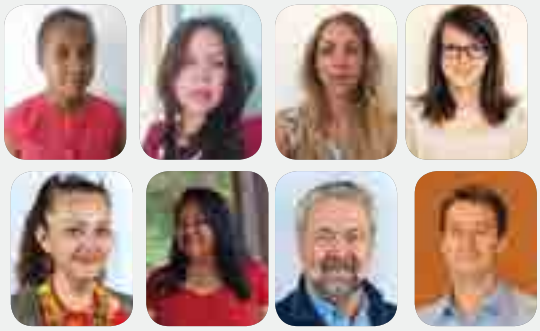

In 2016, the Mérieux Foundation launched a project with the Ministry of Public Health to create a bacteriology laboratory at Befelatanana hospital in Antananarivo (Madagascar).

The objective was to create and ensure the continued viability of operations for an essential package of analyses, to improve diagnosis and produce reliable data on antimicrobial resistance.

The laboratory results have improved patient care and enabled antibiotic stewardship and hospital acquired infection control. Preliminary data show 45% of the *E. coli* and 67% of the *K. pneumoniae* produced extended-spectrum beta-lactamase (ESBL). It provides a baseline for antimicrobial resistance (AMR) surveillance that's being expanded countrywide.

The World Health Organization (WHO) views antimicrobial resistance as one of the greatest threats to global health, responsible for 700,000 deaths per year, mostly in developing countries such as Madagascar *(1)*. WHO therefore recommends that countries develop and implement national strategies to fight against antimicrobial resistance. The Global Antimicrobial Resistance Surveillance System (GLASS), launched by WHO, is starting to be implemented in Madagascar as part of its national strategy.

The Mérieux Foundation has been working in Madagascar since 2007 to strengthen the capacity of its network of clinical biology laboratories, in partnership with the Ministry of Public Health's laboratories department. In particular, the Foundation has renovated and equipped laboratories, trained personnel, and set up a management system using direct cost recovery.

The national laboratory network currently comprises nineteen laboratories in six University Hospitals, eleven Regional Reference Hospitals, and two District Hospitals.

In 2016, we focused on bacteriology by launching a pilot project to establish an essential package of bacteriological analyses at Joseph Raseta Befelatanana University Hospital (HJRB) in Antananarivo. Beyond the technical aspects, we also addressed administrative and financial management to enable the laboratory to become autonomous and thus ensure its sustainability.

The objectives of this pilot project were: i) establish a medical bacteriology laboratory at Befelatanana University Hospital in Antananarivo to improve the diagnosis of bacterial infections

and produce more reliable data on antimicrobial resistance; and ii) ensure its long-term viability.

Material and methods

The medical bacteriology laboratory was established in the following stages:

- **Stage one:** project definition, and collaboration between hospital management and the Ministry of Public Health and their partners: the Mérieux Foundation and the Agence Française de Développement.
- **Stage two:** as soon as the terms of cooperation were defined, the laboratory was renovated to accommodate a fully functional bacteriology laboratory. This required bringing installations up to standard (electricity, laboratory benches, wastewater disposal) and installing equipment (microscopes, autoclaves, incubator, biosafety cabinet, centrifuges) and the supplies needed for bacteriological analyses. The Mérieux Foundation wrote the technical requirements, oversaw the renovation and construction project, and ordered the material and equipment. All this was made possible thanks to the financial support of the partners (the Mérieux Foundation and the Agence Française de Développement).
- **Stage three:** the training of personnel began with a Malagasy doctor who trained for a year at Lariboisière Hospital in Paris (France) to specialize in medical microbiology. Upon his return to Madagascar, he took the civil service exam and was named Clinical Biologist at the HJRB laboratory. In turn, he was able to train the HJRB laboratory personnel, with the help of a young French medical biologist for six months, under the leadership of the Mérieux Foundation. This training made it possible to set up an essential package of bacteriological analyses (direct microscopy, culture - including blood culture, identification using API strips, biochemical tests according to the REMIC 2015 medical microbiology guidelines, antimicrobial susceptibility testing according to CA-SFM / EUCAST guidelines, strain conservation). As a result, three trained technicians were able to begin their work. In parallel, a quality management system started to be put in place with the drafting of standard operating procedures.
- **Stage four:** launch of routine bacteriological analyses, including the production of diagnostic test results, after a phase of technical validation, quality control, and change management. The change management consisted of promoting the medical bacteriology laboratory among clinicians and raising awareness about prescribing bacteriological analyses and compliance with pre-analytic steps.
- **Stage five:** lastly, we trained clinicians on interpreting results and on antibiotic stewardship and raised awareness of hospital hygiene and how to prevent the transmission of multi-resistant bacteria through workshops and clinical case studies.

In addition to the laboratory renovation, we also addressed administrative and financial management. A cost recovery system was created specifically for this new activity. Negotiations took place between the hospital, the Ministry of Public Health, and the partners to provide the medical bacteriology laboratory with budgetary autonomy. As a result of these negotiations, it was agreed that 20% of the laboratory revenues would go to the hospital to contribute to various costs, and 80% would be re-injected into the laboratory to pay for new reagents and supplies and ensure preventive and curative equipment maintenance. The remaining costs (energy, personnel, etc.) would be covered by the hospital. We also set up a joint management committee comprised of representatives from the administration, hospital doctors, and laboratory staff. Its role is to ensure the laboratory runs smoothly.

Results

From December 2015 to March 2018, 4,773 samples were processed by the laboratory. (Figure 1).

Initial data on resistance was established using the diagnostic samples. It shows that for Enterobacteria, 45% of the *Escherichia coli* and 67% of the *Klebsiella pneumoniae* produced extended-spectrum beta-lactamase (ESBL), and 57.6% and 38.8% were resistant to fluoroquinolones. Furthermore, 45% of the *Staphylococcus aureus* strains were resistant to methicillin (MRSA), and 65% of *Acinetobacter baumannii* were resistant to imipenem (IRAB) (Figure 2).

Figure 1: : Total number of bacteriological samples received by the Befelatanana University Hospital laboratory

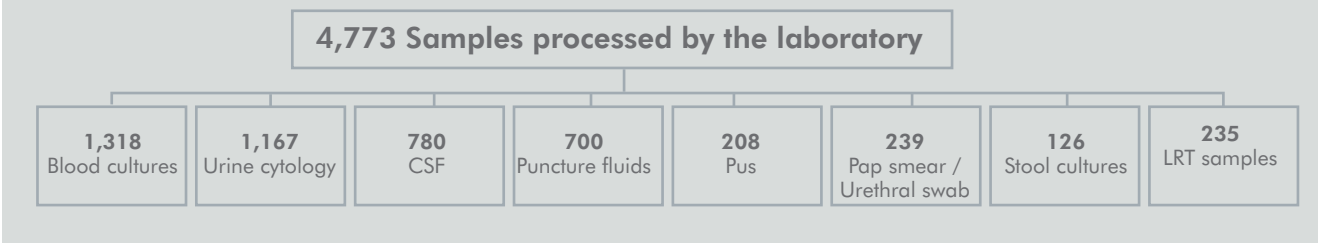

Figure 2: **Comparison of the percentage of bacterial resistance in 2016-2017 at Befelatanana University Hospital and in France, according to InVS in 2016. The key figures are from the 2016 EARS-Net report *(2)***

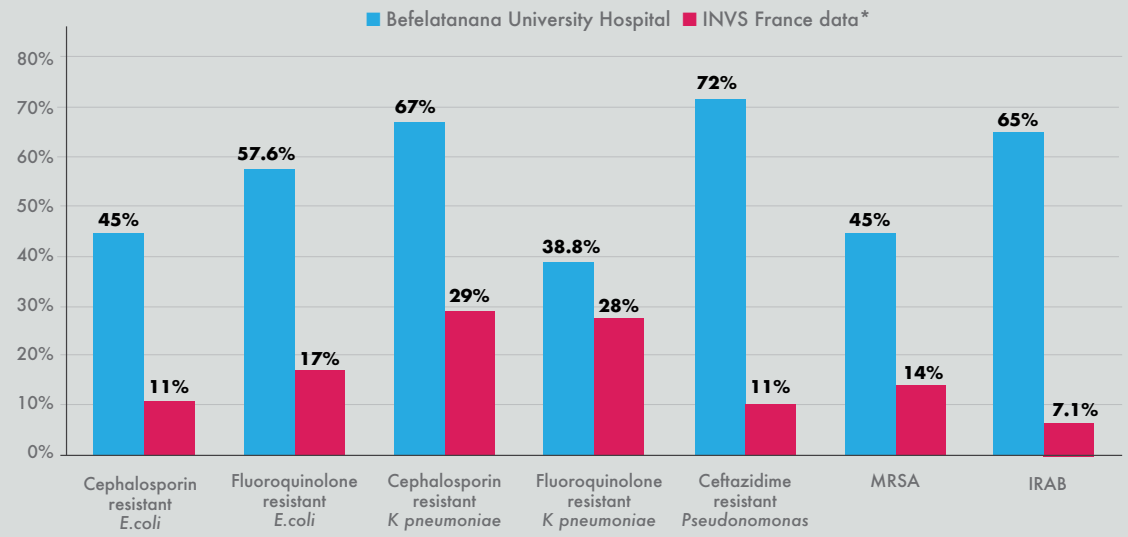

Figure 3: **Financial report for the laboratory's activities in 2016-2017**

	TOTAL	80 % (for the laboratory)	20 % (for the hospital)
Revenues (in euros)	40,590,66	32,472,52	8,118,13
Total expenses (in euros)	29,790,47	24,804,26	4,986,21
Available funds (in euros)	10,800,18	7,668,26	3,131,91

(Oanda exchange rate: 1 euro = 3,960 ariary)

The laboratory generated a total of 40,590.66 euros in revenues for 2016 and 2017. There was a positive balance of revenues (price of the analyses) / expenses (cost of reagents and supplies) for these two years (Figure 3).

The revenues are used to buy new reagents and supplies, and for the preventive and curative equipment maintenance. Since this management system was adopted, the laboratory's activity has thus been continuous, with no shortage of reagents and consumables, all while remaining affordable for patients. Ensuring that the laboratory has budgetary autonomy is key to its long-term viability, since the laboratory is then able to manage its stock and supplies.

Discussion

First, it is important to understand the project's key success factors: i) support from the health authorities, who were involved from the beginning; ii) financial support from the partners for the renovation of the laboratory and the initial contribution of equipment, reagents, and supplies; iii) the competence and motivation of the medical bacteriology laboratory personnel, thanks to the high-level training of the biologist responsible for the laboratory, the organization of the technicians' work, the daily technical support for six months, and coaching and support from the Mérieux Foundation; iv) the value to the hospital, which receives 20% of the laboratory's revenues, has noticed an improvement in patient care, and has access to one of the rare functioning bacteriology laboratories in Madagascar; v) communication and collaboration established between the biologists and clinicians, resulting in increased awareness and understanding of the results obtained, the laboratory's role in patient care, making accurate prescriptions for analyses, the rational use of antibiotics, and basic rules for hospital hygiene; vi) the satisfying performance of the management committee in its monitoring and control of the laboratory's activities and finances, as well as its approval of major decisions, particularly purchases. The laboratory's successful performance is due to all of these factors, so none should be neglected.

The activity and quality of the results produced by the laboratory have led to noticeable improvements in patient care due to the identification of infections and the prescription of appropriate treatment based on the laboratory test results. Looking forward, it would be worth measuring the hospital laboratory's impact on morbidity, mortality, and the duration of hospital stays. For now, such a study has yet to be conducted.

Beyond improving patient care, the laboratory also makes it possible to document hospital-acquired infections and raise awareness about hospital hygiene. As a result, a number of practices have improved, particularly those impacting hand borne transmission in areas at high risk, such as intensive care. Lastly, this work has generated data on antimicrobial resistance

Figure 4: **Laboratories setting up bacteriology testing**

that is useful as an indicator of the country's situation and as a temporal indicator of the impact of all public health measures taken in the country.

The results of this pilot advocate for an extension of bacteriology testing to other laboratories in Madagascar. Six laboratories, in Antananarivo and in the provinces, have expressed interest in replicating this experience by establishing a medical bacteriology laboratory with budgetary autonomy. This interest, expressed both by clinicians, biologists, and their management, is extremely encouraging and motivating, for it shows that there is a real local need. The expansion of this activity will help strengthen the network of clinical biology laboratories.

The project is being conducted in collaboration with and under the authority of the Ministry of Public Health's laboratories department. Future prospects for the laboratory network's development include technical advances, with the establishment of a Laboratory Information Management System (LIMS), such as LabBook *(3)*, to improve monitoring of the laboratory's work, quality, and operations. Implementing an automated and digital data reporting system such as DHIS 2 *(4)* will also further improve and increase the reliability of information sent to the Ministry of Health. The implementation of an External Quality Assessment (EQA) for participating laboratories will also be needed to compare data and increase reliability over time.

Lastly, building this network of medical bacteriology laboratories could lead to the creation of a resistance observatory in Madagascar, through a functional sentinel network. This would be useful to the Ministry of Public Health as well as to projects related to GLASS. The data generated would make it possible to provide recommendations for treatment protocols based on national Malagasy data, inform public health decisions, and initiate studies on research questions this data might raise. A surveillance project including human, animal, and environmental aspects is expected to be launched soon (Tricycle - WHO) *(5)*.

Conclusion

The creation of a medical bacteriology laboratory at Joseph Raseta Befelatanana University Hospital now makes it possible to provide both clinical and laboratory diagnosis. This represents a major progress for hospitalized patients.

Having a functioning bacteriology laboratory in the hospital makes it possible to offer rapid results, reduce hospital stays, optimize antibiotic treatment, and document the hospital's level of hygiene, raising awareness of its importance among medical personnel.

Thanks to this pilot project, we show that the cost recovery system, combined with good revenue management, allows a medical testing lab to cover the preventive maintenance of its equipment and purchase the reagents and supplies it needs to conduct high-quality analyses. This budgetary autonomy means that it can schedule orders, and consequently anticipate stock-outs. Ultimately, treatment of hospitalized patients is improved, which has a direct effect on the hospital's image and reputation. The hospital also receives part of the laboratory's revenues. It therefore has a two-fold reason for supporting the laboratory, creating a virtuous circle between the laboratory-patient-hospital.

Beyond the direct benefit for patients, a bacteriology laboratory makes it possible to assess antimicrobial resistance in Antananarivo, monitor the evolution of resistance over time, and measure the potential impact of various public health recommendations and decisions.

The encouraging results of this pilot project lead us to believe that the Befelatanana University Hospital bacteriology laboratory in Antananarivo will play a central role in antimicrobial resistance surveillance in Madagascar. It is also clear that this experience is worth replicating elsewhere. ■

Saïda Rasoanandrasana has been the head of microbiology at the Befelatanana University Hospital laboratory since 2016. Her role involves setting up a cost recovery system for laboratory management, improving the diagnosis of bacterial infections and producing reliable data on antimicrobial resistance. She has coordinated the RESAMAD laboratory network in Madagascar, which aims to strengthen the capacity of bacteriology laboratories. During her residency, she completed internships in several

national hospitals as well as at Assistance Publique - Hôpitaux de Paris (APHP). An MD and Head of Research (Clinic Director) in microbiology, her research focuses on the resistance of germs to antimicrobials.

A clinical pathologist at the Tsaralalàna Mother-Child University Hospital laboratory since 2012, Lalaina Rahajamanana is currently head of the bacteriology laboratory and is the focal point for monitoring rotavirus and other enteropathogenic diarrhea. She has worked with the Charles Mérieux Center for Infectious Disease in Madagascar since 2013 and is one of the technical advisors within the Madagascar laboratory network (RESAMAD) with the Mérieux Foundation.

Camille Boussioux is a Paris hospital resident in medical biology, specializing in the field of microbiology. She currently works for the Mérieux Foundation in Madagascar as part of the RESAMAD Madagascar laboratory network project. She has a Doctorate in Pharmacy and studied at the Faculté de Pharmacie in Marseille. Her thesis work focused on the analytical and workflow assessment of the establishment of an automated nested multiplex PCR system for multi-pathogen detection in CSF.

Marion Dudez is a medical biologist at the hospital center in Bourg-en-Bresse. After her pharmacy studies, she completed her residency in medical biology at Hospices Civils in Lyon. In 2015, she spent a semester as a resident for the Mérieux Foundation in Madagascar during which she was responsible for developing a bacteriology laboratory in one of the university hospitals in Antananarivo. Her tasks included training the team and setting up analysis and a management system to ensure the laboratory's financial autonomy.

She has a Doctorate in Pharmacy and her thesis work focused on this project.

Odile Ouwe Missi Oukem-Boyer has been working in health research institutions in West and Central Africa, for the past 20 years. Her main research interests are tropical infectious diseases, clinical trials, bioinformatics and health research ethics. Since 2016, she is working for the Mérieux Foundation where she holds a position of country manager for Mali and Niger. Since 2018, she is simultaneously the acting Director General of the Charles Mérieux Center for Infectious Disease in Mali.

Luciana Rakotoarisoa is the Mérieux Foundation's Madagascar country manager.

She graduated as an industrial engineer from Athénée Saint Joseph Antsirabe University and has a master's degree in local development and project management from the University of Antananarivo. She joined the Mérieux Foundation in 2011 after working in the banking sector.

She is responsible for coordinating the foundation's projects in the Malagasy region and managing the local team and expatriate volunteers. She works with technical experts to draft projects and fundraise. As part of her role, she works with the Charles Mérieux Center for Infectious Disease, a center for training and research.

Laurent Raskine, MD, has been the head of specialized biology at the Mérieux Foundation since January 2017. His role is to oversee the microbiology aspect of laboratory capacity building projects by contributing to coordinating and overseeing laboratory network activities, particularly in terms of antimicrobial resistance.

He worked for many years as a hospital practitioner in the Bacteriology Virology Hygiene department at Lariboisière Hospital in Paris, focusing on clinical microbiology.

He works as a specialist at the National Reference Center for Mycobacteria and the Resistance of Mycobacteria to Antituberculosis Drugs and works internationally.

François-Xavier Babin is Diagnostics and Health Systems Director at the Mérieux Foundation since March 2018. A member of the foundation's Management Committee, he is in charge of increasing vulnerable populations' access to diagnostics, by establishing infrastructure, reinforcing skills and processes, improving the management and efficiency of clinical biology laboratories, and assisting health authorities in their governance.

Previously he held roles at the Mérieux Foundation as Director of International Development and Asia Regional Manager based in Cambodia. He started his international work at Institut Pasteur in Cambodia. He did his PharmD residency in biomedical and industrial pharmacy at Hospices Civils in Lyon.

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