ORIGINAL ARTICLE

Installing biosafety level 3 containment laboratories in low- and middle-income countries: challenges and prospects from Mali's experience

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Abstract

In Mali, the incidence of tuberculosis (TB) is estimated at 56 cases per 100 000 people, with a prevalence of multidrug-resistant TB in new cases of 1.7% (range, 0.3–3.1%) and in retreatment cases of 17% (range, 4.4–30%). Appropriate biosafety conditions for performing routine TB culture and antimicrobial susceptibility testing have been lacking. In 2015, a biosafety level 3 (BSL3) laboratory set up in a shipping container was donated to the Malian Ministry of Health and Public Hygiene to provide capacity for TB testing. This laboratory is now managed by Malian laboratory staff and is processing samples at the national level. We explain the necessary steps for establishing and running a BSL3 laboratory. Despite the acute need for functioning and sustainable BSL3 laboratories, low- and middle-income countries are faced with a complex process and must overcome many challenges.

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Introduction

Biosafety level 3 (BSL3) containment laboratories are designed for research and analysis of class 3 pathogens. These infectious agents can spread within the community, but there are prophylactic and curative solutions available for treating and controlling the infections. This level of containment is needed to protect laboratory personnel from the risk of infection and to prevent the spread of pathogens in the environment [1,2].

For this protection to be possible, BSL3 laboratories are technically sophisticated and represent a significant financial cost in terms of construction and equipment. While developed countries are able to invest in this type of infrastructure, this is often not the case for low- and middle-income countries (LMICs), for which there is a discrepancy between the cost of such a laboratory and the population's standard of living [3,4].

In addition to construction and equipment costs, the running and maintenance of a BSL3 laboratory are expensive and complex, and they require real technical expertise. Carrying out and interpreting analyses, procuring reagents and consumables, and cleaning and maintaining these laboratories in LMICs are all challenges that can undermine their long-term viability [2]. Here we focus on the installation of a BSL3 laboratory in Mali for the diagnosis of tuberculosis (TB) by culture and antimicrobial susceptibility testing to identify drug-resistant strains.

In Mali, the incidence of TB is estimated at 56 cases per 100 000 people, with a prevalence of multidrug-resistant (MDR) TB in new cases of 1.7% (range, 0.3–3.1%) and in retreatment cases of 17% (range, 4.4–30%) [5]. According to the National Tuberculosis Control Program (Programme National de Lutte contre la Tuberculose, PNLT), the number of expected cases of MDR-TB in Mali is about 132. In 2012, the diagnosis of TB and MDR-TB cases in particular was performed in only four laboratories across the country [6]. The Charles Mérieux Center for Infectious Disease (CICM) was one of two organizations able to carry out culture and antimicrobial susceptibility testing for the four first-line anti-TB drugs.

At that time, however, the diagnosis of TB was performed under biosafety conditions that were not adapted to the

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FIG. 1. (A) Exterior view, (B) interior view and (C) blueprint of CICM BSL3 laboratory. BSL3, biosafety level 3; CICM, Charles Mérieux Center for Infectious Disease.

pathogens being handled. To address this, the Malian Ministry of Health and Public Hygiene requested support from CICM partners to help them conduct infectious disease diagnostics, especially for mycobacteria, under international biosafety conditions. Thus, in 2015, a BSL3 laboratory was donated to the Malian Ministry of Health and Public Hygiene by the Fondation Christophe et Rodolphe Mérieux and established at the CICM of Mali.

Materials and methods

The CICM's BSL3 laboratory, which qualified in July 2015, is set up in a shipping container at CICM in the capital city of Bamako (Fig. 1). It was officially inaugurated on September 17, 2015, by the Malian minister of health and public hygiene, Ousmane Koné, and the president of the Fondation Christophe et Rodolphe Mérieux, Alain Mérieux, to mark the tenth anniversary of the Mali CICM. A container-type BSL3 was chosen because it is easy to build and is well adapted to the intended use, essentially TB testing, in terms of available work space and equipment layout. In addition, this avoided setting up a construction site in Mali, which would have taken longer and been riskier and more expensive. Once the laboratory installations and operations had been qualified, it was put into service, and a local team was trained in maintenance.

In 2017, additional equipment was provided as part of the DJOMI project, a Global Health Security Agenda (GHSA) initiative funded by the US Centers for Disease Control and Prevention (CDC) through Catholic Relief Services (CRS). At the same time, the Global Fund also helped equip the BSL3 laboratory by providing the necessary equipment and consumables for the production of cultures in liquid medium and first- and second-line antimicrobial susceptibility testing, namely Mycobacteria Growth Indicator Tube 960.

After the equipment had been installed, a team of ten Malian technicians and biologists underwent training in handling mycobacteria in a confined environment and in biosafety rules in a BSL3 laboratory. This training, cofunded by Catholic Relief Services and the Mérieux Foundation, was designed and carried out by three experts from France and Cameroon. Subsequently a partnership was defined between agencies involved in the fight against TB in Mali: the PNLT, CRS, the pneumology department of the Point G hospital and the CICM convened to organize MDR-TB monitoring and the biological sample workflow. In October 2017, diagnostic and culture activities formally started in the BSL3 laboratory. In addition to monitoring patients undergoing treatment and retreatment at the Point G hospital, the CICM set up a research program on MDR-TB in children at the Mali hospital.

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Results

The BSL3 laboratory at the CICM is now functional, with a staff of seven authorized to handle suspected TB samples in a confined environment. A Malian technician who specializes in electronic maintenance ensures that the BSL3 laboratory runs smoothly, supervised by a technical expert from Lyon, France, who is a BSL3 laboratory specialist. The technician regularly checks the parameters of the air conditioning and treatment units and those of the heat pump, and also measures the air pressure of the various laboratory airlocks/modules, along with indoor and outdoor temperature.

To date, samples from 125 patients have been received and analysed: 89 sputum samples mainly from patients in the MDR unit of the Point G pneumology unit, 13 gastric aspirate samples primarily collected as part of the diagnosis of paediatric TB in the paediatric ward of the Mali hospital, 12 pleural fluid samples, five pus samples from abscesses and six urine samples with a suspicion of urinary-tract TB (Table 1). Some patients have been referred by clinics checking for extrapulmonary TB, which is often difficult to diagnose. Some MDR-TB cases have already been diagnosed and the results sent to clinicians so that patients can receive proper care.

The laboratory's activity is carried out under the supervision of the PNLT and in connection with the National Reference Laboratory (Laboratoire National de Référence), which does not yet have the technical capacity (as it lacks a BSL3 lab, equipment and authorized personal), needed to perform culture and antimicrobial susceptibility testing.

TABLE 1. Detail of samples processed in BSL3 laboratory at CICM since start of activities in October 2017

Sample	N	%
Sputum	89	71
Pleural fluid	12	10
Gastric aspirate	13	10
Pus	5	4
Urine	6	5
Total	125	100

BSL3, biosafety level 3; CICM, Charles Mérieux Center for Infectious Disease.

Discussion

By installing a containerized BSL3 laboratory in Mali, a turnkey solution was chosen for reasons of efficiency and speed. Although the purchase cost is not insignificant (about €11 000/m^2 for 30 m^2, or €330 000 excluding transport, installation and qualification expenses), the costs of maintenance and use are moderate, which is important in LMIC settings. However, maintenance of the facility is a major long-term concern, especially because a yearly laboratory qualification is required, which can only be carried out with certified measuring devices as well as independent and properly trained staff.

The power supply for the CICM in general and for the BSL3 laboratory in particular is a major challenge because voltage variations are frequent, even daily; this can cause damage to the equipment. Electrical protection, and preventive maintenance more generally, of the facility is crucial to ensuring its long-term viability.

Multistakeholder funding (Fondation Christophe et Rodolphe Mérieux, the Mérieux Foundation, the US CDC via the GHSA and the Global Fund) should be highlighted. It was needed to acquire all of the components. As a result, there was a 2-year lapse between delivery of the BSL3 laboratory to the CICM and the launch of its operations. This can be explained by the fact that funding for specific equipment had not yet been obtained when the laboratory was delivered, and much had to be done after 2015 to secure all of the additional funding. Once the funding pledges had been obtained by CRS for the GHSA DJOMI project and through the Global Fund, it took a long time for the technical staff of the CICM to identify the equipment and consumables that fulfilled procurement requirements. Procurement channels were particularly complex and tedious, with significant delivery delays. The support of additional staff from the Mérieux Foundation was needed to make the procurement process possible. It is legitimate to question the feasibility of such a process for a national structure that would not benefit from these resources.

Staff training could be considered only once the equipment had been delivered and the laboratory was ready to operate. It was postponed several times, and there was a real risk of losing funding for this important activity. Training finally took place in August and September 2017. It consisted of theoretical lessons, practical work to learn the techniques and best practice in a conventional laboratory, then handling nonpathogenic strains inside the BSL3 laboratory. Certification was granted to laboratory staff who demonstrated their ability to handle suspected TB specimens and understand biosafety procedures and issues related to working in a confined environment. This certification, however, only remains valid if the staff regularly handles such samples in a BSL3 laboratory. For this reason, it is of limited duration, and renewal implies an annual assessment of the staff by training experts.

It is expected that reagents and consumables will be renewed with support from the Global Fund. But given the complexity of the procurement channel via CRS and the Global Fund, it is important to anticipate needs to avoid running out of stock or unusable reagents, as expiration dates are sometimes quite

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short. The specific nature of commodities related to culture in liquid medium and antimicrobial susceptibility testing is such that it is not possible to find solutions via local suppliers. Therefore, a regular supply of reagents and consumables, which is a classic challenge inherent to the operation of any laboratory, is even more crucial for running a laboratory for diagnosing TB.

Currently samples that are analysed at the CICM come from only a few hospitals in Bamako. The ultimate goal is to extend monitoring throughout the country; discussions are ongoing with the PNLT and other partners to organize the collection and delivery of samples to the CICM.

Conclusion

Even with limited resources, LMICs must become autonomous in the fight against infectious diseases. They are the ones most affected by infectious diseases and resistance to antimicrobial drugs. The installation of BSL3 laboratories is essential for patient care and resistance control.

In LMIC conditions, we have shown that it is possible to set up a BSL3 laboratory in accordance with best practice while keeping control of the budget. However, the full execution of the project is difficult. While the number 1 obstacle to the lab operating effectively is the training and availability of competent staff, the number 2 obstacle is the complexity of all the steps required to obtain funding from multiple sources. Finally, although we have shown the feasibility of such a project, the issue of its sustainability remains. Even if it seems guaranteed for the time being, it remains fragile because of the many factors in play.

It is important to take a new approach to establishing laboratories that takes these factors into account and facilitates the whole process. It is critical for LMICs to have functioning laboratories to tackle the challenge of infectious diseases, especially resistance.

Conflict of interest

None declared.

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