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Review

AMR in low-resource settings: Médecins Sans Frontières bridges surveillance gaps by developing a turnkey solution, the Mini-Lab

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ABSTRACT

Background: In low- and middle-income countries (LMICs), data related to antimicrobial resistance (AMR) are often inconsistently collected. Humanitarian, private and non-governmental medical organizations (NGOs), working with or in parallel to public medical systems, are sometimes present in these contexts. Yet, what is the role of NGOs in the fight against AMR, and how can they contribute to AMR data collection in contexts where reporting is scarce? How can context-adapted, high-quality clinical bacteriology be implemented in remote, challenging and underserved areas of the world?
Objectives: The aim was to provide an overview of AMR data collection challenges in LMICs and describe one initiative, the Mini-Lab project developed by Médecins Sans Frontières (MSF), that attempts to partially address them.
Sources: We conducted a literature review using PubMed and Google scholar databases to identify peer-reviewed research and grey literature from publicly available reports and websites.
Content: We address the necessity of and difficulties related to obtaining AMR data in LMICs, as well as the role that actors outside of public medical systems can play in the collection of this information. We then describe how the Mini-Lab can provide simplified bacteriological diagnosis and AMR surveillance in challenging settings.
Implications: NGOs are responsible for a large amount of healthcare provision in some very low-resourced contexts. As a result, they also have a role in AMR control, including bacteriological diagnosis and the collection of AMR-related data. Actors outside the public medical system can actively contribute to implementing and adapting clinical bacteriology in LMICs and can help improve AMR surveillance and data collection. **Jean-Baptiste Ronat, Clin Microbiol Infect 2021;27:1414**

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Introduction

Representative and comparable data for drug-resistant bacterial infections are essential to developing evidence-based treatment guidelines and to measuring the impact of antimicrobial resistance (AMR) control efforts [1]. Yet, these data have proven extremely challenging to obtain in low- and middle-income countries (LMICs), despite the increasing evidence that AMR is rapidly increasing in these contexts [2–5]. AMR poses a uniquely dangerous threat to low-resource settings, with the potential to reverse recent progress towards infectious disease control and to damage healthcare provision generally and threaten the safety of essential services (like surgery) among some of the world's most vulnerable and underserved populations [2,3,6]. We present an overview of current AMR data collection challenges in LMICs and describe an initiative developed by the humanitarian medical organization Médecins Sans Frontières (MSF) that may contribute to this endeavour.

Material and methods

We searched PubMed and Google Scholar for human research and articles in English published from 1 January 2000 to 15 December 2020 using the terms 'Antimicrobial resistance', 'Surveillance', 'Low- and Middle-Income Countries', 'Non-governmental organization' and 'Non-state actors'. All available study types were included, as were 'grey literature' publications (including reports, working papers, evaluations or government documents). We then used this literature to inform our description of MSF's Mini-Lab project, which we illustrate using implementation data from the first 8 months of its use in Haiti.

Gaps in AMR surveillance in LMICs

In publicly available published literature, as well as in MSF's experience across multiple countries, LMIC AMR data lack standardized laboratory and data collection practices and are often not representative [7]. Data are also often collected inconsistently, leading to systematic inaccuracies and underreporting [8]. Quality and coverage are complicated by a lack of infrastructure and expertise [6], especially in laboratory facilities where quality assurance procedures, skilled personnel, laboratory supplies and adequate and functioning equipment are all in short supply [9–13]. Robust data management is also often lacking. As a result, LMIC clinicians frequently distrust and underutilize laboratory services and ignore reported results (such as failing to de-escalate or discontinue a patient's antibiotic even when it is indicated by the laboratory) [7]. Despite a general consensus about the need for improved bacteriological diagnostics in LMICs, they remain underfunded and underdeveloped [7].

Moreover, LMIC microbiology laboratories are usually found in reference hospitals in large cities. AMR data are thus biased towards community-acquired, urban infections and hospital-acquired infections at an advanced level of care. Physicians without access to local bacteriology services are deprived of direct diagnostic support and must rely on aggregated referral centre data or imprecise international data to inform antibiotic guidelines and empirical treatment [14]. More local surveillance could resolve these challenges, establish AMR prevalence rates and have a major impact on individual patients [15,16].

The role for non-state and humanitarian actors in collecting AMR data

To address the challenges of AMR surveillance in LMICs, the World Health Organization's (WHO) Global AMR Surveillance System (GLASS) was created. However, many countries do not have the resources or capacity to meaningfully contribute to the system [17] and restrictions exclude data from independent academic institutions, non-governmental organizations (NGOs) and pharmaceutical companies [6,18]. Significant gaps remain. A variety of non-GLASS AMR surveillance networks have also been created since 2000, including 72 supranational networks for AMR surveillance in bacteria, fungi, HIV, TB and malaria (34 remained active in 2016 [17]. These networks often include non-state actors' data (academic, pharmaceutical companies, contract research organisations, digital disease detection networks, etc.).

Médecins Sans Frontières (MSF), an international medical humanitarian organization, also responds to AMR in the contexts where it operates facilities and contributes to these surveillance initiatives when possible [19]. MSF has established clinical bacteriology laboratories (CBLs) in many low-resource settings, often finding multidrug-resistant (MDR) bacteria at alarming levels [19–26]. MSF currently has five functioning CBLs around the world (Mali, Jordan, Liberia, Central African Republic, Yemen), with laboratory partnerships (private and public) in 14 other sites. Yet, except in the case of Mali (where a Mali GLASS network partnership with the Ministry of Health was recently established), none of the MSF sites are able to share their surveillance data. Usually this is because the country either does not allow private structures to report into their network or because they are not participating members of the global GLASS system. The MSF AMR response focuses on antibiotic and diagnostic stewardship, surveillance and infection prevention and control (IPC) and prioritizes sites that have high-risk patients (burns, neonatology, paediatric and trauma wards) or are in high-risk AMR regions (especially the Middle East and North Africa) [5]. Though resource and time intensive, MSF prioritizes building the capacity of a host country's workforce for both quality and sustainability reasons (establishing a microbiology laboratory with scarce skilled human resources generally takes 1–2 years depending on the sample types they will analyse) [5].

The Mini-Lab: leapfrogging to close the LMIC surveillance gap

MSF has a standardized approach to surveillance and data in its own stand-alone laboratories or when working in partnership with another laboratory. However, some sites have so little access to microbiology that improving it is a key component of AMR response in itself. 'Leapfrog' solutions (diagnostic technologies without the infrastructure requirements of systems used in high-income countries) are much needed in these contexts, such as rapid, affordable and effective point-of-care (POC) diagnostics (especially those that distinguish between viral and bacterial infections) that can identify pathogens and provide antibiotic susceptibility testing (AST). These solutions must be adapted to LMIC constraints, have low maintenance needs and be able to handle varying heat/humidity levels [27]. Yet, these breakthrough products have not yet materialized, mostly because of market failures and barriers to use [6]. As a result, MSF developed its own leapfrog solution: the Mini-Lab. The Mini-Lab adapts manual clinical bacteriology techniques, focusing on ease of use, robustness and clinical relevance in resource-poor contexts. Its goal is to be a turn-key laboratory (i.e. a complete product ready for immediate use) that is self-contained, easily installed, quality assured, adapted to low-resource settings and can be operated by trained laboratory technicians without prior microbiology expertise (Fig. 1). The first Mini-Lab prototype focused on diagnosis and AST for bacterial bloodstream infections [28], and recent studies found it to meet 20 of 25 suitability indicators for use in LMICs (Table 1).

The Mini-Lab project began in response to gaps identified by experts examining the stark microbiology needs in low-resource

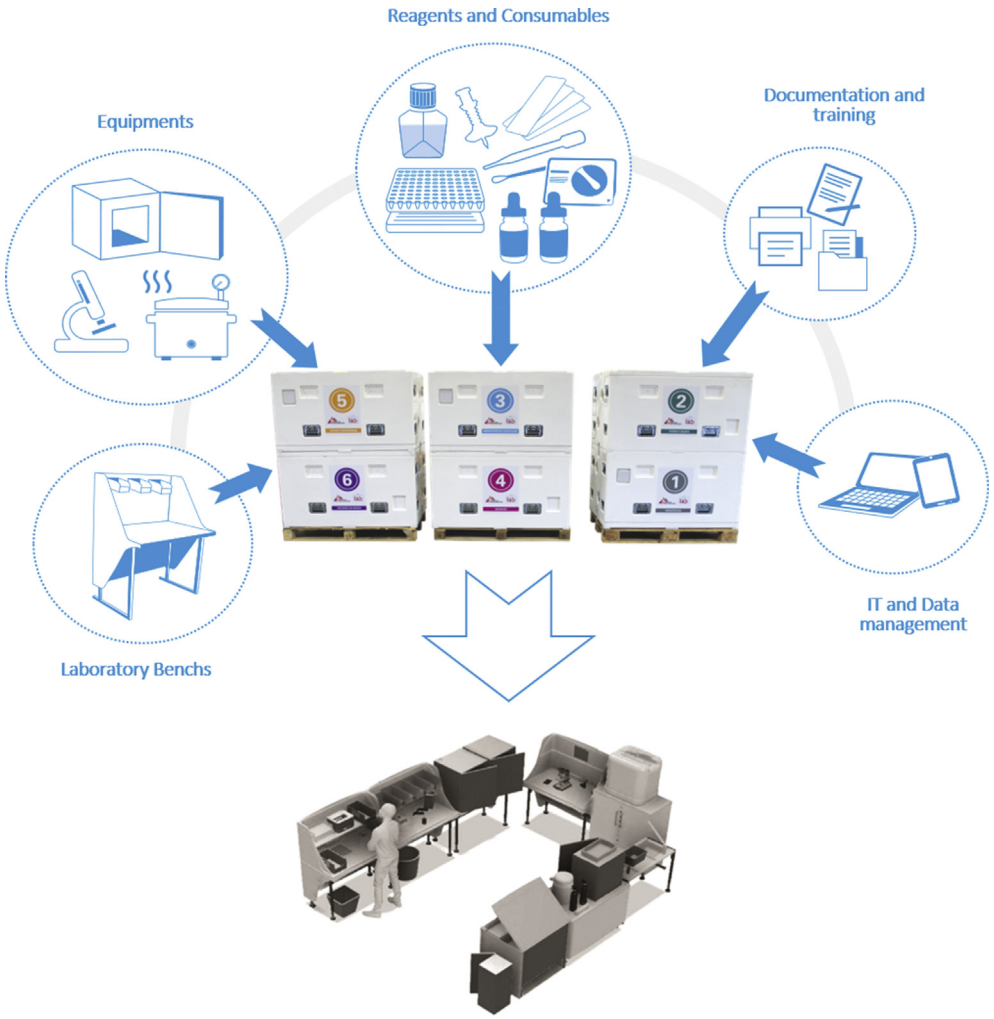

Fig. 1. Mini-Lab components, set-up and target. Box-benches contain all necessary equipment, furniture, data management systems, training, documentation, consumables and reagents. Mini-Lab has six boxes-benches that can be folded to transport material. Unfolded they provide working bench configuration to set up a CBL in a less than 20 m^2 area. The Mini-Lab's goal is to be deployed at first level of care district referral hospitals to improve patient care.

settings [11]. It was created by developing target products profiles, analysing the marketplace, selecting technologies that would work in MSF settings and working with manufacturers to suggest adaptations to existing products when technologies did not yet exist. Rigorous laboratory testing then occurred [29,30] with validation from experts in academia, including a prototype field-test in an MSF burn hospital in Haiti in 2019–2020 (Fig. 2). The Mini-Lab is built around a Quality Management System (QMS) that ensures that all components meet quality requirements and provide accurate results, even in the absence of an on-site microbiologist, and follow the WHO SLIPTA (Stepwise Laboratory Improvement Process Towards Accreditation) and other recommendations [31–34].

The Mini-Lab will soon be used in the Central African Republic (CAR), a conflict affected country with critical health system needs where MSF has 12 medical sites. In CAR, there is not a single CBL outside of the capitol Bangui, and very few national AMR data overall [35]. In 2021, MSF will evaluate its Mini-Lab there as a test of its ability to sustainably establish a CBL in remote hospital facilities, to improve patient care and to bolster AMR surveillance [12]. Key features of the Mini-Lab design are detailed below and in Table 2.

Key features of the Mini-Lab

Installation and safety

All Mini-Lab components are transported in protective boxes that transform into sturdy laboratory benches ('box-benches') with 120 × 80 cm of workspace, meet ISO standards for laboratory furniture [36–41] and undergo thorough risk analysis prior to inclusion. Box-benches include standard safety equipment (e.g. personal protective equipment, extinguishers, eye showers, biohazard spill kits, etc.) and all electrical components provide safe electricity connections. Deployment and installation instructions are designed in an 'Ikea style' didactic document aimed at lay users. Installation of (or dismantling) the Mini-Lab takes 2 days.

Streamlined supplies and inventory

To simplify logistics and supplies, the amount of reagent, consumables and equipment is reduced to what is strictly necessary. A standard, ready-to-order supply list (with quantity specifications) is included, and reagents requiring cold chain are avoided as much as possible. The Mini-Lab core sample workup includes five internationally certificated (CE-IVD or FDA) analytical components: manual biphasic blood culture bottles (Autobio Diagnostics Co., Ltd,

Table 1
Comparing Dailey PJ, Diagnostics 2019 Target Product Profile [53] (TPP) for simplified blood culture in low-resources countries with Mini-Lab prototype achievement

Characteristic	Dailey et all TPP minimum requirements [53]	Mini-Lab prototype Specifications as of December 2020
Global		
Population	Total population with fever	Total population with fever
Health system level	>Level 3	Level 2
Users	Moderately trained lab tech	Lab tech with no experience in bacteriology
Platform cost	<20 k$	Estimation 35 k$ + transport + onsite training
Individual test cost	<10 $ (2 bottles)	Estimation 6 $ for negative BCB, 20–25 $ for positive BCB
Test performance		
System detection	Culture positivity Gram status Antimicrobial susceptibility with additional techniques	Culture positivity Gram Status Antimicrobial susceptibility with ready to use MIC microbroth dilution panels
Pathogen detection	>95% sensitivity for mono or poly	Overall yield = 95.9% [30]
Pathogen identification	90% at species level 95% at genus level	90.25% at species level [29]
Mono. vs. Poly. BC	Not possible	Possible
Interfering substances	Accurate results when malaria infection	Incompatibility of manual blood culture with blood containing malaria parasite has never been described in literature and is so far unkown
Test procedure		
Complexity	2 steps maximum	9 steps (including complete identification and AST)
Sample volume	BC bottle should support <5 mL for paediatric samples or use of separate BC bottles	Minimum of 1 mL of blood for paediatric samples. Same bottle for adults and children
Delayed entry	BC bottles <4 hr at RT before BC	Similar to standard requirements for manual blood culture (delayed incubation decrease yield of positivity). Recent study shown that if blood cultures are stored <24 hr at 25°C there is no significant loss in yield [54]
QC testing	Similar to standard BC	Similar to standard BC (standard kit of 12 ATCC strains included in the Mini-Lab kit)
Test results		
Preliminary results	Report for positive/negative BC	Report for positive, orientation and final ID and AST/preliminary 48H negative BC report and final 7 day negative BC report.
Final results	Pathogen identification	Pathogen identification
AST	Separate methodologies	Included
Interpretation	Alert for preliminary/final reports Paper-based and/or electronic results Results to laboratory, doctors and ward	Alert for preliminary and final reports Electronic and paper-based results Results to laboratory, doctors and ward
Consumables		
Sample collection components	None provided	All blood collection material is provided as a Blood collection kit
Sample identification	Compatible with 2D barcodes and labels	Labels and 2D barcodes
BC bottle storage	6 months at +5/+35°C 70% humidity Including transport stress (48 hr 50°C) No cold chain	18 months at +4/+25°C Avoiding exposure to sunlight
Shipping conditions	No cold chain Transport stress 48 hr, +5/+40°C	Cold chain for 10% of the reagents out of BC bottles Stress studies done on the most at risk reagent following WHO recommended protocol [55]
Waste disposal	Biohazardous waste as specified by WHO or country guidelines	Automatic autoclave integrated; Biohazard waste procedures follow WHO guidelines, all protocol and material for safe waste disposal to hospital waste disposal area included, including procedure on safe destruction of expire reagents and consumable.
Operational characteristics		
Biosafety	Same as standard BC in a closed system Biosafety alert when a pathogen identified	Sealed closed transfer system for steps at biosafety risk. Biosafety alert built in expert system
Operational conditions	+10/+35°C, 70% humidity, +2000 m altitude High dust environment Manual cleaning	Equipment and reagent can work in +10/+35°C, 70% humidity environment but for Human operators' comfort and efficiency, Air conditioning is advised. Manual cleaning operations

Zhengzhou, China), sealed pack sub-culture media (Biomed Diagnostics Co., Ltd, White City, USA), identification and AST microplates (Beckman Coulter Co., Ltd, Sacramento, USA) and other tests for orientation (Gram staining, catalase, oxidase, aminopeptidase). All are compact, ready to use, easy to read and interpret, and can sustain the growth of bacterial pathogens common to low-resource and tropical settings [29,30]. These tests have a long shelf life (12–18 months) and can be stored at 4–25°C. Phenotypic pathogen identification occurs in a unique single microplate combining Gram-positive and Gram-negative testing. AST of all clinically relevant organisms is consolidated on three microplates using a microbroth dilution method to standardize results and reduce cost, volume and storage space.

Tailored equipment

All equipment was selected based on its safety, low maintenance needs and robustness in tropical conditions where power outages, dust, humidity and other challenges are common. The Incudigit SV30 incubators (JP Selecta Co., Ltd., Barcelona, Spain) can withstand 12 hr without electricity without dropping more than 1°C from initial baseline set temperatures [42]. The autoclave (Tuttnauer Co., Ltd., Breda, The Netherlands) includes a predefined cycle for waste sterilization and has safety measures that prevent it from opening when the electricity is out. Detailed maintenance instructions are included (installation, calibration, use, preventive and corrective procedures), as are a maintenance plan and troubleshooting guide.

Fig. 2. Deployment in Drouillard MSF Burn Hospital, Haiti. The Mini-Lab's portability allows its deployment in different types of spaces, from hospital rooms, to a maritime container, or a tent. It can also be used by laboratory technicians without expertise in bacteriology after completing a 1-month on-the-job training (plus mentoring by an expert trained microbiologist for a further 2–3 months).

Table 2
Description of the Mini-Lab characteristics and specifications as of 2020 achievements

Set-up and training	2 days to set-up, 1 month of training for unexperienced technicians before to run clinical samples followed by 2–3 month's mentoring of activities and training of supervisor 1 day of training for nurses on blood culture sampling Continuous education via e-learning platform
Project prerequisite	Programme in place for IPC Clinical staff should have minimum awareness of antibiotic stewardship program (ASP)
Capacity	**Average capacity**: 10 blood samples per day **Possibility to expend** to 20 BCBs/day during activity pick
Staff	**To run** 7 days/week: 2 dedicated lab technicians and 1 supervisor with medical laboratory experience/training, no prior experience in microbiology. Speaking and reading French or English. **Set-up:** 1 experienced Mini-Lab implementer for set-up, training, mentoring (3 months) **Follow-up:** regular visits is advised (every 6–9 months), distance trouble shooting by administrator
Infrastructure prerequisite	**Space**: Clean dust-proof with washable floor stable and walls, 15~20 m^2, Air conditioning desired for operator comfort and efficiency **Structure**: Long-term structure, container (40 F^2), Tent **Equipment to be provided on site**: 1 cupboard, metal, ± 200 × 100 × 40 **Water**: Access to clean and chlorinated water (10 L per day) **Power requirement**: 12 kWh per year. Peak value up to 4.85 kW. Possibility to connect to a fluctuant energy system (UPS and surge protector included) **Internet**: access to internet on weekly basis, minimum monthly access to internet for software up-date. **Waste management**: 2.5 kg/day volume through normal waste disposal facility after autoclaving
Maintenance and support	**Maintenance:** Preventive maintenance conducted by lab technicians. Autoclave annual maintenance to be conducted by trained BIOMED technician. Corrective maintenance to be conducted by field logisticians **Spare part**: kit of principal spare part provided (fuses, light bulbs, etc.) **IT**: 2 computer's, 2 tablets, 2 cameras **Support:** access to Microbiologist advisor by mail for direct support (standard form generated by Mini-LIMS)
Logistics	**The kit includes** all equipment to set-up the lab: bench's, furniture, autoclave, microscope, printer, etc. **Supply:** Consumables stable for >12 months, many articles can be replaced by local components of similar specifications. **International orders**: every 4–5 months (for surveillance of fastidious organism) **Transport**: starter kit 1.2 T (incl. 800 kg possible by boat); every 4 months, supply 400 kg (air) **Pharmacy storage**: controlled temperature 1.5 m^3/Cold chain 0.3 m^3/Dangerous: 0.016 m^3 **Mobility**: repacking in 2 days, possible to move the entire Mini-Lab from one site to another **Modularity**: possible to order specific modules of the Mini-Lab separately to expend activities
Associated cost	**Additional** second- and third-line antibiotics (not included in Mini-Lab kit, to be supplied separately) is advised Antibiotic Stewardship Program and Infection Prevention and Control enforcement

BCB, blood culture bottle; IPC, infection prevention and control.

Staff and organization

Once installed, a trained microbiologist provides 1 month (135 hr) of onsite training for Mini-Lab technicians and 1 month (25 hr) of on-site training for laboratory supervisors through interactive, theoretical, practical and work simulation modules (an e-learning version of is also being developed). This is followed by 2–3 months of onsite staff mentoring and activity monitoring. Other human resource tools are also available for personnel recruitment (job descriptions, questionnaires, etc.) and activity and staff management (task allocation tables, duty rosters, competency assessments, etc.).

Guidance documents

Detailed instruction manuals and visual bench aids (including for installation, best practices, equipment monitoring and quality control) allow Mini-Lab end-users to be fully autonomous, without the need for remote support. A future Laboratory Information Management System (Mini-LIMS) will simplify data entry, process follow-up, support sample management and validate results (the tablet-based format reduces data entry errors, helps laboratory technicians adhere to the workflow, and provides accident and error reports). The Mini-LIMS will embed a microbiology decision support system that is being designed based on international guidelines (European Manual of Clinical Microbiology [43], Clinical Laboratory Standard Institute [44], European Committee on AST [45,46]) and will provide guidance on results interpretation and error and biosafety risk signalling.

Quality control

Internal quality controls (IQCs) systematically detect random errors and prevent false results. A bacterial reference strain kit, composed of 12 ATCC strains (Microbiologics CO, Saint Cloud, USA) controls all analytical process steps. The Mini-Lab is also designed to participate in external proficiency testing and quality assurance (EQA) schemes when desired.

AMR surveillance

The MicroScan (Beckman Coulter. Inc, Sacramento, USA) platform was selected as a ready-to-use, sealed/packaged, lyophilized MIC AST microbroth dilution that is less error-prone than disc diffusion methods, provides refined information [47,48] can be read manually or with an automatic reader, and has high reproducibility and results standardisation because of pre-prepared panels. The antibiotics tested are based on MSF and WHO essential drug lists [49], are embedded by Beckman Coulter on the AST panels and are tailored to the testing needs of the patient

Table 3
Details of the MSF MicroScan Gram Pos panels (C32698) for *Staphylococcus* spp. and *Enterococcus* spp. species, MSF MicroScan Gram Neg panels (C32699) for Gram-negative bacilli isolates and MSF MicroScan Fastidious microplate (C32700) for *Streptococcus* and *Haemophilus* species, with antibiotics molecules classified as per the WHO 2019 Access, Watch, Reserve ('AWaRe') classification of antibiotics and 2019 Essential Medicine List

Antibiotic	Class	AWaRe Category	Listed on EML 2019	MIC POS panel		MIC NEG panel		MIC FAST panel	
				Staphylococci	Enterococci	Enterobacterales	*Non-Fermenting bacilli*	Streptococci	*Haemophilus*
Ampicillin	Penicillins	Access	Yes	X	X	X		X	
Benzylpenicillin	Penicillins	Access	Yes	X				X	
Oxacillin	Penicillins	Access	No	X					
Amoxicillin/clavulanic Acid	Beta lactam - beta lactamase inhibitor	Access	Yes			X			
Chloramphenicol	Amphenicols	Access	Yes			X		X	X
Gentamicin	Aminoglycosides	Access	Yes	X		X	X		
Gentamicin (high level)	Aminoglycosides	Access	Yes		X				
Amikacin	Aminoglycosides	Access	Yes	X		X	X		
Clindamycin	Lincosamides	Access	Yes	X					
Inducible clindamycin resistance	Lincosamides	Access	Yes	X					
Tetracycline	Tetracyclines	Access	No	X					
Trimethoprim	Trimethoprim	Access	No	X		X	X	X	X
Cefoxitin screen	Second-generation cephalosporins	Watch	No	X					
Ceftazidime	Third generation cephalosporins	Watch	Yes			X	X		
Ceftriaxone	Third generation cephalosporins	Watch	Yes			X		X	X
ESBL test	Third generation cephalosporins	Watch	No			X	X		
Piperacillin/tazobactam	Beta lactam - beta lactamase inhibitor	Watch	Yes			X	X		
Ertapenem	Carbapenems	Watch	No			X	X		
Imipenem/cilastatin	Carbapenems	Watch	No			X	X		
Meropenem	Carbapenems	Watch	Yes			X	X	X	X
Ciprofloxacin	Fluoroquinolones	Watch	Yes	X	X	X	X		X
Levofloxacin	Fluoroquinolones	Watch	No					X	X
Teicoplanin	Glycopeptides	Watch	No	X	X				
Vancomycin (IV)	Glycopeptides	Watch	Yes	X	X			X	
Erythromycin	Macrolides	Watch	No	X					
Tigecycline	Glycylcyclines	Reserve	No	X	X				
Daptomycin	Lipopeptides	Reserve	No	X					
Linezolid	Oxazolidinones	Reserve	Yes	X				X	
Fosfomycin (IV)	Phosphonics	Reserve	Yes	X		X			
Colistin	Polymyxins	Reserve	Yes			X	X		
Dalfopristin-quinupristin	Streptogramins	Reserve	No	X	X				

population, to local epidemiology and to antibiotic resistance (ABR) patterns (Table 3). Special attention is given to commonly used antibiotics, antibiotics of last resort and proxy indicators of resistance mechanisms per GLASS requirements [50] and AWaRe classifications [51]. Mini-LIMS will support AST interpretation by incorporating WHONET expert system functionalities in a table-driven approach. AMR data will then feed into high-level surveillance systems with connection to WHONET [52] or DHIS2 platforms for direct data uploading to a country GLASS representative when available. The Mini-Lab's AST system will help clinicians select the correct antimicrobial agent, will support the adaptation of local antimicrobial guidelines and will provide epidemiological surveillance data.

These characteristics ensure that the Mini-Lab is able to (a) correctly diagnose bloodstream infections and improve case management, (b) provide the information required for antimicrobial stewardship and (c) capture data from decentralized, rural areas for AMR surveillance. In CAR, as in many LMICs, the Mini-Lab is expected to fill a gap given the absence of CBL in rural and small city areas. It will also provide valuable data to health authorities and inform their national ABR response plans.

Feedback from the pilot implementation in Haiti

After analytical component evaluations in European laboratories performed satisfactorily [29,30], the first Mini-Lab prototype was deployed and evaluated in the MSF Burn Centre (Drouillard) in Port au Prince, Haiti, from July 2019-April 2020. Its use and robustness overall was evaluated there in field conditions. In particular, each analytical component was assessed for ease-of use by trained laboratory technician who were not microbiology experts. User proficiency was assessed using analytical phase Standardized Operating Procedures (SOPs), including blood culture bottle (BCB) reading, orientation testing (pre-ID), identification (ID) and AST. Furthermore, although not the main objective of the study, some microbiology indicators were obtained through both clinical blood cultures collected from hospitalized patients and simulated blood cultures prepared using low resource settings (LRS) isolates. Results from this initial pilot show that even non-expert laboratory technicians found the Mini-Lab components easy to use (overall score of 96% over 100% maximum user friendliness) and that they improved in their competences in a short period of time (from 68% after training to 91% and 97% after 4 and 6 months, respectively). Most of the analytical components confirmed the performance results obtained during evaluation studies, ensuring the robustness of microbiology results in real-world conditions. Overall, the experience in Haiti showed no major flows and that the Mini-Lab adapted well to MSF operational settings, encouraging its further testing in other resource-constrained or otherwise challenging conditions.

In 2021, the Mini-Lab is only available for blood culture and through MSF. However, the organization is exploring to include other samples (urine, cerebrospinal fluid, one-health, etc.) and how to make this innovation accessible in an open source format or as a turnkey solution in partnership with other actors.

Conclusion

Effective and comprehensive surveillance systems are critical to a better understanding of the global AMR problem, to adapting therapeutic guidelines, to designing and implementing interventions and to assessing the effectiveness of the response. Actors across the public, private, governmental and civil society spheres must all contribute to capturing actionable data. Extending AMR surveillance networks to primary care and utilizing all existing data sources is a key piece of AMR control, yet largely missing in most LMICs.

The Mini-Lab may fill gaps in AMR surveillance in remote settings. When deployed, it will generate standardized, representative, high-quality data on pathogens and drug susceptibility from target populations and improve patients' clinical management in sentinelle site. This will in turn detect and support control of outbreaks in real time.

Laboratory capacity is key in AMR surveillance. Novel innovations, such as MSF's Mini-Lab, are needed to simplify microbiological diagnostics and to provide long awaited solutions for low-resource settings.

Author contributions

J.B.R.: Conceptualization, Methodology, formal analysis, writing – original draft, writing – review and editing, supervision; AN: Methodology, formal analysis, writing – review and editing; T.K.: Methodology, formal analysis, writing – review and editing; A.A.: Methodology, formal analysis, writing – review and editing; W.E.: Methodology, formal analysis, writing – review and editing; L.H.: Methodology, formal analysis, writing – review and editing; R.K.: Methodology, formal analysis, writing – review and editing; J.M.: Methodology, formal analysis, writing – review and editing; C.L.: Methodology, formal analysis, writing – review and editing; O.V.: writing – review and editing; T.N.: Conceptualization, methodology, formal analysis, writing – review and editing, supervision; D.A.: Conceptualization, writing – review and editing, supervision; F.K.: conceptualization, methodology, formal analysis, writing – review and editing, supervision.

Transparency declaration

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References

[1] Clift C, Centre on Global Health Security. Review of progress on antimicrobial resistance. Chatham House: The Royal Institute Of International Affairs; 2019. p. 1–16.
[2] Center for Disease Dynamics, Economics & Policy. State of the world's antibiotics. Washington, D.C: CDDEP; 2015.
[3] World Health Organization. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2016-2017. Geneva: WHO; 2017. p. 1–148.
[4] World Health Organization. Presentation WHO report on antibacterial resistance. Geneva: WHO; 2014.

[5] Ashley EA, Recht J, Chua A, Dance D, Dhorda M, Thomas N, et al. Antimicrobial resistance in low and middle income countries. An analysis of surveillance networks. Infectious Data Observatory; 2016.
[6] Welcome Trust. The Global Response to AMR: Momentum, success, and critical gaps. Welcome Trust; 2020.
[7] Gandra S, Alvarez-Uria G, Turner P, Joshi J, Limmathurotsakul D, van Doorn HR. Antimicrobial resistance surveillance in low-and middle-income countries: progress and challenges in eight South Asian and Southeast Asian countries. Clin Microbiol Rev 2020;33:1–29.
[8] Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. PLoS One 2017;12:1–18.
[9] Saeed DK, Hasan R, Naim M, Zafar A, Khan E, Jabeen K, et al. Readiness for antimicrobial resistance (AMR) surveillance in Pakistan; a model for laboratory strengthening. Antimicrob Resist Infect Control 2017;6:1–7.
[10] Hazim C, Abubeker Ibrahim R, Westercamp M, Alebachew Belete G, Amare Kibret B, Kanter T, et al. Establishment of a Sentinel Laboratory-based antimicrobial resistance surveillance network in Ethiopia. Healt Security 2018;16:S30–6.
[11] Ombelet S, Ronat J-B, Walsh T, Yansouni C, Cox J, Vlieghe E, et al. Clinical bacteriology in low-resource settings: today's solutions. Lancet Infect Dis 2018;18:e248–58.
[12] Ombelet S, Barbé B, Affolabi D, Ronat J, Lompo P, Lunguya O, et al. Best practices of blood cultures in low- and middle-income countries. Front Med 2019;6:131.
[13] Baron EJ. Clinical microbiology in underresourced settings. Clin Lab Med 2019;39:359–69.
[14] Lewis JM, Feasey NA, Rylance J. Aetiology and outcomes of sepsis in adults in sub-Saharan Africa: a systematic review and meta-analysis. Crit Care 2019;23:1–11.
[15] Oldenkamp R, Schultsz C, Mancini E, Cappuccio A. Filling the gaps in the global prevalence map of clinical antimicrobial resistance. Proc Natl Acad Sci USA 2020;118:2020.
[16] Seale AC, Hutchison C, Fernandes S, Stoesser N, Kelly H, Lowe B, et al. Supporting surveillance capacity for antimicrobial resistance: laboratory capacity strengthening for drug resistant infections in low and middle income countries. Wellcome Open Res 2017;2:1–18.
[17] Ashley EA, Recht J, Chua A, Dance D, Dhorda M, Thomas NV, et al. An inventory of supranational antimicrobial resistance surveillance networks involving low- and middle-income countries since 2000. J Antimicrob Chemother 2018. April: 1–13.
[18] Devi S. No time to lower the guard on AMR. Lancet Microbe 2020;1:e198.
[19] Kanapathipillai R, Malou N, Hopman J, Bowman C, Youssef N, Michel J, et al. Antibiotic resistance in conflict settings: lessons learned in the Middle East. JAC-Antimicrobial Resist 2019;1:2–4.
[20] Ronat JB, Kakol J, Khoury MN, Berthelot M, Yun O, Brown O, et al. Highly drug-resistant pathogens implicated in burn-associated bacteremia in an Iraqi burn care unit. PLoS One 2014;9:e0101017. https://doi.org/10.1371/journal.pone.0101017.
[21] Teicher CL, Ronat J-B, Fakhri R, Basel M, Labar A, Herard P, et al. Antimicrobial drug-resistant bacteria isolated from Syrian war-injured patients, August 2011–march 2013. Emerg Infect Dis 2014;20:1949–51.
[22] Murphy RA, Ronat J-B, Fakhri R, Herard P, Blackwell N, Abgrall S, et al. Multidrug-resistant chronic osteomyelitis complicating war injury in Iraqi civilians. J Trauma 2011;71:252–4.
[23] Murphy RA, Nisenbaum L, Labar A, Sheridan R, Ronat J-B, Dilworth K, et al. Invasive Infection and outcomes in a humanitarian surgical burn program in Haiti. World J Surg 2016;40:1–8.
[24] Fily F, Ronat J-B, Kanapathipillai R, Seguin C, Hussein N, Fakhri R, et al. Post-traumatic osteomyelitis in Middle East war-wounded civilians: resistance to first-line antibiotics in selected bacteria over the decade 2006–2016. BMC Infect Dis 2019;19:103.
[25] Langendorf C, Le Hello S, Moumouni A, Gouali M, Mamaty AA, Grais RF, et al. Enteric bacterial pathogens in children with diarrhea in Niger: diversity and antimicrobial resistance. PLoS One 2015;10:e0120275.
[26] Page A-L, De Rekeneire N, Sayadi S, Aberrane S, Janssens A-C, Rieux C, et al. Infections in children admitted with complicated severe acute malnutrition in Niger. PLoS One 2013;8:e68699.
[27] Okeke IN, Feasey N, Parkhil J, Turner P, Limmathurotsakul D, Georgiou P, et al. Leapfrogging laboratories : the promise and pitfalls of high-tech solutions for antimicrobial resistance surveillance in low-income settings. BMJ Glob Heal 2020;5:e003622.
[28] Natale A, Ronat J-B, Mazoyer A, Rochard A, Boillot B, Hubert J, et al. The Mini-Lab: accessible clinical bacteriology for low-resource settings. Lancet Microbe 2020;1:e56–8.
[29] Ombelet S, Natale A, Ronat JB, Vandenberg O, Hardy L, Jacobs J. Evaluation of MicroScan bacterial identification panels for low-resource settings. Diagnostics 2021;11:349.
[30] Ombelet S, Natale A, Ronat J-B, Kesteman T, Vandenberg O, Jacobs J, et al. Biphasic versus monophasic manual blood culture bottles for low-resource settings: an in-depth *in vitro* evaluation using simulated blood cultures. SSRN Electron 2021;1:1–21.
[31] Datema TAM, Oskam L, van Beers SM, Klatser PR. Critical review of the stepwise Laboratory Improvement Process Towards Accreditation (SLIPTA): suggestions for harmonization, implementation and improvement. Trop Med Int Health 2012;17:361–7.
[32] World Health Organization. Quality assurance in bacteriology and immunology. Geneva: WHO; 2012.
[33] Barbé B, Yansouni C, Affolabi D, Jacobs J. Time to implement quality management for clinical bacteriology in sub-Saharan Africa: progress so far and way forward. Clin Microbiol Infect 2017;23:426–33.
[34] World Health Organization. Stepwise Laboratory Improvement Process Towards Accreditation (SLIPTA). 2012. Available: https://www.who.int/tb/laboratory/afro-slipta-checklist-guidance.pdf. [Accessed 12 October 2016].
[35] Bernabé KJ, Langendorf C, Ford N, Ronat JB, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. Int J Antimicrob Agents 2017;50:629–39.
[36] DHHS (NIOSH). 94-110 Applications Manual for the Revised NIOSH Lifting Equation. CDC; 1994.
[37] ISO, NF EN 12464-1. Lumière et éclairage - Éclairage des lieux de travail - Partie 1 : Lieux de travail intérieurs. AFNOR; 2002.
[38] ISO, NF EN 14056. Mobilier de laboratoire, recommandation de conception et d'installation. AFNOR; 2003.
[39] INRS. ED999. Guide de conception des laboratoires d'analyse biologique. 2018.
[40] Miring'u G, Bundi M, Muriithi B, Apondi E, Galata A, Kathiiko C, et al. Knowledge and practices regarding usage of biological safety cabinets. Appl Biosaf 2017;22. 153567601668579.
[41] WHO. Laboratory biosafety manual. 3rd ed. Geneva: CDC; 2004.
[42] Miller AK, Gionea S, Vongsouvath M, Davong V, Mayxay M, Somoskosi A, et al. A robust incubator to improve access to microbiological culture in low resource environments. J Med Devices Trans ASME 2019;13:1–7.
[43] European Society for Clinical Microbiology and Infectious Diseases and Société Française de Microbiologie. European manual of clinical microbiology. 2012.
[44] CLSI. Performance standards for antimicrobial susceptibility testing, vol. 29. Clinical Laboratory Standard Institute; 2020. p. 136.
[45] The European committee and Antimicrobial susceptibility testing, Intrinsic resistance and Unusual Phenotypes version 3.2 February 2020. 2020. p. 1–12. https://Eucast.Org/Expert_Rules_and_Intrinsic_Resistance/.
[46] Giske CG, Martinez L, Canton R, Stefani S, Skov R, Glupczynski Y, et al., EUCAST subcommittee for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. Eur Soc Clin Microbiol Infect Dis 2013:1–40.
[47] Jorgensen JH, Ferraro MJ. Antimicrobial susceptibility testing: a review of general principles and contemporary practices. Clin Infect Dis 2009;49:1749–55.
[48] The European committee and Antimicrobial susceptibility testing. Testing Breakpoint tables for interpretation of MICs and zone diameters, V 10.0. 2020.
[49] World health organization model list of essential medicines vol. 21. World Health Organization; 2019. p. 119–34. https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/essential-medicines-lists.
[50] World Health Organization. GLASS manual for early implementation. Geneva: WHO; 2015.
[51] Sharland M, Pulcini C, Harbarth S, Zeng M, Gandra S, Mathur S, et al. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. Lancet Infect Dis 2018;18:18–20.
[52] Stelling JM. News and notes WHONET: an information system for monitoring recommendations for preventing the spread of antimicrobial resistance. Emerg Infect Dis 1995;1:66–7.
[53] Dailey PJ, Osborn J, Ashley EA, Baron EJ, Dance D, Fusco D, et al. Defining system requirements for simplified blood culture to enable widespread use in resource-limited settings. Diagnostics 2019;9:1.
[54] Ling C, Roberts T, Cusack T-P, Dance D, Lee S, Reed T, et al. Impact of delays to incubation and storage temperature on blood culture results in tropical countries: a multi-centre study. Int J Infect Dis 2020;101:195.
[55] WHO Technical Guidance Series (TGS). Establishing stability of an in vitro diagnostic for WHO Prequalification. vol. 2. Worl Health Organization; 2015. p. 1–25.