

# Clinical bacteriology in low-resource settings: today's solutions



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Low-resource settings are disproportionately burdened by infectious diseases and antimicrobial resistance. Good quality clinical bacteriology through a well functioning reference laboratory network is necessary for effective resistance control, but low-resource settings face infrastructural, technical, and behavioural challenges in the implementation of clinical bacteriology. In this Personal View, we explore what constitutes successful implementation of clinical bacteriology in low-resource settings and describe a framework for implementation that is suitable for general referral hospitals in low-income and middle-income countries with a moderate infrastructure. Most microbiological techniques and equipment are not developed for the specific needs of such settings. Pending the arrival of a new generation diagnostics for these settings, we suggest focus on improving, adapting, and implementing conventional, culture-based techniques. Priorities in low-resource settings include harmonised, quality assured, and tropicalised equipment, consumables, and techniques, and rationalised bacterial identification and testing for antimicrobial resistance. Diagnostics should be integrated into clinical care and patient management; clinically relevant specimens must be appropriately selected and prioritised. Open-access training materials and information management tools should be developed. Also important is the need for onsite validation and field adoption of diagnostics in low-resource settings, with considerable shortening of the time between development and implementation of diagnostics. We argue that the implementation of clinical bacteriology in low-resource settings improves patient management, provides valuable surveillance for local antibiotic treatment guidelines and national policies, and supports containment of antimicrobial resistance and the prevention and control of hospital-acquired infections.

## Introduction

Bacterial sepsis is a leading cause of mortality and critical illness worldwide.<sup>1-3</sup> Antimicrobial resistance is considered a major threat to global health and low-income and middle-income countries<sup>4</sup> are disproportionately burdened.<sup>5,6</sup> Contributing factors include patients' vulnerability to invasive bacterial illness, uncontrolled use of antibiotics, and poor laboratory support for clinical diagnosis resulting in overuse of antibiotics. Further, practices to prevent health care-acquired infections are generally absent in low-resource settings.<sup>5</sup>

Clinical bacteriology is the laboratory work-up needed for identification, quantification, and antibiotic susceptibility testing of bacteria found in clinical patient samples. Doing effective clinical bacteriology supports three of the five strategic objectives identified by WHO for containment of antimicrobial resistance: surveillance, appropriate use of antibiotics (antibiotic stewardship), and infection control in health-care settings.<sup>7</sup> These objectives were reaffirmed at the UN General Assembly's high-level meeting on antimicrobial resistance in September, 2016.<sup>8</sup> Clinical bacteriology contributes substantially to patients' diagnosis and guides antibiotic treatment. For severe sepsis, inappropriate antimicrobial therapy is a major contributor to mortality and sepsis guidelines emphasise the importance of culture-guided therapy.<sup>9</sup> For tropical low-resource settings, inappropriate therapy is particularly problematic because life-threatening bacterial infections, such as non-typhoidal *Salmonella* spp bloodstream infections, are often clinically indistinguishable from severe *Plasmodium falciparum* infection<sup>10-13</sup> and are often

misdiagnosed.<sup>14,15</sup> Identification of bacterial pathogens and antimicrobial susceptibility testing allow optimisation, de-escalation, or discontinuation of antibiotic treatment, resulting in improved patient outcomes, reduced costs, and reduced selection of antimicrobial resistance.<sup>16</sup> Culture data from patient samples can be aggregated to identify common pathogens and determine their susceptibility patterns. Such local surveillance data will support validation of empirical guidelines for antibiotic treatment.<sup>17</sup> In addition, daily reviews of clinical bacteriology data are vital for the detection of hospital-associated or community-associated outbreaks and to monitor emergence of resistance.<sup>18,19</sup>

Diagnostic laboratories in low-income and middle-income countries face challenges of infrastructure, equipment, logistics, quality-assurance, and human resources.<sup>20</sup> In the past decade, considerable efforts have been made to improve laboratory systems in low-resource settings.<sup>21-23</sup> Although diagnostics for tuberculosis, malaria, HIV, and Ebola virus have been successfully disseminated,<sup>5,24</sup> clinical bacteriology covers a wide spectrum of pathogens and cannot be achieved by simple diagnostic and therapeutic algorithms or by a few rapid diagnostic tests or vertical control programmes. Furthermore, the design, development, and clinical validation of new diagnostics for clinical bacteriology can take 2-10 years.<sup>25</sup> The dissemination of diagnostics in low-resource settings comes with additional challenges, including procurement, distribution, and quality control issues.<sup>26</sup> In addition, manufacturers' production capacity and compliance with ISO standards (ISO 13485) are

*Lancet Infect Dis* 2018

Published Online  
March 5, 2018  
[http://dx.doi.org/10.1016/S1473-3099\(18\)30093-8](http://dx.doi.org/10.1016/S1473-3099(18)30093-8)

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often inadequate in such settings.<sup>27</sup> Further, with the advances in mass spectrometry technologies and automated bacterial identification and antimicrobial susceptibility testing in high-resource settings, the gap between these systems and practices of clinical bacteriology in low-resource settings has widened. Pending the implementation of new technologies, conventional culture-based techniques are still the best option for the application of clinical bacteriology in these settings; they are well studied, robust, universally accepted, and most have regulatory certification. Moreover, culture-based techniques are still essential for antimicrobial susceptibility testing, even in the presence of molecular or biomarker tests.

A framework towards the implementation of clinical bacteriology in low-resource settings, including common obstacles and global priorities, is urgently needed. In this Personal View we aim to describe a framework for implementation that is suitable for general referral hospitals in low-resource settings with a moderate infrastructure (ie, a basic diagnostic laboratory operated by laboratory staff without expertise in microbiology).<sup>28</sup> Although focused on operational and technical requirements, this framework will inform clinicians and health-care policy makers. We briefly discuss laboratory services in low-resource settings, such as supranational initiatives involved in funding, accreditation, diagnostic regulations, and manufacturing.<sup>20–22,29–32</sup>

### Clinical bacteriology in low-resource settings: six building blocks

Based on our collective expert opinion and review of the available literature, we propose that six essential building blocks have to be addressed for successful implementation of clinical bacteriology in low-resource settings.

#### Availability of equipment and consumables adapted for use in low-resource settings

Environmental conditions in low-resource settings affect electronic equipment and consumables, such as glassware and dehydrated culture media<sup>33</sup> (table 1, figure 1). Availability of quality-assured diagnostics is further compromised by the absence of onsite production and inadequate supply chains, which are incompatible with the shelf life and cold storage requirements of many diagnostic kits.<sup>41</sup> In addition, there is little commercial interest in the development of new diagnostics adapted for use in low-resource settings because of low profit margins.<sup>5</sup>

Equipment and consumables for diagnostics in low-resource settings need to be adapted so that they are resistant to harsh conditions, such as temperature, humidity, dust, sunlight, and transport. In addition to being robust, safe, and stable, equipment should consume little energy and be easy to maintain. Consumables (such as culture media or test reagents)

need to have a long shelf life and generate little waste. Where possible, internal quality controls should be included in reagent kits. Quality assurance in manufacturing, client support, post-marketing service, and maintenance should be guaranteed.

A first step towards adaptation of diagnostics equipment for use in low-income settings is to draft clear profiles of target products and technical specifications by regulatory agencies, manufacturers, and stakeholders. Some manufacturers have already launched research initiatives for low-cost innovation that target fever-related diagnostics in low-resource settings.<sup>86</sup> Furthermore, manufacturers in growing economies (such as China, Vietnam, and Thailand) are producing a wide range of diagnostics hitherto unknown outside their domestic markets. Some diagnostics used in clinical bacteriology (such as reagents used for phenotypical tests and serotyping) have not been extensively validated for stability and shelf life, which might have been arbitrarily set, for example, at 25°C and 6 months. However, actual use (and some guidelines) suggests a reliable performance outside these specifications<sup>87</sup> and identical products from different manufacturers have different storage and shelf life requirements. Therefore, in line with current practice for pharmaceutical products,<sup>88</sup> extended product stability testing (including temperature and storage stability) should be done to confirm the true limits in low-resource settings.

Other short-term goals are tropicalised packaging (eg, vacuum-sealed packaging to protect against humidity), clear labelling, and adaptation of instructions to an appropriate language and educational level.<sup>89,90</sup> Furthermore, production of quality-assured consumables (such as culture media and phenotypical test reagents) can be outsourced to a centralised facility as has been done in Cambodia.<sup>91</sup>

Medium-term objectives include the development of low tech, low cost, and low maintenance equipment, such as electricity-free incubators,<sup>92</sup> battery-operated centrifuges,<sup>93</sup> and autoclaves powered by solar energy.<sup>94–96</sup> Alternatives for sheep blood, horse blood, and rabbit plasma should be explored; for example, goat, pig, and hair sheep (a breed of sheep adapted to tropical climates) blood are alternatives to sheep blood for homemade culture media,<sup>97,98</sup> but lyophilised or synthetic media should also be considered. Likewise, agar (ie, solidifying substrate in culture media) is obtained from sea algae at a few harvesting sites; substrates such as cellulose produced by engineered bacteria<sup>99</sup> should be assessed as a commercial alternative.

#### Rationalised bacterial identification and antimicrobial susceptibility testing

Because of recent technological advances in identification techniques and continuous improvements to guidelines for antimicrobial susceptibility testing, state-of-the-art identification and testing in low-resource settings remains a major challenge (table 1).<sup>41</sup> Although

	High-resource settings	Low-resource settings
Infrastructure	Infrastructure requirements covered by ISO 15189, Joint Commission International, CLSI QMS01-A4, Clinical Laboratory Improvement Amendments, or an equivalent quality management system <sup>34-37</sup>	Basic requirements frequently not met: <sup>5-30</sup> power, climate control and ventilation, dust reduction, water quality, light sources, biosafety requirements, and internet connectivity
Diagnostics	Increasing development of diagnostics <sup>38,39</sup>	Sales are not lucrative enough for adequate return on investment to create rapid diagnostic solutions <sup>5</sup>
Quality assurance	Quality-assured production and supply by ISO 13485 certified manufacturers <sup>40</sup>	Limited quality assurance of process and products; <sup>41</sup> diagnostics manufacturers are often not certified by ISO 13485 <sup>27</sup>
Consumables	Procurement and supply chain of diagnostics short and reliable	General absence of locally produced consumables; when locally produced, consumables are often substandard with poor quality assurance and irregular availability; <sup>42</sup> some reagents are subject to dangerous goods regulations when shipped by air; <sup>43</sup> long delivery delays in combination with short shelf life and need for cold chain (2–8°C or as low as –20°C) for critical products; high stress conditions (heat, humidity) and limited environmental stability <sup>30</sup>
Logistics	Storage, stock management, and distribution systems in place	Stock management and inventory systems are not in place or inappropriate <sup>30</sup>
Standard operating procedures	Standards for standard operating procedures covered by ISO15189 or equivalent quality management system <sup>34</sup>	The creation of and updating of standard operating procedures and other documents are a significant obstacle; <sup>30</sup> multiple language and cultural barriers to the understanding of such procedures <sup>44</sup>
Reference materials	Reference materials are easily accessible	Reference materials (such as culture type strains) are expensive, subject to strict shipment requirements <sup>40</sup> and difficult to maintain
Documents	Guideline documents, standards and norms are affordable	Documents from the International Organization for Standardization and guidelines from CLSI are for sale but expensive. Recently, CLSI has made their key document, M100:S27, freely available online <sup>45</sup>
Culture-based growth	Automated blood culture systems with continuous growth monitoring and automated detection, <sup>46</sup> identification with MALDI-TOF, and automated antimicrobial susceptibility testing have substantially decreased turnaround time <sup>47,48</sup> and have increased simplicity	Automated equipment and MALDI-TOF are rarely used because of high cost and stringent requirements for infrastructure; <sup>5-49</sup> service contracts are unavailable or unaffordable in many settings; <sup>5</sup> manual blood culture systems require training and experience; many manual diagnostic products are no longer commercialised
Identification	Identification systems validated with bacterial collections obtained in high-resource settings	Identification methods not validated with bacterial collections from low-resource settings; <sup>49-50</sup> some tropical bacteria cannot be reliably identified with commercial identification methods <sup>51,52</sup>
Antimicrobial susceptibility testing of bacteria	Harmonised criteria by international guidelines (CLSI, EUCAST) integrated in automated antimicrobial susceptibility testing methods assuring correct and updated use of breakpoints and expert rules <sup>33,54</sup>	Guidelines are often temporary, not well disseminated, only available in English, and poorly followed; <sup>41</sup> expert rules are too complicated to be mastered by staff without expertise in microbiology
Laboratory processes	Streamlined and automated trajectory with the help of Laboratory Information Management Systems contributes to shortening of preanalytical phase and post-analytical phase <sup>55,56</sup>	Piecemeal sampling, paper-based systems, with hardcopy results collected too late or not at all; <sup>57</sup> accuracy of results is seen as more important than speed and short turnaround time
Laboratory criteria	Clinically relevant criteria for sampling <sup>58</sup>	No laboratory guidance for selection, sampling, and transport of specimens results in inadequate sampling (eg, fistula and wound swabs, long transport delays); sampling biased to patients who are severely ill, failed initial treatment, or can afford testing
Communication	Proactive communication and reporting by the clinical microbiologist <sup>59</sup>	Poor communication between laboratory staff and clinicians <sup>60</sup>
Hours of operation	24/7 specimen processing, consultative role including out-of-hours call for a clinical microbiologist <sup>41</sup>	Laboratory activities mostly limited to office hours
Quality indicators	Quality indicators for sampling processing and reporting embedded in quality management systems	Quality indicators not systematically monitored (eg, blood culture contaminants)
Professional standards	Professional standards for clinical microbiologist and biomedical staff <sup>61</sup> and professional societies at the international and national levels	No professional standards or profiles for clinical microbiologists; few professional societies and postgraduate activities
Laboratory staff	Dedicated, well trained, and experienced biomedical staff; clinical microbiology experts are involved in training of staff and management of laboratory	Frequent understaffing and poor staff retention; <sup>5,30,63,64</sup> clinical microbiology experts are non-existent or scarcely involved; absent preservice training and education; <sup>64</sup> few available training or teaching sites for clinical bacteriology
Patients	The patient is knowledgeable and has health insurance; clinical and nursing staff familiar with indications	Out-of-pocket payment, cultural differences, and insufficient knowledge from both patients and staff result in reluctance to take samples from patients <sup>32,65-67</sup>
Clinicians	Clinicians are familiar with indications and interpretation of laboratory results; and trust and rely on the laboratory results as part of evidence-based clinical algorithms	Clinicians have a high reliance on clinical judgment, are reluctant to request laboratory tests, and tend to deny laboratory results <sup>57,68</sup> because of negative perceptions of the laboratory, which include slow turnaround, <sup>14,69,70</sup> poor accuracy of laboratory tests, <sup>14,69,70</sup> inadequate laboratory capacity, and unavailability of consumables <sup>20,67</sup>
AMR	High awareness of AMR and infection control among clinicians, nursing staff, and hospital staff	AMR is considered mainly a worldwide or nationwide problem, but less of a problem within clinicians' own hospitals <sup>71,72</sup>
Antibiotics	Patients educated on appropriate and restrictive use of antibiotics	Pressure from patients to prescribe antibiotics; <sup>71,72</sup> issues with self-medication because of widespread availability of antibiotics
Clinical decision making	Clinical microbiologist is an active member of the antibiotic stewardship committee <sup>73</sup>	Antibiotic stewardship committees or activities are mostly absent; few studies on non-use of antibiotics or de-escalation through the use of clinical bacteriology; <sup>5</sup>

(Table 1 continues on next page)

	High-resource settings	Low-resource settings
	(Continued from previous page)	
Antibiotic stewardship	AMR surveillance reports generated by the results of routinely submitted samples and aggregated in (supra)national or regional networks	AMR surveillance data based on poor data quality and representativeness, especially in Africa and the western Pacific; <sup>5,24,75</sup> AMR surveillance focused on intensive care units and vulnerable populations <sup>5</sup>
Infection control	Real-time alert function for infection control (community and hospital-based outbreaks) <sup>76</sup>	Infection control committees rarely work with laboratory data for outbreak investigation and management <sup>5,74</sup>
Surveillance	All laboratories take part in surveillance of (re-)emerging pathogens and vaccine-preventable diseases <sup>77</sup>	Public health surveillance is mostly confined to reference laboratories
Accreditation	Certification, accreditation, and regulation of clinical laboratories	WHO Regional Office for Africa provides an accreditation process as an interim pathway to meet international laboratory standards; <sup>78</sup> other tools, such as Stepwise Laboratory Improvement Process Towards Accreditation and Laboratory Quality Stepwise Implementation tool, focus on malaria, tuberculosis, and HIV and have few applications to clinical bacteriology <sup>79,80</sup>
External quality control	External quality control programmes available	Existing external quality programmes for microbiology are scarce, expensive, and address mostly HIV, tuberculosis, and malaria <sup>42,81-85</sup>
Reference laboratories	Functional reference laboratories	Few reference laboratories, mainly oriented to research and outbreak management; referral of specimens for clinical bacteriology is more demanding (sampling, shipment) than for tuberculosis and HIV testing

AMR=antimicrobial resistance. CLSI=Clinical and Laboratory Standards Institute. EUCAST=European Committee for Antimicrobial Susceptibility Testing. MALDI-TOF=matrix assisted laser desorption ionisation–time of flight.

**Table 1: Clinical bacteriology in high-resource settings compared with low-resource settings**

For more on the International Organization for Standardization see <http://www.iso.org/iso/home.html>



**Figure 1: Adapted consumables for use in low-income settings**  
At high relative humidity, glass slides for microscopy become opaque because of the development of condensation within the glass. Photograph taken in DR Congo.

some guidelines on antimicrobial susceptibility testing are now open access,<sup>45,100</sup> building local capacity to implement annual revisions of such guidelines is a major challenge.

The relevance of the need to identify all bacteria to the species level is debatable;<sup>101</sup> grouping genera and species according to their clinical relevance might be more useful.<sup>47</sup> We propose the adoption of a two-tier approach consisting of first-line identification to the group level

with preliminary antimicrobial susceptibility testing, followed by a more advanced identification and testing at national reference laboratories. Practical guidelines for grouping bacteria according to clinical relevance, antimicrobial resistance profile, hospital epidemiology, and public health importance should be undertaken. Table 2 shows how Gram-negative enteric bacteria can be grouped according to clinical and infection control relevance.<sup>48,101,117,118</sup> In most laboratories, the detail and level of identification of bacteria will be dependent also on the technical and economic feasibility of the identification system used.

The grouping of bacteria would encourage technologies for abbreviated identification through so-called spot tests, which are single substrate biochemical or enzymatic tests that can be read via colour, fluorescence, or turbidity. Spot tests, already available for key pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, are reliable and can contribute to clinical decision making.<sup>58,119,120</sup> Valuable documents, such as the Clinical and Laboratory Standards Institute guidelines for the identification for bacteria and yeasts,<sup>119</sup> should be updated, extended to tropical bacteria (eg, *Salmonella* spp, *Burkholderia pseudomallei*), validated with geographically representative strains, and made open access.

Testing panels for antimicrobial susceptibility should be adapted to the requirements of low-resource settings (eg, harmonised with the country's essential drug list). Disk diffusion testing has advantages of cost, flexibility, simplicity, and reliability. However, simplified tests for minimal inhibitory concentration—such as lyophilised microbroth dilution methods—could be less prone to error and are sometimes required (eg, ceftriaxone for *Streptococcus pneumoniae*). Simple and affordable reading apparatus would be helpful for accurate interpretations,

	Clinical relevance	Infection control relevance	Antimicrobial resistance profile	Public health importance
<i>Citrobacter</i> spp; <i>Cronobacter</i> spp; <i>Enterobacter</i> spp; <i>Hafnia alvei</i> spp; <i>Serratia</i> spp*	Pneumonia; post-operative site infections; urinary tract infections; wound colonisation or infection	Mostly health care-associated <sup>102</sup>	Multidrug resistant: AmpC expression (cephalosporin resistance); <sup>103</sup> included on WHO's priority pathogen list† <sup>104</sup>	No particular public health importance apart from health care-associated infections
<i>Klebsiella</i> spp; <i>Raoultella</i> spp	Bloodstream infections; pneumonia; pyogenic infections; urinary tract infections; wound colonisation or infection	Often health care-associated (hospital outbreaks); <sup>103</sup> community-associated strains (pyogenic infections) <sup>105</sup>	Multidrug resistant: ESBL and carbapenemase production; <sup>106</sup> included on WHO's priority pathogen list† <sup>104</sup>	Global dissemination of antibiotic resistance genes; <sup>104,106</sup> clonal spread of multidrug resistant (sequence type 258) <sup>107</sup> hypervirulent community-associated strains <sup>105</sup>
<i>Escherichia coli</i>	Bloodstream infections; enteritis; urinary tract infections	Mostly community-associated <sup>102</sup>	Multidrug resistant: ESBL, carbapenemase production; <sup>107</sup> included on WHO's priority pathogen list† <sup>104</sup>	Clonal spread of multidrug resistant sequence type 131 in community <sup>107,108</sup>
<i>Salmonella typhi</i> ; <i>Salmonella Paratyphi A</i> *	Enteric fever	Community-associated	Multidrug resistant, decreased ciprofloxacin resistance and occasionally ESBL; <sup>109</sup> included on WHO's priority pathogen list† <sup>104</sup>	Human-to-human transmission; <sup>109</sup> clonal spread of multidrug-resistant H58 strain <sup>110</sup>
Non-typhoidal <i>Salmonella</i> spp	Bloodstream infections; enteritis	Community-associated; hospital outbreaks	Multidrug resistant, decreased ciprofloxacin resistance, and occasionally ESBL; <sup>109</sup> included on WHO's priority pathogen list† <sup>104</sup>	Major cause of bloodstream infection in children in sub-Saharan Africa; associated with more deaths than malaria; <sup>111,112</sup> clonal spread of invasive <i>Salmonella typhimurium</i> (sequence type 313) <sup>113</sup>
<i>Morganella</i> spp; <i>Proteus</i> spp; <i>Providencia</i> spp	Post-operative site infections; urinary tract infections	Healthcare-associated	Antimicrobial susceptibility profile differs from other Enterobacteriaceae (eg, intrinsic colistin resistance) <sup>114</sup>	No particular public health importance apart from health care-associated infections
<i>Shigella</i> spp	Dysentery; enteritis; haemolytic-uremic syndrome	Community-associated	Included on WHO's priority pathogen list† <sup>104</sup>	<i>Salmonella dysenteriae</i> serotype 1 is frequently involved in epidemics <sup>115</sup>

Detail and level of identification is dependent on technical and economic feasibility of the identification system used. We focused on isolates recovered from bloodstream pathogens. Multidrug resistance is defined as resistance to at least one agent in three or more antibiotic classes.<sup>116</sup> ESBL=extended spectrum beta-lactamase. \*If technically feasible and affordable, separate identification of this species would be desirable. †WHO's priority pathogen list is a global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.

**Table 2: Proposed grouping of bacterial species by clinical and infection control relevance; example of Gram-negative enteric bacteria**

particularly when coupled to an open-access expert system, such as the system available in WHONET software.

### Communication between the laboratory and clinicians

The interface between clinicians and the diagnostic laboratory is poorly studied in low-resource settings.<sup>60,69,121</sup> Guided by their reliance on clinical algorithms and syndromic approaches, clinicians are reluctant to request laboratory tests (table 1); a tendency that is aggravated by their perception that tests are expensive, slow, and often irrelevant.<sup>65</sup> In some regions, patients fear blood sampling and invasive procedures (figure 2).<sup>65,66</sup> Additionally, senior managers in hospitals are typically academic clinicians, which increases the gap in communication between decision makers, clinicians, and laboratory staff. Laboratory staff often feel underappreciated and have limited professional opportunities.<sup>69,121</sup>

In high-resource settings, clinical bacteriology is closely integrated with patient management and infection prevention and control.<sup>59,122</sup> Such integration does not exist in low-resource settings, where trained clinical microbiologists are rare and the main focus of the laboratory work is on the analytical phase, with little professional collaboration and communication between laboratory staff and clinicians.<sup>20,60</sup> Therefore, even when good quality diagnostic laboratories exist in low-resource settings, their impact is frequently compromised by

underuse, inadequate specimen collection, or post-analytical issues (such as ineffective reporting of results).<sup>5,33,65,69</sup>

We advocate regular person-to-person interactions between clinicians and laboratory staff to address the communication gap and further highlight the importance of this interaction through pre-service and continuous training.<sup>123,124</sup> The Strengthening Laboratory Management Toward Accreditation (SLMTA) programme provides useful strategies on how to improve communication between clinicians and laboratory staff.<sup>78,125</sup> Likewise, the modules for specimen collection and test result reporting in the SLMTA toolkit could help to strengthen clinical bacteriology activities in low-resource settings.

### Prioritisation of clinically relevant specimens

Although key to performance,<sup>78</sup> the minimal number of samples (critical volume) that should be processed to acquire expertise in clinical bacteriology is not defined. Clinical bacteriology relies on the competence and experience of laboratory staff; for example, the Gram stain, which provides crucial information during diagnosis of blood cultures,<sup>126,127</sup> is notoriously prone to error in inexperienced hands.<sup>128</sup> Further, laboratories in low-resource settings tend to process few samples and often use inappropriately selected specimens (table 1).

For more on WHONET see <http://whonet.org/>



Jan Jacobs

**Figure 2: Lumbar puncture**

This procedure requires sterile gloves, a specialised needle, and assistance from a nursing team. Photograph taken in DR Congo.

When resources are limited, we propose the prioritisation of key clinical specimens (table 3)—for example, blood cultures are highly relevant for patient management and for antimicrobial resistance surveillance.<sup>18</sup> By contrast, culture of cerebrospinal fluid, with its stringent culture requirements, might not have added clinical value (ie, after cell count and Gram stain testing) because standard treatment with third generation cephalosporins in the postneonatal period covers most bacterial pathogens.<sup>133,141,142</sup>

Specimens from empyema, abscesses, and osteomyelitis, and surgical samples can guide clinical care, but procedures for these specimens are considerably more complex than laboratory work-up of blood culture samples or urine samples.<sup>136</sup> Clear sampling procedures and acceptance criteria need to be formalised, communicated, and implemented.<sup>124</sup>

#### Provision of accessible and affordable training and reference materials

Training materials dedicated to clinical bacteriology in low-resource settings are scarce, seldom updated, and sometimes expensive. Training (both theoretical and practical) and reference materials should be specific to the setting, open access, available in local languages,

and be readable and comprehensible for non-expert users of various cultural backgrounds.<sup>44</sup> End-user feedback and validation is useful to refine and improve teaching materials.<sup>44</sup>

Established guidance and toolkits should be linked to reference materials, including SLMTA toolkit modules, the Stepwise Laboratory Improvement Towards Accreditation checklist,<sup>79</sup> and WHO's Laboratory Quality Stepwise Implementation tool<sup>80</sup> can be complemented with real-life scenarios of clinical bacteriology. Clinical reference documents, such as WHO guidelines for hospital care of children and adults,<sup>141,142</sup> should include recommendations for clinical bacteriology (indications, sampling, and transport) and use of antibiotics. New programmes adapted to low-resource settings, such as WHO's Laboratory Assessment Tool,<sup>143</sup> also offer guidance on how to assess laboratories and national laboratory systems.

Onsite training of clinicians, nurses, and laboratory staff will encourage the highest efficiency and retention. Experiences from the implementation of clinical medicine in low-resource settings highlight the value of onsite support through educational outreach and mentoring visits.<sup>144</sup> The role of bench-side coaching by experienced professionals cannot be underestimated as a way of teaching good clinical practice.<sup>145</sup> Remote learning with video is a valuable complement to bench-side exposure;<sup>146</sup> for example, the European Committee for Antimicrobial Susceptibility Testing has released instruction videos for disk diffusion.<sup>147</sup> Telemicrobiology, which is the transfer of images of cultures and microscopy, allows for real-time analysis, expert consultation, training, and quality assurance at an affordable cost.<sup>148,149</sup>

#### Onsite validation and field adoption

As highlighted in the 2016 O'Neill report on antimicrobial resistance, more effort should be put into the development of new diagnostics for bacterial detection, identification, and antimicrobial susceptibility testing.<sup>150</sup> Promising new technologies are increasingly being used in clinical bacteriology (table 1), but when applied to low-resource settings there are budgetary, technical, human resource, and behavioural constraints and such technologies are rarely implemented outside of reference laboratories.<sup>25</sup> Furthermore, in low-resource settings, clinical performance studies are a major bottleneck to the development of diagnostics.<sup>151</sup> Specifically, many diagnostics are not tested in low-resource settings because of financial or operational constraints; therefore, their implementation in these settings is delayed.

Some manufacturers are forming partnerships and investing in research exploring low-cost diagnostic innovation<sup>86</sup> and some of those technologies might develop into valuable diagnostics for low-resource settings. Rather than awaiting accreditation in resource-rich settings, new diagnostics could be evaluated in field settings in low-resource setting. Some of these

For an example of such partnerships see <http://www.finddx.org/partners>

	Preanalytical and analytical feasibility	Relevance for individual patient management	Relevance for surveillance
Blood	++++ Technical requirements feasible; mostly one pathogen, top five pathogens account for most isolates <sup>129-132</sup>	++++ Unequivocal interpretation (except contaminants); high clinical impact; <sup>9</sup> amenable to antibiotic stewardship <sup>9</sup>	++++ Indications for sampling are standardised; quality indicators allow for inter-laboratory harmonisation and surveillance over time <sup>6</sup>
Cerebro-spinal fluid	+++ Sampling requires skills and expertise; specific transport are required for cold-vulnerable pathogens	+++ Little value of culture over white blood cell count and Gram stain <sup>133</sup>	+++ Epidemics ( <i>Neisseria meningitidis</i> ) or serotype distribution ( <i>Streptococcus pneumoniae</i> ) <sup>134,135</sup>
Empyema, closed abscess, joint fluid	+++ Mixed, fastidious, and anaerobic flora possible; specific transport needs; selective media and considerable expertise required	+++ Gram stain and culture can guide diagnosis and treatment, particularly in severe infections and when complete drainage is not possible	+++ Variability in patient selection
Bone tissue	++ Surgically obtained samples; requires grinding of specimens; <sup>136</sup> often polymicrobial infections <sup>137</sup>	++ Can guide treatment; some flora are difficult to interpret (eg, coagulase-negative staphylococci)	++ Variability in patient selection (eg, trauma, prosthesis material)
Respiratory tract (non-tuberculosis)	+ Useful for mixed flora and cold-vulnerable pathogens; contaminating oral flora; requires selective media and expertise	+ Difficult to determine difference between colonisation and infection	+ Variability in patient selection and contaminating or colonising flora
Urine	+ Long transport delay requires cold chain	++ Can alert to resistant bacteria; contaminating flora	++ Variability in patient selection (bias to antimicrobial resistance)
Stool	+ Challenging transport needs; selective culture media, microaerophilic incubation conditions ( <i>Campylobacter</i> spp); considerable expertise required	+ Diarrhoea frequently of non-bacterial origin; <sup>138</sup> long turnaround time; relatively low sensitivity for bacterial pathogens of greatest interest <sup>138</sup>	++ Suspected outbreaks of dysentery or cholera; confirmation of epidemic and antibiotic resistance patterns <sup>139,140</sup>

Grades of relevance and feasibility are shown as ++++ (high), +++ (moderate), ++ (low), or + (very low). Preanalytical feasibility refers to indications, sampling, and transport; analytical feasibility refers to technical (eg, selective culture media or incubation conditions) and human (training or expertise) requirements.

**Table 3: Relevance of different clinical specimens collected through routine patient care in low-resource settings**

innovations might then diffuse to high-resource settings, a process called reverse innovation.<sup>152,153</sup>

Well-functioning quality assured diagnostic laboratories could constitute reliable study sites to carry out clinical diagnostic studies in the target population. Beyond strict diagnostic performance, such studies should address the adoption of new diagnostics into practice, their integration into clinical care, and cost-effectiveness.<sup>154</sup>

### Beyond the six building blocks

Other factors can influence the implementation of clinical bacteriology in low-resource settings. Political commitment is essential to instal and equip clinical laboratories at all levels of health care and to strengthen health systems. It is therefore worth noting the recent resolution of the UN General Assembly, wherein Heads of State agreed to a broad, coordinated approach to tackle the root causes of antimicrobial resistance.<sup>8</sup> The announcement by WHO of a forthcoming Essential Diagnostics List could also help to integrate diagnostic resources better adapted to low-income settings into national programmes.<sup>155</sup>

In addition, the professional, academic, and regulatory environment should facilitate implementation of clinical bacteriology in health-care organisation and biomedical curricula. Reference laboratories in low-resource settings should extend their capacity to support basic bacteriology

and antimicrobial resistance,<sup>156</sup> rather than perpetuating existing silos through the restriction of their activities to HIV, tuberculosis, or malaria reference work.<sup>41,145</sup> Further opportunities to support the implementation of clinical bacteriology are linkage to the WHO prequalification programme of in-vitro diagnostics<sup>157</sup> and extension of the Maputo Declaration goals to include clinical bacteriology.<sup>23</sup>

Furthermore, in response to the 2016 O’Neill report on antimicrobial resistance,<sup>150</sup> wherein a Global Innovation Fund for non-commercial research was proposed, there have been calls for the development of a Global Antimicrobial Conservation Fund.<sup>158</sup> We strongly endorse this initiative, which—in collaboration with the UK Fleming Fund—would further support the provision of basic bacteriology services in low-resource settings.<sup>159</sup>

### Conclusions

Given the global attention given to antimicrobial resistance and several calls to action,<sup>7,160,161</sup> it is time to address the issue of strengthening clinical bacteriology in low-resource settings. The benefits of clinical bacteriology are numerous, not only for individual patient care, but also for surveillance of outbreaks and emerging resistance, and also management of hospital infections and antimicrobial usage. The reference laboratories and networks, which were established in response to WHO’s Maputo declaration on laboratory strengthening for the

diagnosis of HIV, tuberculosis, and malaria, could be used to include clinical bacteriology—since little clinical bacteriology is currently being done in most of these reference laboratories.<sup>23,41,145</sup>

We have outlined some challenges that might be encountered during the implementation of clinical bacteriology in low-resource settings and provide a framework as to how these difficulties could be overcome. The substantial progress made in the diagnosis and management of HIV, tuberculosis, and malaria has shown that non-expert staff can effectively deliver services that were previously considered too complicated and demanding.<sup>162</sup> With similar concerted international efforts on an international scale, we believe such progress could be achieved for clinical bacteriology.

#### Contributors

JJ and J-BR had the rationale for this work. JJ did the literature review, wrote the initial draft, and supervised the manuscript revisions. SO contributed to manuscript preparation, writing of the draft, revision, data compilation, literature review, and project administration. J-BR contributed to manuscript preparation, literature review, revision, and project administration. TW, CPY, OV, DM, EV, JC, and MS wrote substantial paragraphs, attributed literature, and provided critical review and commentary. The members of the bacteriology in low-resource settings working group are: Octavie Lunguya (National Institute for Biomedical Research, DR Congo); Marie-France Phoba (National Institute for Biomedical Research, DR Congo); Palpouguini Lompo (Institut de Recherche en Science de la Santé—Clinical Research Unit of Nanoro, Burkina Faso); Thong Phe (Sihanouk Hospital Center of Hope, Cambodia); Samuel Kariuki (Kenya Medical Research Institute, Kenya); Paul N Newton (Lao–Oxford–Mahosot Hospital, Wellcome Trust Research Unit, Laos); David A B Dance (Lao–Oxford–Mahosot Hospital, Wellcome Trust Research Unit, Laos); Claude Muvunyi (University of Rwanda, Rwanda); Sayda El Safi (University of Khartoum, Sudan); Barbara Barbe (Institute of Tropical Medicine, Belgium); Dadi Falay (University Hospital of Kisangani, DR Congo); Dissou Affolabi (Centre National Hospitalier Universitaire Hubert Koutoucou Maga, Benin); Maurice Page (independent consultant); Céline Langendorf (Médecins Sans Frontières, France); Yves Gille (Biologie Sans Frontières, France); Tjalling Leenstra (National Institute for Public Health and the Environment, Netherlands); John Stelling (Brigham & Women's Hospital, MA, USA); Thierry Naas (Hôpital de Bicêtre, France); Thomas Kesteman (Fondation Mérieux, France); Daniel Seifu (Addis Ababa University, Ethiopia); Elisabeth Delarocque-Astagneau (Institut Pasteur, France); Constance Schultsz (Academic Medical Center of the University of Amsterdam, Netherlands); Heidi Schutt-Gerowitt (University of Cologne, Germany); Joanne Letchford (Diagnostic Microbiology Development Program, Cambodia); Heiman Wertheim (Department of Clinical Microbiology, Radboudumc, Netherlands); Gunnar Kahlmeter (EUCAST Development Laboratory, Sweden); and Awa Aidara Kane (World Health Organization, Switzerland).

#### Declaration of interests

MS reports non-financial support from bioMérieux. CPY reports non-financial support from bioMérieux, and BD Molecular Diagnostics. All other authors declare no competing interests.

#### Acknowledgments

This study was supported in part by the Baillet-Latour fund. We would like to thank Nada Malou and Rupa Kanapathipilai (Médecins Sans Frontières, New York, NY, USA) for their support.

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