Laboratory strengthening efforts key to combat antimicrobial resistance

Antimicrobial resistance (AMR) is of increasing international concern. It threatens the effectiveness of existing treatments against many infectious diseases. Low- and middle-income countries are most at risk, particularly as local and national healthcare approaches are often not set up to tackle the problem. Makeda Semret, Cédric Yansouni, and colleagues at McGill University, Canada, partnered with Addis Ababa University, Ethiopia, to develop a sustainable clinical bacteriology sector at the Tikur Anbessa Specialised Hospital in Addis Ababa. The project's success demonstrates that local interventions can lead to sustainable improvements in approaches to AMR.

Causing 700,000 deaths every year, antimicrobial resistance (AMR) has been declared one of the top 10 global public health threats facing humanity by the World Health Organization. AMR occurs when microorganisms change the structure of their DNA by mutation or gene transfer over time, developing resistance to the medicines traditionally used to treat them. This is mainly driven by antimicrobials being prescribed incorrectly or unnecessarily (overuse). Antimicrobial resistance is already widespread in many parts of the world. It is most pressing in hospital settings where hospital-associated infections are increasingly due to drug-resistant organisms such as methicillin-resistant *S. aureus* (MRSA), extended-spectrum ß-lactamase (ESBL) *E. coli*, as well as emerging new multidrug-resistant bacteria – leading to morbidity and mortality that is directly attributable to resistance.

The project at work in Ethiopia.

AMR threatens the effectiveness of existing treatments against very common infectious illnesses like urinary tract infections, appendicitis, or infected wounds. Treatments then become costly or even impossible for previously curable diseases, leading to prolonged illness or death in susceptible patients. Without effective antimicrobials, medical procedures, such as surgeries and cancer chemotherapy become risky, as the risk of infections increases.

Even though there are innovative antimicrobials in clinical development, their development is not fast enough to combat the exponentially growing threat of AMR. If no significant measures are taken to curb the rising threat of AMR, it is estimated that the burden of AMR will increase to 10 million deaths per year by 2050. This dwarfs the number of fatalities caused by malaria, tuberculosis, and HIV combined.

Currently, the highest rates of AMR are reported from low- and middle-income countries (LMICs). Of those, sub-Saharan African countries are the least prepared to face the socioeconomic costs of AMR due to a lack of health infrastructure in place, particularly diagnostic testing capacity. Among other factors, the focus on single-disease control programmes instead of overall health systems has led to many aspects of patient care being neglected.

The WHO's Global Strategy for Containment of Antibiotic Resistance recognises that clinical microbiology diagnosis is essential to combat AMR. This is because identifying the exact


The team undertaking blood culture testing in Ethiopia.

cause of infections and identifying only the patient populations that require antimicrobials ensure the appropriate use of antimicrobials, which then prevents overuse. The committee addresses three strategies: data for surveillance, appropriate use of antibiotics (antibiotic stewardship), and infection control. Sub-Saharan Africa, however, has almost no clinical hospital laboratories that provide bacteriology diagnostics services to international standards.

DIAGNOSTIC TESTING IN ETHIOPIA

Let's explore a case study in sub-Saharan Africa: Ethiopia. With 110 million inhabitants, Ethiopia is the second most populous country in Africa. Access to basic health care services has improved over the past two decades, but advanced therapies are only available in specialised hospitals in urban areas. Even in urban referral centres, there is little access to bacteriology diagnostic testing. The lack of diagnostic results means healthcare providers are working with a blindfold, unable to identify the specific infection a patient may be suffering from and unable to determine whether patients would benefit from antibiotics. As a result, patients are often put on multiple, broad-spectrum antibiotics or prescribed antibiotics unnecessarily. This has led to significant overuse; in Ethiopia, up to 85% of hospitalised patients are on antibiotics on any given day.

Ethiopia also lacks the infrastructure and institutional capacity to monitor trends of AMR, as data collection is limited to local hospitals and small cohort studies. Consequently there are large gaps in understanding the actual burden of AMR in the community, making it difficult to formulate effective treatment strategies.

THE IMPORTANCE OF DIAGNOSTIC TESTING

Cédric Yansouni from McGill University, along with researchers from institutions across the United States and Canada, such as Harvard Medical School and University of British Columbia, recently published a compelling study in the *Annals of Internal Medicine*. The study provided data that described the loss of key information when antibiotics were prescribed before microbiologic testing in patients with life-threatening infections. By monitoring 325 patients with severe sepsis, they found that approximately 50% of patients who had positive blood cultures before treatment had falsely negative cultures after administration of a single dose of antibiotics. This signified that treatment can skew the detection of bacterial infection and underscored the importance of bacteriology testing before starting antibiotic treatment. Prescribing antibiotics without a bacteriology diagnostic test massively reduces the sensitivity of blood cultures, which in turn reduces healthcare professionals' ability to detect the specific source of bacterial infection. The significance of this study has gathered attention from major publications, such as *NEJM Journal Watch* and *The Quebec Research Funds*.

The lack of diagnostic results means healthcare providers are working with a blindfold, unable to determine whether patients would benefit from antibiotics.

In order to assess the clinical impact of such missed diagnoses, the team led a separate study in Ethiopia. They performed blood-culture testing on 777 patients admitted to hospital. Among these, the probability of having bacteria in the bloodstream was highest among patients who had received the most antimicrobials prior to testing – ie all patients for whom antimicrobials were prescribed as a "best guess" instead of being informed by specific results. Of greatest concern, around 80% of patients harboured bacteria resistant to the most commonly prescribed drug, ceftriaxone. Having ceftriaxone-resistant bacteria in the blood was associated with a 15-fold increase in the odds of death. Earlier testing would have allowed more effective treatment by detecting these resistant bacteria.

Being able to target treatment is key to controlling AMR and has knock-on effects, as correct diagnoses can minimise the patient's stay in hospital and the resources needed for treatment. Using bacteriology testing to guide treatment, also known as culture-guided therapy, can significantly decrease mortality in conditions like severe sepsis, as inappropriate antimicrobial use has been recognised as a major contributor to deaths.

LABORATORY STRENGTHENING IN ETHIOPIA

Despite international recognition of AMR and the value of diagnostic testing, solutions are not straightforward. High-level recommendations from WHO on AMR containment are frequently in direct conflict with local institutional priorities

and with the attitudes and experience of individual healthcare providers in LMICs. Makeda Semret, Cédric Yansouni, and a team from McGill University worked with researchers from Addis Abba University to understand the factors needed to ensure sustainable change.

They established the Addis Ababa–McGill Partnership in Infectious Diseases to address training gaps, provide opportunities for innovative research and, importantly, focus on measures that would improve the quality of care and safety of patients in LMICs. They conducted a project to strengthen the clinical bacteriology service at the Tikur Anbessa Specialised Hospital (TASH), the largest referral hospital in Ethiopia with approximately 20,000 admissions annually.

Before this project, TASH had few quality measures in place, communication between clinicians and laboratory staff members as well as credibility of the laboratory results were weak. Protocols from the McGill University Health Centre (MUHC) were adapted for healthcare professionals at TASH, with local realities including availability of reagents and equipment in Ethiopia, level of training and language proficiency of personnel in mind. Three microbiologists from MUHC (Semret, Yansouni, and Michael Libman) visited TASH on a regular basis to provide direct supervision and formal training sessions with local technologists, instilling a SOP culture in TASH healthcare professionals. The Ethiopian Public Health Institute assisted with the introduction of quality control and quality assurance processes. The team used existing online resources to improve technologists' knowledge and organised regular clinician-focused hospital lectures on AMR topics. Through practical application of quality assurance processes, a quality mindset was nurtured throughout the care team.

Within 18 months of implementing these interventions, bacteriology laboratory use increased from an average of 15 to 75 samples per day. Standardised automated blood cultures and antimicrobial susceptibility testing are now routine procedures, with up to 50 blood culture specimens processed every day. Data from these routine tests were recorded and submitted for national and global AMR surveillance, as part of the Global Antimicrobial Surveillance System. Following the success at TASH, efforts are underway to scale-up versions of this intervention in other large hospitals in Ethiopia.

As well as strengthening the laboratory, the team implemented a number of new initiatives, such as antimicrobial stewardship to steer clinicians towards evidence-based prescribing of antimicrobials. Taken together, all these measures resulted in a 50% reduction in antibiotic use in hospitalized patients. Strikingly, the savings resulting from lower antimicrobial use were slightly greater than the annual cost of laboratory reagents, making the intervention financially feasible in addition to clinically beneficial.

Quality-assured laboratory results made it possible to safely discontinue 50% of the antibiotics prescribed to admitted patients, because the team could determine they were not needed.

SCALING-UP BACTERIOLOGY AS THE CORNERSTONE OF AMR CONTAINMENT

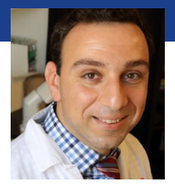
The team's short-term success at TASH demonstrates that local interventions to strengthen clinical bacteriology laboratories are feasible in low income countries. However, it also highlights the pertinence of taking a holistic approach and gaining support from organisational leadership to ensure the changes in culture and practice are sustainable.

The team at Tikur Anbessa Specialised Hospital (TASH).

For example, providing the clinical and financial impact of this work to policymakers yields the information they need to provide the appropriate budget and support to diagnostic bacteriology laboratories, so they can adopt routine quality-assured bacteriology testing as essential to AMR containment. If clinical microbiology is recognised as a speciality in sub-Saharan Africa, expertise in this area can be fostered to produce a new generation of skilled microbiologists.

The major factors that contribute to widespread AMR still remain in Ethiopia and across sub-Saharan Africa. Weak supply chains for bacteriology reagents, lack of comprehensive policies that address regulatory and fiscal obstacles for the diagnostic sector outside the laboratory, and a perennial lack of advancement opportunities for trained laboratory staff will require strong collaborative effort and urgency from national- and hospital-level policymakers. Now Tikur Anbessa Specialised Hospital has shown change is feasible. In addition to feasibility, however, the jump to sustainability requires adequate prioritization of bacteriology diagnostics at local and ministerial levels, as well as a proven toolkit for reaching the goal of AMR containment.

Behind the Research



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Research Objectives

Informing policy on diagnostics for severe and emerging infections in low-resource or remote communities, and assessing the impact of interventions to limit AMR in high- and low-income settings.

Detail

Bio

Cédric Yansouni is Assistant Professor in the Department of Medicine, McGill University, Montreal, Canada, and co-leads Montreal's JD MacLean Centre for Tropical Diseases.

Makeda Semret leads the Antimicrobial Stewardship Program and the Infectious Diseases/Medical Microbiology Training Program at the McGill University Health Centre.

They are both founding members of AAU-McGill Partnership for Infectious Diseases, which includes Ethiopia's first post-graduate infectious diseases training program.

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Collaborators

Workeabeba Abebe, Tinsae Alemayehu, Gebremedhin Beedemariam, Temesgen Beyene, Michael Libman, Wondwossen Amogne, Solomie Deribessa, Daniel Seifu, Oystein Haarklau, the study team and laboratory, nursing and admin colleagues.

Personal Response

What future initiatives or studies are planned in or beyond Ethiopia to further provide support for laboratory-based containment of AMR in LMICs?

"Our research programme aims to support global efforts towards better strategies for implementing bacteriology laboratories, in order to contain antimicrobial resistance (AMR) in low-and-middle income countries (LMIC). Our work evaluates specific laboratory tools or larger intervention bundles. Examples include assessing rationalised "AMR toolkit" that can be scaled-up in LMIC, studying the diagnostic accuracy and clinical impact of new tools for AMR diagnostics as they become available, or evaluating electronic decision support tools to help clinicians interpret key information at the point of antibiotic prescription. We believe this work fills a current vacuum between high-level recommendations and the reality of large parts of the LMIC healthcare landscape."

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