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TRIANGULATE HEALTH

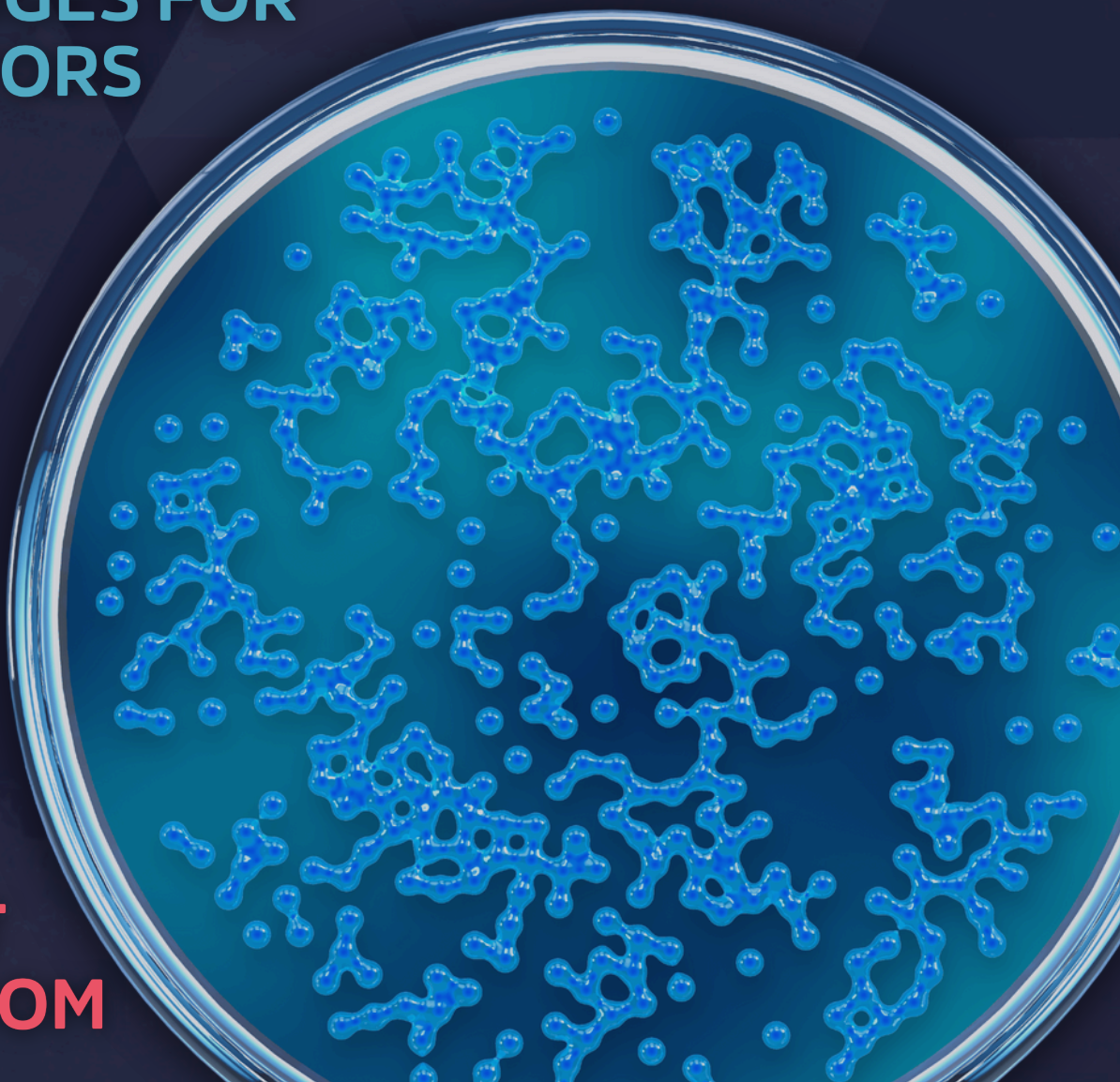
AMR NAVIGATOR

SPOTLIGHT ON AMR DIAGNOSTICS

THE ROLE OF DIAGNOSTICS IN AMR

WHAT IS THE POINT OF THE POINT-OF-CARE?

CHALLENGES FOR INNOVATORS



WITH **PRODUCT SHOWROOM**

"Today, antibiotics are rarely prescribed based on a definitive diagnosis. Diagnostic tests can show whether or not an antibiotic is actually needed, and which one. Having rapid, low-cost and readily available diagnostics is an essential part of the solution to this urgent problem."

- Dr Margaret Chan,
Former Director General of the World Health Organization

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In this issue, we include insights and excerpts from interviews with:

- **Jayne Bailey, Senior Director at Cepheid**
- **Jonathan Pearce, CEO of Antibiotic Research UK**
- **Dr Emma Hayhurst, CEO of Llusern Scientific**

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The role of diagnostics in AMR

"Receiving a result and getting clarity on the cause of a problem that generates so much discomfort provides peace of mind to the patient in a timely manner."
- Dr Emma Hayhurst, CEO, Llusern Scientific

Antimicrobial resistance (AMR) is one of the most challenging threats to the future of health, partly caused by the misuse of antibiotics. Rapid diagnostics are crucial to curbing unnecessary antibiotic use and their development is becoming ever more critical. Currently, nearly half (47%) of the world's population have little to no access to diagnostics. In the absence of diagnostics, many prescribing decisions are based on empirical diagnoses, resulting in the reliance on non-targeted or broad-spectrum antibiotics that may not be effective, thus contributing to an increase in AMR. In the US, 27 million out of 40 million people were given unnecessary antibiotics for respiratory issues. Meanwhile, standard in-vitro diagnostics can take days to yield results. Whilst waiting for test results, doctors sometimes prescribe antibiotics as an interim decision which can often lead to taking the wrong drug for a short period of time.

A diagnostic test to help prevent AMR must therefore do several things: check what type of infection is present at the point-of-care (POC) and test for antimicrobial susceptibility so appropriate treatment can be prescribed. This is valuable knowledge for both the patient, the clinician and AMR researchers.

"Receiving a diagnosis can become a long, drawn out, frustrating process for patients to be able to find out what's wrong with them and how the infection can be treated. Diagnostics would help people understand, get an accurate diagnosis and treatment, and if it's not a straightforward treatment and cure, support and help to manage their condition."
- Jonathan Pearce, CEO, Antibiotic Research UK

An investment in knowledge pays the best interest

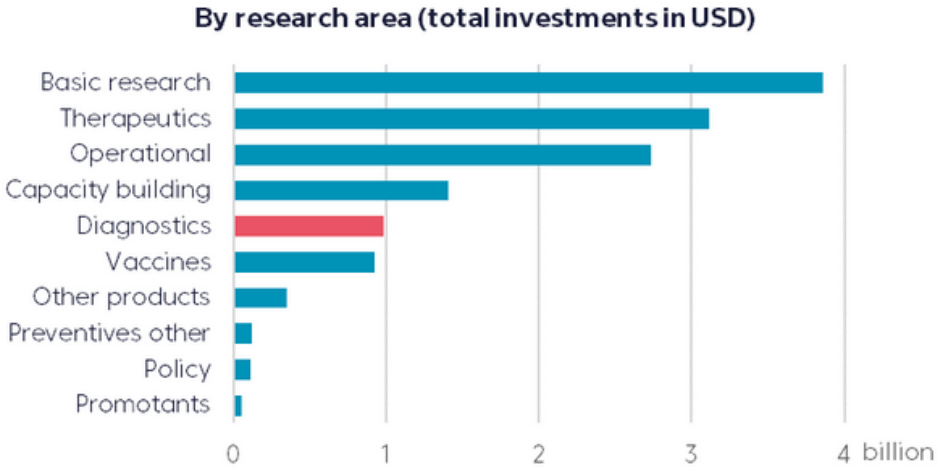

Figure 1: Amount of R&D investment in the field of AMR by research type, in billion US$.
Source: Adapted from Global AMR Hub, 2020

Diagnostic development has historically been overlooked until the COVID-19 pandemic when lateral flow tests became part of everyday life. The standard culture diagnostic test has been practiced for the past half century and only 7% of research and development (R&D) funding for AMR was dedicated to diagnostics from 2017 to 2023 (Figure 1).

The diagnostics pipeline is improving

- **In October 2022**, the US National Academies of Sciences, Engineering, and Medicine developed a list of recommendations aimed at accelerating the development and uptake of rapid diagnostics to address antimicrobial resistance.
- **Also in October 2022**, the World Health Organization (WHO) launched the Global Antimicrobial Resistance and Use Surveillance System (GLASS). GLASS aims to support countries to build capacity for detecting pathogens and their drug susceptibility, as well as to improve global AMR surveillance and diagnostic stewardship.
- **In March 2024**, at the 8th annual AMR Conference, Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (Carb-X), a global non-profit partnership accelerating the development of antibacterial products, launched their latest funding round to improve the pool of diagnostics in several therapeutic areas. In June 2024, the rapid, instrument-free diagnostic for chlamydia and drug-resistant gonorrhoea from Fuse Diagnostics became the third recipient of the Carb-X grant.

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What's the point of the point-of-care?

"Rapid testing reduces onward transmission, enables prompt isolation of patients and ensures the right patient in the right bed at the right time to improve patient flow."

- Jayne Bailey, Senior Director, Cepheid

For a new diagnostic to be effective, it should be easily integrated into the clinical care pathway at the 'point-of-care'. Dr Emma Hayhurst of Llusern Scientific adds that urinary tract infections (UTIs) specifically are a hugely under-researched area and so many women (and men) often suffer the consequences of a UTI as if it were a normal part of life. Llusern hopes to change the public's perception by developing an affordable diagnostic tool for UTIs: "*There are currently no highly accurate diagnostic tools for UTI at the POC, and we think creating one could help reduce recurrent UTIs, a rate which currently stands at 25%.*"

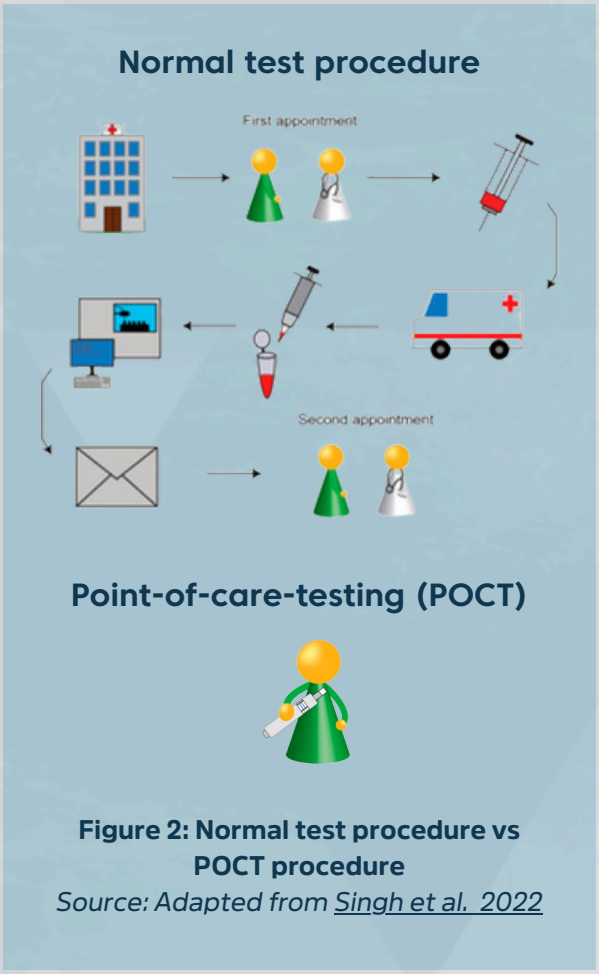


Figure 2: Normal test procedure vs POCT procedure

Source: Adapted from Singh et al. 2022

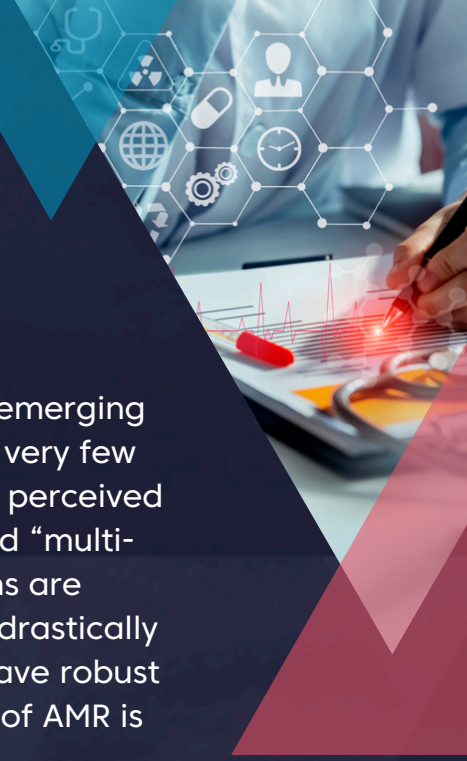
Another benefit of POCT is that it aims to complement the clinical care pathway and potentially save time. Dr Emma Hayhurst stresses that a key benefit of Llusern's UTI test is that it does not have to be conducted by a doctor or a nurse, it can be used by prescribing pharmacists as well as other support staff in an acute or community setting, circumventing the need for additional administrative resources and reducing the pressure on testing laboratories, GPs and nurses.

Jonathan Pearce, CEO of Antibiotic Research UK, has been studying the impact of poor UTI diagnostic pathways on patient experience and shares his insight.

"What we see is people who describe their lives shrinking, they describe a massive impact on every aspect of their lives, whether it's their personal ability to socialise, work, enjoy family life, go on trips, get out and about and avoid isolation."

- Jonathan Pearce, CEO, Antibiotic Research UK

Challenges for innovators



At the time of writing (August 2024), in the Carb-X directory of emerging diagnostic tests (Figure 3), there were 1075 tests registered. Yet very few of these tests circulate in clinical care pathways. In addition to a perceived lack of market incentives for AMR research, AMR is a complex and "multi-layer" problem that cannot be solved with a single test. Infections are heterogeneous, and the microbial profile of one country can be drastically different from another, hence the gold-standard test needs to have robust performance against a wide array of pathogens. The landscape of AMR is also constantly changing, with new pathogenic resistant genes continuously evolving. Diagnostic tests therefore need to adapt to the new AMR challenges. In addition, certain practicalities need to be considered, and at the very basic level, a diagnostic test needs to be:

- Affordable and cost-effective
- Show sensitivity and specificity
- Be rapid and robust
- Demonstrate user friendliness, including ease of specimen collection and sample preparation.

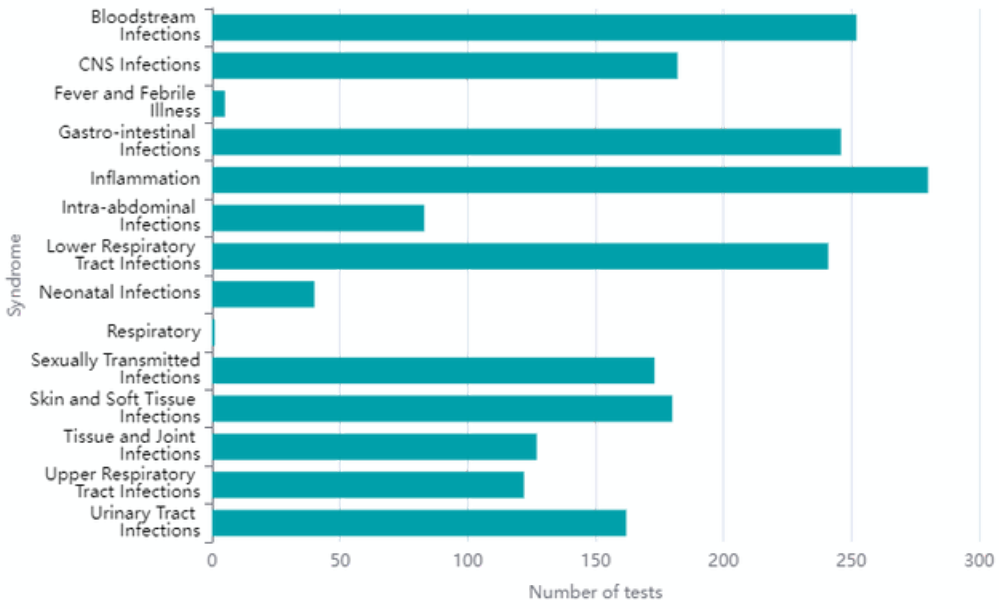


Figure 3: AMR test directory by syndrome.
Source: FIND

Challenges for innovators

During a UK based AMR diagnostics event "Moving Forward in Infection Diagnostics" co-hosted by the National Health Service (NHS) England and other stakeholders in 2023, many innovators spoke to the regulatory barriers to approving and reimbursing an infection diagnostic.

In the UK, product developers are encouraged to engage with the Medicines and Healthcare Regulatory Agency (MHRA) to develop target product profiles based on what and where (in the care pathway) diagnostics are needed. It is hoped that focusing on clinical needs may facilitate timely reimbursement and use in the health system. A study looking at barriers and facilitators to pricing and funding of respiratory POC testing found a lack of price regulation and weak purchasing power due to regional procurement processes as barriers to reimbursement.

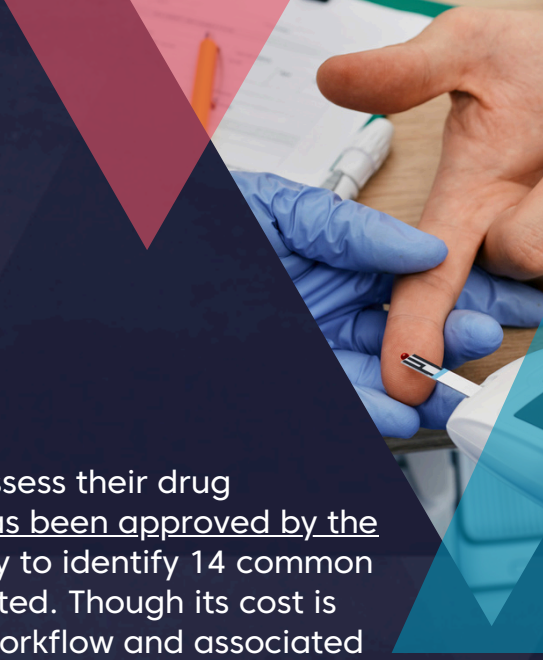
The American National Academies also suggests simplifying the process of obtaining regulatory approval for infection diagnostics, in a similar way to what the United States Food and Drug Administration (FDA) granted during the COVID-19 pandemic.

Jonathan Pearce, CEO of Antibiotic Research UK, highlighted the importance of aligning the interests of various stakeholders to improve the availability of diagnostic tests:

"When you talk to the other people that are involved in making a diagnostic and treatment pathway work, you start to understand there are different perspectives. For GPs, it's got to be a test that is meaningful and useful for them.[...] The NHS [UK] tends not to implement new initiatives at the moment, unless it can see a cost benefit to it or a reduction in costs. [...] And then there's a pushback from GPs in terms of new diagnostic systems if it means that each GP practice or surgery has to bring in a new diagnostic process or a machine that they have to staff and then run and look after."

Even if a high-performance diagnostic test is developed, integration into the health system remains challenging. For example, demonstrating the value of diagnostics during the health technology assessment (HTA) stage, where it is the norm for value assessment frameworks to be designed for medicines.

Product showroom



Creating a diagnostic test that can distinguish between bacterial and viral infections is one challenge. Another is identifying the causative pathogen and understanding its resistance profile. We explore here some of the diagnostic products in development or on the market.

1. With the ability to identify pathogens in 1.5 hours and assess their drug susceptibility in 7 hours, **Accelerate PhenoTest BC Kit**, has been approved by the FDA and shown to be effective in a clinical trial. Its ability to identify 14 common bacterial and two fungal infections has been demonstrated. Though its cost is unknown, it could reduce the complexity of laboratory workflow and associated costs.

2. Llusern's first product is a UTI test panel, the **Lodestar DX UTI test system**, capable of detecting >95% of uropathogens at POC in 20 minutes. Currently, Llusern is conducting trials of the kit at GP surgeries, and it has also been included in National Institute for Health and Care Excellence (NICE) guidelines in development for POC testing technologies.

3. Cepheid's real-time PCR system, **GeneXpert**, which can test patients for a range of infections at the POC. These include respiratory infections such as influenza and also rectovaginal infections such as trichomoniasis. Jayne Bailey, Senior Director at Cepheid, mentioned the focus of GeneXpert to identify carriers of antibiotic-resistant bacteria, so they can be treated appropriately or managed within the current care pathways.

4. Abbott's **Determine TB LAM Ag test** for tuberculosis (TB) detection, has been shown to be effective, easy to use and affordable as part of care pathways since WHO's recommendation in 2015 and the uptake by some countries with a high TB burden. However, 70% of the 37 high TB burden countries have not adopted the technology five years after WHO's recommendation, highlighting the lack of funds, regulatory barriers and a narrow target population as some of the barriers.

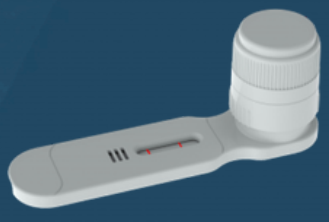


Figure 4: AMR DetecTool for detecting multi-drug resistant bacteria, the product of collaboration between 15 European institutes.
Source: AMR DetecTool

5. The **AMR DetecTool** is a lateral flow test that can detect bacteria with multi-drug resistance with high specificity and sensitivity, all within 30 minutes. While it is still under extensive testing, it has shown promising potential to be cheap and easy to produce, while requiring no pre-treatment of samples.

Are they cost-effective?
Affordability of POC diagnostics

An effective POC diagnostic has the potential to reduce patients' length of stay and save doctors' time, which can subsequently be cost-saving and optimise resource allocation in a healthcare system.

At an event on AMR Diagnostics in 2023, Professor Chris Whitty, Chief Medical Officer for England highlighted the importance of using cost-benefit analyses to not only assess the costs of using the test, but how they are used in the health service with consideration for behavioural variables.

One study in the Netherlands showed that rapid diagnostics can reduce the time spent in isolation rooms in the intensive care unit (ICU) by more than 40%. All these benefits translate to savings in healthcare resources and staff time, which hints they could be cost-effective.

A C-reactive protein test, which can differentiate between bacterial and viral infections, only costs around £4-5 in the UK, with low costs of equipment and staff training. Meanwhile, these tests have been shown to reduce antibiotic prescriptions by around 20% in two separate studies. In Norway and Sweden, C-reactive protein tests for LRTI showed an incremental cost-effectiveness ratio (ICER) of €9,391/QALY, indicating a highly cost-effective implementation.

A review published by Ockhuisen et al. also suggested that POC tests such as GeneXpert are likely cost-effective.

Dr Emma Hayhurst of Llusern estimates that the POC UTI test panel they are developing has an upfront, one-time cost of £1,500 with test strips costing ~£30 per patient. This is comparable to current laboratory testing for UTIs which currently stands at £37 per patient.

There are other ongoing studies that aim to ascertain the effectiveness of new diagnostics. For example, the TOUCAN study, run by the University of Oxford, set out to evaluate the performance of new diagnostics for UTIs in GP practices. In collaboration with the NICE committee, their data will inform future guidance and recommend specific technologies for use in the NHS.

"The traditional, treatment-based analysis using QALYs does not really demonstrate the true value of diagnostics. We need a review of the assessment of the value of diagnostic."

– Jayne Bailey, Senior Director, Cepheid

Diagnostic testing in low- and middle-income settings

Many of the diagnostic tests in development are also only suitable for use in high-income settings. In reality, there is a considerable demand in low- and middle-income countries (LMICs). The Lancet Commission on diagnostics has estimated that reducing the number of patients with no access to diagnostics by 10% (currently at 47%) could reduce the annual number of premature deaths by 2.5%.

In LMICs, misdiagnosis of infection is a threat. For example, malaria and COVID-19 often present with similar symptoms such as fever, pain and diarrhoea. A randomised trial in Tanzania showed that the integration of POC tests in the standard care pathway reduced antibiotic prescriptions from 30% to 11% while achieving significantly better patient outcomes. Some important features of the trial were the use of relatively affordable tests (such as C-reactive protein and procalcitonin antigen tests) that are widely accepted by physicians and the use of electronic systems for recording test results.

Pricing of diagnostic tests remains a key issue in LMICs. Cepheid—in collaboration with donors such as the Bill & Melinda Gates Foundation and FIND—has established a global access programme aiming to bring rapid molecular testing to communities in LMICs at a lower price. These include a multi-drug resistant TB test and TB-HIV co-infection tests. In 2023, the Global Fund also worked with Cepheid in an attempt to renegotiate the pricing structure of TB diagnostic tests to further improve coverage in LMICs. The Global Fund negotiations resulted in more than a 20% reduction in the price of two tests, with final prices being US$14.90 and US$7.97 per unit. These costs could still be considered high to LMICs given the Access to COVID-19 Tools (ACT) Accelerator—a global access collaboration —reduced the cost of COVID-19 tests for LMICs to less than US$3.

In addition to making diagnostics affordable, new initiatives are also needed to support the growth of the diagnostics market in LMICs. One proposed solution, outlined in the Review on Antimicrobial Resistance, is a “diagnostic market stimulus” system. This system would offer a per-unit subsidy to diagnostics manufacturers with the goal of promoting the uptake and use of high-quality diagnostic tests, enhancing market growth and accessibility.

AMR diagnostics: To the future

The following measures could be adopted promptly to promote new, rapid diagnostics to reduce the unnecessary use of antimicrobials.

1. **Focus multinational efforts to fund early research in AMR diagnostics.**
2. **In LMICs, where access is poor, there is a clear call for continued efforts to make diagnostic tests more affordable and accessible to underserved populations globally. A "diagnostic market stimulus" can be used to provide top-up payments to diagnostics manufacturers for each unit sold.**
3. **Create target product profiles to facilitate the development of diagnostic tools.**
4. **Better cost-effectiveness analysis to establish the cost-effectiveness of POC testing for infections. This includes conducting more studies, generating economic evidence and considering behavioural variables.**
5. **Call for regulatory agencies and policymakers to recognise the value of diagnostic tests and develop appropriate frameworks for their assessment and reimbursement, considering the unique characteristics of diagnostics compared to medicines.**
6. **Collaboration among stakeholders including innovators, regulators, healthcare providers and policymakers, is crucial to overcome regulatory barriers and ensure timely reimbursement and use of diagnostic tests in healthcare systems.**

Diagnostics milestone

The Longitude Prize, which aims to incentivise the development of a rapid POC test, welcomed its winner, PA-100 AST System (Sysmex Astrego AB) in June 2024, a whole decade after the launch of the Prize.

Next issue

Next time, we aim to explore the role of vaccines in managing AMR. By immunising individuals against common bacterial and viral pathogens, vaccines help to decrease the incidence of infections, thereby reducing the demand for antimicrobial drugs.

We would very much like to thank the following individuals for sharing their experience and insights with Triangulate Health Ltd:

- **Jayne Bailey, Senior Director at Cepheid**
- **Jonathan Pearce, CEO of Antibiotic Research UK**
- **Dr Emma Hayhurst, CEO of Llusern Scientific**

Useful links

- **DRIVE-AB** (Europe's Innovative Medicines Initiative)
- **Antimicrobial Resistance (AMR): Diagnostics** (Global AMR R&D Hub)
- **Tackling Antimicrobial Resistance** (European Observatory on Health Systems and Policies)
- **Study on bringing AMR medical countermeasures to the market** (European Commission, PwC EU Services EEIG)
- **CARB-X Annual Report 2023: Accelerating the Global Response to Antimicrobial Resistance** (CARB-X)
- **AMR DetecTool** (EIT Health - European Institute of Innovation and Technology)
- **Molecular methods for antimicrobial resistance (AMR) diagnostics to enhance the Global Antimicrobial Resistance Surveillance System, GLASS** (WHO)
- **Key resources on diagnostics for AMR** (The Global Health Network)
- **Tackling Drug-resistant Infections Globally: Final Report and Recommendations** (The Review on Antimicrobial Resistance)
- **AMR Test Directory** (FIND)
- **Tackling antimicrobial resistance in low-income and middle-income countries** (Pokharel, Raut and Adhikari, BMJ Global Health)
- **Antimicrobial resistance could be the next pandemic – here's what we're doing about it** (Legal and General Investment Management (LGIM))

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