DIAGNOSTIC SOLUTIONS CRITICAL TO LIMIT ANTIMICROBIAL RESISTANCE DEVELOPMENT

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Today, patients with suspected infections receive empirical treatment, unguided by laboratorial bacteriology, resulting in the overuse of antimicrobials, the emergence of drug resistance and a rapidly dwindling inventory of effective antimicrobials. Emerging diagnostic technologies have the potential to ameliorate this situation by fostering rapid and precise diagnosis and the early refinement of antibiotic therapy, making diagnosis central to the battle against antimicrobial resistance. While innovative technology platforms exist that enable the differentiation of pathogen classes and the detection of specific pathogens and their resistance profile with speed, sensitivity and ease of use, there are major challenges to the development, regulatory pathway and clinical integration of diagnostic tests that employ these recent technological advancements. In order to foster the development of appropriate diagnostics necessary to address the AMR crisis, creative solutions are needed. Specifically, we need to make a better case for the economic benefits of diagnostics to induce changes in the funding landscape, attract new funding partners, and enhance funding coordination among donors. Furthermore, we need to create incentives to attract manufacturers to this field. This includes addressing regulatory challenges and improving the diagnostic ecosystem, notably in low-income countries, to accelerate uptake of new tools.

Despite significant advances in diagnostic technologies, many patients with suspected infections receive empiric antimicrobial therapy without prior identification of the causative agent. The result is overuse of a small arsenal of effective antibiotics, and the spread of antimicrobial resistance (AMR) at an alarming pace, with more than 500,000 deaths from resistant infections in the world annually.

The world health community has been increasingly sounding a clarion call for taking action against the dangers of AMR, and it has become clear that we cannot rely solely on new drugs or vaccines emerging from the development pipeline, but need a multifaceted and global response to combat AMR. The actions necessary to deal with the AMR threat have been identified by health authorities and principally come down to the following:

- Create awareness among stakeholders of the AMR threat and align them on the principles of antibiotic stewardship and appropriate use of antibiotics;
- Through regulation, avoid the overuse of antibiotics in humans and farm animals and restrict use to the appropriate infections;
- Improve sanitation, hygiene, infection prevention and control measures to increase the likelihood that infection is prevented, thereby reducing the need for antibiotics;
- Enhance surveillance of resistance and monitoring of antibiotic usage in humans and animals to achieve a better understanding of the magnitude of the AMR problem.

A central component and enabler of all four action points is appropriate diagnosis to clarify the etiology of the illness in order to target treatment and quantify the problem, and create an effective public health surveillance and response mechanism. Today, we do not have the diagnostic tools to effectively address AMR. We need easy-to-use and affordable tests that are rapid enough to have a positive

impact on patient care, can identify a specific pathogen or, at a minimum, distinguish between bacterial, viral and parasitic infections, and also provide information on susceptibility to antimicrobial agents. Connectivity and electronic health aspects are critical to ensuring that the results can be effectively communicated to health-care providers, and are actually used to guide care and control efforts.

Challenges to better diagnostics

The rapid and accurate establishment of a microbial cause is central to providing quality care. However, the process of clinical bacteriology remains antiquated, with timing determined by the speed of bacterial growth. Usually, it takes one day to grow bacteria from the clinical specimen and another to identify and measure antibiotic susceptibility; for diseases like tuberculosis, it takes from two to eight weeks to grow the bacteria and several more weeks to determine the resistance profile. Emerging diagnostic technologies have the potential to ameliorate this situation by fostering rapid and precise diagnosis and the early refinement of antibiotic therapy. For example, new antigen detection methods can improve the accuracy of detecting pneumococcal antigens in urine and thus enable rapid diagnosis of pneumonia. Molecular tools may hold even greater promise to increase the speed and sensitivity of pathogen identification and can be combined with drug resistance detection. In the case of tuberculosis, for example, the time to diagnosis of multidrug resistance has decreased from several months to two hours through the introduction of Xpert MTB/RIF, a game-changing molecular test. The utilization of molecular assays is increasing for the detection of all infectious organisms, in particular for the diagnosis of viral illnesses. Newer automated tests allow for use at the point of care and can detect multiple different causative organisms to provide a comprehensive diagnostic panel for major clinical syndromes (e.g. fever and respiratory symptoms or unspecified fever). In addition, there are alternative methods, such as mass spectrometry, that hold great potential to improve the ability to detect infectious organisms and resistance, and to do so rapidly. While these types of tests are currently confined to high-resource settings miniaturization efforts are underway.

Such tests need to be complemented with triaging tests that can be used by clinical staff to differentiate between causative organism classes (i.e. viral, bacterial or parasitic) and thus guide initial empiric therapy prior to the availability of more comprehensive results. More research and development is urgently required to identify differentiating biomarkers. Inflammatory markers, such as a white blood cell count or acute phase proteins (e.g. C-reactive protein) are not specific enough. Procalcitonin (PCT) is thus far the only potentially more specific marker for bacterial infections. It is released in response to bacterial infections and correlates with their extent and severity. However, all data available to date has evaluated the use of PCT in the context of pneumonia or sepsis in high-resource settings. There are currently no data available from low-resource settings where, for example, malaria or tuberculosis are endemic and co-infections are often present. Therefore, the utility of PCT in these contexts remains to be proven. Other approaches to triaging markers to differentiate viral, bacterial or parasitic diseases have been studied, but no marker besides PCT has penetrated clinical care to date.

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without extensive technical skills and potentially by the patient in the home. Besides these test design challenges in terms of robustness and automation, there are multiple other obstacles for manufacturers to achieving commercialization, notably in developing countries. These include a complex regulatory approval landscape, weak health systems and a chronic lack of funding for procurement. In addition there are numerous phases where development may confront significant hurdles: biomarker selection, prototype development and technical validation; manufacturing validation; performance evaluation and clinical validation; and endorsement and scale-up. The successful introduction of a new diagnostic will require effective collaboration with companies, the health-care sector, the World Health Organization, and health ministries, leaving private firms with numerous impediments when attempting to bring new tests to market in the various settings.

Recommendations to accelerate the development of diagnostics

In order to foster the development of the appropriate diagnostics necessary to address the AMR crisis, creative solutions are needed. These include the following:

- Make the case for the economic benefits of diagnostics. All stakeholders need to be better educated on the importance of diagnostics in the fight against AMR. If they gain a better understanding of the value of diagnostics to world health, they are more likely to increase their investments in diagnostic development, and ensure appropriate levels of reimbursement for diagnostic testing.
- Attract new funding sources. Historically, funding sources for diagnostics development has been concentrated in the public sector, with the philanthropic sector providing limited funding. More funders will need to be brought into the AMR diagnostic initiative in order to bring diagnostics to fruition. While the health world community has articulated the steps for preventing the spread of drug-resistant bacteria, the risk is that the funding for AMR diagnostics, if prior experience is a guide, is likely to turn out to be inadequate to develop the necessary diagnostics for dealing with AMR. Therefore, if the world health community is to seriously address AMR, it will have to provide sufficient funds for the development programmes necessary to create diagnostics. In the past, the focus has been on the development of new antibiotics, and diagnostics are likely to be insufficiently emphasized.
- Enhance funding coordination among donors. As AMR is a global issue, it would behoove governmental bodies and private donors to coordinate funding for diagnostics to establish common priorities and avoid multiple grant applications, underfunding of projects and duplicative research and support. A coordinated network could share information, resulting in better funding decisions.
- Create incentives to attract manufacturers. There is a need to incentivize the development of POC diagnostics that could differentiate between a bacterial and viral infection, and at the same time diagnose specific resistance pattern within hours. While this challenge is a difficult one, if achieved it would be transformational. While diagnostic development costs generally are less expensive than antibiotics or vaccines, price is still a deterrent for manufacturers to enter the marketplace. If manufacturers were provided with scientific and regulatory expertise and funding assistance, they would be incentivized to commercialize diagnostics, and product development would be accelerated. This assistance is of critical importance to smaller or nascent diagnostic manufacturers. Resources for this purpose are already in existence – the diagnostic-focused product development partnerships (PDPs) funded by the Bill and Melinda Gates Foundation and a number of governmental agencies. PDPs, such as the Foundation for Innovative New Diagnostics (FIND) in Geneva, have the requisite experience to assist manufacturers in a) establishing the initial target product profiles; b) conducting clinical trials; c) providing mentoring services; and d) developing other supporting activities to help overcome obstacles to achieve development, adoption and eventual roll-out.
- Address regulatory challenges and accelerate uptake of new tools. There is a need for governmental bodies to clarify and revise conflict of interest policies to allow

collaboration among diagnostic manufacturers, laboratories and opinion leaders in order to meet various regulatory requirements. Other reforms should focus on: better regulatory guidance for development of diagnostics; the harmonization of regulations to enable manufacturers to more rapidly develop and introduce diagnostics worldwide, and strengthen recommendations and training schemes on the use of new tests, with emphasis on changing clinical practices.

Conclusion

Improved diagnostic solutions for the identification of pathogens and resistance patterns are urgently required to limit the spread of AMR in the globalized world and preserve the available drugs to treat infectious diseases. The novel technologies that have emerged in recent years should be leveraged and adapted to develop diagnostic tools that are appropriate for use in developed countries and in low-resource settings to address both direct patient care needs and surveillance. To achieve this, significant funding will be required to integrate diagnostic solutions as a critical tool in a larger AMR control strategy. The world health community has recognized that the need for a solution to AMR has never been greater, but the question remains as to whether there is the political will to limit the unregulated use of antimicrobials in patient care and the nontherapeutic antimicrobial consumption in livestock. Without increased political commitment and funding, the battle against infectious diseases is not likely to be won. •

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