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editorial

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Fighting AMR with Host Immune Response Technology

The COVID-19 (SARS-CoV-2) pandemic has forced governments and healthcare systems to manage their resources in an environment of significant uncertainty. But now, as the world begins to adjust and reflect on the magnitude of the crisis, we are starting to appreciate the collateral damage caused by some of the measures taken to manage the outbreak. These measures have affected every aspect of our lives, including our healthcare and health delivery systems. AMR was an urgent issue long before the emergence of COVID-19 and has neither disappeared nor diminished during the pandemic. AMR has, in fact, both contributed to, and been aggravated by, the crisis.

AMR Puts Modern Medicine at Risk

Long before the COVID-19 pandemic featured in our daily headlines, antibiotic misuse and its contribution to AMR was defined as a global healthcare threat. It is well understood that the continuing evolution of pathogens driven by the overuse of antibiotics results in antibiotics that are less and less effective over time, which in turn makes infections increasingly difficult to treat. This increases the risk of disease spread, severe illness, and death. Here are a few key facts on AMR:

- Annually, approximately 700,000 [1] people die from antibiotic-resistant infections around the globe. The renowned economist Jim O'Neill in his AMR report commissioned by the UK government projects that, at current rates, this number could increase to roughly 10 million [2] people a year by 2050.
- Alarming levels of drug-resistant infections have been reported across continents and socioeconomic groups [3].
- The emergence and spread of microorganisms that cause drug-resistant infections is compounded by over prescription of antibiotics [4] in humans as well as their overuse in livestock [5].
- These antibiotic-resistant ''superbugs'' cause a range of bacterial infections that can be lethal. Every year, around the world, 230,000 people die [6] from antibiotic-resistant tuberculosis alone. E. coli, for example, causes millions of urinary-tract infections every year. If an antibiotic-resistant strain of E. coli emerges, it has the potential to quickly spread and kill patients.

As global consumption of antibiotics increases and the antibiotic pipeline continues to dry up, AMR is becoming not just a challenge to infectious disease management, but a threat to modern medicine. We cannot imagine medical fields like oncology, obstetrics, orthopedics and even dentistry without the mainstay of effective antibiotics. For example, routine surgeries could lead to life-threatening bacterial infections requiring antibiotics, and AMR might jeopardize our ability to effectively utilize chemotherapy as a treatment option for cancer patients. The ramifications of antibiotics losing effectiveness are potentially orders of magnitude more severe and difficult to deal with than the pandemic caused by SARS-COV-2.

The Basis for Solutions

Beyond improving our ability to prevent infections, it is widely accepted that a solution to the AMR crisis must involve breakthroughs across two key dimensions: Discovery of new antibiotics

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with different modes of action, which would expand the available treatment options, and the development of actionable tools to support improved antibiotic stewardship so that the right antibiotics are used only if and when needed. This may sound like a simple plan, but the clinical, scientific and technological realization of it involve significant complexities.

Discovering and developing new antibiotics is an onerous task. While many new antibiotic compounds have been introduced into clinical practice in the last 30 years, since 1989 none of these antibiotics have targeted a novel bacterial mechanism. Recent advances in the generation of omics data and computational molecular design are accelerating the identification of novel antimicrobial compounds, but their development and availability for clinical use still require many years of work and enormous financial investments, which are accompanied by a high failure rate along the way. As a point of reference, it takes 10-15 years on average, and over $1 billion to develop a new drug.

There is no doubt that discovering new effective therapies for drug-resistant bacteria is essential to containing the AMR challenge. However, new drugs can only be one part of the solution, as bacteria will eventually acquire resistance to these new compounds too. Staying ahead in the race against superbugs means we must also integrate accessible, actionable, and fast diagnostic tools into clinical workflows to enable better antibiotic stewardship. Only by reducing the massive overuse of antibiotics can we attenuate the selective pressure that drives the creation of resistant bacteria.

The challenge of properly utilizing antibiotics is based in part on the ability to effectively distinguish bacterial from viral infections. Unfortunately, in many cases, bacterial and viral infections are clinically indistinguishable, presenting with very similar symptoms. Given that only bacterial infections benefit from antibiotics and most infections are viral, improved tools to accurately differentiate between these infection types can dramatically reduce antibiotics use by up to 50% [7].

Despite the introduction of numerous novel diagnostic technologies over the last decades, the rates of antibiotic overuse and AMR unfortunately remain unchanged. And even with a seemingly simple clinical question to address, developing an effective diagnostic remains challenging because the tool must meet many different requirements including:

1. Accuracy of the test (>90%)
2. Short time to results (minutes rather than hours/days)
3. Solution for inaccessible infection sites
4. Inert to the presence of the natural flora
5. Robust to rapidly evolving pathogens
6. Accessibility at the point of need, where and when care is sought
7. Cost-effective
8. Easy to use

While many recent technologies improved one or more of these aspects, no single technology has ticked every box. Just missing one of these requirements impacts the utility of the tool in real-life clinical scenarios, quickly diminishing its value with little to no impact on antibiotic stewardship.

One novel and promising diagnostic approach is the utilization the host-immune response, based on its potential to meet all the above-mentioned requirements. The underlying concept is that the body's response to the microbe is decoded, such that rapid and accurate measurement of a few biomarkers distinguishes between bacterial and viral infections, providing actionable insights to guide physician decision-making. Host immune response-based diagnostics can not only provide insights on the type of infection, but also on infection severity. This additional and complementary information can assist physicians in determining if a patient is likely to deteriorate, supporting decisions on hospital admission and treatment escalation, among other things

The COVID-19 effect on AMR

A study published in *Clinical Infectious Diseases* in May [8] found that among a sample of 2,010 SARS-CoV-2 hospitalized patients worldwide, 72% received antibiotics. However, another sample of 806 patients showed that only 8% had an actual documented bacterial infection. In the face of the pandemic and with resources limitations, it is necessary to determine who is carrying a virus, and whether they have a bacterial co-infection to improve the utilization of antibiotics. The mentioned above numbers might suggest up to 10-fold overuse of antibiotics as described above present a real drawback in the fight against AMR.

The ability to rapidly and accurately identify the minority of patients that require the most medical assistance can also help to better manage the utilization of resources, treat early, reduce mortality, and indirectly reduce antibiotics usage. Here too, host-based technology can come into action by flagging if a patient is likely to deteriorate, thus facilitating both better individual treatment and system resources utilization. These actionable insights can help physicians make better treatment decisions for SARS-CoV-2 positive patients and support better resource allocation and improved patient outcomes. At the same time, these insights can also help in reducing the overuse of antibiotics in COVID-19 patient management, which are being given in many cases as an unnecessary prophylaxis due to great uncertainty regarding patients' clinical course and expected disease severity.

Looking to the Future

As we turn our attention to rebuilding our healthcare systems and economies and fortifying them to better cope with the next pandemic, we must make tackling AMR with a global approach a major priority. We must invest in and promote the use of medical tools that will expand our armory against AMR, not only new drugs, but also devices that can ensure the proper use and retained effectiveness of antibiotics.

Declaration of Competing Interest

Dr. Kfir Oved is a shareholder and employee of MeMed.

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Dr. Kfir Oved has over 15 years of combined industry and academic experience, leading interdisciplinary teams combining biotechnology and biochemistry, applied immunology, engineering, and big data in multiple clinical applications. Kfir co-founded MeMed and serves as its Chairman of the Board. For over a decade, he served as CTO of MeMed, where he led the inception, development, and clinical validation of the entire MeMed technology suite, including the MeMed BV^{TM} test, and the MeMed Key^{TM} point-of-need platform, from an idea on a napkin to development completion. Kfir holds a B.A. in Biology (Summa Cum Laude), B.Sc. in medicine (Magna Cum Laude), and Ph.D. in molecular immunology, and trained for six years at the Technion School of Medicine. Kfir is the co-author of over 100 granted and pending patents, the author of over 20 peer-reviewed publications, and the recipient of multiple research excellence awards, including the Gutwirth Excellence award and Wolf Award for research students, and was listed as one of the top 25 voices in Precision Medicine for 2019 by BIS research. He was among the inceptors of the AI-based health data company Navina and serves as its chief strategy and innovation officer. Last year, he founded Canopy Immuno-Therapeutics, a stealth mode biotech company engaged in developing a novel immunotherapeutic approach for autoimmunity and life-threatening allergy.

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