MORE SHOTS ON GOAL: TOWARDS AN INNOVATION ECOSYSTEM SUFFICIENT FOR THE FIGHT AGAINST ANTIMICROBIAL RESISTANCE

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Johnson & Johnson is the world's most broadly based health-care company, with a longstanding commitment to and leadership in innovative technology platforms that advance human health. These include pharmaceuticals, biologicals and vaccines, as well as device and surgical innovations in orthopaedics, trauma and general surgery. As such, we understand the challenges in developing novel technologies to combat antibiotic and antiviral resistance against transmissible health security threats like tuberculosis, and the risks that resistant micro-organisms pose to patients in emergency and elective surgeries. We understand the scope of these dangers and their potential to claim millions of lives across both advanced and less developed health-care systems. We are committed to advancing the policies and technologies that will drive forward progress in this field.

This year, from the World Health Assembly to the G7 meetings, world leaders have rightly emphasized the importance of an urgent, global response to the growing tide of antimicrobial resistance (AMR).

The threats AMR pose to human health are real and increasingly visible. A stream of recent reports illustrates their seriousness. In Nigeria, for example, 88% of Staphylococcus aureaus infections can no longer be treated successfully with methicillin *(1)*. In India, of the 30 health-care workers who contracted tuberculosis at one hospital this year, 26 of them were diagnosed with multidrug-resistant TB (MDR-TB) *(2)*. And containment of *clostridium difficile* (C. diff) and *methicillin-resistant staphylococcus aureaus* (MRSA) continues to prove difficult for a majority of hospitals in the United States *(3)*.

Per Keiji Fukuda, the World Health Organization's (WHO) assistant director-general for health security, said "This is the greatest challenge in infectious disease today. All types of microbes, including many viruses and parasites, are becoming resistant" *(4)*.

The scale of the problem lends credence to calls for comprehensive approaches to combatting it. In the design of these comprehensive approaches, we recommend that policy-makers 1) place innovation on par with stewardship in terms of priority and importance; 2) endorse bolder incentive models to help stimulate investment in AMR-related research and development (R&D); 3) consider lessons from recent case studies, including SIRTURO™, in shaping AMR innovation policies for the future.

Place innovation on par with stewardship in the policy discourse on AMR

Stakeholders have widely embraced the idea of combining multiple solutions to address AMR. Disagreement exists, however, regarding the relative ranking of proposed solutions, and the order in which solutions should be pursued.

In recent months especially, some have argued that antibiotic stewardship be considered the primary and predominant strategy for combating AMR *(5)*. Stewardship programmes indeed play a vital role in managing the overuse of antibiotics and preserving their effectiveness over time. Nonetheless, rather that slanting AMR strategies almost entirely toward stewardship, we suggest that stewardship measures be pursued in parallel with, and be seen as on par with, programmes that promote a vibrant innovation ecosystem for AMR-related R&D.

Neither stewardship nor R&D can stem the tide of AMR on its own, within the timeframe in which progress must be achieved. A stewardship-only approach has clear limitations. As Sally Davies, England's chief medical officer, has explained: "Bacteria have a capacity to adapt in ways that defeat any antibiotic eventually," even where robust stewardship practices are in place *(6)*. Ramanan Laxminarayan, director of the Center for Disease Dynamics, Economics and Policy, has underscored the point: "People should understand that no matter how good we are as antibiotic stewards, antibiotic resistance is a natural evolutionary phenomenon that will proceed, albeit at a slower pace. But nonetheless, we will need better tools to fight infection, so research for new antibiotics, diagnostics and

vaccines is still very important *(7)*".

Of course, research toward new and better tools is itself subject to limitations: scientific exploration towards market-ready technologies is a lengthy, risky and expensive process. Whereas stewardship practices can be implemented with relative quickness, technological innovation is almost invariably a longer-term strategy. It is important to understand notions of "stewardship first, drug development later" *(8)* in terms of pursuing both strategies now, understanding that drug development investments are likely to bear fruit over a longer time horizon.

Today, many countries have committed to developing national plans to combat AMR within the next two years.[1] We suggest that in these formal plans, countries place equal emphasis on both stewardship and innovation as paired strategies of equal importance. Global institutions can help to encourage such an approach.

Assemble, test and implement a bold collection of incentive models, sufficient to attract the world's best and brightest to the challenge of AMR

An innovation ecosystem adequate to combat the AMR challenge remains a far-off ideal at present. To move the field forward, we recommend the following to policy-makers:

- **Reshape the incentives paradigm for antibiotics R&D.** As referenced above, the development process for any innovative therapy is recognized for its cost, risk, complexity and lengthy duration. Importantly, innovators must absorb the economic impacts of failures in the R&D process, sometimes amounting to hundreds of millions of dollars or more. Less than one of every 10 drug candidates entering Phase I clinical trials ever makes it to market. Extensive and expensive clinical testing is necessary and, for those drugs that do succeed to the point of market approval, post-market research requirements can be extensive and costly.

  The distinctiveness of R&D for drug-resistant infectious disease places new points of strain on this already challenging innovation model. The development shift forced by drug resistance demands a targeted approach that is very different from the approaches employed for broad-spectrum antibiotics in the past. Failure risks and rates are higher than average.

  For these reasons and more, current incentive models are insufficient to stimulate the level of new antibiotic R&D investments necessary to strike back at drug-resistant infections. Changes in public policy toward the creation of new incentive frameworks specific to AMR-related R&D can help to offset these challenges.
- **Seek out a broader, bolder "basket" of incentive options. For drug-resistant diseases especially, the need for more R&D across the board remains stark.** To address this need, we must explore an array of options for stimulating antibiotic drug and vaccine development, and the development of adjacent technologies such as companion diagnostics. In short, we must create a broad set of highly attractive incentives to engage many biomedical innovator companies – large and small – in this work.

  There are many relevant proposals already available for policy-makers' consideration. However, most options remain in concept form only, yet to be implemented or tested. Until such testing occurs and programmes are assessed and refined, the key questions of what will work? And how, when and where will it work best? will be impossible to answer.

  Thus, a multidimensional or "package" approach – making several or more incentive options available to prospective innovators – would best allow for their efficient testing, evaluation and refinement. Indeed, finding what "works" within an acceptable period of time will almost certainly require testing several options simultaneously.
- **Solicit the advice of innovator companies in the policy development process; they are best positioned to assess the likely success of various incentive programmes ahead of implementation.** Innovators of different sizes and character will almost certainly have different perspectives on what conditions would prompt their participation in AMR-related R&D.

  Similarly, different types of diseases related to drug-resistant bacteria – each with its own set of risks, markets and cost profiles – will require different incentive models. Hence, again, the importance of advancing a variety of incentive options to enlarge the pool of participating firms.

Consider lessons from relevant case studies, including SIRTURO™, in shaping AMR-related innovation policies for the future

We recommend that policy-makers look to relevant case study examples, including SIRTURO™, in the design of AMR-related innovation policies for the future.

SIRTURO™ is a new antimycobacterial drug indicated as part of combination therapy in adults with pulmonary MDR-TB. The first medicine for TB with a new mechanism of action to be developed in more than 40 years, SIRTURO™ is the first new drug specifically indicated to treat a drug-resistant form of tuberculosis.

Our company's experiences with SIRTURO™ – today and since its discovery in our labs more than a decade ago –

1. Ly, Thu. "US pledges to support Vietnam to combat anti-microbial resistance." VietnamNet. 27 June 2015.

illustrate the progress that is possible against drug-resistant infectious disease, and also the challenges associated with the development of new antibiotics.

Regarding challenges in cost recovery and the current commercial model

From discovery through its post-market phase, SIRTURO™ is a product for which we expect to see no "return on investment" as the term is traditionally defined. Traditional sales and marketing strategies are inappropriate for a drug such as this, and out of concert with stewardship principles set by our company, regulatory agencies and the World Health Organization.

Considering return on investment and also stewardship, the SIRTURO™ experience highlights the expansive post-approval responsibilities and sustained investments required of market authorization holders to ensure a new antibiotic's appropriate use worldwide. We estimate that approximately half of all investments necessary to develop and support SIRTURO™, amounting to several hundreds of millions of dollars, will be required after the point of US regulatory approval in December 2012.

Regarding responsible market introduction of AMR-related new products

The sustainable access strategy for SIRTURO™ incorporates a wide range of measures to support post-market surveillance and research, appropriate use, and affordability. Last December, our company forged a new collaboration with the United States Agency for International Development (USAID) to mutually advance the fight against MDR-TB.

Under the agreement, Janssen will contribute an estimated US$ 30 million of SIRTURO™, or about 30,000 courses. USAID will work with Janssen, national TB programmes and their implementing partners to ensure responsible access to and appropriate use of the treatment.

This type of multi-sectoral collaboration may offer a potential model for the market introduction of other new antibiotics developed over time.

Regarding existing incentives in support of AMR-related R&D

Of note, our company received a Priority Review Voucher (PRV) with the accelerated FDA approval of SIRTURO™. The PRV programme marked an important step forward in the development of new incentives to spur R&D in areas of high unmet medical need.

At the same time, it is important to recognize that the PRV provides limited incentives to invest in high-risk early research because, in considering such investments, the Voucher value is discounted both by the high risk of programme failure and the substantial delay (typically over a decade) before the Voucher would be received.

We believe the Priority Review Voucher would be most effective as an incentive for innovator firms if it were part of a more complete, diverse and integrated set of incentives that policy-makers can help to make available.

Conclusion

Solutions to the AMR challenge must be multi-pronged; bold in their design; and built upon lessons derived from case studies in AMR-related innovation.

In the design of policies to meet this challenge, alongside companion strategies, due attention must be given to facilitating more therapeutic and preventive options for patients, sooner. To achieve this, stakeholders should aim to foster more "shots on goal," galvanizing and mobilizing the larger innovator community to apply its time, talents and resources to the challenge of AMR. ■

References

1. Tan, Annabel. Antimicrobial Resistance: The End of the Antibiotics Era. Asian Scientist. 3 June 2015.
2. Five Sewri TB staffers got drug resistant TB this year. The Times of India. 11 Sept 2015. At http://timesofindia.indiatimes.com/city/mumbai/Five-Sewri-TB-staffers-gotdrug-resistant-TB-this-year/articleshow/48906073.cms
3. Bird, Julie. Majority of hospitals rate poorly in controlling C.diff, MRSA. Consumer Reports. 29 Jul 2015. At http://www.fiercehealthcare.com/story/majority-hospitalsrate- poorly-controlling-cdiff-mrsa/2015-07-29
4. Kelland, Kate. Most countires woefully unprepared to fight resistant superbugs: WHO. Reuters. 29 Apr 2015.
5. Per an author of the recent CDDEP report, The State of the World's Antibiotics, 2015: "We need to focus 80 percent of our global resources on stewardship and no more than 20 percent on drug development. No matter how many new drugs come out, if we continue to misuse them, they might as well have never been discovered." This tilted approach to stewardship over innovation is, in our view, misplaced.
6. Min-ho, Jung. "'Koreans use antibiotics too much.'" The Korea Times. At http://www.koreatimes.co.kr/www/news/people/2015/09/178_186631.html
7. Tan, Annabel. Antimicrobial Resistance: The End of the Antibiotics Era. Asian Scientist. 3 June 2015.
8. Per Jim O'Neill: "The cost of a global effort to raise awareness of the threat of antimicrobial resistance would be miniscule compared to the amount being spent to develop new drugs and tehcnologies, which in any case will take years to become available. Countries should urgently put in place educational campaigns and begin to change behaviors. Together, we can break our bad antibiotic habits." Found at https://www.project-syndicate.org/commentary/using-antibiotics-wisely-by-jim-oneill- 2015-09. As a point of argument and clarification, we urge policymakers to urgently put in place both stewardship campaigns and incentives-for