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Antibiotic development & economic, regulatory and societal challenges

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Antibiotic development — economic, regulatory and societal challenges

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Antibiotic resistance is undoubtedly one of the greatest challenges to global health, and the emergence of resistance has outpaced the development of new antibiotics. However, investments by the pharmaceutical industry and biotechnology companies for research into and development of new antibiotics are diminishing. The public health implications of a drying antibiotic pipeline are recognized by policymakers, regulators and many companies. In this Viewpoint article, seven experts discuss the challenges that are contributing to the decline in antibiotic drug discovery and development, and the national and international initiatives aimed at incentivizing research and the development of new antibiotics to improve the economic feasibility of antibiotic development.

Q *We are facing an antibiotic resistance crisis as the emergence of resistance is outpacing the development of new antibiotics. What economic, regulatory and societal factors and challenges are contributing to the decline in antibiotic drug discovery and development?*

Christine Årdal and David McAdams. Developing a new antibiotic is difficult, with an estimated failure rate of 95%[1], and costs hundreds of millions of US dollars, if not more[2,3]. However, this is not unique to antibiotics. New medicines in other therapeutic areas are similarly risky and costly. The major challenge with antibiotics is profitability. As older antibiotics are still effective for treating most infections[4], the primary value of new antibiotics is to treat multidrug-resistant infections and provide a protective benefit against emerging pathogens. As the development of resistance is hastened by use[5], new antibiotics are stewarded as a last resort, which results in low unit sales. Whereas medicines for rare diseases have used high unit-pricing strategies to achieve profitability, these are often unavailable to antibiotic developers due to clinical trial design (it is difficult to demonstrate the superiority of new antibiotics as resistance is still relatively uncommon) and bundled hospital reimbursement structures (whereby hospitals are incentivized to prescribe lower-cost antibiotics). Large pharmaceutical companies have largely abandoned the market, accounting for only 4 of the 42 antibiotics currently under development[6]. This in turn puts pressure on small and medium-sized enterprises (SMEs), as there is little chance that their candidate antibiotics will be purchased by larger companies. Achaogen, an SME, went bankrupt in April 2019 after launching a new antibiotic, plazomicin, against carbapenem-resistant Enterobacteriaceae (CRE) in the United States in 2018 (REF.[7]). CRE is one of three priorities identified by the World Health Organization (WHO) as critically requiring new antibiotics[8]. Almost US$500 million was raised through both public and private funds to develop plazomicin[9], but now its future accessibility is in jeopardy, before it has even been registered in any country outside the United States. Many SMEs developing promising new antibiotics are on the brink of bankruptcy as private-sector investors further contract in reaction to Achaogen filing for bankruptcy. To avoid a broader collapse of antibiotic innovation, new revenue models are urgently needed that enable antibiotic developers to earn a profit that more closely aligns with the value they deliver to society.

Manica Balasegaram. Misuse and overuse of drugs in human and animal medicine and in food production, poor infection prevention and control, and the availability and distribution of poor-quality medicines have led to the emergence of high numbers of drug-resistant bacteria. Yet, despite much international attention and many policy discussions, programmes to develop new antibiotics continue to be abandoned due to scientific challenges, regulatory issues and limited commercial attractiveness, which is often due to unsustainable low prices of the drug, short treatment courses and the need for conservation. Many large pharmaceutical companies have exited the market, and SMEs are struggling to finance their efforts, as demonstrated by recent high-profile bankruptcies. This situation is compounded by insufficient public support for research into and development of new drugs.

Although 42 antibiotics are under clinical development, only 11 of these have the potential to treat pathogens on the WHO's critical threat list[10]. Support is needed to ensure studies can be conducted for not just regulatory trials but also public health and postregulatory trials to best understand how to use new antibiotics.

Infectious diseases are a major cause of morbidity and death in children, but only a few paediatric treatment strategies are being developed. Developing treatment approaches for children is particularly challenging and exacerbated by the scarcity of guidelines and evidence-based treatments to manage paediatric infections. Children require treatments that are adapted in terms of the regimen, dose and formulation. Although regulatory agencies require companies to develop paediatric plans to evaluate new antibiotics, few new drug development projects in children are implemented. Importantly, steps are now being taken by regulatory agencies to provide guidance on the paediatric-specific requirements for the evaluation of medical products to treat bacterial infections. However, this guidance alone is not enough to address clinical needs globally.

Much of the discussion about antibiotics focuses on developing new treatments; however, old antibiotics have a crucial role in everyday clinical practice. Limited

availability, supply shortages and pricing are serious global problems that restrict access to effective treatment for common bacterial infections, which may not only worsen clinical outcomes but are potentially accelerating the development of antibiotic resistance.

Ramanan Laxminarayan. The slowdown in new antibiotic development in the 1980s was not accidental. First, the regulatory cost of bringing any new drug to market has been climbing, and this is not specific to antibiotics. Second, there was the perception that there were 'enough' antibiotics and that new antibiotic development was not needed. Although there was certainly talk of drug resistance, there were no meaningful numbers of cases to encourage pharmaceutical companies to make an investment. The regulatory barriers to developing antibiotics and the need to prove that an antibiotic has value in the face of drug-resistant infections have been written about extensively. Some progress has been made by the regulatory bodies in addressing these issues, but their hands are tied by the overarching intent of enabling legislation that is designed to protect patient safety, and rightly so.

Third, a substantial challenge for a manufacturer of a new antibiotic is that the manufacturer has to compete in a marketplace where there are roughly 200 existing antibiotics with good brand name recognition that mostly work. When I say 'mostly', what I mean is that true multidrug resistance is a rare phenomenon as a proportion of all bacterial infections. Certainly, the value of an antibiotic that will save the patient's life from a multidrug-resistant infection when no other antibiotic will work is extremely high, yet the proportion of all bacterial infections that fall in this category is extremely small. That said, the number of bacterial infections that do not respond to any available antibiotic is increasing. Add to this the fact that bacterial infections are acute and of short duration with early onset of adverse outcomes. In this numbers game, it is difficult for an antibiotic manufacturer to be able to precisely identify the small proportion of patients who both really need the antibiotic and are willing to pay a high price for it.

Fourth is the cost of capital. Any investment in a new antibiotic is seen as a high-risk proposition, and consequently the returns expected by prospective investors are high to account for this risk premium. The era of purely private investment in new antibiotics seems to be coming to a close, and what we see now are co-investments by the public and private sectors, with publicly financed investors such as the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and the Global Antibiotic Research and Development Partnership (GARDP) occupying the centre stage in antibiotic development all the way from preclinical and regulatory stages to product registration.

Kevin Outterson. The most pressing problems for antibiotic research and development are economic, not scientific or regulatory. Support for basic science has given us more than 400 preclinical projects globally, with remarkable diversity and ambition. For many years, regulators at the Food and Drug Administration (FDA) and European Medicines Agency have been leading reforms that have addressed many of the regulatory challenges. Lowering standards is not a reasonable path for science-based agencies; a race to the bottom will not fix this crisis. As mentioned above, the key problems are economic. Companies are making so much money from the sales of other drug classes, including immuno-oncology therapeutics, that antibiotic development projects compare poorly when management allocates capital. Due to the threat of the emergence of resistance, new antibiotics are 'kept on the shelf', not being sold. In no other drug class do we lock up the most innovative new products to keep sales as low as possible. Large companies have been making entirely rational decisions to exit this market, at least from the perspective of the individual company. For society, these individual commercial decisions threaten the global ability to research, develop and produce new antibiotics. We are destroying a key global infrastructure and threatening our health security.

The contributors

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Manica Balasegaram trained as a medical doctor at the University of Nottingham, United Kingdom, and from 2001 onwards worked as a doctor and researcher in several countries in sub-Saharan Africa and southern Asia with Médecins Sans Frontières. In 2007, he joined the Drugs for Neglected Diseases initiative as Head of the Leishmaniasis Clinical Program before returning to Médecins Sans Frontières as Executive Director of the Access Campaign. He joined the Global Antibiotic Research and Development Partnership in June 2016, and is a board member of the Medicines Patent Pool as well as FIND's Scientific Advisory Committee. He is also the executive director of GARDP.

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Kevin Outterson is a professor of law and N. Neal Pike Scholar in Health and Disability Law at Boston University, United States, and Executive Director of CARB-X. He has grappled for a dozen years with issues peculiar to antibiotic research and development, especially relating to intellectual property, reimbursement and business models. He now leads the world's largest push incentive for antibacterial research and development, CARB-X, with a 5-year budget exceeding US$500 million. The views expressed herein are personal, and do not necessarily represent the views of CARB-X or any CARB-X funder.

John H. Rex is a physician and drug developer with more than 30 years of development and policy experience focused on antimicrobial agents. He is currently Chief Medical Officer of F2G Ltd (an antifungal biotechnology company), an expert-in-residence for the Wellcome Trust and an operating partner with a venture capital group (Advent Life Sciences) and was (2015–2019) a voting member of the US Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria. He blogs regularly at http://amr.solutions/blog.html.

Nithima Sumpradit is a pharmacist and lead coordinator for development and implementation of Thailand's National Strategic Plan on Antimicrobial Resistance 2017–2021. She is also a programme manager of the Royal Thai Government–WHO Country Cooperation Strategy Programme on Antimicrobial Resistance.

John H. Rex. Antibiotic research and development has two core challenges. First, antibiotics are incredibly hard to discover. Only two classes of drugs, namely antimicrobials and anticancer agents, are used with the aim to kill a living organism. Although living organisms are readily eliminated by gross means (steam, fire or bleach), these approaches are obviously not applicable for the treatment of patients. Finding molecules that are just right — toxic to the bacteria but not (too) toxic to the patient — is very challenging. Second, antibiotics hit an economic hurdle in that these life-saving medicines are greatly undervalued. If antibiotics would be appreciated as being equivalent to anticancer drugs — but curative! — we would have no trouble ascribing a value equal to many years of life regained. However, as antibiotics have been so effective since at least the 1950s, most adults do not realize that a seemingly simple pneumonia or skin infection could be fatal. We now expect infections to be cured at a small cost with a handful of pills, and it is hard to argue that we should suddenly start paying for the true societal and personal value of a course of antibiotics.

Nithima Sumpradit. The economic factors for the research into and development of new antibiotics are less attractive compared with those for medicines for chronic conditions. A major reason is that antibiotics have a limited lifespan due to the emergence of drug-resistant pathogens, whereas other drugs are not affected by factors that limit their lifespan (except when better products are introduced to the market). In addition, the duration of antibiotic treatment for individual patients is relatively short (for example, 1–2 weeks or up to 1 month), whereas the treatment for chronic conditions can be continuous over many years. In terms of regulatory factors, discrepancies of regulatory capacity across countries can affect the lifespan of new antibiotics as well. Countries with limited regulatory capacity may lose control of antibiotic distribution. As a result, some antibiotics that need to be reserved as a last-line treatment option are sold without a prescription. Additionally, the limited regulatory capacity can result in the rampant availability of substandard and falsified antibiotic products, which further promote the emergence of resistant pathogens. Social factors are usually associated with the demand for antibiotics. Individuals living in poverty are susceptible to infections, and under the poor living conditions (for example, no access to basic sanitization facilities or health care), infections can spread faster. Thus, the demand for antibiotics in those areas is high — not only to treat infections but also for being a quick solution for poor infection prevention and control. In addition, it is important to note that the overuse of antibiotics has become a social norm in many countries as it is influenced by the beliefs and attitudes of the individuals towards antibiotics as well as sociocultural factors, regardless of medical justifications. Evidence on this matter is plenty and mentioned elsewhere. In conclusion, these three factors are intertwined in a complex way and pose a dilemma for research into and development of new antibiotics, and in the future all those aspects need to be addressed to meet the public health need and the business interest.

Q *What are the current strategies to incentivize and aid the development of new antibiotics and successful research and development outcomes? What barriers are stopping the implementation of these programmes and what future initiatives are needed to improve the economic feasibility of antibiotic development? What roles do the public sector and the private sector have? How should those sectors combine their efforts to promote antibiotic development at a global scale?*

C.Å. and D.M. The European Union, Germany, the United Kingdom and the United States have all commissioned reports laying out strategies to incentivize antibiotic innovation[11–14]. The recommendations of these reports are largely aligned around two main themes: more public investment is needed in antibacterial research and development ('push' funding); and incentives are needed to ensure that new antibiotics that meet unmet public health needs can be profitable ('pull' incentives).

Governments have responded to the first recommendation with substantial new investments in push funding, through new organizations such as CARB-X and existing initiatives such as the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). The result is a strengthened pipeline with a global developer base of SMEs[15]. Yet, the call for pull incentives has been met with scepticism due to the high 'price tag' of US$1 billion per antibiotic (excluding public funding received for clinical trials)[11]. Whereas this estimate is meant to secure global access and stewardship for the lifetime of the patent, it is politically unattractive to reward the pharmaceutical industry with such sums, given recent high-profile cases of exorbitant medicine prices[16].

Despite these challenges, there is some progress in implementing pull incentives on a national basis. The United States is currently pursuing several regulatory options to allow newer antibiotics to be reimbursed at higher prices[17]. More promising still, Sweden and the United Kingdom have made commitments to pilot incentives that pay an annual fixed fee to secure access to important new antibiotics ('access pilots')[18,19]. This is an important development that demonstrates a change in thinking regarding antibiotic reimbursement, from paying for consumption to paying to ensure access to a critical antibiotic. If other countries join Sweden and the United Kingdom, this may have a stabilizing influence on the market, easing investor concerns.

The future development of new antibiotics is currently at risk, with investors leery after Achaogen's backruptcy filing. The AMR Industry Alliance states that its members invested US$2 billion in antibacterial innovation in 2016 (REF.[20]). To maintain or hopefully increase such investment, the public sector needs to demonstrate a willingness to pay for those antibiotics that meet unmet public health needs. National or regional access pilots are a good first step.

M.B. The traditional business model to develop new drugs does not work for antibiotics. Alternative approaches proposed include push and pull incentives such as market entry rewards and transferable exclusivity vouchers. These have yet to be implemented, in part because they are perceived as too costly or political unviable. One promising new approach is a subscription or Netflix-type model which offers the prospect of a defined revenue stream and secure access for existing and new antibiotics. Although critical questions remain, including appropriate subscription rates, sustainable financing, qualifying criteria and scalability, such incentives could be an economically and politically feasible way to help maintain a research and development ecosystem, particularly for SMEs and manufacturers.

A successful strategy will require a mixture of push and pull incentives with long-term sustainable financing tailored

to meet specific needs focused on public health priorities while ensuring access and stewardship. A coordinated global effort is urgently needed as new and remaining companies, academic institutions, governments and not-for-profit organizations (actors) in the antibiotic development landscape struggle to mobilize financing. Investment needs to focus on optimizing use, access and quality of both existing and new antibiotics. More people currently die because of lack of access to antibiotics than of drug-resistant infections.

We need sustainable and substantial public investment in antibiotic research and development to address the rapid increase in antibiotic-resistant infections. No one actor can address the challenge of antibiotic resistance and lack of effective drugs alone. It is crucial to bring complementary actors together.

Effective antibiotic treatments must be made sustainably accessible to all who need them.

The not-for-profit GARDP was created to address this global challenge. GARDP accelerates the development of treatments by taking a portfolio approach, making a long-term commitment to partners and projects by building global collaborations. Partnerships are key to GARDP's strategy, and include partnerships with industry, research institutions and/or academia, governments and civil society.

By conducting research and development with partners through preclinical and clinical studies, pharmaceutical quality and chemistry, manufacturing and control, regulatory activities, production and supply, GARDP can absorb substantial development risks. GARDP can also separate the cost of developing new treatments from traditional sales approaches, ensuring appropriate margins while establishing sustainable access measures with partners.

R.L. The era of purely private investment in new antibiotics is coming to an end for the reasons described already. There is an opportunity to rethink the antibiotics business to ensure that new generations of antibiotics are both brought to market and used in ways that ensure responsible access to those who could benefit the most from these antibiotics. At the heart of the resistance problem is the market failure associated with the 'commons' nature of antibiotic effectiveness. In other words, no single patient, doctor, hospital, health-care payer or pharmaceutical company is incentivized to take into account their actions on the effectiveness of antibiotics for others. That often results in overuse and misuse and is an important rationale for the entry of public funds into the antibiotic development space.

How might the public and private sectors work together on new drug development? There are examples of how to do this from other areas, including defence, which is also a 'public good'. The public sector has a role in identifying areas of public health needs and providing resources and knowhow from government and research institutions as well as appropriate guardrails for responsible access and stewardship to the process of bringing new antibiotics to market. The private sector excels at identifying drug candidates that are likely to succeed, determining appropriate risk–return ratios, and also in running the process of drug development and product registration in various geographical areas. Now these are very general descriptors of complementary skills and may vary depending on the country and context. But it is safe to say that not only are public funds needed for the development of new antibiotics but also that there is a strong rationale for these funds to be pooled globally. It makes little sense for the United States alone to make investments in new antibiotics that will benefit the entire world when other countries stand ready to co-invest and collaborate, both to increase the likelihood of useful and novel antibiotics coming to market and to ensure stewardship and responsible access. We have now recognized that vaccines are a global public good as is global public health. This is why we make investments in the Gavi Alliance and the WHO. We have to realize that antibiotic effectiveness is also a global public good, and it makes little sense to determine public investments in novel antibiotics through the lens of a national perspective alone.

K.O. Incentives for antibiotics are categorized as either 'push' or 'pull'. Push incentives occur before regulatory approval by the FDA or European Medicines Agency, and the funding supports many projects, including the many that fail before approval. Pull incentives are paid only after regulatory approval and hence only successful products are supported. Both push and pull incentives are required to address our pressing problems.

At present, the United States and the European Union have initiated an admirable array of push incentives, including support of basic science at the US National Institute of Allergy and Infectious Diseases (NIAID), the UK Medical Research Council, and other national funding agencies, as well as specialized support for preclinical and clinical antibacterial research by the US Biomedical Advanced Research and Development Authority (BARDA), CARB-X, the European Gram Negative AntiBacterial Engine (ENABLE), the REPAIR Impact Fund and GARDP. These efforts have been led by BARDA in the United States and by the Wellcome Trust, the Innovative Medicines Initiative and the Novo Nordisk Foundation in Europe, with substantial additional funding from the UK's Global AMR Innovation Fund, the German Federal Ministry of Education and Research and the Bill & Melinda Gates Foundation, among others.

These efforts are succeeding. The preclinical pipeline is shifting to higher-quality products targeting the most urgent clinical needs, de-risking projects for private development. Without these programmes, the fragile pipeline would become entirely moribund. However, the bankruptcy of Achaogen in April 2019 provided a moment of clarity for the antibiotics industry: the finish line is not FDA approval, but break-even profitability. Because novel antibiotics are rightfully held in reserve for years, sales revenues are very low in the first 5–7 years. During this period, the company must pay for postapproval costs such as clinical studies to fulfil paediatric commitments, expanded label indications, global registration and the infrastructure to support commercialization. These postapproval expenses will be at least several hundred million US dollars. For most new drugs, companies cover these expenses through aggressive sales. For antibiotics, companies have no way to pay for them without positive net revenues in an environment that hinders their ability to raise additional funds. For Achaogen, scientific and regulatory achievement ended in economic disaster. A similar fate awaits other antibiotic companies unless governments enact meaningful pull incentives in the next year.

Pull incentives are being actively discussed in the United States and Europe, building on the release of the DRIVE-AB final report in 2018 (REF.[11]), a study funded by the Innovative Medicines Initiative.

In the United States, the Administrator of Medicare[17] announced new reimbursement reforms to the largest health insurance system in the United States, designed to better support antibiotic innovation. In the United Kingdom, the Department of Health and Social Care has been working with the National Health Service and the National Institute for Clinical and Care Effectiveness to pilot a Netflix-type subscription model which would pay for two innovative antibiotics without regard to the volume of the drugs used. This payment mechanism is called 'delinkage', and is uniquely salient for antibiotics that could be undermined by resistance through inappropriate commercial incentives to sell. Paying for antibiotics on a national level is a powerful pull incentive, paying for value as opposed to volume.

The broken market for antibiotics requires both push and pull incentives. The former are well understood, and admirable efforts are in place and funded at scale. The latter remain mostly inchoate and much work needs to be done immediately to combat the antibiotic crisis.

J.H.R. Starting about 10 years ago (I date it to the autumn of 2009, when Sweden held the presidency of the Council of the European Union and convened a conference entitled 'Innovative Incentives for Effective Antibacterials'), there has been a concerted global effort to provide funding for antibacterial research and development. Creation of early-stage funding, also known as push funding, has been successful, exemplified by the creation of the Innovative Medicines Initiative New Drugs for Bad Bugs (IMI ND4BB) projects (launched in 2012; funds made available €223 million), CARB-X (launched in 2016; funds made available US$455 million) and the Novo Holdings REPAIR Impact Fund (launched in 2018; funds made available US$165 million).

Now, corresponding pull incentives are needed that reward the innovator and ensure that the antibiotic is available on the market. Once an antibiotic has been developed, we must ensure that it is used sparingly but is also readily available in the pharmacy. This latter point has led to us to refer to antibiotics as the 'fire extinguishers' of medicine: they need to be put in place before the fire starts. We do not pay for them on a per-fire basis; instead we see them as vital infrastructure akin to roads and water. The debates on how to implement pull incentives are now central to many discussions, and one of the Innovative Medicines Initiative projects (DRIVE-AB) spent 3 years working through possible approaches. On the basis of this and other work (for example, the review on antimicrobial resistance in the United Kingdom and the reports from the Duke–Margolis project in the United States), I am hopeful that some concrete examples of pull incentives will emerge in the near future. A very exciting initial step was the announcement by the US government detailing the changes to reimbursements of antibiotics in hospital; although this is not a delinked model, those changes should make a difference when they are put into action beginning in October 2019.

Importantly, I think it is critical that both push and pull funding sources continue to use a blend of public and private funds to ensure projects progress (or do not progress) on the basis of achieving clear milestones. Having 'skin in the game' is a key feature of successful projects — it must be possible for a project to fail (and be stopped) so that efforts are transferred to other work. An ongoing debate concerns the role of non-profit companies in antibiotic research and development, and I can certainly see a value for such as long-term support for antibiotics. That said, my experience leads me to believe that private investment and a corresponding potential for private return are critical both to the creation of exciting new projects and knowing when to terminate a failing project.

N.S. We need strategies at both the global and the country level to address this issue. At the global level, we need a reconfiguration of the financial incentives for both new and existing antibiotics to prolong the lifespan of all antibiotics and ensure accessibility to quality antibiotics. As a result, balancing the interests among the public sector, the private sector, civil society partners and other relevant stakeholders should be discussed to find new ways to provide reasonable return of investment and ensure product development and market entry as well as to delink antibiotic revenue from sales volume. At the country level, a focus should be on strengthening the regulatory system to control antibiotic distribution and promoting social innovation to ensure appropriate access and use of antimicrobials. For countries where antibiotics can be accessed without a prescription, controlling antibiotic distribution should be highly prioritized. However, caution is warranted when a prescription system is introduced, especially when the demand for antibiotics is still high, as it can lead to unintentional consequences (such as the distribution of antibiotics on the black market) that are even harder to control. Thus, a regulatory transition taking into account the context of each individual country is essential. Specifically, the transition should fully engage key stakeholders and take scientific information (for example, the national antimicrobial resistance situation), access to medicine matters, and costs and societal impacts associated with patients, pharmacies, clinics, hospitals and drug companies into account. Additionally, the AWaRe concept of the WHO should be applied for antibiotic reclassification to ensure consistency from antimicrobial regulation to procurement and use. Currently, this approach is being tested in Thailand. For social innovation, financial incentives (such as capitation and pay for performance) and peer approval (such as benchmarking patterns of antibiotic use) are found to be effective for prescribers to improve use of antibiotics. Meanwhile, social innovation for patients (such as a mirror toolkit for self-assessing whether their sore throat symptom is caused by a bacterial or a non-bacterial infection) enables them to make informed decisions and refrain from requesting antibiotics from prescribers/pharmacists, and eventually leads to reduction of unnecessary use of antibiotics. Thus, research into and development of social innovation to prolong lifespan of antibiotics are very crucial as well.

Q *Even when new antibiotics will reach the market, the problem of resistance emergence remains. Therefore, what factors should be considered to circumvent the global health crisis associated with drug resistance?*

C.Å. and D.M. Antibiotic resistance will always emerge as bacteria continue to evolve. Yet, due to advances in diagnostics, it is becoming possible in some cases to identify and target resistant strains with directed interventions that reduce opportunities for transmission, thereby slowing and perhaps even reversing the spread of resistant bacteria[21,22]. Examples include successful directed-control efforts against hospital-associated CRE in the United States[23] and community-associated

penicillin-resistant pneumococcus in Sweden[24].

The past decade has seen remarkable advances in resistance-diagnostic technology; recently, Unitaid announced a five-country effort to deploy whole-genome sequencing for tuberculosis diagnosis[25]. At the same time, exciting yet costly new treatment technologies are being developed, for example CRISPR-modified bacteriophages aiming to provide personalized treatment for identified infections[26,27]. Thus, at least in countries with strong public health systems and the ability to pay, it may one day be possible to reverse the rise of resistance and maintain the effectiveness of our existing antibiotic arsenal.

But what about low-income and middle-income countries with weaker health systems? These countries may well be trapped in a vicious cycle, unable to stop resistance from growing even more prevalent because their health systems are already overburdened. Worse still, if high-income countries are able largely to escape the antibiotic resistance crisis, the private sector will have even less incentive to develop new antibiotics than it does now and people in low-income and middle-income countries may be stuck in a postantibiotic world — a nightmare scenario with tremendous geopolitical implications.

Of course, the die is not yet cast. If we embrace the right priorities as a global community — reliable access to all antibiotics regardless of market size, so that our full antibiotic armamentarium is available wherever needed; affordable resistance diagnostics, to ensure that all infections are treated as effectively as possible; affordable public health interventions that can be directed against resistant bacteria; and steady innovation to meet unmet public-health needs — we may be able to turn the tide against antibiotic resistance together.

M.B. The fact that bacteria can evolve to survive exposure to antibiotics is an inevitable part of nature and means that new treatments alone will not halt the evolution and transmission of antibiotic resistance. Developing new treatments to tackle resistance is of course an important global priority. But doing so in isolation of stewardship, access and infection prevention and control jeopardizes the public health return on investment to develop treatments. The steps taken by GARDP include limiting indications for new treatments, improving formulations and drug profiles, and providing an evidence base for the use of antibiotics and to develop stewardship guidelines that include conditions in relation to access and stewardship in contracts with industrial partners. The WHO's AWaRe tool has been developed to contain drug-resistant infections and make antibiotic use safer and more effective. The tool classifies antibiotics into three groups: namely 'Access', which should be used as first choice for most infections, 'Watch', and 'Reserve', for use as a last resort. The WHO recommends that Access group antibiotics should account for at least 60% of every country's total antibiotic use[28].

In a recent study supported by GARDP[29], researchers analysing the sales of oral antibiotics for children in high- and middle-income countries found that consumption differs widely, with little correlation between countries' wealth and the types of antibiotics. Of concern is the relatively low use of amoxicillin, an antibiotic that can treat the most common childhood infections. Providing national policymakers with evidence on the antibiotics prescribed in their country is an important step to help countries tackle inappropriate prescribing of antibiotics. This in turn helps countries deliver their national action plan on antimicrobial resistance and ensure antibiotics will remain available and effective for generations to come.

We need to adopt a holistic approach to address antibiotic resistance. Action is required to improve infection prevention and control, limit unnecessary use of antibiotics and use existing antibiotics appropriately in humans, animals and agriculture. Without harmonized and immediate action on a global scale across all sectors, the world is heading towards a postantibiotic era in which fatal bacterial infections are common.

R.L. Resistance is always going to emerge in response to any new antibiotic but we can certainly do more to extend the useful therapeutic life of antibiotics. In the current situation, no single pharmaceutical company has an incentive to invest in stewardship as the consequences of overselling antibiotics extend to all antibiotics in the class. This is much like asking fishermen to voluntarily limit their fishing when the impact of their overfishing is really a problem for everyone and not just them. But that will have to change if we are to aspire to a portfolio of effective antibiotics for future generations or until the next technological solution to combat bacterial pathogens comes along. Going forward, it is clear that public funds will have to support new antibiotic development because of the substantial public health consequences associated with antibiotic resistance. However, public support will have to be accompanied by conditions on how antibiotics developed with these funds will be used. Both CARB-X and GARDP already require their pharmaceutical partners to agree to conditions that govern stewardship and responsible access. We do need to ensure that antibiotics reach those who need them, but we need to have a clear understanding of what 'need' means. Does 'need' mean only life-threatening situations? Or does 'need' refer to situations when there is a small risk of adverse outcomes without the antibiotic? Who will make these determinations? These are challenging questions especially when the existing paradigm has been one where access to antibiotics was determined largely by the ability to pay and to be able to access the services of a medical professional.

Some have claimed that stewardship reduces the incentives to innovate new antibiotics but this is not a good argument to make. Should we be wasting oil just because energy conservation reduces incentives to discover new sources of oil? What we should be looking for is ways whereby innovation of new antibiotics can be incentivized without the pharmaceutical company having to push sales to recover its investment. We have made tremendous progress in discussing these issues in recent years, but we have yet to deploy a working model in the real world of simultaneously incentivizing a new antibiotic to come to market while also ensuring appropriate and responsible use and access. That is the challenge that lies ahead of us, but I am confident that it will be addressed.

K.O. Resistance is inevitable, but our work is not futile. We can reduce the rate at which clinically relevant resistance emerges through three groups of practices: infection prevention and control (the best infection is the one that never happened, due to clean food and water, vaccinations, WASH procedures at health-care facilities, and other public health interventions against infectious diseases); antibiotic stewardship (the right drug administered to the

right patient at the right time, without unnecessary use, in humans, animals, agriculture and the environment); and discovering new drugs to which even the worst bacteria are fully susceptible. The first two interventions reduce the evolutionary pressure antibiotics place on bacteria, but improvements will require substantial change in many social systems: human behaviour must change. The third intervention requires higher-risk research into and development of new antibiotics without existing bacterial resistance, including new classes, and novel bacterial targets and mechanisms of action. Society would be wise to hold these new drugs in reserve until needed, which is good stewardship, but will accentuate the economic problems described earlier unless delinked pull incentives are adopted.

J.H.R. First, I think it is obvious that resistance will continue to develop, and we are going to need a steady stream of innovative products. Second, we have to realize that the most important form of stewardship is not limiting drug use (we should of course use drugs judiciously) but rather preventing the infections in the first place. Antibiotics have been so successful that we have used them as substitutes for clean food, clean water, vaccines and diagnostics. It is helpful to recall that infection rates began to fall in the early 1900s, long before antibiotics, on the basis of just implementing better sanitation.

N.S. First, we should be aware that the global health crisis relating to antimicrobial resistance is not only the occurrence of resistance in microorganisms caused by the use of antibiotics but also the spread of resistant pathogens and resistance genes from place to place or from country to country. Indeed, the latter may happen faster and may be more complex to control. Thus, factors relating to both the appropriate use of antibiotics and transmission control of resistant micro-organisms under the views of the One Health approach should be considered to address antimicrobial resistance challenges. Second, to solve problems associated with antimicrobial resistance, we need both technical and political arms. The technical arm (for example, the Global Action Plan on Antimicrobial Resistance) guides us on 'what to do' and 'how to do it', whereas the political arm (for example, the Political Declaration of the United Nations High-Level Meeting of the General Assembly on Antimicrobial Resistance) facilitates the establishment of multi-sectoral governance mechanisms, expands multisectoral collaborations and provides policy directions as well as resource allocation. Thus, factors to sustain and booster the global policy momentum with regard to antimicrobial resistance and the policy interface between the global level and the national level are needed to advocate antimicrobial resistance for a global high-level agenda and simultaneously support national actions to address antimicrobial resistance. Finally, we need a scientific as well as a monitoring and evaluation platform based on the One Health approach to generate and provide evidence for guiding policy decisions and strategic implementation. Examples of evidence include, but are not limited to, the rates and epidemiological patterns of antimicrobial resistance, the trends of antimicrobial consumption and use, and integration of these two pieces of information. Additionally, system and process evaluation such as the Joint External Evaluation Tool for International Health Regulation, the Country Self-assessment Questionnaire for Global Monitoring of Country Progress on Antimicrobial Resistance and the country midterm review to monitor and evaluate the progresses and outcomes of implementation is also useful to identify implementation gaps and guides further steps.

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Competing interests

R.L. is a voting member of the US Presidential Advisory Council for Combating Antibiotic-Resistant Bacteria and Board Chair of the Global Antibiotic Research and Development Partnership, which works to bring new antibiotics to market. J.H.R. is Chief Medical Officer and a director of F2G Ltd, a non-executive director of and a consultant for Adenium Biotech ApS, an operating partner of and a consultant for Advent Life Sciences and an expert-in-residence for the Wellcome Trust. He sits on the scientific advisory boards of Macrolide Pharmaceuticals, Bugworks Research Inc., Basilea Pharmaceutica, Forge Therapeutics Inc., Novo Holdings and Roche Pharma Research & Early Development. He is a shareholder in AstraZeneca Pharmaceuticals, F2G Ltd, Adenium Biotech ApS, Advent Life Sciences, Macrolide Pharmaceuticals and Bugworks Research Inc. He has received consulting fees from Phico Therapeutics, ABAC Therapeutics, Polyphor Ltd, Heptares Therapeutics Ltd, Gangagen Ltd, Meiji Seika Pharma, Basilea Pharmaceutica International Ltd, Allecra Therapeutics GmbH, Forge Therapeutics Inc., SinSa Labs, AtoxBio, Peptilogics, F. Hoffmann-LaRoche Ltd, Novo Holdings, Innocoll, Vedanta, Progenity, Nosopharm SA, Roivant Sciences and Shionogi Inc. C.Å., M.B., D.M., K.O. and N.S. do not declare competing interests.

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