

To the G20: incentivising antibacterial research and development



The antibiotic pipeline is insufficient. For example, only about five truly novel antibiotic classes are in clinical development for critical or high unmet public health needs defined by WHO.^{1,2} Given attrition rates,³ only two of these antibiotic classes are likely to receive regulatory approval during the next 7 years. The earlier, preclinical-phase pipeline is hard to assess, but might include more than a dozen novel antibiotics. However, their chances of success are even more remote than those currently in development, and are probably more than a decade away from being approved.³ Meanwhile, resistance rates to the world's current stock of antibiotics are rising, not only threatening the ability to treat infections, but also jeopardising the ability of modern health-care to safely treat cancer and undertake many surgeries.^{4,5} Deliberate and coordinated action is needed now to ensure continuous availability of effective antibiotics.

In 2016, the G20 committed to “unlock research and development into new and existing antimicrobials from a G20 value-added perspective”.⁶ DRIVE-AB, a 3-year research project financed by the European Union's Innovative Medicines Initiative (IMI), is close to concluding its work on incentives and policies to stimulate innovation, sustainable use, and equitable availability of novel antibiotics to meet unmet public health needs. In this Comment, we summarise some of DRIVE-AB's findings that are pertinent to the G20 commitments, including a market entry reward (MER). DRIVE-AB's complete findings will be published and presented at the DRIVE-AB conference in Brussels on Sept 5–6, 2017. These include detailed findings and recommendations regarding new economic models, the societal value of antibiotics, forecasting the development of resistance, and responsible use measures.

Incentives to stimulate antibacterial innovation can be grouped into two types: push incentives that pay for the research and development (R&D), and pull incentives that reward an outcome such as regulatory approval. Substantial investments are already occurring to push innovation, including grant financing—eg, the Biomedical Advanced Research and Development Authority, IMI, Joint Programming Initiative on Antimicrobial Resistance,

the Horizon 2020 research programme, and most recently the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator and the Global Antibiotic R&D Partnership, which acts as a virtual developer. These efforts are laudable, necessary, and must continue. They ensure that the pipeline is directed at public health needs. Yet the success of these initiatives in bringing novel antibiotics to market depends on continued private investment. Our stakeholder analyses identify that the willingness of companies and other private investors to invest in antibacterial R&D is primarily driven by anticipated market rewards—ie, the pull incentives.

The traditional pull incentive is revenues from unit-based sales. Yet for new antibiotics, revenues alone might not be sufficient to encourage companies to invest in the development of new antibiotics. In clinical practice, novel antibiotics should be reserved for use against bacteria that are resistant to existing antibiotics. If infection prevention efforts are successful, such infections might be relatively rare, so sales volumes will be low. Therefore, new pull incentives are needed that effectively reward innovation and reduce revenues derived from sales volume—a so-called delinked model. Without an effective pull incentive, private sector investment will continue to decline, and the few remaining companies will leave antibacterial R&D, further diminishing innovation.

Panel: Next steps for G20 members to incentivise antibacterial research and development (R&D)

- Immediately fill the gap of US\$250 million per year in push funding; existing mechanisms require additional financing and are well suited for an immediate in-flow of extra financing
- Implement market entry reward pilots to learn about the operationalisation of such models
- Request that regional and global banking institutions (such as the European Investment Bank and the World Bank) examine potential novel financial instruments to support further antibacterial R&D funding
- Establish a mechanism for multinational coordination and collaboration
- Develop health technology assessment processes and rules of reimbursement to consider the resistance situation and capture antibiotic societal value

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A fully or partly delinked MER (ie, a financial payment to the developer or intellectual property holder for a novel antibiotic that meets the predefined target product profile, addressing the most pressing public health threats) can be an effective pull mechanism. The decision on behalf of an innovator to apply for a MER will be voluntary. The size of the reward should be commensurate with the level of predefined need using public health criteria such as WHO's Priority Pathogen List. Additionally, antibiotics that meet more challenging criteria such as a new class, should receive higher rewards than those meeting less challenging criteria. Based on our current models (final versions to be presented in September, 2017), we estimate an MER of between US\$750 million and \$2000 million, paid out to developers in instalments over 5 years. Grants from public funds and foundations for preclinical and clinical trials must be accounted for in calculating the MER so that the public does not pay twice for innovation. Developers that receive MER will also be bound by transparent and implementable sustainable use and equitable access obligations.

Although substantial public sector investment in antibacterial R&D is already occurring, estimated at \$520 million annually (unpublished data), our models suggest that the public and philanthropic sectors must invest an additional \$250 million in push funding annually into targeted priority antibacterial R&D areas¹ to maintain a healthy pipeline. This excludes investments in diagnostics, vaccines, or products for animal health, which are also needed. Banking institutions such as the European Investment Bank and the World Bank could raise capital by financing medicines in other therapeutic areas and using a portion of the returns to reinvest in antibiotics.

Private investment must also increase. The implementation of an MER will help to attract and retain private capital. Additionally, health technology assessment procedures need to be expanded to account for drug resistance prevalence and to capture the societal benefit of a specific antibiotic, allowing for value-based pricing based on societal benefits of the particular antibiotic (eg, resistance and cross-resistance rates). With these incentives, our models suggest that private sector investment will at least double the public sector push contribution.

Implementation of an MER is complex and unprecedented. DRIVE-AB and others⁷⁻⁹ have extensively

explored multiple implementation options, ranging from country-level arrangements to the transfer of intellectual property to a global organisation. All options have their pros and cons and cost-benefit implications, which will be fully articulated in our final report.

Setting up infrastructure to implement MERs will take financial investment and time. We see that different models can be introduced as infrastructure and expertise is built up. In the near term, different national and multinational solutions need to be designed to work synergistically with others. Piloting MERs can help to understand these synergies and the operationalisation. Yet implementing a forum for global coordination is urgent, because innovators need clear messages about global priorities. Next steps for incentivising antibacterial R&D that can be taken by the G20 countries immediately are noted in the panel. DRIVE-AB's detailed recommendations will be available in September.

**Christine Årdal, Enrico Baraldi, Francesco Ciabuschi, Kevin Outterson, John H Rex, Laura JV Piddock, David Findlay, on behalf of the DRIVE-AB Steering Committee*
 Division for Infection Control and Environmental Health, Norwegian Institute of Public Health, Oslo 0403, Norway (CÅ); Department of Engineering Sciences, Industrial Engineering and Management (EB), and Department of Business Studies (FC), Uppsala University, Uppsala, Sweden; School of Law, Boston University, Boston, MA, USA (KO); CARB-X, Boston, MA, USA (KO, JHR); Institute of Microbiology and Infection, University of Birmingham, Birmingham, UK (LJVP); and GlaxoSmithKline, London, UK (DF)
 christine.ardal@fhi.no

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