Roche position on incentivising the development and appropriate use of new antibiotics

Background

Antimicrobial resistance (AMR) occurs when microbes (e.g. bacteria, fungi, viruses, parasites) are able to resist the effects of medications that were once successfully able to kill them or inhibit their growth.[1] AMR leads to antibiotics and other antimicrobial medicines becoming ineffective and infections become increasingly difficult or impossible to treat, increasing the risk of disease spread, severe illness and death.[2] AMR is not a future threat, it already kills at least 700,000 people each year[3], with a 2022 study published in the Lancet estimating that there were over 1.2 million deaths attributable to bacterial AMR in 2019 alone.[4] According to the WHO, if no action is taken, AMR could claim as many as 10 million lives per year by 2050.[2] With the impact on patients increasing and few new antibiotic classes for 50 years, there is an urgent need to take action on AMR now.

Antibiotics play a crucial role in modern medicine and without them, many common treatments and procedures will not be feasible, such as basic surgery or cancer treatment. We have a duty to society as well as patients to work with industry, government and health system partners to discover and develop new novel diagnostics and novel antibiotics and ensure they are available for patients when they need them. This position statement sets out Roche's commitment to finding new market models for AMR and sets out the principles we feel should underpin industry incentive schemes in the future, focusing on demand side measures, also known as pull incentives.

For clarity, this position statement does not address incentives for greater R&D, also known as push incentives, which although equally important to contributing to a sustainable long-term antibiotics ecosystem, are already relatively well established[5].

The challenge with current market models for antibiotics

The innovation gap between the tools we need to fight AMR and the tools we have is widening, due to the high failure rate of novel antibiotics and few incentives for new R&D. Considering the approval success rate, only 10 of the 51 new antibiotics and biologicals currently in clinical development identified by the WHO can be expected to reach the market within the next 10 years, and none of these therapies will represent new classes of antibiotics.[6]

---

[1] Wellcome Trust (2021), *How is modern medicine being affected by drug resistant infections?* RAND Europe, UK, Available at: https://www.rand.org/pubs/external_publications/EP68730.html [Last accessed October 2021]
[2] World Health Organisation (WHO) (2020), Health Topics, Antimicrobial resistance, Available at: *https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance* [Last accessed October 2021]
[3] Centre for Disease Control and Prevention (2013), ANTIBIOTIC RESISTANCE THREATS in the United States, 2013. Available at: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf [Last accessed December 2021]
[4] The Lancet. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. 2022. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02724-0/fulltext#%20
[5] Global Coalition on Aging (2021), *2021 AMR Preparedness Index* (p.32). Available at: https://www.ifpma.org/wp-content/uploads/2021/06/2021_AMR_Prepardness_Index_GCOA_IDSA.pdf [Last accessed January 2021]
[6] World Health Organisation (2017)The world is running out of antibiotics, WHO report confirms. Available at: https://www.who.int/news/item/20-09-2017-the-world-is-running-out-of-antibiotics-who-report-confirms [Last accessed December 2021]

Filling this innovation gap and ensuring that there is a long term, sustainable pipeline of antibiotics available to patients when they need them, requires a multi-sectoral approach to, i) bolster the pipeline of new novel diagnostics and novel antibiotics and ensure that these therapies reach patients who need them, and ii) ensure careful stewardship of both existing and new therapies in health systems – ensuring "the right drug for the right bug" and that treatments are used for the correct duration.

Good stewardship must sit at the heart of AMR strategies. The conventional pharmaceutical business model, in which revenues are based on volume sales, is not appropriate for therapies that must be used sparingly. In recent years, two main types of market interventions have been explored to, a) catalyse R&D for novel antibiotics (push incentives) and, b) create new commercial models that stimulate sustained investment in novel antibiotics while encouraging their responsible use in health systems (pull incentives).

Pull incentives

Pull incentives are measures that aim to increase the number and speed of antibiotics being made available by 'pulling' them through the system from market authorisation. The most common pull incentives also support stewardship efforts across the health system by de-linking the manufacturer's return on investment from volume of sales.[7] In practice, they work by providing a known and predictable return on investment for the successful development of new antibiotics, ideally those that address an unmet medical need - i.e. conditions with few treatment options or where multi-drug resistance is common.

Models currently being trialled include Market Entry Rewards (MERs) that pay an upfront amount and/or fixed scheduled payments to manufacturers when new antibiotics enter the market. NHS England's subscription model pilot is an example of this. Another model being explored are Transferable Exclusivity Extensions (TEEs). These models would reward manufacturers for bringing vital new antibiotics to market by giving them a transferable right to extend patent protection on another product.

In order to be effective, pull incentives need to be accompanied by different types of health technology assessment (HTA) and reimbursement models that ensure the amount paid by governments or insurers for novel antibiotics truly reflects their societal, as well as their clinical, value. Pull incentives also need to be proportionate to the revenue that manufacturers would have otherwise got from volume sales. The GAIN Act in the US is an example of bespoke assessment pathways for antibiotics.

Roche Position

The Roche Group is uniquely placed to help counter the threat of AMR by investing in both diagnostic technologies and new antibiotic agents, as well as by working with a range of partners to ensure there is both a global response and real action in countries. We are

---

[7] IFPMA (2018), Policy Position, The need for AMR R&D pull incentives, Available at: https://www.ifpma.org/wp-content/uploads/2018/09/IFPMA_AMR_Position_Incentives_Pull_2018.pdf [Last accessed December 2021]

matching our investment in scientific innovation in AMR with new thinking on market models and reimbursement systems that will ensure there is a sustainable pipeline of innovative diagnostics and novel antibiotics, ready when patients need them. As well as working with global industry partners to fund research and drive international support for market interventions such as pull incentives, we also have local partnerships at a country level to help build ecosystems that support R&D, access and good stewardship.

We know that the challenges involved in AMR are broad, including use of antibiotics in agriculture and in the food chain which requires multi-sectoral coordination. Roche is fully committed to address the issues in healthcare, from developing new, novel antibiotics and developing new diagnostic tools which support stewardship.

There is no one size fits all model for pull incentives that will suit every country. Governments must choose the best combination of market incentives and regulatory and reimbursement schemes that fit their environment and health system structures and that drive optimal behaviours in terms of R&D investment, access and stewardship across the ecosystem. There are, however, some key attributes that underpin fit-for-purpose pull incentive schemes that we would point to:

- Includes holistic value assessment of novel antimicrobials
- Delinks revenue from sales
- The size and timing of incentives are sufficient to drive industry's behaviour change towards investing in antibiotic development
- Supports good principles of stewardship
- Co-ordinated efforts to deliver impact

Holistic value assessment

Any discussion on pull incentives must start with an appropriate valuation of the antibiotic in question to ensure that it is truly fulfilling an unmet need whilst recognising the positive benefits that antibiotics bring beyond the individual patient and that consequently society is receiving what it is paying for. There are some key features that we consider to be important:

- Value assessment of novel antibiotics must capture their broader value to public health, as well as their clinical value to individual patients
- Value assessment must recognise the innovative nature of novel antibiotics, with priority given to those that target high priority pathogens, have a new mode of action or come in convenient formulations that enable their easy administration in target populations. The "STEDI" values of antibiotics concept[8] provides a useful framework highlighting the attributes of novel antibiotics that should be rewarded:
    - **S**pectrum – narrow spectrum antibiotics that reduce damage to the good bacteria in the gut (microbiome)
    - **T**ransmission – avoiding pathogen spread to the wider population

[8] Outterson K, Rex JH (2020) Evaluating for-profit public benefit corporations as an additional structure for antibiotic development and commercialisation. *Translational Research*, Available at: https://pubmed.ncbi.nlm.nih.gov/32165059/ [Last accessed December 2021]

    - **E**nablement – ability of antibiotic to enable other medical interventions such as surgery
    - **D**iversity – having a range of antibiotic treatment options to reduce selection pressure
    - **I**nsurance – having an agent available in case of a sudden or significant increase in the prevalence of pathogens resistant to existing agents
- Value assessment needs to be able evaluate the costs and benefits of *both* antibiotics *and* complementary diagnostics that, when used together, improve patient identification and the chance of successful treatment – also underpinning the principles of good stewardship.
- Finally, in order to provide a fully holistic assessment of value, the evaluation must include indirect as well as direct costs and benefits. For example, the ability of people to continue working and contributing to society as a result of their treatment. This will require assessments to include different types of evidence beyond clinical trial data e.g. non-clinical data.

Delinkage of revenue from sales

An optimal pull incentive needs to delink a manufacturer's return on investment from volume of sales. Subscription or one-off payment models (as being piloted in England) that reflect the broader value to society of antibiotics and replace the revenue that the manufacturer might otherwise have generated present opportunities to incentivise innovation while supporting principles of good stewardship. A shift from traditional sales models to de-linked schemes is an essential market reform where government intervention is required.

Appropriate size and timing of pull incentives

Pull incentives will only work if they are large enough in size and activated at an appropriate time point in a product's lifecycle. For example, Market Entry Rewards (MER) pull incentives such as advance payment or subscription models need to be activated at market entry, to provide a return on investment to manufacturers while ensuring that the products are not used until they are needed. There will also need to be long term reimbursement models, particularly in partially de-linked models, that will ensure access to novel antibiotics when they are needed while maintaining principles of good stewardship.[9]

Principles of good stewardship

Good stewardship is a minimum requirement of any pull incentive and diagnostics can play a key role in achieving this. Pull incentives must not only incorporate, but actively reward, feasible, impactful and best-practice stewardship with appropriate diagnostic technologies to ensure the "right drug for the right bug", and for the right duration, with accompanying monitoring and tracking mechanisms so health systems can record and analyse the effectiveness of stewardship policies and the spread of drug resistant bacteria.

---

[9] Outterson, K (2021) Estimating The Appropriate Size Of Global Pull Incentives For Antibacterial Medicines, *Health Affairs,* Vol 40, No 11, available here: https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2021.00688 [Last accessed December 2021]

Co-ordinated efforts to deliver impact

AMR is a global problem that cannot be solved by one country or region alone - it requires a collective, global response. National governments need to be empowered to take action on stewardship and market reforms in their own markets, while coordinating their response with other countries and global organisations to multiply their impact. Global manufacturers can play an important role in bringing national stakeholders together and spreading good practice – helping build a global ecosystem that supports investment and stewardship in AMR.

This position paper was endorsed by Bill Anderson, CEO Roche Pharmaceuticals, on July 5th 2022, and entered into force the same day.