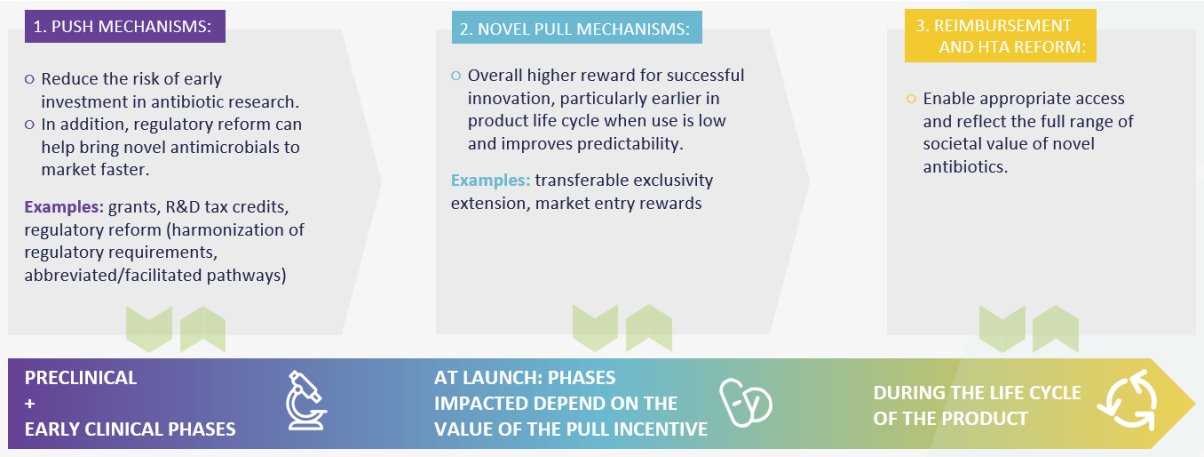
Policy Position

The need for AMR R&D pull incentives

Antimicrobial resistance (AMR) has emerged as a significant threat to global health security and, if left unaddressed, could undermine the achievements of modern medicine. New antibiotics, vaccines, and other innovations are urgently needed; however, there are relatively few in development. Over the past two decades, there has been a considerable decline in the number of companies conducting antibiotic and antifungal R&D due to the significant scientific, regulatory, and economic challenges specific to this therapeutic area.

If governments can create market conditions where there is a sustainable return on investment, the pharmaceutical industry and private investors have demonstrated their willingness to take on the risk and uncertainty that comes with the development and commercialization of a new medicine or a vaccine. Adoption by governments of sustainable and substantial pull incentives, as part of a suite of incentives including push mechanisms and reform of reimbursement and Health Technology Assessment (HTA) systems, must be achieved if industry is to continue to invest and take on the risk in research, development, and commercialization for new medicines and vaccines to address AMR.

Figure 1: Suite of incentives



Novel pull incentives

The unique challenges and dynamics of the antibiotics market require unique measures to establish an economic environment that will incentivize new antibiotic R&D and sustain current R&D investment. One of the key and unique market challenges is that uptake of novel antibiotics is slow, in part due to the importance of supporting appropriate stewardship of any novel antibiotic. This product stewardship is critical to preserving the long-term effectiveness of the antibiotic, especially while resistant infections are relatively rare and diagnostics and surveillance data to guide appropriate use is limited. Novel pull incentives are needed to drive innovation and increase revenue earlier in the product life cycle, when use is low. There are also economic challenges that limit private investment into vaccines, diagnostics, and novel approaches that could address AMR – some of which are similar to novel antibiotics and some of which may be different. Recognizing the important role these products play, we support the exploration of new incentives for vaccines, diagnostics, and novel approaches and the inclusion of these products, as appropriate, in the novel pull mechanisms described below.

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Novel pull mechanisms should reward successful delivery of innovative products to the market, and should ensure a predictable return on investment. Transferable Exclusivity Extensions (TEE) and Market Entry Rewards (MERs) are two novel pull incentives that would create supportive market conditions for product development. These market-based novel pull incentives maintain shared risk between governments and the pharmaceutical industry. By only rewarding companies that succeed in bringing a product that meets an unmet medical need, these mechanisms preserve competition between companies, which will drive development and delivery of antimicrobial innovation. The degree to which these novel pull incentives (whether MER or TEE) impact continued existing investment, support late-stage development, or attract companies into R&D is related to the overall size of the incentive. Other factors that may influence the size of the incentive include the public health need and the potential return expected from other components of the suite of incentives, including revenue from sales. Both TEE and MERs can include provisions that support appropriate use and access. Additionally, both incentives reduce or partially uncouple the proportion of manufacturer revenue that is derived from antibiotic sales volume. Finally, both TEE and MERs can be designed to focus on only the highest-priority antimicrobials to treat or prevent urgent or serious health threats.

Stewardship and access commitments

- The structure of TEE and MERs can include stewardship and access commitments. Both TEE and MERs are novel pull incentives that reward innovation for the successful development of novel antimicrobial medicines and vaccines outside of the traditional drug reimbursement systems. They offer an opportunity for partnership between governments and the private sector to not only ensure development of high-priority products addressing an unmet public health need (as determined by public health and regulatory agencies) but also promote appropriate use of these products.
- Consistent with the commitment of the Industry Declaration[i] and Roadmap[ii], we will continue to support access through approaches which may include: Tiered pricing strategies (both within and between countries), increased product registration in priority countries, non-exclusive voluntary licensing approaches and product donations.
- Maintain supply of antibiotics and vaccines for the patent period;
- Ensure that promotional activities are aligned with the goal of advancing stewardship and eliminate those that do not, in order to protect the utility of antibiotics by encouraging their appropriate use;
- Implement activities to support antimicrobial stewardship, such as the appointment of a Chief Stewardship Officer, development of a stewardship strategy including education of health care providers, and implementation of a surveillance study.

Transferable Exclusivity Extensions

TEE[iii] rewards a company with a transferable exclusivity voucher that can be used for any other product in its portfolio or sold to another company. The nature of the exclusivity extension will depend on adoption and implementation of these programs within their national contexts (and will be consistent with TRIPS and existing international patent law). There are a number of tools that could be used to confer this extension. The preferred option should fit best within each national context: it may be through a regulatory mechanism; a data exclusivity extension or a patent exclusivity extension. By transferring the exclusivity extension to a higher-revenue product (or through the sale of a transferable exclusivity voucher), TEE provides an important incentive that would support sustainable investment into AMR-relevant research and development. Similar to a market entry

reward, a TEE incentive can be coupled to public health provisions to support access and appropriate use. A central feature of this novel pull incentive is that it does not require upfront or annual government appropriations, since the revenue comes from extending current reimbursement of a product to which the TEE is transferred. Given the time needed to develop new antibiotics and vaccines, TEE would provide a predictable, reliable and sustainable source of revenue to effectively incentivize investments. The ability to sell the exclusivity extension to another company would ensure the incentive is equally applicable to both large pharmaceutical companies with broad portfolios and smaller, more focused biotechnology companies.

A number of key stakeholders and influential reports have endorsed the concept of a transferable exclusivity voucher[iv,v,vi,vii,viii,ix,x,xi], particularly as part of a suite of incentives. This mechanism could be implemented both in countries like the U.S. with a significant private sector insurance market (which would reduce the additional public expenditure due to TEE), as well as in other countries with single-payer health care systems.[xii]

Discussion on TEE in the U.S.[xiii] have led to a framework that provides elements that could also apply in other regions. This framework includes:

- A requirement that relevant regulatory and public health authorities establish a list of "priority antimicrobials" to treat or prevent bacterial or fungal infections.
- A company that obtains regulatory approval for a drug or biological product (e.g. antibiotics, vaccines) will receive a 12-month exclusivity conveyance that can be used to extend one existing exclusivity associated with a product of the company's choosing, subject to certain restrictions.
- The exclusivity conveyance may be transferred/licensed/sold to another company to be used for a small molecule of their choosing.

TEE can be linked to provisions designed to support stewardship and access of new products[xiv, xv] as well as other measures to address potential challenges and stakeholder concerns (Table 1).

Table 1: Solutions for potential TEE concerns

Concerns	Potential solutions
Increases costs in other potentially unrelated areas of healthcare	• Limit the term on transferable exclusivity to 12 months. • Independently assess value and impact of incentive 10 and 20 years following implementation. • Raise awareness of the broader public health risk of AMR and the indispensable role antibiotics play to support other parts of health care (oncology, basic surgery, neonatal care) to build support for the broader health system to bear a share of the costs to bring new antibiotics to the market[xvi].
Delay the market entry of other generic drugs	• The exclusivity extension cannot be applied to any product with a set number of years of exclusivity remaining to provide a reasonable amount of time for businesses in the marketplace and payers to adjust to the extended exclusivity of a chosen product. This provision will help mitigate the delay of the market entry by other generic drugs.

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	• The TEE will only impact one product for a limited amount of time (12 months) therefore limiting its cost. • To delay the impact of the incentive, the extension can only be applied to products approved after an agreed upon date.
Negatively impacts access of medicines	Maintain or expand efforts to enhance access to the product receiving the exclusivity voucher, including through a range of potential mechanisms most relevant for each country.

Market Entry Rewards

A MER is a single payment or series of payments to a pharmaceutical developer for successfully achieving regulatory approval for an antibiotic that meets specific criteria to address a defined public health need. A number of key stakeholders and influential reports have endorsed the concept of Market Entry Rewards[xvii,xviii,xix,xx,xxi,xxii]. MERs provide significant revenue early in the product life cycle when antibiotic sales volumes are generally low – a key economic challenge to antibiotic R&D.

International evaluations have recommended that MERs of between US$1-4 billion[xxiii,xxiv,xxv,xxvi,xxvii] globally could incentivize antibiotic development while also encouraging sustainable use of novel antibiotics. The degree to which a MER would impact continued existing investment, support late-stage development, or attract companies into R&D is related to the overall size of the incentive as well as the impact of the broader suite of incentives (push, reimbursement HTA). In most of these models, the developer would retain rights to the drug which would maintain market-based aspects to incentivize further development and would allow market demand through sales to determine a product's value in the treatment armamentarium over its life-cycle rather than a single upfront incentive payment. When combined with additional push funding, reimbursement and HTA reform, as proposed by the recent IMI DRIVE AB report, MERs could form part of the suite of incentives needed to enable sustainable private investment in innovation to address AMR.

To maximize impact, MERs will need to be linked to sustainable funding sources, should have transparent eligibility and selection criteria, be predictable and the funding for the awards needs to be sustainable over the long 10-15 year product development timeline. Following approval of an eligible antimicrobial that addresses an identified public health need, the government(s) would administer the MER payments. These payments could be made in installments to ensure a predicable return and fulfillment of any access and stewardship requirements included as conditions of the MER.

Call to action

Given the growing public health and economic burdens posed by antimicrobial resistance, there is an urgent need to reinvigorate the antimicrobial pipeline. This is particularly critical given the long development times (10 – 15 years) for new medicines and vaccines. TEE and MERs, as part of a suite of incentives, address key economic challenges to antimicrobial and vaccine development and have the potential to significantly increase investment in R&D across all stages of development. Recognizing the global consensus on the need for novel pull mechanisms to incentivize investment into antimicrobial development, we call on governments to move forward with the adoption and implementation of these programs within their regional or national contexts.

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