

Solutions to incentivize antibiotics R&D – No "one-size-fits-all"

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Introduction

Several characteristics of the current business model for antibiotics have been responsible for the failure to adequately reward innovation and have led to the pharmaceutical industry's hesitancy to invest in antibiotic R&D. Sustainable solutions that balance economic, social and environmental systems must address these economic challenges while supporting antibiotic stewardship and equitable access.

Key Economic Challenges

Demand for novel antibiotics is highly uncertain. Most chronic diseases have well-studied epidemiology projections, but predicting the rate at which multi-drug resistance (MDR) will rise 10-15 years in the future is extremely difficult. The tendency to preserve novel antibiotics for last resort use, so as to delay the emergence of resistant strains, further exacerbates the uncertainty. Additionally, if a new derivative of an existing class treating the same resistance is introduced to the market, demand for the novel antibiotic evaporates as guidelines are likely to further reserve use to curb the emergence of resistance to the new class. While reserving novel antibiotics for later line use is considered appropriate stewardship practice in most cases, the result is that the business case of antibiotic R&D projects are less favorable when compared to investments in other therapeutic areas.

The true value of novel antibiotics to patients and society is under-recognized. Off-patent antibiotics are likely to be effective for the majority of patients who are not infected by MDR pathogens. This fact, combined with "non-inferiority" trial designs for novel antibiotics, means that differentiation versus standard of care, a key requirement to achieve favorable benefit assessments by Health Technology Assessment (HTA) agencies and hospitals, is difficult. In addition, several key benefits brought by new antibiotics, such as transmission value (reducing overall incidence of infections), enablement value (enabling other treatments such as surgery, cancer chemotherapy which would not be safe to perform without effective antibiotics) and insurance value (providing protection when every other therapy fails), are not systematically considered in value assessment. This negatively impacts pricing and reimbursement negotiations.

The current Diagnosis-Related Group (DRG)-based hospital reimbursement system in the U.S. and most of Europe imposes a significant economic constraint on antibiotics used to treat serious infections in the hospital settings. Diagnostic Related Groups (DRGs) provide a set payment to hospitals for a given patient diagnosis, encompassing both labor and non-labor costs, including pharmaceuticals. Since the cost of antibiotics included in the DRG payment is mainly driven by generics that are cheaply available, use of higher priced novel antibiotics would mean the cost of antibiotics could consume significant portion of the payment, or even more. This creates pressure for hospitals to minimize costs and add restrictive steps in the protocol to delay use of higher priced novel antibiotics. Patients may therefore receive delayed appropriate treatment due to these restrictions.

The economic challenges of AMR are multifaceted. Sustainable solutions to make antibiotic R&D attractive must address these economic challenges while supporting antibiotic stewardship and equitable access. There is no "one-size-fits-all" solution. Solutions that require global coordination urgently need a forum for implementation. In the meantime, national authorities should seize opportunities to enhance their existing systems so that incentives for antibiotic innovation can be improved in the near term.

Challenges	Uncertain Demand	Full Value not Recognized	Reserved Use for Non-Clinical Reasons
Antibiotics most impacted	Antibiotics covering rare resistance, especially with novel mechanisms	Antibiotics covering rare resistance	Novel antibiotics for inpatient use
Potential Solutions	Fully or partially delinked models	Health Technology Assessment Reform	Reimbursement Reform
Time to establish	Medium to long term	Near term	Near term

Conclusions/Discussion

The economic challenges of AMR are multifaceted, and the consequence of our failure to address them is enormous. To stay ahead of the bacteria, we must consider all the necessary levers. A transparent and sustainable delinked model such as Market Entry Reward (MER) could improve the predictability of economic returns for developers who take the long view to pursue novel antibiotics that address priority pathogens and rare resistance. Implementation of a MER is complex and will take significant coordination across countries with different health systems and priorities. A global forum for implementation is urgent. In the meantime, national authorities should seize the opportunities to enhance their existing systems so that incentives for antibiotic innovation can be improved in the near term. Health technology assessment processes need to be developed to include the full value of new antibiotics and rules of reimbursement amended to better capture the recognized value of antibiotics. Barriers to access posed by bundled-payment mechanisms that discourage the appropriate use of novel antibiotics within hospitals should be removed. This market-based mechanism can complement and reinforce key antimicrobial stewardship components, including the use of diagnostics, de-escalation, regimen monitoring, and surveillance.