FOSTERING CLINICAL DEVELOPMENT AND COMMERCIALISATION OF NOVEL ANTIBIOTICS

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Summary: Novel antibiotics are desperately needed to combat progressively resistant strains of bacteria, but there are too few innovative antibiotics in the clinical pipeline because of ongoing scientific, regulatory and economic challenges inherent to the antibiotics market. Global and national antibiotic incentive programmes are making progress in revitalising the pipeline but there are gaps in the incentivisation agenda. The pipeline could be improved by increasing funding of clinical trials to help drugs reach market approval, creating a market entry reward programme to facilitate commercialisation, and supporting coordinated international and national action on repairing the antibiotic pipeline and market.

Keywords: Antibiotics, Antimicrobial Resistance, Drug Discovery, Drug Development

Introduction

In the past, developing new antibiotics appeared to be the easiest solution to overcome resistant pathogens. As bacteria evolved to become resistant to certain antibiotics, treatment for these infections could be supplemented or replaced by newer generations of the same antibiotic or by a new, more effective class of antibiotic. The world saw a boom in new antibiotics and classes between 1940 and 1990 as pharmaceutical companies leveraged scientific breakthroughs and were rewarded with high-value patents.

However, due to a combination of financial, regulatory, and scientific barriers to continued development of new antibiotics, the focus of research and development (R&D) shifted away to other therapeutic areas. In 1990, there were 18 major pharmaceutical companies active in antibiotic R&D, but by 2020 this number has fallen to eight and they continue to divest from the market. The number of new antibiotics marketed each decade has also significantly decreased and no novel classes of antibiotics with distinct chemical structures have been developed. In conjunction, global antibiotic consumption increased by 65% between 2000 and 2015, mostly driven by low- and middle-income countries. The void in R&D alongside uncontrolled use has meant that the
antibiotic pipeline is frighteningly thin relative to the unrelenting advance of antibiotic resistance.

This article provides a brief summary of our recently published chapter in the book “Challenges to Tackling Antimicrobial Resistance.” We review the current state of the global market for antibiotics and antibiotic innovation, as well as identifying progress and challenges in fostering antibiotic R&D. We highlight some key policy gaps that must be addressed and put forth possible solutions.

The most current pipeline assessment is conducted by The Pew Charitable Trusts. As of September 2019, there are 21 drugs in the pipeline that are expected to have activity against a WHO critical threat or CDC urgent pathogen: 7 in Phase I clinical trials, 5 in Phase II, and 9 in Phase III. The Pew Trusts has also recently published a five-year longitudinal analysis of the antibiotic pipeline between 2014 and 2018 and concluded that the pipeline is stagnant and insufficient to meet the growing threat of antibiotic resistance. Over this period, 67 antibiotics were in clinical development, 10 of which stalled in development and 15 were discontinued. Ten drugs were approved during this period, but none of them targeted a WHO critical pathogen.

There is no single definition of what makes an antibiotic novel or innovative. Bacteria develop resistance to antibiotics through exposure and create protective mechanisms against frequently encountered antibiotics. The more unique a new antibiotic is compared to existing antibiotic structures means that bacteria are unlikely to have encountered the chemical components of the new antibiotic. Consequently, there is less risk for baseline resistance levels in target bacteria, known as cross-resistance, for these more unique antibiotics. Problematically, almost all of the pipeline drugs are redevelopments of classic antibiotic compounds or are combination therapies of existing antibiotic molecules. Of the 10 antibiotics approved between 2014 and 2018, only two drugs meet at least one of the WHO criteria for innovation: (1) known absence of cross-resistance to existing antibiotics; (2) new chemical class; (3) new target; or (4) new mechanism of action in terms of the biochemical process through which a drug produces its pharmacological effect.

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Current antibiotic pipeline

In 2017, the World Health Organization (WHO) published a priority pathogens list, which outlines the antibiotic-resistant bacteria that pose the greatest threat to global public health. This list aims to guide antibiotic R&D based on medical need as opposed to the economic factors that have traditionally directed antibiotic investment. At the top of this list, categorised as “critical”, are the gram-negative, carbapenem-resistant strains of A. baumannii, P. aeruginosa, and the Enterobacteriaceae family, which are important causes of community and hospital-acquired infections. Carbapenems are a class of highly effective antibiotics that are often used as a last resort drug for treatment of severe bacterial infections. In 2013, the United States (US) Centers for Disease Control and Prevention (CDC) had published a US-focused urgent threats list for antibiotic resistance, which highlighted many of the same pathogens.

Barriers to antibiotic R&D

The success rate of moving an antibiotic from basic research to market approval is estimated to be between 1.5–3.5% and can take 15 years. The economic, regulatory, and scientific barriers to antibiotic R&D can best be categorised based on the steps of the antibiotic value chain: initial research, preclinical trials, clinical trials, market approval, and, finally, commercialisation.

The basic science and discovery research behind understanding and identifying new molecules for candidate drugs has been scientifically challenging. Bacteria, particularly gram-negative varieties, have proven highly resilient to recent experimental research on destruction mechanisms. Discovery research has predominantly been tackled by academics funded by the public sector, while clinical trials have been the domain of private pharmaceutical companies, thus leaving a gap in funding and appropriate actors in the preclinical phase.

Antibiotic clinical trials and post-approval follow-on trials have been estimated to cost on average $130 million and $146 million (about €117 million and €131 million), respectively. Many drug candidates will be discarded on the way at a financial loss. These costs and uncertainties are often prohibitively high for small and medium sized enterprises (SMEs). Despite the challenge of economies of scale, SMEs own a significant share of antibiotics in clinical development. An added practical challenge is that recruiting patients with acute bacterial infections for clinical trials is logistically difficult due to the short treatment windows and lack of rapid point-of-care diagnostic tools to identify participants.

Market approval of new antibiotics is necessary for ensuring the drug’s quality, safety and efficacy. However, there are procedural differences between national drug regulatory agencies in approving antibiotics that make global licensing time-consuming and expensive. These differences relate to patient selection criteria, definitions of clinical endpoints, specification of statistical parameters, and rules regarding expedited approvals.

Finally, the economic reward for commercialising a new antibiotic is minimal or negative relative to other therapeutic areas, such as neurologic, diabetes, and cardiovascular drugs. At present, novel antibiotics are not destined to generate significant revenue even with their immense public health value. Potential sales volumes are restricted by short treatment durations and hospital stewardship programmes that limit access. In addition, the large overlap in clinical

application of newly patented antibiotics with existing generic alternatives places downward pressure on prices.

**Incentive mechanisms for antibiotic R&D**

Push and pull incentives are broadly used to classify the two main types of mechanisms for supporting antibiotic R&D. Push incentives, such as research grants, reduce the cost of researching and developing new antibiotics. In contrast, pull mechanisms increase the potential revenue of a successfully marketed antibiotic. This may be through outcome-based rewards that directly increase revenue such as monetary prizes, reimbursement premiums, advanced market commitments to purchase the drug, and patent buyouts by governments. If large enough, outcome-based pull rewards could replace the traditional revenue stream generated by the sales volumes of a licensed antibiotic. This concept is referred to as ‘delinkage’ since the antibiotic’s revenue would be delinked or decoupled from its sales, thus removing the incentive to promote the drug’s use. Alternatively, pull mechanisms may be legal or regulatory, providing incentives such as accelerated procedures for marketing approval or extensions to the patent period.

A recent systematic review identified at least 47 different push and pull mechanisms, each with unique advantages and disadvantages. These mechanisms must work together to target the economic criteria necessary for rebalancing the market: (1) improve profitability; (2) make market participation feasible for SMEs; (3) encourage investment by large pharmaceutical companies; and (4) facilitate cooperation across all stakeholders. In addition, an effective incentive package will support antibiotic sustainability and facilitate patient access to new antibiotics.

**Programmes supporting antibiotic R&D**

Promisingly, government agencies, non-governmental organisations, and drug developers have come together to form major international and national programmes to strengthen the antibiotic pipeline. There are now over 58 different initiatives that incentivise the development of antibiotics, operating either at multilateral, European Union (EU), or national levels. At the multilateral level, key initiatives include the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the Global Antibiotic Research and Development Partnership (GARDP), the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the European and Developing Countries Clinical Trial Partnership (EDCTP), and the Global Antimicrobial Resistance Innovation Fund (GAMRIF). Other important initiatives are the EU’s Innovative Medicines Initiative (IMI) and its subsidiary New Drugs for Bad Bugs Program (ND4BB), as well as the US Biomedical Advanced Research and Development Authority (BARDA).

Charitable organisations such as the Wellcome Trust and the Bill and Melinda Gates Foundation have been strong champions for combatting antimicrobial resistance and co-finance many of these initiatives. Finally, from a regulatory perspective, the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), a working group of technical experts from Canada, the EU, US, and Norway, has been collaborating and sharing strategies to support the antibiotic pipeline and improve the market approval process.

**Policy implications and next steps**

The extensive array of antibiotic R&D programmes and incentives is commendable, and strides are being made towards reviving the antibiotics pipeline. However, major antibiotic developers, such as Novartis and Sanofi, continue to divest from the market indicating that the antibiotics market is still highly dysfunctional and unappealing to developers. The end goal should be a continuum of incentivisation that reflects the economic need, cost distribution, and barriers of the entire antibiotic value chain. Our chapter delves into multiple ways this continuum can be repaired. However, for the purposes of this article we will discuss three of the most critical policy objectives that need to be addressed: (1) augment push-funding of antibiotic clinical trials; (2) implement a strong pull incentive in the form of a global market entry reward for successful commercialisation of novel antibiotics; and (3) facilitate coordinated international and national action on repairing the antibiotic pipeline and market.

Most push-funding for antibiotic R&D is directed towards basic antimicrobial science and less so towards clinical development. While early-stage push-funding of antimicrobial science is integral to the R&D process, there is a need for more late-stage push-funding of preclinical and clinical trials to help translate scientific innovation into marketable products. As more drug candidates transition to clinical development, it may be beneficial to pool disparate early-stage push-funding and re-allocate it to late-stage push-funding to ensure viable antibiotics make it to the market approval stage. In addition, programmes like BARDA and the IMI, which specifically fund clinical trials, could be further expanded. SMEs would particularly benefit from this improvement in clinical funding.

Market entry rewards (MERs) have been repeatedly endorsed by health policy experts as an effective pull incentive for commercialisation and distribution of licensed antibiotics. A MER is a financial prize for the successful development of an innovative antibiotic that meets pre-defined criteria and adheres to conditions related to sustainability and patient access. A MER would offer the same revenue stream otherwise generated by a novel, patented drug on the market while removing the incentives for developers to drive up sales volumes.
for profit. MER rewards can be tailored based on the degree of delinkage, total reward size, payout timeline, access and stewardship requirements, and other features. 

It is expected that a MER would need to be approximately $1 to 2 billion (about €900 million to €1.8 billion) per first-entrant novel antibiotic to entice developers to invest in R&D and gamble on inventive antibiotic projects. With the ten-year goal of bringing 10 to 15 novel antibiotics to market, a MER programme is estimated to cost between $10 and $30 billion (about €9 billion and €27 billion). Despite the abundance of expert literature calling for an international MER programme, no nation has been willing to take the lead in establishing such a global fund or make a firm financial commitment. This inaction stems from the large sums involved, insufficient political support, the complexity of coordinated action, and a lack of capacity and expertise to implement such a scheme.

Intra- and international cooperation and communication will be essential to increasing push funding efficiently and developing a global MER programme. Presently, national governments, global institutions, non-governmental organisations, and industry are independently investing their resources in antibiotic R&D projects and funding programmes. This is partially responsible for the current mismatched and incomplete global incentives. In addition, many of the antibiotic R&D initiatives operate in isolation from other initiatives despite their commonalities. There is a clear risk of duplicating efforts with initiatives that have similar mandates and receive interweaving funding from different payers.

Born out of the 2017 G20 Summit, The Global Antibiotic R&D Hub is an international partnership that aims to coordinate antibiotic R&D under a unified One Health continuum. The Hub is comprised of 19 countries, the European Commission, Wellcome Trust, and Bill and Melinda Gates Foundation. While still in its early stages of development, the Hub is well positioned to actively facilitate a more balanced complement of incentive mechanisms. They could press for greater clinical development funding as well as implement and advocate for a global MER programme. This collaborative Hub is a large step towards unifying efforts; however, the Hub will need continued and growing political and financial support from many countries for it to become an effective international instrument against antibiotic resistance.

Countries should also be developing their own national action plans (NAPs) on antimicrobial resistance that reinforce global guidance from the Hub and other international organisations such as WHO, The Food and Agriculture Organization of the UN, and the World Organization for Animal Health. Anderson, et al. have proposed a framework that can help policy makers design, implement, monitor, and evaluate their national action plan. Part of a comprehensive national action plan involves creating a viable market for novel products within the country and fostering national R&D of antibiotics.

References


