TRIAL WATCH

The small-molecule antibiotics pipeline: 2014–2018

As new types of resistance mechanisms and multidrug-resistant bacteria continue to emerge and spread globally, the need for new antibiotics has never been greater. And yet, nearly every antibiotic available today is based on scientific discoveries from more than 30 years ago. Development of new antibiotics has slowed because of scientific barriers as well as lowered returns on investment, leading many large pharmaceutical companies to abandon their antibiotic discovery programmes. Together, these factors have led to an anaemic pipeline. In 2014, The Pew Charitable Trusts' antibiotic resistance project began tracking the clinical pipeline of small-molecule antibiotics semi-annually to shed light on the landscape of products in clinical development. This analysis can be useful to demonstrate the need for policies aimed at spurring antibiotic innovation. Here, we present data collected by Pew over the past 5 years to provide insights into the flow of candidates through the pipeline (FIG. 1; see Supplementary information for details). We also provide an interactive visualization of this data (see Related links).

This longitudinal analysis emphasizes longstanding concerns about too few antibiotics in development to address current and anticipated patient needs. Of the 67 antibiotics that have been in some stage of clinical development since 2014, 20 new candidates have entered the pipeline and 10 products have been approved, while 17 have been either suspended or discontinued. An additional 10 candidates have stalled (defined as remaining in the same clinical development stage since 2014). Reasons for why candidates are discontinued or stalled are not always clear, but generally are due to change in public health priorities, and also challenges with confirming safety or securing funding for further development.

Approximately 60% of candidates are targeted at Gram-positive bacteria. Although most scientific challenges are encountered in the discovery of new classes of antibiotics against Gram-negative bacteria, nearly 75% of stalled or discontinued candidates targeted Gram-positive bacteria, primarily *Staphylococcus aureus* or *Clostridioides difficile*. Also, of 17 candidates representing novel chemical classes, nearly half were either stalled or discontinued, compared with the remaining 50 antibiotics based on previous classes, of which less than a third were stalled or discontinued over the same time period.

A continued area of unmet need is new treatments for bacterial infections caused by multidrug- or extensively drug-resistant Gram-negative pathogens. Furthermore, a subset of these pathogens has shown increased resistance to carbapenems (one of the antibiotics of last resort), and has been identified by the WHO as a critical need for R&D: carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPA). Just 18 of the 67 compounds in this analysis have the potential to address at least 1 of these pathogens; 4 of these have been discontinued. Of the remaining 14 still-active or approved drugs during this time period, the majority have potential activity against most CRE with *Klebsiella pneumoniae* carbapenemase production (13 compounds), but a few also have potential to address CRAB (4 compounds) and CRPA (3 compounds). Acinetobacter and Pseudomonas present major challenges to drug developers owing to their particularly complex outer membrane structures, including penetration barriers, and wide variety of efflux pumps. Moreover, even with in vitro or in vivo activity against subsets of species, conducting clinical trials to show efficacy against these resistant pathogens is extremely difficult, and none of the ten approvals since 2014 are indicated against CRE, CRAB or CRPA on their FDA drug labels.

Overall, this longitudinal analysis of antibacterial development highlights key gaps that still exist in the pipeline. However, promising initiatives focused on accelerating research and discovery of new antibiotics led by the US government's National Institute of Allergy and Infectious Diseases and Biomedical Advanced Research and Development Authority, ongoing public–private partnerships to support development of new antibacterials by the Innovative Medicines Initiative and CARB-X, and nonprofits including the Global Antibiotic Research and Development Partnership, The Pew Charitable Trusts and The Wellcome Trust provide hope for combating antibiotic resistance. Innovative economic models are now vital to ensure the availability of novel antibiotics.

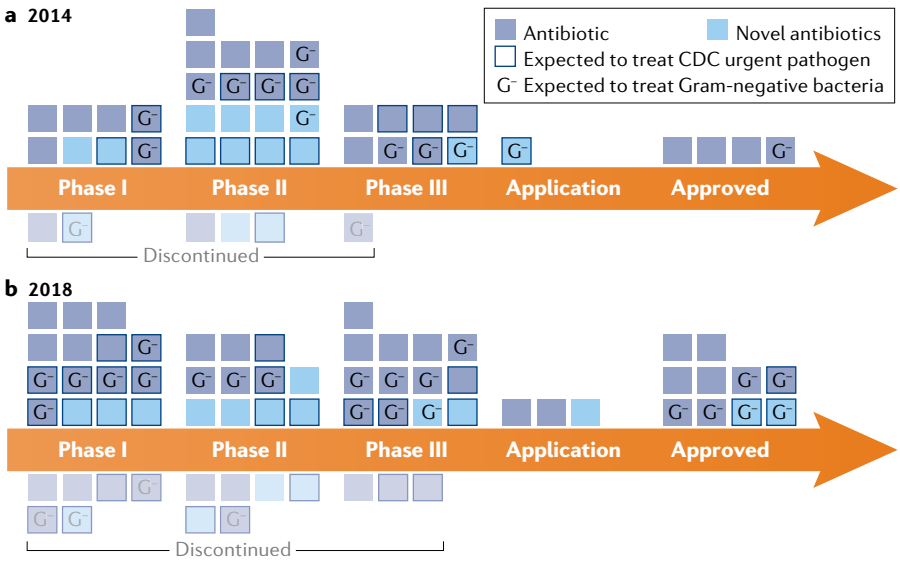

Fig. 1 | **Changes in the antibiotic development pipeline from 2014–2018.** The snapshot for 2014 (**a**) provides the baseline for the analysis, with changes to the overall pipeline in the following 5 years added to the snapshot for 2018 (**b**). The year-over-year changes for this 5-year period can be seen in the associated visualization (see Related links).

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