Antibiotic resistance is high on the political agenda and improving the antibiotic R&D pipeline is one of the major action points. The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) supports antibacterial projects through early preclinical development, with a 5-year budget totalling US$455 million (Nat. Rev. Drug Discov. 15, 589–590; 2016). Since its inception in July 2016, 368 applications from around the world have been submitted. This pool of information provides a reasonable approximation of global preclinical antibiotic R&D activities and was used for this analysis. Of 368 submitted projects, we excluded funding requests for diagnostics and out-of-scope applications, leaving 254 applications for analysis (FIG. 1).

More than 50 small-molecule preclinical projects among the CARB-X submissions focused on at least one of the critical priority pathogens on the WHO global priority list that was recently published to guide antibiotic R&D, which are all extensively drug-resistant Gram-negative bacteria. The small molecules being investigated by these projects belong to new chemical and/or functional classes with no anticipated cross-resistance to existing classes (FIG. 1a). These projects exhibit considerable diversity, with several clusters (FIG. 1b) as well as a large group of projects classified as ‘other’. The largest cluster are membrane-targeting agents, including compounds modelled on natural antimicrobial peptides. There is also a substantial cluster of agents that inhibit LpxC, the enzyme responsible for the first committed step in the biosynthesis of lipid A—a key component of the outer membrane of Gram-negative bacteria.

Another prominent trend is the strong focus on biologics, including antibodies, antibacterial vaccines, antibody–drug conjugates and other large molecules (FIG. 1a). Such pathogen-specific strategies are usually intended for pre-emptive use. Some of these biologics target bacterial virulence factors, and it is notable that there are also multiple small-molecule projects targeting bacterial virulence mechanisms in other ways. Phage-related products are also prominent (FIG. 1a). In contrast to earlier years, there are fewer projects with phage cocktails, and more genetic engineering efforts, using phages for delivery and phage products such as endolysins as starting points.

Innovation in antibiotics against Gram-positive bacteria is also needed for future resistance problems. Several novel chemical scaffolds and targets for Gram-positive bacteria are present in the pipeline (FIG. 1a). In contrast to the preclinical pipeline a decade ago, the decrease in the...
number of submitted funding applications in the Gram-positive field may reflect the CARB-X focus on Gram-negative bacteria, but also the shift in global priority to Gram-negative bacteria and the availability of several current and future antibiotic options for infections caused by Gram-positive bacteria.

Overall, the analysis of this project sample shows reasonable convergence with the WHO critical priority pathogens and a promising trend of innovative projects that has not been seen in the clinical pipeline (see the WHO report in Further information). Although innovative projects are riskier than modifications of known chemical scaffolds, such innovative drugs are urgently needed against the most-resistant bacteria. Many innovative non-traditional approaches may not translate into a measurable benefit for patients in the near future, but may still provide valuable insights for future progress in treatment strategies. Finally, most projects were submitted by small companies (FIG. 1c) and were at the hit-to-lead stage (FIG. 1d).

Given this, and that the attrition rates are extremely high for innovative approaches, more incentives and support are needed to maintain this positive momentum as these projects move towards clinical studies.

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Competing interests statement

The authors declare no competing interests.

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