

World Health Organization

# ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

An analysis of the antibacterial clinical development pipeline, including tuberculosis



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## **Abbreviations and acronyms**

**BLI** β-lactamase inhibitor

**CRAB** carbapenem-resistant Acinetobacter baumannii

CRE carbapenem- and third-generation cephalosporin-resistant Enterobacteriaceae

CRPA carbapenem-resistant Pseudomonas aeruginosa

**DBO** diazabicyclooctane

**DHFR** dihydrofolate reductase

**ESBL** extended-spectrum  $\beta$ -lactamase

**GARDP** Global Antibiotic Research and Development Partnership

IV intravenous

KPC Klebsiella pneumoniae carbapenemase

LeuRS leucyl-tRNA synthetase

MBL metallo-β-lactamase

MIC minimum inhibitory concentration

MmpL3 mycobacterial membrane protein large 3

MoA mode of action

MRSA methicillin-resistant Staphylococcus aureus

**NBTI** novel bacterial topoisomerase II inhibitor

NDA new drug application

**NDM** New Delhi metallo-β-lactamase

OPP other priority pathogens on the WHO priority pathogens list ("high" and "medium" priority)

**PBP** penicillin-binding protein

**PDF** peptide deformylase

PK/PD pharmacokinetics/pharmacodynamics

**PPL** priority pathogens list

**R&D** research and development

TB tuberculosis

tet tetracycline resistance encoding gene

VIM Verona integron-encoded metallo-β-lactamase

## **Executive summary**

As part of implementation of the Global Action Plan on Antimicrobial Resistance, WHO drew up a list of priority antibiotic-resistant pathogens (priority pathogens list; PPL) to guide research into and the discovery and development of new antibiotics. As a further step, WHO reviewed the publically available information on the current clinical development pipeline of antibacterial agents to assess the extent to which the drug candidates act against these priority pathogens, *Mycobacterium tuberculosis*, and *Clostridium difficile*.

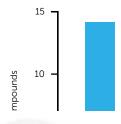
The review shows that the current clinical pipeline is still insufficient to mitigate the threat of antimicrobial resistance:

- More investment is needed in basic science, drug discovery and clinical development, especially for Mycobacterium tuberculosis and the critical priority Gram-negative carbapenem-resistant pathogens Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae.
- Most of the agents in the pipeline are modifications of existing antibiotic classes. They are only short

- term solutions as they usually cannot overcome multiple existing resistance mechanisms and do not control the growing number of pan-resistant pathogens.
- More innovative products are required against pathogens with no cross- or co-resistance to existing classes.
- Although oral formulations for community diseases associated with high morbidity are essential globally, few oral antibiotics for infections caused by Gram-negative pathogens are in the pipeline.

As of May 2017, a total of 51 antibiotics (including combinations) and 11 biologicals were in the clinical pipeline with 42 new therapeutic entities (33 antibiotics and nine biologicals) that target priority pathogens, seven products for tuberculosis (TB) and nine for C. difficile infections (seven antibiotics and two biologicals) (Fig. 1). The qualitative analysis shows a lack of potential treatment options for priority resistant bacteria, especially for multidrug- and extensively drug-resistant Gram-negative pathogens.

Fig 1. Antibacterial agents currently in phases 1-3 of clinical development<sup>a</sup>





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