ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

An analysis of the antibacterial clinical development pipeline, including tuberculosis

World Health Organization

ANTIBACTERIAL AGENTS IN CLINICAL DEVELOPMENT

An analysis of the antibacterial clinical development pipeline, including tuberculosis

World Health Organization

WHO/EMP/IAU/2017.12

Suggested citation. Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.12). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see http://www.who.int/about/licensing.

Design and layout: it's B. blossoming.it

Printed in Geneva, Switzerland

Contents

Acknowledgements

This publication was prepared by the WHO Department of Essential Medicines and Health Products (EMP) under the leadership of Peter Beyer (WHO/EMP). Ursula Theuretzbacher (Centre for Anti-infective Agents, Austria) was the leading scientific expert. She prepared the documentation for the advisory group and drafted the final report with the support of Simon Gottwalt (WHO/EMP), who was also responsible for planning the project, collecting data and preparing the advisory group meeting.

We thank the members of the advisory group, which met in Geneva, Switzerland, on 12–13 June 2017 to review the data, discuss and assess the compounds referred to and provide feedback on the report. The advisory group consisted of:

- Dr Mark Butler, Senior Researcher, Institute for Molecular Bioscience, University of Queensland, Brisbane, Australia
- Dr Lloyd Czaplewski, Director, Chemical Biology Ventures, Abingdon, United Kingdom of Great Britain and Northern Ireland
- Professor Stephan Harbarth, Associate Professor, Division of Infectious Diseases and Infection Control Programme, Geneva University Hospitals, WHO Collaborating Centre, Geneva, Switzerland (Chair)
- Dr Jean-Pierre Paccaud, Director, Business Development and Corporate Strategy, Drugs for Neglected Diseases *initiative*, Geneva, Switzerland
- Professor Mical Paul, Director, Infectious Diseases Institute, Rambam Health Care Campus, and Associate Professor, The Ruth and Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel
- Dr John H. Rex, Chief Strategy Officer, CARB-X, Boston, United States of America (USA), and Chief Medical Officer, F2G Ltd, Manchester, United Kingdom
- Dr Lynn Silver, Owner, LL Silver Consulting, Springfield, NJ, USA
- Dr Melvin Spigelman, President and Chief Executive Officer, Global Alliance for TB Drug Development, New York City, NY, USA (technical resource person)
- Dr Ursula Theuretzbacher, Centre for Anti-infective Agents, Vienna, Austria.
- Professor Guy Thwaites, Director, Oxford University Clinical Research Unit, Ho Chi Minh City, Viet Nam, and Professor of Infectious Diseases, University of Oxford, Oxford, United Kingdom

We would like to thank Nicole Homb (WHO/EMP) for her contribution to managing conflicts of interest and the development of the methodology; Christian Lienhardt (WHO/ Global TB Programme) for contributions on the tuberculosis research and development pipeline; and Nicola Magrini (WHO/EMP), Lorenzo Moja (WHO/EMP) and Sarah Paulin (WHO/EMP) for their contributions to development of the method and for reviewing and finalizing the report. We also thank Gilles Forte (WHO/EMP), Sarah Garner (WHO/EMP), Suzanne Hill (WHO/EMP) and Elizabeth Tayler (WHO/Antimicrobial Resistance Secretariat) for reviewing the report.

We thank Enrico Tognana and Marco Cavaleri (European Medicines Agency) for conducting the search on the Adis Insight database. We are grateful to the following organizations and individuals who provided advice on the method for this pipeline analysis and/or reviewed draft pipeline data: **Access to Medicines Foundation** (Clarke Cole, Damiano de Felice), **BEAM Alliance** (Marie Petit), Bio (Arthur Phyllis), CARB-X (Kevin Outterson, Barry Eisenstein), **Global Antibiotic Research and Development Partnership** (Jean-Pierre Paccaud, Manica Balasegaram, Gabrielle Landry), IFPMA (Nina Grundmann), **JPIAMR** (Laura Marin), **NIAID/NIH** (Dennis M. Dixon), **Norwegian Public Health Institute** (Christine Ardal), **ReAct group** (Anthony So, Otto Cars), **TB Union** (Grania Brigden), **The Pew Charitable Trusts** (David Visi, Joe Thomas), **Treatment Action Group** (Erica Lessem, Mike Frick); Evelina Tacconelli, Johan Mouton, David Livermore

The WHO Secretariat takes full responsibility for any omissions, any errors in the data or other shortcomings in this document. We would welcome any feedback and additional information for future iterations of this pipeline analysis. Please send any comments to: iauinfo@who.int

Funding for this report was kindly provided by the Government of Germany.

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 β-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[a]