Overview of Antibacterial Agents in Preclinical and Clinical Development

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WHO annual antibacterial R&D pipeline review

**Data collection:** literature & desk review, survey, targeted outreach, online data call (preclinical)

**Inclusion criteria**

*New therapeutic entities* in clinical and preclinical development worldwide

*Traditional* (direct-acting small molecules) and *non-traditional antibacterial agents* (antibodies, bacteriophages, lysins, live biotherapeutics oligonucleotides etc.)

**Activity** - WHO bacterial priority pathogens

- *Mycobacterium tuberculosis*
- *Clostridioides difficile*

**Innovation assessment:** no cross-resistance, new chemical class/target/mode of action
Results: preclinical pipeline

- 217 antibacterial agents/programs are in preclinical stage
- WHO critical pathogens: 69 agents (31.8%) have activity against \textit{Pseudomonas aeruginosa}, 50 agents (23%) against \textit{Acinetobacter baumannii} and 28% target key \textit{Enterobacterales}
- A significant number of products (44%) focus on a single pathogen
- The majority (70%) are being developed as single agents
- The large majority of preclinical developmental research projects are being conducted in Europe and the Americas (mostly the USA and Canada)
- The preclinical pipeline is dominated by companies (n = 103; 85.1%), of which the majority (~80%) have < 50 employees
- From one year to the next, one third of development programmes are discontinued

Source: \textit{2021 Antibacterial agents in clinical and preclinical development}
Results: traditional and non-traditional agents in clinical development by clinical development phase (Phases 1–3 and NDAs)

Most of the products are traditional agents in early phases

77 products in Phases 1-3
- 45 traditional
- 32 non-traditional
3 NDAs (= 80 candidates overall)

Source: 2021 Antibacterial agents in clinical and preclinical development
Results: traditional and non-traditional agents in clinical development by intended target

Traditional products: activity
- ~60% products in Phases 1-3 against BPP target at least one critical Gram-ve pathogen

Critical priorities:
- CRAB = 7 candidates
- CRPA = 5 candidates
- CRE = 11 candidates

Other priorities:
- 13 candidates target MDR-TB
- 5 CDIs

Source: 2021 Antibacterial agents in clinical and preclinical development
Diversity in non-traditional approaches: 34 products

Non-traditional antibacterials present diverse and novel mechanisms of action and most of them are intended for use in combination with standard antibiotics.

Development stage
- Most are in early clinical stages
- 2/34 are in NDA stage

Nontraditional products: activity
90% pathogen-specific
- P. aeruginosa (13)
- C. difficile (n = 12)
- S. aureus (n = 7)
- E. coli (4)
- One agent targets MDR-TB

Source: 2021 Antibacterial agents in clinical and preclinical development
Innovation assessment of traditional agents

RECENTLY APPROVED ANTIBIOTICS

12 new antibiotics approved in last 5 years
10 Belong to existing antibiotic classes
1 addresses all critical priority pathogens
2 are considered innovative and one is intended against a critical priority

Source: 2021 Antibacterial agents in clinical and preclinical development

ANTIBIOTICS IN CLINICAL PIPELINE

27 Trad. products in Phases 1-3 for BPPs
6 fulfil at least 1 of the WHO innovation criteria
2 of these six are active against at least one “critical” Gram-negative bacteria
The clinical pipeline for antibiotics is stagnant

Source: 2021 Antibacterial agents in clinical and preclinical development
Since 2017, only twelve products have been authorized with 2 considered innovative.

**Few candidates** in pipeline (27) and few (4) with a **novel mechanism of action**.

**Innovation**
- Few new innovative antibiotics are expected in the coming years with no silver bullets
- Most traditional agents don’t meet the innovation criteria as they are evolutions of existing classes

**Target**
- Major gap in products addressing MDR pathogens such as *A. baumannii* and *P. aeruginosa* (one agent authorized against all the critical pathogens and few in the pipeline)
- Very few agents target metallo-β-lactamases which continue to grow in prevalence

**Formulations**: appropriate oral formulations and optimized paediatric formulations are lacking.

Products recently approved/in clinical development are insufficient to tackle increasing emergence and spread of AMR.
Thank you