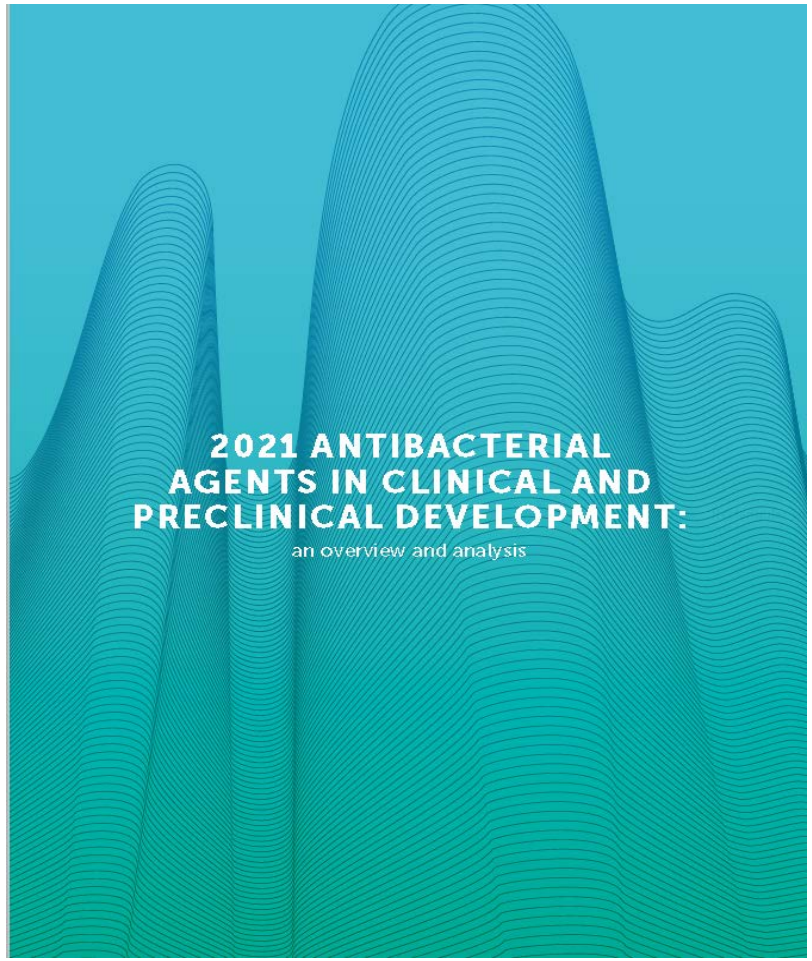
Overview of Antibacterial Agents in Preclinical and Clinical Development

Dr Alexandra Cameron

Senior Expert and Unit Head a.i., Impact Initiatives and Research Coordination, Global Cooperation and Partnerships Department, AMR Division, WHO

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

World Health Organization

WHO innovation criteria

- Objective: identify products‘ potential to overcome existing mechanisms of drug resistance
- Applicable to **traditional** agents recently approved and in clinical development

4 WHO innovation criteria

No cross resistance

New chemical class

New target

New Mode of Action

Results: preclinical pipeline

- 217 antibacterial agents/programs are in preclinical stage
- WHO critical pathogens: 69 agents (31.8%) have activity against *Pseudomonas aeruginosa*, 50 agents (23%) against *Acinetobacter baumannii* and 28% target key *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

Distribution of declared microbiological activity of species-specific programmes by WHO priority pathogen

Organism	Total products*	Species-specific products	WHO PPL
P. aeruginosa	69	21	Critical
A. baumannii	50	8	
E. coli	62	10	
K. pneumoniae	58	4	
Enterobacter spp.	51	1	
Enterobacterales spp.	22	0	
Salmonella spp.	20	0	High
N. gonorrhoeae	22	4	
H. pylori	6	1	
Campylobacter spp.	6	0	
S. aureus	74	19	
E. faecium	38	1	
Shigella spp.	18	0	Medium
H. influenzae	14	0	
S. pneumoniae	37	1	
M. tuberculosis	28	20	
C. difficile	20	5	
Not disclosed	9		
Broad G+/G-**	13		
Gram-negative**	3		
Total		95	

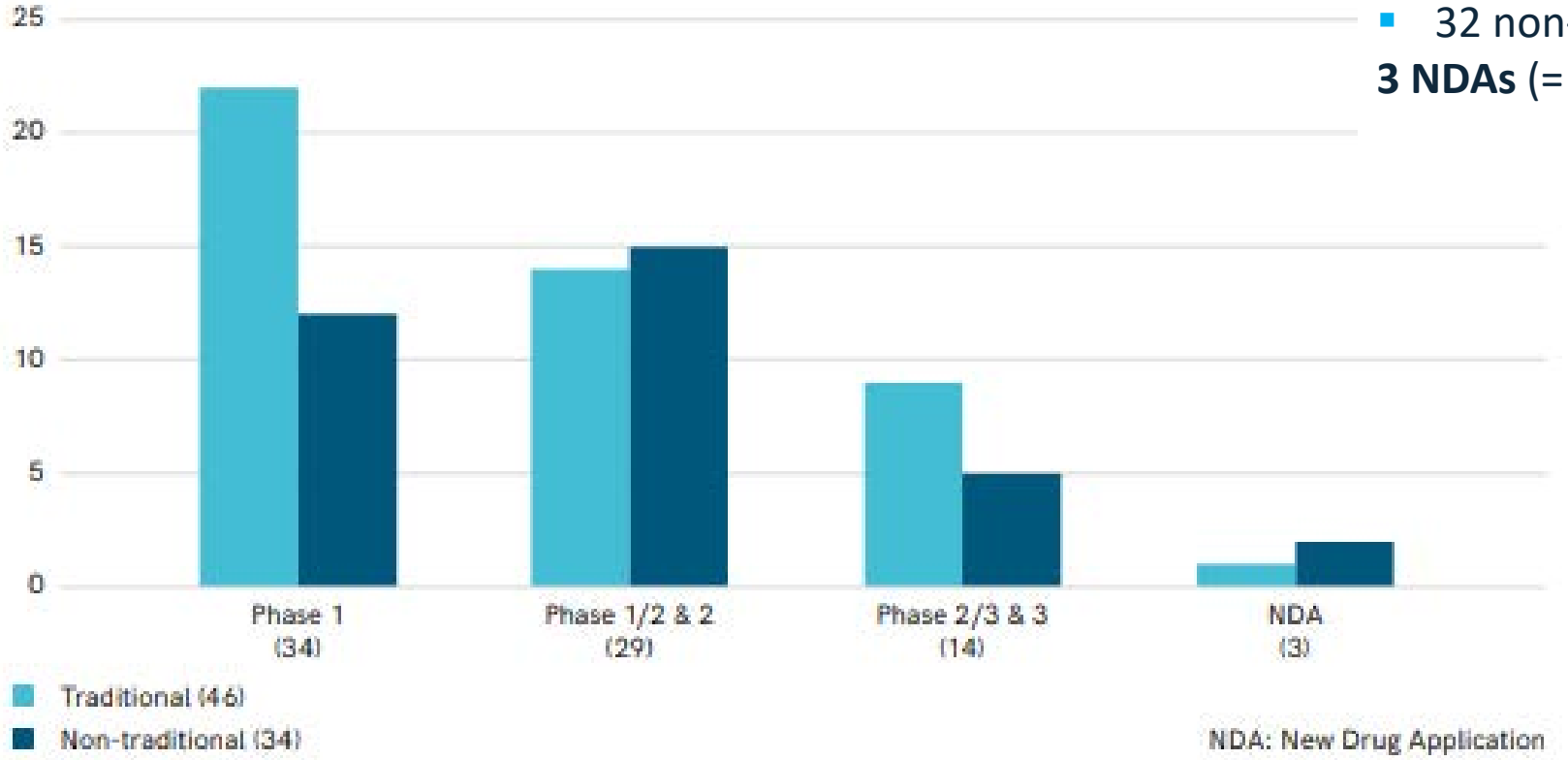
*Note that products with activity against multiple species will be counted against each species.
**Activity against individual bacterial species was not provided.
G+/G-: Gram-positive and Gram-negative bacteria; PPL: priority pathogens list; spp.: species; WHO: World Health Organization.

Source: *2021 Antibacterial agents in clinical and preclinical development*

World Health Organization

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

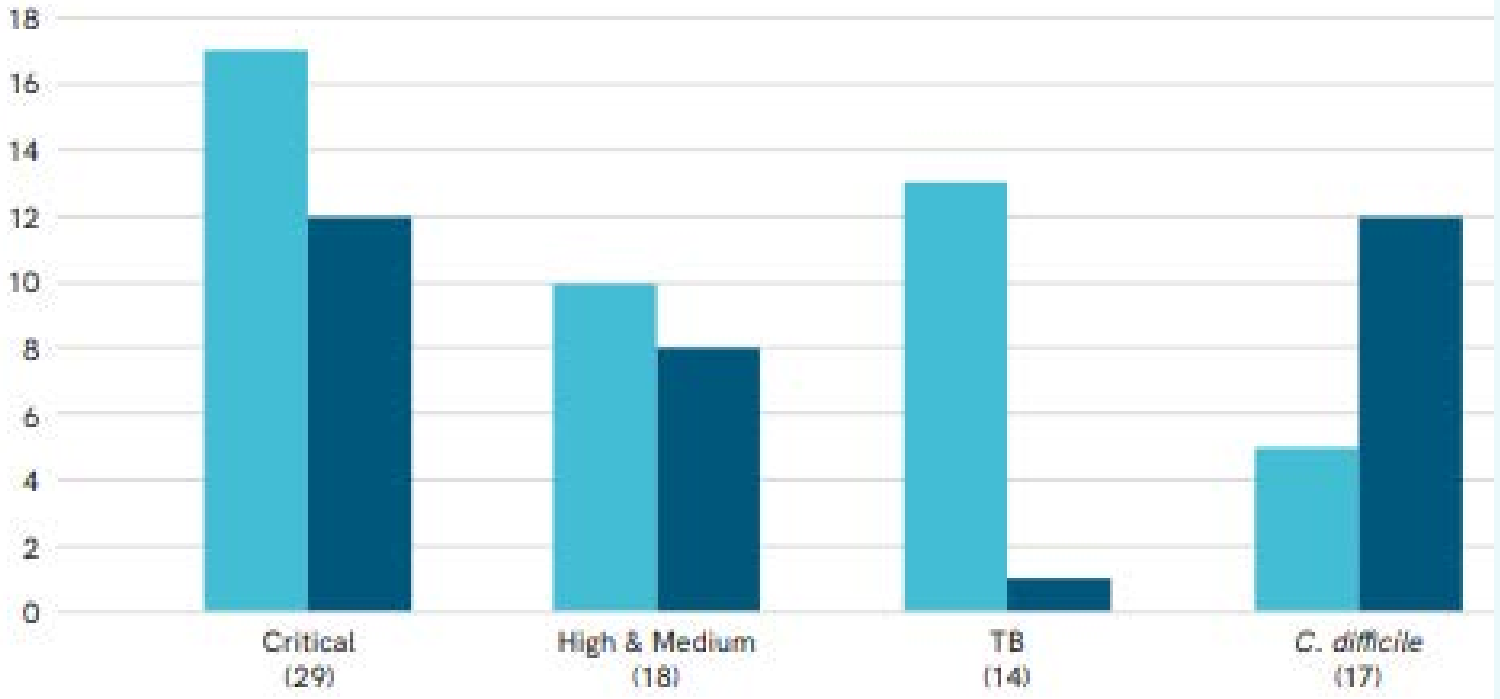
- 45 traditional
- 32 non-traditional

3 NDAs (= 80 candidates overall)

Source: *2021 Antibacterial agents in clinical and preclinical development*

World Health Organization

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

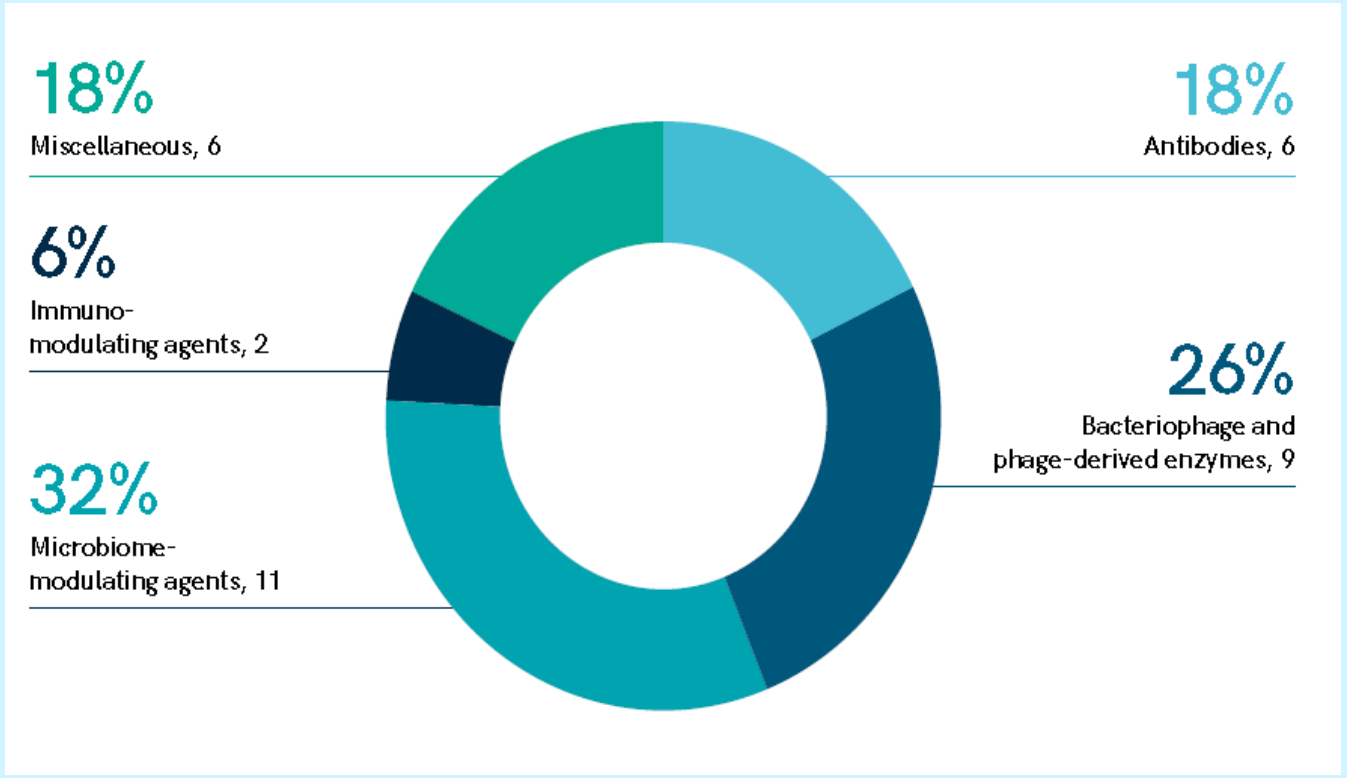
Other priorities:

- 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



Source: *2021 Antibacterial agents in clinical and preclinical development*

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

World Health Organization

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

ANTIBIOTICS IN CLINICAL PIPELINE

27 Trad. products in Phases 1-3 for BPPs

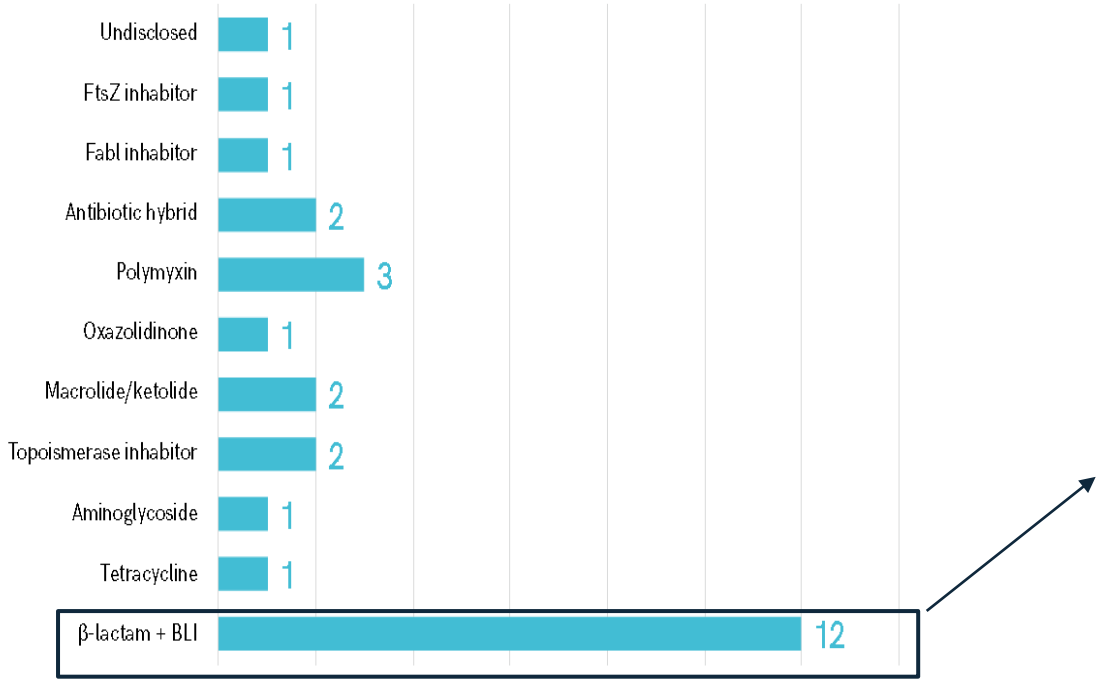
6 fulfil at least 1 of the WHO innovation criteria

2 of these six are active against at least one “critical” Gram-negative bacteria

Source: *2021 Antibacterial agents in clinical and preclinical development*

World Health Organization

Nearly 50% of antibiotics in clinical pipeline that target priority pathogens are β-lactam/BLI combinations



BLI: β-lactamase inhibitor; FabI: enoyl-acyl carrier protein reductase; FtsZ: filamenting temperature-sensitive Z; WHO: World Health Organization.

Source: *2021 Antibacterial agents in clinical and preclinical development*

Activity of the β-lactam/BLI combinations and gaps

	CRE					
	A	A	D	B		
	ESBL (CTX-M)	KPC (KPC-2,-3)	OXA (OXA-48)	MBL (NDM)	CRAB	CRPA
Vaborbactam + meropenem	●	●	●	○	○	○
Relebactam + imipenem + cilastatin	●	●	●	○	○	?
Cefiderocol	●	●	●	●	●	●
Durlobactam (ETX-2514) + sulbactam	○	○	○	○	●	○
Enmetazobactam (AAI-101) + cefepime	●	?	○	○	○	○
Sulopenem	●	○	○	○	○	○
Taniborbactam (VNRX-5133) + cefepime	●	●	●	●	-	●
Benapenem	○	○	○	○	○	○
Zidebactam + cefepime	●	●	●	?	○	?
ARX-1796 (oral avibactam prodrug)	●	●	●	○	○	○
ETX-0282 + cefpodoxime proxetil	●	●	●	○	○	○
OP0595 (nacubactam) + meropenem	●	●	●	?	○	○
QPX7728 + QPX2014	●	●	●	●	●	●
QPX7728 + QPX2015	●	●	●	●	○	○
XNW4107 + imipenem + cilastatin	?	?	?	?	?	?
VNRX-7145 + ceftibuten	●	●	●	○	○	○

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

- 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

World Health Organization

World Health Organization

Thank you

Acknowledgements:

Dr Valeria Gigante, Team Lead

Dr Hatim Sati, Technical Officer

Impact Initiatives and Research Coordination, Global Cooperation and Partnerships Department, AMR Division, WHO

#WHO #AMR #R&D