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Overview of Antibacterial Agents in Preclinical and Clinical Development

Global Leaders Group on AMR Information Session

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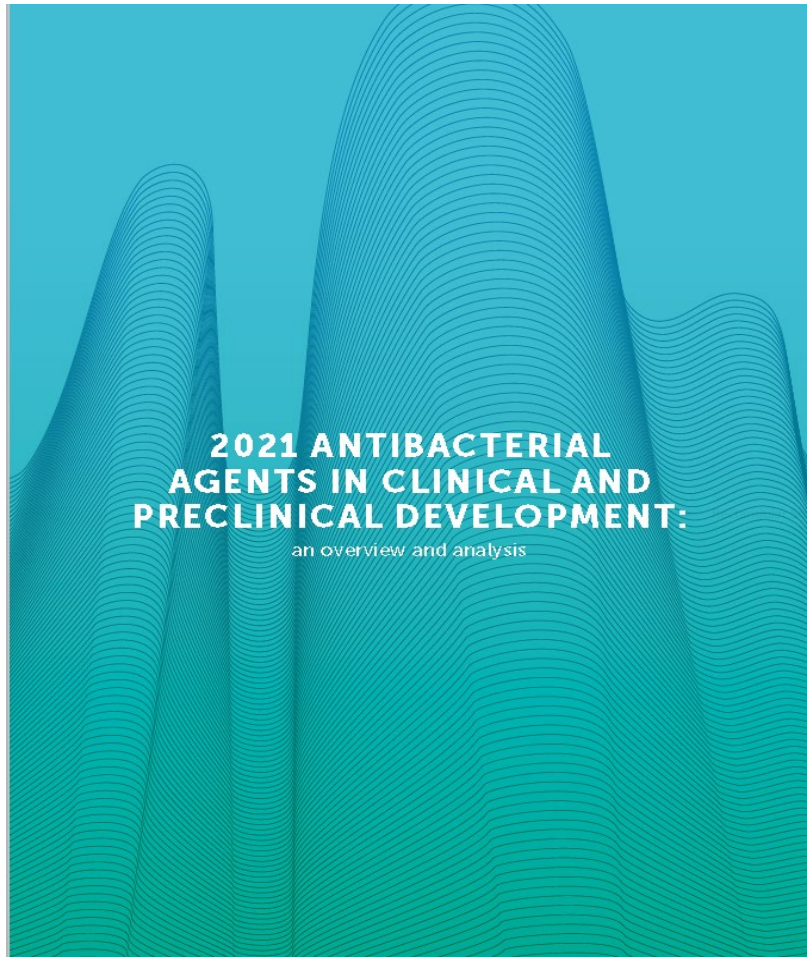
Acknowledgements:

Dr Valeria Gigante, Team Lead

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

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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*

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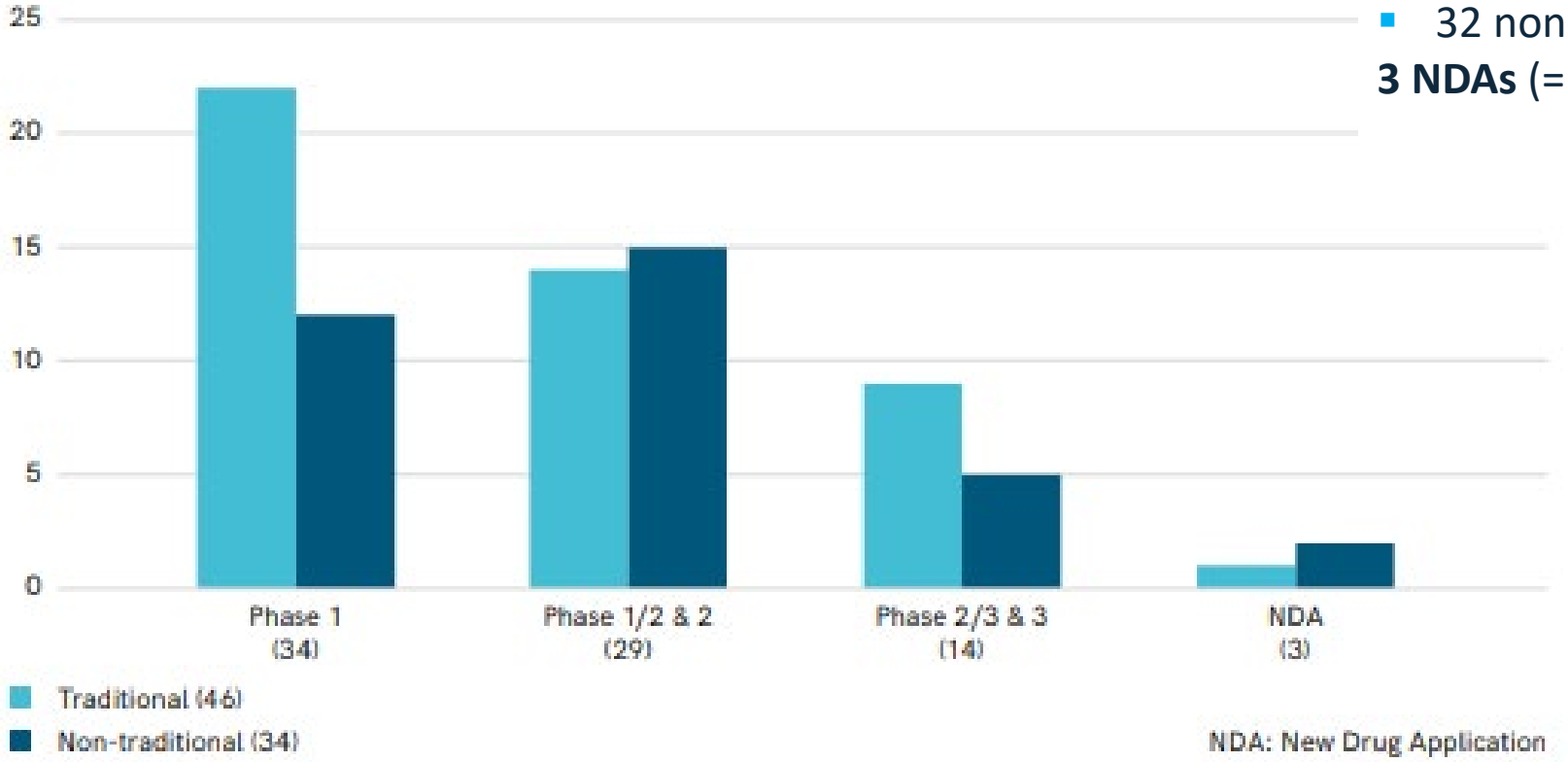
Results: traditional and non-traditional agents in clinical development by clinical development phase (Phases 1–3 and NDAs)

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*

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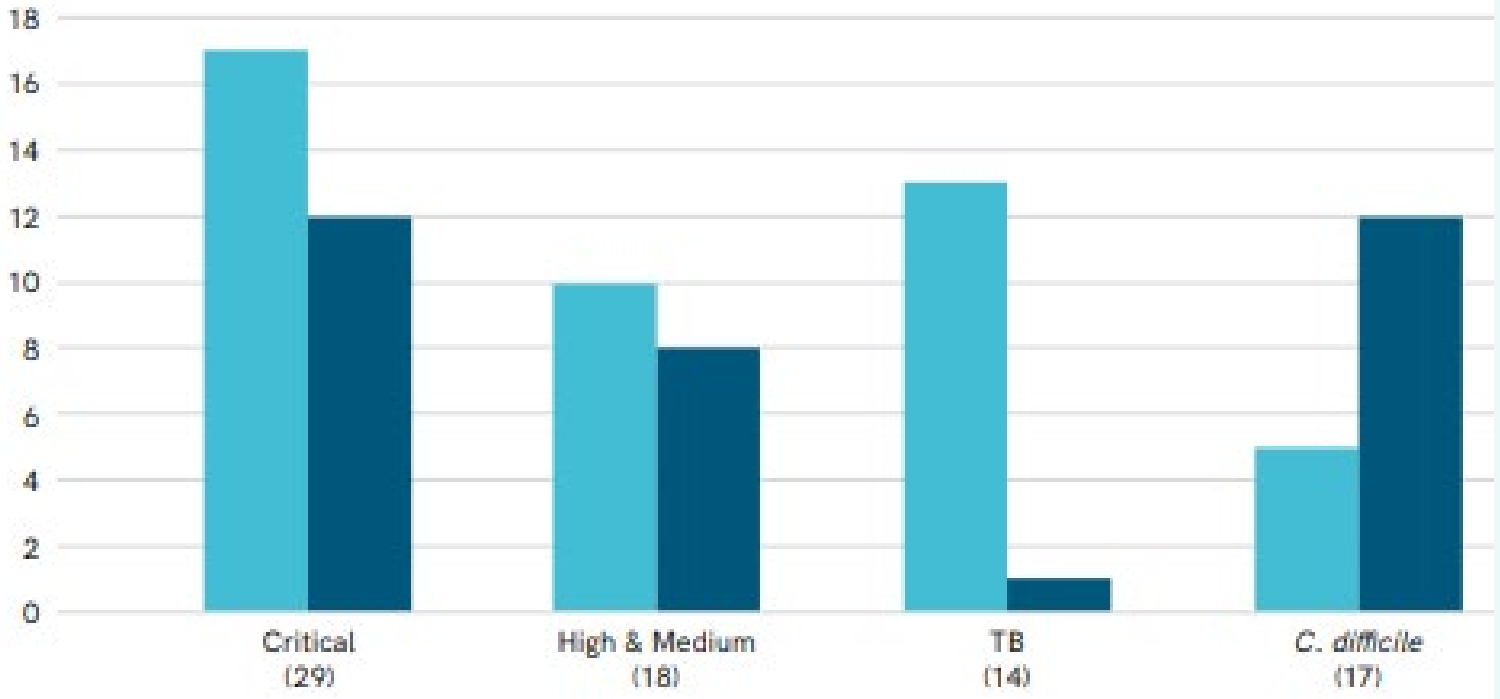
Results: traditional and non-traditional agents in clinical development by intended target



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

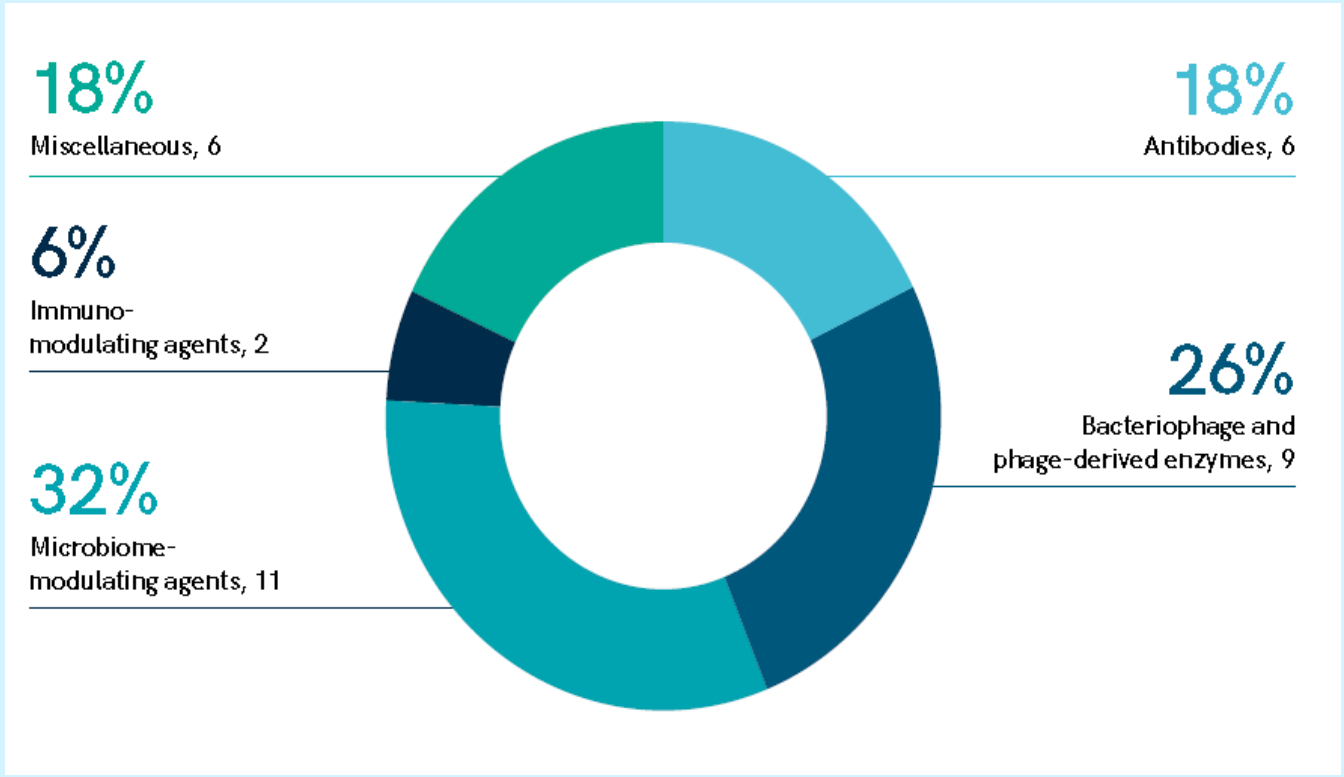
Other priorities:

- 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

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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*

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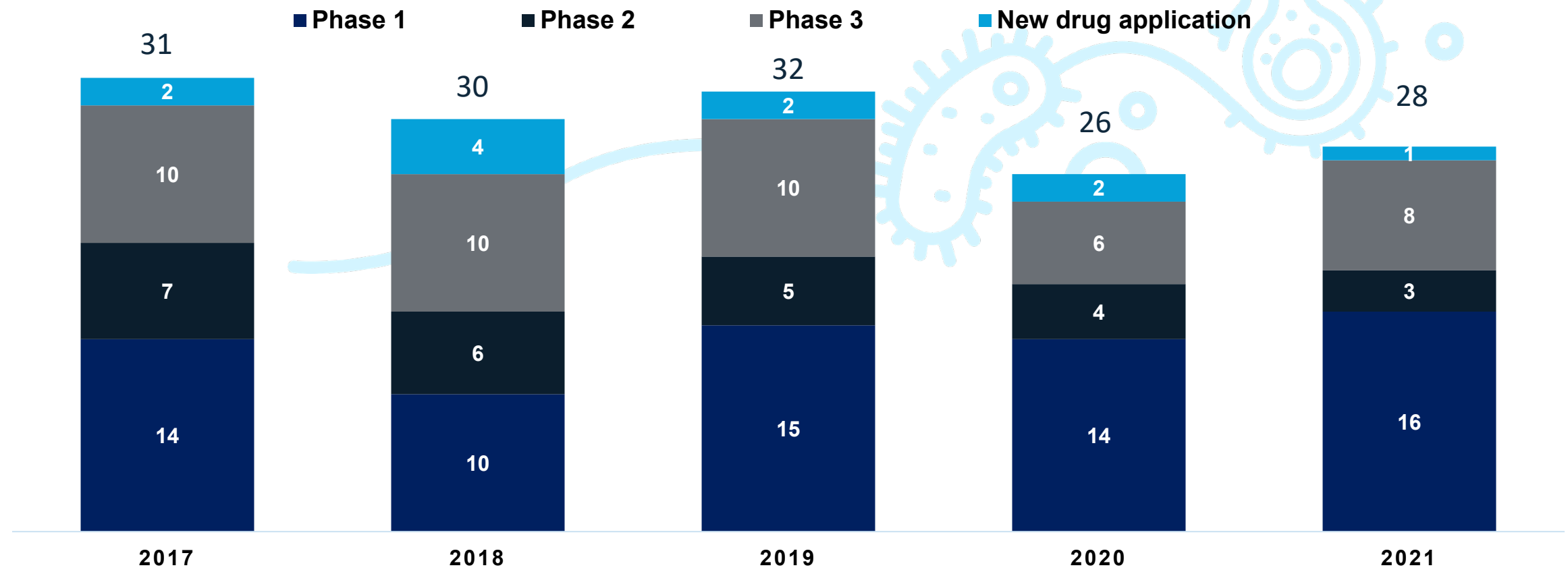
The clinical pipeline for antibiotics is stagnant



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

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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

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Thank you

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