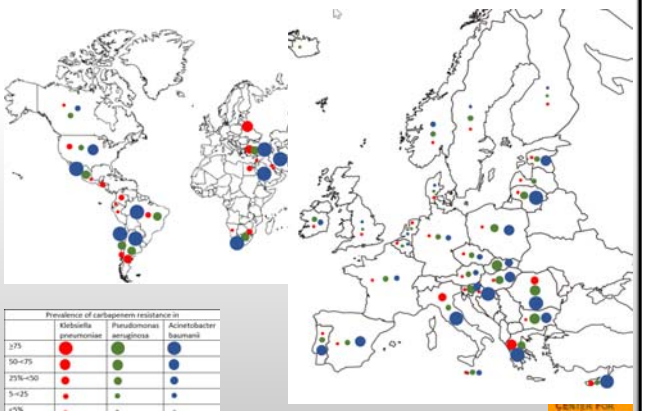
BioInfect, Alderley Park 2017

Antibacterial Drug R&D

Medical Need and Public Support

U. Theuretzbacher – Center for Anti-Infective Agents, Vienna, Austria

Resistance in Gram-negative bacteria



Prevalence of carbapenem resistance in	Klebsiella pneumoniae	Pseudomonas aeruginosa	Acinetobacter baumanii
≥75			
50–<75			
25%–<50			
5–<25			
<5%			

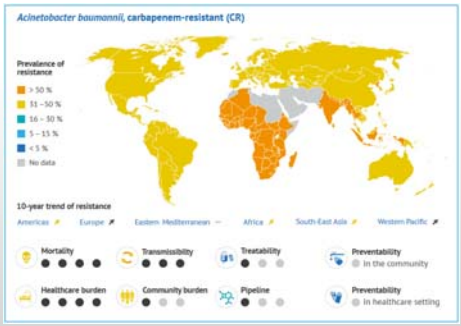
U. Theuretzbacher: Curr Opin Microbiology Nov 2017, in press

who priority pathogens list

Prioritization: Multi-criteria decision analysis

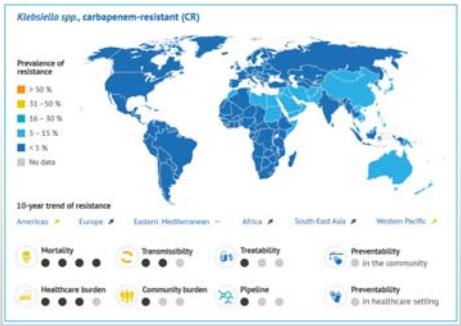
 http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf

Critical Priority Pathogens



 http://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf

Critical Priority Pathogens



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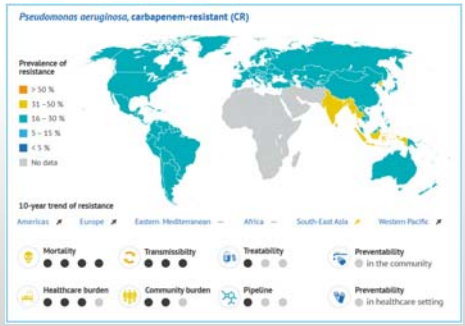
Critical Priority Pathogens



 http://www.who.int/medicines/areas/rational_use/PPLreport_2017_09_19.pdf

Innovation

- Innovation
- Novelty
- Usefulness

New App

Scientific definition

No cross-resistance to existing antibiotics
- New class/target/MoA
- Substantial improvement of existing class without cross-resistance

Improved antibiotics from existing classes
- Reduced class-specific resistance

Improved features, e.g.
- Oral formulation
- Improved pharmacokinetics

Definition not uniformly agreed!

U. Theuretzbacher Antibiotic innovation for future public health needs. Clin Microbiol Infect. 2017 Jun 24.
U. Theuretzbacher: New drugs – will they solve the problem of resistance to antibiotics? Clin Microbiol Infect. 2017 August 19

Clinical pipelines - WHO critical priority pathogens

ß-lactams, ß-lactam-inhibitor combinations

Ph	Class	Compound	Pathogen activity CR-E | CR-PA | CR-AB
✓	Carbapenems	Vaborbactam/merop	
3		Relebactam/imip	
1		VNRX-5133/merop	
3		Sulopenem	
1	Cephalosporins	Zidebactam/cefep	
1		Nacubactam/cefep	
2		AAI-101/cefep	
1		Tazo/cefep	
1		C-Scape	
3	Ceph-siderophore	Cefiderocol	
2	Monobactams	Avibactam/aztreon	
1		LYS228	
1	BLIs	ETX-2514SUL	

KPC | NDM

WHO critical priority pathogens
Carbapenem resistant
CR-E: Enterobacteriaceae
CR-PA: Pseudomonas aeruginosa
CR-AB: Acinetobacter baumannii group

Activity
Unclear
No or insufficient activity

Pipeline: Specific solutions for specific patients for specific situations in specific regions

Based on the WHO pipeline analysis 2017

Clinical pipelines - WHO critical priority pathogens

			WHO critical priority pathogens CR-E | CR-PA | CR-AB
✓	Delafloxacin	Fluoroquinolone	
3	Sulopenem	Carbapenem	ESBL
3	Plazomicin	Aminoglycoside	
3	Lascufloxacin	Fluoroquinolone	
3	Eravacycline	Tetracycline	
3	Omadacycline	Tetracycline	
3	Solithromycin	Macrolide	
3	Iclaprim	DHFR-inhibitor	
3	Lefamulin	Pleuromutilin*	
2/3	MRX-I/MRX-IV	Oxazolidinone	
2	Gepotidacin	NBTI (Triazaacenaphthylene)	
2	Zoliflodacin	NBTI (Spiropyrimidenetrione)	
2	Murepavidn	Novel membrane targeting AB	
2	Brilacidin	Novel membrane targeting AB	
2	Afabicin	FabI inhibitor	
2	Nafithromycin	Macrolide	
2	Finafloxacin	Fluoroquinolone	
1	SPR-741 + antibiotic?	Polymyxin + antibiotic?	
1	TP-271	Tetracycline	
1	TP-6076	Tetracycline	
1	KBP-7072	Tetracycline	
1	TNP-2092	Rifamycin-quinolone hybrid	

Gram-pos

New chemical or functional class

Carbapenem resistant
CR-E: Enterobacteriaceae
CR-PA: Pseudomonas aeruginosa
CR-AB: Acinetobacter baumannii group

Activity
Unclear
No or insufficient activity

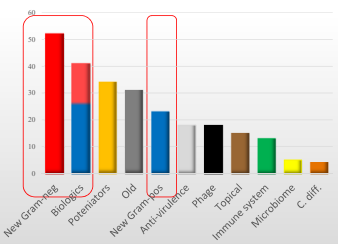
Mostly developed by companies with <500 employees (most companies <100)

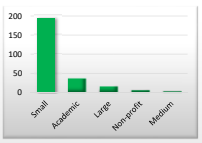
Biologics, C. diff. drugs, combinations or off-patent drugs not included

Based on the WHO pipeline analysis 2017

Preclinical pipelines, n=254

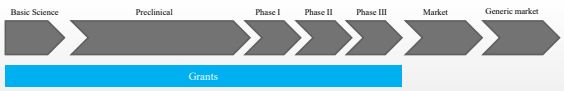
CARB-X submissions 2016, n=254





U. Theuretzbacher et al: Innovation potential of the preclinical antibiotic pipeline. Nature Reviews Drug Discovery. Oct 2017

DRIVE-AB's recommended models



Grants

Pipeline Coordinator

MER | Continuity

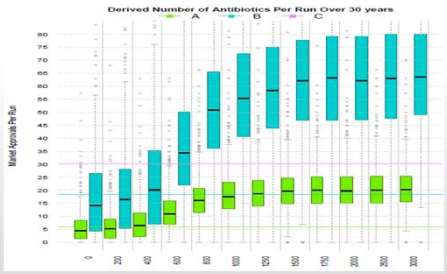
Push mechanisms ICO

Increase, Coordinate, Optimise resources
- **Address drug discovery and early development hurdles: scientific and financial**
- **Global coordination hub**

Discovery grants improve the entry rates into the preclinical phase, improve the effect of pull mechanisms

Additional annual push funding ~200-500 million

Market Entry Reward – Simulation



Summary

- Medical need is not reflected in the clinical pipelines
- The preclinical pipelines are encouraging but not robust enough
- More innovation is required
- Need for support is apparent

Acknowledgements: