

# **Nouveaux antibiotiques**

# **2021**

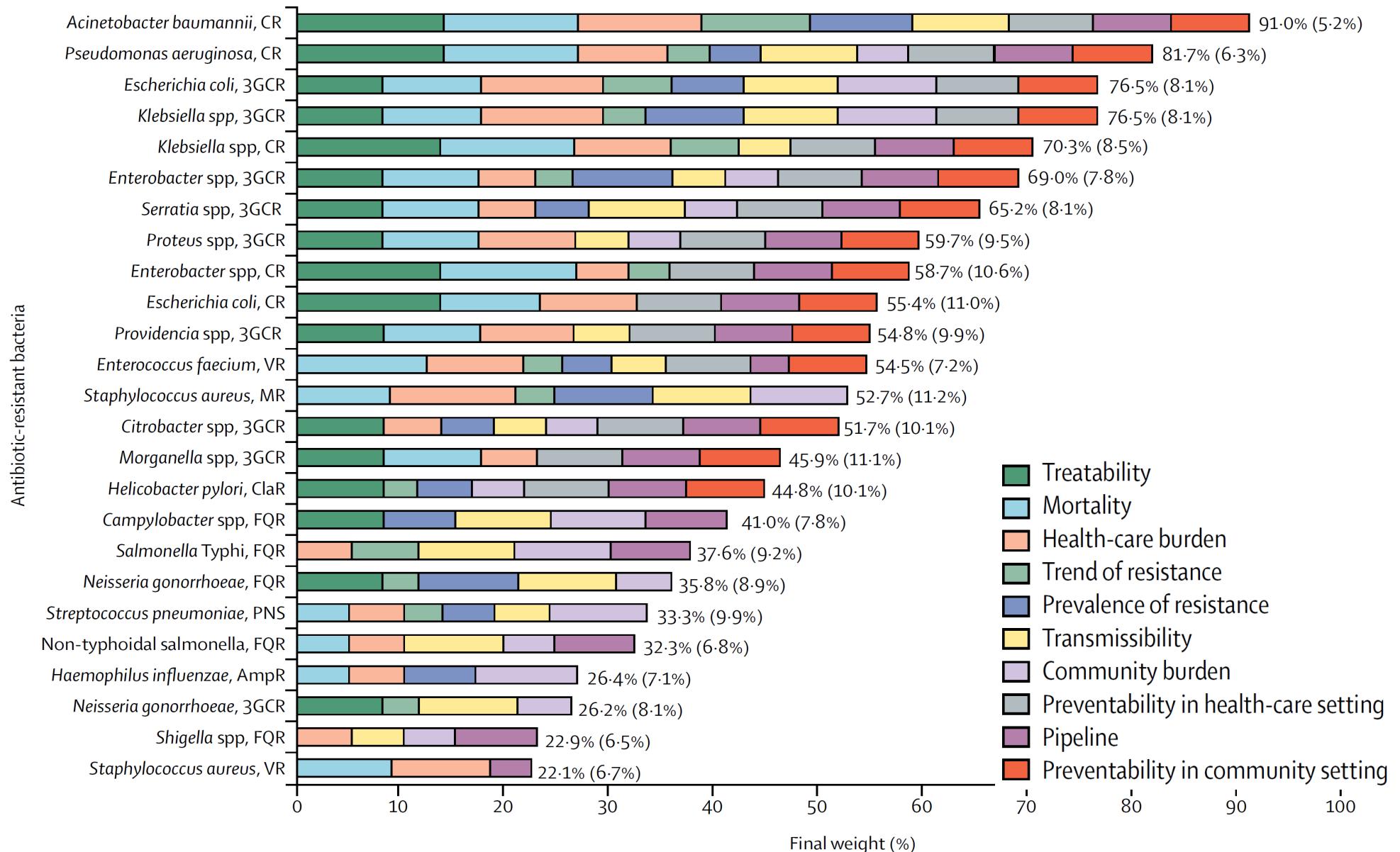
P Chavanet

Dijon

# Image globale des problèmes

- █ Treatability
- █ Mortality
- █ Health-care burden
- █ Trend of resistance
- █ Prevalence of resistance
- █ Transmissibility
- █ Community burden
- █ Preventability in health-care setting
- █ Pipeline
- █ Preventability in community setting

# Image globale des problèmes



Tacconelli E et al

Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis

Lancet Infect Dis 2018; 18; 318–27

# Les menaces « OMS » (2019)

(hormis tuberculose)

France

Hôpital/soins de suite

« ville »

## Priorité « critique »

Acinetobacter	penem-R	Faible mais ↑	rare
Pseudomonas	penem-R	≈ 20-30%	rare
Enterobactéries	penem-R C3G-R	≈ 30% ≈ 20-30%	rare 10-20%

## Priorité élevée

E.Faecium vanco-R	
S.aureus vanco-R	
Helicobacter pylori Clarithro-R	
Campylobacter sp fluoroQ-R	↑
Salmonella sp fluoroQ-R	↑
Gono C3G-R/fluoroQ-R	↑

## Priorité « moyenne »

Pneumocoque SDP
H.Influenzae ampi-R
Shigella sp fq-R

# Vue globale du potentiel actuel (antibiotique)

<b>Direct-acting small molecules</b> <ul style="list-style-type: none"><li>• ~70% new and ~20% old targets</li><li>• ~50% targeting Gram-negative bacteria</li></ul>	<b>Potentiators</b> <ul style="list-style-type: none"><li>• <math>\beta</math>-Lactamase or efflux pump inhibitors</li><li>• Expanding spectrum</li><li>• Enhancing or restoring activity</li><li>• Protectors</li></ul>	<b>Repurposed drugs</b> <ul style="list-style-type: none"><li>• FDA-approved drugs</li></ul>	<b>Antibodies and vaccines</b> <ul style="list-style-type: none"><li>• Against select pathogens</li></ul>	<b>Immuno-modulators</b> <ul style="list-style-type: none"><li>• Support pathogen elimination</li></ul>	<b>Antivirulence approaches</b> <ul style="list-style-type: none"><li>• Adjunctive</li><li>• Targeting different virulence factors and strategies</li><li>• Against select pathogens</li></ul>	<b>Phages and microbiota</b> <ul style="list-style-type: none"><li>• Phages against select pathogens</li><li>• Endolysins</li><li>• Modulators of microbiota (mostly gut)</li></ul>
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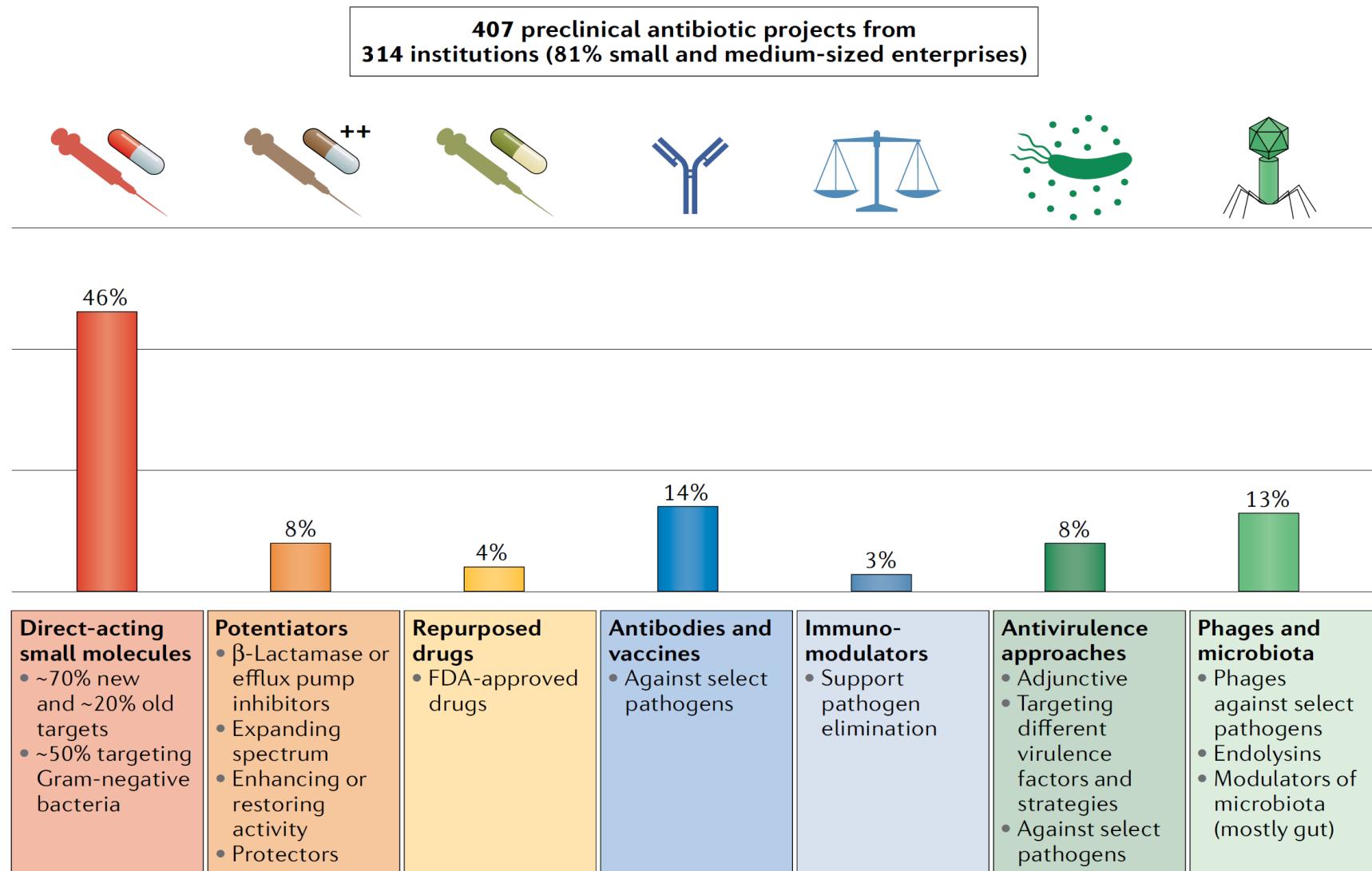
Ursula Theuretzbacher, Kevin Outterson, Aleks Engel and Anders Karlén

The global preclinical antibacterial pipeline

NaTuRe RevleWS | **MicrObiOlogy** volume 18 | May 2020

<https://doi.org/10.1038/s41579-019-0288-0>

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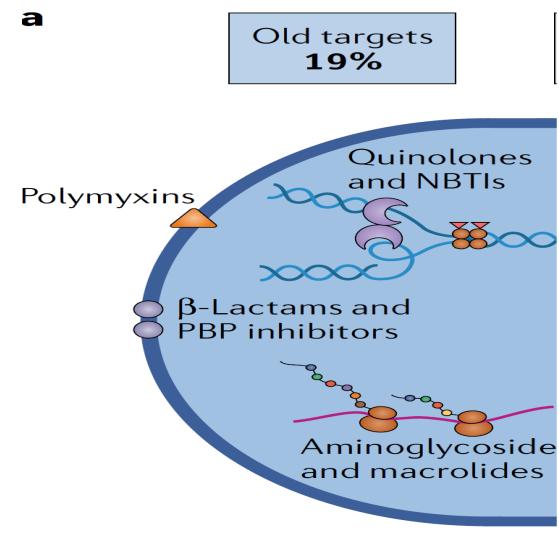


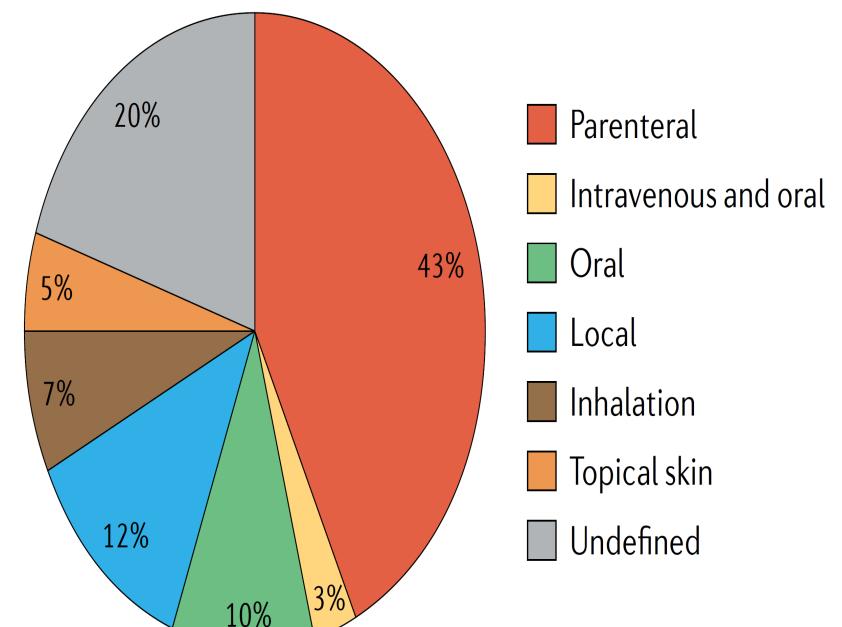
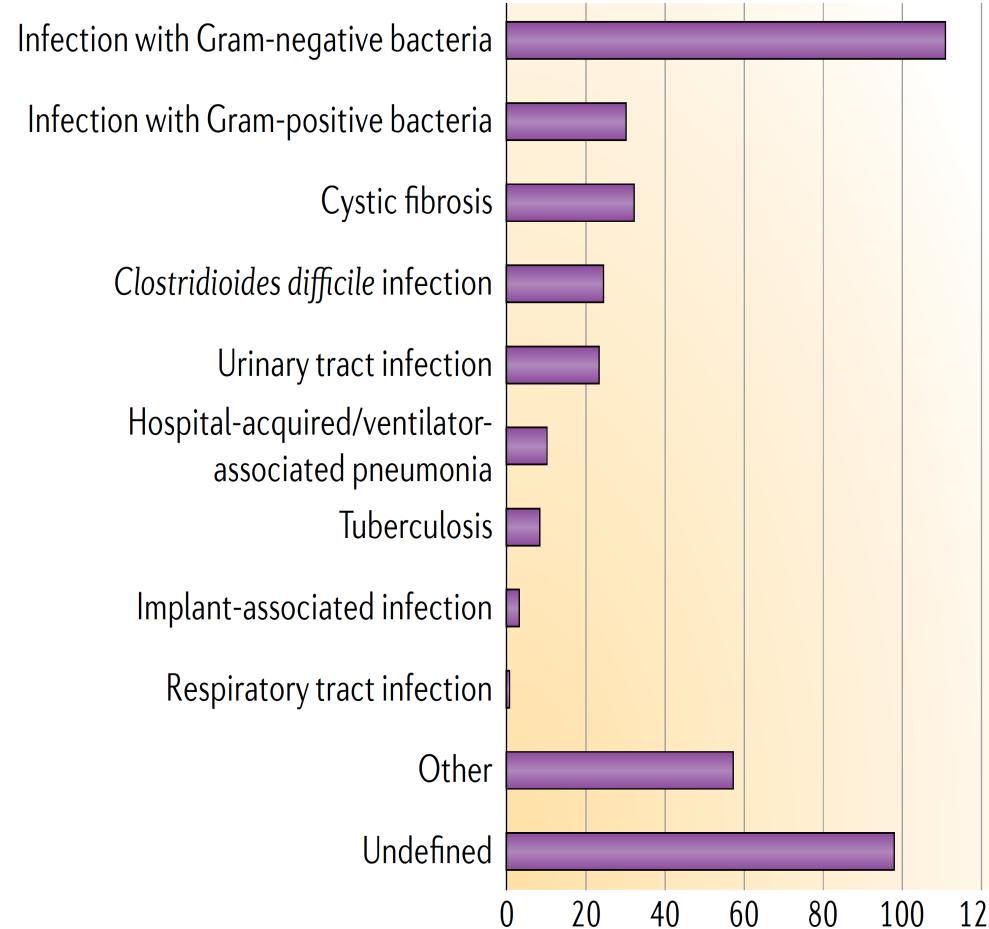
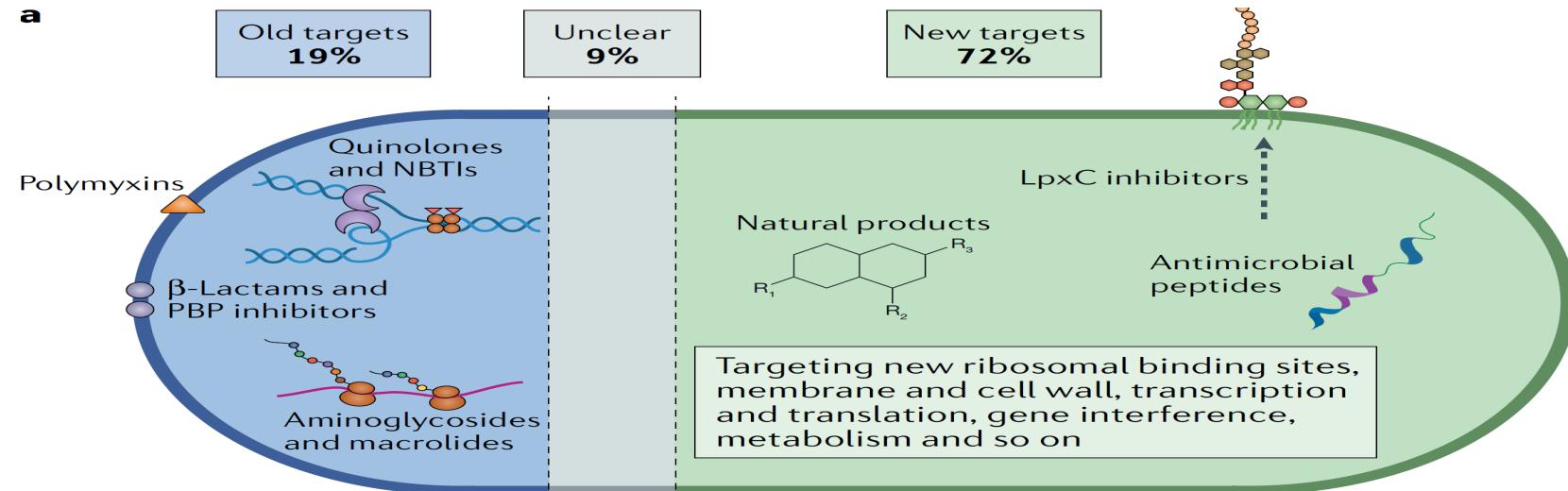
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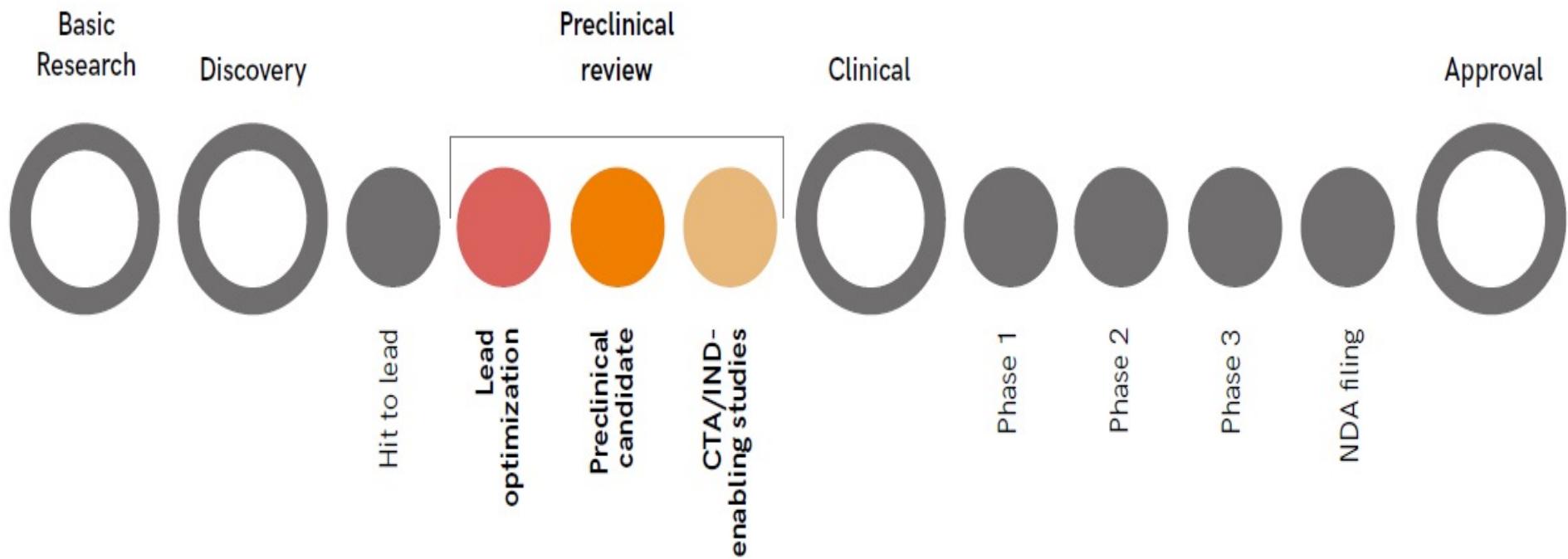
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# Petit rappel « découverte »

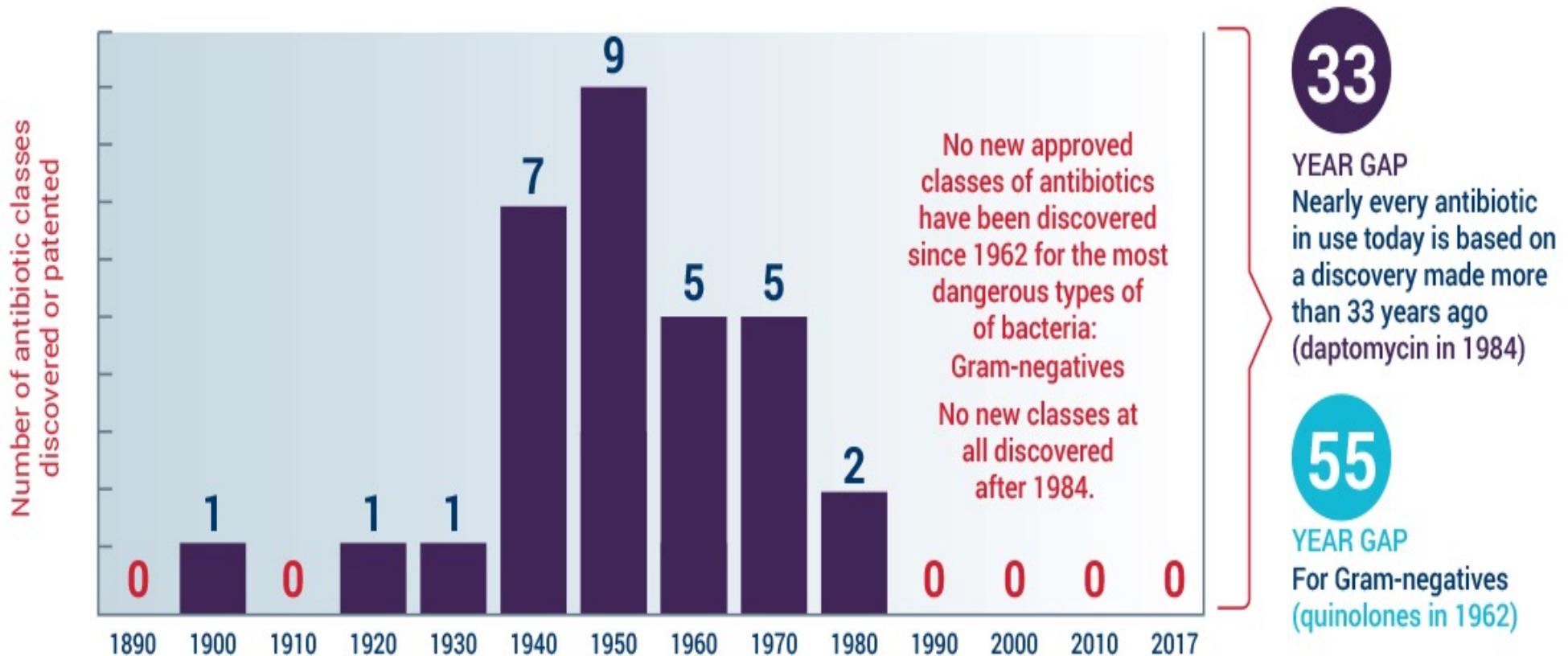


# Des idées – beaucoup d'échecs



Source: Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL. Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nat Rev Drug Discov. 2007;6(1):29-40; Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, et al. Alternatives to antibiotics-a pipeline portfolio review. Lancet Infect Dis. 2016;16(2):239-51.

# Pas (peu) de nouvelles classes d'antibiotiques

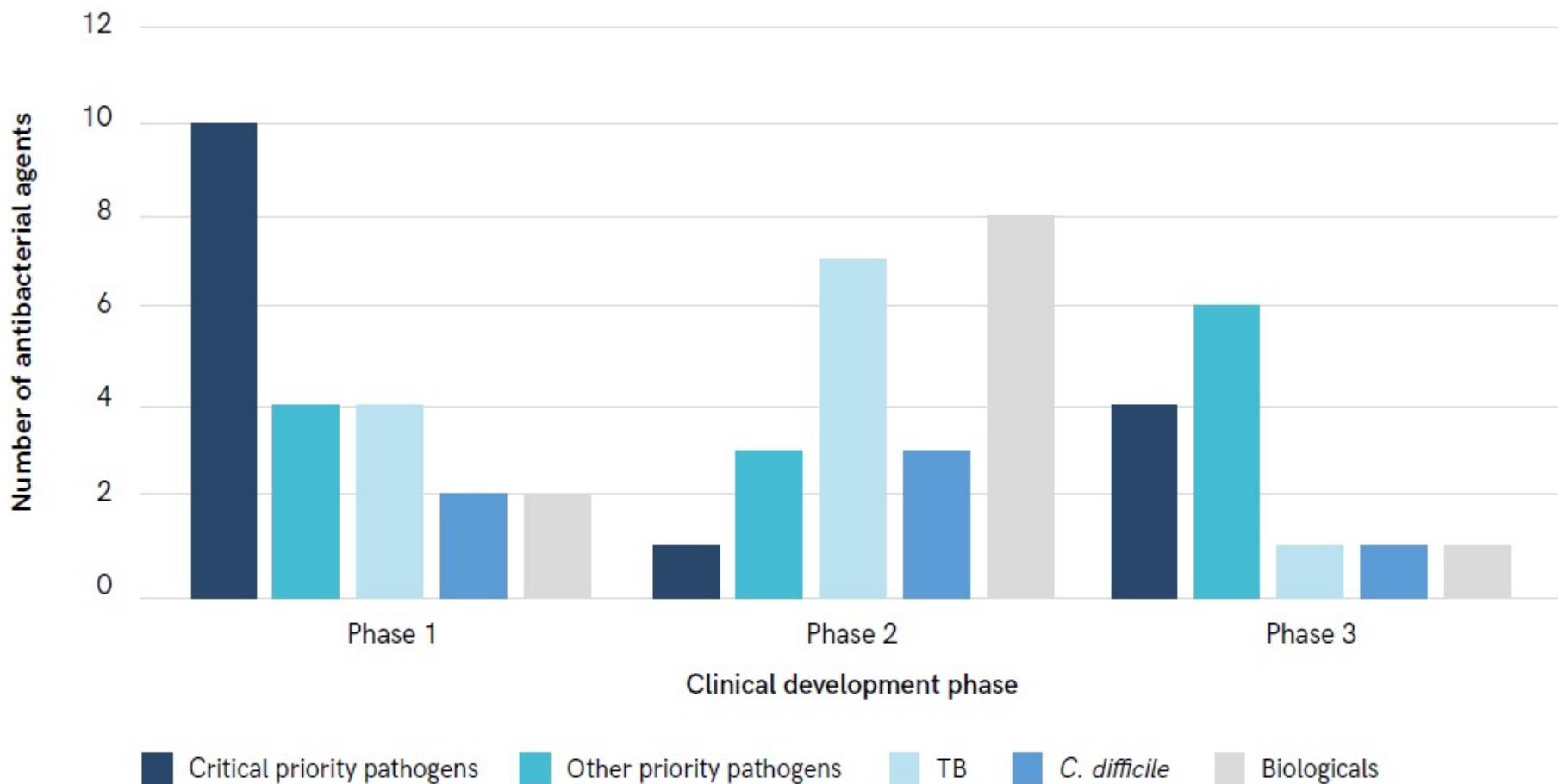


\*This chart excludes bedaquiline, which is the first drug in a new class to treat tuberculosis.

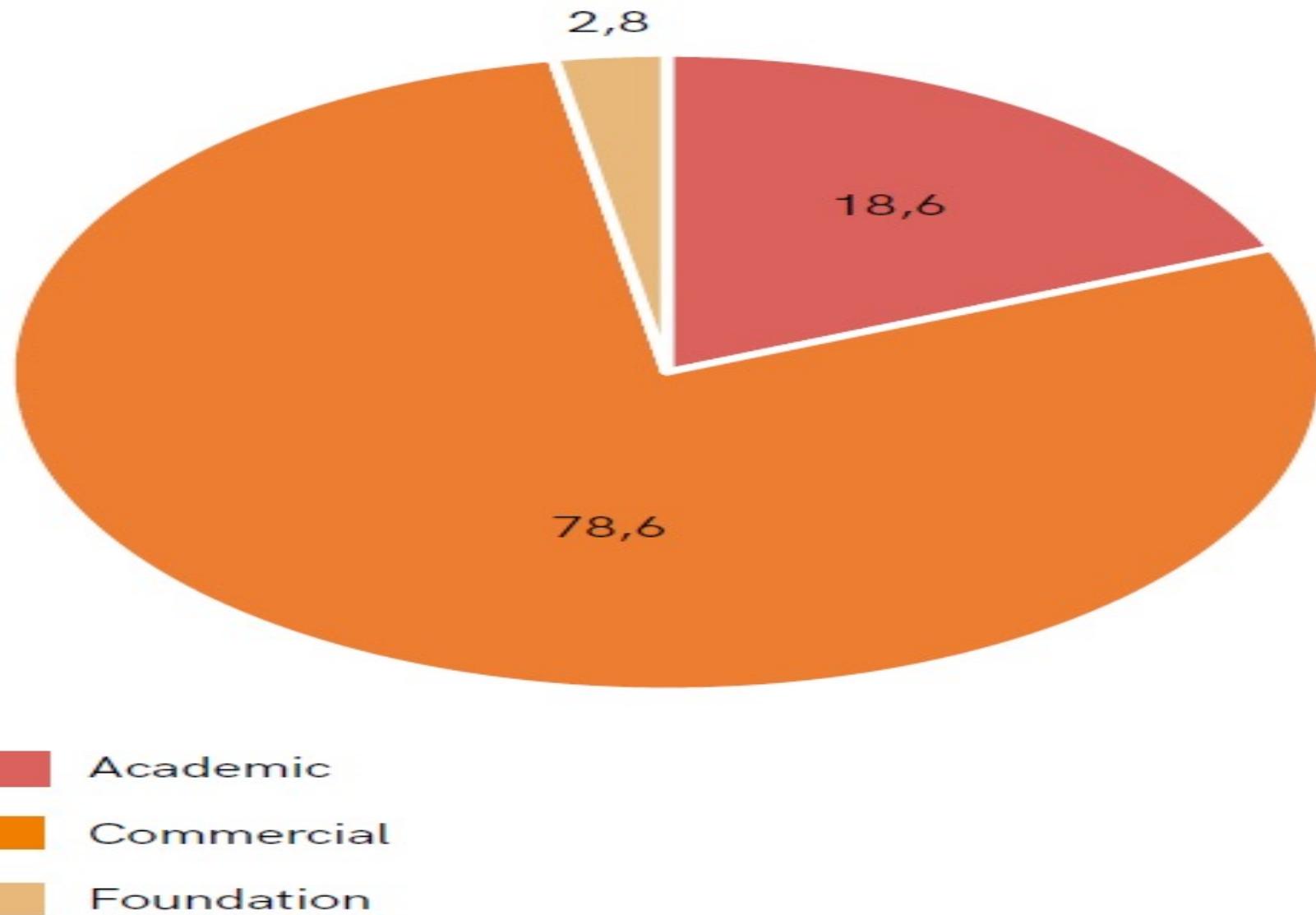
Source: Pew Charitable Trusts; Deak D, Powers JH, Outterson K, Kesselheim AS. Progress in the Fight Against Multidrug Resistant Bacteria?: A Review of FDA Approved Antibiotics 2010-2015. ANNALS OF INTERNAL MED. 2016 MAY 31. DOI: 10.7326/M16-0291.

# Situation actuelle des développements cliniques

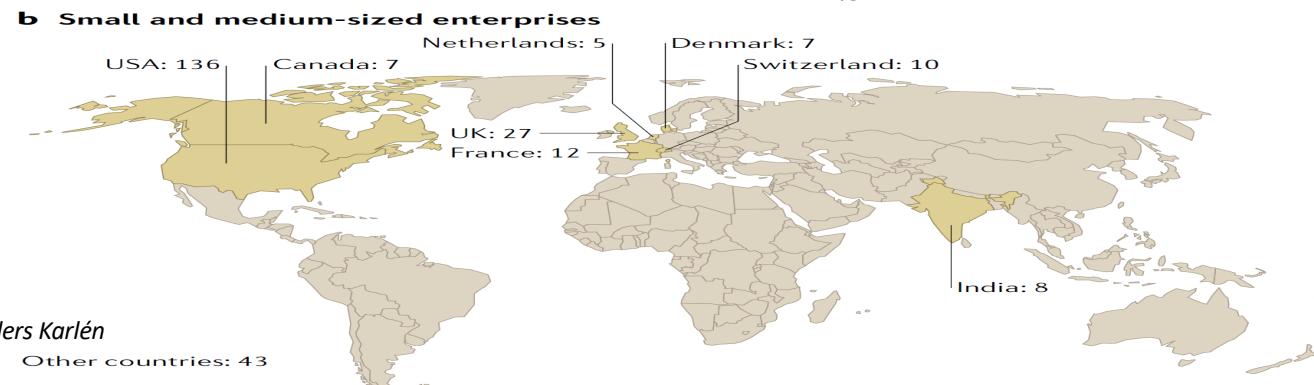
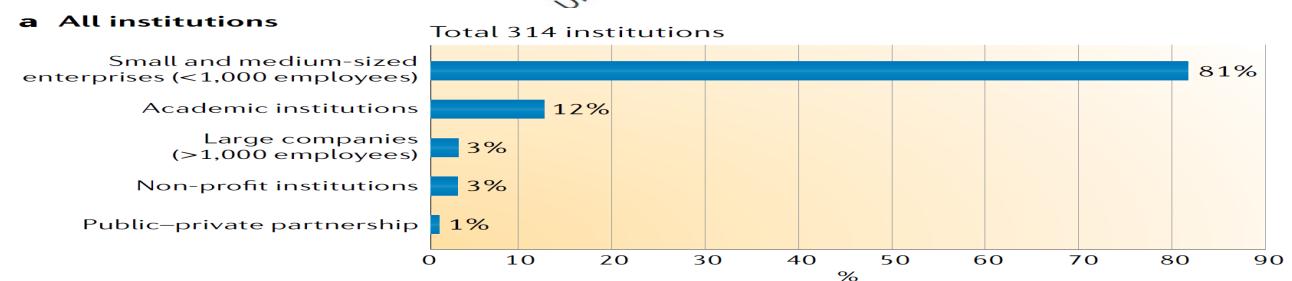
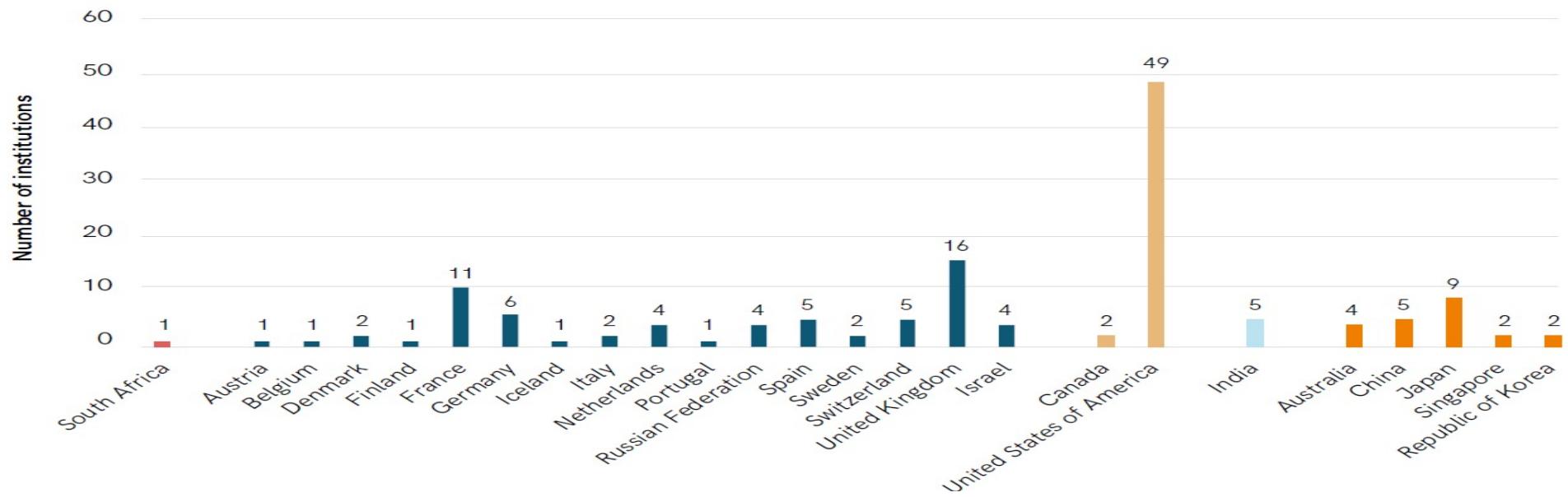
(phase 1, 2 ou 3)



# Qui inventent ?



# Effort « antibiotique » - quels pays ?



Ursula Theuretzbacher, Kevin Outterson, Aleks Engel and Anders Karlén

The global preclinical antibacterial pipeline

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# Il y a des investissements « risqués »

Table 2. Distribution of programmes by mode of action and preclinical development stage

Mode of action	Total (%)	Development stage		
		LO	PCC	CTA/IND
Cell wall synthesis	50 (19.8)	12	22	16
Cell membrane	36 (14.3)	13	19	4
DNA replication	8 (3.2)	3	4	1
Protein synthesis	21 (8.3)	12	7	2
Cell metabolism	18 (7.2)	8	8	2
Immunomodulation	11 (4.4)	5	4	2
Bacteriophage	28 (11.1)	10	17	1
Other	47 (18.7)	26	15	6
Not disclosed	33 (13.1)	19	12	2
Total	252 (100)	108	108	36

LO: lead optimization; PCC: preclinical candidate; IND: IND enabling studies

Table 2. Antibiotics that are being developed against WHO priority pathogens

Name (synonym)	Phase	Antibiotic class	Route of administration (developer)	Expected activity against priority pathogens			
				CRAB	CRPA	CRE	OPP
Lascufloxacin	NDA <sup>1</sup>	Fluoroquinolone	iv & oral (Kyorin)	○	○	○	?
Cefiderocol <sup>12</sup>	NDA <sup>2</sup> MAA <sup>2</sup>	Siderophore cephalosporin	iv (Shionogi)	●	●	●	/
Sulopenem, Sulopenem etzadroxil/ probenecid	3	Penem	iv (Iterum) oral (Iterum)	○	○	○ <sup>3</sup>	/
Durlobactam (ETX-2514) + sulbactam	3	DBO-BLI/PBP2 binder + β-lactam-BLI/PBP1,3 binder	iv (Entasis)	●	○	○	/
Taniborbactam (VNRX-5133) + cefepime	3	Boronate-BLI + cephalosporin	iv (VenatoRx)	○	?	●	/
Enmetazobactam (AAI-101) + cefepime	3	β-lactam BLI + cephalosporin	iv (Allegra)	○	○	○ <sup>4</sup>	/
Zoliflodacin	3	Topoisomerase inhibitor (spiropyrimidene-trione)	oral (Entasis/GARDP)	/	/	/	●
Gepotidacacin	3	Topoisomerase inhibitor (triazaacenaphthylene)	iv & oral (GSK)	/	/	/	●
Levonadifloxacin Alalevonadifloxacin	3 <sup>5</sup>	Fluoroquinolone	iv oral (Wockhardt)	○	○	○	?
Cefilavancin (TD-1792)	3 <sup>6</sup>	Glycopeptide-cephalosporin conjugate	iv (Theravance/R Pharm)	/	/	/	●
Solithromycin	3 <sup>7</sup>	Macrolide	iv & oral (Melinta/Fujifilm Toyama Chemical)	/	/	/	●
Contezolid Contezolid acefosalim	2/3 <sup>8</sup>	Oxazolidinone	oral (MicuRx) iv & oral (MicuRx)	/	/	/	●
Afabicin (Debio-1450)	2	FabI inhibitor	iv & oral (Debiopharm)	/	/	/	●
BOS-228 (LYS-228)	2	Monobactam	iv (Boston Pharmaceuticals)	○	○	●	/
Nafithromycin (WCK-4873)	2	Macrolide	oral (Wockhardt)	/	/	/	●
TNP-2092	2	Rifamycin-quinolizinone hybrid	iv & oral (TenNor)	/	/	/	?
Benapenem	2 <sup>9</sup>	Carbapenem	iv (Sichuan Pharmaceutical)	○	○	○	/
Zidebactam + cefepime	1	DBO-BLI/PBP2 binder + cephalosporin	iv (Wockhardt)	○	?	●	/
Nacubactam + meropenem	1	DBO-BLI/PBP2 binder + meropenem	iv (NacuGen Therapeutics)	○	○	● <sup>10</sup>	/
ETXO282 + cefpodoxime	1	DBO-BLI/PBP2 binder + cephalosporin	oral (Entasis)	○	○	● <sup>10</sup>	/
VNRX-7145 + ceftibuten	1	Boronate-BLI + cephalosporin	oral (VenatoRx)	○	○	●	/
SPR-741 + β-lactam	1	Polymyxin (potentiator) + β-lactam	iv (Spero)	?	?	?	/
SPR-206	1	Polymyxin	iv (Spero)	●	●	●	/
KBP-7072	1	Tetracycline	oral (KBP BioSciences)	○	○	○	●
TP-271	1	Tetracycline	iv & oral (Tetraphase)	?	○	○	●
TP-6076	1	Tetracycline	iv (Tetraphase)	●	○	?	/
EBL-10031 (apramycin)	1 <sup>10</sup>	Aminoglycoside	iv (Juvabis)	?	-	?	/
AIC-499 + unknown BLI	1	β-lactam + BLI	iv (AiCuris)	?	?	?	/
TNP-2198	1	Rifamycin-nitroimidazole conjugate	oral (TenNor)	/	/	/	●
TXA-709	1	FtsZ inhibitor	oral & iv (Taxis)	○	○	○	●
BCM-0184	1	?	oral (Biocidium)	○	○	○	●
ARX-1796 (oral avibactam prodrug)	1	DBO-BLI + α-lactam	oral (Arixa Pharmaceuticals)	○	○	● <sup>11</sup>	/

Name (trade name)	Market authorization holder	Approved by (date)	Antibiotic class	Route of administration	Indication/s	WHO EML & AWaRe	Expected activity against priority pathogens			
							CRAB	CRPA	CRE	OPP
Delafloxacin (Baxdela)	Melinta	FDA (6/2017 ABSSI, 10/2019 CAP) MAA	Fluoroquinolone	iv & oral	ABSSI, CAP	AWaRe: Watch	0	0	0	●
Vaborbactam + meropenem (Vabomere)	Melinta	FDA (8/2017) EMA (11/2018)	Boronate BLI + carbapenem	iv	cUTI	WHO EML & AWaRe: Reserve	0	0	● <sup>1</sup>	/
Plazomicin (Zemdri)	Achaogen	FDA (8/2018)	Aminoglycoside	iv	cUTI	WHO EML & AWaRe: Reserve	0	0	●	/
Eravacycline (Xerava)	Tetraphase	FDA (8/2018) EMA (9/2018)	Tetracycline	iv	cIAI	AWaRe: Reserve	?	0	●	/
Omadacycline (Nuzyra)	Paratek	FDA (10/2018)	Tetracycline	iv & oral	CAP (iv), ABSSI (iv, oral)	AWaRe: Reserve	0	0	0	●
Relebactam + imipenem/ cilastatin (Recarbrio)	MSD	FDA (7/2019)	DBO-BLI + carbapenem/ degradation inhibitor	iv	cUTI, cIAI		0	?	● <sup>1</sup>	/
Lefamulin	Nabriva	FDA (8/2019)	Pleuromutilin	iv & oral	CAP		/	/	/	●
Pretomanid (PA-824)	TB Alliance	FDA (8/2019)	Nitroimidazole	oral	XDR TB		/	/	/	● <sup>3</sup>

	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	●	●	●	●	●	●
Sulopenem	●	-	-	-	-	-
Durlobactam (ETX-2514) + sulbactam	-	-	-	-	●	-
Taniborbactam (VNRX-5133) + cefepime	●	●	●	●	-	?
Enmetazobactam (AAI-101) + cefepime	●	?	-	-	-	-
BOS-288	●	●	●	●	-	-
Zidebactam + cefepime	●	●	●	?	-	?
Nacubactam + meropenem	●	●	●	?	-	-
ETX-0282 + cefpodoxime	●	●	●	-	-	-
VNRX-7145 + ceftibuten	●	●	●	-	-	-
ARX-1796 (oral avibactam prodrug)	●	●	●	-	-	-

# vs BGN (hôpital)

- Imipenem (cil)/relebactam
- Meropenem/varbobactam
- Ceftazidime/avibactam
- Ceftolozan/tazobactam
- Aztreonam/avibactam.....+ ?
- Cefiderocol
- Plazomicin
- eravacycline

# vs BGN (BLSE – « ville »)

- *E coli*
  - Oral fosfomycin versus ciprofloxacin in women with E.coli febrile urinary tract infection, a double-blind placebo-controlled randomized controlled non-inferiority trial (FORECAST)
  - Nitrofurantoin
  - Pivmecillinam
  - Amox-clav,
- *Klebsiella sp*
  - Pivmecillinan
  - Finafloxacin
  - sitafloxacin

Existant Japon / futur proche ?

## Dans le futur : antibiotiques oraux

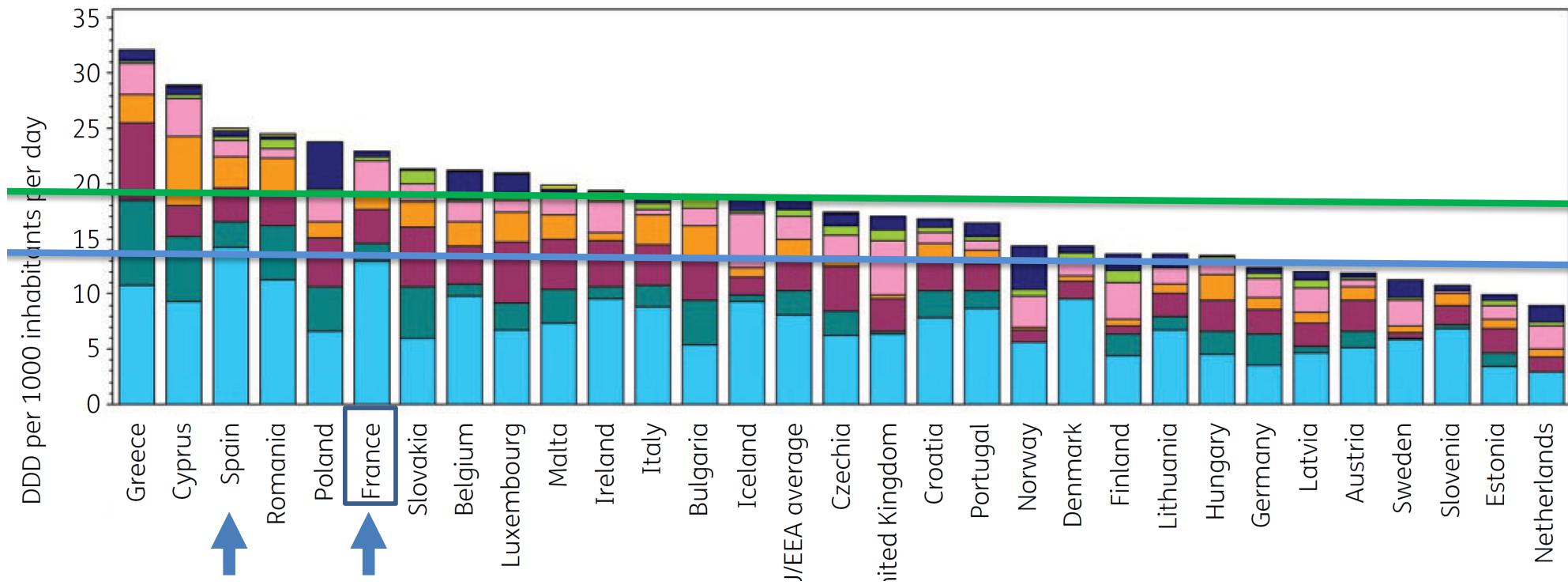
- Tebipenem
  - Tebipenem pivoxyl hydrobromide
- Sulopenem
  - solupenem etzadroxil / probenecid

**Oral bombs ??**

# Autres approches

- Formulations:
  - Nanoparticules
- Molécules « antivirulence »
  - Sortase inhibiteurs vs S aureus
- Peptides
  - Risin, en association
- Phages
- Immunothérapie passive
  - Passive:
    - $\gamma$ globuline: choc streptococcique
    - Ac monoclonaux
    - Prophylaxie PVAM
- Vaccin
  - Staphylocoque
  - E coli
  - Streptocoque
- Inactivation enzymatique – tube digestif

# Antibio « ville » Europe



█  $\beta$ -lactam antibacterials (J01C)

█ Macrolides, lincosamides, streptogramins (J01F)

█ Tetracyclines (J01A)

█ Other antibacterials (J01X)

█ Other  $\beta$ -lactam antibacterials (J01D)

█ Quinolone antibacterials (J01M)

█ Sulphonamides and trimethoprim (J01E)

█ Other antibiotics (J01B, J01G and J01R combined)

# Autres approches -1

- **Abstentiomycine** (dci = réflexomycine)
  - ✓ Très active sur la prévention des résistances
  - ✓ Facilement disponible
  - ✓ Non remboursée car évite de nombreux effets secondaires et surcoûts

# Autres approches -2

- **Rabaudmycine**

- Spectre lorrain et national
- Très active sur l'organisation des environnements hospitalo-universitaires
- Encore disponible

Non masqué



partiellement masqué



# Autres approches -3

- **Thierry.May.cine**
  - Moins disponible
  - Toujours active
  - Très large spectre

