Annual Joint Meeting SGINF

Lausanne, September 19, 2019

Pfizer Satellite Symposium

The challenge of combatting resistant gram negative infections: From research and development to the clinical application of new drugs

The rise and spread of carbapenem-resistance enhances the need of innovative antibacterial drugs: Why is it so difficult to develop and get them to the market?

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DISCLOSURE

Nothing to disclose:

No conflict of interests with commercial entities

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Agenda

1. Carbapenem resistance: what do we mean?
2. The rise of carbapenem resistance in CH and elsewhere
3. Do we need new, innovative antibiotics?
4. Why is it so difficult?

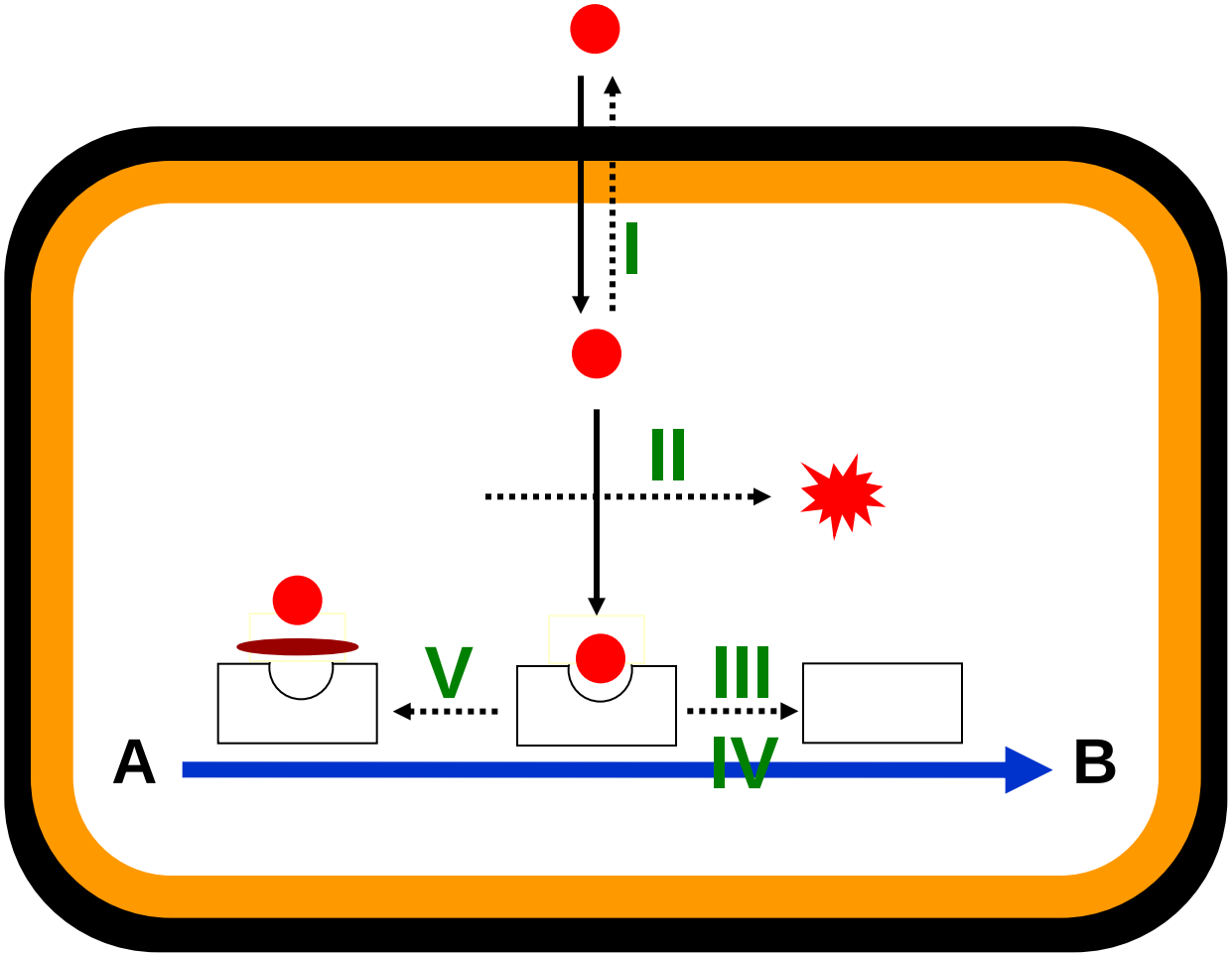
Bacterial resistance to antibiotics: genetic mechanisms

Intrinsic resistance — Innate ability of a bacterial species to resist the action of an antibiotic as a consequence of the bacteria's structural or functional characteristics

Acquired resistance

- Mutation
- Horizontal gene transfer
  - Conjugation
  - Transformation
  - Transduction

Antibiotic resistance mechanisms



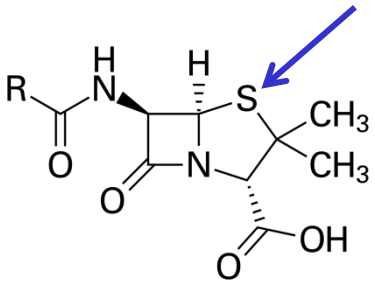
I: Concentration decrease
II: Inactivation, destruction
V: Target protection

III: Modification of the target
IV: By-pass

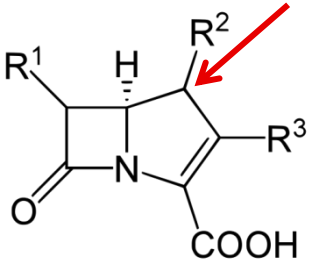
Some classes of antibiotics to which Gram-negative bacteria can acquire resistance:

1. (Ureido)penicillins
2. 3rd or 4th generation cephalosporins
3. Carbapenems
4. Fluoroquinolones
5. Polymyxins
6. Aminoglycosides
7. Glycylcycline
8. Tetracyclines
9. Chloramphenicol
10. Sulphonamides
11. Fosfomycin

Imipenem
Meropenem
Ertapenem
Doripenem



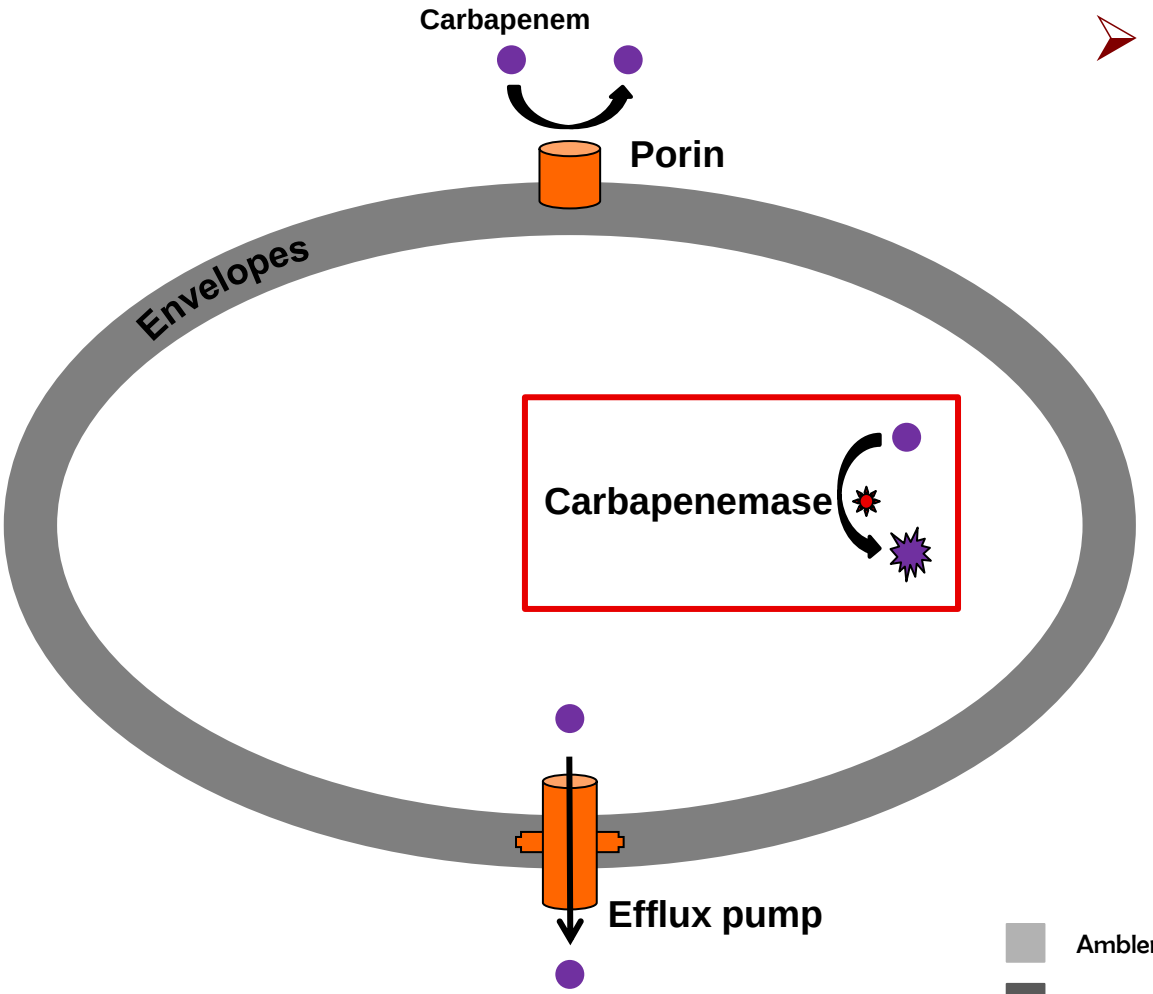
Penicillin



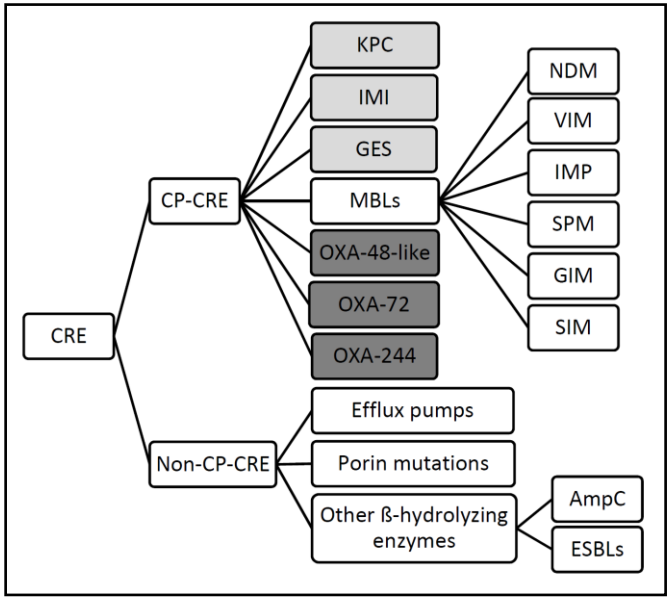
Carbapenem

Carbapenem resistance in *Enterobacteriaceae*

- **Mutation**
- **Horizontal transfer**



CRE: Carbapenem-Resistant *E.*; CP: Carbapenemase Producing



Antibiotics 2019, 8:122

Ambler class A
Ambler class D
Ambler class B

KPC: *K. pneumoniae* carbapenemase
MBLs: Metallo-β-lactamase
NDM: New Delhi metallo-β-lactamase
OXA-48: Oxacilinase

Comparison of epidemiological stages of carbapenemase-producing Enterobacteriaceae in European countries, 2010–2018

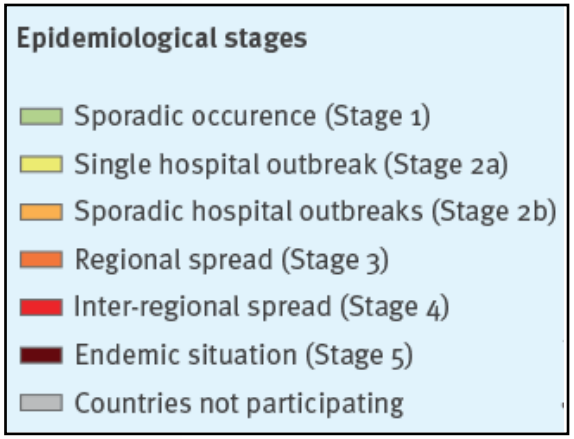
Country	Epidemiological stage for the spread of carbapenemase-producing Enterobacteriaceae				Change in epidemiological stage 2015–18
	2010 [11]	2013 [9]	2014–15 [8]	2018	
Albania	NA	2a	1	1	→
Austria	0	2b	2b	2b	→
Belgium	2b	3	4	4	→
Bosnia and Herzegovina[a]	1	1	0	2b	↑
Bulgaria	0	2a	2a	2b	→
Croatia	1	3	3	4	↑
Cyprus	2a	2a	1	2a	↑
Czech Republic	1	2b	2b	3	↑
Denmark	1	2a	4	4	→
Estonia	0	2a	1	1	→
Finland	1	2a	2a	3	↑
France	3	3	4	4	→
Germany	3	3	3	3	→
Greece	5	5	5	5	→
Hungary	3	4	4	4	→
Iceland	0	0	0	1	↑
Ireland	1	4	3	4	↑
Italy	4	5	5	5	→
Kosovo[b]	NA	2b	0	1	↑
Latvia	1	1	1	1	→
Lithuania	1	1	1	1	→
Luxembourg	NA	1	1	1	→
Malta	1	5	5	5	→
Montenegro	NA	0	1	1	→
The Netherlands	2a	2b	2a	2b	→
North Macedonia	NA	0	1	2a	↑
Norway	2a	2a	1	1	→
Poland	4	3	4	4	→
Portugal	1	1	2b	3	↑
Romania	1	1	4	4	→
Serbia	1	1	2b	4	↑
Slovak Republic	NA	2a	4	4	→
Slovenia	0	1	2a	1	↓
Spain	2b	3	4	4	→
Sweden	2a	2b	2a	2b	→
Turkey	NA	2a	5	5	→
United Kingdom[c]	2b	3	3	3	→

↑: increase in the epidemiological stage between 2015 and 2018

→: unchanged epidemiological stage between 2015 and 2018

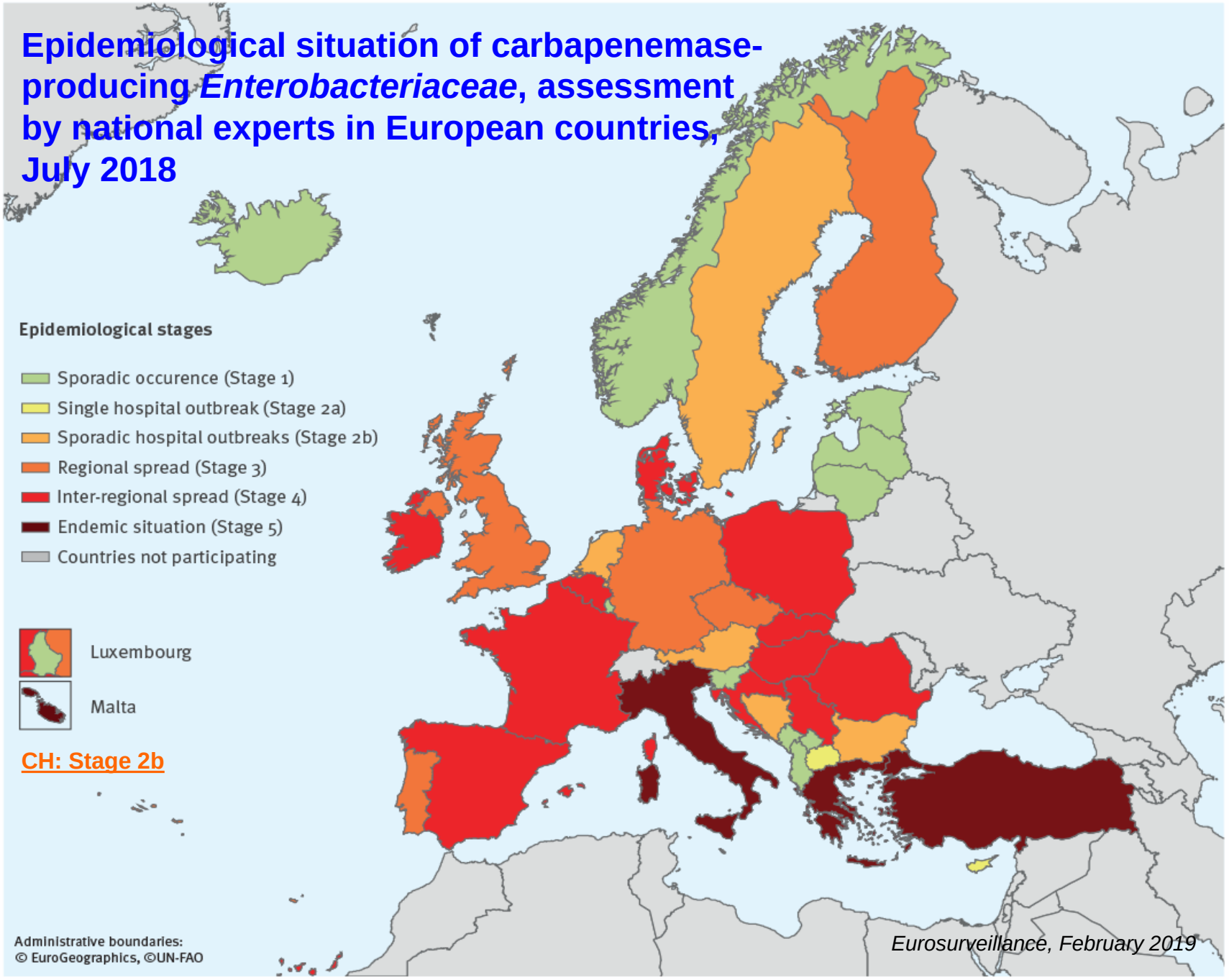
↓: decreased epidemiological stage between 2015 and 2018

CH: Stage 2b



Eurosurveillance, February 2019

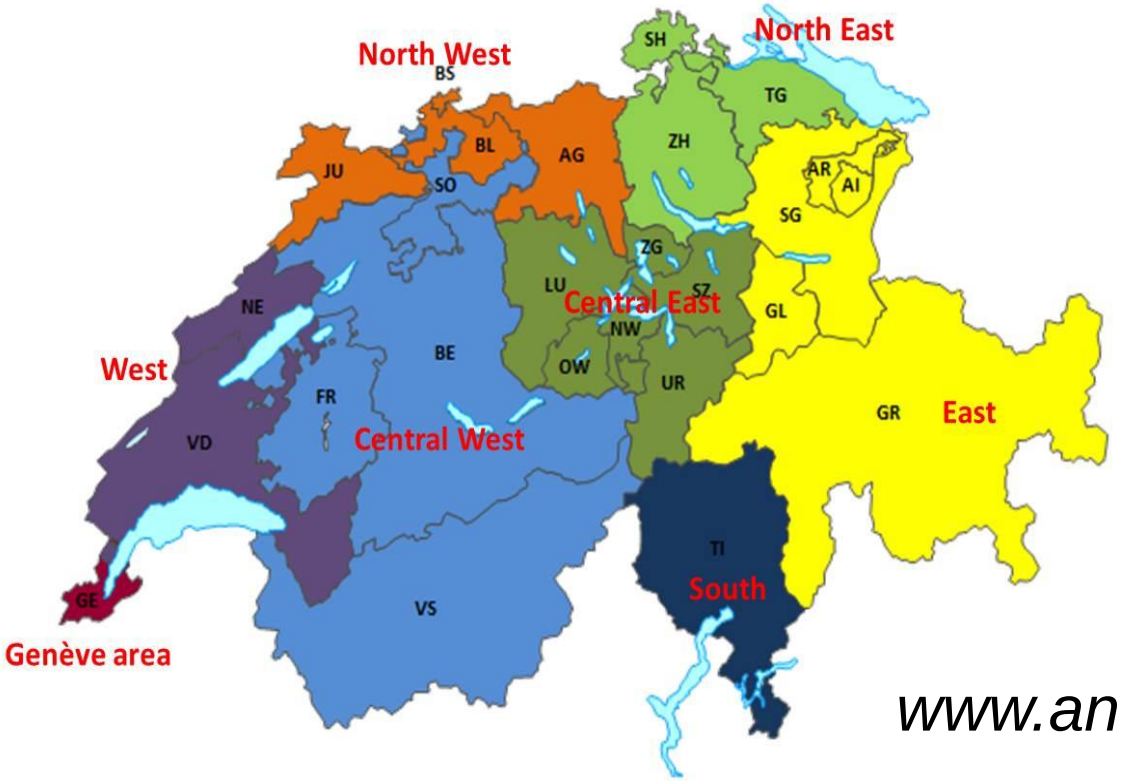
Epidemiological situation of carbapenemase-producing *Enterobacteriaceae*, assessment by national experts in European countries, July 2018



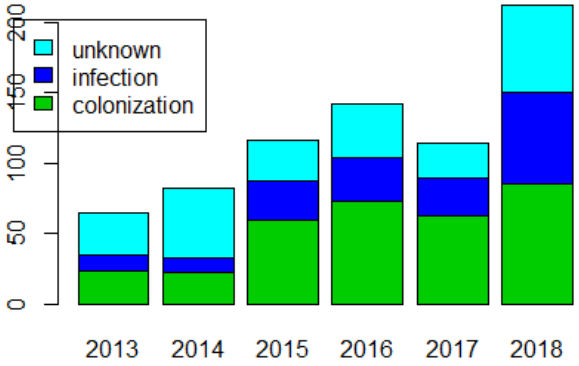
Eurosurveillance, February 2019

Carbapenem resistance in Switzerland

2018

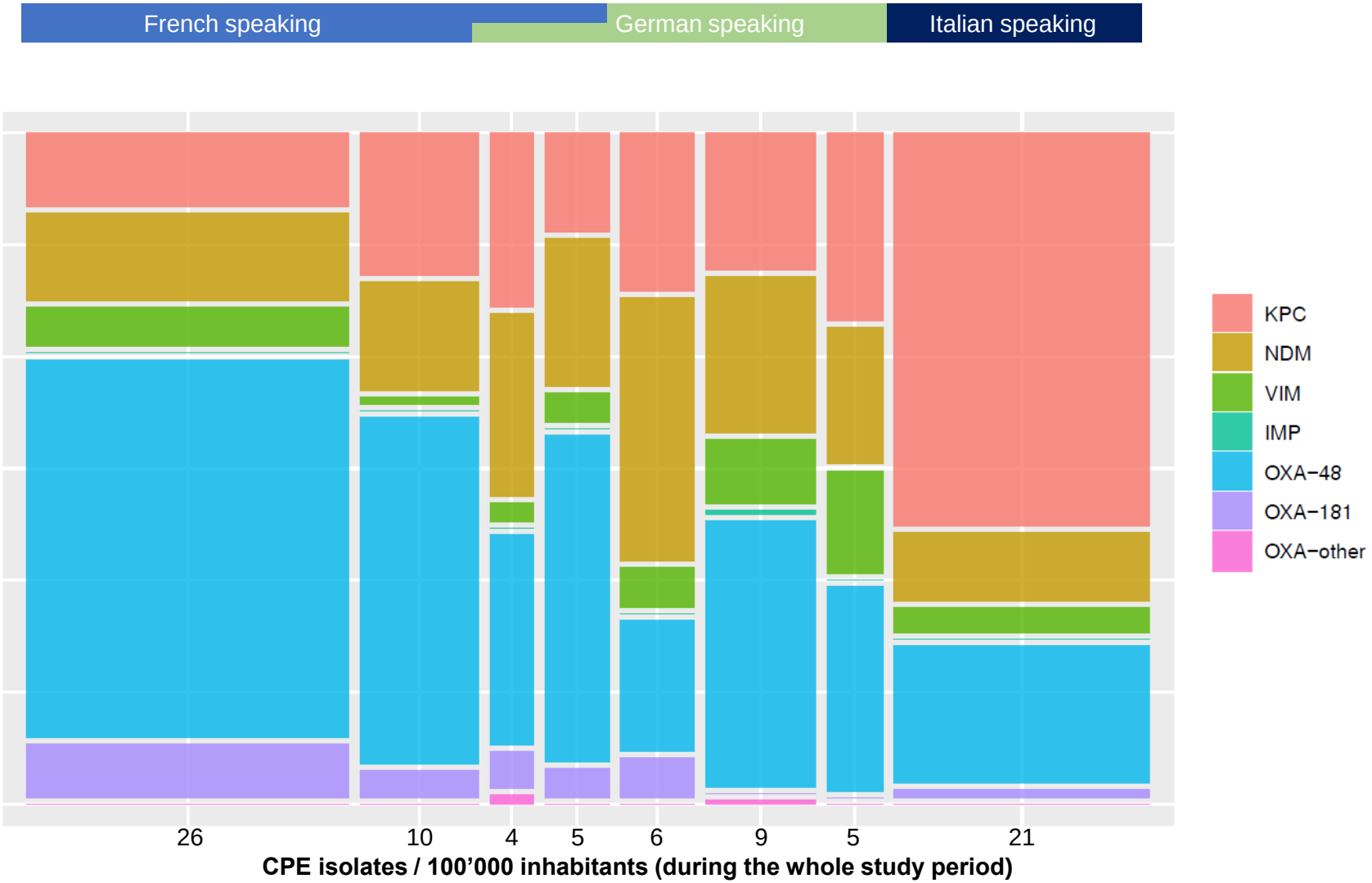


www.anresis.ch



Ramette A, Gasser M et al. 2019, manuscript in preparation

CPE isolates in Switzerland 2013-2018



Ramette A, Gasser M et al. 2019, manuscript in preparation

Criteria for defining MDR, XDR and PDR in *Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter* spp.

MDR: non-susceptible to ≥1 agent in 3 antimicrobial categories
XDR: non-susceptible to ≥1 agent in all but ≤2 categories
PDR: non-susceptible to all antimicrobial agents listed

Categories: Aminoglycosides, ES3,4-G cephalosporins, carbapenems, fluoroquinolones, glycylcyclines, phenicols, polymixins, etc.

MDR: multidrug-resistant
XDR: extensively drug-resistant
PDR: pandrug-resistant

Clin. Microbiol. Infect. 2012; 18: 268

WHO priority pathogens list for R&D of new antibiotics (2018)

- Hospitals
- Nursing homes
- Patients with medical devices

Priority 1: CRITICAL

***Acinetobacter baumannii*, carbapenem-resistant**
***Pseudomonas aeruginosa*, carbapenem-resistant**
***Enterobacteriaceae*, carbapenem-resistant, ESBL-producing**

Priority 2: HIGH

***Enterococcus faecium*, vancomycin-resistant**
***S. aureus*, methicillin-resistant, vancomycin-intermediate and resistant**
***Helicobacter pylori*, clarithromycin-resistant**
***Campylobacter* spp., fluoroquinolone-resistant**
***Salmonellae*, fluoroquinolone-resistant**
***N. gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant**

Priority 3: MEDIUM

***Streptococcus pneumoniae*, penicillin-non-susceptible**
***Haemophilus influenzae*, ampicillin-resistant**
***Shigella* spp., fluoroquinolone-resistant**

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

Innovation criteria

- **No cross-resistance**
- **New chemical class**
- **New target**
- **New mode of action**

A few actions to fight AMR: a one-health approach

- Increase of the knowledge of potential reservoirs of resistance genes and efficiency of transmission
- Development of rapid diagnostic techniques
- Development of alternative treatments and vaccines
- Development of efficient intervention measures
- Discovery of novel antibacterial molecules

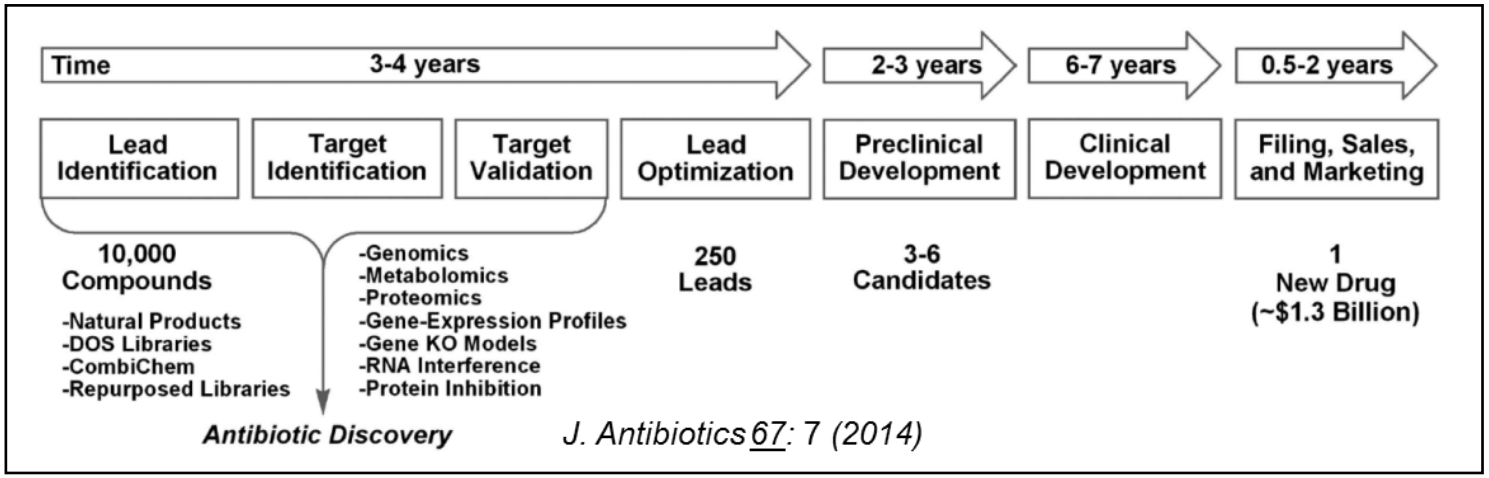
→ **Promotion of antimicrobial stewardship / Decrease of antibacterial consumption**

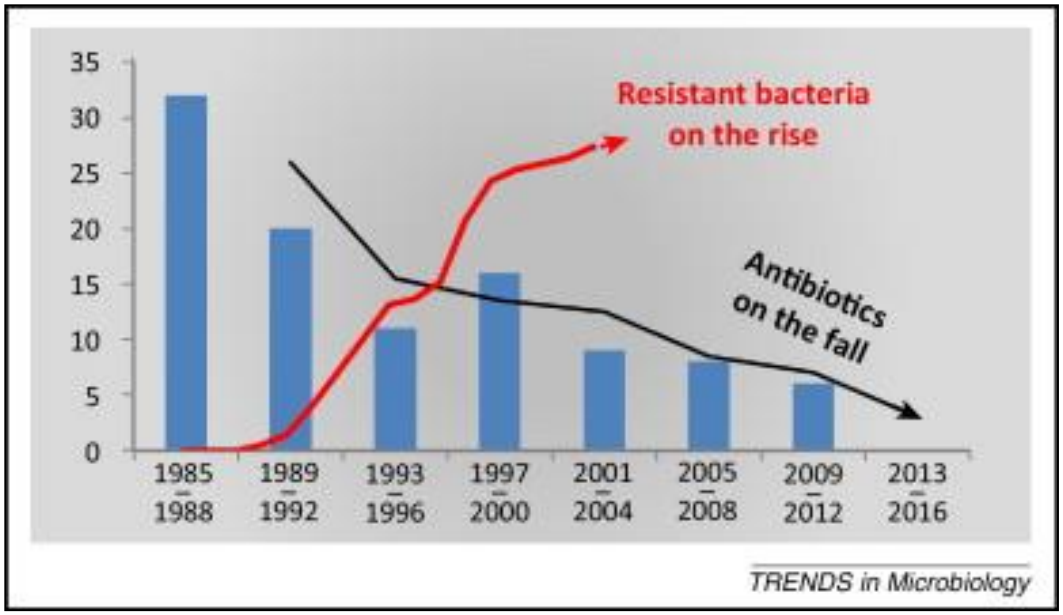
Identification and development of novel antibiotics are dramatically slow

- **Difficult research strategies**
- **Financial gaps between lead identification and pre-clinical, clinical research, introduction into the market**
- **Cost of clinical research**
- **20-year life of a patent**
- **Potential competition between new dugs**
- **Low to modest interest of pharmaceutical companies**
- **…**

GAIN Act: Generating Antibiotic Incentives Now

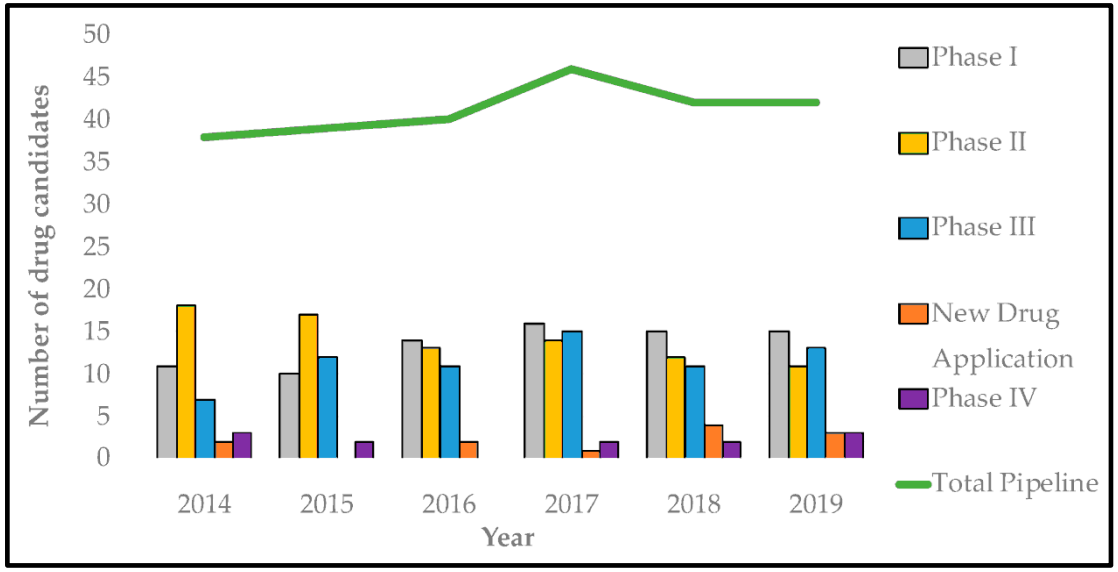
Antibiotic discovery: the long way from the lead to marketing





Reverse development of new antibiotics versus resistant bacteria.

Evolution of the total antibiotic pipeline and the antibiotic pipeline by stage of development



Ribeiro da Cunha, B. et al.; Antibiotics 2019, 8: 45

Agents with market authorization

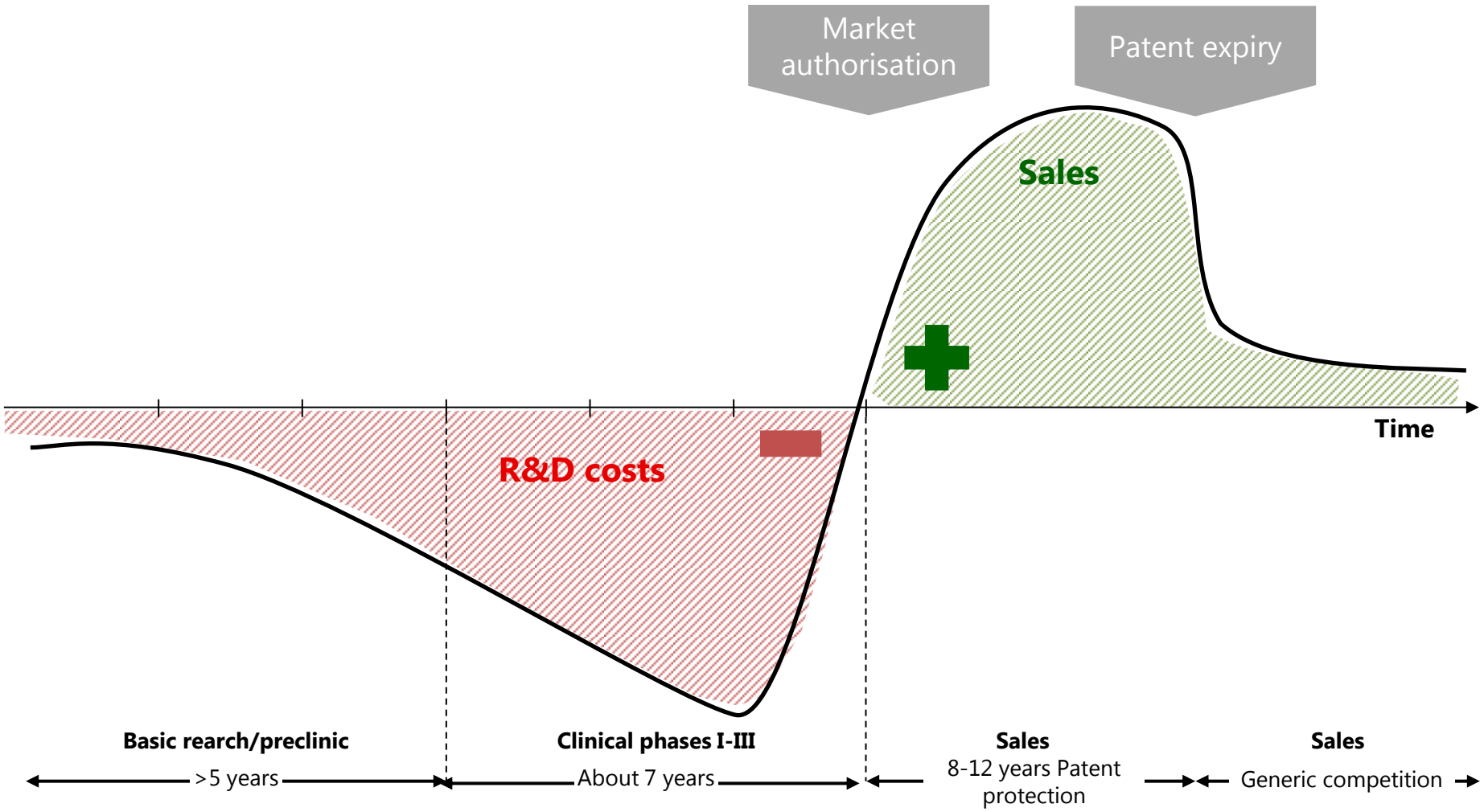
Table 1. Antibiotics and combinations containing a new chemical entity that have gained market authorization since June 2017

Name (trade name)	Approved by (date)	Antibiotic class	Route of administration (market authorization holder)	Expected activity against priority pathogens				Innovation			
				CRAB	CRPA	CRE	OPP	NCR	CC	T	MoA
Delafloxacin (Baxdela)	FDA (6/2017)	Fluoroquinolone	iv & oral (Melinta)	○	○	○	●	–	–	–	–
Vaborbactam + meropenem (Vabomere)	FDA (8/2017)	Boronate BLI + carbapenem	iv (Melinta)	○	○	●[1]	/	?	✓	–	–
Plazomicin (Zemdri)	FDA (6/2018)	Aminoglycoside	iv (Achaogen)	○	○	●	/	–	–	–	–

Pathogen activity: ● *active;* **?** *possibly active;* ○ *not or insufficiently active;* **/** *activity not assessed as the antibiotic is focused and developed for only either Gram-positive cocci or Gram-negative rods.*
Innovation assessment: ✓ *criterion fulfilled;* **?** *inconclusive data or no agreement among the advisory group;* – *criterion not fulfilled.*
Abbreviations: *BLI, β-lactamase inhibitor; CC, new chemical class; CRAB, A. baumannii, carbapenem-resistant; CRE, Enterobacteriaceae-, carbapenem- and third-generation cephalosporin-resistant; CRPA, P. aeruginosa-, carbapenem-resistant; FDA, Food and Drug Administration; iv, intravenous; MoA, new mode of action; NCR, no cross-resistance to other antibiotic classes; OPP, other priority pathogens on the WHO priority pathogens list (PPL) ("high" and "medium" priority); T, new target.*
Underlined agents: *New chemical class.*
[1] *Active against K. pneumoniae carbapenemase (KPC) but not metallo-β-lactamase-producing Enterobacteriaceae.*

Novartis drops antibiotic development program

Expenses and earnings structure over the lifecycle of a normal drug (non-antibiotics)

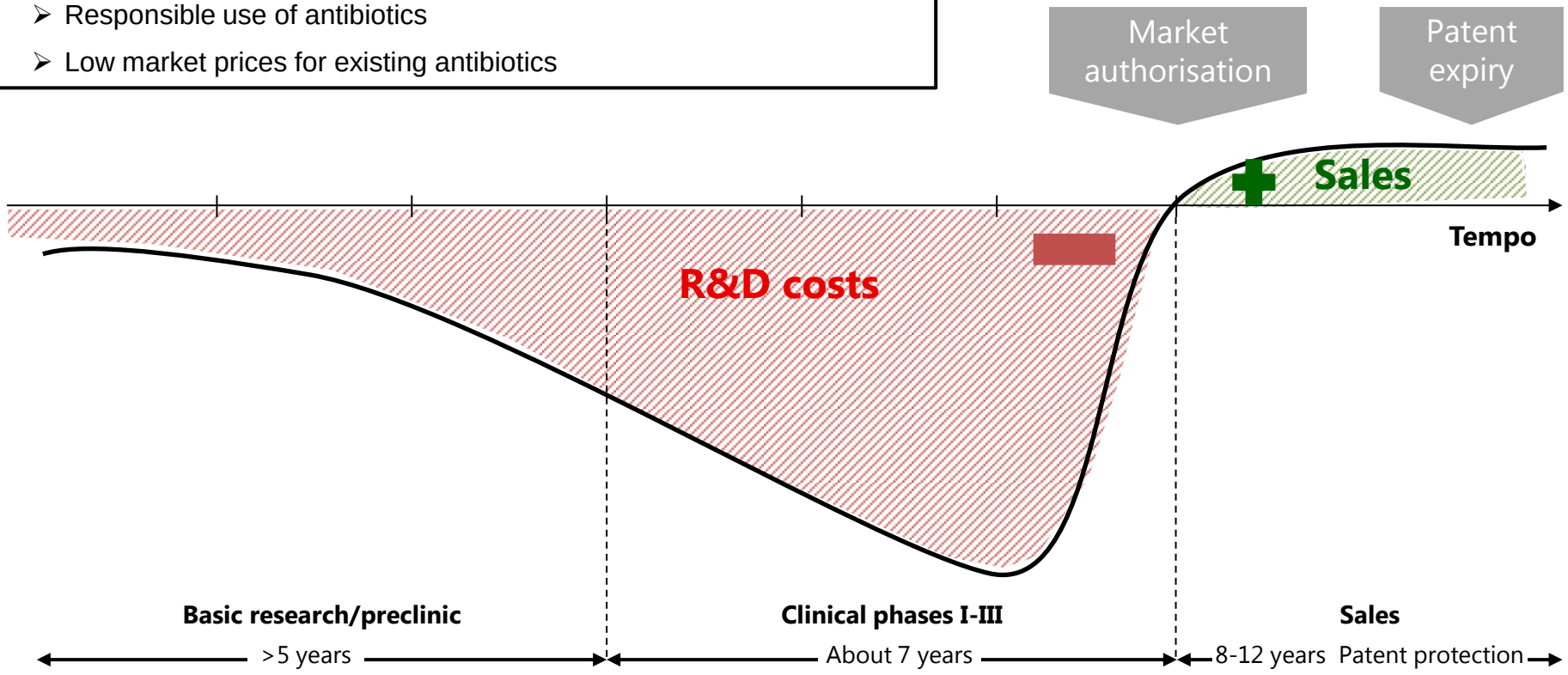


Courtesy of R. Blankart, Bern

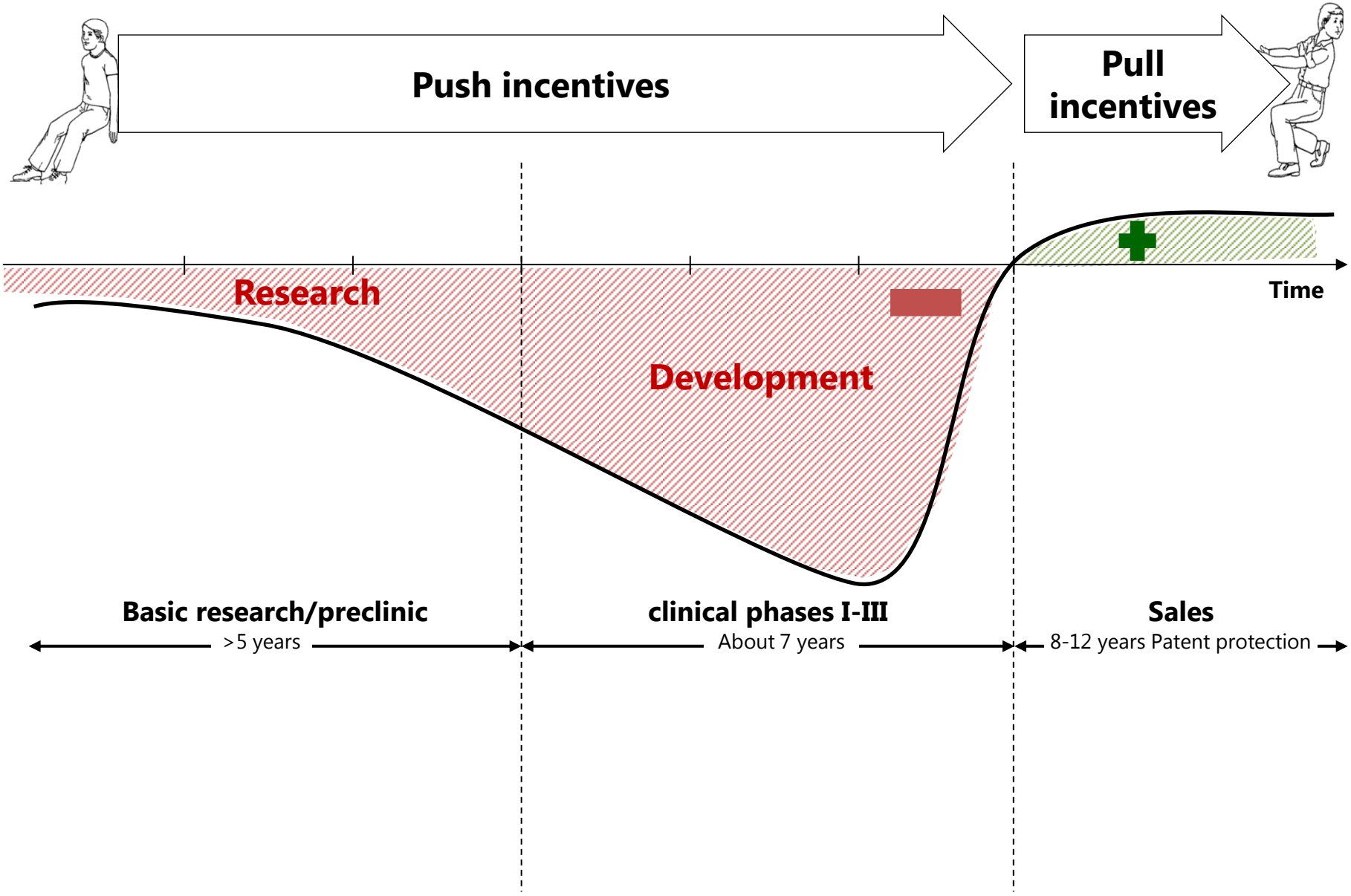
Expenses and earnings structure over the lifecycle of an antibiotic

Reasons for market failure:

- Link between the use of antibiotics and the development of resistance
- Low incentives for R&D
- Responsible use of antibiotics
- Low market prices for existing antibiotics



Courtesy of R. Blankart, Bern



The government should take regulatory actions in order to achieve a socially desirable result.

Courtesy of R. Blankart, Bern

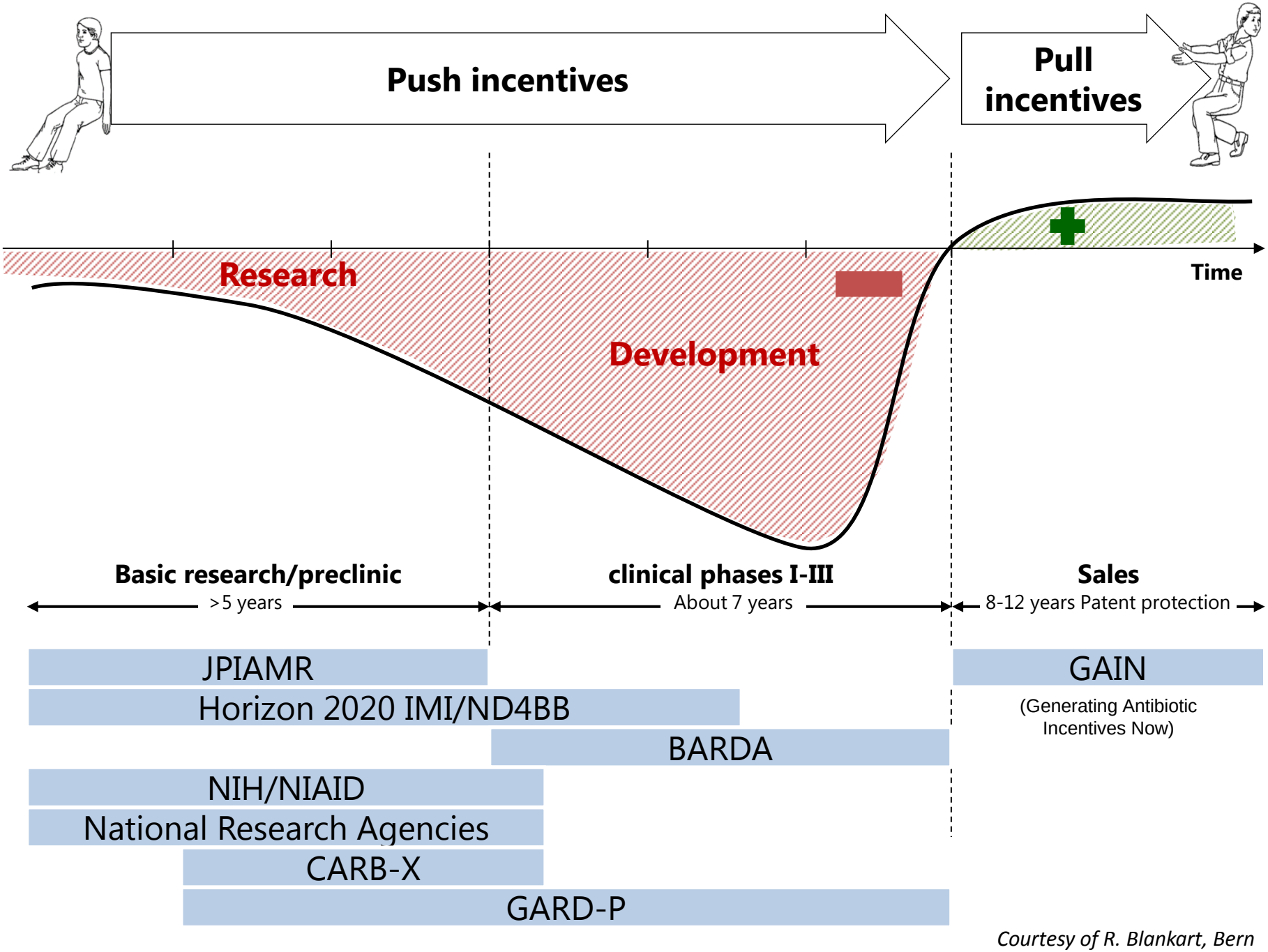
Push and Pull incentives

- **Push incentives aim to promote projects in the R&D phase**
- **Pull incentives aim to replace the incentives normally generated by the sales of drugs in the market**

- **Push incentives fund inputs; push strategies should focus on cultivating partnerships and collaborations**
- **Pull incentives fund or reward outputs; pull strategies should focus on increasing market sustainability**

J. Guyton, PRTM

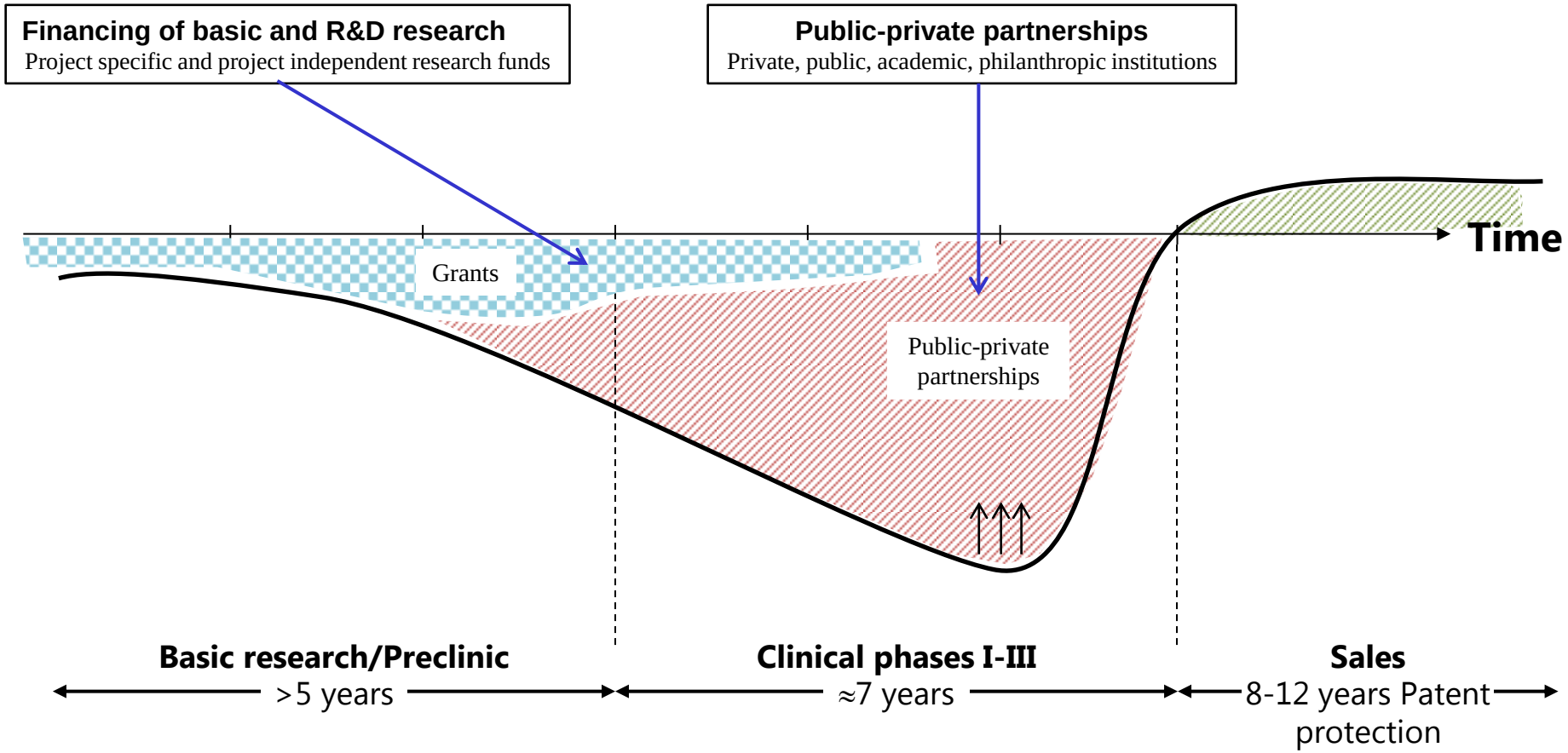
Pull incentives can be designed so that the rewards to companies are not based solely on sales volume, thus reducing the incentive to maximize sales of a drug while under patent



Courtesy of R. Blankart, Bern

The government should take regulatory actions in order to achieve a socially desirable result.

Basic research is funded in particular at universities and university hospitals, as well as SME



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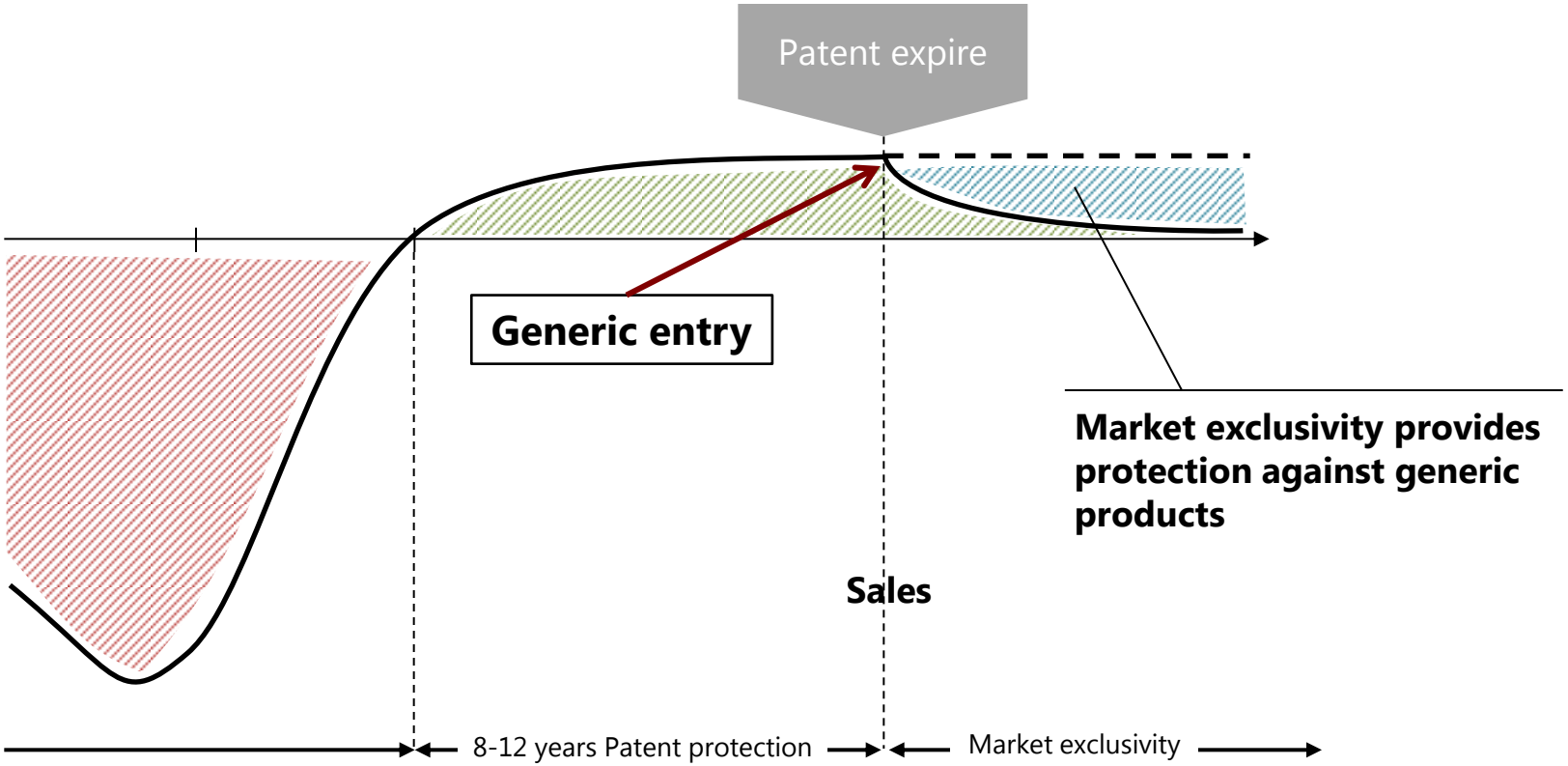
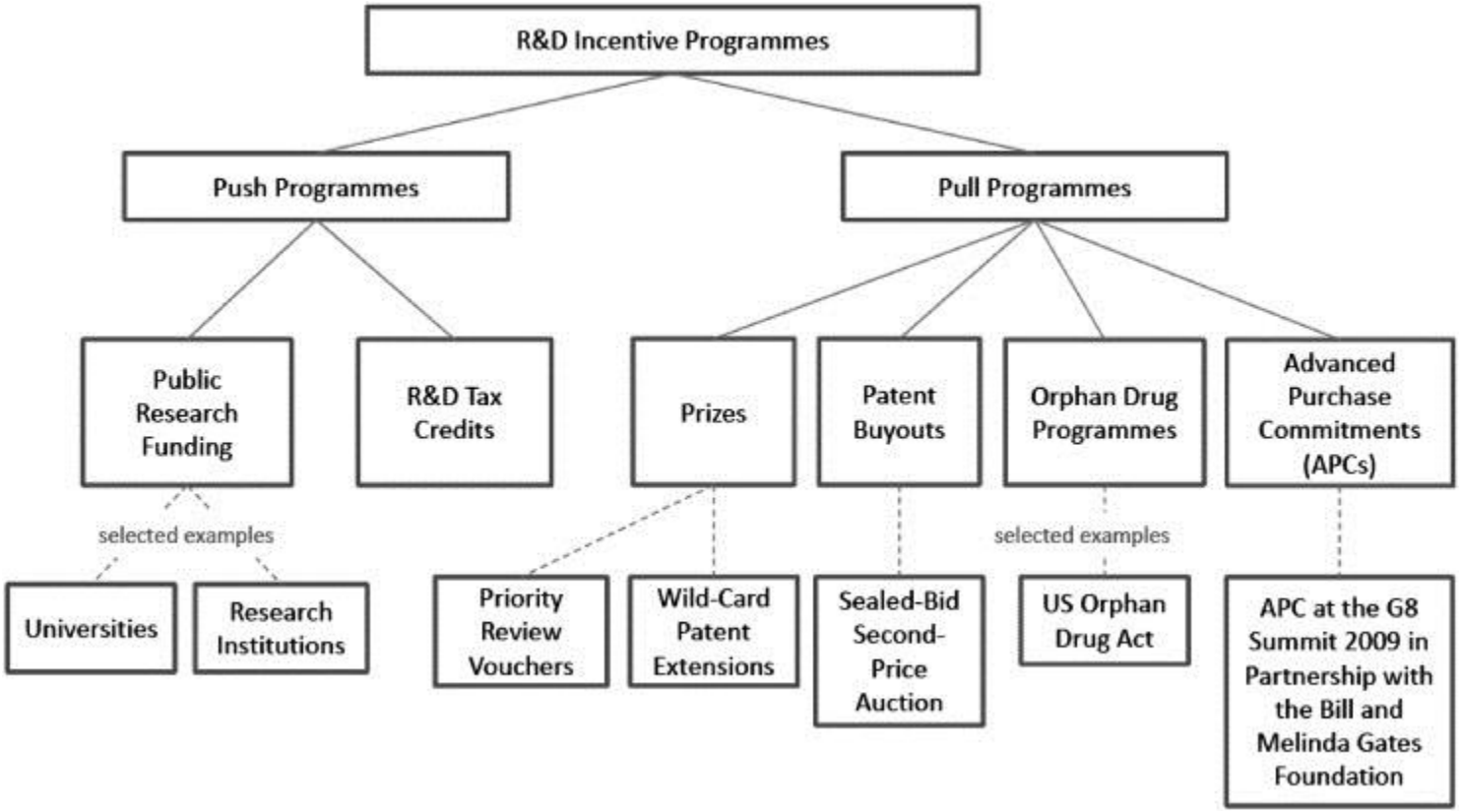
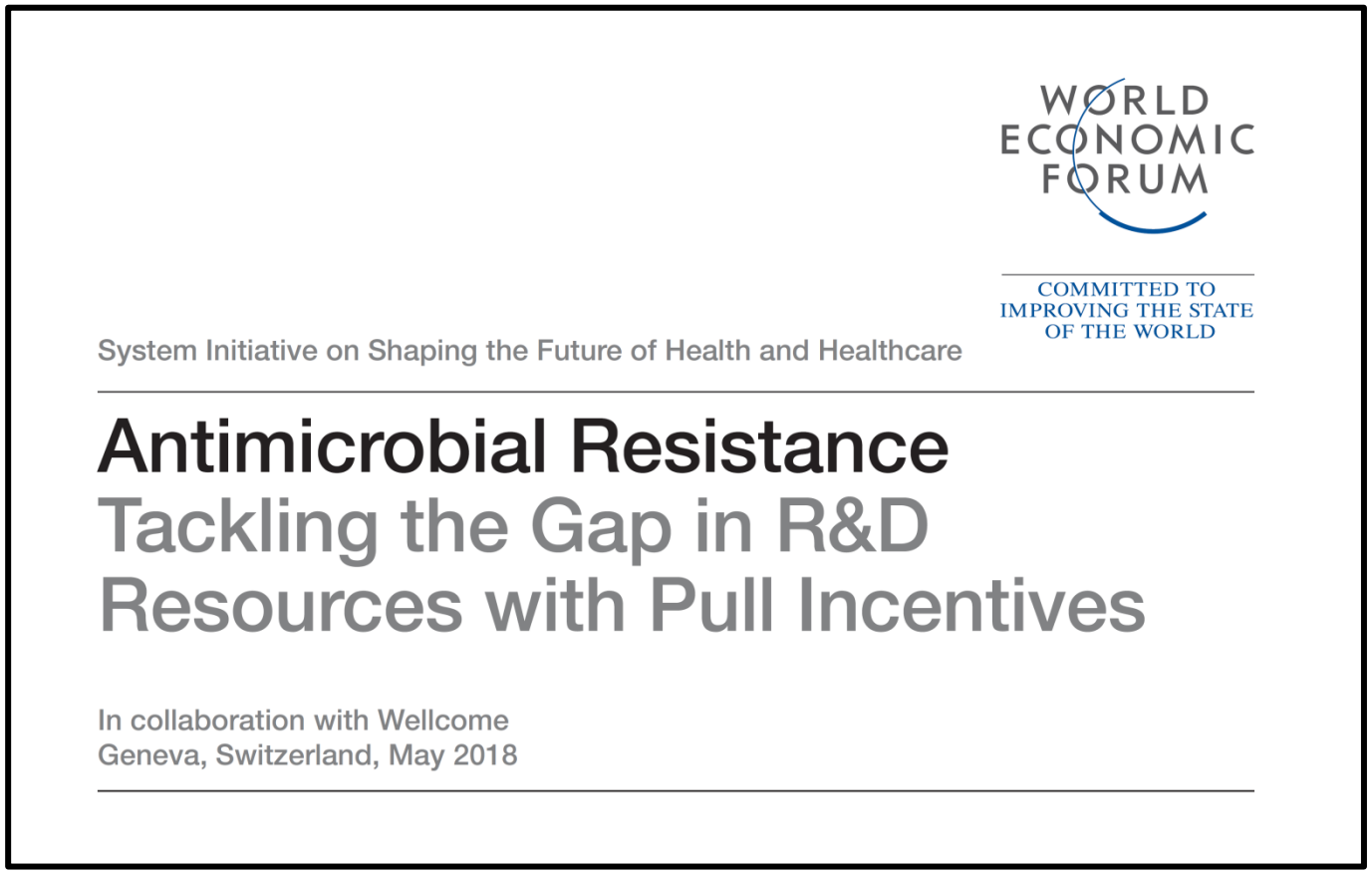
Pull incentives: effect of market exclusivity



Push and pull R&D incentive programmes and selected examples



Mueller-Langer F., Health Economics, Policy and Law (2013), 8:185–208



- An appropriate reward size
- An appropriate balance of risk between the private and public sectors
- Prioritization of development of antibiotics which meet public health priorities
- Enabling stewardship of new antibiotics
- Enabling availability and access to new antibiotics

Pull mechanisms

Summary

- **In addition to decrease the use of antibiotics (one-health approach), we urgently need new, innovative antimicrobials**
- **The current economic model to finance R&D up to the market should be revisited**
- **Public / Private partnership should be enhanced, considering mainly the interests of the community**
- **Politics should take charge of the issue!**
- **www.roundtableantibiotics.ch**

Appeal by science and industry to make more effective use of Switzerland's innovative capacity to fight antibiotic resistance and to develop new antibiotics

The increasing number of antimicrobial resistant infections, combined with the lack of new antimicrobial agents, is one of the greatest public health challenges of our time. While basic research identifies new potential antimicrobial molecules and develops rapid diagnostic tests, the translation of this knowledge into market-ready and cost-efficient products often fail due to the unanswered questions of financing and profitability.

ROUND TABLE ANTIBIOTICS

The Round Table on Antibiotics is an interdisciplinary group of experts in medicine, research and economics coming from almost all Swiss universities and polytechnic schools, as well as of committed personalities from industry. It aims to stimulate Switzerland's contribution to innovation, research and development in the field of antibiotic resistance, in particular by promoting the development and release to the market of new active antimicrobial drugs. The stagnating progresses in this area for decades show that the current approaches and the research programmes on national and international levels are not sufficient. The Round Table Antibiotics is firmly convinced of the need in Switzerland, as well as elsewhere, to better coordinate and expand the activities aimed to introduce and bring to the market new antimicrobials and new rapid diagnostic tests.