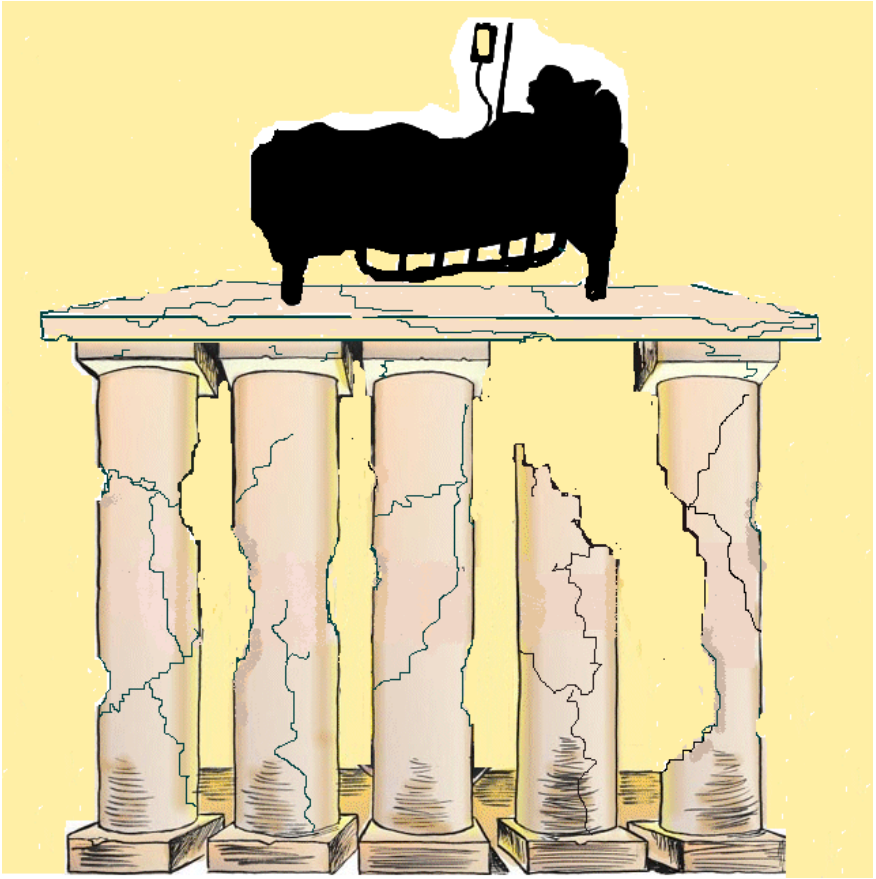
Are new antibiotics the solution?

Andreas Heddini, MD, PhD
Nordic Cluster Medical Lead



Modern medicine is built on access to effective antibiotics…

Source: ReAct; www.reactgroup.org

The antibiotic pipeline has been drying up…

Antibiotic susceptibility proportions for NDM-1-positive Enterobacteriaceae isolated in the UK and India

	UK (n=37)	Chennai (n=44)	Haryana (n=26)
Imipenem	0%	0%	0%
Meropenem	3%	3%	3%
Piperacillin-taz	0%	0%	0%
Cefotaxime	0%	0%	0%
Ceftazidime	0%	0%	0%
Cefpirome	0%	0%	0%
Aztreonam	11%	0%	8%
Ciprofloxacin	8%	8%	8%
Gentamicin	3%	3%	3%
Tobramycin	0%	0%	0%
Amikacin	0%	0%	0%
Minocycline	0%	0%	0%
Tigecycline	**64%**	**56%**	**67%**
Colistin	**89%**	**94%**	**100%**

From Kumarasamy *et al.* Lancet Infect Dis 2010

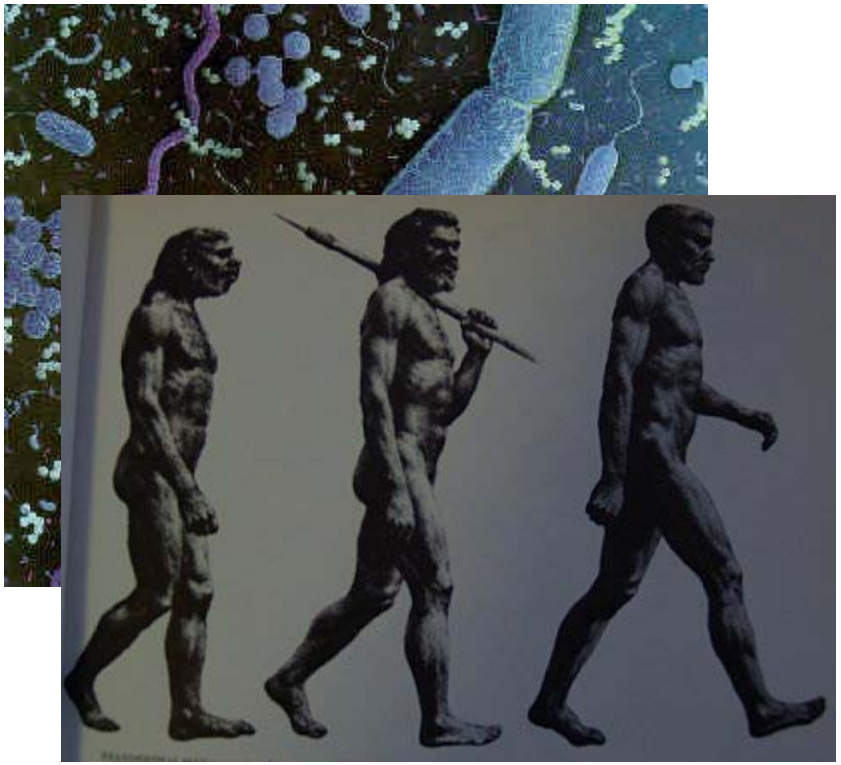
Development of antibiotics

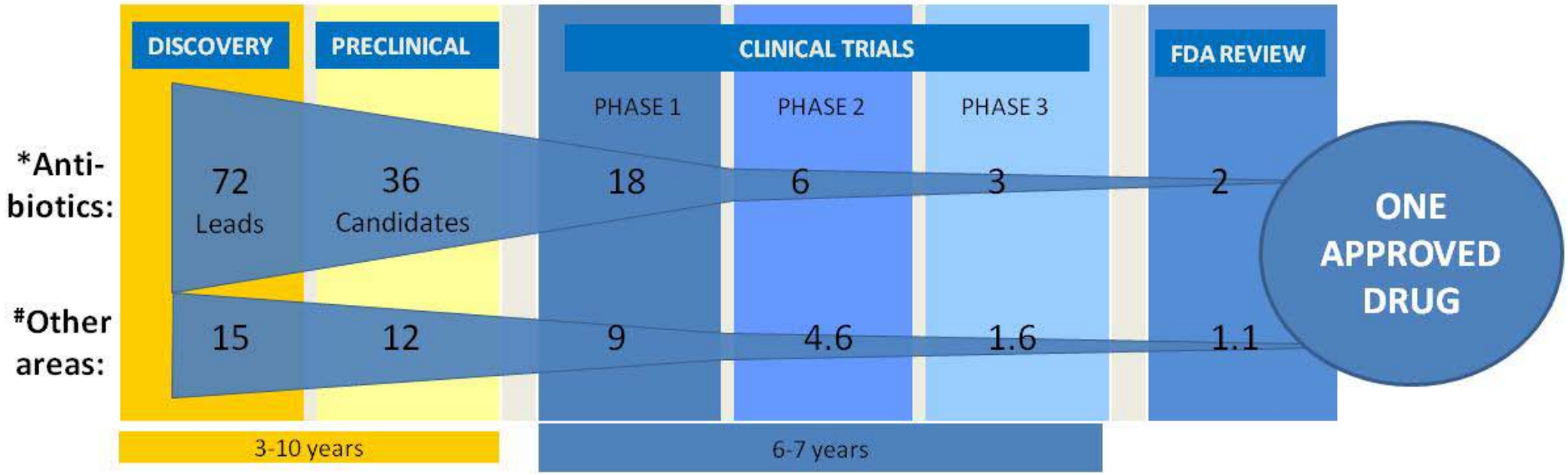
Wright D, *Nature Reviews Microbiology* **5**, 175-186, 2007

Why is it so difficult to develop novel antibiotics?

- Business model not appropriate
- Difficult to predict future needs
- Global problem
  - Balance access to medicines with rational use of antibiotics

➢ **<u>Significant scientific challenges</u>**




DISCOVERY
PRECLINICAL
CLINICAL TRIALS
PHASE 1
PHASE 2
PHASE 3
FDA REVIEW
*Anti-biotics:
72 Leads
36 Candidates
18
6
3
2
#Other areas:
15
12
9
4.6
1.6
1.1
ONE APPROVED DRUG
3-10 years
6-7 years

Other options

Other novel antibacterials:

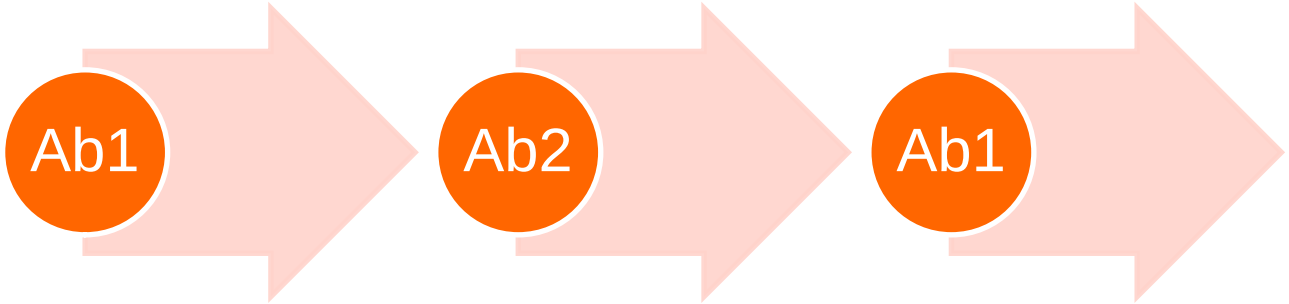
- Antibacterial peptides
  - Often short half-life, making them unsuitable for systemic use
  - Toxic
- Bacteriophages
- Small molecules
  - E.g. inhibiting virulence factors (would leave normal flora unharmed), TTS, QS, adhesion etc
- ?

Strategies for preserving drug efficacy

- Dosage based on revisiting pharmacokinetic (pk) and pharmacodynamic (pd) principles
  - Exposure over time
- Finding the right dose for old antibiotics
  - Obtain exposure-response relationships
  - Re-evaluate registration and indication for available antibiotics
  - Create a mandatory process of re-evaluating indications and dosing, e.g. 5-year intervals

Antibiotic cycling?

- Rotation of one class of antibiotics with one or more different classes exhibiting comparable spectra of activity



- Time needs to be many years (at least 2-3 yrs, probably longer)
- Disappointing results so far; resistance genes seem not to be easily lost
- Necessary to apply when introducing new antibiotics?

Requirements

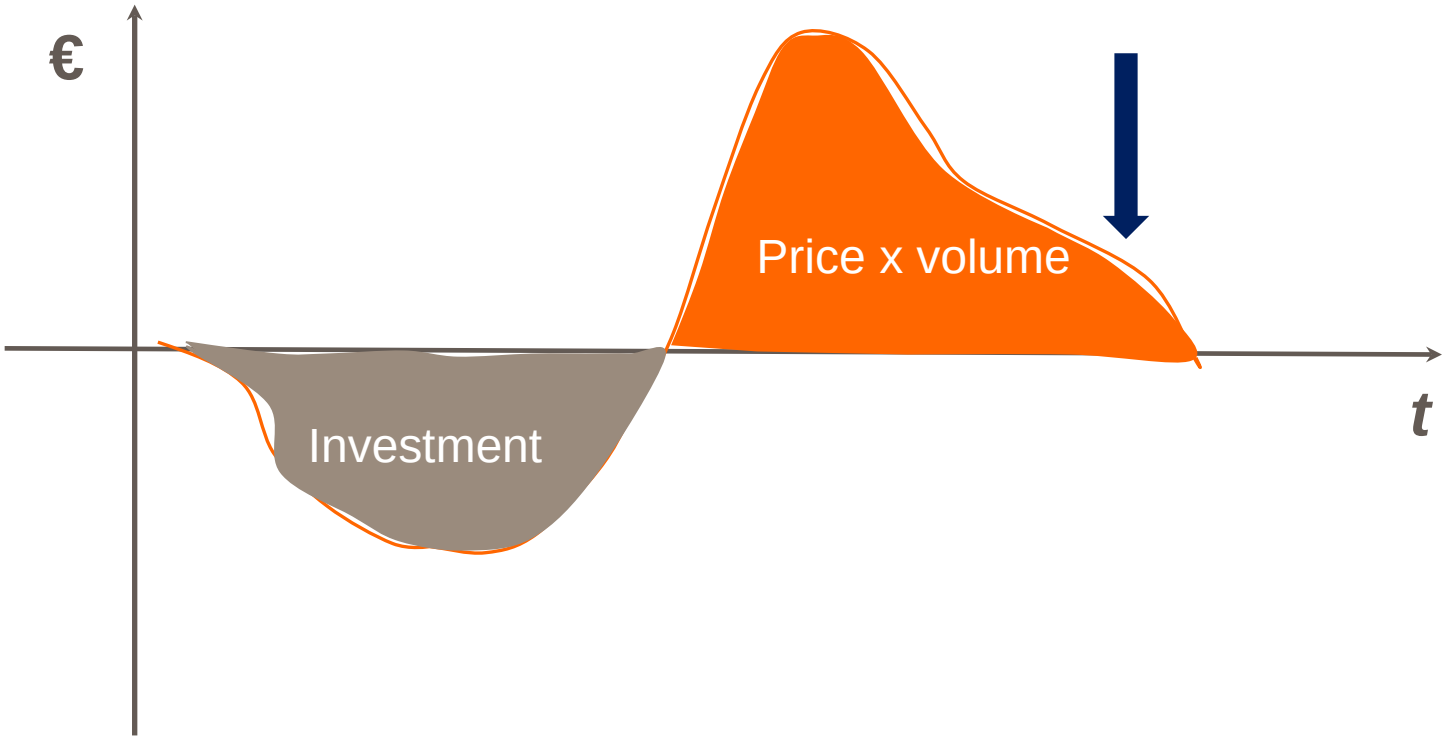
- A sustained, systematic effort of discovery and development – many years
- Financing mechanisms for clinical trials?
- A mechanism for prioritizing amongst different antibiotics, diagnostics and other health technologies needs to be based on:
  - Surveillance -> information on global prevalence of resistant pathogens
  - Predictions, modelling and analyses of trends

Reasons for optimism

- Regulatory agencies
  - New routes for faster approval
- Public sector, governments, agencies & legislation
  - PPPs, e.g. IMI
- Media, international health organisations, NGOs etc
  - Advocacy, stimulate discussion on solutions
- Academia
  - Research efforts
- Industry
  - New openness and new ways of working

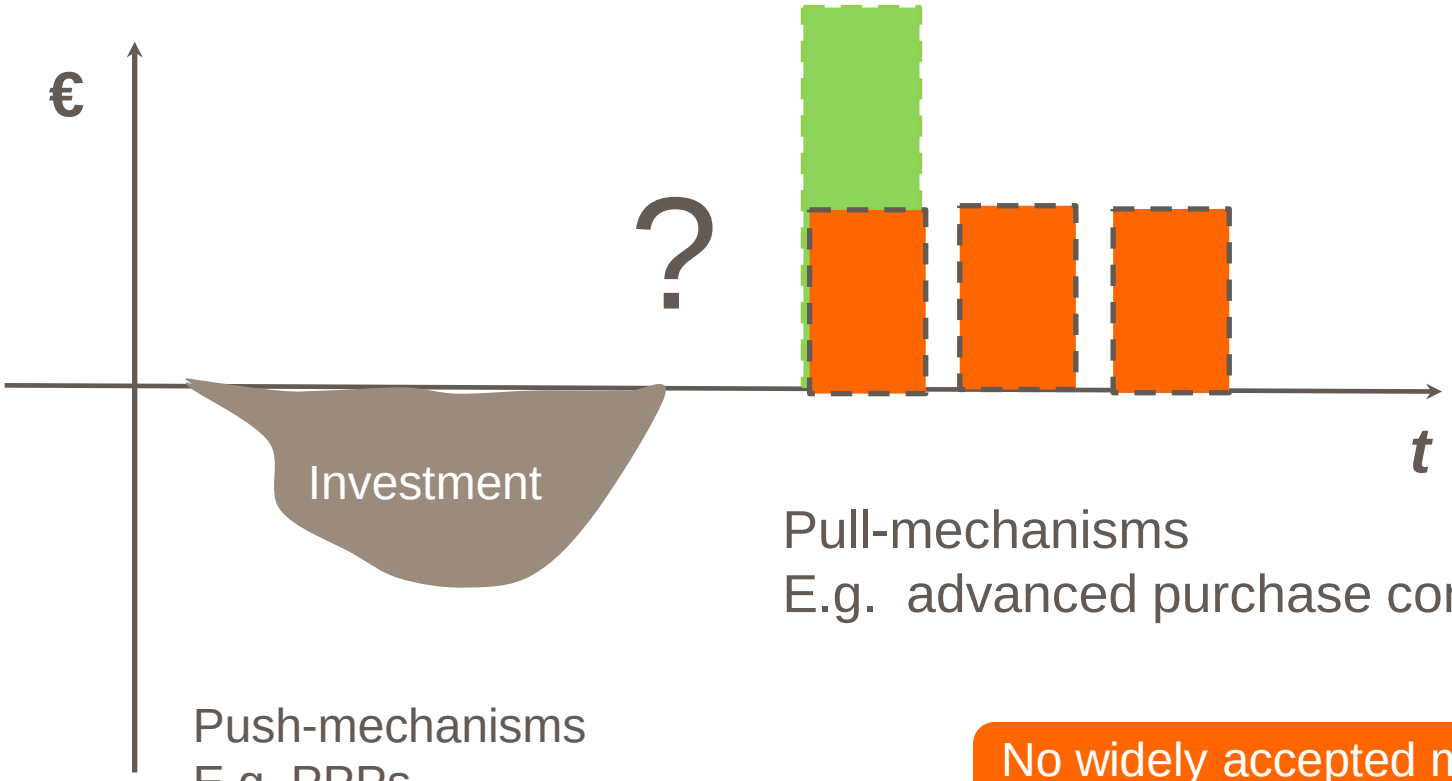
Need for new business model

- Traditionally:



Need for new business model – ”de-linkage”

- De-link R&D investments from marketing and sales



Pull-mechanisms
E.g. advanced purchase commitments

Push-mechanisms
E.g. PPPs
Cooperation, reduce risk

No widely accepted model exists today!

Key strategies to ~~stop~~ manage antibiotic resistance

- Minimize irrational use of antibiotics
  - Measure resistance and use
  - Promote rational use
  - Animal use

- Prevent infections and bacterial spread
  - Hospital hygiene
  - Agriculture and animal industry

- Development of new antibiotics and alternatives, including new diagnostic tools

How shall novel antibiotics be made available?

- In parallell with the process to develop new antibiotics we need mechanisms to make potential new drugs available in a *controlled* manner
- At the same time *access* for those in need must be addressed
- Global problem – needs global solutions!

Image: Christine Daniloff