The Antibiotic Pipeline
What Can we Expect?

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The antibiotic era

- **1950-60s**: Small spectrum
  - Gram positive
  - Gram negative

- **1970-90s**: Broad spectrum
  - Gram positive
  - Gram negative

- **2000s**: Small spectrum
  - Gram positive
  - Gram negative (targeted)

- **2010s**: Small spectrum
  - Gram positive

- **Golden years of pills and profits**
  - Fixing selected resistance problems

- **Natural products**
- **Medicinal chemistry, Semisynthetic products**
- **Target based**
- **Natural products? Alternative approaches?**

MS Kinch et al: Drug Discovery Today 2014, 19 (9)
Novel antibiotics and derivates

QUARTZ, Keith Collins
New antibiotics approved by the FDA but subsequently withdrawn or discontinued, 1980-2009

Outterson et al 2013
Recent approvals

FDA approvals

- **Linezolid**
- **Daptomycin**
- **Ceftaroline**
- **Telavancin**
- **Fidaxomicin**
- **Ceftolozane+Tazobactam**
- **Ceftazidine+Avibactam**
- **Tedizolid**
- **Oritavancin**
- **Dalbavancin**

Drugs and their approvals over time:

- Gram-positive: Linezolid, Daptomycin, Ceftaroline, Telavancin, Fidaxomicin
- Gram-negative: Ceftolozane+Tazobactam, Ceftazidine+Avibactam
- Other: Tedizolid, Oritavancin, Dalbavancin
Extensively resistant Gram-negatives

Percentage of carbapenem-resistant Klebsiella, 2011-2014
Medical need

Major public health needs to address bacterial resistance

- Extensively drug-resistant Gram-negative bacteria
  - Klebsiella, E. coli, Pseudomonas, Acinetobacter
  - Critically ill patients

- Carbapenem-sparing treatment, i.v., oral
  - Klebsiella, E. coli, other Enterobacteriaceae
  - Urinary tract infections due to multi-drug resistant bacteria
  - Infections due to ESBL producers

- Specific indications
  - E.g. oral antibiotic against gonorrhoea
What to expect?

Gram-positive

Ph 1
Ph 2
Ph 3

old
new
What to expect?

Gram-negative

- Ph 1
- Ph 2
- Ph 3

old  new
β-Lactamase Inhibitors

Class ACD | Class B
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Preclinical: 4 | 1
Discovery: 3 | 2
Phase 1: 3 | 1
Phase 2: 1 | 1
Phase 3: 1 | 1
What to expect?

C. difficile

Ph 1  Ph 2  Ph 3

old  new
Antibacterial R&D pipelines

- New classes against MDR Gram-negative bacteria intended for systemic use (mostly research)
- New classes against MDR Gram-positive bacteria intended for systemic use; Mycobacterium tuberculosis
- Old class: Improving well-known classes or repurposing approved drugs, combinations
- C. difficile: different approaches
Antibacterial R&D pipelines

- Potentiators (mostly beta-lactamase inhibitors, resistance modifying) and adjunctive therapies
- Topical drugs incl. inhalation, mostly skin/wound formulations, OTC
- Vaccines, antibodies against MDR bacteria
- Immunsystem or microbiome modifying strategies
- Phage cocktails, modified phages or phage products
- Discovery or screening platforms
Where is innovation coming from?

- **Basic research:** Universities

- **Drug discovery**
  - SMEs
  - Publicly funded research institutes (Institute Pasteur, Frauenhofer, Deutsches Zentrum für Infektionsforschung,...)
  - Public-Private-Partnerships (Bioaster, IMI Lead factory,...)
  - Big Pharma
    Small scale teams: GSK, Novartis, Merck, Genentech
    Discovery partnerships: Roche, Sanofi-Aventis
Current antibacterial pipelines

Scientific challenges

Research
Drug discovery

Alternative approaches, modifications
Quantity vs need

Economic models
Clinical evidence
Pipelines are insufficient

Discrepancy between antibiotic R&D pipelines and public health needs

Scientific challenges

Economic model