Redeveloping Old Antibiotics
European Initiative

U. Theuretzbacher
Center for Anti-Inf ective Agents, Vienna, Austria

Reviving old antibiotics
Reviving old antibiotics: how old?

Approved in:
- Japan 1951
- Europe 1959
(Science Laboratories Roger Bellon → Rhône-Poulenc + Hoechst = Aventis + Sanofi-Synthelabo → SanofiAventis)
- US 1962

Why revive old antibiotics?

- 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
Typical knowledge gaps

- 1962 FDA approves a marketing application
- 1981 FDA requires preclinical testing before clinical trials
- Europe: National agencies
- EMA since 1995

- Dosage regimens
- PK
- PK/PD – exposure-effect relationships
- Clinical efficacy
- Safety

Reviving old antibiotics: anti-resistance strategies

(1) improving our surveillance of the rise of antibiotic-resistant bacteria to enable effective response, stop outbreaks, and limit the spread of antibiotic-resistant organisms, and acting on surveillance data to implement appropriate infection control;

(2) increasing the longevity of current antibiotics, by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria and scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics;

(3) increasing the rate at which new antibiotics, as well as other interventions, are discovered and developed.
Re-developing process

- Prioritize
- Identify the knowledge gaps, assess quality of information
- Form collaborative groups with extensive complementary skills
- Assure public funding
- Use cutting-edge methods to close the knowledge gaps
- Create an open information and data hub

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Re-developing process

- Disseminate and communicate to all stakeholders
- Share knowledge with regulatory agencies
- Produce guidelines
- Monitor appropriate use, organize resistance surveillance programs
AIDA: “Re-developing” of old antibiotics

14 partners from 11 different countries, complimentary expertise

Example AIDA:
- critically ill patients
- outpatients
- nursing home patients

Colistin
Nitrofurantoin
Fosfomycin trometamol
Rifampicin
Minocycline oral

http://www.aida-project.eu
“Re-developing” of old antibiotics: Principles
http://www.aida-project.eu

Aims:
- Dosing recommendations
- Efficacy (superiority, non-inferiority)
- PK
- Safety
- Combination therapy
- Emergence of resistance
- Breakpoints
- Valid comparators for new antibiotics

Non-clinical
Single drugs, combinations
PK/PD index
magnitude
exposure-res

population PK
exposure relationships
- exposure-clinical outcome
- exposure-safety
- exposure-res
MCS, PTA

PK
- sparse
sampling

RCT
endpoints
- microbiol
- clinical
  - efficacy
  - safety
  - res

microbiol
- res mechan
- colonisation

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Conclusion

- Using old antibiotics without updating knowledge may harm patients
- Coordinated process for „re-developing“ is necessary
- Integrate preclinical and clinical studies
- Translate evidence-based study results to clinical practice