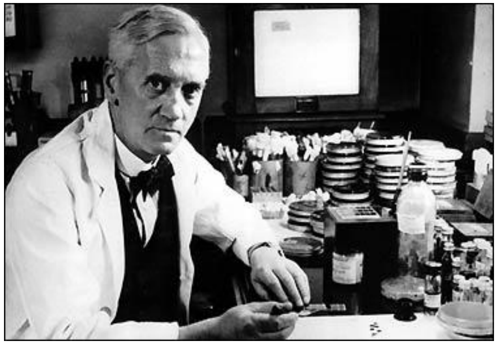
Specific a and empiric therapy

Otakar Nyč

The modern history of antibiotic begins…



- Fleming changed the course of history
- Mould contaminated an experiment – contained penicillin
- Killed the *Staphylococcus aureus* that had been growing in the dish
- Penicillin altered the treatment of bacterial infections
- Discovery of antibiotics – revolutionary event that saved millions of lives

1928, Sir Alexander Fleming

“When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer. But I suppose that was exactly what I did.”

20^{th} Century

- Golden age of antibiotics
  - Discovery
  - Development
  - Clinical exploitation
- Arguably the most significant medical advance of the century
- Considerable pharmaceutical investment
  - 11 distinct antibiotic classes
  - >270 antibiotics in clinical use

21st Century

- Prospects of a post-antibiotic era?
- Evolving resistance with antibiotic use
- Emergence of superbugs
- Unmet needs of the hospital treatment market

BBC NEWS

HEALTH

David Cameron calls for action on antibiotic resistance

2 July 2014 Last updated at 02:14 BST

FACT SHEET: Obama Administration Takes Actions to Combat Antibiotic-Resistant Bacteria

BBC NEWS

HEALTH

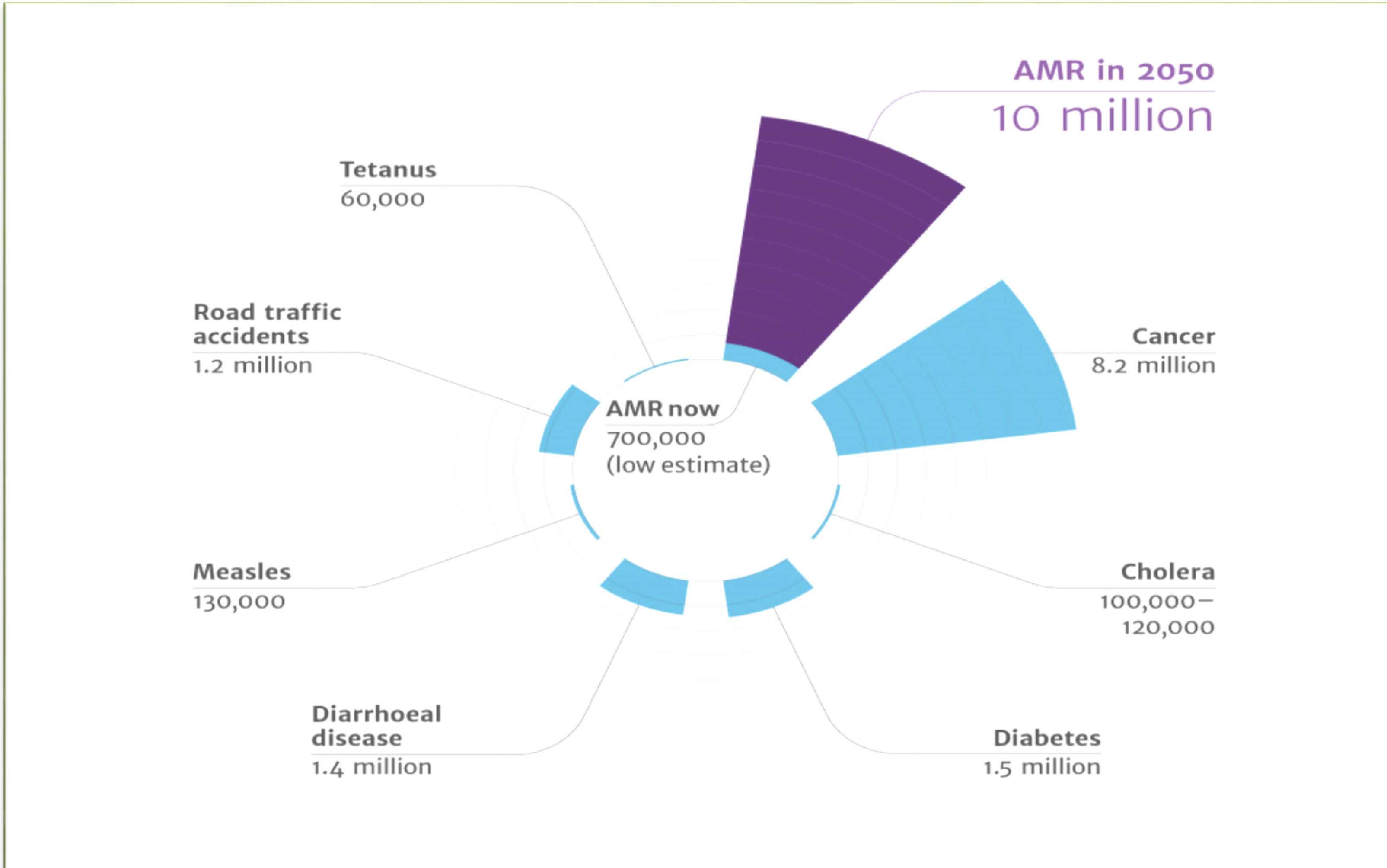
30 April 2014 Last updated at 13:05

Antibiotic resistance now 'global threat', WHO warns

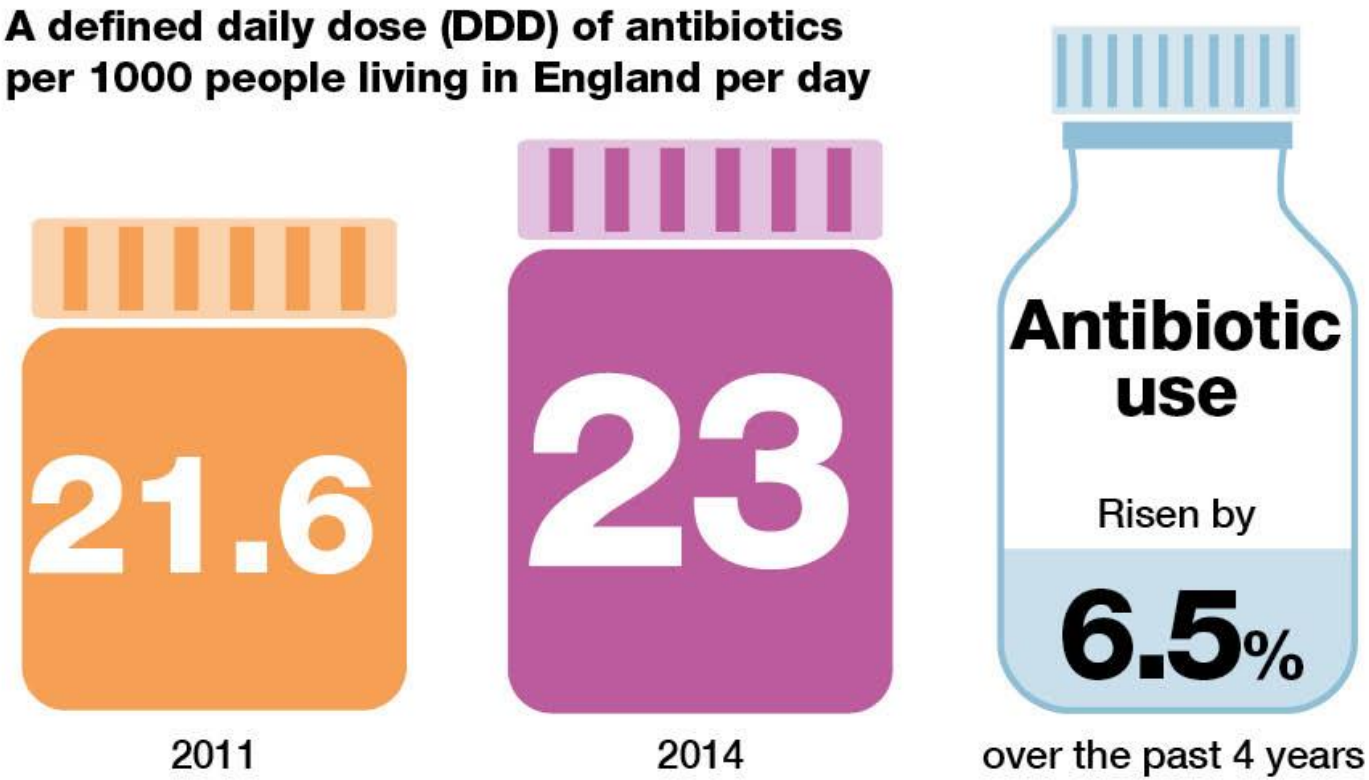
theguardian

Call for new generation of antibiotics to fight off superbugs

- Antibiotic **resistance** (AMR) is increasing….



Consumption of antibiotics…



Worldwide 2000 -2010 by 36 %…. human medicine and veterinary medicine, agriculture

https://www.gov.uk/government/organisations/public-health-england

The main problem…

- 40 – 50 % of all antibiotic are uses unnecessarily or inappropriately

Unnecessary administration

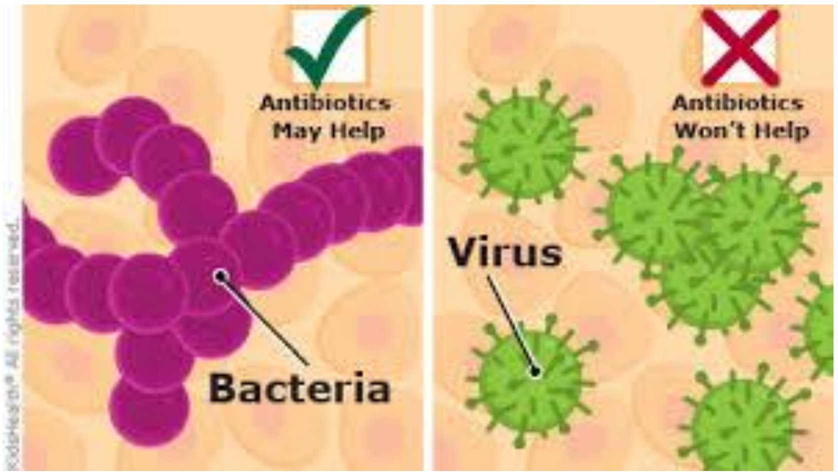
- **40 - 50% used unnecessarily or badly**
- treatment of viral infections
- use of antibiotics in the prevention
- treatment of fever (antipyretics x antibiotics)
- Treatment of positive serological findings .. mycoplasma, Lyme...

Bad use of antibiotics

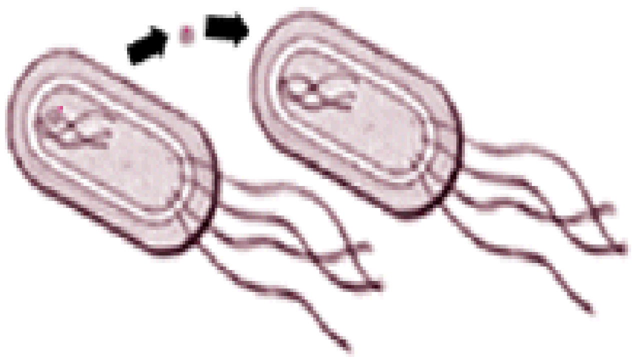
- unworthy choice - unnecessarily broad spectrum
- long duration of administration
- inappropriate application interval
- wrong (low) dose …

STOP THE OVERUSE OF ANTIBIOTICS

"This is America. It seems to rain antibiotics."



Bacterial evolution and resistance - natural defense process



- Adult humans contains 10^{14} cells, only 10% are human – the rest are bacteria
- Antibiotic use promotes Darwinian selection of resistant bacterial species
- Bacteria have efficient mechanisms of genetic transfer – this spreads resistance
- Bacteria double every 20 minutes,
- Bacterial adaptation to changing conditions
- Development of new antibiotics has slowed – resistant microorganisms are increasing

Antibiotic resistance…

- Antibiotic resistance develops
  - Through natural mutations of bacterial genes
  - Through transfer of resistance genes between different bacteria via plasmids, transposons, etc.
- If a bacterial population with newly resistant bacteria are exposed to a specific antibiotic, they will be selected and develop a new resistant strain

Resistance

- Hospitals
  - vancomycin-resistant enterococci (VRE’s)
  - multi-resistant *Staph. aureus* (MRSA)
  - multi-resistant *Enterobactericeae, Pseudomonas* aeruginosa..NF gram negative rods

Gram-negative superbugs

Resistant Gram-negative bacteria terminology	
ESBL-producing Enterobacteriaceae	Extended spectrum beta-lactamases producing Enterobacteriaceae, e.g. Escherichia coli, Klebsiella pneumoniae
CPE	carbapenemase-producing Enterobacteriaceae….
MRPA (MDR-PA)	Multidrug resistant Pseudomonas aeruginosa
MRAB (MDR-AB)	Multidrug resistant Acinetobacter baumannii
	Pan-resistant Pseudomonas aeruginosa / Acinetobacter baumannii

Gram-pozitive superbugs

Resistant Gram-positive bacteria terminology	
PRSP	Penicillin resistant Streptococcus pneumoniae
MDRSP	Multidrug resistant Streptococcus pneumoniae
MRSA	Methicillin resistant Staphylococcus aureus
VRSA	Vancomycin resistant Staphylococcus aureus
VISA (GISA)	Vancomycin (Glycopeptide) intermediate Staphylococcus aureus
VRE (GRE)	Vancomycin (Glycopeptide) resistant Enterococcus

Polymixin

- Colistin (polymixin E) : **An example of antimicrobial resistance**
- The antibiotic colistin is a prime example of increasing antimicrobial resistance (AMR). For many years it was rarely used on humans because of its harmful effects on the kidneys, although it has been used extensively in **veterinary medicine**. In recent years, however, colistin has again become a last-resort treatment for some patients with specific hard-to-treat bacterial infections. Worryingly, and reflecting the decreasing efficacy of antibiotics in general, the effectiveness of colistin is now also diminishing.

  In November 2015, scientists announced the emergence of **E. coli bacteria in China carrying the mcr-1 gene**, which makes bacteria resistant to colistin. An infection with E. coli bacteria can cause gastroenteritis and even kidney failure. A study in The Lancet medical journal describes this as the ‘breach of the last group of antibiotics’. A woman from Pennsylvania in the US was also found with E. coli bacteria carrying the mcr-1 gene, although the patient proved not to be resistant to all antibiotics. As scientists have succeeded in transferring this colistin resistance to other bacteria, they are now more concerned than ever before that **pan-resistant bacteria could develop**

The consequences of antibiotic resistance

- Increased morbidity & mortality
  - "best-guess" therapy may fail with the patient's condition deteriorating before susceptibility results are available
  - no antibiotics left to treat certain infections
- Greater health care costs
  - more investigations
  - more expensive, toxic antimicrobials required
  - expensive barrier nursing, isolation, procedures, etc.
- Therapy priced out of the reach of some third-world countries

Clinical impact of resistance

- Increased morbidity
- Increased mortality
- Extended hospital stay
- Increased admission to intensive care
- Loss of bed days

Resistance and limitations in the development of key medical disciplines

- As immunosuppressive diseases and use of immunosuppressive agents become more prevalent, opportunistic infections becomes more common, esp. by organisms rarely encountered previously
  - Diseases: e.g. HIV, leukemia
  - Drugs: e.g. in solid organ transplants, bone marrow transplants, rheumatoid disorders
  - Critical patients in intensive care…
- untreatable opportunistic infections !
- stagnation in the development of leading medical fields

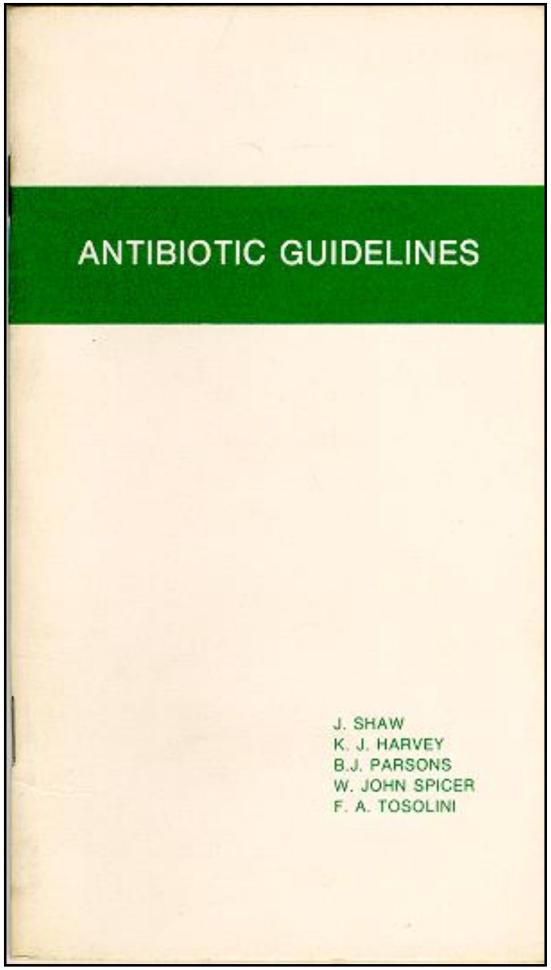
Social factors fuelling resistance

- Poverty encourages the development of resistance through under use of drugs
  - Patients unable to afford the full course of the medicines
  - Sub-standard & counterfeit drugs lack potency
- In wealthy countries, resistance is emerging for the opposite reason – the overuse of drugs.
  - Unnecessary demands for drugs by patients are often eagerly met by health services and stimulated by pharmaceutical promotion
  - Overuse of antimicrobials in food production is also contributing to increased drug resistance. Currently, 50% of all antibiotic production is used in animal husbandry and aquiculture
- Globalization, increased travel and trade ensure that resistant strains quickly travel elsewhere. So does excessive promotion.

Postponing the end of the antibiotic era

- Antibiotic stewardship (prudent use)
- Include preventing the spread of resistant microorganisms and the corresponding genes (infection control)
- Develop new antibiotics that have novel modes of action or circumvent bacterial mechanisms of resistance (research)

Antibiotic stewardship



Antibiotic Stewardship Program

- Optimal selection, dosage, and duration of antimicrobial treatment that
  - Results in the best clinical outcome for the treatment or prevention of infection
  - With minimal toxicity to the patient and
  - With minimal impact on subsequent resistance

Antibiotic Stewardship Program

- Involves
  - Prescribing antimicrobial therapy only when it is beneficial to the patient
  - Targeting therapy to the desired pathogens
  - Using the appropriate drug, dose, and duration

What are Antibiotic Guidelines?

- Best practice recommendations concerning the treatment of choice for common clinical problems
- Written by national or local experts
- Evidence based where possible
- Regularly updated every 2 years
- Used for medical education, problem look-up and drug audit

Types of antibiotic uses

- **Empirical therapy**
  - Without the knowledge of pathogen
- **Pathogen-directed therapy**
  - Knowing the pathogen and susceptibility to antibiotics
- Prophylaxis
  - Surgical
  - Medical

Empirical therapy

- emergency administration of antibiotics – meningitis, sepsis, VAP…
- typical clinical signs - streptococcal tonsillitis…
- in most other situations it is possible to wait for the results of the microbiological examination
- but clinicians are often not interested for microbiological examination, or is not avavilable

Data for empirical treatment

- Clinical manifestations
- Epidemiological data
- Reports of resistance to antibiotics – local, national, international
- Pneumonia
- UTI
- streptococcal pharyngitis

Disadvantages of empirical treatment

- Mostly broad spectrum antibiotic
- Risk of errors -bacteria is not susceptible to the antibiotic chose
- Side effects - resistance, dysmicrobia (diarrhea, candida infections, superinfection..), CDI
- Treatment costs…

Principles of Antibiotic Guidelines

- Empiric antibiotics should be reviewed once Gram stain/ microscopy/culture/sensitivity or PCR available. **Empiric therapy should be changed to directed therapy as soon as possible**. Directed/specific therapy should be the narrowest spectrum antibiotic to adequately cover the known pathogens

Deescalation

- changing broad-spectrum treatment to targeted
- the second or third day when the results of the microbiological examination are known
- principle used mainly in the treatment of severe infections – sepsis, VAP, complicated urinary infections

Principles of Antibiotic Guidelines

- Specimens for microbiology should be taken prior to commencement of empiric treatement. In an emergency, at a minimum a set of blood cultures should be taken e.g meningitis, sepsis, pneumonia…

- Ensure any history of allergy is documented…

Factors to consider when prescribing an antibiotic

- Any history of allergy, toxicity?
- Is it appropriate for the spectrum I want to cover?
- What route of admin: oral or i.v?
- Any factors affecting absorption ?
- Is it going to reach the site of infection?
- Any drug interactions?
- Any serious toxicity eg, hepatic, renal?
- Does it need monitoring eg aminoglycosides, vancomycin?

Inappropriate prescribing

- *Example of a drug not required:*
  - A patient with suspected infected burns received oral oxacillin and penicillin V. Therapy was continued for 10 days despite the failure. Culture of the swab grew methicillin-resistant *Staphylococcus aureus* (MRSA).

Inappropriate prescribing

Example of inadequate cover:

A patient received gentamicin for peritonitis, thereby ignoring the anaerobic flora of the bowel. Metronidazole or clindamycin should have been added…

Infection control

- Infection control is of utmost importance in reducing risk of infection, use of antibiotics and hence emergence of bacterial resistance
  - Hand hygiene !!!
  - Appropriate isolation / contact restriction
  - Prompt reporting of certain infectious diseases (e.g. MRSA infections, *Clostridium difficile* infection)
  - Many more!

Stewardship: Role of the Microbiology Laboratory, Antibiotic centre

- Regular reporting of changing resistance patterns
  - Newsletters
  - Specialty-specific data
- Restricted antibiotic reporting
  - Routinely only first line antibiotics
  - Reserve antibiotics only if pathogen is resistant to first line antibiotics
- Patient specific data (culture & sensitivity) to optimise treatment
- Categorization….reserve antibiotics - must be approved by antibiotic centers

- Clinical microbiologist assess the accuracy of the indication

- provides advice on antibiotic treatment

Trends in antibacterial development

number of newly licenced products in decline

few agents under development compared to other therapeutic areas in all sectors

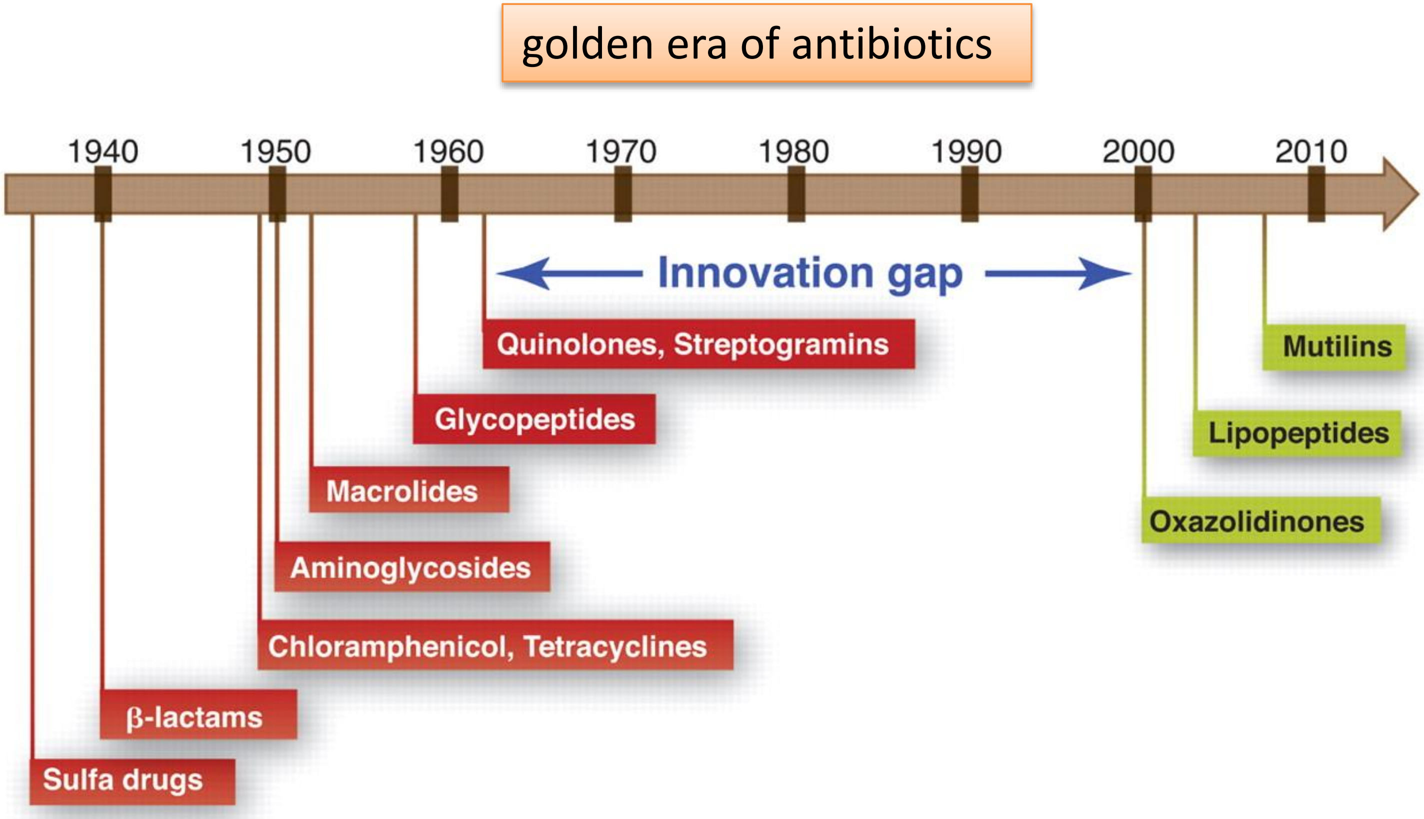
drugs in late development still focused on community RTI sector

very little agents for MDR Gram-negative infection

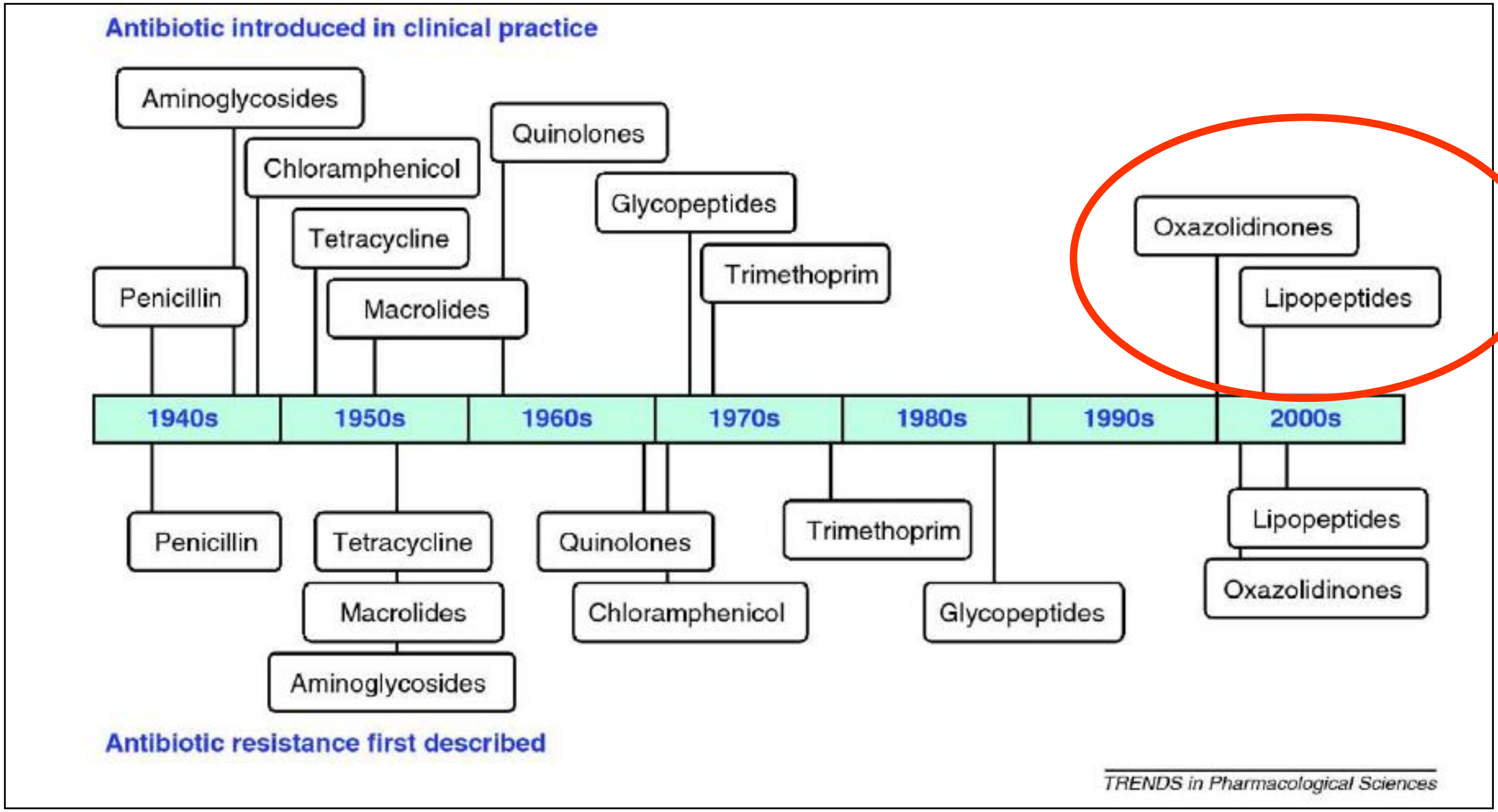
New antibiotics

- A few novel antibiotics have shown promising results / are undergoing clinical studies
- Ceftolozan/tazobactam
- Ceftazidim/avibactam (inhibition of ESBL and carbapenemases)
- Dalbavancin

History of and Innovation Gap in Antibiotics…



Development of antibiotics and resistance…



DEFINITION OF RATIONAL USE OF ANTIBIOTICS (WHO)

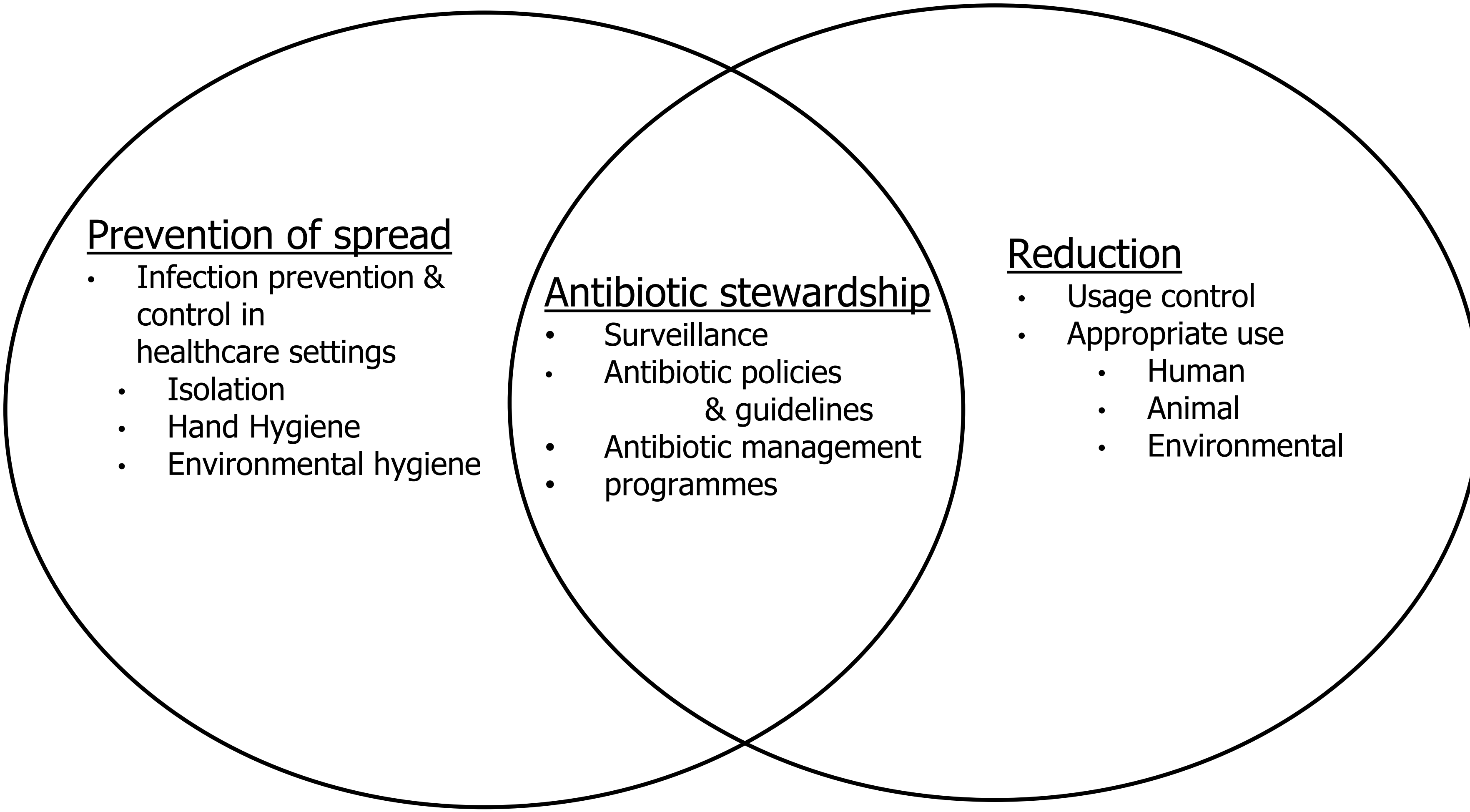
PROPER INDICATION

PROPER DRUG

PROPER DOSAGE

MONITORING

Dealing with resistance



Conclusion

- Discovery of antibiotics – revolutionary event that saved millions of lives
- Emergence of resistance – reduced effectiveness, increased toxicity, increased costs
- To preserve susceptibility – or to postpone development of resistance – antibiotics should be used rationally