Solving the Resistance Problem

Prof Jan Verhoef : AMR 2019, Amsterdam

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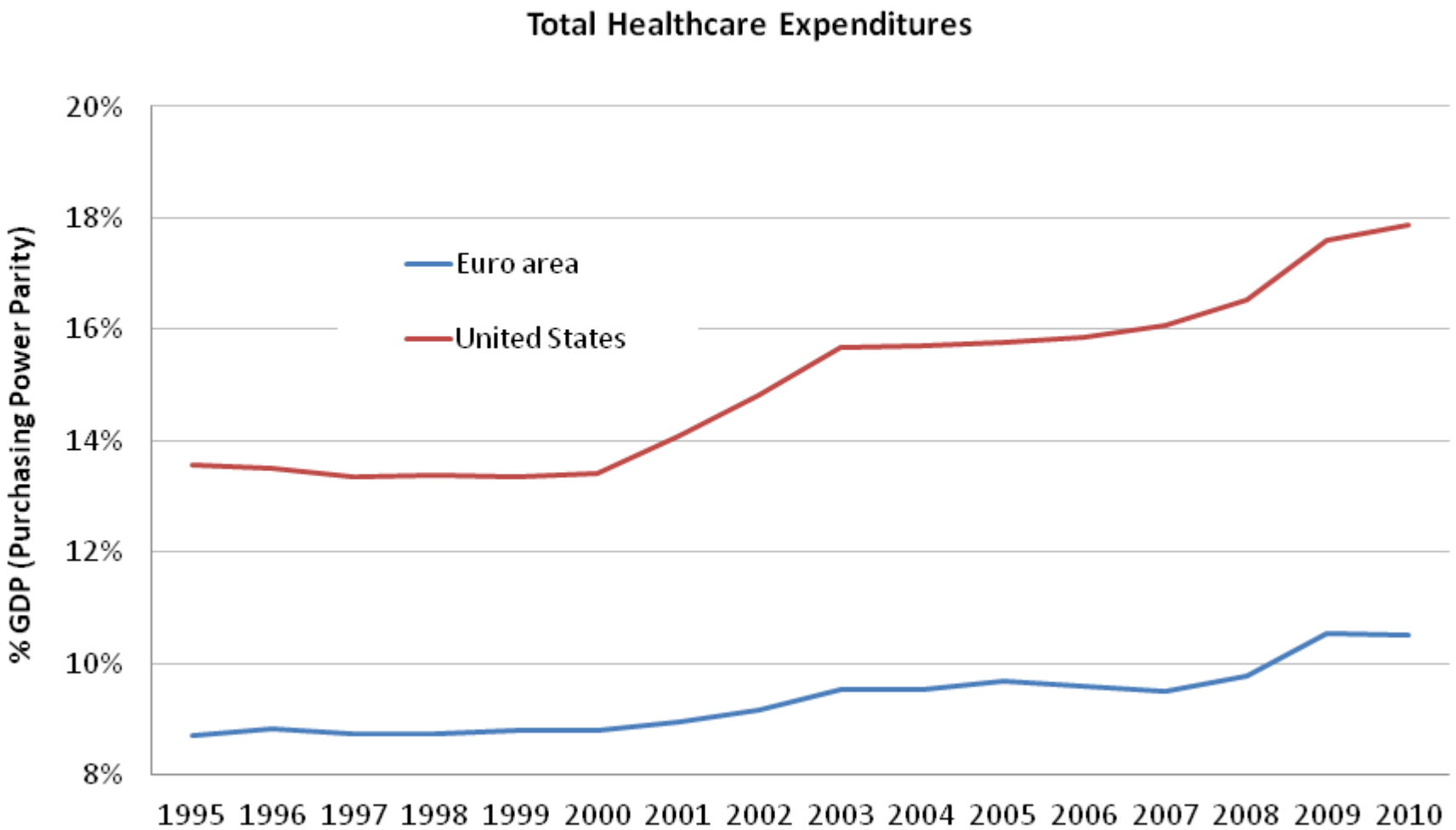
Chart 1: Spending on health care is rising in Europe as well as in the U.S.



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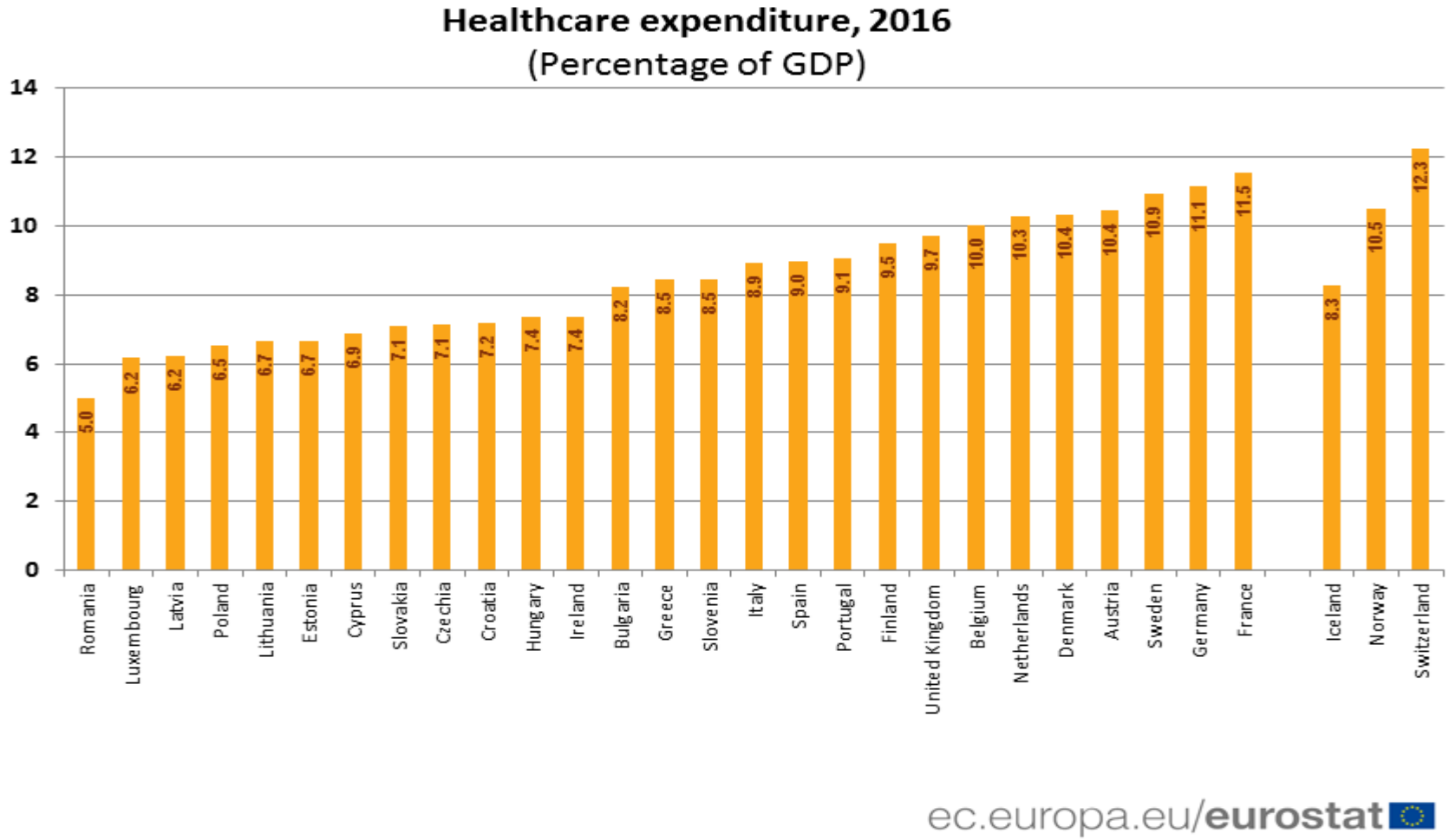
Sources: World Health Organization, The GailFosler Group LLC

In EU: Healthcare Expenditure between 5-13% of GDP (unsustainable levels)



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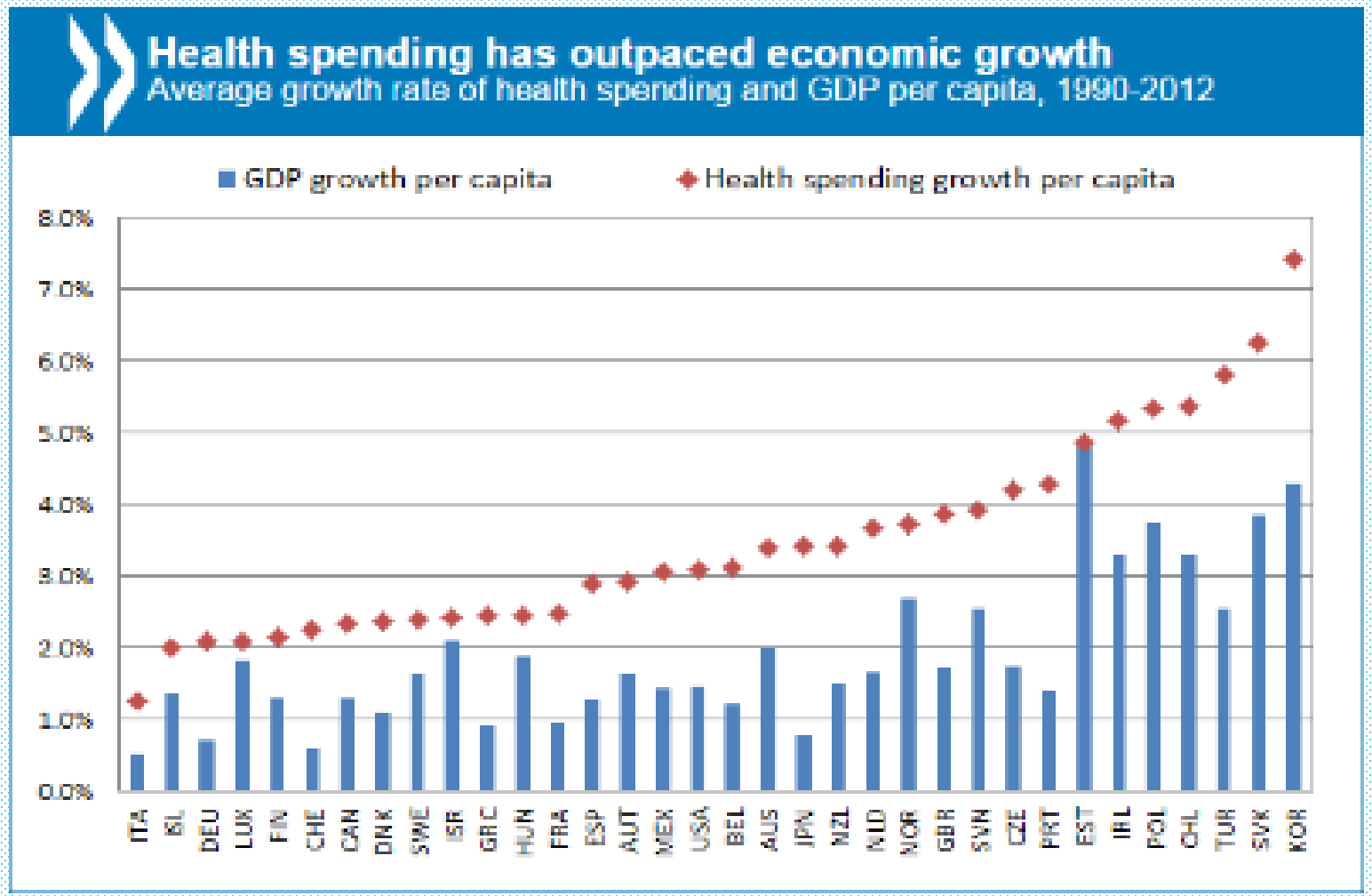
Healthcare costs are rising faster than the economic Growth



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Unsustainable rise in Healthcare Cost

Therefore emphasis on PREVENTION

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- E.g. EU millenum goal 10% fewer Type 2 Diabetes patients

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First and Foremost was/is Prevention in number of Patients with Infectious Diseases

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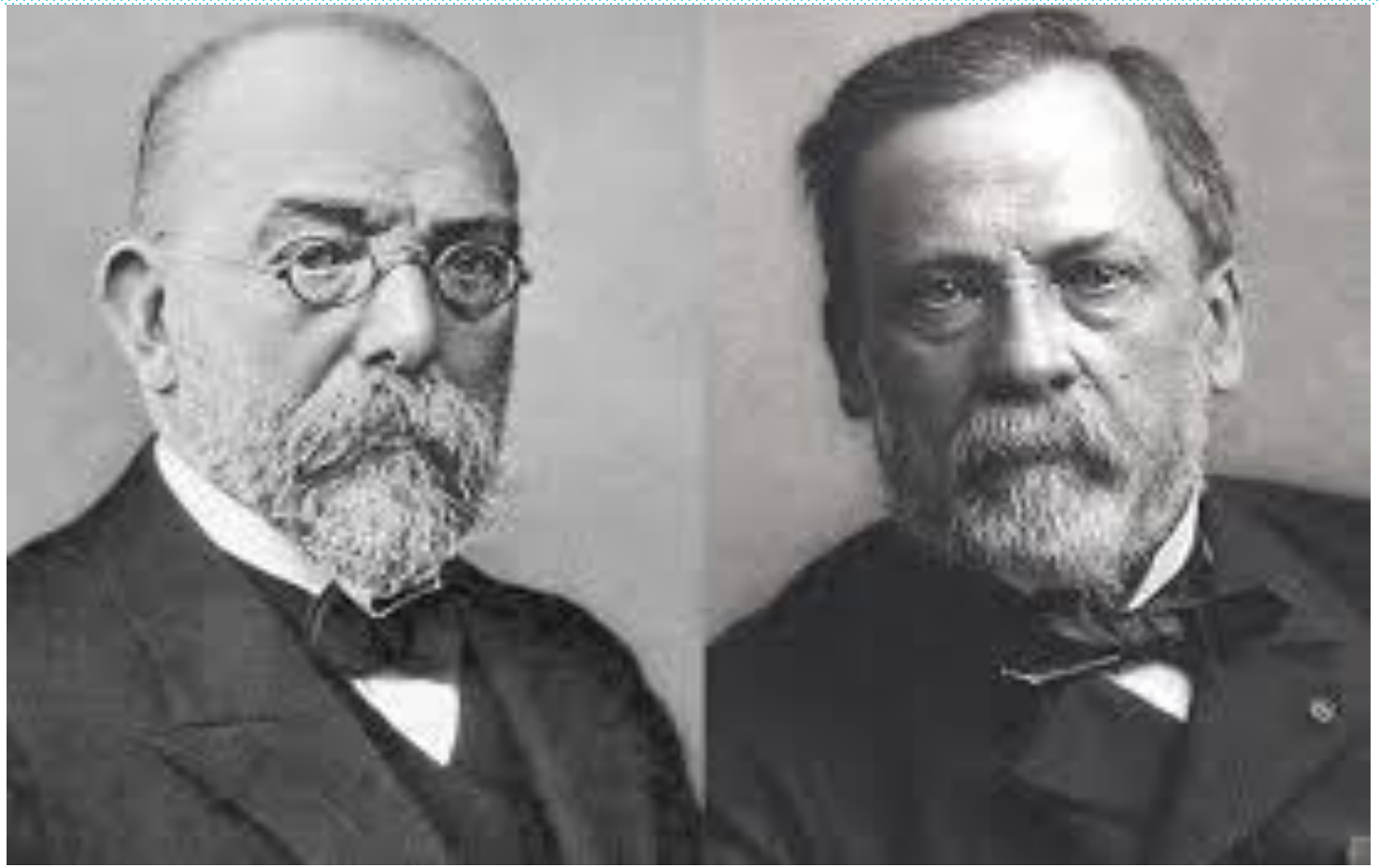
Prevention started with Pasteur and Koch



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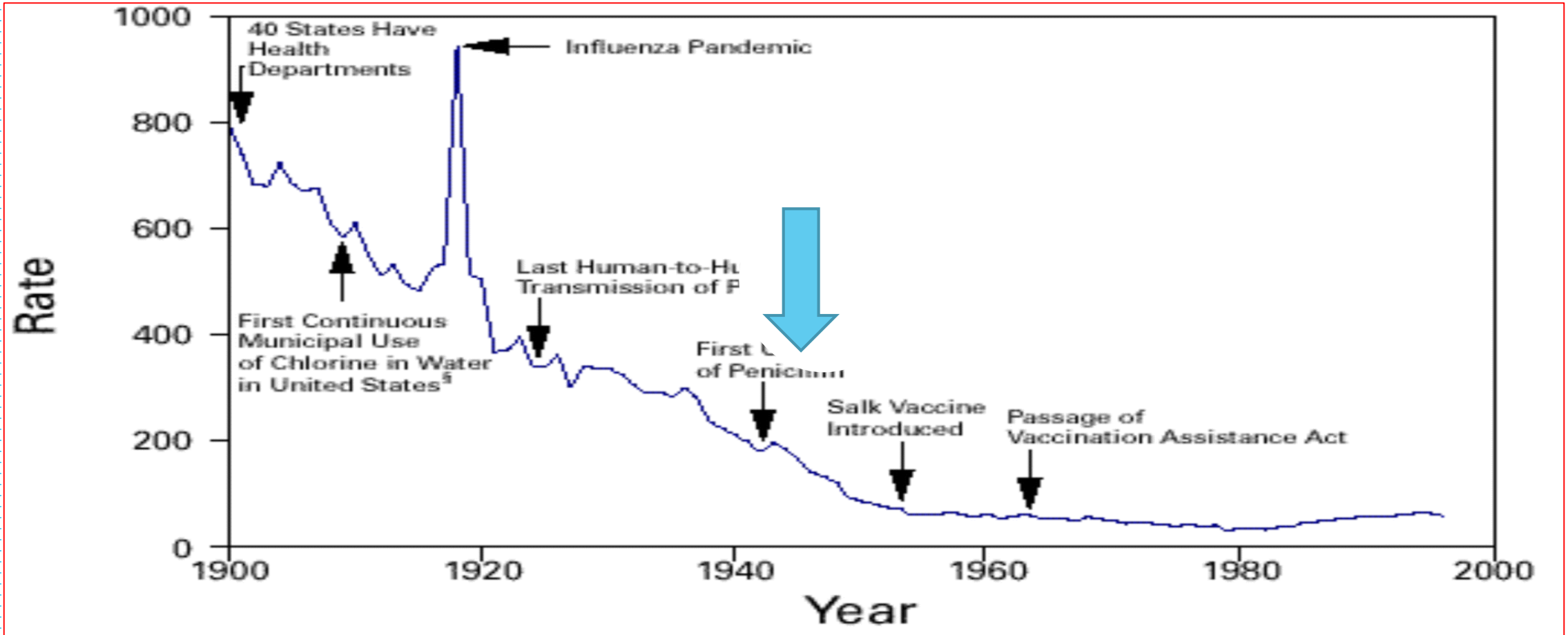
Decrease in Mortality of Infectious diseases
mainly due to to prevention



*Per 100,000 population per year.
†Adapted from Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999:281;61–6.
§American Water Works Association. Water chlorination principles and practices: AWWA manual M20. Denver, Colorado: American Water Works Association, 1973.

Prevention of infectious diseases: great success

- Hygienic measures: sewage, safe drinking water, save food
- Immunizations
- Better diagnostics
- antibiotics

First and Foremost was/is Prevention in number of Patients with Infectious Diseases

- However, without antimicrobial agents, progress in medicine would have come to a complete stop
  - No progress in surgery
  - No progress in oncology
  - No progress in transplantation medicine
  - Treatment of the elderly
  - No progress there where prevention failed

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The Nobel Prize
Physiology/Medicine 1945

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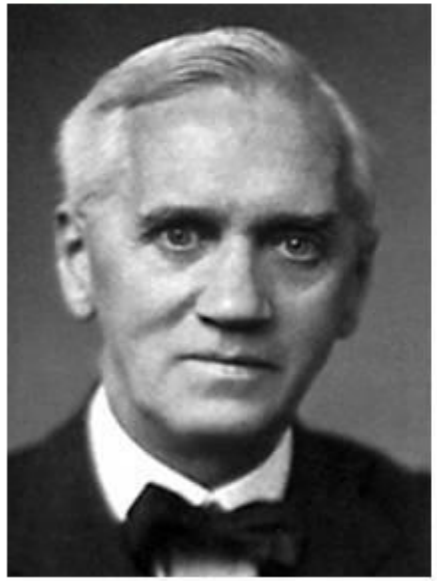
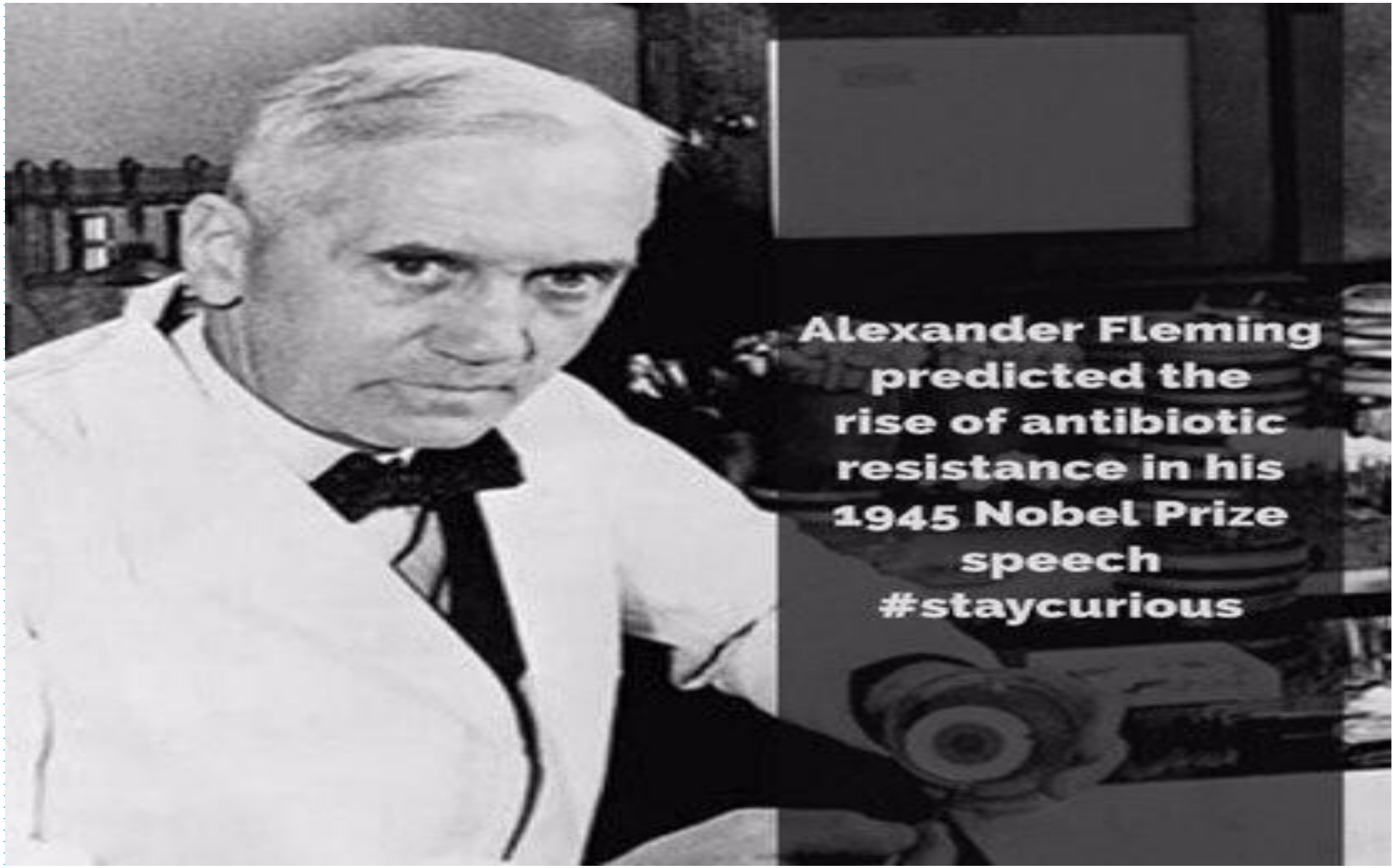


Sir Alexander Fleming
1881 - 1955

Sir Howard Walter Florey
1898 - 1968

Ernst Boris Chain
1906 - 1979

Alexander Fleming discovered the antimicrobial properties of penicillin in 1928. Twelve years later, Howard Florey and Ernst Chain developed the processes to produce penicillin in sufficient quantity for it to become widely available


Alexander Fleming predicted the rise of antibiotic resistance in his 1945 Nobel Prize speech
#staycurious

Emergence of antibiotic resistance

"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body." Sir Alexander Fleming, 1945

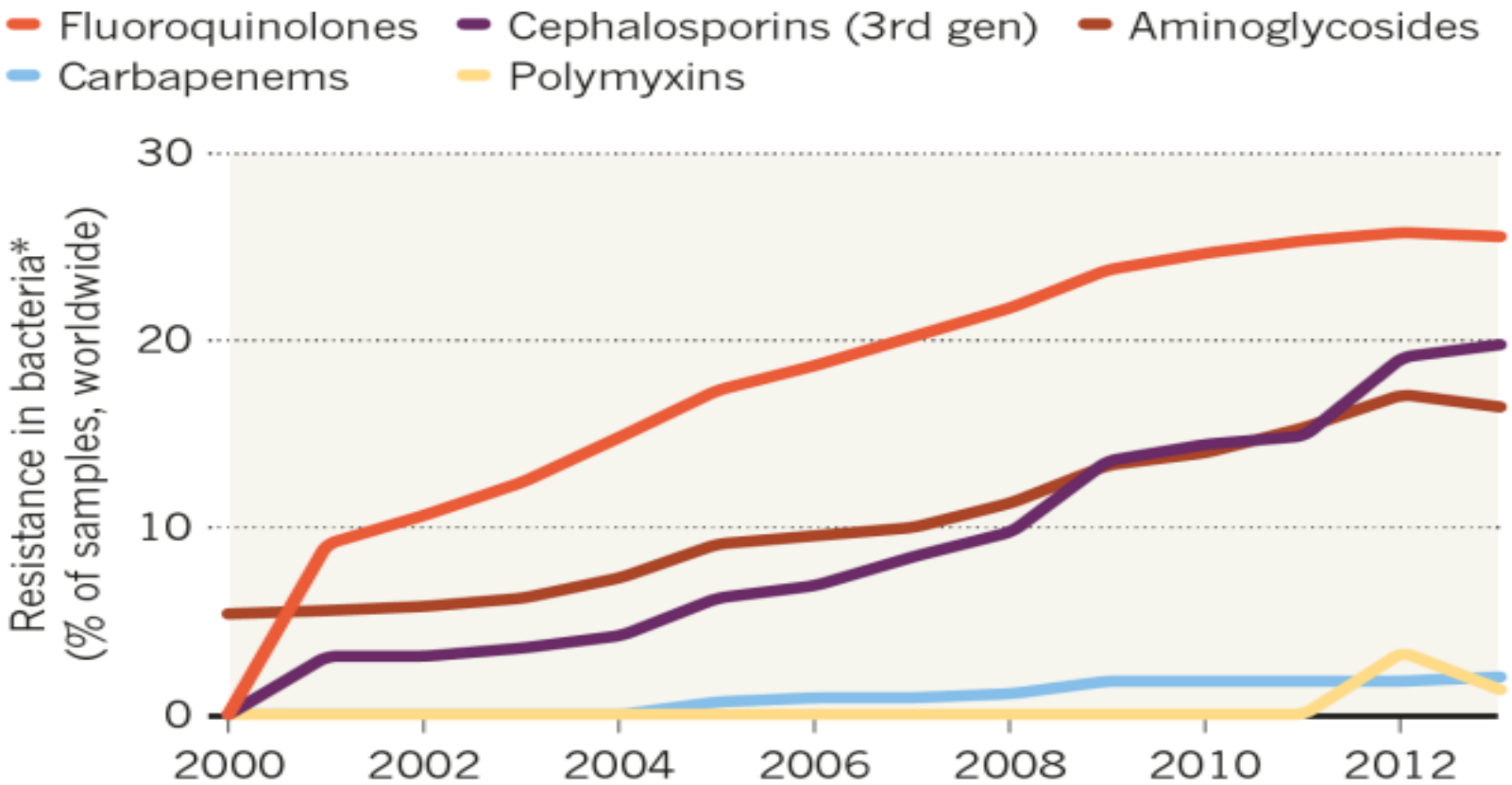
The issue of antibiotic resistance was recognised early in the 'antibiotic era'. It threatens our ability to control infection.

ANTIBIOTIC AWARENESS WEEK
18–24 NOVEMBER 2013
Preserve the Miracle

4. Sir Alexander Fleming, Nobel Lecture, December 1945

THE SPREAD OF ANTIBIOTIC RESISTANCE

An increasing proportion of bacteria display resistance to common antibiotics.



*Enterobacteriae, including *Escherichia coli*, *Klebsellia pneumonia*, *Enterobacter* and *Salmonella*

1958: first pandemic of Pen-Res staphylococci

1959 development of Meticilline against Penicilline resistant Staphylococci

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first epidemics MRSA: 1965

1965: Kopenhagen 25% of Staphylococci MRSA

1965: Zurich 25% MRSA

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However both in Zurich as in Kopenhagen after 5 years the percentage dropped to less than 5%

Why?

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First epidemic MRSA UMCUtrecht 1984,1987
(we developed protocols which are used world wide)

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Martinair Crash in 1992 (Faro) determining factor for protocols

Colonization of Dutch crash victims after stay in a Portuguese hospital

No., victims	no. of days in hospital	MRSA positive
5	1	2
7	2 - 5	4
12	5 - 14	5

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Hospitals with MRSA

Protocol Basics:

- Ward with MRSA is closed
- Patient isolated
- Search and destroy
- Staff with MRSA is send home (not allowed to work)
- Patients from a hospital abroad first in Isolation

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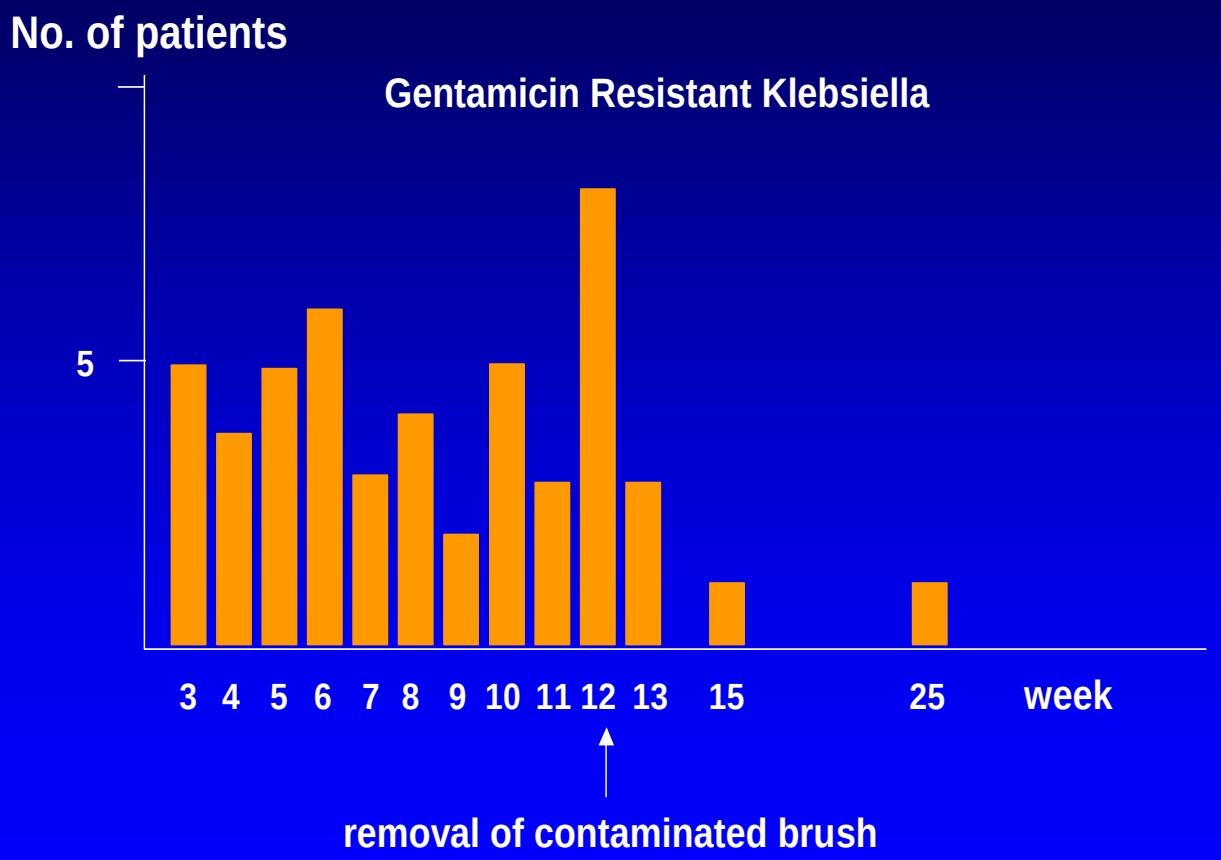
Hygiene prevents spread of multiresistant microbes



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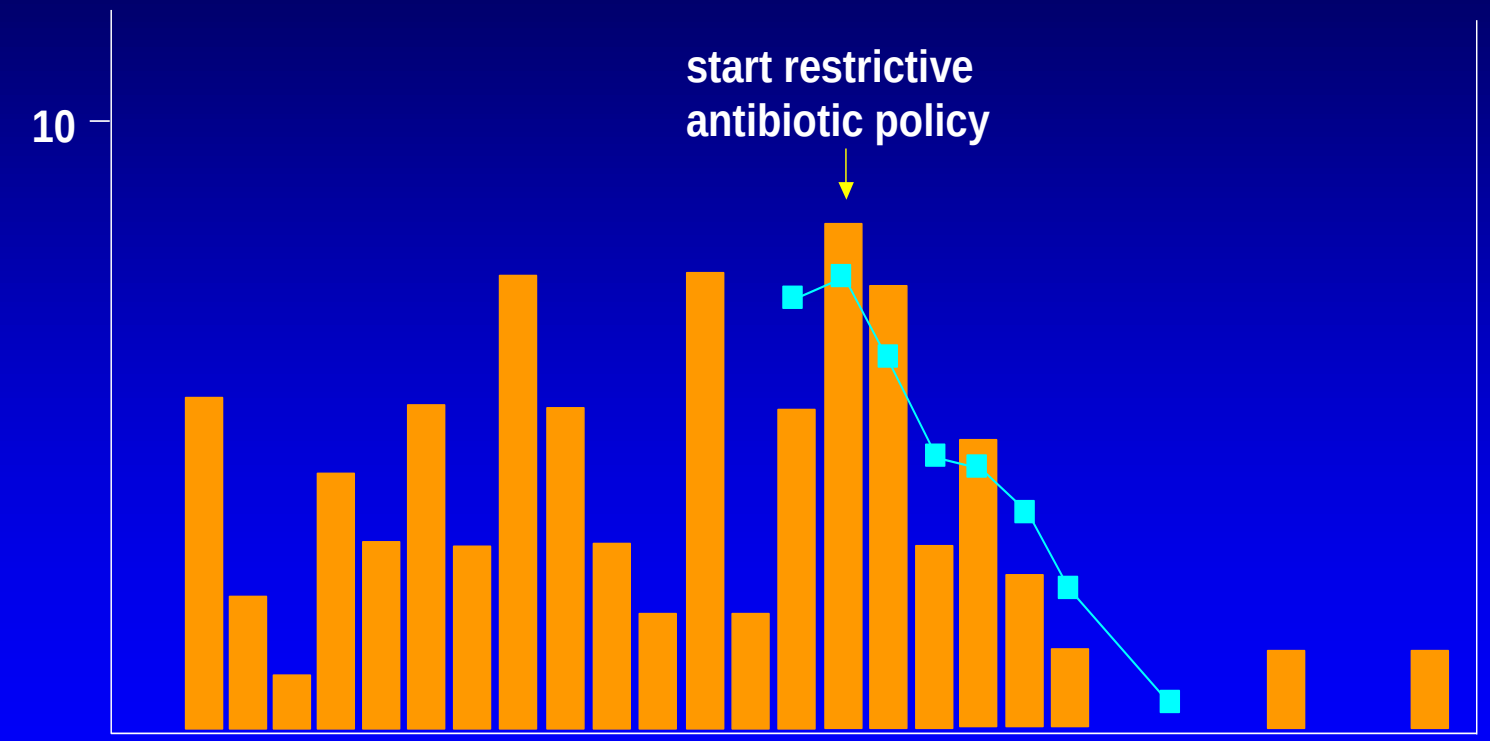
Restrictive antibiotic policy decreases spread of Gentamicine resistant gram-negative bacteria



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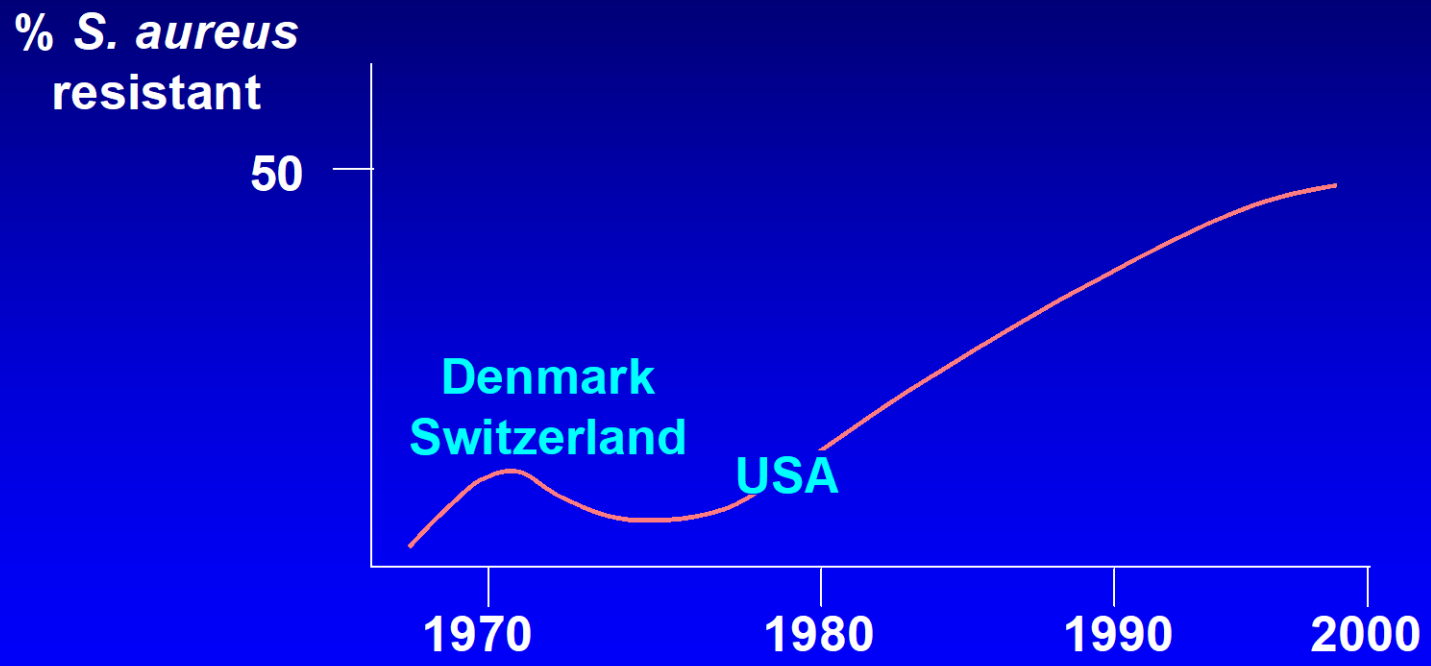
MRSA: on the rise Worldwide



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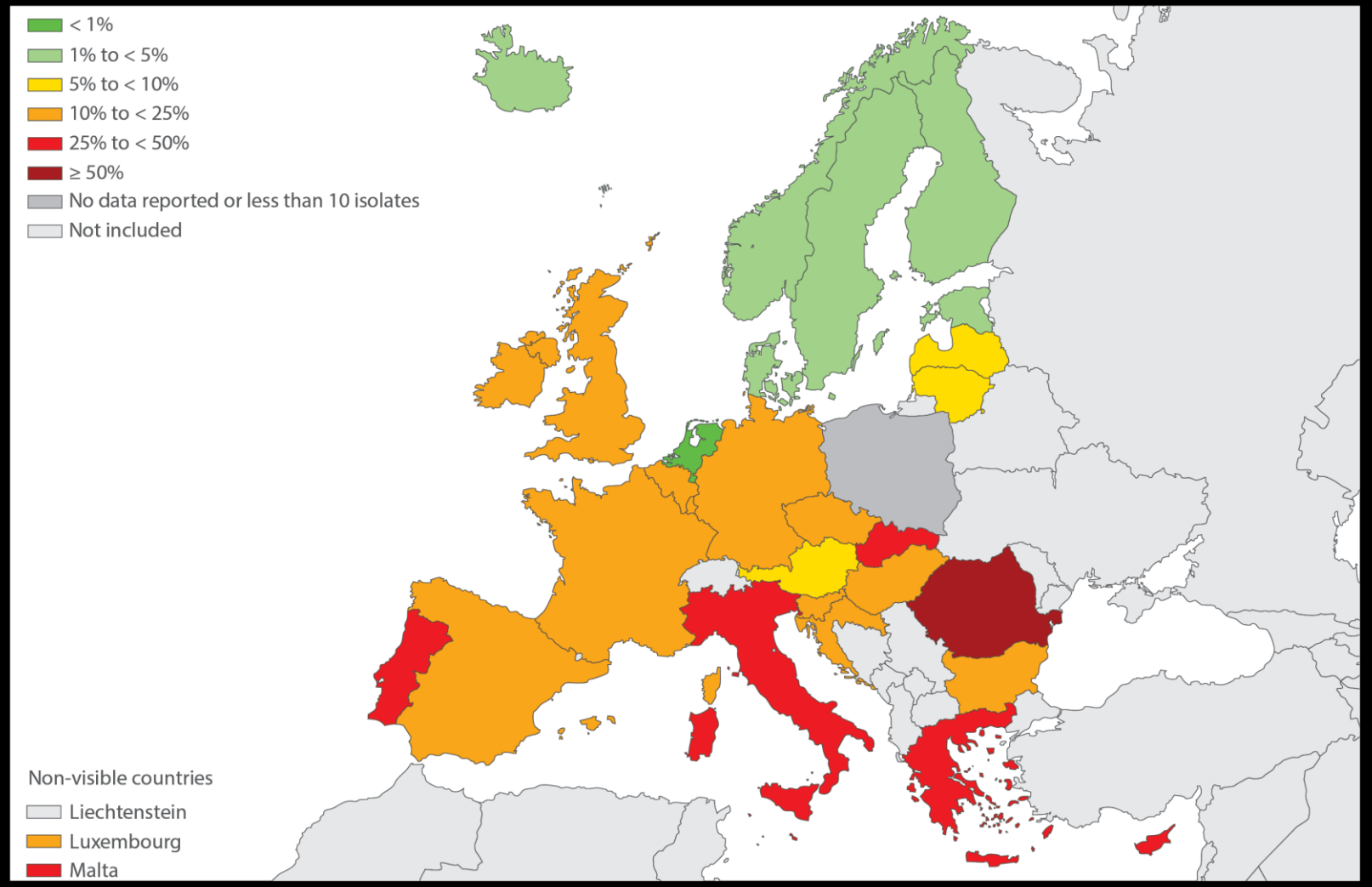
Staphylococcus aureus.

INVASIVE ISOLATES EU resistance 1-50%



Source: European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2014. Stockholm: ECDC, 2015

However MRSA at the farm (> 50% ?) "One health"

- MRSA cattle variant from cattle to farmer. However the cattle variant is less virulent
- This needs to be studied

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Resistance problem from 1960-1990 often manageable;
(almost every year a new antibiotic licenced)

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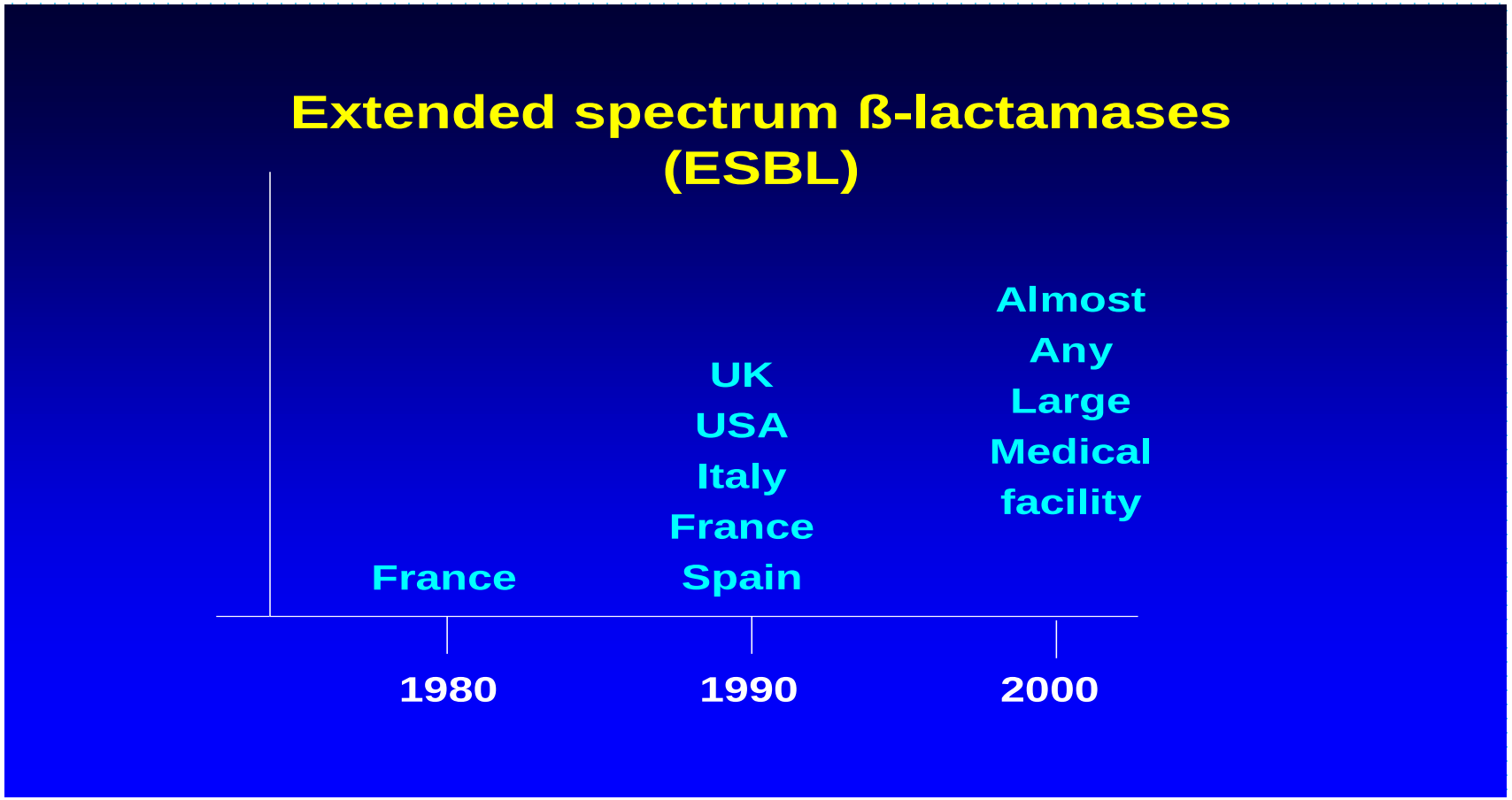
From MRSA to the Gram negatives



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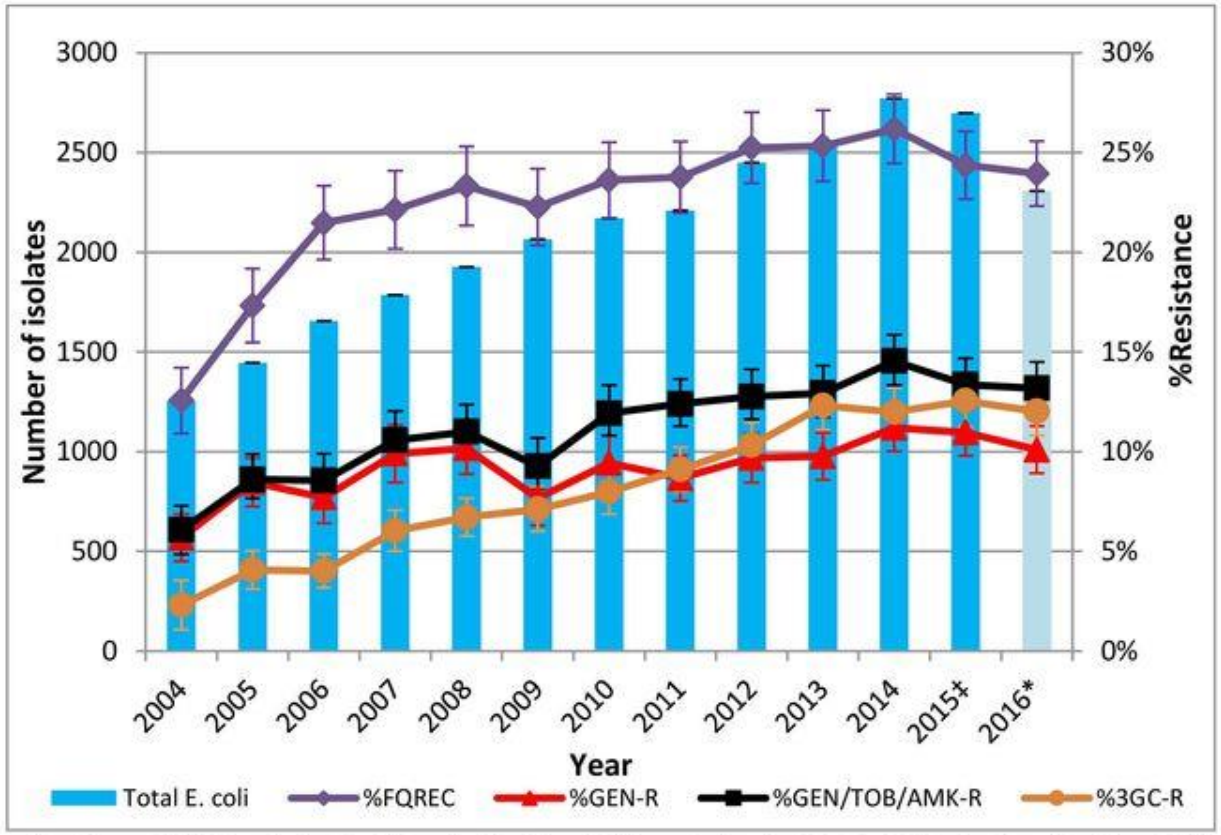
Trends in *E. coli* invasive infections showing percentage resistance to fluoroquinolones, aminoglycosides and 3rd-generation cephalosporins



* 2016 data are provisional to the end of Q3 only (note: data missing from 2 laboratories for Q3); ‡ 2015 missing data from 3 laboratories for 2 quarters each

FQREC, fluoroquinolone (e.g. ciprofloxacin)-resistant E. coli; GEN, gentamicin, TOB, tobramycin; AMK, amikacin (GEN, TOB and AMK are aminoglycosides); 3GC, 3rd-generation cephalosporins (e.g. cefotaxime, ceftazidime)

Resistance is indeed not a new phenomenon

THE LANCET

1970: Infections due to Klebsiella resistant to all available agents

"CONTROL OF INFECTION DUE TO KLEBSIELLA AEROGENES IN A NEUROSURGICAL UNIT BY WITHDRAWAL OF ALL ANTIBIOTICS"

December **1970**, Pages 1213-1215 !

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Carbapenem last resort: however the superbug is becoming resistant against Carpapenems

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Import of ESBLs after visit abroad

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

Asia including India: 46%

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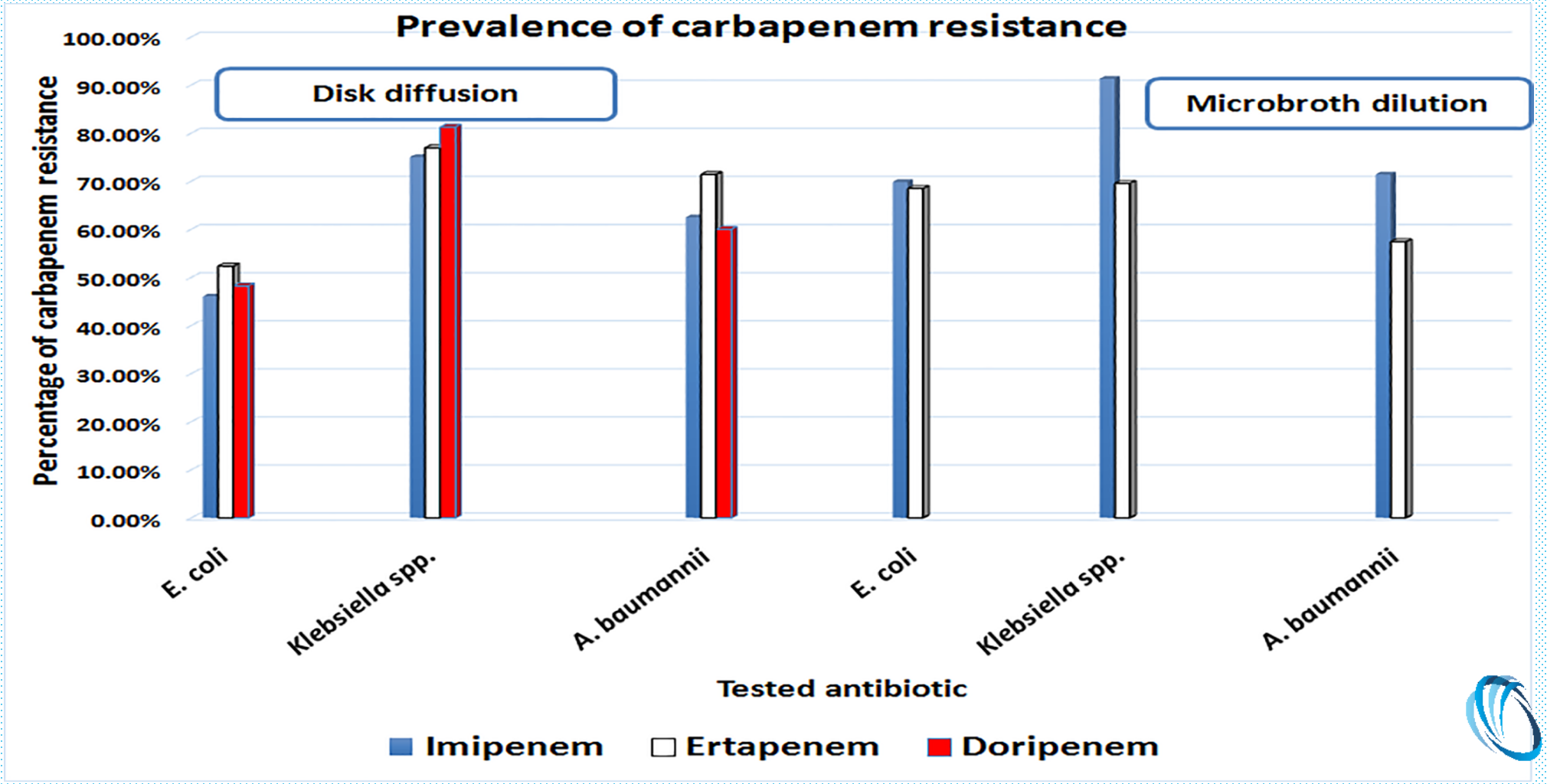
Highly AMR in EGYPT 2015



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Epidemics are very expensive:

- Prevention: Hygiene extremely important
- Proper (restricted) use of antimicrobials
- Rapid diagnostics would lead to proper use of antibiotics
- A need for new antibiotics
- A new business modell for these new antibiotics
- “One Health” and the environment

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Limitations of present rapid diagnostics

- Many samples from patients carry more than one species of bacteria
- Which bacteria in the sample is the pathogen?
- A resistant gene can be detected on the spot from a patient's sample, However
- how do we know that the resistance gene comes from the genome of the pathogen?

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New antibiotics urgently needed, preventive measures and rapid antibiotics are not solving the problem for the time being

- However few companies are working on new antibiotics
- A looming disaster: a new businessmodel is needed

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Business model for new antibiotics

- New antibiotics used only when bacteria are very resistant thus:
- Limited use of new antibiotics does lower the ambition of the Pharma industry to develop new antibiotics

- HOWEVER:

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A much more attractive Business plan is is much more attractive and based on following facts

- New antibiotics for lifethreatening infections
- Often blind therapy can not be avoided
- In all hospitals with AMR new antibiotic that are active against AMR will become drug of choice in any hospital acquired infection
- Thus:

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New Broad spectrum antibiotics developed must be shown first to be as good as old ones against **susceptible** strains.

If that is the case these new antibiotics will be used in patient with serious hospital infections

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In conclusion:

- Prevention is extremely important especially to prevent hospital acquired infections
- However prevention does not solve the problem of AMR
- New Antibiotics are urgently needed
- These new antibiotics must be as good as old ones against infections caused by susceptible micro-organisms and

  active against multiresistant micro-organisms

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In conclusion (2)

- Antimicrobial treatment will become more expensive
- But in a new businessmodel the path to registration will be simpler and cheaper
- And: the use of new antibiotics may lead to a decrease in AMR (at least temporarily)

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