# Epidemiology and Economics of Antibiotic Resistance

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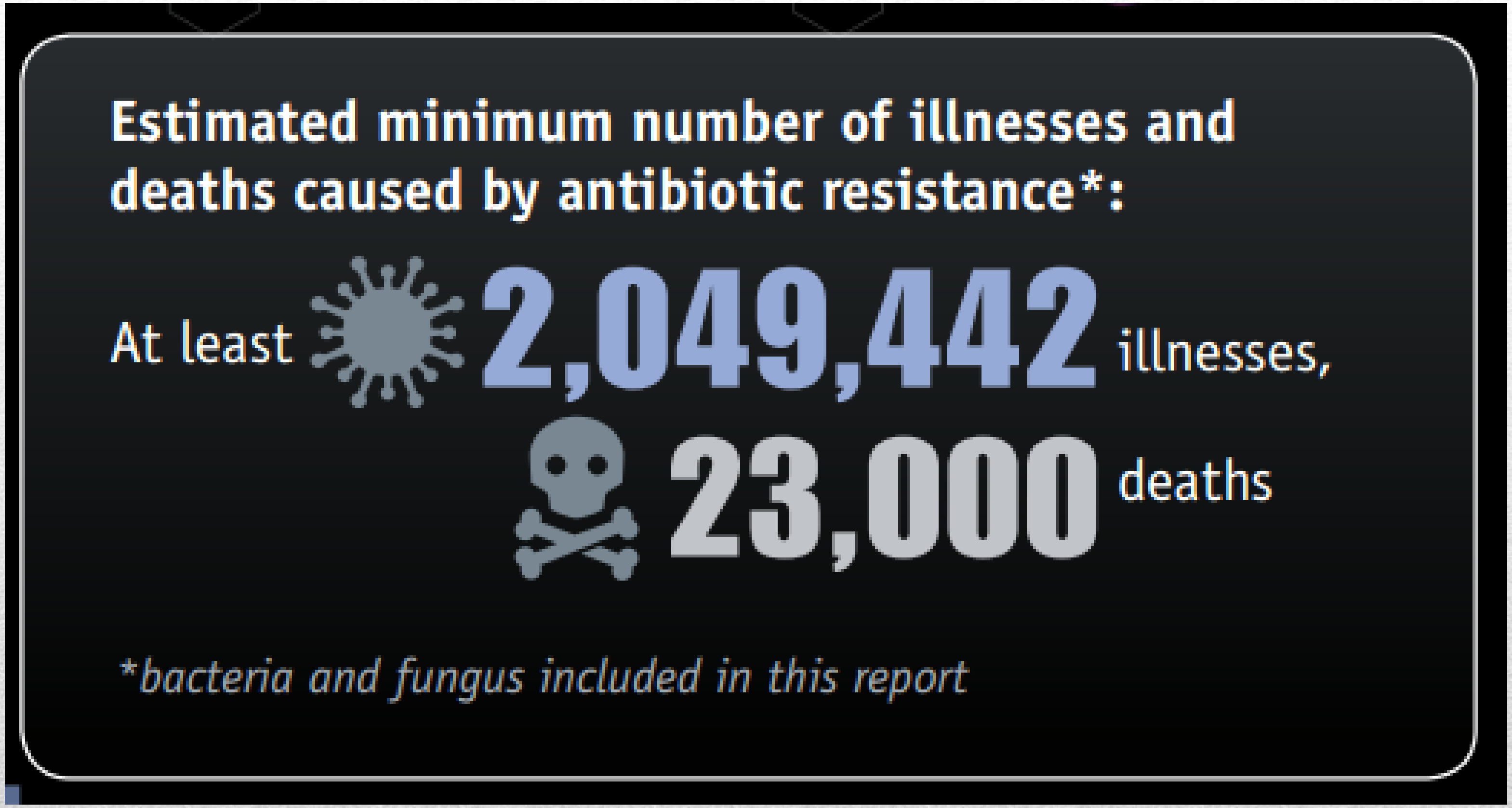
*February 17, 2016*

Health Watch USA Meeting

CDDEP
CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

I. The burden of antibiotic resistance is a growing global threat, but hard numbers are lacking as to the magnitude of the problem

# Burden of Antibiotic Resistance in the United States



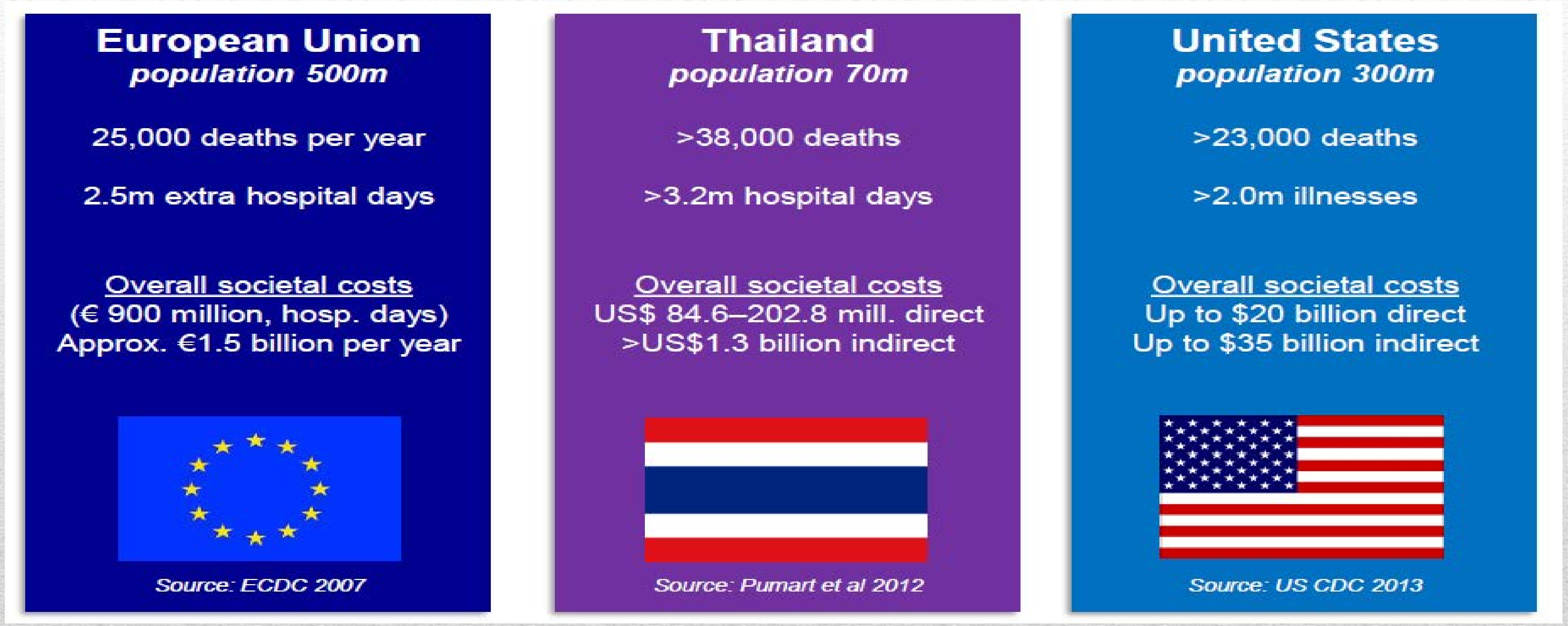

Centers for Disease Control 2013

# Burden by Resistant Pathogen, US

## What is the best measure of burden?

| Pathogen | Infections | Deaths |
|---|---|---|
| Streptococcus pneumoniae | 1,200,000 | 7,000 |
| Drug-resistant Campylobacter | 310,000 | 28 |
| Drug-resistant Neisseria gonorrhoeae | 246,000 | <5 |
| Drug-resistant non-typhoidal Salmonella | 100,000 | 40 |
| Methicillin-resistant Staphylococcus aureus (MRSA) | 80,000 | 11,000 |
| Drug-resistant Shigella | 27,000 | <5 |
| Extended-spectrum β-lactamase producing Enterobacteriaceae (ESBLs) | 26,000 | 1,700 |
| Vancomycin resistant Enterococcus (VRE) | 20,000 | 1,300 |
| Carbapenem-resistant Enterobacteriaceae (CRE) | 9,300 | 610 |
| Clindamycin-resistant Group B Streptococcus | 7,600 | 440 |
| Others | 23,547 | 1,380 |
| **Total** | **2,049,447** | **23,508** |

# Burden of Antibacterial Resistance




Global Estimates Not Available

# Measuring the Cost of Resistance

European Union:

| Extra in-hospital costs | Extra outpatient costs | Productivity losses due to absence from work | Productivity losses due to patients who died from their infection | TOTAL |
|---|---|---|---|---|
| € 927.8 million | € 10 million | € 150.4 million | € 445.9 million | **€ 1.5 billion** |

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For the US: If one assumes that there are 2,000,000 ARI per CDC, that $20 billion is an excess cost of $10,000 per infection. (Europe would be €750)

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US CDC estimate based on one hospital in which costs for ~1,000 patients with antibiotic resistant infections was estimated to be:

Hospital: $3.4–$5.4 million

Mortality: $7.0–$9.2 million

Lost productivity: $162,624–$322,707

Total: $10.7–$15.0 million

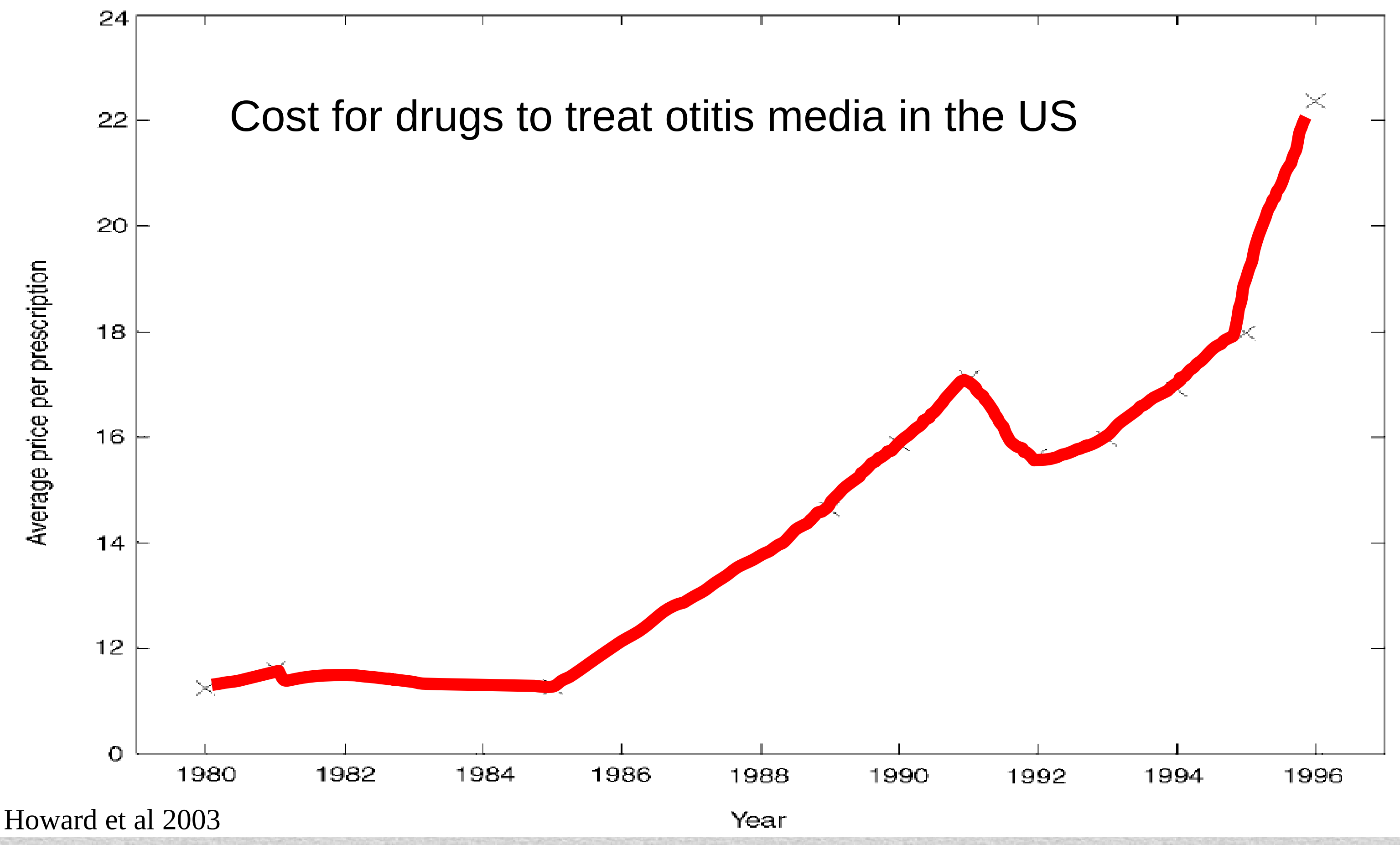
# Measuring the Cost of Resistance

## Excess costs of resistance by pathogen

| Resistant Organism | Range of Excess Cost |
|---|---|
| Methicillin-resistant *Staphylococcus aureus* | $695 – $29,030 |
| Vancomycin-resistant *Enterococcus* | $16,711 – $60,988 |
| *Pseudomonas aeruginosa* | $627 – $45,256 |
| *Acinetobacter baumannii* | $5,336 – $126,856 |
| Multiple organisms | $9372 – 18,990 |
| ESBL-producing *Enterobacteriaceae* | $3,658 – $4,892 |

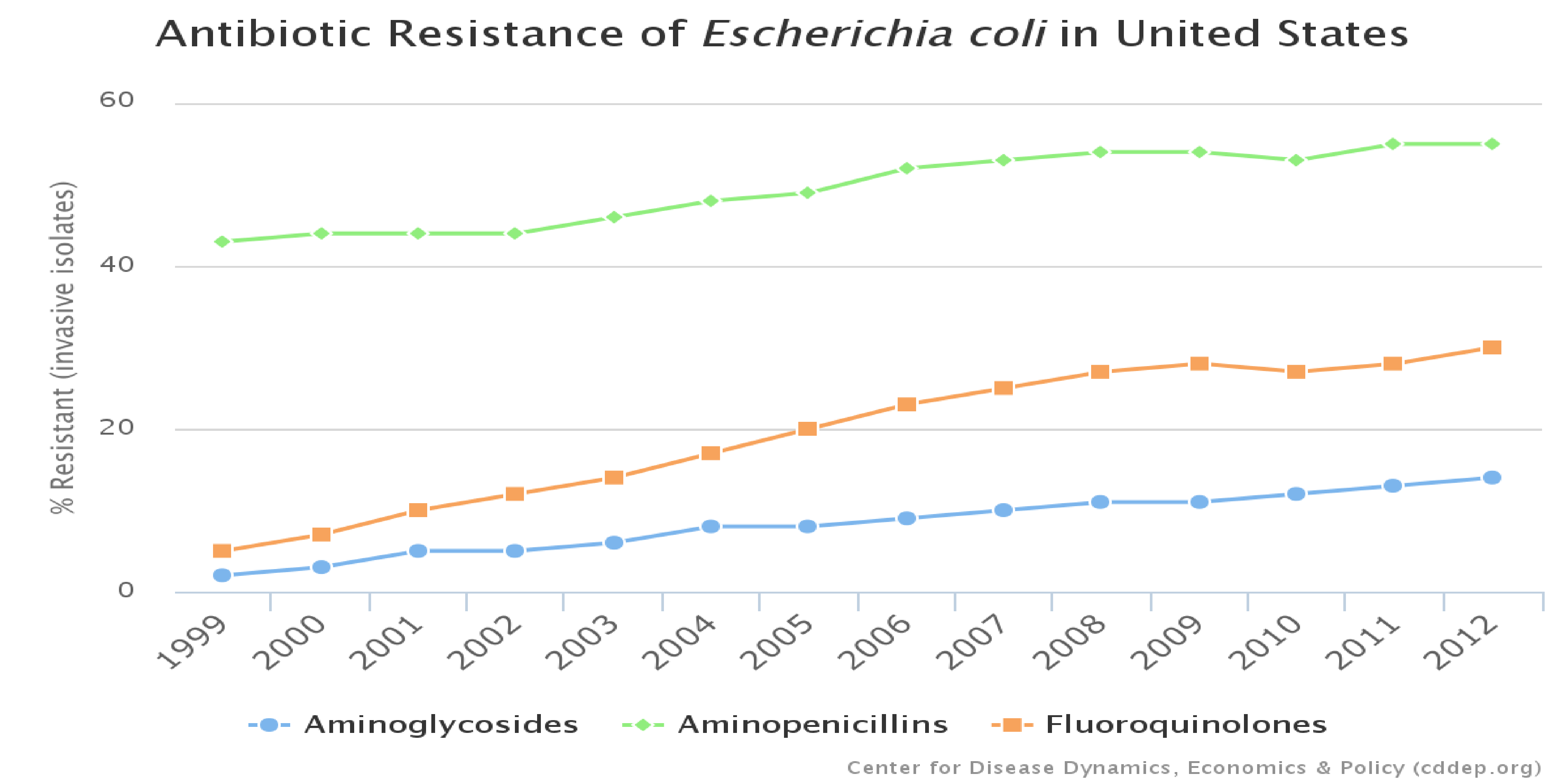
# Unconsidered Costs

## Costs of drugs for patients with non-resistant infections




Howard et al 2003

# A Growing Problem



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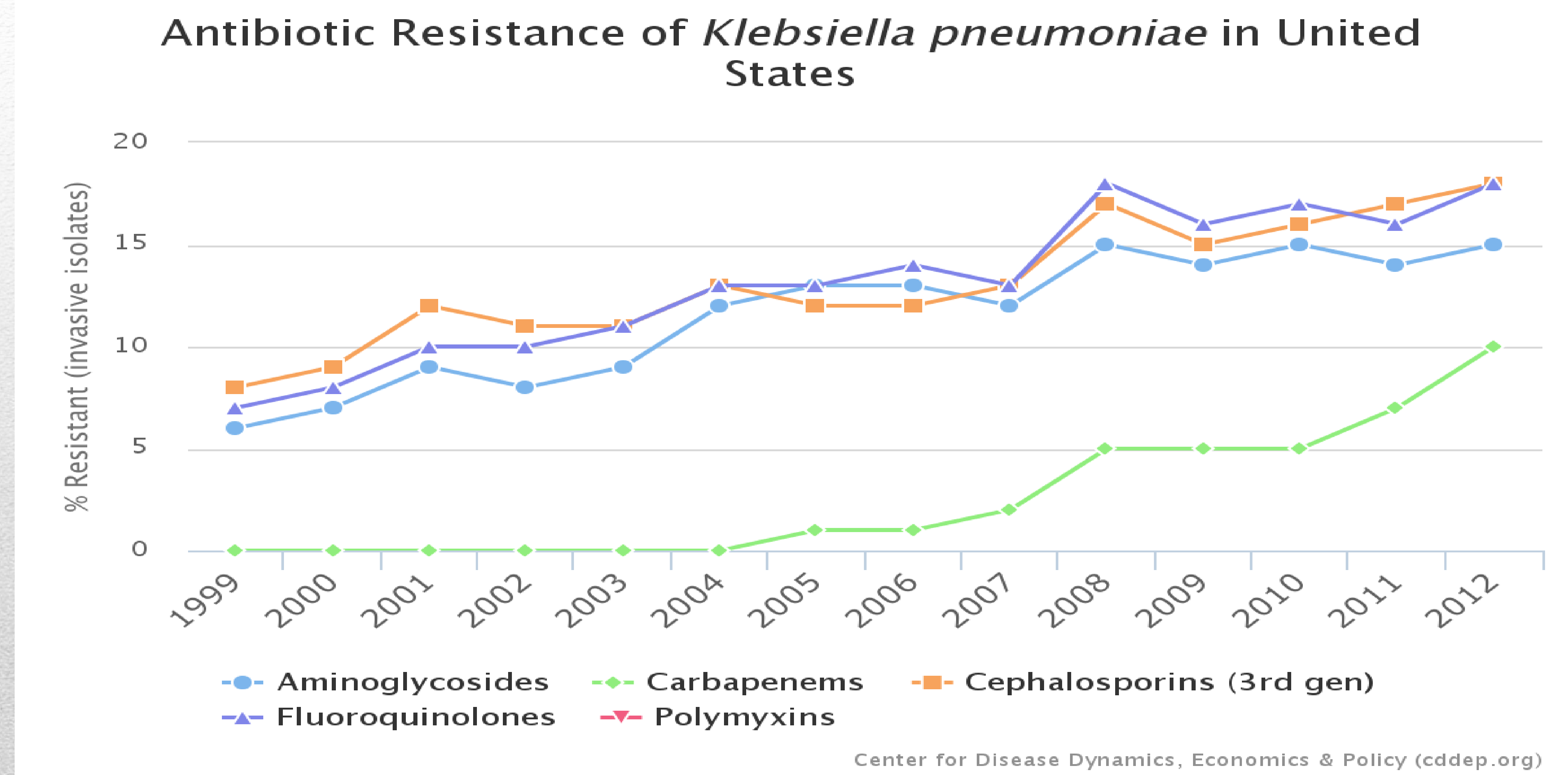


resistancemap.cddep.org

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# A Global Problem

## Methicillin-Resistant *Staphylococcus aureus*

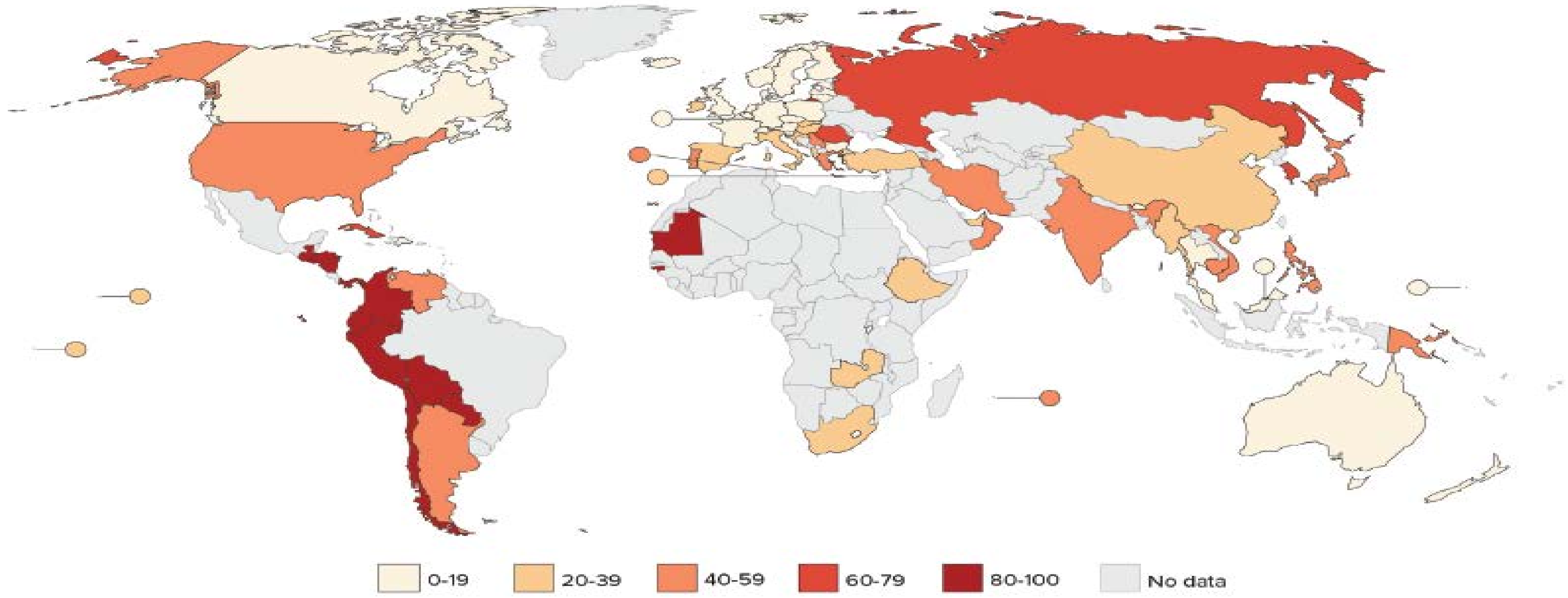



**FIGURE 1-1[1]: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA), by country (most recent year, 2011–14)**

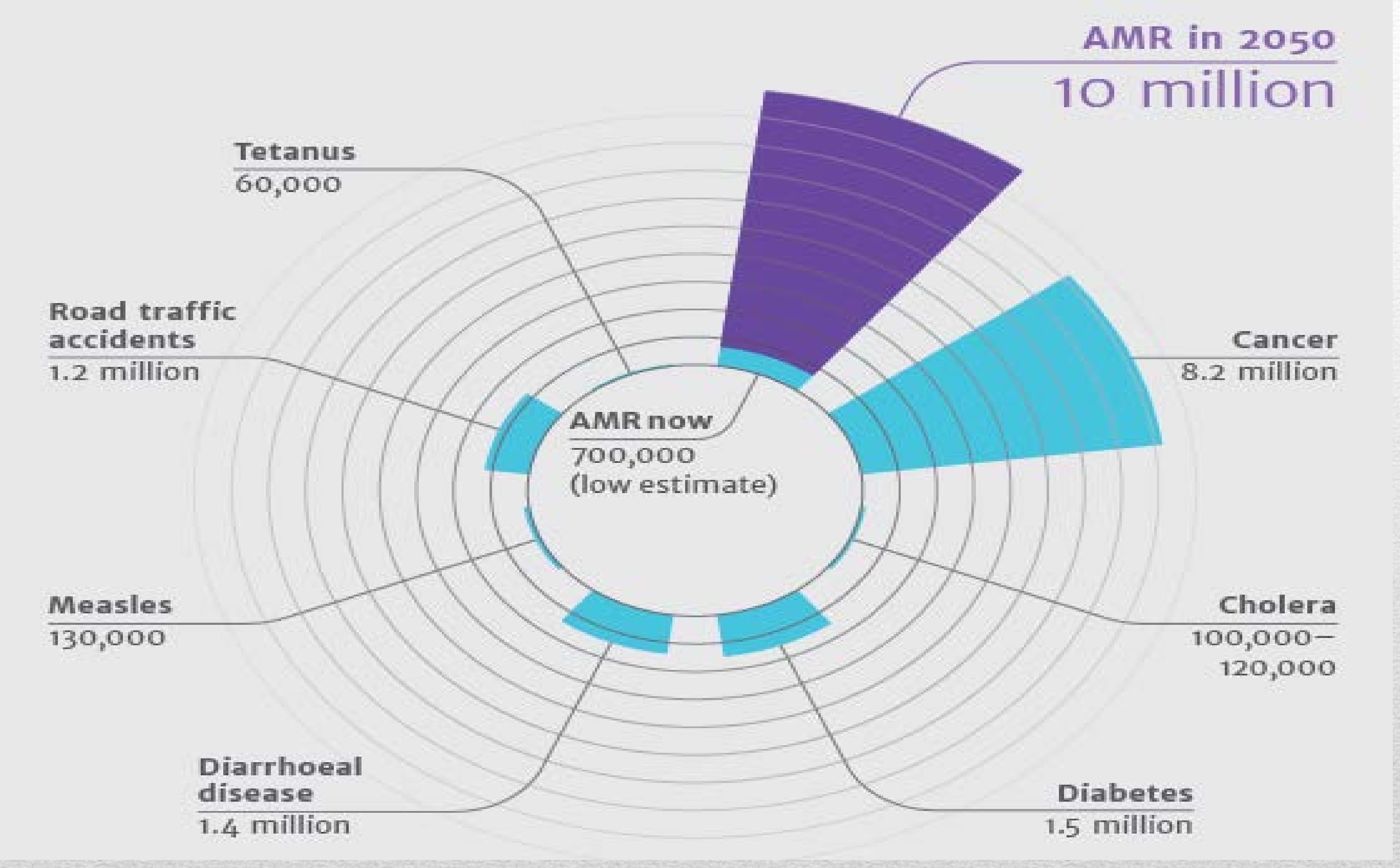
*Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming*

# Antimicrobial Resistance Worldwide

## More than just antibiotics at risk

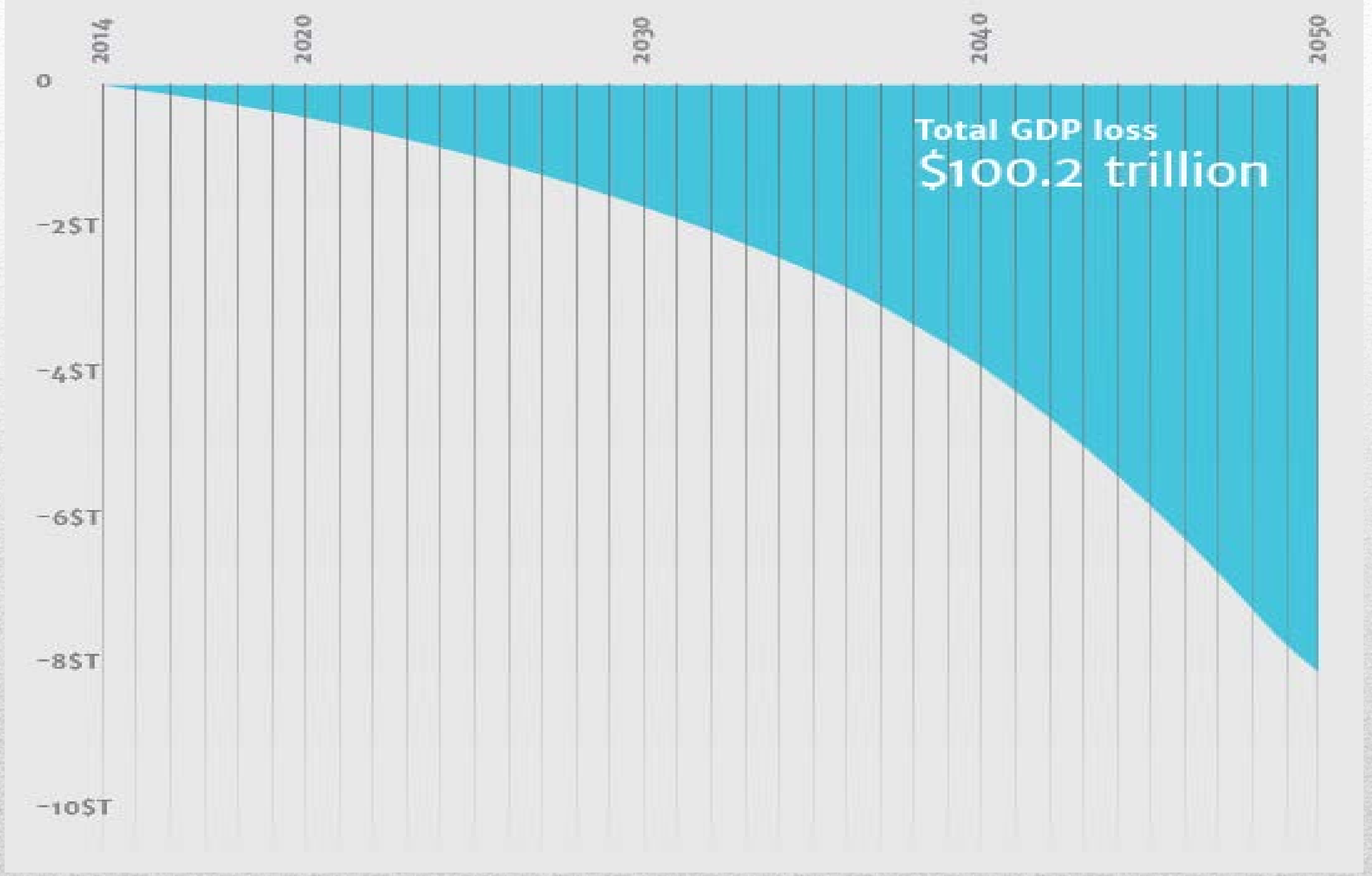
| Example of mycobacterium: | Example of parasite: | Example of viruses: |
|---|---|---|
| **Tuberculosis** | **Malaria** | **HIV and influenza** |
| Increased morbidity and mortality, increased costs, threatened disease control | Threatened disease control | Threatened disease control |

# Worldwide Deaths Due to AMR




Source: UK Review on AMR

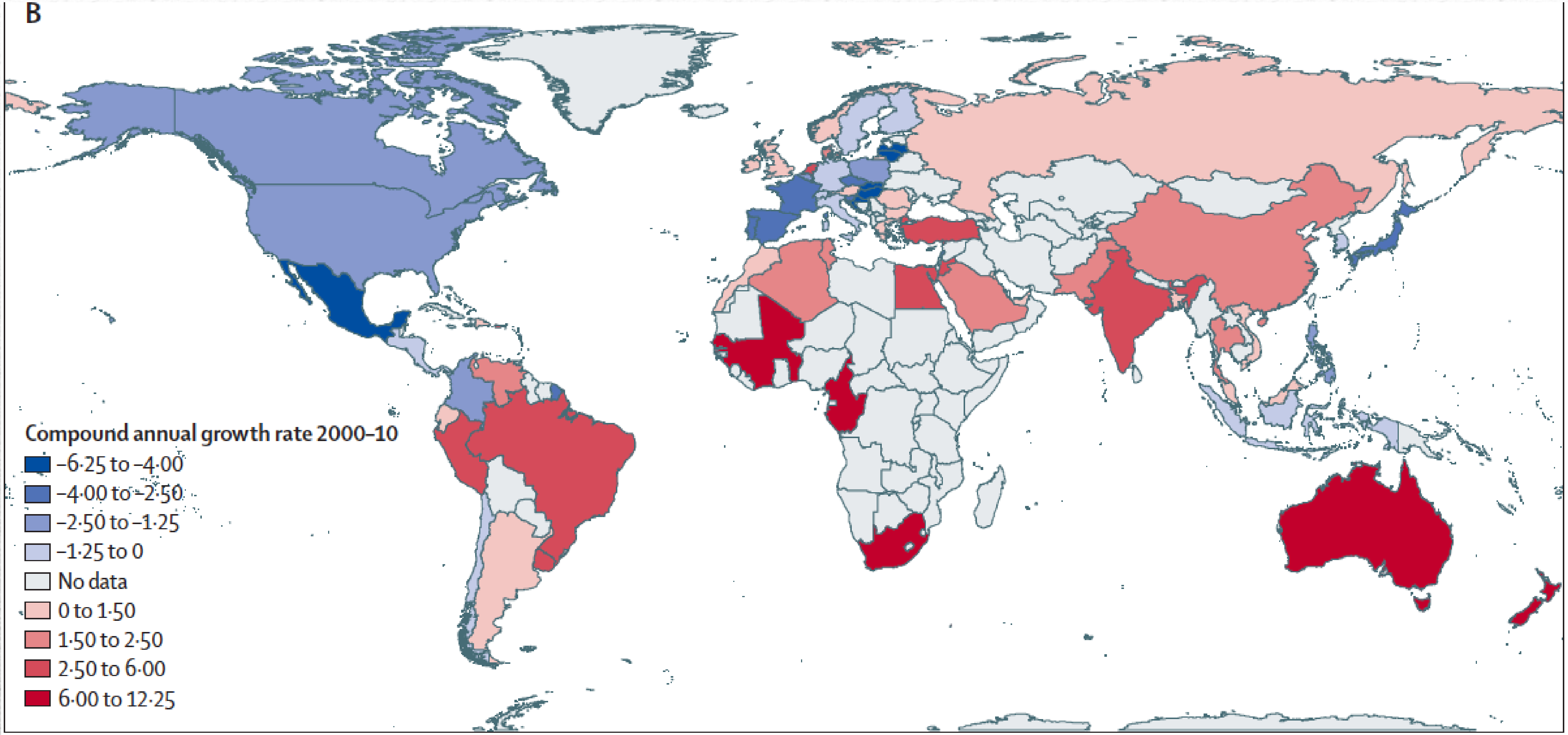
# Economic Cost of AMR




Source: UK Review on AMR

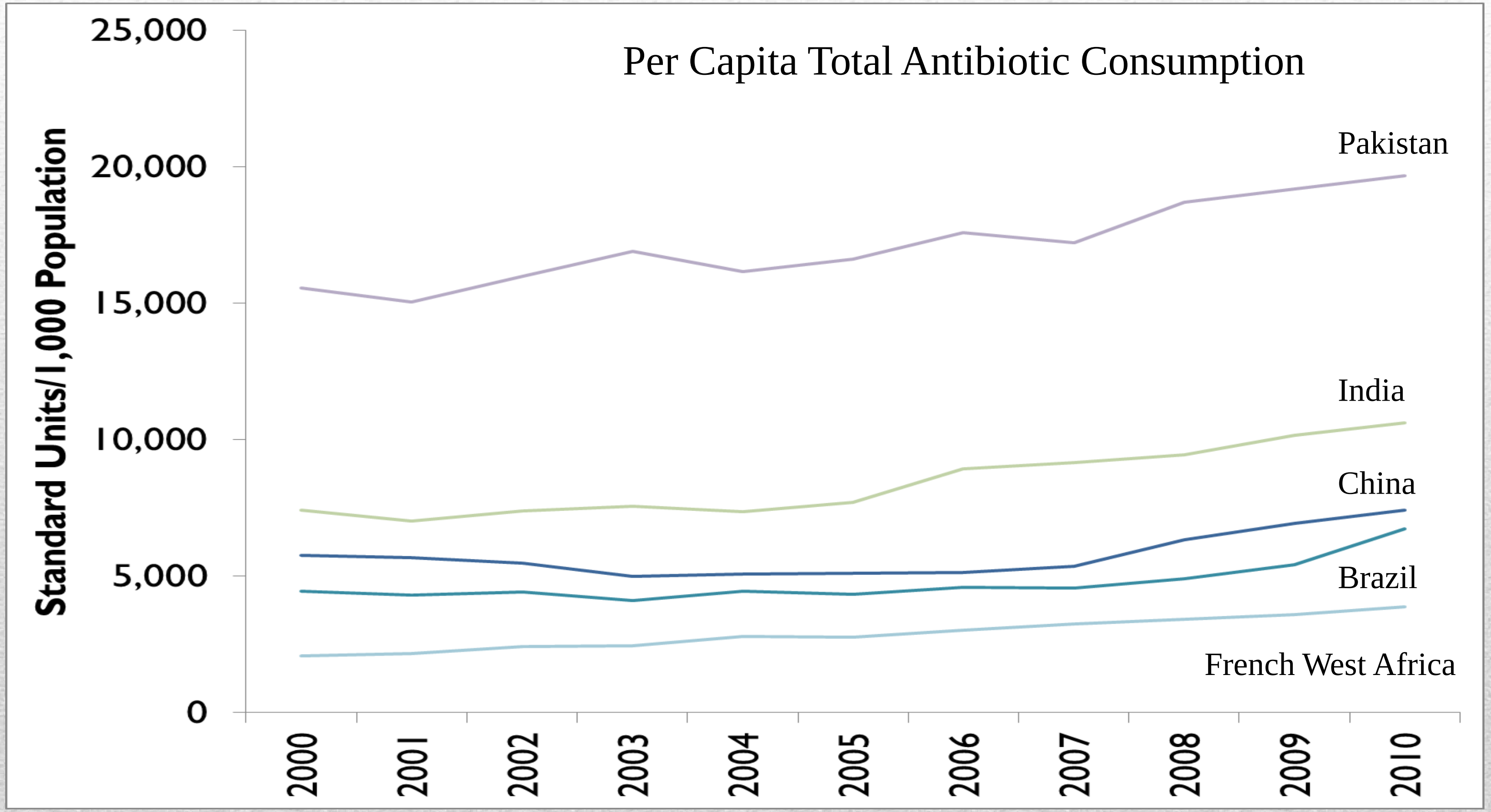
II. Increasing incomes are increasing access to antibiotics and saving lives - but they are not a good substitute for public health

# Changes in Global Consumption 2000-2010




Van Boeckel et al, *Lancet Inf. Dis.*, 2014

# Antibiotic Consumption is Increasing in Developing Countries

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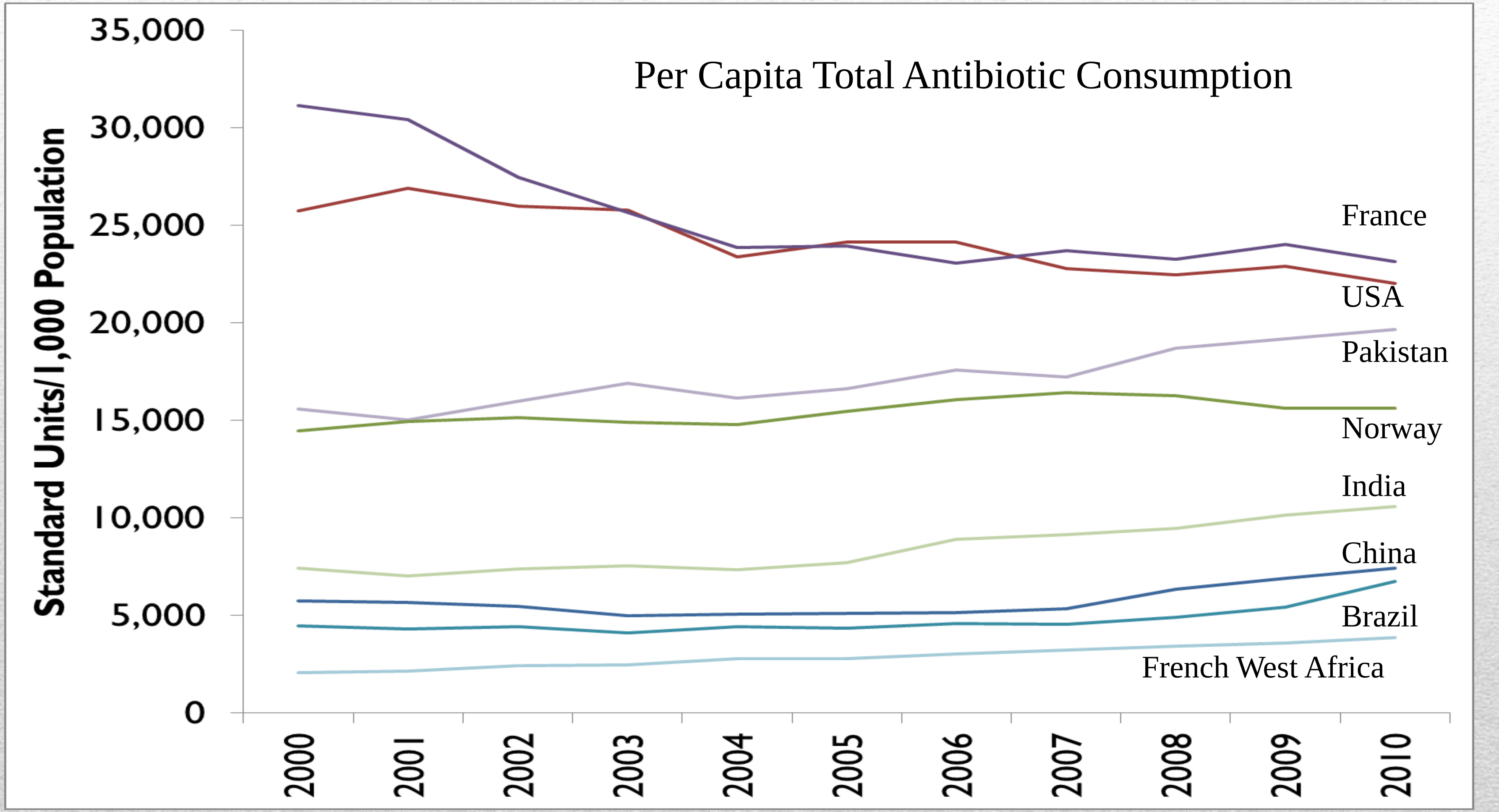


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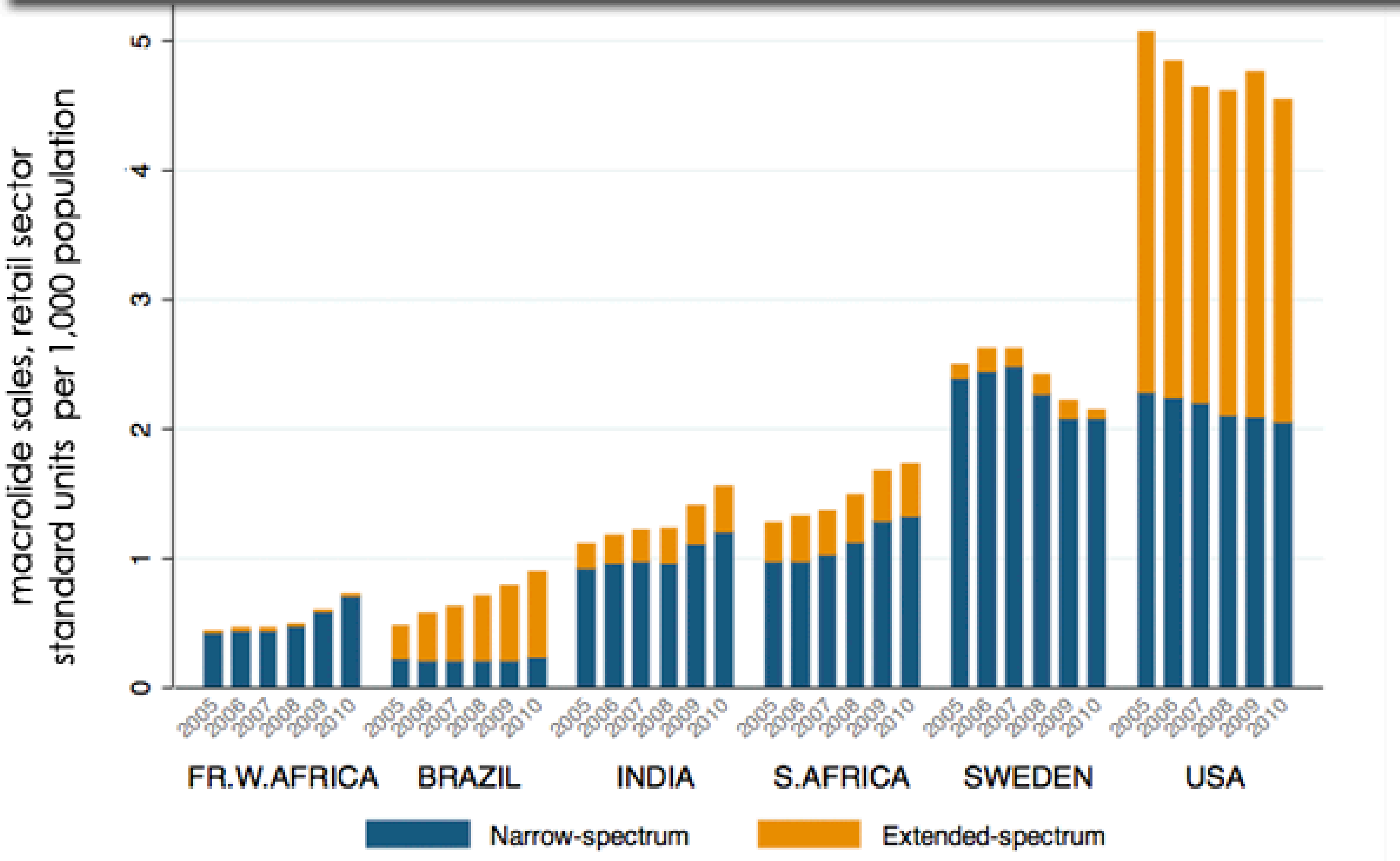
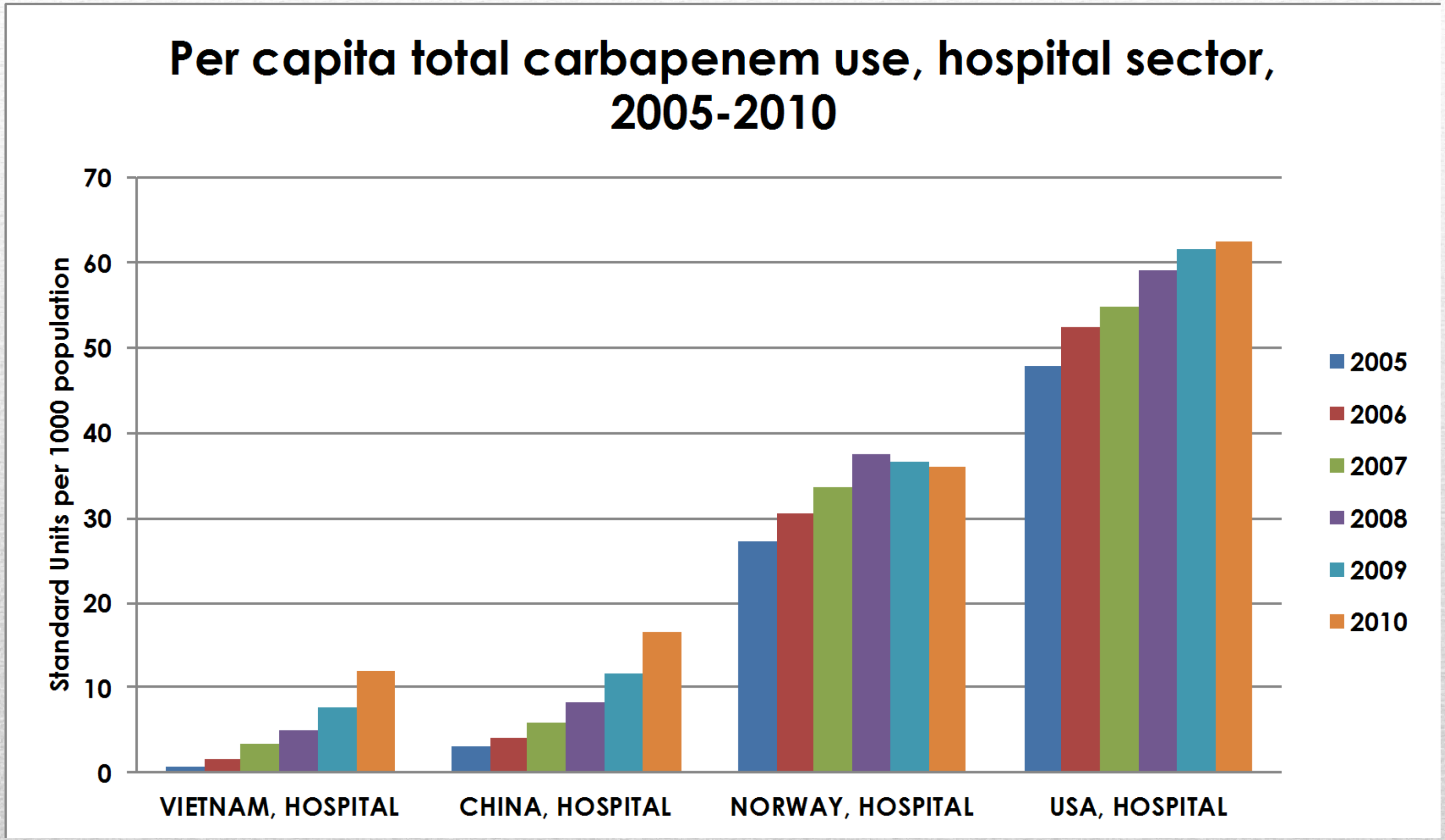
# Extended-spectrum macrolide use is highly prevalent in the United States, and increasing in developing countries

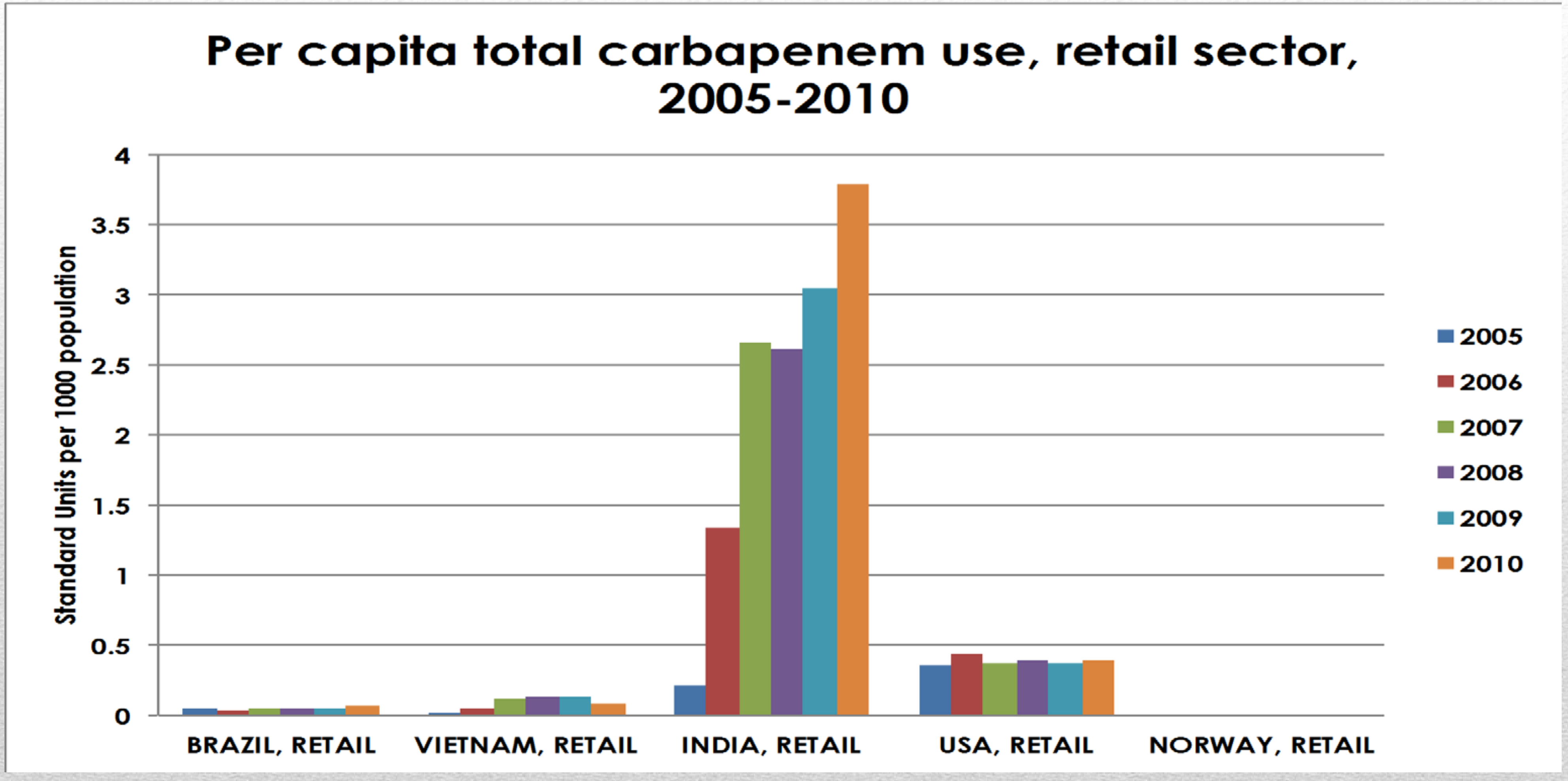



Data source: Based on data obtained under license from IMS Health MIDAS ™ (January 2005-December 2010); IMS Health Incorporated. 

# Carbapenem use is increasing in the hospital



# But carbapenems are also sold on the retail market

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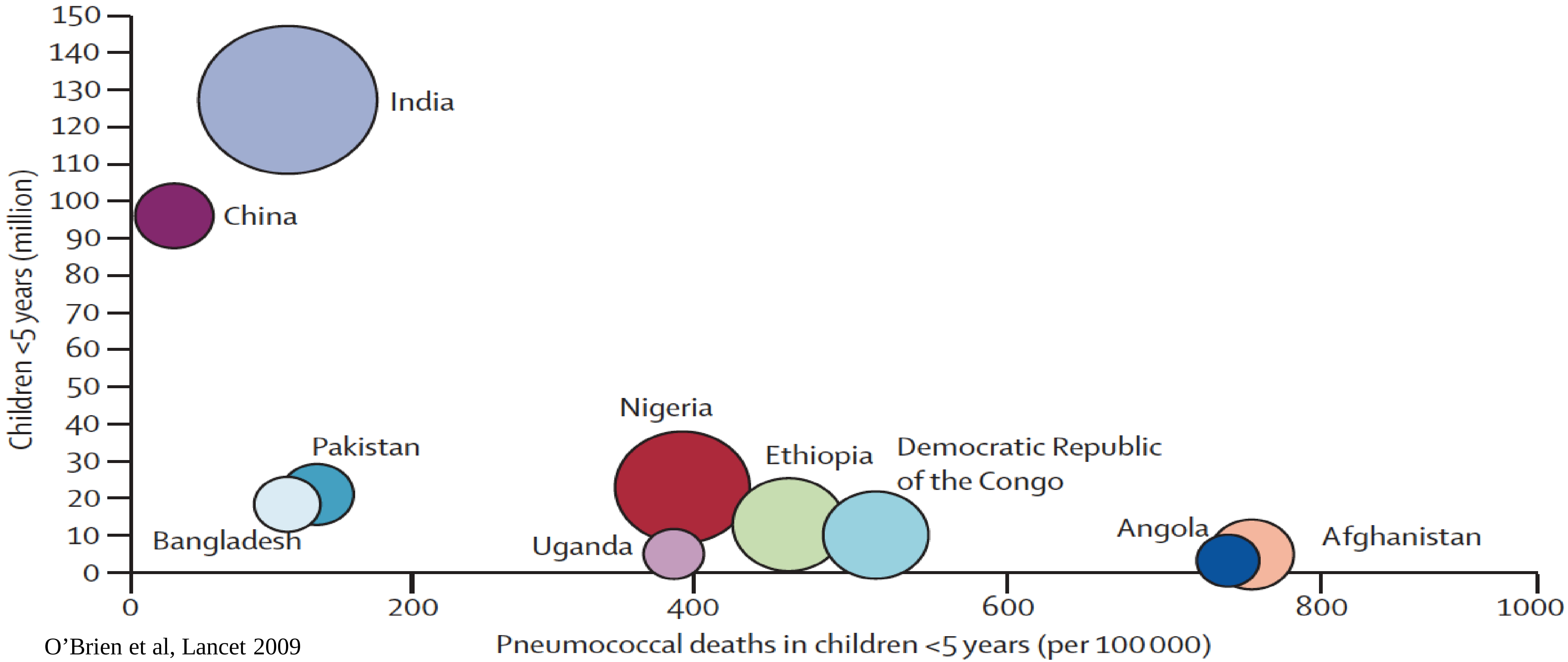
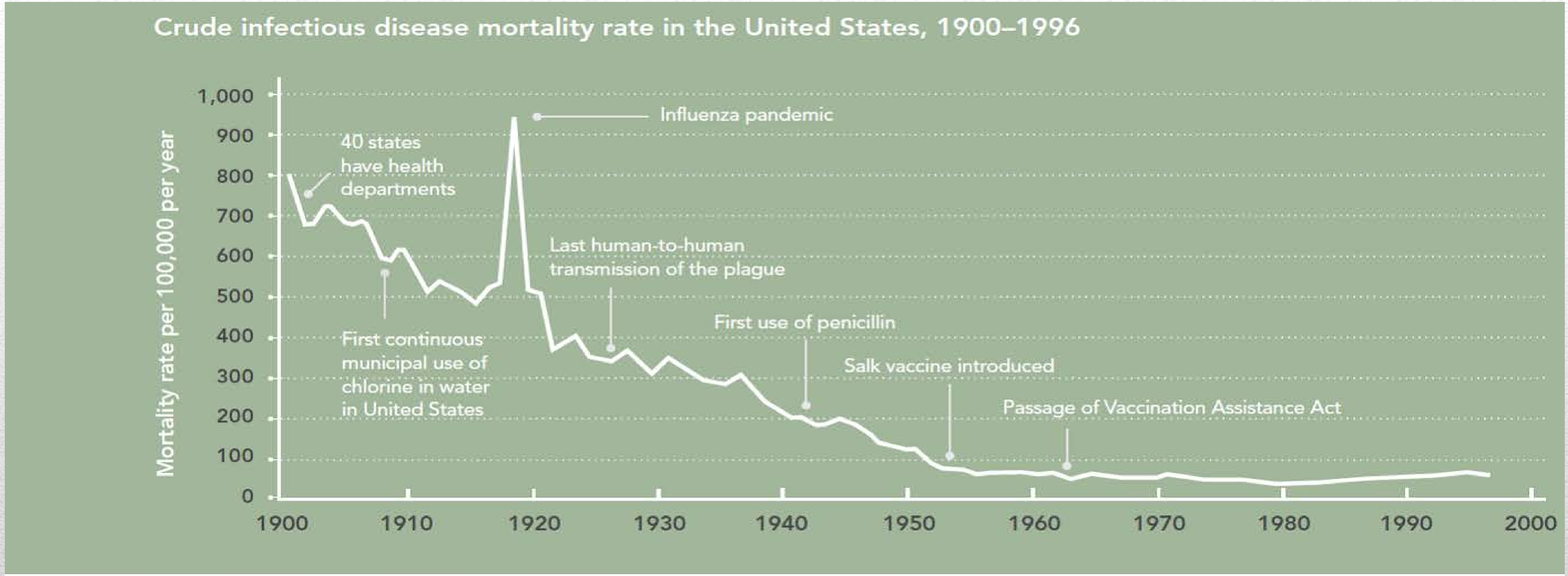
# Bacterial diseases are still major killers in developing countries because of lack of access to antibiotics




O'Brien et al, Lancet 2009

# What are We Asking of Antibiotics?




**Source:** Adapted from Armstrong, Conn et al. (1999).

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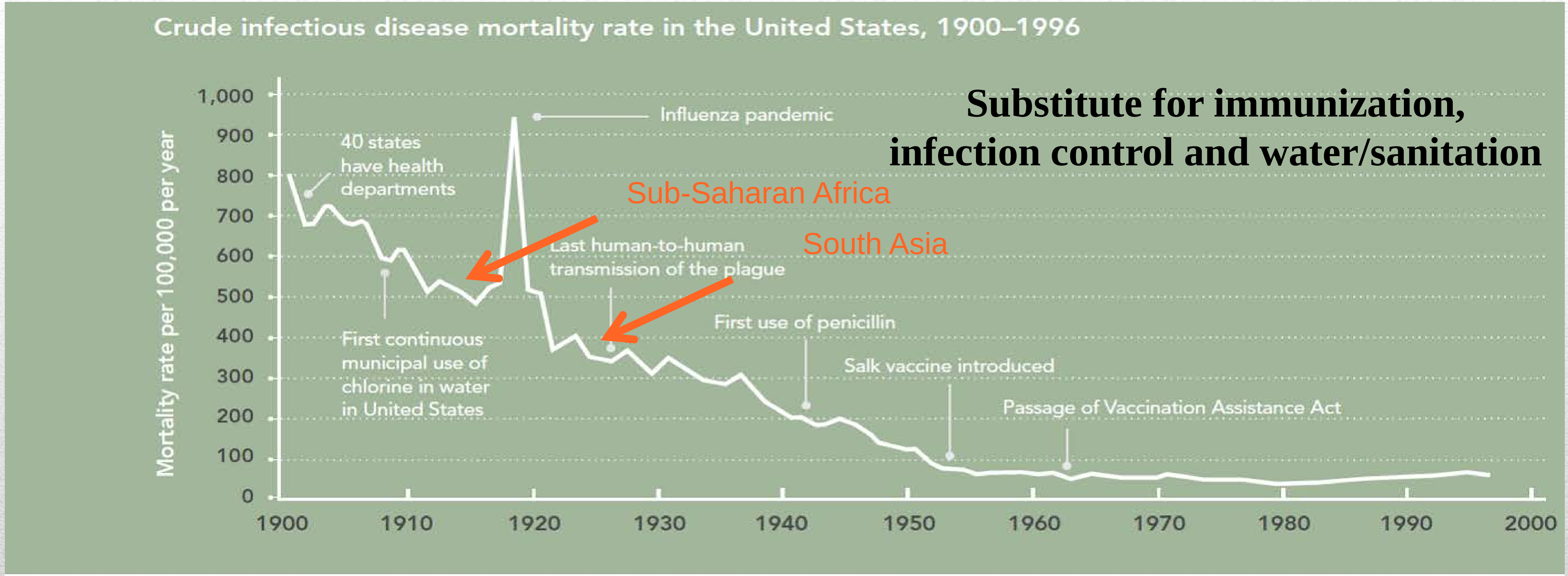



Source: Adapted from Armstrong, Conn et al. (1999).

III. More antibiotic use is associated with increasing rates of antibiotic resistance

# Antibiotic Use and Resistance

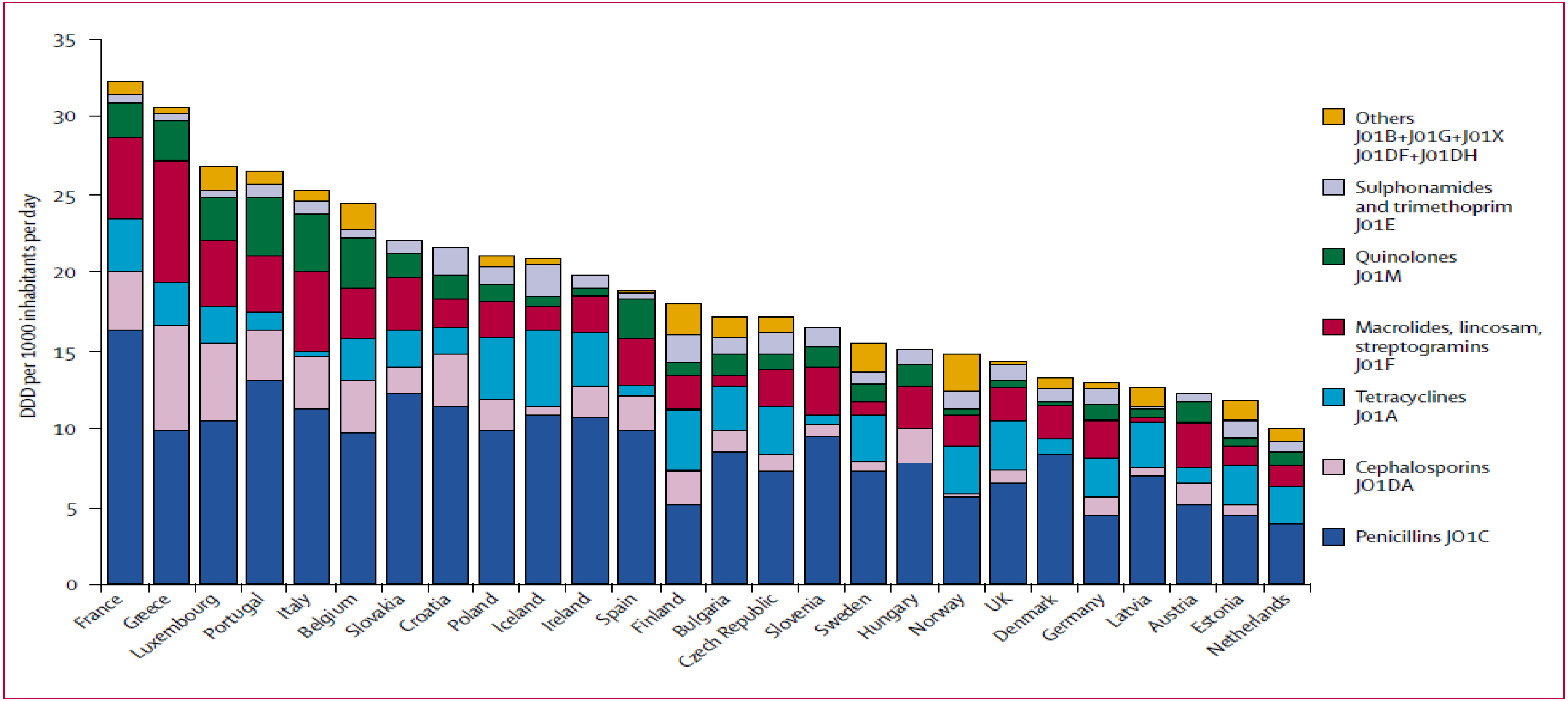



***Figure 1:*** **Total outpatient antibiotic use in 26 European countries in 2002**

Gossens et al 2005

# Antibiotic Use ar

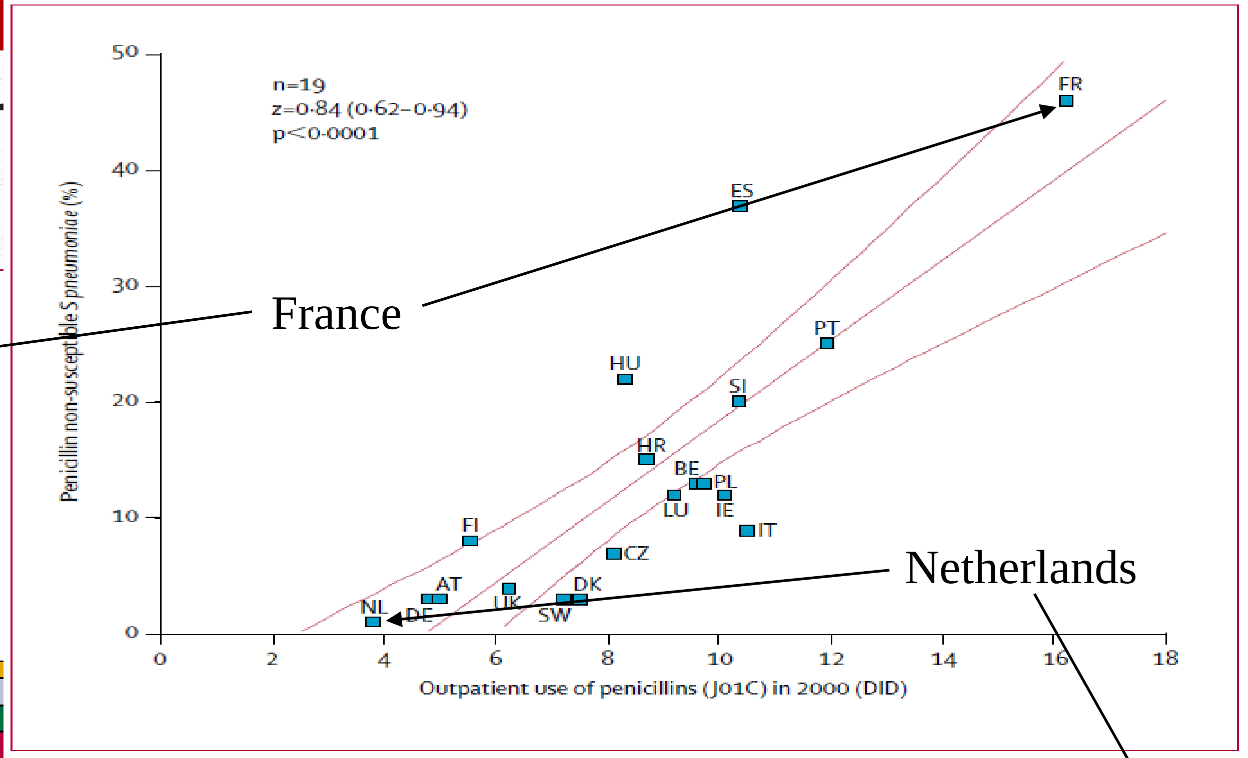
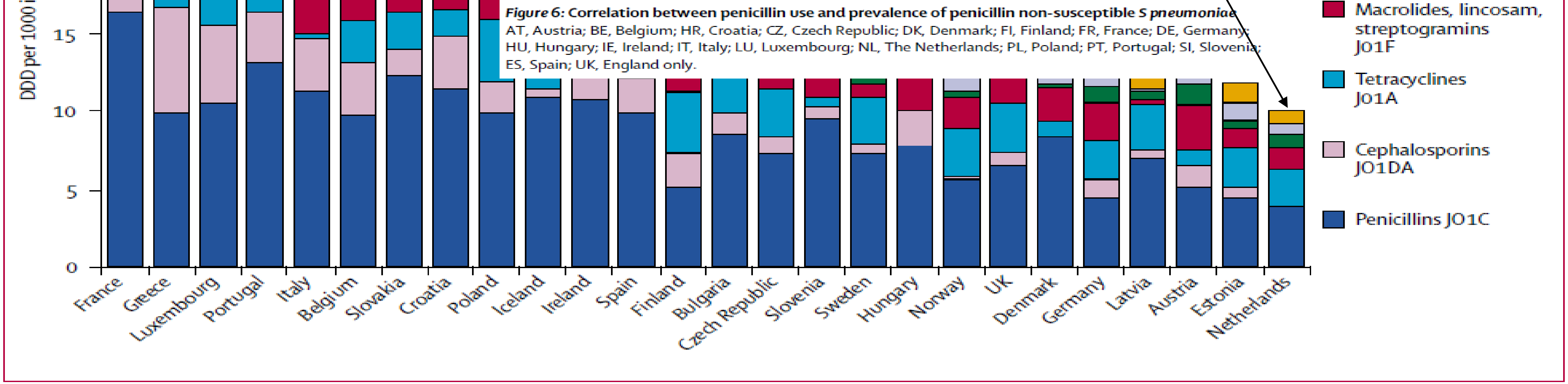



*Figure 6:* **Correlation between penicillin use and prevalence of penicillin non-susceptible *S pneumoniae***
AT, Austria; BE, Belgium; HR, Croatia; CZ, Czech Republic; DK, Denmark; FI, Finland; FR, France; DE, Germany; HU, Hungary; IE, Ireland; IT, Italy; LU, Luxembourg; NL, The Netherlands; PL, Poland; PT, Portugal; SI, Slovenia; ES, Spain; UK, England only.

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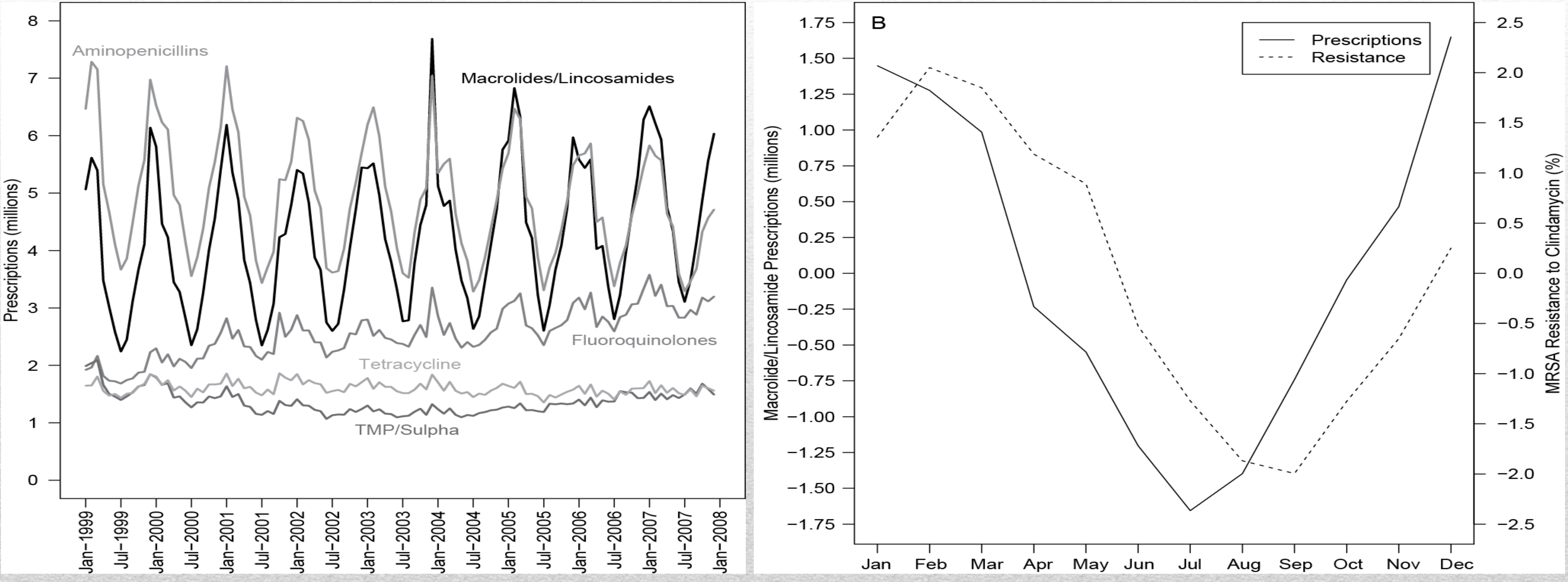
# Antibiotic Use and Resistance




Source: Sun et al 2012

IV. Drivers of antibiotic use relate to incentives and behavior of patients, physicians, pharma, payers and healthcare institutions.

# Drivers of Antibiotic Use

## How do incentives affect antibiotic prescribing?

### Patient Expectations/Satisfaction

- Patients more likely to get a prescription if they expect antibiotics
- Physicians more likely to give a prescription if they believe patient expects antibiotics regardless of patient expectation

# Drivers of Patient Expectations

**Germs are germs**: e.g., bacteria and viruses are the same

**Why Not Take a Risk?:** e.g., “I don’t know if antibiotics will make me better, but it’s better to be safe than sorry so I should take them”

**Others:**

- **Prior Knowledge:** “I got better last time I got ABX”
- **WebMD:** “Someone (i.e. internet/friend) told me that antibiotics will make me better”
- **Trust:** "I trust the doctor to give me antibiotics if I am sick (when I need them)“
- **Seriousness:** "If the doctor takes me seriously, they will give me a prescription“
- **Veni, Vidi, Vici:** "Only a prescription is worth the wait“

# Why Not Take a Risk?

Motivated by Fuzzy Trace Theory

Status quo: patient is already sick

Two options

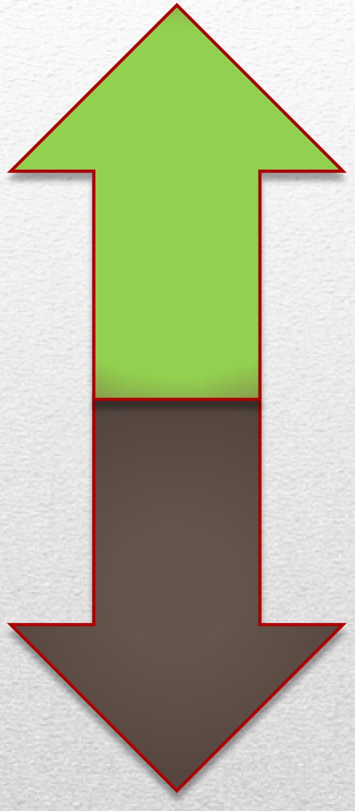
1. Stay sick for sure (by avoiding antibiotics)
2. Maybe stay sick; maybe get better (by taking antibiotics)

Getting better is preferred over staying sick, so choose antibiotics

Underlying assumptions:

- There is some chance that antibiotics could make them feel better
- Antibiotics are essentially harmless to the individual

Get Better



Stay Sick

# Drivers of Antibiotic Use

## How do incentives affect antibiotic prescribing?

- Patient Expectations/Satisfaction
- Patient Socioeconomics
  - Health insurance increases prescribing
  - Free programs increase antibiotics

# Drivers of Antibiotic Use

## How do incentives affect antibiotic prescribing?

Patient Expectations/Satisfaction

Patient Socioeconomics

Legal Ramifications

Physician Remuneration

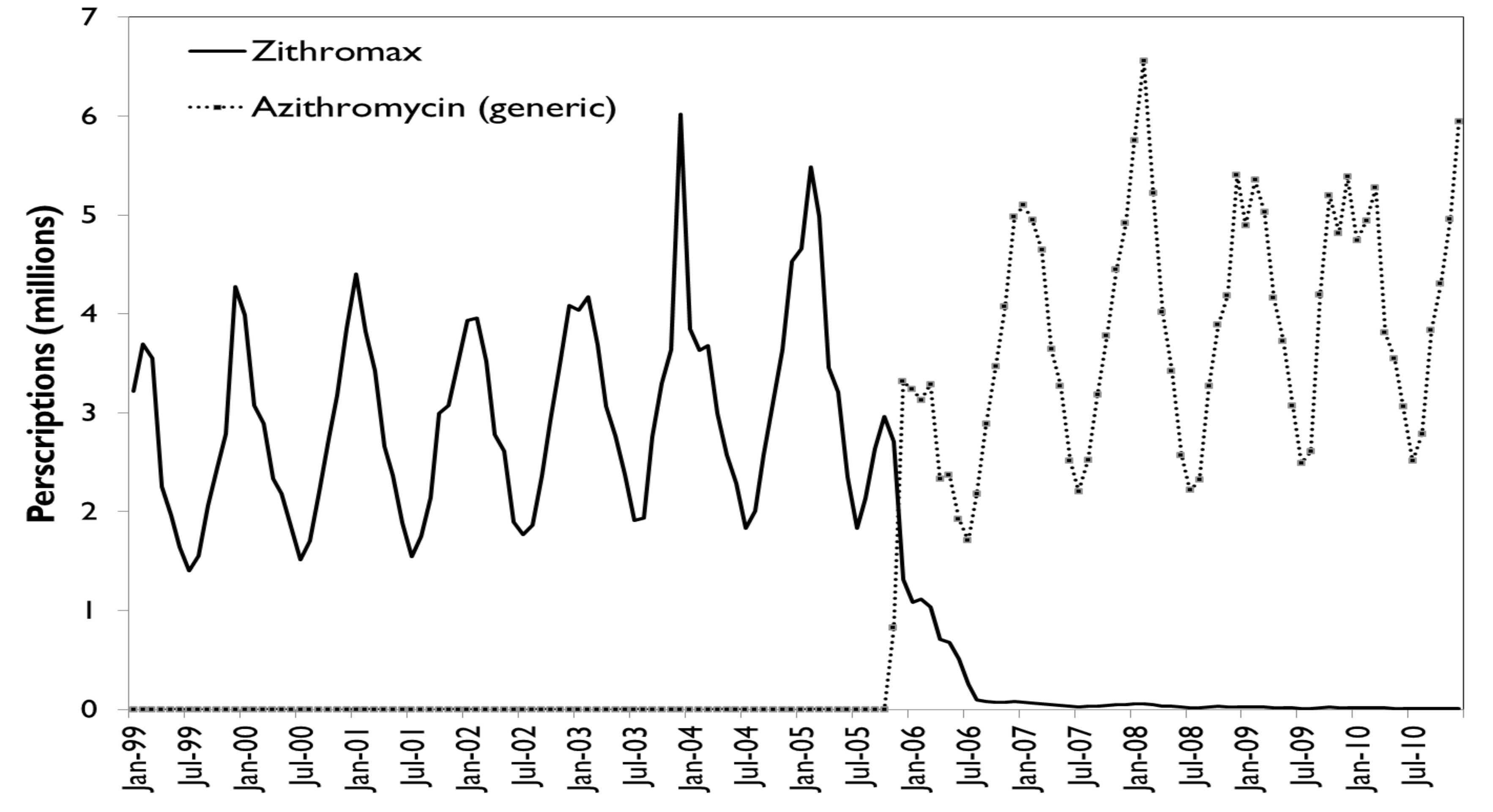
# Hospital Incentives

Antibiotics may be a substitute for infection control

Infection control is often not compensated but longer hospital stays are beneficial to the hospital

# Pharmaceutical Incentives

## Patents



# Externalities of Antibiotics

## and how they relate to incentives

Positive Externalities

- Reduce the transmission of disease

Negative Externalities

- The more antibiotics are used, the greater the selective pressure placed on bacteria to evolve

The problem is the absence of economic incentives for individuals/hospitals/companies to take into account the negative impact of their use of antibiotics on social welfare

V. There is no silver bullet for maintaining antibiotic effectiveness. There are tradeoffs to every approach.

# So what can we do?

Maintaining antibiotic effectiveness in the long term requires

1. Conservation: Technological, medical, and incentive-based solutions to keep existing antibiotics working
2. Innovation: Develop new antibiotics

But these two approaches are linked in a negative feedback loop
Increased innovation reduces the need for conservation and vice versa

# Conservation

Antimicrobial stewardship

New clinically relevant tests that identify both the cause of an infection and its sensitivity to common antibiotics

Vaccines



J. Am. Soc. Mass Spectrom. (2013) 24:1194–1201
DOI: 10.1007/s13361-013-0609-x

FOCUS: MS IN THE CHARACTERIZATION OF MICROORGANISMS: RESEARCH ARTICLE

**Establishing Drug Resistance in Microorganisms by Mass Spectrometry**

Plamen A. Demirev, Nathan S. Hagan, Miquel D. Antoine, Jeffrey S. Lin, Andrew B. Feldman

Johns Hopkins University Applied Physics Laboratory, 11100 Johns Hopkins Rd., Laurel, MD 20723, USA

# Other types of solutions?

Combination therapies that target both essential functions and resistance factors

- Eg. amoxicillin-clavulanate

Repurpose old drugs to optimize dosing levels and the duration, and route of administration

- E.g. optimized dosing of colistin to reduce toxicity and improve efficacy

Prevent resistance by protecting non-target bacterial flora during treatments

# Antibiotics as a Natural Resource

The cost of discovering new sources of oil becomes more expensive as the resource is depleted (because harder to find and environmental regulations)

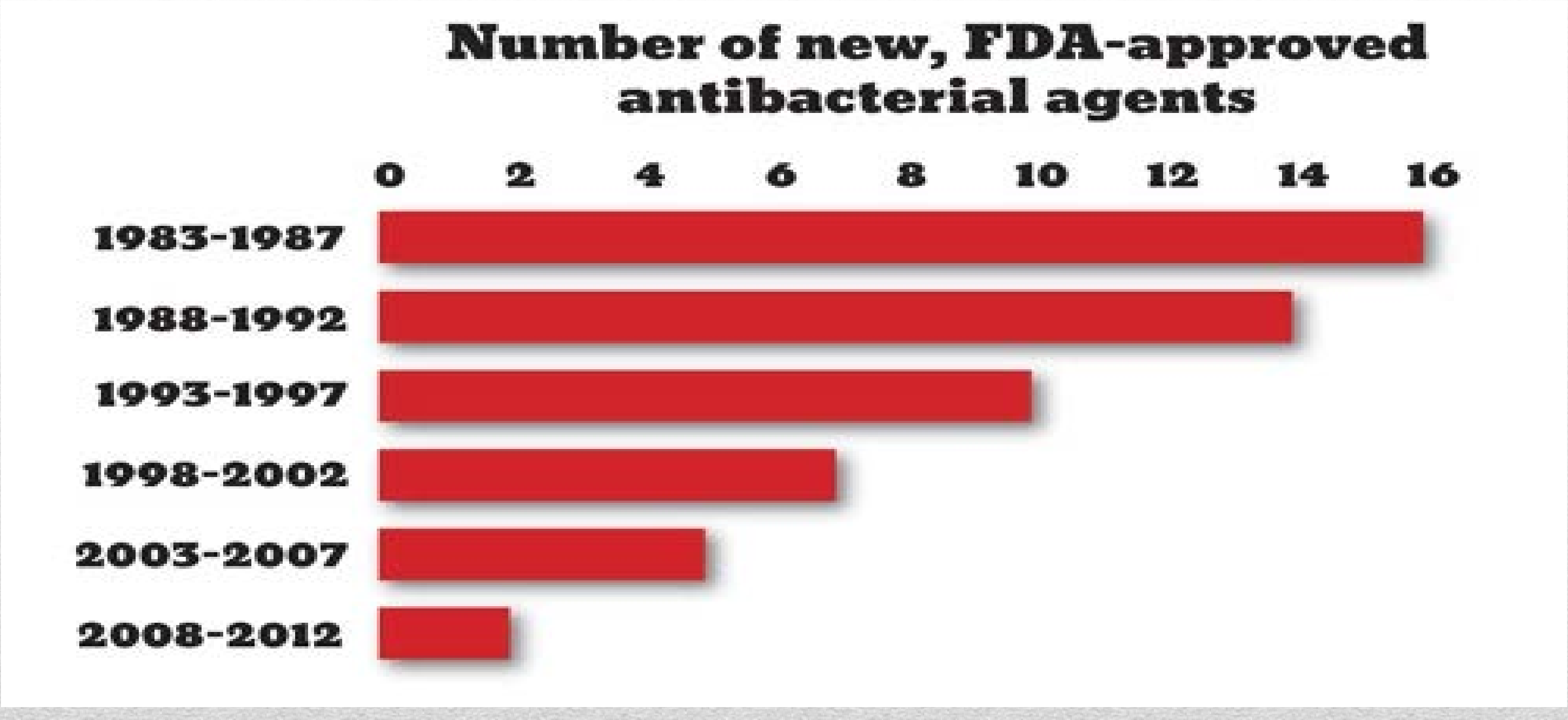
Increased incentives for finding new oil reserves reduces incentives to conserve oil

# Antibiotics as a Natural Resource

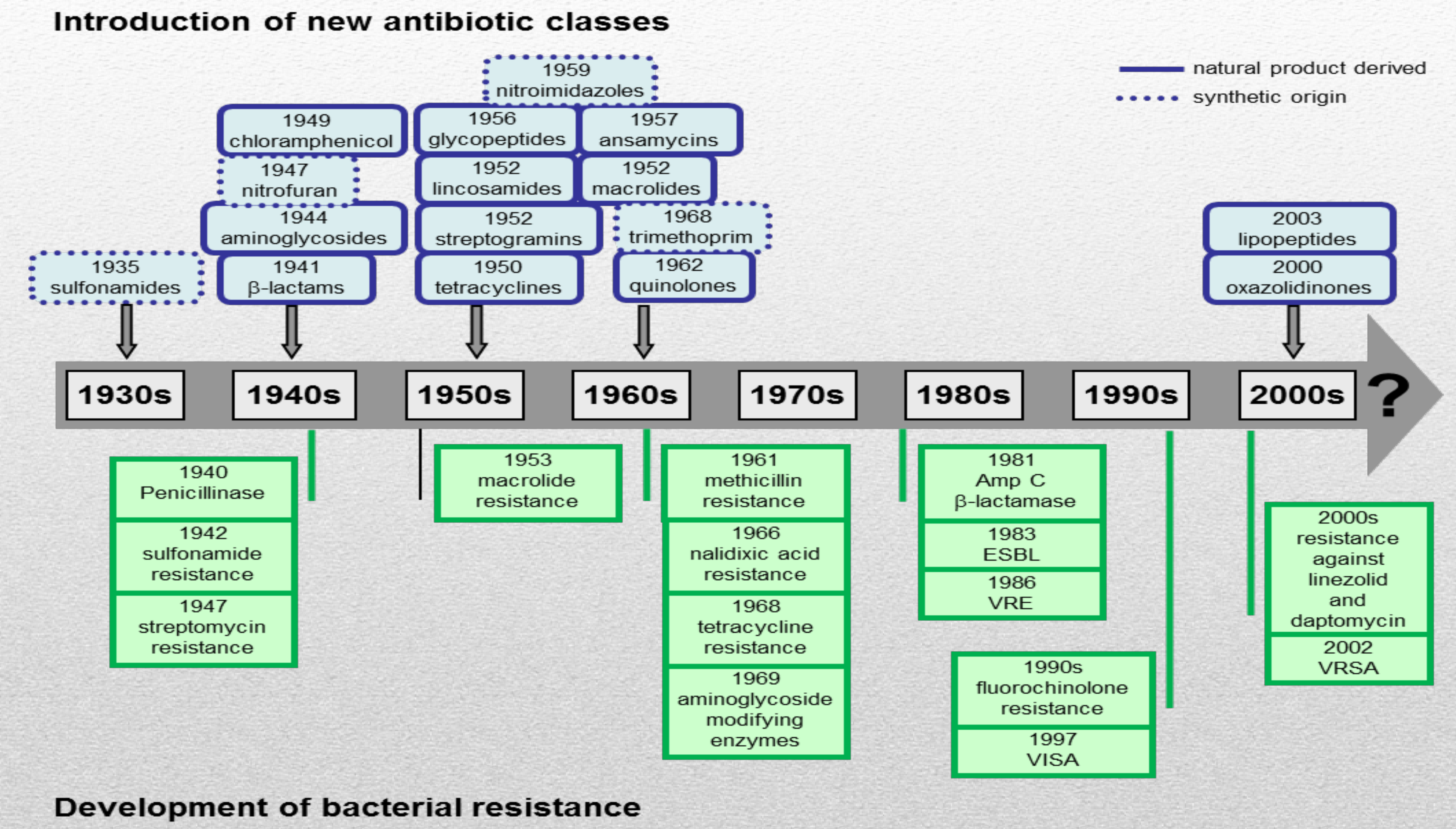
New antibiotics are likely to cost more than existing ones (because harder to discover and increased regulatory costs)

Subsidies for new drug development discourage efforts to improve how existing antibiotics are used

# Dwindling Antibiotic Development



# Once an antibiotic is introduced, resistance is not far behind



# Incentives to develop new antibiotics

Decrease cost of development (e.g. tax credits, grants, contracts, liability protection)

- Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) – BARDA partnership

Increase income linked to antibiotics (e.g. extend exclusivity, patent extensions, prizes)

- Under the Generating Antibiotic Incentives Now (GAIN) Act in the United States new antibiotics are given 5 years of additional market exclusivity for designated Qualified Infectious Disease Products

# Important questions

Do we need public subsidies for new antibiotic development or will the market respond on its own?

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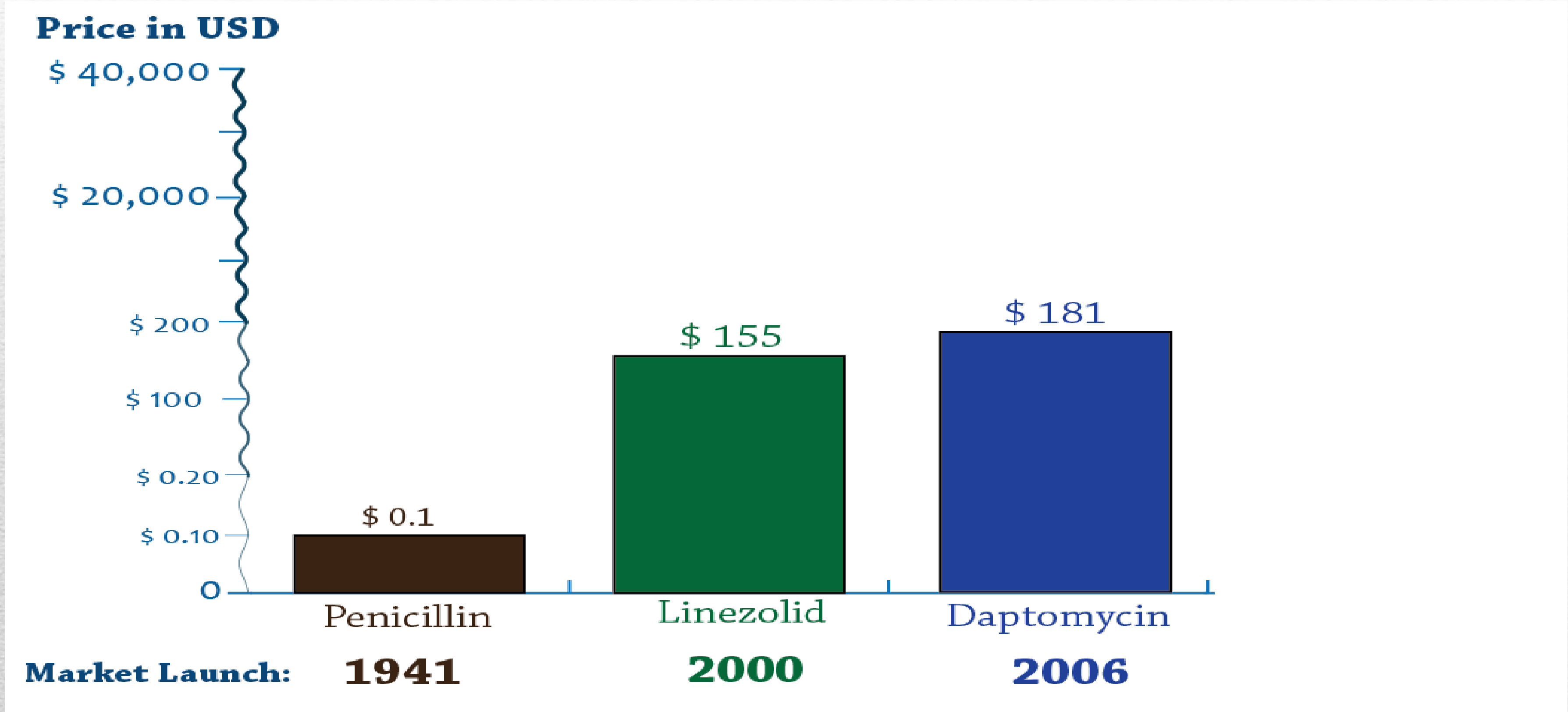

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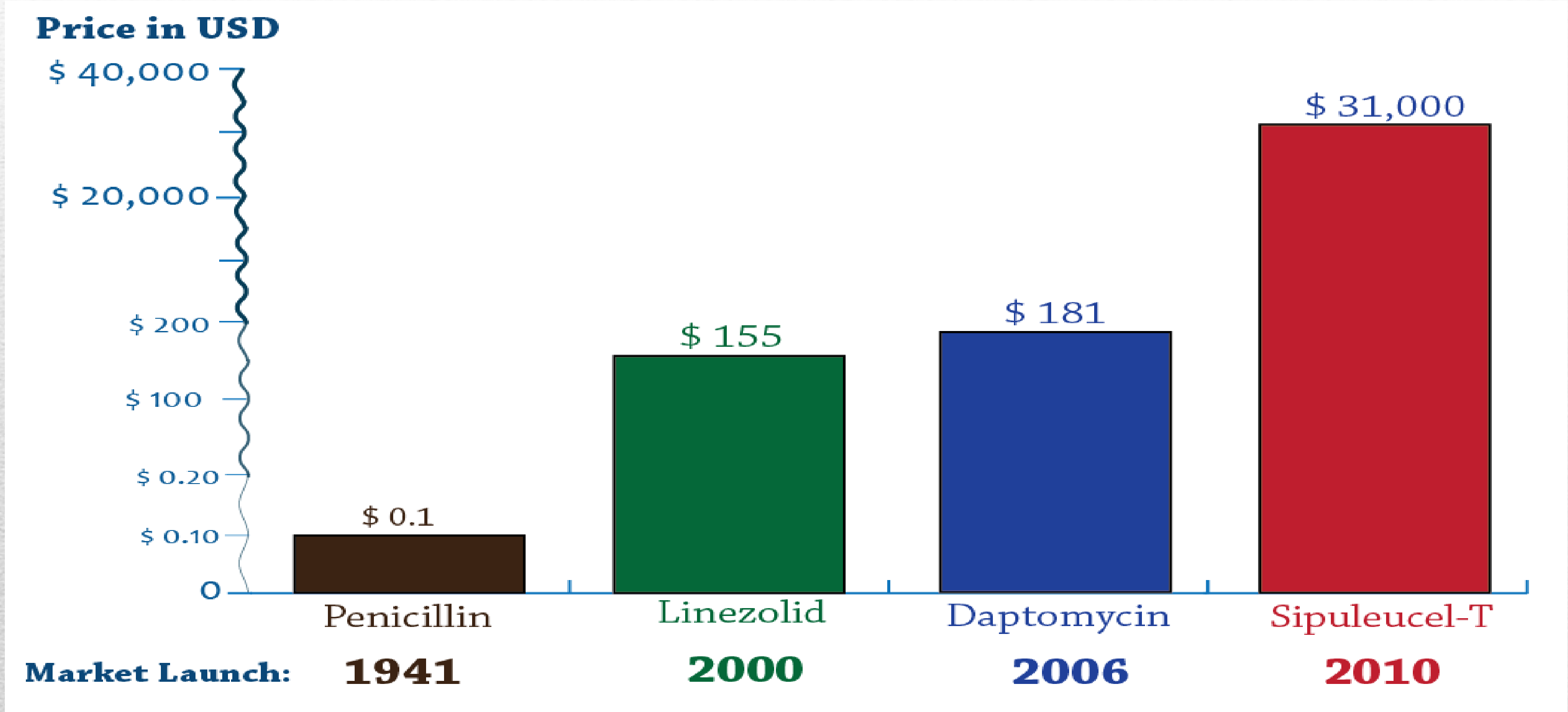

# Important questions

Do we need public subsidies for new antibiotic development or will the market respond on its own?

What is the impact of public subsidies for new drug development on stewardship?

How can we change the rules of the game to incentivize appropriate use of new (and existing) antibiotics?

How do we balance access with concerns about resistance?

For research, updates and tools on drug resistance and other global health topics,
visit:

**www.cddep.org**

Thank you!

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