Economics of Antibiotic Resistance

Ramanan Laxminarayan

Latsis Symposium, 2015

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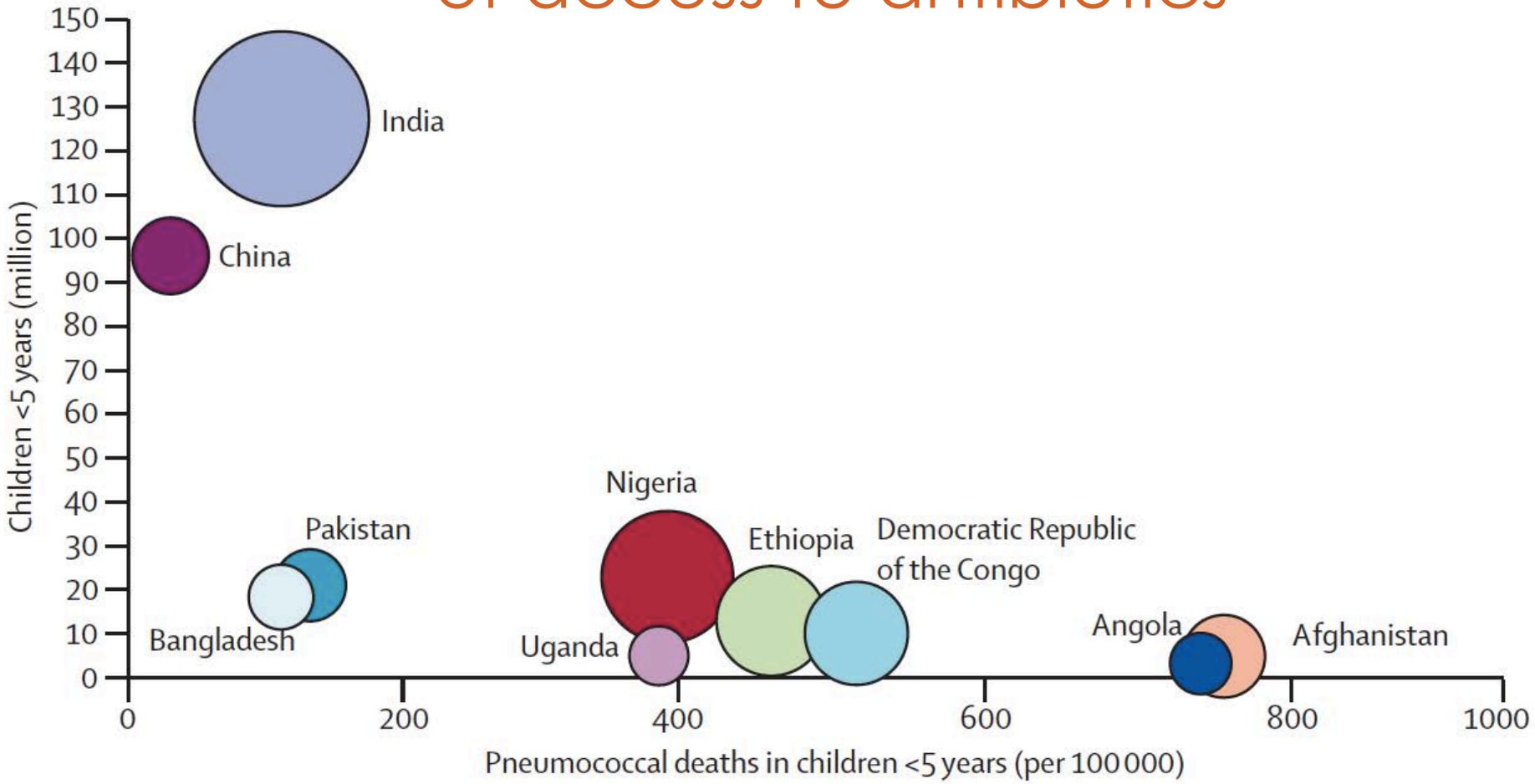
I. Increasing incomes and access to antibiotics are saving lives but are not a good substitute for public health

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



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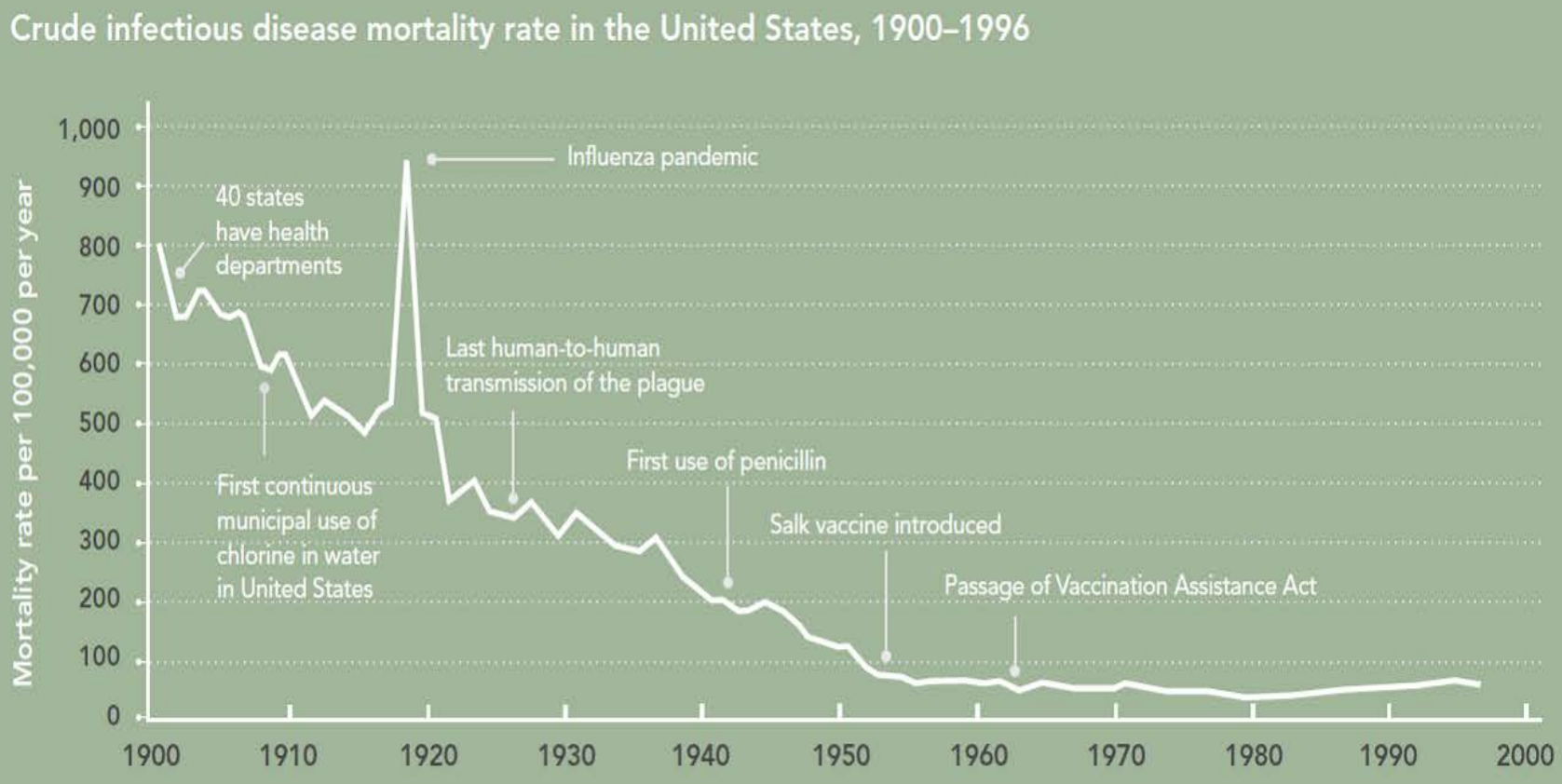
O'Brien et al, Lancet 2009

What are we asking of antibiotics?

FIGURE 1.1

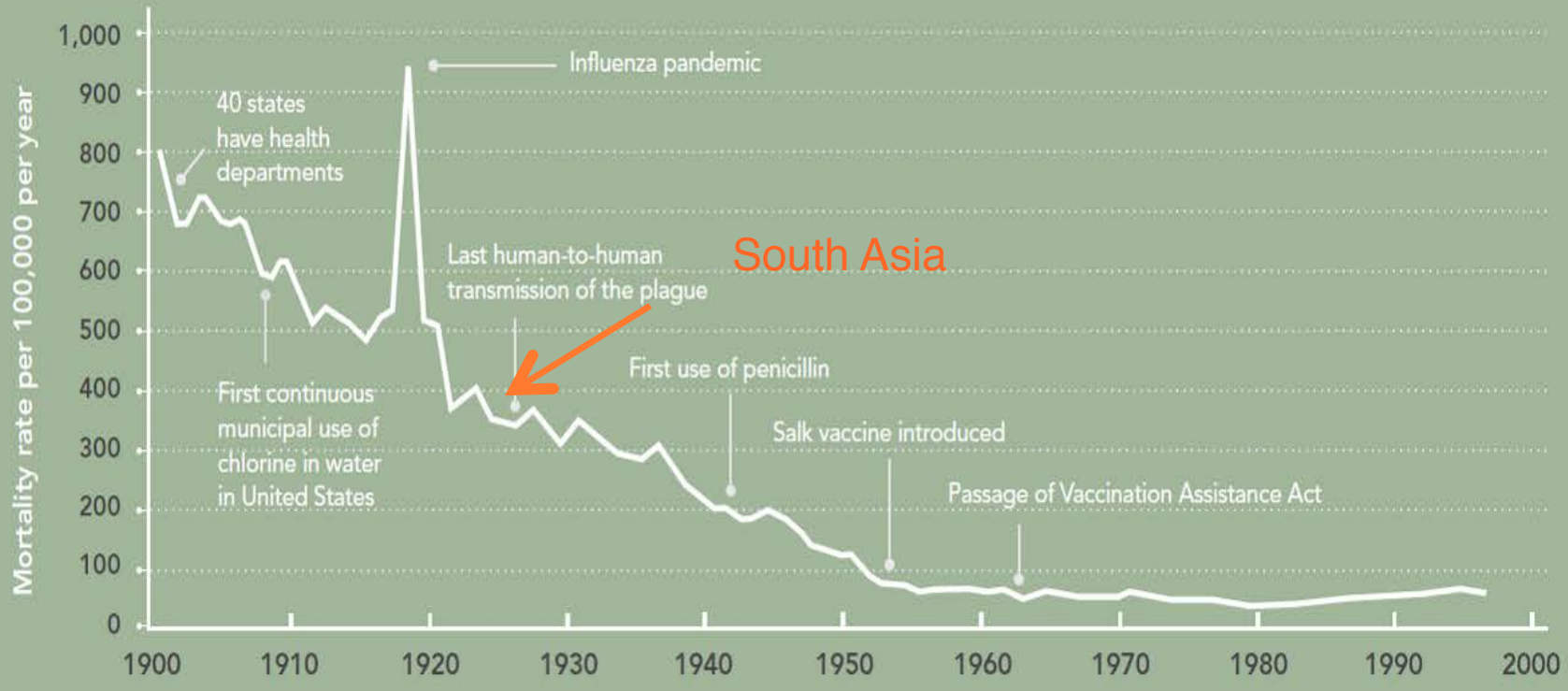


Source: Adapted from Armstrong, Conn et al. (1999).

Substitute for immunization, infection control and water/

FIGURE 1.1

Crude infectious disease mortality rate in the United States, 1900–1996



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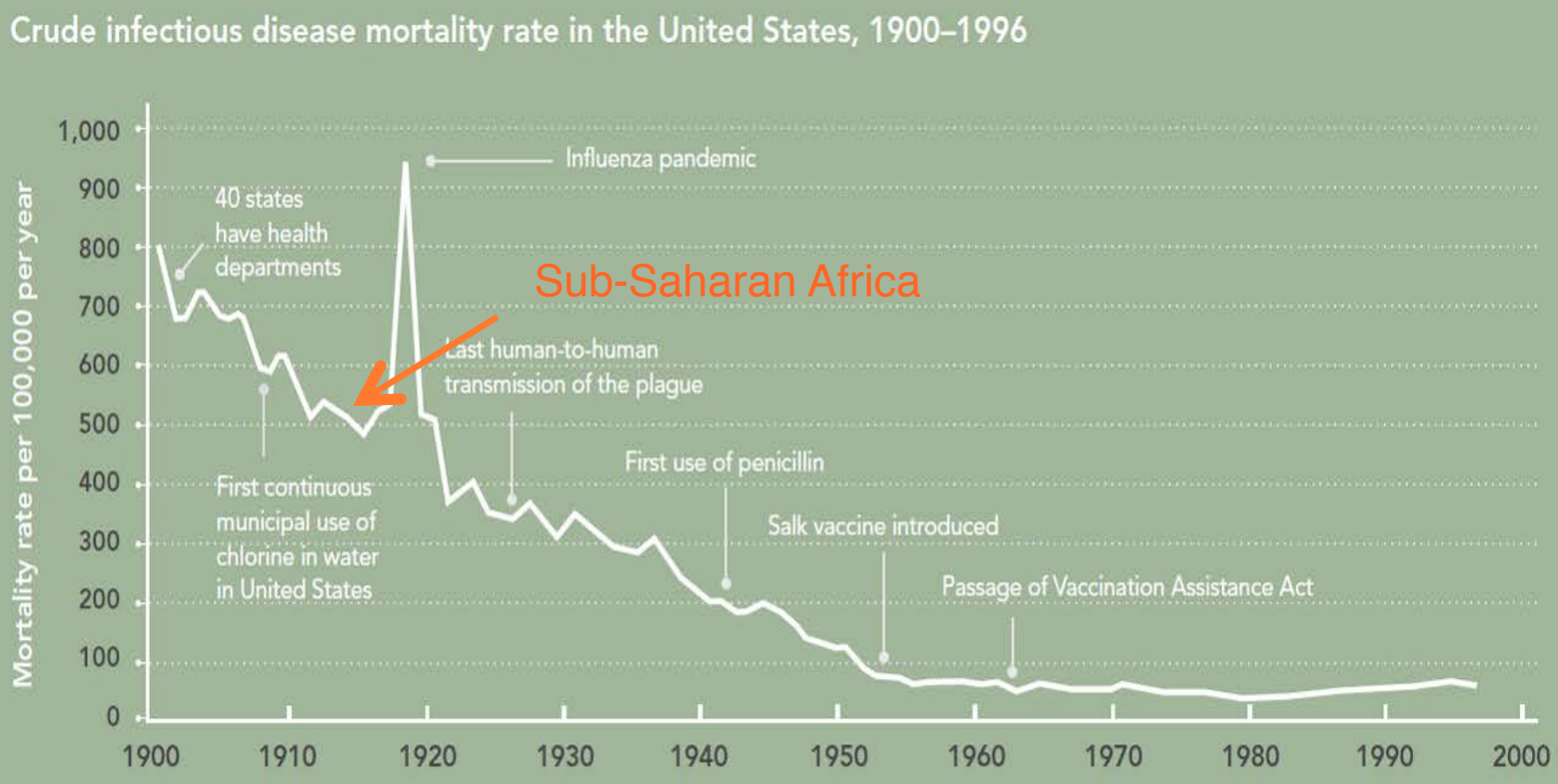
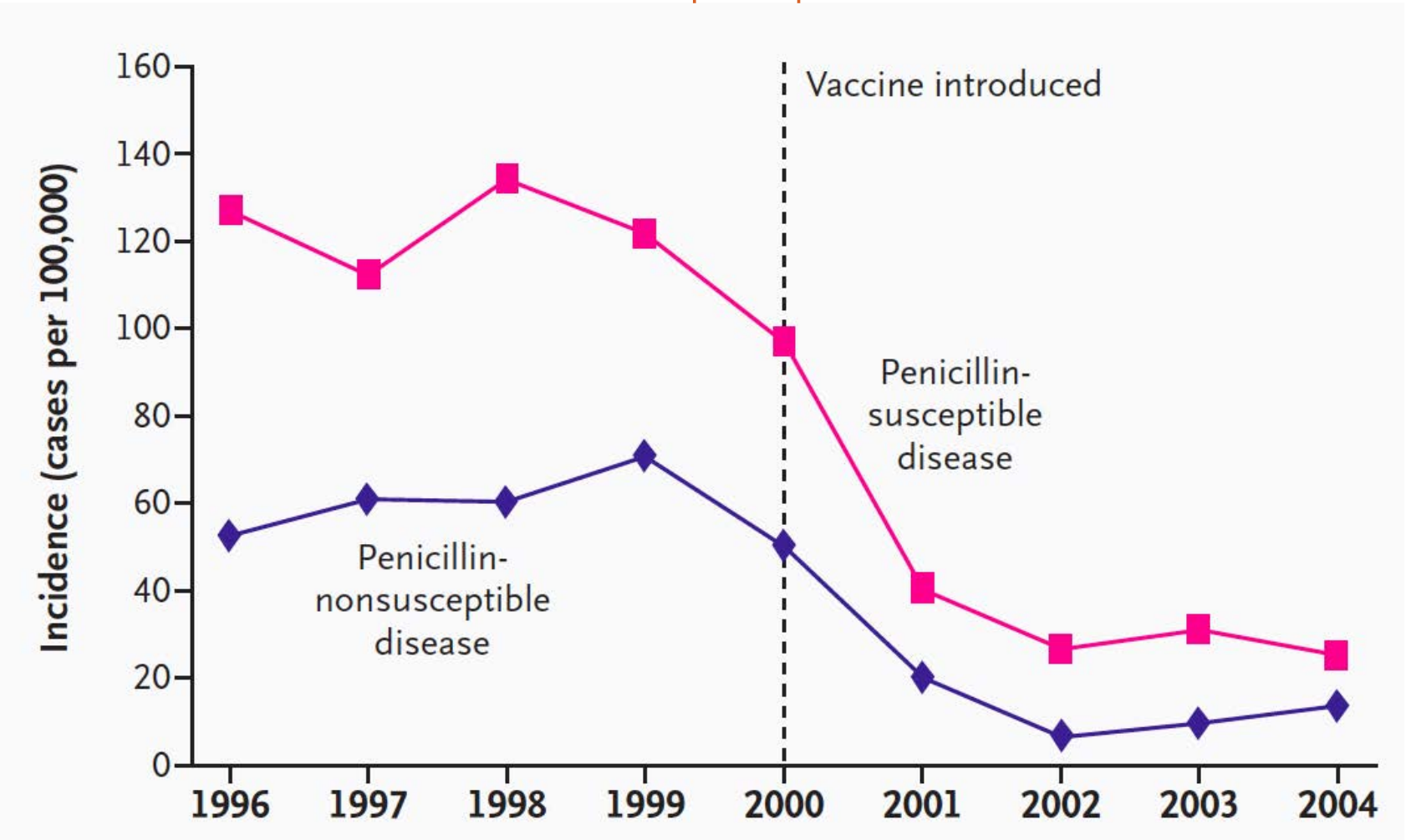


Source: Adapted from Armstrong, Conn et al. (1999).

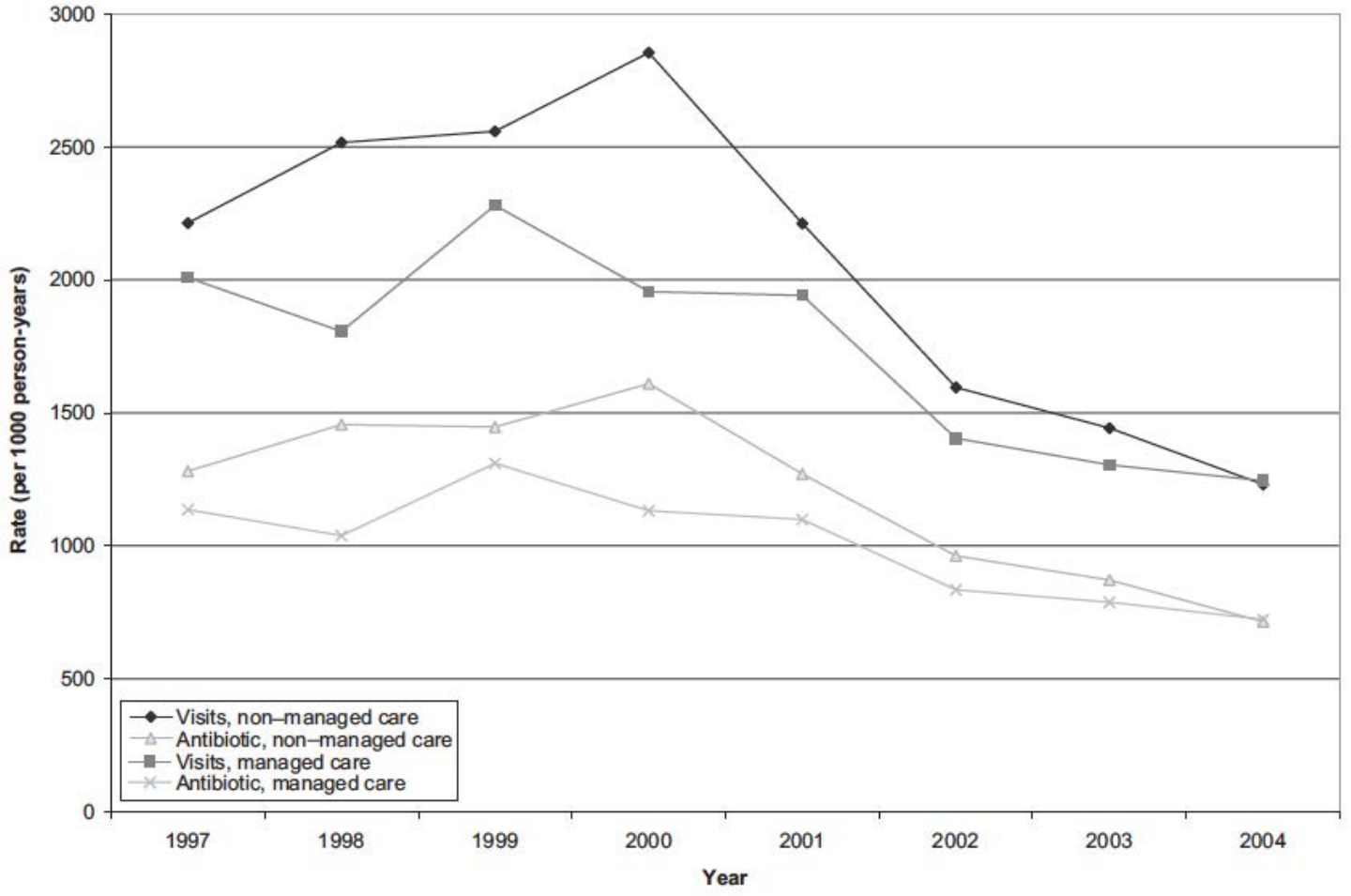
Vaccines can be effective

Invasive disease caused by Pneumococci in children under two declined in the US post pneumo vaccination



Kyaw MH et al. N Engl J Med 2006;354:1455-1463.

Effect of PCV7 introduction on antibiotic prescriptions and ambulatory care visits



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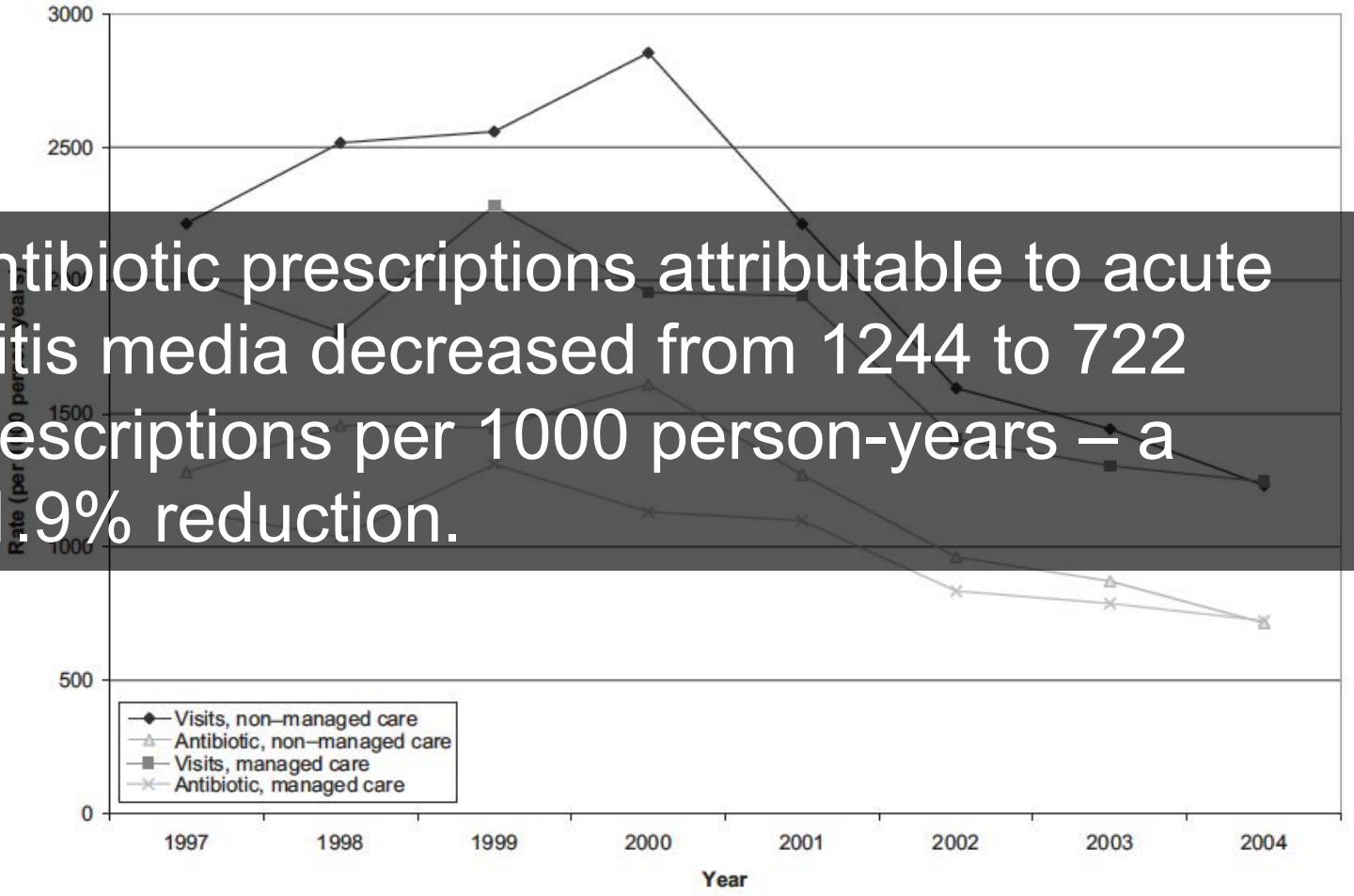
Zhou et al, Pediatrics 2008

Effect of PCV7 introduction on antibiotic prescriptions and ambulatory care visits



Antibiotic prescriptions attributable to acute otitis media decreased from 1244 to 722 prescriptions per 1000 person-years – a 41.9% reduction.

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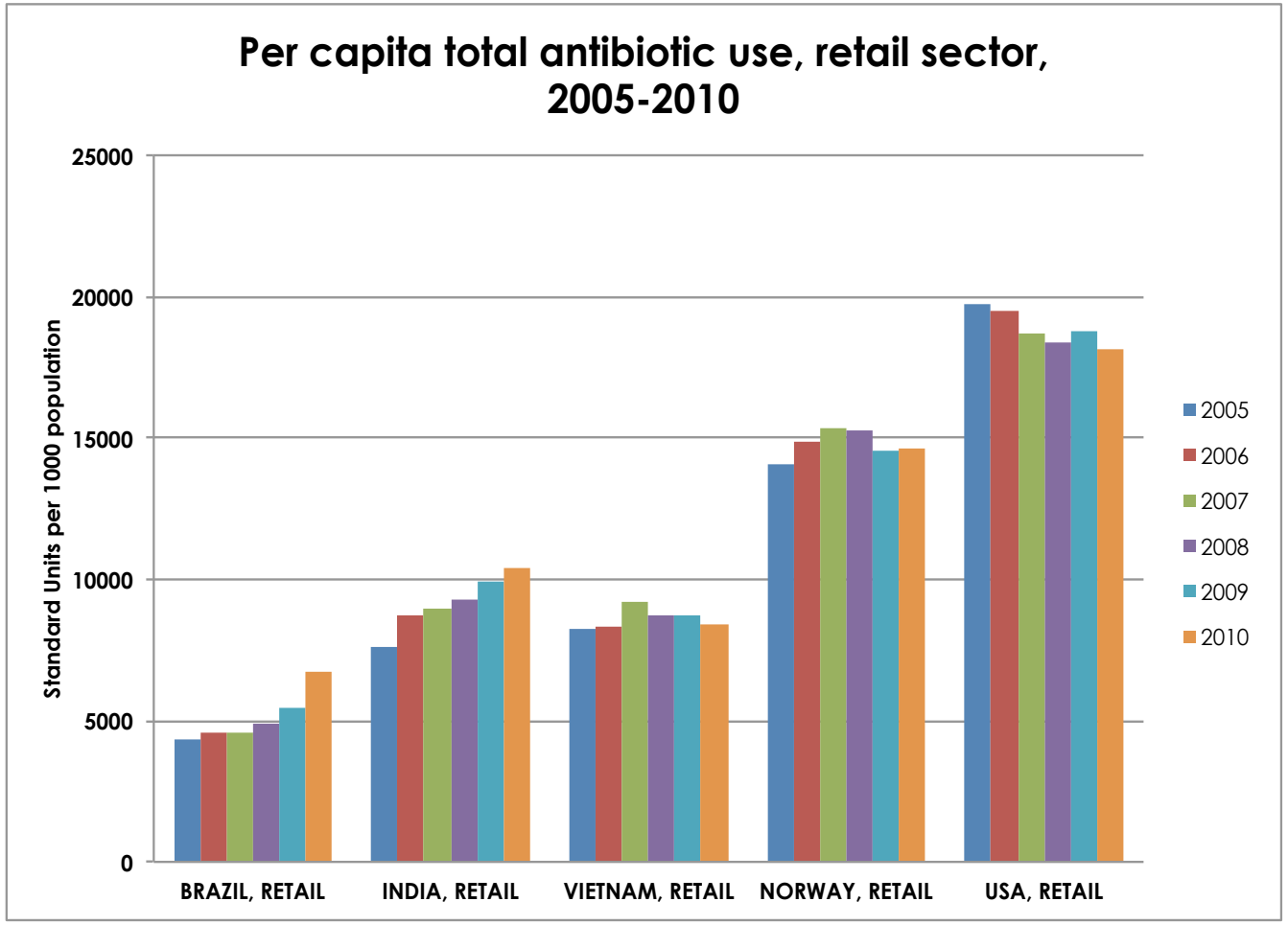
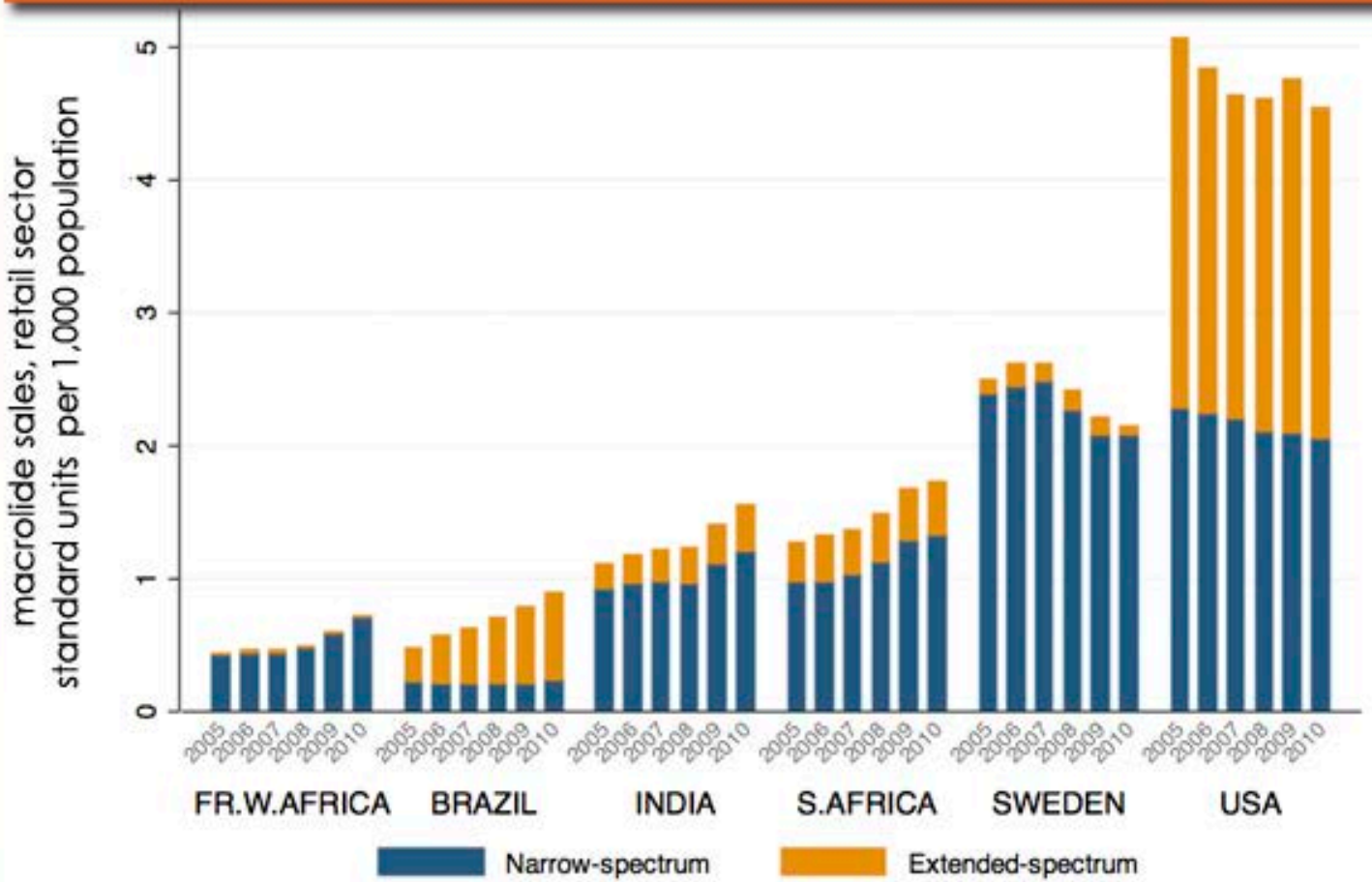
Zhou et al, Pediatrics 2008

Antibiotic consumption is increasing in developing countries…



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. All rights reserved.

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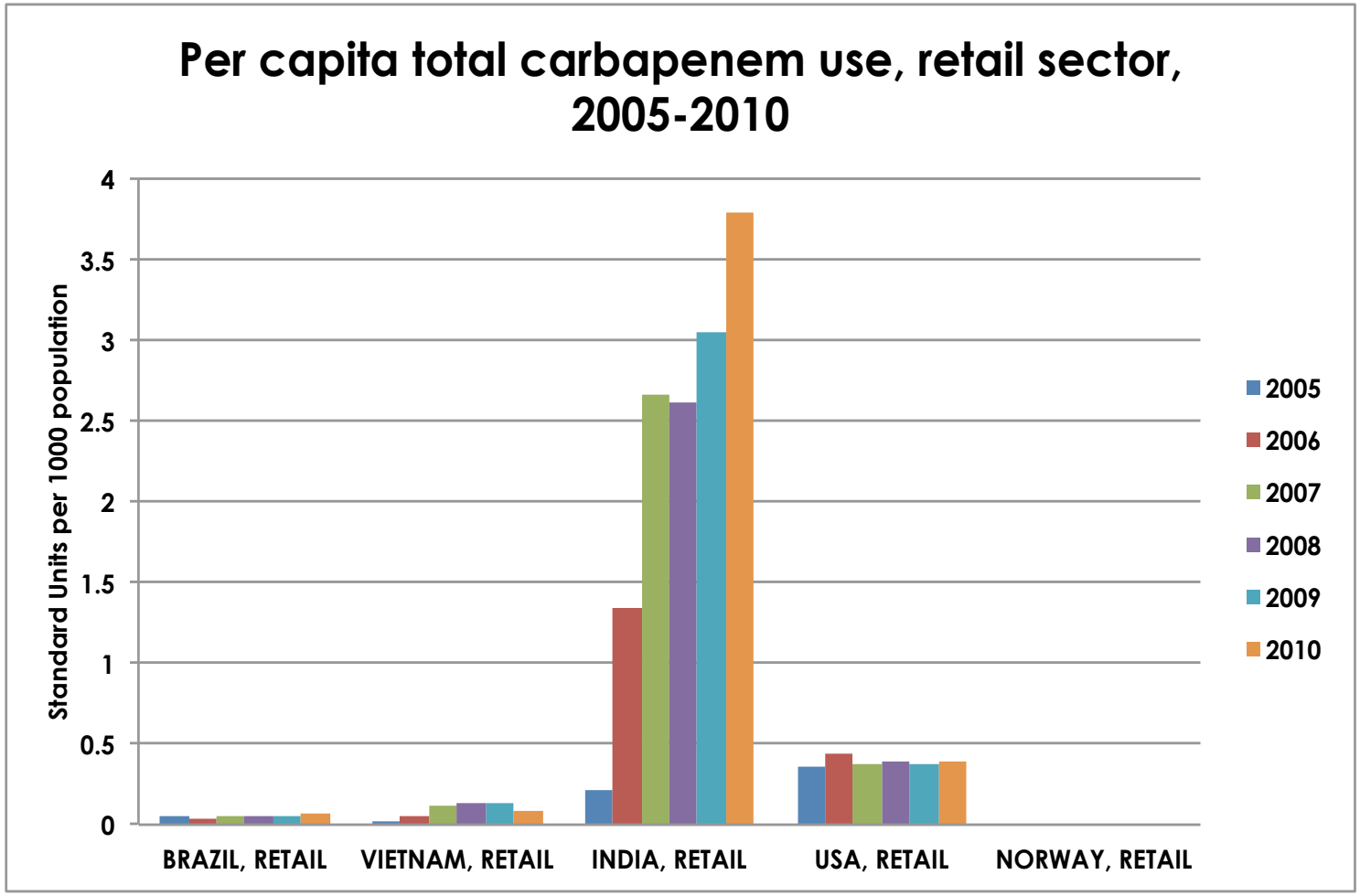
Last-resort drugs are widely sold on the retail market..



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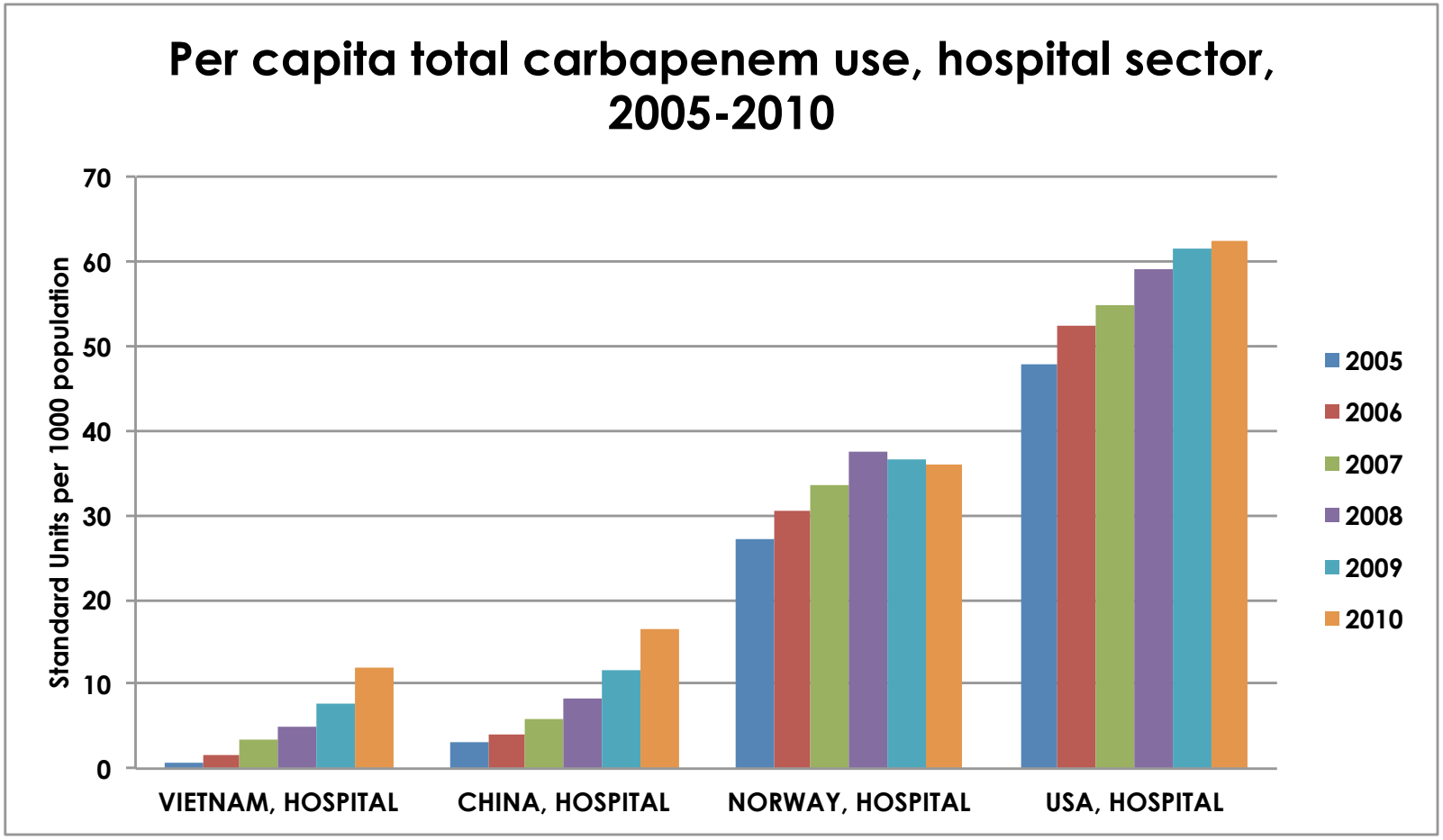
Hospital use of carbapenems is rapidly growing



Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

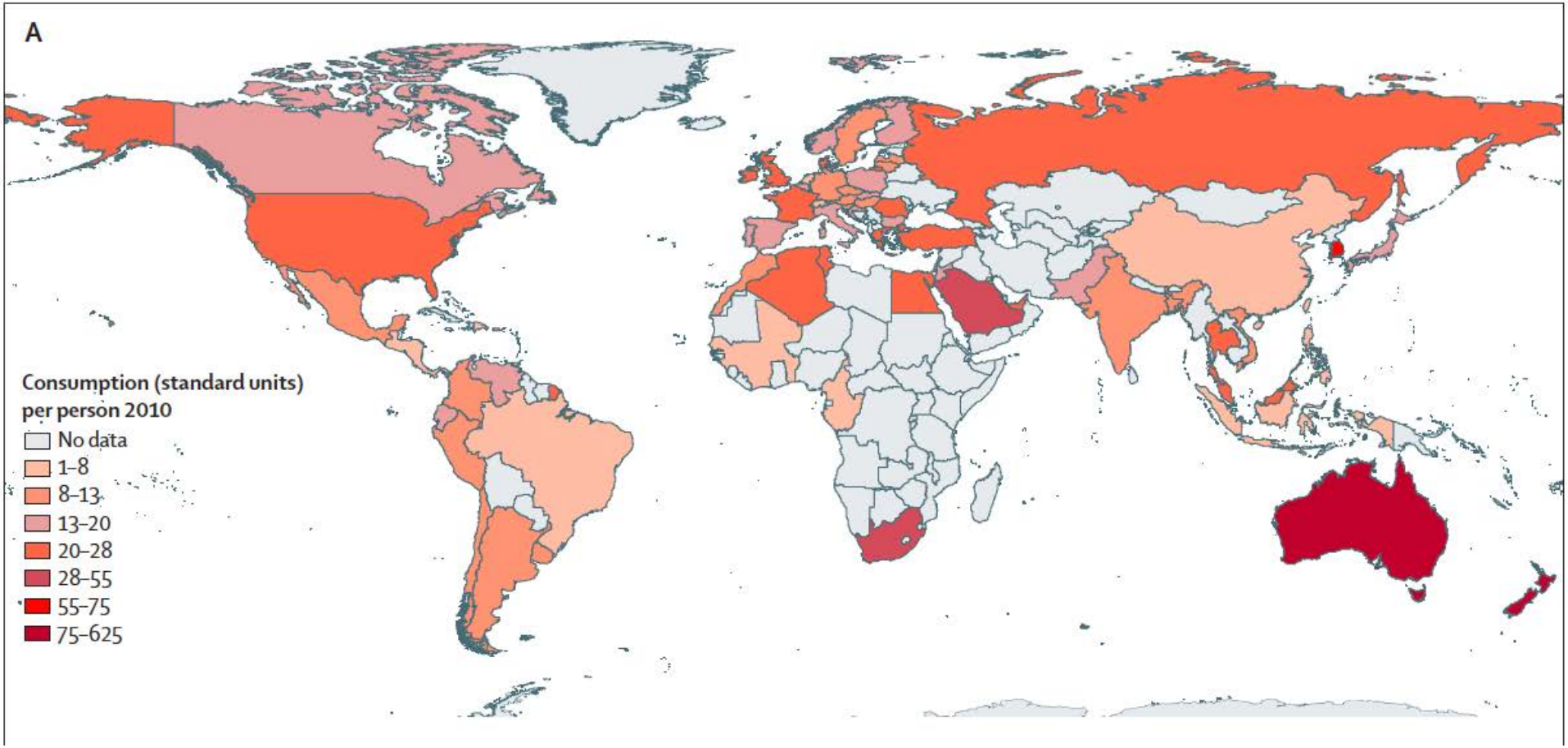
Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

Summary

Background Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption. We aimed to assess variations in consumption to assist monitoring of the rise of resistance and development of rational-use policies and to provide a baseline for future assessment.

Lancet Infect Dis 2014

Published Online
July 10, 2014
http://dx.doi.org/10.1016/S1473-3099(14)70780-7



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

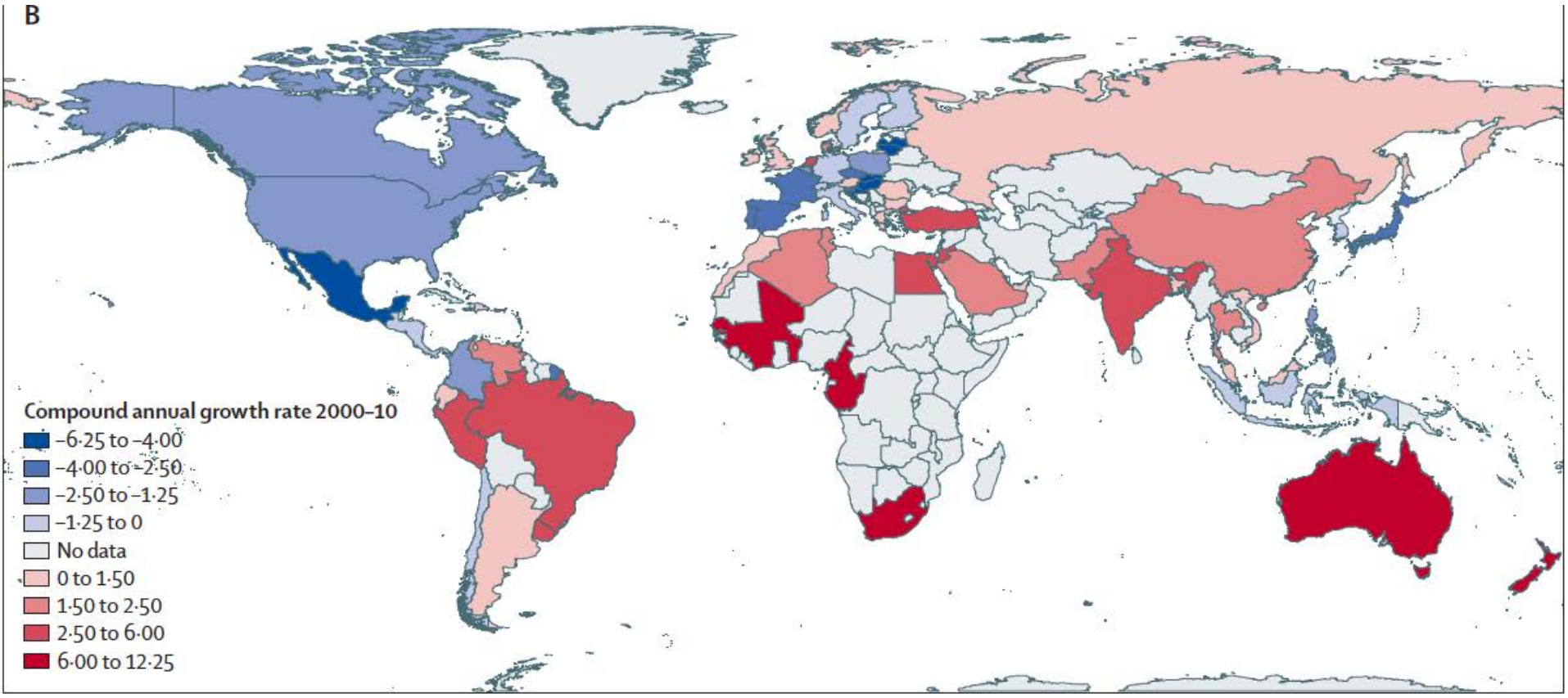

Figure 2: Consumption of antibiotics in 2010

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

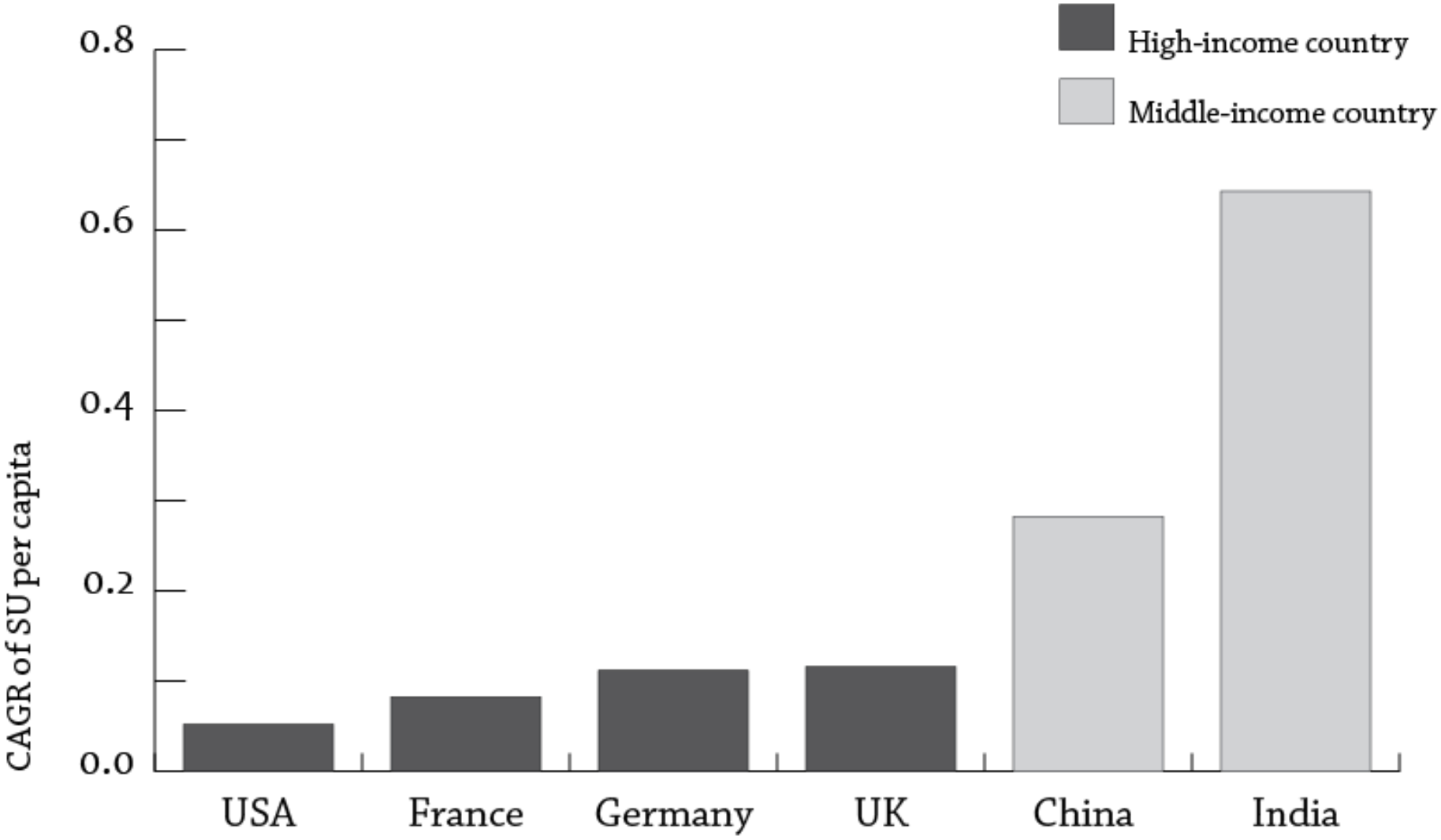
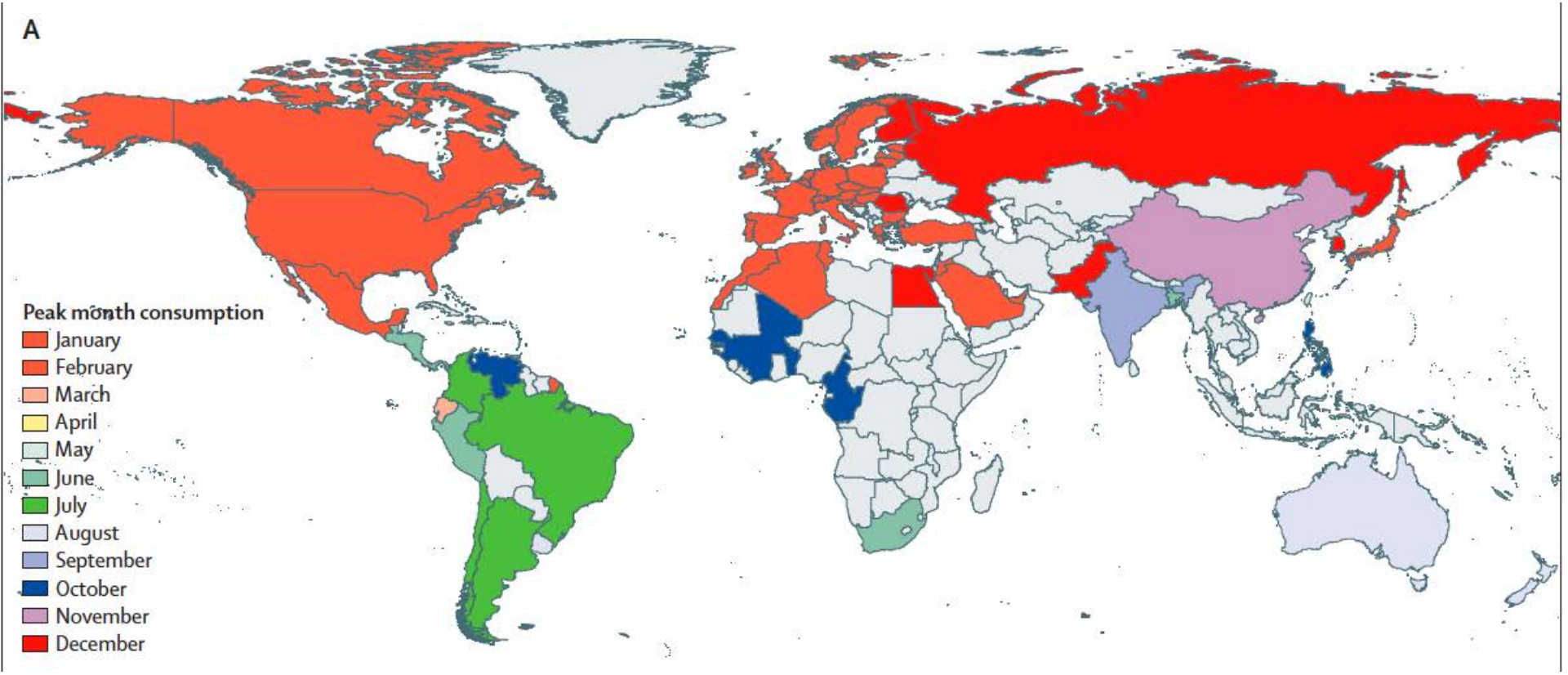


Figure: Compound annual growth rate (CAGR) of total antibiotic consumption in Standard Units (SU) per capita for the period 2000-2010 across select countries.



Van Boeckel et al, Lancet Inf Dis, 2014

Antibiotic sales data can predict influenza in the United States

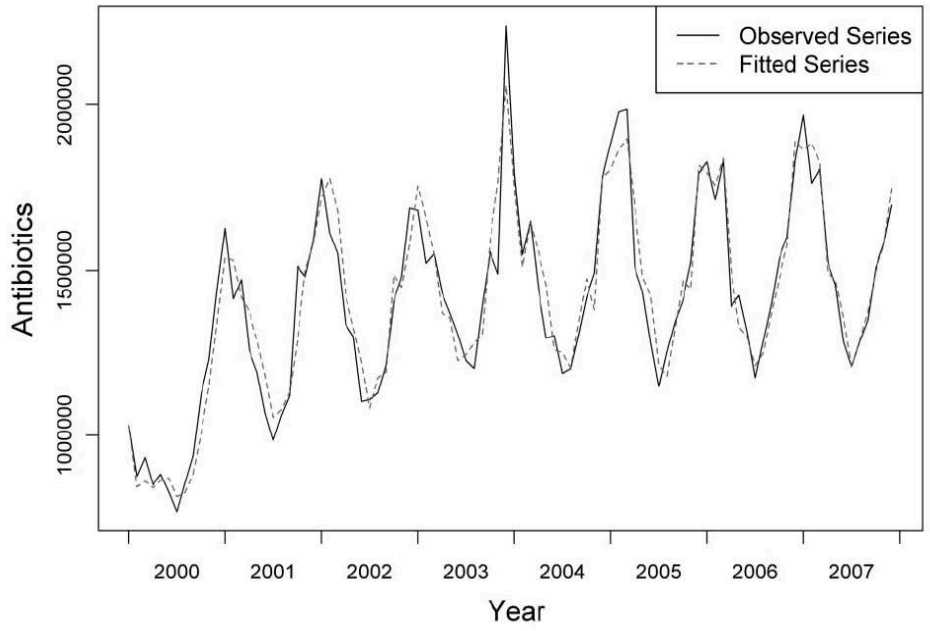


FIGURE 1. Observed and fitted antibiotics series from 2000 to 2007. The solid line represents the actually observed antibiotics series; the dashed line represents the fitted antibiotics series from the time series regression model that uses influenza-like illness as an explanatory series.

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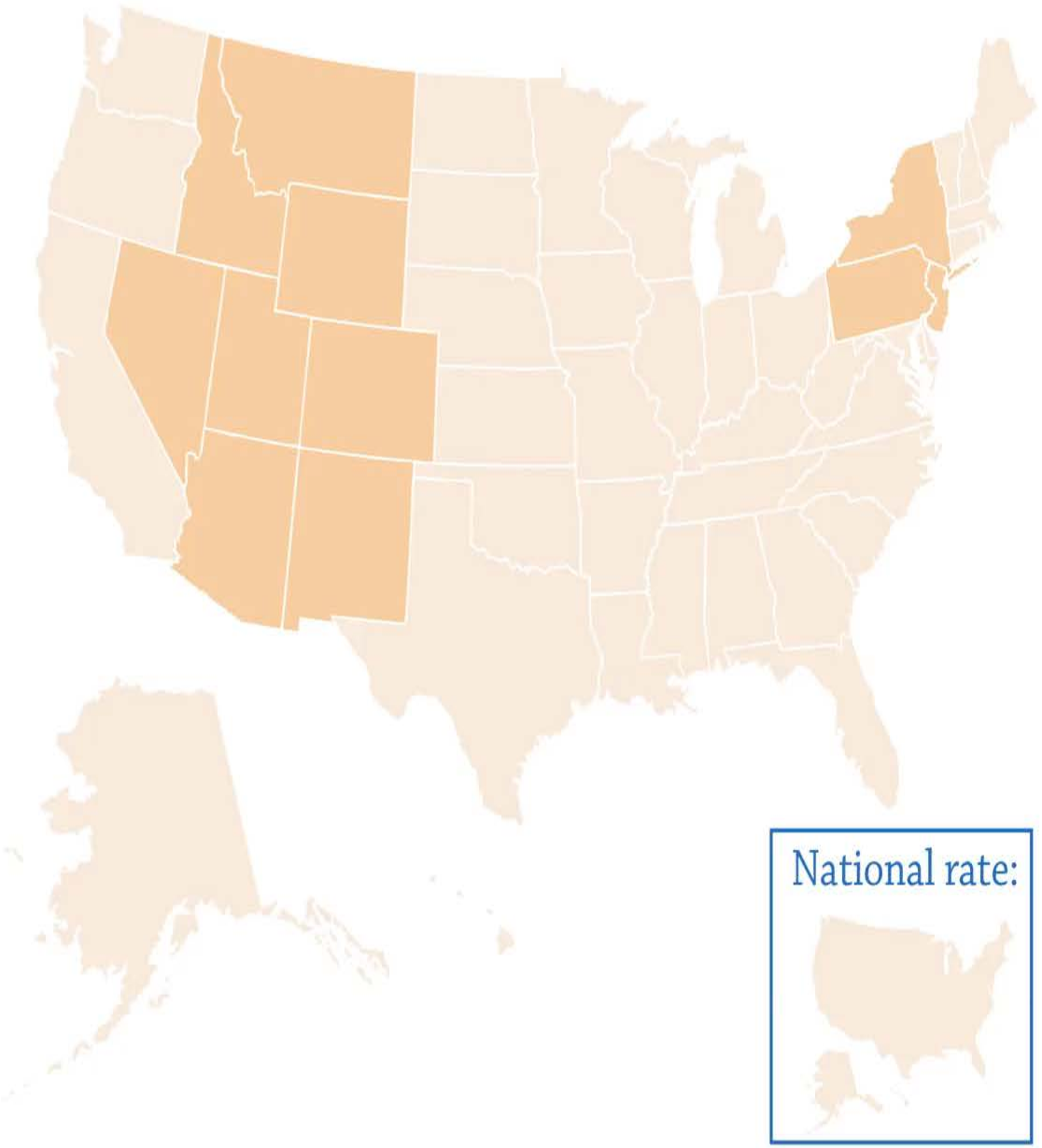
Polgreen, Laxminarayan et al. ICHE, 2010

Carbapenem-resistant *Acinetobacter baumannii*

Year: **1999**

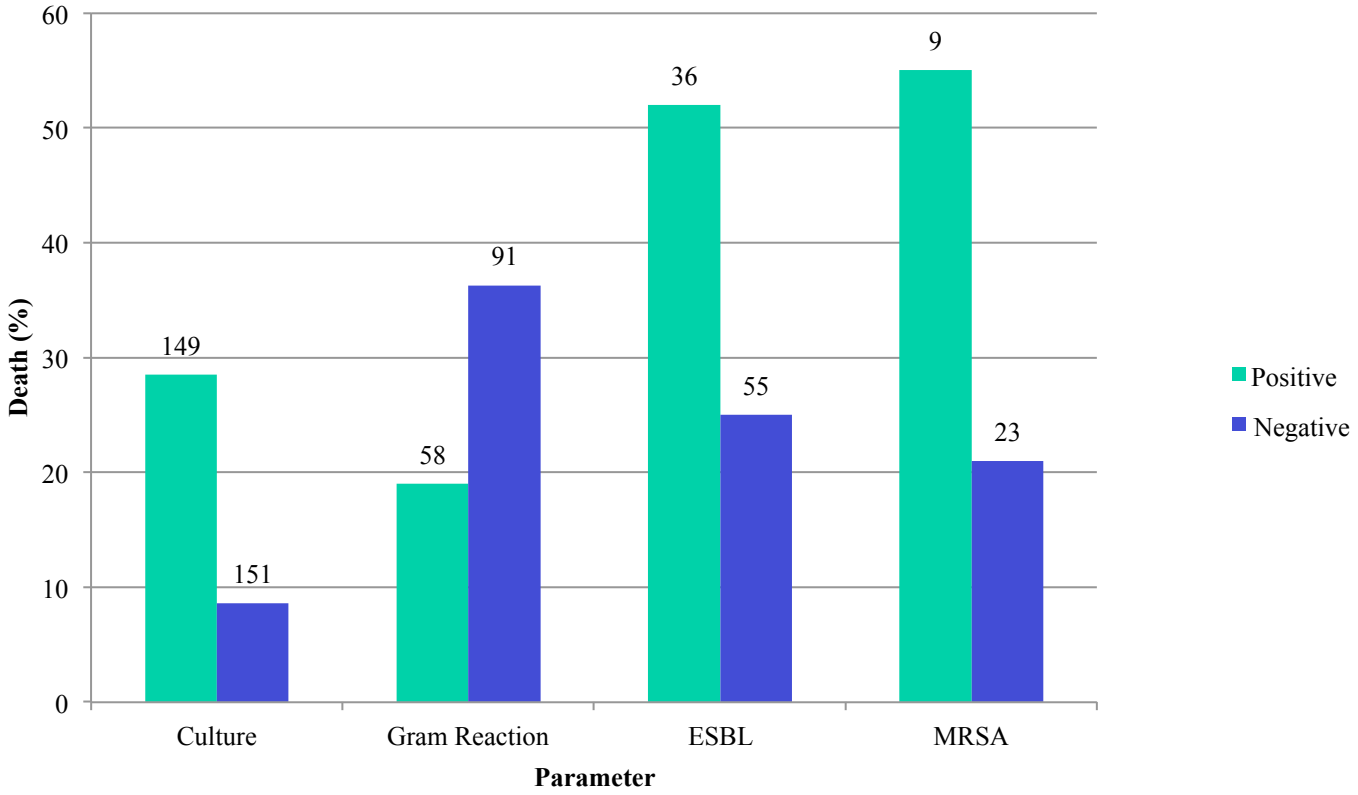


Percentage resistant:

- < 10%
- 10 - 20%
- 20 - 40%
- 40 - 60%
- > 60%
- Inadequate data

National rate:

Mortality outcomes are worse in neonates with resistant infections



Kayange M, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. 2010. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza-Tanzania. BMC Pediatrics 10: 39.

"All the News That's Fit to Print"

The New York Times

Late Edition
Today, a chillier day, sunshine mixing with some clouds, high 42. Tonight, mostly cloudy, low 34. Tomorrow, mostly cloudy, chilly, high 43. Weather map is on Page B16.

VOL. CLXIV . . . No. 56,705 + NEW YORK, THURSDAY, DECEMBER 4, 2014 $2.50

TODD HEISLER/THE NEW YORK TIMES

Protesters at Grand Central Terminal on Wednesday after a grand jury decided not to indict a police officer in Eric Garner's death.

NEW YORK OFFICER FACING NO CHARGES IN CHOKEHOLD CASE

Grand Jury's Decision in Fatal Encounter Draws Protests — U.S. to Investigate

By J. DAVID GOODMAN and AL BAKER

A Staten Island grand jury on Wednesday ended the criminal case against a white New York police officer whose chokehold on an unarmed black man led to the man's death, a decision that drew condemnation from elected officials and touched off a wave of protests.

The fatal encounter in July was captured on videos and seen around the world. But after viewing the footage and hearing from witnesses, including the officer who used the chokehold, the jurors deliberated for less than a day before deciding that there was not enough evidence to go forward with charges against the officer, Daniel Pantaleo, 29, in the death of the man, Eric Garner, 43.

Officer Pantaleo, who has been on the force for eight years, appeared before the grand jury on Nov. 21, testifying that he did not intend to choke Mr. Garner, who was being arrested for allegedly selling loose cigarettes. He described the maneuver as a takedown move, adding that he never thought Mr. Garner was in mortal danger. [Page A29.]

The decision came barely a week after a grand jury found no criminality in the actions of another white police officer, Darren Wilson, who shot and killed Michael Brown, an unarmed 18-year-old black man in Ferguson, Mo.

After the news from Staten Island, a wave of elected officials renewed calls for Justice Department intervention, saying the grand jury's finding proved that justice could be found only in the federal courts. By the evening, the department announced it would open a civil rights inquiry.

On the streets of the city, from Tompkinsville to Times Square, many expressed their outrage with some of the last words Mr. Garner uttered before being wrestled to the ground: "This stops today," people chanted. "I can't breathe," others shouted.

While hundreds of angry but generally peaceful demonstrators took to the streets in Manhattan as well as in Washington and other cities, the police in New York reported relatively few arrests, a stark contrast to the riots that unfolded in Ferguson in the hours after the grand jury decision was announced in the

Continued on Page A28

VIA ASSOCIATED PRESS

Mr. Garner, in an undated family photo, died at age 43.

U.S. and Iran Both Attack ISIS, But Try Not to Look Like Allies

By TIM ARANGO and THOMAS ERDBRINK

BAGHDAD — Iranian fighter jets struck extremist targets in Iraq recently, Iranian and American officials have confirmed, in the latest display of Tehran's new willingness to conduct military operations openly on foreign battlefields rather than covertly and through proxies.

The shift stems in part from Iran's deepening military role in Iraq in the war against the Sunni extremists of the Islamic State. But it also reflects a profound

gets in a buffer zone that extends 25 miles into Iraq.

The new military approach highlights an unusual confluence of interests in both Iraq and Syria, where Tehran and Washington find themselves fighting the same enemy in an increasingly public fashion. While there is no direct coordination between Iran and the United States, there is a de facto nonaggression pact that neither side is eager to acknowledge.

'Superbugs' Kill India's Babies And Pose an Overseas Threat

By GARDINER HARRIS

AMRAVATI, India — A deadly epidemic that could have global implications is quietly sweeping India, and among its many victims are tens of thousands of newborns dying because once-miraculous cures no longer work.

These infants are born with bacterial infections that are resistant to most known antibiotics, and more than 58,000 died last year as a result, a recent study found. While that is still a fraction of the nearly 800,000 newborns

world, and this will require treating an increasing number of neonates who have sepsis and pneumonia," said Dr. Vinod Paul, chief of pediatrics at the All India Institute of Medical Sciences and the leader of the study. "But if resistant infections keep growing, that progress could slow, stop or even reverse itself. And that would be a disaster for not only India but the entire world."

In visits to neonatal intensive care wards in five Indian states,

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

Incentives for Physicians

- Satisfying patient expectations

TABLE 5

Frequency of Antibiotic Prescribing by Factors Related to Patients' Expectations of Antibiotics (N = 482)

Factor	No.* (%)	Antibiotic Prescribed No. (%)	OR (95% CI)
Patient expects antibiotic			
Yes	290 (60)	213 (73)	2.6 (1.7-3.9)
No	150 (31)	78 (52)	reference
No answer	42 (9)	28 (67)	
Clinician believes patient expects an antibiotic			
Yes	298 (62)	236 (79)	4.7 (3.2-7.1)
No	182 (38)	81 (45)	reference
No answer	2 (<1)	2 (100)	
Antibiotic helped similar illness in the past			
Yes	284 (59)	212 (75)	4.5 (2.9-6.9)
No	170 (35)	88 (52)	reference
Don't know	19 (4)	12 (63)	
No answer	9 (2)	5 (56)	

NOTE: Because some questions were unanswered, the numbers may not add up to 482.
*In outpatients with nonspecific upper respiratory infections, acute bronchitis, or acute sinusitis.
OR denotes odds ratio; CI, confidence interval.

Dosh, J
Fam Pr 1999

CDD

Health insurance increases prescribing

Table 4. Use of oral, injected, and all antibiotics per person per year by level of family income and insurance plan

Antibiotic use and income tertile*	Free plan ($N = 1935$)		Cost-sharing plans ($N = 3830$)		Ratio of free to cost-sharing (95% confidence interval)†
	Number of antibiotics	Number per person	Number of antibiotics	Number per person	
Oral antibiotics					
Upper one-third	548	0.94	723	0.58	1.63 (1.55, 1.72)
Middle one-third	577	0.93	669	0.57	1.62 (1.53, 1.71)
Lower one-third	442	0.72	386	0.33	2.17 (1.97, 2.39)
All incomes	1670	0.85	1825	0.48	1.79 (1.72, 1.86)
Injected antibiotics					
Upper one-third	45	0.08	89	0.07	1.09 (0.77, 1.54)
Middle one-third	69	0.11	75	0.06	1.73 (1.27, 2.36)
Lower one-third	38	0.06	45	0.04	1.60 (1.05, 2.44)
All incomes	187	0.10	221	0.06	1.67 (1.39, 2.01)
All antibiotics					
Upper one-third	593	1.02	812	0.65	1.57 (1.51, 1.63)
Middle one-third	646	1.04	744	0.64	1.63 (1.57, 1.70)
Lower one-third	480	0.78	431	0.37	2.11 (1.94, 2.30)
All incomes	1857	0.96	2046	0.53	1.80 (1.75, 1.86)

*Numbers shown for income tertiles do not sum to totals because income was unknown for 138 claims on the free plan and 59 on the cost-sharing plans.

†Taylor's series 95% confidence intervals [12]; ratio and confidence intervals calculated using 8 significant digits.

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Foxman et, RAND Corporation,1987

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Foxman et, RAND Corporation,1987

What happens when antibiotics are provided free?

Table 2: Average Percentage Change in prescriptions 1 year into the program

	Percentage Change Before and After		Diff-in-Diff
	Treatment Group	Control Group	
All Antibiotics	7.67 (0.40)	2.74 (0.31)	4.93 (0.50)
Covered Antibiotics	11.73 (0.43)	4.62 (0.31)	7.10 (0.54)
Not-covered Antibiotics	-8.75 (0.66)	-4.76 (0.39)	-3.99 (0.76)
No-equivalent Antibiotics	-4.76 (0.82)	-0.32 (0.56)	-4.44 (0.99)

Note: The changes before the program are calculated using data from November 2005 to October 2006, and the changes after the program are based on data from November 2006 to October 2007.

Overall increase in antibiotic prescriptions as well as substitutions to covered antibiotics from not-covered antibiotics.

Li and Laxminarayan, *Health Economics*, 2013

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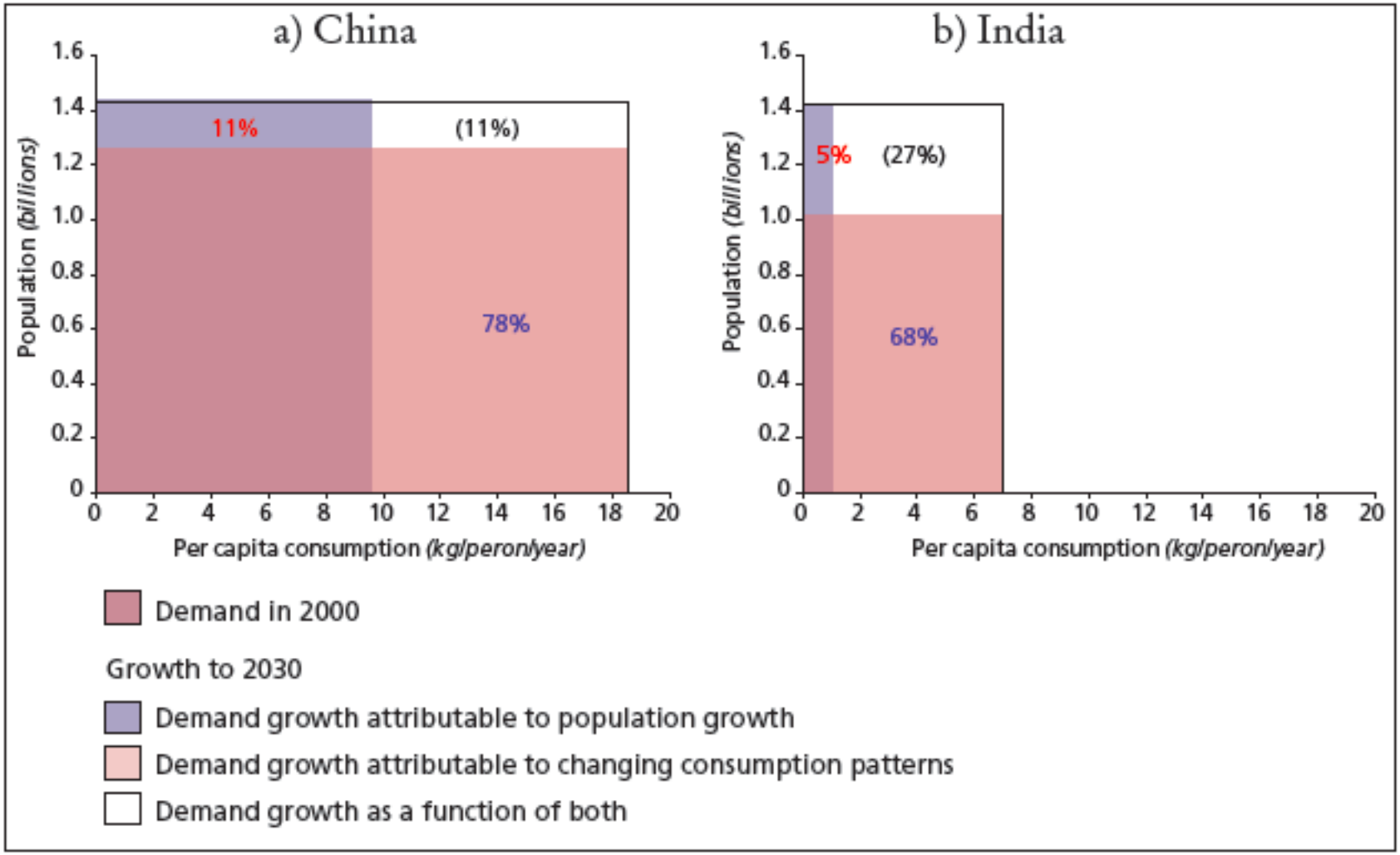
Li and Laxminarayan, *Health Economics*, 2013

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

III. In the livestock sector, the tremendous increase in demand for animal protein will drive continued use of antibiotics in sub-therapeutic concentrations without changes in regulatory policy

Increase in demand for poultry in India and China between 2000 and 2030



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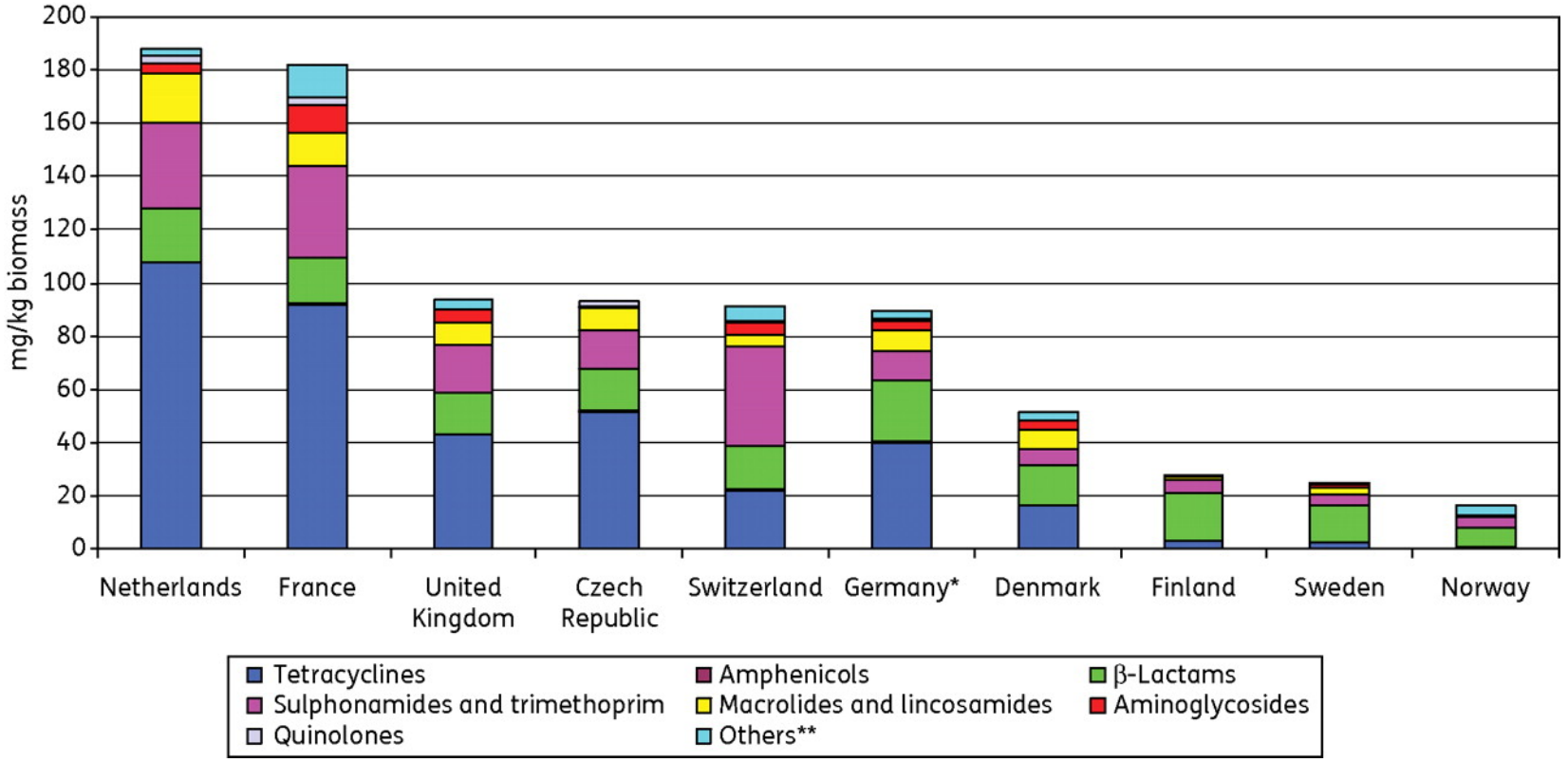
FAO, 2011

Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.



Grave K et al. J. Antimicrob. Chemother. 2010;65:2037-2040

Global trends in antimicrobial use in food animals

Thomas P. Van Boeckel[a,1], Charles Brower[b], Marius Gilbert[c,d], Bryan T. Grenfell[a,e,f], Simon A. Levin[a,g,h,1], Timothy P. Robinson[i], Aude Teillant[a,e], and Ramanan Laxminarayan[b,e,j,1]

[a]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; [b]Center for Disease Dynamics, Economics & Policy, Washington, DC 20036; [c]Universite Libre de Bruxelles, B1050 Brussels, Belgium; [d]Fonds National de la Recherche Scientifique, B1000 Brussels, Belgium; [e]Princeton Environmental Institute, Princeton, NJ 08544; [f]Fogarty International Center, National Institutes of Health, Bethesda, MD 20892; [g]Beijer Institute of Ecological Economics, 10405 Stockholm, Sweden; [h]Resources for the Future, Washington, DC 20036; [i]International Livestock Research Institute, 00100 Nairobi, Kenya; and [j]Public Health Foundation of India, New Delhi 110070, India

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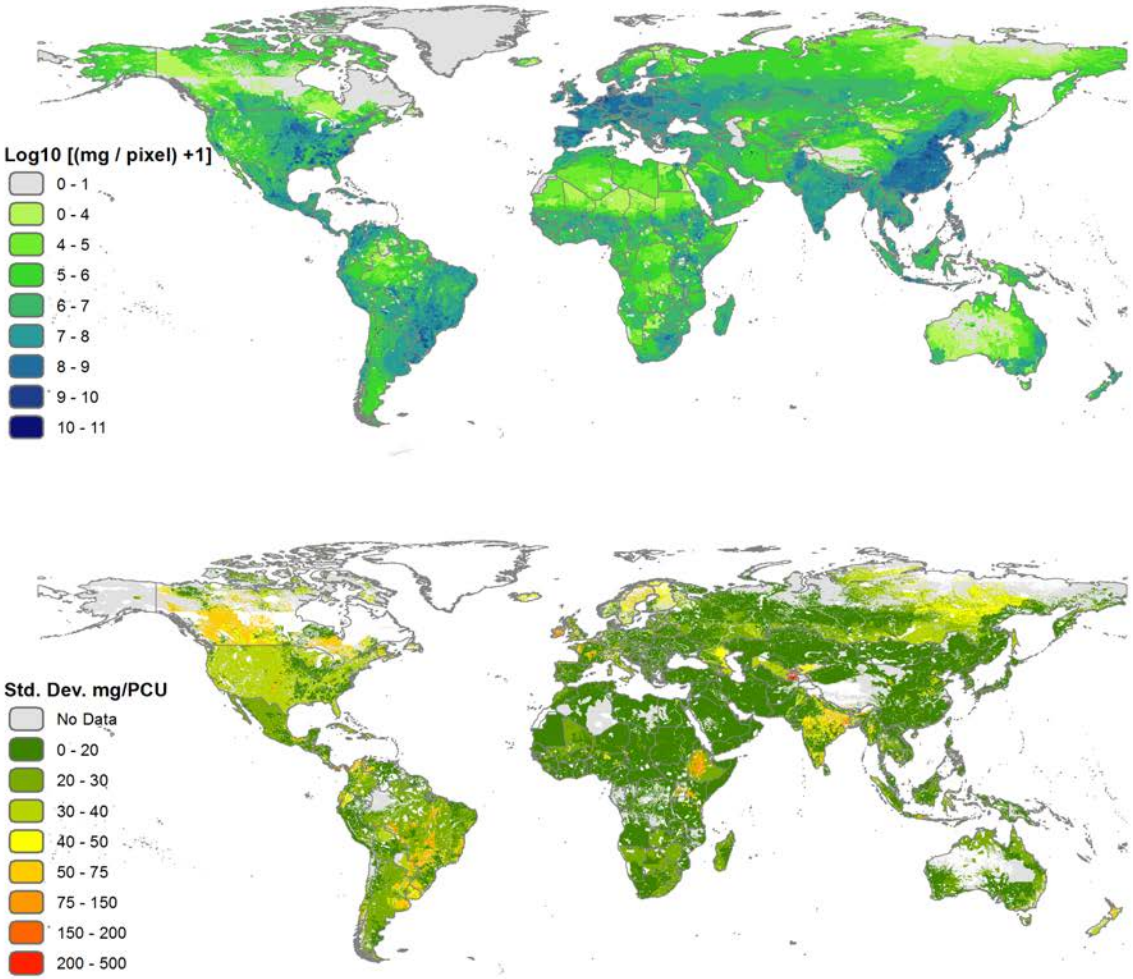
Global antimicrobial consumption in livestock (top) and average standard deviation of estimates (bottom)



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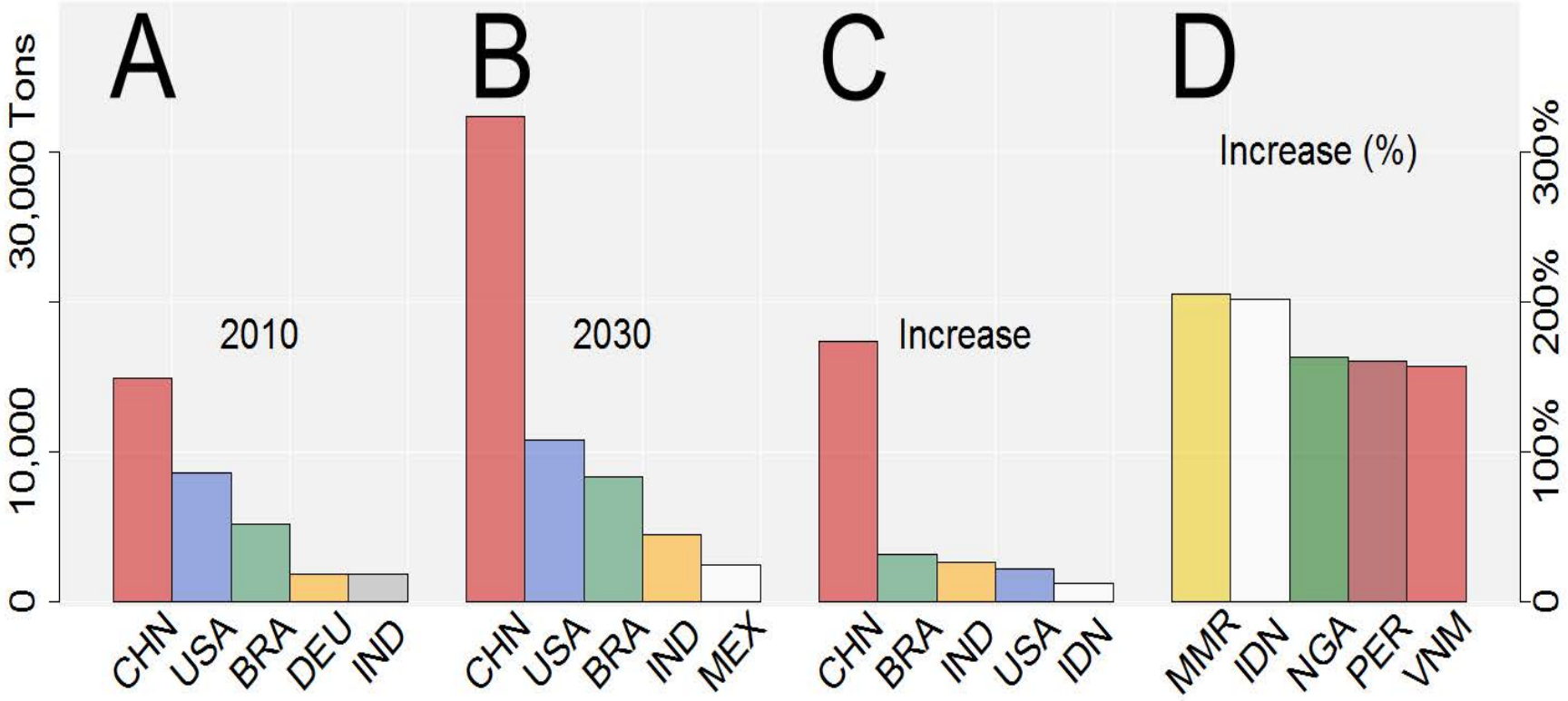
van Boeckel et al, *PNAS*, 2015

Largest consumers of antimicrobials in livestock in 2010 and 2030



A) Largest five consumers of antimicrobials in livestock in 2010
B) Largest five consumers of antimicrobials in livestock in 2030 (projected).
C) Largest Increase in antimicrobial consumption between 2010 and 2030,
D) Largest relative increase in Antimicrobial consumption between 2010 and 2030.

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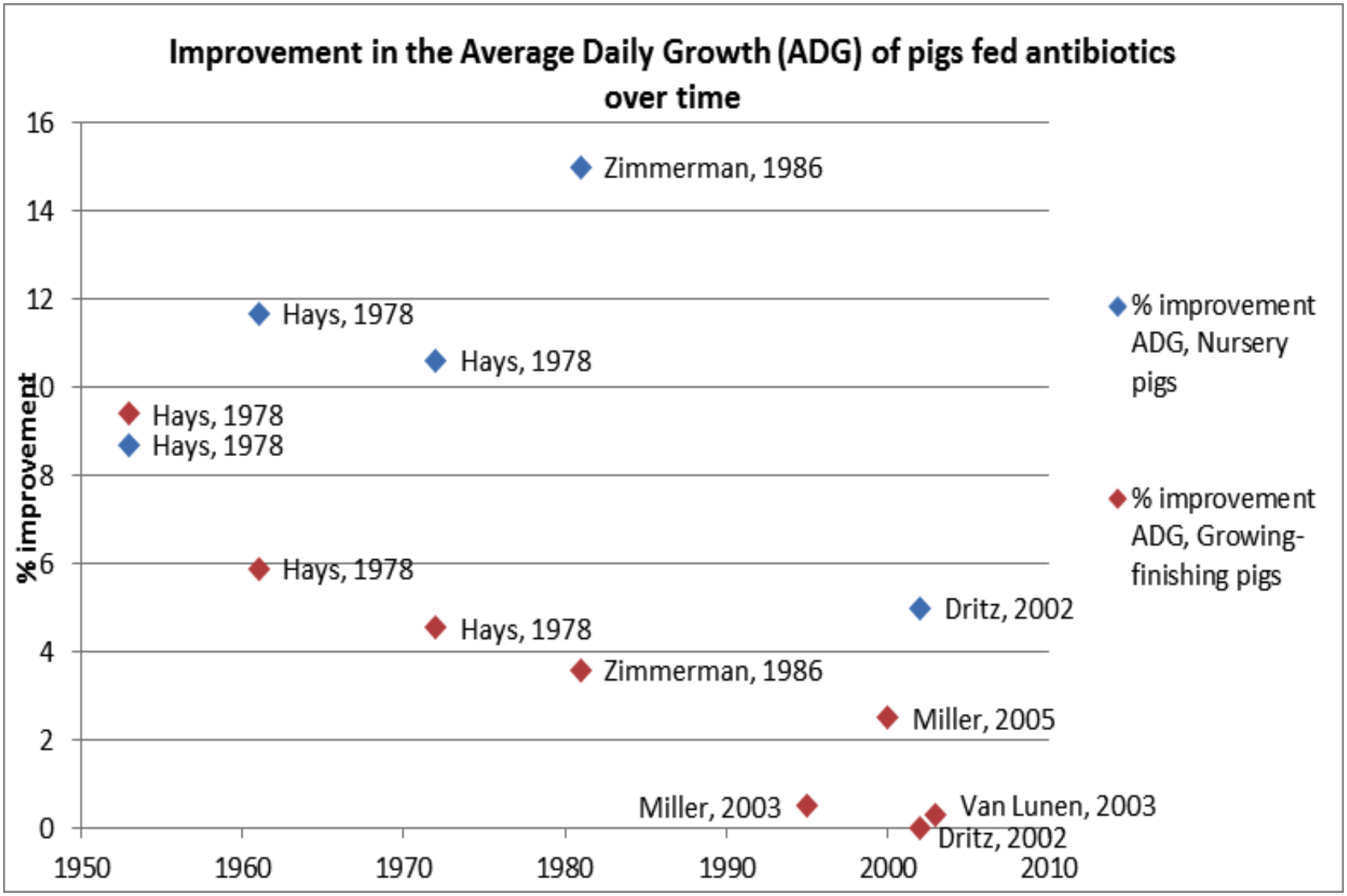
van Boeckel et al, *PNAS*, 2015

- Global average annual consumption of antimicrobials per kilogram of animal produced was 172 mgs per kg for cattle, chicken and pigs
- Global consumption of antimicrobials in food animal production was estimated at 63,151 (±1,560) tonnes in 2010 and is projected to rise by 67%, to 105,596 (±3,605) tonnes by 2030,
  - In hotspots like India where areas of high consumption (30 kg per km2) for industrial poultry production are expected to grow 312% by 2030

(van Boeckel et al, *PNAS*, 2015).

van Boeckel et al, *PNAS*, 2015



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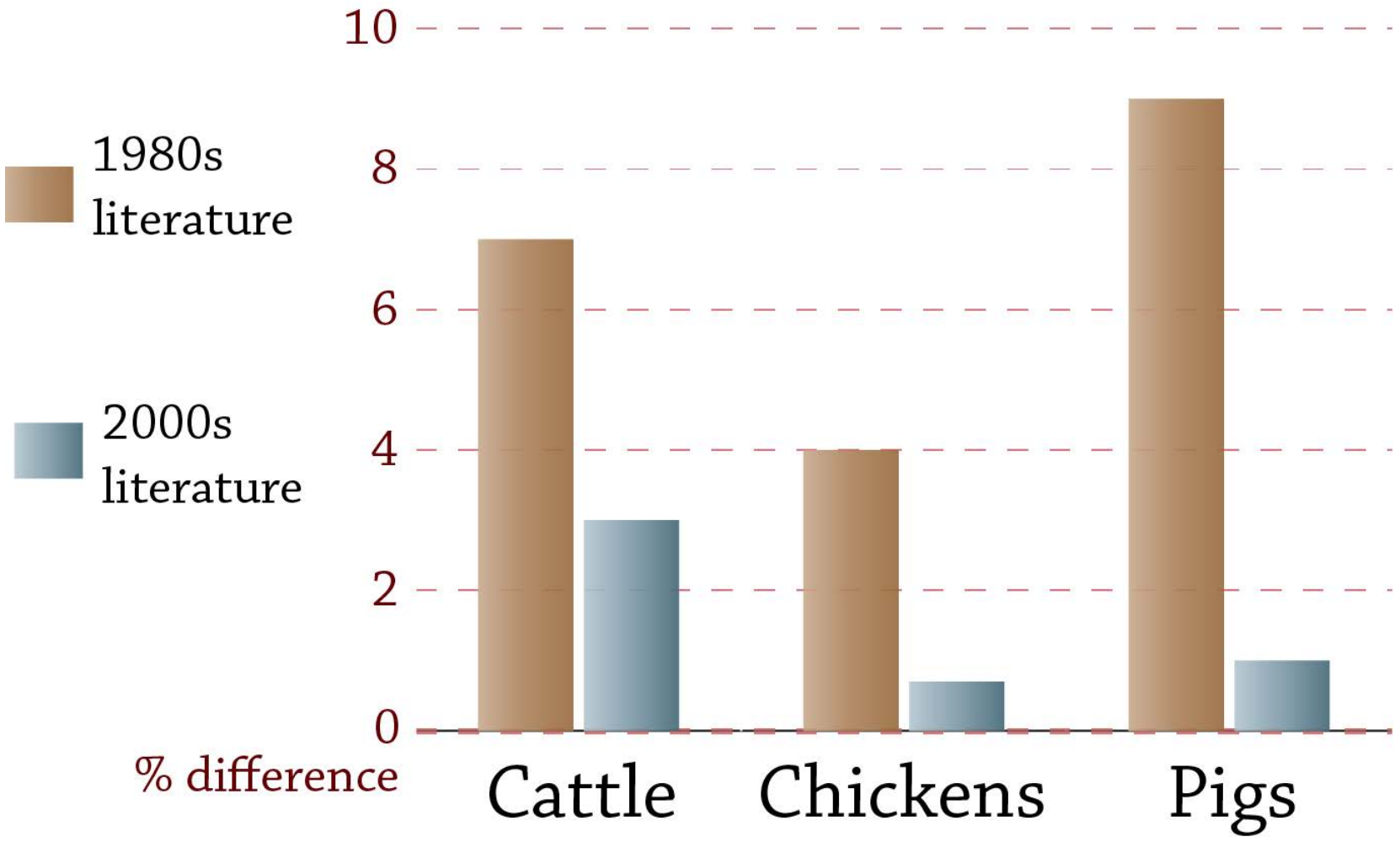
Laxminarayan et al OECD Report, 2014

Difference in average daily growth between animals raised with and without AGPs



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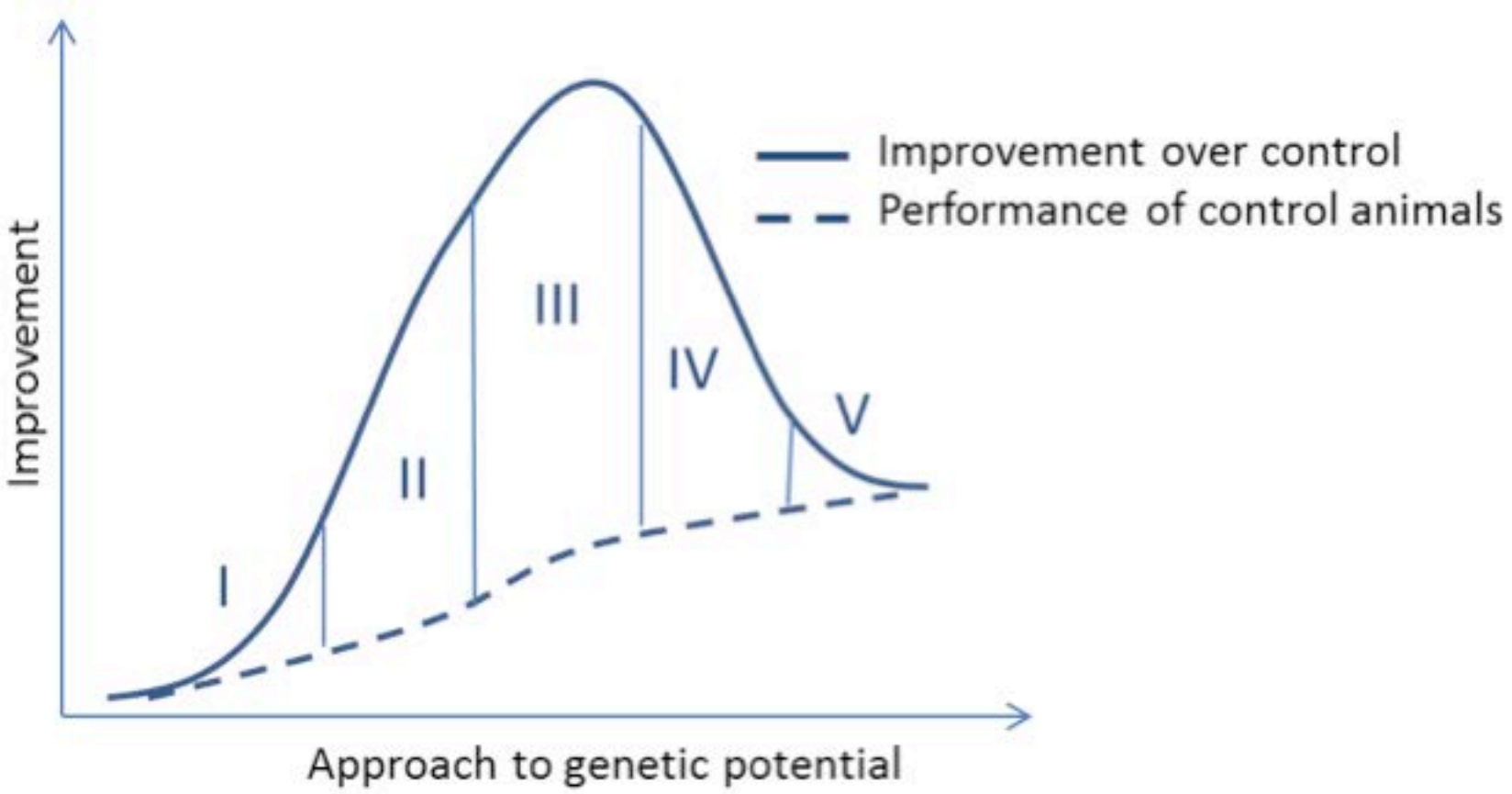
Response by livestock to supplementation with growth promoters



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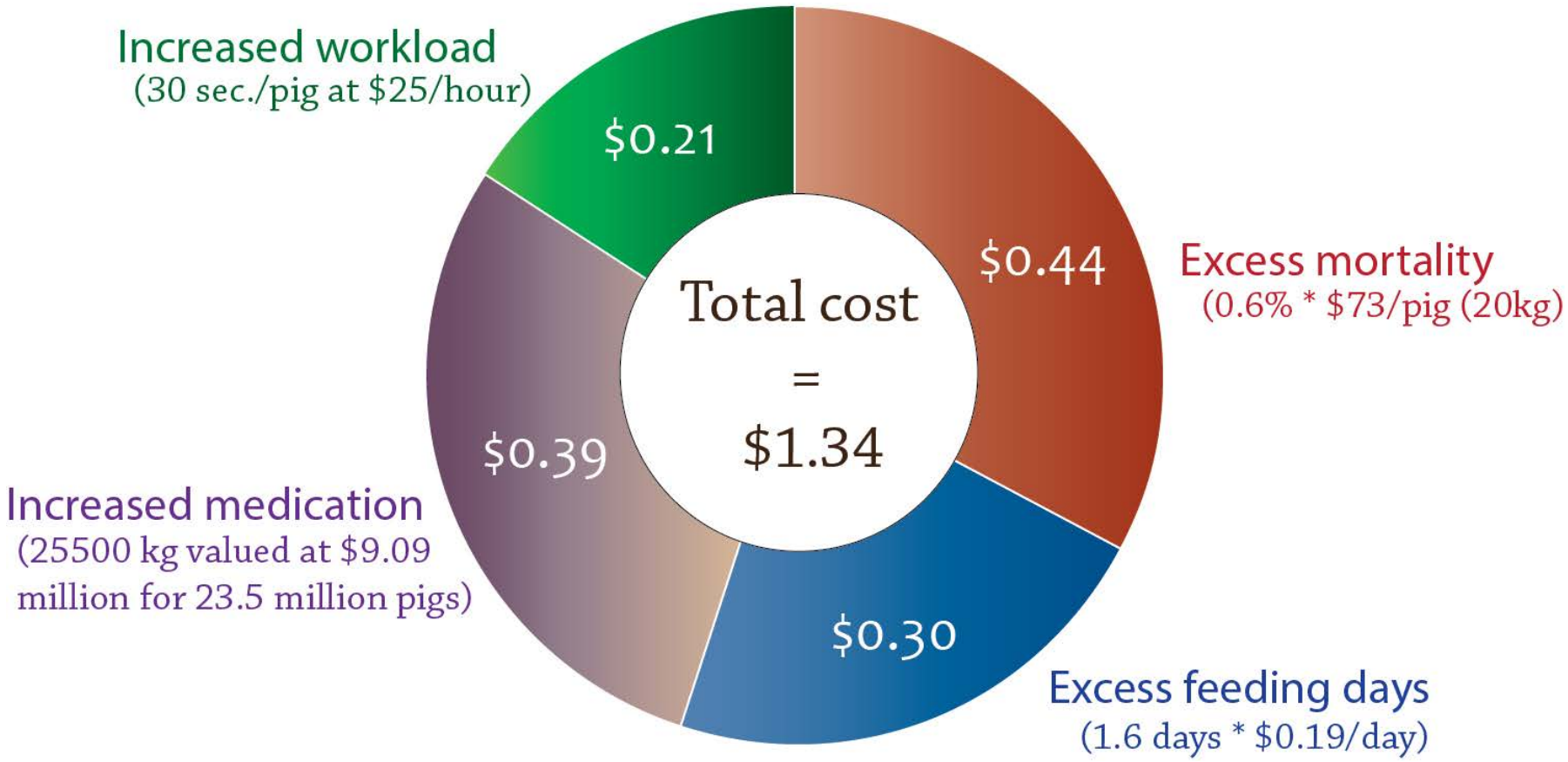
Barug et al., 2006

Productivity reductions and costs per produced pig incurred by removing AGPs



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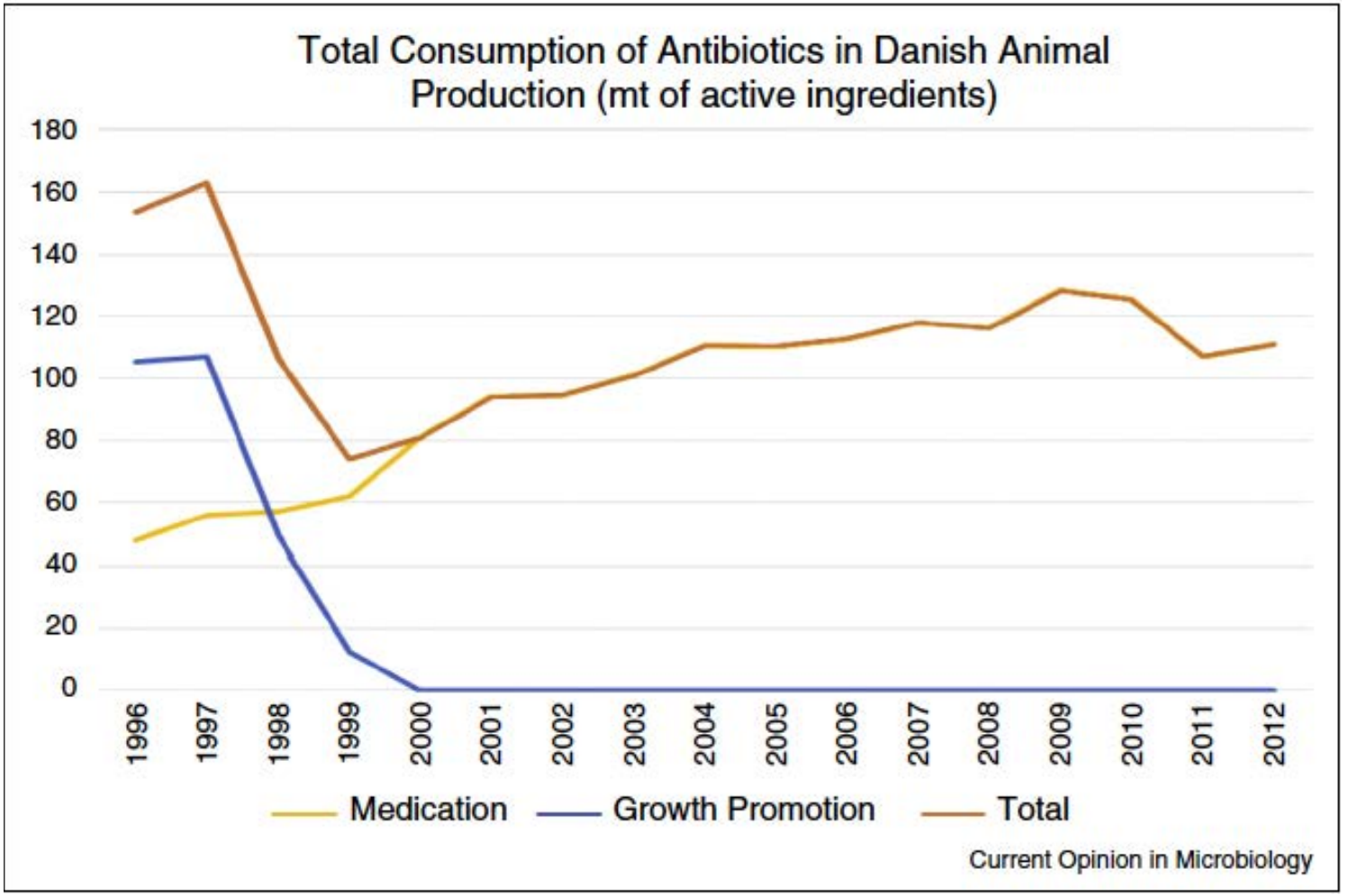
Effect of Danish ban on AGPs



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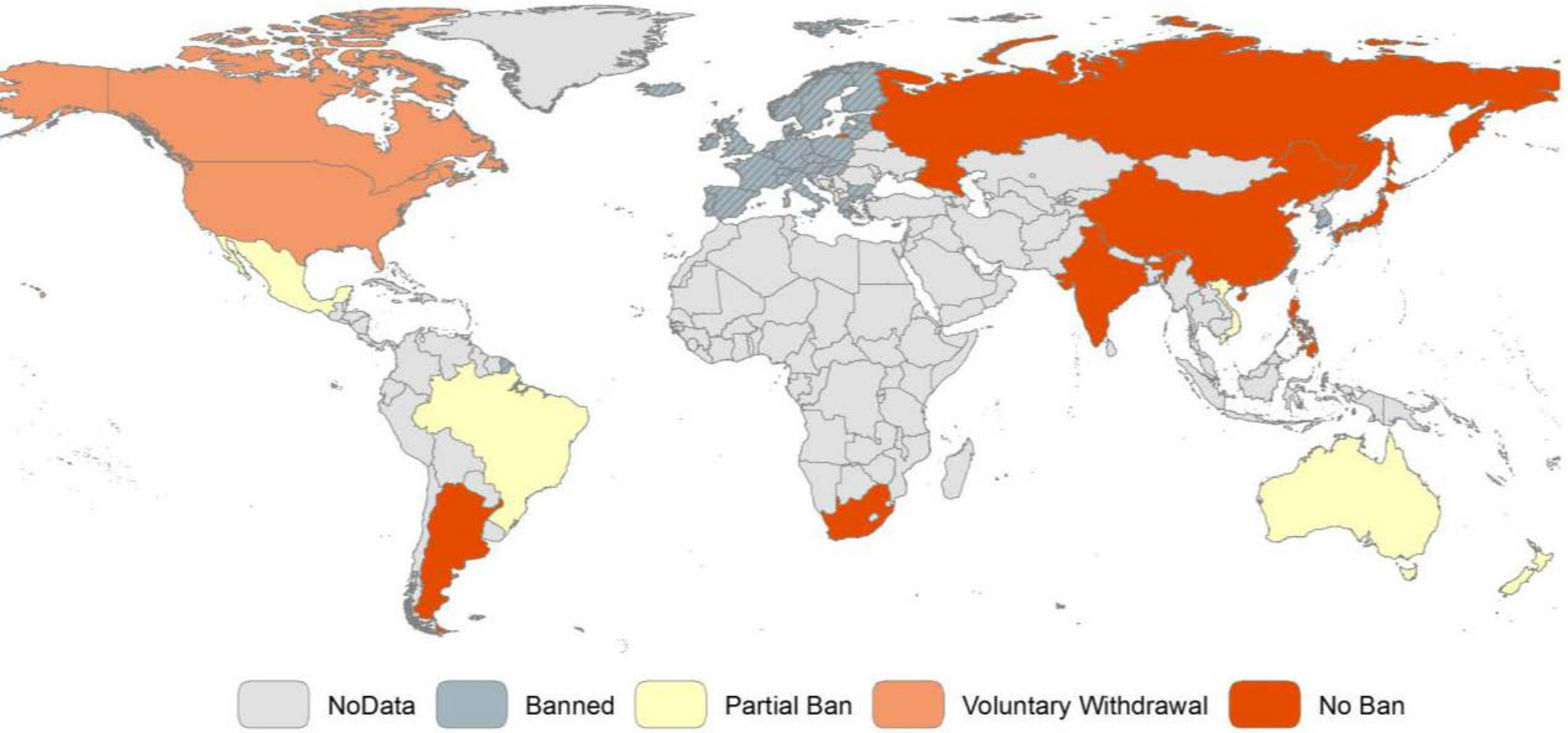
DANMAP 97 (1998) DANMAP 2012 (2013); DANMAP 2004 (2005)

Categories of regulatory framework for the use of antimicrobial for growth promotion



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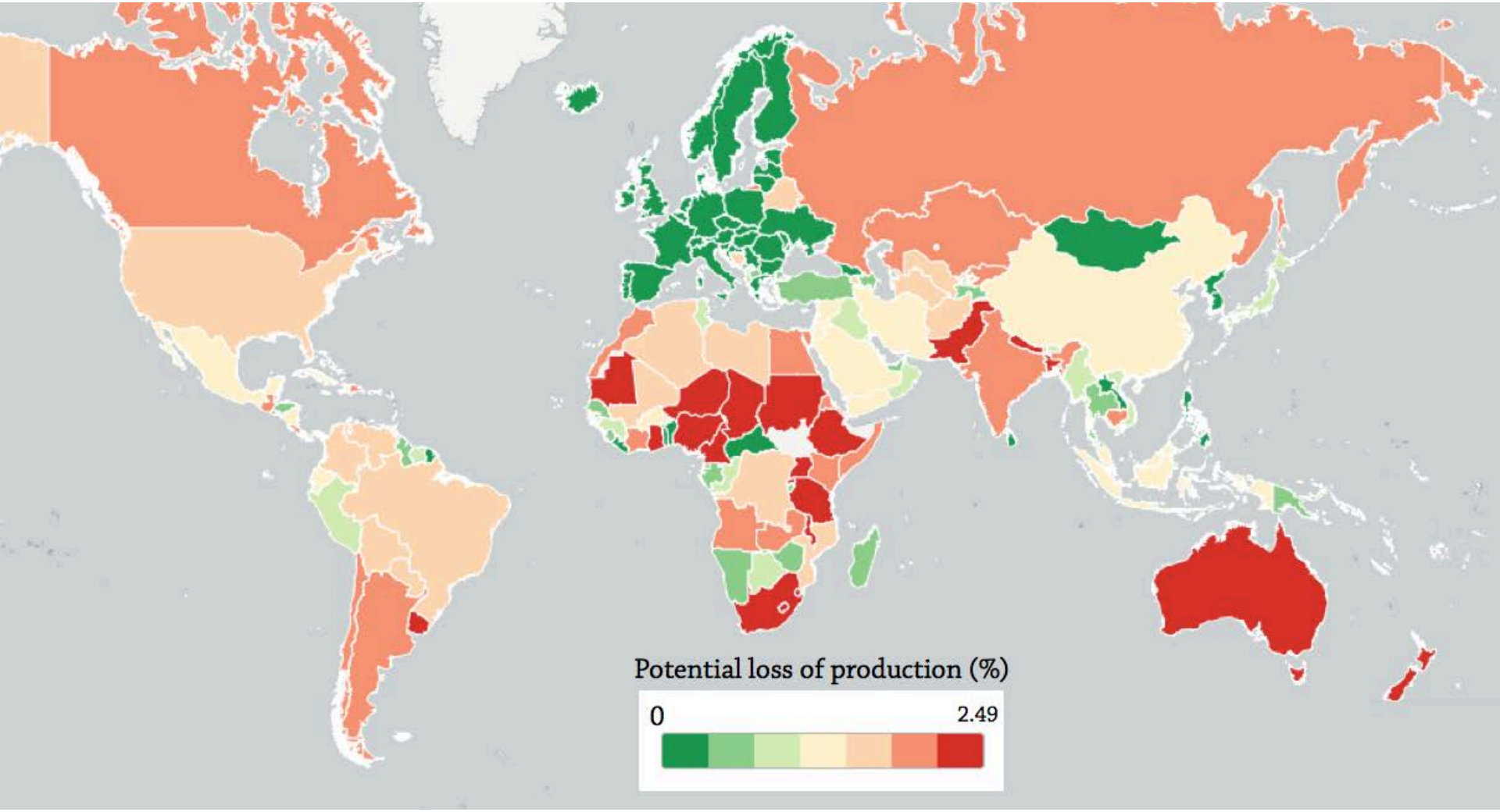
Potential loss in annual meat production following AGP withdrawal (in %)



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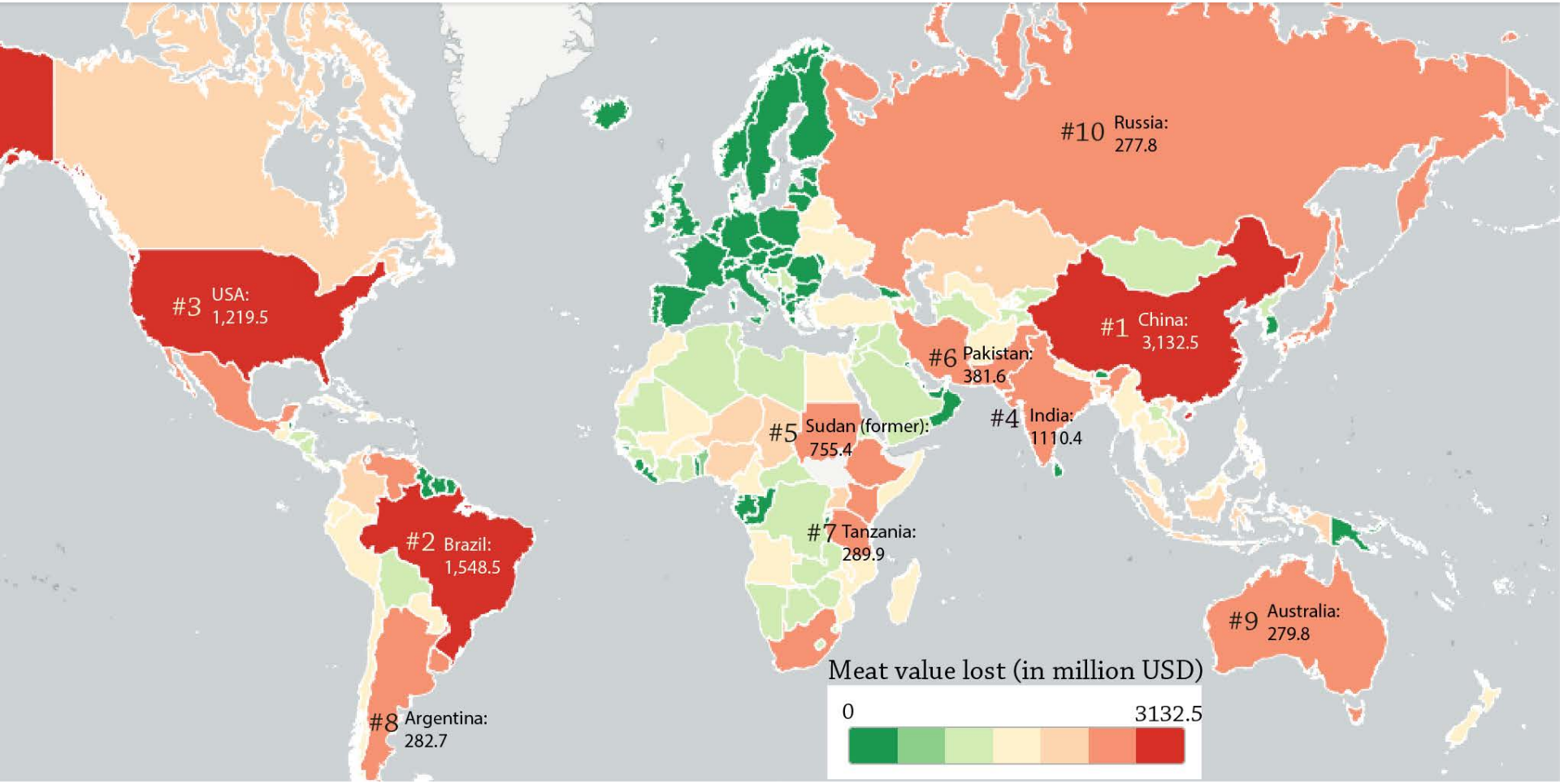
Potential loss in the value of annual meat production following AGP withdrawal



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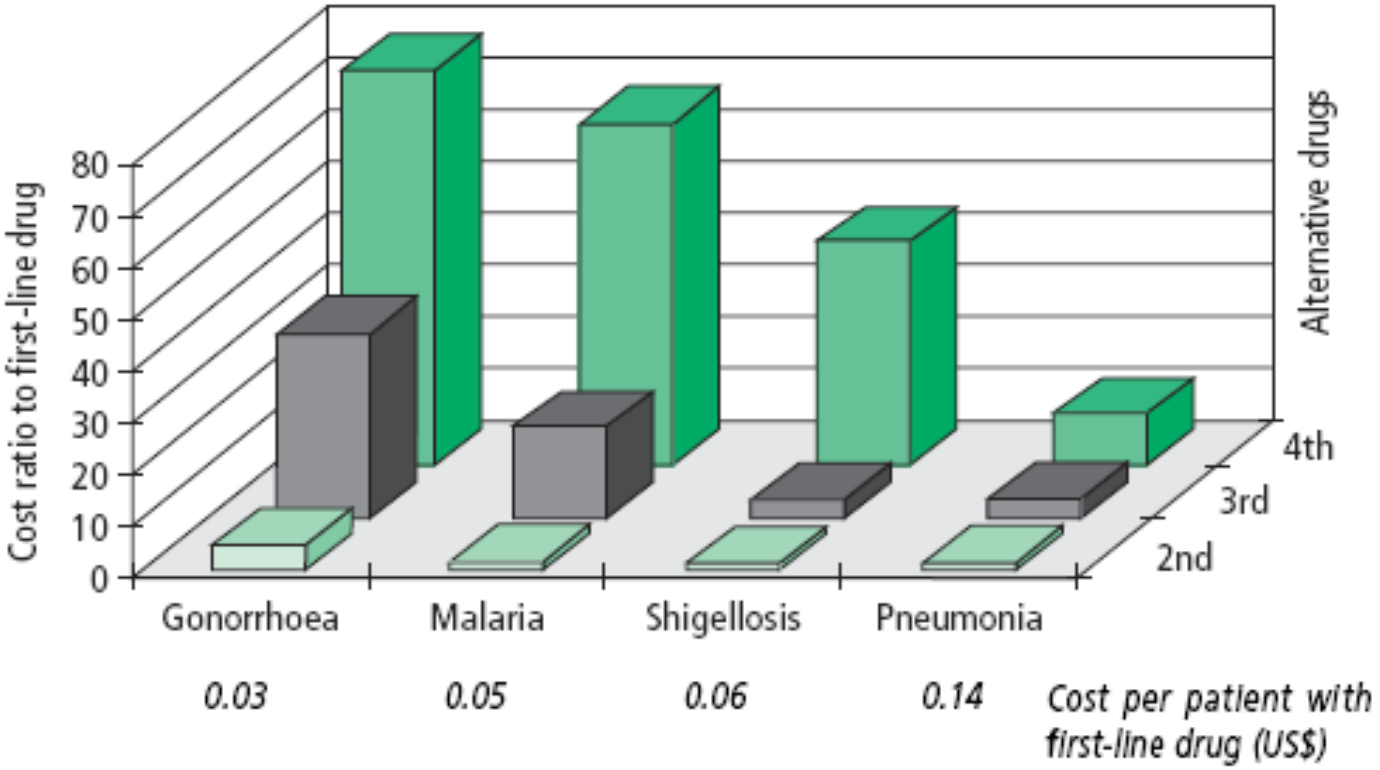
IV. Who will pay the price of rising resistance – implications of AMR.

Loss of first line drugs increases drug costs



Source: WHO Policy Perspective 2005, adapted from WHO Model Formulary, WHO Clinical Guidelines and Management Sciences for Health's 2004 International Drug Price Indicator Guide (slide courtesy: David Heymann)

Annual health gain (QALYs) in the US from procedures requiring antibiotic prophylaxis

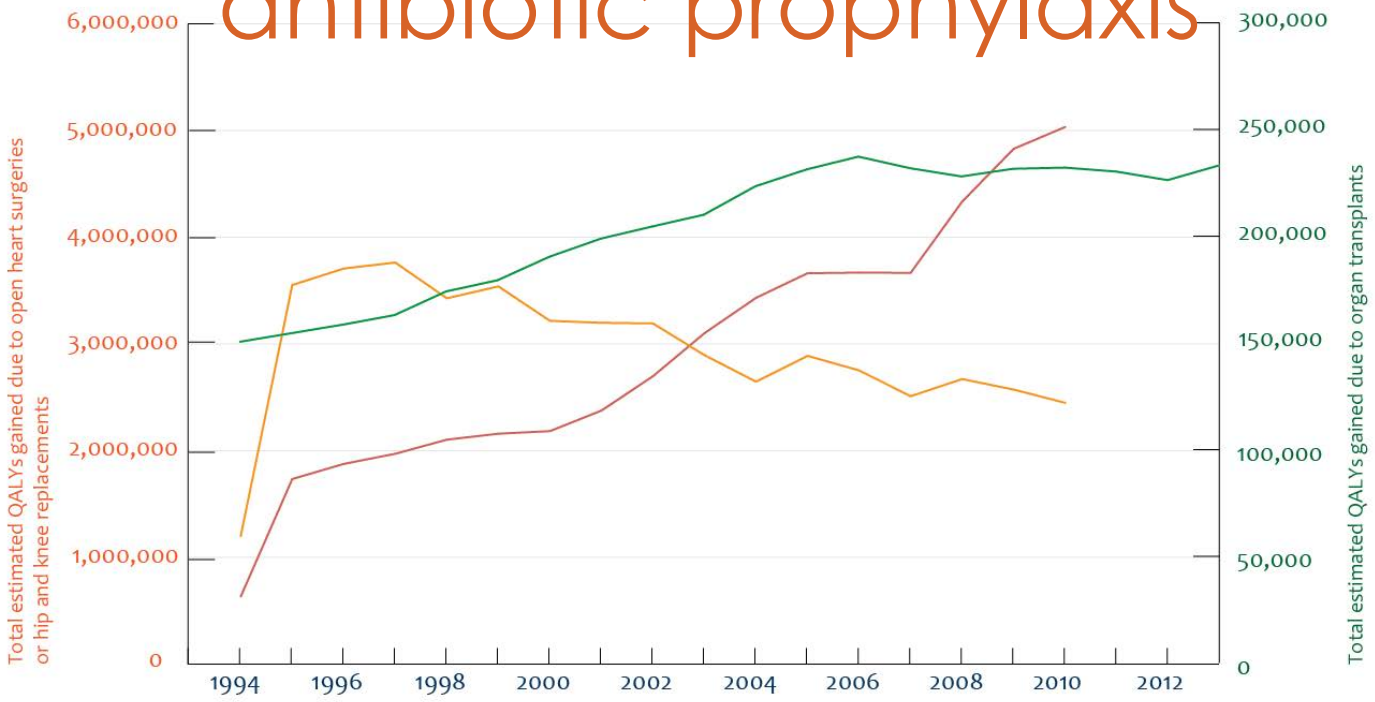


Figure: Trends in the estimated total gains in quality-adjusted life years due to organ transplants, hip and knee replacements and open heart surgeries performed annually in the US during 1994-2013.

Data source: Data on organ transplants is obtained from the online database published by the Organ Procurement and Transplantation Network. Annual reports on National Hospital Discharge Survey are used to calculate estimates for open heart surgeries and hip and knee replacements. Estimates on total quality adjusted life years (QALYs) are calculated by multiplying QALYs per procedure obtained from studies in the US and Europe.

Organ transplants*
Open heart surgeries**
Hip and knee replacements

*For organ transplants, QALYs due to simultaneous heart and lung transplants are not included, and QALY per procedure for pancreas after kidney transplantation is used as the QALY per procedure for pancreas transplantation.

**For open heart surgeries, QALYs are only from coronary artery bypass graft (CABG).

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V. Solving the problem – what can economics bring to the table?

Make better use of existing antibiotics

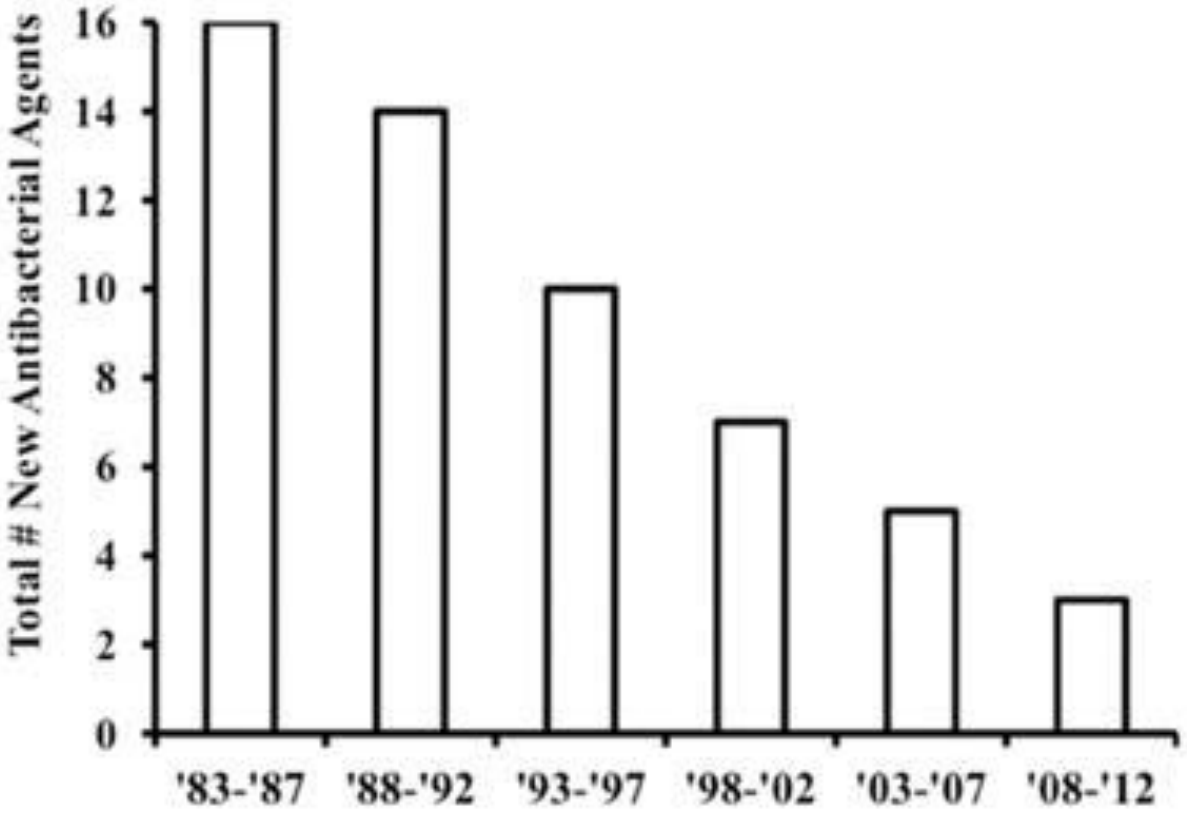
Image Courtesy of Shutterstock

Image Courtesy of Shutterstock

Is the rate of new drug development declining?

FIGURE 1: The FDA Reboot of Antibiotic Development

Antimicrobial agents approved by FDA. The number of new antibacterial agents is shown from 1983 to 2012. (Courtesy of The American Society for Microbiology)



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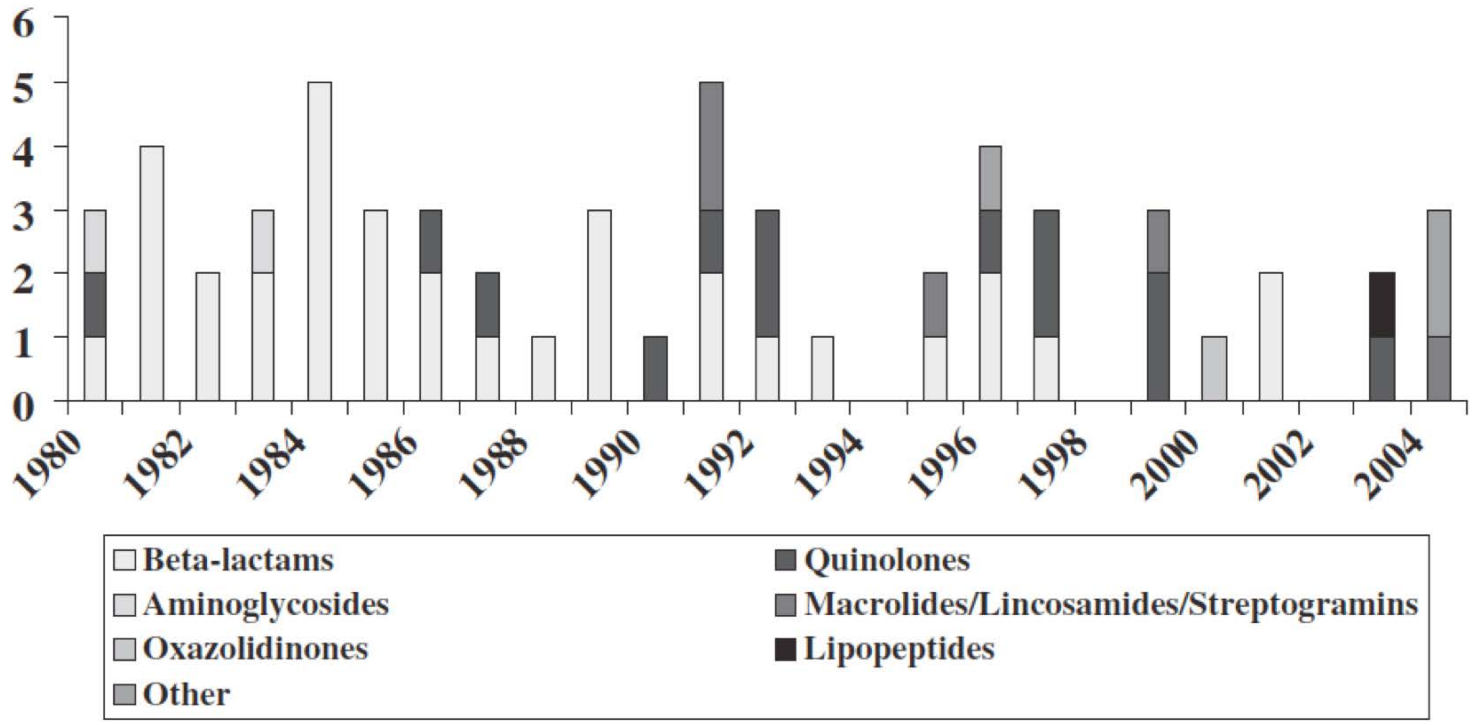
Trends in development of new antibiotics



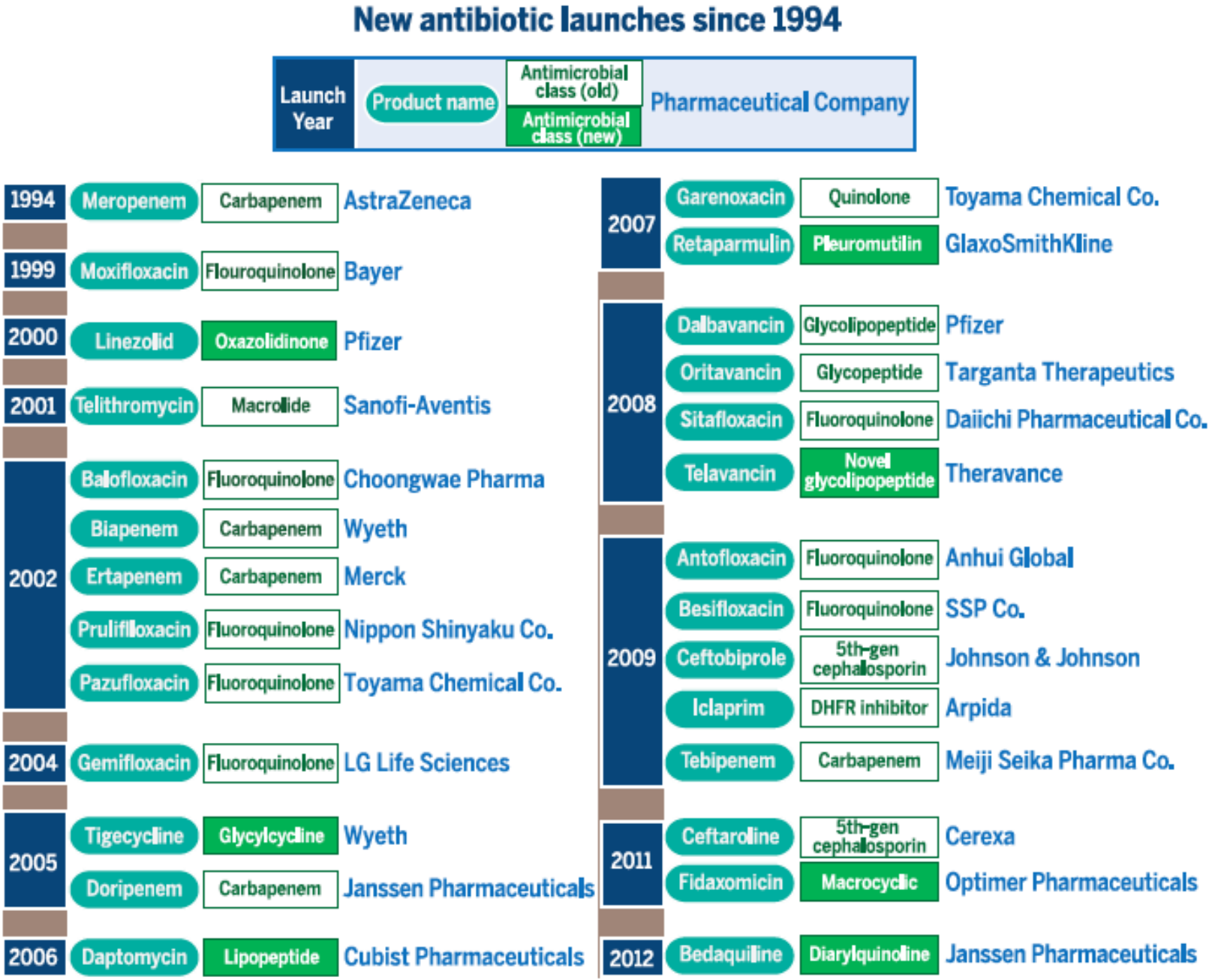


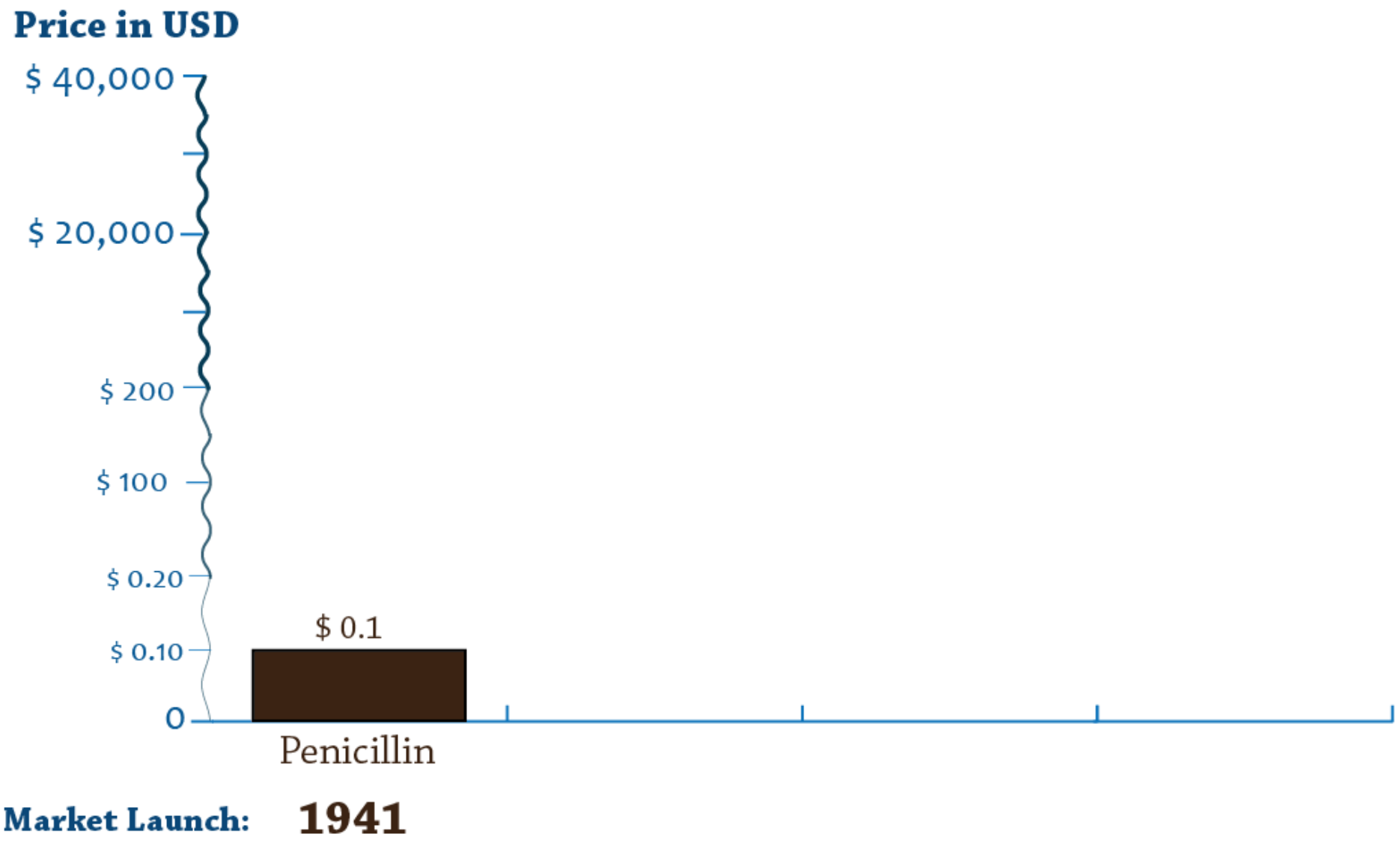
Fig. 3. Antibiotic pipeline for the past 20 years.

Laxminarayan, *Science*, 2014

Consider this

- Of the 61 new antibiotics approved between 1980 and 2009, 26 (43%) were withdrawn either because of toxicity or lack of market, compared with a 13% withdrawal rate for other therapeutic categories (Outterson et al 2013)

- 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



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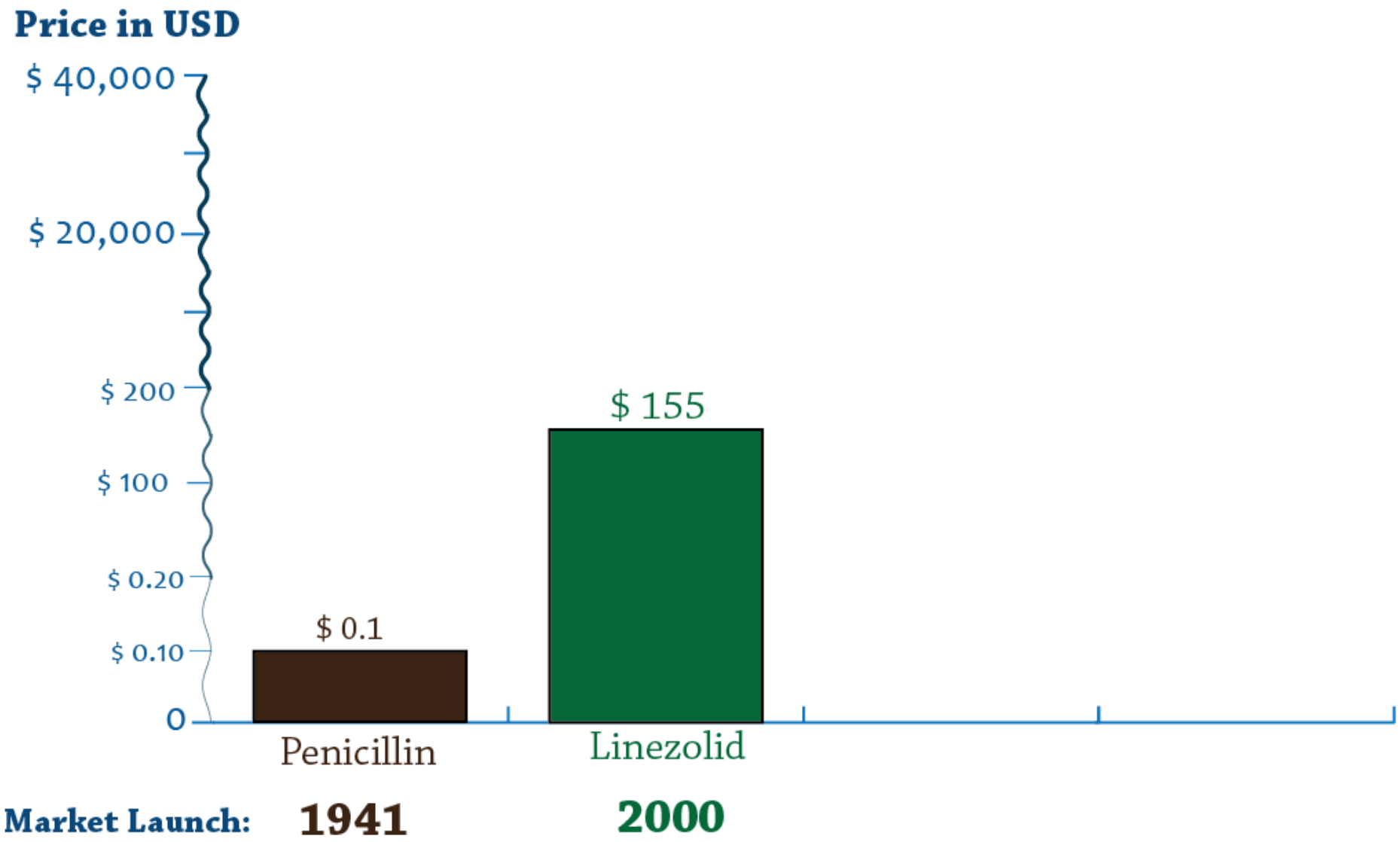

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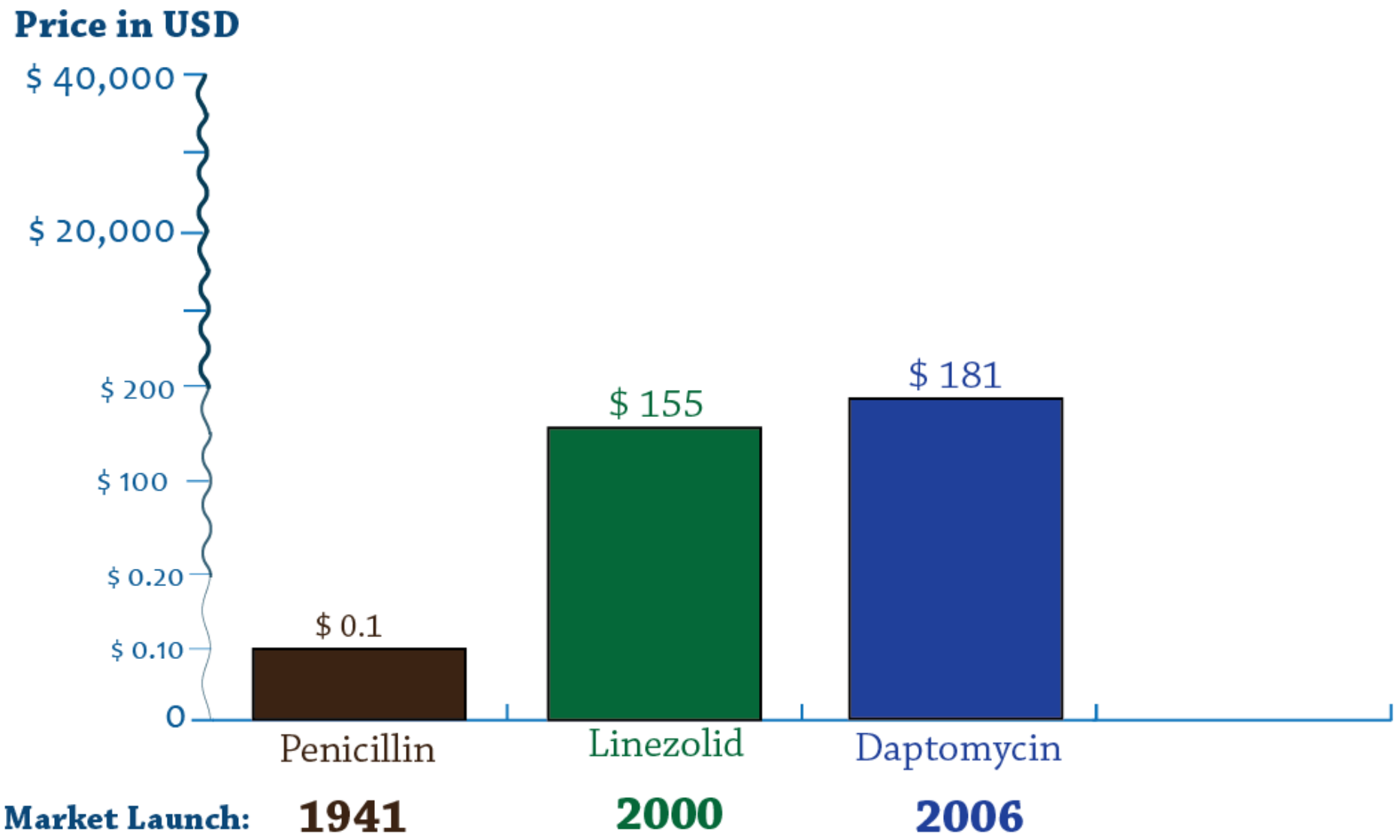

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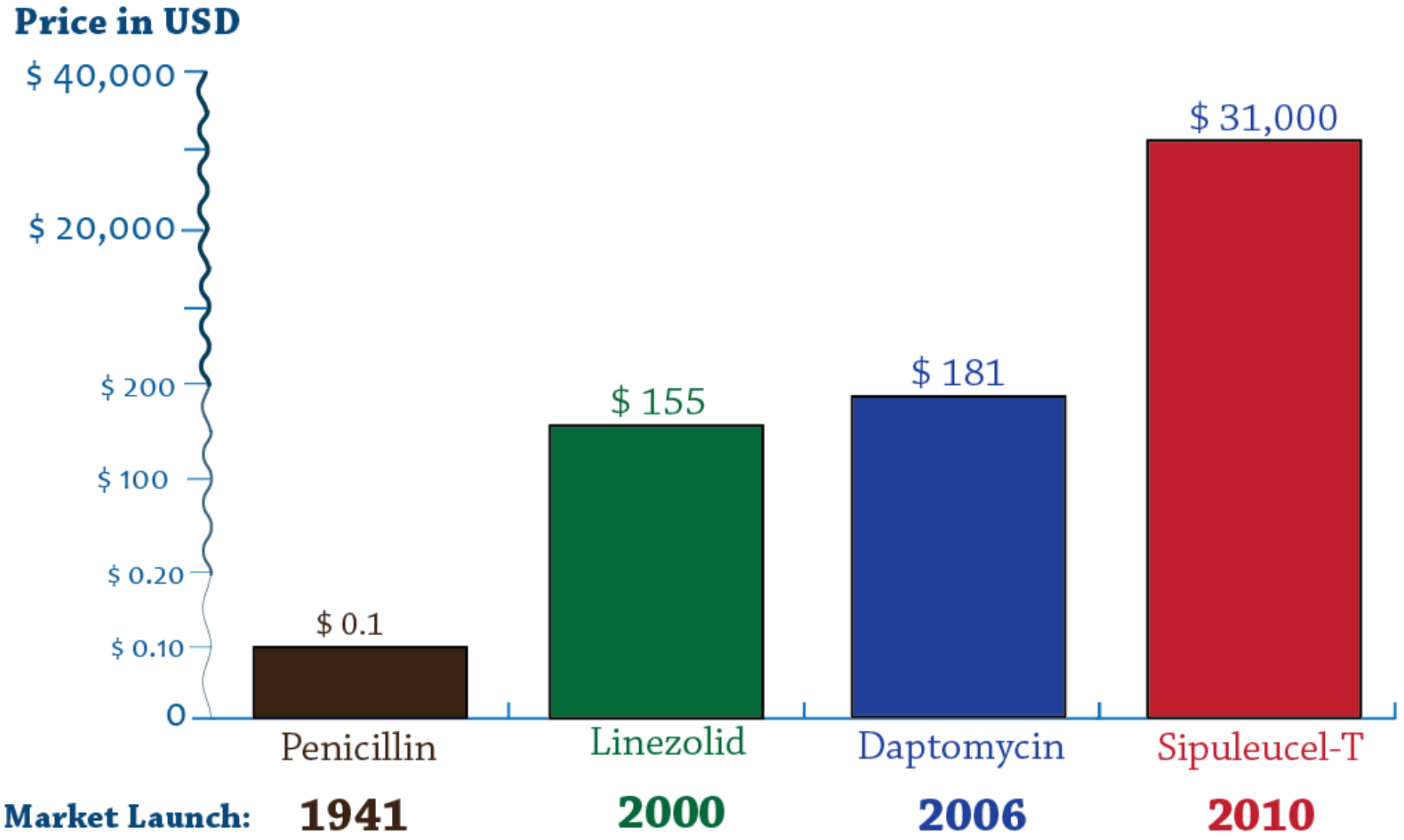

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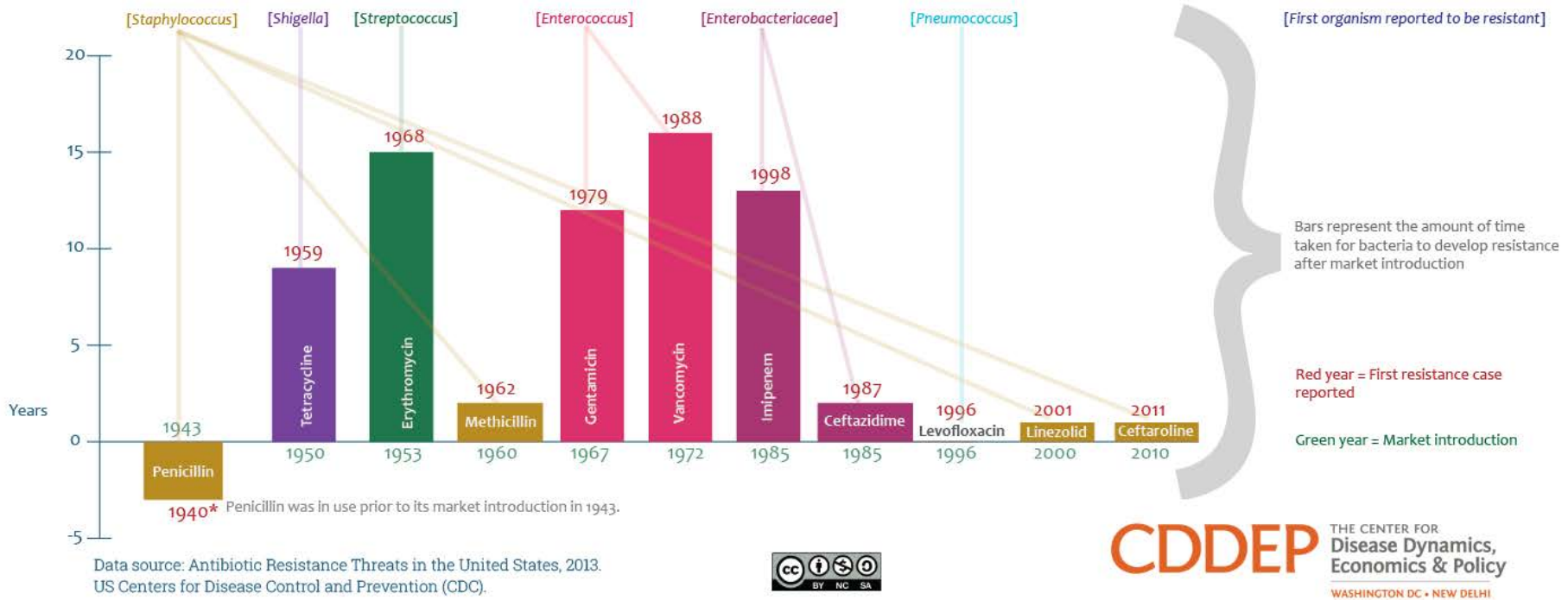
Important questions

- 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?

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



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What kind of innovation?

- 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
- Point-of-care diagnostics
  - to identify both the cause of an infection and its sensitivity to common antibiotics

Q: What should we be willing to pay for a stewardship program that would enable a 1-year delay in the need for a $1billion investment in a new antibiotic?

A: Roughly $60 million, at a modest 6% discount rate

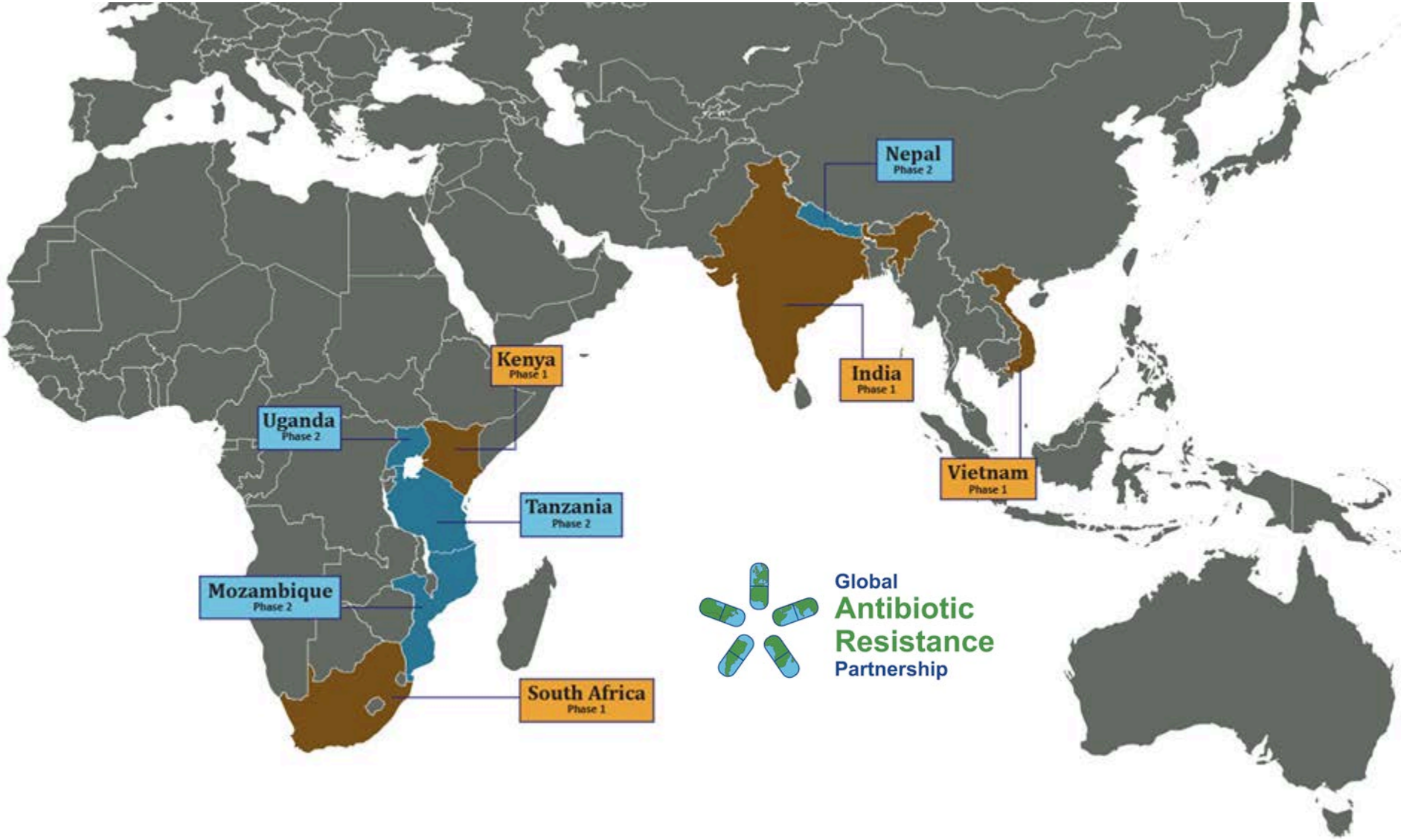
Q: What does the US Government allocate for antimicrobial stewardship programs?

A: Zero

Q: What does the Indian Government allocate for antimicrobial stewardship programs?

A: What is a stewardship program?

Closing thoughts



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www.cddep.org/garp
www.extendingthecure.org

Thank you