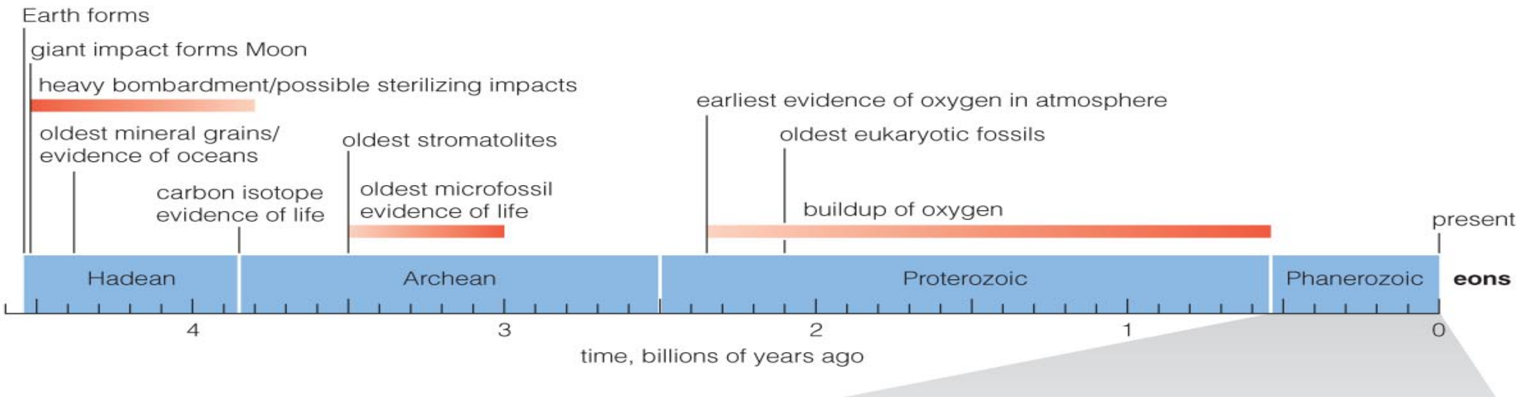
Antimicrobial Resistance

Ramanan Laxminarayan

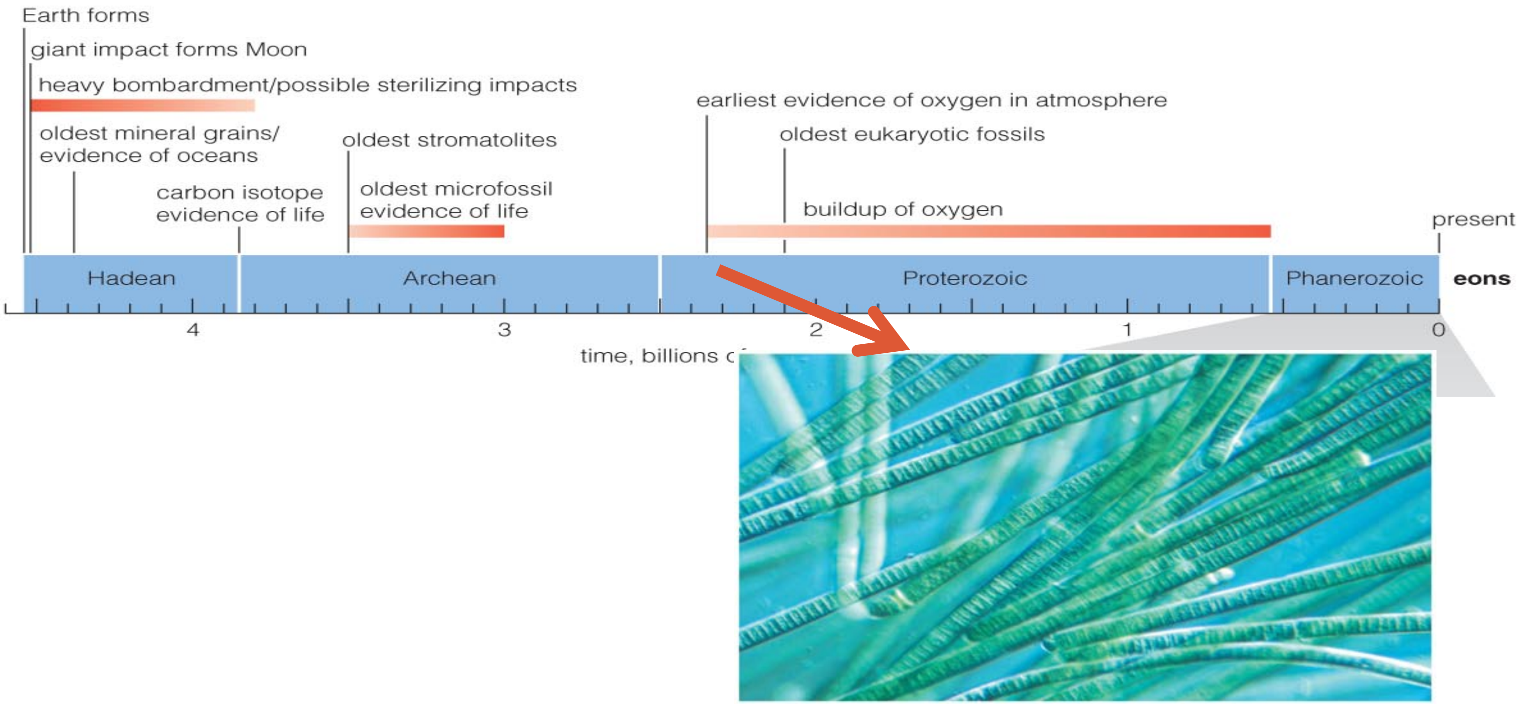
Singapore International Infectious Disease Conference 2017

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

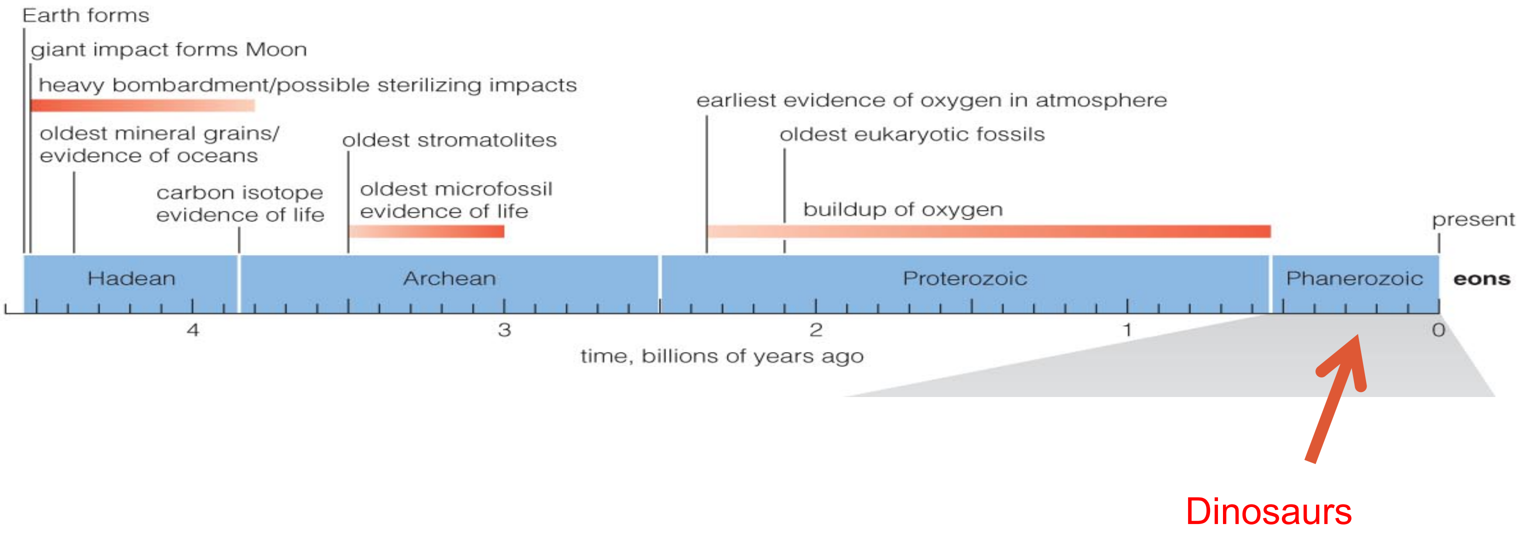
In the beginning…



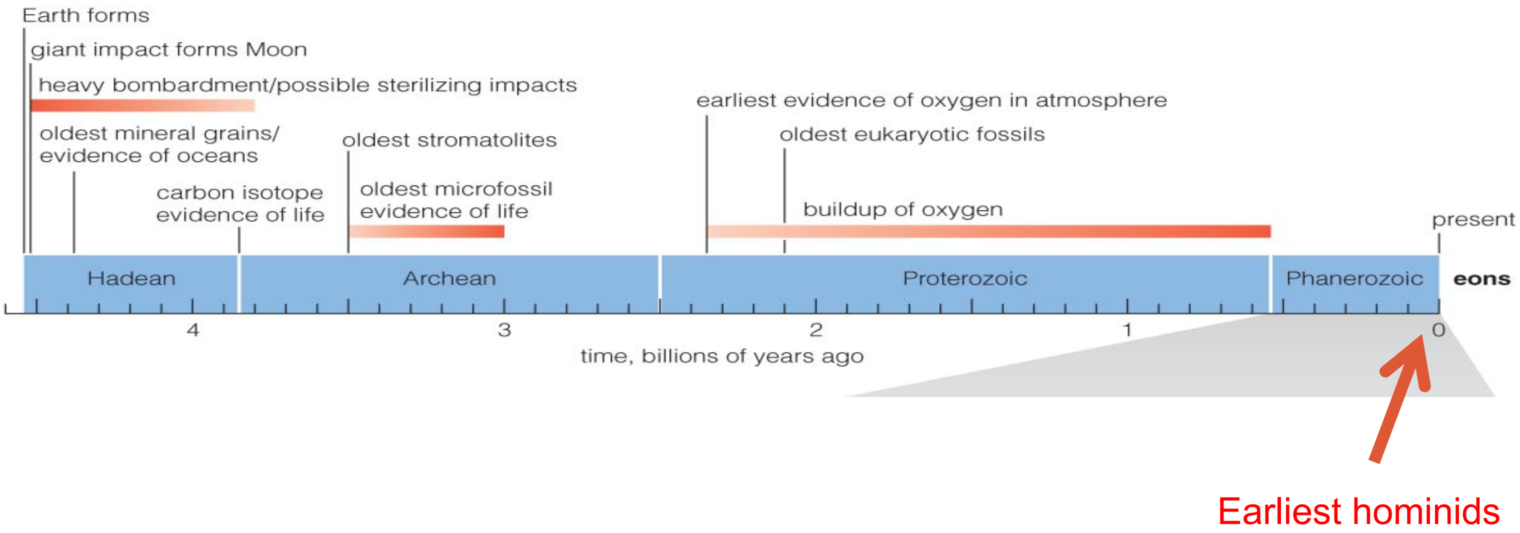
Cyanobacteria release oxygen into the atmosphere via photosynthesis paving the way for more complex life forms



Dinosaurs appears 265 million years ago



Hominids arrived a few million years ago



Life depends on microbes

- Microbes outnumber all other species and make up most living matter (~60% of the earths biomass).
- Less than 0.5% of the estimated 2 to 3 billion microbial species have been identified.
- Microbes generate half the oxygen that we breathe

Microbes were also the cause of death

All causes (United States, 1900)	**1548.4 1**
1- Tuberculosis	174.2
2- Pneumonia and influenza	161.3
3- Heart disease	145.4
4- Diarrhea, enteritis, ulcers	104.9
5-Intrachrania lesions – vascular	103.9
6- Nephritis	90.6
7- Accidents excluding automobile	72.5
8- Cancer	66.3
9- Senility	45.2

CDC/NCHS – National Vital Statistics Mortality vol48

But no longer

All causes (United States, 2000)	864.7
1- Heart Disease	268.2
2 - Malignant neoplasm's (cancer)	200.3
3 - Cerebrovascular diseases	58.6
4- COPD	41.7
5- Accidents Automobile/Others	16.1/20
6- Pneumonia and influenza	34.0
7- Diabetes mellitus	24.0
8- Suicide	11.3
9 - Nephritis	9.7
10 - Chronic Liver Di	

CDC/NCHS – National Vital Statistics Mortality vol48

Death Rates for Common Infectious Diseases in the United States

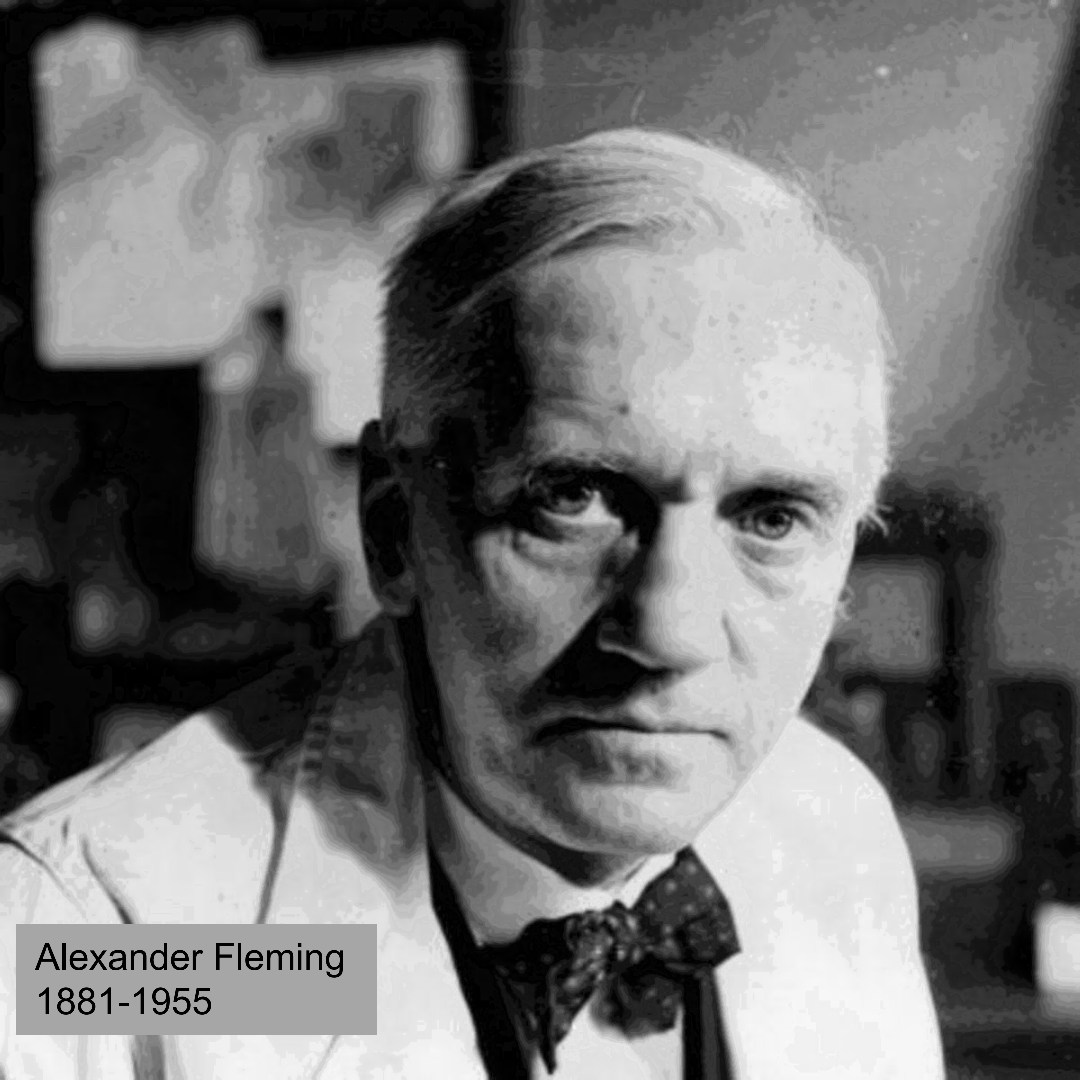
(per 100,000 Population)

	1900	1935	1970
Influenza and Pneumonia	202.2	104	31
Tuberculosis	194.4	55	3
Gastroenteritis	142.7	14	1
Diphtheria	40.3	3	0
Typhoid fever	31.3	3	0
Measles	13.3	3	0
Dysentery	12	2	0
Whooping Cough	12	4	0
Scarlet fever (including strep throat)	9.6	2	0
Meningococcal infections	6.8	2	0

Tetracycline-Labeled Human Bone from Ancient Sudanese Nubia (A.D. 350)

Abstract. *Nubian bone recovered from an X-group cemetery (A.D. 350 to 550) exhibits a pattern of fluorescence identical to that of modern tetracycline-labeled bone. When it is viewed under ultraviolet light at 490 angstroms, fluorophors are visible as a characteristic yellow-green fluorescence on surfaces that were actively mineralizing at the time of exposure. Contamination of stored grains provided the proper environment for cultivation of tetracycline-producing Streptomycetes. Evidence for exposure to antibiotics in an archeological population is relevant to studies of the evolution of R factors and to the interpretation of health and disease within the population.*

Bassett et al, Science, 1980



Alexander Fleming
1881-1955

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.

— Alexander Fleming

THE BRITISH JOURNAL
OF
EXPERIMENTAL
PATHOLOGY
VOLUME TEN
1929

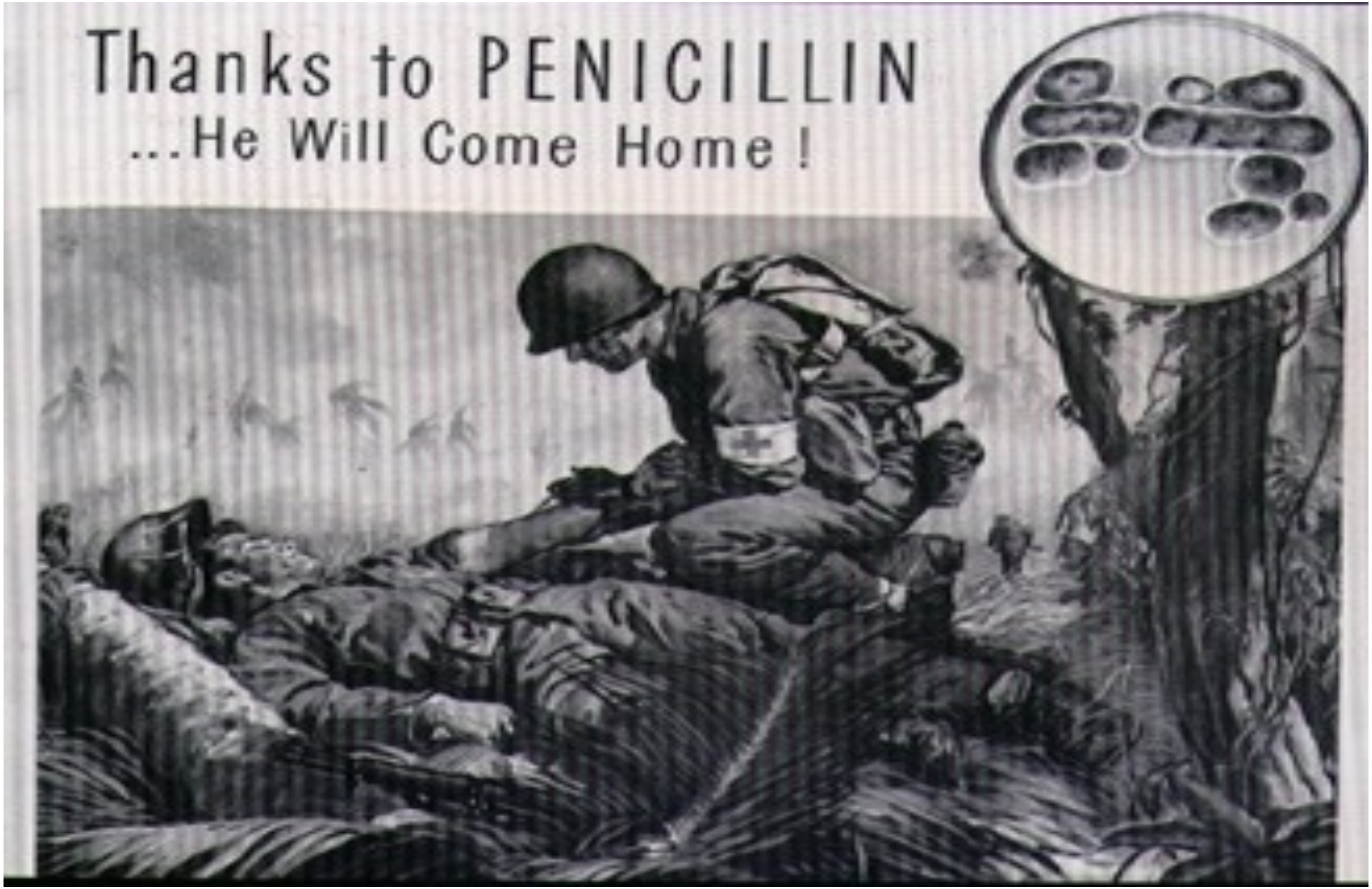
Reproduced from pages 226–236.

ON THE ANTIBACTERIAL ACTION OF CULTURES OF A PENICILLIUM, WITH SPECIAL REFERENCE TO THEIR USE IN THE ISOLATION OF *B. INFLUENZÆ.*

ALEXANDER FLEMING, F.R.C.S.

From the Laboratories of the Inoculation Department, St Mary's Hospital, London.

Received for publication May 10th, 1929.


Thanks to PENICILLIN
...He Will Come Home!


1
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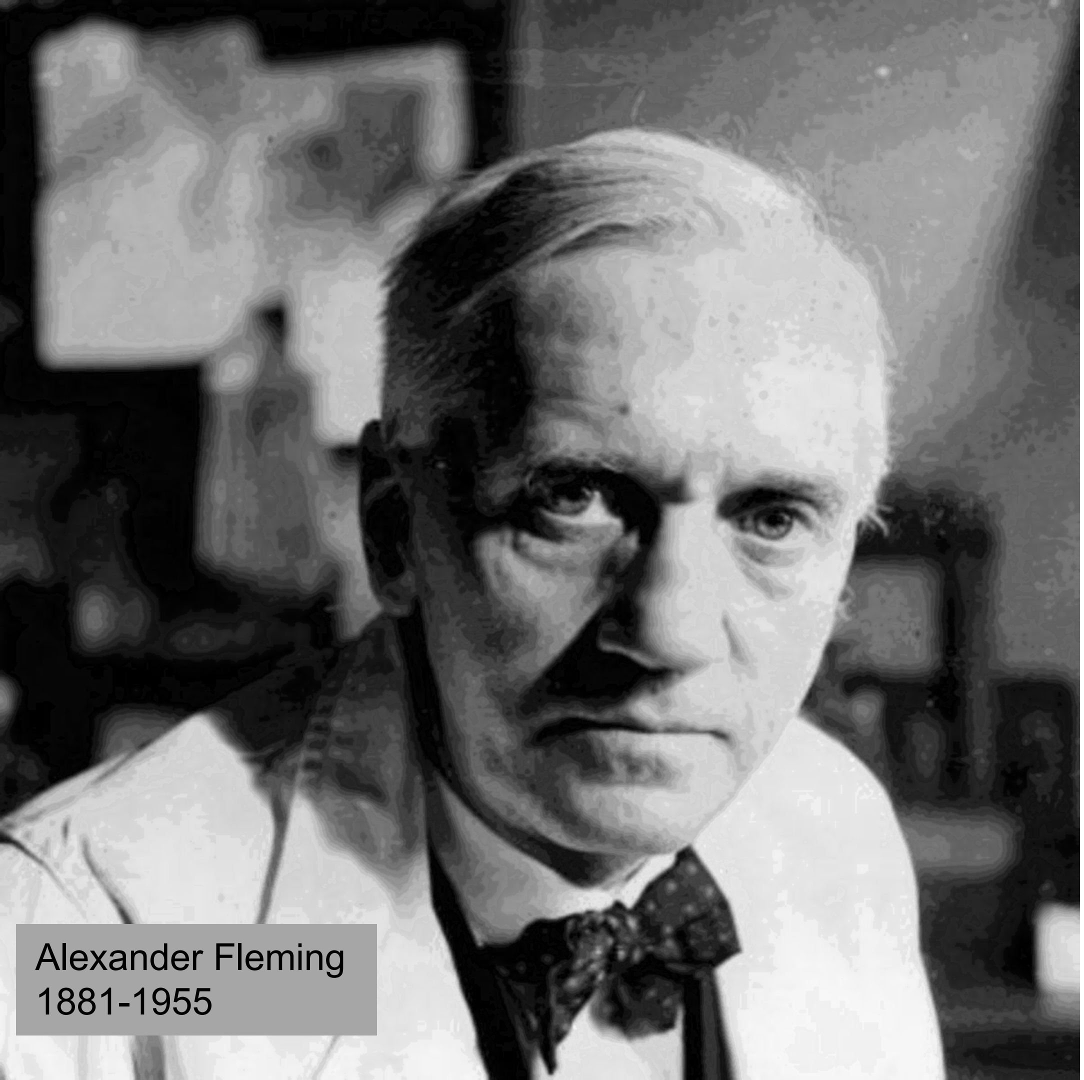
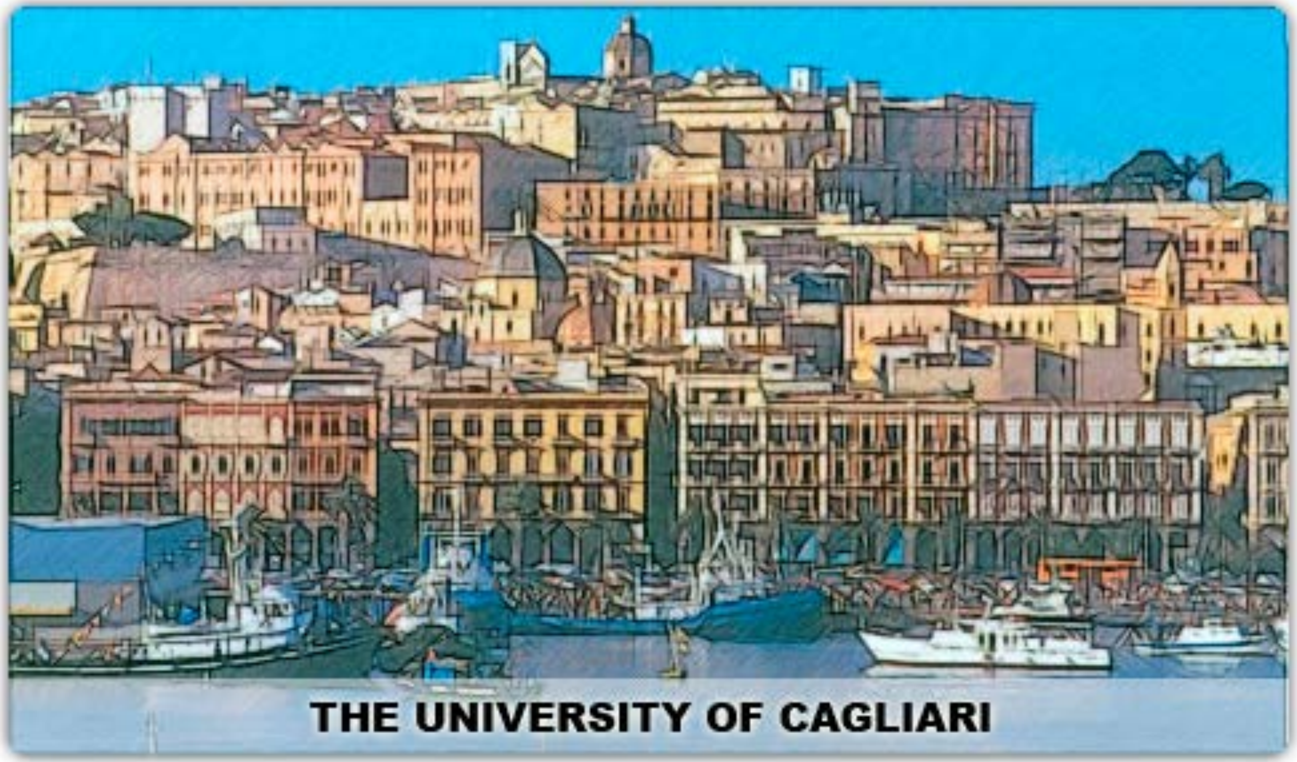

Alexander Fleming
1881-1955


Giuseppe Brotzu
1895-1976


THE UNIVERSITY OF CAGLIARI

Cephalosporium acremonium

LAVORI DELL'ISTITUTO D'IGIENE DI CAGLIARI

RICERCHE SU DI UN NUOVO ANTIBIOTICO

Prof. GIUSEPPE BROTZU

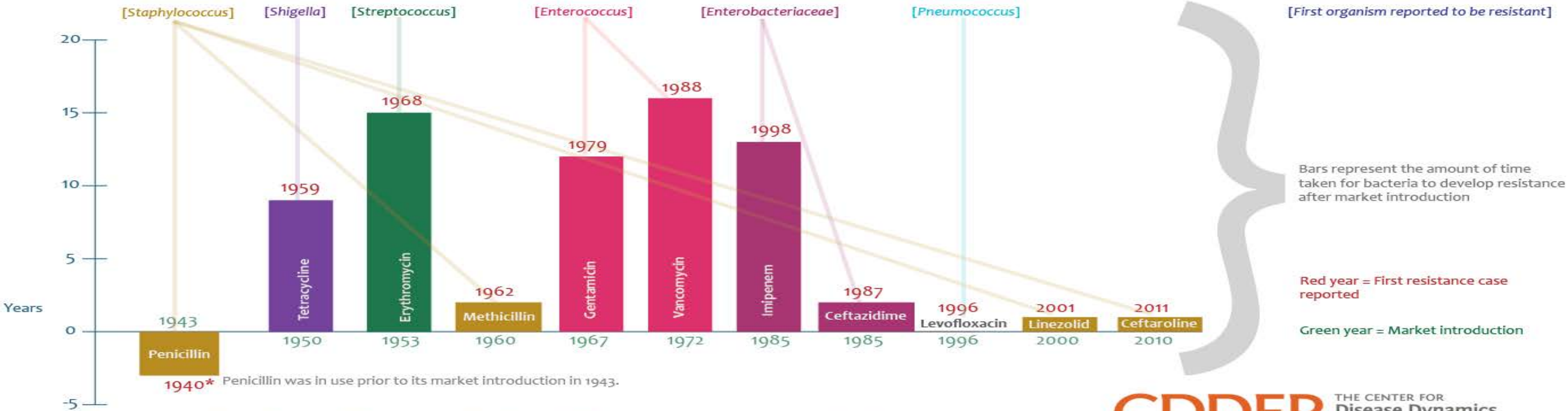
Mortality rates of patients with bacteremic pneumococcal pneumonia

Treatment	No.	% mortality
Symptomatic[1]	356	80
Penicillin[1] (1940s)	333	17

[1]M. Finland. Clinical Pharmacology and Therapeutics 13:469-511, 1972.

I. Drug resistance is rising worldwide and threatens gains made in reducing the burden of infectious diseases

First reported cases of bacterial resistance against key antibiotics



Data source: Antibiotic Resistance Threats in the United States, 2013.
US Centers for Disease Control and Prevention (CDC).

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LETTER

doi:10.1038/nature10388

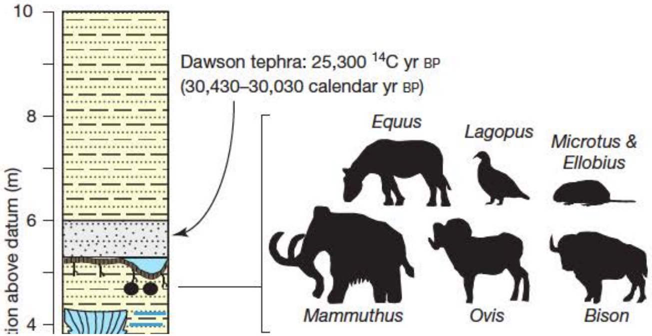
Antibiotic resistance is ancient

Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes[1,2]. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics[3]. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Recent studies of modern environmental and human commensal microbial genomes have a much larger concentration of antibiotic resistance genes than has been previously recognized[4–6]. In addition, with high concentrations of *Escherichia coli* harbouring the *gfp* (green fluorescent protein) gene from *Aequorea victoria* (Supplementary Information).

After fracturing of the samples (Supplementary Fig. 3), total DNA was extracted from a series of five subsamples taken along the radius of each core (Supplementary Information). Quantitative polymerase



D'Costa, Nature, 2011

START | infoporn

The Bug Wars

In the battle of bad bacteria vs. antibiotics, the drugs usually lose.

Infectious diseases give us a stunning demonstration of evolution in action: The fittest bacteria – the ones that survive an antibiotic onslaught – transfer their resistance to new generations and across species. Their ability to fight back usually strengthens with each mutation, allowing them to thwart even the most intelligently designed drugs. Over the past 63 years, deadly bugs like *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Escherichia coli* have evolved to withstand medicines like penicillin, tetracycline, and ciprofloxacin. So scientists are now planning a flank attack – precisely targeted drug-delivery systems and bacteria-eating nanorobots. But if history repeats itself, the bugs will ultimately win. – **Patrick Di Justo**

BEHIND ENEMY LINES: A LOOK AT RESISTANCE TACTICS

Genetic mutations enable bacteria to adapt to new threats. Here are three ways they evolve to combat antimicrobial agents.

CAMOUFLAGE
A bacterium's protein receptors morph so the antibiotic can't lock into them. (Staph used this method to evade the penicillin family.)

ROADBLOCKS
The cell membrane changes to keep the antibiotic out. (Bacteria like staph and strep fended off tetracyclines this way.)

DISARMAMENT
A bacterium produces enzymes that turn off the action part of the antibiotic. (This is how *E. coli* trumped cephalosporins.)

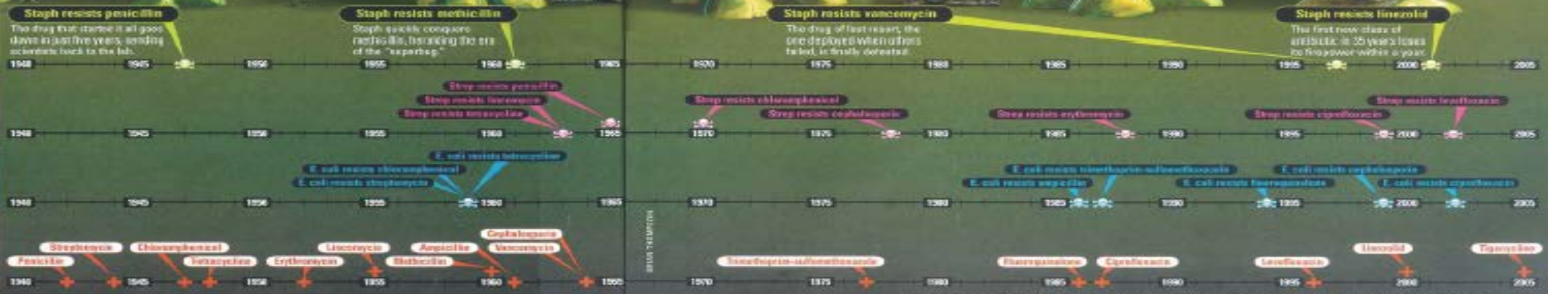
HOW FAST BACTERIA EVOLVE TO THWART DRUGS

Staphylococcus aureus
S. aureus causes everything from skin infections to toxic shock syndrome. More than half of all staph infections found in intensive care units today can be linked to a drug-resistant strain.

Streptococcus pneumoniae
Besides the much-loathed strep throat and the much-feared flesh-eating bacteria, strains of *Streptococcus* cause over 125,000 cases of pneumonia a year that require hospitalization.

Escherichia coli
Dangerous forms of *E. coli* cause all sorts of maladies, from GI distress to meningitis. In June 2005, the FDA approved tigecycline, a new type of antibiotic designed to fight resistant *E. coli*.

Antibiotics
More than 110 million antibiotic prescriptions are written annually in the US. The Centers for Disease Control and Prevention discourages the use of antibiotics to treat viral diseases like the flu. The drugs are ineffective against viruses.



Sources: Alliance for the Prudent Use of Antibiotics; Centers for Disease Control and Prevention; *Clinical Infectious Diseases*; Mark Fischetti and Stuart Levy, *The New Killer Diseases*; Jeffrey Fisher, *The Plague Makers*; Stuart Levy, *The Antibiotic Paradox*; National Library of Medicine


MONEYWEEK
WHITEWATER
COSMOPOLITAN
November 1995
At Last! Something Pleasurable That's Good for You. The Health Benefits of Sex
The Heart-Pounding Bawdiness of Brad Pitt, Who Couldn't Care Less
Cosmo's Update on Antibiotics. What's Okay and What's Dangerous
Why Marry Instead of Just Fooling Around?
Makeup Tricks
$2.95
MUTUAL FUNDS: 1ST QUARTER STARS
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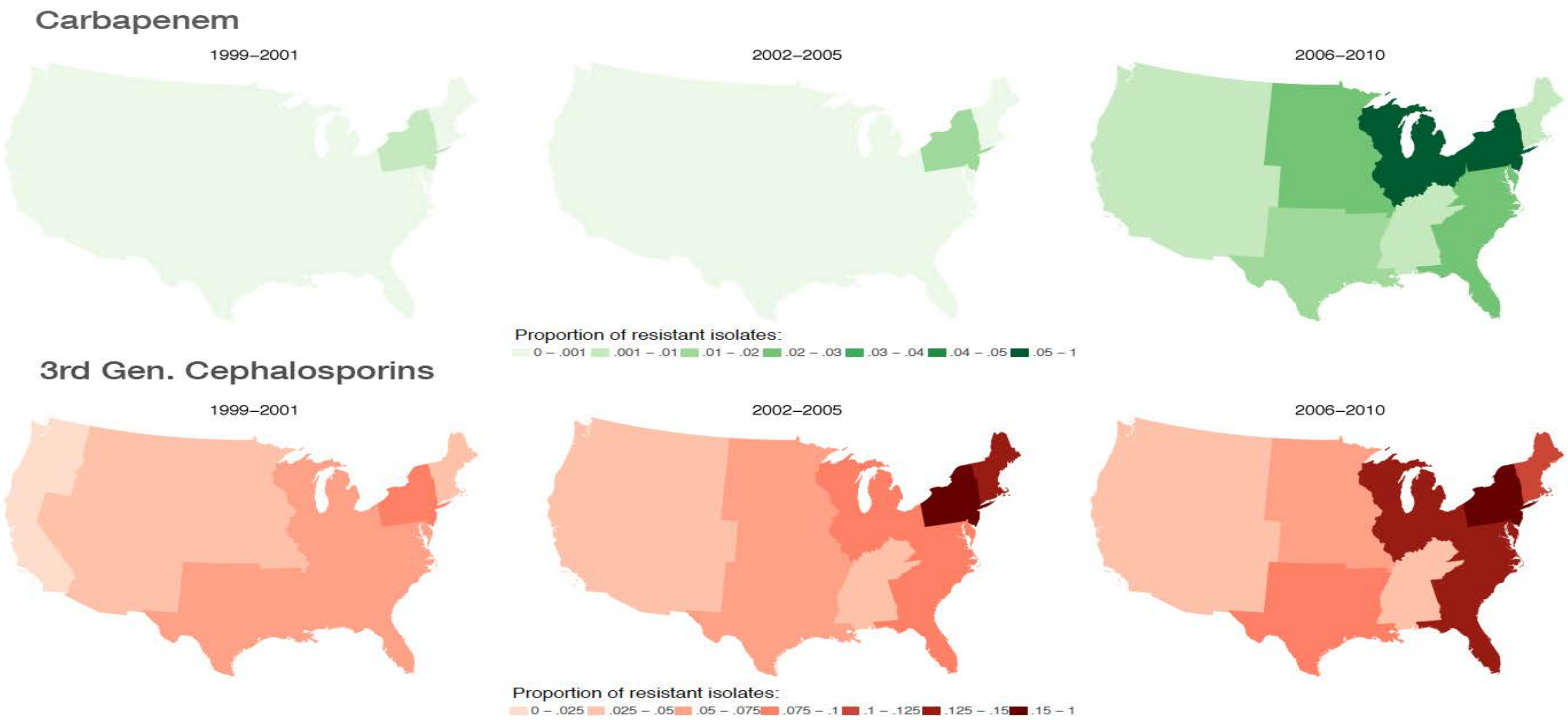
DR. DAVID SHLAES OF WYETH-AYERST

Carbapenem and 3rd. gen. cephalosporin resistance among *K. pneumoniae* highest along the East Coast, but present in all regions of the country



Note: Data for 2010 available through July.

Data source: Braykov NB, Eber MR, Klein EY, Morgan DJ, Laxminarayan R. Trends in Resistance to Carbapenems and Third- Generation Cephalosporins among Clinical Isolates of Klebsiella pneumoniae in the United States, 1999-2010. Infect Control and Hospital Epidemiology. 2013; 34(3)

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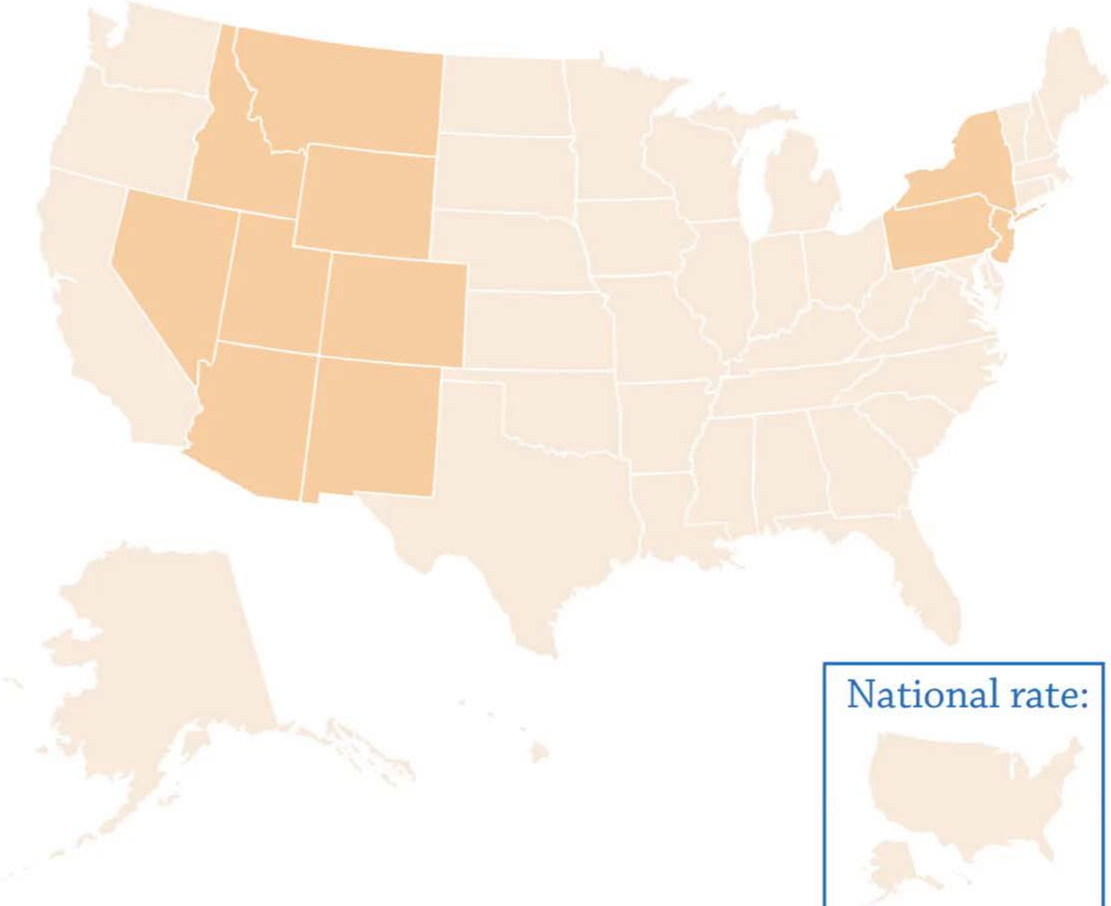
Carbapenem-resistant *Acinetobacter baumannii*

Year: **1999**

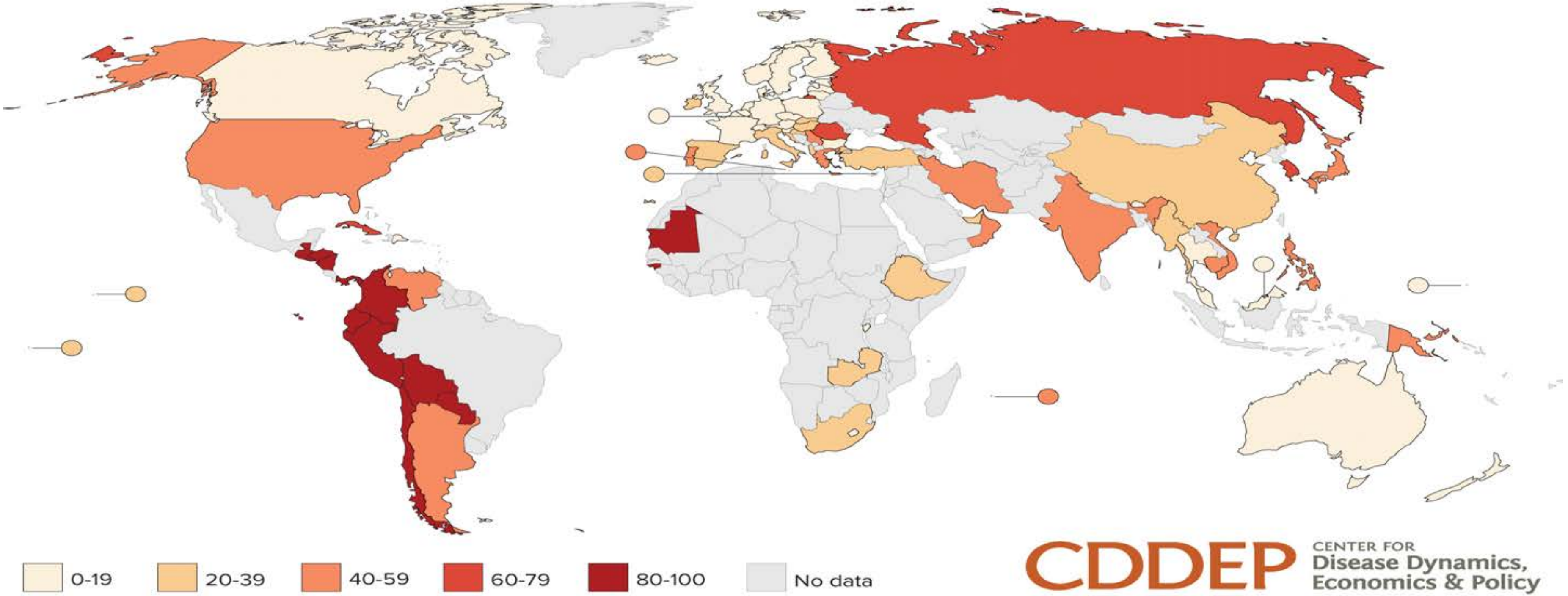


Percentage resistant:

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

National rate:

Percentage of *Staphylococcus aureus* that are methicillin resistant (MRSA), by country (most recent year, 2011-14)



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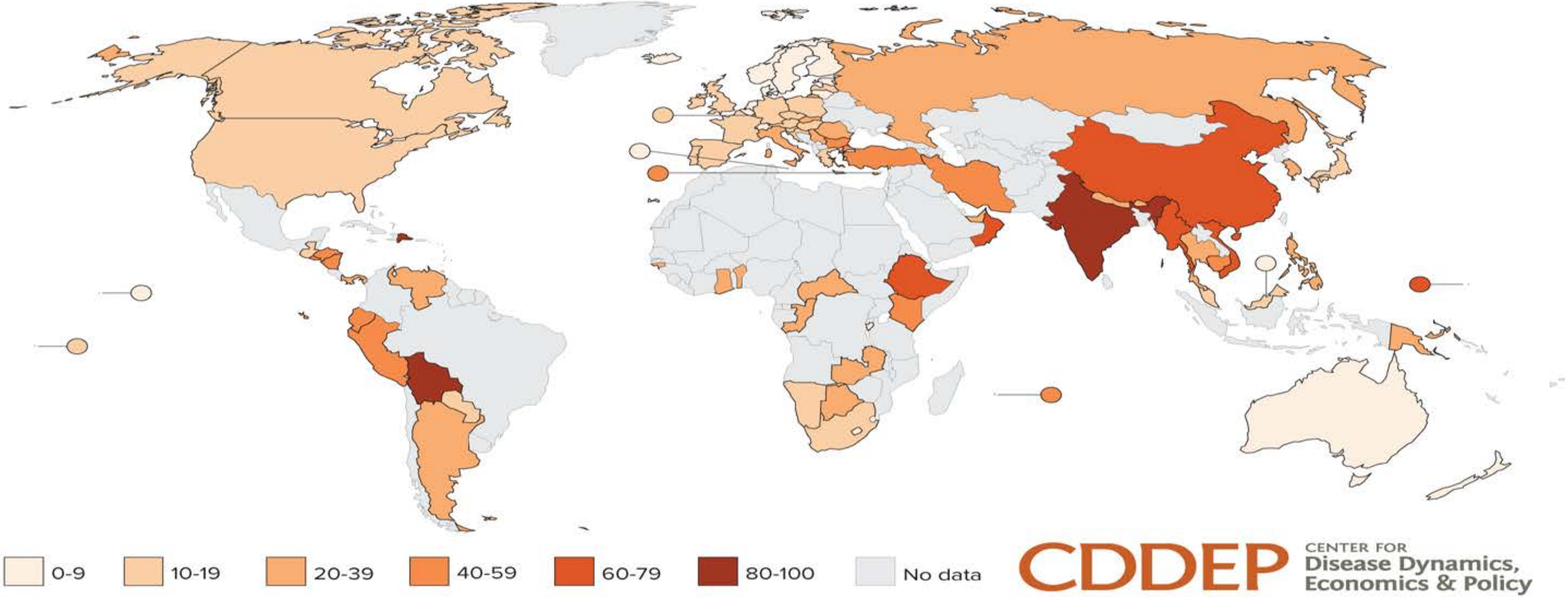
Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from hospital-associated MRSA and invasive isolates have been used. In their absence, data from community-associated MRSA or all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used to test for MRSA: Oxacillin, cefoxitin, flucloxacillin, cloxacillin, dicloxacillin, and methicillin. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

Percentage of extended-spectrum beta-lactamase producing *Escherichia coli**, by country (most recent year, 2011-2014)



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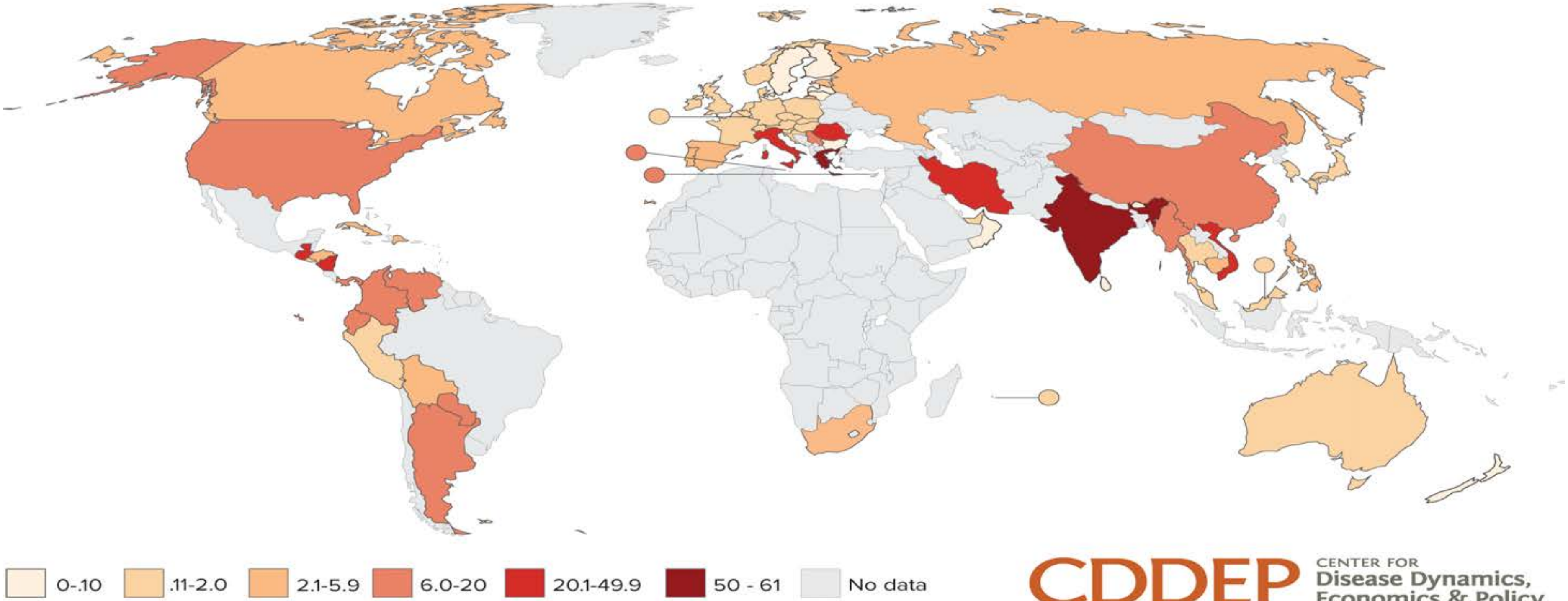
Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: Ceftazidime, ceftriaxone and cefotaxime. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

*Indicated by third-generation cephalosporin resistance

Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011-2014)



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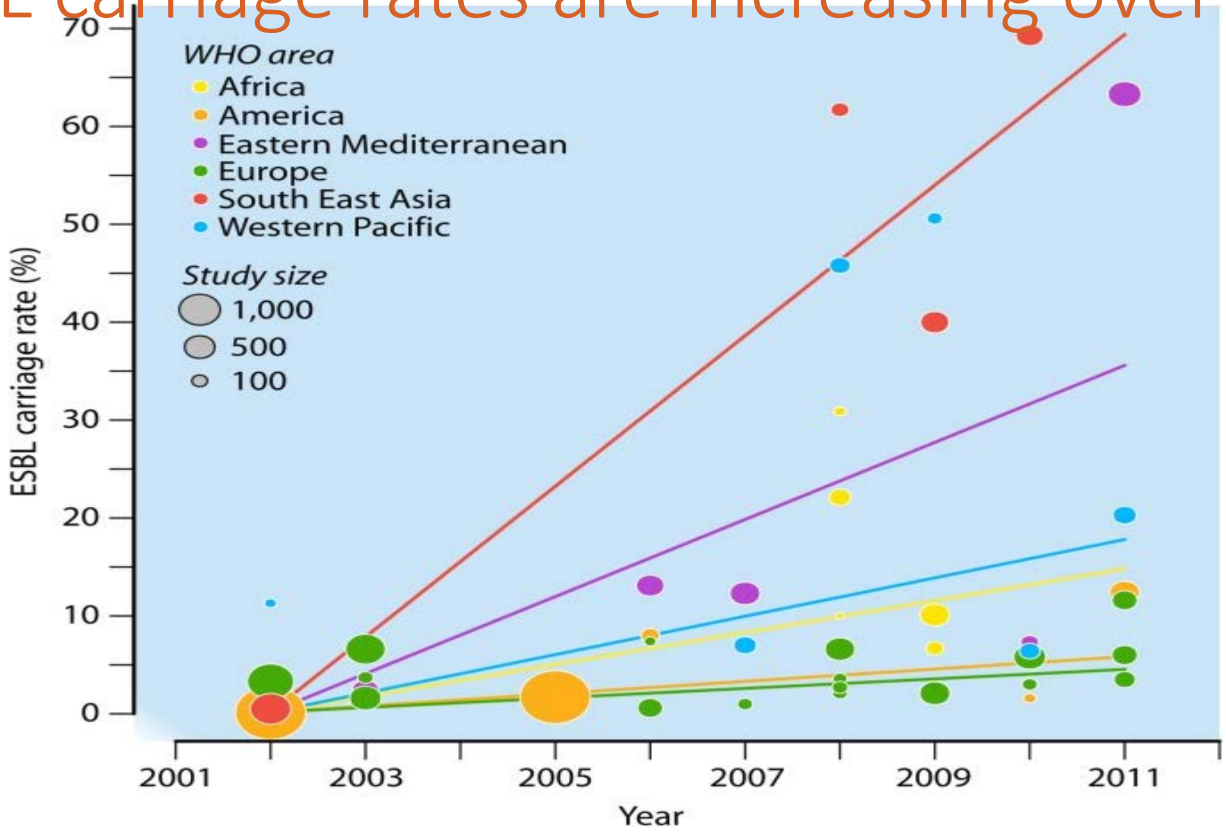
Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: imipenem, meropenem, ertapenem and doripenem. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

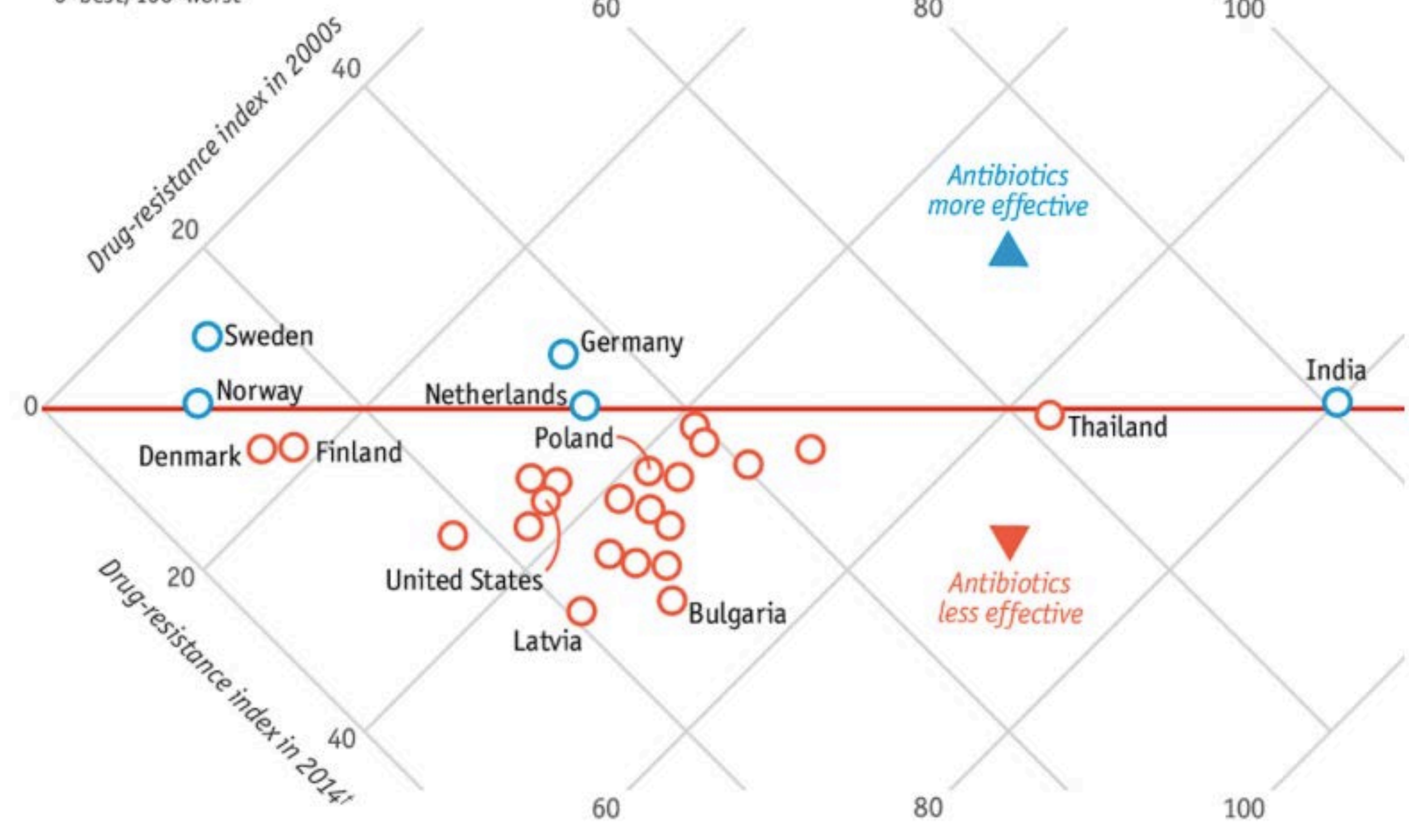
ESBL carriage rates are increasing over time



Woerther, Clin Microbiol Rev. 2013

The drugs work less

Effectiveness of antibiotics* in selected countries
0=best, 100=worst

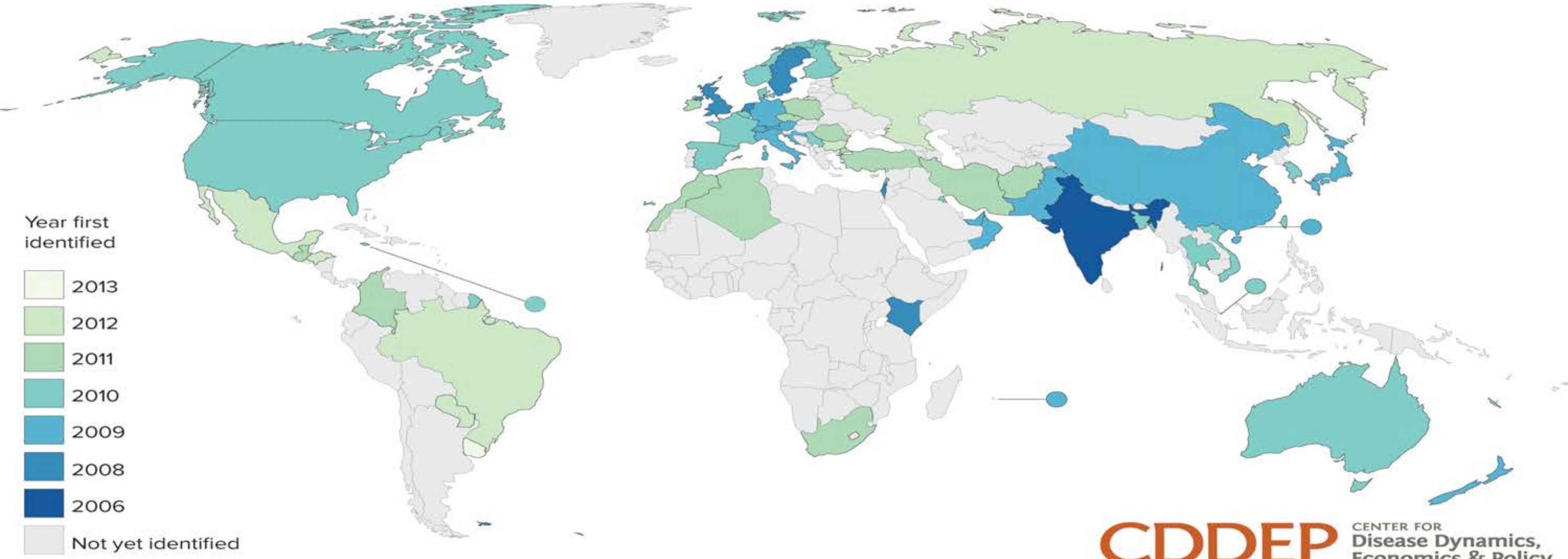


*By index of six bacteria's resistance to six classes of drug
†Except US (2012), Poland (2013) and Thailand (2013)

Source: Centre for Disease Dynamics, Economics & Policy

Economist.com

Spread of New Delhi metallo beta-lactamase: first detection, by country



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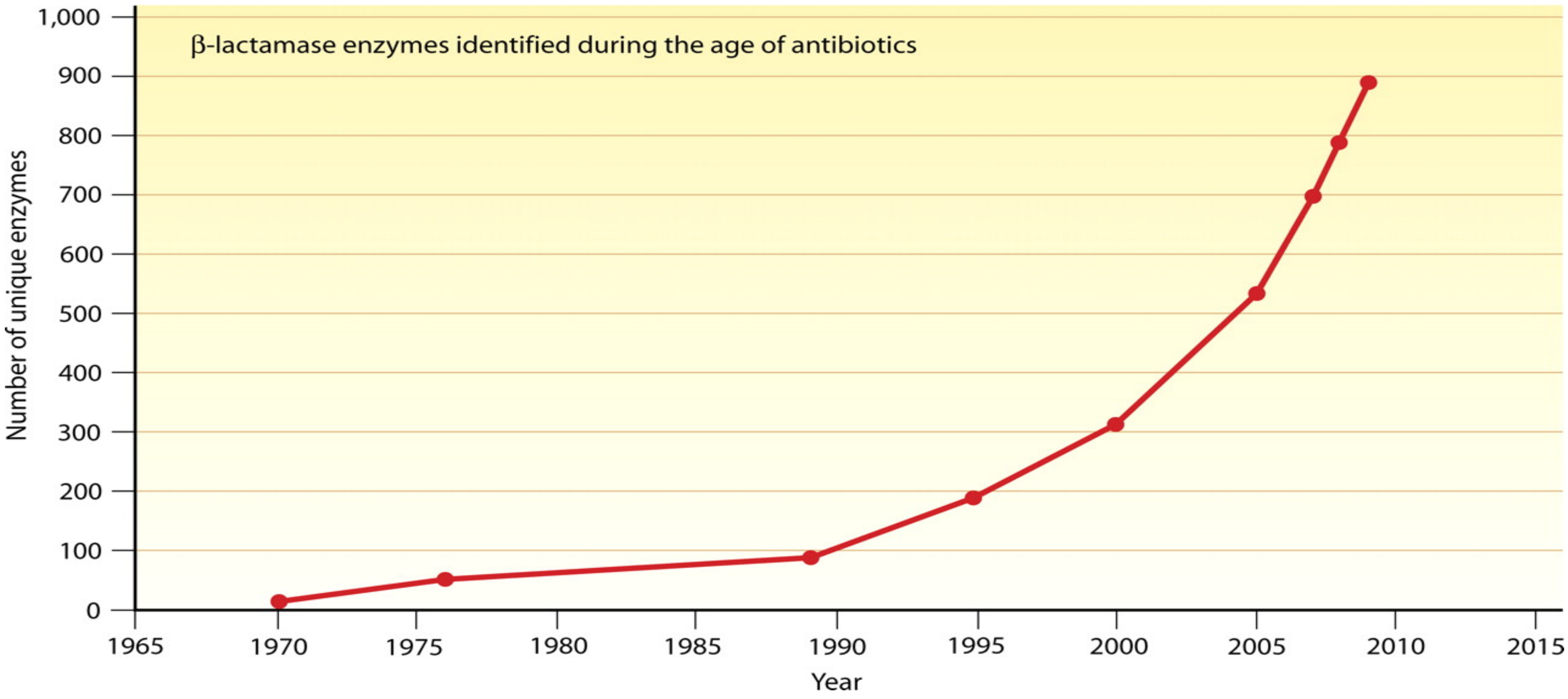
Source: Johnson and Woodford 2013 (adapted)

Clonal spread of *S. pneumoniae* 23F

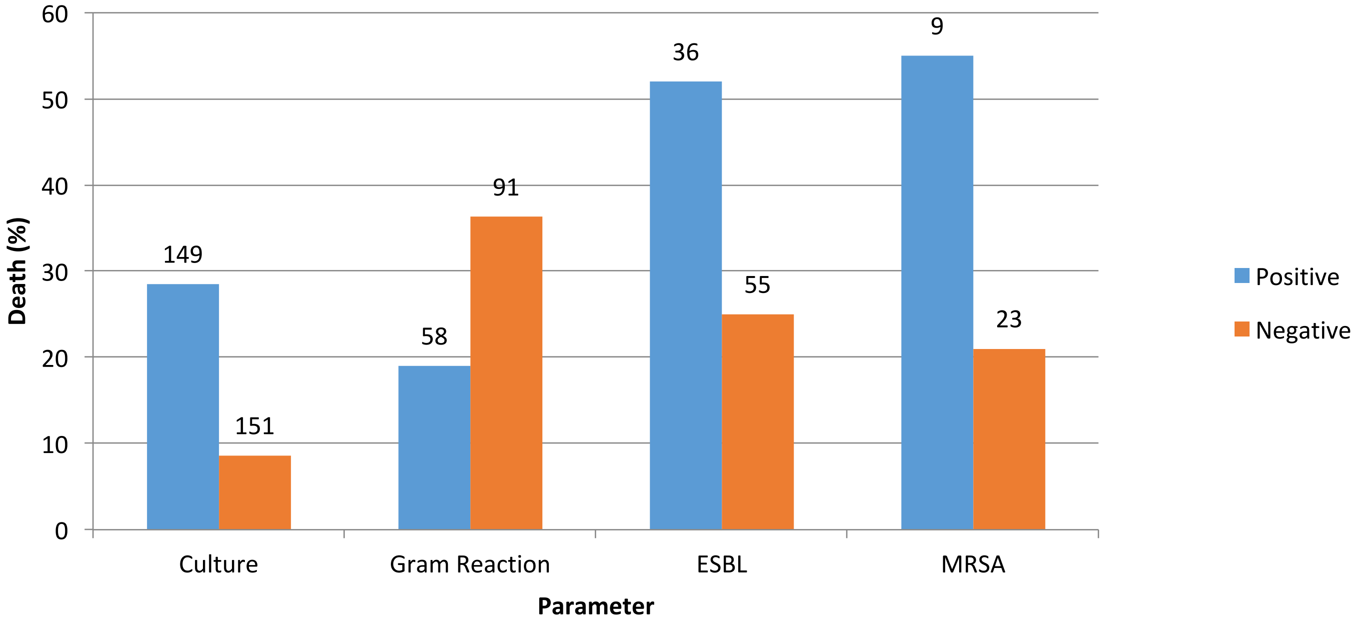
Slide courtesy: Keith Klugman

Numbers of unique β-lactamase enzymes identified since introduction of first β-lactam antibiotics



Davies and Davies, Microbiol. Mol. Biol. Rev. 2010.

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.

	Number of resistant isolates	CFR in culture-positive sepsis due to resistant pathogens	CFR in culture-positive sepsis due to sensitive pathogens
Gram negative			
Acinetobacter spp (n=222)			
ES cephalosporins	85/222 (38%)	59/85 (69%)	71/137 (52%)
Carbapenems	174/222 (78%)	106/174 (61%)	24/48 (50%)
MDR	181/222 (82%)	112/181 (62%)	18/41 (44%)
Klebsiella spp (n=169)			
ES cephalosporins	105/169 (62%)	57/104 (55%)	38/65 (58%)
Carbapenems	59/169 (35%)	36/59 (61%)	59/110 (54%)
MDR	91/169 (54%)	52/91 (57%)	43/78 (55%)
Escherichia coli (n=137)			
ES cephalosporins	65/137 (47%)	40/64 (63%)	43/73 (59%)
Carbapenems	21/137 (15%)	12/21 (57%)	71/116 (61%)
MDR	52/137 (38%)	30/52 (58%)	53/85 (62%)
Pseudomonas spp (n=68)			
ES cephalosporins	32/68 (47%)	29/32 (91%)	24/36 (67%)
Carbapenems	21/68 (31%)	19/21 (90%)	34/47 (72%)
MDR	13/68 (19%)	11/13 (85%)	42/55 (76%)

DeNIS Study, Lancet ID, 2016

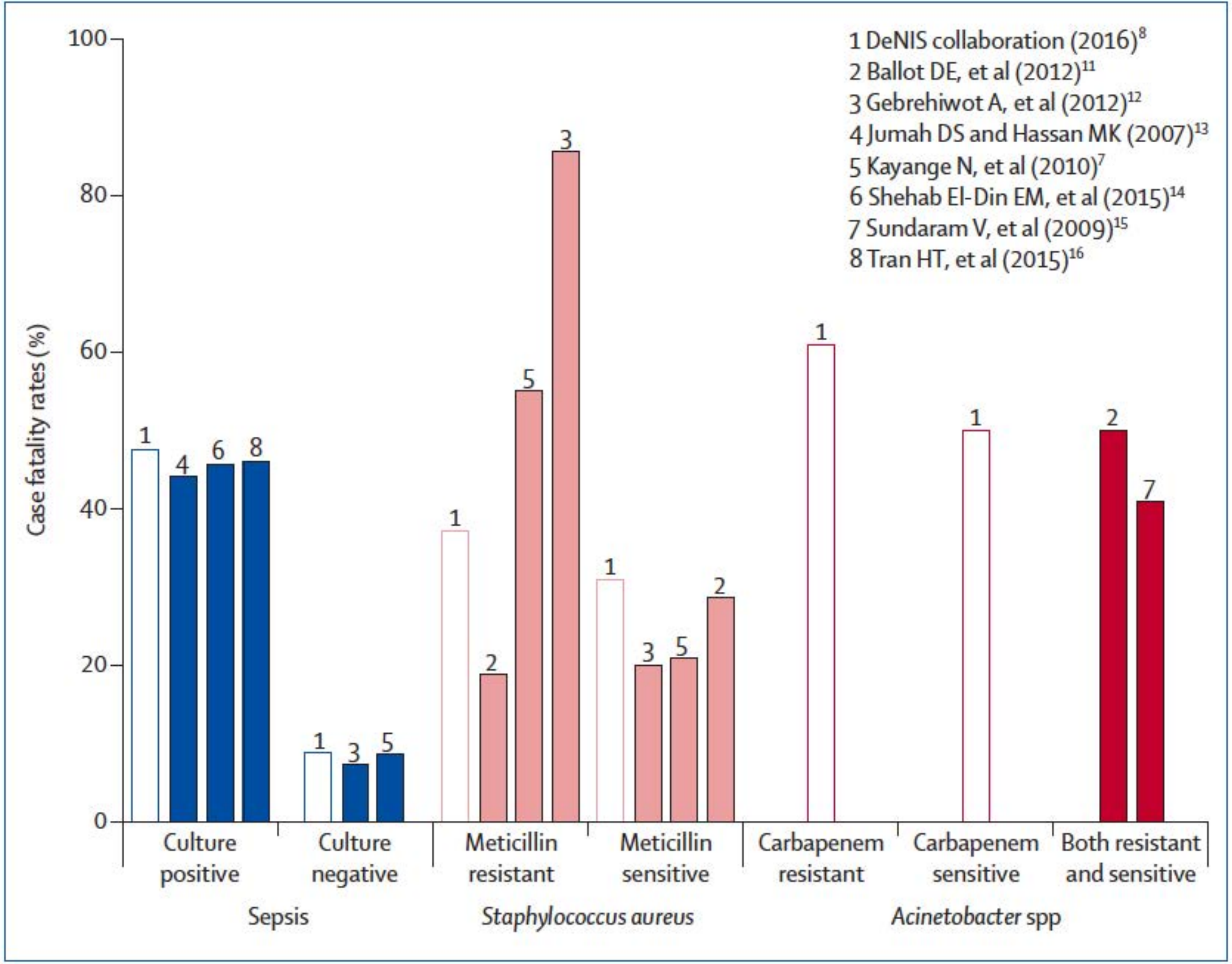


Figure: **Case fatality rates from the DeNIS study (unshaded) compared with earlier studies (in solid colours)**

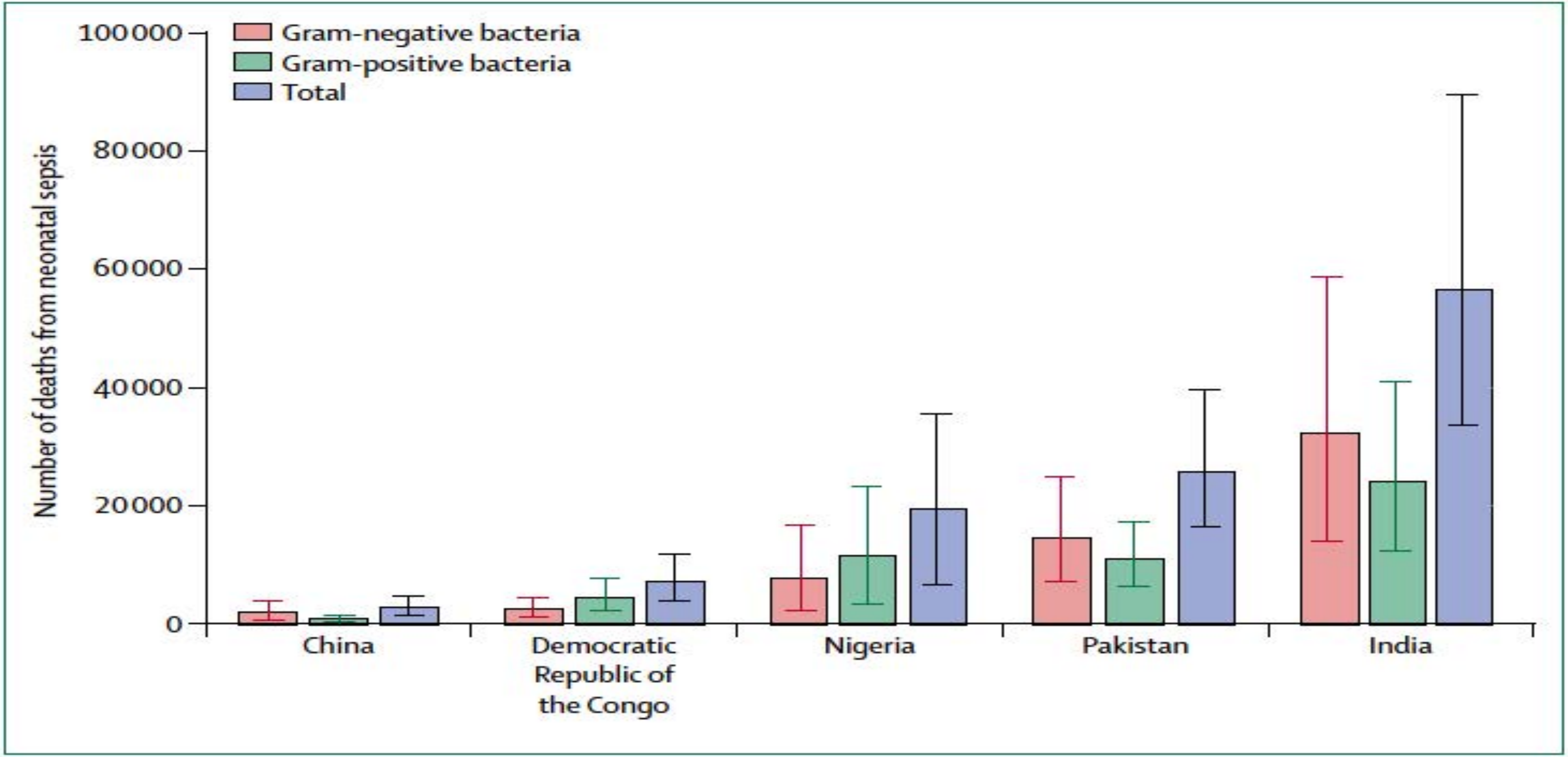


Figure 2: **Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries**

Laxminarayan et al Lancet, 2015

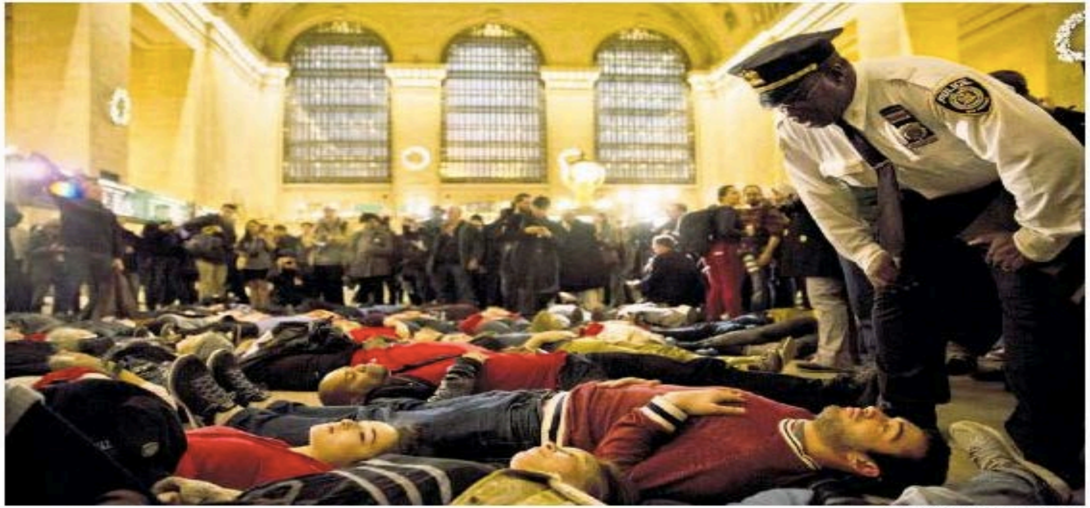
"All the News That's Fit to Print"

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 + ©2014 The New York Times 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

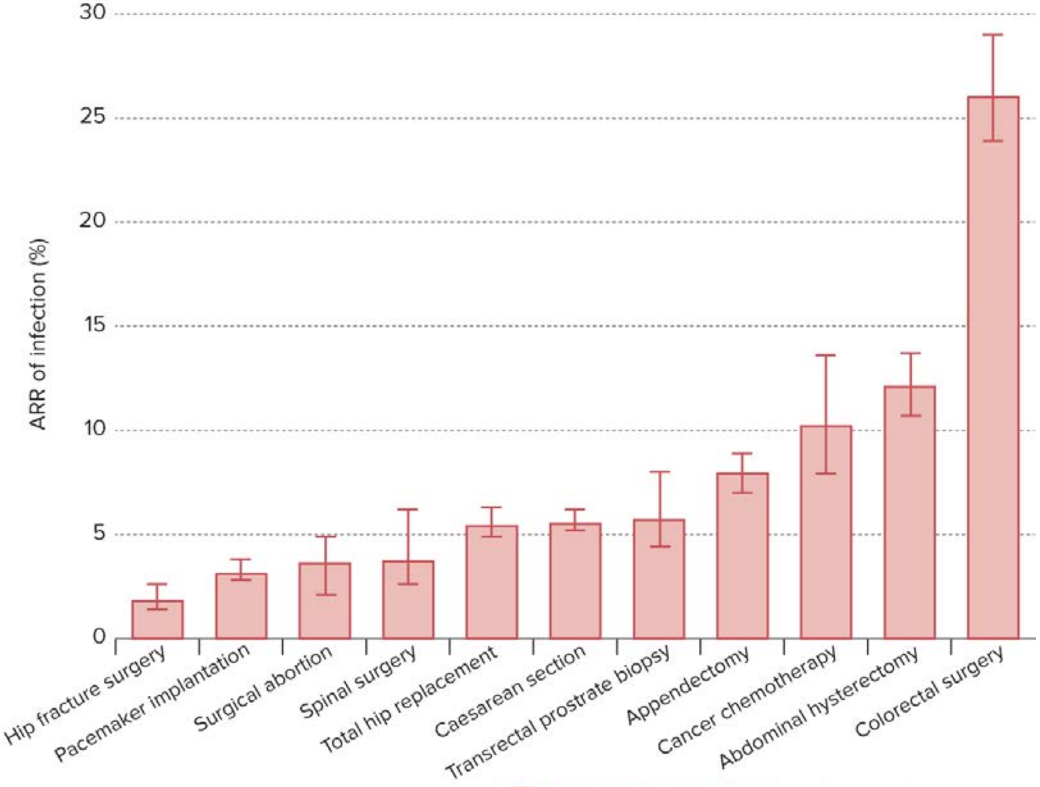
AMRAVATI, India — A deadly epidemic that could have global implications is quietly sweeping India, and among its many victims are tens of thousands of newborns dying because once-miraculous cures no longer work.

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,

Absolute risk reduction (ARR) of infection with antibiotic prophylaxis in common surgical procedures and blood cancer chemotherapy in the USA



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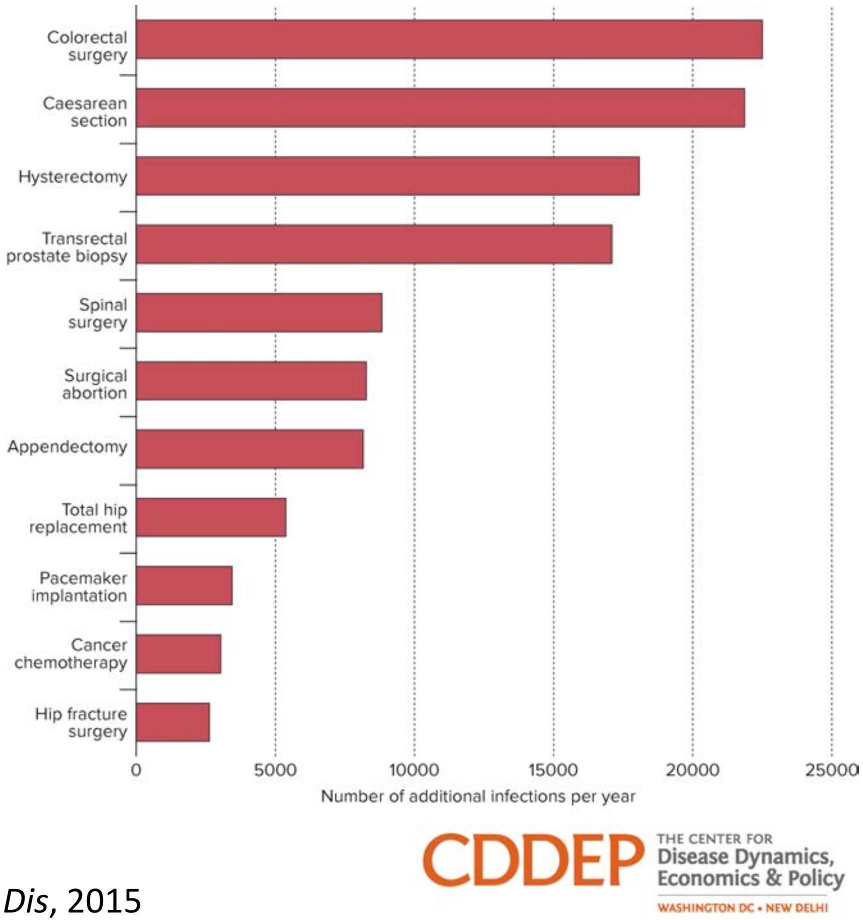
Teillant et al, *Lancet Infect Dis*, 2015

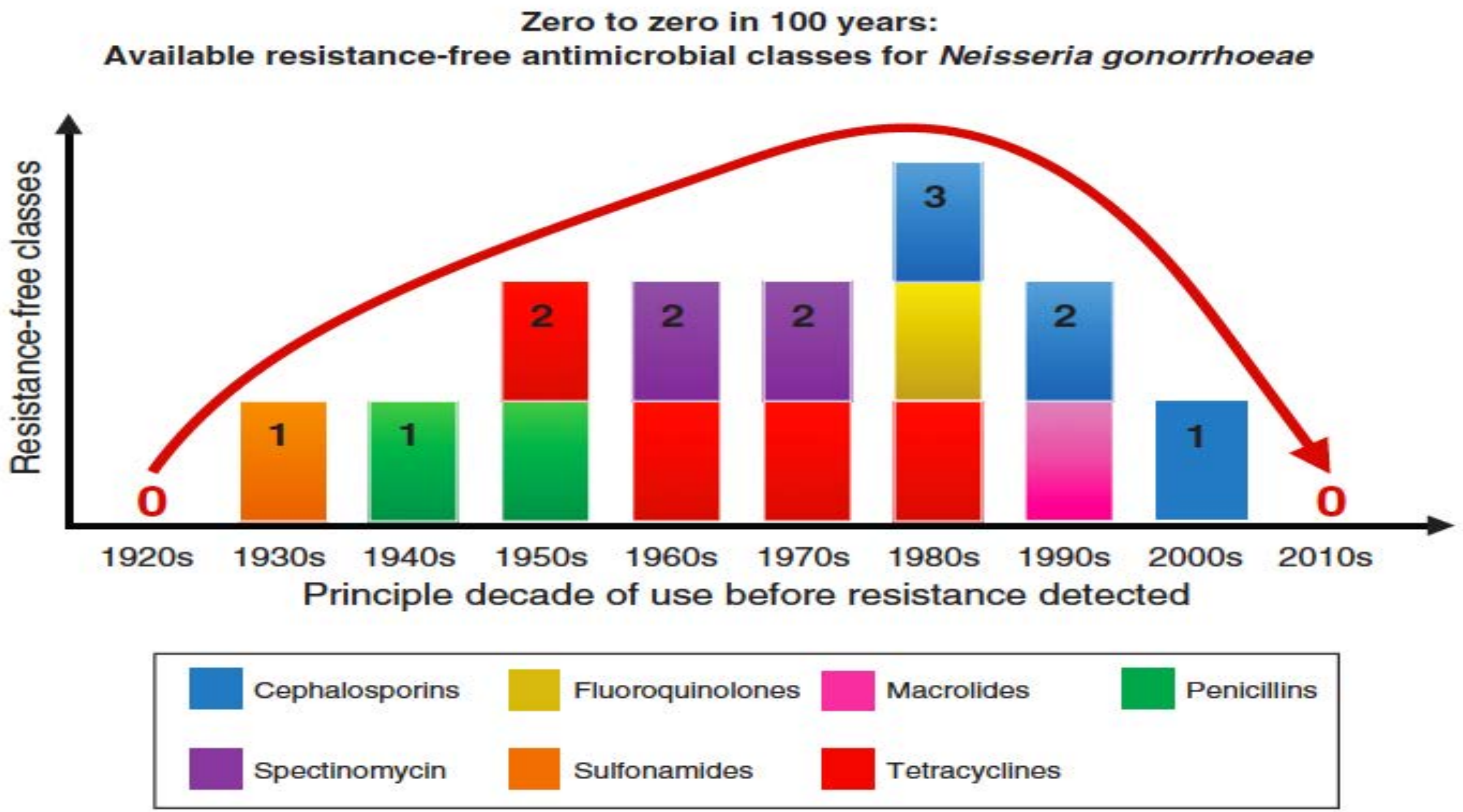
Number of additional infections per year in the USA under a 30% decreased efficacy of antibiotic prophylaxis



Teillant et al, *Lancet Infect Dis*, 2015

Surgical site infections

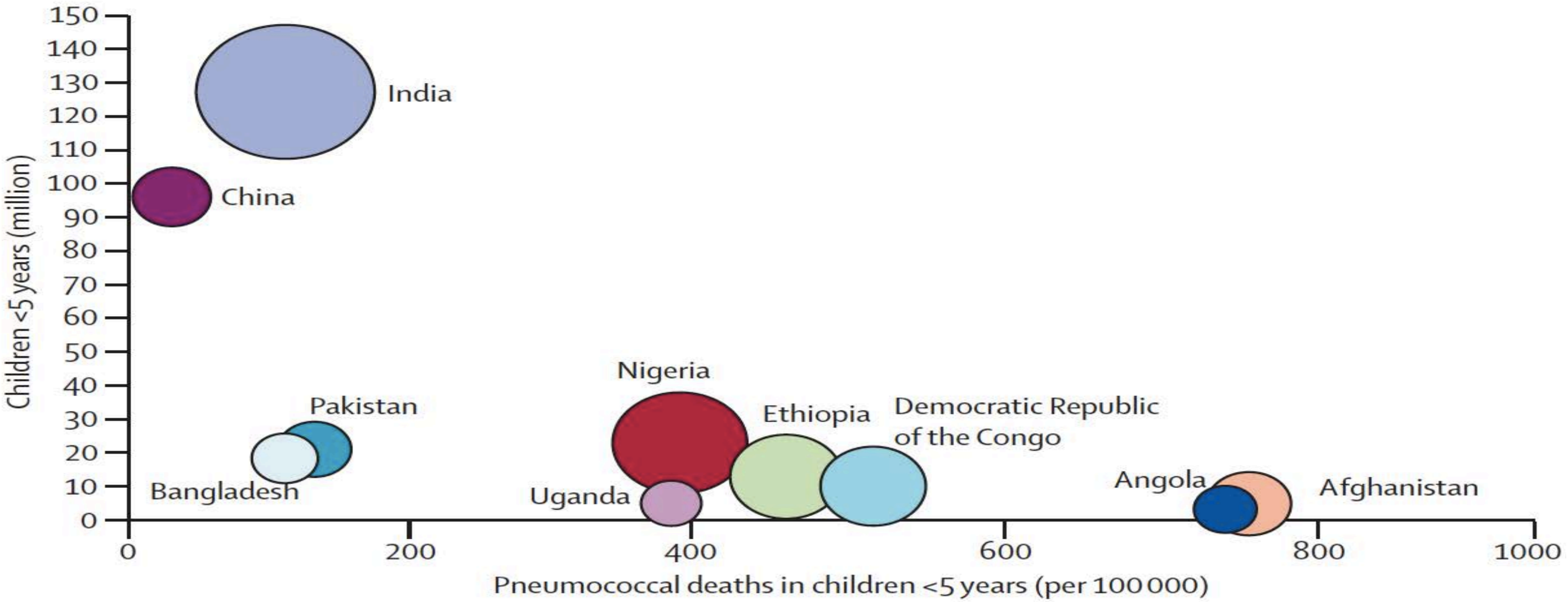
- There are 92 million surgeries in low-income countries each year
- 5.5 million surgical site infections or SSIs (6 per 100 procedures) – about a third of all healthcare associated infections
- SSIs are the leading cause of infection in settings with limited resources
- Mortality rate from SSI Rates of mortality from surgical site infections are 3% in the US and between 8 and 20% in low-income countries
- Between 400,000 and a million deaths from SSIs each year with an increasing number caused by resistant pathogens.



Lahra et al, Microbiology Australia, Nov 2016

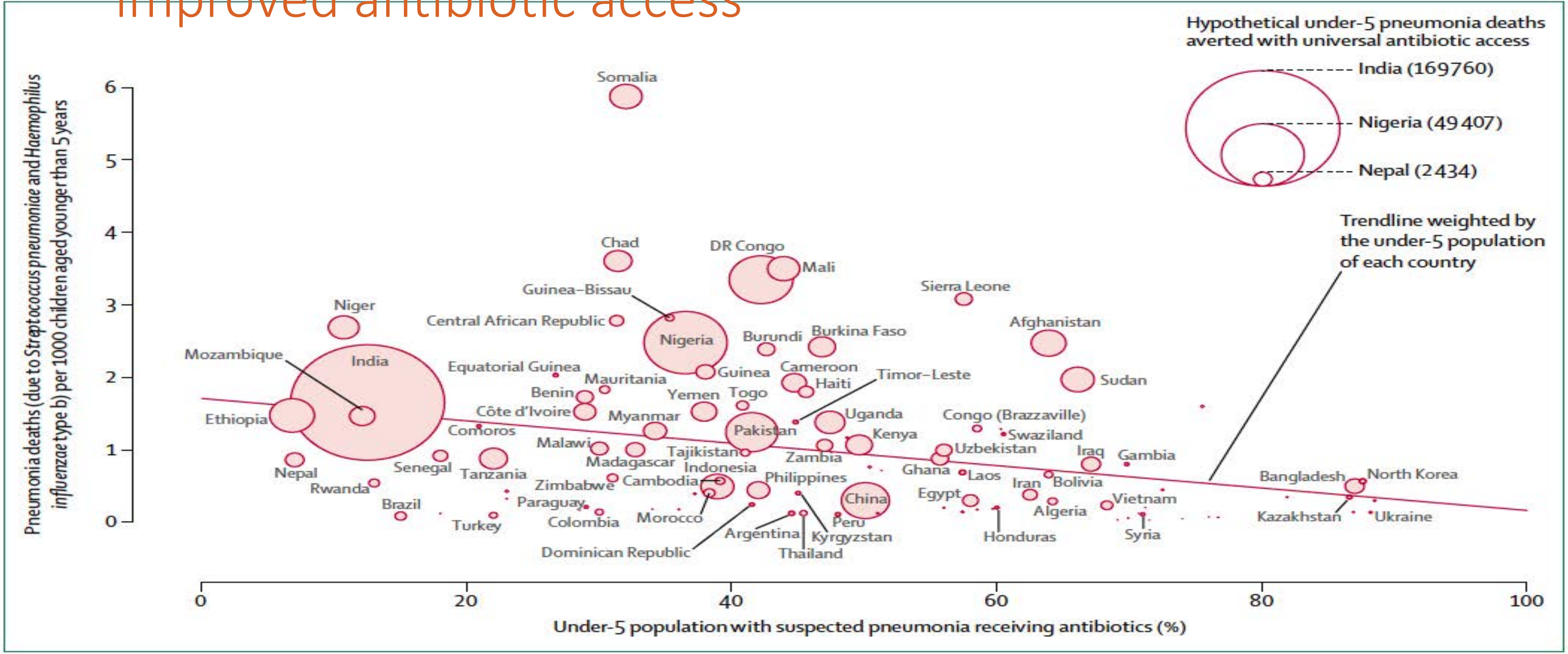
II. Rising incomes and increasing access to antibiotics are saving lives (although lack of access still kills more people than antibiotic resistance) but are not a good substitute for public health

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



O'Brien et al, Lancet 2009

Pneumococcal pneumonia deaths avertable with improved antibiotic access

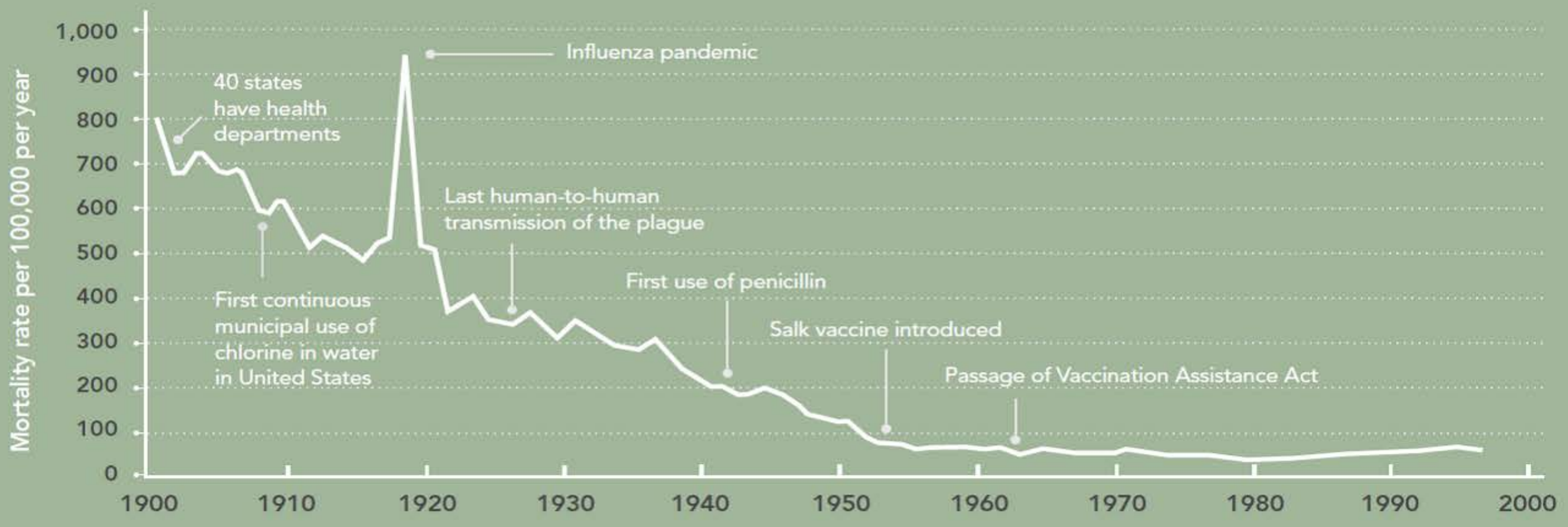


Laxminarayan et al, Lancet, 2015

What are we asking of antibiotics?

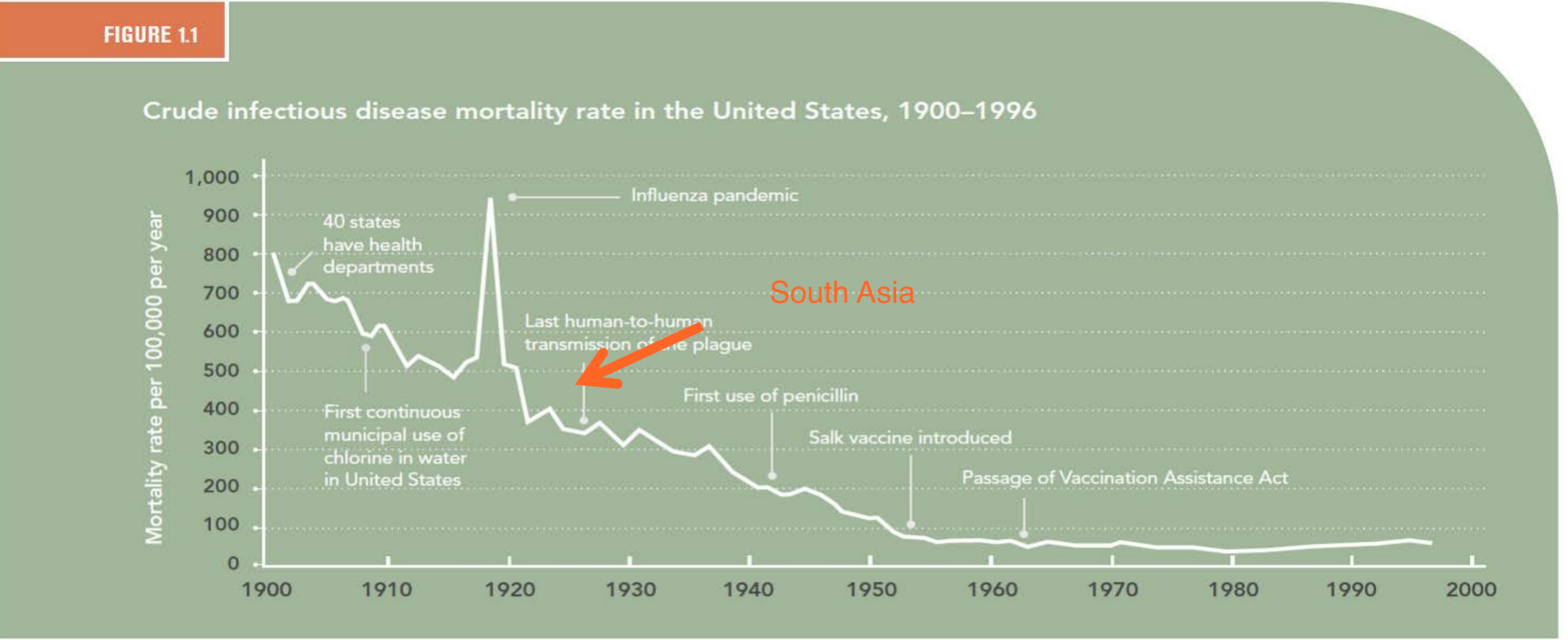
FIGURE 1.1

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



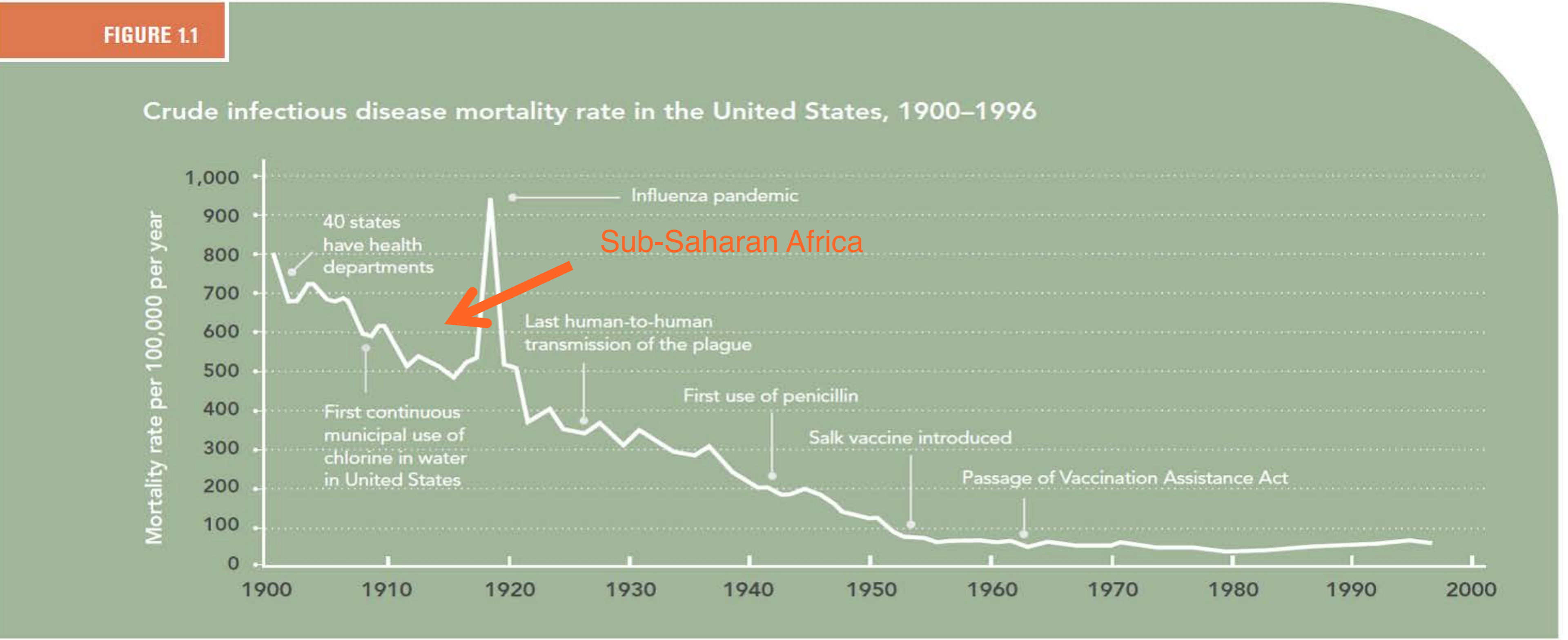
Source: Adapted from Armstrong, Conn et al. (1999).

Substitute for immunization, infection control and water/sanitation



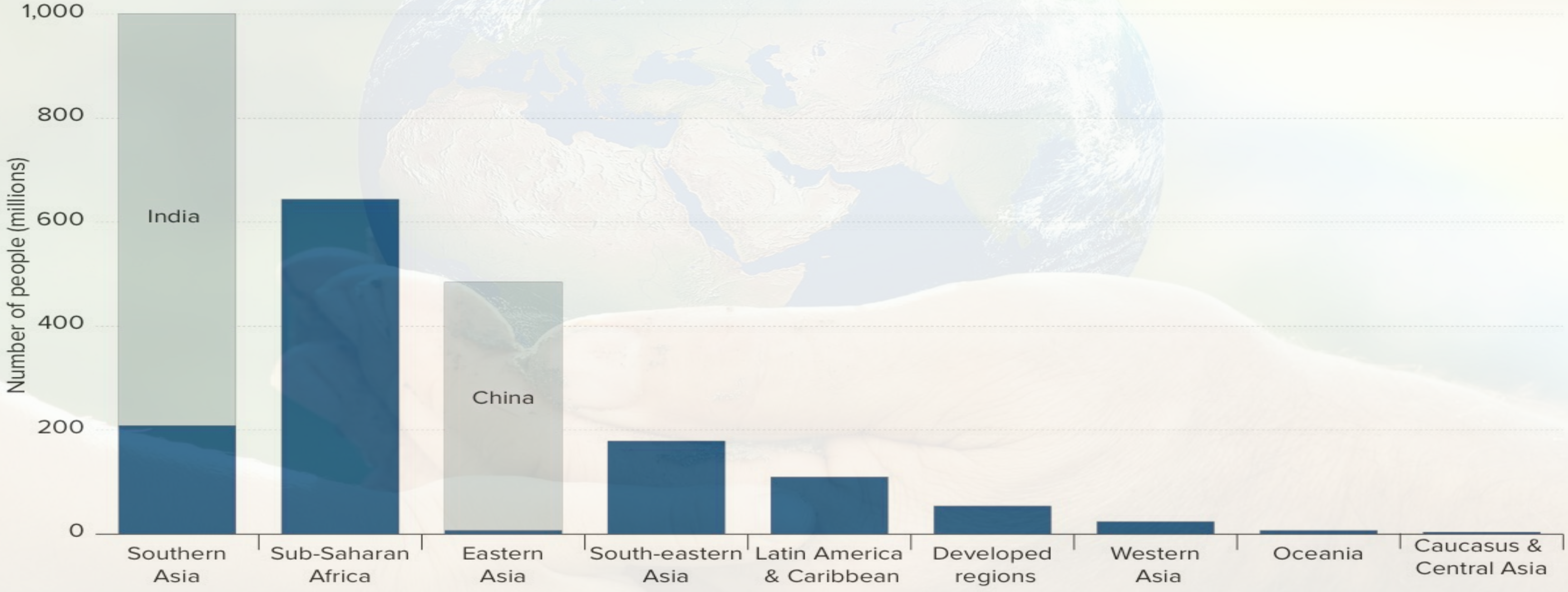
Source: Adapted from Armstrong, Conn et al. (1999).

Substitute for immunization, infection control and water/sanitation



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

Population without access to improved sanitation, by MDG region 2012



Source: WHO/UNICEF 2014

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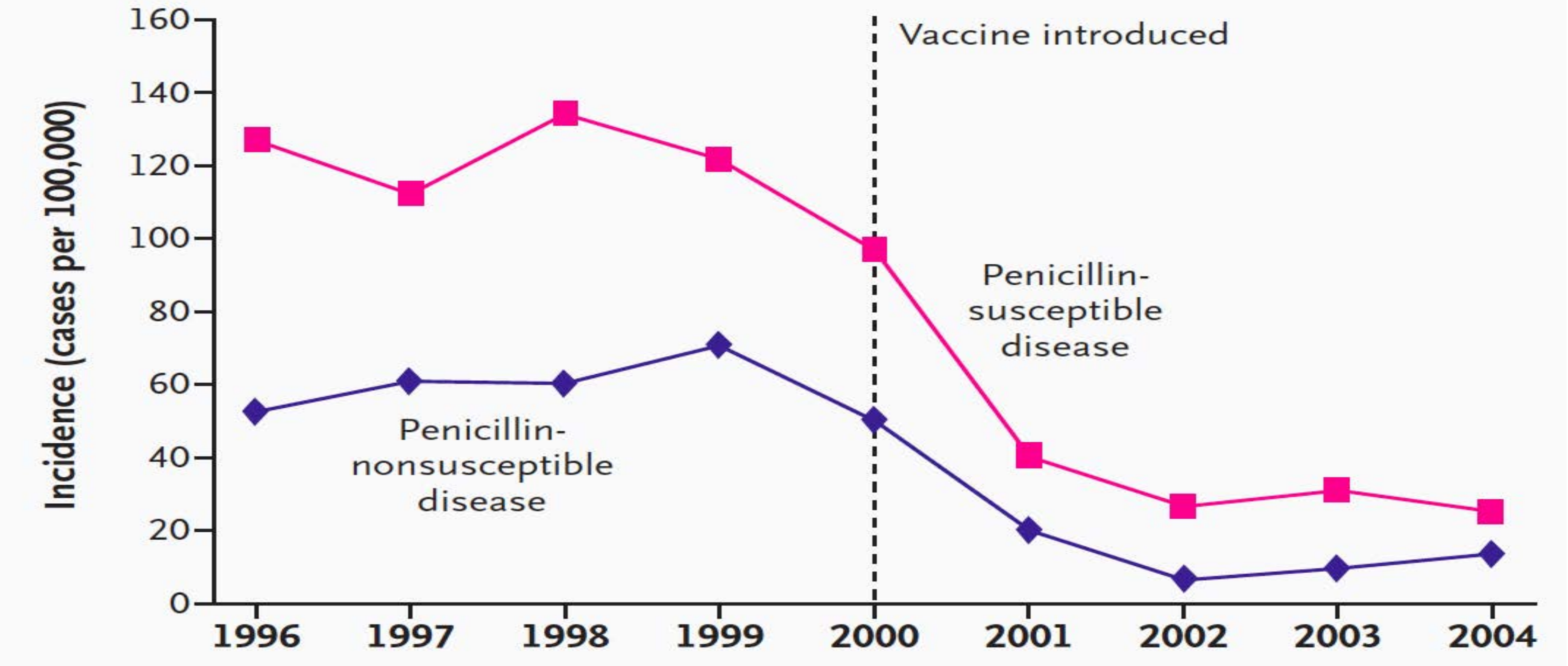
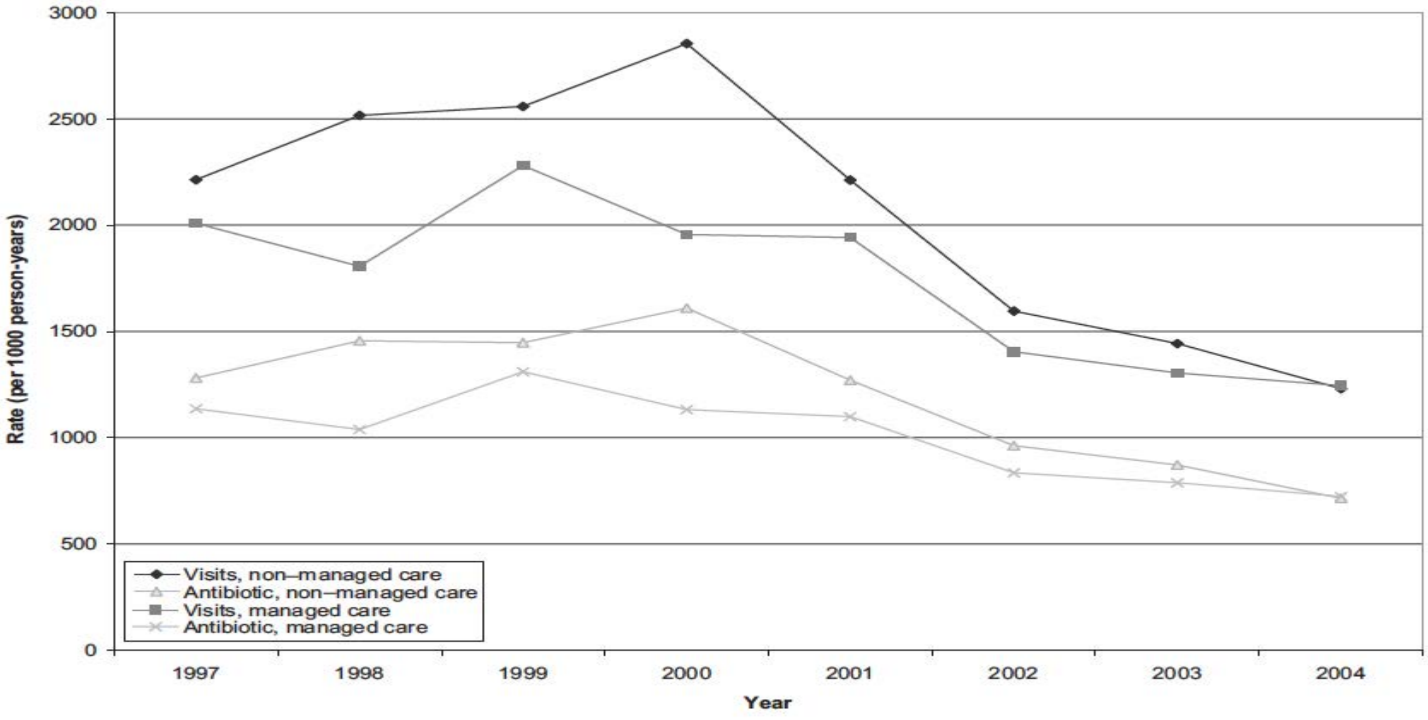
Vaccines can be effective

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



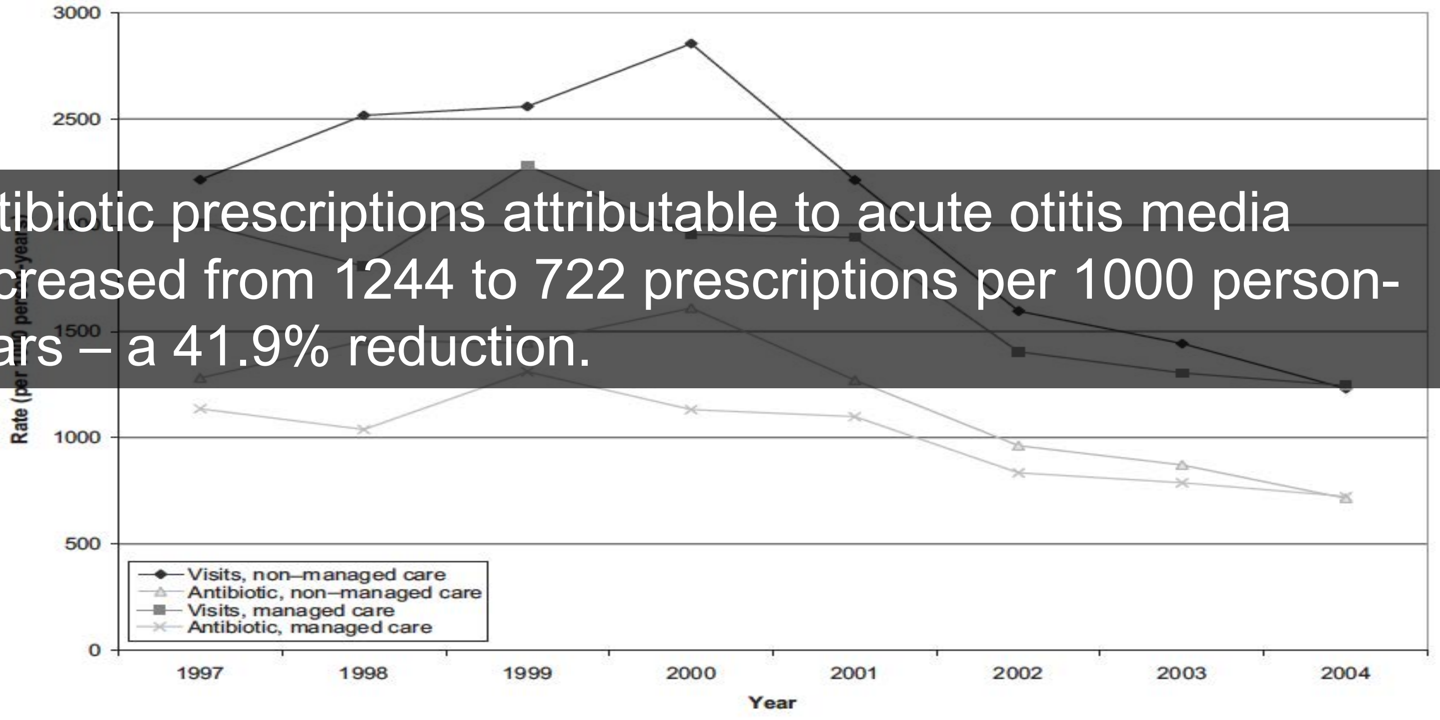
Kyaw MH et al. N Engl J Med 2006;354:1455-1463.

Effect of PCV7 introduction in 2000 on antibiotic prescriptions and ambulatory care visits



Zhou et al, Pediatrics 2008

Effect of PCV7 introduction in 2000 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.

Zhou et al, Pediatrics 2008

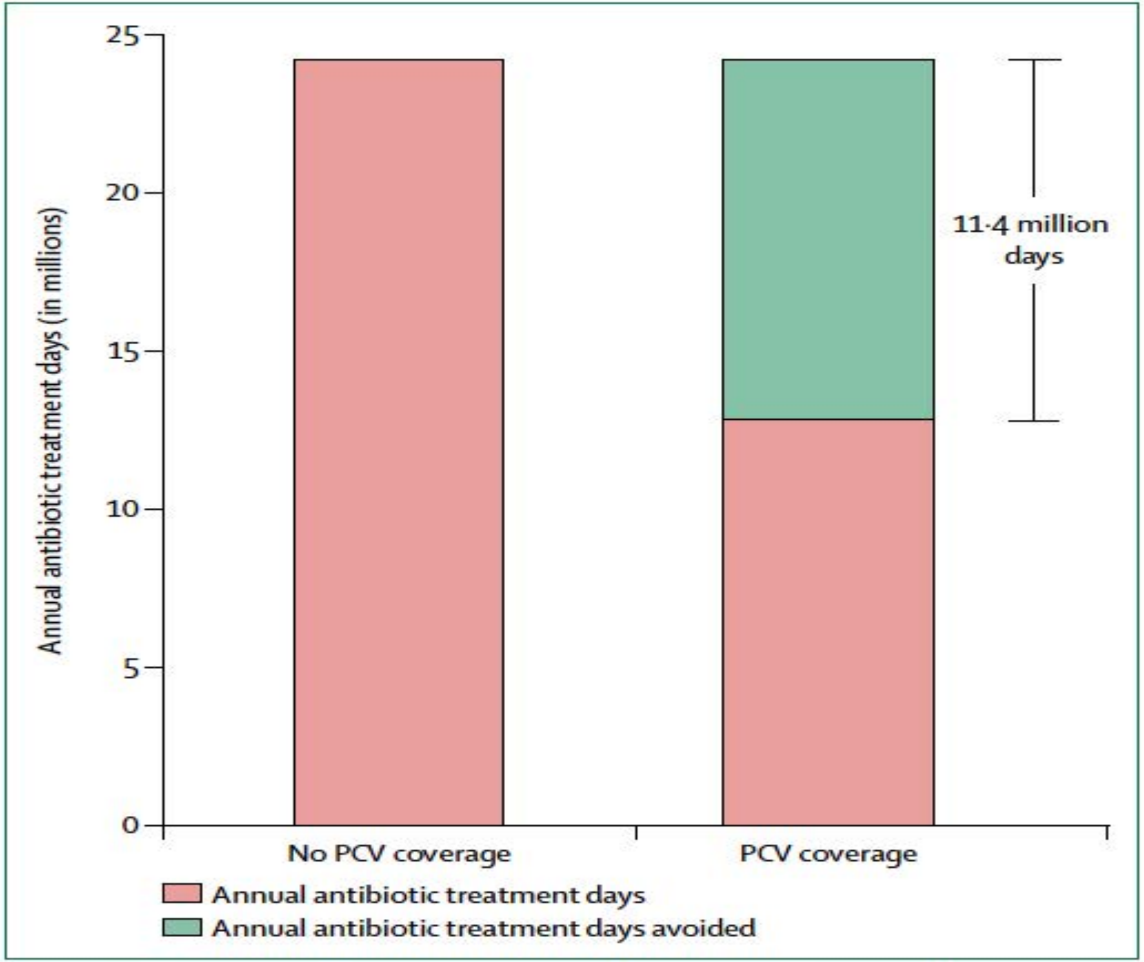
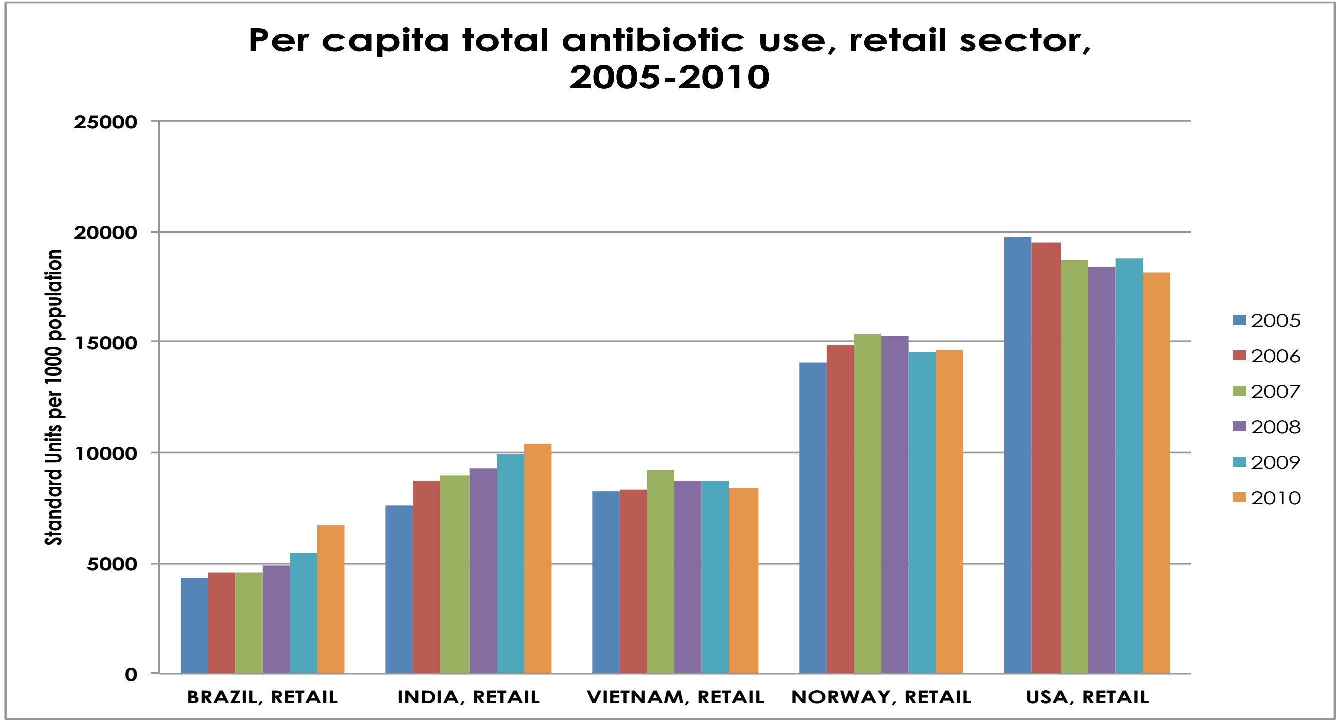


Figure 3: **Days on antibiotics for suspected pneumonia, averted by provision of pneumococcal conjugate vaccine (PCV)**
Bar represents antibiotic days avoided with PCV coverage.

Laxminarayan et al Lancet, 2015

Antibiotic consumption is increasing in developing countries…



Source: Based on data obtained under license from IMS Health MIDAS ™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.

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.

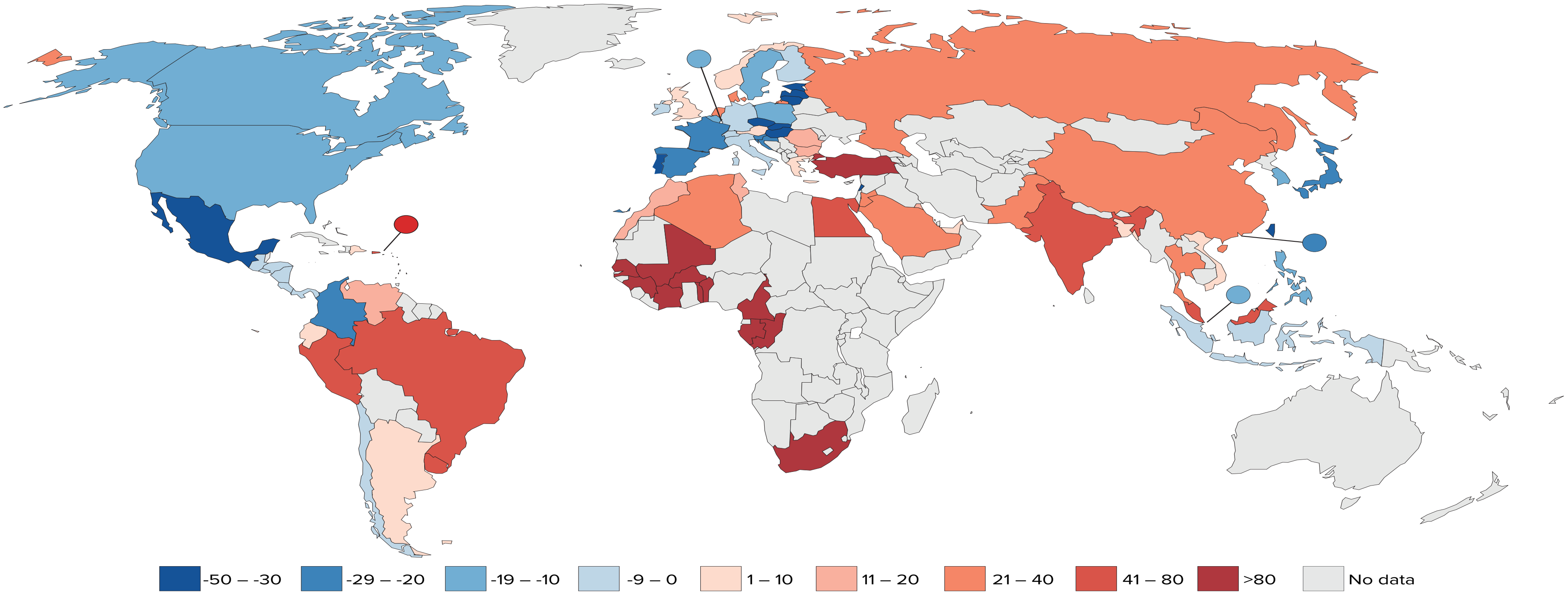
Lancet Infect Dis 2014

Published Online

July 10, 2014

http://dx.doi.org/10.1016/S1473-3099(14)70780-7

Percentage change in antibiotic consumption per capita 2000–2010*, by country



Source: Van Boeckel et al. 2015 (adapted; based on IMS MIDAS)

*Data for Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama were available only as a group classified as Central America. Similarly, data for Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo were grouped and classified as French West Africa. The data for these countries represent the estimates for the corresponding regional groupings they belong to. For countries that did not have data available for 2000, the values for the earliest years for which data were available after 2000 were used to calculate the percentage changes. These countries and initial years are Algeria (2002), Bangladesh (2007), Croatia (2005), Netherlands (2005), and Vietnam (2005).

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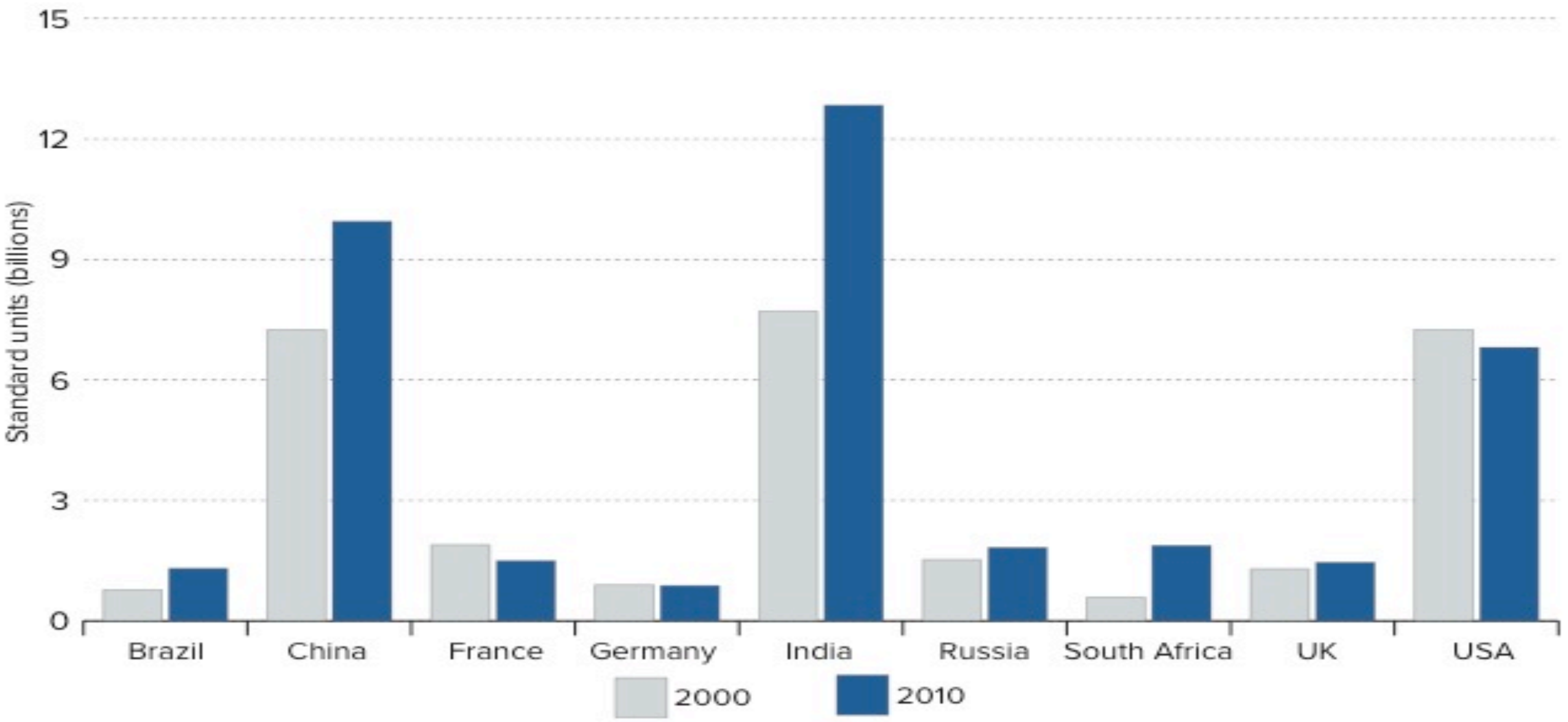
Total antibiotic consumption in selected countries, 2000 and 2010



Van Boeckel et al. 2014 (based on IMS MIDAS)

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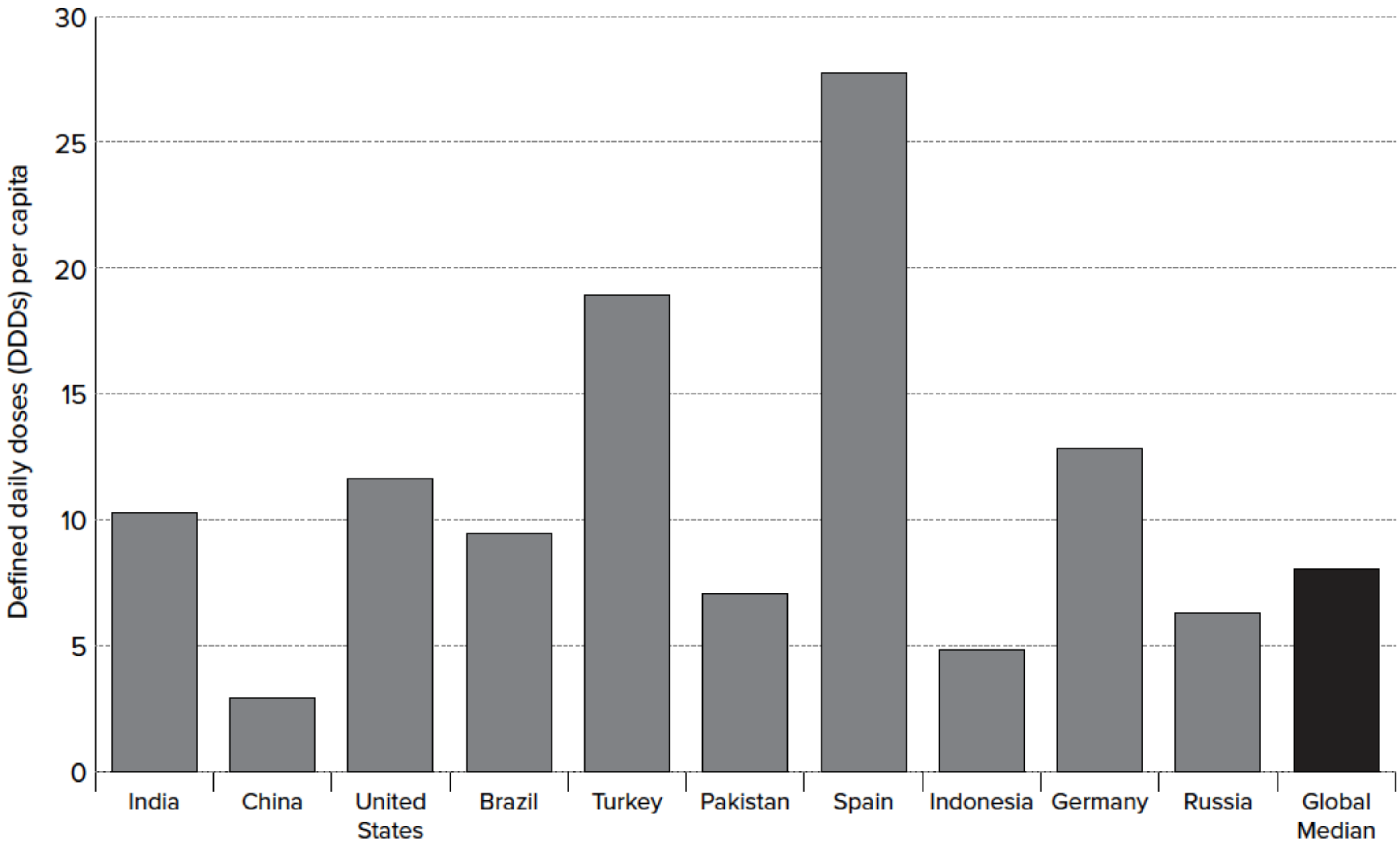
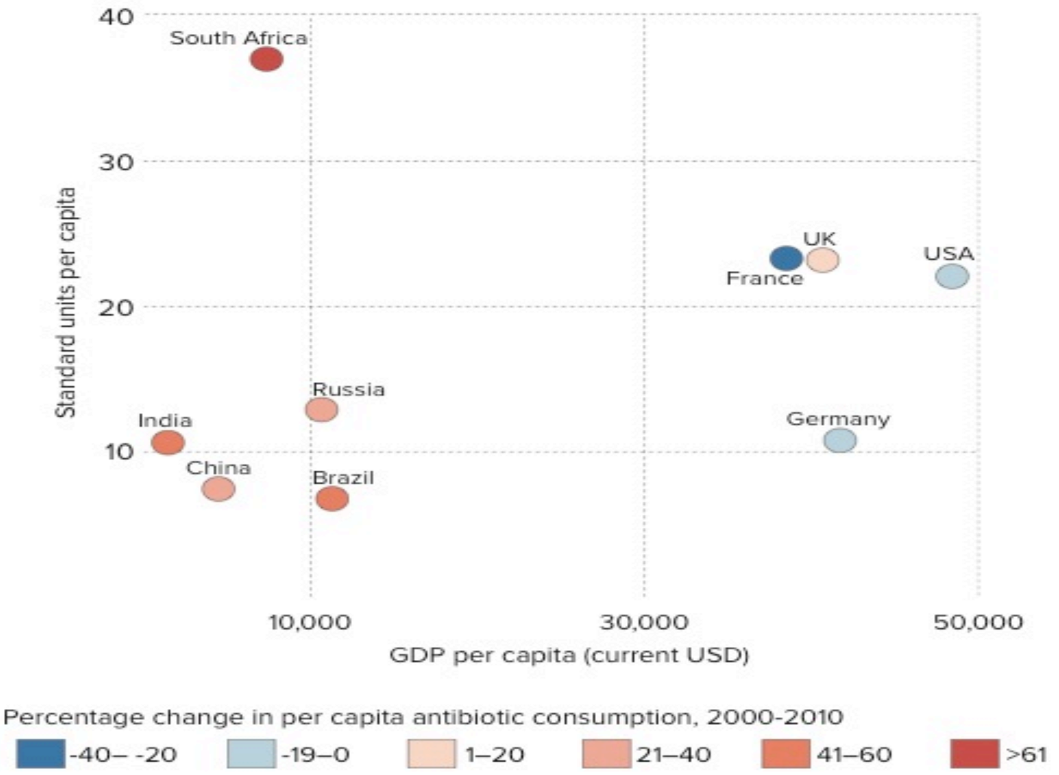


Top 10 antibiotic consumers in 2014, ordered by total consumption, and global median consumption per capita.

Antibiotic use per capita by income in selected countries, 2010



Source: Van Boeckel et al. 2014 (based on IMS MIDAS) and World Bank 2015

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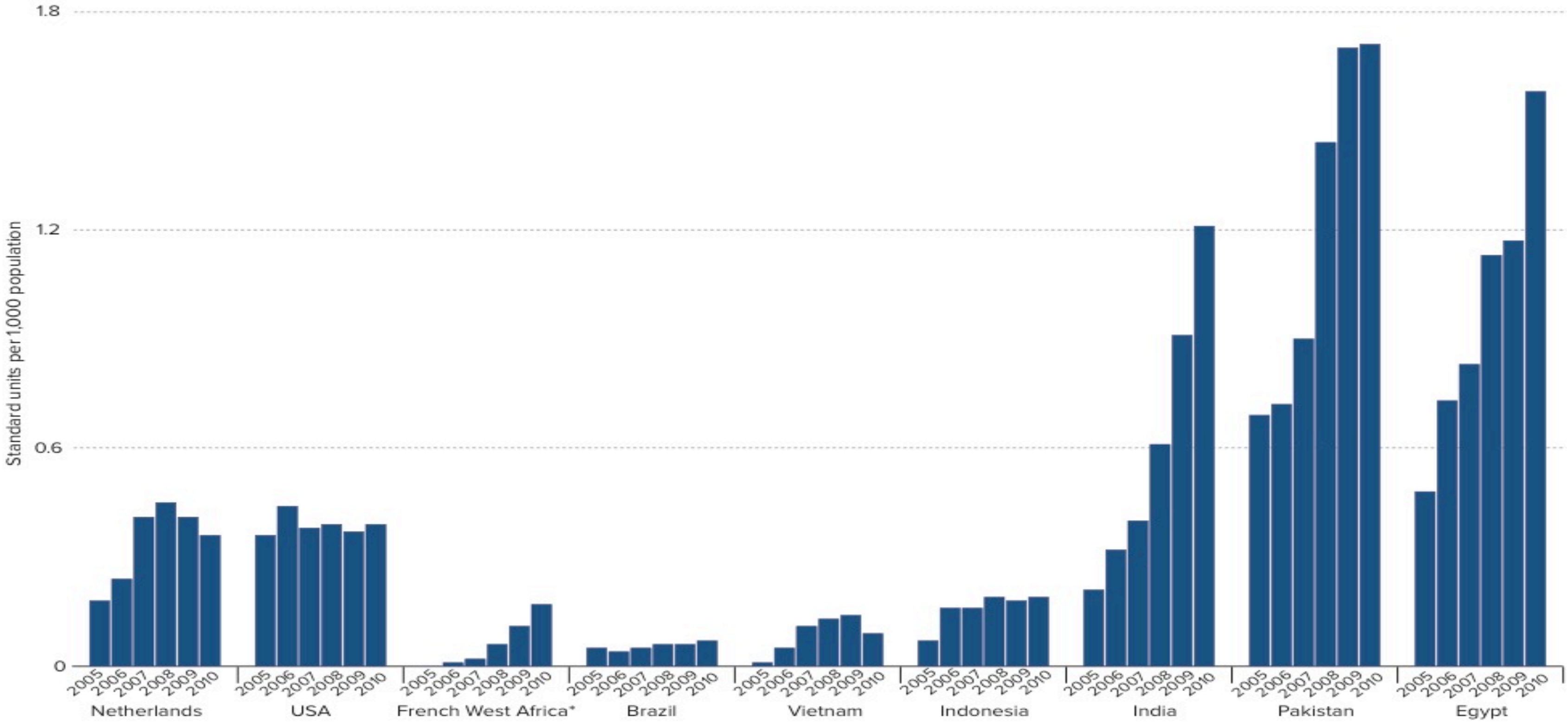
Carbapenem retail sales in selected countries, 2005–2010 (per 1,000 population)



Source: Laxminarayan et al. 2013 (based on IMS MIDAS)

*An IMS grouping of Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo

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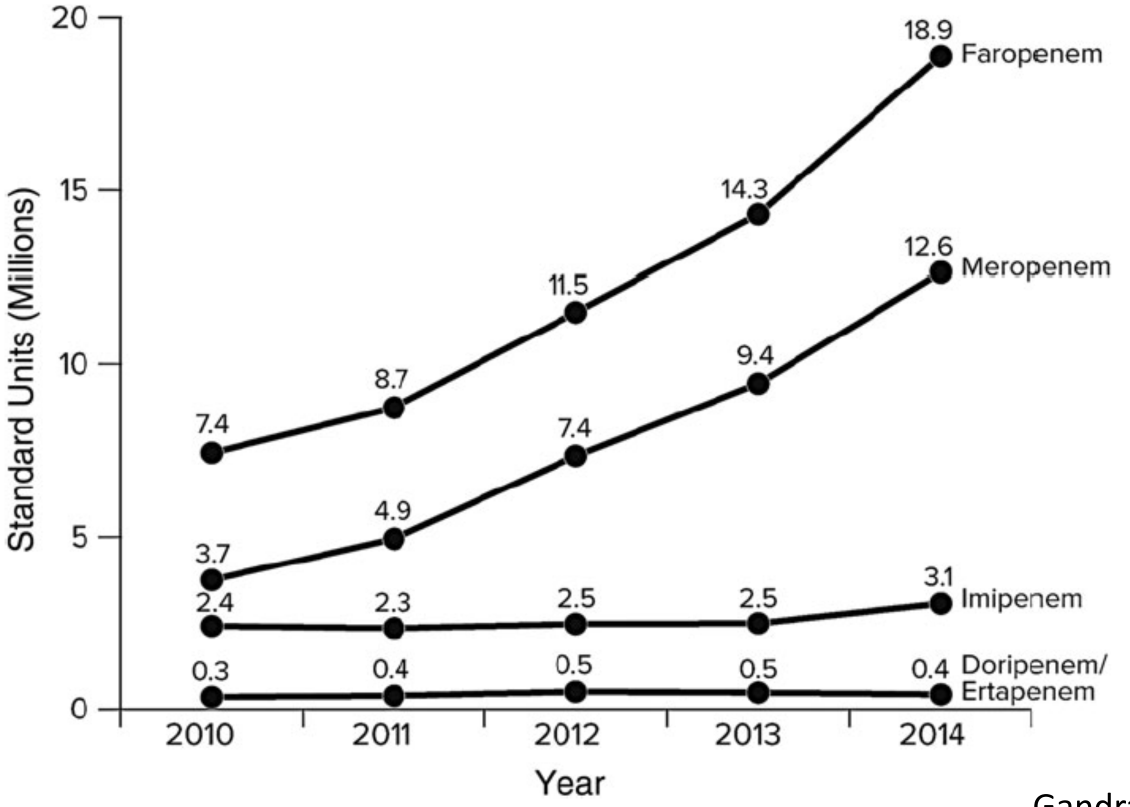
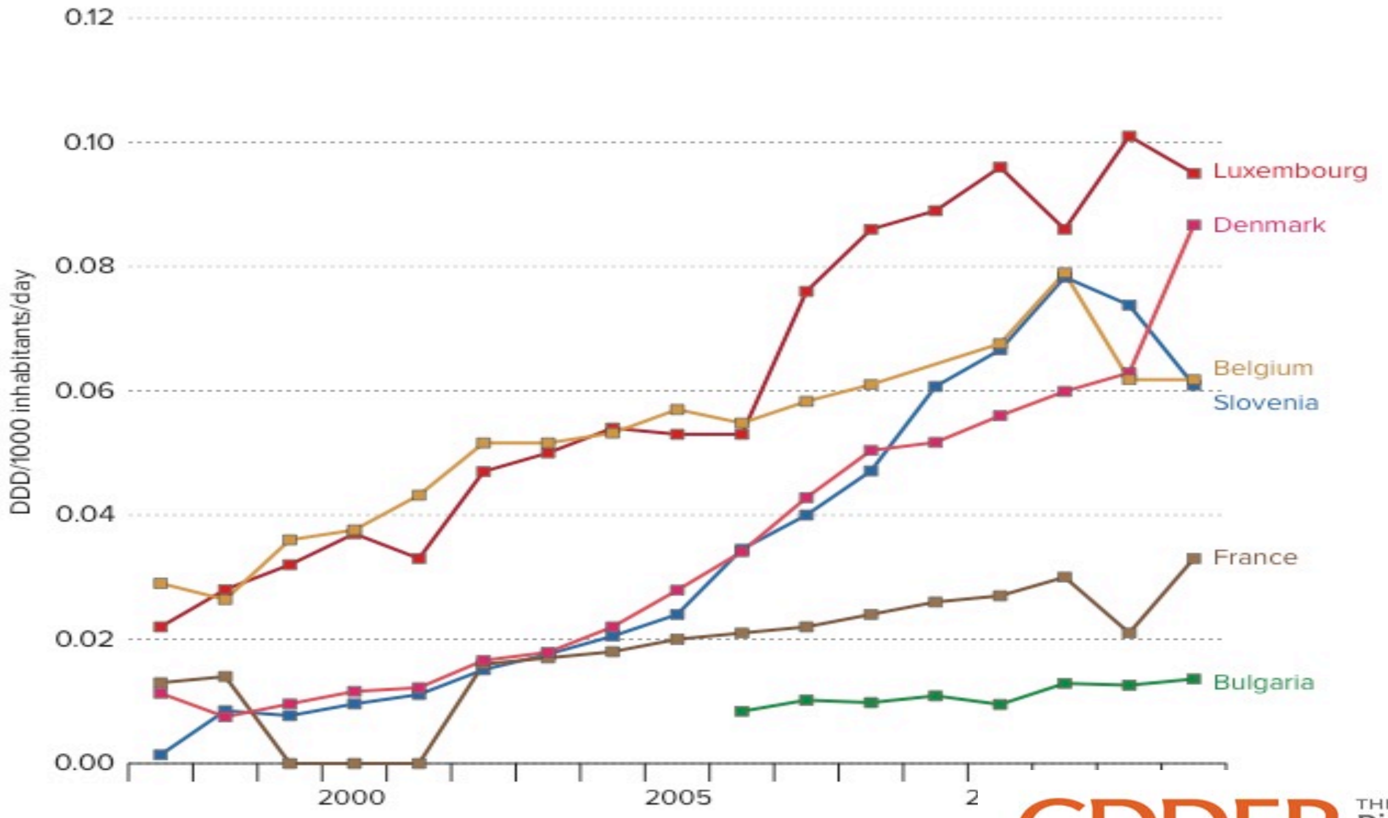
Faropenem consumption has increased by 154% since it was approved for use in India in 2010



Gandra et al, Clin Inf Dis, 2016

Carbapenem consumption in the hospital sector in selected European countries, 1997–2013



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ESAC-Net 2015

Non-prescription use of antimicrobials is common

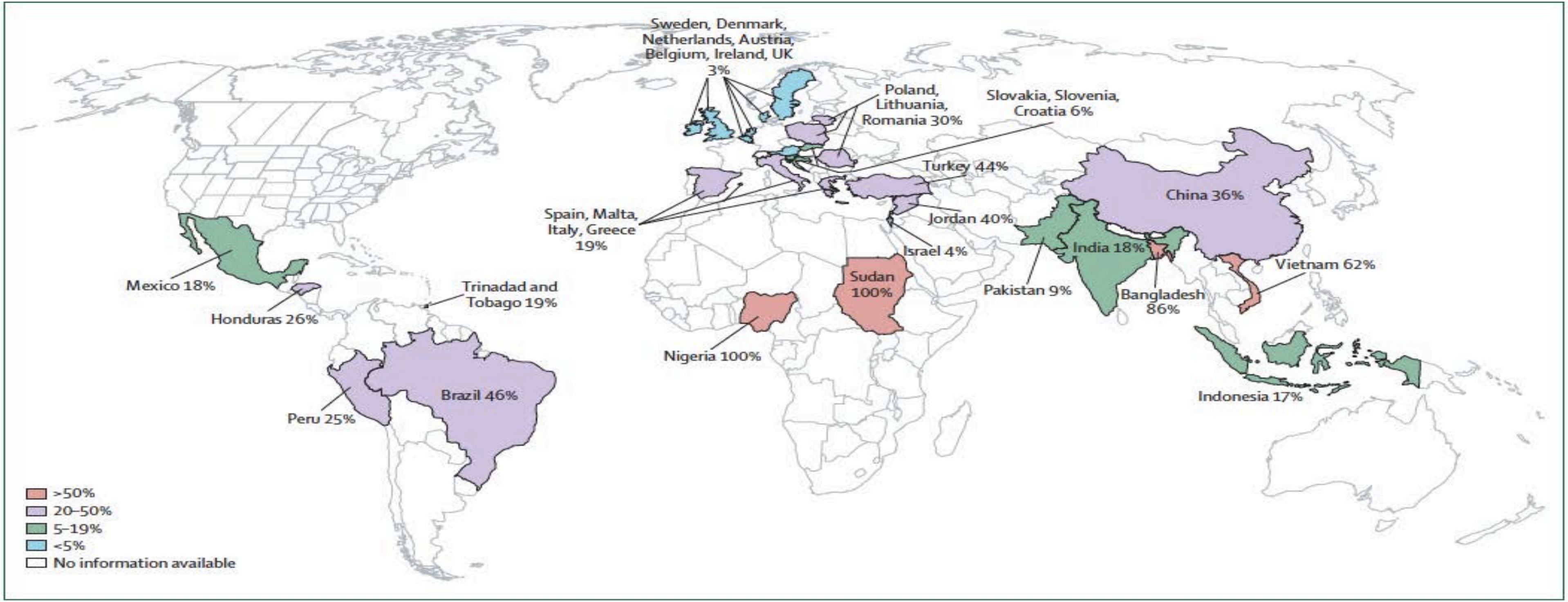

Figure 2: Frequency of non-prescription use of antimicrobials in the general population based on published works
In small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

Morgan et al, Lancet ID, 2011

Table 1. Workforce of Doctors and Nurses According to Country or Region in 2010.*

Country or Region	Population	Doctors	Nurses	Doctors and Nurses/ 1000 Population	Nurse-to-Doctor Ratio
	in millions	*in thousands*			
Country					
China	1338	1915	1,864	2.8	0.97
India	1225	768	1,179	1.6	1.54
United States	309	756	3,064	12.3	4.05
Brazil	195	338	1,278	8.3	3.78
United Kingdom	62	166	626	12.7	3.77
South Africa	50	37	198	4.7	5.30
Region					
Americas	937	1974	4,947	7.4	2.5
Europe	899	2744	5,870	9.6	2.1
Middle East and North Africa	590	654	894	2.6	1.4
Southeast Asia	1795	997	1,810	1.6	1.8
Sub-Saharan Africa	847	150	778	1.1	5.2
Western Pacific	1821	2696	3,814	3.6	1.4
World	6888	9216	18,114	4.0	2.0

* A doctor or nurse is defined as a person with the appropriate qualifications recognized in his or her own country. In this table, the nurse workforce includes nurses and midwives. Data are from the World Health Organization.[9]

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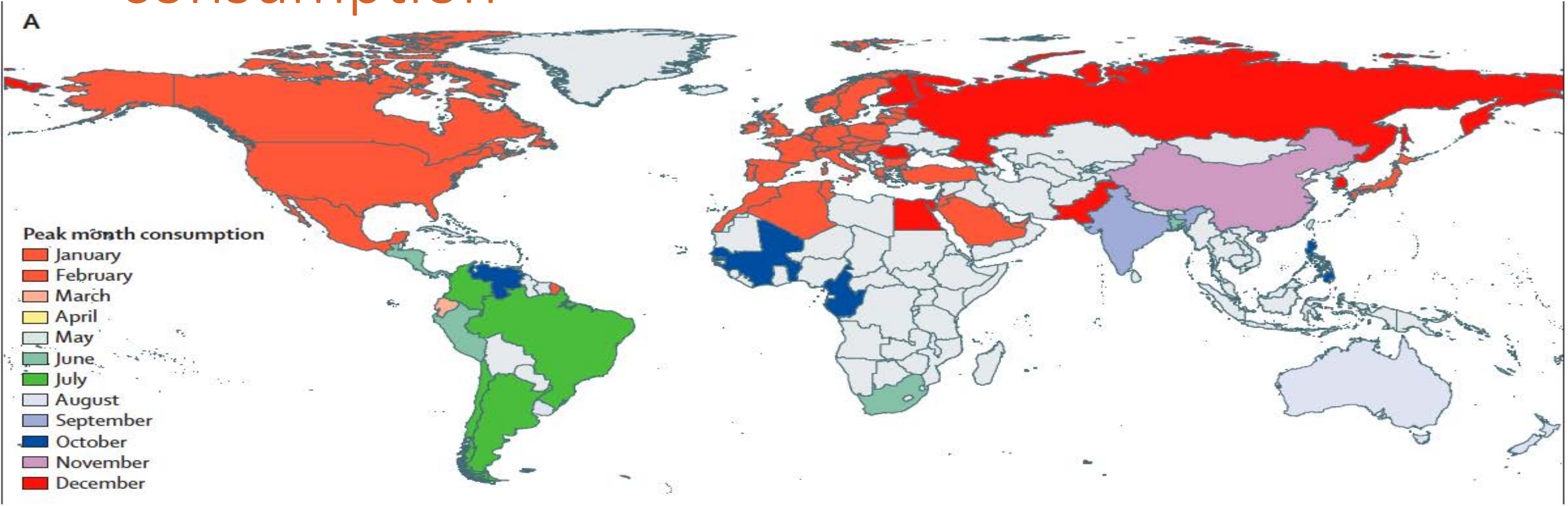
The flu season is a key driver of antibiotic consumption



Van Boeckel et al, Lancet Inf Dis, 2014

Influenza in the United States is nearly perfectly predicted by antibiotic sales data

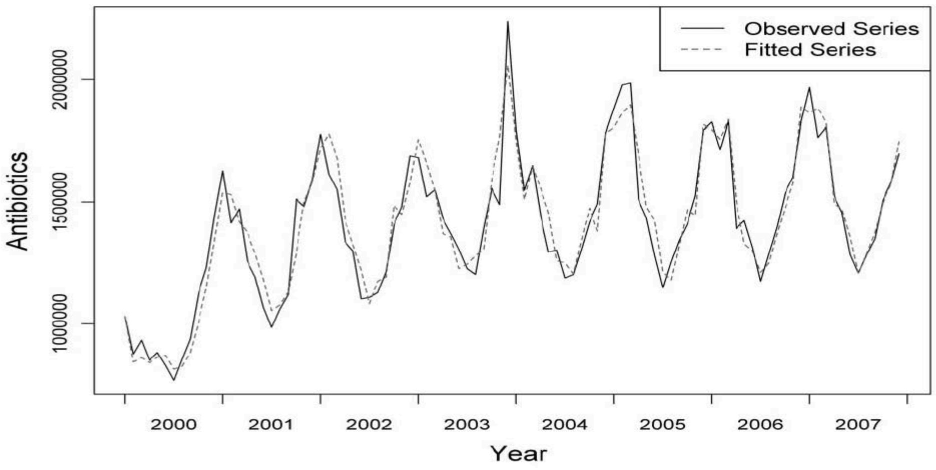
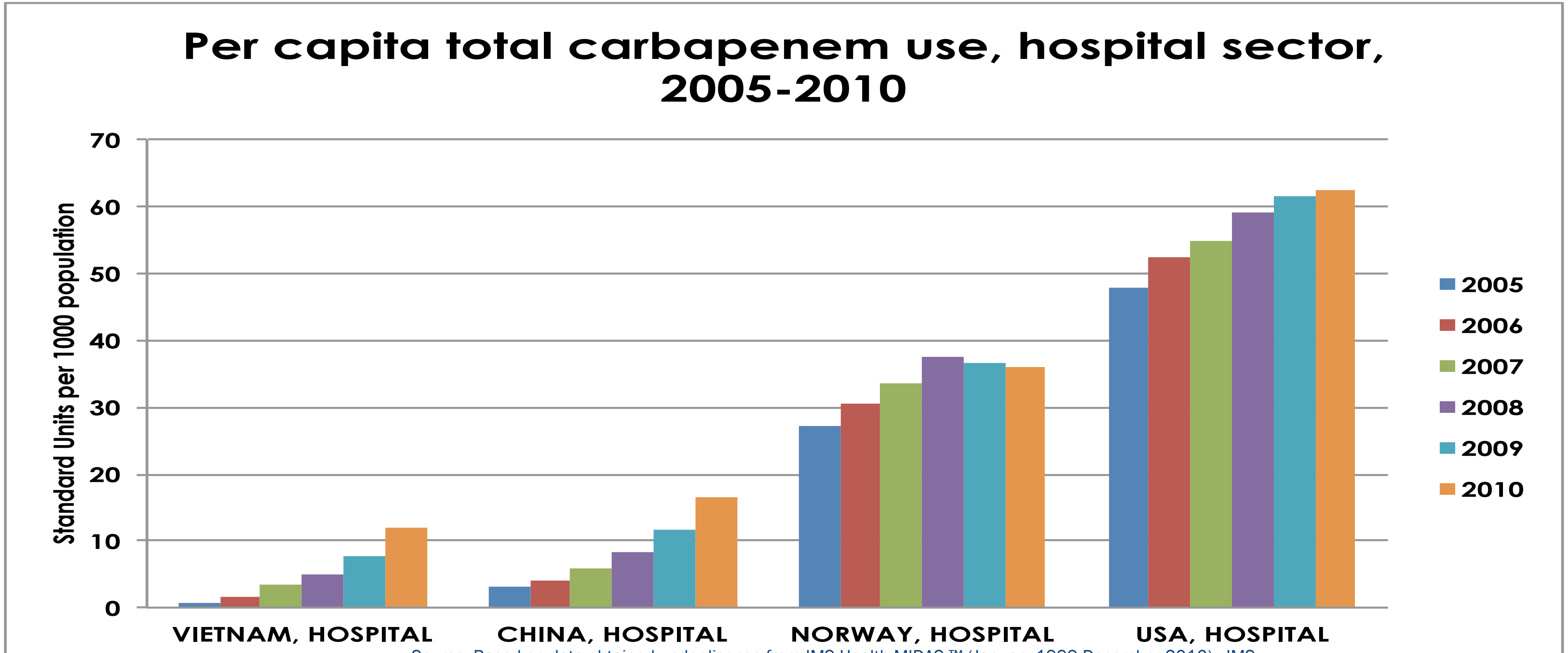


FIGURE 1. Observed and fitted antibiotics series from 2000 to 2007. The solid line represents the actually observed antibiotics series; the dashed line represents the fitted antibiotics series from the time series regression model that uses influenza-like illness as an explanatory series.

Polgreen et al Inf Cont Hosp Epi, 2011

Hospital use of carbapenems is rapidly growing



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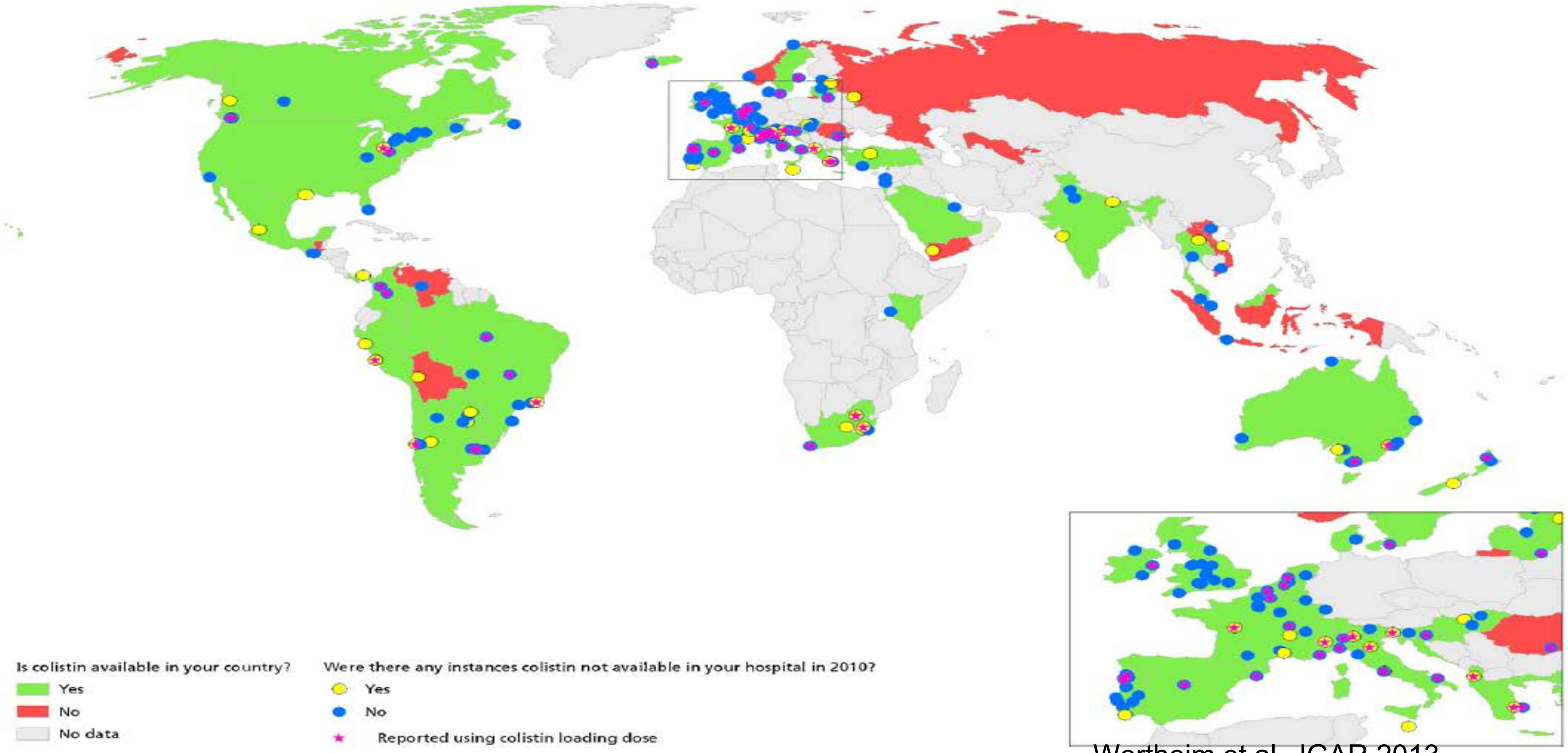
Global availability of colistin



Wertheim et al, JGAR 2013

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Summary

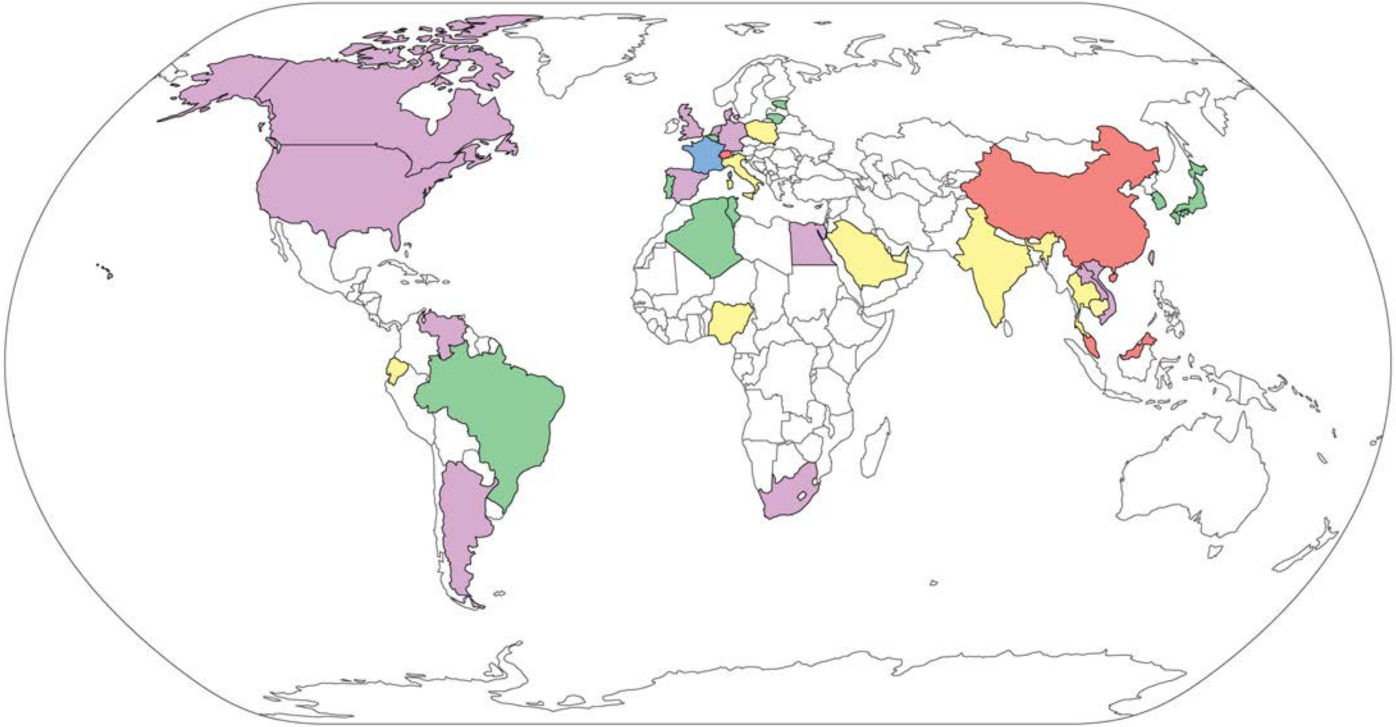
Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Lancet Infect Dis 2015

Published Online November 18, 2015 http://dx.doi.org/10.1016/S1473-3099(15)00424-7

See Online/Articles http://dx.doi.org/10.1016/S1473-3099(15)00463-6

Countries reporting plasmid-mediated colistin resistance encoded by *mcr-1*



Isolate source(s):

- Animals
- Humans
- Animals and humans
- Animals and environment
- Animals, humans and environment

Data source: Al-Tawfiq, J. A., Laxminarayan, R. & Mendelson, M. How should we respond to the emergence of plasmid-mediated colistin resistance in humans and animals? Int. J. Infect. Dis. (2016). doi:10.1016/j.ijid.2016.11.415

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III. 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

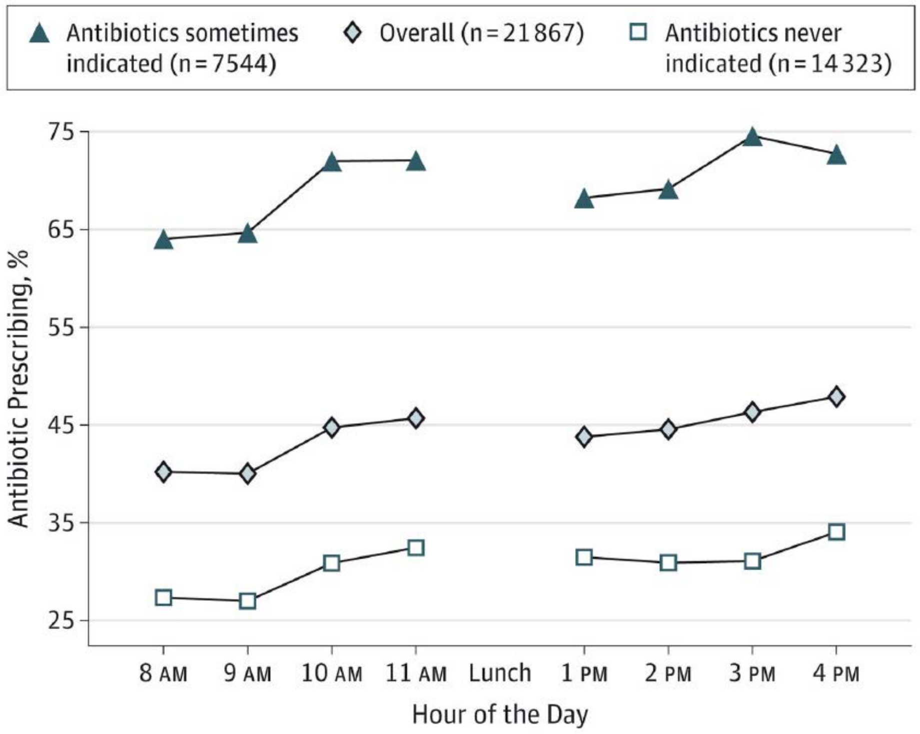
Frequency of Antibiotic Prescribing by Factors Related to Patients' Expectations of Antibiotics (N = 482)

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

Decision fatigue increases inappropriate prescribing



Relative to the first hour of a session, the adjusted odds ratios of antibiotic prescribing in the fourth hour was 1.26 (95% CI, 1.13–1.41)

Linder et al, JAMA IM, 2014

Hospital Incentives

- Antibiotics are a substitute for infection control
- Infection control is often not compensated

What proportion of hospitalized patients in the United States are administered an antimicrobial?

A. 25%
B. 40%
C. 55%
D. 70%

What proportion of hospitalized patients in the United States are administered an antimicrobial?

A. 25%
B. 40%
C. 55%
D. 70%

Relationship Between Occurrence of Surgical Complications and Hospital Finances

Sunil Eappen, MD
Bennett H. Lane, MS
Barry Rosenberg, MD, MBA
Stuart A. Lipsitz, ScD
David Sadoff, MBA
Dave Matheson, JD, MBA
William R. Berry, MD, MPP, MPH
Mark Lester, MD, MBA
Atul A. Gawande, MD, MPH

Importance The effect of surgical complications on hospital finances is unclear.

Objective To determine the relationship between major surgical complications and per-encounter hospital costs and revenues by payer type.

Design, Setting, and Participants Retrospective analysis of administrative data for all inpatient surgical discharges during 2010 from a nonprofit 12-hospital system in the southern United States. Discharges were categorized by principal procedure and occurrence of 1 or more postsurgical complications, using *International Classification of Diseases, Ninth Revision*, diagnosis and procedure codes. Nine common surgical procedures and 10 major complications across 4 payer types were analyzed. Hospital costs and revenue at discharge were obtained from hospital accounting systems and classified by payer type.

Compared with absence of complications, complications were associated with a **$39 017** higher contribution margin per patient with private insurance ($55 953 vs $16 936) and a **$1749** higher contribution margin per patient with Medicare ($3629 vs $1880).

Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study

Nikolay P Braykov, Daniel J Morgan*, Marin L Schweizer, Daniel Z Uslan, Theodoros Kelesidis, Scott A Weisenberg, Birgir Johannsson, Heather Young, Joseph Cantey, Arjun Srinivasan, Eli Perencevich, Edward Septimus, Ramanan Laxminarayan*

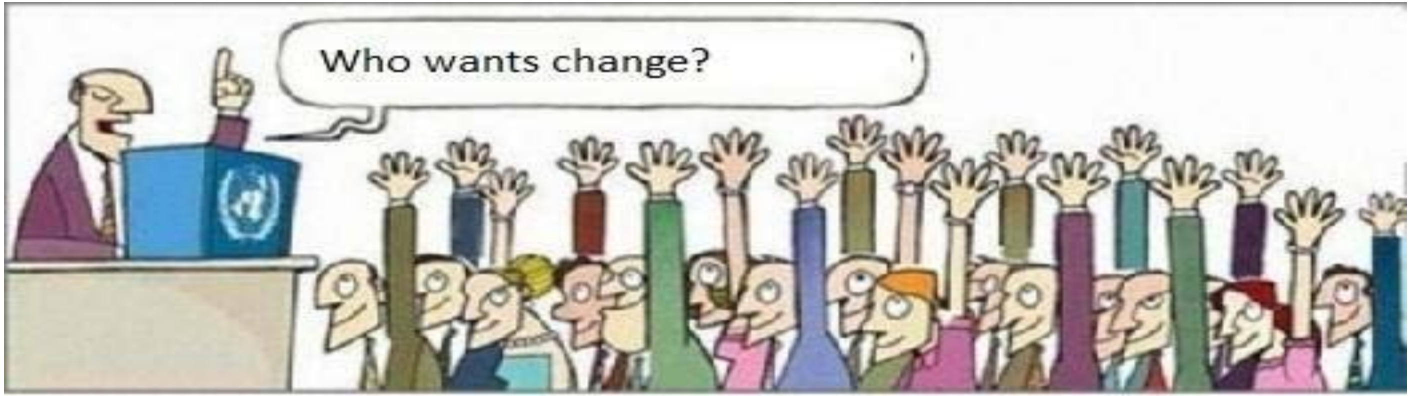
Lancet Infect Dis 2014; 14: 1220–27

See Comment page 1168

Summary

Background Modification of empirical antimicrobials when warranted by culture results or clinical signs is recommended to control antimicrobial overuse and resistance. We aimed to assess the frequency with which patients were started on empirical antimicrobials, characteristics of the empirical regimen and the clinical

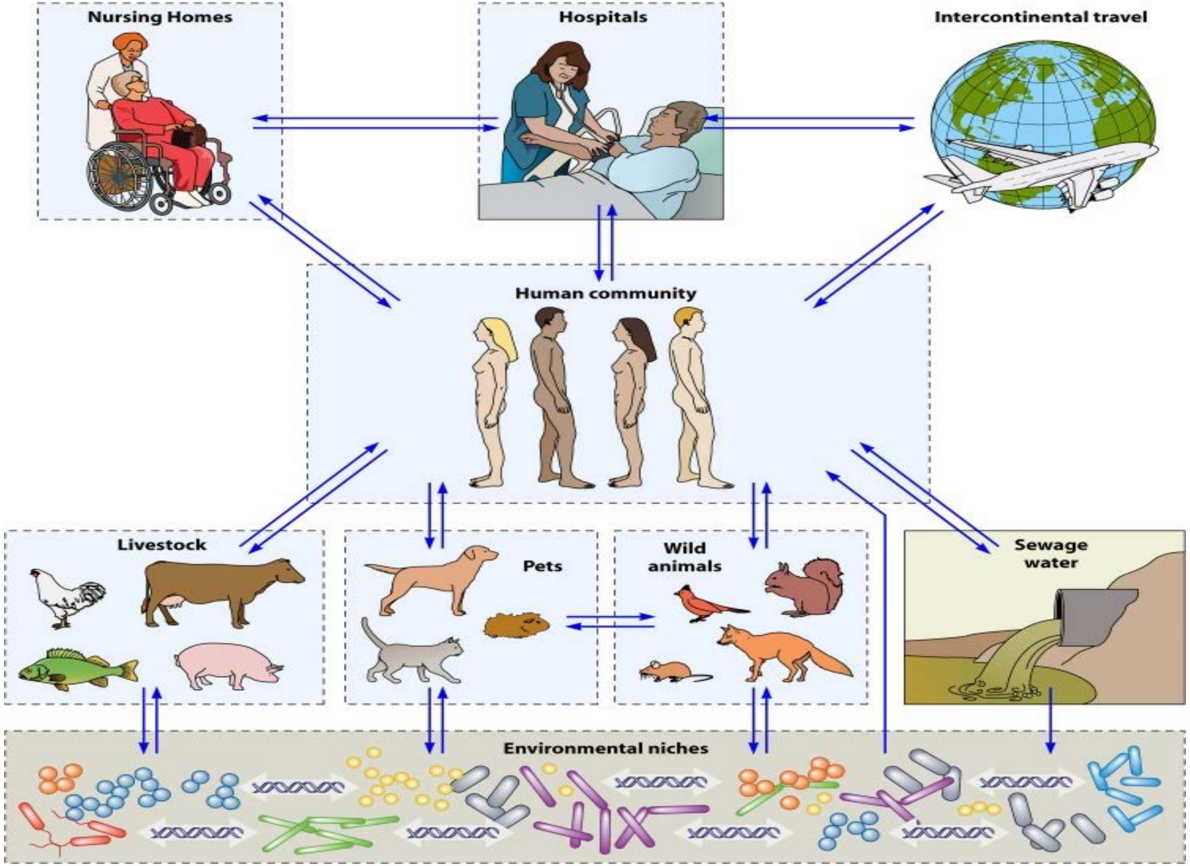
- At the start of therapy, 220 (30%) patients were afebrile and had normal white blood cell counts.
- Appropriate cultures were collected from 432 (59%) patients, and 250 (58%) were negative.
- By the 5th day of therapy, 12.5% of empirical antimicrobials were escalated, 21.5% were narrowed or discontinued, and 66.4% were unchanged.
- Narrowing or discontinuation was more likely when cultures were collected at the start of therapy and no infection was noted on an initial radiological study.


Who wants change?


Who wants change?
Who wants to change?
qcme.me/ZGtjZGL
Créé sur Québecmeme

IV. Antibiotic use in animal sector is increasing globally in response to the tremendous growth in demand for animal protein.

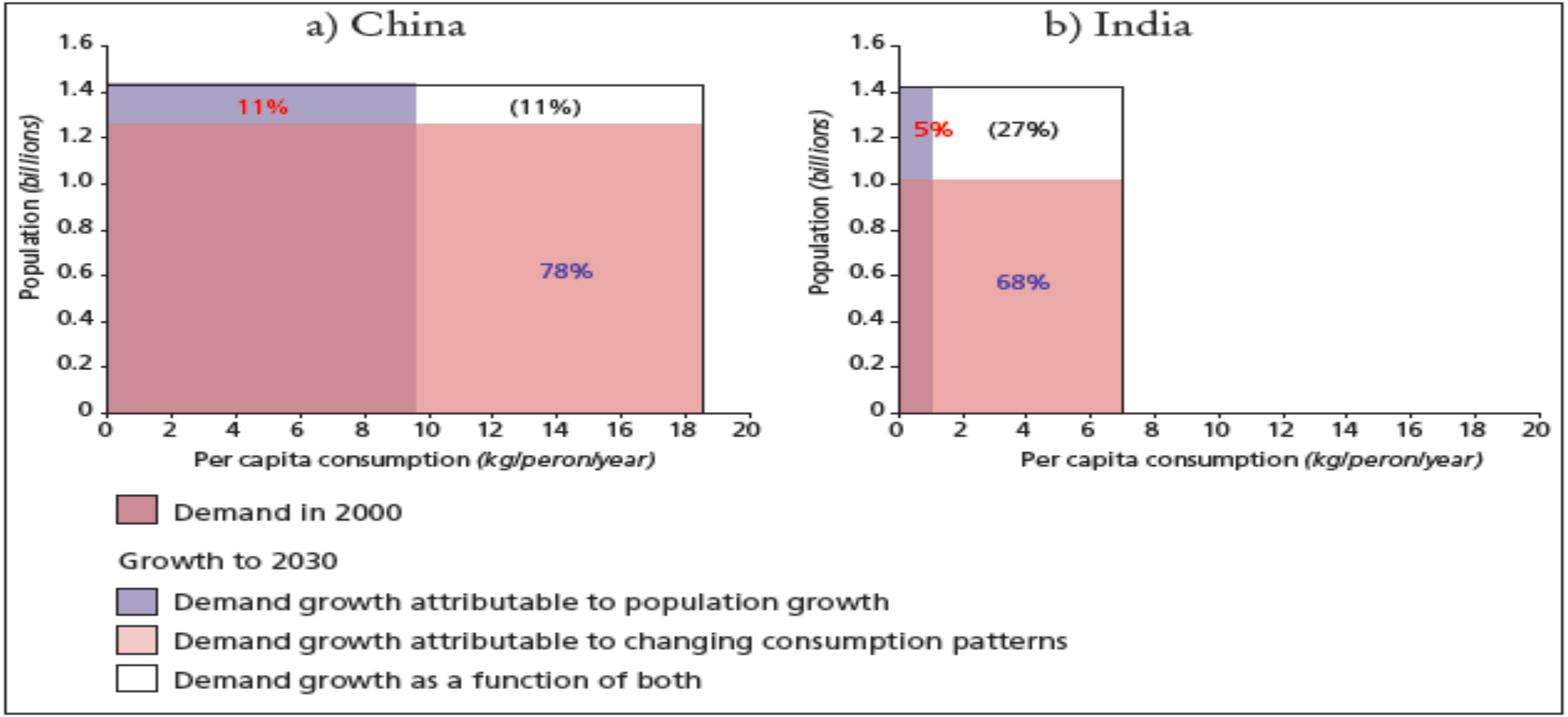
Meanwhile antibiotic manufacturing is expediting the accumulation of resistance genes in the environment.


Nursing Homes
Hospitals
Intercontinental travel
Human community
Livestock
Pets
Wild animals
Sewage water
Environmental niches

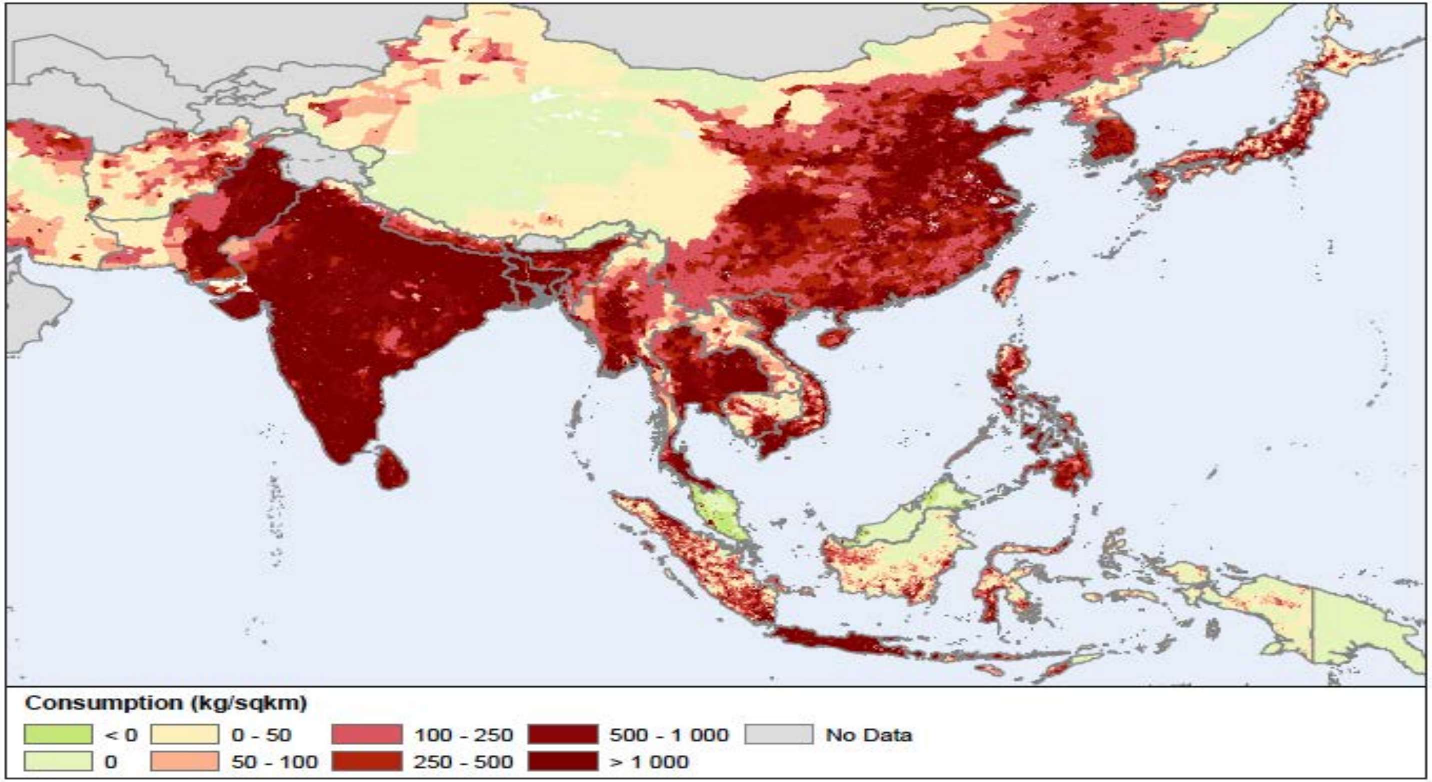
Antibiotic use for growth promotion and disease prevention

2/3rds of the tonnage of antibiotics sold worldwide are used in agriculture

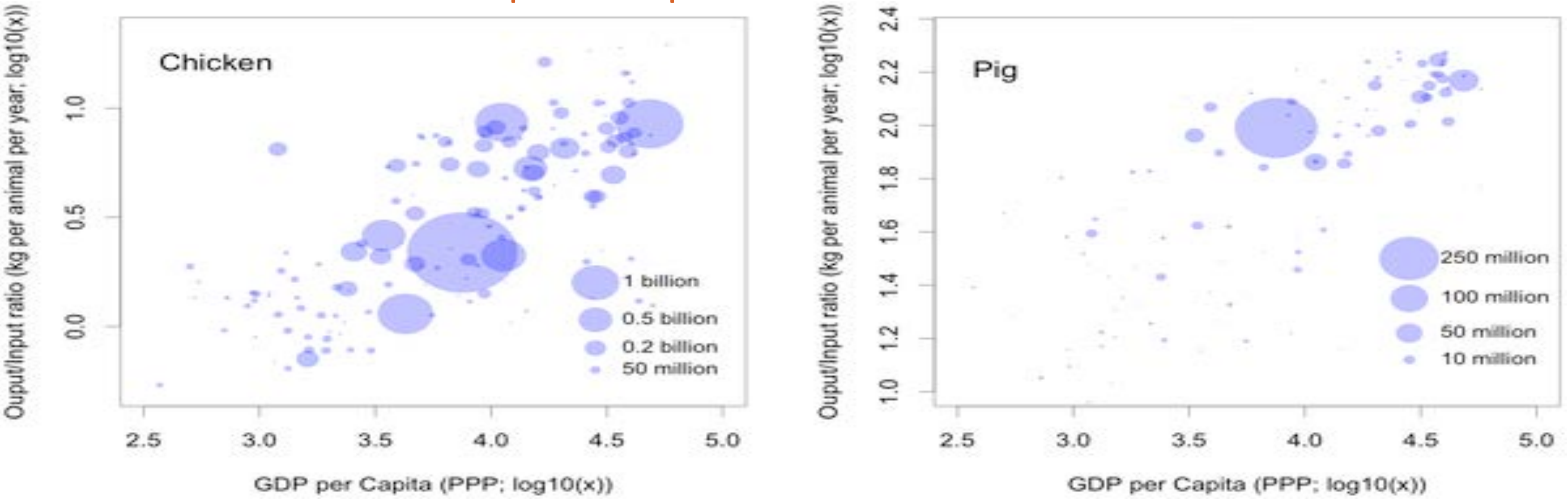
Demand for poultry in India and China is set to increase two to seven fold between 2000 and 2030



Growth in demand for poultry meat from 2000 to 2030 in Asia



Productivity (kg of meat per animal per year) as a function of GDP per capita

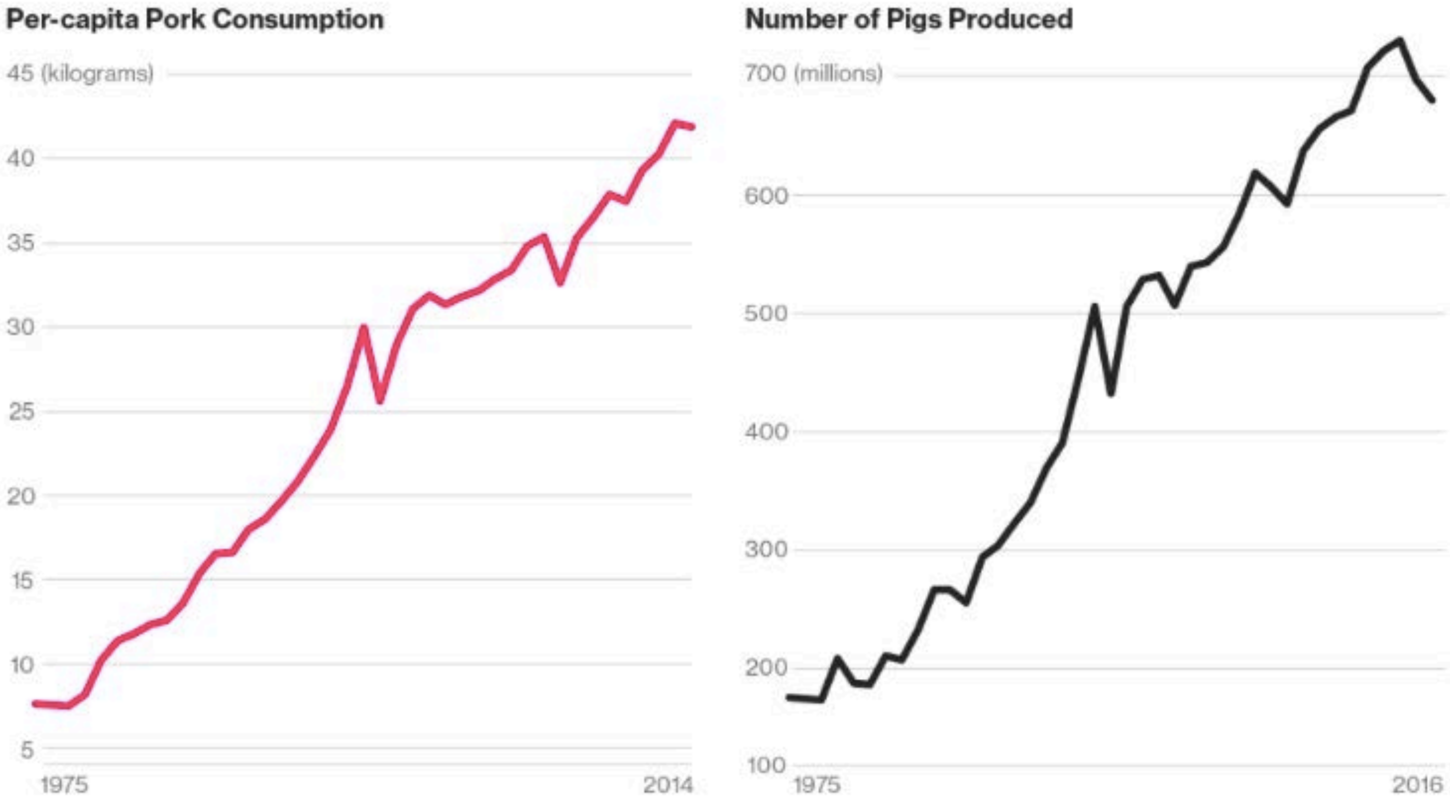


Gilbert M, Conchedda G, Van Boeckel TP, Cinardi G, Linard C, et al. (2015) Income Disparities and the Global Distribution of Intensively Farmed Chicken and Pigs. PLOS ONE 10(7): e0133381. https://doi.org/10.1371/journal.pone.0133381
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0133381

PLOS | ONE
TENTH ANNIVERSARY

Pig Run

Swine output has surged to feed pork-hungry China



Source: Bloomberg data

Bloomberg

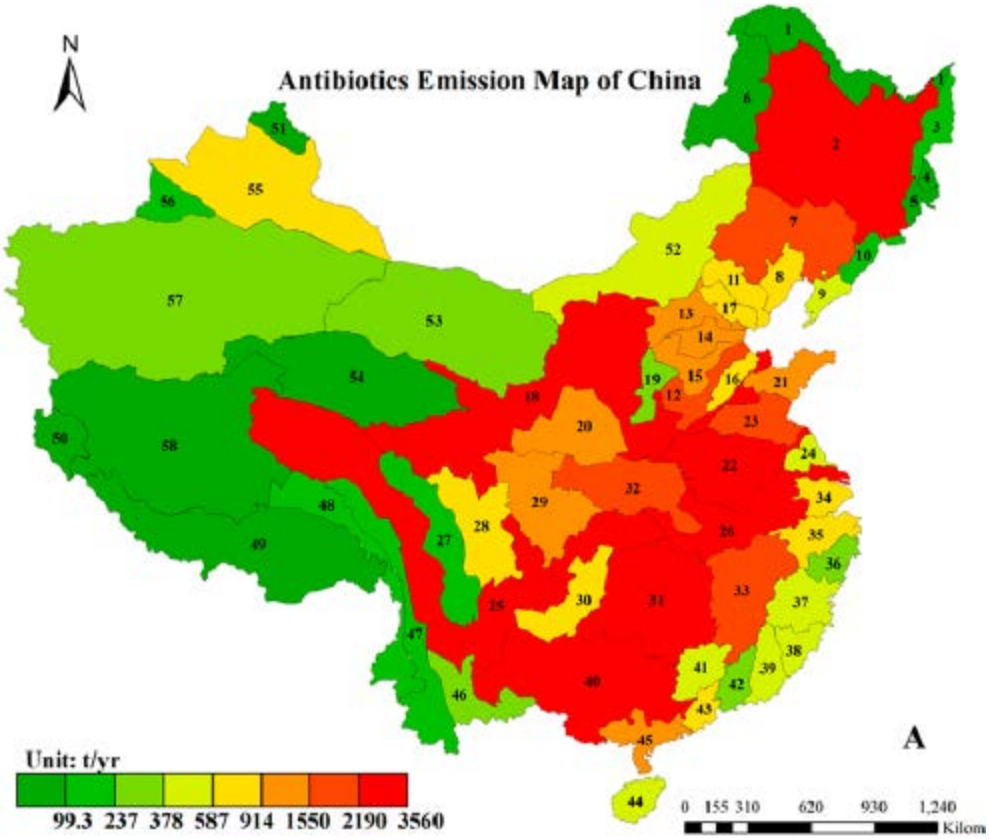
Drug Binge

China consumes half the world's antibiotics, with the majority administered to animals

Antibiotics consumed (metric tons) in 2013

Source: Ying Guang-Guo et al in Environmental Science & Technology, May 2015

Bloomberg



- Total consumption in China - 92700 tons in 2013,
- 54000 tons of antibiotics excreted by human and animals - much of this entered into the receiving environment following various wastewater treatments into 58 river basins of China

Zhang et al, Env Sci Tech, 2015

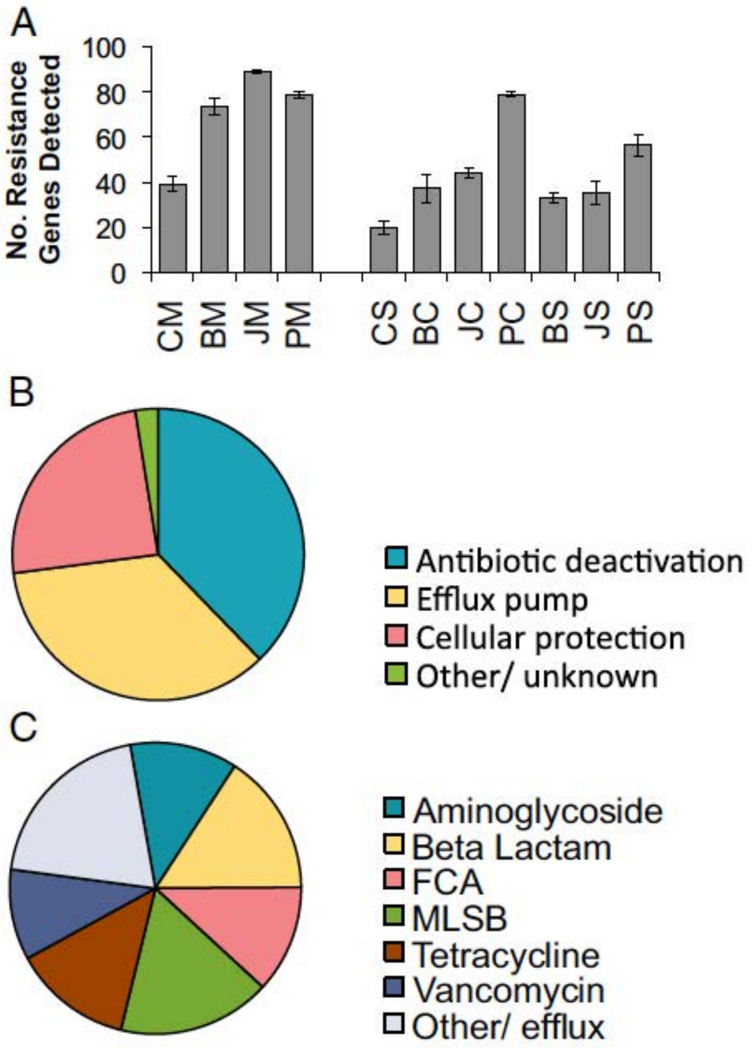
Diverse and abundant antibiot in Chinese swine farms

Yong-Guan Zhu[a,b,1,2], Timothy A. Johnson[c,d,1], Jian-Qiang Su[a], Min
Syed A. Hashsham[c,e], and James M. Tiedje[c,d,2]

[a]Key Lab of Urban Environment and Health, Institute of Urban Environment, Chinese
Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; and [c]Ce
Sciences, and [e]Civil and Environmental Engineering, Michigan State University, East L

Contributed by James M. Tiedje, December 31, 2012 (sent for review October 31, 201

High-capacity quantitative PCR arrays detected 149 unique resistance genes among all of the farm samples, the top 63 ARGs being enriched 192-fold (median) up to 28,000-fold (maximum) compared with their respective antibiotic-free manure or soil controls.



Pharmaceuticals and Personal Care Products in the Environment

CONTAMINATION OF SURFACE, GROUND, AND DRINKING WATER FROM PHARMACEUTICAL PRODUCTION

JERKER FICK,*† HANNA SÖDERSTRÖM,† RICHARD H. LINDBERG,† CHAU PHAN,† MATS TYSKLIND,† and D.G. JOAKIM LARSSON‡

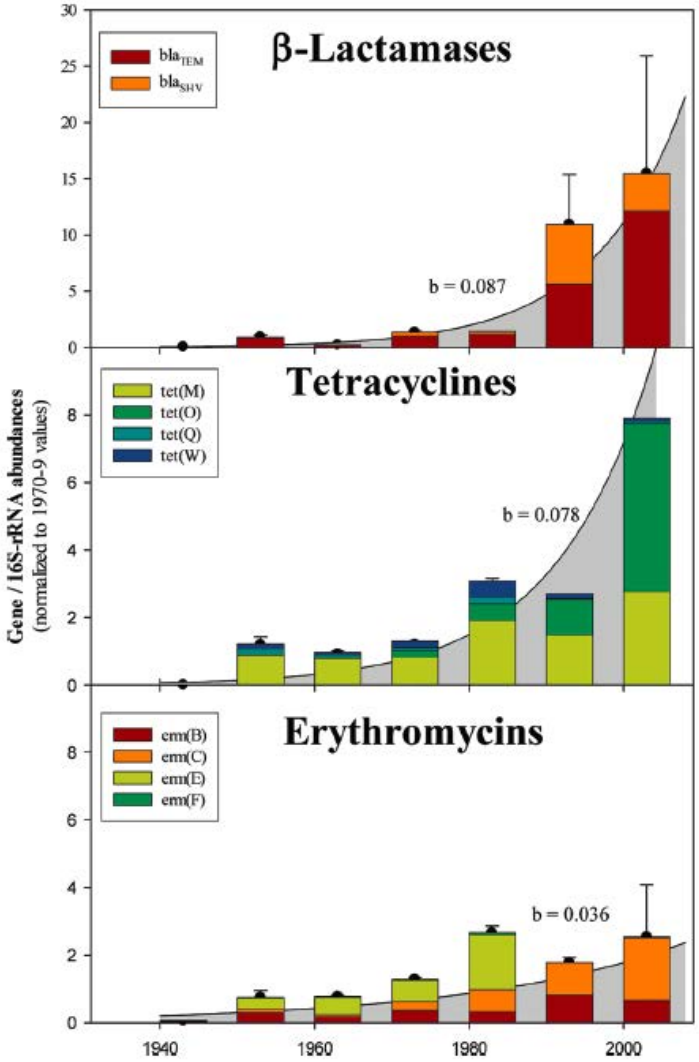
†Department of Chemistry, Umeå University, Linneausväg 6, SE-90187 Umeå, Sweden

High amounts of four antibiotics were measured in the lakes that do not take in wastewater from the sewage plant. The levels of ciprofloxacin (2.5 mg/L) and cetirizine (20 µg/L) in one of the lakes was higher than previously measured levels in the blood of people taking the medications, report the authors. This suggests there are other unknown sources – perhaps illegal dumping – of wastewater responsible for polluting the lakes.

In addition, effluents from a wastewater treatment had concentrations of ciprofloxin of 14 milligrams per liter (mg/L) and cetirizine as high as 1.2 mg/L. These concentrations are approaching therapeutic doses (concentratios that would kill some microorganisms outright). Concentration reported in the US range in the nanograms per liter (ng/L), which are one million fold less.

contaminated by the treatment plant. Water samples were also taken from wells in six nearby villages. The samples were analyzed for the presence of 12 pharmaceuticals with liquid chromatography–mass spectrometry. All wells were determined to be contaminated with drugs. Ciprofloxacin, enoxacin, cetirizine, terbinafine, and citalopram were detected at more than 1 µg/L in several wells. Very high concentrations of ciprofloxacin (14 mg/L) and cetirizine (2.1 mg/L) were found in the effluent of the treatment plant, together with high concentrations of seven additional pharmaceuticals. Very high concentrations of ciprofloxacin (up to 6.5 mg/L), cetirizine (up to 1.2 mg/L), norfloxacin (up to 0.52 mg/L), and enoxacin (up to 0.16 mg/L) were also detected in the two lakes, which clearly shows that the investigated area has additional environmental sources of insufficiently treated industrial waste. Thus, insufficient wastewater management in one of the world's largest centers for bulk drug production leads to unprecedented drug contamination of surface, ground, and drinking water. This raises serious concerns regarding the development of antibiotic resistance, and it creates a major challenge for producers and regulatory agencies to improve the situation.

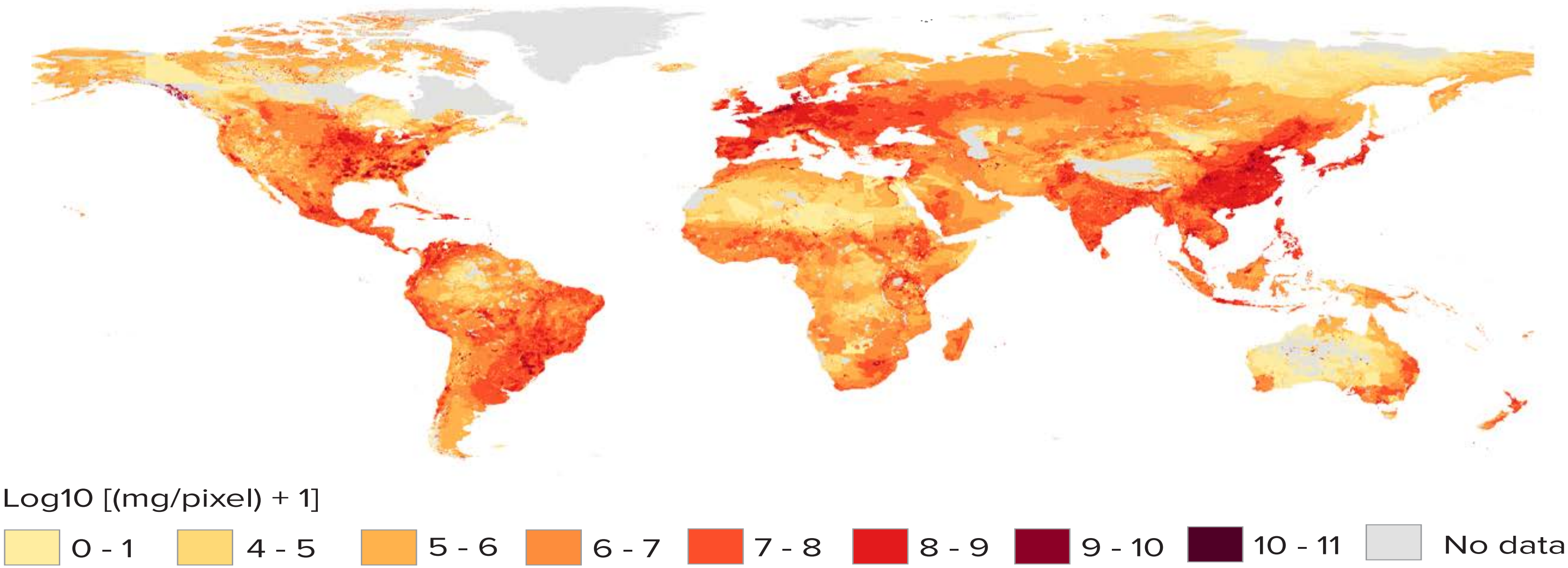
Fick et al Env Tox and Chem, 2009



Increase of antibiotic resistance genes among soils collected at five sites in The Netherlands from 1940 to 2008.

Knapp et al Env Sci Tech, 2010

Global antibiotic consumption in livestock (mg per 10 km² pixels) 2010



Van Boeckel et al., PNAS, 2015

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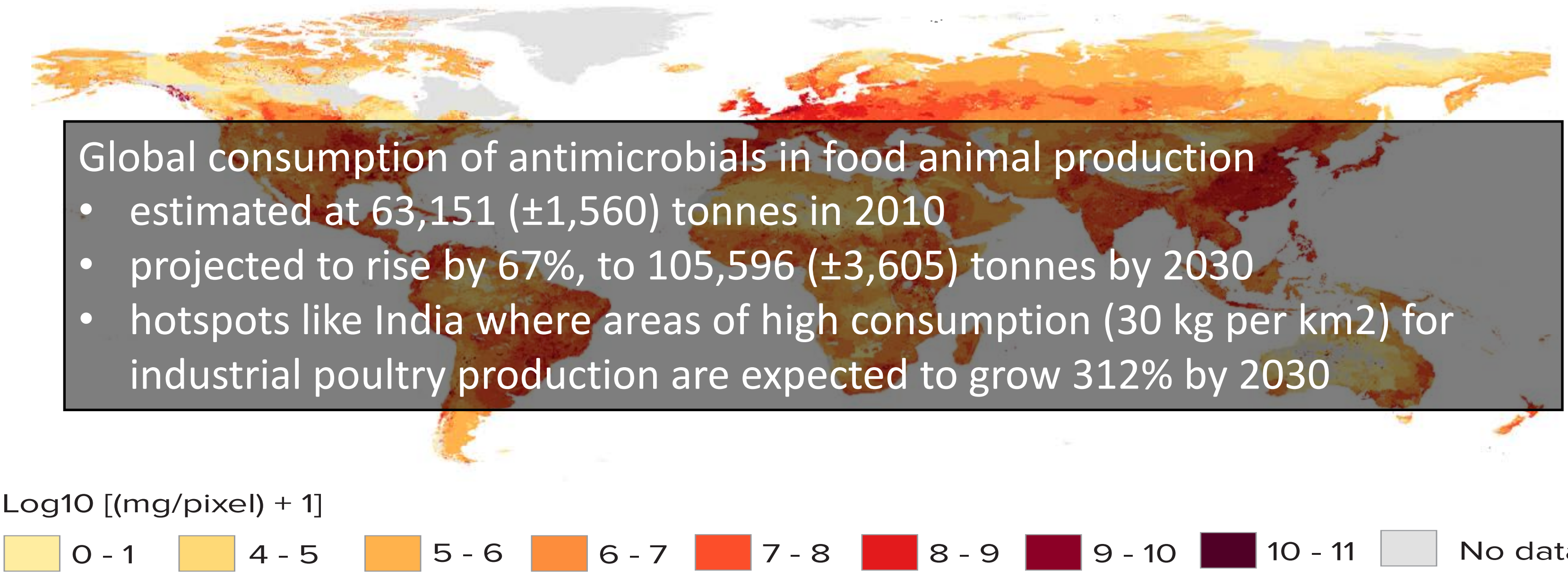
Global antibiotic consumption in livestock (mg per 10 km^2 pixels) 2010



Global consumption of antimicrobials in food animal production

- estimated at 63,151 (±1,560) tonnes in 2010
- projected to rise by 67%, to 105,596 (±3,605) tonnes by 2030
- 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

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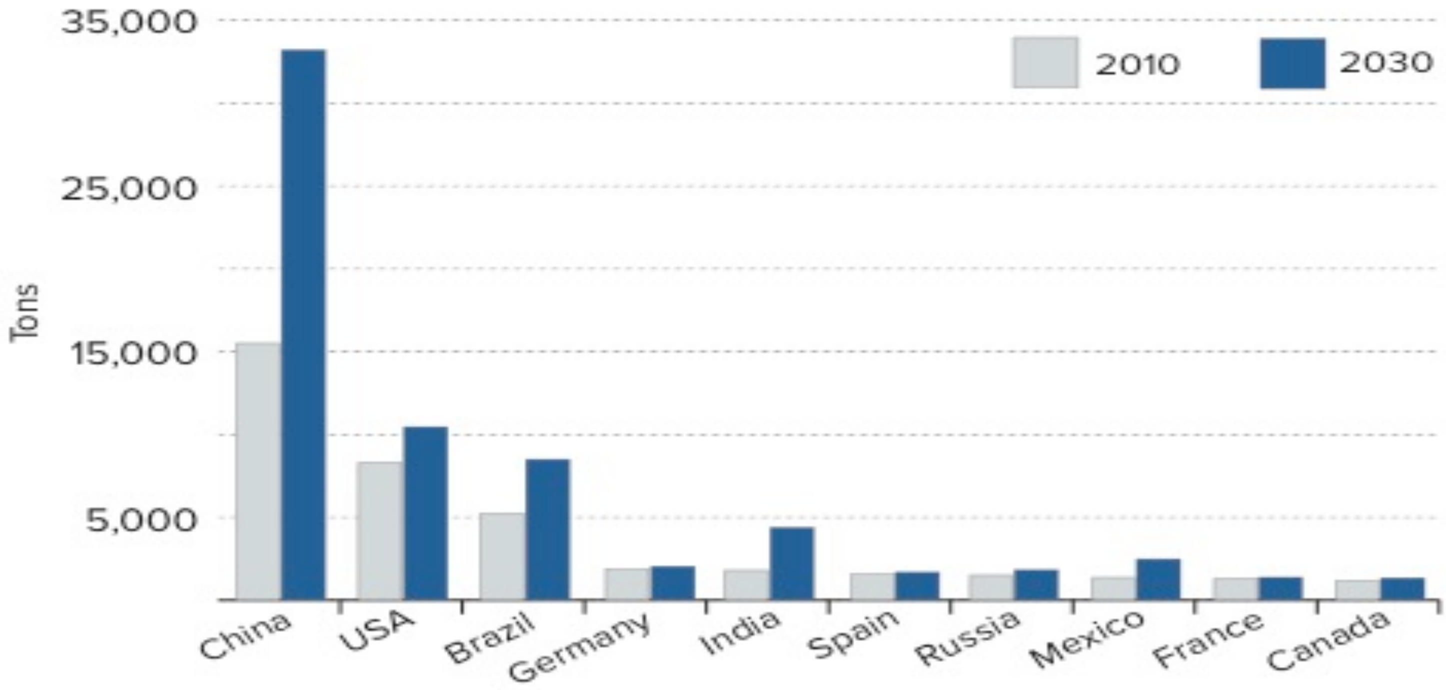
Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)



Van Boeckel et al., PNAS, 2015

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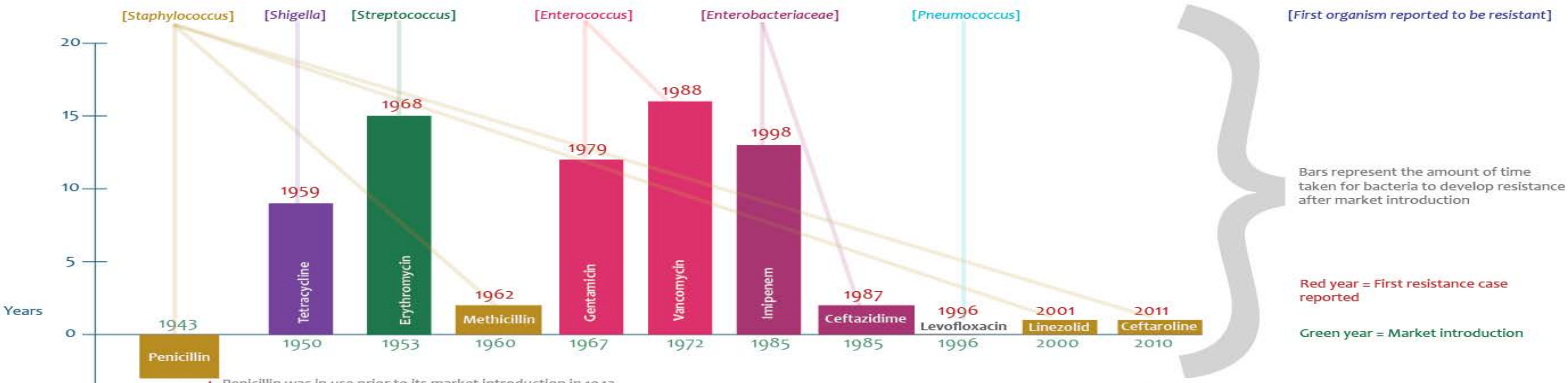
V. Is finding new antibiotics the answer?

First reported cases of bacterial resistance against key antibiotics



* Penicillin was in use prior to its market introduction in 1943.

Data source: Antibiotic Resistance Threats in the United States, 2013.
US Centers for Disease Control and Prevention (CDC).

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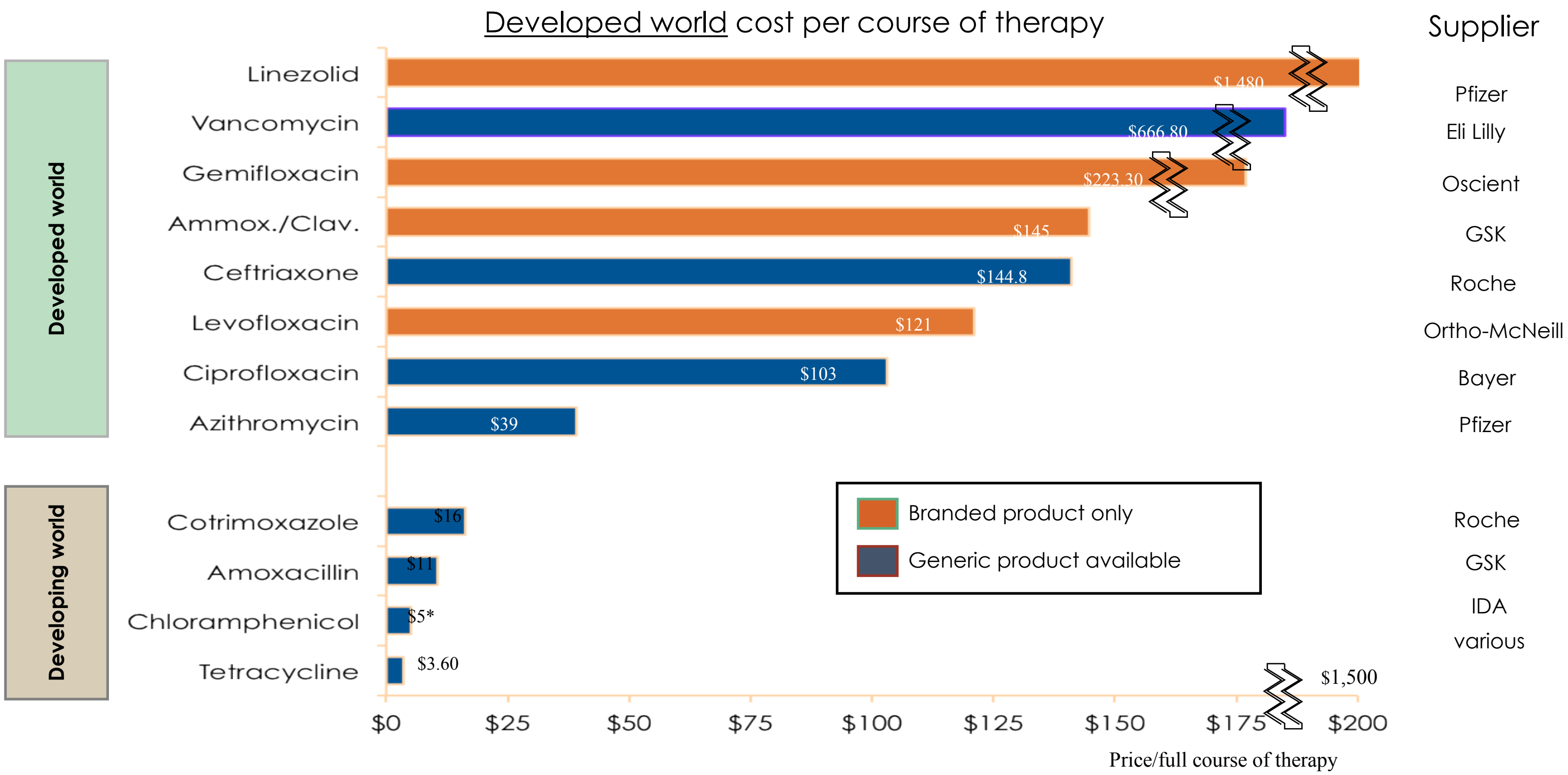
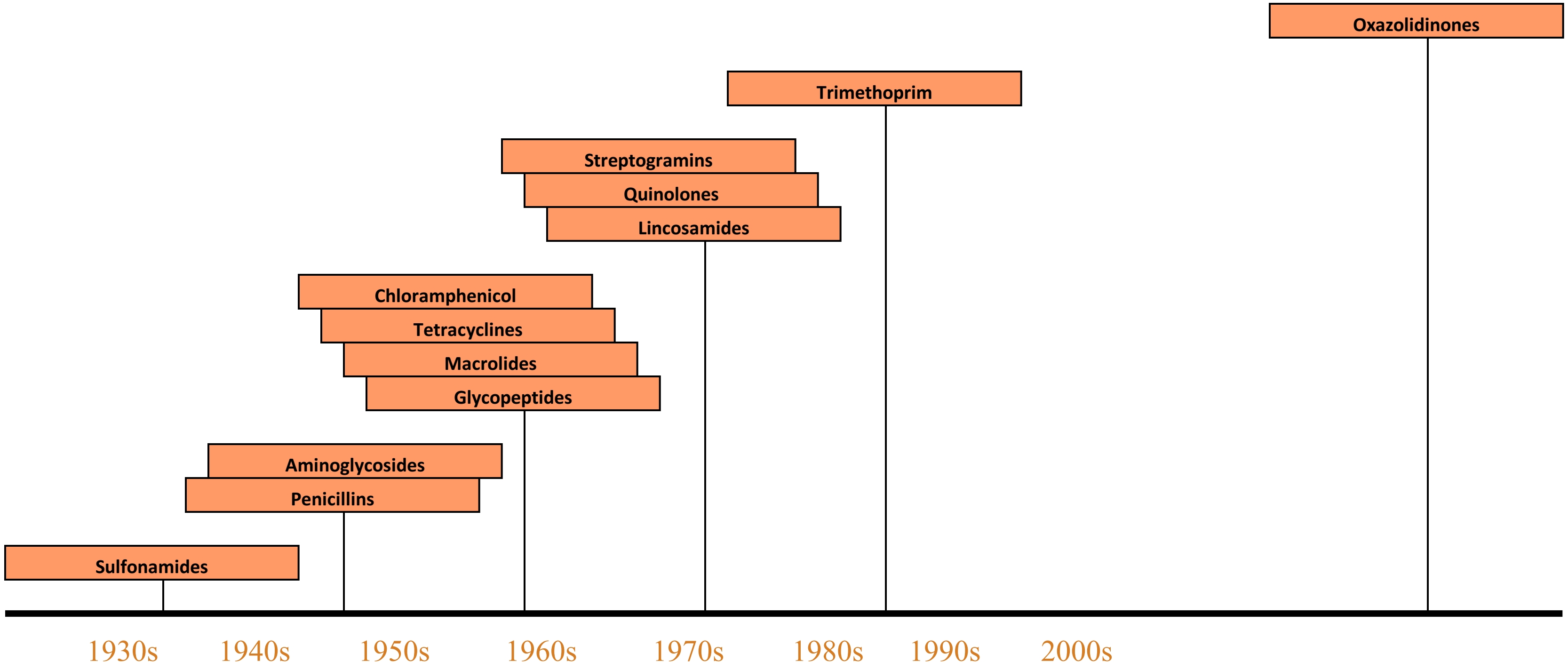
The rich pay with their wallets, the poor with their lives



Notes: *Chloramphenicol is not available in developed world—price is therefore estimated. †Ceftriaxone and ciprofloxacin may be available in some tertiary settings in developing world.
Source: The Medical Letter (2006), Disease control priorities in developing countries, Lancet (2006), Expert interviews.

Discovery of new classes of antibiotics



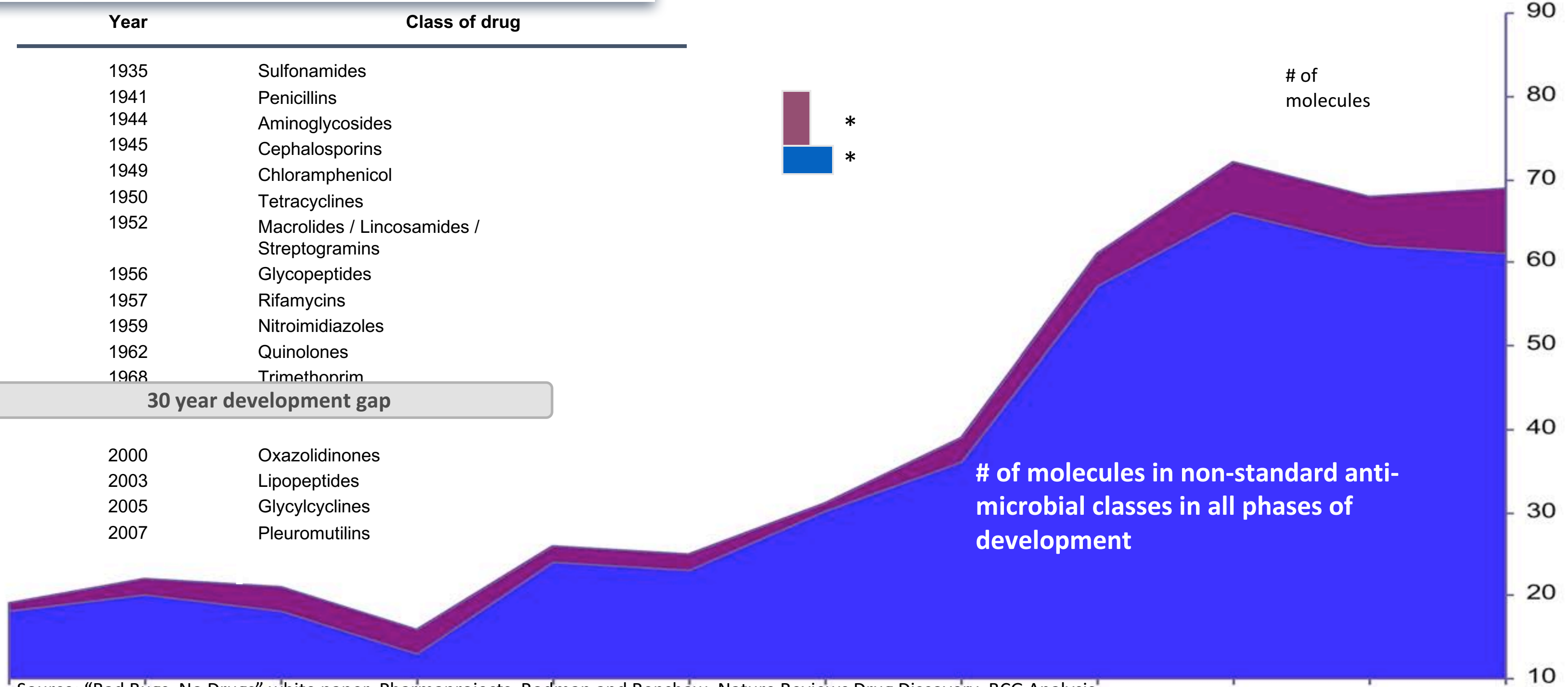
Pipeline of new anti-microbial drugs growing after a long lag

But prices are likely to be high

Significant gap in first introduction of new antimicrobial classes...

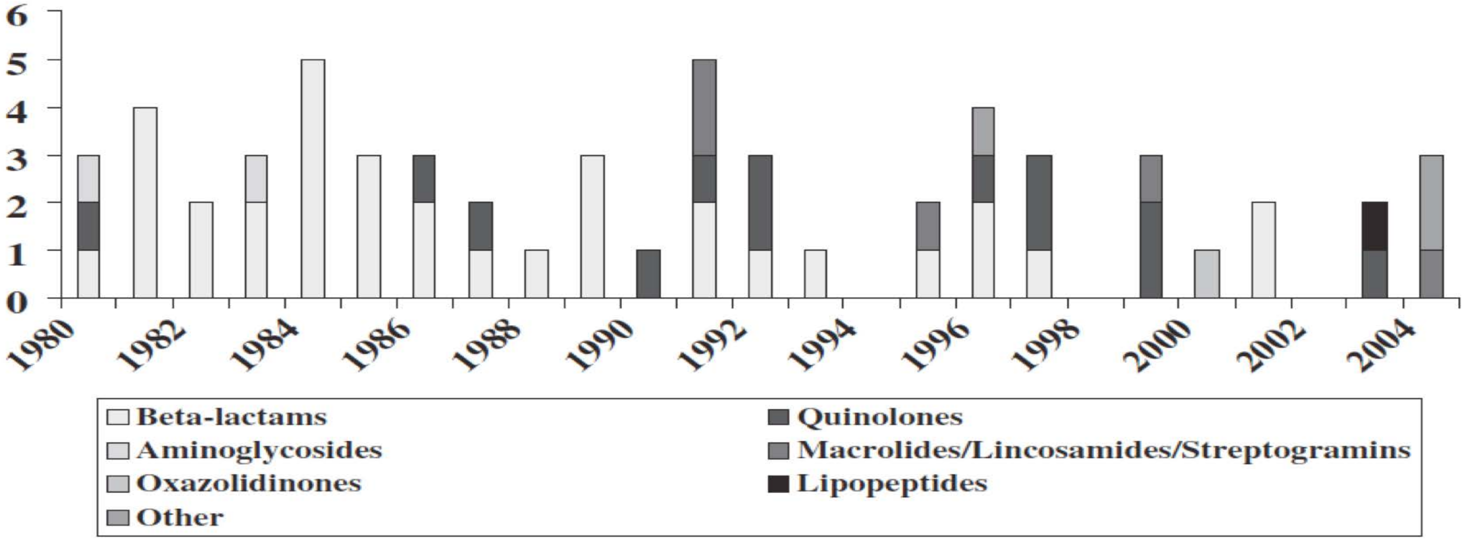
Year	Class of drug
1935	Sulfonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides / Lincosamides / Streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidiazoles
1962	Quinolones
1968	Trimethoprim
30 year development gap	
2000	Oxazolidinones
2003	Lipopeptides
2005	Glycylcyclines
2007	Pleuromutilins

...Is being addressed by large recent reinvestment in novel mechanism development

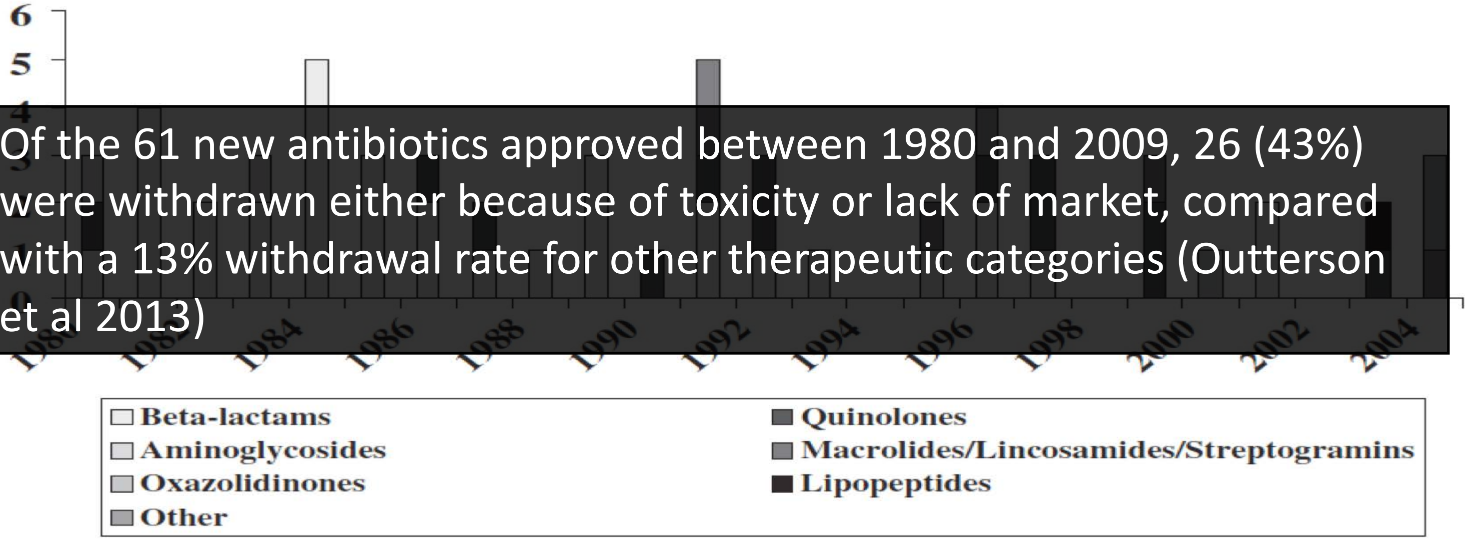


Source: “Bad Bugs, No Drugs” white paper, Pharmaprojects, Rodman and Renshaw, Nature Reviews Drug Discovery, BCG Analysis

Trends in development of new antibiotics



Trends in development of new antibiotics



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)

New antibiotic launches since 1994

Launch Year	Product name	Antimicrobial class (old) / Antimicrobial class (new)	Pharmaceutical Company
1994	Meropenem	Carbapenem	AstraZeneca
1999	Moxifloxacin	Flouroquinolone	Bayer
2000	Linezolid	Oxazolidinone	Pfizer
2001	Telithromycin	Macrolide	Sanofi-Aventis
2002	Balofloxacin	Fluoroquinolone	Choongwae Pharma
2002	Biapenem	Carbapenem	Wyeth
2002	Ertapenem	Carbapenem	Merck
2002	Prulifloxacin	Fluoroquinolone	Nippon Shinyaku Co.
2002	Pazufloxacin	Fluoroquinolone	Toyama Chemical Co.
2004	Gemifloxacin	Fluoroquinolone	LG Life Sciences
2005	Tigecycline	Glycylcycline	Wyeth
2005	Doripenem	Carbapenem	Janssen Pharmaceuticals
2006	Daptomycin	Lipopeptide	Cubist Pharmaceuticals
2007	Garenoxacin	Quinolone	Toyama Chemical Co.
2007	Retaparmulin	Pleuromutilin	GlaxoSmithKline
2008	Dalbavancin	Glycolipopeptide	Pfizer
2008	Oritavancin	Glycopeptide	Targanta Therapeutics
2008	Sitafloxacin	Fluoroquinolone	Daiichi Pharmaceutical Co.
2008	Telavancin	Novel glycolipopeptide	Theravance
2009	Antofloxacin	Fluoroquinolone	Anhui Global
2009	Besifloxacin	Fluoroquinolone	SSP Co.
2009	Ceftobiprole	5th-gen cephalosporin	Johnson & Johnson
2009	Iclaprim	DHFR inhibitor	Arpida
2009	Tebipenem	Carbapenem	Meiji Seika Pharma Co.
2011	Ceftaroline	5th-gen cephalosporin	Cerexa
2011	Fidaxomicin	Macrocyclic	Optimer Pharmaceuticals
2012	Bedaquiline	Diarylquinoline	Janssen Pharmaceuticals

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

Laxminarayan, *Science*, 2014

Incentives for new antibiotics, as proposed by BARDA and EU may encourage new drug development but don’t impact incentives for using drugs appropriately

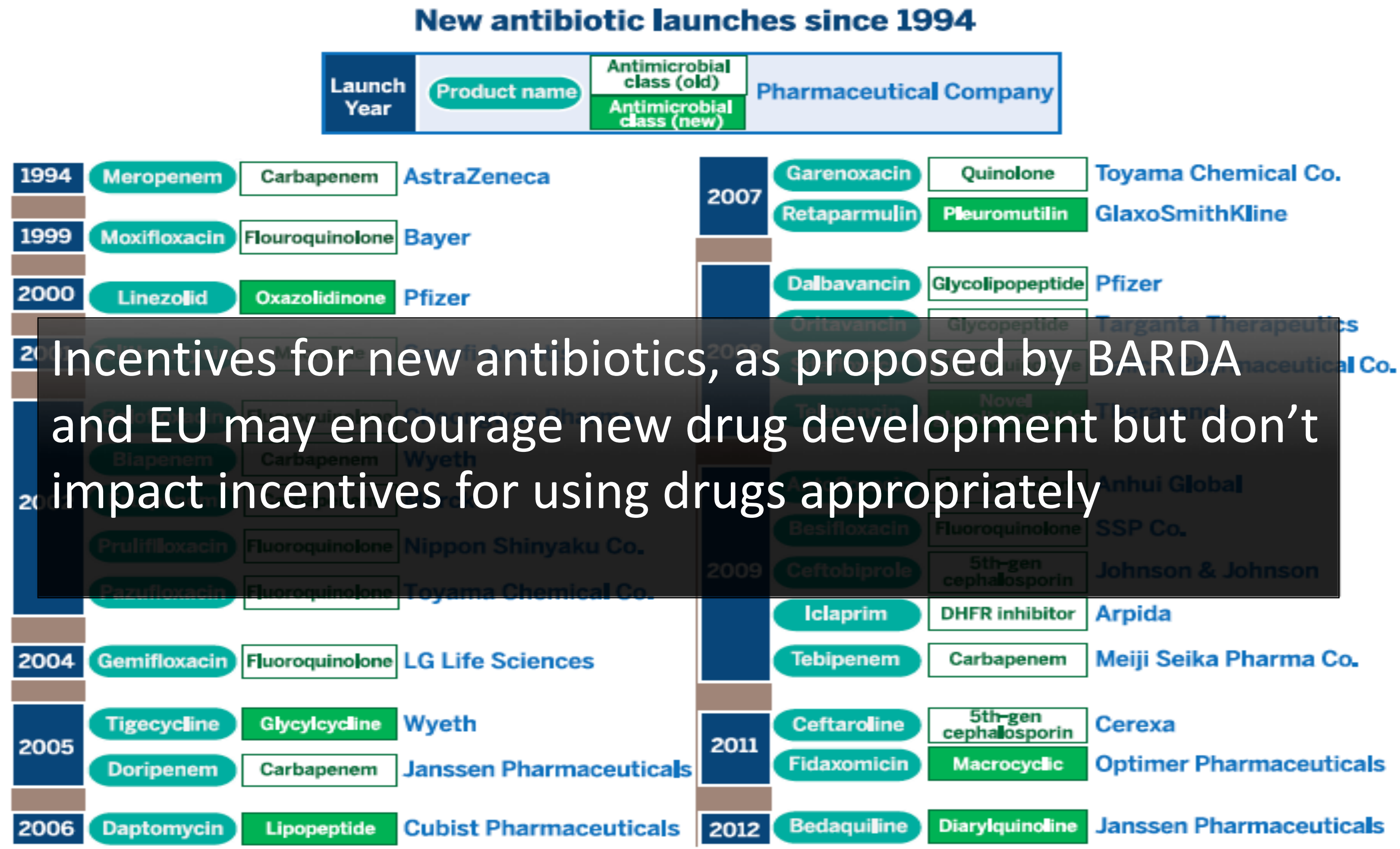
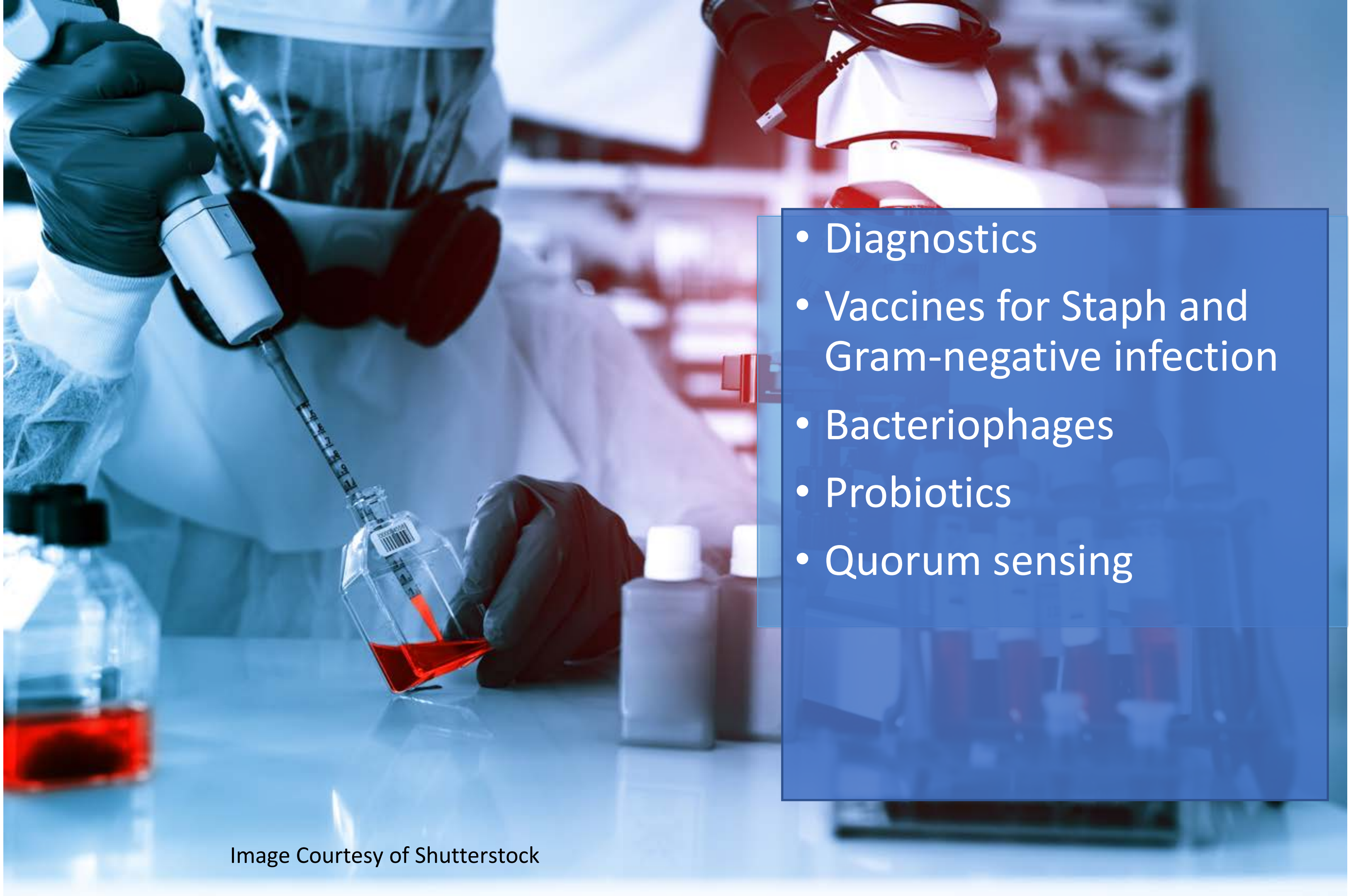


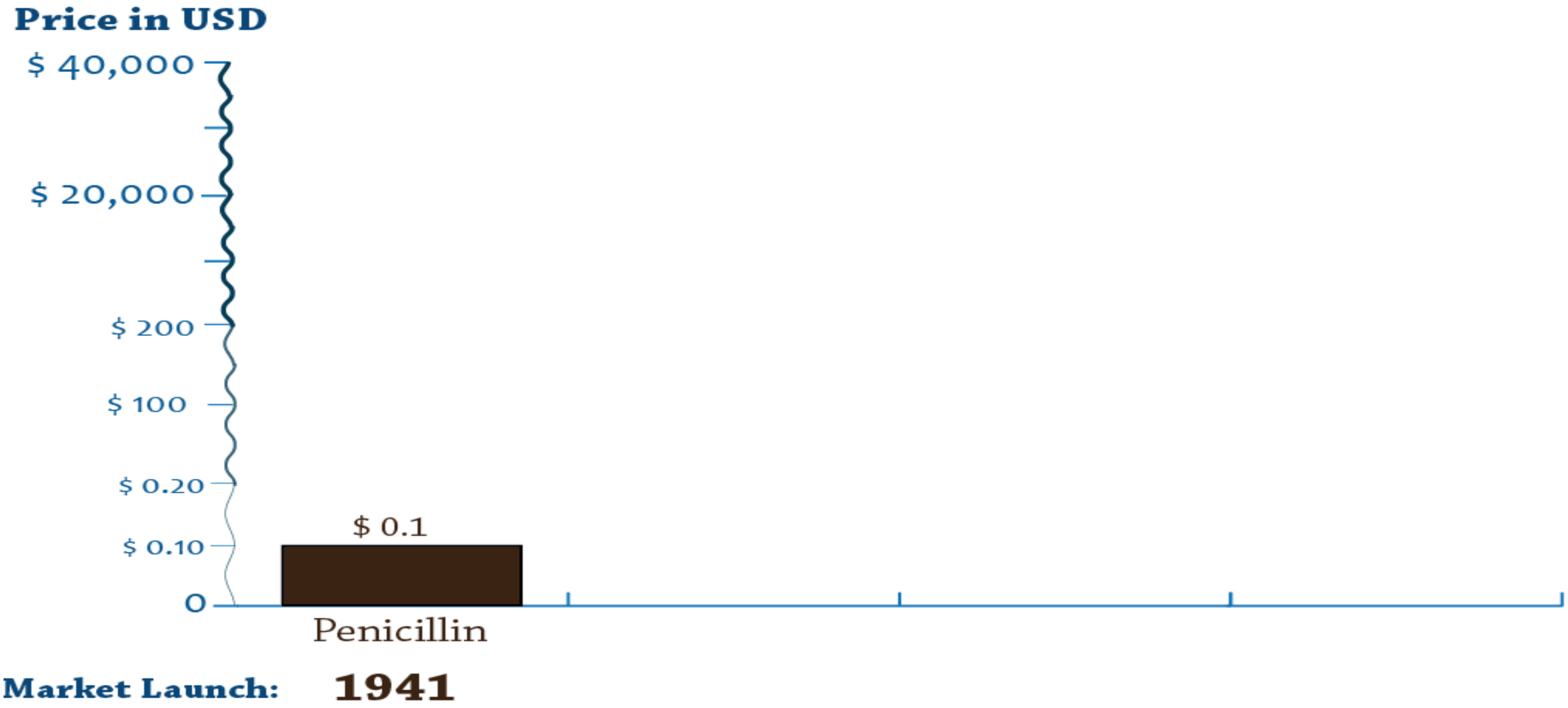
Fig. 3. Antibiotic pipeline for the past 20 years.

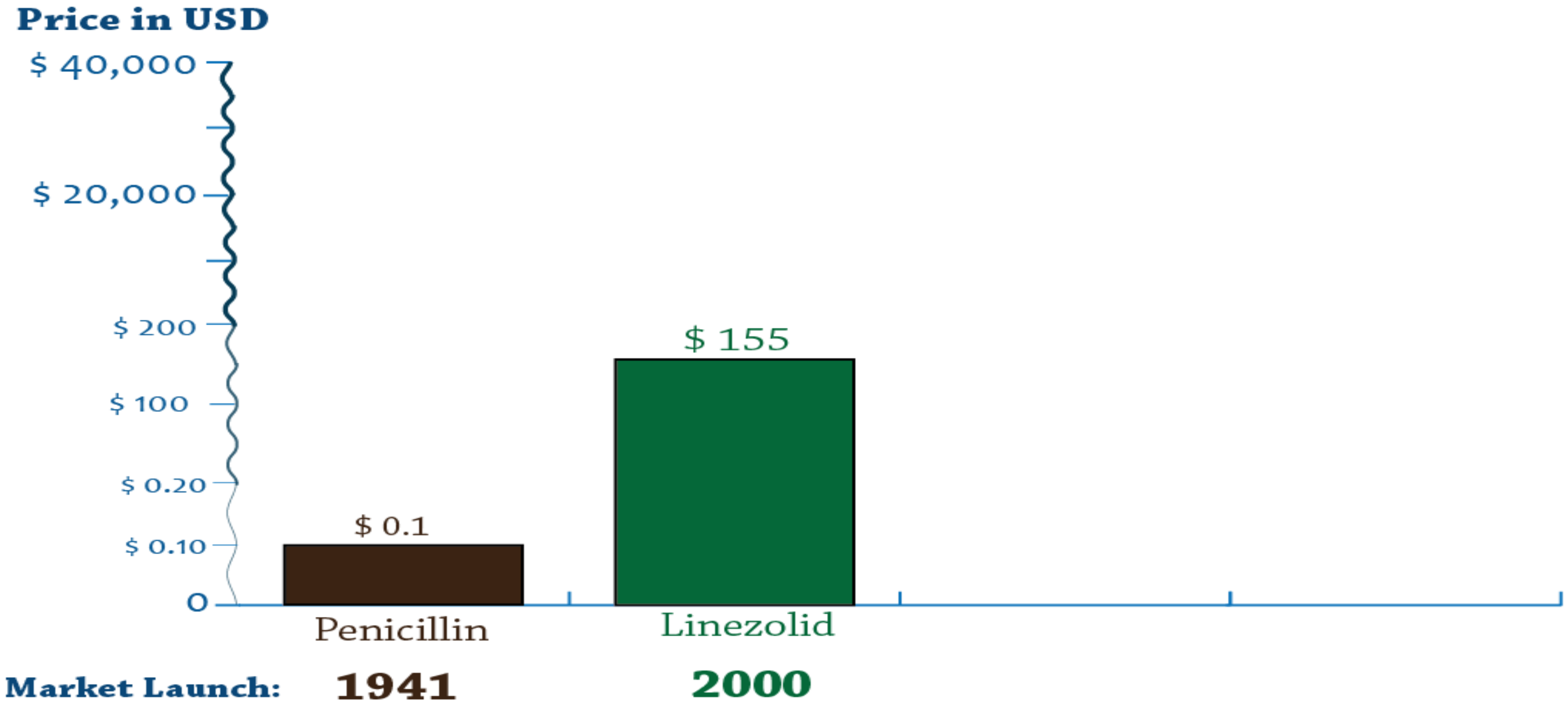
Laxminarayan, *Science*, 2014



- Diagnostics
- Vaccines for Staph and Gram-negative infection
- Bacteriophages
- Probiotics
- Quorum sensing

Image Courtesy of Shutterstock


Price in USD
$ 40,000
$ 20,000
$ 200
$ 100
$ 0.20
$ 0.10
0
$ 0.1
Penicillin
Market Launch:
1941


Price in USD
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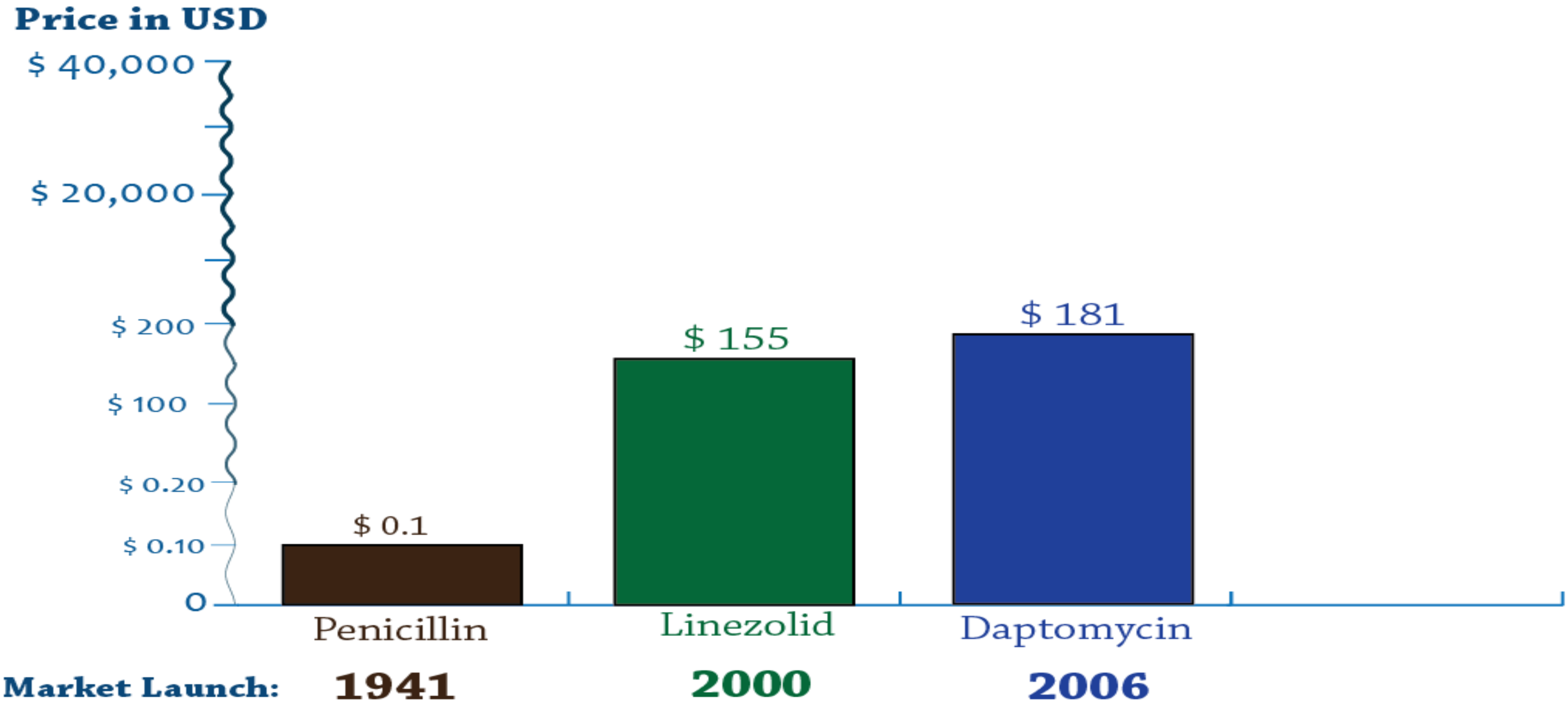
$ 0.1
$ 155
Penicillin
Linezolid
Market Launch:
1941
2000


Price in USD
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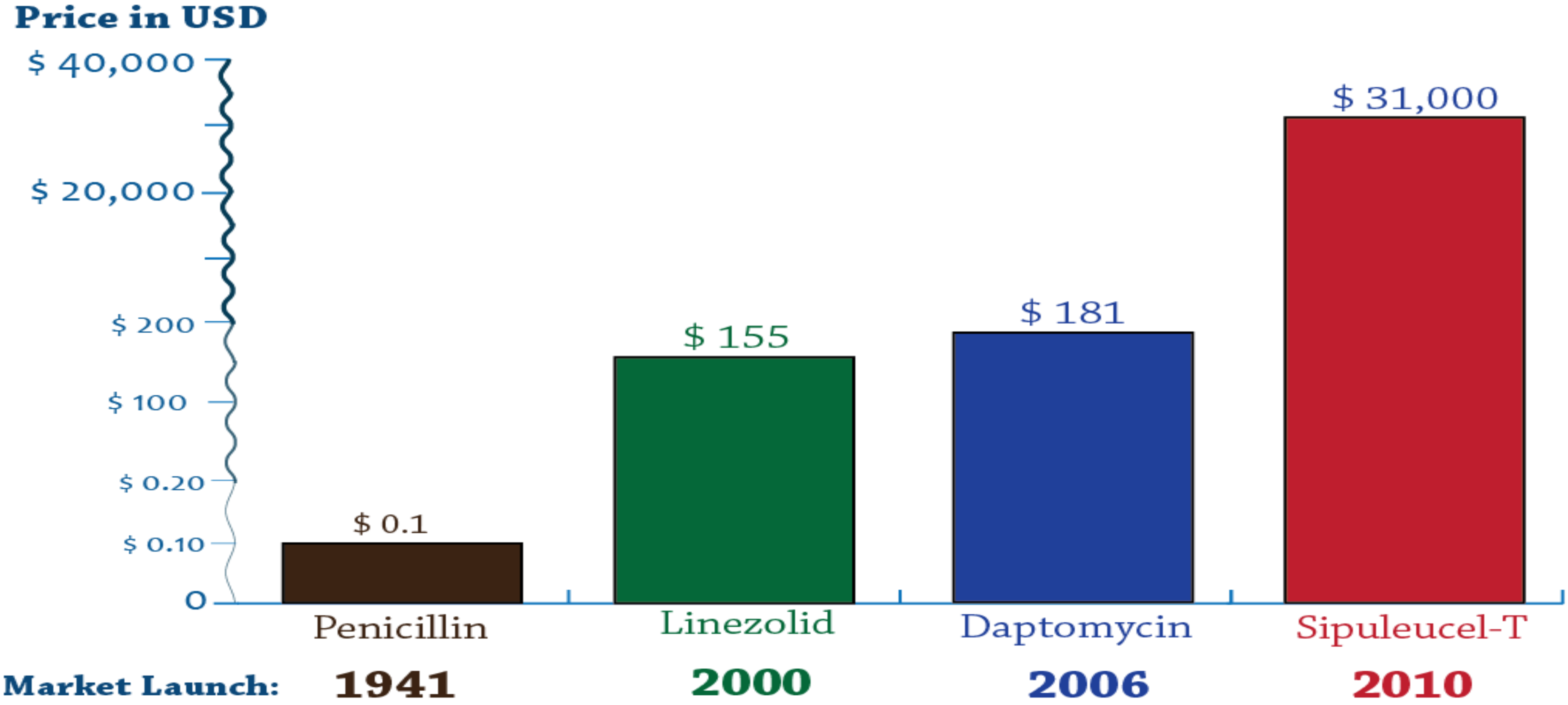
$ 20,000
$ 200
$ 100
$ 0.20
$ 0.10
0
$ 0.1
$ 155
$ 181
Penicillin
Linezolid
Daptomycin
Market Launch:
1941
2000
2006


Price in USD
$ 40,000
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Penicillin
Linezolid
Daptomycin
Sipuleucel-T
Market Launch:
1941
2000
2006
2010

United Nations A/71/L.2

General Assembly

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Seventy-first session
Agenda item 127
Global health and foreign policy

Draft resolution submitted by the President of the General Assembly

Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance

BLADE OF GRASS IS RESPONSIBLE FOR LOSS OF FOOT

C. W. Jones, athletic director of the Athens Y. M. C. A. yesterday suffered the loss of his right foot, the member having been amputated just above the ankle.

Mr. Jones, it seems, recently was exercising on a plot of grass, dew on a blade of grass cutting him slightly just under the little toe. The cut did not heal as quickly as it should have and medical attention was called, but to no avail. Blood poisoning had set in, and it was imperative that the foot be amputated to prevent the poison spreading further.

Weekly Banner, 18 July 1899, p. 2, col. 2.

©Athens-Clarke County Heritage Room, 2011.

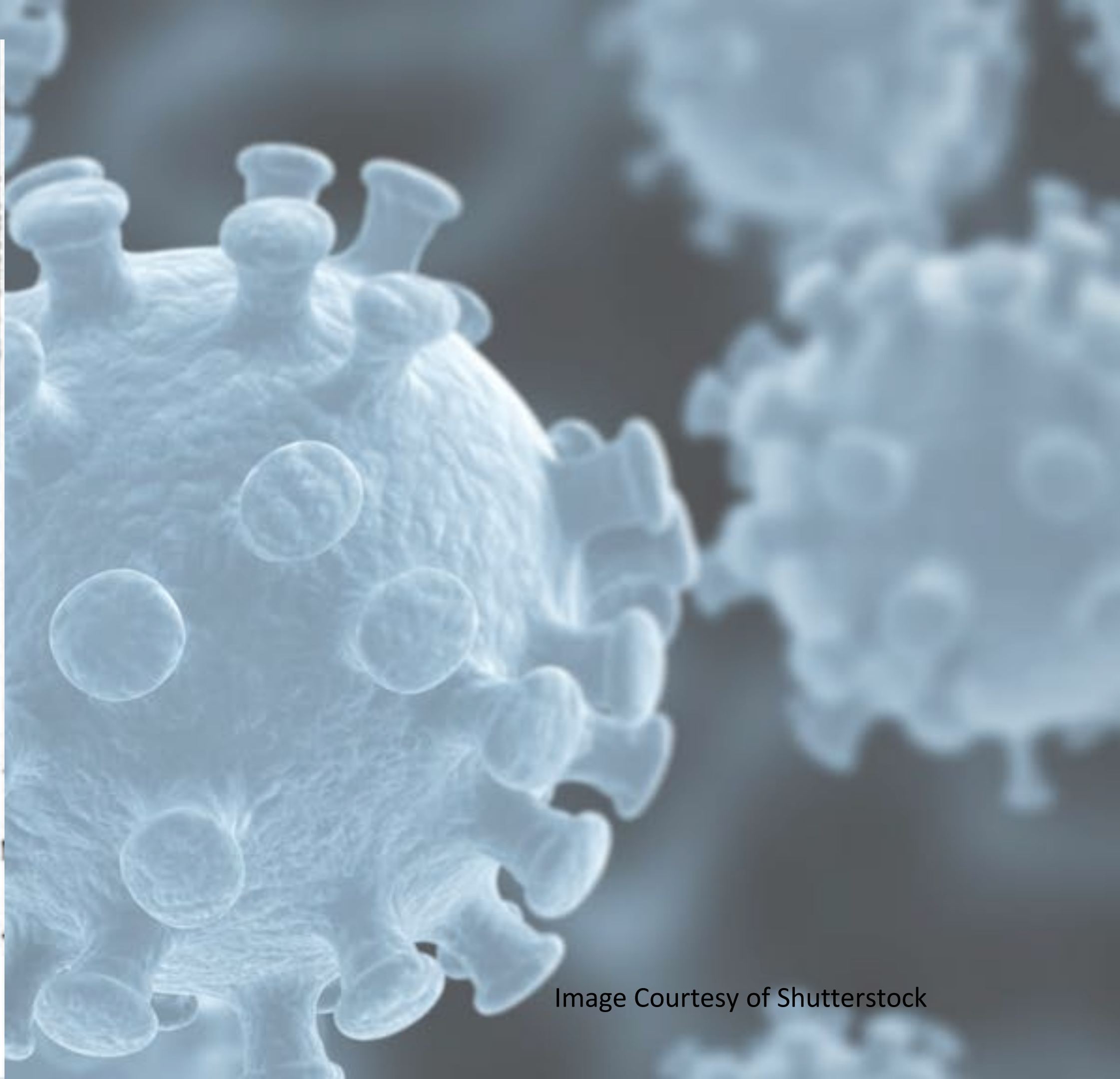
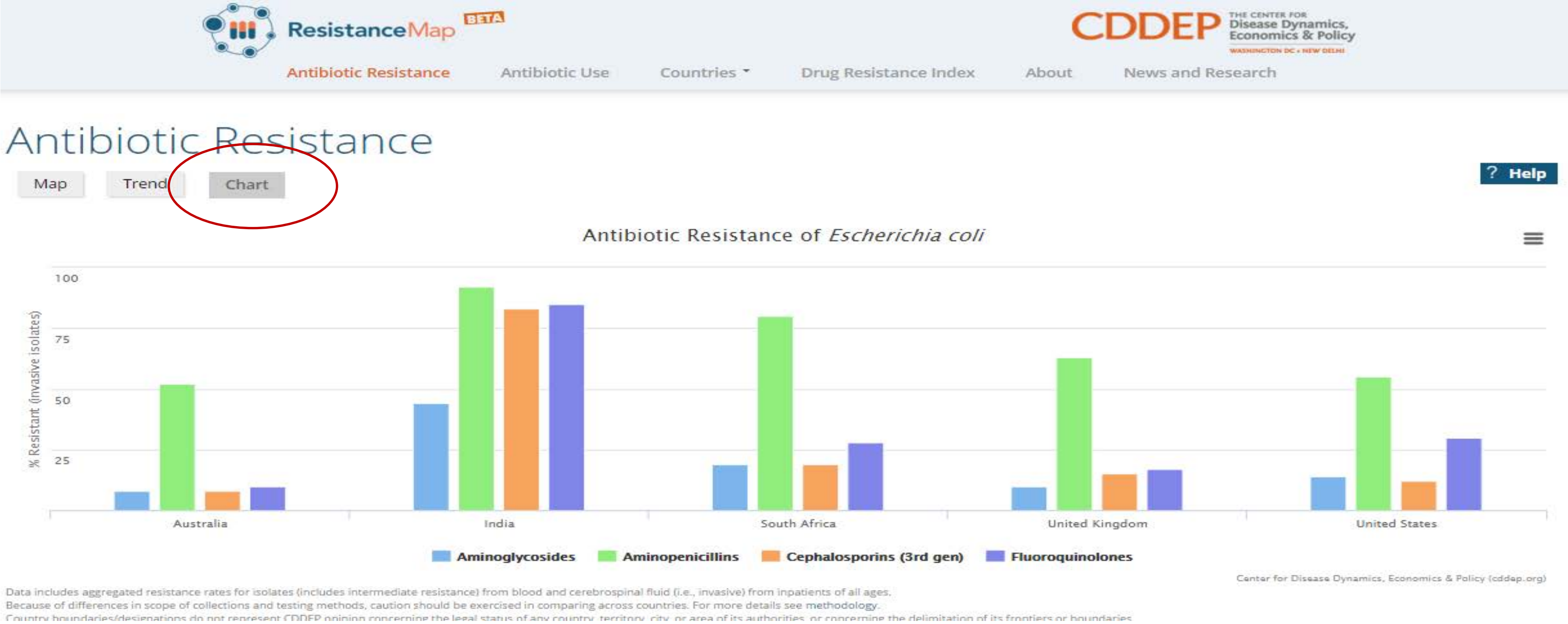


Image Courtesy of Shutterstock

Resistancemap.org

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