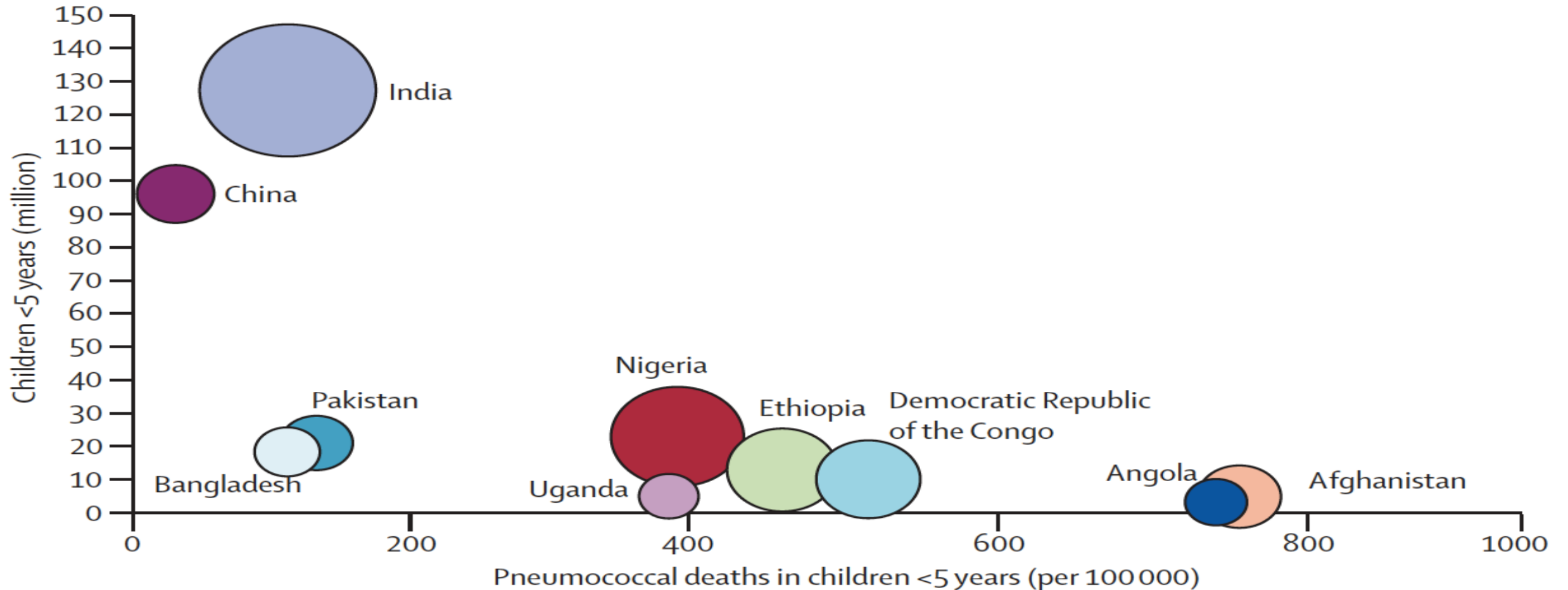


The Global Challenge of Antimicrobial Resistance

Ramanan Laxminarayan
GARP Regional Meeting, Kathmandu

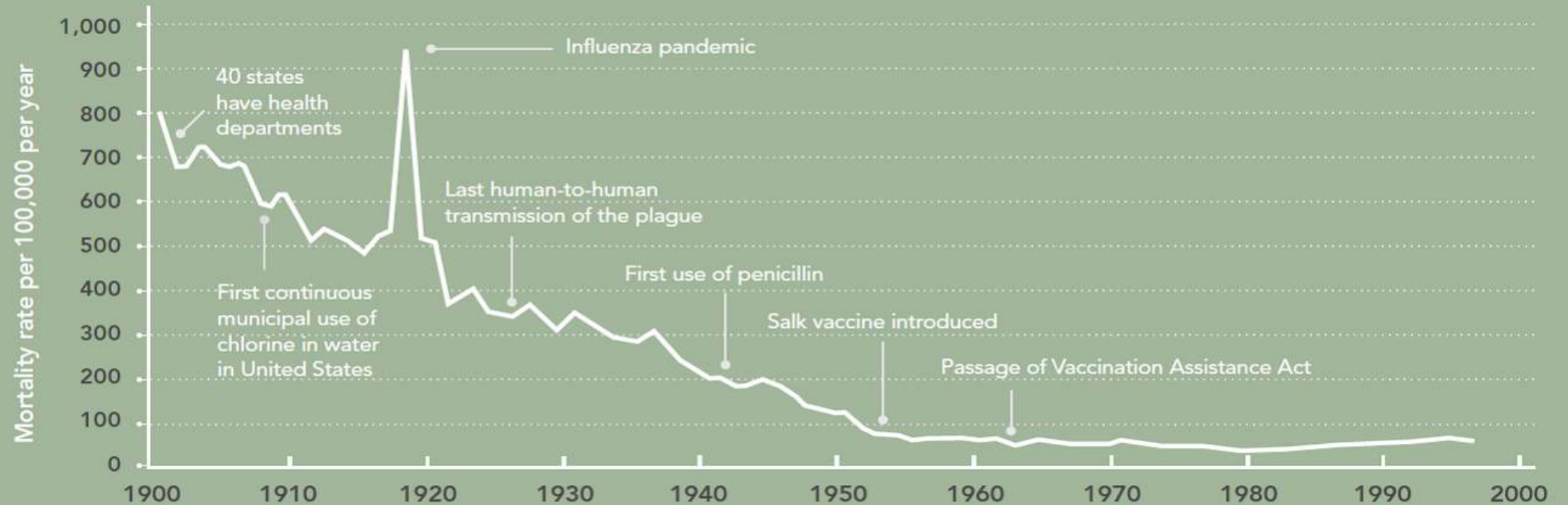
Bacterial diseases are still major killers in developing countries because of lack of access to antibiotics



What are we asking of antibiotics?

FIGURE 1.1

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

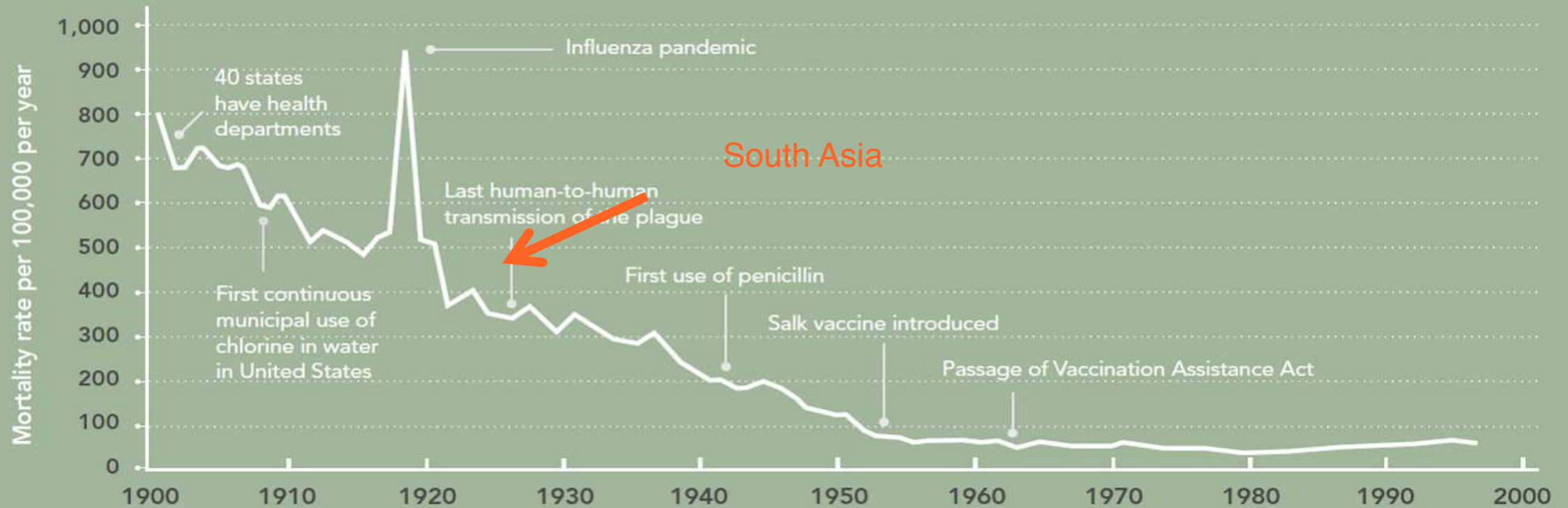


Source: Adapted from Armstrong, Conn et al. (1999).

Substitute for immunization, infection control and water/sanitation

FIGURE 1.1

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

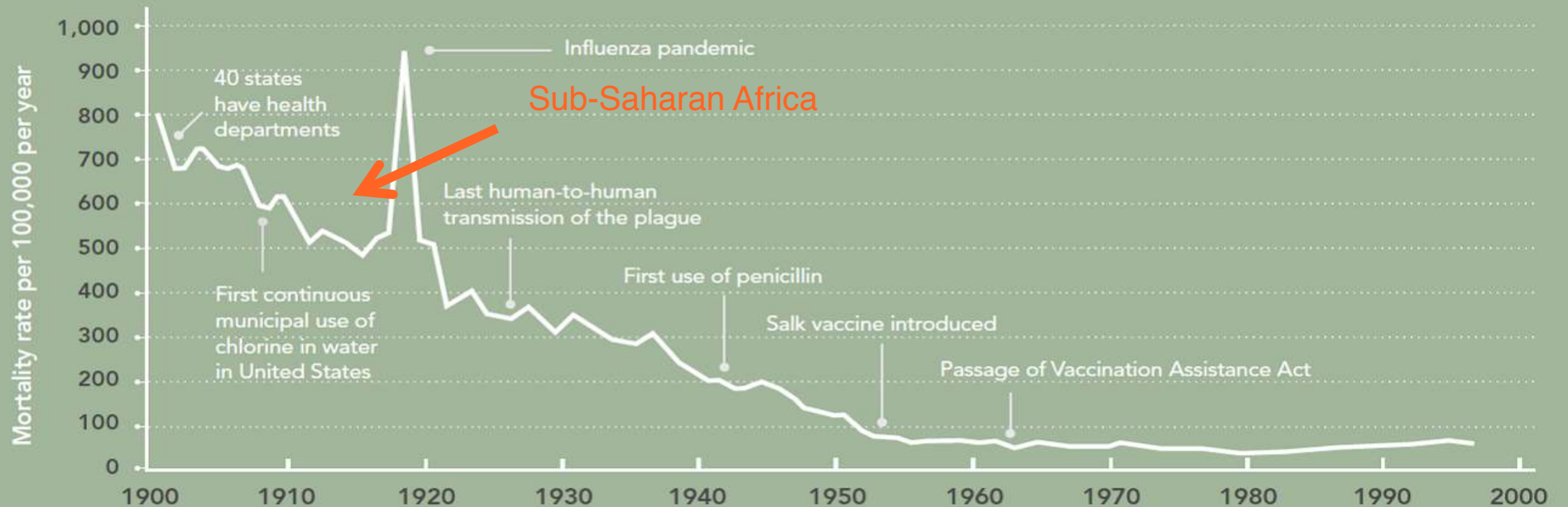


Source: Adapted from Armstrong, Conn et al. (1999).

Substitute for immunization, infection control and water/sanitation

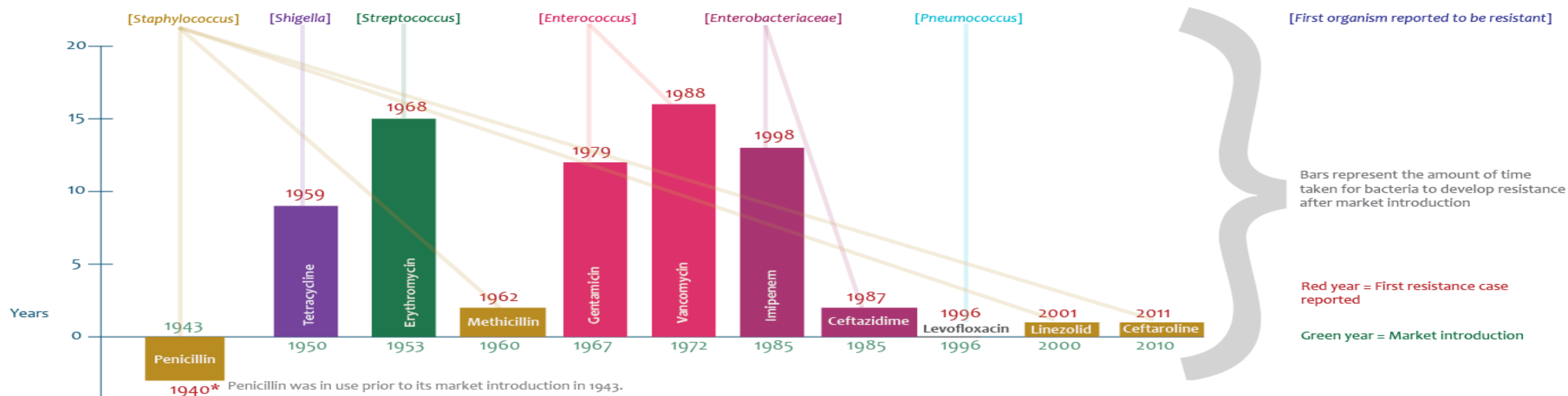
FIGURE 1.1

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



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

First reported cases of bacterial resistance against key antibiotics

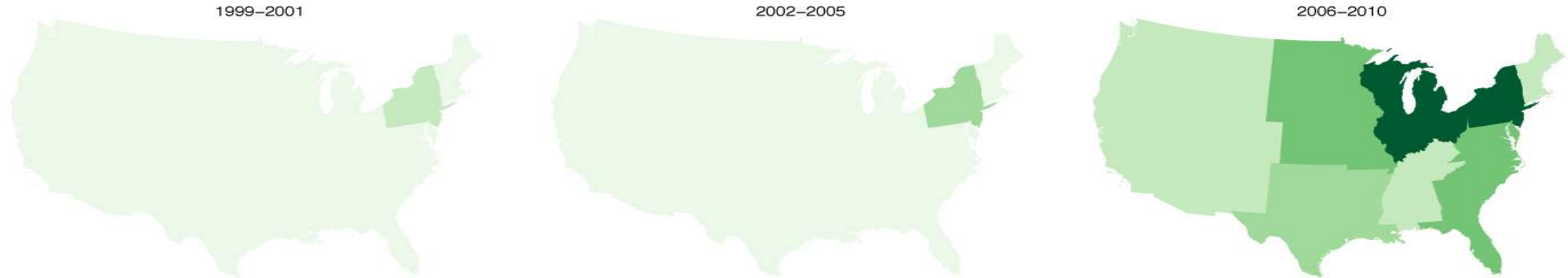


Data source: Antibiotic Resistance Threats in the United States, 2013.
US Centers for Disease Control and Prevention (CDC).



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

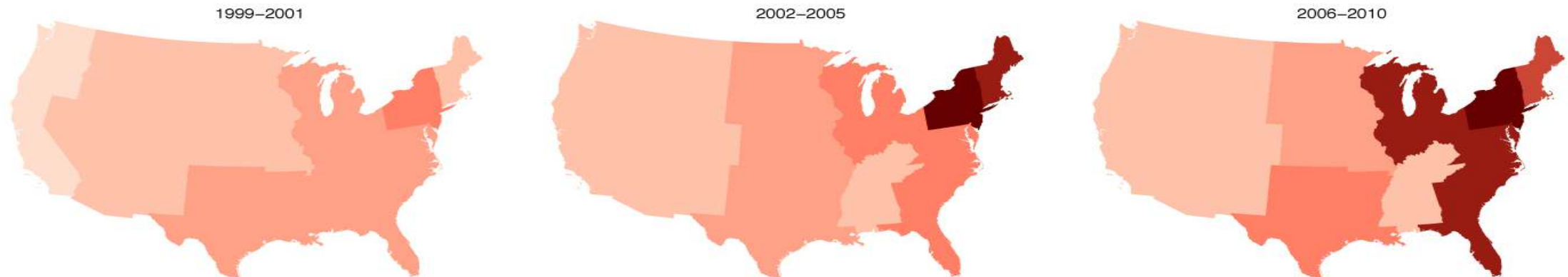
Carbapenem



Proportion of resistant isolates:

0 - .001	.001 - .01	.01 - .02	.02 - .03	.03 - .04	.04 - .05	.05 - 1
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3rd Gen. Cephalosporins



Proportion of resistant isolates:

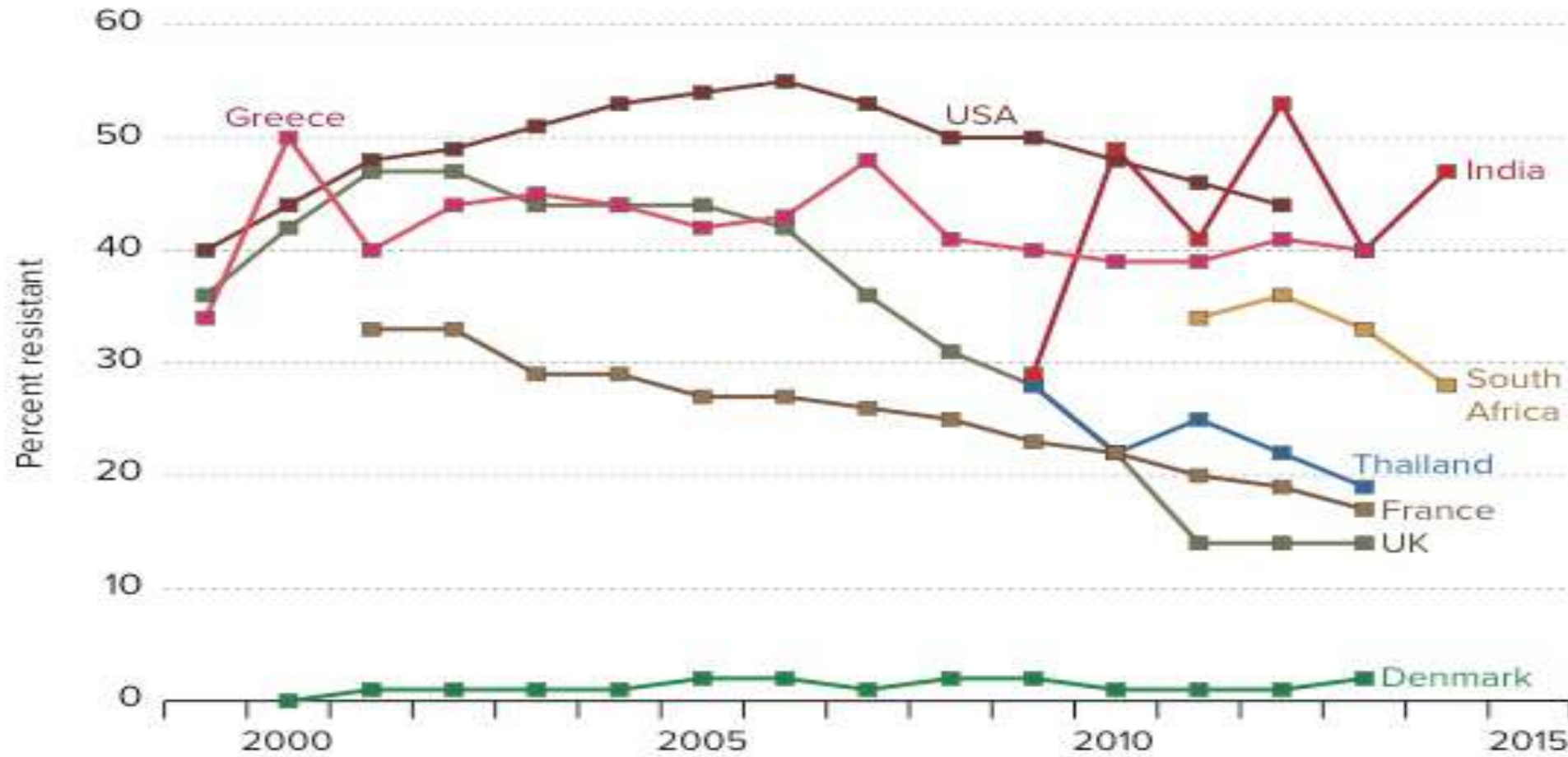
0 - .025	.025 - .05	.05 - .075	.075 - .1	.1 - .125	.125 - .15	.15 - 1
----------	------------	------------	-----------	-----------	------------	---------

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)



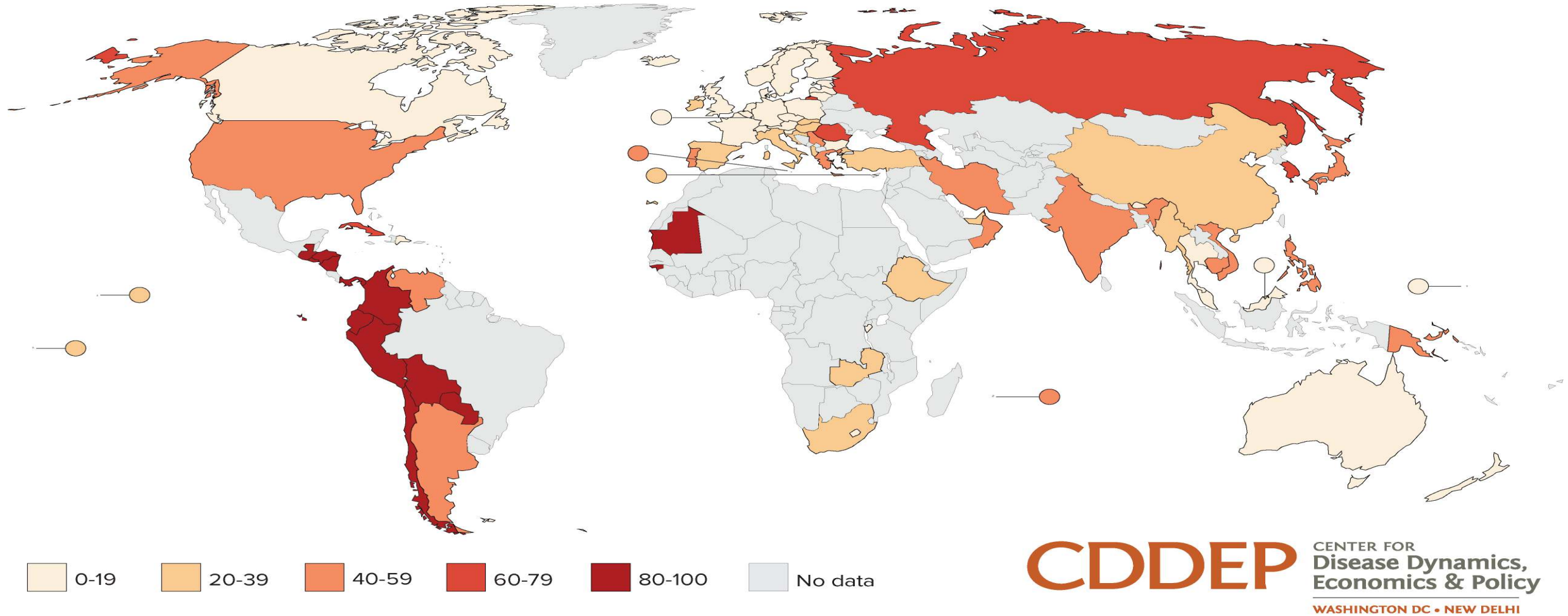
Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014



Source: CDDEP 2015

Depending on the country, resistance to one or more of the following drugs may have been used to test for MRSA: Oxacillin, cefoxitin, flucloxacillin, cloxacillin, dicloxacillin, and methicillin. Intermediate-resistant isolates are included as resistant

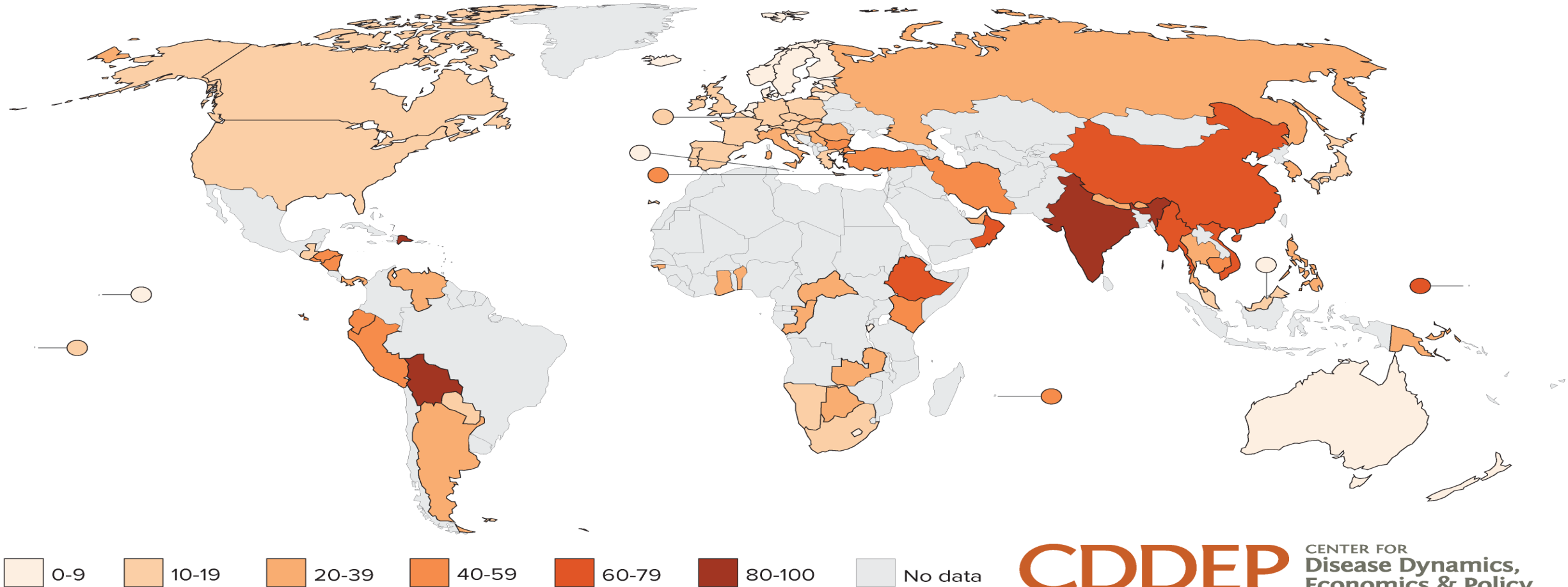
Percentage of *Staphylococcus aureus* that are methicillin resistant (MRSA), by country (most recent year, 2011-14)



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, ceftioxin, 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)

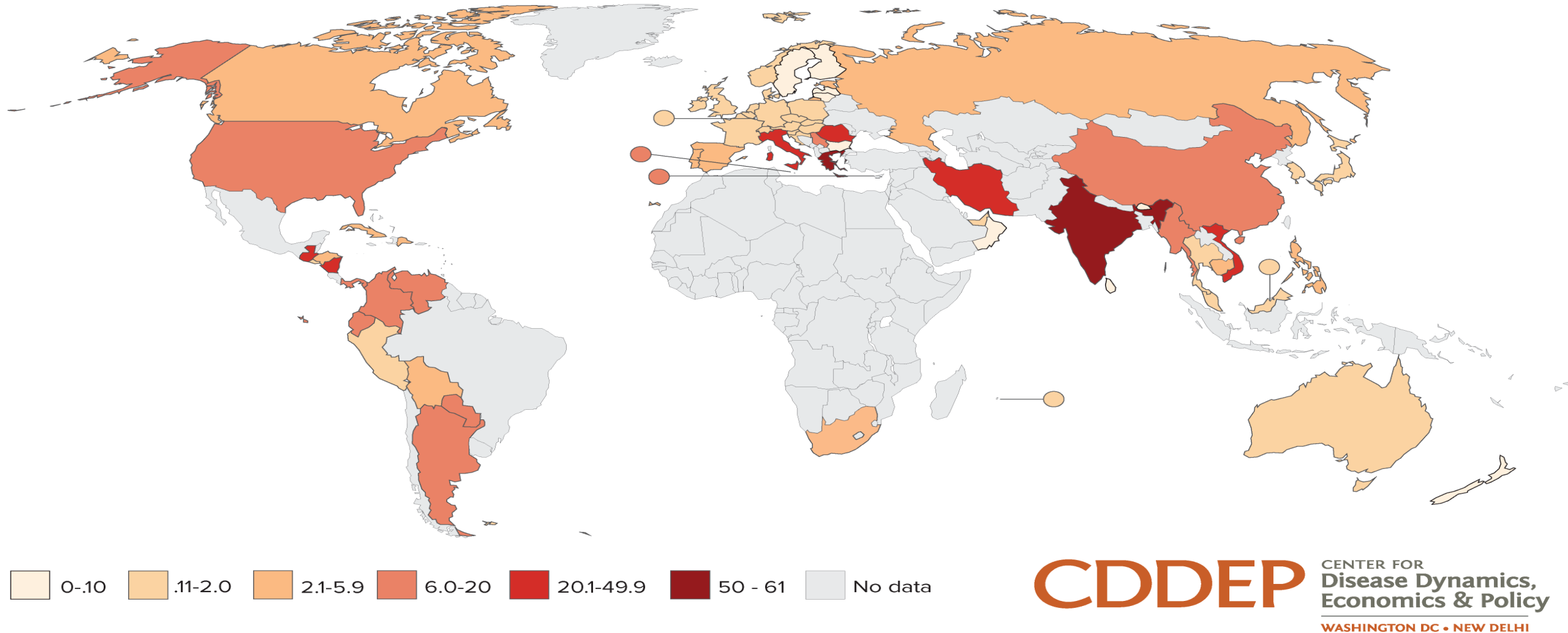


Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

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: Cefotaxime, ceftazidime and ceftriaxone. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

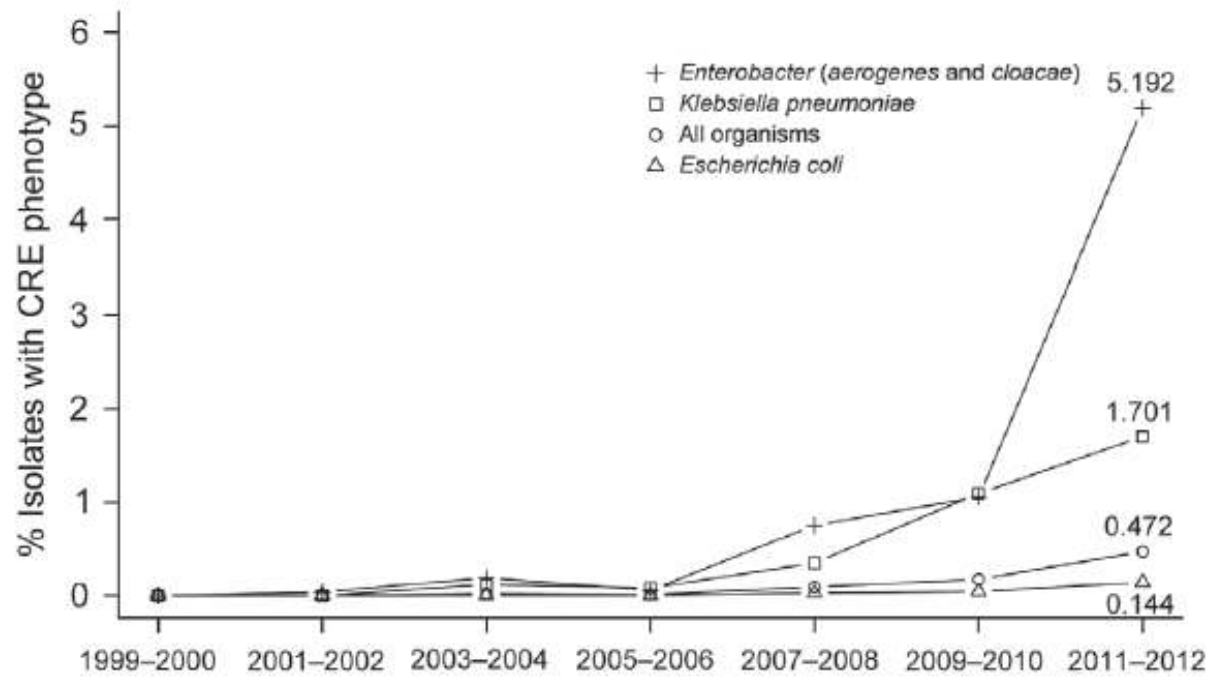
*Indicated by third-generation cephalosporin resistance

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

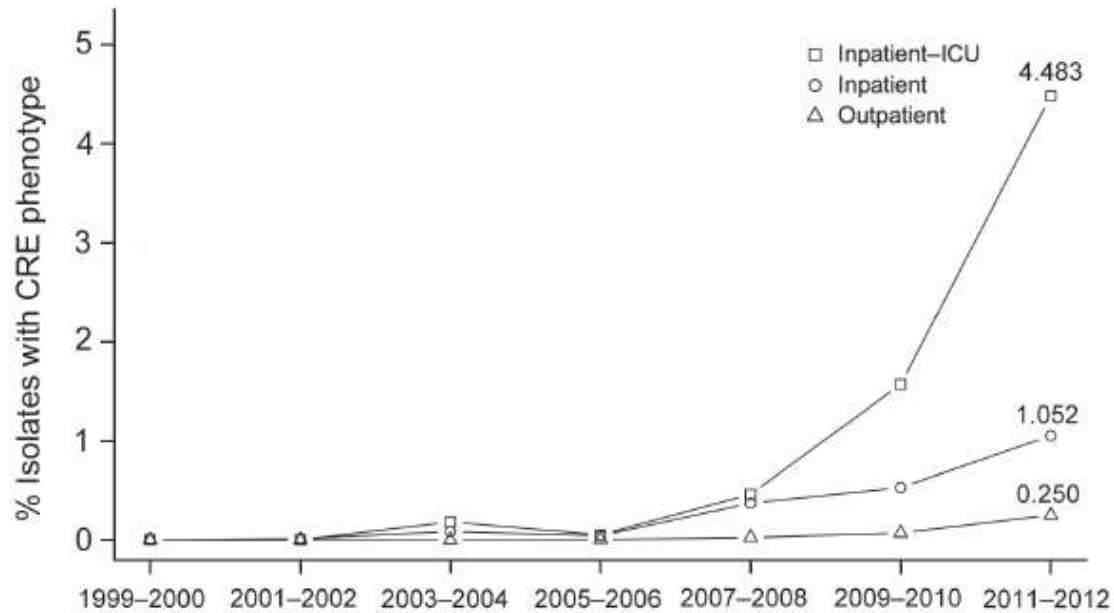


Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

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.

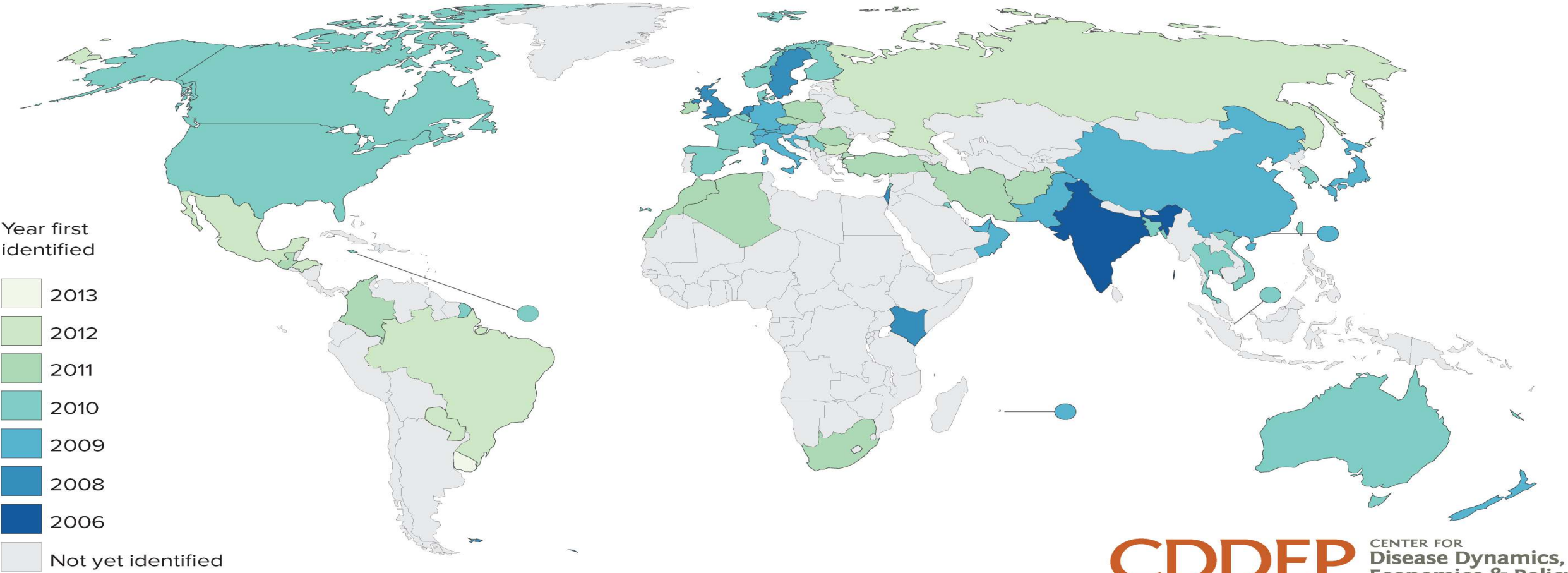


CRE rates in children grew between 2000 and 2012



Logan et al, EID, 2015

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

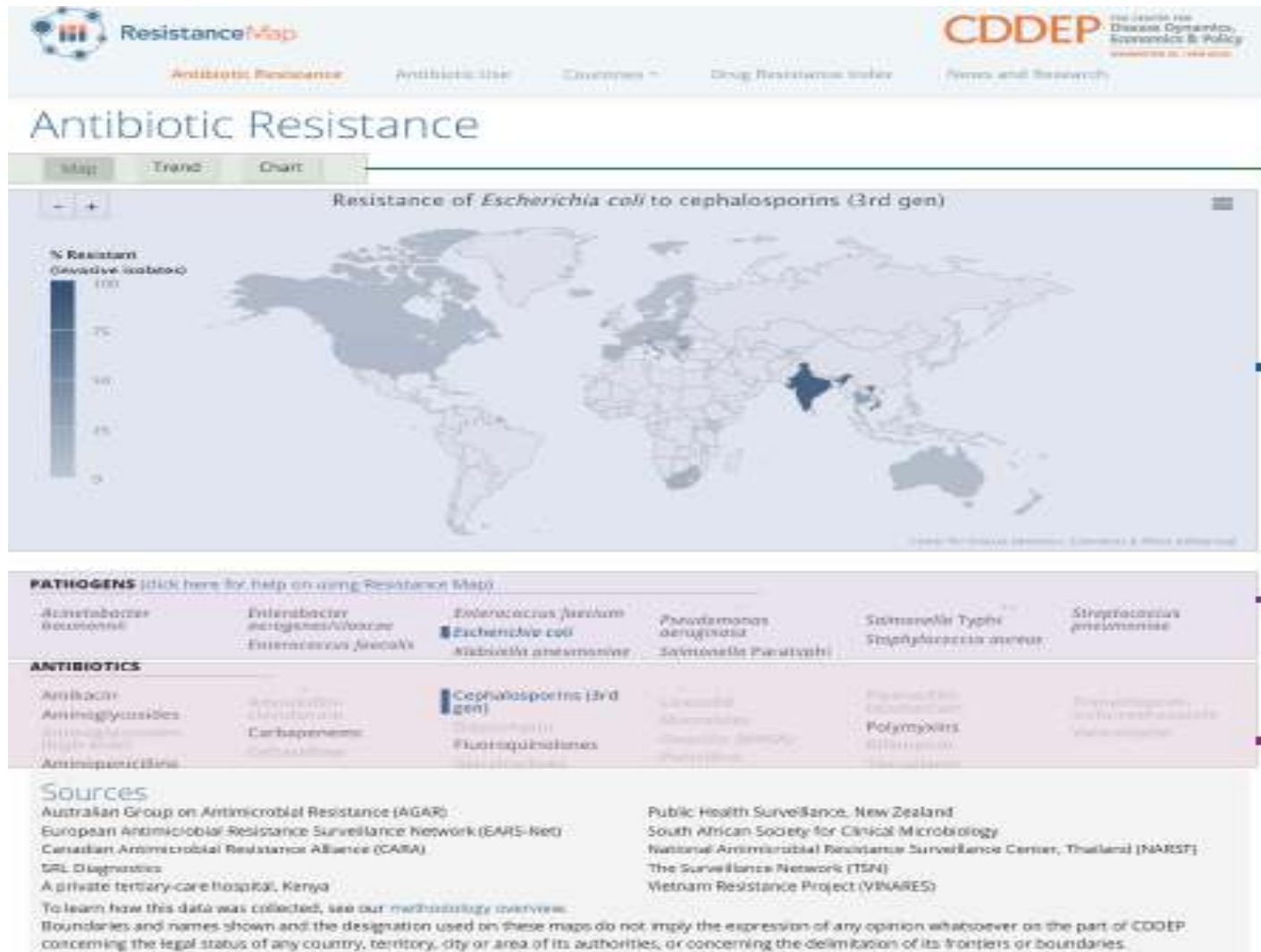


Source: Johnson and Woodford 2013 (adapted)

Clonal spread of *S. pneumoniae* 23F



ResistanceMap webpage



Select map, trend or chart.

The landing view on the resistance section displays a map with the most recent resistance data. By default, *E. coli*'s resistance is displayed.

Click on a pathogen to explore its resistance.

Antibiotics that have resistance data available are displayed in black. Antibiotic whose data is currently displayed is highlighted in blue.

Resistance rates in various countries on global map



Antibiotic Resistance

Antibiotic Use

Countries ▾

Drug Resistance Index

About

News and Research

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

Antibiotic Resistance

Map

Trend

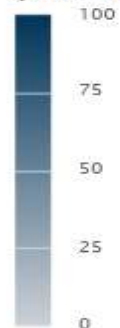
Chart

? Help



Resistance of *Escherichia coli* to Fluoroquinolones

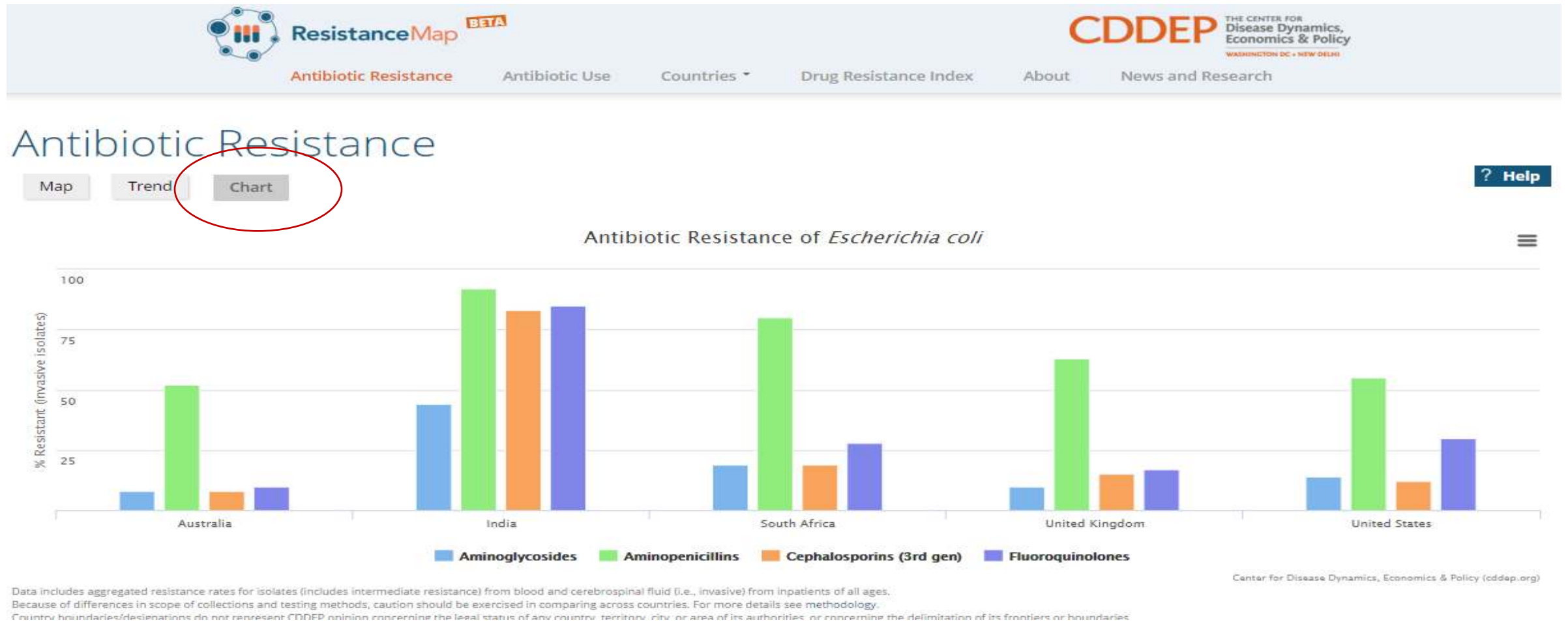
% Resistant
(invasive isolates)



Data includes aggregated resistance rates for isolates (includes intermediate resistance) from blood and cerebrospinal fluid (i.e., invasive) from inpatients of all ages. Because of differences in scope of collections and testing methods, caution should be exercised in comparing across countries. For more details see methodology. Country boundaries/designations do not represent CDDEP opinion concerning the legal status of any country, territory, city, or area of its authorities, or concerning the delimitation of its frontiers or boundaries.

Center for Disease Dynamics, Economics & Policy (cddep.org)

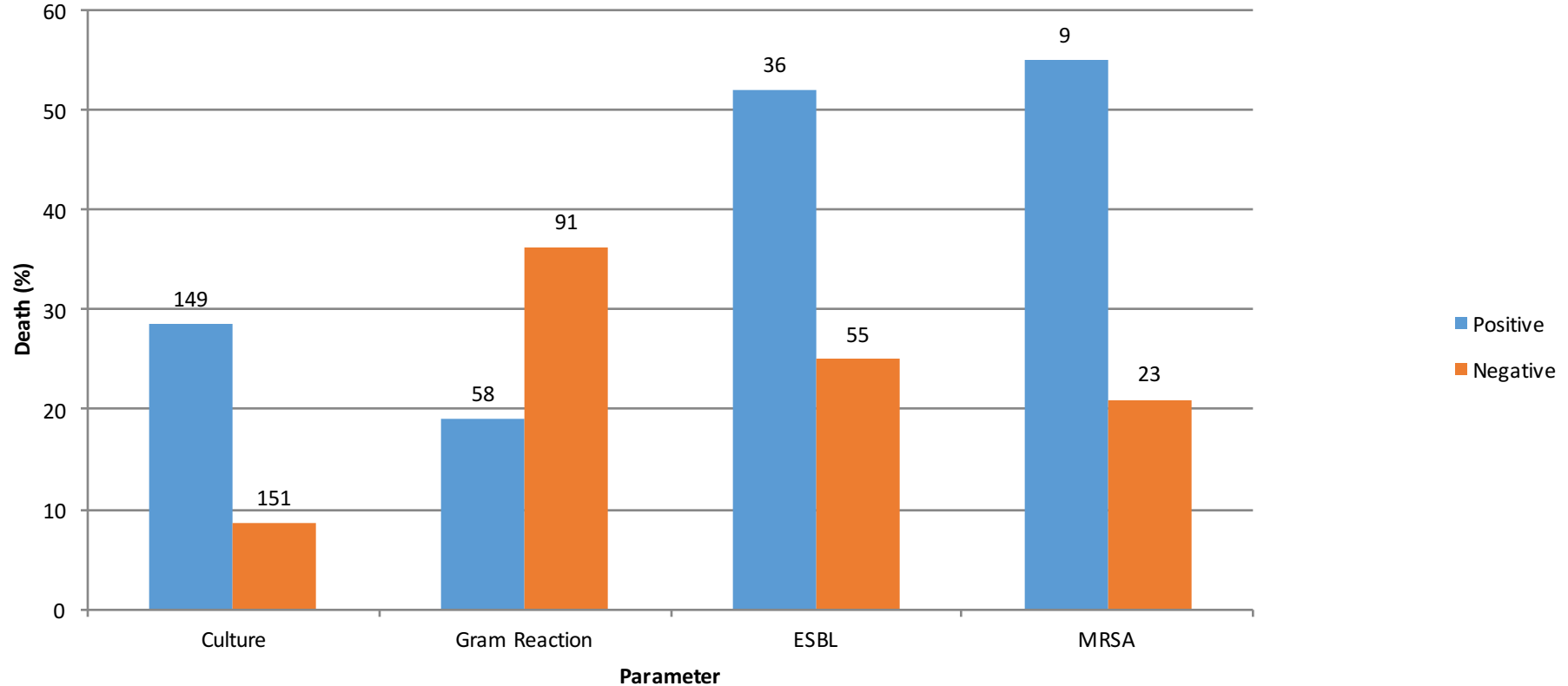
Resistance rates comparison among countries



Where does the burden of
resistance lie?

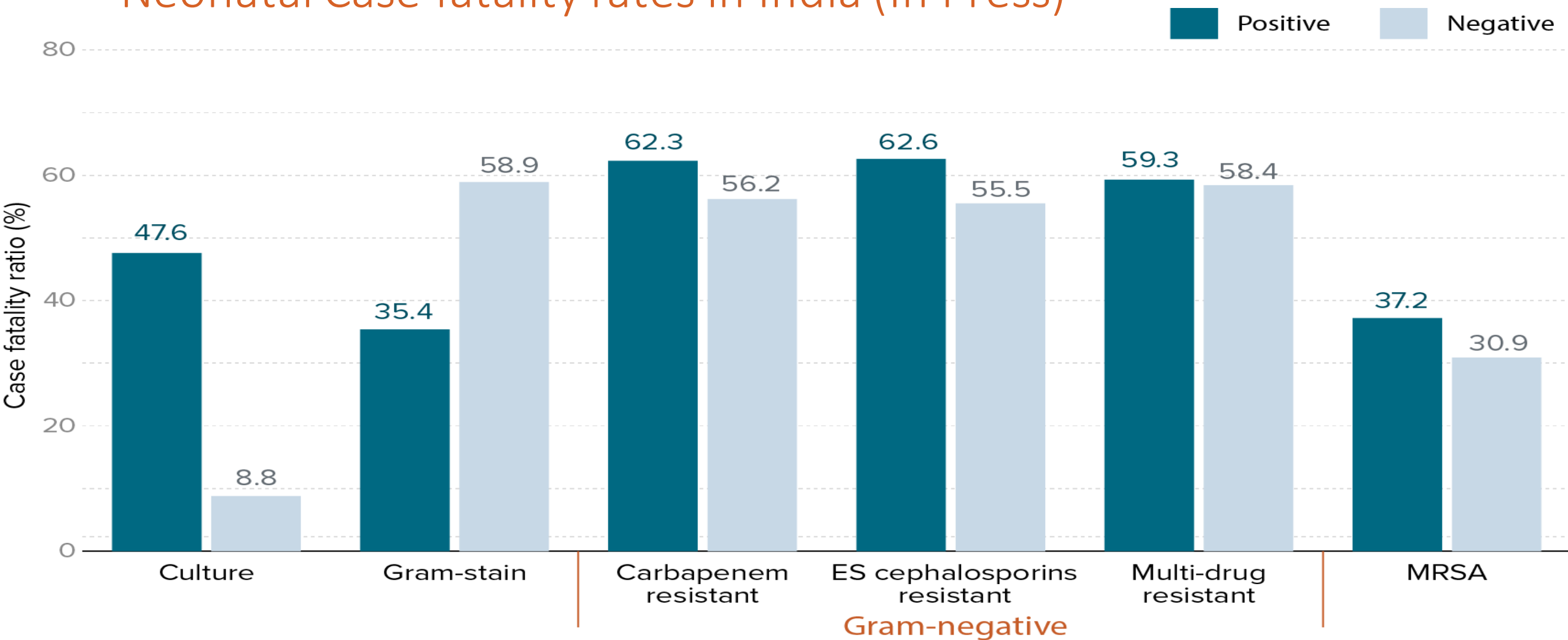
Neonatal sepsis – 421,000 deaths
globally

Mortality outcomes are worse in neonates with resistant infections

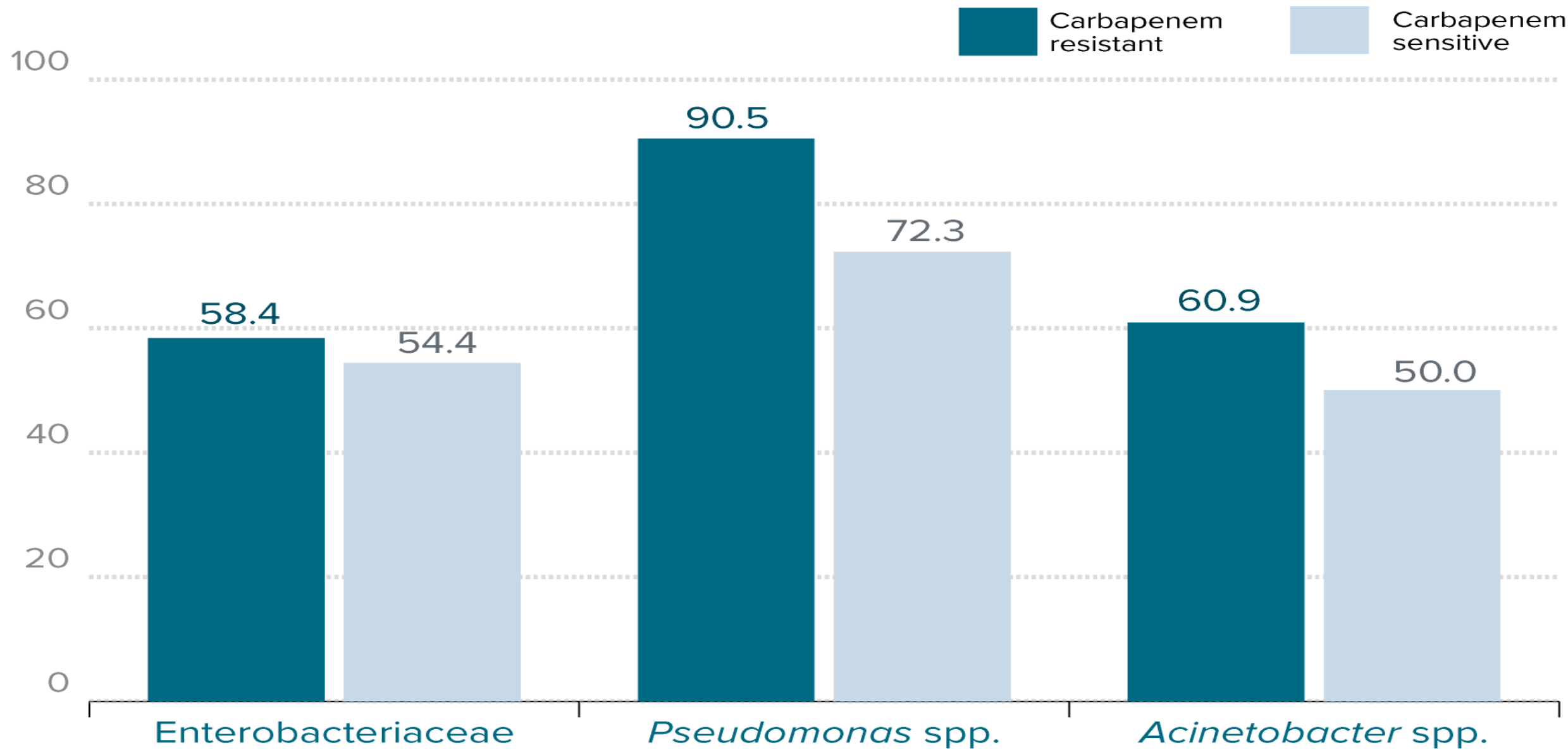


Kayange M, Kamugisha E, Mwizamholya DL, Jeremiah S, Mshana SE. 2010. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza- Tanzania. BMC Pediatrics 10: 39.

Neonatal Case fatality rates in India (In Press)



Case fatality ratio (%)



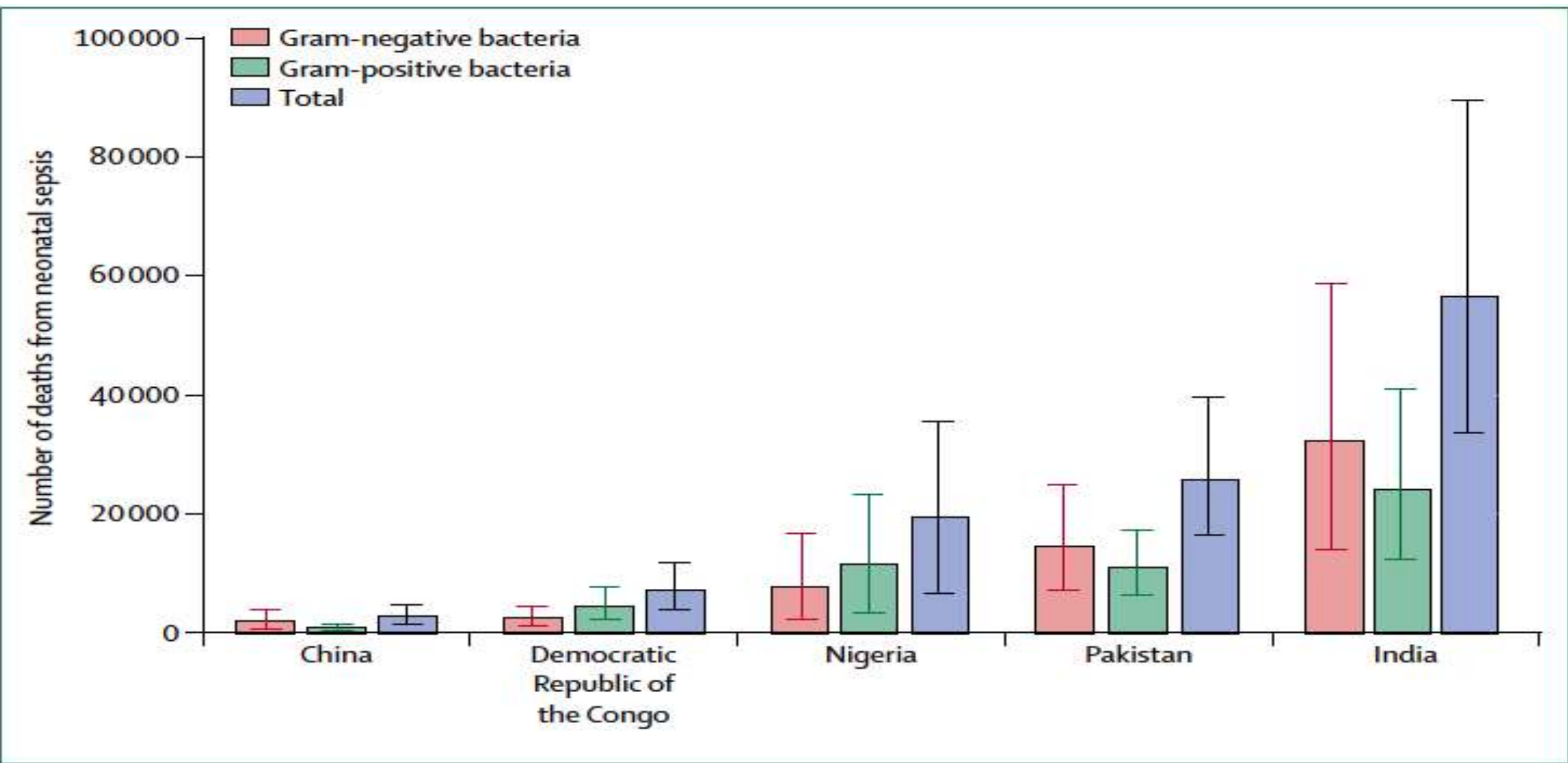


Figure 2: Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries

Laxminarayan et al Lancet, 2015



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

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,

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 take-down 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



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

Typhoid and para typhoid –
400,000 deaths, 16 million cases

Fig. 1. **Distribution of typhoid fever, by age group, at various incidences**

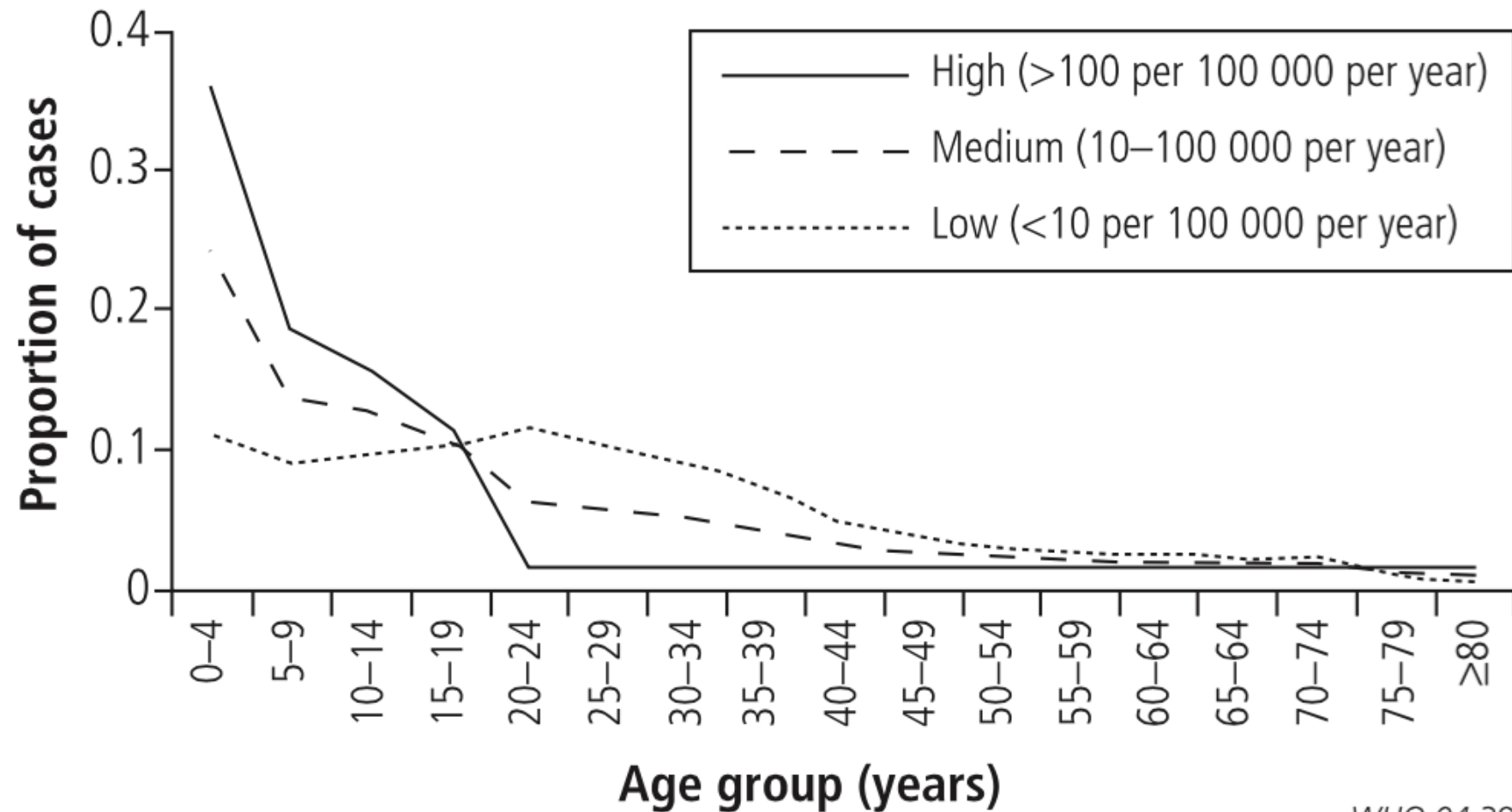
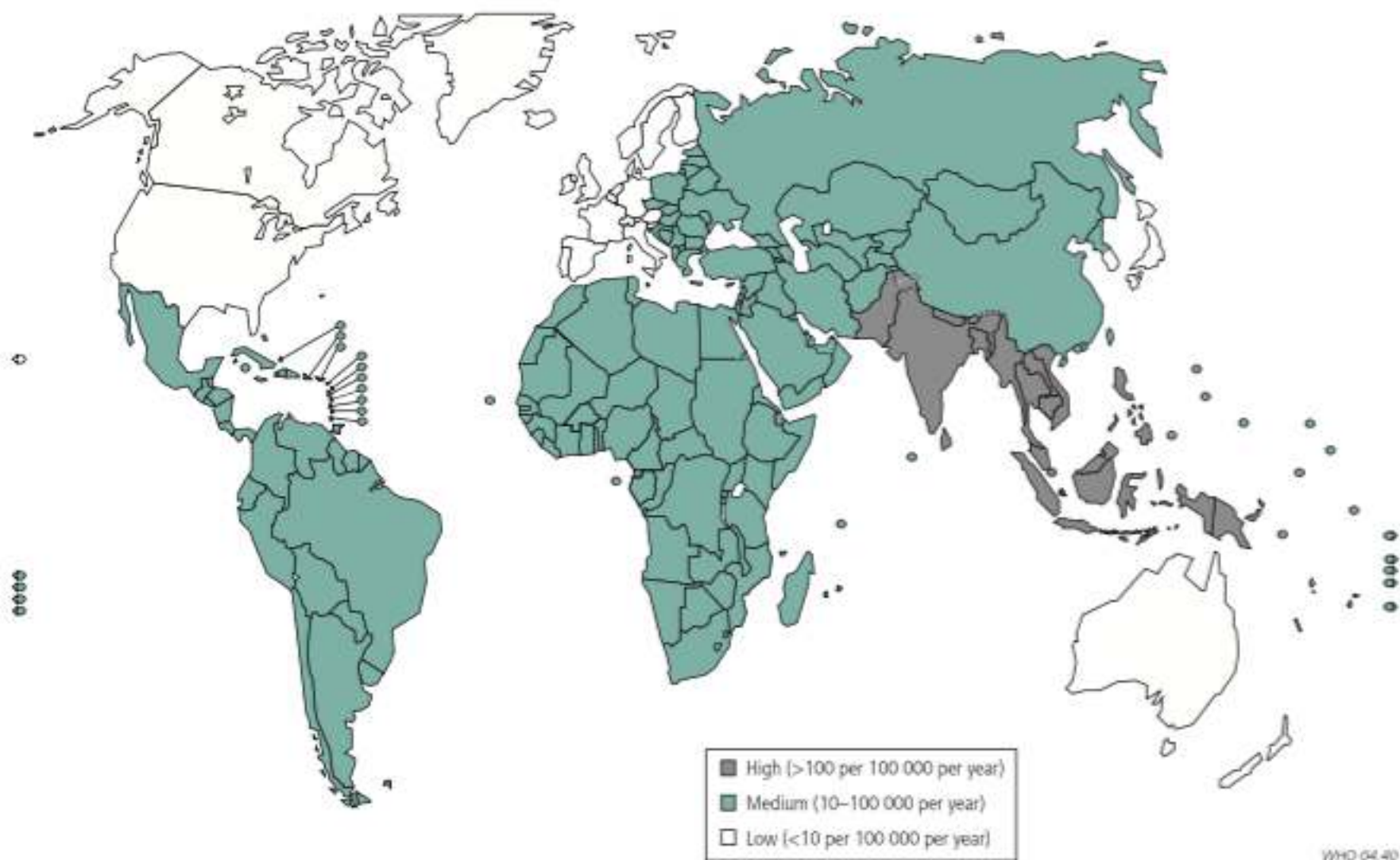


Fig. 2. Geographical distribution of typhoid fever



Antimicrobial resistance and management of invasive *Salmonella* disease



Samuel Kariuki^{a,b,*}, Melita A. Gordon^{c,d}, Nicholas Feasey^{d,e}, Christopher M. Parry^{f,g}

A B S T R A C T

Invasive *Salmonella* infections (typhoidal and non-typhoidal) cause a huge burden of illness estimated at nearly 3.4 million cases and over 600,000 deaths annually especially in resource-limited settings. Invasive non-typhoidal *Salmonella* (iNTS) infections are particularly important in immunosuppressed populations especially in sub-Saharan Africa, causing a mortality of 20–30% in vulnerable children below 5 years of age. In these settings, where routine surveillance for antimicrobial resistance is rare or non-existent, reports of 50–75% multidrug resistance (MDR) in NTS are common, including strains of NTS also resistant to fluoroquinolones and 3rd generation cephalosporins. Typhoid (enteric) fever caused by *Salmonella* Typhi and *Salmonella* Paratyphi A remains a major public health problem in many parts of Asia and Africa. Currently over a third of isolates in many endemic areas are MDR, and diminished susceptibility or resistance to fluoroquinolones, the drugs of choice for MDR cases over the last decade is an increasing problem. The situation is particularly worrying in resource-limited settings where the few remaining effective antimicrobials are either unavailable or altogether too expensive to be afforded by either the general public or by public health services. Although the prudent use of effective antimicrobials,

Resistance is increasing and associated with worse outcomes

- In Kenya, proportion of *S typhi* in Kenya that are multidrug resistant and resistant to nalidixic acid and with decreased susceptibility to fluoroquinolones had risen from 1% in 2000 to nearly 25% in 2008.
- Fluoroquinolone resistance is increasing in India (44%) and Pakistan (58%).
- Case fatality rates associated with multidrug-resistant *S typhi* in south Asia are 10% (close to the 12.8% recorded in the pre-antibiotic era)
***Lancet Infect Dis* 2005; 5: 481–93**

Surgical site infections – over
400,000 deaths

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.

Maternal deaths caused by sepsis
– about a tenth of all maternal
deaths

Future

DEVELOPMENT

Economics to End Poverty

[Bloggers](#)[Tags](#)[Contact](#)

Are Institutional Births Institutionalizing Deaths?



SUBMITTED BY **JISHNU DAS** ON THU, 11/20/2014
CO-AUTHORS: **JEFFREY HAMMER**

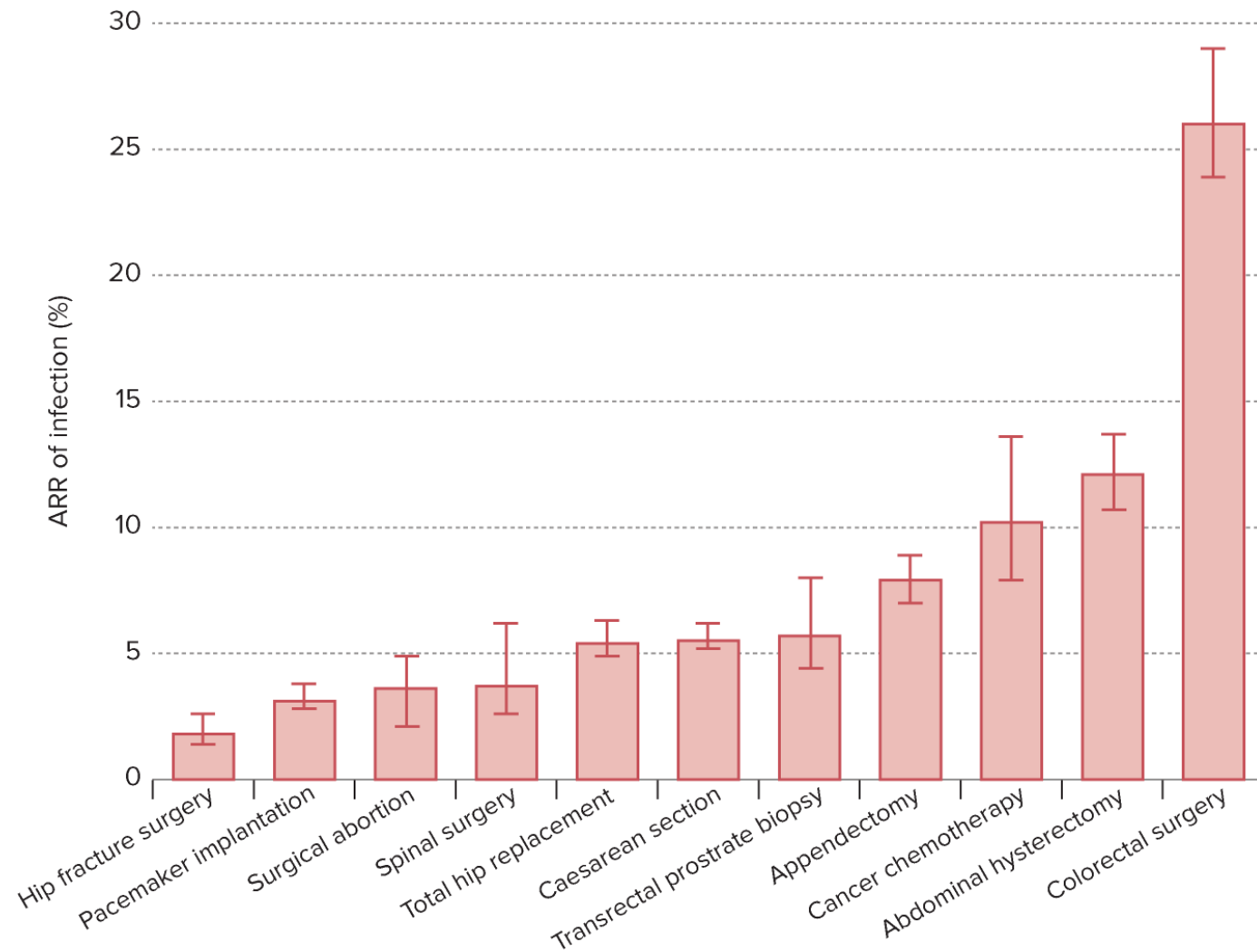
[f Share](#)[Tweet](#)[in SHARE](#)

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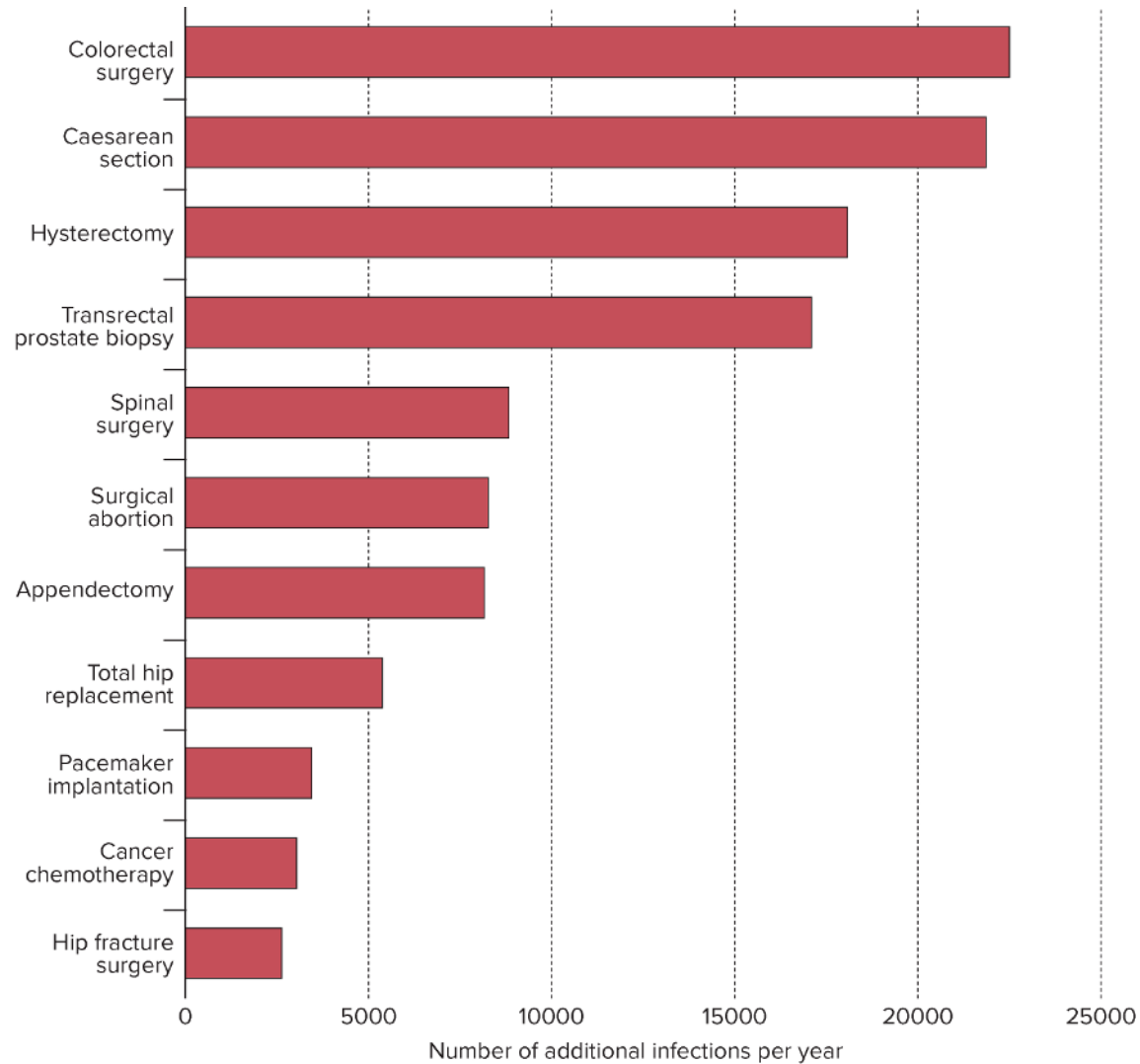


Increasing rates of institutional deliveries place a greater burden on infection standards in health care institutions.

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



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



Malaria – 420,000 deaths

Impact of chloroquine resistance on malaria mortality

Impact de la résistance à la chloroquine sur la mortalité palustre

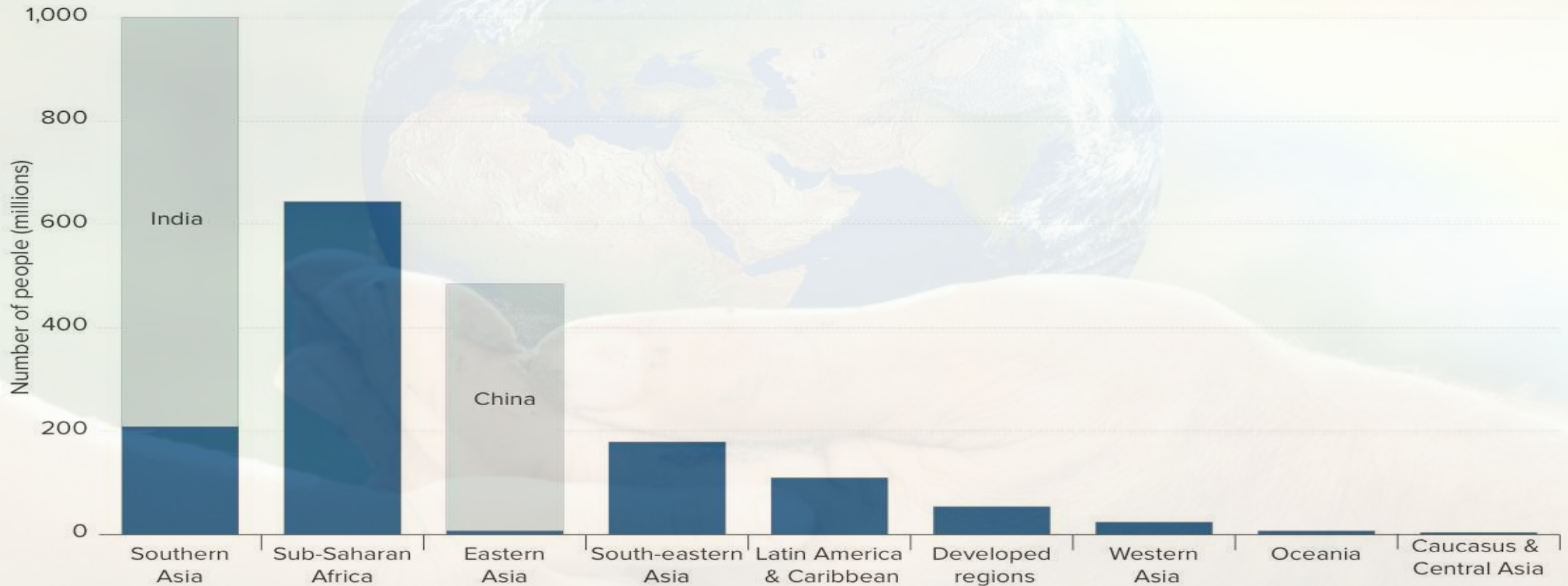
Jean-François Trape^{a*}, Gilles Pison^b, Marie-Pierre Preziosi^c, Catherine Enel^b, Annabel Desgrées du Loû^a, Valérie Delaunay^c, Badara Samb^c, Emmanuel Lagarde^b, Jean-François Molez^a, François Simondon^a

Risk of malaria mortality in children under 10 went up between two and five-fold in three populations in Senegal following emergence of chloroquine resistance.

Anticipated impact of drug resistance in the near term

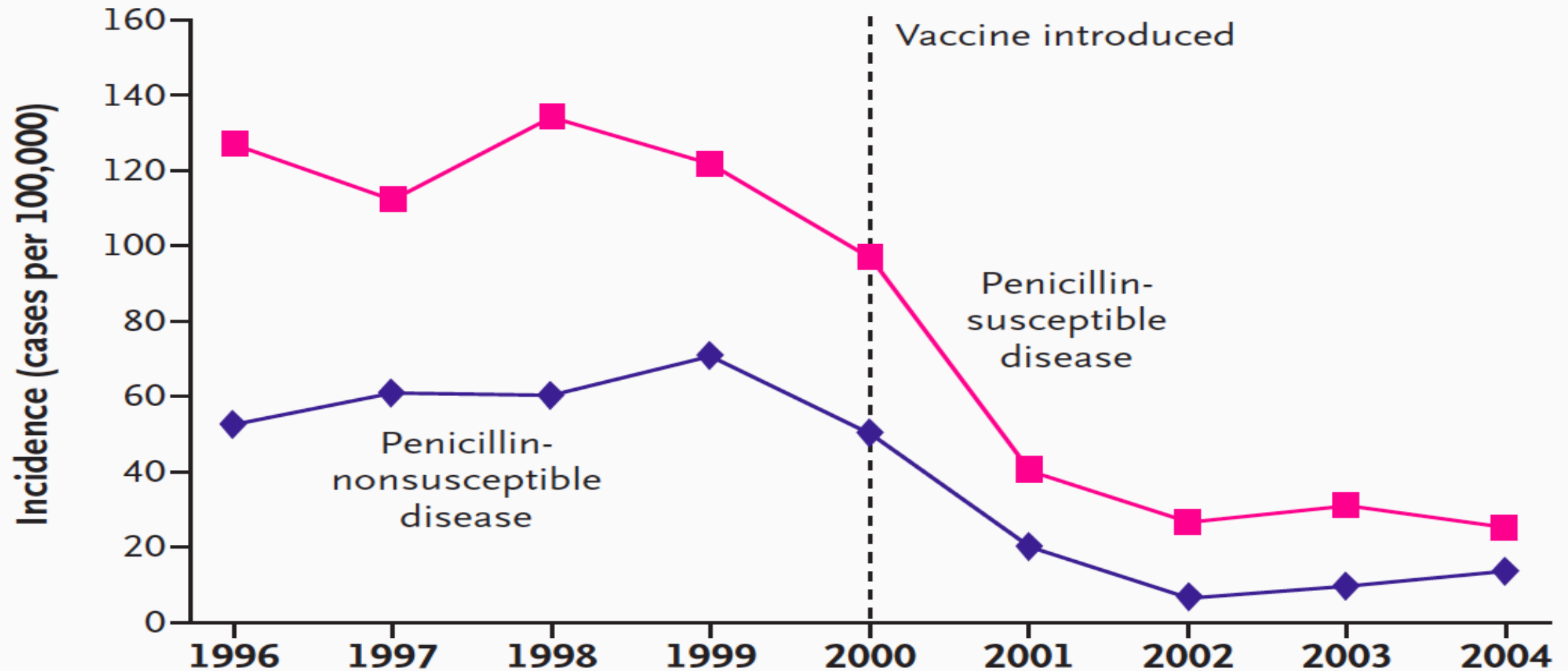
- Neonatal sepsis
- Enteric pathogens
- Surgical site infections
- Maternal mortality associated with obstetrics
- Malaria
- Tuberculosis
- HIV

Population without access to improved sanitation, by MDG region 2012



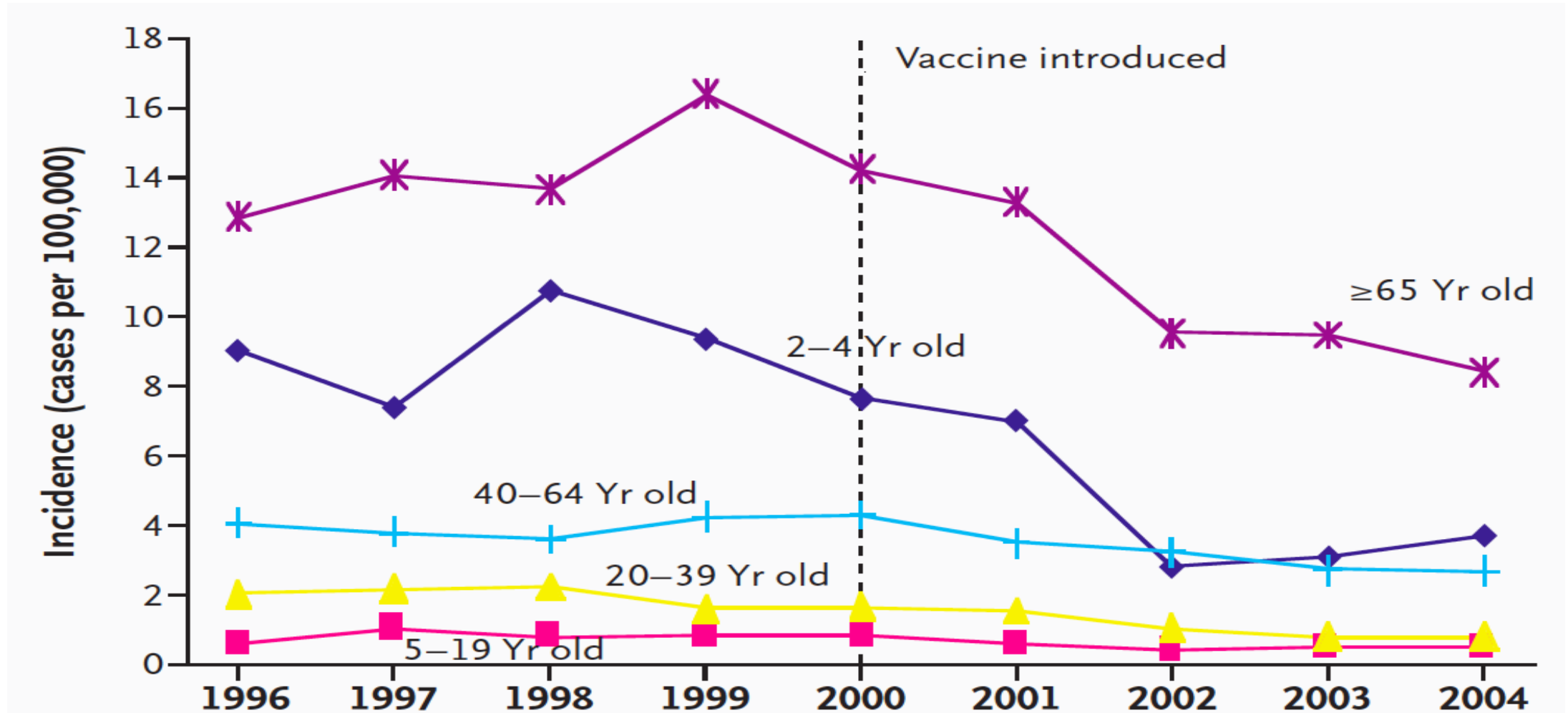
Vaccines can be effective

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



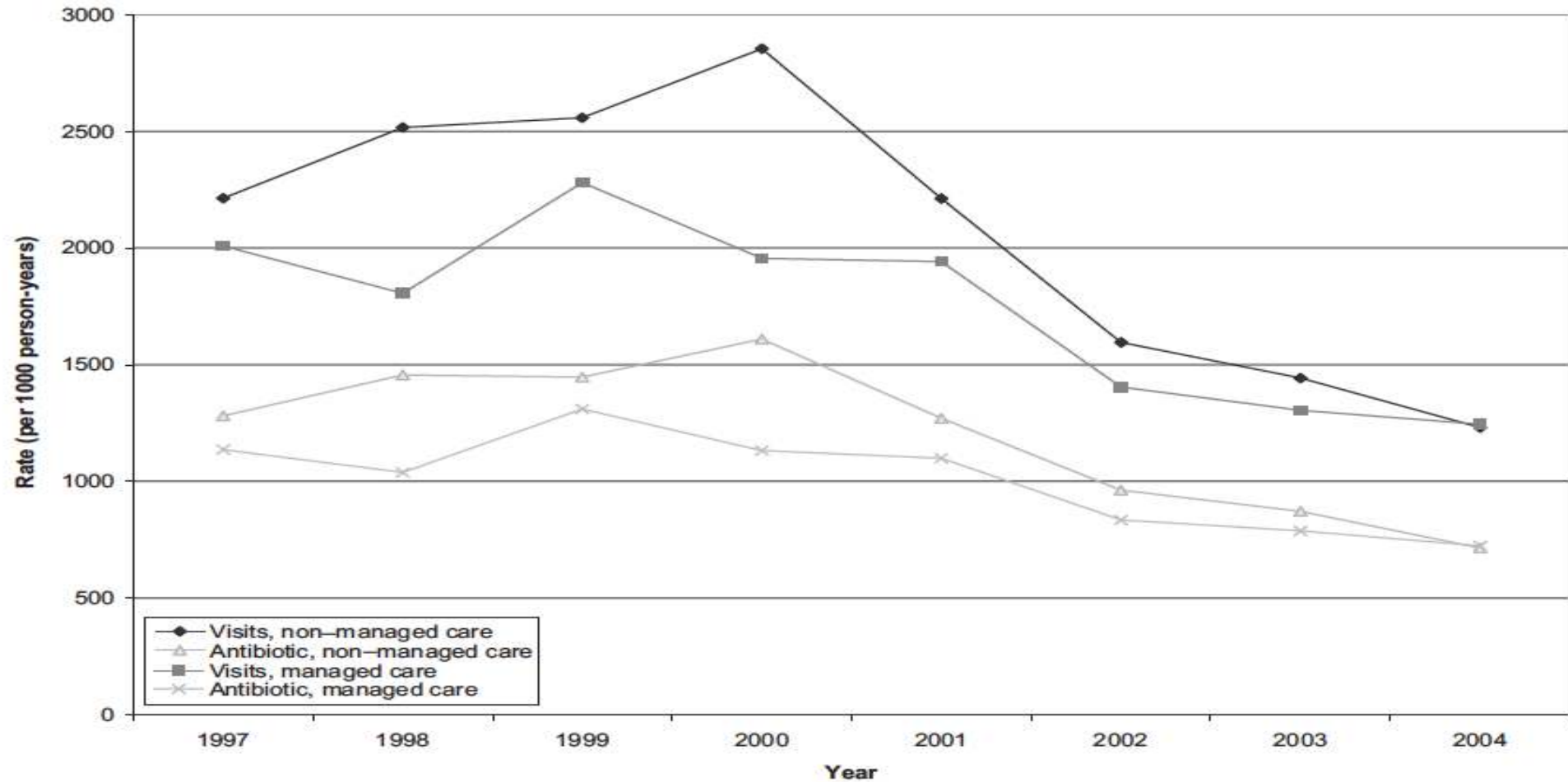
Kyaw MH et al. N Engl J Med 2006;354:1455-1463.

Invasive disease caused by non-susceptible Pneumococci, US



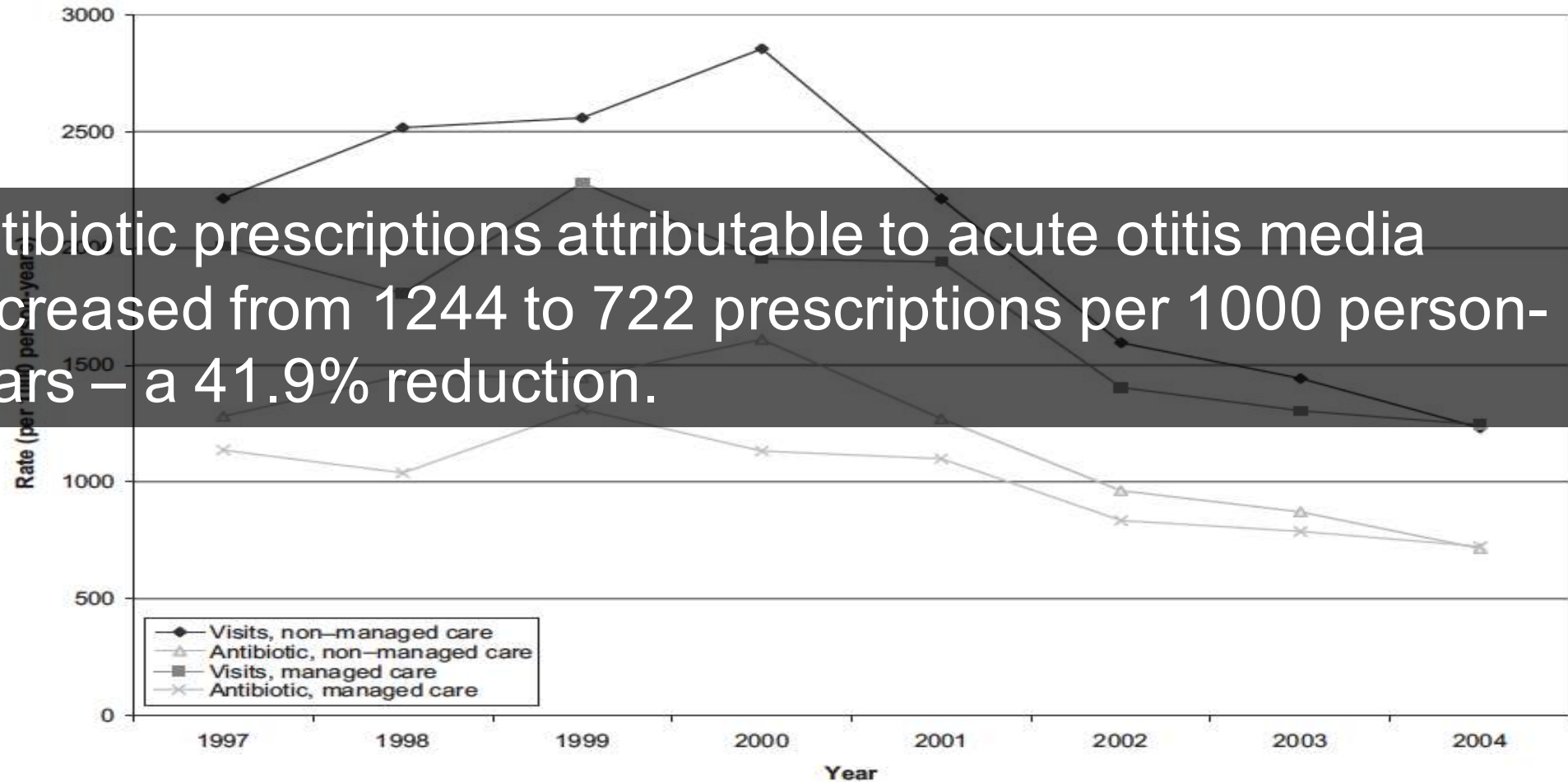
Kyaw MH et al. N Engl J Med 2006;354:1455-1463.

Effect of PCV7 introduction on antibiotic prescriptions and ambulatory care visits



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.



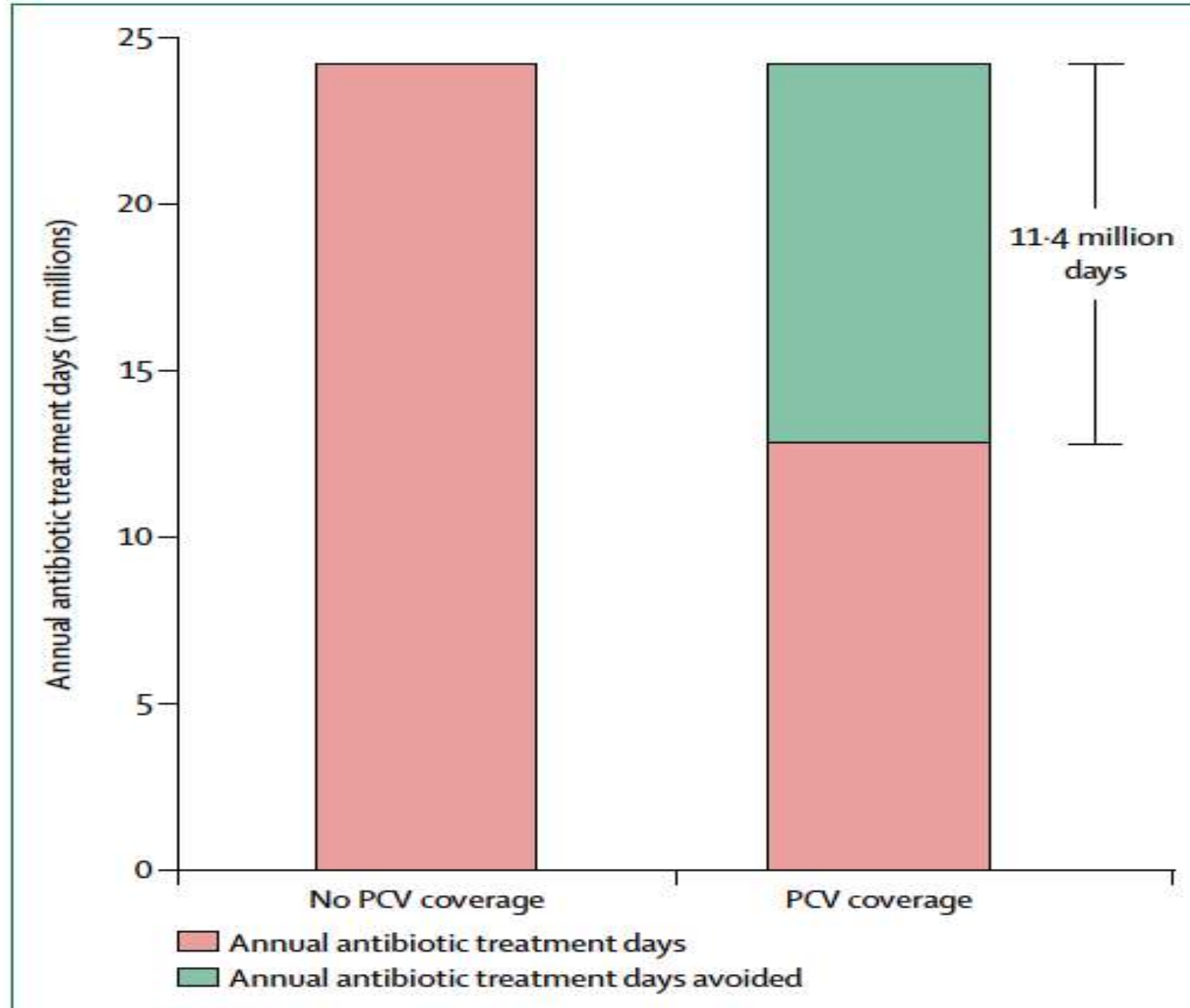
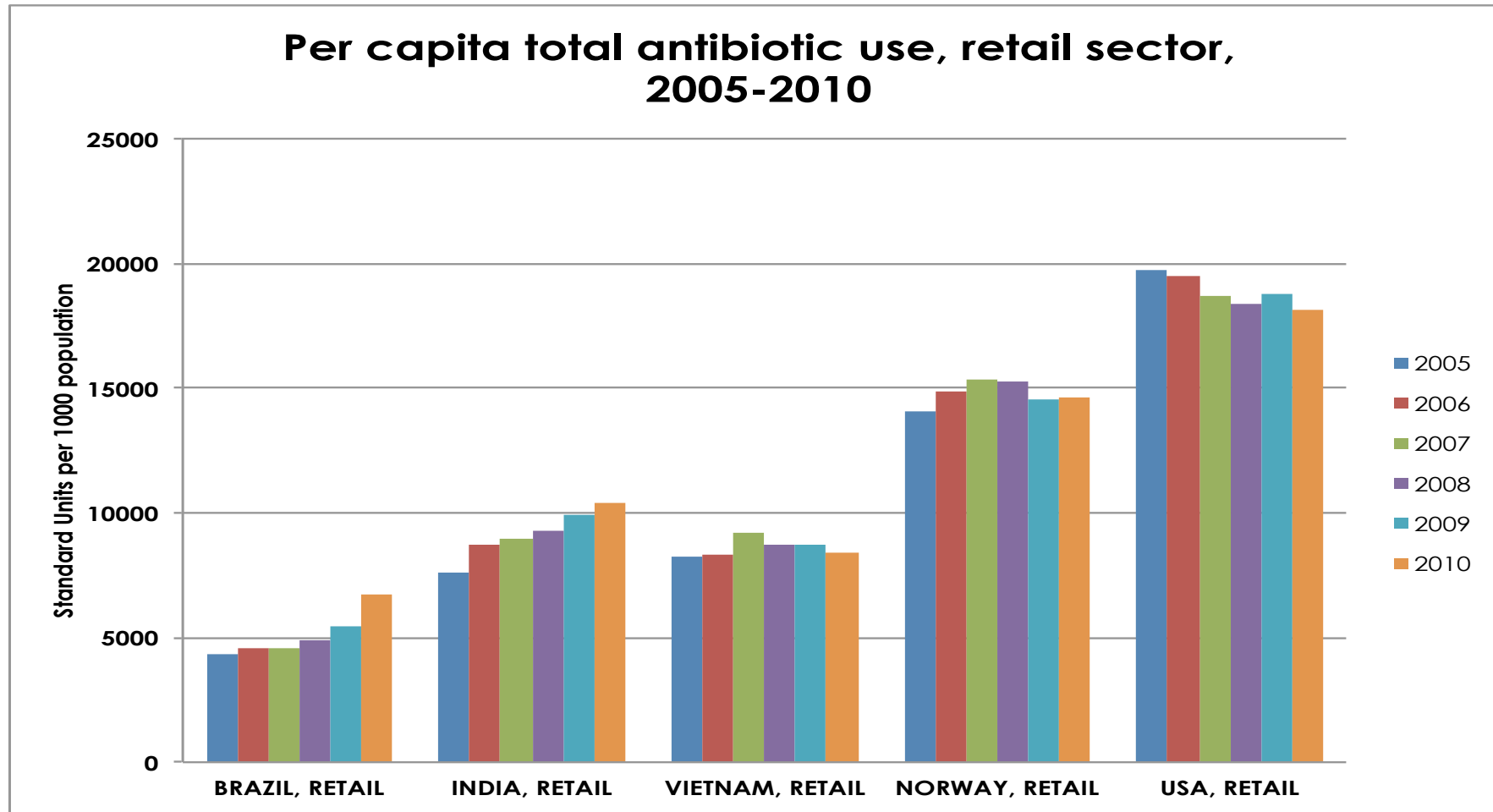


Figure 3: Days on antibiotics for suspected pneumonia, averted by provision of pneumococcal conjugate vaccine (PCV)

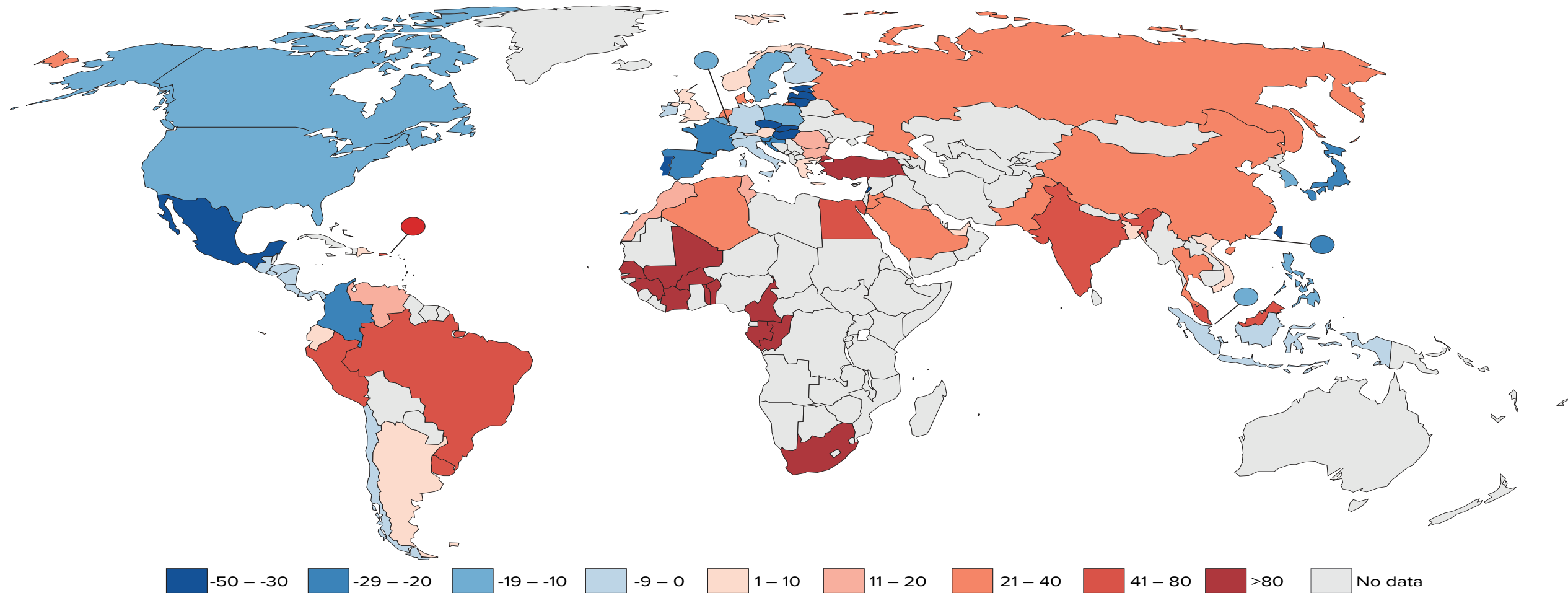
Bar represents antibiotic days avoided with PCV coverage.

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.

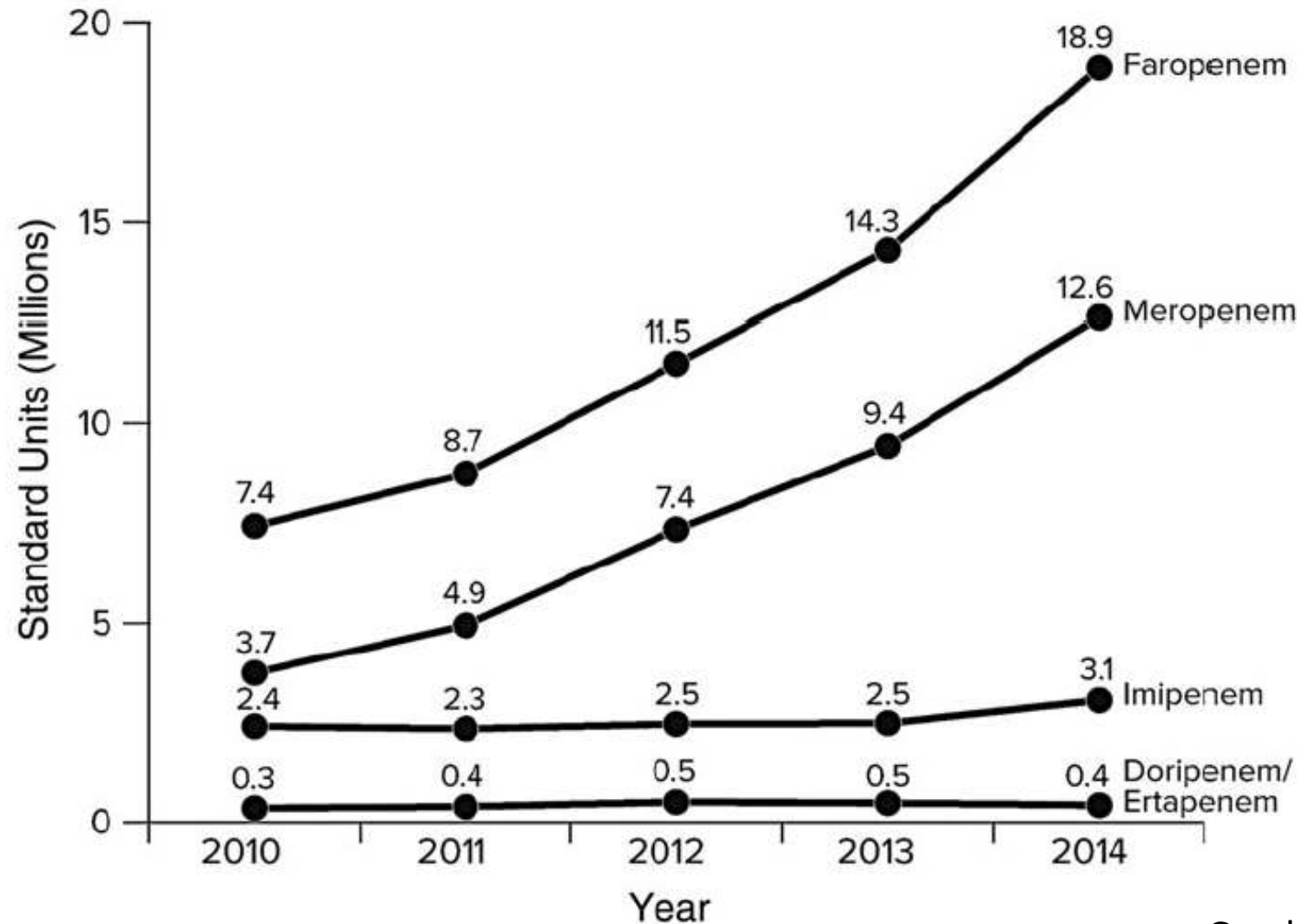
Percentage change in antibiotic consumption per capita 2000–2010*, by country



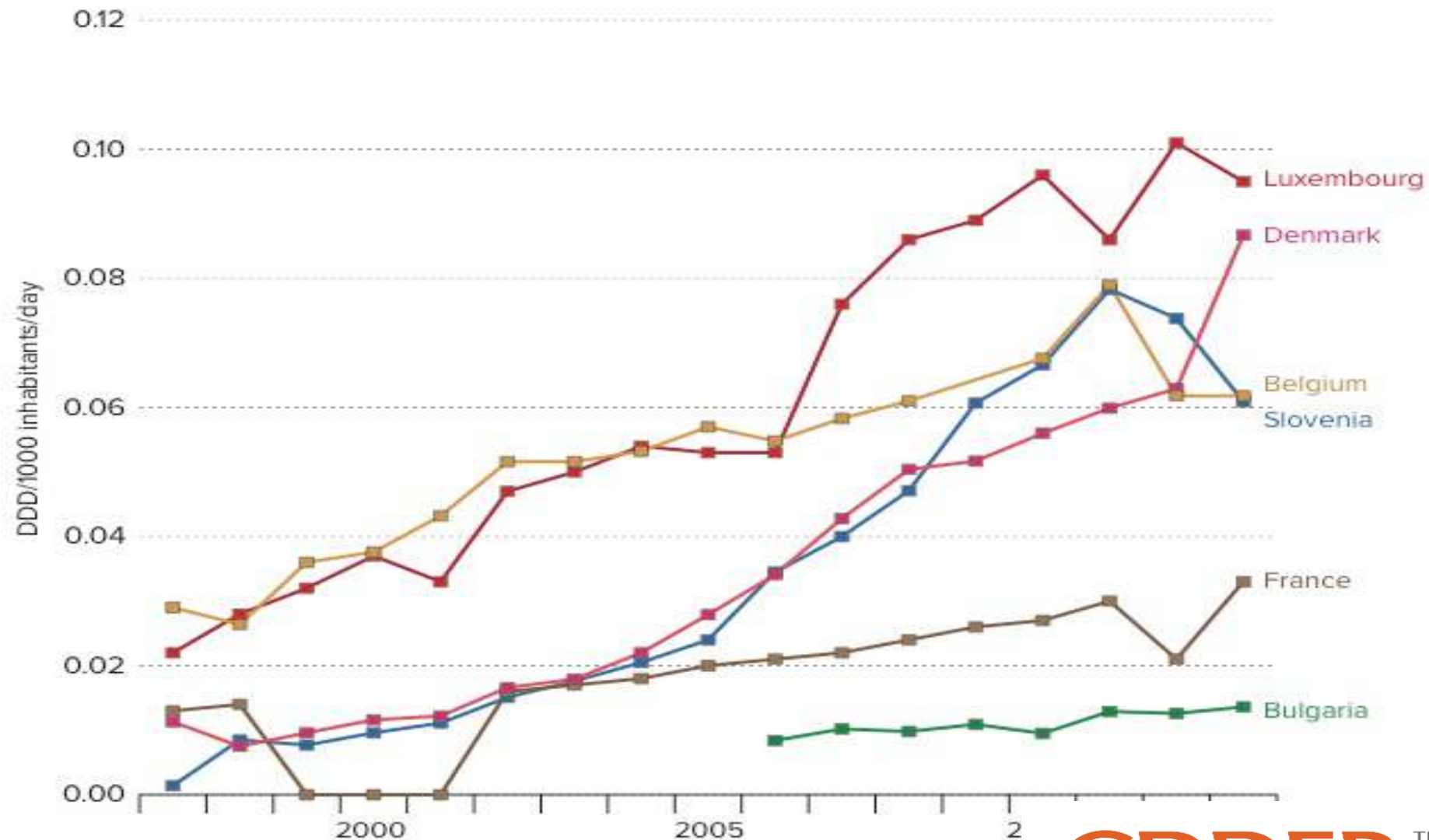
Source: Van Boeckel et al. 2015 (adapted; based on IMS MIDAS)

*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).

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



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



Non-prescription use of antimicrobials is common

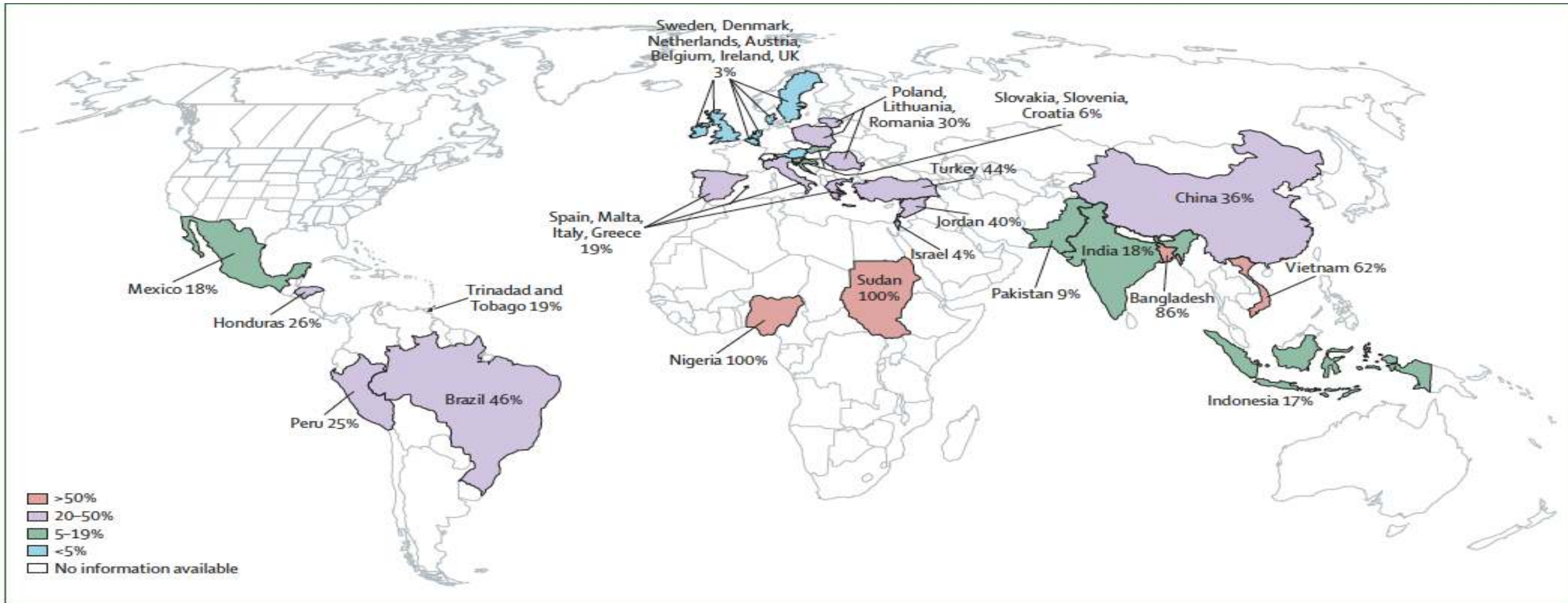


Figure 2: Frequency of non-prescription use of antimicrobials in the general population based on published works
In small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

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

Country or Region	Population <i>in millions</i>	Doctors <i>in thousands</i>	Nurses	Doctors and Nurses/ 1000 Population	Nurse-to-Doctor Ratio
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

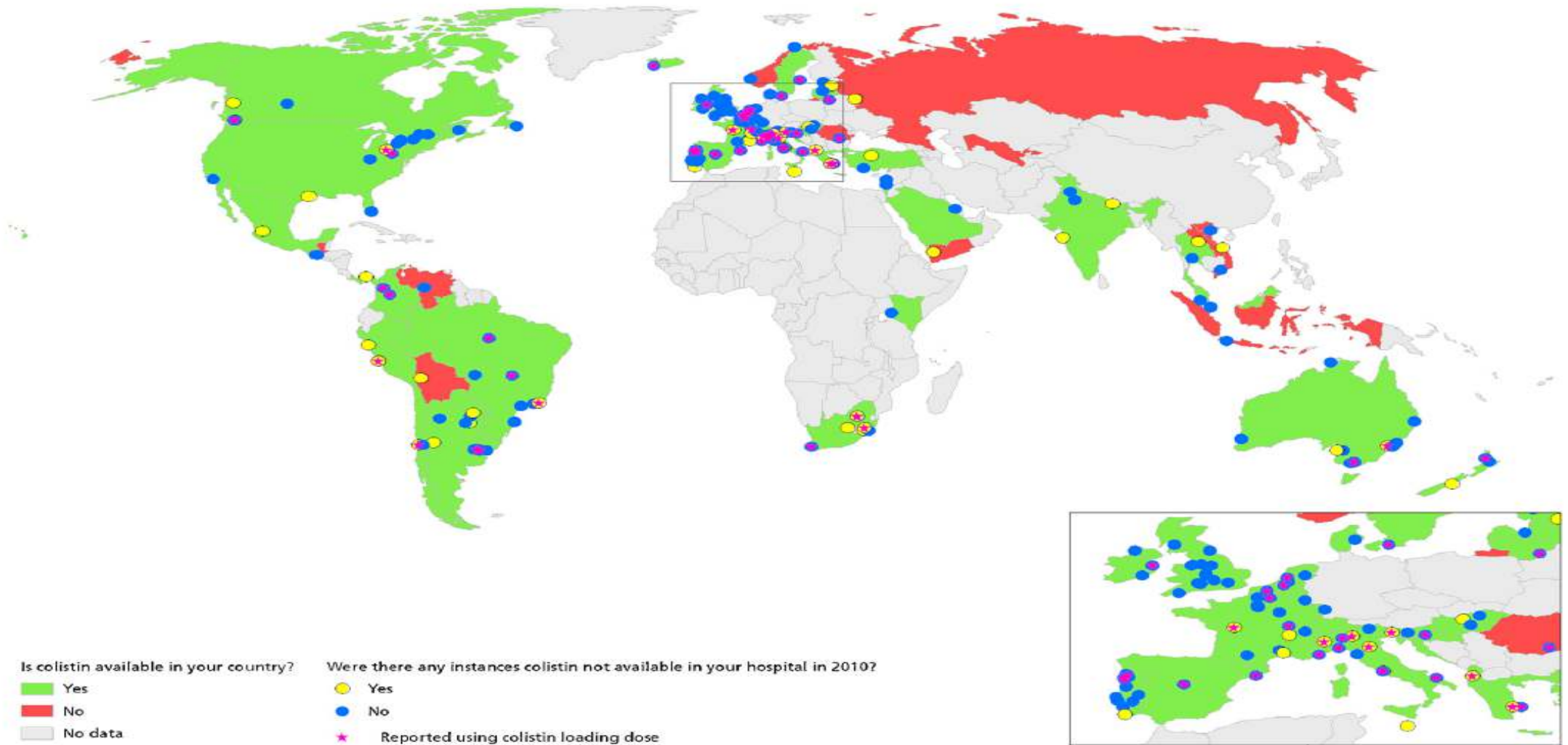
* A doctor or nurse is defined as a person with the appropriate qualifications recognized in his or her own country. In this table, the nurse workforce includes nurses and midwives. Data are from the World Health Organization.⁹

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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.

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[http://dx.doi.org/10.1016/S1473-3099\(15\)00424-7](http://dx.doi.org/10.1016/S1473-3099(15)00424-7)

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[http://dx.doi.org/10.1016/S1473-3099\(15\)00462-6](http://dx.doi.org/10.1016/S1473-3099(15)00462-6)

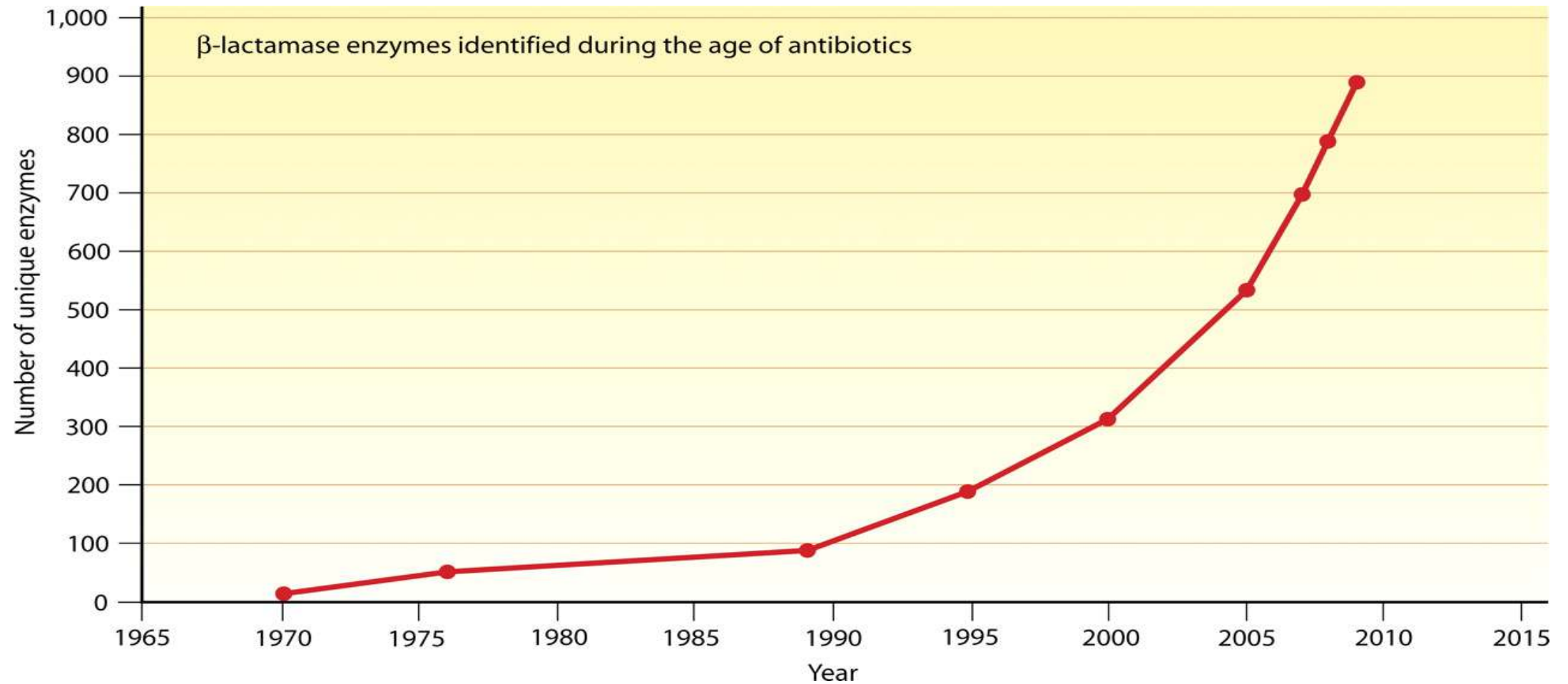
Antibiotic use for growth promotion and disease prevention

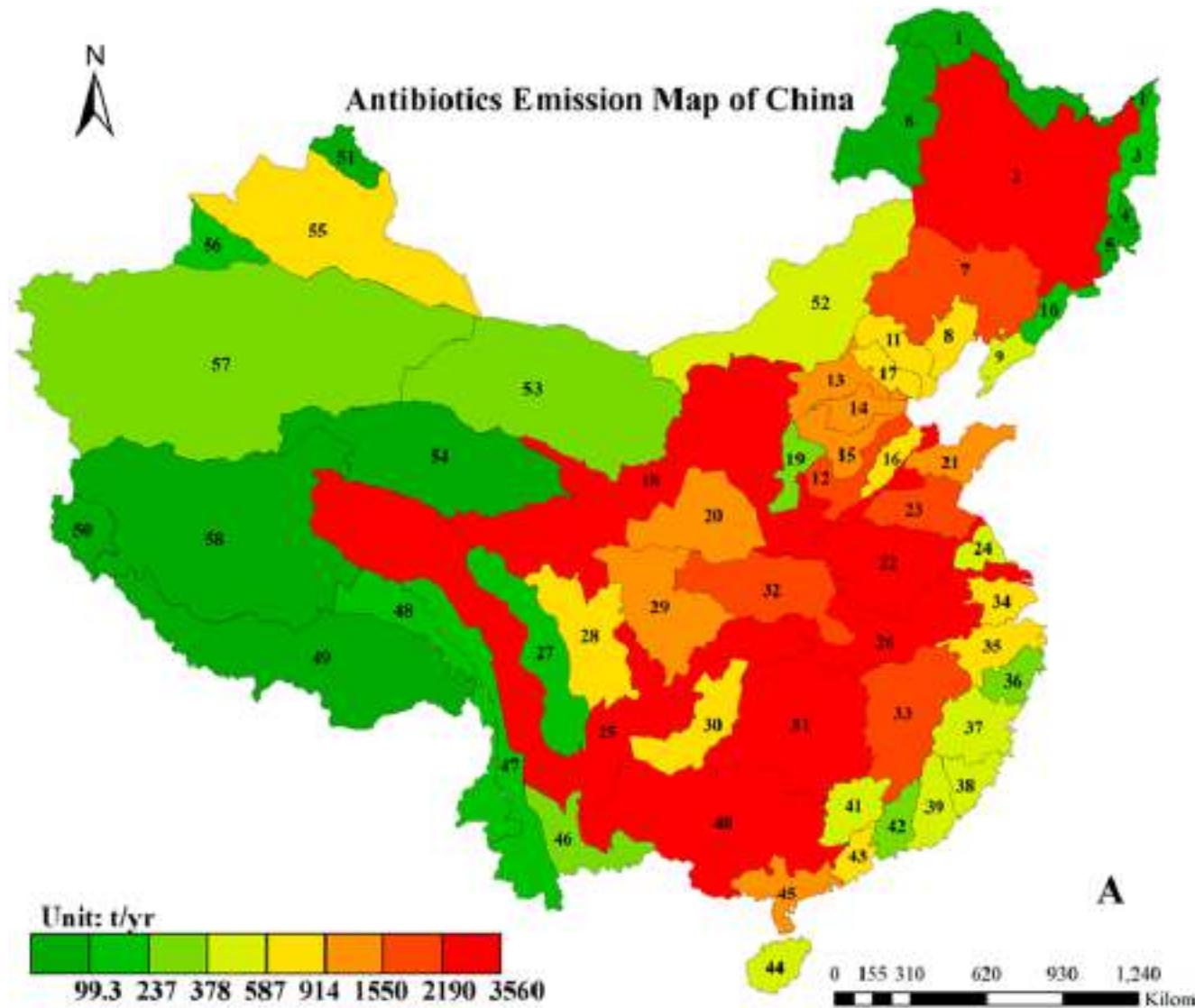


2/3^{rds} of the tonnage of antibiotics sold worldwide are used in agriculture



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





- 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

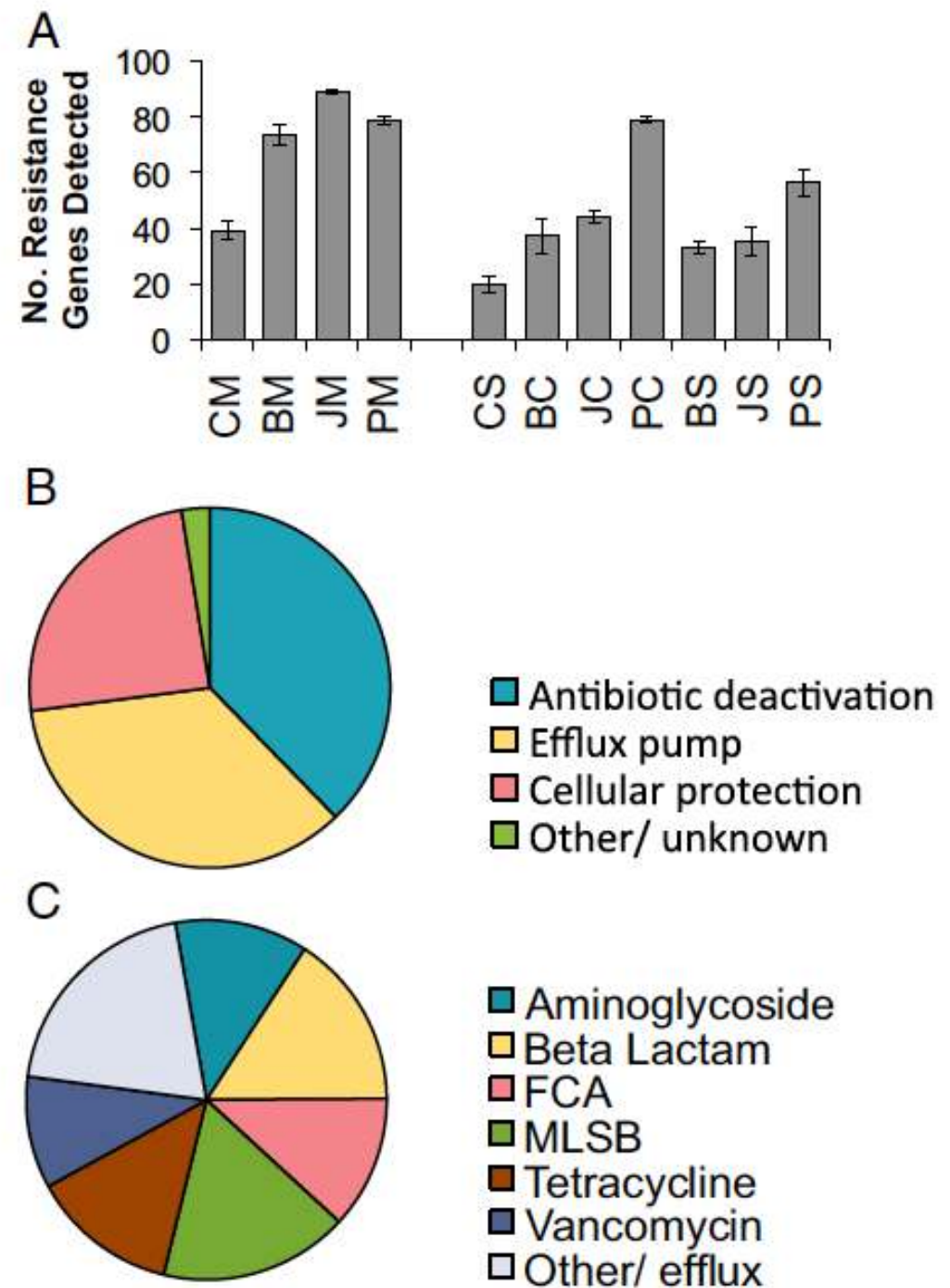
Diverse and abundant antibiotic resistance genes in Chinese swine farms

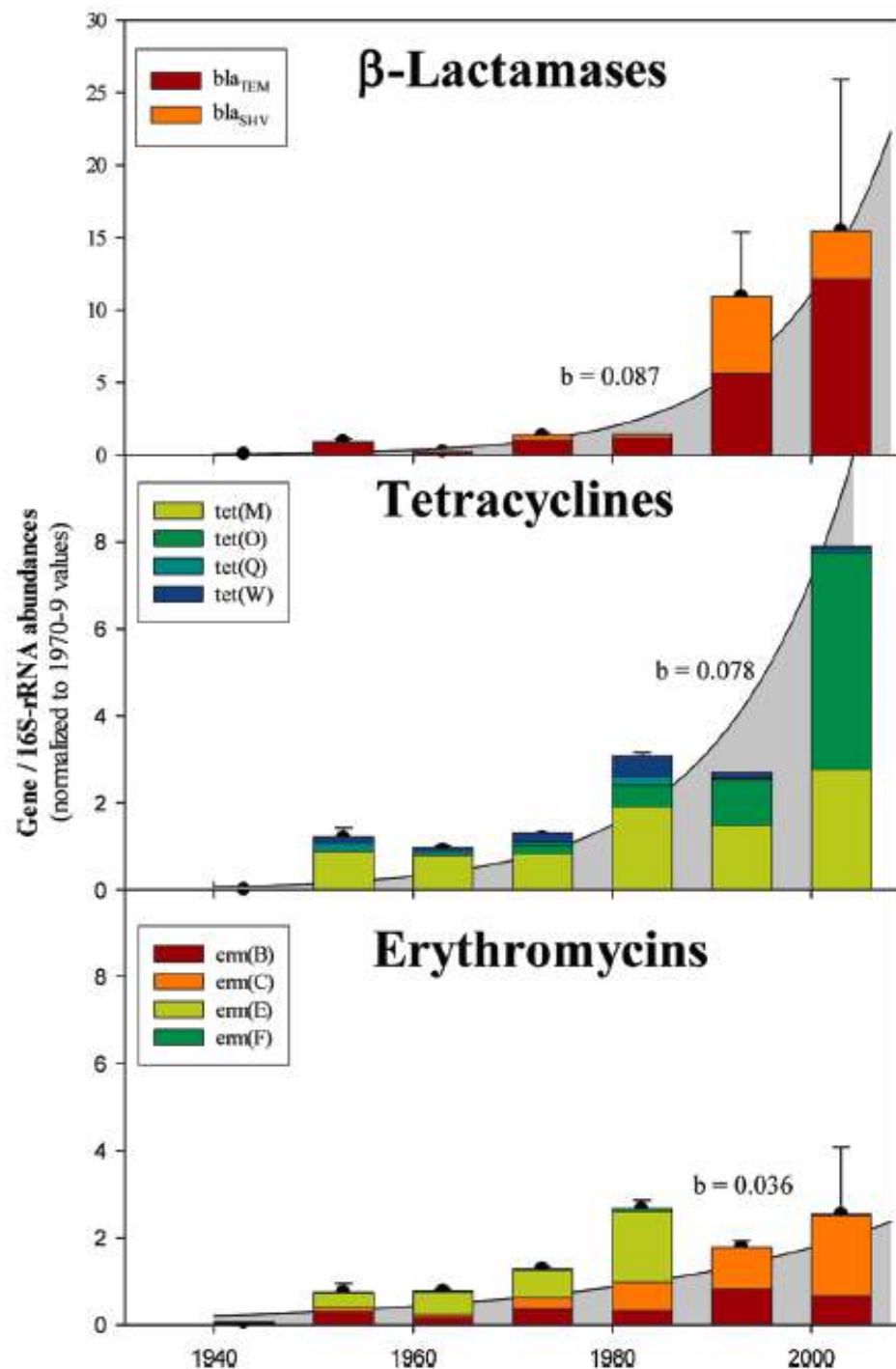
Yong-Guan Zhu^{a,b,1,2}, Timothy A. Johnson^{c,d,1}, Jian-Qiang Su^a, Min Syed A. Hashsham^{c,e}, and James M. Tiedje^{c,d,2}

^aKey Lab of Urban Environment and Health, Institute of Urban Environment, Chinese Academy of Sciences, Beijing 100085, China; and ^cCellular and Environmental Sciences, and ^eCivil and Environmental Engineering, Michigan State University, East Lansing, Michigan 48824, USA

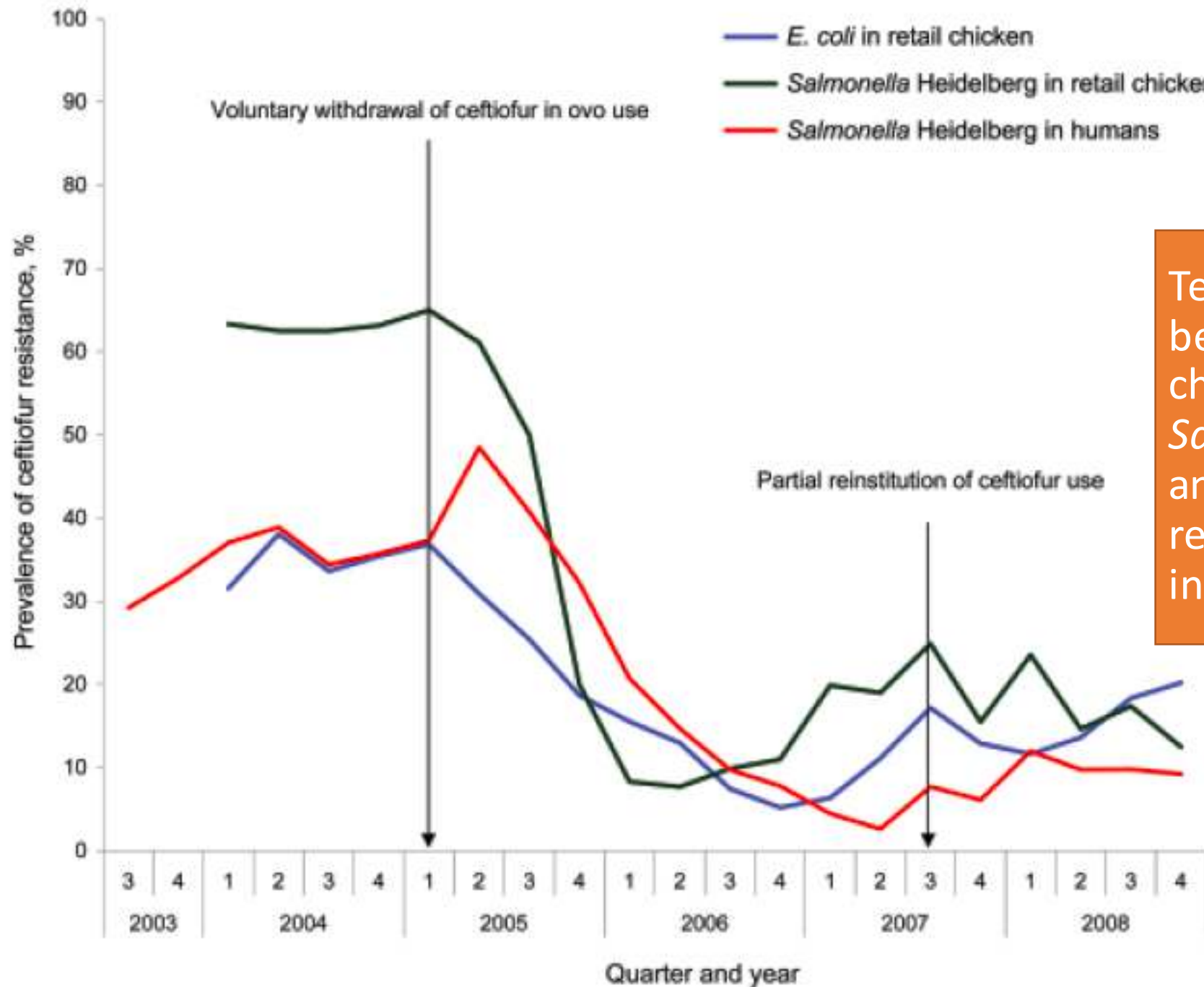
Contributed by James M. Tiedje, December 31, 2012 (sent for review October 31, 2012)

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.



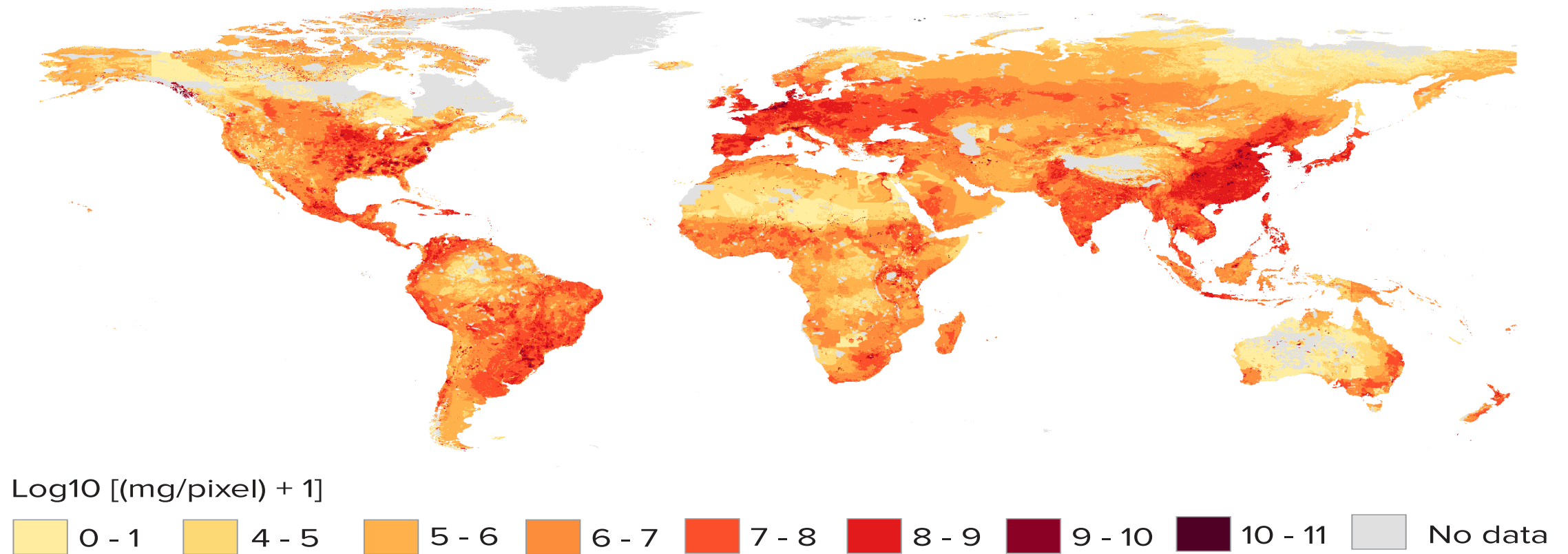


Increase of antibiotic resistance genes among soils collected at five sites in The Netherlands from 1940 to 2008.

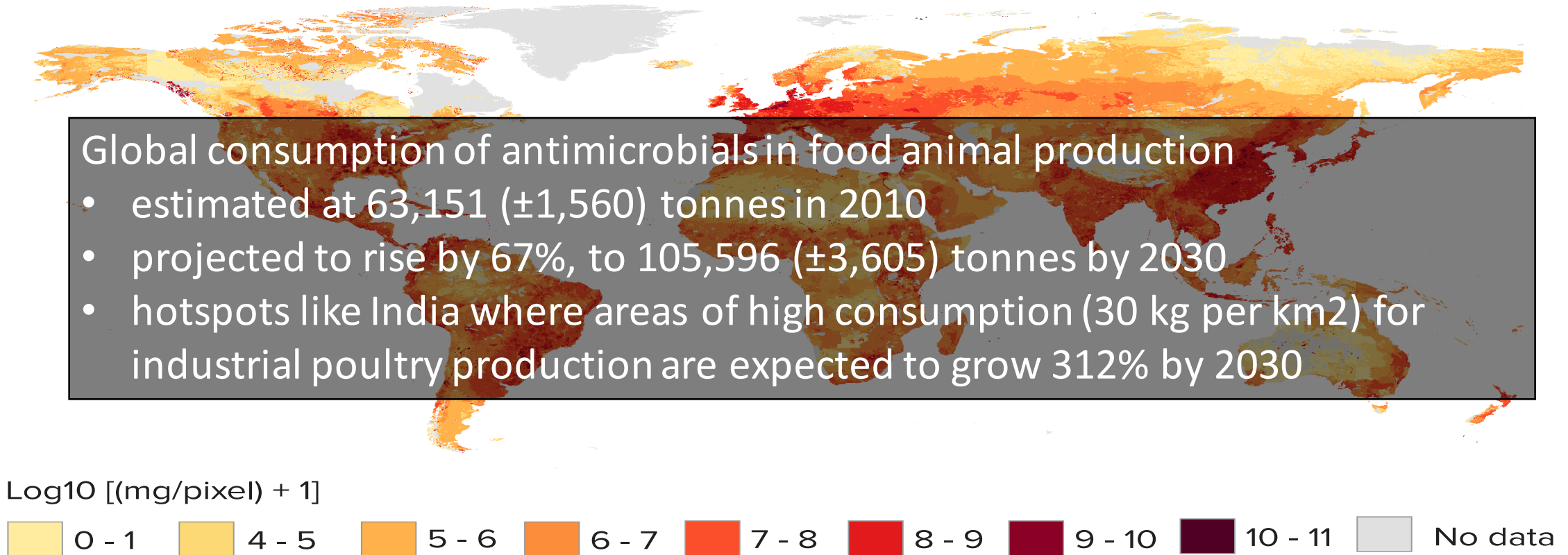


Temporal association between contamination of retail chicken with ceftiofur-resistant *Salmonella* Heidelberg strains and incidence of ceftiofur resistant *Salmonella* Heidelberg infection in humans

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



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



Price in USD

\$ 40,000

\$ 20,000

\$ 200

\$ 100

\$ 0.20

\$ 0.10

0

\$ 0.1

Penicillin

Market Launch: 1941



Price in USD

\$ 40,000

\$ 20,000

\$ 200

\$ 100

\$ 0.20

\$ 0.10

0

Penicillin

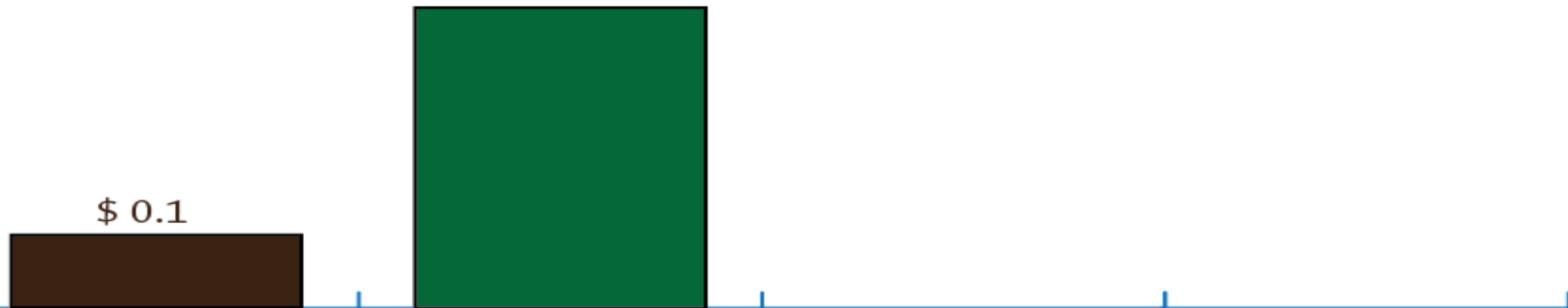
Linezolid

\$ 0.1

\$ 155

Market Launch: **1941**

2000



Price in USD

\$ 40,000

\$ 20,000

\$ 200

\$ 100

\$ 0.20

\$ 0.10

0

Penicillin

Linezolid

Daptomycin

\$ 0.1

\$ 155

\$ 181

Market Launch: **1941**

2000

2006

Penicillin

Linezolid

Daptomycin

\$ 0.1

\$ 155

\$ 181

Market Launch: **1941**

2000

2006

Price in USD

\$ 40,000

\$ 20,000

\$ 200

\$ 100

\$ 0.20

\$ 0.10

0

Penicillin

Linezolid

Daptomycin

Sipuleucel-T

\$ 0.1

\$ 155

\$ 181

\$ 31,000

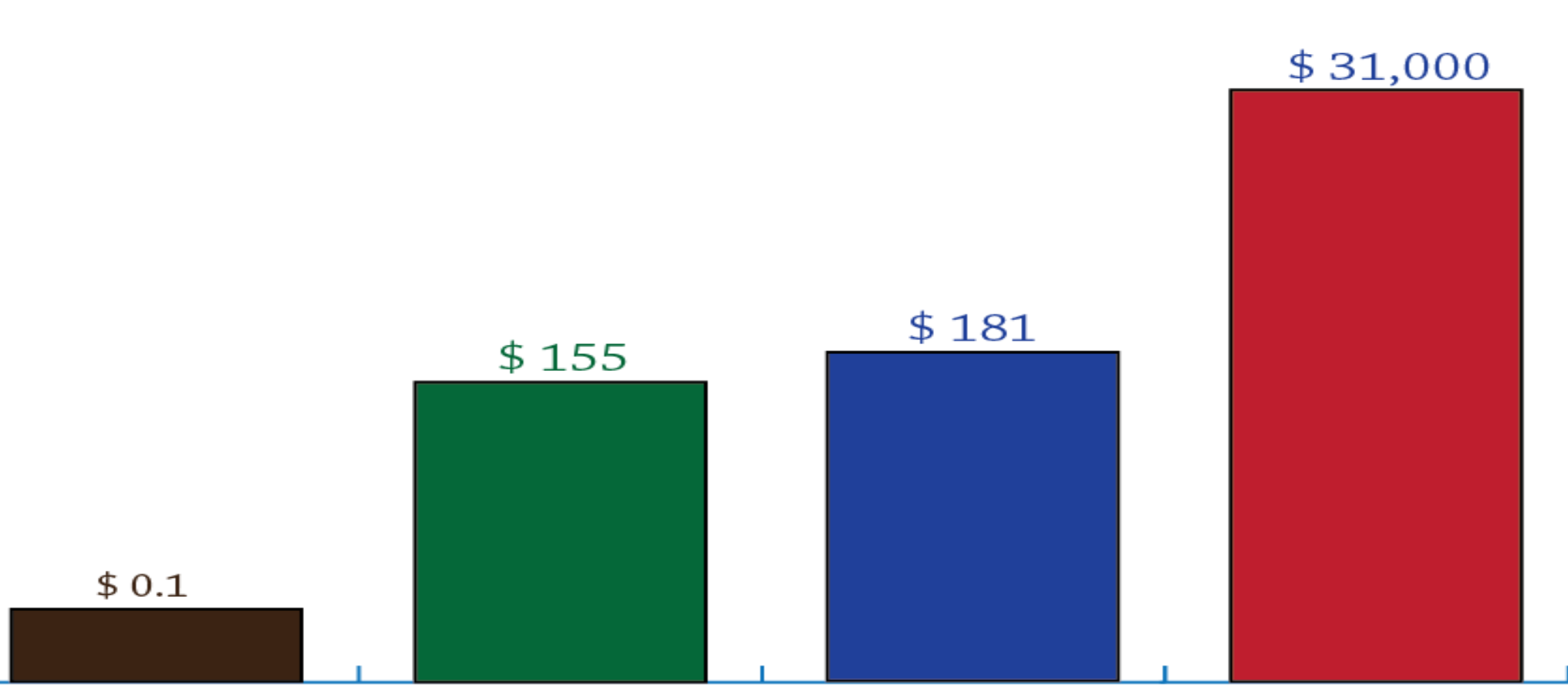
Market Launch:

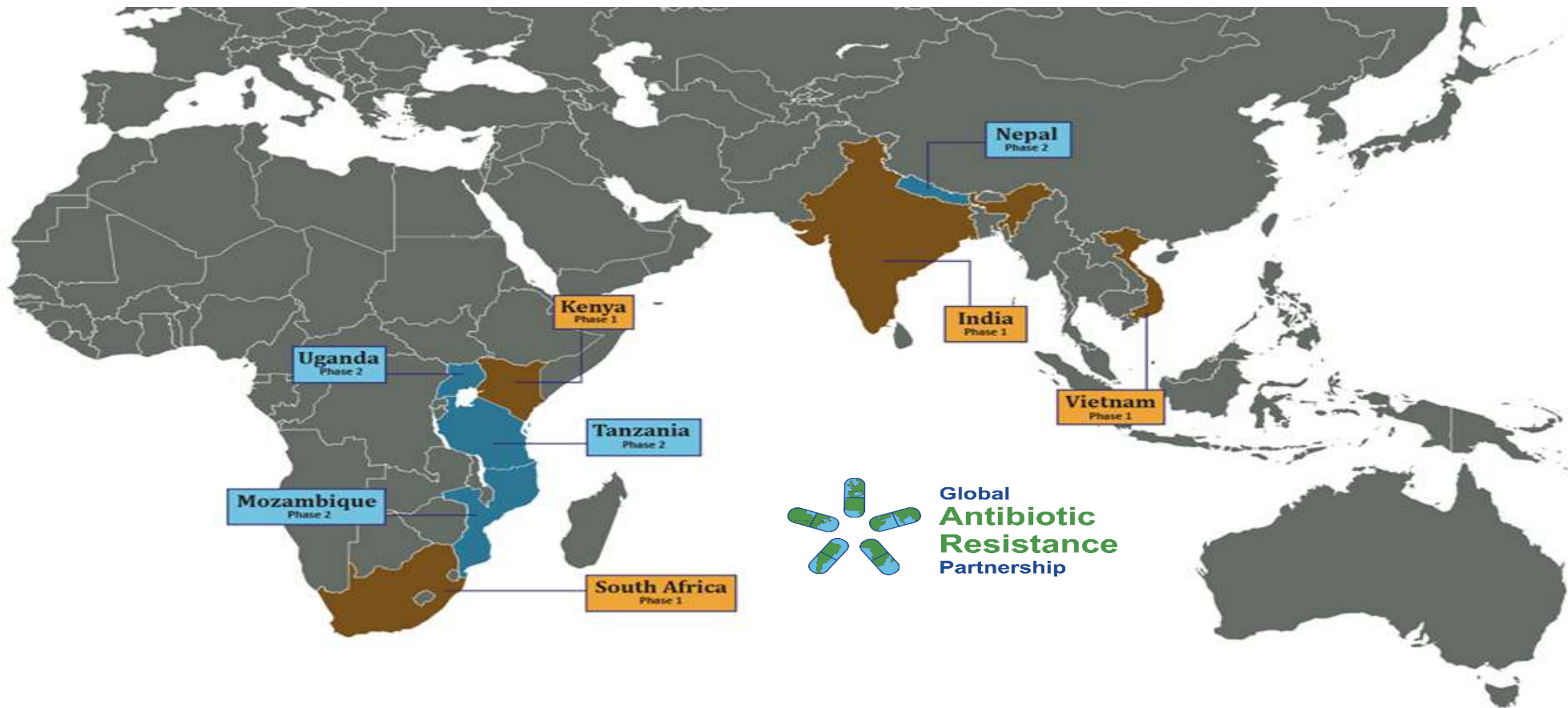
1941

2000

2006

2010





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Global
Antibiotic
Resistance
Partnership



THE STATE OF THE WORLD'S ANTIBIOTICS 2015

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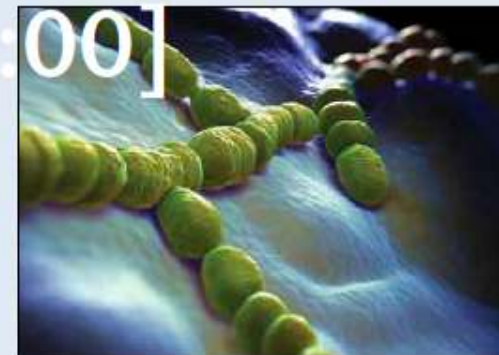
November 2015

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Antimicrobials: access and
sustainable effectiveness



**EMBARGO:
NOVEMBER 18, 2015**



[14:00]

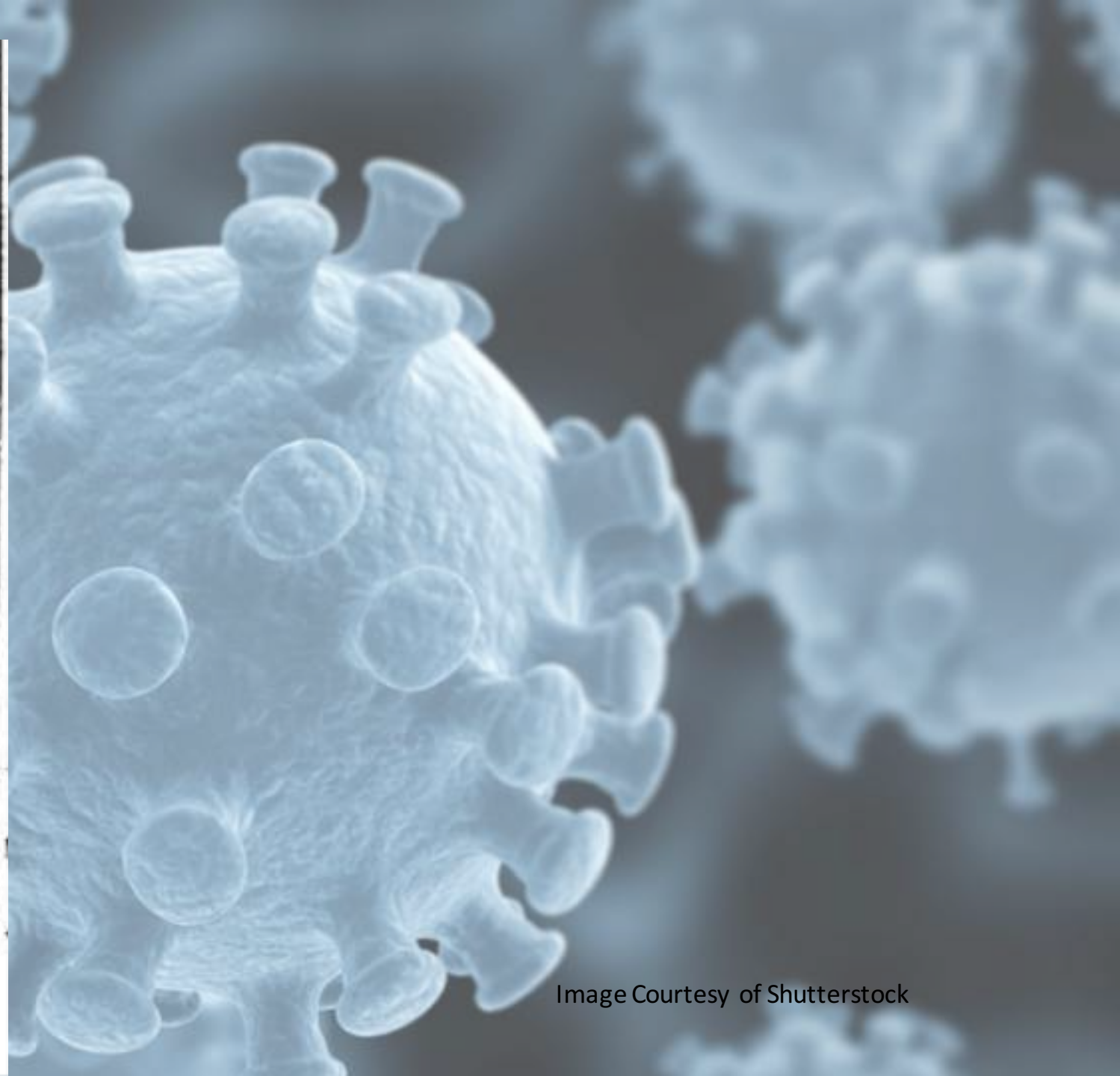
"Our intention is to redefine and reposition antimicrobial resistance into a broader and more appropriate context, especially given the new era of sustainable development...Our Series defines two dimensions: sustainable access, as well as sustainable effectiveness."

Reprint Reprint

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.



Slides are downloadable @
www.cddep.org

More on the Global Antibiotic Resistance
Partnership @

www.cddep.org/garp