What Explains Differences in Resistance Rates?
Economics

Ramanan Laxminarayan

ECCMID

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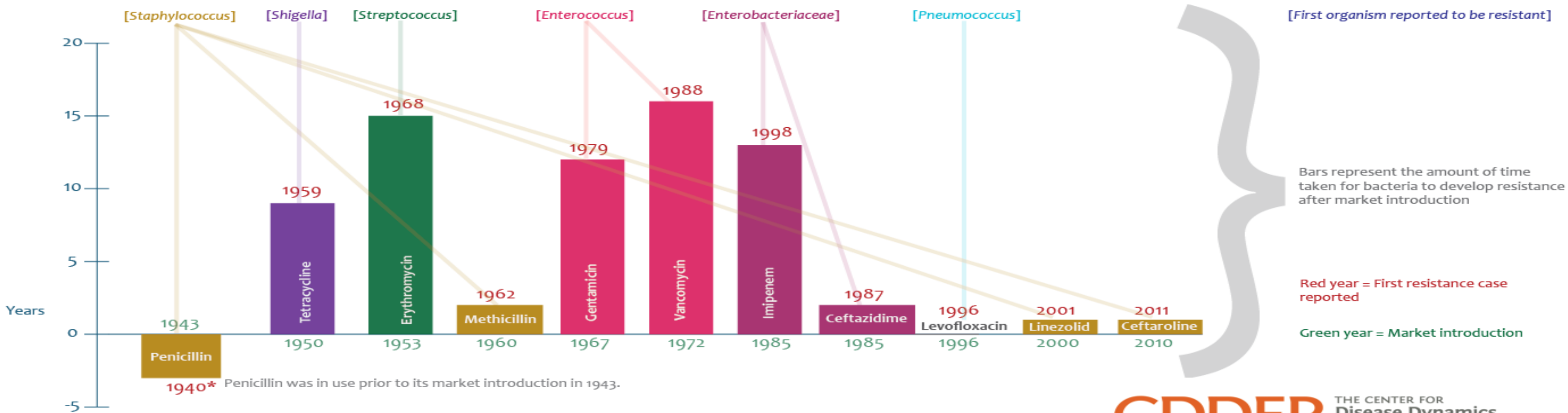
Resistance rates are determined by

- Infection prevention (IPC or vaccines)
- Use of antibiotics in humans and animals

First reported cases of bacterial resistance against key antibiotics



1940* 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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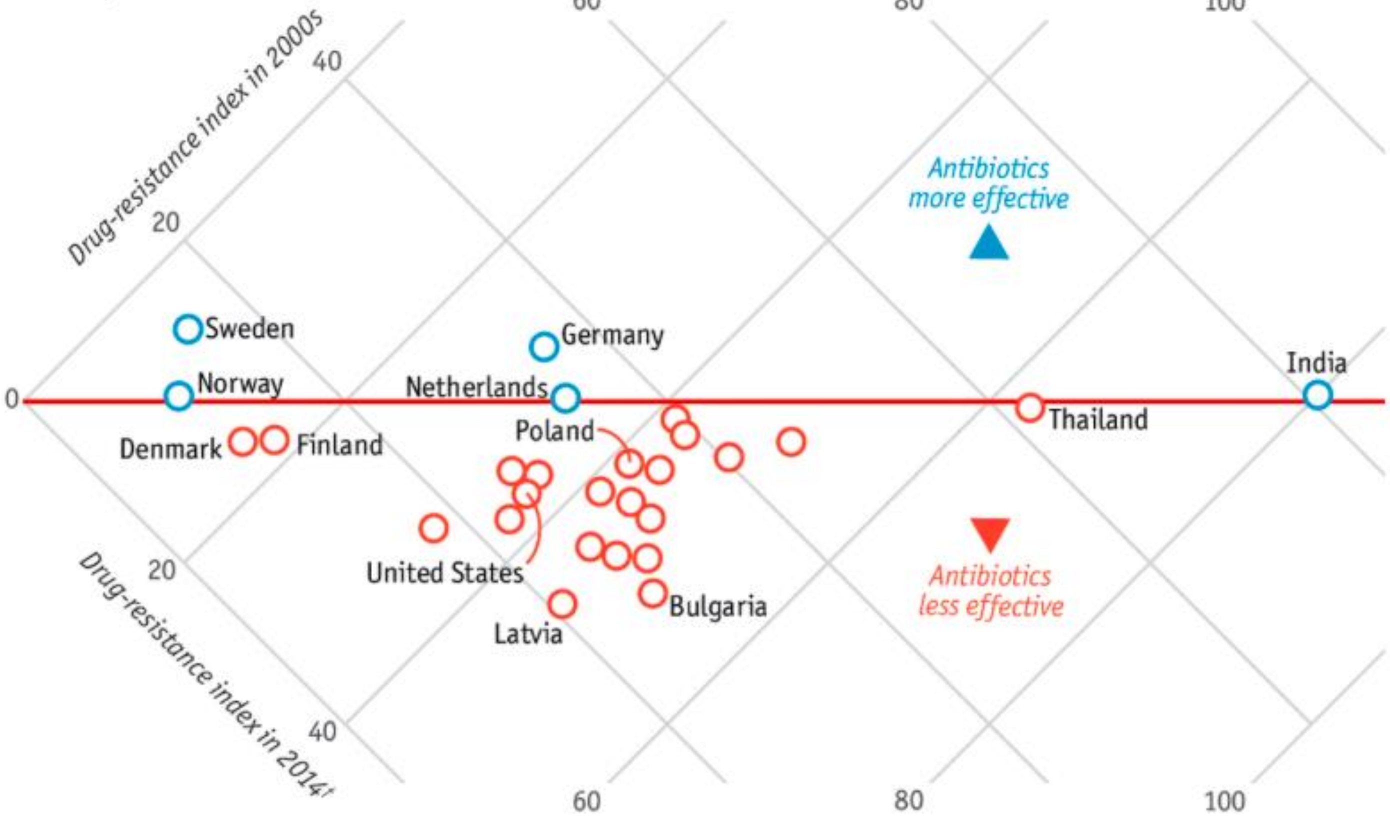
The drugs work less

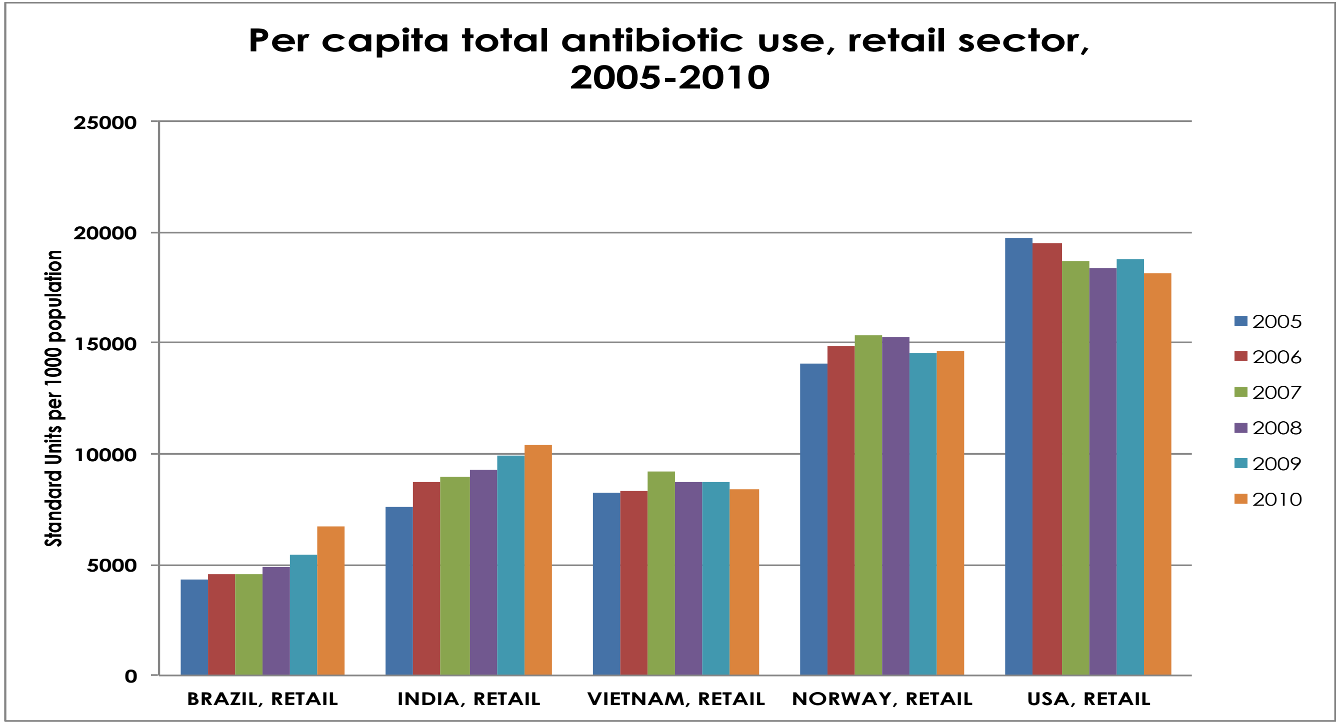
Effectiveness of antibiotics* in selected countries
0=best, 100=worst



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

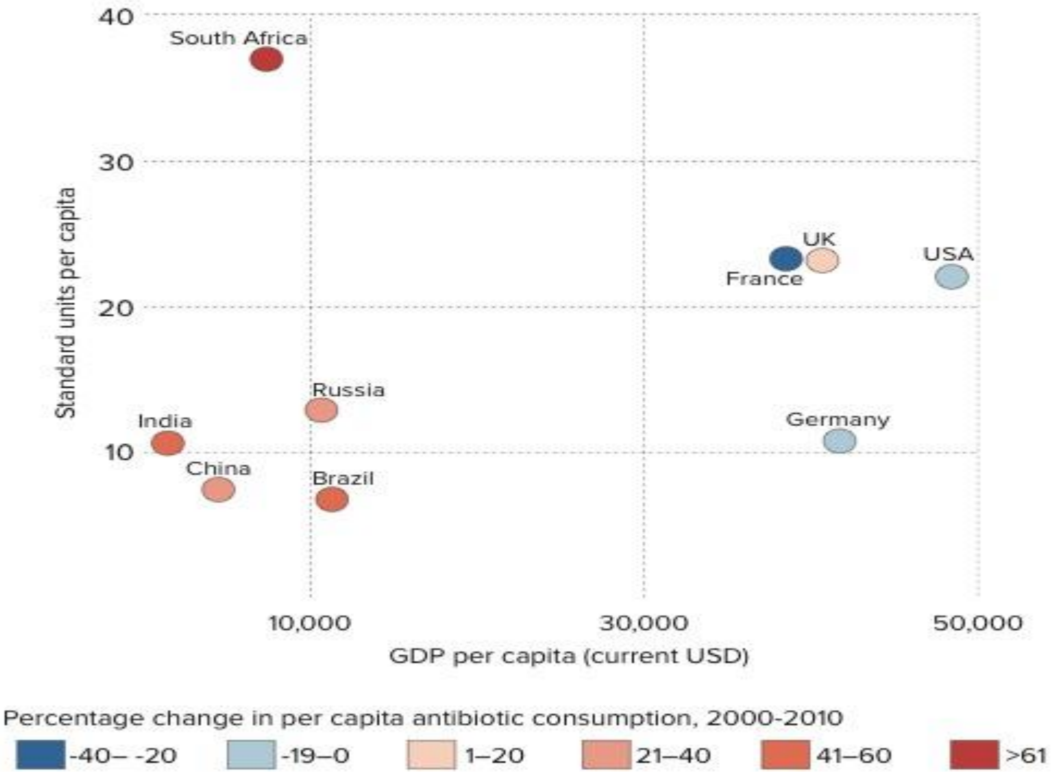
Source: Centre for Disease Dynamics, Economics & Policy

Rising incomes drive antibiotic consumption



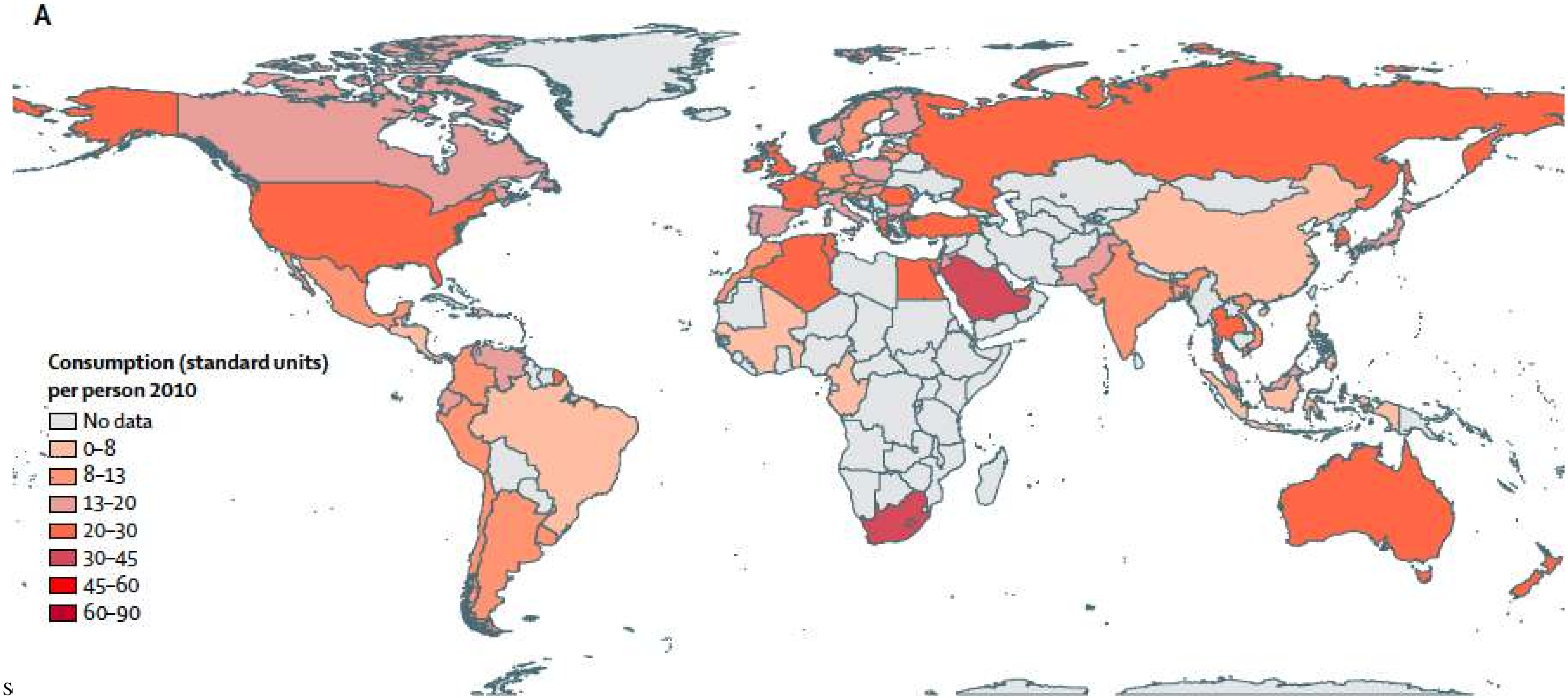
Source: Based on data obtained under license from IMS Health MIDAS ™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.

Antibiotic use per capita by income in selected countries, 2010



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

Per capita antibiotic consumption 2010*, by country



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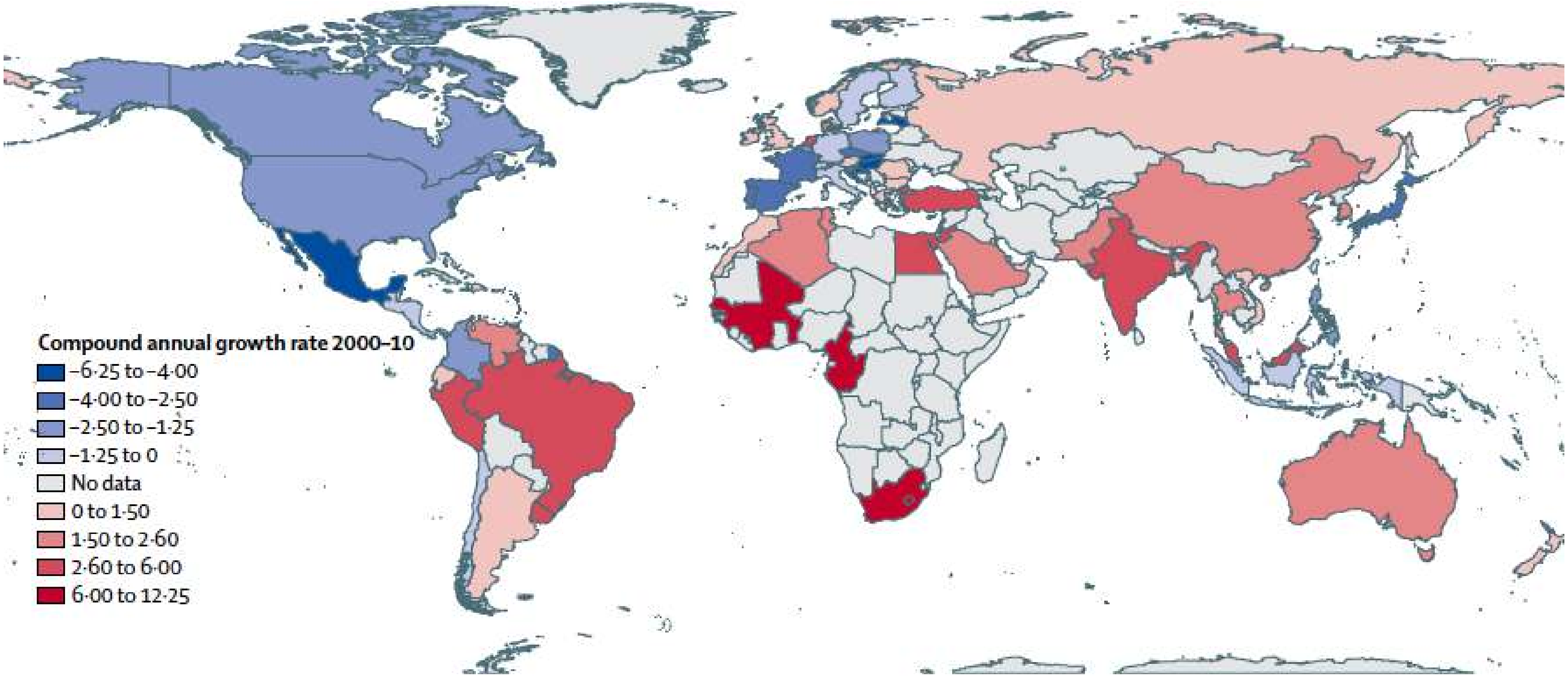
Percentage change in antibiotic consumption per capita 2000–2010*, by country



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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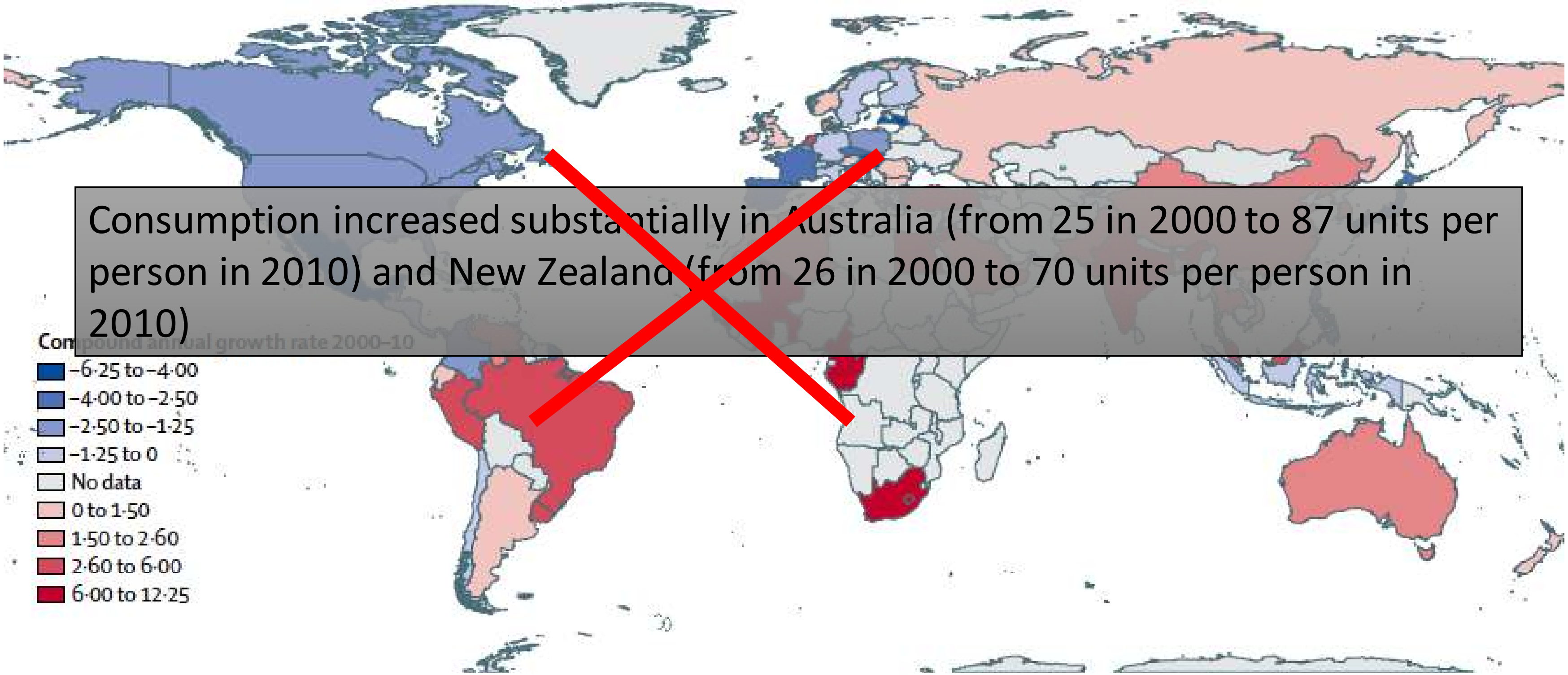

Source.

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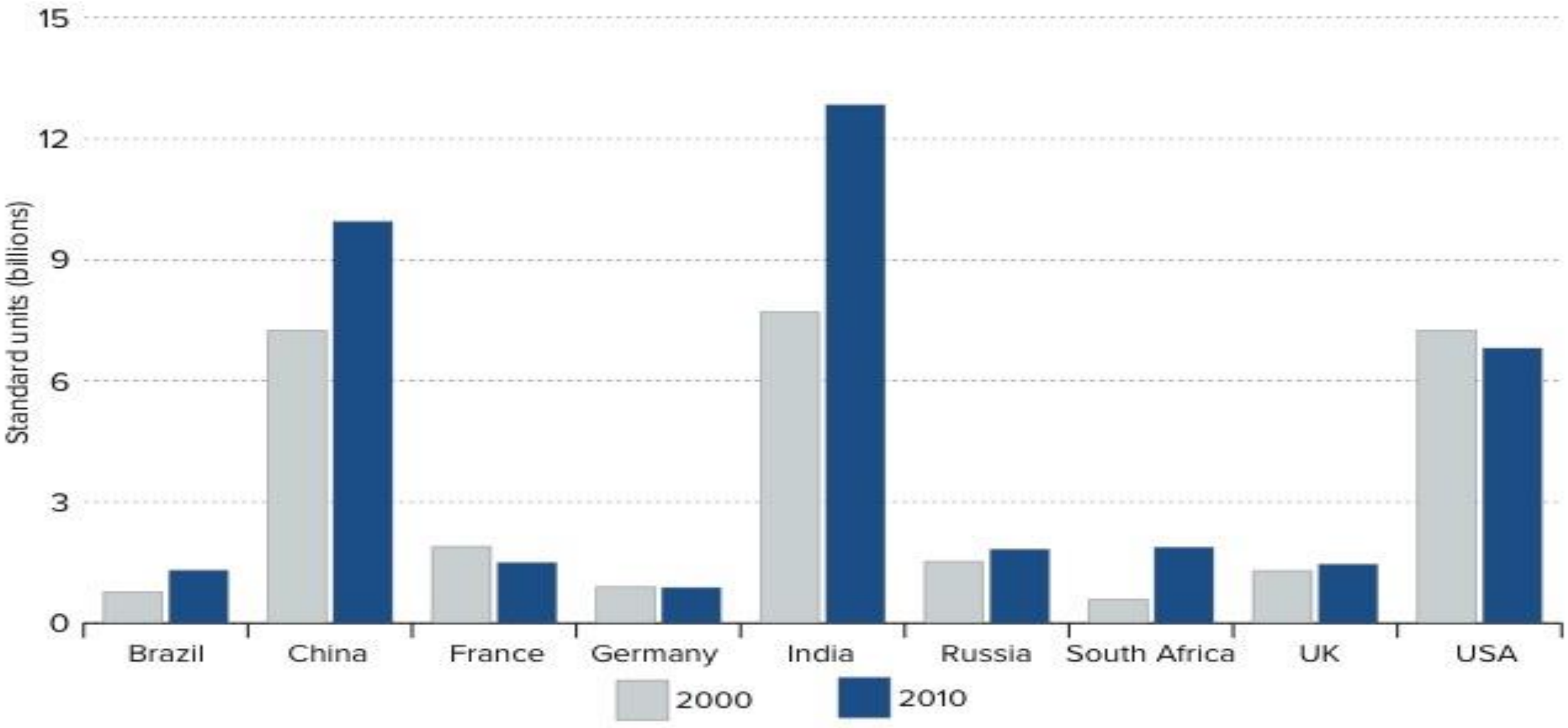
Total antibiotic consumption in selected countries, 2000 and 2010



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

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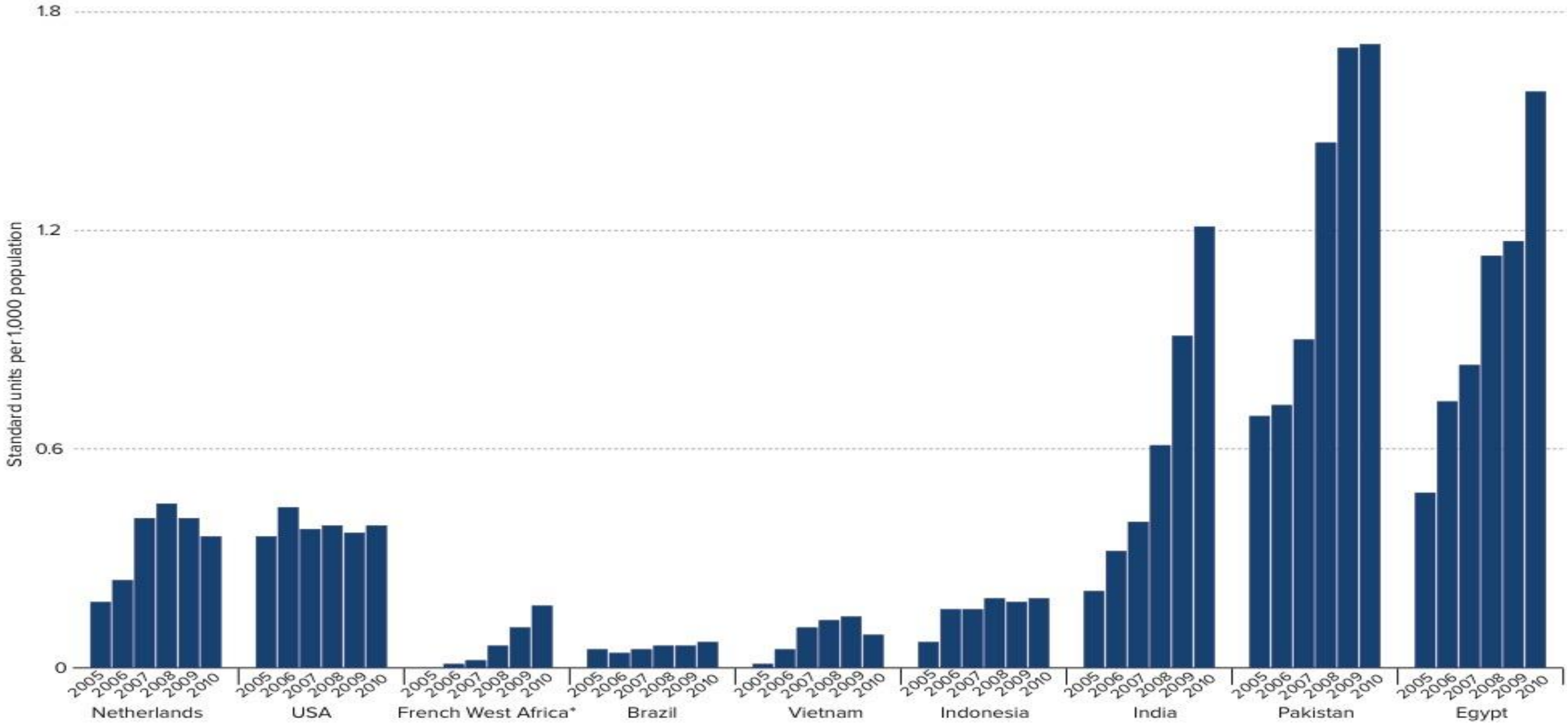
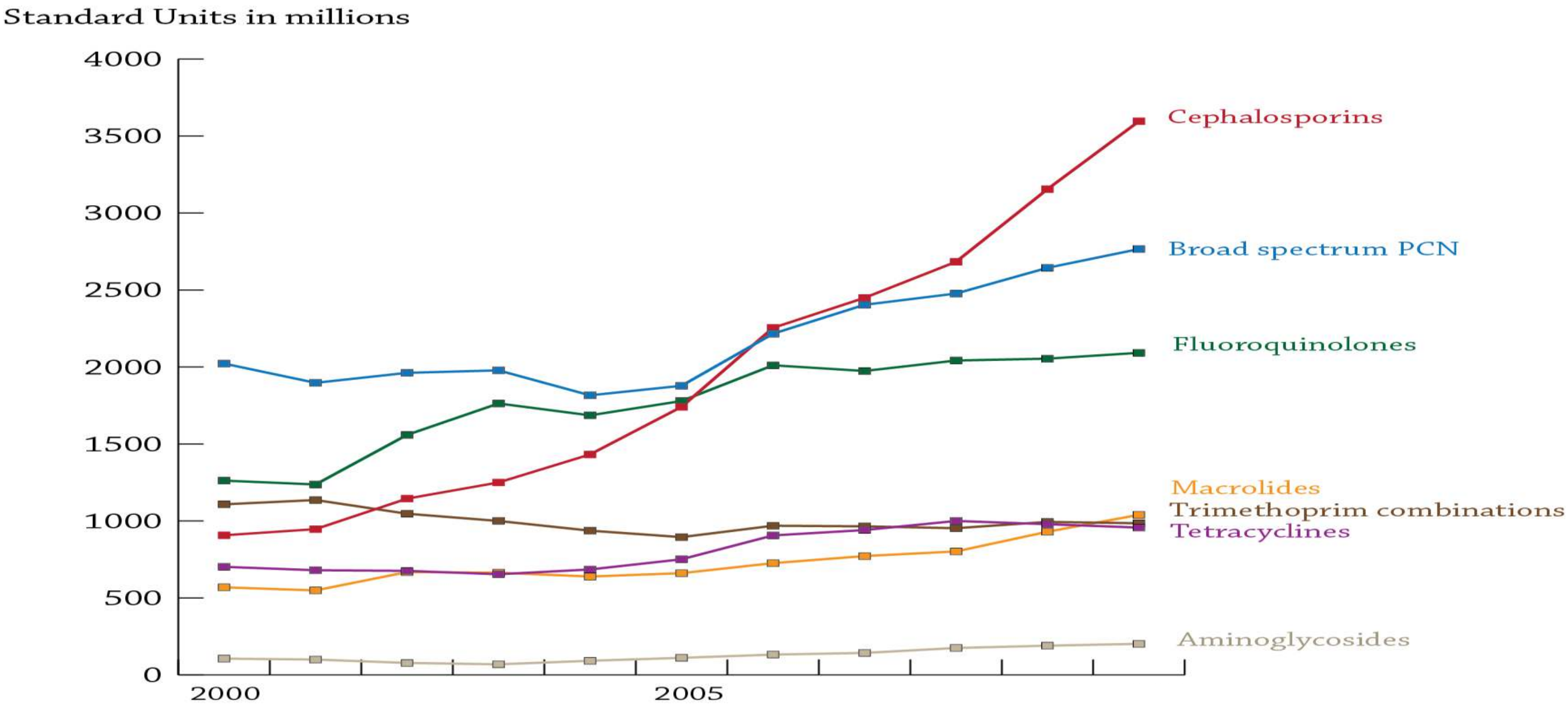
Carbapenem retail sales in selected countries, 2005–2010 (per 1,000 population)



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 To go

Use of cephalosporins and broad spectrum penicillins is rising in India:



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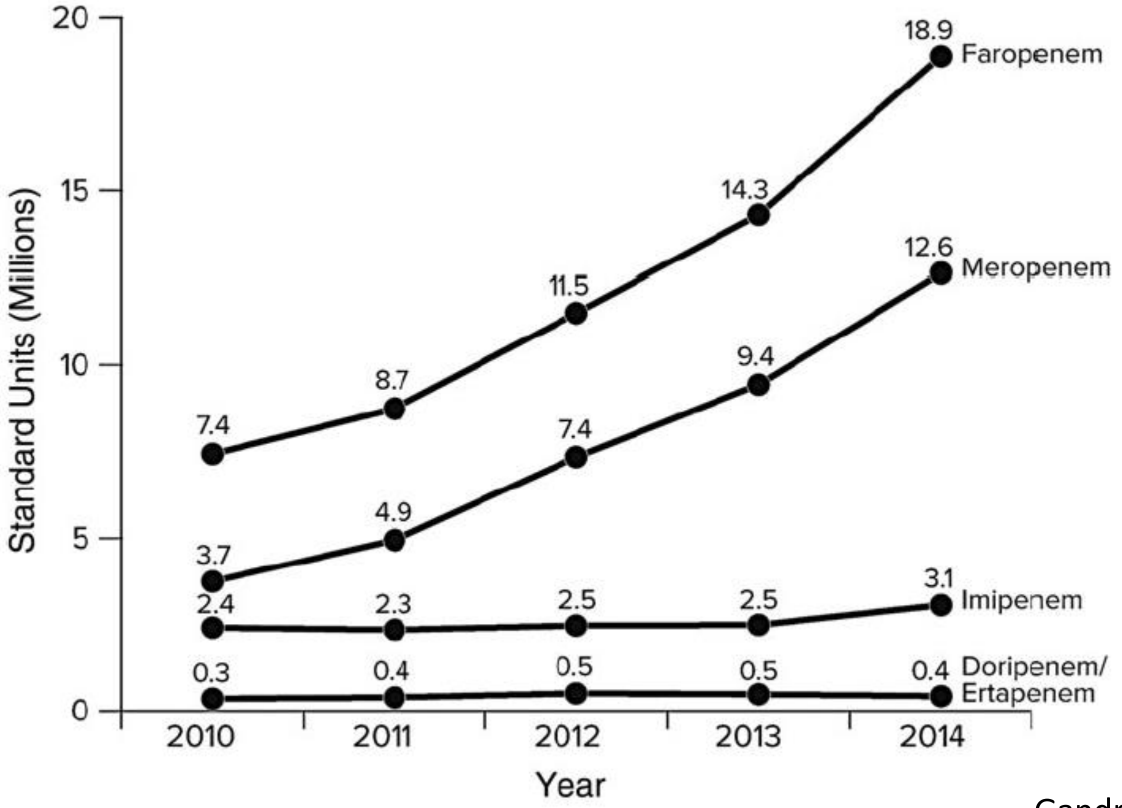
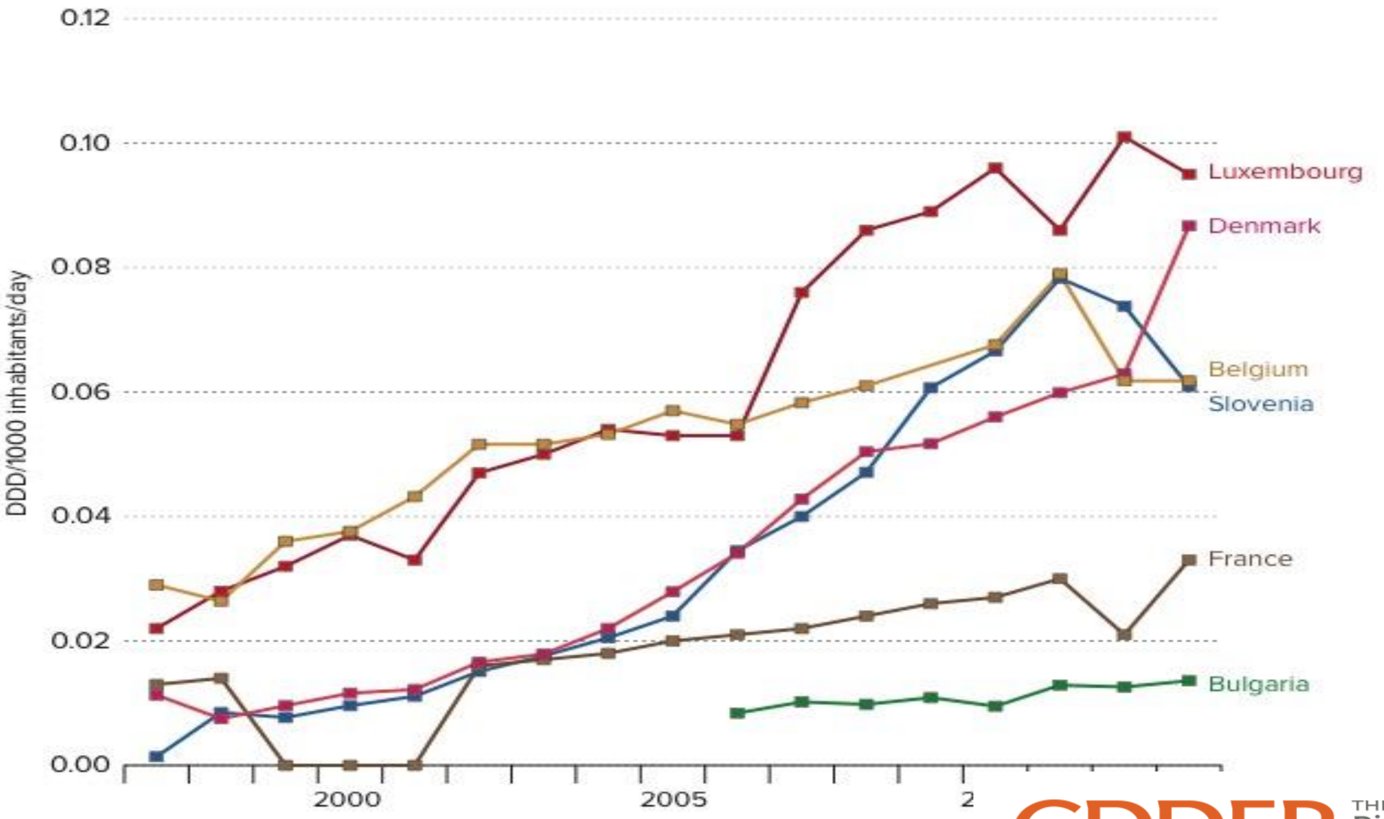
Faropenem consumption has increased by 154% since it was approved for use in India in 2010



Gandra et al, Clin Inf Dis, 2016

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



ESAC-Net 2015

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Non-prescription use of antimicrobials is common

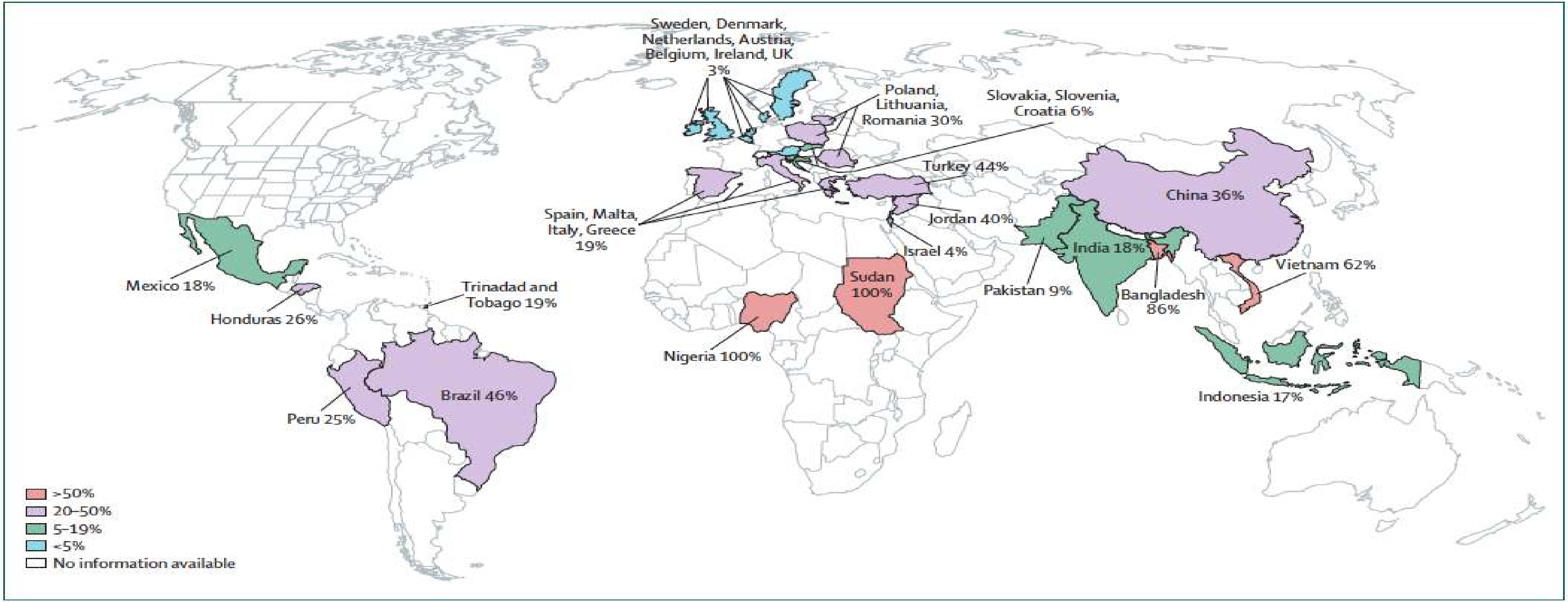
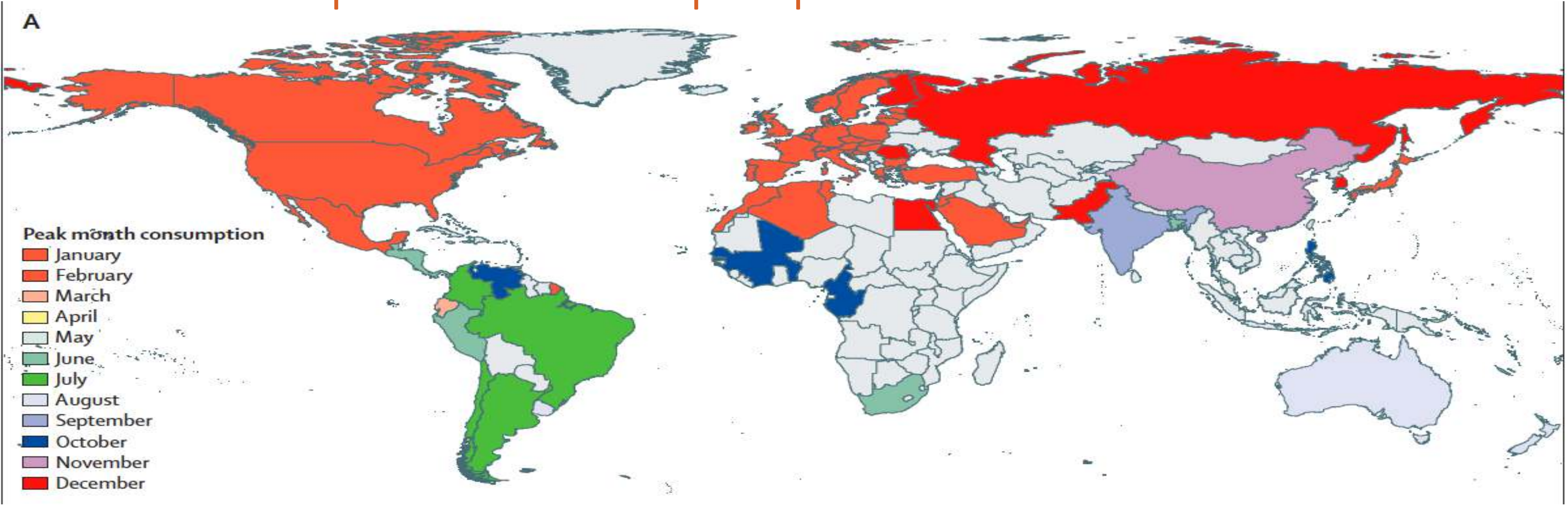


***Figure 2*: Frequency of non-prescription use of antimicrobials in the general population based on published works**
In small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

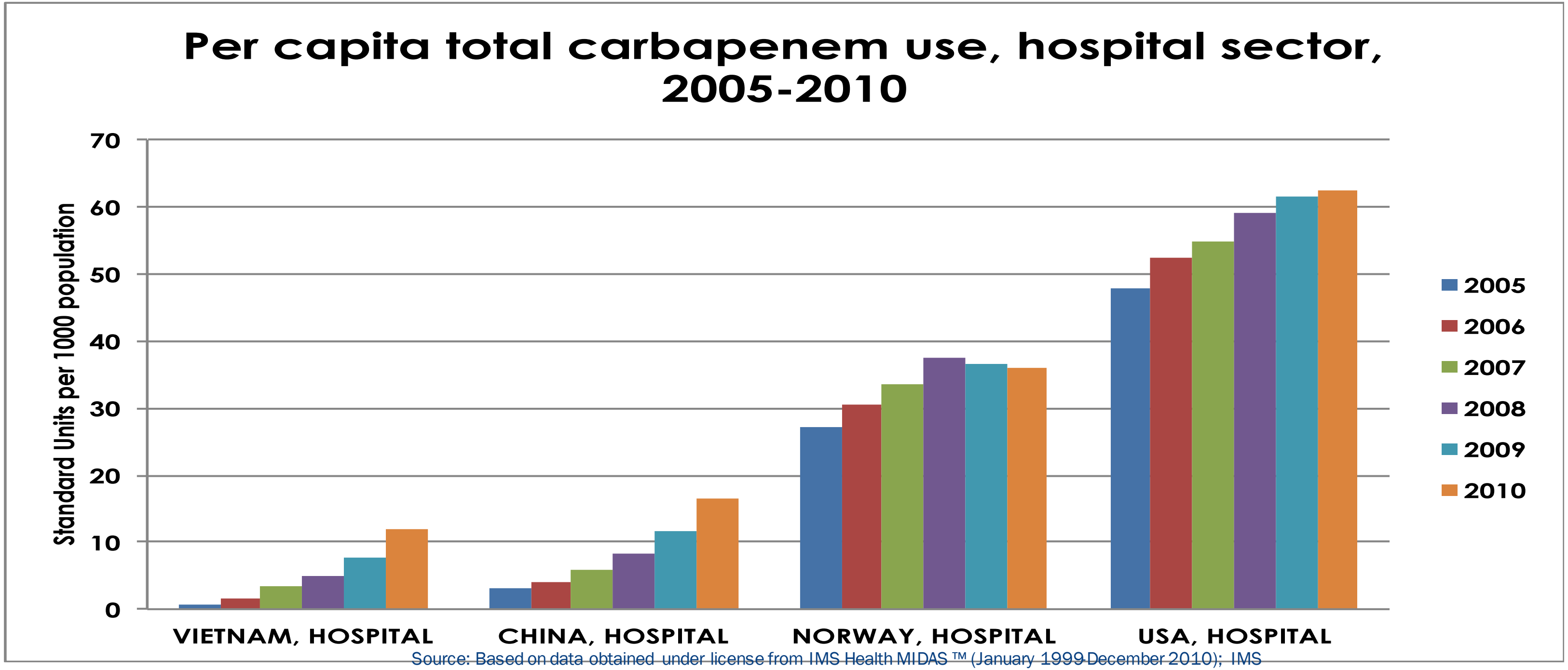
Morgan et al, Lancet ID, 2011

The flu season is a key driver of antibiotic consumption – when people can afford antibiotics



Van Boeckel et al, Lancet Inf Dis, 2014

Hospital use of carbapenems is rapidly growing



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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

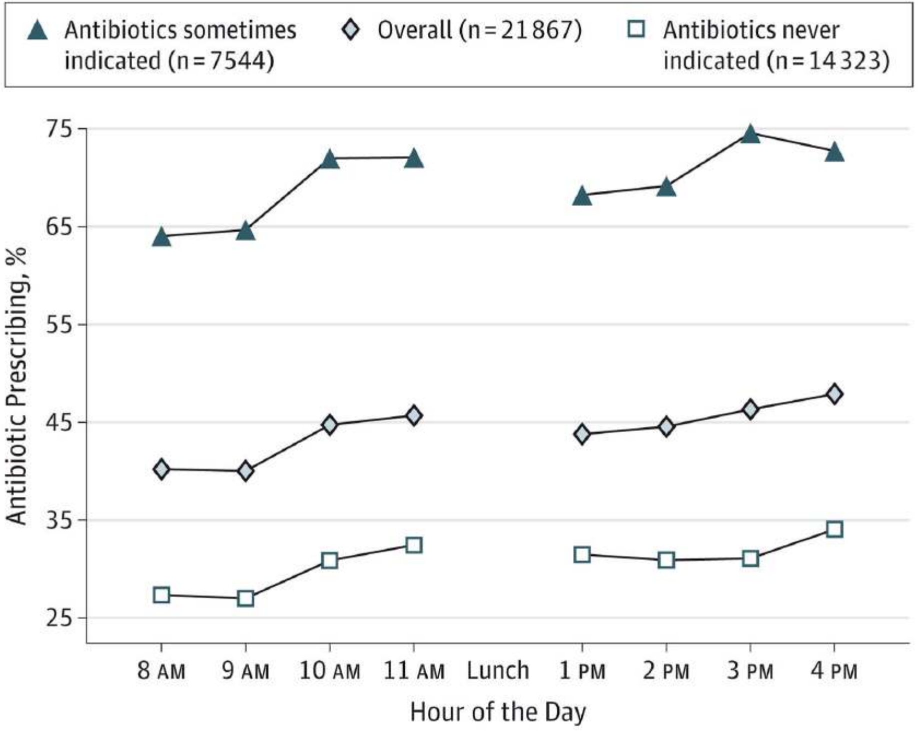
Frequency of Antibiotic Prescribing by Factors Related to Patients' Expectations of Antibiotics (N = 482)

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

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).

China

- A study of 230,800 outpatient prescriptions in 28 Chinese cities found that
  - nearly half the prescriptions written between 2007 and 2009 were for antibiotics
  - ten percent were for two or more antibiotics

Li, Yongbin, Jing Xu, Fang Wang, Bin Wang, Liqun Liu, Wanli Hou, Hong Fan, Yeqing Tong, Juan Zhang, Zuxun Lu, 2012. Overprescribing in China, Driven by Financial Incentives, Results in Very High Use of Antibiotics, Injections, and Corticosteroids. Health Affairs 31(5), 1075-1082.

Currie, Lin, Meng (2014)

- Baseline (no expectations) Patient A did not ask for an antibiotic
- Patient B directly asked the doctor for an antibiotic prescription to be filled at the pharmacy
- Patient C asked for a prescription (not specifically antibiotics) but indicated that he/she would buy any drugs prescribed in another pharmacy
- Patient D both asked specifically for antibiotics and indicated that he/she would buy any drugs prescribed elsewhere

Currie, Lin, Meng (2014)

- Baseline (no expectations) Patient A did not ask for an antibiotic (55% prescribed)
- Patient B directly asked the doctor for an antibiotic prescription to be filled at the pharmacy (88%)
- Patient C asked for a prescription (not specifically antibiotics) but indicated that he/she would buy any drugs prescribed in another pharmacy (12%)
- Patient D both asked specifically for antibiotics and indicated that he/she would buy any drugs prescribed elsewhere (16%)

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) Number of antibiotics	Free plan (N = 1935) Number per person	Cost-sharing plans (N = 3830) Number of antibiotics	Cost-sharing plans (N = 3830) Number per person	Ratio of free to cost-sharing (95% confidence interval)†
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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Association between health insurance and antibiotics prescribing in four counties in rural China

Hengjin Dong [a,*], Lennart Bogg [b], Clas Rehnberg [c], Vinod Diwan [b,d]

Table 5
Types of antibiotics by financing groups

Systems	Insurance (%)	Out-of-pocket (%)	Total (%)	χ^2	*P*
Total cases				11.6	0.04
Penicillin	97 (37.9)	209 (45.3)	306 (42.7)		
Gentamicin	35 (13.7)	74 (16.1)	109 (15.2)		
Norfloxacin	27 (10.5)	37 (8.0)	64 (8.9)		
Cephalosporins	22 (8.6)	17 (3.7)	39 (5.4)		
Sulfonamides	13 (5.1)	21 (4.6)	34 (4.7)		
Others	62 (24.2)	103 (22.3)	165 (23.0)		
County hospital				2.0	0.16
Newer drugs	25 (30.5)	15 (20.5)	40 (25.8)		
Old drugs	57 (69.5)	58 (79.5)	115 (74.2)		
Township hospital				1.5	0.21
Newer drugs	16 (12.1)	30 (17.2)	46 (15.0)		
Old drugs	116 (87.9)	144 (82.8)	260 (85.0)		
Village health station					0.003[a]
Newer drugs	8 (19.0)	10 (4.7)	18 (7.0)		
Old drugs	34 (81.0)	204 (95.3)	238 (93.0)		
Respiratory infections				7.5	0.01
Newer drugs	20 (18.9)	19 (8.5)	39 (11.8)		
Old drugs	86 (81.1)	205 (91.5)	291 (88.2)		
Digestive system infections				1.0	0.32
Newer drugs	14 (23.0)	18 (16.7)	32 (18.9)		
Old drugs	47 (77.0)	90 (83.3)	137 (81.1)		

[a] Fisher's exact test (two-tailed).

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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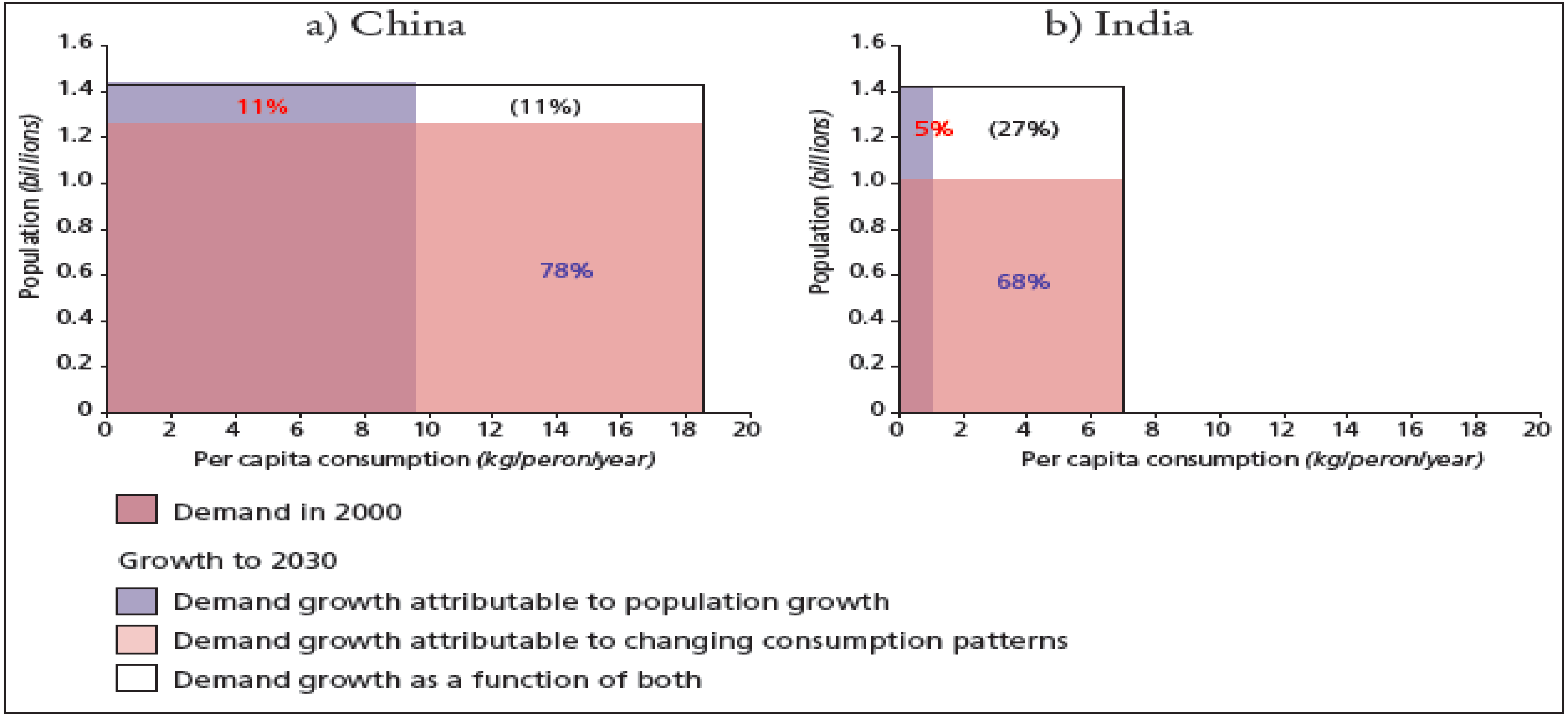
Li and Laxminarayan, *Health Economics*, 2013

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

Antibiotic use for growth promotion and disease prevention

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

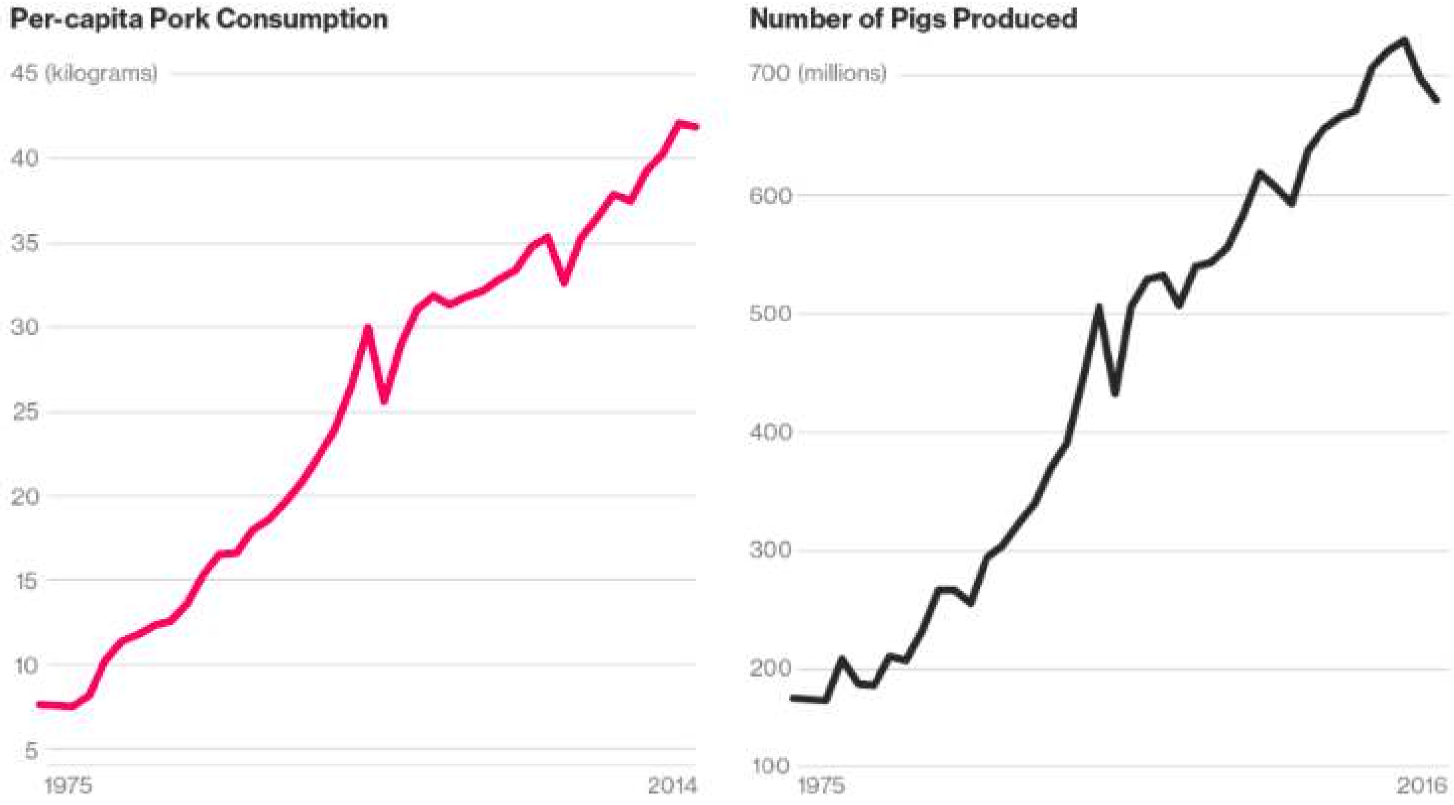
Demand for poultry in India and China is set to increase two to seven fold between 2000 and 2030



FAO, 2011

Pig Run

Swine output has surged to feed pork-hungry China



Source: Bloomberg data

Bloomberg

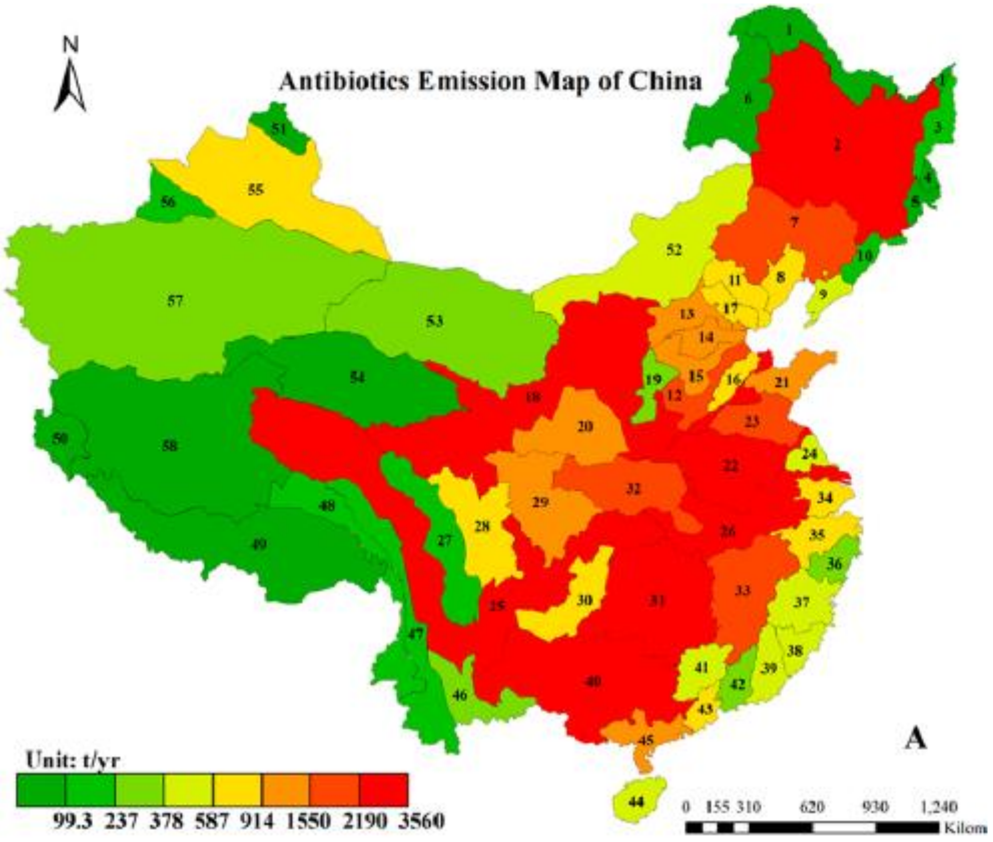
Drug Binge

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

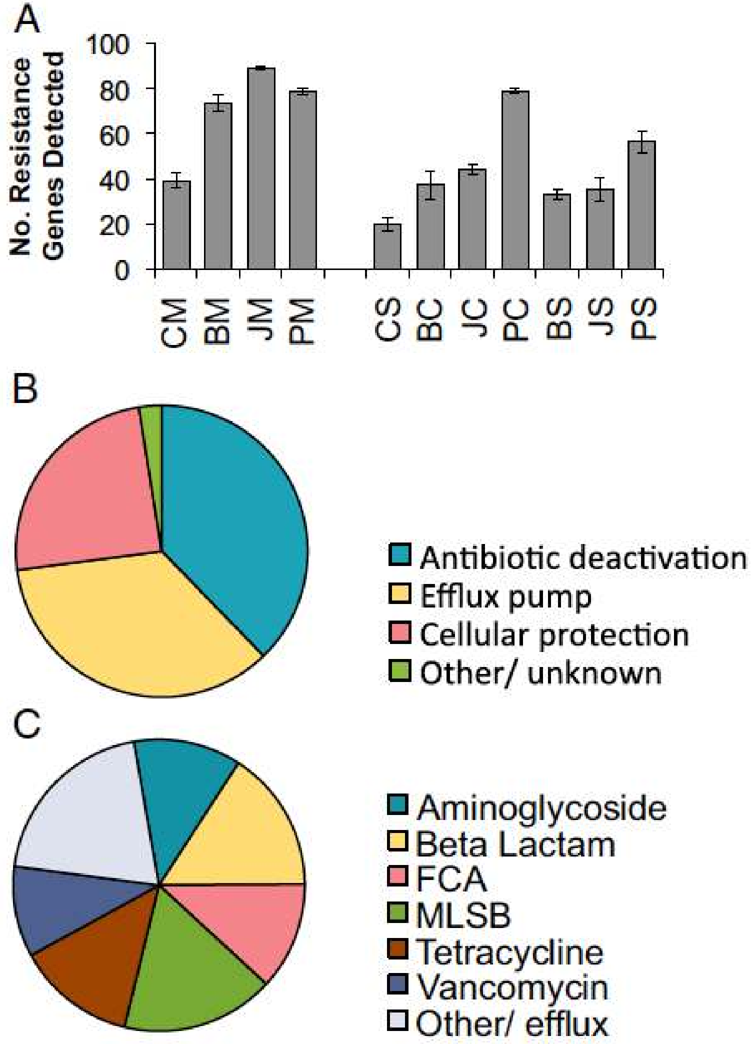
Diverse and abundant antibiot in Chinese swine farms

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]

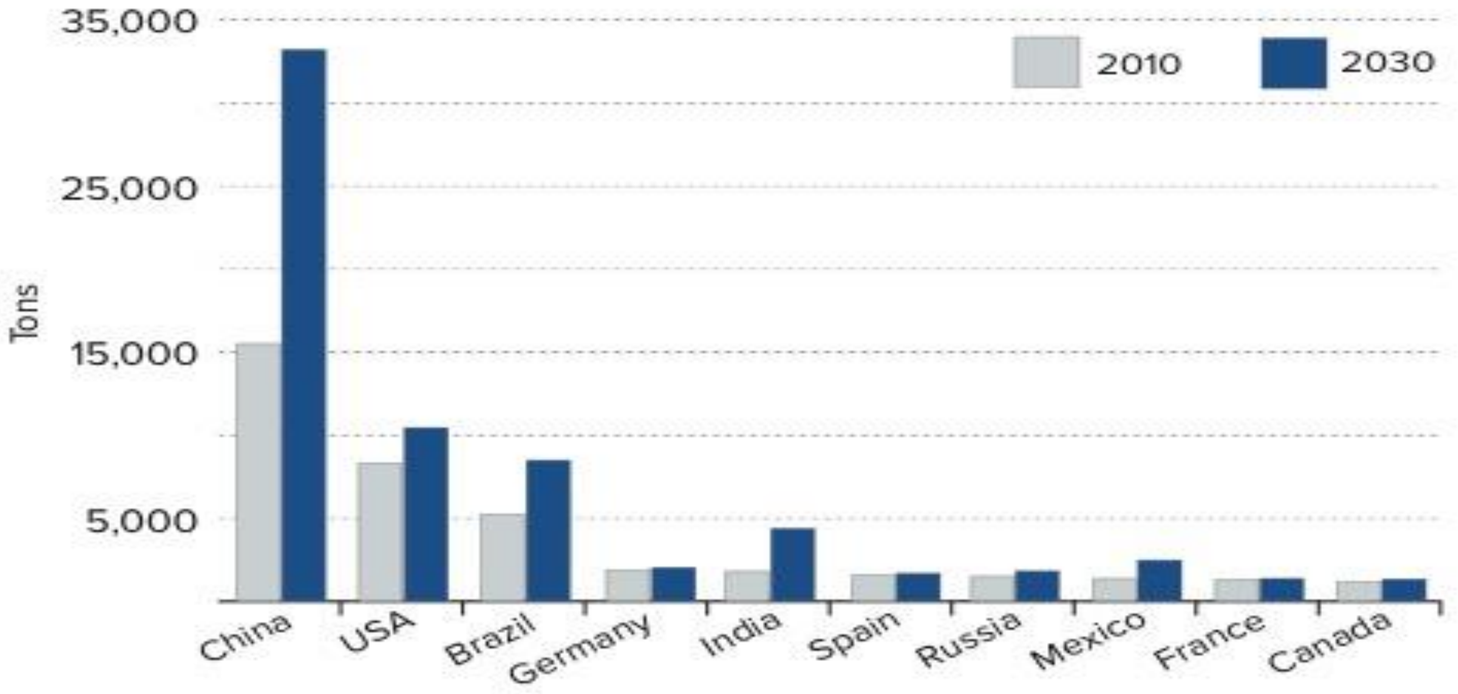
[a]Key Lab of Urban Environment and Health, Institute of Urban Environment, Chinese A
Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China; and [c]Ce
Sciences, and [e]Civil and Environmental Engineering, Michigan State University, East La

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.



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



Van Boeckel et al., PNAS, 2015

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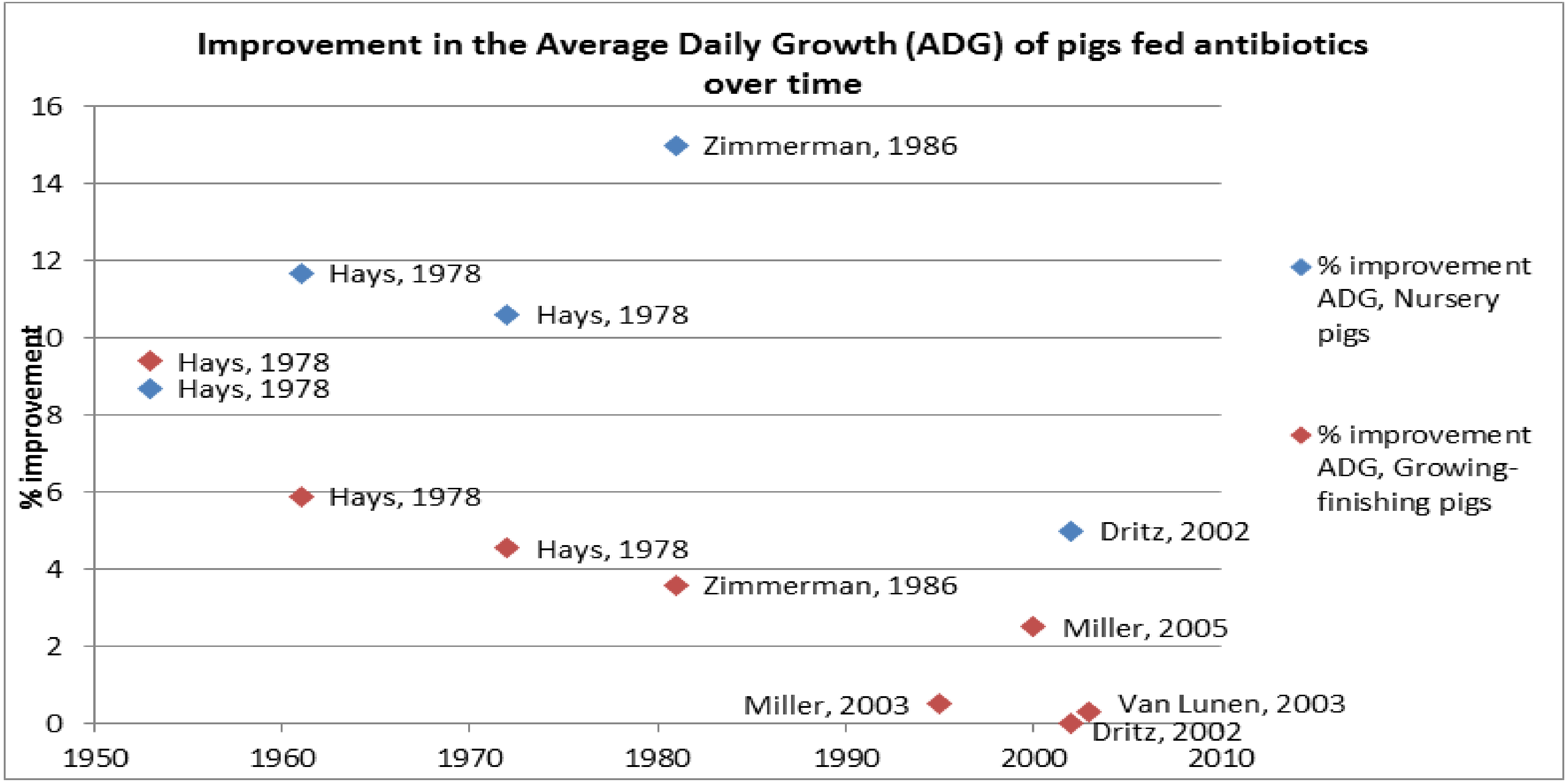
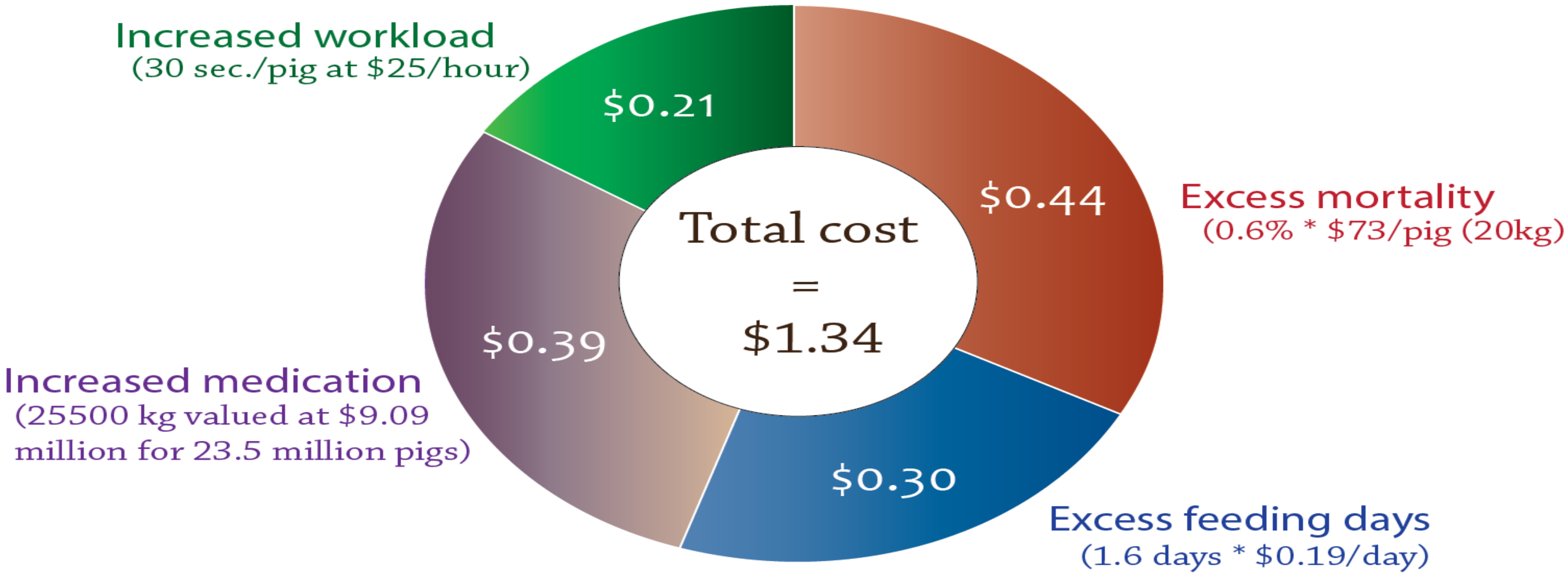


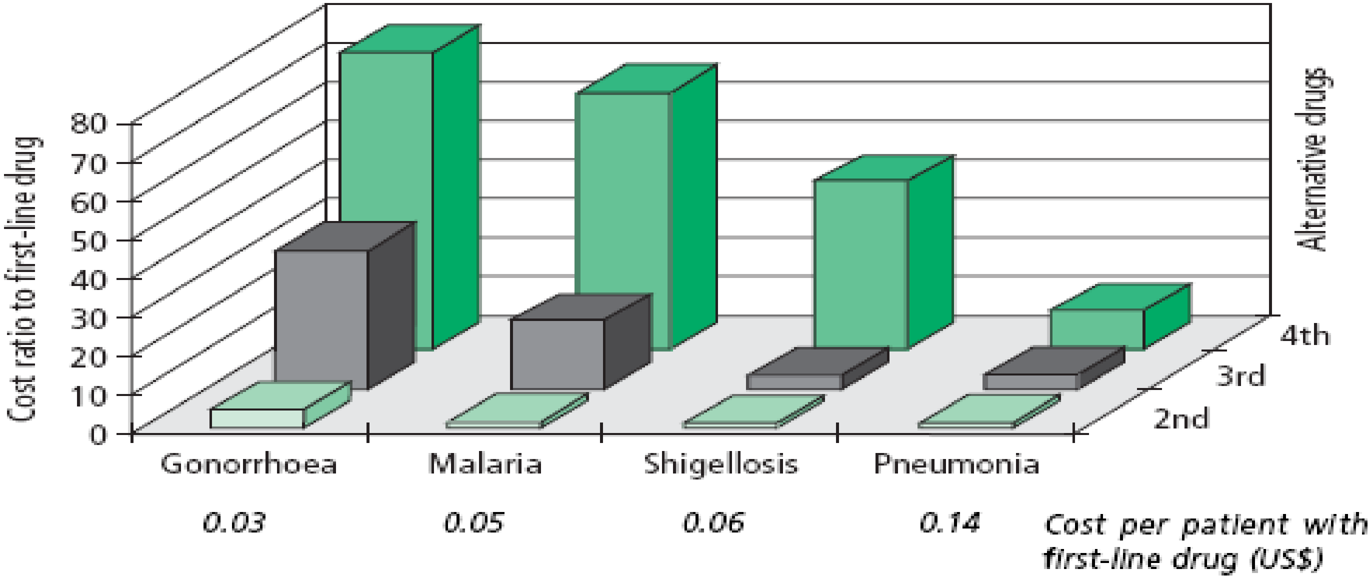
Laxminarayan et al, OECD Report, 2015

Productivity reductions and costs per produced pig incurred by removing AGPs



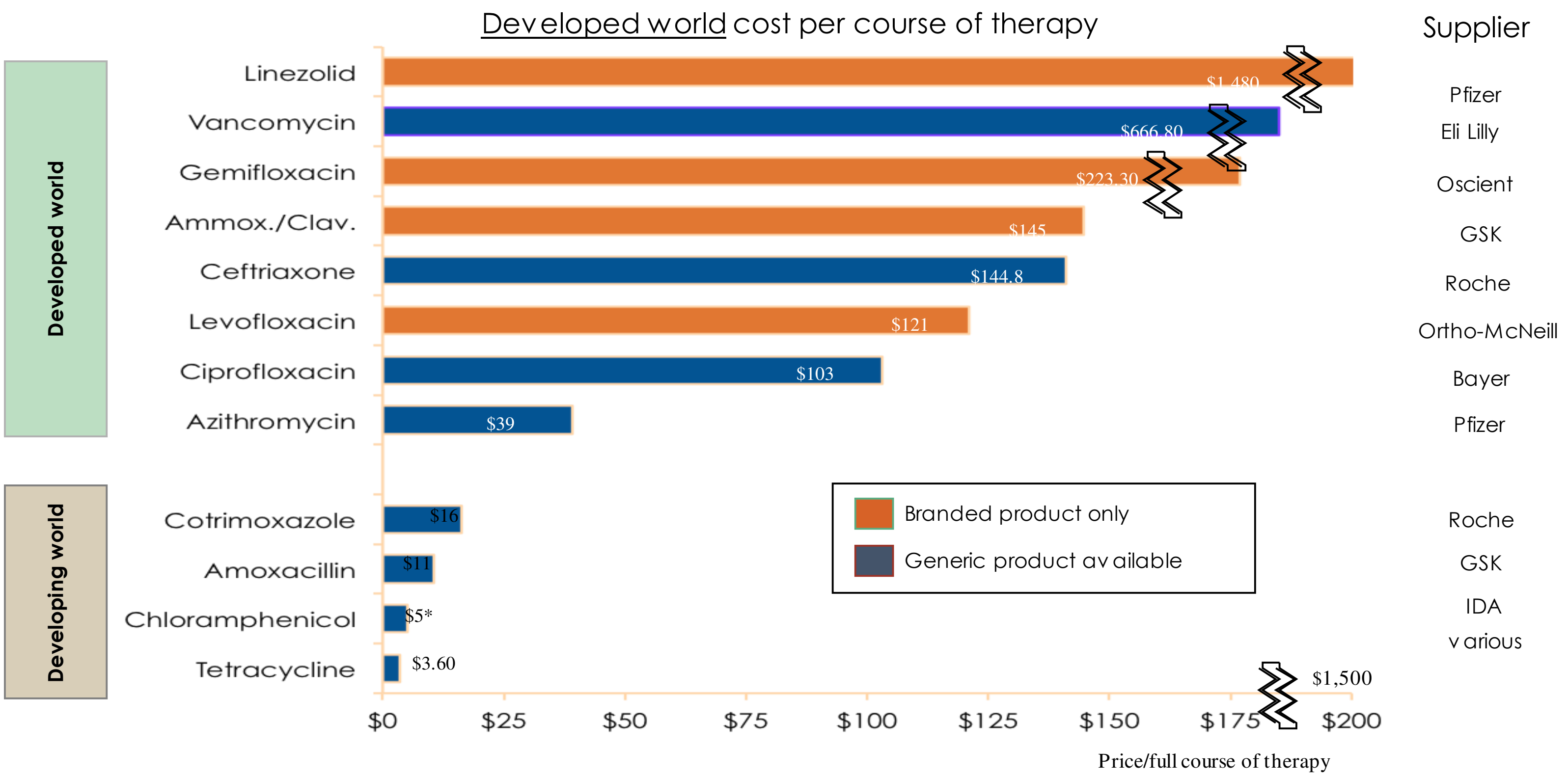
Laxminarayan et al, OECD Report, 2015

Were first line antibiotics too inexpensive?

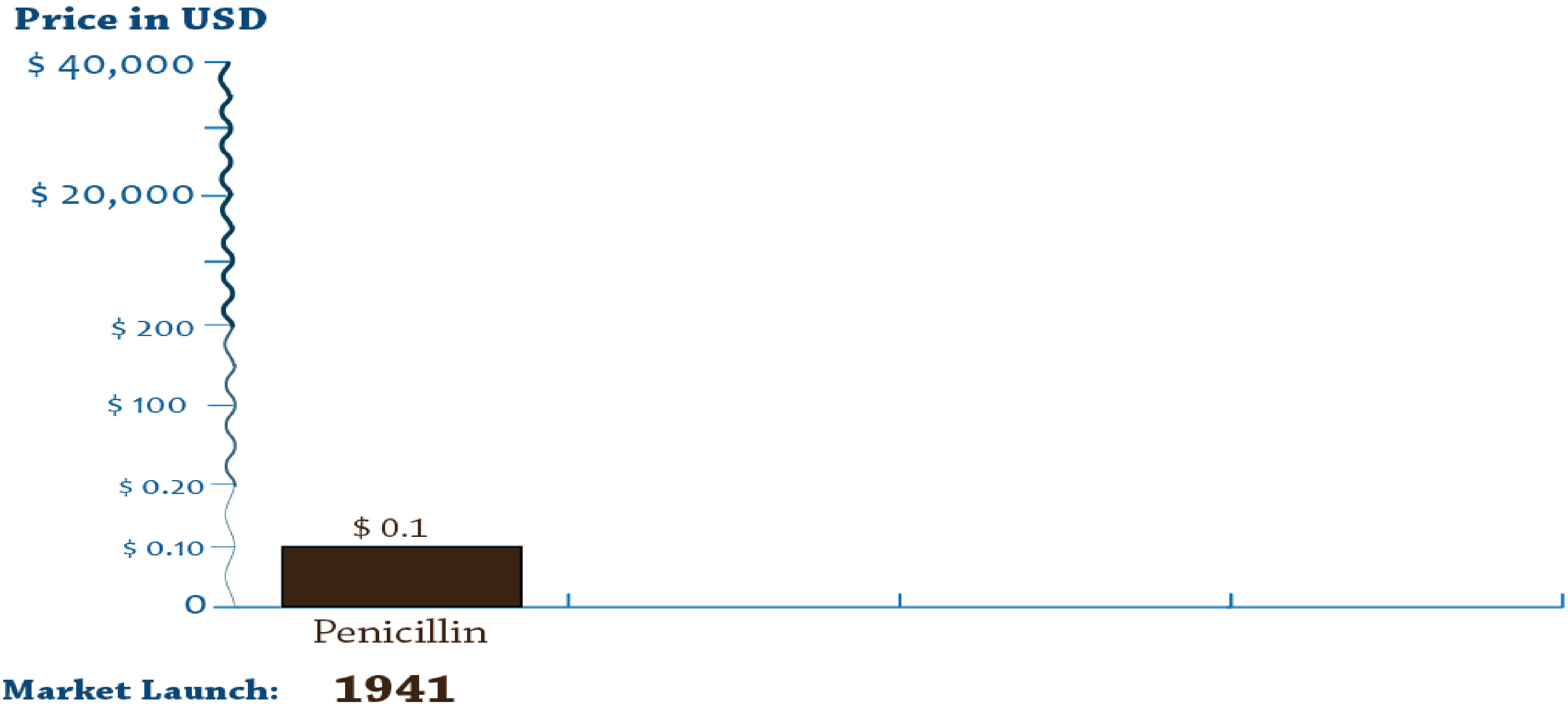


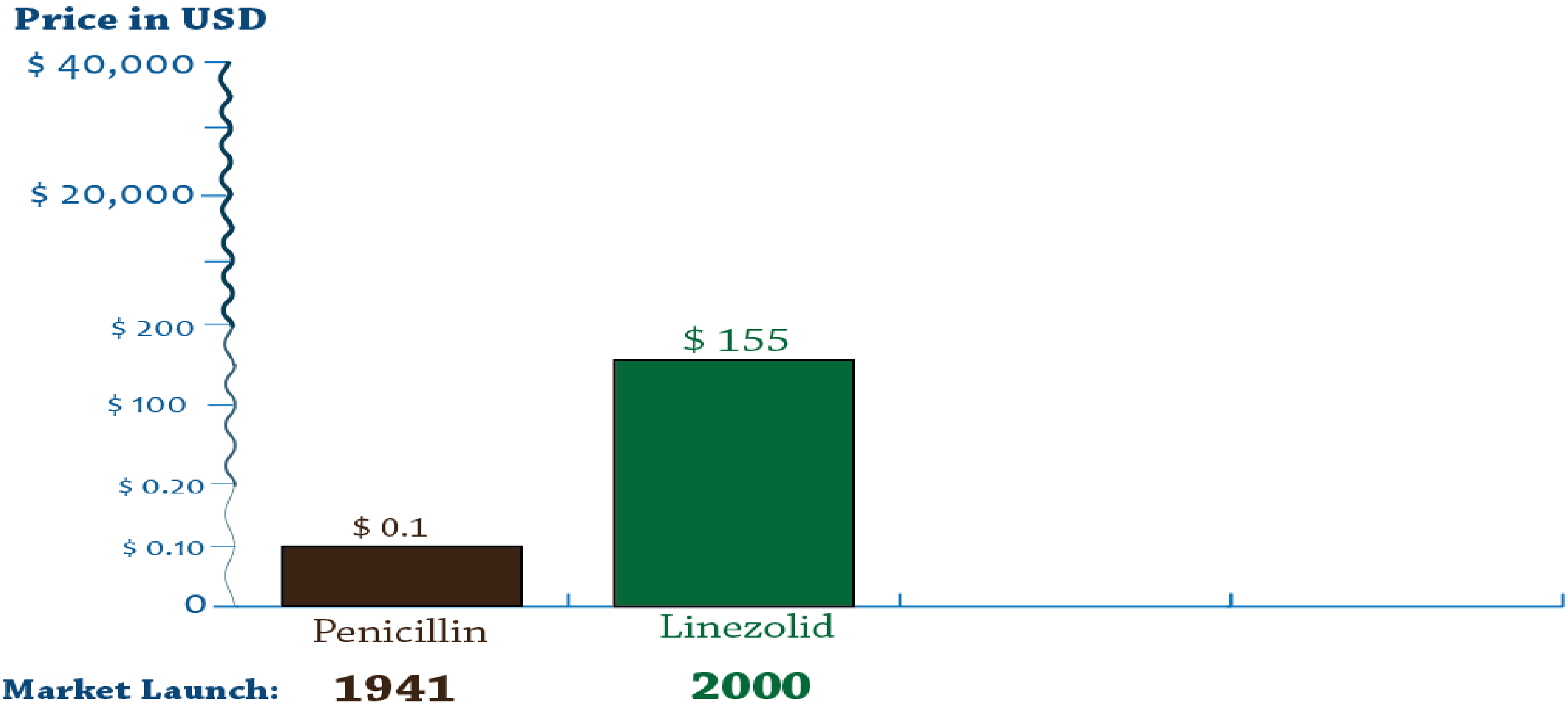
Source: WHO Policy Perspective 2005, adapted from WHO Model Formulary, WHO Clinical Guidelines and Management Sciences for Health's 2004 International Drug Price Indicator Guide (slide courtesy: David Heymann)

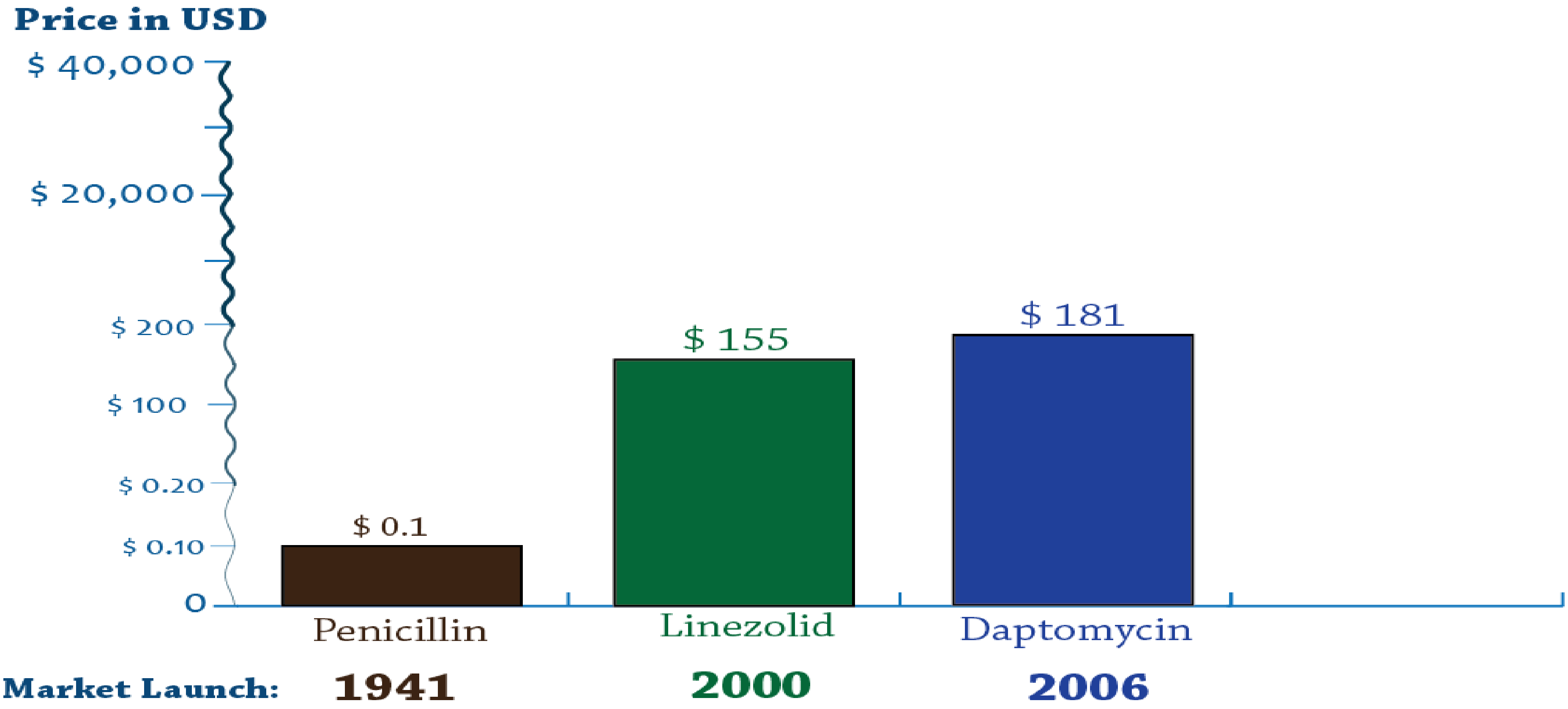
The rich pay with their wallets, the poor with their lives



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.


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
$ 0.1
$ 155
Penicillin
Linezolid
Market Launch:
1941
2000



Price in USD
$ 40,000
$ 20,000
$ 200
$ 100
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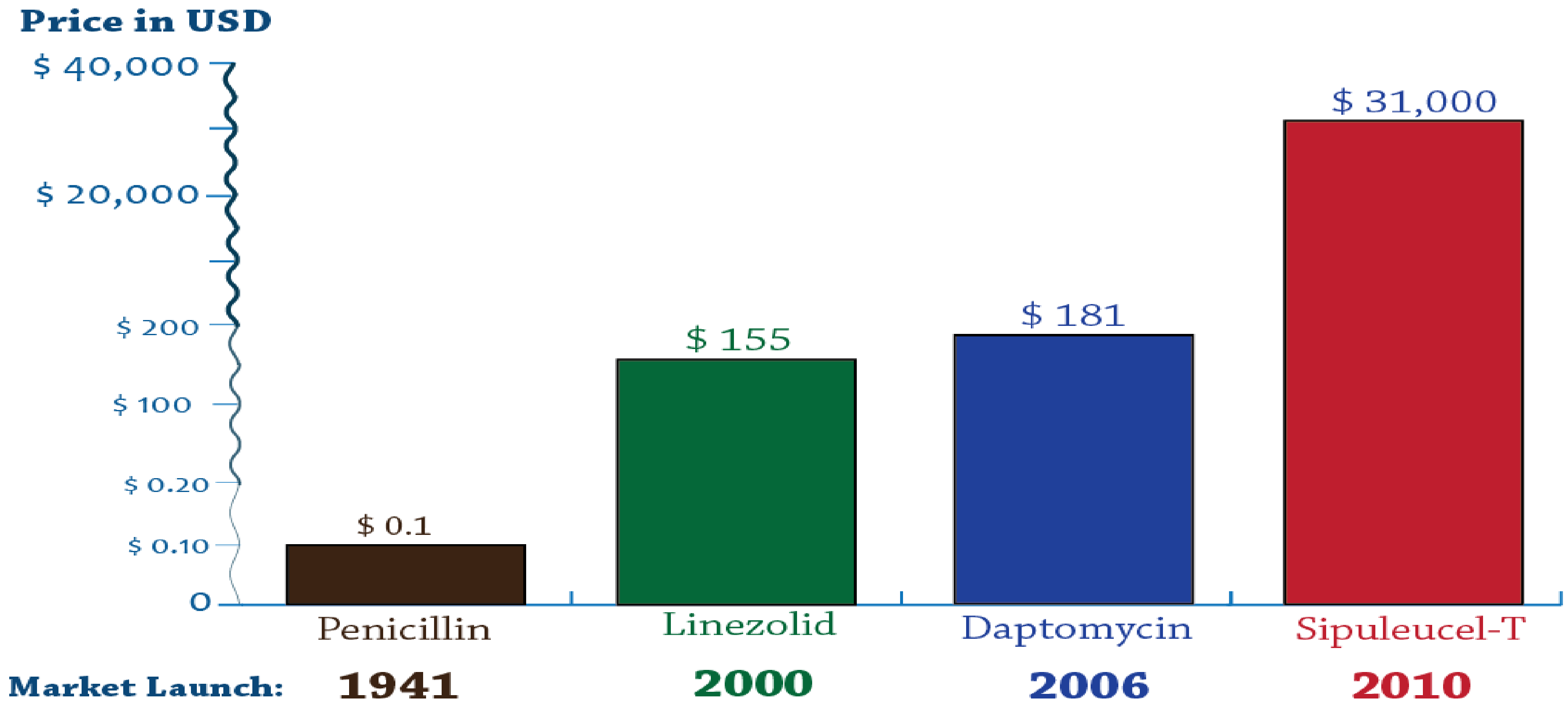
$ 155
$ 181
Penicillin
Linezolid
Daptomycin
Market Launch:
1941
2000
2006


Price in USD
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$ 20,000
$ 200
$ 100
$ 0.20
$ 0.10
0
$ 0.1
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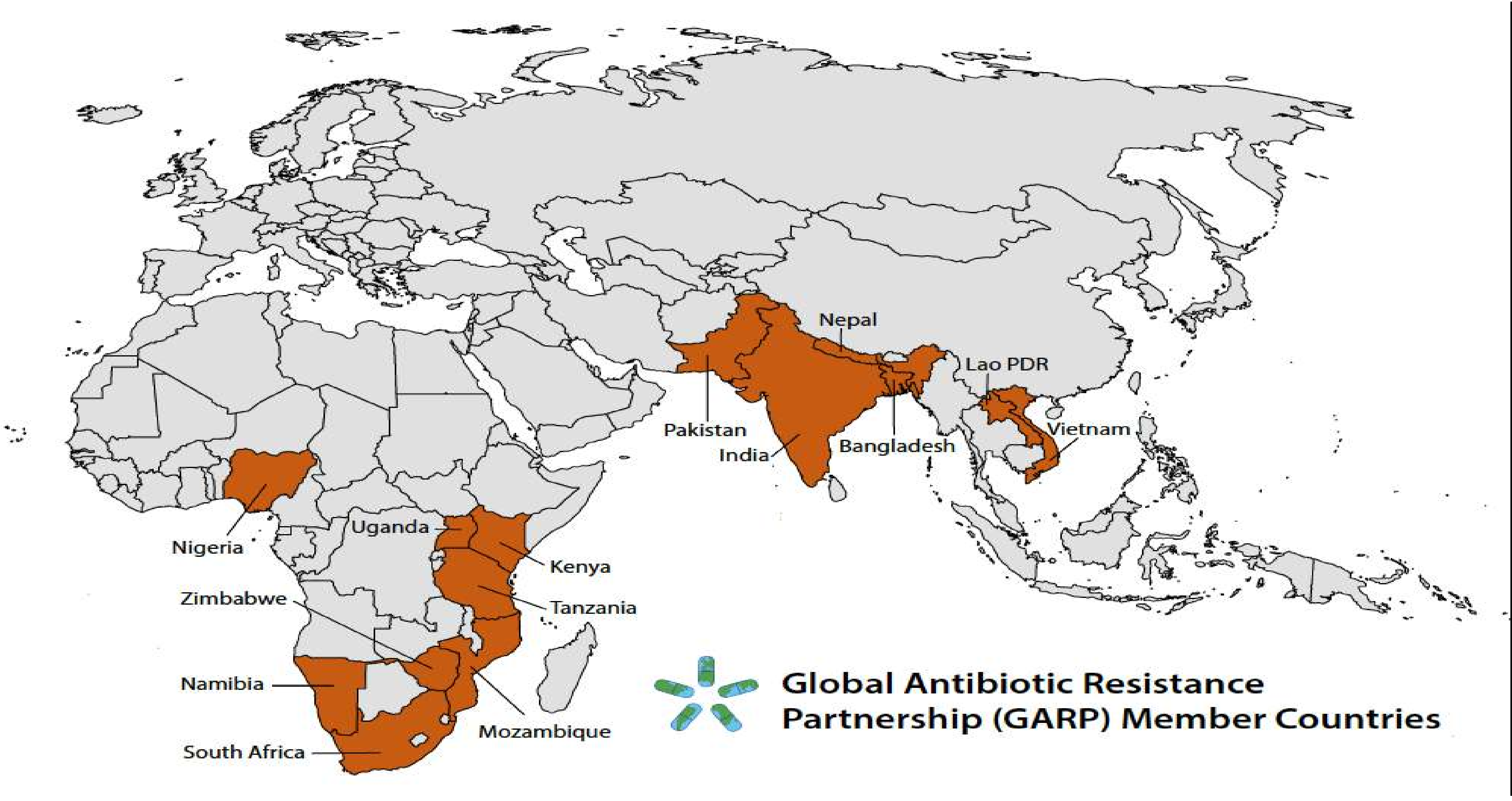
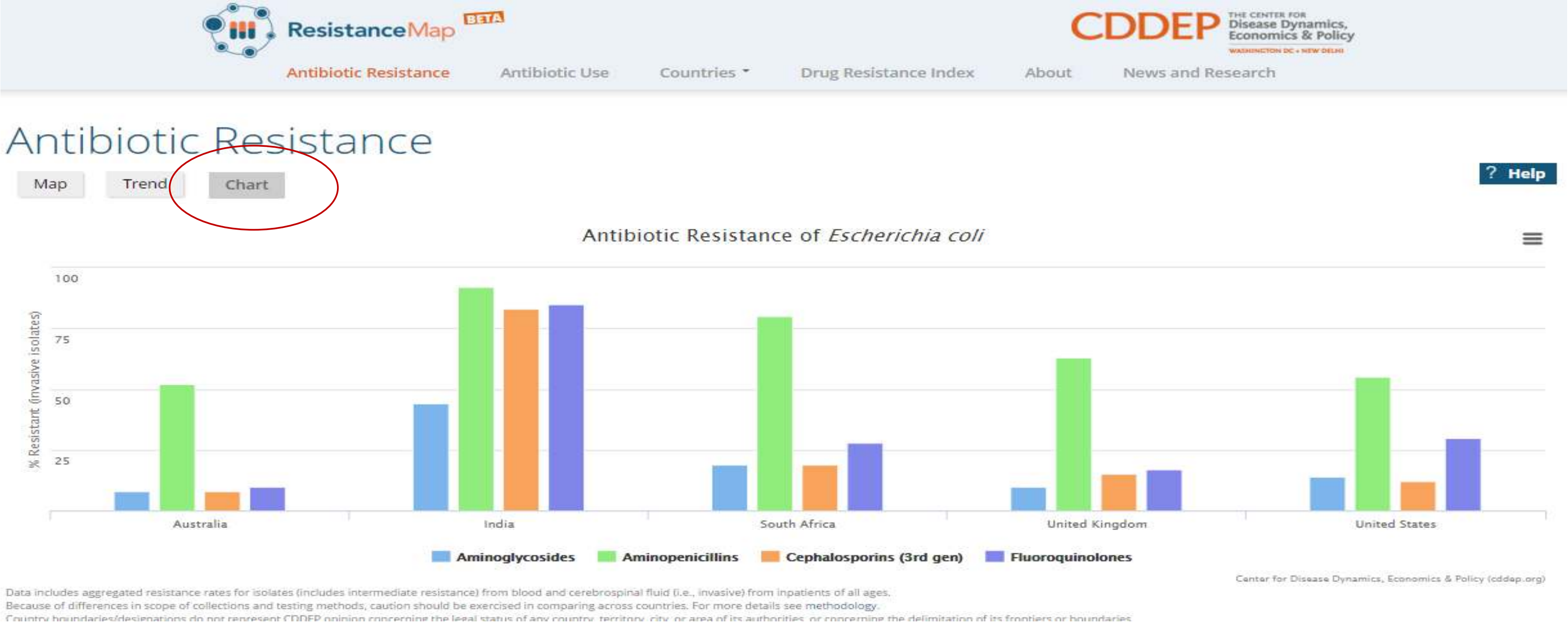
$ 31,000
Penicillin
Linezolid
Daptomycin
Sipuleucel-T
Market Launch:
1941
2000
2006
2010


Nepal
Lao PDR
Pakistan
India
Bangladesh
Vietnam
Nigeria
Uganda
Kenya
Tanzania
Zimbabwe
Namibia
Mozambique
South Africa
Global Antibiotic Resistance
Partnership (GARP) Member Countries

Resistancemap.org



Slides are downloadable @ www.cddep.org

Thank you