Antimicrobial Stewardship

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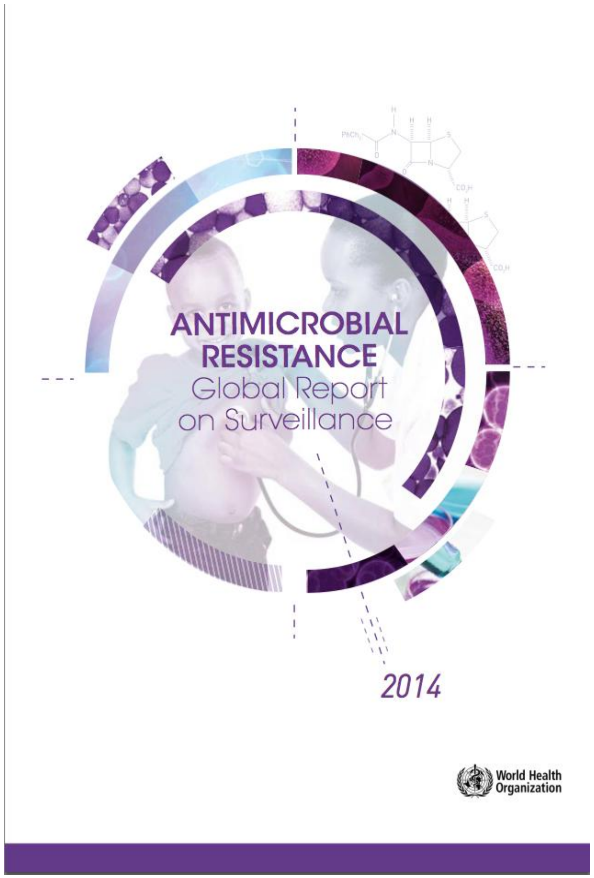
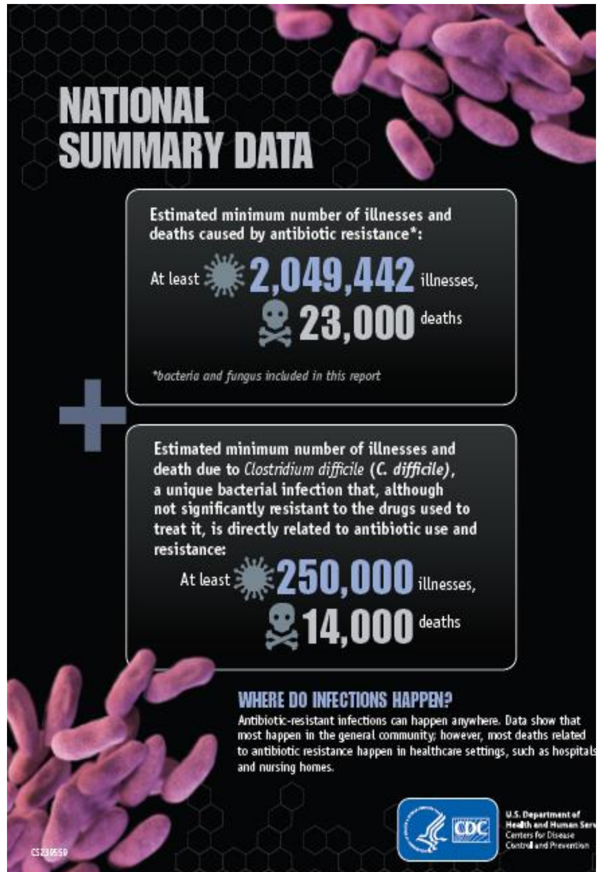
Overview

- The Problem – Antimicrobial Resistance
- The Solution – Antimicrobial Stewardship
  - Evidence for benefits of stewardship
  - Implementation of stewardship

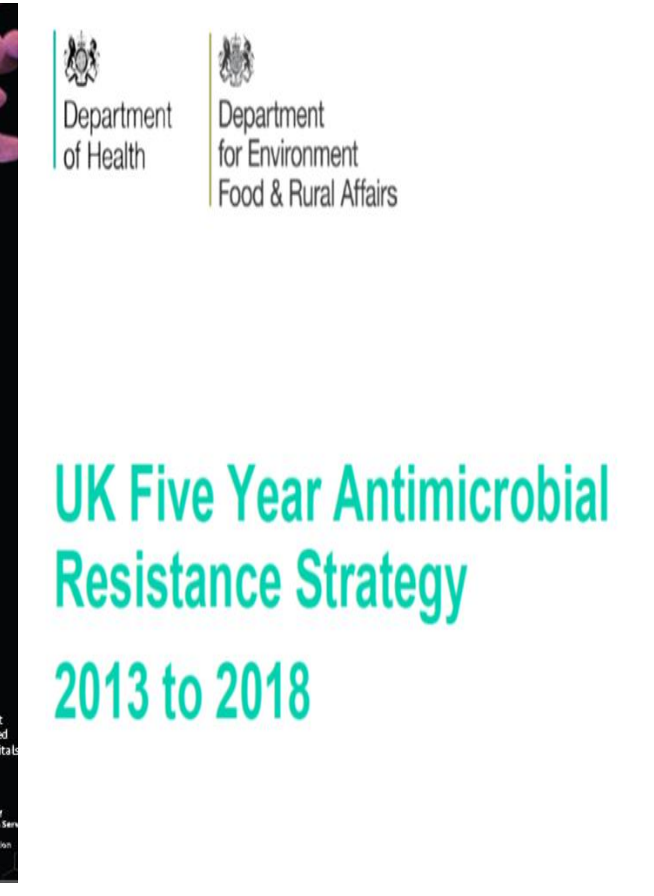
Antibiotic resistance is a global concern



WHO 2014



CDC (USA) 2013



DH (UK) 2013

What is the cost of antibiotic resistance in lives and money?

Antibiotic resistance in Europe and the world

European Union
population 500m

25,000 deaths per year

2.5m extra hospital days

<u>Overall societal costs</u>
(€ 900 million, hosp. days)
Approx. €1.5 billion per year

Source: ECDC 2007

Thailand
population 70m

>38,000 deaths

>3.2m hospital days

<u>Overall societal costs</u>
US$ 84.6–202.8 mill. direct
>US$1.3 billion indirect

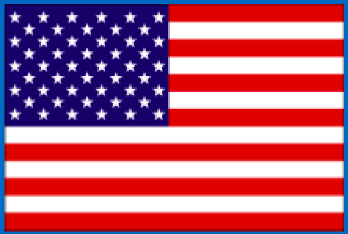
Source: Pumart et al 2012

United States
population 300m

>23,000 deaths

>2.0m illnesses

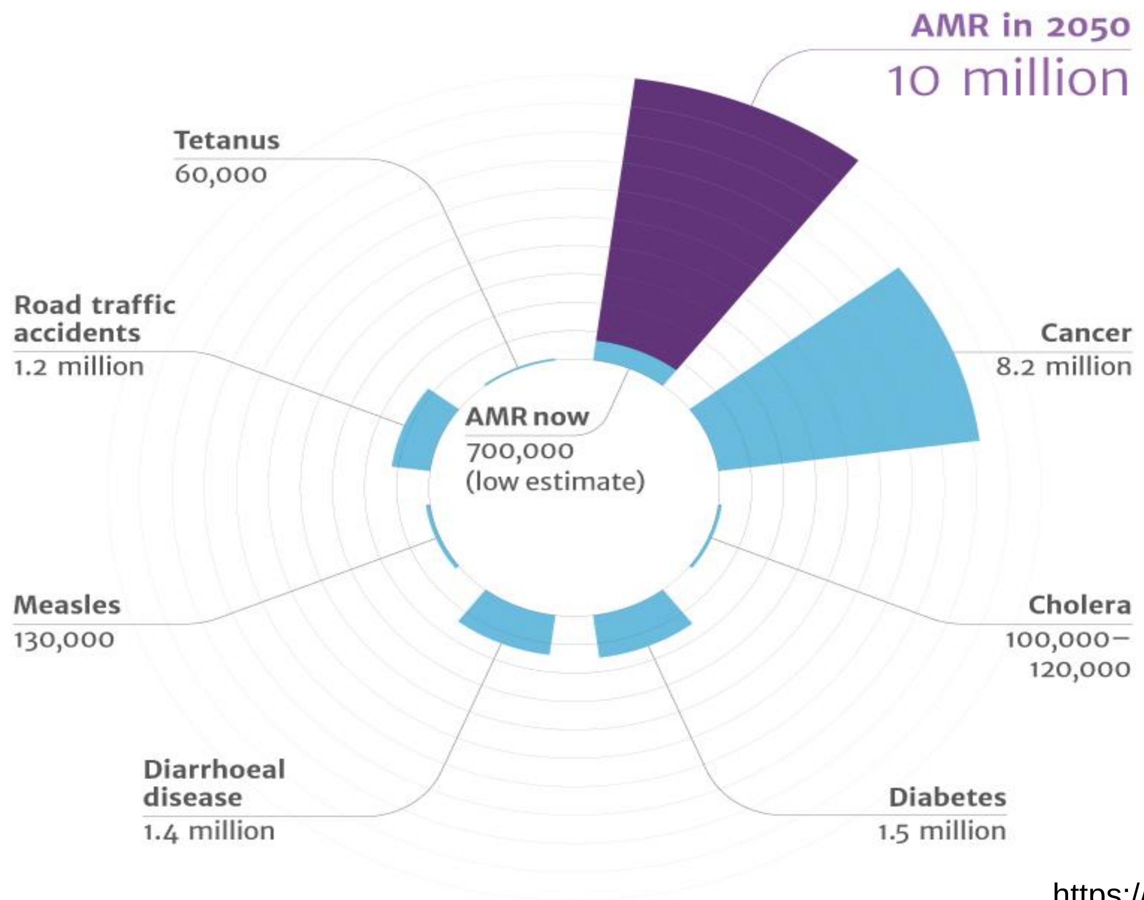
<u>Overall societal costs</u>
Up to $20 billion direct
Up to $35 billion indirect



Source: US CDC 2013

https://amr-review.org

Antimicrobial Resistance and Mortality



https://amr-review.org

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

Summary

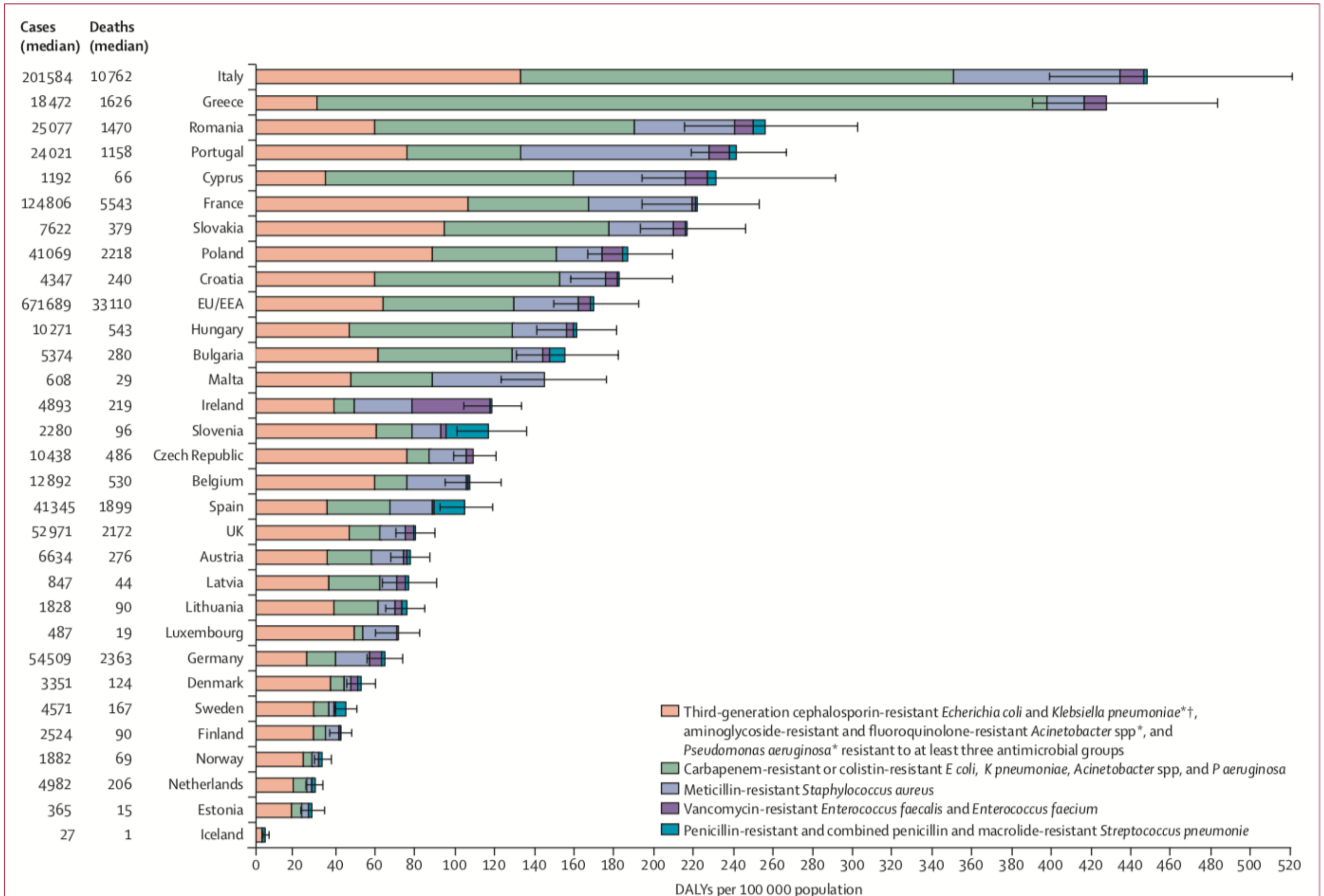


Figure 3: **Burden of infections with antibiotic-resistant bacteria in DALYs, EU and European Economic Area, 2015**

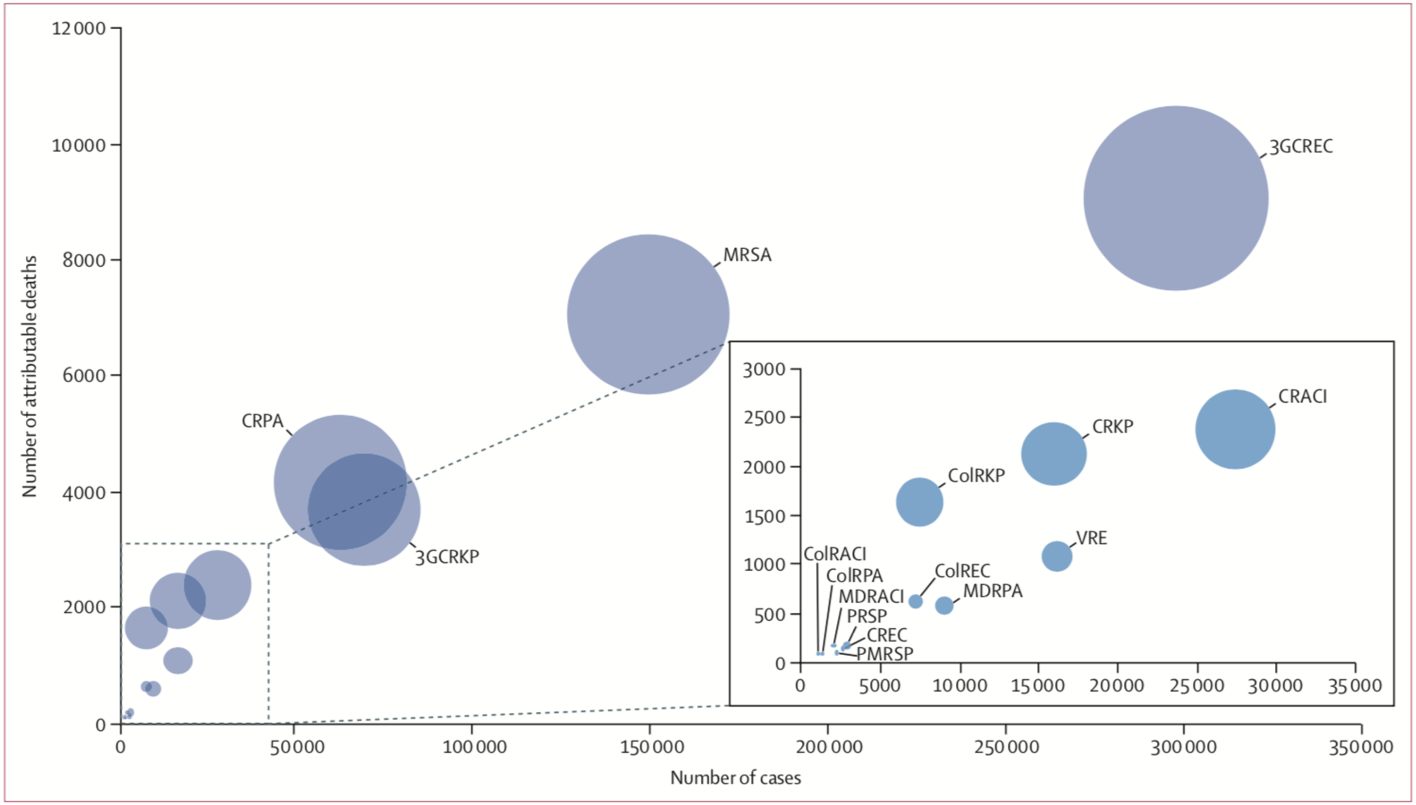


Figure 1: Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015

Diameter of bubbles represents the number of disability-adjusted life-years. ColRACI=colistin-resistant *Acinetobacter* spp. CRACI=carbapenem-resistant *Acinetobacter* spp. MDRACI=multidrug-resistant *Acinetobacter* spp. VRE=vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. ColREC=colistin-resistant *Escherichia coli*. CREC=carbapenem-resistant *E coli*. 3GCREC=third-generation cephalosporin-resistant *E coli*. ColRKP=colistin-resistant *Klebsiella pneumoniae*. CRKP=carbapenem-resistant *K pneumoniae*. 3GCRKP=third-generation cephalosporin-resistant *K pneumoniae*. ColRPA=colistin-resistant *Pseudomonas aeruginosa*. CRPA=carbapenem-resistant *P aeruginosa*. MDRPA=multidrug-resistant *P aeruginosa*. MRSA=meticillin-resistant *Staphylococcus aureus*. PRSP=penicillin-resistant *Streptococcus pneumoniae*. PMRSP=penicillin-resistant and macrolide-resistant *S pneumoniae*.

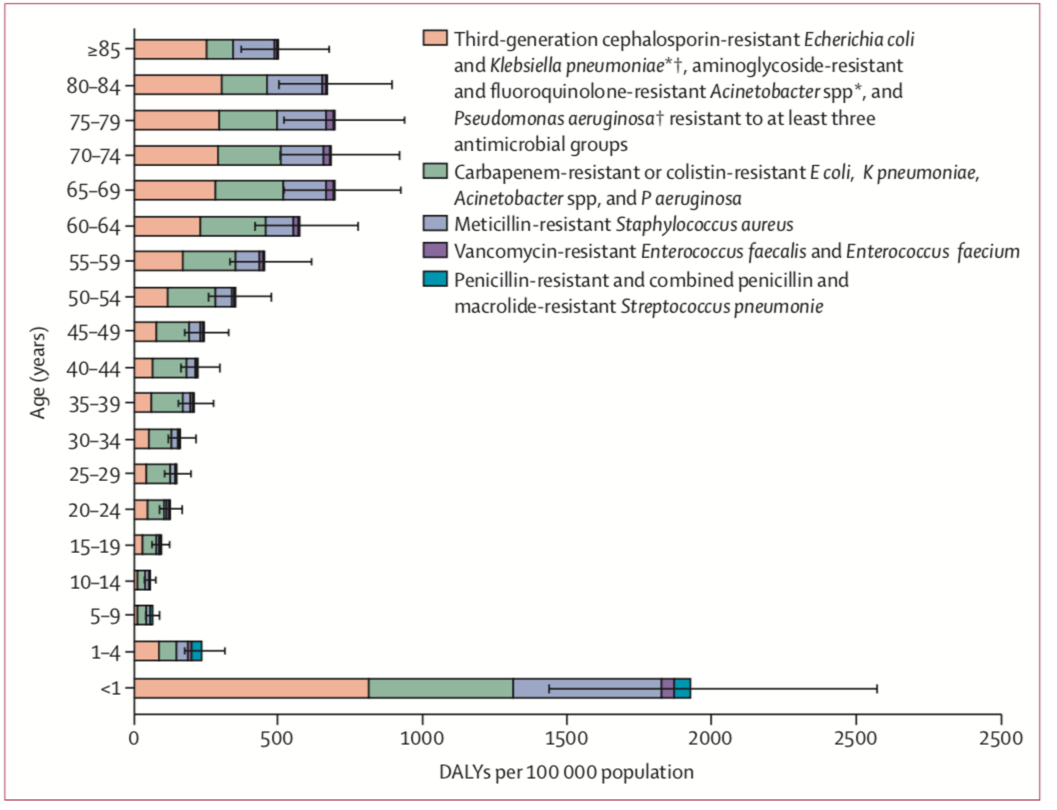


Figure 2: **Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015**

Error bars are 95% uncertainty intervals. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E coli* (88·6%) and *K pneumoniae* (85·3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum β-lactamase.[9]

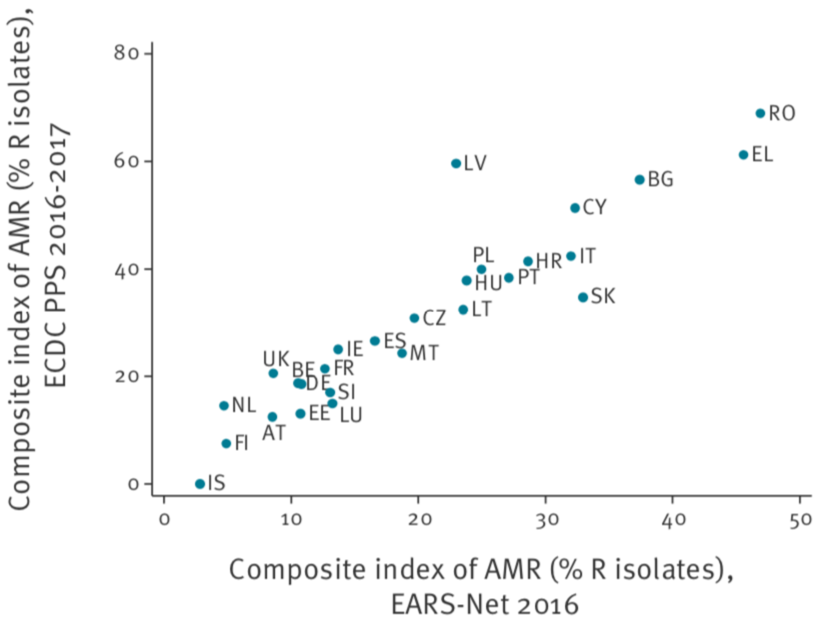
SURVEILLANCE AND OUTBREAK REPORT

Prevalence of healthcare-associated infections, estimated incidence and composite antimicrobial resistance index in acute care hospitals and long-term care facilities: results from two European point prevalence surveys, 2016 to 2017

Carl Suetens[1], Katrien Latour[2], Tommi Kärki[1], Enrico Ricchizzi[3], Pete Kinross[1], Maria Luisa Moro[3], Béatrice Jans[2], Susan Hopkins[4], Sonja Hansen[5], Outi Lyytikäinen[6], Jacqui Reilly[7,8], Aleksander Deptuła[9], Walter Zingg[10], Diamantis Plachouras[1], Dominique L Monnet[1], the Healthcare-Associated Infections Prevalence Study Group[11]

1. European Centre for Disease Prevention and Control, Solna, Sweden
2. Sciensano, Brussels, Belgium
3. Agenzia sanitaria e sociale regionale – Regione Emilia Romagna, Bologna, Italy
4. Public Health England, London, United Kingdom
5. Institute of Hygiene and Environmental Medicine, Charité – University Medicine Berlin, Berlin, Germany
6. National Institute for Health and Welfare, Department of Health Security, Helsinki, Finland
7. National Services Scotland, Health Protection Scotland, Glasgow, United Kingdom
8. Glasgow Caledonian University, Glasgow, United Kingdom
9. Department of Propaedeutics of Medicine, Nicolaus Copernicus University, Toruń; Ludwik Rydygier Collegium Medicum; Bydgoszcz, Poland
10. Imperial College London, London, United Kingdom
11. Members of the Healthcare-Associated Infections Prevalence Study Group are listed at the end of this article

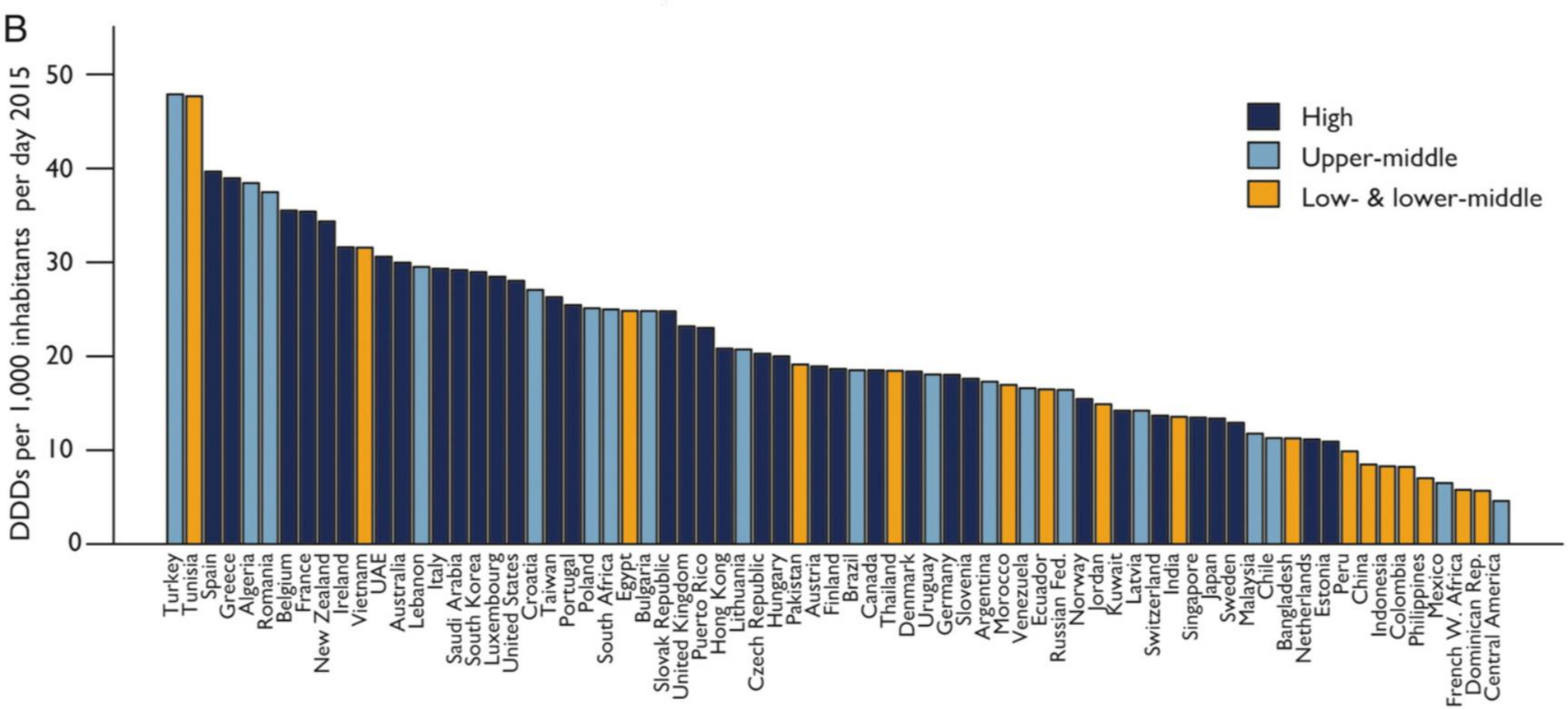
A. Correlation between the composite indices of AMR from the PPS in acute care hospitals, 2016-2017 and EARS-Net, 2016 (n = 27 countries)



Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

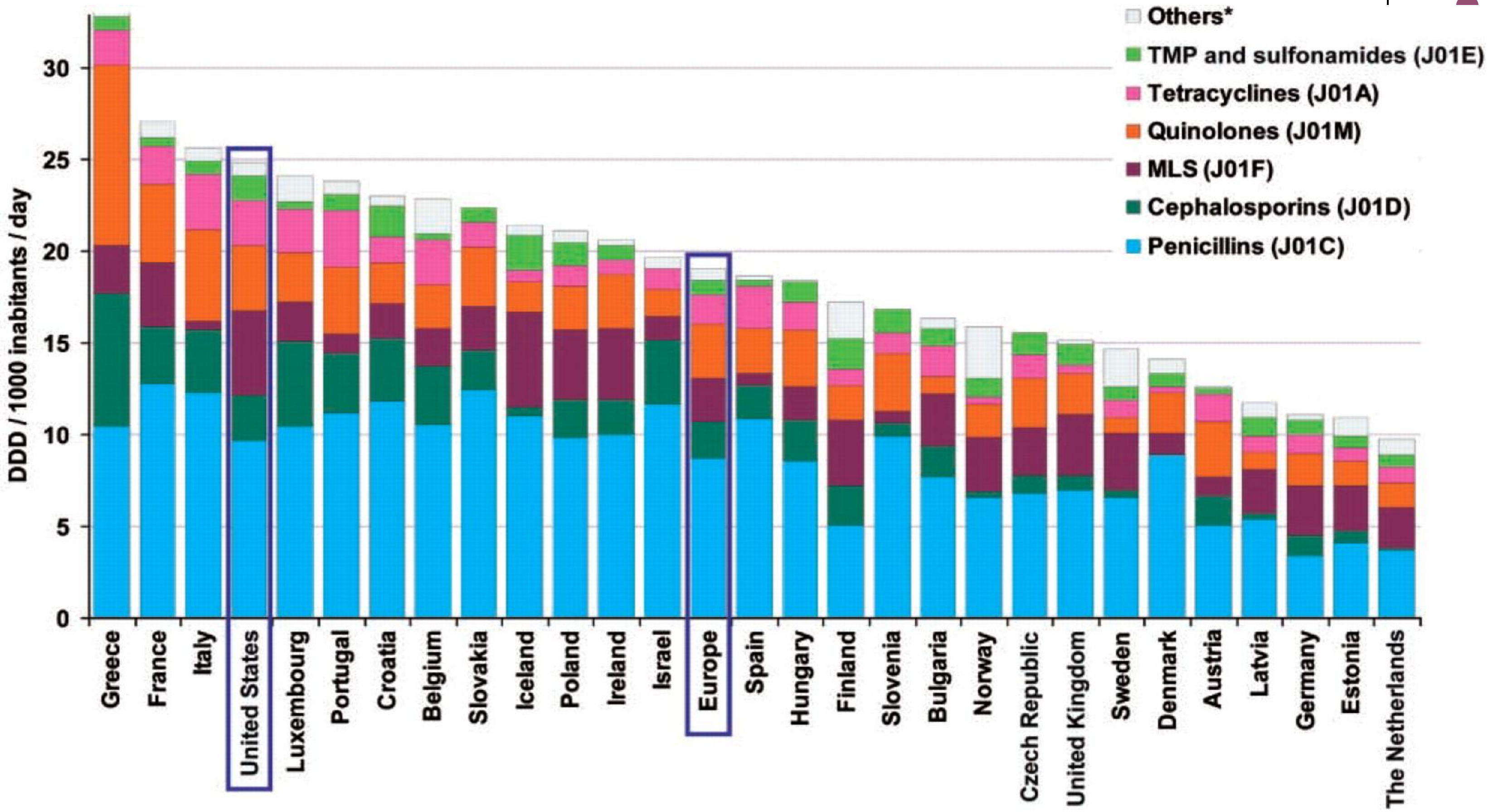
Eili Y. Klein[a,b,c,1], Thomas P. Van Boeckel[d], Elena M. Martinez[a], Suraj Pant[a], Sumanth Gandra[a], Simon A. Levin[e,f,g,1], Herman Goossens[h], and Ramanan Laxminarayan[a,f,i]

[a]Center for Disease Dynamics, Economics & Policy, Washington, DC 20005; [b]Department of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21209; [c]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; [d]Institute of Integrative Biology, ETH Zürich, CH-8006 Zürich, Switzerland; [e]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; [f]Princeton Environmental Institute, Princeton University, Princeton, NJ 08544; [g]Beijer Institute of Ecological Economics, SE-104 05 Stockholm, Sweden; [h]Laboratory of Medical Microbiology, Vaccine & Infectious Diseases Institute, University of Antwerp, 2610 Antwerp, Belgium; and [i]Department of Global Health, University of Washington, Seattle, WA 98104


B
DDDs per 1,000 inhabitants per day 2015
0
10
20
30
40
50
High
Upper-middle
Low- & lower-middle
Turkey
Tunisia
Spain
Greece
Algeria
Romania
Belgium
France
New Zealand
Ireland
Vietnam
UAE
Australia
Lebanon
Italy
Saudi Arabia
South Korea
Luxembourg
United States
Croatia
Taiwan
Portugal
Poland
South Africa
Egypt
Bulgaria
Slovak Republic
United Kingdom
Puerto Rico
Hong Kong
Lithuania
Czech Republic
Hungary
Pakistan
Austria
Finland
Brazil
Canada
Thailand
Denmark
Uruguay
Germany
Slovenia
Argentina
Morocco
Venezuela
Ecuador
Russian Fed.
Norway
Jordan
Kuwait
Latvia
Switzerland
India
Singapore
Japan
Sweden
Malaysia
Chile
Bangladesh
Netherlands
Estonia
Peru
China
Indonesia
Colombia
Philippines
Mexico
French W. Africa
Dominican Rep.
Central America

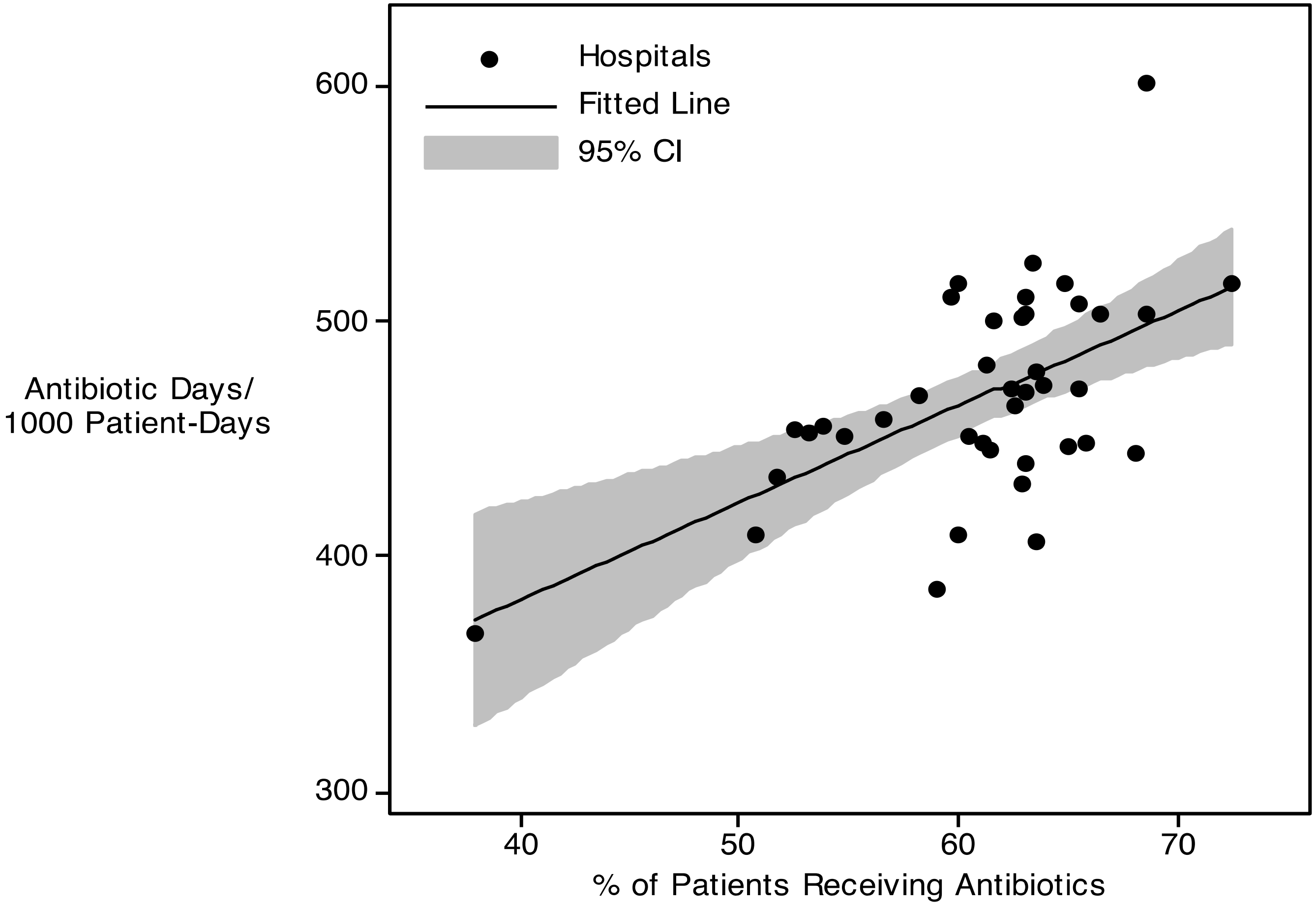
Variability in Antibiotic Use: Do we really know what we are doing?

Total outpatient antibacterial use in the USA and European countries



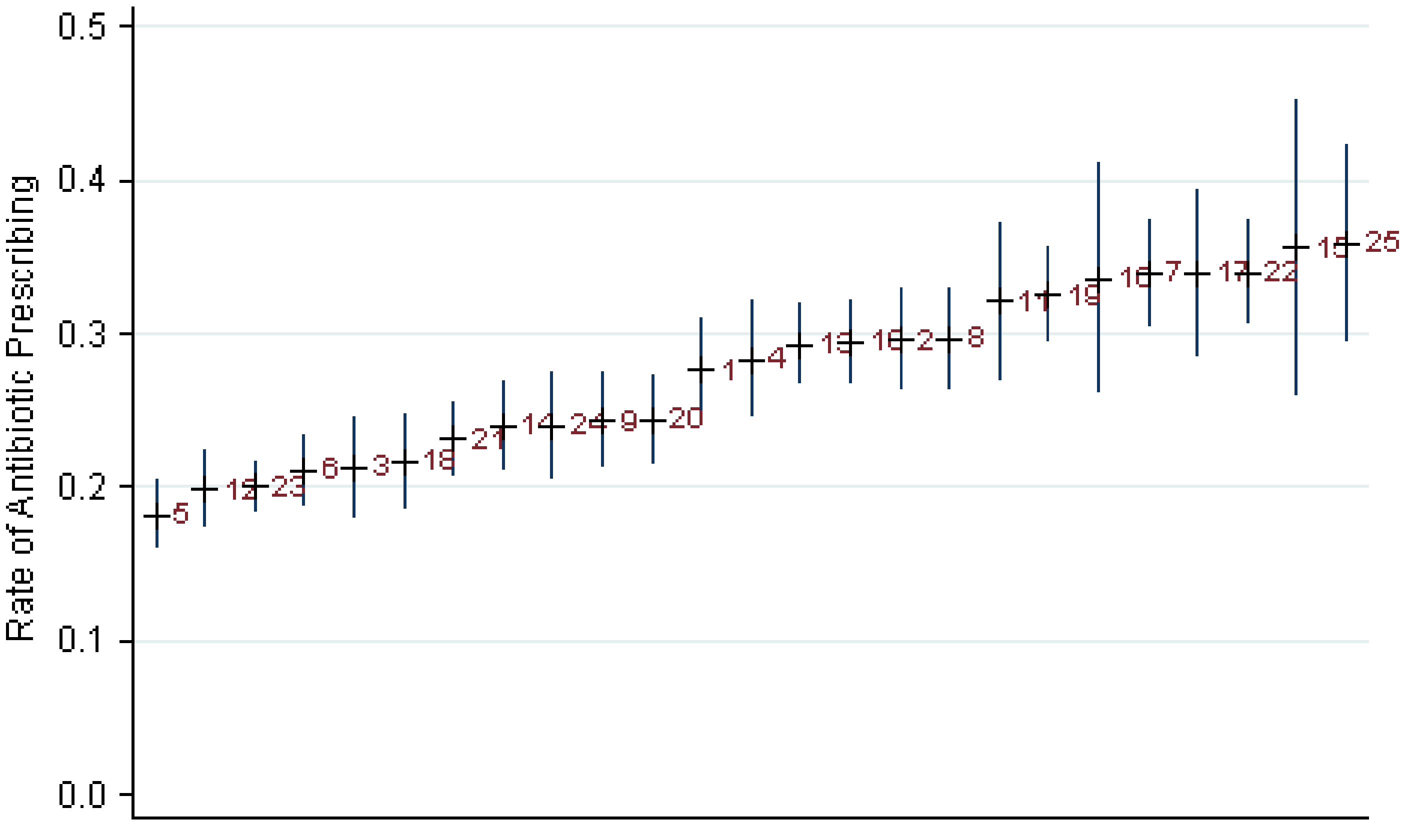
Goossens H et al. Clin Infect Dis. 2007;44:1091-1095

Variability in Antibiotic Use in Hospitalized Children



Gerber JS, et al. Pediatrics 2010

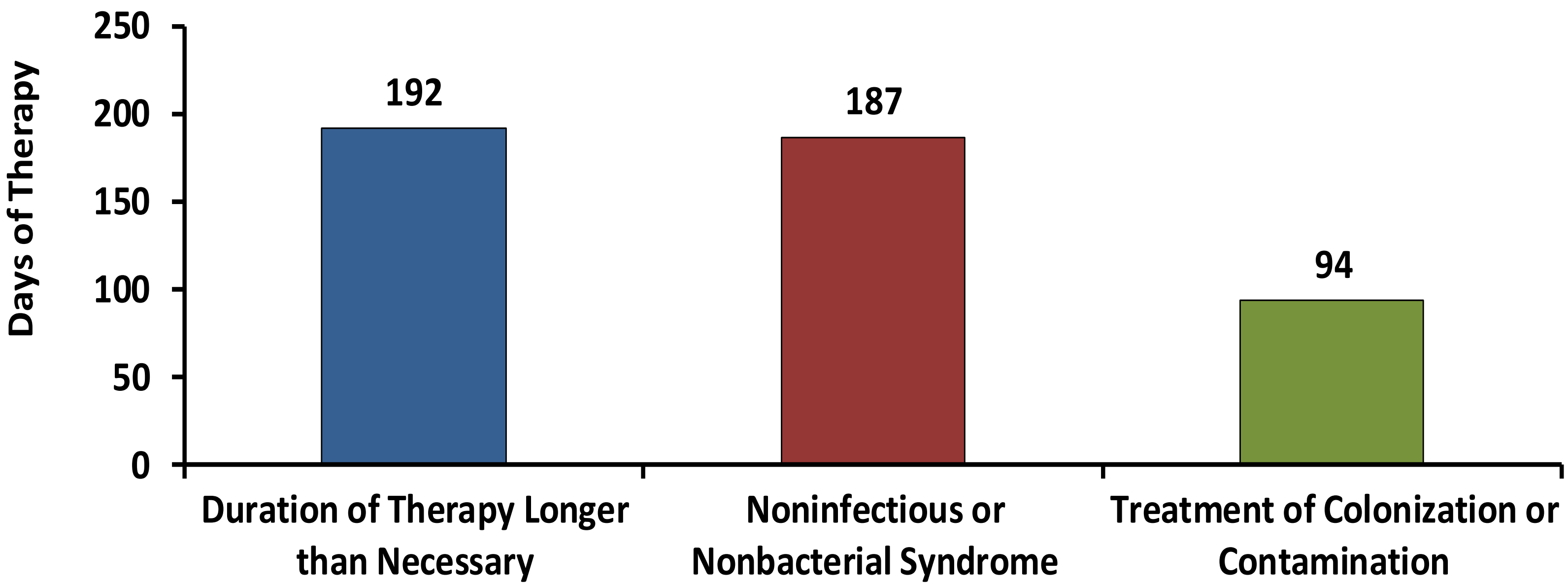
Antibiotic Prescribing in the Outpatient Setting



Gerber JS, et al. JPIDS in press

Most Common Reasons for Unnecessary Days of Therapy in Inpatients

576 (30%) of 1941 days of antimicrobial therapy deemed unnecessary



Hecker MT1, Aron DC, Patel NP, Lehmann MK, Donskey CJ. Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med. 2003 Apr 28;163(8):972-8.

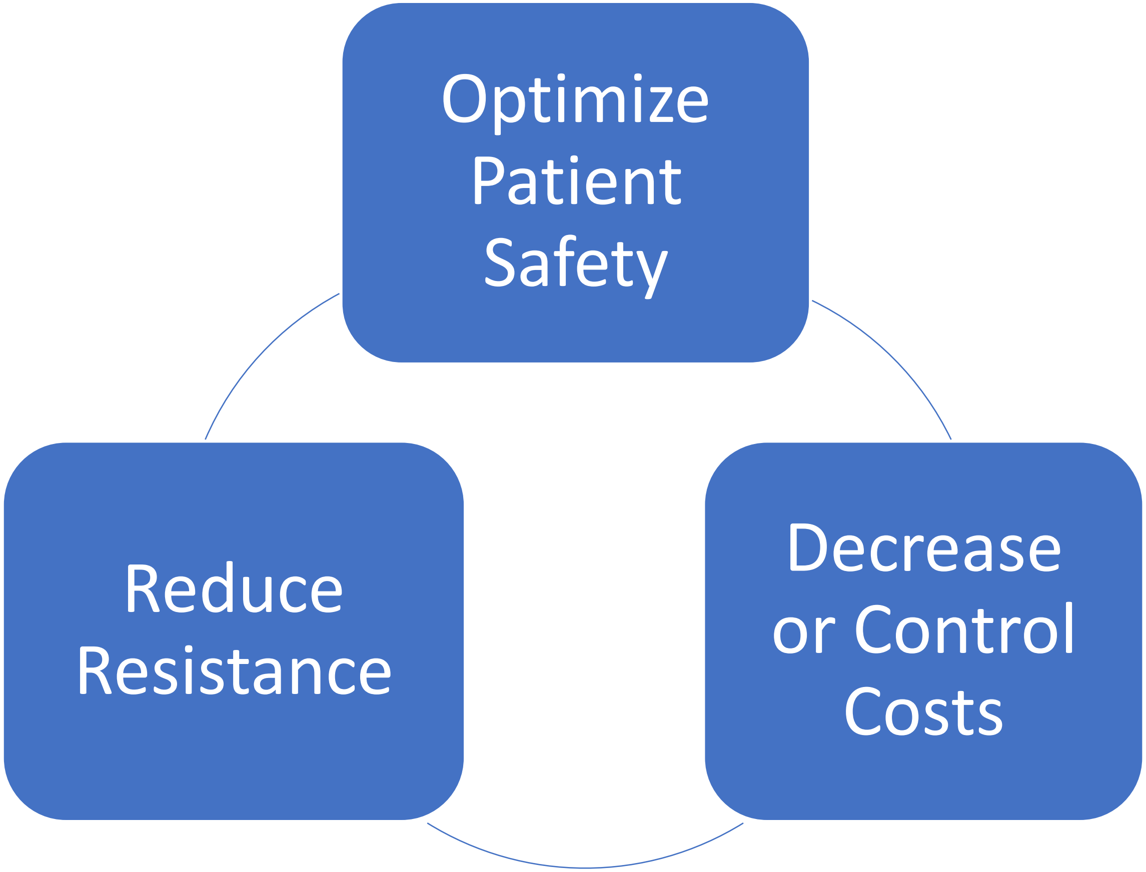
Core Actions to Combat Resistance

1. Preventing Infections, Spread of Resistance
   - Immunization, infection control, handwashing, safe food preparation
2. Tracking
3. Improving Antibiotic Use/Stewardship
   - **Perhaps most important action needed**
4. Development of drugs and diagnostic tests

Definition: Improving Stewardship

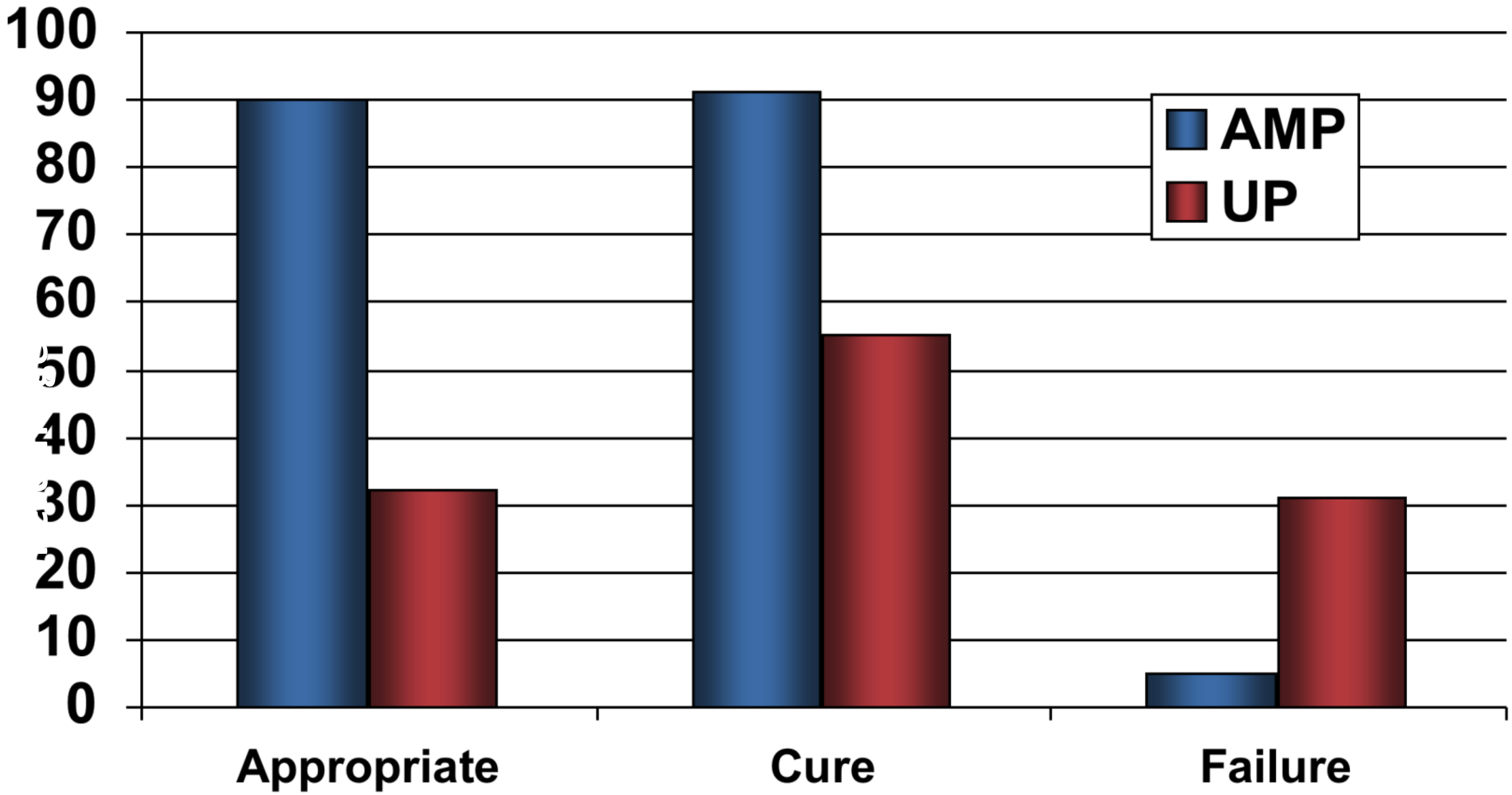
- The use of antibiotics is the single most important factor leading to antibiotic resistance and the single most important action needed to greatly slow the development and spread of resistance
- Commitment to always use antibiotics appropriately and safely-only when they are needed to treat disease, and to chose the right antibiotics and to administer them in the right way in every case = antibiotic stewardship

ASP Objectives



Benefits of Stewardship: The Evidence

Optimize Patient Safety: Improved Clinical Outcomes



AMP=antibiotic management program; UP=usual practice; RR=relative risk; CI=confidence interval.

Fishman N. Am J Med. 2006;119(6 suppl 1):S53-S61.

Optimize Patient Safety: Decreased C. difficile

- **The Netherlands:** restricted use of cephalosporins and a complete ban on fluoroquinolones plus infection control ended NAP1 outbreak

- **Canada:** education about limiting use of targeted antibiotics (cephalosporins, ciprofloxacin, clindamycin, and macrolides) but not infection control ended NAP1 outbreak

Debast SB1, Vaessen N, Choudry A, Wiegers-Ligtvoet EA, van den Berg RJ, Kuijper EJ. Successful combat of an outbreak due to Clostridium difficile PCR ribotype 027 and recognition of specific risk factors. Clin Microbiol Infect. 2009 May;15(5):427-34

Valiquette L1, Cossette B, Garant MP, Diab H, Pépin J. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of Clostridium difficile-associated disease caused by the hypervirulent NAP1/027 strain. Clin Infect Dis. 2007 Sep 1;45 Suppl 2:S112-21.

Stewardship Decreases Resistance

- Ben Taub General Hospital, 1994
- ID faculty held approval pager 24/7

  - All broad-spectrum antibiotic required approval (ticar/clav, imipenem, aztreonam, ceftazidime, ciprofloxacin, ofloxacin, amikacin, IV fluconazole)
- Increased susceptibility of Gram negatives

P. aeruginosa susceptibilities, 1/93-12/93 vs. 7/94-6/95

Ticar/clav	Imipenem	Aztreonam	Ceftazidime	Cipro
83 → 89	83 → 95	70 → 88	76 → 92	83 → 87

White AC Jr, Atmar RL, Wilson J, Cate TR, Stager CE, Greenberg SB. Effects of requiring prior authorization for selected antimicrobials: expenditures, susceptibilities, and clinical outcomes. Clin Infect Dis. 1997 Aug;25(2):230-9.

Stewardship Decreases Costs

Strategy	Type of Institution	Annual Cost Savings
Pre-prescription approval	County teaching hospital	$803,910
	Tertiary care hospital	$302,400
Post-prescription review	Tertiary care hospital	Decrease abx charge per patient ($1287 vs. $1873, $p<0.04$)
	VA hospital	$145,942
	Community hospital (175 beds)	$200,000-250,000
	Community hospital (120 beds)	$177,000
	Argentinean hospital (250 beds)	$913,236

White AC et al. Clin Infect Dis. 1997;25:230-239. Fishman N. Am J Med. 2006;119:S53-S61.
Fraiser GL et al. Arch Intern Med. 1997;157:1689-94. Gentry CA et al. Am J Health Syst Pharm. 2000;57:268-74.
LaRocco A. Clin Infect Dis. 2003;37:742-3; Bantar C et al. Clin Infect Dis. 2003;37:180-6.
Carling P et al. Infect Control Hosp Epidemiol. 2003;24:699-706.

Current data from pediatric antimicrobial stewardship programs

Inpatient antimicrobial stewardship in pediatrics: a systematic review

- Systematic review of PubMed
- Articles related to pediatric ASP
- 9 original articles related to formal pediatric ASP's
- Reductions in:
  - antimicrobial utilization
  - cost
  - prescribing errors
- No apparent negative impact on patient safety

Smith MJ, Gerber JS, Hersh AL, JPIDS 2015 in Press.

Inpatient Stewardship Programs: Core Elements

The New Model:
A Spectrum of Activities

Comprehensive program led by ID trained physician and pharmacist

Individual interventions based on goals of institution led by individual (s) with interest

Many approaches in between

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CPCE
The Center for Pediatric Clinical Effectiveness

Who Can Be A Steward?

- Not realistic to expect that all institutions have ID trained physicians
- and pharmacists
- Basic requirements:
  1. Interest in stewardship/patient safety/performance improvement
  2. Basic knowledge of antibiotics
  3. Dedicated time
- Alternatives to ID physician: hospitalist, microbiology director, surgeon, intensivist
- Alternatives to ID pharmacist: pharmacist with advanced training (e.g. critical care, medicine), pharmacist with training in stewardship
- Activities scalable to comfort level

Primary Approaches

Approach	Definition	Pros	Cons
Formulary management	Eliminate unnecessary duplication of agents	•Control over how and why antibiotics are used •Better pricing	Impact on good use of antibiotics likely minimal
Pre-prescription approval	Phone call placed or form filled out before pharmacy dispenses antibiotic	•Reduces starting unnecessary antibiotics •Useful way to deal with high cost antibiotics	•Impacts use of restricted agents only •Addresses empiric use >> downstream use •Resource intensive in real time

Primary Approaches

Approach	**Definition**	**Pros**	**Cons**
Post-prescription review	Downstream review of appropriateness of antibiotic therapy, usually at 24-72 hours	•More clinical data available to enhance uptake of recommendations •Greater flexibility in timing of interventions	Recommended action is optional and may not be followed by prescribers

Examples

- **Formulary management**
  - Pick one antibiotic in class
- **Pre-prescription review**
  - Restrict expensive agents such as daptomycin, linezolid, carbapenems, echinocandins
- **Post-prescription review**
  - Focus on use of an expensive drug (see above) or commonly used agent like vancomycin
  - Focus on a disease state such as bacteremia, asymptomatic bacteriuria, CAP
  - Focus on IV to PO conversion

Antibiotic Stewardship and Behavior Change

- Antibiotic Stewardship (AS) interventions use different strategies (both persuasive and restrictive) to **change the prescribing behaviors** of frontline clinicians
  - Education
  - Audit and Feedback
  - Restricted Formularies
  - Prior Approval

- Prescribing behavior is a complex, multifactorial process

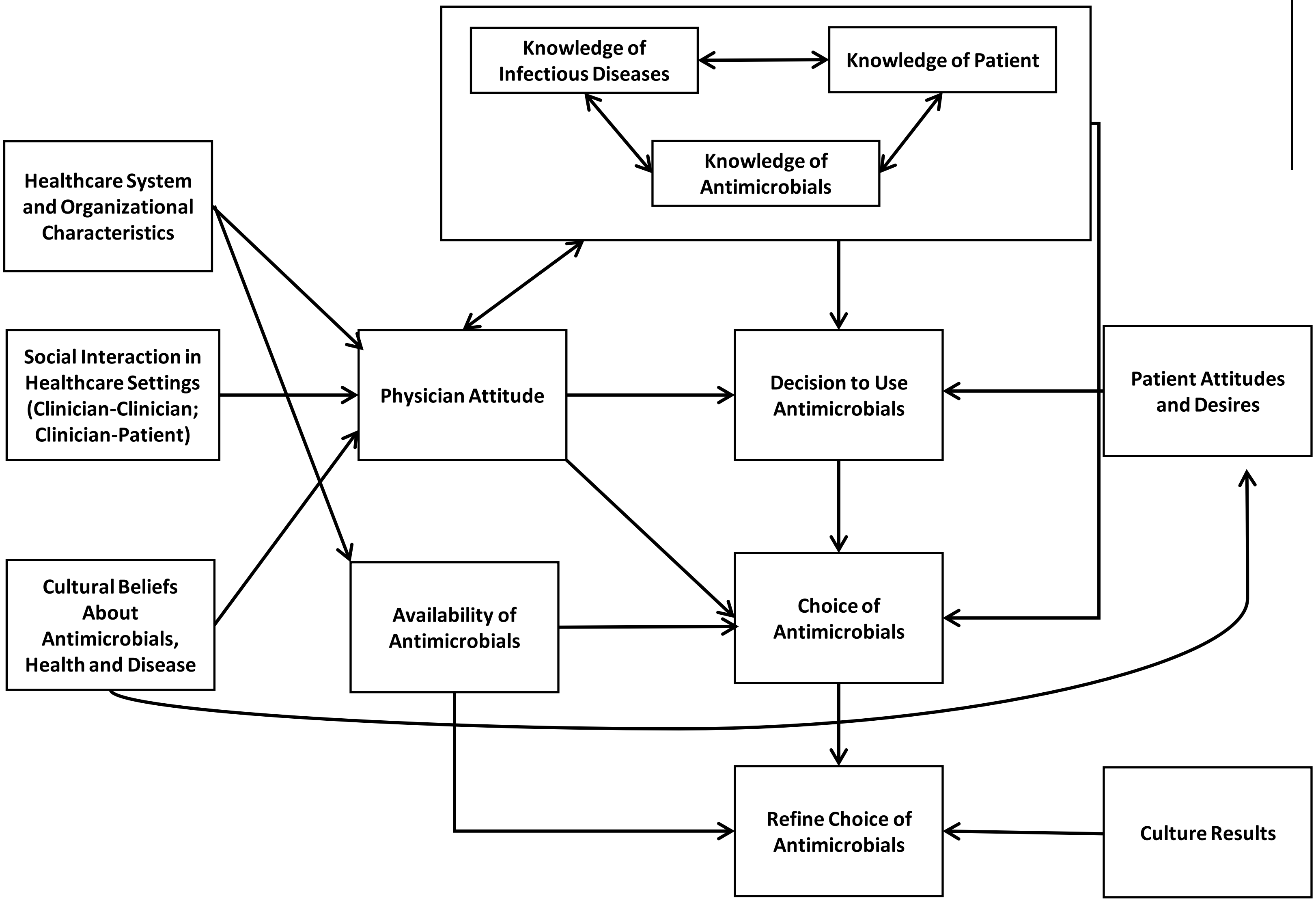
Social Determinants of Antibiotic Prescribing

- Emerging literature identifies factors that drive antibiotic prescribing decisions **beyond clinician knowledge** of appropriate practice or **medical need**

- Medical sociologists and anthropologists have long-identified that prescribing a drug is **a highly social as well as clinical act**[1]

[1]van der Geest et al. Ann Rev Anthropology 1996 (25): 153-178.

Conceptual Framework for Antibiotic Use



Adapted from Fishman, N. 2006. "Antimicrobial Stewardship" American Journal of Infection Control. 34(5)S1: S55-63

Social Determinants of Antibiotic Prescribing

1.) Relationships between clinicians

2.) Relationships between clinicians and patients

3.) Risk, fear, anxiety and emotion

4.) (Mis)perception of the problem

5.) Contextual and environmental factors

Measurement

"Measure Something"

Neil Fishman, 2010

- Measurement for internal institutional use
  - Show effectiveness of a stewardship program or initiative (e.g. improved patient safety, decreased antimicrobial use)
  - Internal benchmarking of antibiotic use
- Measurement for external benchmarking
  - Antibiotic use
  - Quality improvement measures

What to Measure: Examples

- Number and type of interventions
- Results of a specific initiative
  - Improvement in peri-operative antibiotic use (% of cases where antibiotic given correctly)
  - Improvement not treating asymptomatic bacteriuria (% of patients treated inappropriately before and after an intervention)
- Decrease in (or stable) use of antimicrobials
  - Need to normalize antibiotic use data (e.g. per 1000 patient days)
  - Can attach costs to the antimicrobial use

Basics: Antibiotic Use (DDD vs. DOT)

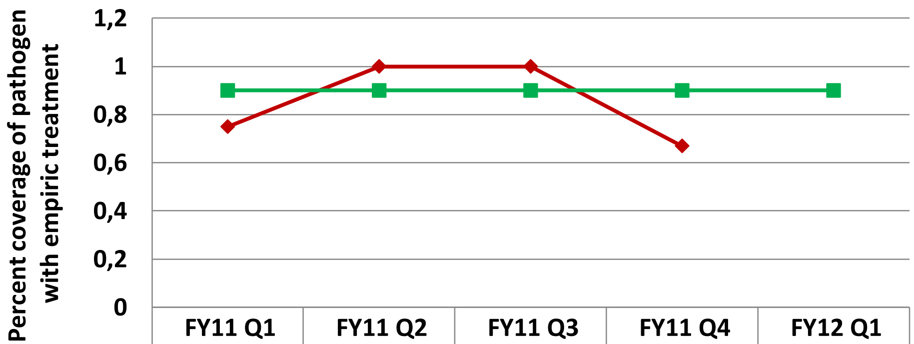
- **Defined daily dose (DDD):** the usual daily dose for adults as defined by the World Health Organization (WHO)
  - Vancomycin DDD = 2 grams.1
  - A patient receives 2 grams/day for 5 days; total use (10 grams) ÷ DDD (2 grams) = 5 DDDs
  - A hospital "uses" 1000 grams of vancomycin (e.g., purchases, dispenses, administers) in the 1st quarter of 2010, for a total of 4,500 patient days, then: [1000 grams/2 grams /4,500 patient days] X 1000 = 111 DDD/1000 patient days
- **Days of therapy (DOT):** 1 DOT is administration of a single agent at least once that day
  - If a patient receives 2 agents, she receives one DOT for each
  - Normalize to 1000 patient days

CHOP ASP Quality Initiatives

	ABX Management for CLABSI	Blood Stream Infections (BSI)
Structure/Guideline	Antibiotics for presumed CLABSI	Empiric ABX management of BSI
Process	According to guidelines: 1. % empiric ABX choice 2. % definitive ABX choice 3. % duration ABX therapy	% BSI with appropriate empiric antibiotic
Outcome	90% coverage of culture positive CLABSI with empiric treatment	1. 90% coverage of culture positive CA-BSI with empiric treatment 2. 90% coverage of culture positive HA-BSI with empiric treatment

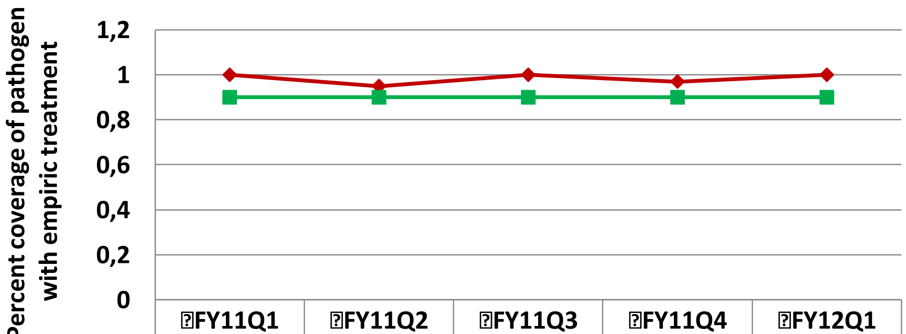
CHOP ASP Quality Initiatives

Appropriate Coverage of Pathogen with Empiric Treatment for HA-BSI



	FY11 Q1	FY11 Q2	FY11 Q3	FY11 Q4	FY12 Q1
% Appropriate	0,75	1	1	0,67	
Target	0,9	0,9	0,9	0,9	0,9

Appropriate Coverage of Pathogen with Empiric Treatment for CA-BSI



	FY11Q1	FY11Q2	FY11Q3	FY11Q4	FY12Q1
% Appropriate	1	0,95	1	0,97	1
Target	0,9	0,9	0,9	0,9	0,9

Indicator Status Color Coding:

=At or above Target

=Within 15% away from Target

=Greater than 15% away from Target

Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial

Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE:

JAMA. 2013 Jun 12;309(22):2345-52

From: **Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial**

JAMA. 2013;309(22):2345-2352. doi:10.1001/jama.2013.6287

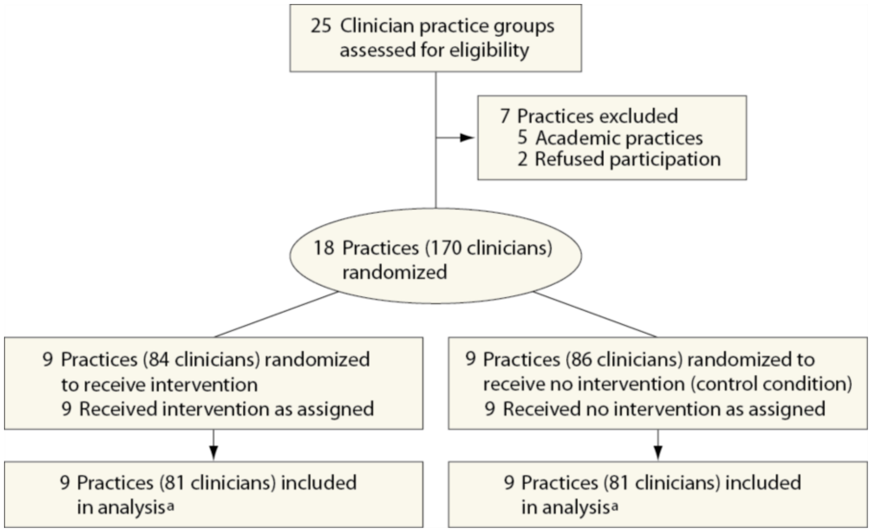
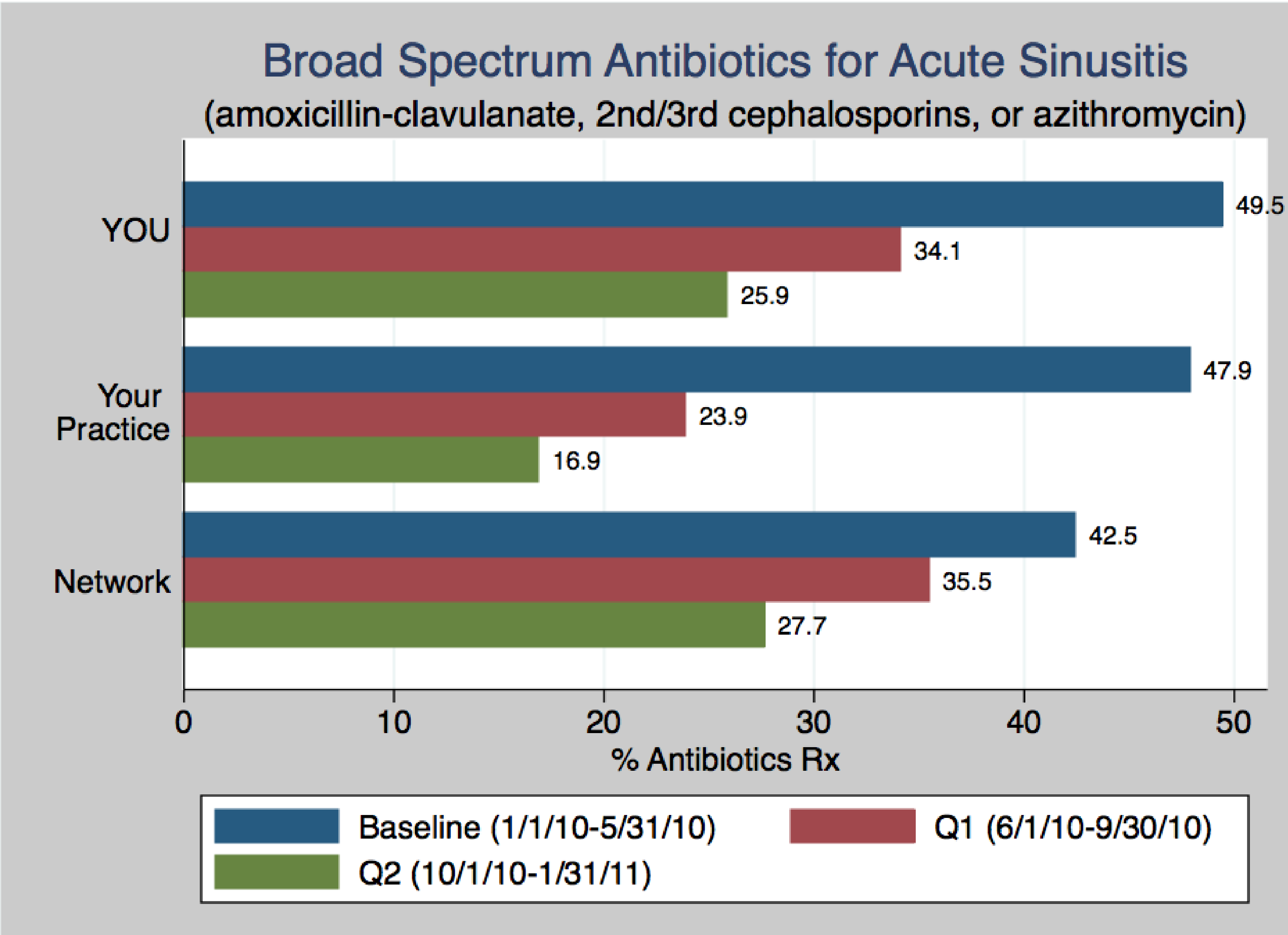


Figure Legend:

[a]Three clinicians in the intervention group and 5 in the control group did not attend acute-care encounters during the study period.

Antimicrobial Stewardship Intervention

- Guideline development
- Education
- **Prescribing Audit and Feedback**



Broad Spectrum Antibiotics for Acute Sinusitis
(amoxicillin-clavulanate, 2nd/3rd cephalosporins, or azithromycin)
YOU
49.5
34.1
25.9
Your Practice
47.9
23.9
16.9
Network
42.5
35.5
27.7
0
10
20
30
40
50
% Antibiotics Rx
Baseline (1/1/10-5/31/10)
Q1 (6/1/10-9/30/10)
Q2 (10/1/10-1/31/11)

The JAMA Network

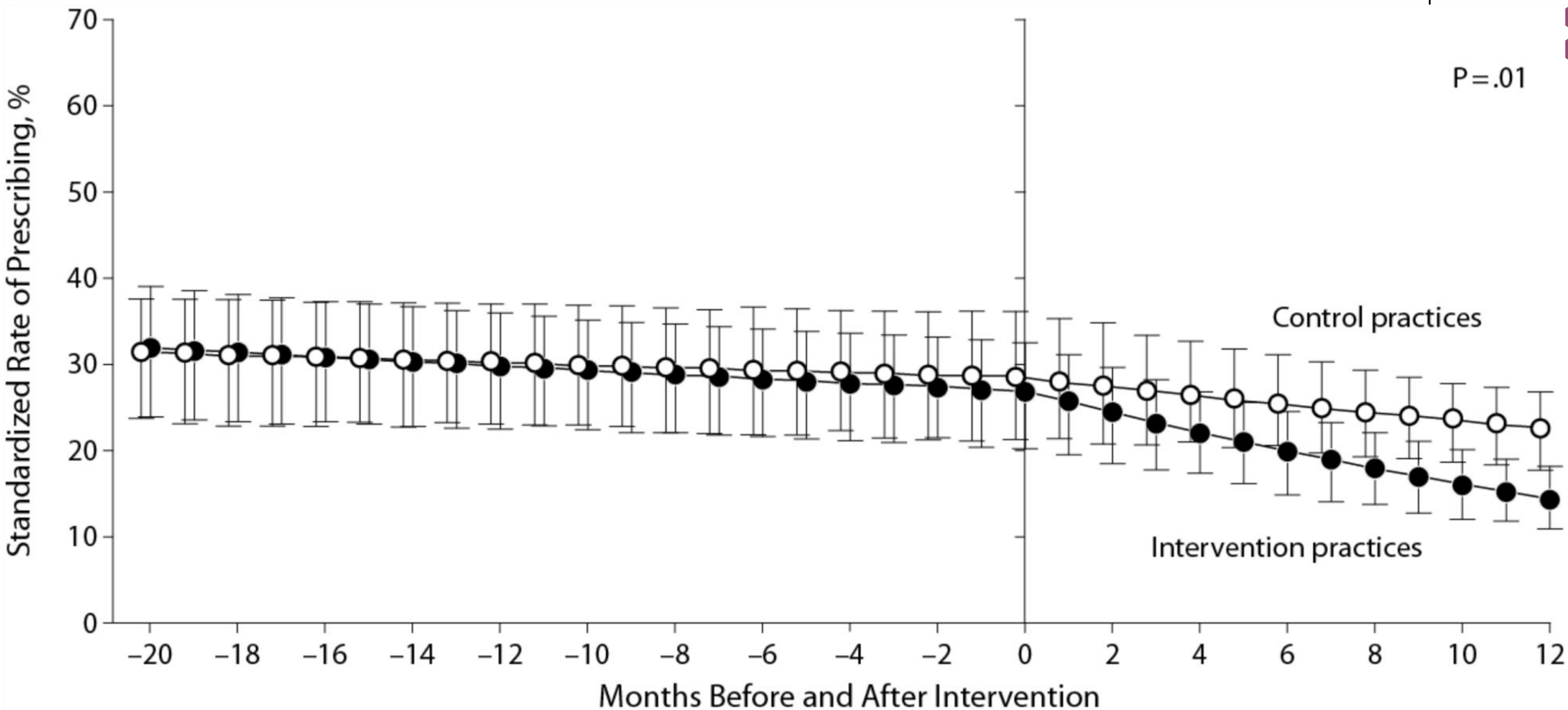


Figure Legend:

The estimate of interest (and associated P value) is the treatment × time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs.

Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE: Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA. 2013 Jun 12;309(22):2345-52

The JAMA Network

From: **Durability of Benefits of an Outpatient Antimicrobial Stewardship Intervention After Discontinuation of Audit and Feedback**

JAMA. Published online October 10, 2014. doi:10.1001/jama.2014.14042

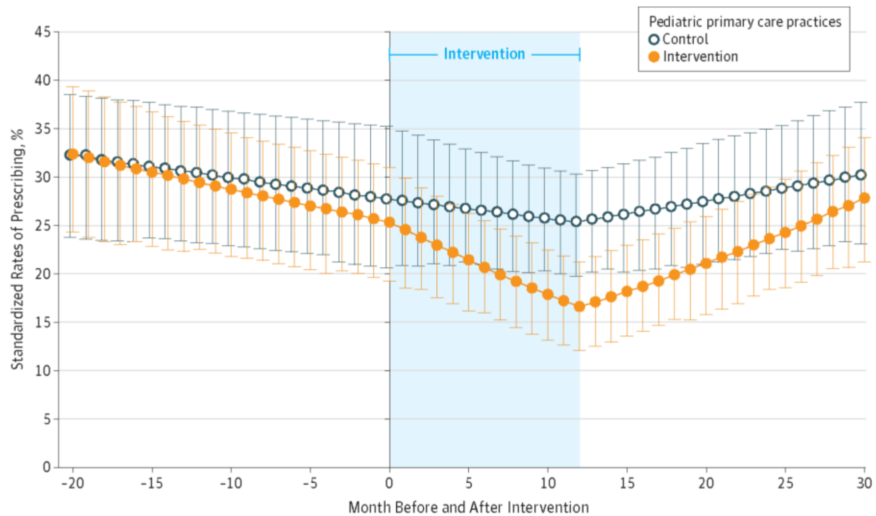
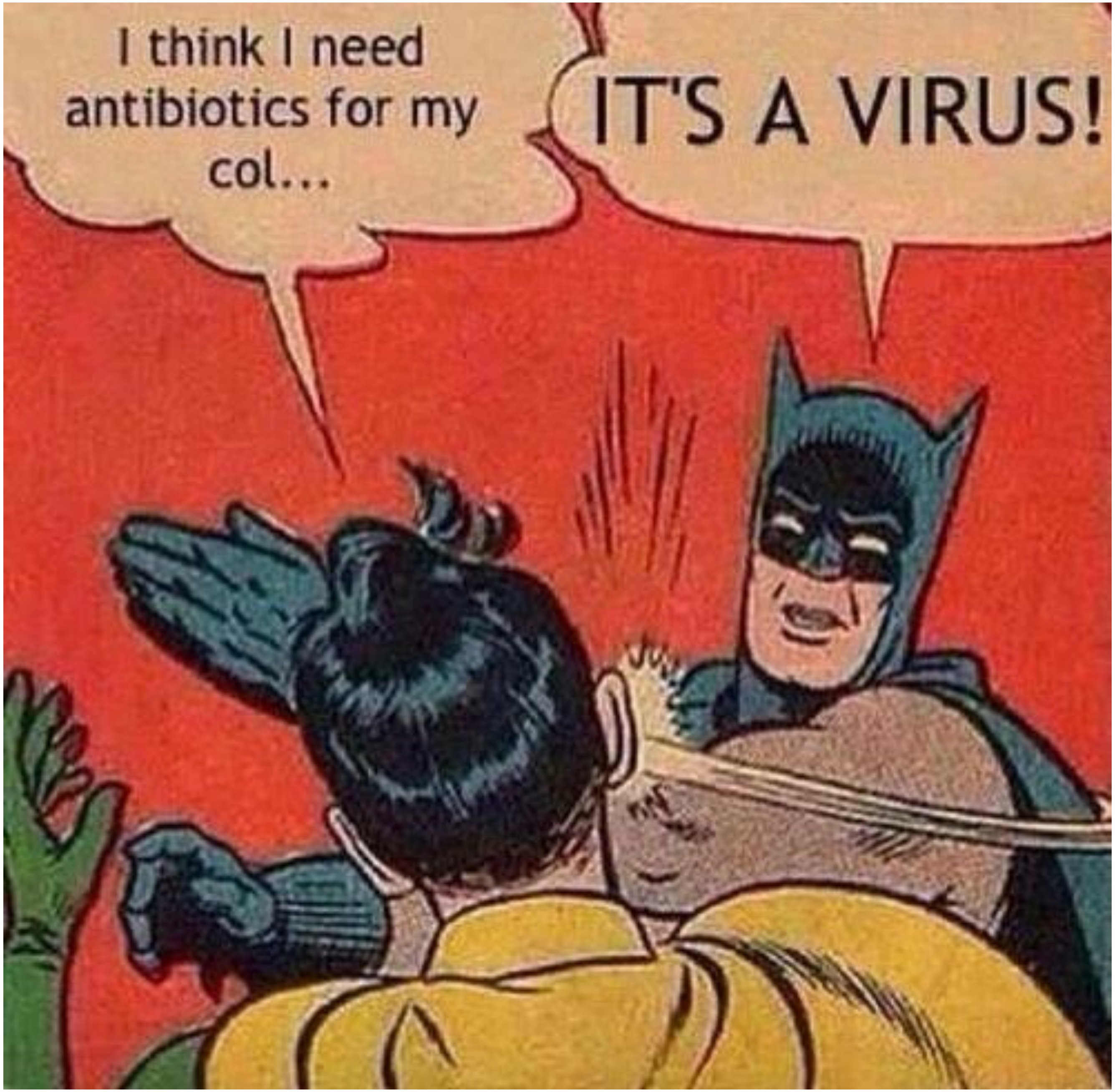


Figure Legend:

Standardized Rates of Broad-Spectrum Antibiotic Prescribing Before, During, and After Audit and FeedbackThe estimate of interest is the treatment × time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs.

Summary

- Antimicrobial resistance is major public health threat
- Variability in use = opportunity
- Antimicrobial stewardship is vital patient quality and safety initiative
- Antimicrobial stewardship is effective across different outcomes
- Implementation, implementation, implementation…!


I think I need antibiotics for my col...
IT'S A VIRUS!