Tackling Antibiotic Resistance: A Global Priority

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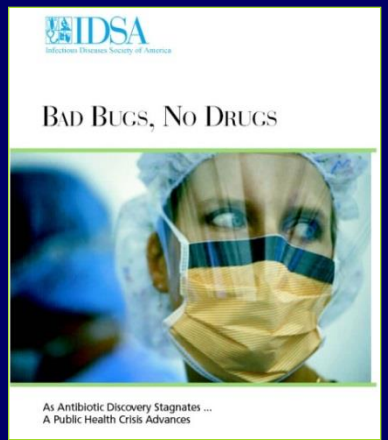
10x'20

Tufts Medical Center



Disclosures

- Adjudication Committee – NIH
- Data Monitoring Committee
  - Actelion
- Editor
  - ID Clinics of North America
  - Antimicrobial Agents and Chemotherapy
- Treasurer, Infectious Diseases Society of America
- Member, ID Board and ID Test Writing Committee, American Board of Internal Medicine
- Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)

Have We Returned to the Pre-antibiotic Era? Recent Case

71 year old lady with laryngeal cancer post larengectomy, chemotherapy and radiation in 2012, COPD on home oxygen, and recent admission for tracheobronchitis now transferred from rehabilitation with fever, flank pain and respiratory failure

- **Cured of cancer**

Have We Returned to the Pre-antibiotic Era? Recent Case

History:

- **12/2015 Cough, sputum production with acute on chronic respiratory failure**
- **She had no fever, chills or other constitutional symptoms**
- **Evaluation for viruses, other infections negative**
- **Blood and sputum cultures grew GNR ultimately identified as MDR *K. pneumoniae,* + metallo-carbapenemase**
- **Did well, cleared blood cultures, did not need re-intubation**
- **Treated for 2 weeks with**
  - **IV tigecycline**
  - **IV colistin**
  - **inhaled colistin**
- **January, 2016 switched from colistin IV/inhaled to IV minocycline**

Have We Returned to the Pre-antibiotic Era? Recent Case

Admitted with pneumonia again in late January and in May

She presented with respiratory failure and tracheobronchitis along with a urinary tract infection

- **Discharged on a 5 day course of levofloxacin**
- **Sputum and urine cultures subsequently grew a carbapenemase-producing *Klebsiella pneumoniae***
- **4 days later, she was found to have an increased oxygen requirement**
- **ER: reports feeling very tired, still has urinary symptoms (dark, foul-smelling, with right flank pain), T 38.5C, increased oxygen requirements**
- **Urine culture >=100,000 CFU/mL *Klebsiella pneumoniae*, + Carbapenem resistance, MDR organism**

Have We Returned to the Pre-antibiotic Era? Recent Case

Culture Urine >=100,000 CFU/mL *Klebsiella pneumoniae*,
+ Carbapenem resistance, multidrug resistant (MDR) organism
<u>Resistant to:</u>

- **Ampicillin**
- **Ampicillin/sulbactam**
- **Piperacillin/tazobactam**
- **Cefazolin**
- **Cefoxitin**
- **Ceftazidime**
- **Ceftriaxone**
- **Cefepime**
- **Meropenem**
- **Amikacin**
- **Gentamicin**
- **Tobramycin**
- **Ciprofloxacin**
- **Nitrofurantoin**
- **Trimethoprim/Sulfa**
- **Ceftolozane-tazobactam**
- **Ceftazidime-avibactam**

Have We Returned to the Pre-antibiotic Era? Recent Case (continued)

After discussion re: limited options, predictable renal, neurological and other toxicity, patient and her family decided on hospice care

Case

47 year old female school teacher presents with pain upon urination, lower abdominal pain

- Started on standard oral therapy - ciprofloxacin

Two days later she comes back and appears ill with new chills, nausea and back pain

- High fever, exam notable for new right flank tenderness
- Urine shows signs of infection
- Labs: elevated white blood cells with left shift

Therapy advanced to guideline therapy for pyelonephritis; she looked well enough to go home

- One dose IV ceftriaxone, then oral TMP/SMX

http://cid.oxfordjournals.org/content/52/5/e103.full.pdf+html

Case continued…
Two days later

Substantially worse, acutely ill, high fever, low BP, requires hospitalization for intravenous hydration as unable to eat or drink; 2 episodes of vomiting

- **Exam – T 38.7, BP 90/60, elevated HR, ill appearing, mild distress due to pain; worsening right flank tenderness**
- **Despite antibiotic therapy, urine culture grows > 100,000/mL *K. pneumoniae***
- ***K. pneumoniae* identified as ESBL+**
  - **Resistant to ciprofloxacin, ceftriaxone, TMP/SMX**

- **Admitted to hospital and treated with imi/meropenem**
  - **Drugs of choice for ESBLs**

Have we returned to the pre-antibiotic era?

Maybe so…

- **mcr-1/mcr-2**
  - **Transmissible (plasmid) colistin resistance**
  - **Already associated with KPC; true MDR/XDR possible**
- **We should be scared**
- **Forced to use drugs with extremely limited/negative data – e.g.,**
  - **Inhaled/parenteral colistin**
  - **Fosfomycin for ESBL infections**
  - **Tigecycline for MDR infections (despite warning re: death)**
- **Infection prevention, stewardship, surveillance of paramount importance**
  - **Progress is being made through CARB, WHO, others**

McGann, et al. Antimicrob. Agents Chemother 2016; DiPlato et al. Antimicrob. Agents Chemother 2016

public health

Infections With 'Nightmare Bacteria' Are On The Rise In U.S. Hospitals

MARCH 05, 2013 2:56 PM ET

By RYAN JASLOW / CBS NEWS / March 5, 2013, 3:18 PM

CDC: Deadly drug-resistant bacteria on rise in U.S. hospitals

ELSEVIER

Water Research

Volume 37, Issue 8, April 2003, Pages 1685–1690

Antibiotic resistance of *E. coli* in sewage and sludge

F.F Reinthaler, J Posch, G Feierl, G Wüst, D Haas, G Ruckenbauer, F Mascher, E Marth

Occurrence of Antibiotic-Resistant Uropathogenic *Escherichia coli* Clonal Group A in Wastewater Effluents

Laura A. Boczek[1], Eugene W. Rice[1], Brian Johnston[2] and James R. Johnson[2]

Carbapenem-Hydrolyzing GES-5-Encoding Gene on Different Plasmid Types Recovered from a Bacterial Community in a Sewage Treatment Plant

Delphine Girlich[a], Laurent Poirel[a], Rafael Szczepanowski[b], Andreas Schlüter[c] and Patrice Nordmann[a]

And we now face a global crisis

- CDC 2013
- Other reports are similar (ECDC, WHO, CDDEP)

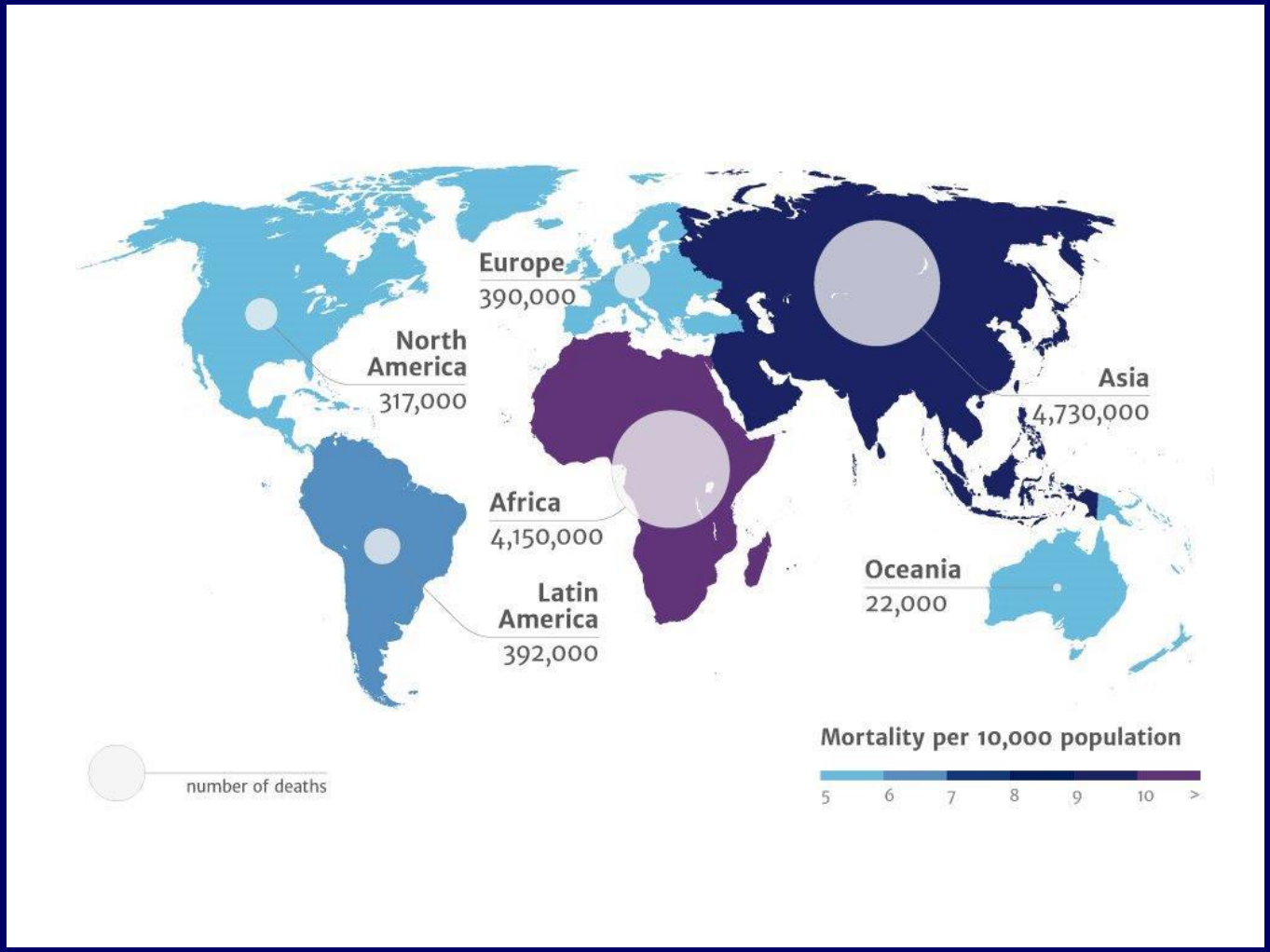
In the United States, each year we have

23,000 deaths/year

≅

One jumbo jet crash every week

Global Deaths Attributable to AMR Every Year by 2050



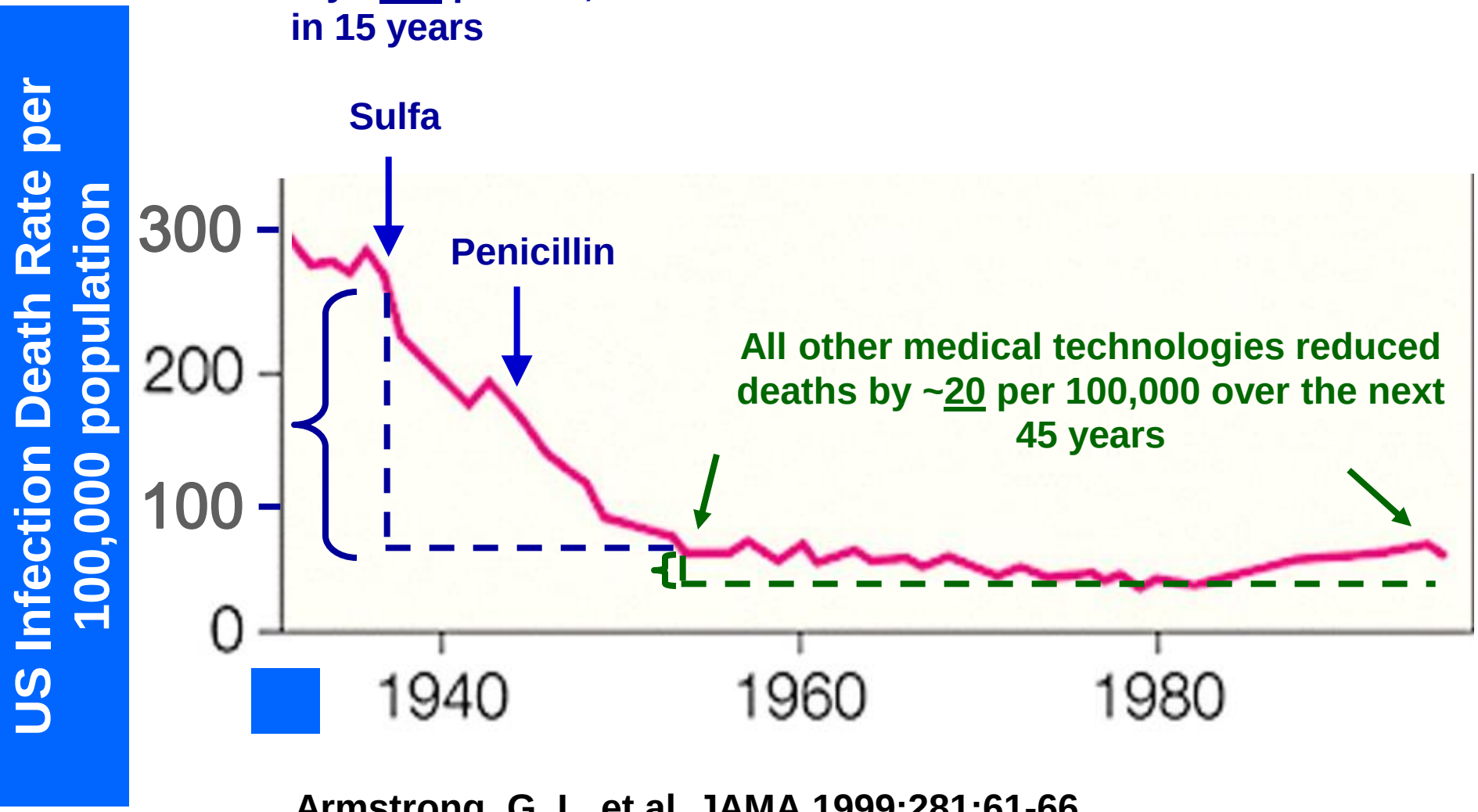
www.amr-review.org

Cost of AMR

- Deaths
  - 25,000/year in the United States
  - 500,000/year globally
- Costs
  - US health care costs $20 billion/year
- Lost productivity
  - $3.5 billion/year in the US
  - €1.5 billion/year in the EU

Impact of Antibiotics on Mortality

Antibiotics caused US deaths to decline by ~220 per 100,000 in 15 years



Armstrong, G. L. et al. JAMA 1999;281:61-66.

Power of Antibiotics

Disease	Pre-Antibiotic Death Rate	Death With Antibiotics	Change in Death
Community Pneumonia[1]	~35%	~10%	-25%
Hospital Pneumonia[2]	~60%	~30%	-30%
Heart Infection[3]	~100%	~25%	-75%
Brain Infection[4]	>80%	<20%	-60%
Skin Infection[5]	11%	<0.5%	-10%
By comparison…treatment of heart attacks with aspirin or clot busting drugs[6]			*-3%*

[1]IDSA Position Paper '08 Clin Infect Dis 47(S3):S249-65; [2]IDSA/ACCP/ATS/SCCM Position Paper '10 Clin Infect Dis In Press; [3]Kerr AJ. Subacute Bacterial Endocarditis. Springfield IL: Charles C. Thomas, 1955 & Lancet 1935 226:383-4; [4]Lancet '38 231:733-4 & Waring et al. '48 Am J Med 5:402-18; [5]Spellberg et al. '09 Clin Infect Dis 49:383-91 & Madsen '73 Infection 1:76-81; [6]'88 Lancet 2:349-60

Antibiotics for Cellulitis Save More Lives Than Aspirin or Streptokinase for Myocardial Infarction!

Disease	Death No Treatment	Death With Treatment	Reduction in Death	NNT to Save a Life*
Cellulitis	11%	0.3%	>10%	9
MI†	12%	9%	3%	33

Spellberg et al. Clinical Infectious Diseases 2009

*Number of patients Needed to Treat (NNT) to save a life

†From ISIS-2 Study published in 1988 in Lancet 2:349-60

Antibiotics and Medical Progress

Ability to control infection is critical to other advances in medicine including:

- Neonatal care
- Transplantation
- Chemotherapy
- Immunosuppression
- Complex and routine surgery
  - Joint replacement
- Obstetric care
- Intensive care interventions

Antibiotics
A limited resource

- ↑ Increasing antibiotic resistance
- ↑ Overuse of antibiotics
- ↓ Poor access for many LMIC
- ↓ Dry antibiotic pipeline

IDSA PUBLIC POLICY

The Epidemic of Antibiotic-Resistant Infections: A Call to Action for the Medical Community from the Infectious Diseases Society of America

Brad Spellberg,[1,2] Robert Guidos,[3] David Gilbert,[4] John Bradley,[5,6] Helen W. Boucher,[7] W. Michael Scheld,[8] John G. Bartlett,[2] and John Edwards, Jr.,[1,2] for the Infectious Diseases Society of America

[1]Division of Infectious Diseases, Harbor–University of California–Los Angeles (UCLA) Medical Center, Torrance, [2]Geffen School of Medicine, UCLA, Los Angeles, and [3]Children's Hospital San Diego and [4]University of California at San Diego, California; [5]Infectious Diseases Society of America, Alexandria, and [6]Division of Infectious Diseases, University of Virginia Health System, Charlottesville, Virginia; [7]Division of Infectious Diseases, Providence Portland Medical Center and Oregon Health Sciences University, Portland, Oregon; [8]Tufts–New England Medical Center, Boston, Massachusetts; and [9]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

The ongoing explosion of antibiotic-resistant infections continues to plague global and US health care. Meanwhile, an equally alarming decline has occurred in the research and development of new antibiotics to deal with the threat. In response to this microbial "perfect storm," in 2001, the federal Interagency Task Force on Antimicrobial Resistance released the "Action Plan to Combat Antimicrobial Resistance: Part 1: Domestic" to strengthen the response in the United States. The Infectious Diseases Society of America (IDSA) followed in 2004 with its own report, "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, A Public Health Crisis Brews," which proposed incentives to reinvigorate pharmaceutical investment in antibiotic research and development. The IDSA's subsequent lobbying efforts led to the introduction of promising legislation in the 109th US Congress (January 2005–December 2006). Unfortunately, the legislation was not enacted. During the 110th Congress, the IDSA has continued to work with congressional leaders on promising legislation to address antibiotic-resistant infection. Nevertheless, despite intensive public relations and lobbying efforts, it remains unclear whether sufficiently robust legislation will be enacted. In the meantime, microbes continue to become more resistant, the antibiotic pipeline continues to diminish, and the majority of the public remains unaware of this critical situation. The result of insufficient federal funding: insufficient surveillance, prevention, and control; insufficient research and development activities; misguided regulation of antibiotics in agriculture and, in particular, for food animals; and insufficient overall coordination of US (and international) efforts could mean a literal return to the preantibiotic era for many types of infections. If we are to address the antimicrobial resistance crisis, a concerted, grassroots effort led by the medical community will be required.

We are in the midst of an emerging crisis of antibiotic resistance for microbial pathogens in the United States and throughout the world [1–4]. Epidemic antibiotic resistance has been described in numerous pathogens in varying contexts, including—but not limited to—a global pandemic of methicillin-resistant *Staphylococcus aureus* (MRSA) infection [5–12]; the global spread of drug resistance among common respiratory pathogens, including *Streptococcus pneumoniae* [13–19] and *Mycobacterium tuberculosis* [20–29]; and epidemic increases in multidrug-resistant (and, increasingly, truly pan-resistant) gram-negative bacilli [30–39]. Infections caused by these and other antibiotic-resistant microbes impact clinicians practicing in every field of medicine. Given their breadth of effect and significant impact on morbidity and mortality, multidrug-resistant microbes are considered a substantial threat to US public health

Received 27 September 2007; accepted 29 September 2007; electronically published 5 December 2007

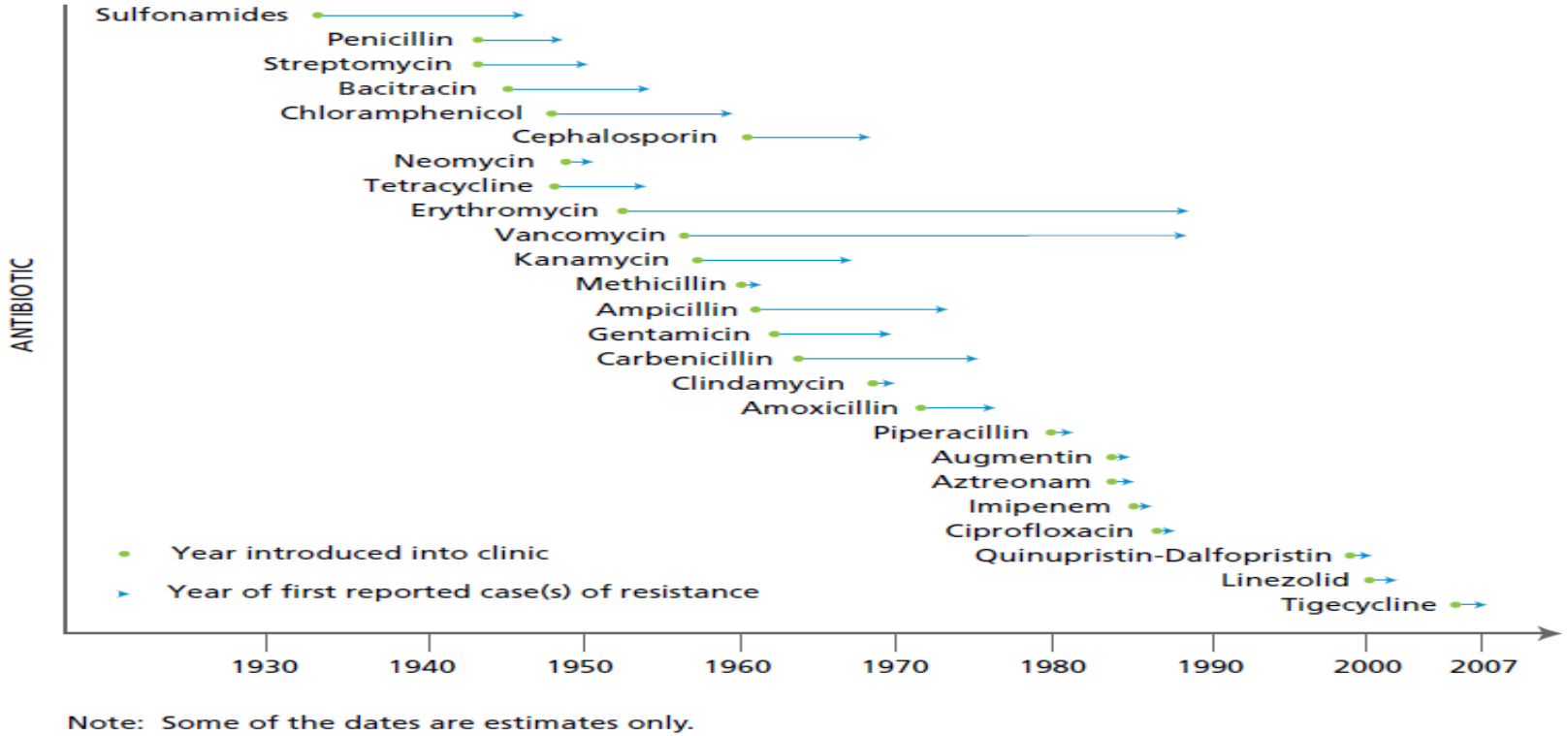
Reprints or correspondence: Dr. John Edwards, Jr., Div. of Infectious Diseases, Harbor-UCLA Medical Center, 1124 W. Carson St., RB2, Torrance, CA 90502 (EdwardsJ@ucla.edu)

Clinical Infectious Diseases 2008; 46:155–64

1058-4838/2008/4602-0001$15.00
DOI: 10.1086/524891

Spellberg, B. et al. Clinical Infectious Diseases 2008; 46 (2):155-64

Emergence of antibiotic resistance threatens ability to control infection

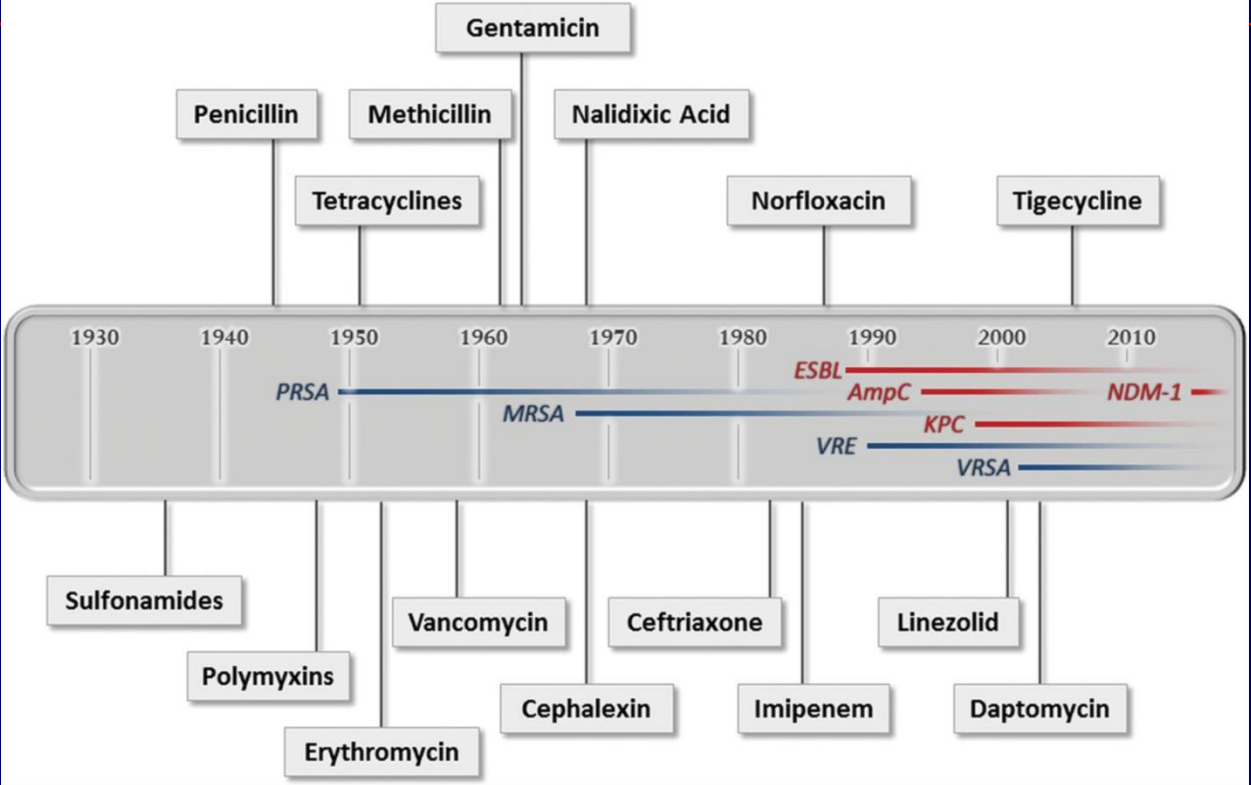


"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body."

Sir Alexander Fleming, 1945

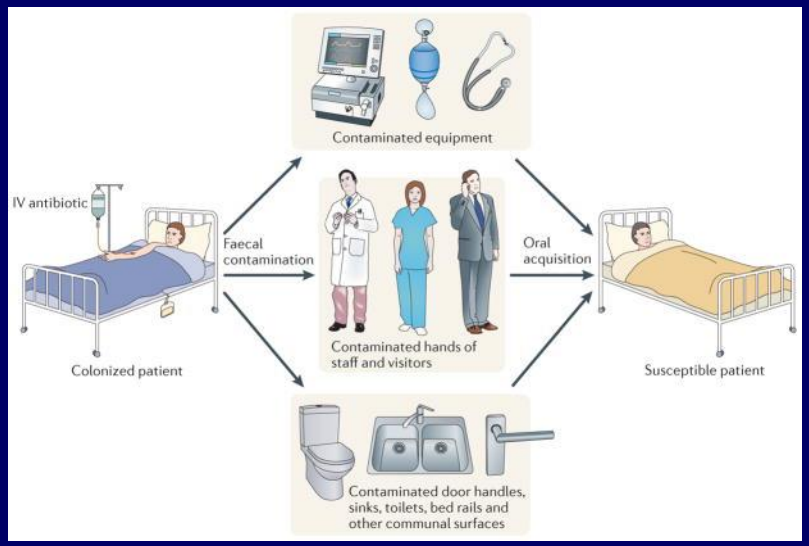
4. Sir Alexander Fleming, Nobel Lecture, December 1945
5. Pray LA Insight Pharma Reports 2008, in Looke D 'The Real Threat of Antibiotic Resistance' 2012

Emergence of Antibiotic Resistance



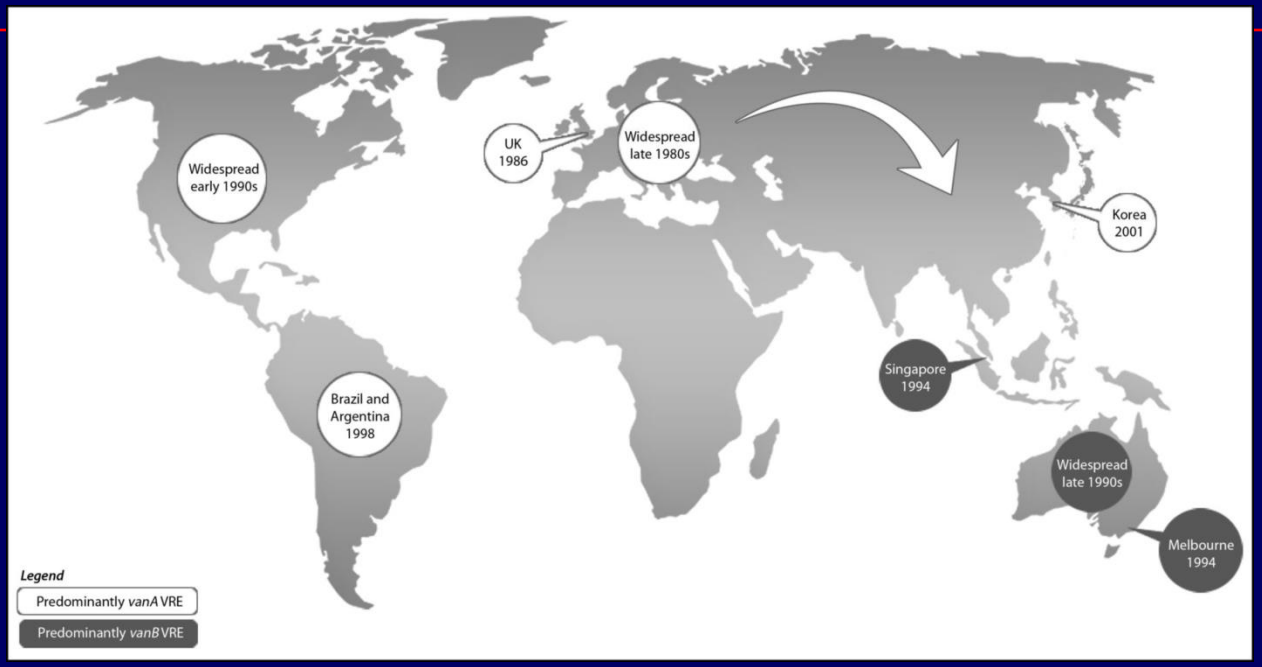
Clin Infect Dis. 2013;56(9):1310-1318. doi:10.1093/cid/cit020

Spread of VRE Healthcare Environment



C. A. Arias and B. E. Murray.
Nat Rev Microbiol. 2012 Mar 16; 10(4): 266–278

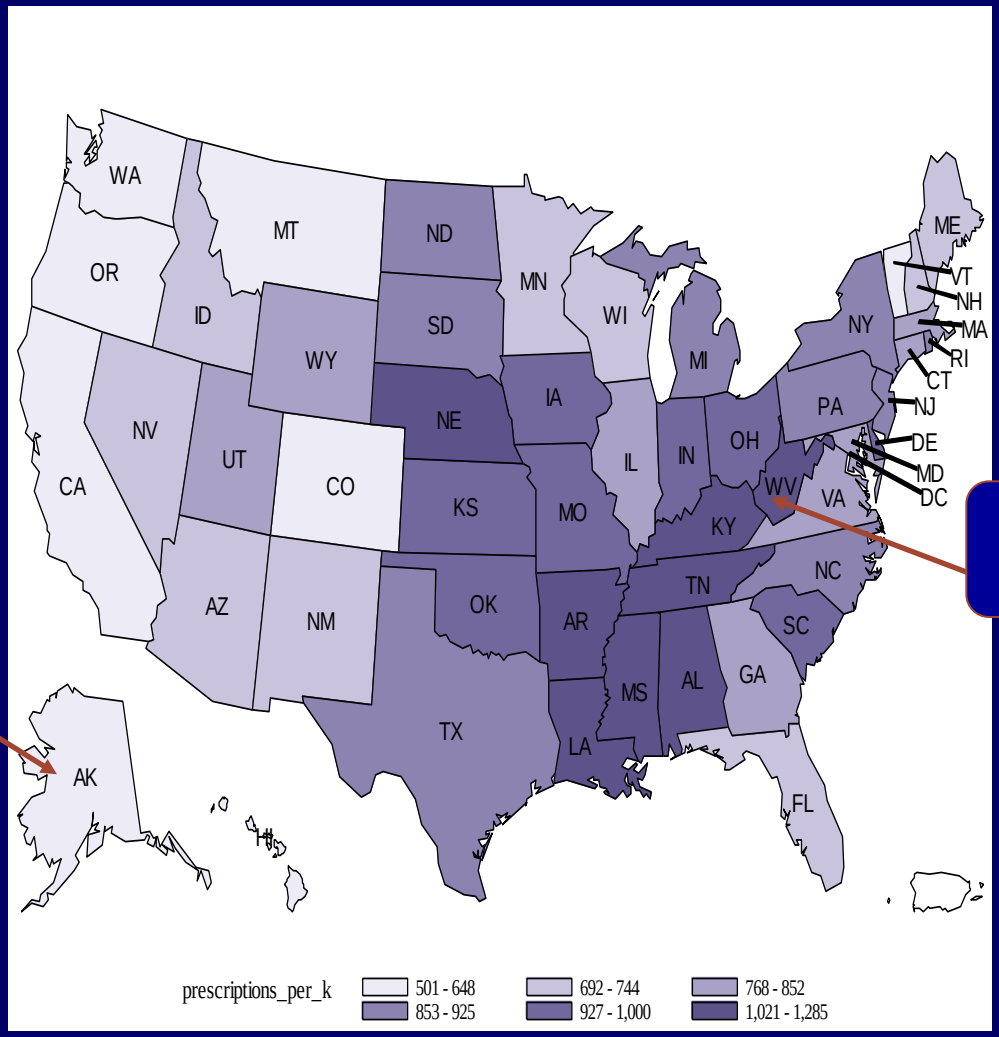
Global Spread of VRE



Clin Infect Dis. 2013;56(9):1310-1318. doi:10.1093/cid/cit020

Overuse of Antibiotics

Community Antibiotic Prescribing Rates per 1000 Population — United States, 2014



Lowest state: 501 per 1000

Highest state: 1,285 per 1000

Dr. Lori Hicks, CDC; Data: IMS Health Xponent
http://www.cdc.gov/getsmart/community/programs-measurement/measuring-antibiotic-prescribing.html

What We Know about U.S. Outpatient Antibiotic Use

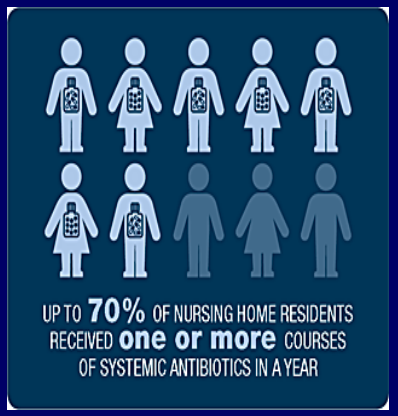
- The U.S. uses lots of outpatient antibiotics compared to other countries
- There is a lot of geographic variability within the U.S.
- There is a lot of unnecessary use, especially for respiratory conditions, in doctors' offices and emergency departments

What We Don't Know and are Working to Address

- Where there are opportunities to improve antibiotic use in dental offices, retail clinics, and urgent care centers

What We Know about U.S. Nursing Home Antibiotic Use

- Up to 70% of residents receive an antibiotic each year
- Estimate 40-75% of antibiotic use in inappropriate or unnecessary
  - Lack national data

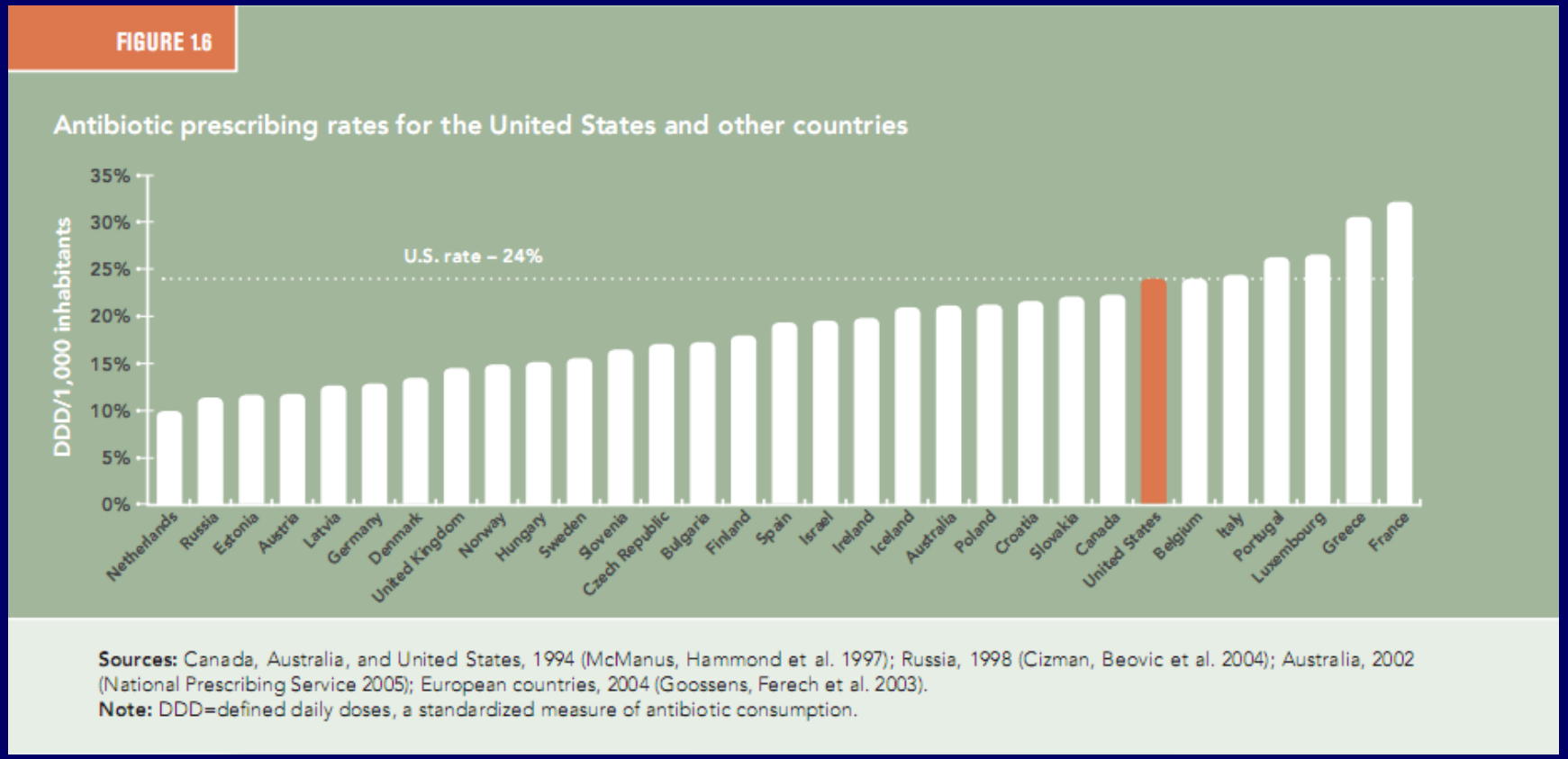


What We Don't Know and are Working to Address

- What's being used?
- For what indications?
- In what types of nursing home patients?

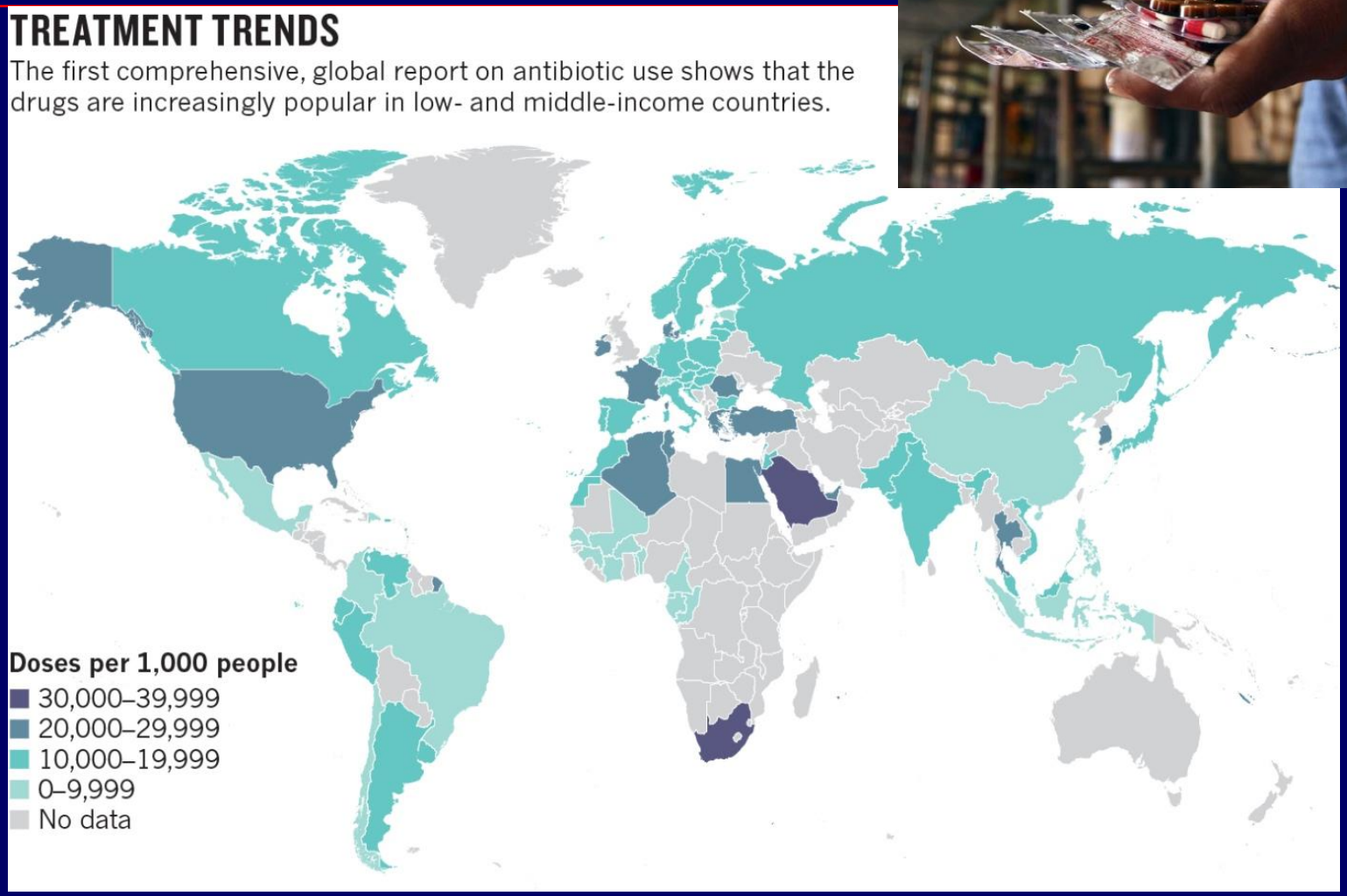
http://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html

Global Antibiotic Prescribing CDDEP



https://www.cddep.org/tool/antibiotic_prescribing_rates_country/

Antibiotic Exposure Global Populations



Global antibiotic consumption grew 30% between 2000 and 2010.Growth is driven mostly by countries such as South Africa and India, where antibiotics are widely available over the counter and sanitation in some areas is poor

https://www.nature.com/news/dramatic-rise-seen-in-antibiotic-use-1.18383; CDDEP

Use/Overuse in Animals

- > 60,000 tons of antimicrobials used in animals globally/year
  - Therapy
  - Prevention/growth promotion
- 40 countries have policies to limit use of antimicrobials in livestock
- Major differences between species
  - Pork, beef, poultry (chickens/turkey)
  - Companion animals

Major use of antibiotics on plants

Bacterial spot of peach and nectarine (*Xanthomonas arboricola* pv. *pruni*)

~15% of quantity of antibiotics
~6,000 kg annually
Three sprays on 15% of acreage

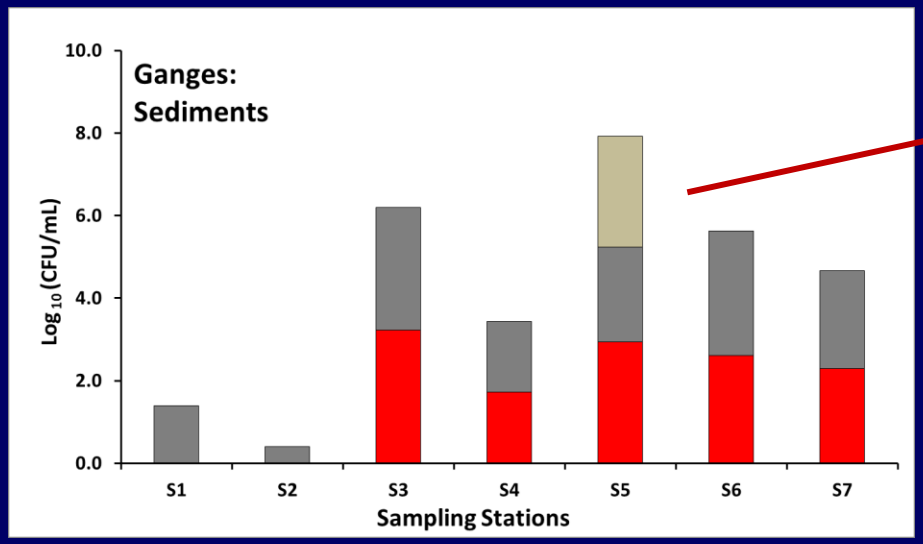
Fire blight of pear and apple (*Erwinia amylovora*)

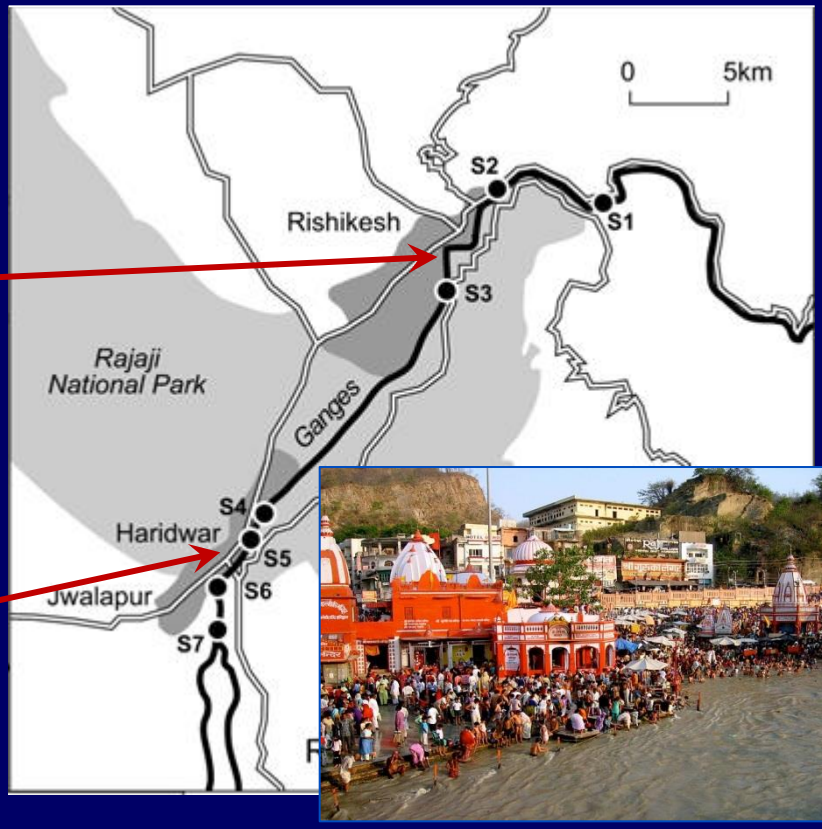
~85% of quantity of antibiotics
~29,500 kg annually
Pear: Three sprays on 45% of acreage
Apple: One spray on 18% of acreage
<u>Intervene if fire blight risk high</u>: warm temperatures coincide with open flowers in orchards with recent history of disease.

Virginia Stockwell, PACCARB presentation, June, 2016

Carbapenem-resistant isolates of apparent fecal origin

Newcastle University
UK | Malaysia | Singapore

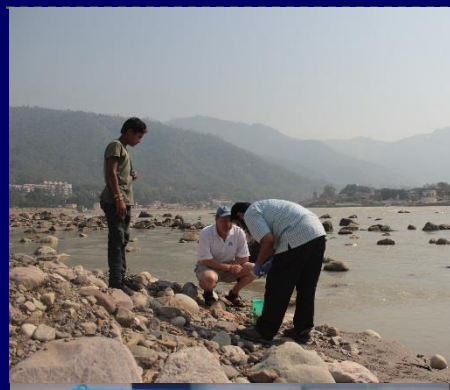




including numerous *bla*$_{NDM-1}$ positive pathogens

Observations

- Antibiotic use and regionally poor water quality drive the global spread of AR
- Developed countries are complacent because of locally clean water
  - AR is massively discharged in wastes where management is limited
  - International travel (human, wildlife) spreads local AR to global scales



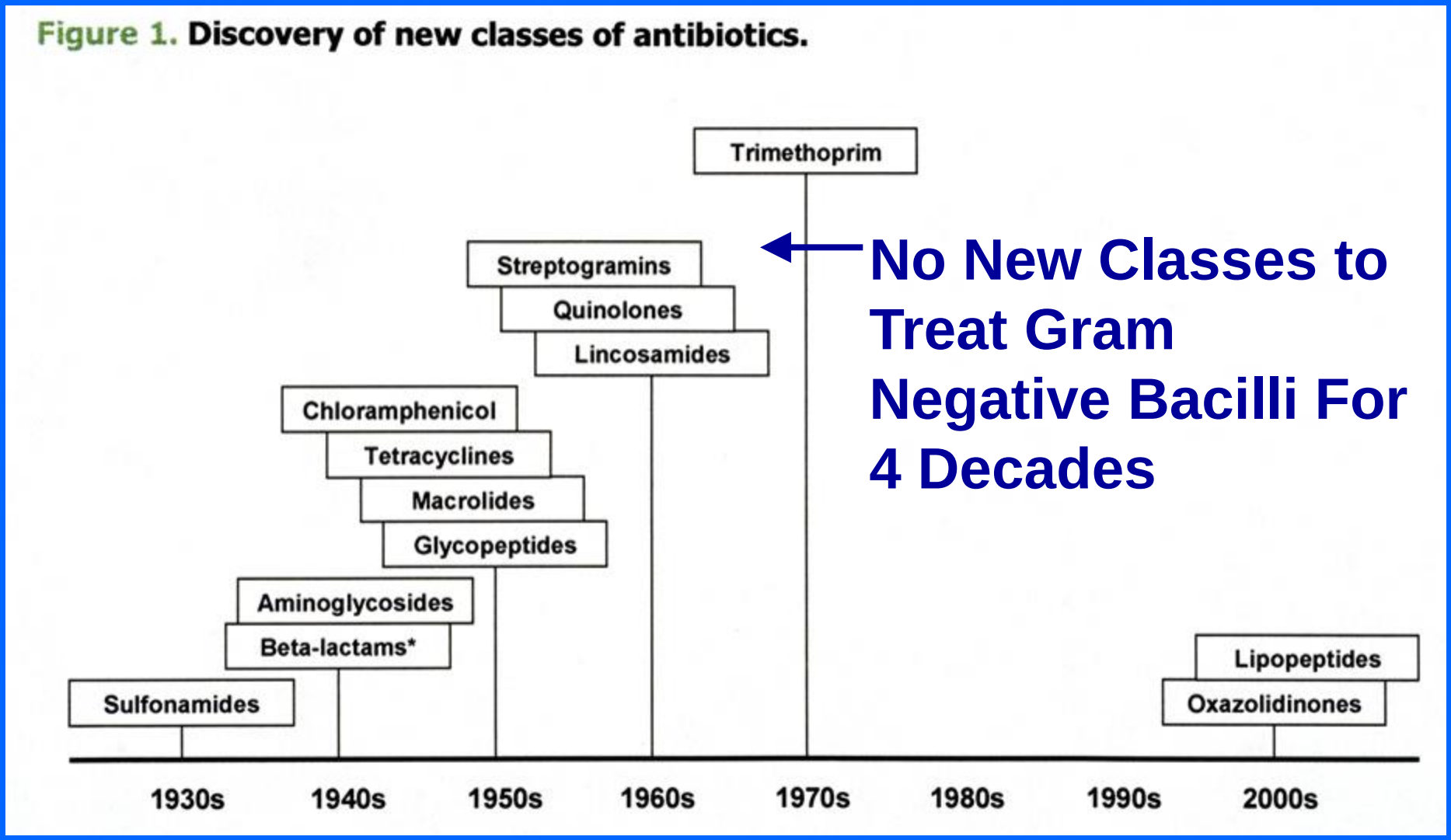
http://www.creativefibrotech.com/frp-toilet-modules.html

http://www.bbc.co.uk/news/health-27695242

AMR
Problem of Access to Antimicrobials

- Low and Middle Income Countries
- Unacceptably high mortality due to untreated infection
- Access = major priority for WHO and other global agencies

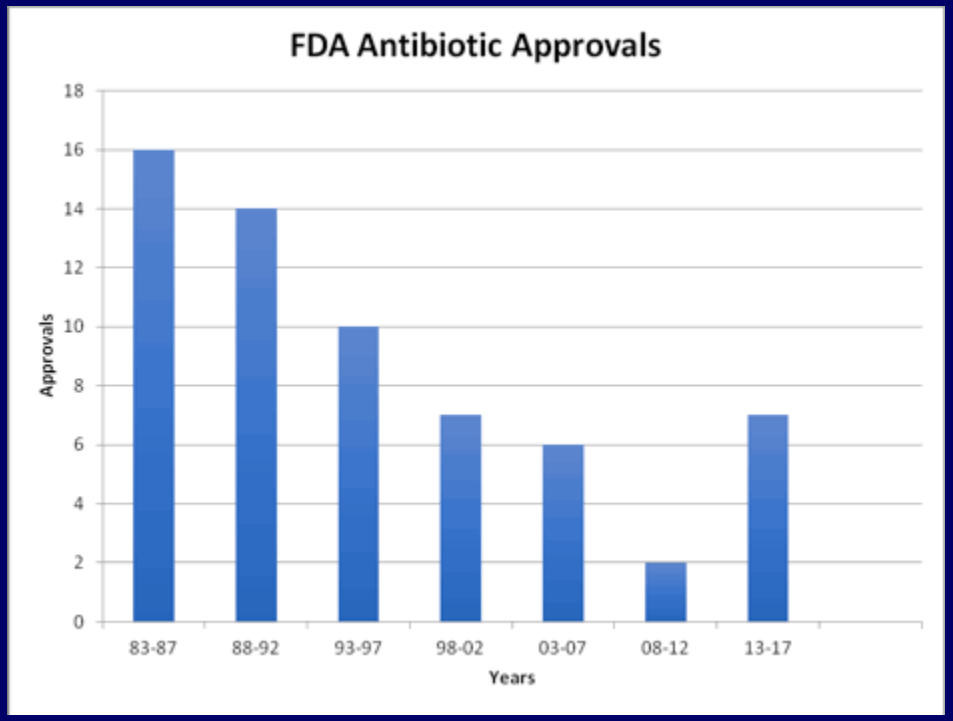
Antibiotic Discovery



No New Classes to Treat Gram Negative Bacilli For 4 Decades

Courtesy J.G. Bartlett

Rate of New Antibacterials Approved by US FDA Over 30 Years



Boucher et al. Clin Infect Dis 56:1685-94, 2013; Pew; D. Shlaes, Antibiotics: The Perfect Storm

Antibiotic resistance: Global Priority

2014: WHO Global Report on Surveillance

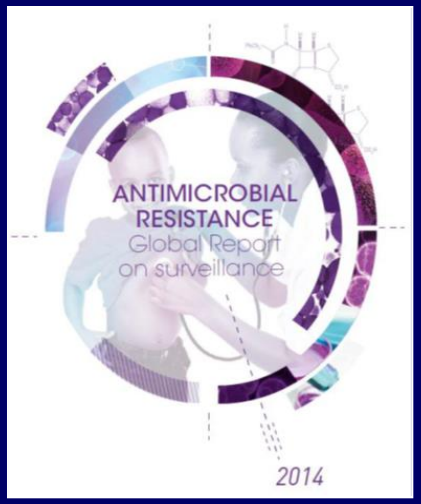
- **Very high rates of resistance observed for common bacteria that cause healthcare associated and community-acquired infections in all WHO regions**
- **Significant gaps in surveillance**
- **Urgent need to strengthen collaboration on global surveillance to address antimicrobial resistance (AMR)**

May 2015

- **World health assembly endorses global action plan to tackle AMR**

September 2016

- **193 countries sign UN Declaration to take action on AMR, reaffirming their commitment to develop national action plans on AMR, based on the global action plan.**

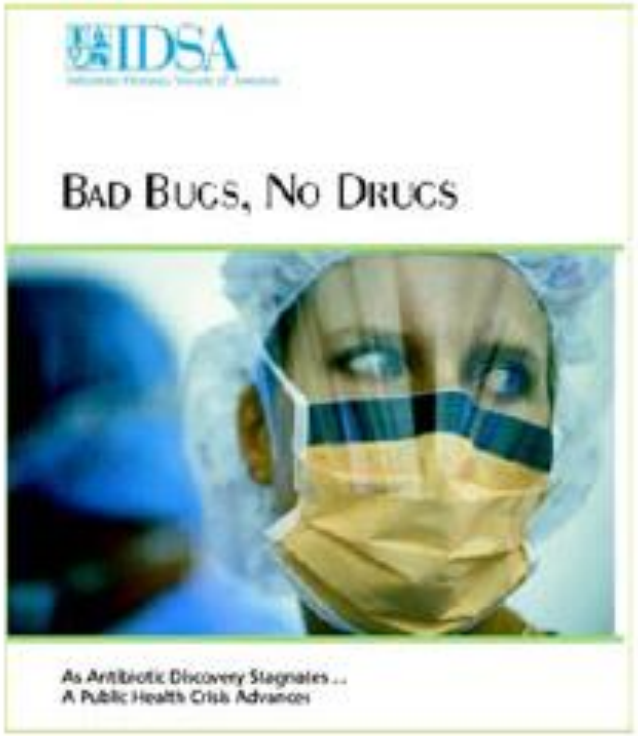


6. World Health Organization 2014 . Antimicrobial Resistance: Global Report on Surveillance. http://www.who.int/drugresistance/documents/surveillancereport/en/ Last accessed 21/9/14
7. http://www.who.int/antimicrobial-resistance/global-action-plan/en/
8. http://www.who.int/mediacentre/news/releases/2016/commitment-antimicrobial-resistance/en/

Combating Antimicrobial Resistance: Policy Recommendations to Save Lives

Infectious Diseases Society of America (IDSA)*

Clinical Infectious Diseases 2011;52(S5):S397–S428



IDSA Calls to Action on AMR

- **Bad Bugs, No Drugs. As Antibiotic Discovery Stagnates ... A Public Health Crisis Brews**
  - **Infectious Diseases Society of America. July 2004**
- **Bad Bugs Need Drugs: What's in the Development Pipeline? An Update from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America**
  - ***Clin Infect Dis* 2006; 42: 657-68**

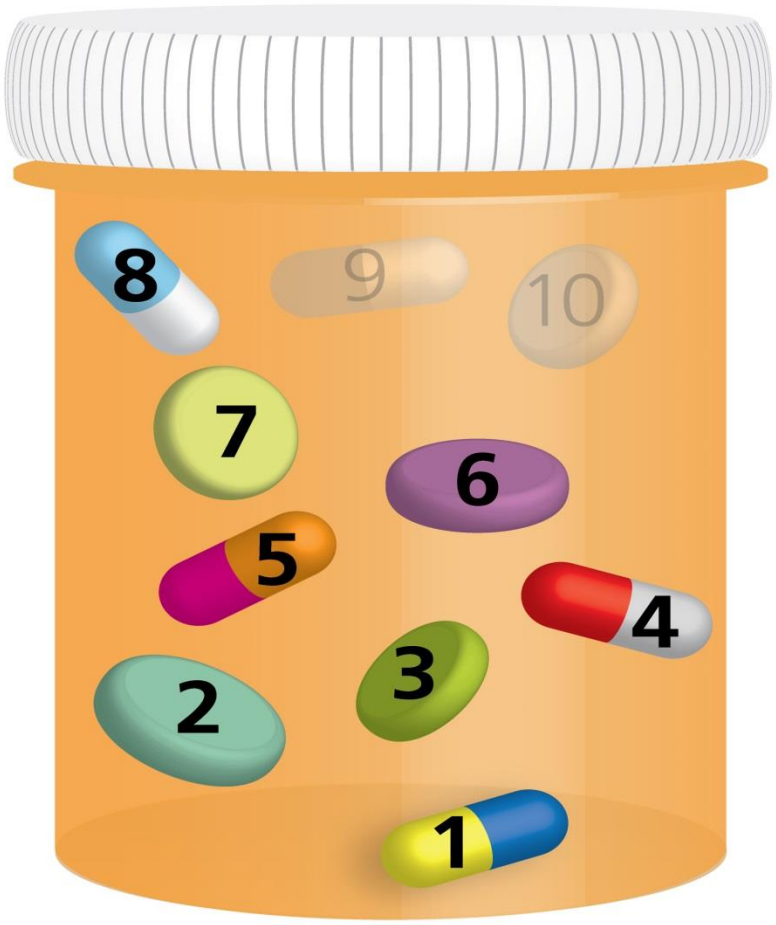
IDSA REPORT

Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America

Helen W. Boucher,[1] George H. Talbot,[2] John S. Bradley,[3,4] John E. Edwards, Jr,[5,6,7] David Gilbert,[8] Louis B. Rice,[9,10] Michael Scheld,[11] Brad Spellberg,[5,6,7] and John Bartlett[12]

[1]Division of Geographic Medicine and Infectious Diseases, Tufts University and Tufts Medical Center, Boston, Massachusetts; [2]Talbot Advisors, Wayne, Pennsylvania; [3]Division of Infectious Diseases, Rady Children's Hospital San Diego, and [4]University of California at San Diego, San Diego, [5]Division of Infectious Diseases, Harbor–University of California at Los Angeles (UCLA) Medical Center, and [6]Los Angeles Biomedical

Status of IDSA 10 x '20 Initiative



Bad Bugs Need Drugs

10x'20

Ten new ANTIBIOTICS by 2020

10

9

8 meropenem and vaborbactam
The Medicines Company; Approved: August 30, 2017

7 delafloxacin
Melinta Therapeutics; Approved: June 17, 2017

6 ceftazidime and avibactam
Actavis plc; Approved: February 25, 2015

5 ceftolozane and tazobactam
Cubist Pharmaceuticals, Inc.; Approved: December 19, 2014

4 oritavancin
The Medicines Company; Approved: August 6, 2014

3 tedizolid phosphate
Cubist Pharmaceuticals, Inc.; Approved: June 20, 2014

2 dalbavancin
Durata Therapeutics; Approved: May 23, 2014

1 ceftaroline fosamil
Forest Laboratories, Inc.; Approved: October 29, 2010

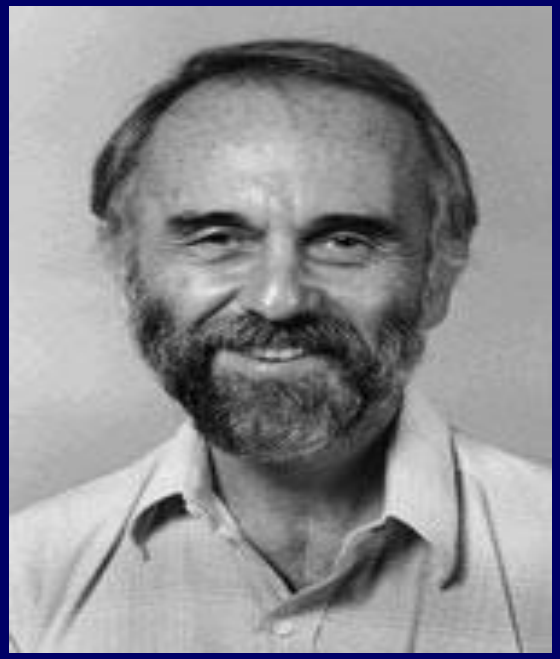
Progress, but unmet needs remain, all of these drugs have gaps, and we remain at high risk

Combating AMR: Multiprong One Health Approach

One Health

- Human medicine
- Veterinary medicine
- Environmental health
- Ecology
- Public health
- Molecular and microbiology
- Health economics
- Translational medicine

One Health History - Founders Veterinary Epidemiology and One Medicine-One Health



Sir Calvin Schwabe
1927-2006

Dr. James H. Steele

1912-2013

Prof Emeritus
UT School of Public Heatlh

Source: CDC, 2011

Organizations working on One Health

- World Health Organization (WHO)
- Food and Agriculture Organization (FAO)
- World Organization for Animal Health (OIE)
- One Health Initiative
- US Centers for Disease Control
- EcoHealth Alliance

Tripartite Alliance

AMR Review May, 2016 "The O'Neill Report"

- Recommendations across 10 areas
- Most aim to reduce demand for antimicrobials
  - Vaccines
  - Alternatives to antibiotics
  - Diagnostics
- Need a global workforce!

https://amr-review.org/

Progress on Antimicrobial Resistance United States Policy

- President Obama's Executive Order (9/18/14)
- President's Council of Advisors for Science and Technology (PCAST) Report
- National Strategy from White House
  - Combating Antibiotic Resistant Bacteria (CARB)

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015

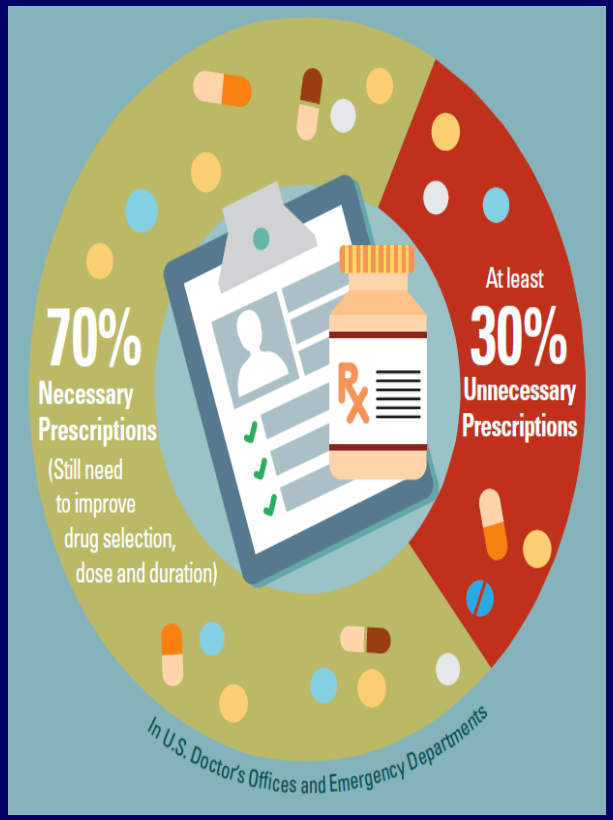
THE WHITE HOUSE
WASHINGTON

CARB National Action Plan

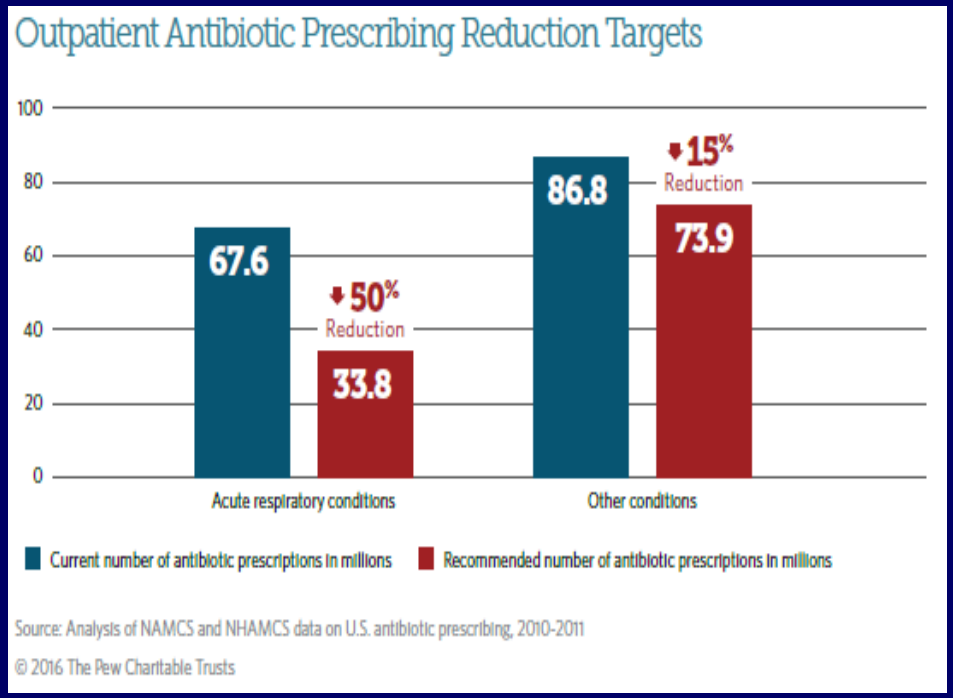
Five Goals:

1. **Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections**
2. **Strengthen National One-Health Surveillance Efforts to Combat Resistance**
3. **Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria**
4. **Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines**
5. **Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development**

Setting National Targets: Outpatient Antibiotic Prescribing



47 million unnecessary antibiotic prescriptions per year



By 2020, significant outcomes of Goal 1 will include: **(CARB National Action Plan)**

- Establishment of antibiotic stewardship programs in all acute care hospitals and improved antibiotic stewardship across all healthcare settings.
- Reduction of inappropriate antibiotic use by 50% in outpatient settings and by 20% in inpatient settings.

Fleming-Dutra et al. JAMA 2016;315(17): 1864-1873; The Pew Charitable Trusts; CARB Action Plan

INITIAL ASSESSMENTS OF THE NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2016

PACCARB

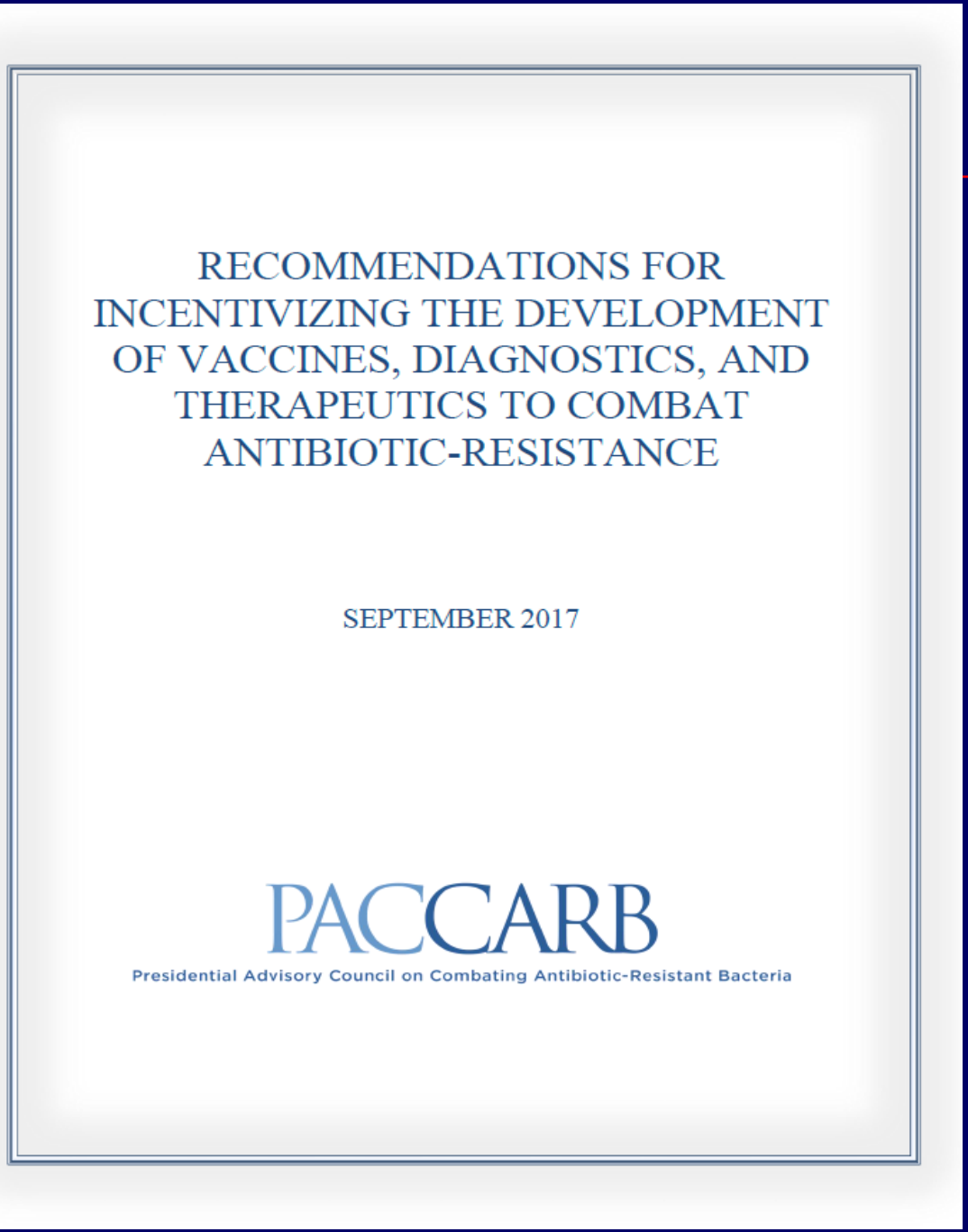
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

PACCARB Initial Report March, 2016

Recommendations:

- **Fully embrace One Health approach**
- **Lead Federal champion of CARB initiative**
- **Coordination of federal response**
- **Resource allocation**
- **Development of critical partnerships**
- **Economic incentives for developing/deploying new diagnostic, preventative and therapeutic tools**

https://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf


RECOMMENDATIONS FOR INCENTIVIZING THE DEVELOPMENT OF VACCINES, DIAGNOSTICS, AND THERAPEUTICS TO COMBAT ANTIBIOTIC-RESISTANCE
SEPTEMBER 2017
PACCARB
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

PACCARB Top 10 Recommendations*

Human Health	Incentives to Develop	Animal Health
Provide additional funding for the development of new product pipelines for vaccines that prevent viral or bacterial syndromes that drive antibiotic use Optimize the interactions among sponsors, regulatory agencies (such as FDA), and use policy committees (e.g., the ACIP) Incentivize the uptake of vaccines by influencing behavior, such as reimbursement to ensure "first-dollar coverage"	 Vaccines	Develop and fund a National Policy and Innovation Institute under USDA whose main functions will include the following: Supporting basic research on immunology across species for the development of vaccines
Include the development of a concomitant AST as part of any new antibiotic funding (or funding for new antibiotics) Provide financial support for diagnostic manufacturers to bring new tests to market Continue funding for clinical trial networks with common rules or shared IRBs	 Diagnostics	Promoting educational programs for veterinarians on the use and interpretation of diagnostic tests
Develop new economic models (pull incentives) for therapies to support the currently available push incentives	 Therapeutics / Alternatives	Providing resources to conduct, evaluate, and create a database of efficacy studies of alternative products

* The comprehensive list of PACCARB recommendations, including the top 10 listed here, begins on page 4.
Abbreviations: ACIP, Advisory Committee on Immunization Practices; AST, antimicrobial susceptibility test; FDA, U.S. Food and Drug Administration; IRB, institutional review board; USDA, U.S. Department of Agriculture

https://www.hhs.gov/sites/default/files/paccarb-final-report-03312016.pdf

TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEAR

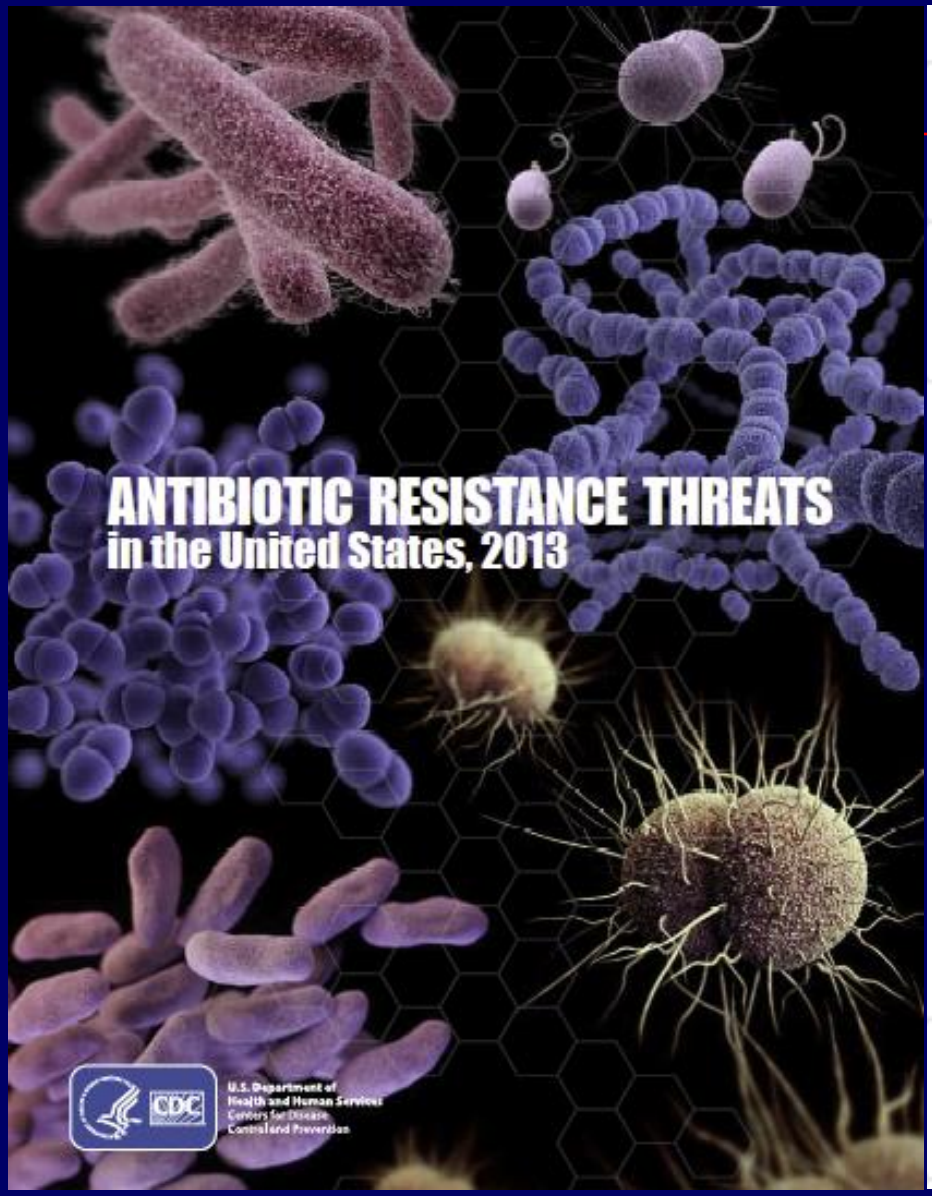
FIVE REASONS WHY

Tuberculosis (TB) is the number one global infectious disease killer today, causing 1.8 million deaths per year. Drug-resistant TB is the most common and lethal airborne AMR disease worldwide today, responsible for 250 000 deaths each year.

Patients with multidrug-resistant TB (MDR-TB[1]) need complex and prolonged multidrug treatment with costly, highly toxic, and much less effective second-line medicines. There is a limited number of second-line medicines to treat MDR-TB and only 52% of patients are successfully treated globally.

In about 50% of MDR-TB patients worldwide, treatment regimens are already compromised by second-line drug resistance. Treatment of extensively drug-resistant disease (XDR-TB[2]) is successful in only one in three patients at best.

ELOPMENT OF NEW ANTIBIOTICS



Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

2017 WHO Priority List of Bacteria For Which New Antibiotics are Urgently Needed

Three categories according to urgent need for new antibiotics:

Critical priority

- ***Acinetobacter baumannii*, carbapenem-resistant**
- ***Pseudomonas aeruginosa*, carbapenem-resistant**
- ***Enterobacteriaceae*, carbapenem-resistant, ESBL-producing**

High priority

- ***Enterococcus faecium*, VRE**
- ***Staphylococcus aureus*, MRSA, VISA/VRSA**
- ***Helicobacter pylori*, clarithromycin-resistant**
- ***Campylobacter* spp., fluoroquinolone-resistant**
- **Salmonellae, fluoroquinolone-resistant**
- ***Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant**

Medium priority

- ***Streptococcus pneumoniae*, penicillin-non-susceptible**
- ***Haemophilus influenzae*, ampicillin-resistant**
- ***Shigella* spp., fluoroquinolone-resistant**

27 February 2017; www.who.int

Bacteria (WHO category)	WHO (2017)	CDC (2013)	ESKAPE (2008-9)
Acinetobacter baumannii, carbapenem-R	Critical	Serious (MDR)	Yes
Pseudomonas aeruginosa, carbapenem-R	Critical	Serious (MDR)	Yes
Enterobacteriaceae, carbapenem-R, 3rd-gen ceph-R (ESBL+)	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Yes
Enterococcus faecium, vancomycin-R	High	Serious (VRE)	Yes
Staphylococcus aureus, methicillin-R, vancomycin-I/R	High	Serious (MRSA) Concerning (VRSA)	Yes
Helicobacter pylori, clarithromycin-R	High		
Campylobacter spp., fluoroquinolone-R	High	Serious (drug-R)	
Salmonellae spp., fluoroquinolone-R	High	Serious (drug-R)	
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	High	Urgent (drug-R)	
Streptococcus pneumoniae, penicillin-NS	Medium	Serious (drug-R)	
Haemophilus influenzae, ampicillin-R	Medium		
Shigella spp., fluoroquinolone-R	Medium	Serious	
Clostridium difficile		Urgent	
Candida spp. fluconazole-R		Serious (Flu-R)	
M. tuberculosis		Serious (drug-R)	
Group A *Streptococcus*		Concerning (erythro-R)	
Group B *Streptococcus*		Concerning (clinda-R)	

J Rex

Powered by CARB-X

8 new classes of antibiotics

5 Non Traditional Approaches

10 New Targets

CARB-X Portfolio

Powered by CARB-X

The CARB-X portfolio comprises 18 early stage R&D projects investigating 8 new classes of antibiotics, 5 non-traditional antibiotics, 10 new molecular targets and a rapid diagnostic to determine the type of drug-resistant bacteria that is causing an infection.

Company/ Research Team	Project	Novelty*			Project description	Urgency/ Priority**	Bacteria Targeted / Stage of Early Development			
		New Class	Non-traditional	New Target			Hit to Lead	Lead Optimization	Pre-Clinical	Phase 1
Achaogen	AKAO-LpxC	✓		✓	LpxC Inhibitor	✓	*Pseudomonas aeruginosa*			
Antabio	PEI		✓	✓	Pseudomonas Elastase inhibitor	✓	*Pseudomonas aeruginosa*			
Bugworks Research	Gyrox	✓			Gyrase-topoisomerase inhibitor	✓	Gram-negative activity			
Cidara Therapeutics	CD201		✓	✓	Bifunctional immunotherapy	✓	Acinetobacter + *P. aeruginosa* + Enterobacteriaceae			
ContraFect	Gram-negative lysins		✓	✓	Recombinant lysin protein	✓	*P. aeruginosa*			
Debiopharm	Debio 1453	✓		✓	Narrow-spectrum inhibitors of FabI	✓	*Neisseria Gonorrhoeae*			
Eligochem	Helical AMP	✓			Helical Antimicrobial Peptide	✓	Gram-negative activity			
Entasis Therapeutics	ETX000				Oral Gram-negative combination	✓	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✓		✓	LpxC Inhibitor	✓	Gram-negative activity			
Iterum	Sulopenem				Oral and IV penem	✓	Gram-negative activity			
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	*Pseudomonas aeruginosa*			
Oppilotech	LPS	✓		✓	Targets synthesis of LPS	✓	Gram-negative activity			
Redx Pharma	NBTI	✓			Dual-acting topoisomerase inhibitor	✓	Acin. + *P. aerug* + Enterobacteriaceae			
Spero Therapeutics	SPR741			✓	Potentiator	✓	Gram-negative activity			
Tetraphase Pharm	TP-6076				Next-generation tetracycline	✓	Acinetobacter + Enterobacteriaceae			
					ß-lactamase Resistant PBP Inhibitor	✓	Entero-bacteriaceae			
				✓	Antibody-drug conjugate	✓	*Pseudomonas aeruginosa*			

tion	Development Stage			
	Feasability Demonstration	Optimization and Preparation for Development	Product Development	System Integration and Testing
	POC Diagnostic			

t are established by CARB-X following the Pew Trusts pipeline analysis model. Pew defines a novel chemical class re molecular structure. Non-traditional products include lysins and monoclonal antibodies.
nined by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO).
✓ Serious/Medium priority.

BOSTON UNIVERSITY · BARDA · RTI INTERNATIONAL · MassBio · AMR CENTRE · CLSI · BROAD INSTITUTE · NIH National Institute of Allergy and Infectious Diseases · wellcome trust

CARB X

A portfolio of ~20 antibacterial candidates

Private sector approach to funding/portfolio management

A minimum of 2 candidates progress to clinical development

CARB-X 2nd Round of Funding July, 2017

"Scientists developing promising new antibiotics in India, Ireland, France, Switzerland, the US and UK are to share up to $17.6m to speed treatments for the world's deadliest superbugs"

The seven projects supported include:

- **Five potential new class antibiotics for Gram-negative bacteria**
- **Potential new treatment for drug-resistant gonorrhea**
- **New molecule targeting a superbug causing serious infections in cystic fibrosis patients**
- **Phase 1 clinical trial of a new oral broad-spectrum antibiotic"**

CARB-X funding for global scientists racing to discover new antibiotics to treat superbugs

Table 1 | **The CARB-X pipeline**

Drug name	Sponsor	Properties	Indication	Status
Traditional antibiotics				
LPS*‡	Oppilotech	Targets LPS synthesis	Gram-negatives	Hit to lead
Debio1453*‡	Debiopharm	Narrow-spectrum FabI inhibitors	*Neisseria gonorrhoeae*	Lead optimization
FG-LpxC*‡	Forge Therapeutics	LpxC inhibitor	Gram-negatives	Lead optimization
AKAO- LpxC*‡	Achaogen	LpxC Inhibitor	*Pseudomonas aeruginosa*	Preclinical
VNRX-PBP*	VenatoRx	β-Lactamase resistant PBP inhibitor	Enterobacteriaceae	Hit to lead
Gyrox*	Bugworks Research	Gyrase–topoisomerase inhibitor	Gram-negatives	Lead optimization
NBTI*	Redx Pharma	Dual-acting topoisomerase inhibitor	*Acinetobacter*, *P. aeruginosa* and Enterobacteriaceae	Lead optimization
Helical AMP*	EligoChem	Helical antimicrobial peptide	Gram-negatives	Lead optimization
SPR741	Spero Therapeutics	Potentiator	Gram-negatives	Preclinical
ETX0282 CPDP	Entasis Therapeutics	Oral combination	Gram-negatives	Preclinical
Sulopenem	Iterum Therapeutics	Oral and intravenous penem	Gram-negatives	Phase I
TP-6076	Tetraphase Pharmaceuticals	Next-generation tetracycline	*Acinetobacter* and Enterobacteriaceae	Phase I
Non-traditional antibiotics				
Gram-negative lysins‡	ContraFect	Recombinant lysin protein	*P. aeruginosa*	Hit to lead
PEI‡	Antabio	*Pseudomonas* elastase; virulence modifier	*P. aeruginosa*	Lead optimization
T3SS inhibitor‡	Microbiotix	Type III secretion system inhibitor; virulence modifier	*P. aeruginosa*	Lead optimization
VIS705‡	Visterra	Antibody–drug conjugate	*P. aeruginosa*	Lead optimization
CD201‡	Cidara Therapeutics	Bifunctional immunotherapy	*Acinetobacter*, *P. aeruginosa* and Enterobacteriaceae	Preclinical

LPS, lipopolysaccharide; PBP, penicillin-binding protein. *New chemotype. ‡Novel mechanism of action. Pipeline as of 1 October 2017.

https://www.eurekalert.org/pub_releases/2017-07/wt-cff072417.php

Public-Private Partnerships and Other Global R&D Efforts

- The European Union (EU) Innovative Medicines Initiative (IMI) -- NewDrugs4BadBugs
  - Knowledge sharing at pre-competitive research stage
  - Goals: better networks of researchers, more fluid trial designs and incentives for companies
  - IMI will provide $149.6 million, private companies will contribute $144.1 million for first phase
- GARDP/DNDi established May 2016 (WHO/DNDi)
  - Sept ‘17 - 5 countries+Wellcome+others pledged €56.5 mil
- Diagnostics prizes
  - £10 mil Longitude Prize (UK); $10 AMR Diagnostic Challenge (US)
- Global R&D Hub (German leadership)
- UK & China joint R&D venture (tot £17 mil)

Market Entry Rewards Needed to Establish a Pull Incentive

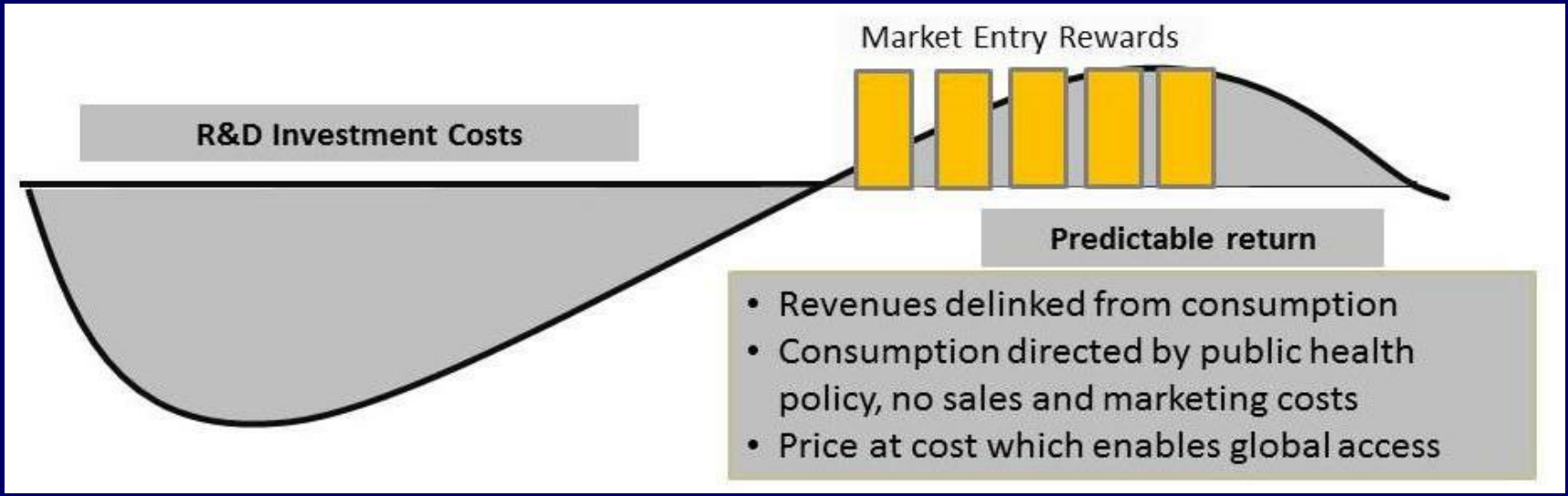
- Antibiotics are one of the only class of drugs whose use diminishes utility overtime
- How do we ensure antibiotics are available while not driving inappropriate use?
- Market Entry Rewards models seek to uncouple profit of antibiotics from the number of units sold
  - Allow a reasonable return on investment (ROI)
  - Can build in provisions for stewardship and conservation

August 2016

September 2017

64

Market Entry Rewards



Other Pull Incentives

- Priority Review Vouchers (PRV)
- Transferrable IP Rights (TIPR)
- Lump sum Market Entry Reward

Davos Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance

Call on governments to work with them to develop new and alternative market structures that provide more dependable and sustainable market models for antibiotics, and to commit the funds needed

- **Provide appropriate incentives (coupled with safeguards to support antibiotic conservation) for companies to invest in R&D to overcome the formidable technical and scientific challenges of antibiotic discovery and development**
- **These include mechanisms to ensure that**
  - **pricing of antibiotics more adequately reflects their benefits**
  - **novel payment models that reduce the link between the profitability of an antibiotic and the volume sold**
  - **An integral part of these models is a reduced need for promotional activity by companies**

- **85 companies, 9 industry associations 18 countries; http://amr-review.org/industry-declaration**

Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating AMR – 3 Areas

- Reducing the development of drug resistance
  - Stewardship; including principles set out by the World Health Organization (WHO) Global Action Plan on antimicrobial resistance (AMR), and via improved education of clinicians…extends to promoting judicious use of antibiotics in livestock, as part of a 'one health' approach
- Increasing investment in R&D that meets global public health needs
  - Commitment to continuation and extension of collaborative initiatives between industry, academia and public bodies to improve R&D
- Improve access to high-quality antibiotics for all
  - Commitment to supporting initiatives aimed at ensuring affordable access to antibiotics in all parts of the world, at all levels of income

http://amr-review.org/industry-declaration


HOLY SEE
HIGH-LEVEL MEETING ON
ANTIMICROBIAL RESISTANCE
21 SEPTEMBER 2016, UN HEADQUARTERS, NEW YORK
OBSERVER
OBSERVER
OBSERVER

United Nations High Level Meeting on AMR – September 2016

- 4th High Level Meeting for infectious diseases
- Reaffirmed WHO Global Action Plan on AMR
- Priorities
  - Innovation of novel therapeutics and diagnostics
  - Ensuring access to current and future treatments and diagnostics
  - Improving surveillance systems
    - Antimicrobial use
    - Antimicrobial resistance
  - Developing metrics to assess progress

UN Declaration: Global Governance Responses

- WHO, FAO and OIE to finalize a global development and stewardship framework
- Establish the **Interagency Coordination Group on Antimicrobial Resistance (IACG)**
  - co-chairs: UN Deputy Secretary-General and the Director-General of the WHO
  - Mandate: to provide practical guidance for ensuring sustained effective global action to address AMR
  - Founded on 17 March 2017, incorporating 27 organisations and 15 independent experts
  - Three conveners: Professor Junshi Chen, Professor Dame Sally Davies and Ms Martha Gyansa-Lutterodt
-

Interagency Coordination Group on Antimicrobial Resistance (IACG)

- First meeting in New York on 2–3 May 2017
- Adopted a Framework for Action, based on over 150 interviews
  - establishes a comprehensive view on 14 different issues mapped against the SDGs and the WHO's Global Action Plan (GAP) on AMR
  - presents five levers that can help address them

Interagency Coordination Group on Antimicrobial Resistance (IACG)

Five primary objectives:

1. **Support implementation of UNGA Political Declaration and the GAP and link them to the SDGs by advocating for action against AMR at the highest political level**
2. **Coordinate mapping of the actions being taken towards achieving measurable results, and to identify opportunities for collaboration, as well as gaps, redundancies and duplication**
3. **Promote, plan and facilitate collaborative action to align activities so that gaps are closed and resources optimally distributed**
4. **Explore feasibility of developing global goals and ambitions related to AMR for UN agencies, component members and, where appropriate, other stakeholders, for priorities set out in the declaration**
5. **Report regularly on progress/IACG meetings and issue a full report to the Secretary-General during the 73rd session of the UNGA**

May, 2017, Meeting of the G20 Health Ministers - Recommendations

- National Action Plans based on One Health approach “well underway” by 2018
- Raise awareness of AMR through prevention and stewardship campaigns as part of balanced approach to addressing the five objectives of the WHO Global Action Plan on AMR
- Act to strengthen infection prevention and control measures
- Promote participation in the WHO global “Save Lives: Clean Your Hands” campaign
- Foster R&D for priority pathogens and TB via Global R&D Hub (Germany)
- Promote development , support implementation of antimicrobial stewardship programs to reduce inappropriate antibiotic consumption by humans and require that antibiotics must be prescribed/dispensed by domestically certified health professionals

https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf

May, 2017, meeting of the G20 Health Ministers - Recommendations

- Strengthen One Health approach within the G20
- Reactivate R&D pipeline through incentive mechanisms that avoid the reliance on high price/volume combinations
- Promote prudent and responsible use of antimicrobials
- Support ongoing initiatives, examining push and pull mechanisms that take into account needs of all countries and stress the need for a better coordination of existing initiatives
- Build on the work of existing product development partnerships and funding initiatives such as the Global Antibiotic Research and Development Partnership (GARDP), launched May 2016 by the WHO and the Drugs for Neglected Diseases initiative (DNDi), UNITAID, the Joint Programming Initiative on AMR (JPIAMR), Combating Antibiotic Resistance Bacteria Biopharmaceutical Accelerator (CARB-X), Innovative Medicines Initiative (IMI), the TB Alliance for new anti-tuberculosis medicines

https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G20-Gesundheitsministertreffen/G20_Health_Ministers_Declaration_engl.pdf

WHO Progress

- Established GLASS
  - Global Antimicrobial Resistance Surveillance System
    - First call for data: April ‘16-July ‘17
- Tripartite organizations (WHO/FAO/OIE) developing joint monitoring and evaluation approach
- Expert meeting on indicators for monitoring/evaluation of country/global efforts
- Expert meeting on workforce and AMR education
  - Established subcommunity on Health Workforce AMR Education & Training
  - 91 educational tools available

Progress on National Action Plans

WHO country self-assessment on NAPs

- **151/195 WHO member states responded**
  - **85% countries developing or have NAPs**
  - **52% fully developed NAP addressing full One Health spectrum**
  - **52% LMICs national-level measures in place on IPC in human healthcare; 7% in animals/foods**
  - **19% multisectoral AMR action plan with monitoring**
  - **5% multisectoral AMR action plan that has been implemented with $$$ and monitoring**

Progress in Animal AMR Industry/Non-profits

- Gates Foundation, World Veterinary Association, AAVMC
- Natural Resources Defense Council, consumer groups Sept 2016
  - Graded top 25 US restaurant chains re: meat raised with antibiotics
  - 9 passed assessment; Panera and Chipotle exemplary
  - Tyson, McDonalds, KFC, Taco Bell, Burger King all pledged to cut down or cut out antibiotics in food animals

AMR Call to Action – Berlin 2017
Wellcome Trust, UK, Ghanian Thai Govts

- AMR is now recognised at highest political levels
  - High-level UNGA meeting September 2016
  - Renewed commitments - G20 Health Ministers'/G20 Leaders' Declaration, May/July 2017
- Political rhetoric not consistently translated into action
  - Progress in just 1/3 priority areas in 2016 AMR Review
- AMR poses a threat to all in today's interconnected world, and is deeply tied up with the achievement of the Sustainable Development Goals (SDGs), universal health coverage and health security
- Call to Action on AMR builds momentum towards concrete and tangible actions by acting as the first step to an effective and coordinated response that transcends borders
- Community present at the Call to Action on AMR and beyond must support and input into the work of the IACG to achieve these goals

AMR: A Global Priority

- Human Health
- Animal Health
- Environmental Protection
- National and Global Security

AMR: A Global Priority
Future Goals

- Coordinate AMR and TB activities
- Facilitate multinational research networks
- Promote research that leads to improved use of existing antibiotics while maintaining access
  - Global stewardship
- Advance “push” and “pull” incentives for antimicrobial therapeutics, diagnostics and vaccines
- Secure an expert infectious diseases workforce to address AMR
- Make AMR activity map publicly available
- Create a mechanism to facilitate collaboration and sharing of resources and knowledge

Thank You!

- Antimicrobial Resistance Committee, IDSA
- Cesar Arias
- Sara Cosgrove
- James Hughes
- Amanda Jezek
- Ramanan Laxminarayan
- Kevin Outterson
- John Rex
- George Talbot

Helpful Resources

- Wellcome Trust Wellcome.ac.uk
- www.amr-review.org
- Pew Charitable Trust www.pewtrusts.org
- WHO 2017 PPL (aka, Priority Bacterial Pathogens List)
  - Downloaded 27 Feb 2017 from http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf
- CDC 2013 Threat List
  - Downloaded 28 Feb 2017 from https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf
- ESKAPE
  - Rice LB. Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE. J Infect Dis. 2008;197(8):1079-81.
  - Boucher HW et al. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clinical Infectious Diseases. 2009;48(1):1-12
- http://www.who.int/antimicrobial-resistance/en/