One Health and the control and prevention of antimicrobial resistance: Perspectives from human medicine

Cornelius J. Clancy, M.D.

Chief, Infectious Diseases

VA Pittsburgh Healthcare System

Director, XDR Pathogen Lab and

Mycology Research Unit

University of Pittsburgh

One Health, One Planet 2019
Phipps Conservatory and Botanical Gardens
Pittsburgh, PA
14 March 2019

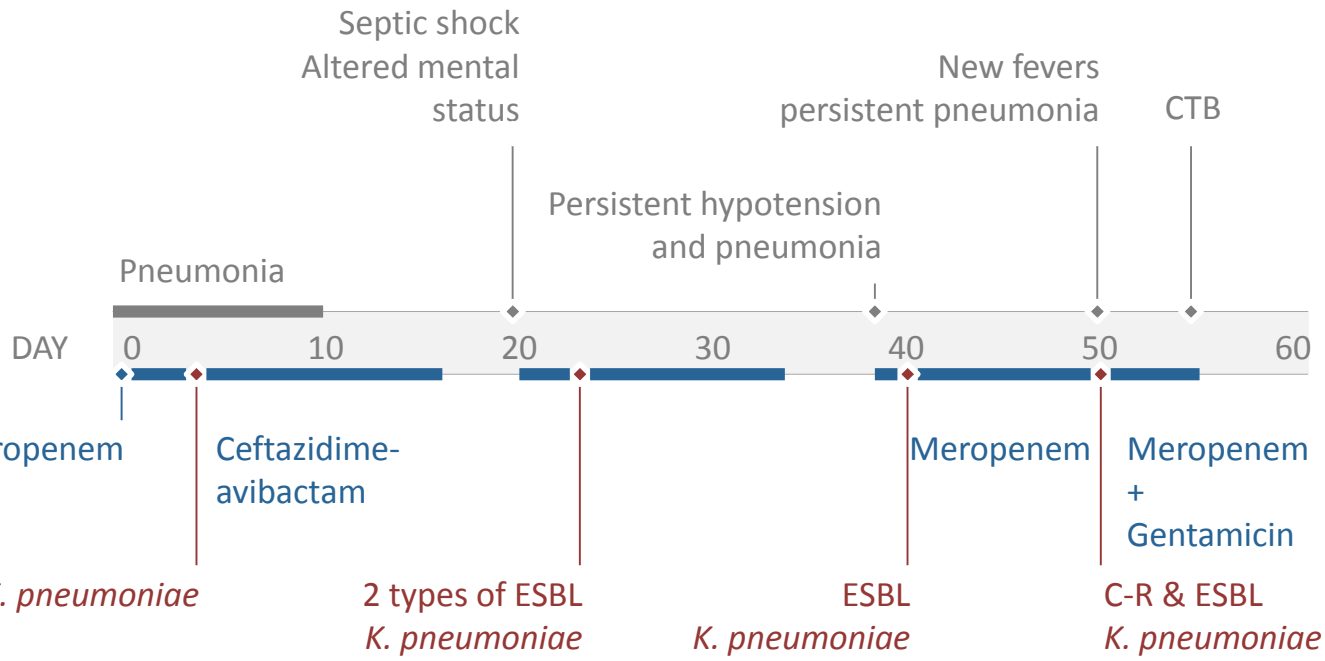
Pitt

VAPHS
VA Pittsburgh Healthcare System

An illustrative case, 2019

65 y/o woman; double lung transplant for COPD.

Fever; shortness of breath. On admission required ventilation.



The rise of CRE* superbugs

NBC NEWS

HEALTH
MAR 5, 2015, 12:27 AM ET

Two More Hospitals Report 'Superbugs' on Endoscopes

By MAGGIE FOX

Hospitals Plagued by Unbeatable 'Superbugs'

Nov 29, 2012 11:11 AM CST

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'USA TODAY' FINDS THOUSANDS OF CASES IN RECENT YEARS

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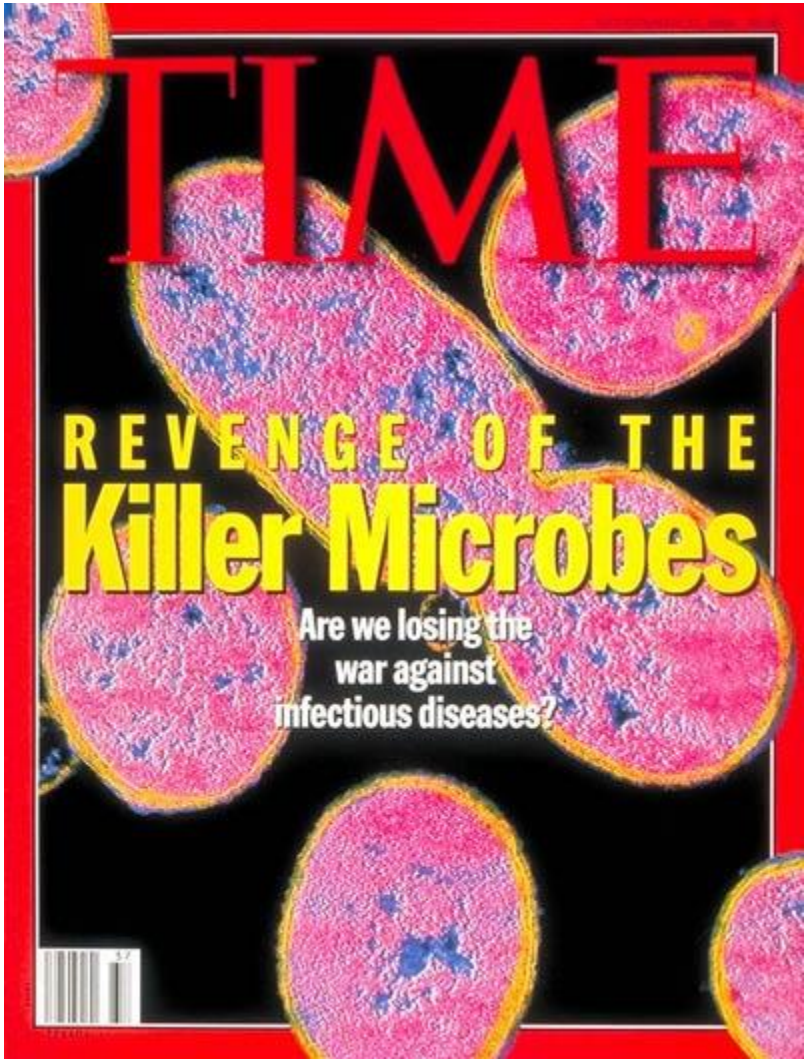

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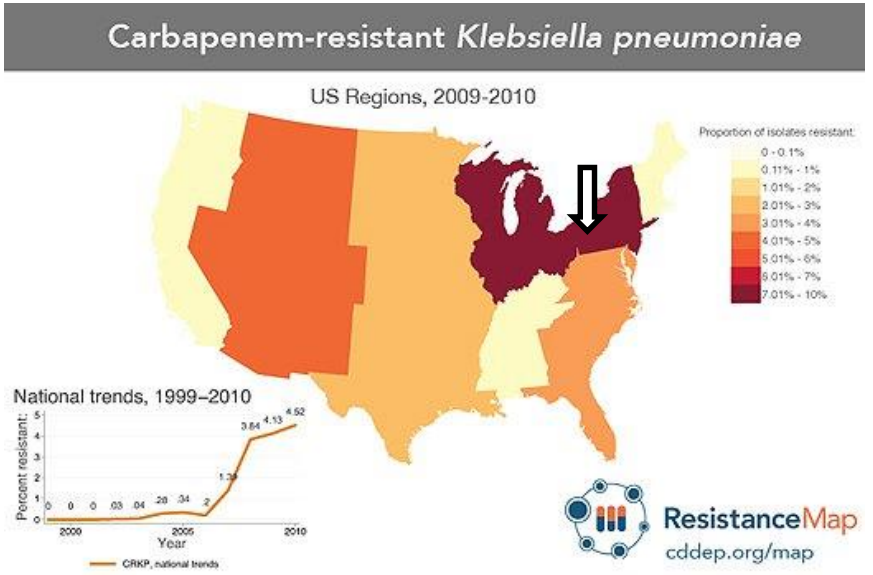

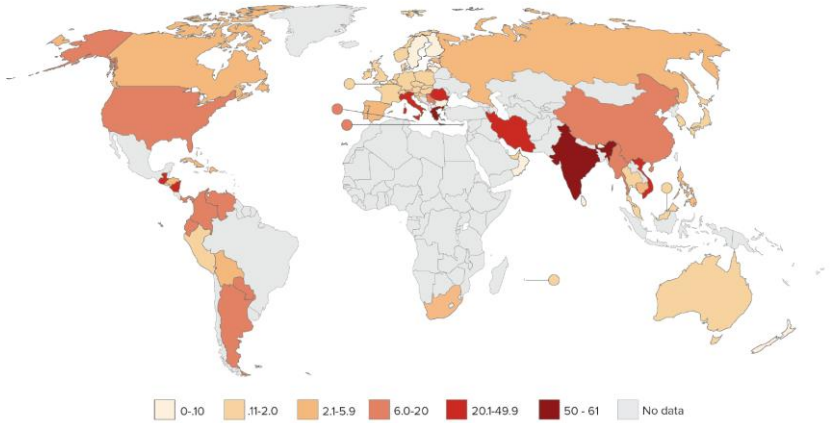

FIGURE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011–2014)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

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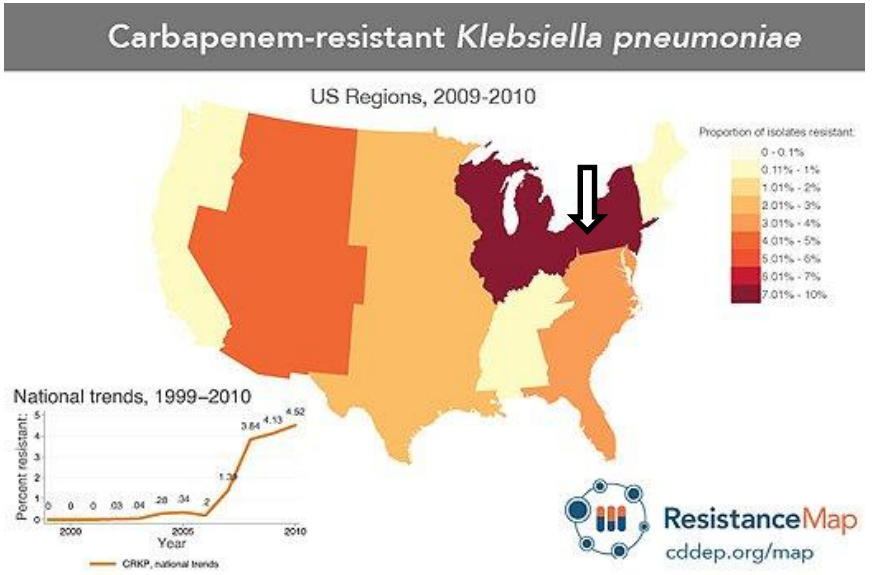
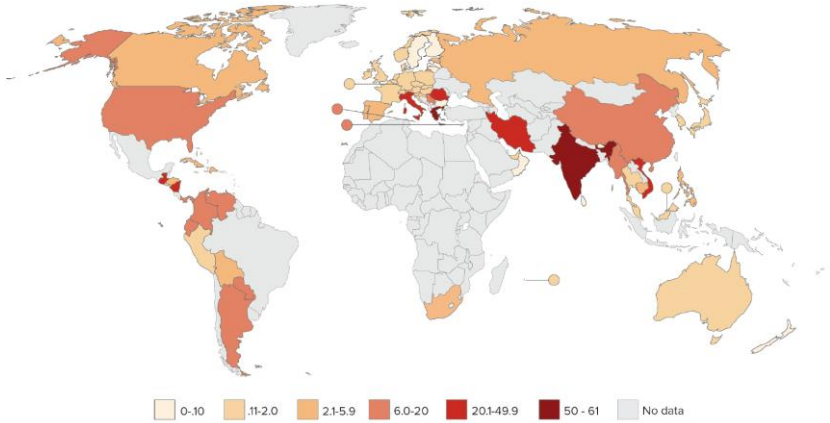
10 million deaths due to drug-resistant infections per year in 2050





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Review on Antimicrobial Resistance, Wellcome Trust and UK Department of Health

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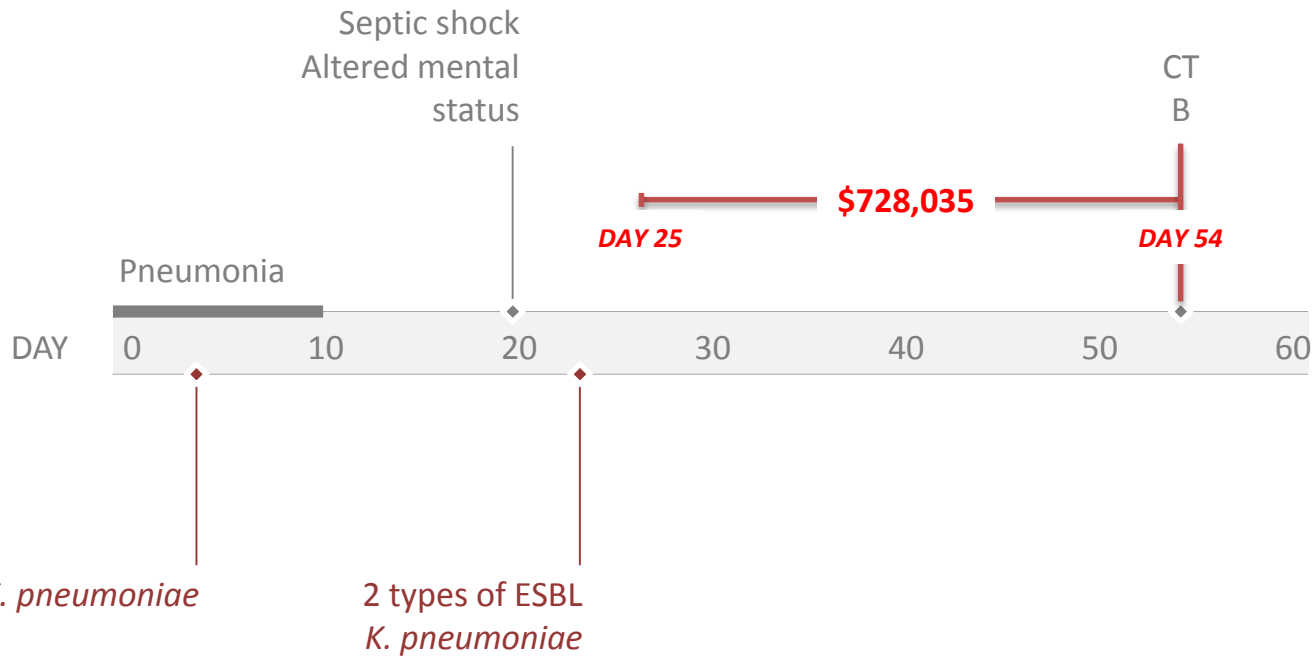

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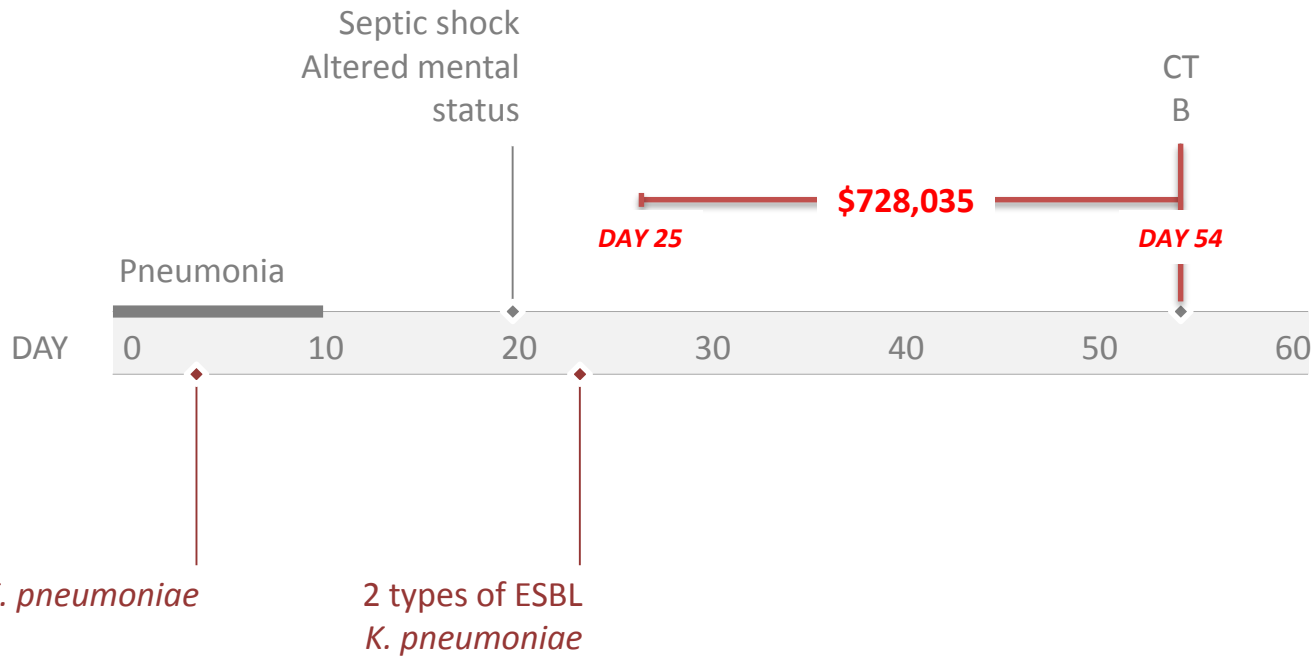


Lost global production due to antimicrobial resistance 2016-2050: $100 trillion

Review on Antimicrobial Resistance, Wellcome Trust and UK Department of Health

Antibiotic resistance threats

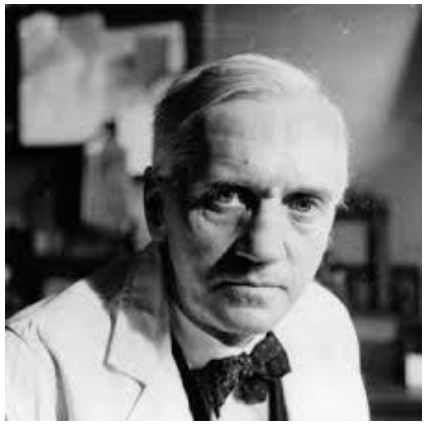
table.2

Urgent Threats
Clostridium difficile
Carbapenem-resistant Enterobacteriaceae
Neisseria gonorrhoeae
Serious Threats
Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant *Candida*
Extended spectrum Enterobacteriaceae
Vancomycin-resistant *Enterococcus*
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant nontyphoidal *Salmonella*
Drug-resistant *Salmonella* serotype Typhi
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus*
Drug-resistant *Streptococcus pneumoniae*
Drug-resistant tuberculosis
Concerning Threats
Vancomycin-resistant *Staphylococcus aureus*
Erythromycin-resistant Group A *Streptococcus*
Clindamycin-resistant Group B *Streptococcus*

Table 2. US Centers for Disease Control and Prevention list of the greatest drug-resistant microbial threats in the United States.[6]

CDC: Antibiotic Resistance Threats in the US, 2013 (http://www.cdc.gov/drugresistance/threat-report-2013/index.html)

History of penicillin resistance



"… the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism."
26 June, 1945

"Surveys of hospitals have found that practices to improve antimicrobial use are frequently inadequate and not routinely implemented"

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

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Clin Infect Dis 2007; 44:159-77

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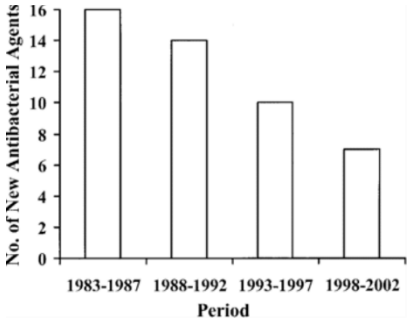
Clin Infect Dis 2007; 44:159-77

MAJOR ARTICLE

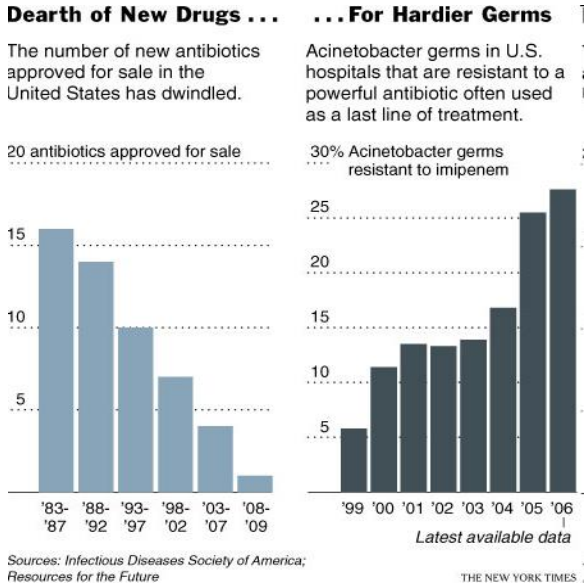
Trends in Antimicrobial Drug Development: Implications for the Future

Brad Spellberg,[1] John H. Powers,[2] Eric P. Brass,[1,2] Loren G. Miller,[1,2] and John E. Edwards, Jr.[1,2]

[1]Research and Education Institute and Department of Medicine, Harbor–University of California, Los Angeles (UCLA), Medical Center, Torrance, and [2]David Geffen School of Medicine, UCLA, Los Angeles, California; and [3]Office of Drug Evaluation IV, Center for Drug Evaluation and Research, US Food and Drug Administration, Rockville, Maryland

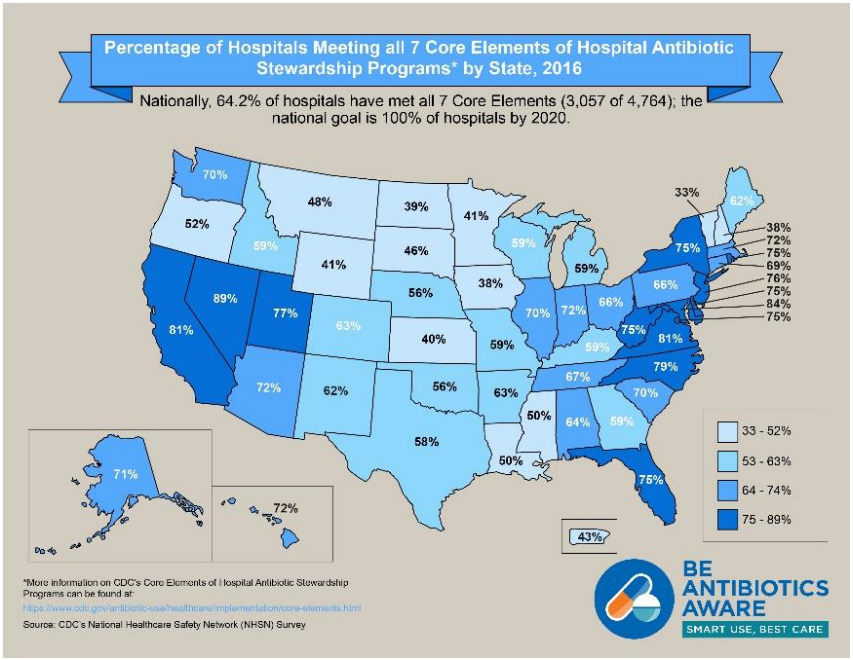


Clin Infect Dis 2004; 38:1279-86



Mandates for Antimicrobial Stewardship (AMS)

CDC Core Elements of AMS
Hospitals
Nursing homes
Outpatient

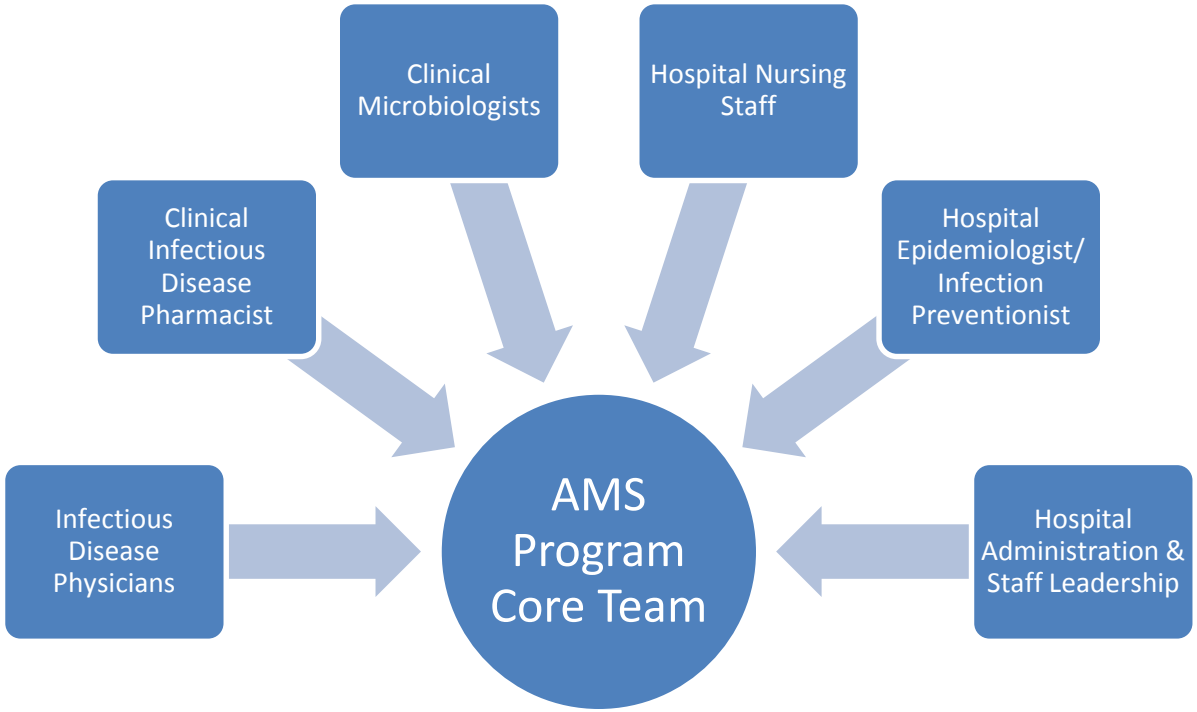


Core elements of AMS programs

- Leadership commitment
  - Human, financial, IT resources
- Accountability
  - Single leader (M.D.) responsible for program outcomes
- Drug expertise
  - Single leader (Pharmacist) responsible for improved antibiotic use
- Action
  - Implementing at least one recommended action
- Tracking
  - Monitoring prescribing and resistance
- Reporting
  - Regular reporting on antibiotic use and resistance
- Education
  - Optimal prescribing and resistance

E. Friestrom, E. McCreary

Core AMS team



E. Friestrom, E. McCreary

"There is no single template for a program to optimize antibiotic prescribing"

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Does AMS work?

J Antimicrob Chemother 2011; **66**: 1223–1230
doi:10.1093/jac/dkr137 Advance Access publication 2 April 2011

Journal of Antimicrobial Chemotherapy

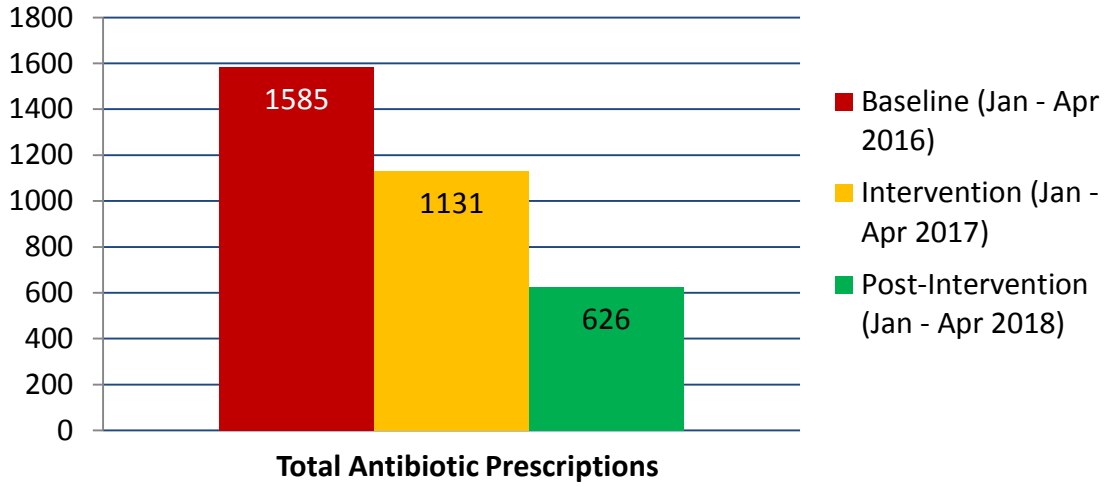
Impact of antimicrobial stewardship in critical care: a systematic review

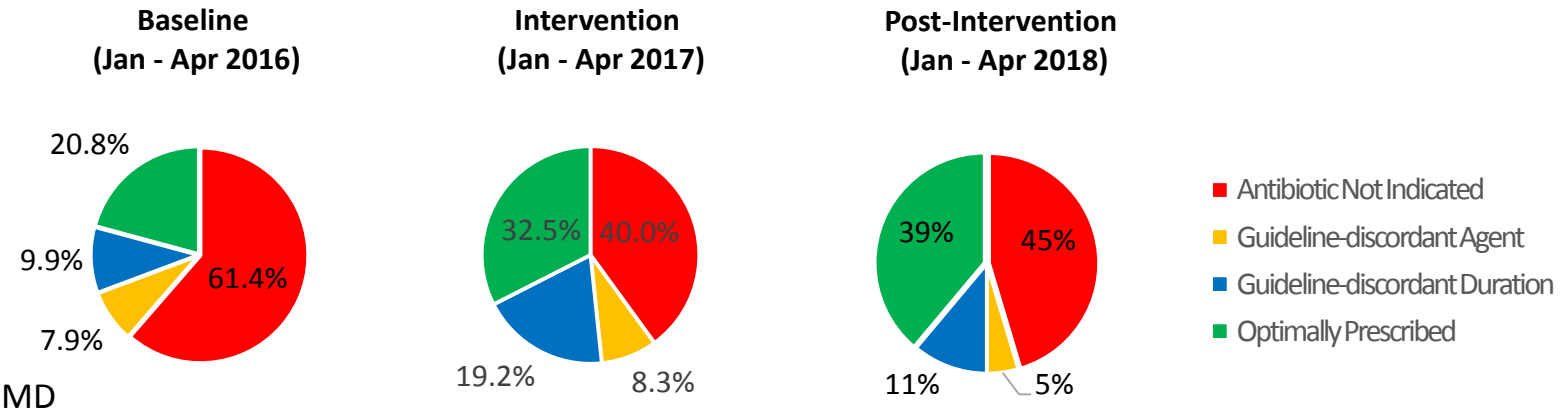
Reham Kaki[1], Marion Elligsen[2], Sandra Walker[2–4], Andrew Simor[1,4], Lesley Palmay[2] and Nick Daneman[1,4]*

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada; [3]Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; [4]Division of Infectious Diseases, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

- 38 studies, 6 AMS intervention types
- Reduced utilization (11%-38%), lowered costs (US$5-10/patient-day), shortened duration of treatment, reduced inappropriate use and adverse events/toxicity
- Not associated with increased nosocomial infection rates, lengths of stay, or mortality
- Interventions beyond >6 mos were associated with reduced resistance

AMS: Still a lot of work to do





Brooke Decker, MD

VA Pittsburgh Healthcare System

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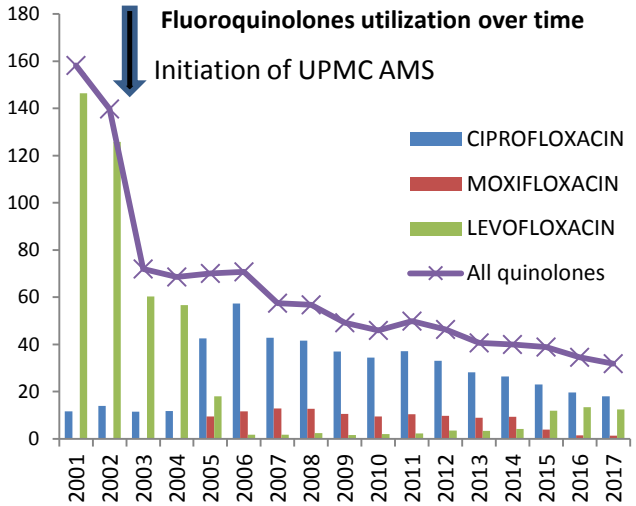
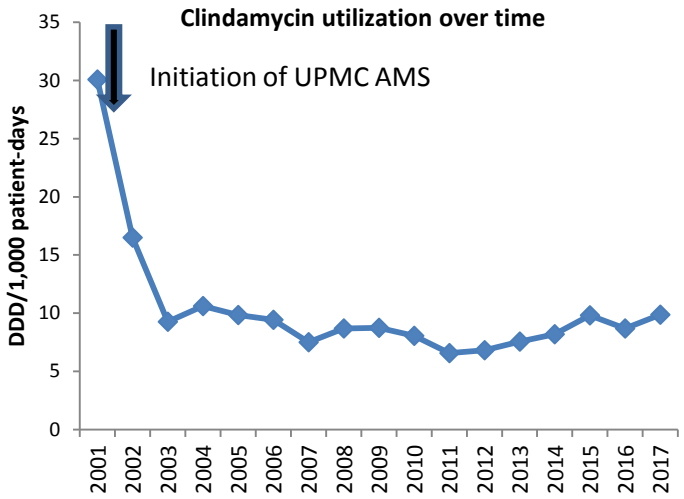
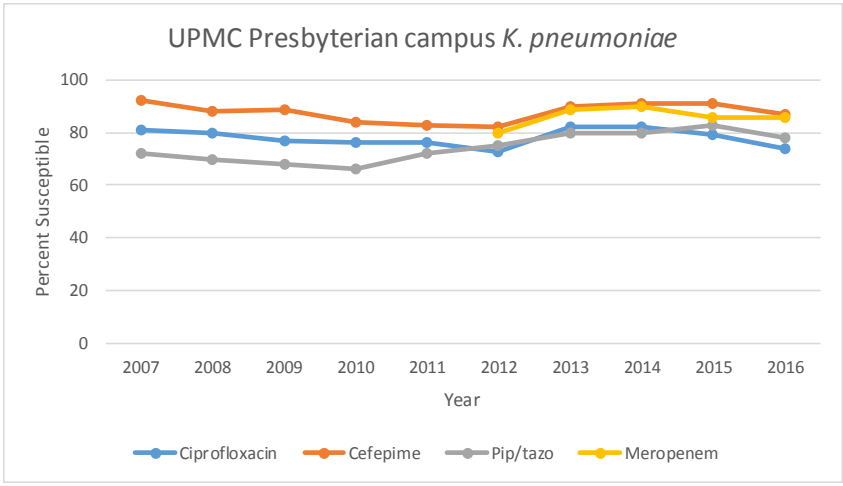
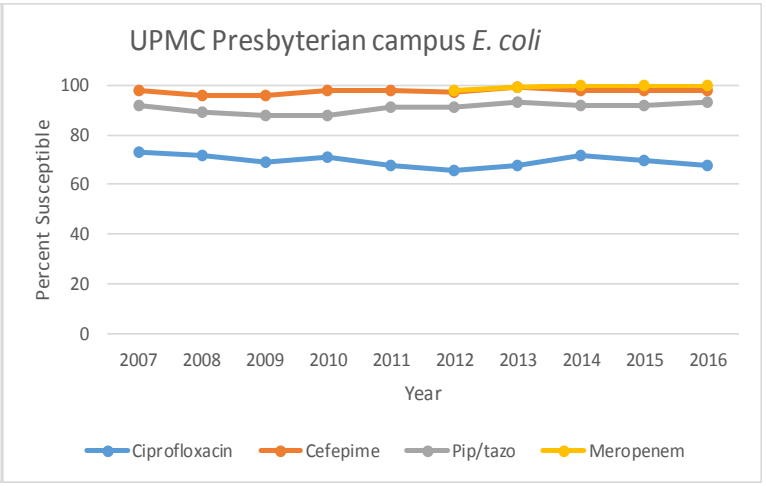


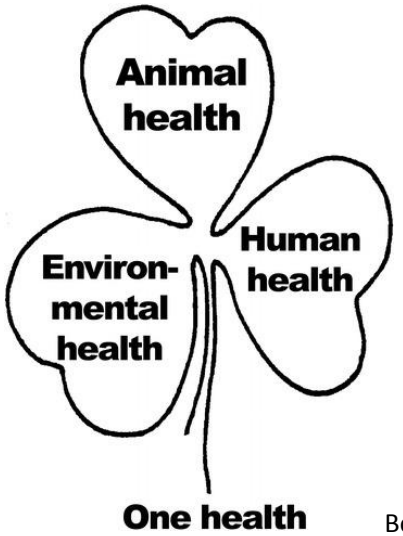




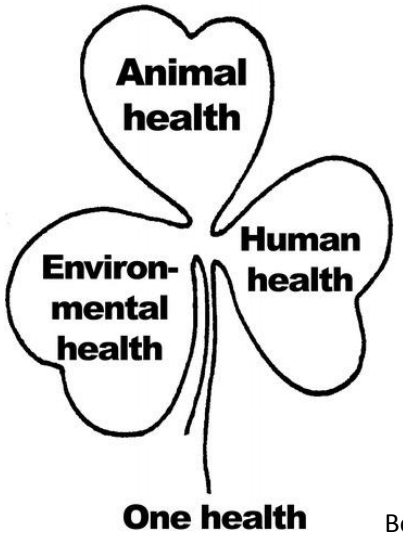


M. Hong Nguyen, MD

UPMC



Boqvist, Acta Vet Scand 2018



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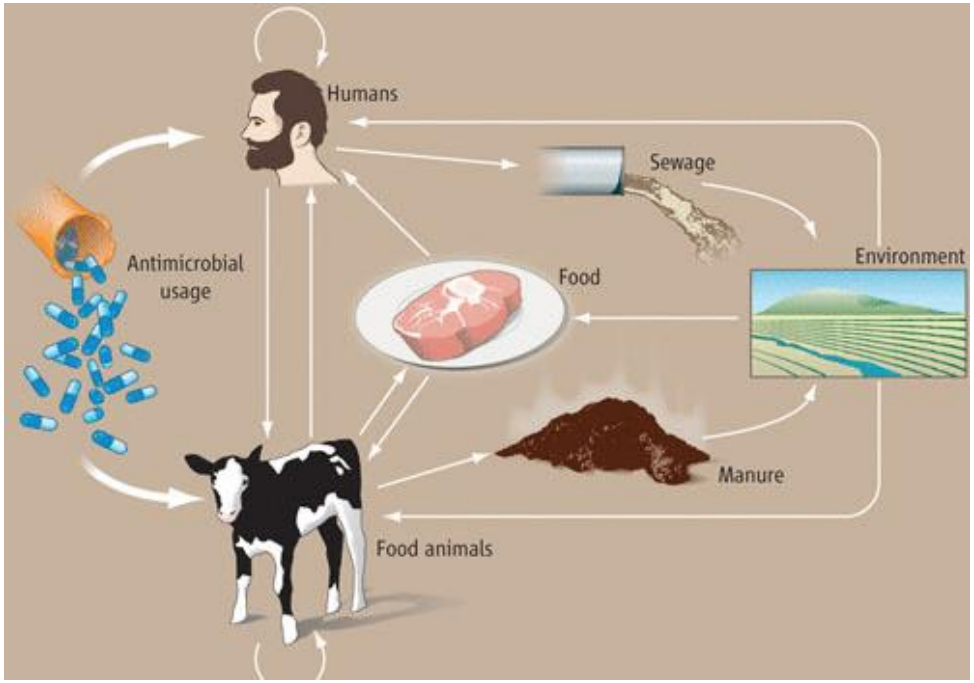

McEwen, Microbiol Spectrum 2018

One Health AMR Case Study 1: Colistin

Health

Antibiotic resistance: World on cusp of 'post-antibiotic era'

By James GallagherHealth editor, BBC News website
19 November 2015

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

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Lancet Infect Dis 2016; 16: 161–68

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

INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz, Section Editor

Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections

Matthew E. Falagas[1,2,3] and Sofia K. Kasiakou[1]

[1]Alfa Institute of Biomedical Sciences (AIBS) and [2]Department of Medicine, "Henry Dunant" Hospital, Athens, Greece; and [3]Tufts University School of Medicine, Boston, Massachusetts

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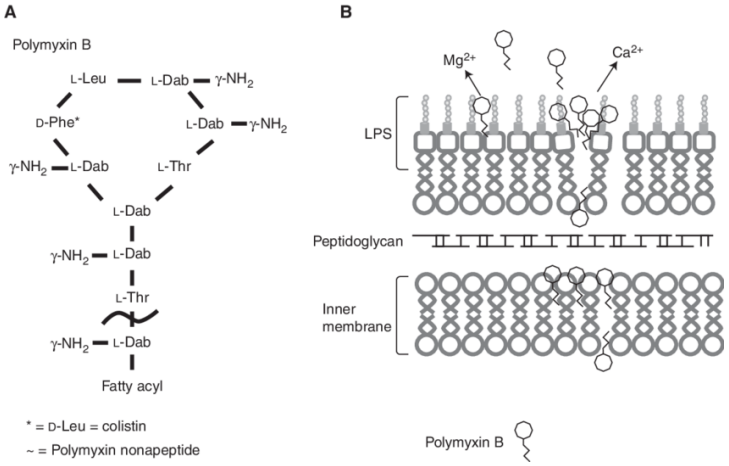

- China, Brazil, Europe (certain countries)
  - Administered orally to pigs, poultry, calves for treatment, prophylaxis, metaphylaxis of diarrhea, and/or as growth promoter
  - Vastly exceeds use in humans (12,000 tonnes in China)
- Phenotypic resistance testing is technically difficult
  - Not included in routine surveillance of animals, environment, food, humans

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

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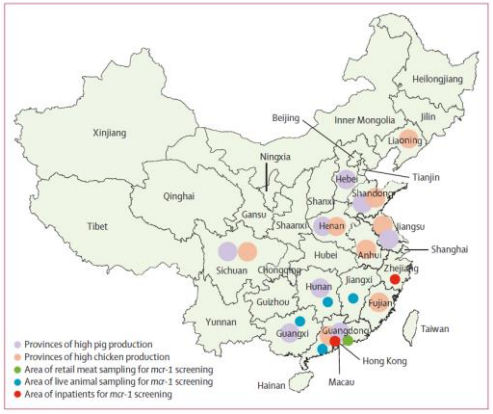

Figure 1: Map of China

	Year	Positive isolates (%)/number of isolates
Escherichia coli		
Pigs at slaughter	All	166 (20·6%)/804
Pigs at slaughter	2012	31 (14·4%)/216
Pigs at slaughter	2013	68 (25·4%)/268
Pigs at slaughter	2014	67 (20·9%)/320
Retail meat	All	78 (14·9%)/523
Chicken	2011	10 (4·9%)/206
Pork	2011	3 (6·3%)/48
Chicken	2013	4 (25·0%)/16
Pork	2013	11 (22·9%)/48
Chicken	2014	21 (28·0%)/75
Pork	2014	29 (22·3%)/130
Inpatient	2014	13 (1·4%)/902
Klebsiella pneumoniae		
Inpatient	2014	3 (0·7%)/420

Table 2: Prevalence of colistin resistance gene *mcr-1* by origin

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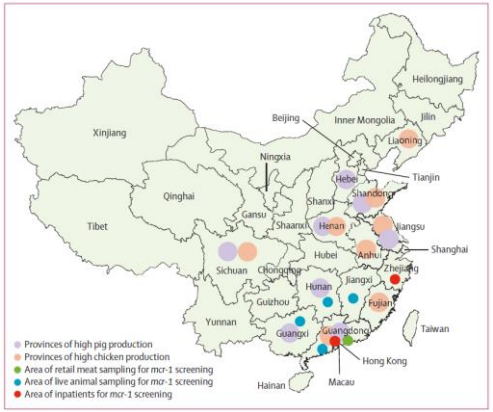

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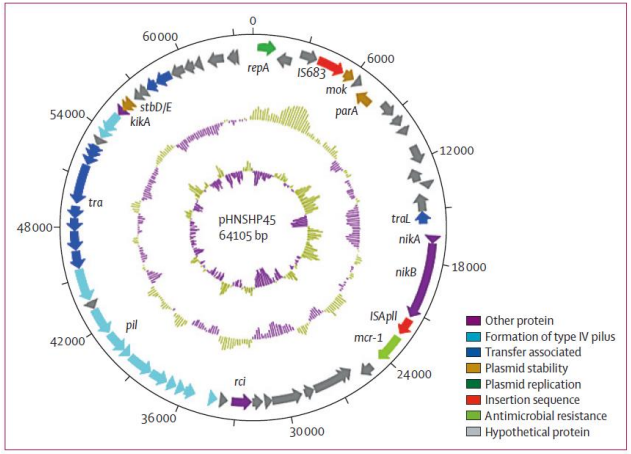

Figure 2: Structure of plasmid pHNSHP45 carrying *mcr-1* from *Escherichia coli* strain SHP45

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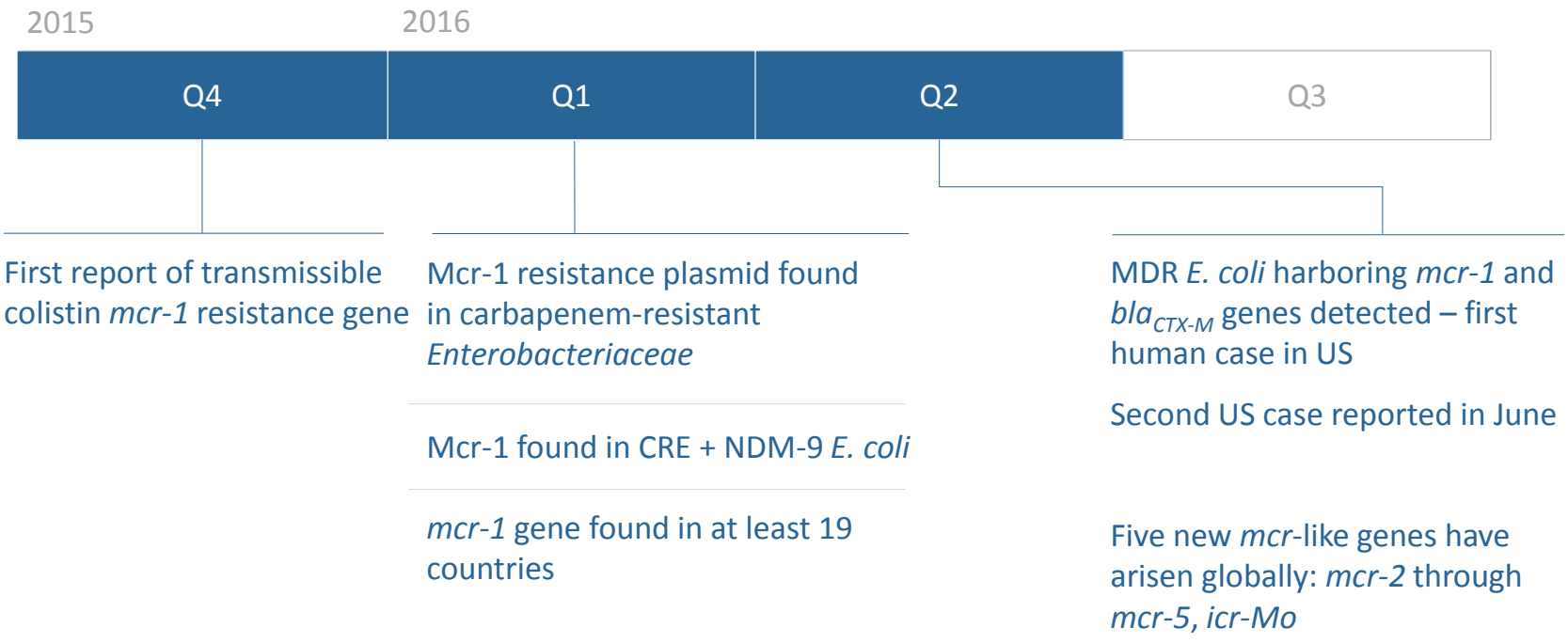
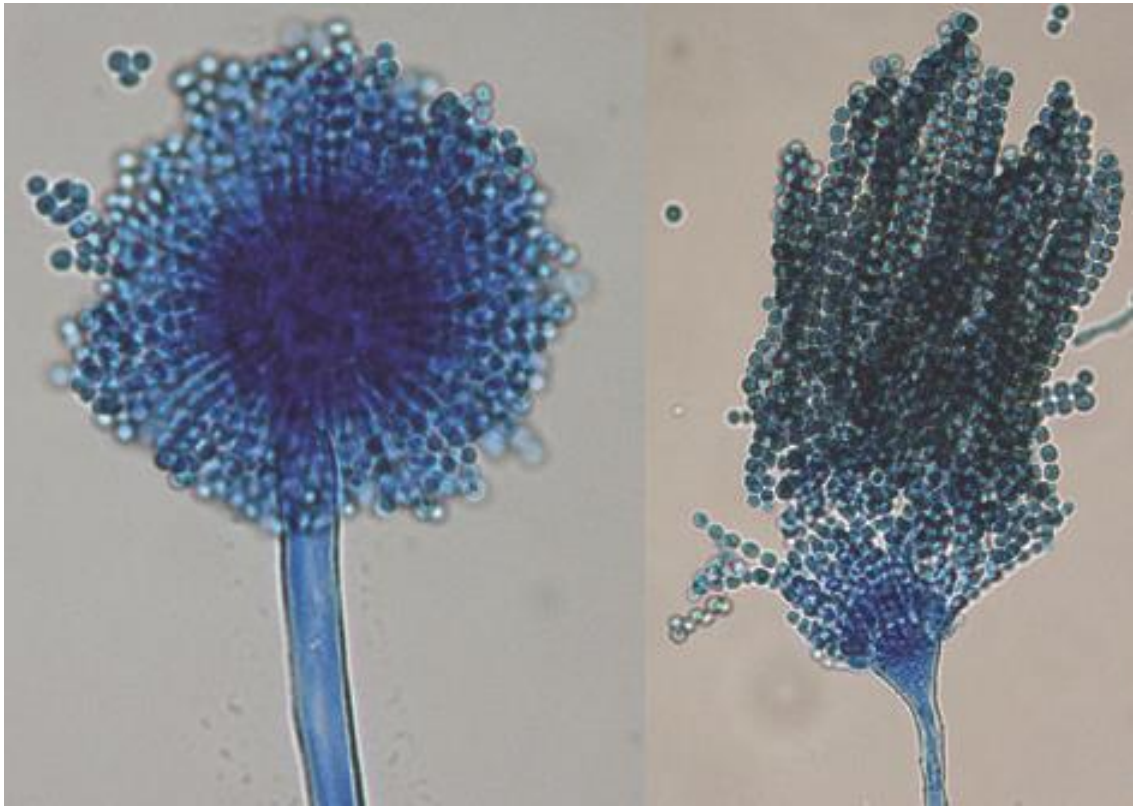
CRE: Our last line of defense is breached

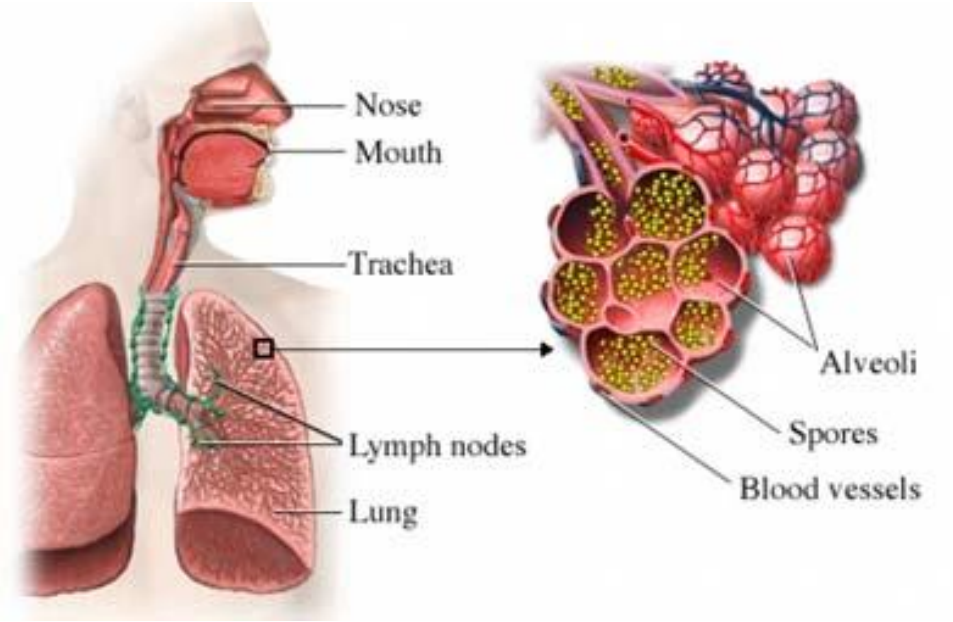


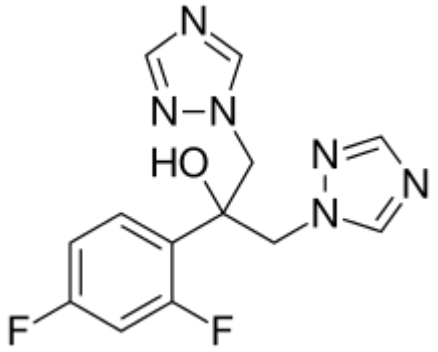
Liu YY et al. Lancet Infect Dis. 2016 Feb;16(2):161-8.
Du H Lancet Infect Dis. 2016 Jan 29. Yao X et al. Lancet Infect Dis. 2016 Jan 29, Bloomberg.
AAC 2016 May 26 online; doi:10.1128/AAC.01103-16

Case Study 2: Azole-R *Aspergillus*



Case Study 2: Azole-R *Aspergillus*

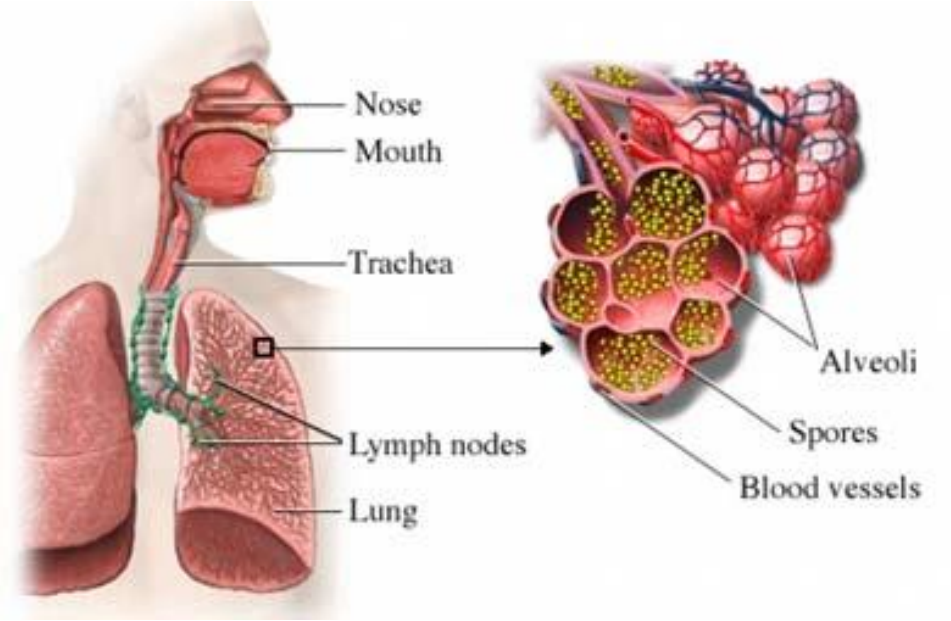


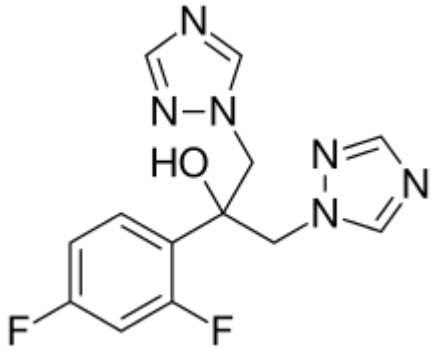


Azole antifungals

Chowdhary Plos Pathogens 2013

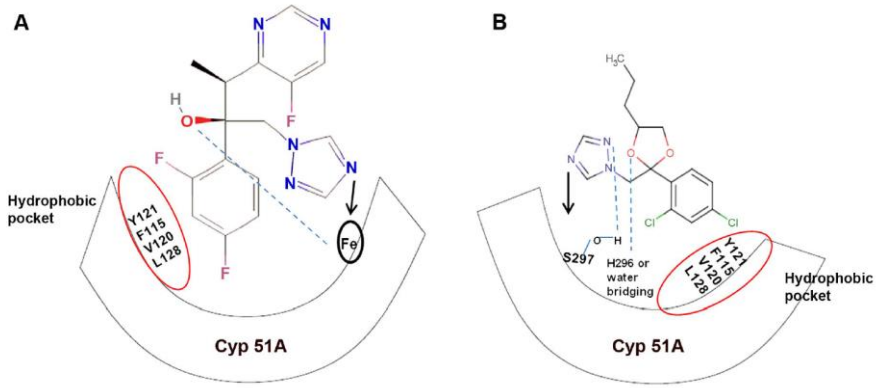
Case Study 2: Azole-R *Aspergillus*





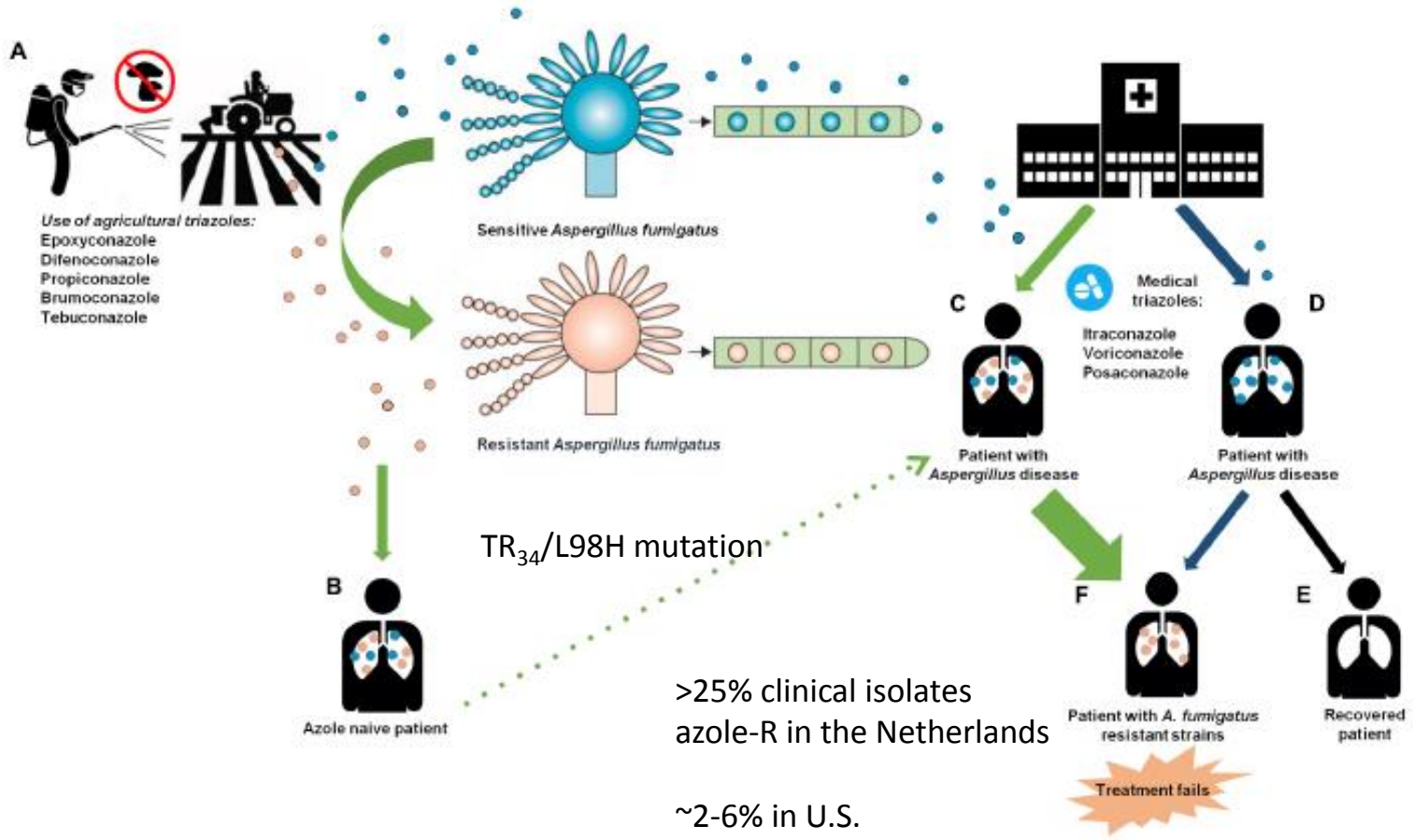
Azole antifungals

Crop protection, wood preservation, fruit and vegetable mildew and rust



Chowdhary Plos Pathogens 2013

Case Study 2: Azole-R *Aspergillus*



>25% clinical isolates azole-R in the Netherlands

~2-6% in U.S.

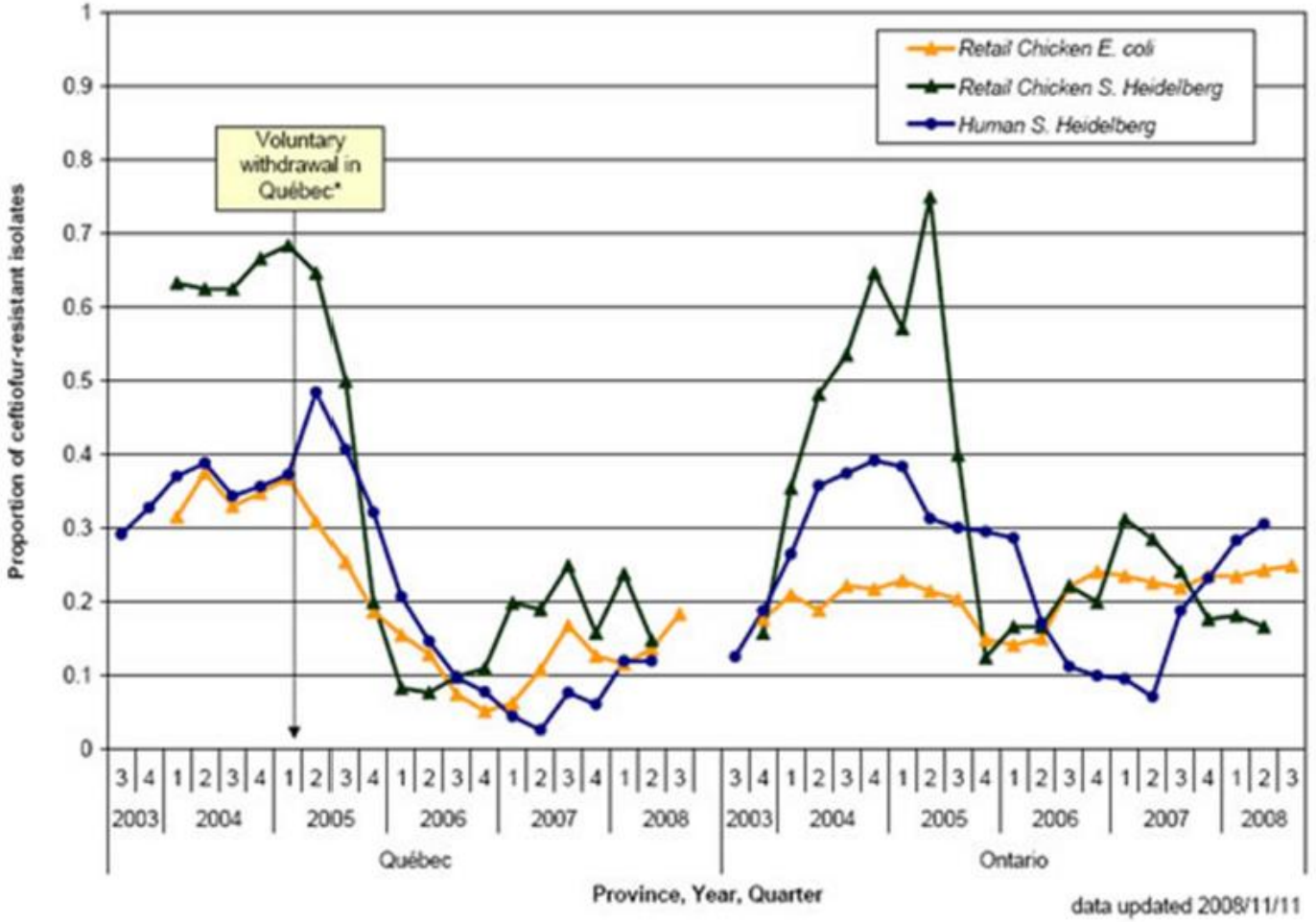
Berger Frontiers Micro 2017

Case Study 3: AMS in the poultry industry

- Ceftiofur was administered to eggs or day-old hatchery chicks as prophylaxis against *E. coli* or egg yolk infections
  - Canadian Integrated Program for Antimicrobial Resistance Surveillance
    - High rates of ceftiofur resistant *Salmonellla*
    - Ceftriaxone cross-resistance

McEwen, Microbiol Spectrum 2017; CPIARS 2009

Case Study 3: AMS in the poultry industry



McEwen, Microbiol Spectrum 2017; CIPARS 2009

Case Study 3: AMS in the poultry industry

- Japan, 2012
  - Voluntary withdrawal of ceftiofur use in hatcheries
    - Decrease in cephalosporin-R *E. coli* in broilers
- Canada, 2014
  - Ceftiofur voluntary ban by Canadian poultry industry http://www.chickenfarms.ca/wjat-we-do/antibiotics/faq/
- Europe
  - Label claim for ceftiofur use in day-old chicks withdrawn
- U.S.
  - Off-label use of 3rd generation cephalosporin banned

McEwen, Microbiol Spectrum 2017

One Health strategies against AMR

- Drug classification
  - Limit use of medically important antibiotics

TABLE 1 Classification of importance of antimicrobial classes for human health and animal health

Category	Human health (WHO) (42)	Animal health (OIE) (162)
Critically important	Aminoglycosides Ansamycins Carbapenems and other penems Cephalosporins (3rd and 4th generation) Phosphonic acid derivatives Glycopeptides Glycylcyclines Lipopeptides Macrolides and ketolides Monobactams Oxazolidinones Penicillins (natural, aminopenicillins, and antipseudomonal) Polymyxins Quinolones Drugs used solely to treat tuberculosis or other mycobacterial diseases	Aminoglycosides Amphenicols Cephalosporins (3rd and 4th generation) Macrolides Penicillins (natural, aminopenicillins, aminopenicillins with beta-lactamase inhibitor, antistaphylococcal) Fluoroquinolones Sulfonamides Diaminopyrimidines Tetracyclines
Highly important	Amidinopenicillins Amphenicols Cephalosporins (1st and 2nd generation) and cephamycins Lincosamides Penicillins (antistaphylococcal) Pleuromutilins Pseudomonic acids Riminofenazines Steroid antibacterials Streptogramins Sulfonamides, dihydrofolate reductase inhibitors, and combinations Tetracyclines	Ansamycin—rifamycins Cephalosporins (1st and 2nd generation) Ionophores Lincosamides Phosphonic acid Pleuromutilins Polymyxins (including bacitracin and other polypeptides) 1st-generation quinolones (flumequin, miloxacin, nalidixic acid, oxolinic acid)
Important	Aminocyclitols Cyclic polypeptides Nitrofurantoins Nitroimidazoles	Aminocoumarin Arsenical Bicyclomycin Fusidic acid Orthosomycins Quinoxalines Streptogramins Thiostrepton

One Health strategies against AMR

- AMS
  - Align medical, animal, agricultural activities
  - Regulatory
    - Antimicrobials in animal growth promotion
    - Extra-label fluoroquinolone, 3rd generation cephalosporin use in animals
    - Prescription-only antibiotics for veterinary use
- Surveillance and research
- Improved sanitation, hygiene and infection prevention
- New therapeutics, diagnostic tests, vaccines

One Health strategies against AMR

- Communication, education, and training
  - Views on moral implications of antibiotic use
    - Physicians, Veterinarians
      - Limit inappropriate use and resistance (“do no harm”)
    - Poultry industry leaders
      - Responsibility to business and employees
  - Interviews with farmers in India indicated that antibiotics are viewed as vitamins and feed supplements

One Health strategies against AMR

- Communication, education, and training
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  - Interviews with farmers in India indicated that antibiotics are viewed as vitamins and feed supplements
- Human medicine needs to get its own house in order

Acknowledgments

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VAPHS AMS

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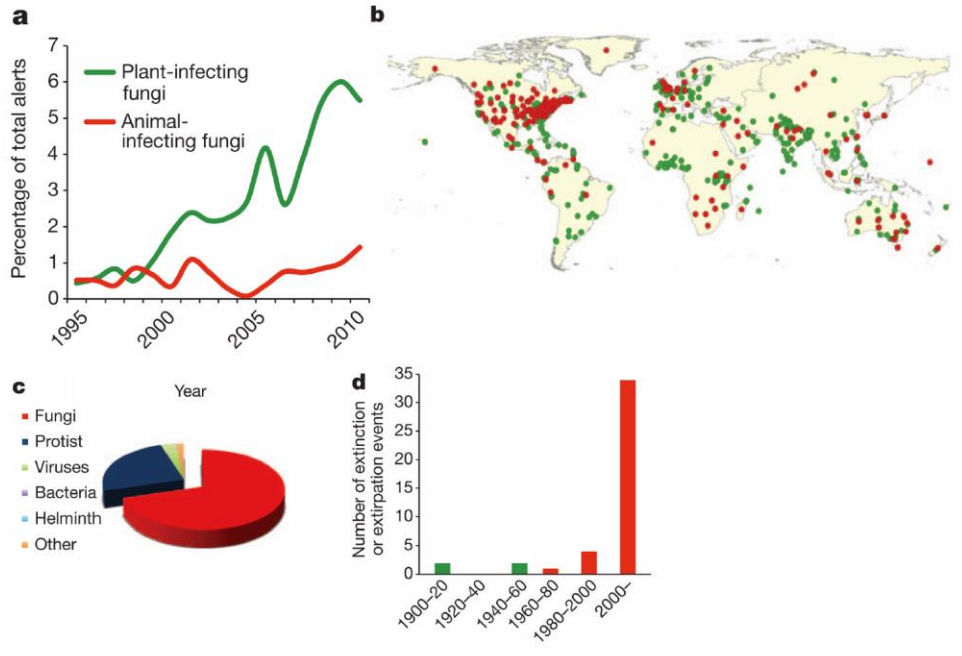
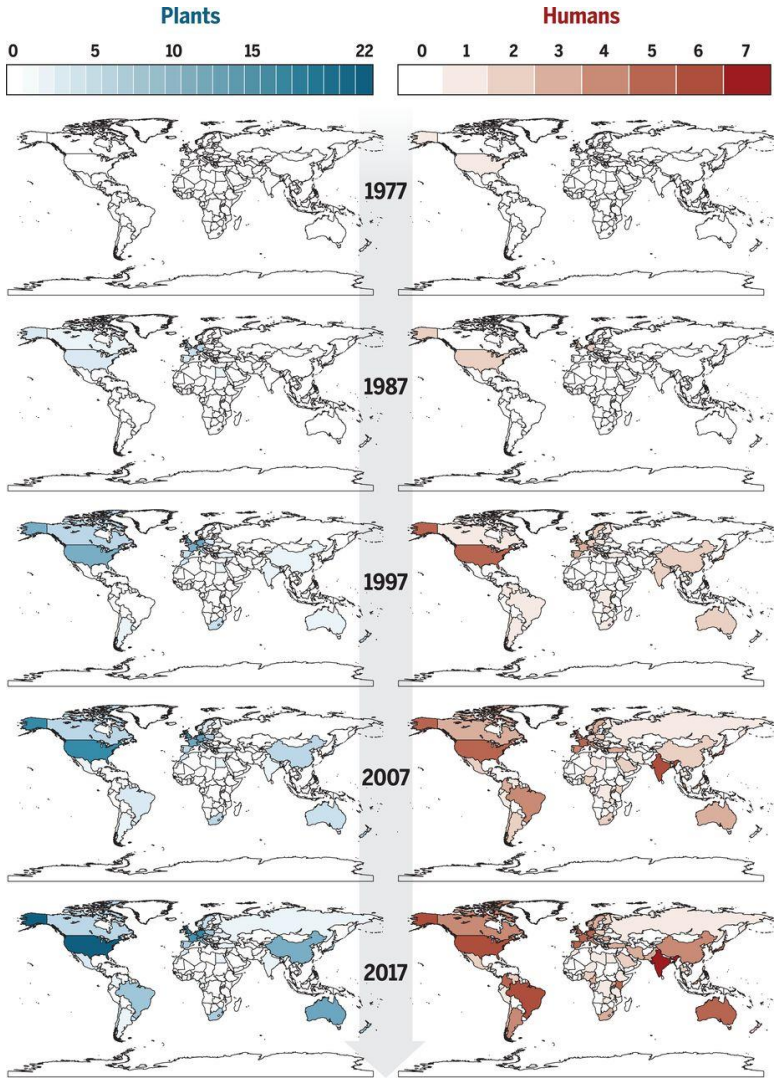
Worldwide emergence of fungal disease and antifungal-R





Fisher, Science 2018