

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

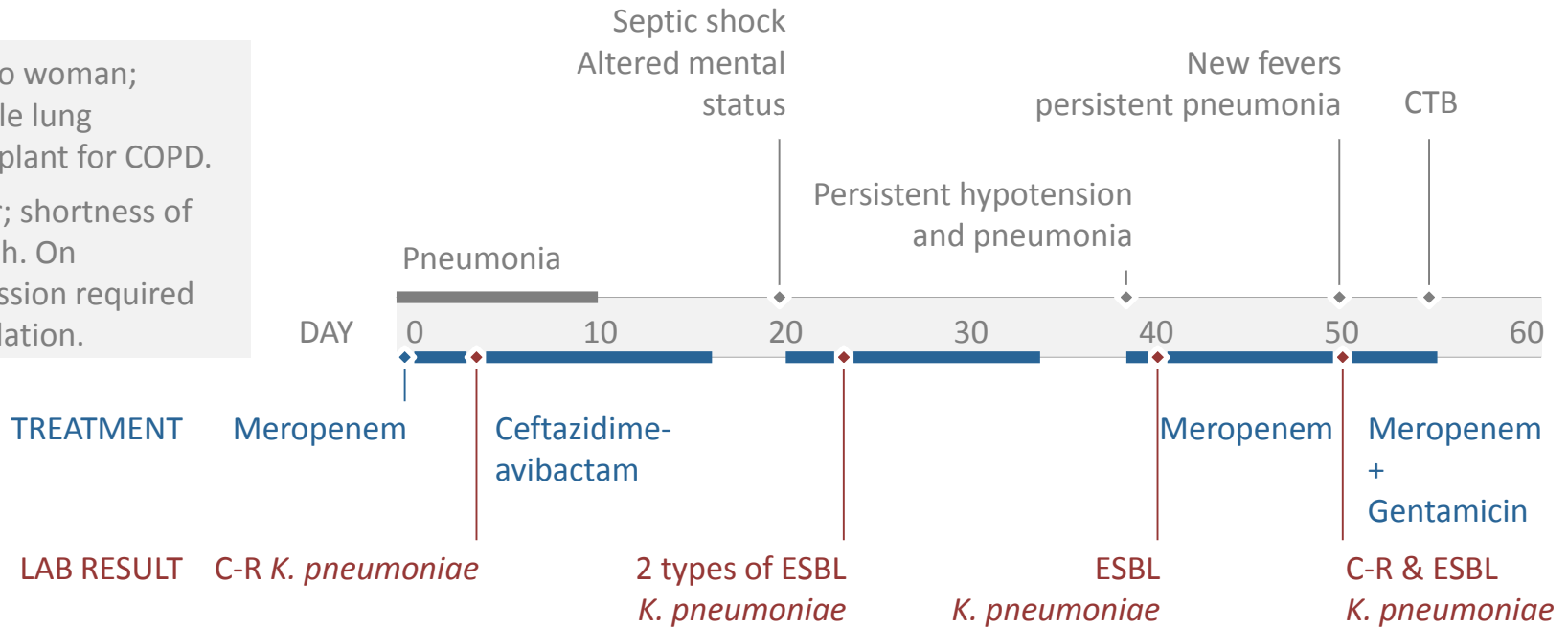
Pittsburgh, PA

14 March 2019



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



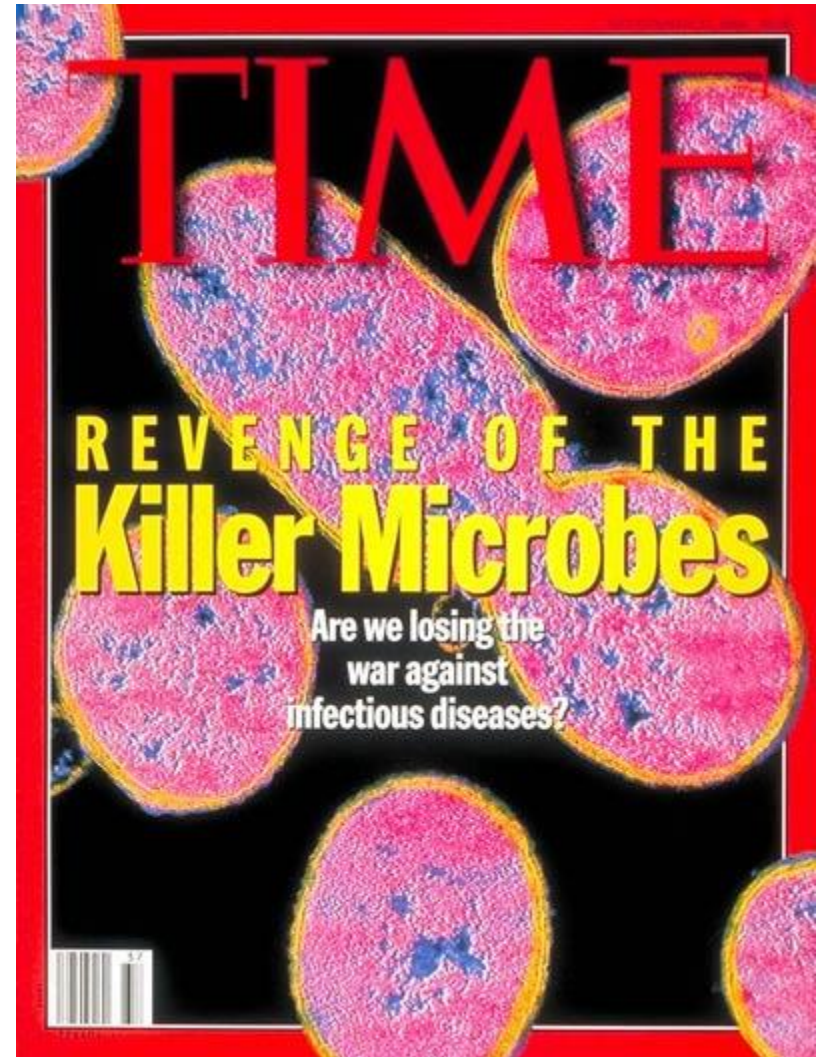
Hospitals Plagued by Unbeatable 'Superbugs'

Nov 29, 2012 11:11 AM CST

Hospitals Plagued by Unbeatable 'Superbugs'

'USA TODAY' FINDS THOUSANDS OF CASES IN RECENT YEARS

(NEWSER) - US hospitals are quietly fighting an incredibly high stakes war that they look unlikely to win against "superbugs" that resist even the most potent antibiotics available, a *USA Today* investigation has concluded. The paper has compiled evidence showing that hospitals across the country have seen thousands of infections from... [More »](#)



*Carbapenem Resistant Enterobacteriaceae

The rise of CRE* superbugs



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

Hospitals Plagued by Unbeatable 'Superbugs'

'USA TODAY' FINDS THOUSANDS OF CASES IN RECENT YEARS

(NEWSER) - US hospitals are quietly fighting an incredibly high stakes war that they look unlikely to win against "superbugs" that resist even the most potent antibiotics available, a *USA Today* investigation has concluded. The paper has compiled evidence showing that hospitals across the country have seen thousands of infections from... [More »](#)

Carbapenem-resistant *Klebsiella pneumoniae*

US Regions, 2009-2010

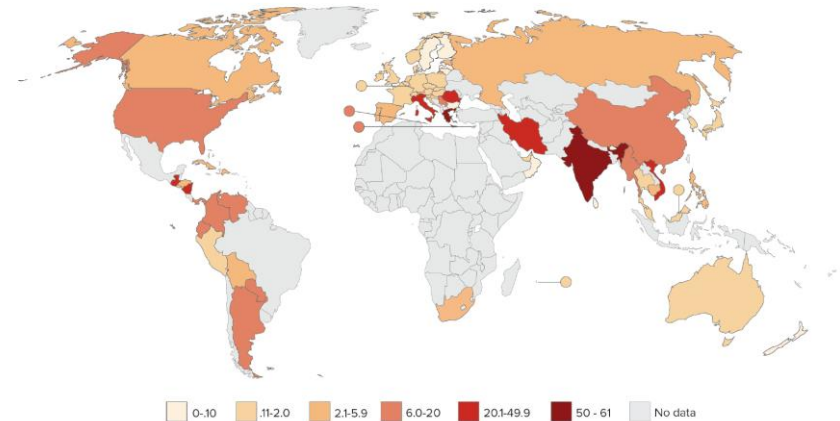
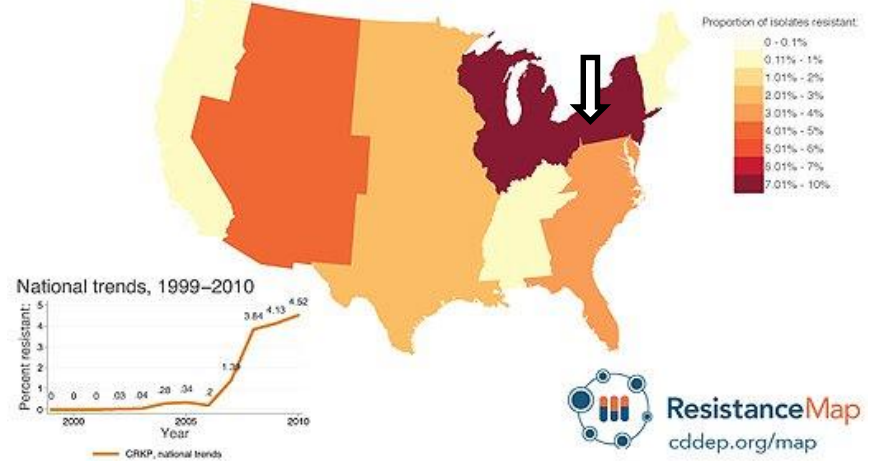


FIGURE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011-2014)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

*Carbapenem Resistant Enterobacteriaceae

The rise of CRE* superbugs



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

Hospitals Plagued by Unbeatable 'Superbugs'

'USA TODAY' FINDS THOUSANDS OF CASES IN RECENT YEARS

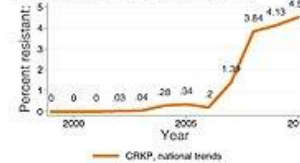
(NEWSER) - US hospitals are quietly fighting an incredibly high stakes war that they look unlikely to win against "superbugs" that resist even the most potent antibiotics available, a *USA Today* investigation has concluded. The paper has compiled evidence showing that hospitals across the country have seen thousands of infections from... [More »](#)

Carbapenem-resistant *Klebsiella pneumoniae*

US Regions, 2009-2010



National trends, 1999-2010



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

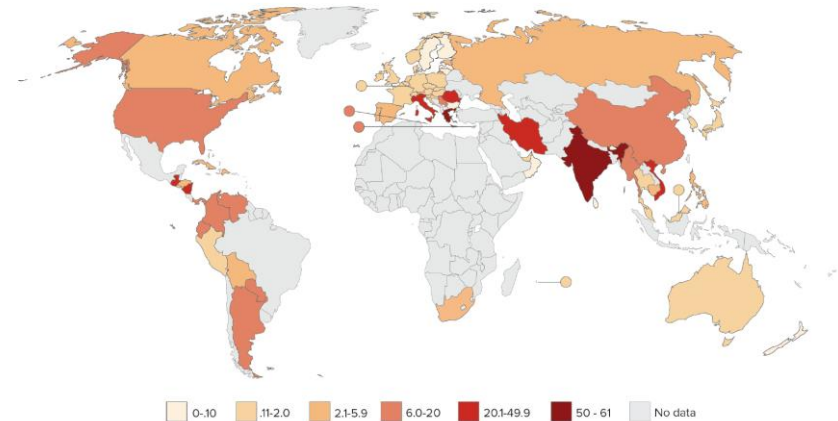


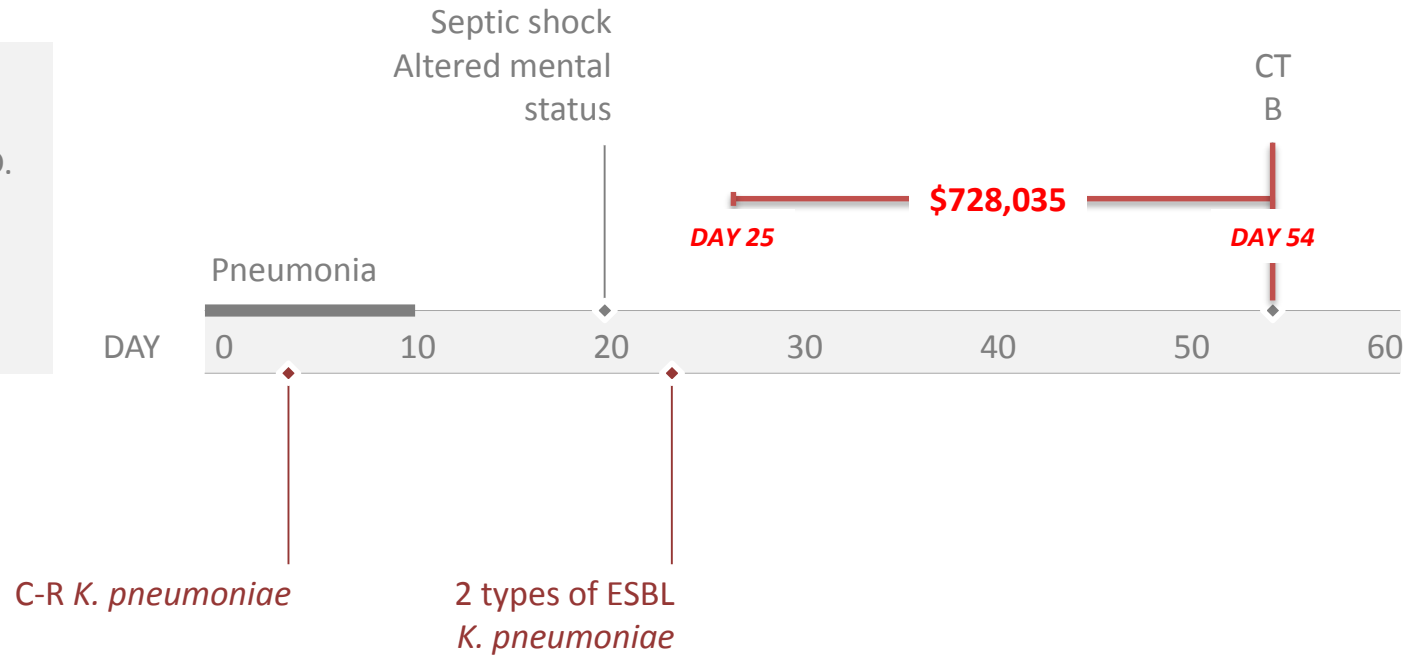
FIGURE 1-3: Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011-2014)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

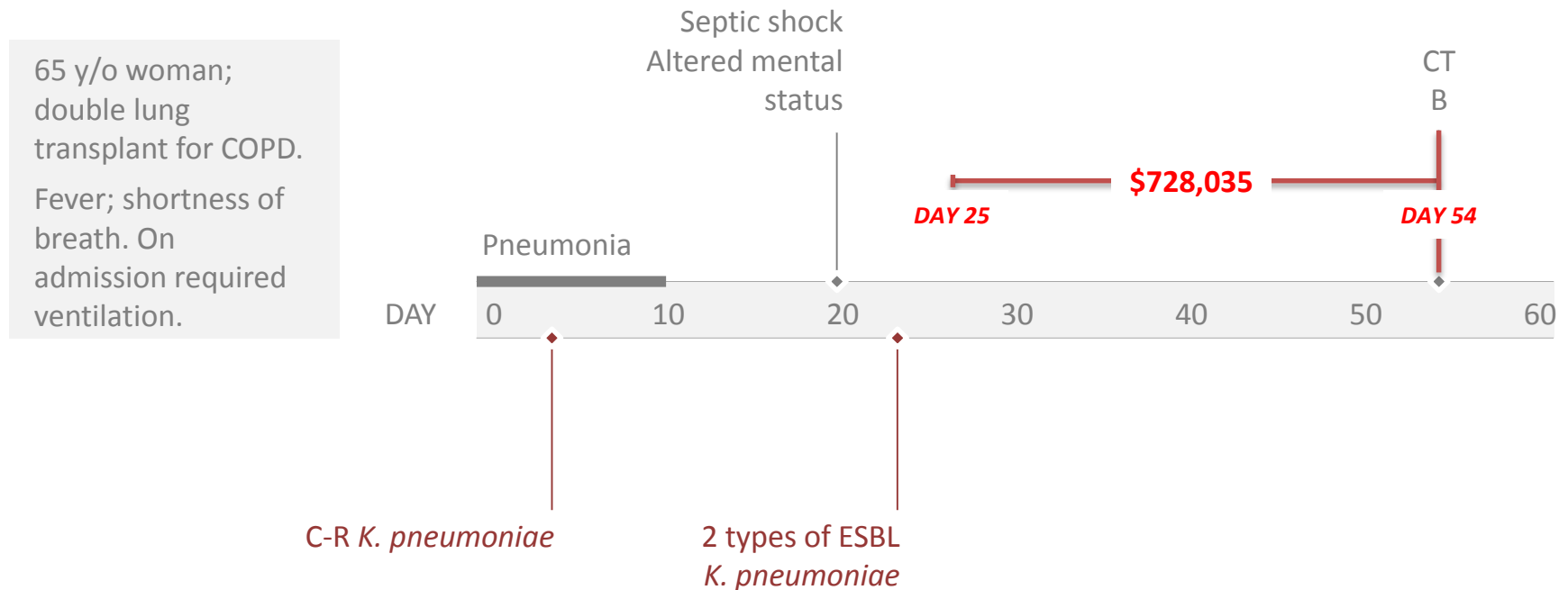
*Carbapenem Resistant Enterobacteriaceae

An illustrative case, 2019

65 y/o woman;
double lung
transplant for COPD.
Fever; shortness of
breath. On
admission required
ventilation.



An illustrative case, 2019



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

Antibiotic resistance threats



table.2

Urgent Threats

Clostridium difficile
Carbapenem-resistant Enterobacteriaceae
Neisseria gonorrhoeae

Serious Threats

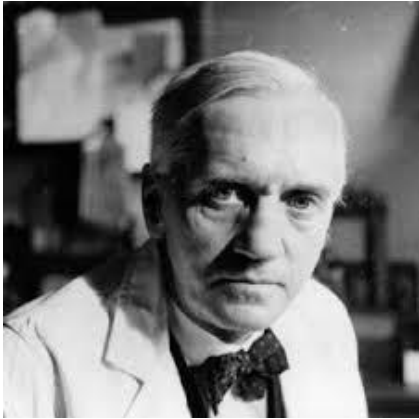
Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant *Candida*
Extended spectrum Enterobacteriaceae
Vancomycin-resistant *Enterococcus*
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant nontyphoidal *Salmonella*
Drug-resistant *Salmonella* serotype Typhi
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

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,³
Marianne Billeter,¹¹ and Thomas M. Hooton¹²**

¹Harborview Medical Center and the University of Washington, Seattle; ²Maine Medical Center, Portland; ³Emory University, Atlanta, Georgia; ⁴Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and ⁵Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; ⁶University of Utah, Salt Lake City; ⁷Mayo Clinic College of Medicine, Rochester, Minnesota; ⁸University of Pittsburgh Medical Center, Pittsburgh, and ⁹University of Pennsylvania, Philadelphia, Pennsylvania; ¹⁰William Beaumont Hospital, Royal Oak, Michigan; ¹¹Ochsner Health System, New Orleans, Louisiana; and ¹²University of Miami, Miami, Florida

Clin Infect Dis 2007; 44:159-77

“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,¹¹ Marianne Billeter,¹¹ and Thomas M. Hooton¹²

¹Harborview Medical Center and the University of Washington, Seattle; ²Maine Medical Center, Portland; ³Emory University, Atlanta, Georgia; ⁴Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and ⁵Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; ⁶University of Utah, Salt Lake City; ⁷Mayo Clinic College of Medicine, Rochester, Minnesota; ⁸University of Pittsburgh Medical Center, Pittsburgh, and ⁹University of Pennsylvania, Philadelphia, Pennsylvania; ¹⁰William Beaumont Hospital, Royal Oak, Michigan; ¹¹Ochsner Health System, New Orleans, Louisiana; and ¹²University of Miami, Miami, Florida

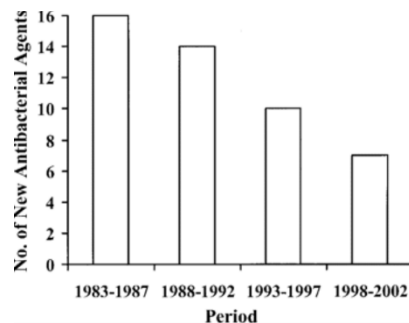
Clin Infect Dis 2007; 44:159-77

MAJOR ARTICLE

Trends in Antimicrobial Drug Development: Implications for the Future

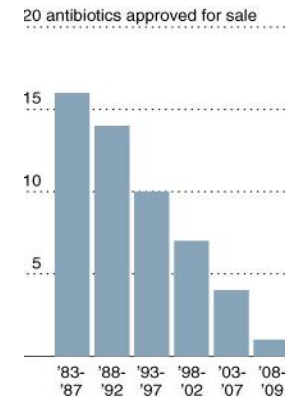
Brad Spellberg,¹ John H. Powers,² Eric P. Brass,^{1,2} Loren G. Miller,^{1,2} and John E. Edwards, Jr.^{1,2}

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



Dearth of New Drugs ...

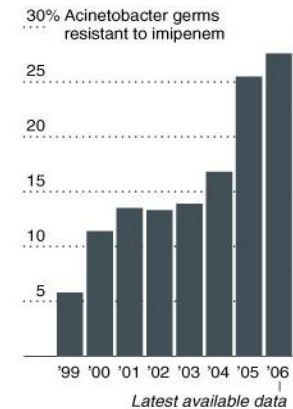
The number of new antibiotics approved for sale in the United States has dwindled.



Sources: *Infectious Diseases Society of America; Resources for the Future*

... For Hardier Germs

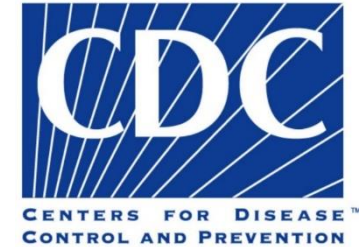
Acinetobacter germs in U.S. hospitals that are resistant to a powerful antibiotic often used as a last line of treatment.



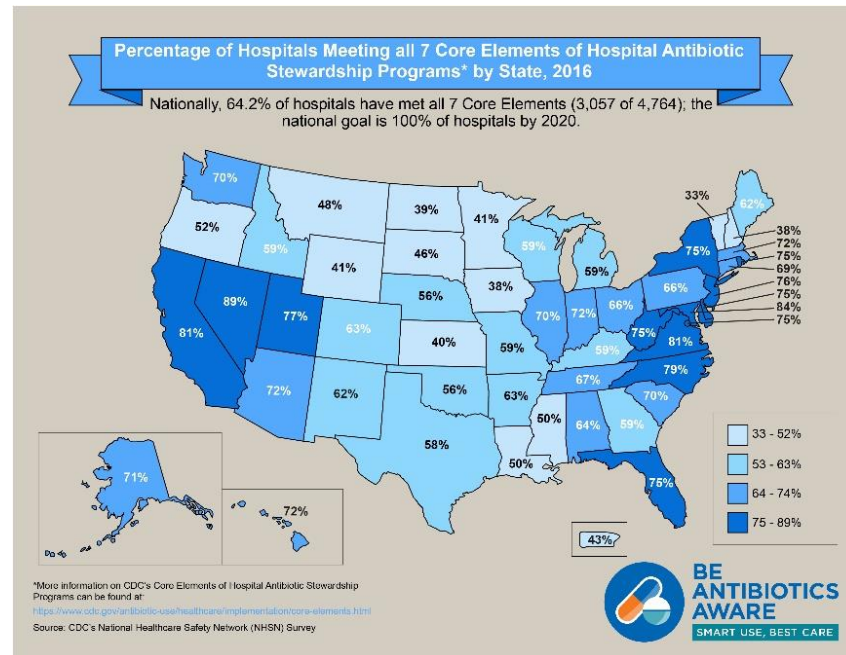
Latest available data

THE NEW YORK TIMES

Mandates for Antimicrobial Stewardship (AMS)



CDC Core Elements of AMS
Hospitals
Nursing homes
Outpatient

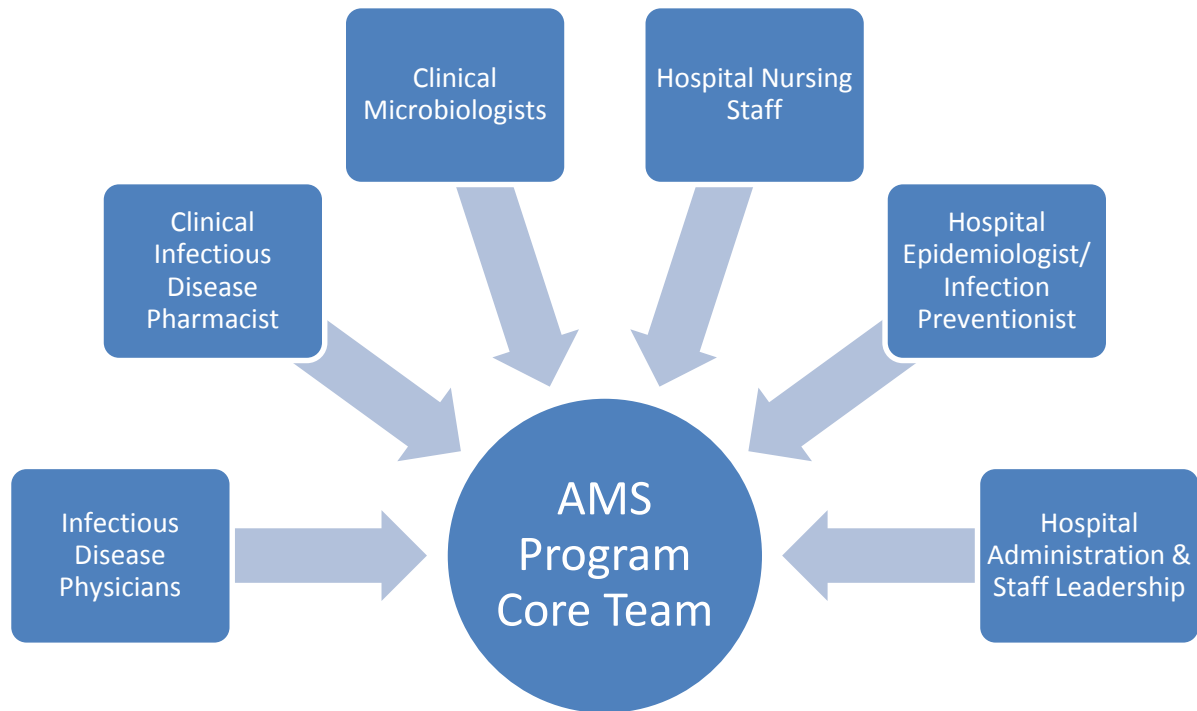


Core elements of AMS programs

- 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

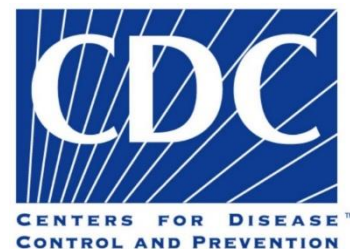


Core AMS team



E. Friestrom, E. McCreary

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



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**

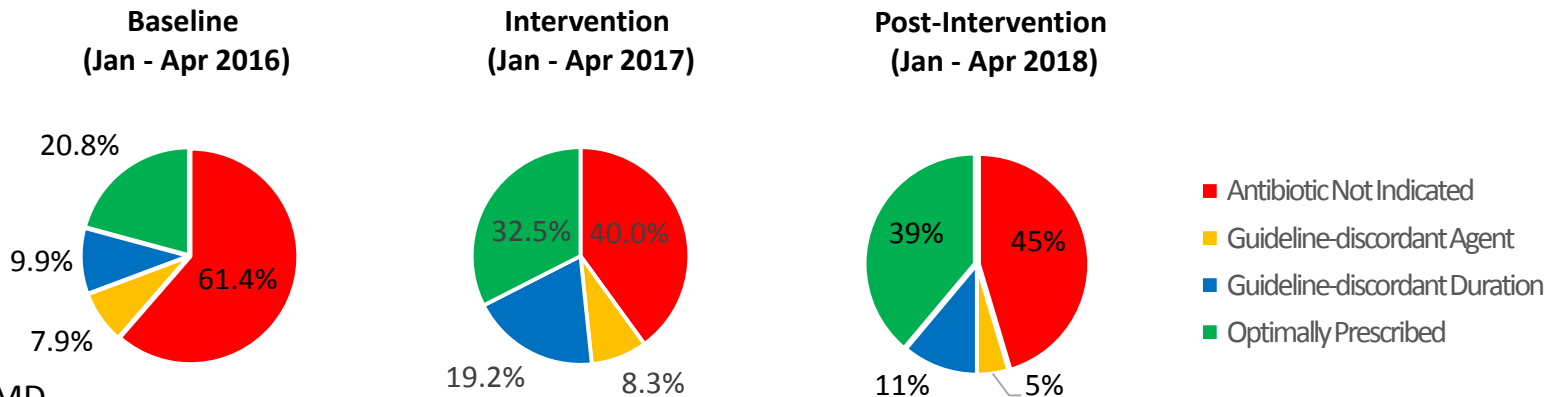
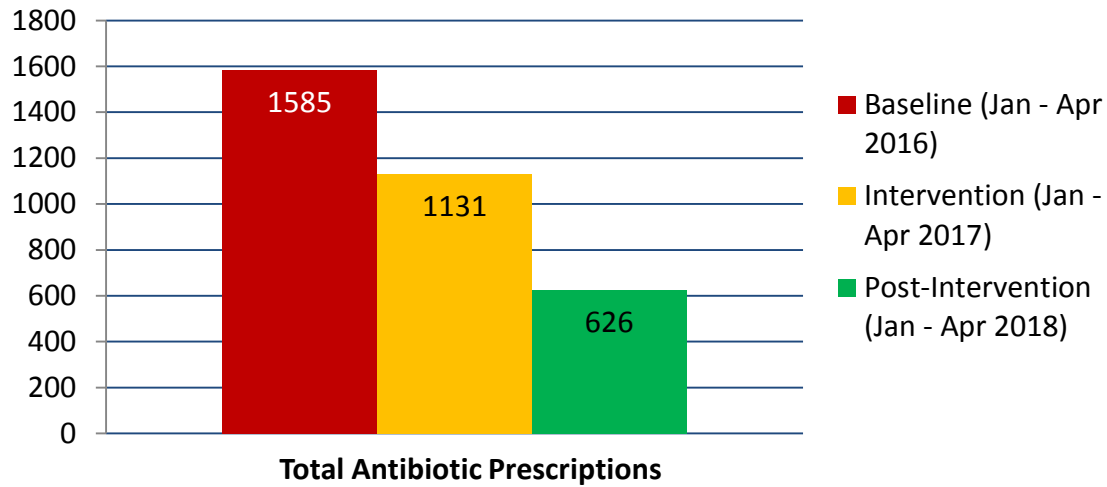
Impact of antimicrobial stewardship in critical care: a systematic review

Reham Kaki¹, Marion Elligsen², Sandra Walker²⁻⁴, Andrew Simor^{1,4}, Lesley Palmay² and Nick Daneman^{1,4*}

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

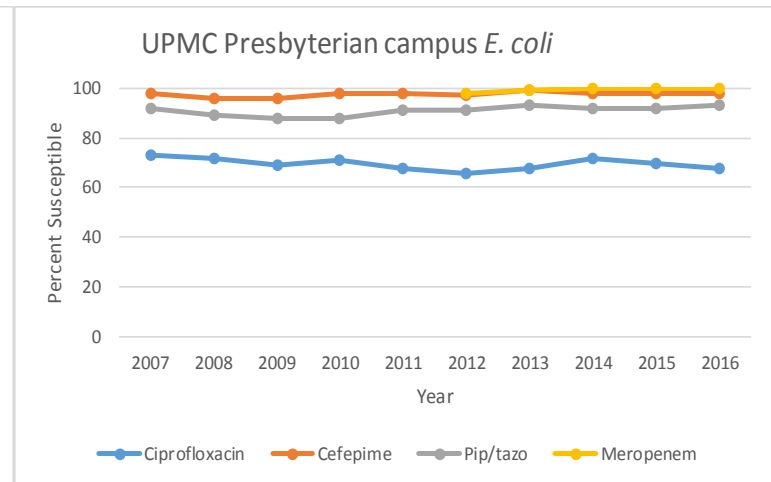
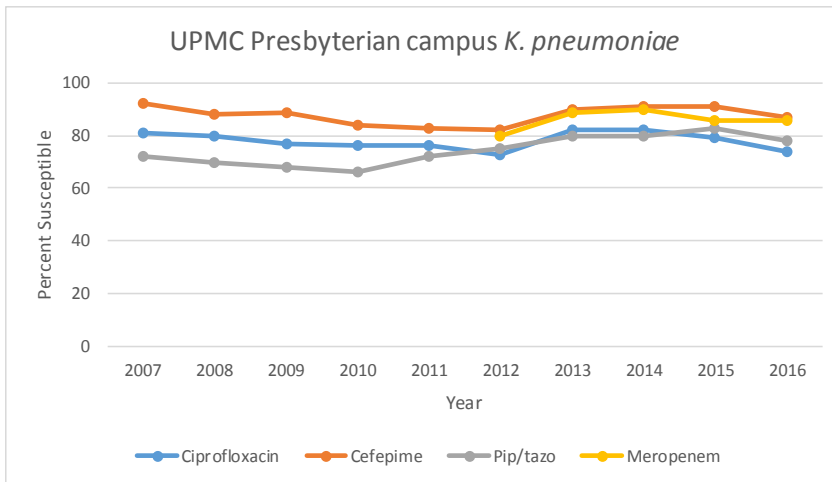
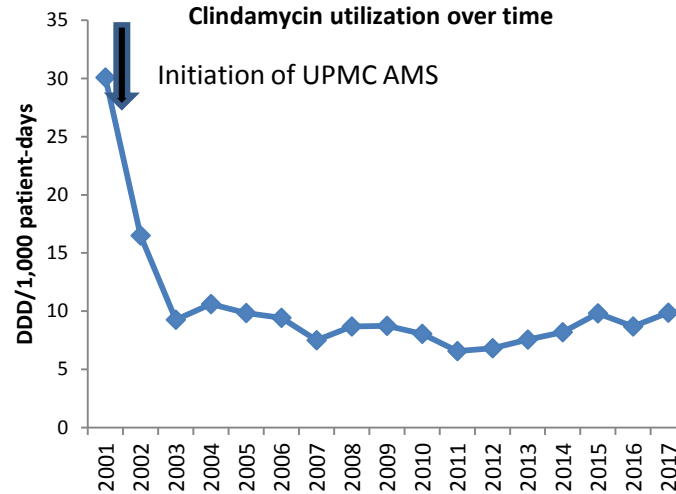
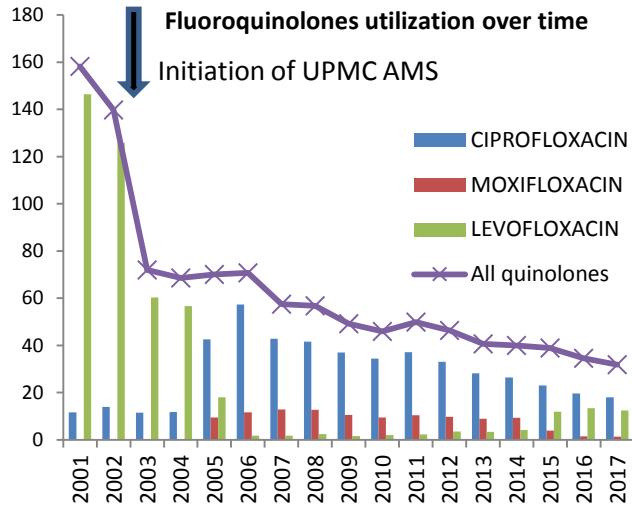
- 38 studies, 6 AMS intervention types
- Reduced utilization (11%-38%), lowered costs (US\$5-10/patient-day), shortened duration of treatment, reduced inappropriate use and adverse events/toxicity
- Not associated with increased nosocomial infection rates, lengths of stay, or mortality
- Interventions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

AMS: Still a lot of work to do



Brooke Decker, MD

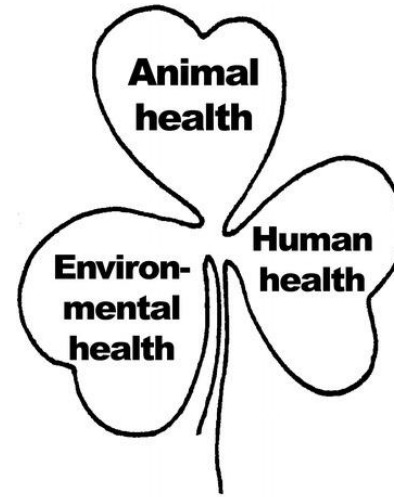
AMS: Still a lot of work to do



M. Hong Nguyen, MD



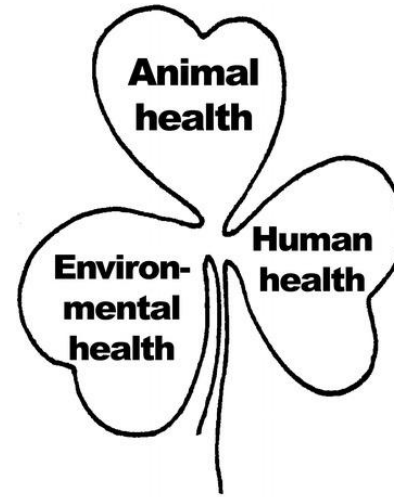
One Health



One health

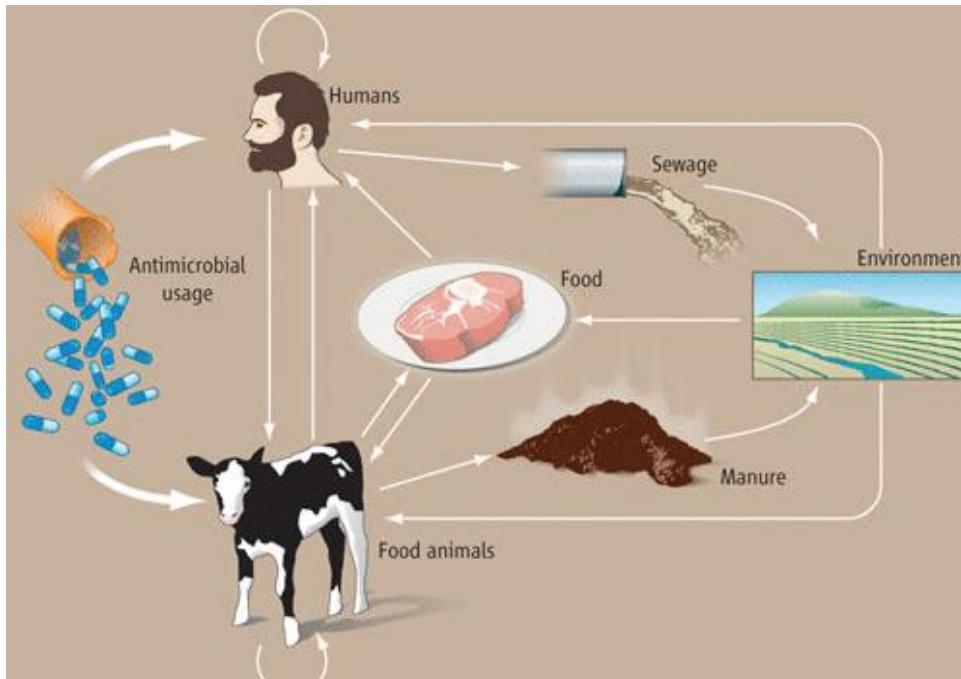
Boqvist, Acta Vet Scand 2018

One Health



One health

Boqvist, Acta Vet Scand 2018



McEwen, Microbiol Spectrum 2018

Antibiotic Resistance in Humans and Animals

A National Academy of Medicine Perspective

Antibiotics purchased for livestock in the U.S. in 2014



15.4
million
kilograms

Antibiotics purchased for humans in the U.S. in 2014



3.5
million
kilograms

"Antimicrobials for livestock account for 80% of the antimicrobials purchased in the United States. To pretend that we can address antibiotic resistance that results from antimicrobial use by focusing on the 20% that occurs in humans and ignoring the 80% that occurs in animals is to fail as a society.

We have a crisis of antibiotic resistance."

@theNAMedicine

www.nam.edu/Perspectives

Source: FDA, 2015

One Health AMR Case Study 1: Colistin



[Health](#)

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

By James Gallagher Health editor, BBC News website
19 November 2015

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

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

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Lancet Infect Dis 2016;
16: 161-68

Published Online

November 18, 2015

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

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

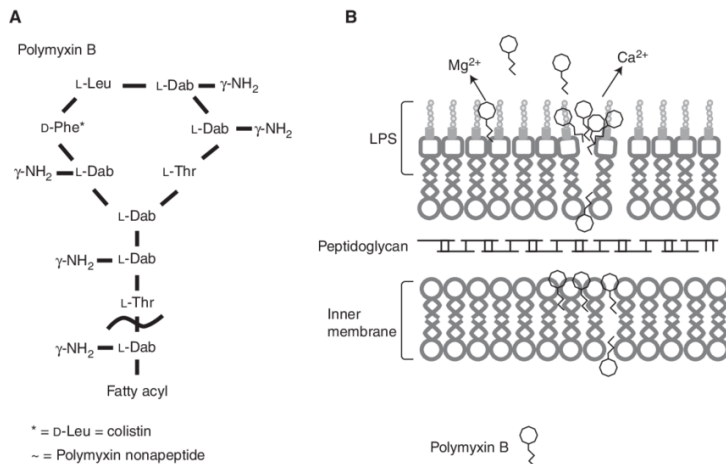
Matthew E. Falagas^{1,2,3} and Sofia K. Kasiakou¹

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

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

Matthew E. Falagas^{1,2,3} and Sofia K. Kasiakou¹

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



- 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

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

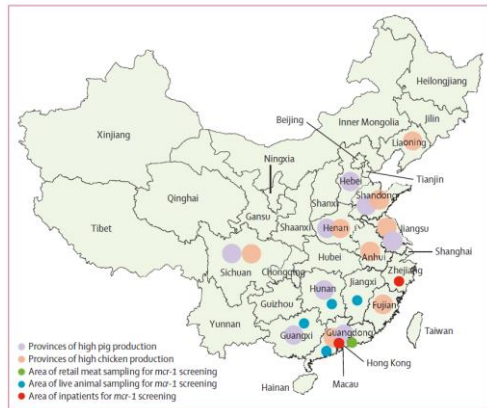


Figure 1: Map of China

	Year	Positive isolates (%)/number of isolates
<i>Escherichia coli</i>		
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
<i>Klebsiella pneumoniae</i>		
Inpatient	2014	3 (0.7%)/420

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

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

Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

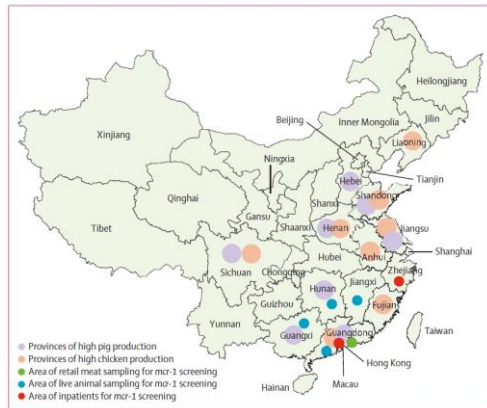


Figure 1: Map of China

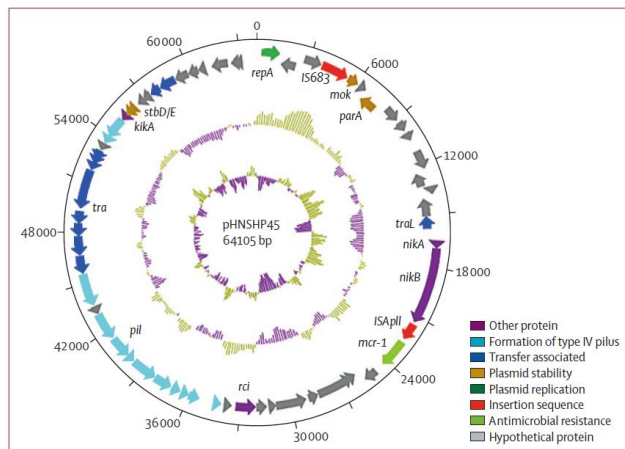
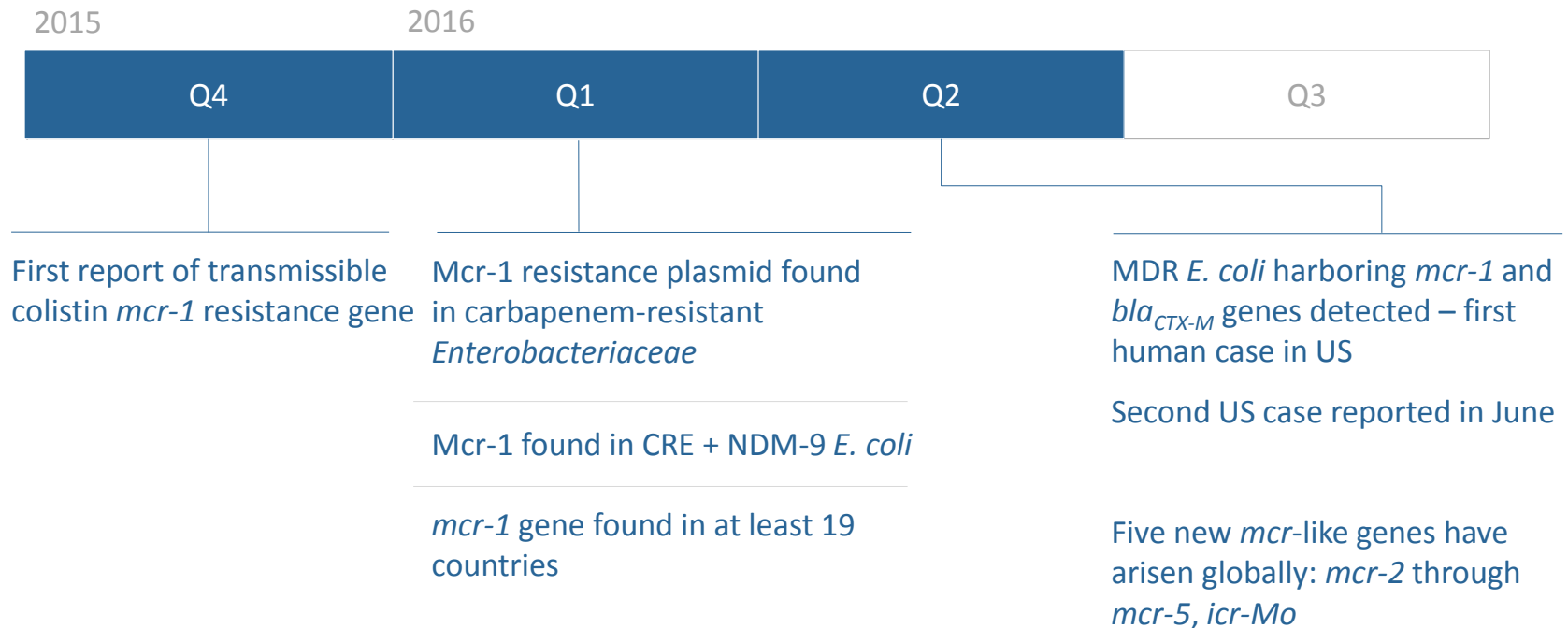


Figure 2: Structure of plasmid pHNSHP45 carrying mcr-1 from *Escherichia coli* strain SHP45

	Year	Positive isolates (%) / number of isolates
<i>Escherichia coli</i>		
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
<i>Klebsiella pneumoniae</i>		
Inpatient	2014	3 (0.7%) / 420

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

CRE: Our last line of defense is breached



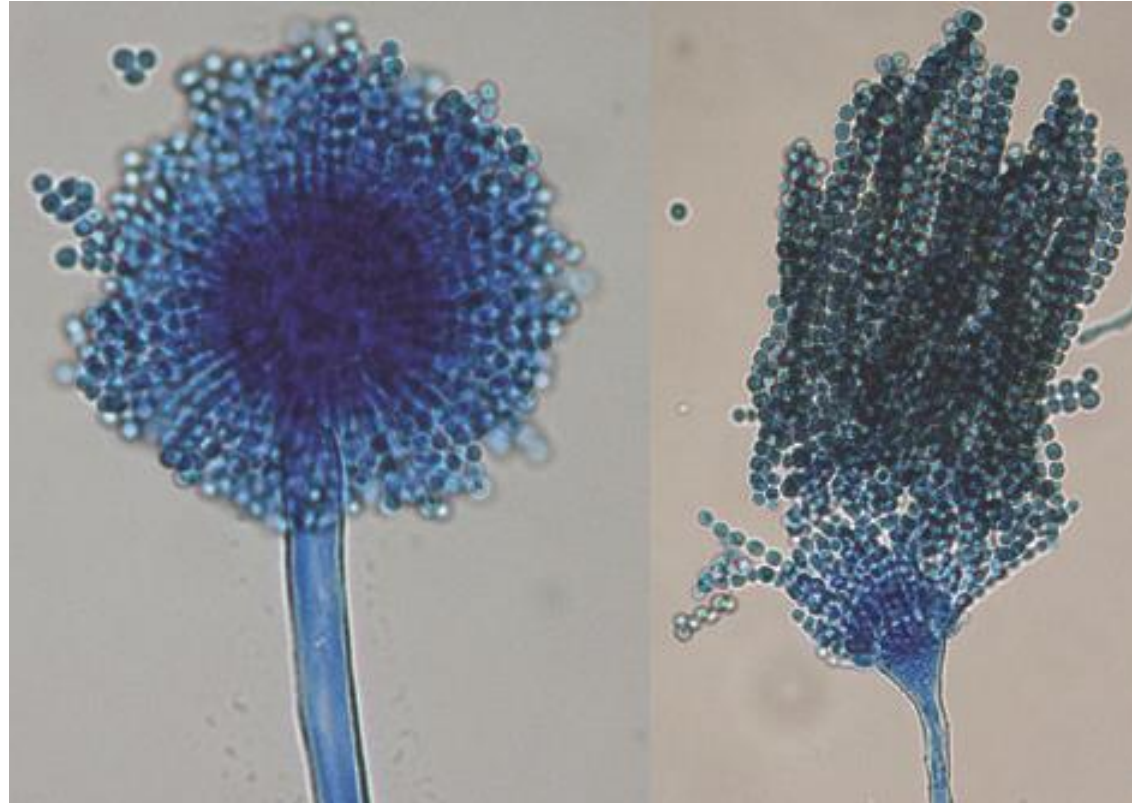
Liu YY et al. Lancet Infect Dis. 2016 Feb;16(2):161-8.

Du H Lancet Infect Dis. 2016 Jan 29. Yao X et al. Lancet Infect Dis.

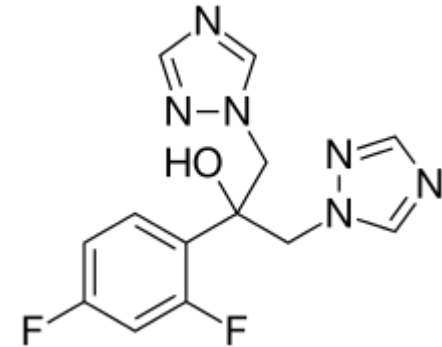
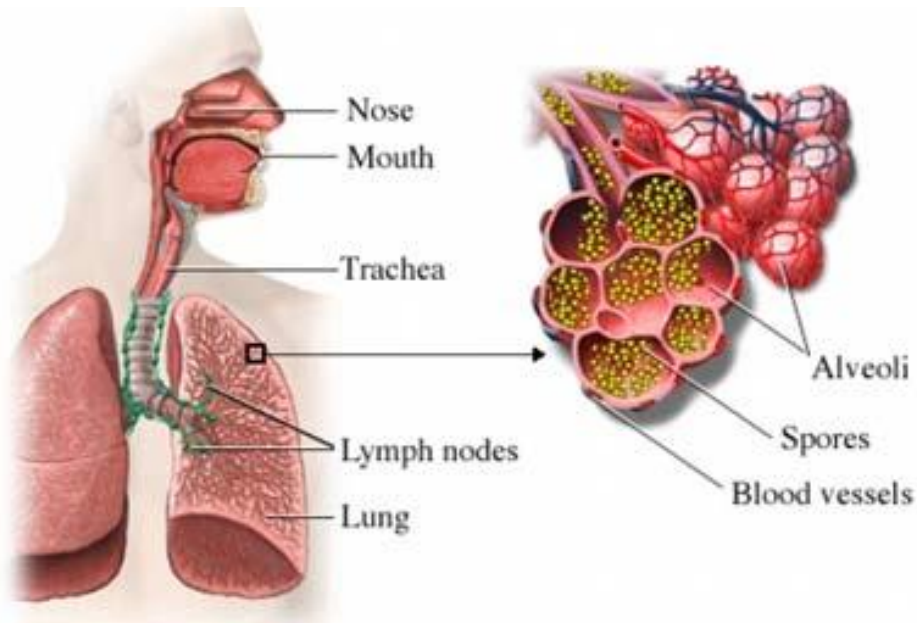
2016 Jan 29, [Bloomberg](#).

AAC 2016 May 26 online; doi:10.1128/AAC.01103-16

Case Study 2: Azole-R *Aspergillus*

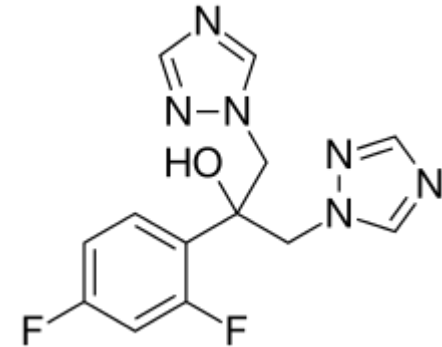
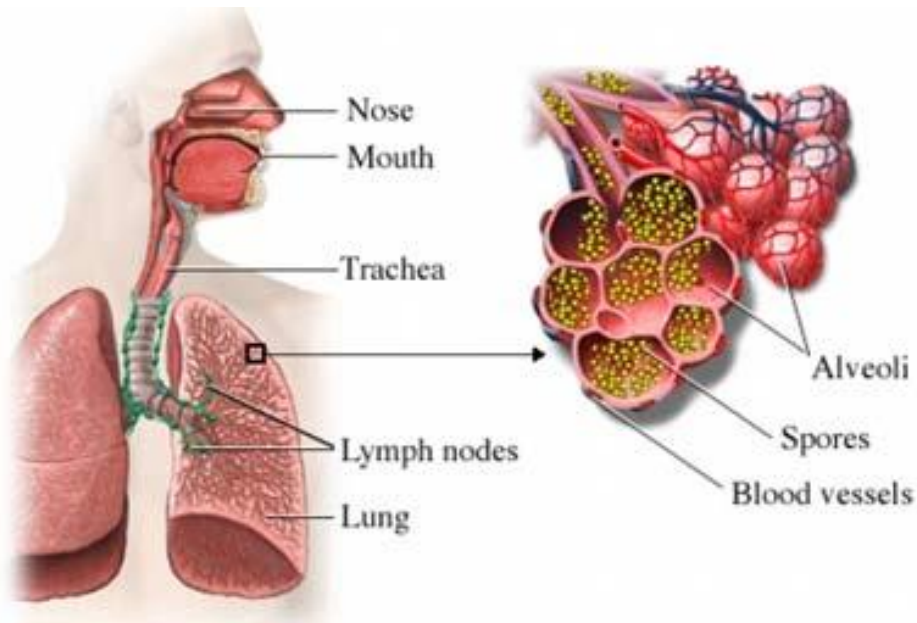


Case Study 2: Azole-R *Aspergillus*



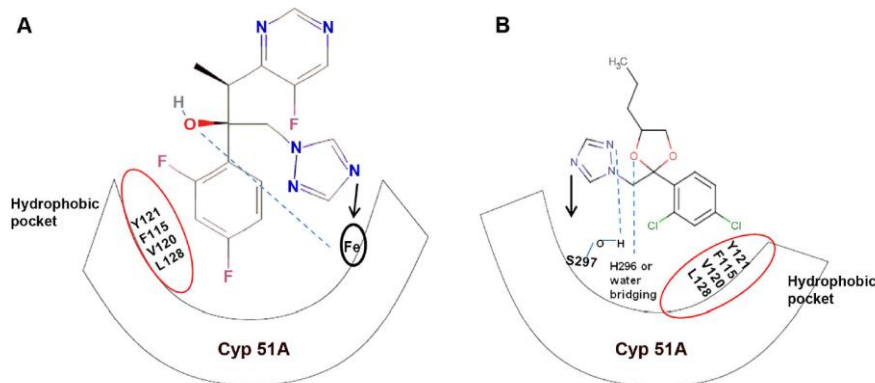
Azole antifungals

Case Study 2: Azole-R *Aspergillus*

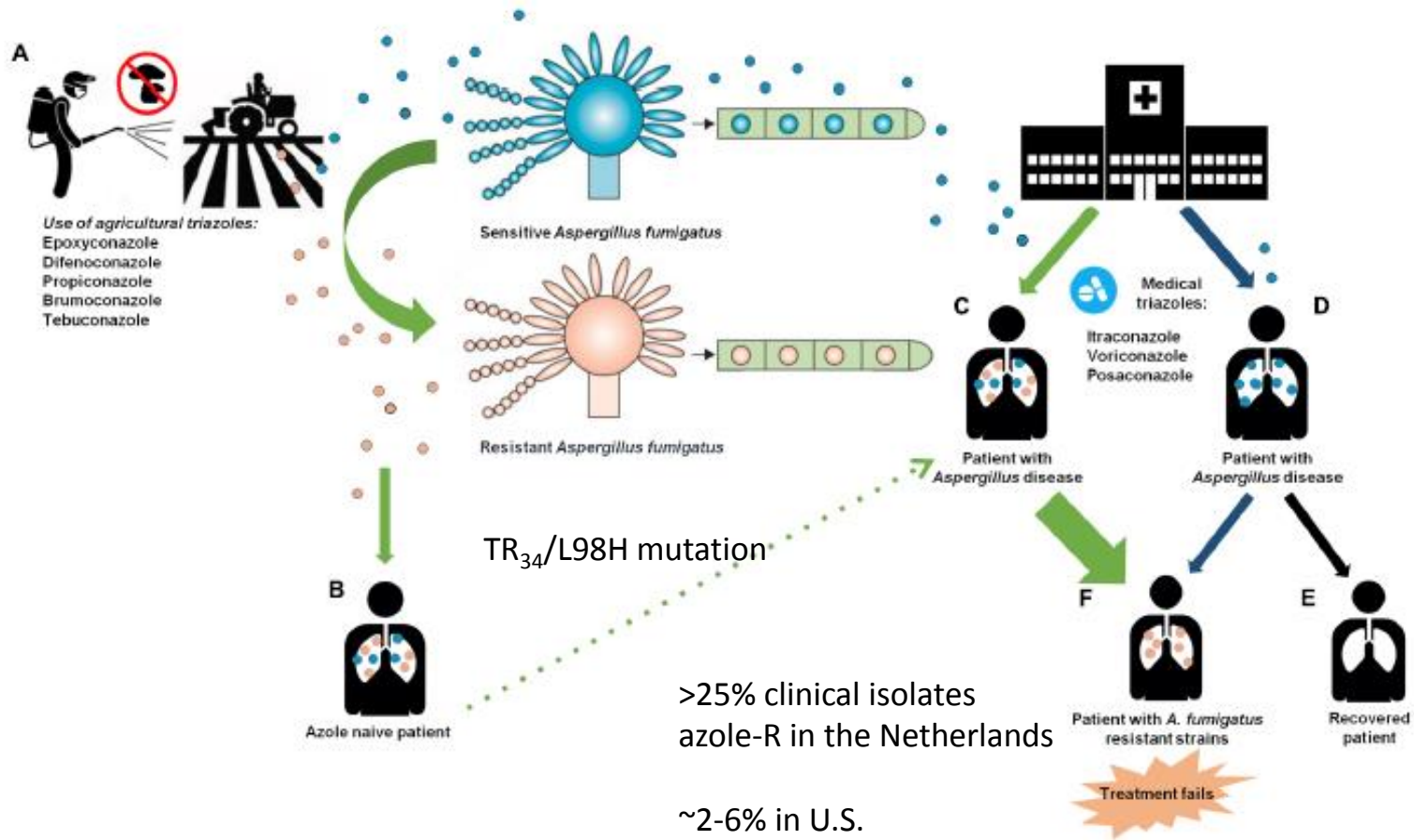


Azole antifungals

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



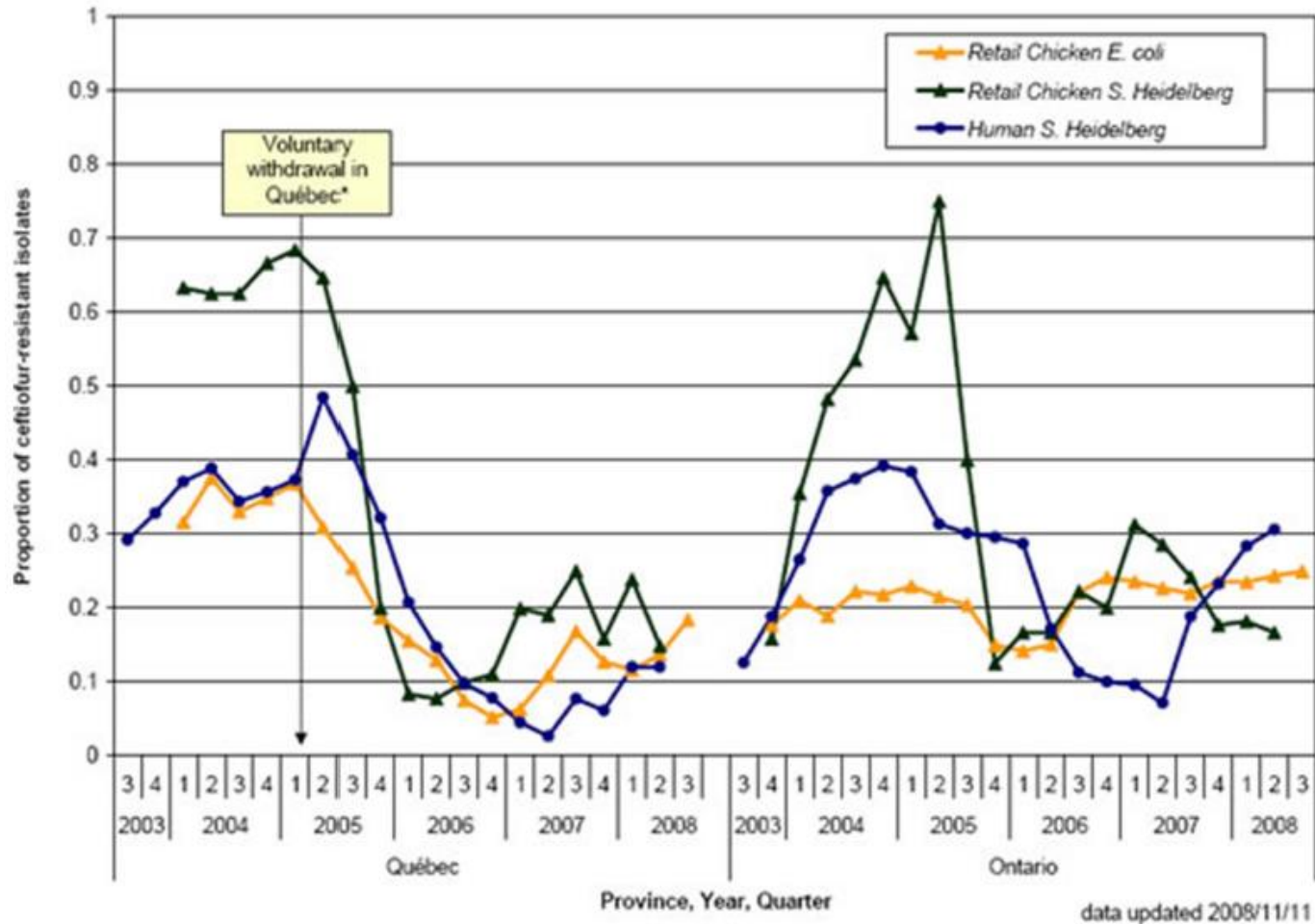
Case Study 2: Azole-R *Aspergillus*



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 *Salmonella*
 - Ceftriaxone cross-resistance

Case Study 3: AMS in the poultry industry



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

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 Riminoenzines 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 Nitrofurantoin 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
 - 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
- Human medicine needs to get its own house in order

Acknowledgments

UPMC AMS and XDR Pathogen Lab VAPHS AMS

UPMC AMS

- **M. Hong Nguyen MD (Director)**
- Ryan Bariola MD (System AMS)
- Brian Potoski PharmD,
- Ryan Shields PharmD
- Erin McCreary PharmD, Rachel Marini PharmD, Tina Khadem PharmD, Greg Eschenauer PharmD, Bonnie Falcione PharmD, Ryan Rivosecchi Pharm D
- Ghady Haidar MD, EJ Kwak MD, Alex Viehman MD
- Lloyd Clarke, Diana Pakstis, Ellen Press

UPMC XDR Pathogen Lab

- Binghua Hao PhD, Shaoji Cheng PhD

VAPHS AMS

- **Brooke Decker MD (Director)**
- Deanna Buehrle PharmD
- Jae Hong, MD



Worldwide emergence of fungal disease and antifungal-R

