



Infectious Diseases Update 2015

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Primary Care Update, October 24, 2015

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Learning Objectives

- Brief highlight of major events in infectious diseases in past year
- Discuss an emerging infectious threat important to your daily practice
- Discuss 2 infection prevention strategies to reduce surgical infections
- Discuss 3 important advances in antimicrobial management

Disclosures

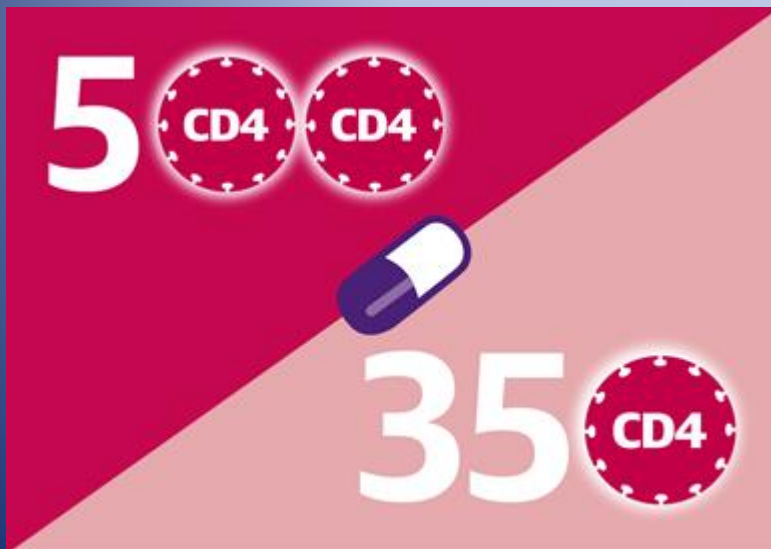
- Research funding from Rebiotix Inc
- Editor in Chief, AOA
- Employee , Mayo Foundation



Epidemic Infections

- Lyme disease
- West Nile Virus
- Coccidioidomycosis
- Measles
- Pertussis
- Mumps
- Norovirus
- Ebola
- MERS
- Borrelia miyamotoi
- Hartland virus
- RMSF in AZ
- Bourbon Virus
- Chikungunya
- Legionnaires – Bronx
- SLE – Arizona
- Plague - Yellowstone

Top 3 Advances in ID 2015



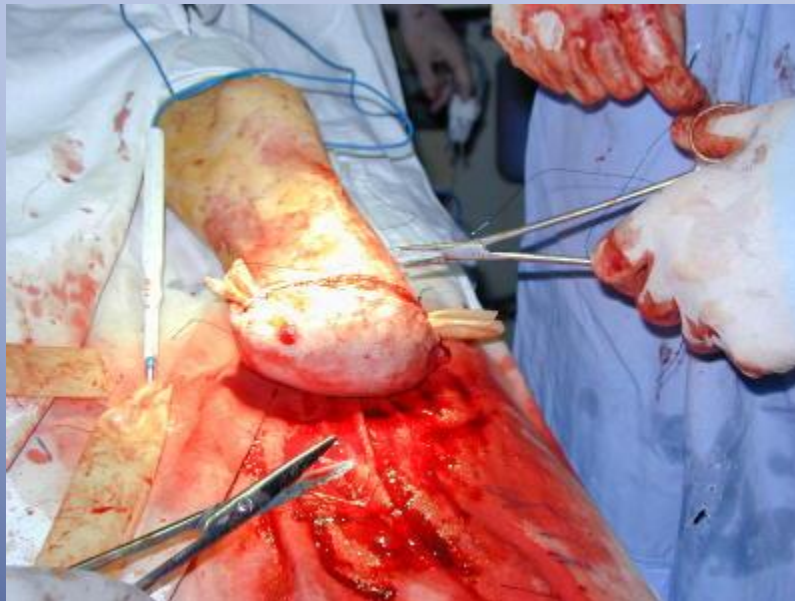
Which is the most important emerging threat to human health?

- A. Ebola-virus disease
- B. HIV infection
- C. Multiply resistant bacterial infections
- D. Middle Eastern Respiratory Syndrome Corona Virus Infection (MERS-CoV)
- E. Lyme disease

Emerging Threats

- *Multiply resistant pathogens*
- Healthcare associated infections

1 in 25 inpatients



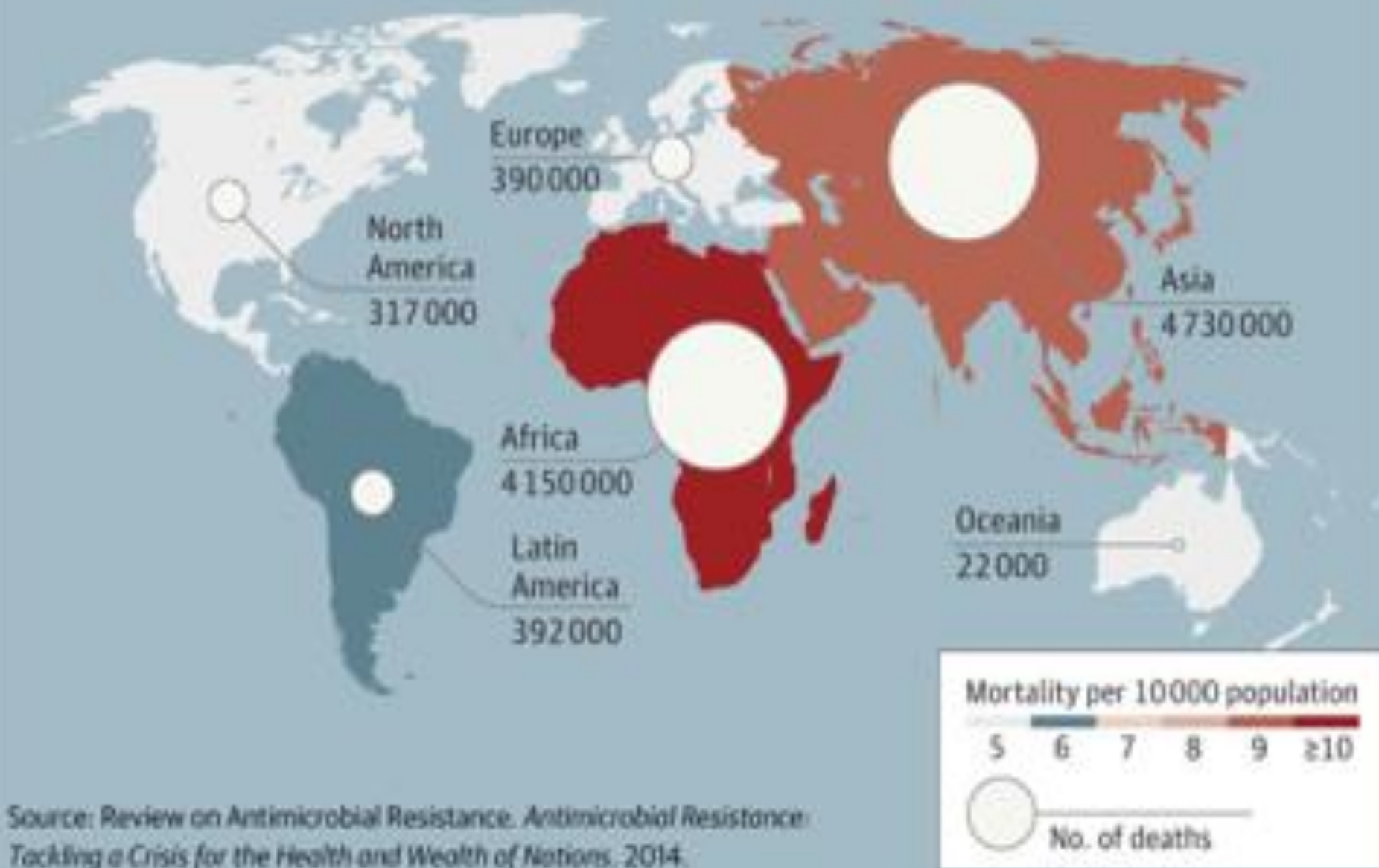


“It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body...there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.”

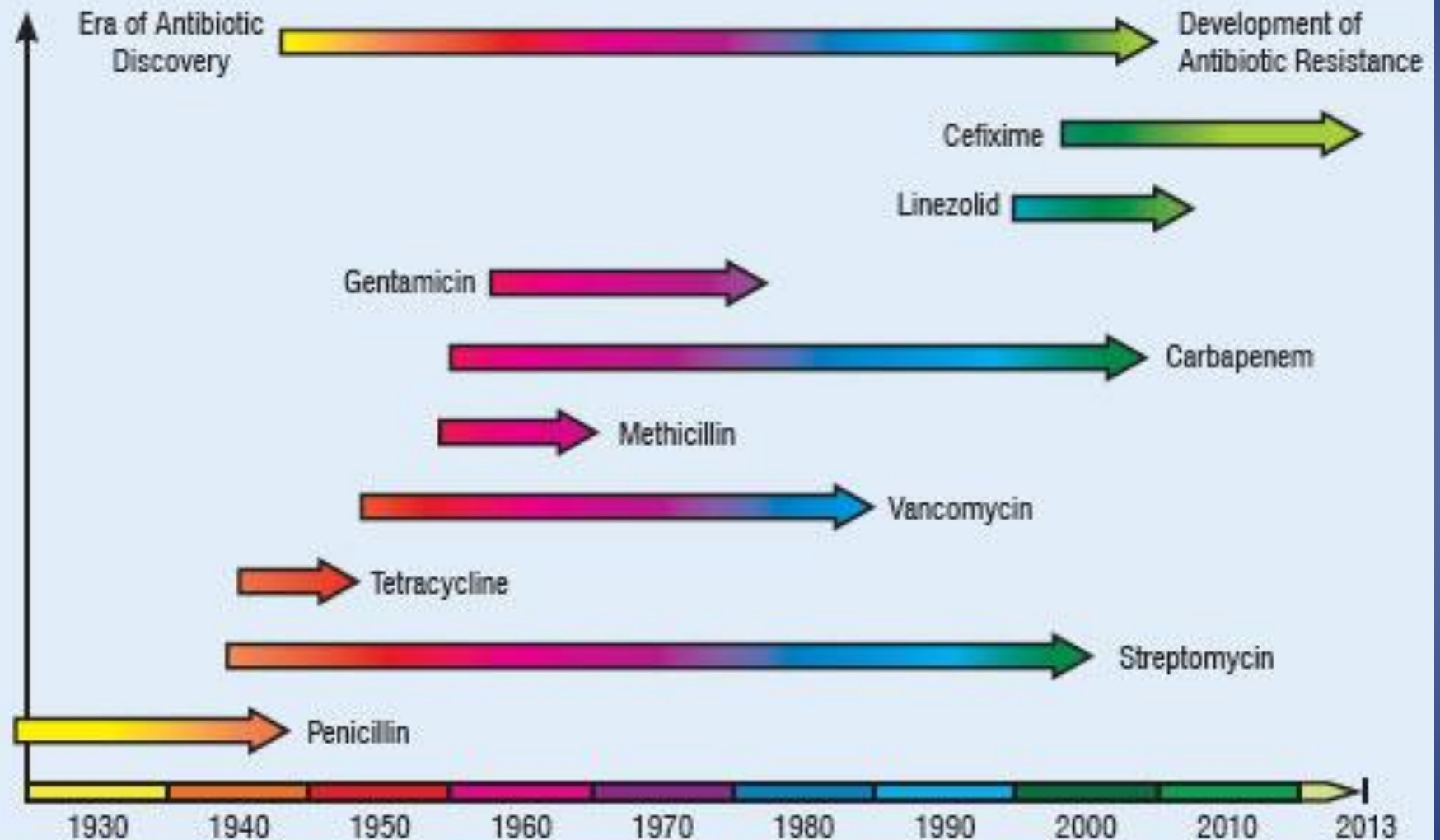
-Alexander Fleming, Nobel prize lecture, 1945



Deaths Attributable to Antimicrobial Resistance Every Year by 2050



The Discovery and Consequent Development of Antibiotic Resistance



Current Top 5 Healthcare Associated Infections

- Pneumonia = #1 22% of all HAI
- Surgical Site = #1 22%
- Gastrointestinal = #3 17%
- UTI (esp CAUTI) = #4 13%
- Primary BSI = #5 10%

***Clostridium difficile* = #1 HAI**

Magill SS et al *N Engl J Med* 2014;370:1198

Rise of the Superbugs



BBC Health

Call to punish GPs over antibiotics

BBC News website 8/15/2015

- "Soft-touch" and "hazardous" doctors should be disciplined for prescribing too many antibiotics, a leading NHS figure says.
- Prime Minister David Cameron has warned: "We are looking at an almost unthinkable scenario where antibiotics no longer work and we are cast back into the dark ages of medicine where treatable infections and injuries will kill once again."

Causative Pathogens

<u>Pathogens</u>	<u>Percent</u>
• <i>Clostridium difficile</i>	12%
• <i>Staph aureus</i>	11%
• <i>Klebsiella pneumonia</i>	10%
• <i>E. coli</i>	9%
• Enterococcus	9%

"The last decade has seen the inexorable proliferation of a host of antibiotic resistant bacteria, or bad bugs, not just MRSA, but other insidious players as well.

...For these bacteria, the pipeline of new antibiotics is verging on empty. 'What do you do when you're faced with an infection, with a very sick patient, and you get a lab report back and every single drug is listed as resistant?' asked Dr. Fred Tenover of the Centers for Disease Control and Prevention (CDC). 'This is a major blooming public health crisis.'"

—Science magazine; July 18, 2008

Who Cares?



Opportunities

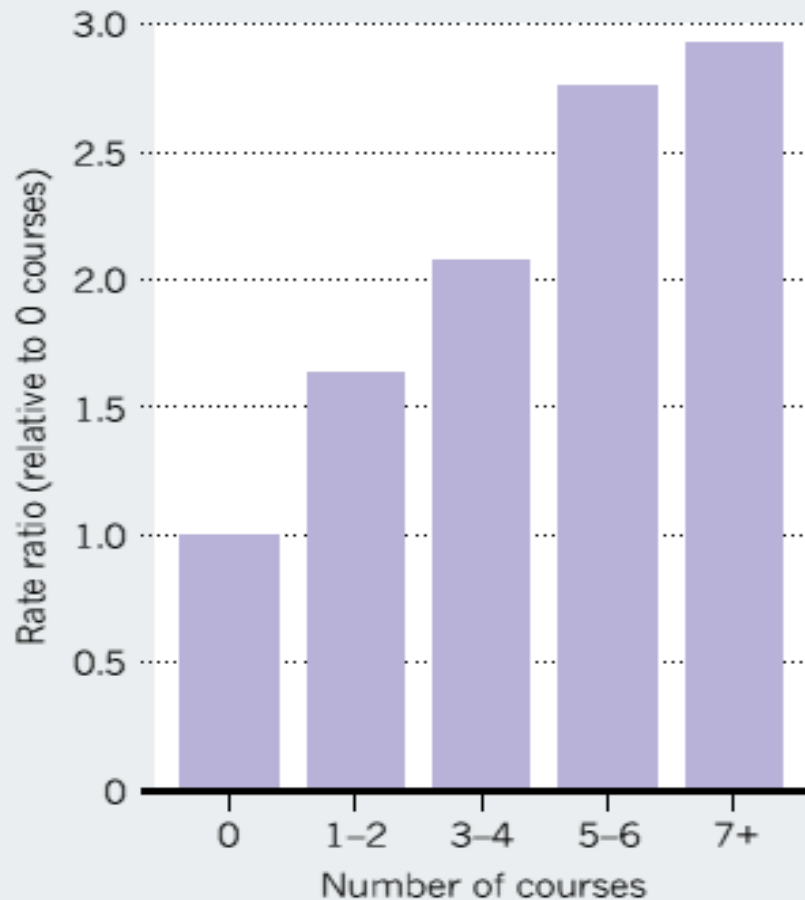
- Has anyone in this room prescribed Azithromycin for a URI?
- Has anyone given ciprofloxacin for asymptomatic bacteriuria?
- Has anyone prescribed Amoxicillin or Clindamycin to prevent Prosthetic hip infections before dental work?



Stop killing beneficial bacteria

TROUBLING CORRELATION

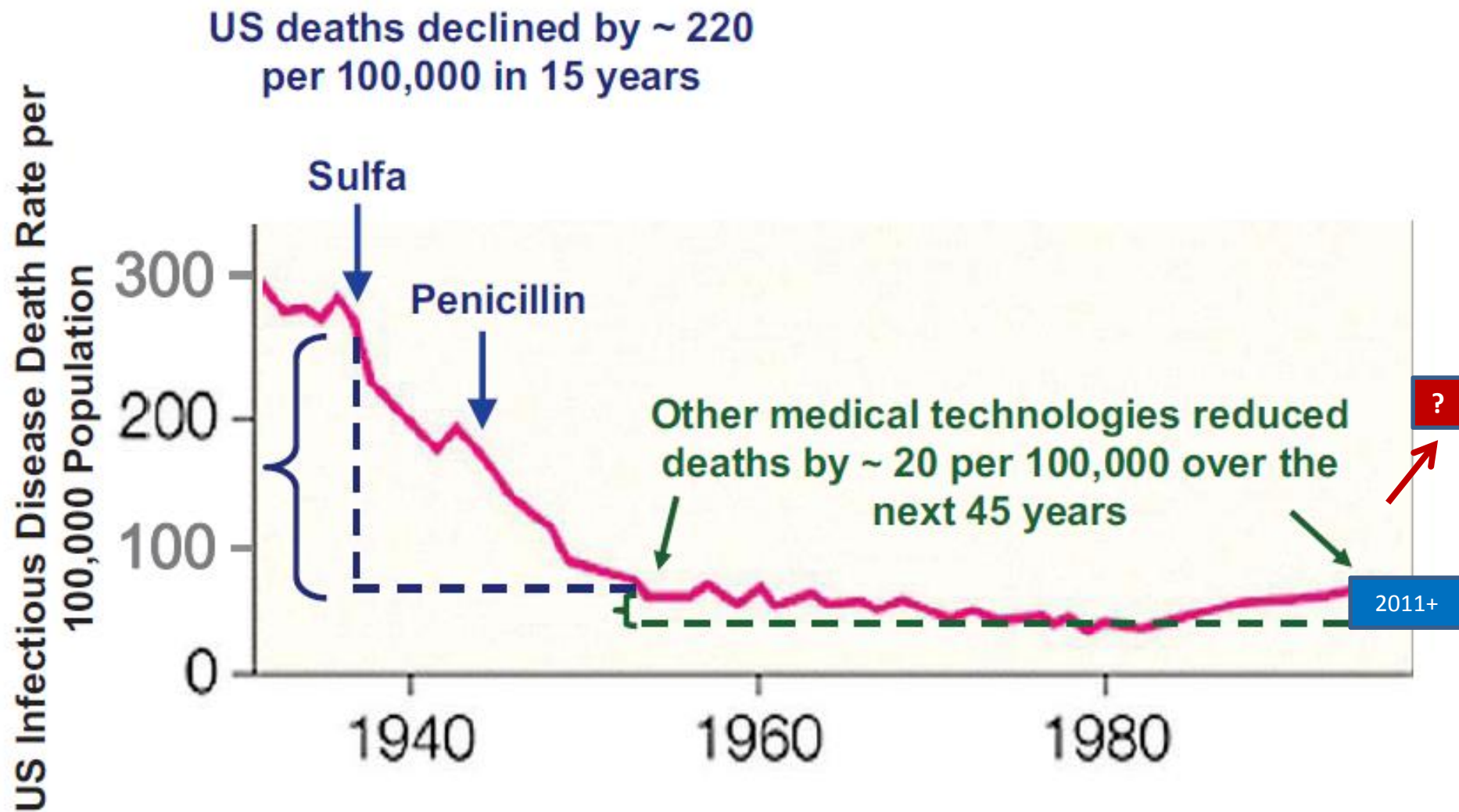
The risk of inflammatory bowel diseases in children rises with the number of courses of antibiotics taken.



Collateral Damage

- Average child receives 10-20 courses of antibiotics before age 18
- Antibiotics affect our resident microbiota and may not fully recover after a course of antibiotics
- Overuse of antibiotics may be contributing to obesity, DM, IBD, allergies, and asthma

Infectious Disease Mortality in the United States During the 20th Century



Modified from Armstrong, G. L. et al. JAMA 1999;281:61-6.

Why We Need to Improve Antibiotic Use

- Antibiotics are misused across the continuum of care
- Use of antibiotics in animals
- Antibiotic misuse adversely impacts patients and society
- **Antibiotics are the only drug where use in one patient can impact the effectiveness in another.**
- Improving antibiotic use improves patient outcomes and saves money
- Improving antibiotic use is a public health imperative-
WHO considers AR an emerging threat to global stability

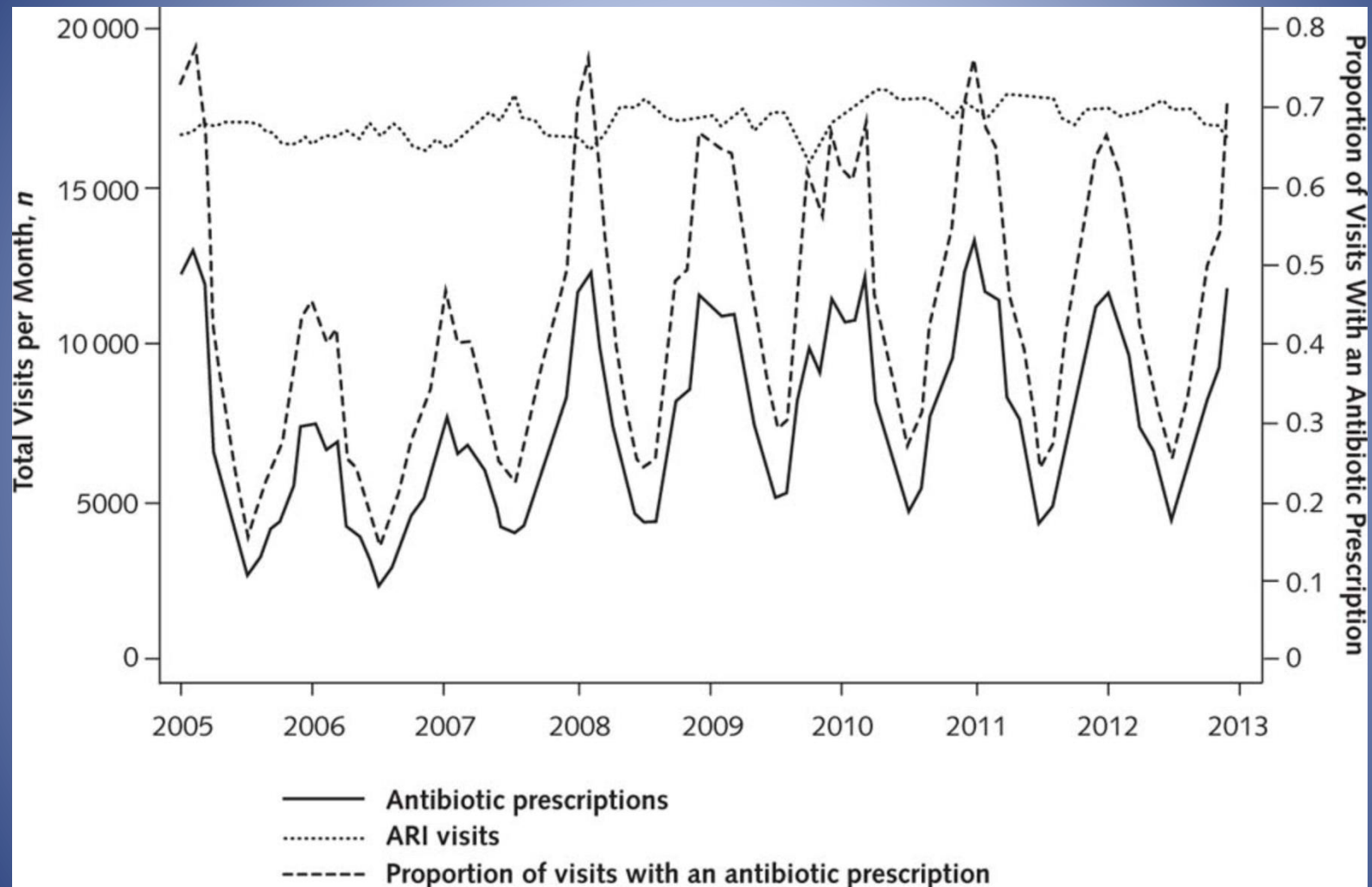
How Big is the Problem?

- Antibiotics are the second most commonly used class of drugs in the United States
- More than 8.5 billion dollars spent annually
 - 200-300 million antimicrobials prescribed annually
 - 53% for outpatient use
 - Bronchitis, pharyngitis and sinusitis account for 75% of all office-based Rx for antibiotics
- Almost half of hospitalized patients receive antibiotics
- **50%** of antibiotic use is either unnecessary or inappropriate across all type of health care settings

BMC Med 2014;12:96

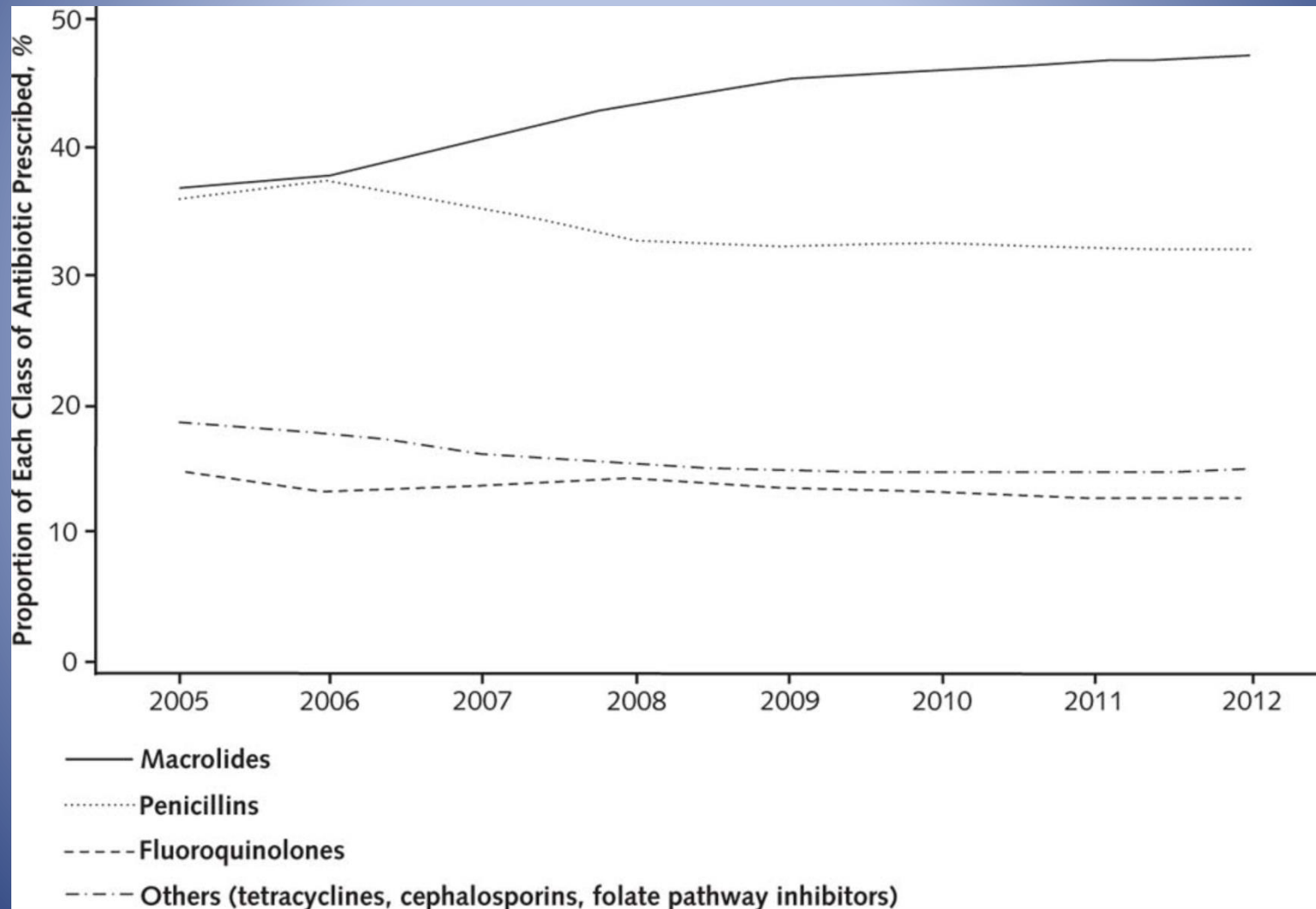
Clin Infect Dis 2007; 44:159-177

Trends in overall antibiotic prescribing.



Temporal trends in the proportion of all antibiotics prescribed for each antibiotic class.

Ann Intern Med. 2015;163(2):73-80. doi:10.7326/M14-1933



Prevention of Unnecessary Abx Use

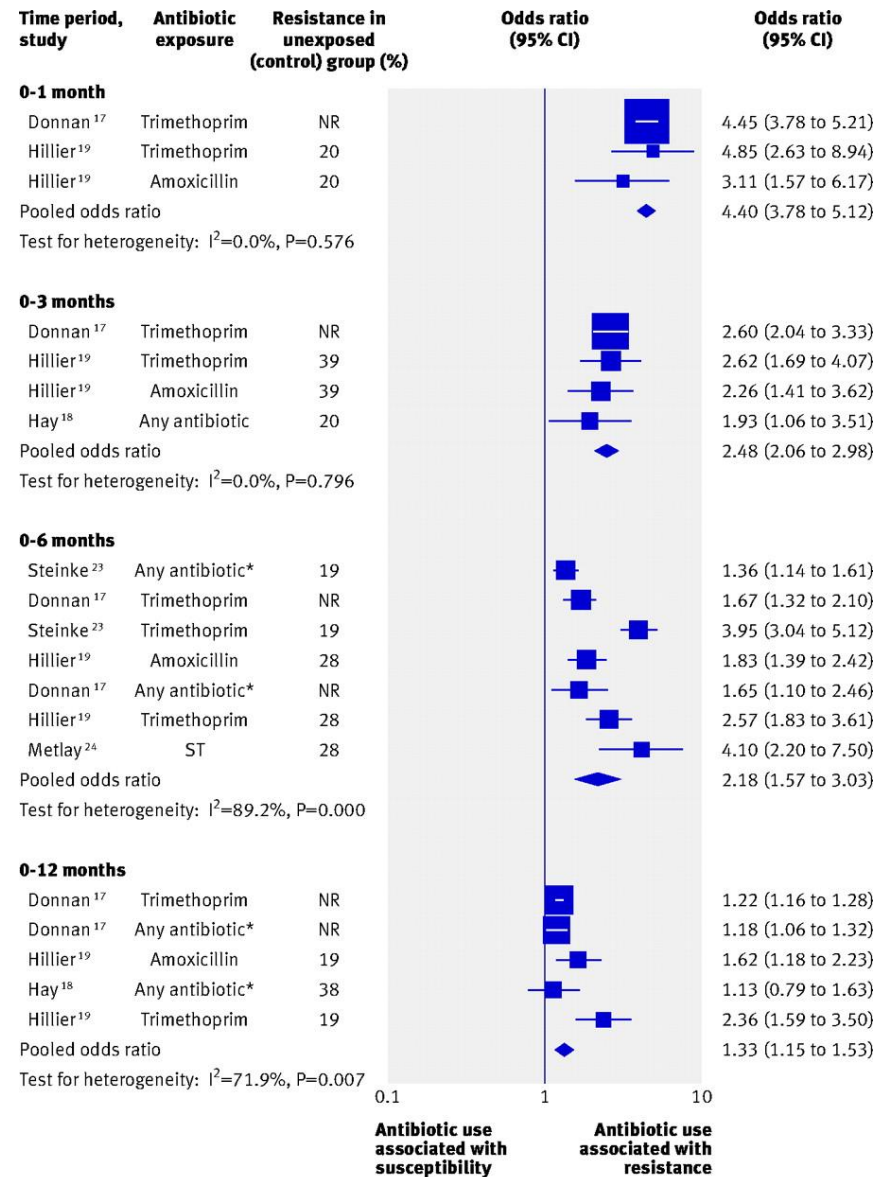
- URTIs - >50% Rxs are inappropriate
- Pharyngitis – adults – not Strep
- UTI – 30-50% are inappropriate
- Prophylaxis –not in line with guidelines

But it won't impact MY patients..

- Impact on urinary, respiratory and skin flora
- Effect is greatest in month after but may last 12 months
- Potential driver of community resistance
- Dose response for Amox and TMP-SMX

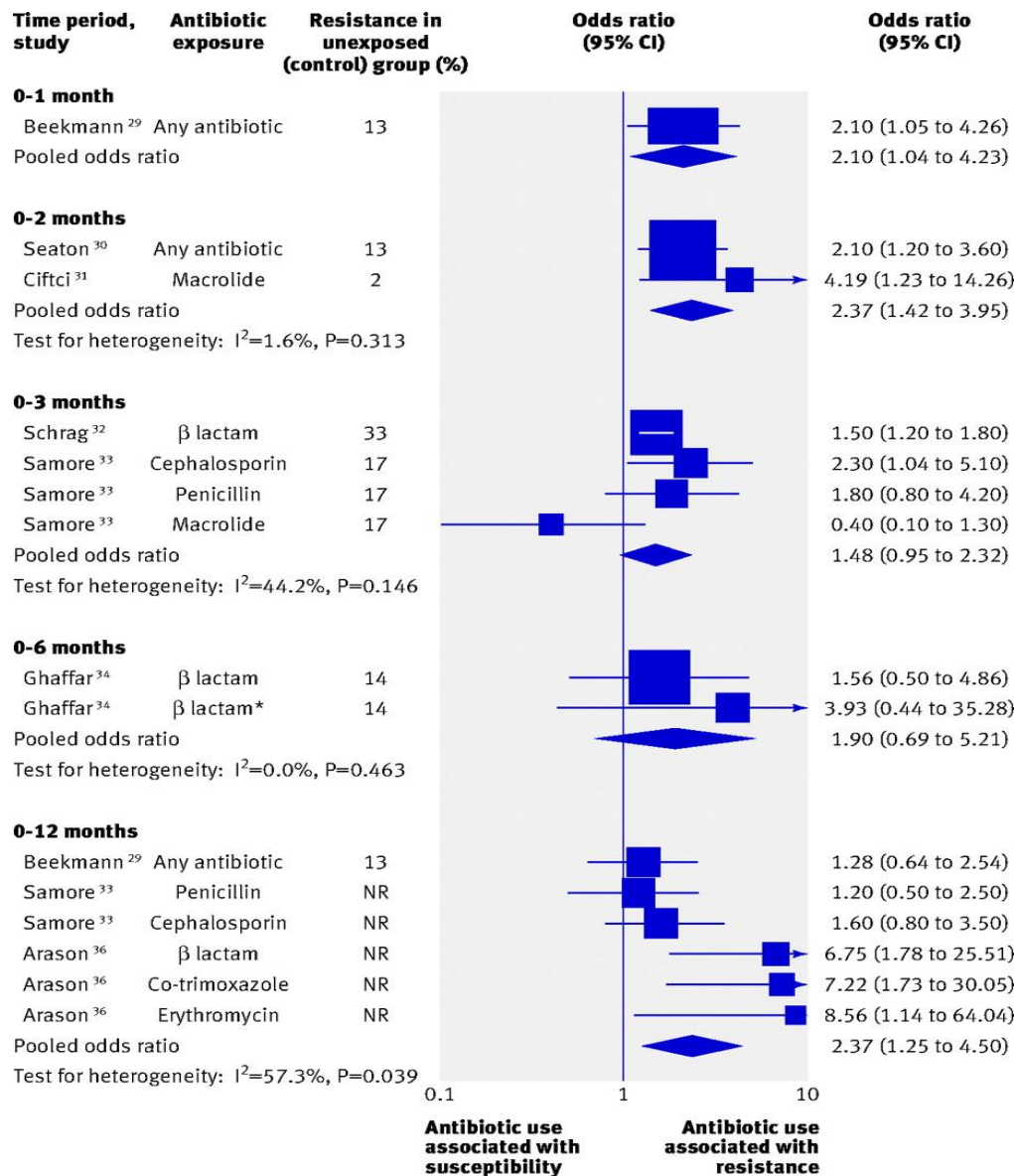
Fewest Abx for shortest duration

Forest plot showing individual study and pooled ORs (log scale) for resistance in urinary tract bacteria (E coli) and antibiotic exposure.



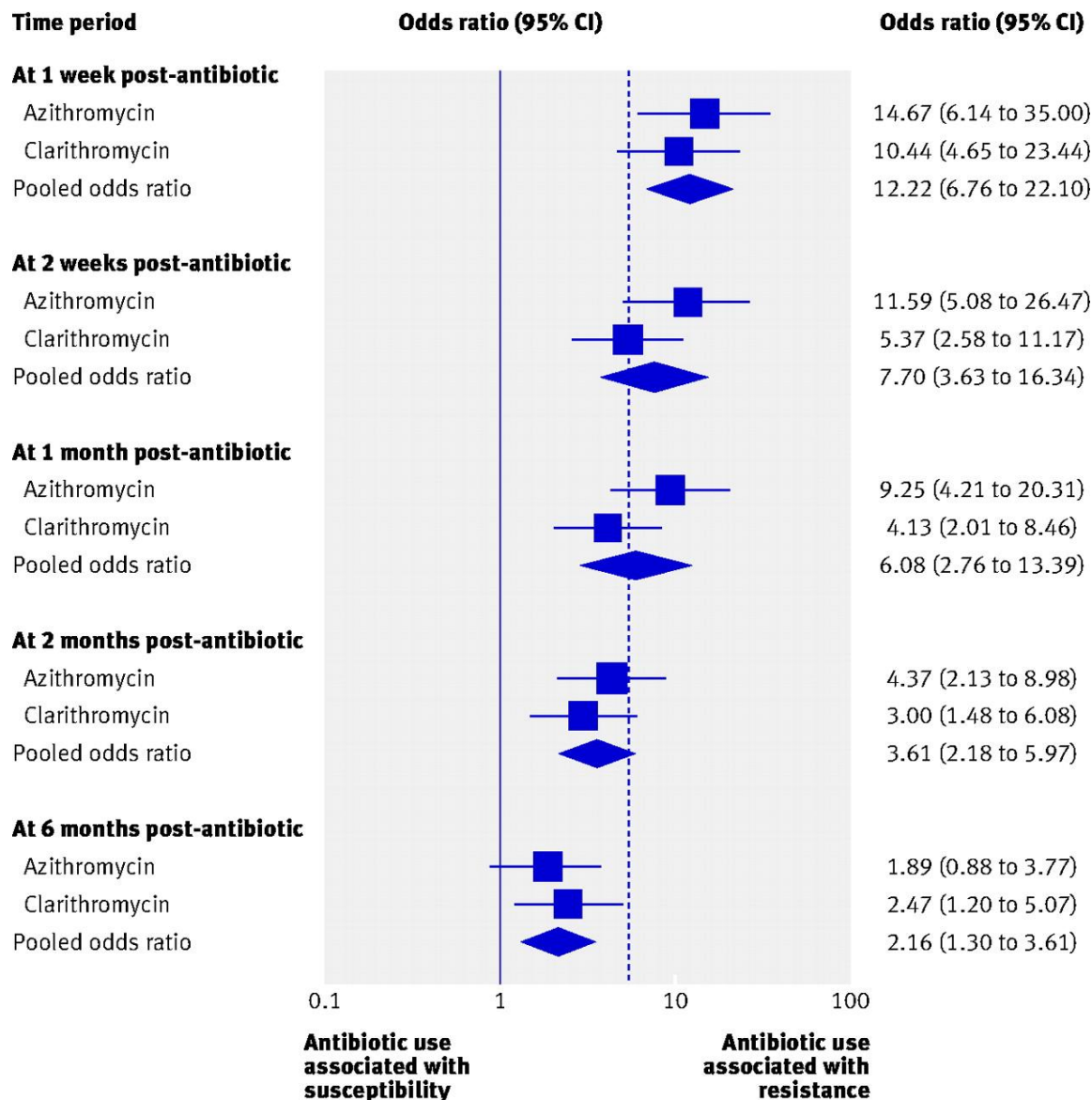
* Any antibiotic other than trimethoprim. ST=sulfamethoxazole-trimethoprim. NR=not reported

Forest plot showing individual study and pooled ORs (log scale) for resistance in respiratory tract bacteria and previous antibiotic prescribing.



* β lactam plus another antibiotic. NR=not reported

Forest plot showing individual analytic and pooled ORs (log scale) for resistance in respiratory tract streptococci of healthy volunteers from the Malhotra-Kumar study and previous antibiotic prescribing.



The Response

- Prevention
 - Screening and surveillance
 - Hygiene and Environmental controls
- Dx/Treatment
 - Differentiate bacterial infections from others
 - Biomarkers
 - Reliable bacterial identification and resistance tests
- Outbreak Management
- Education

The FilmArray BCID Panel

Simultaneous detection of 27 targets:



Gram + Bacteria

- *Staphylococcus*
- *Staphylococcus aureus*
- *Streptococcus*
- *Streptococcus agalactiae*
- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- *Enterococcus*
- *Listeria monocytogenes*



Gram - Bacteria

- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Serratia*
- *Proteus*
- *Acinetobacter baumannii*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Enterobacteriaceae*
- *Escherichia coli*
- *Enterobacter cloacae* complex



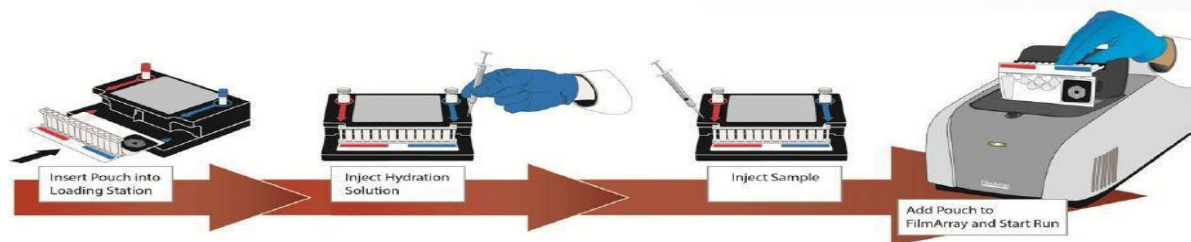
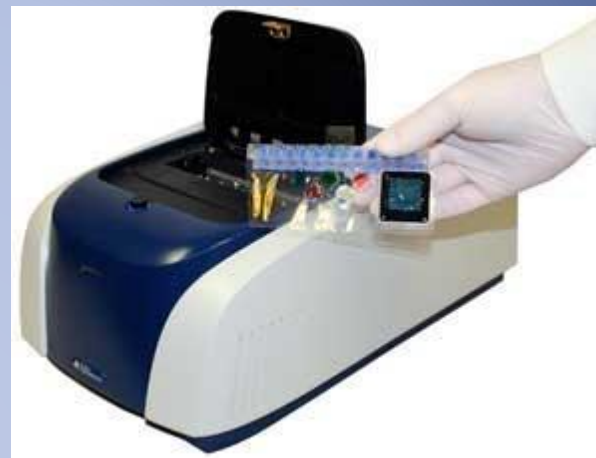
Fungi

- *Candida albicans*
- *Candida glabrata*
- *Candida krusei*
- *Candida parapsilosis*
- *Candida tropicalis*



Antibiotic Resistance

- *mecA*
- *vanA / vanB*
- *KPC*



Simple:
Only 2 minutes of
hands-on time

Easy:
No precise
pipetting required

Fast:
Run time of
only 1 hour

Rapid Tests for MRSA

Test	Time	Sites
GeneOhm MRSA ACP Assay	2 hrs	Nasal, Groin, Wound
GeneOhm StaphSR Assay	2 hrs	Blood*
Xpert MRSA/SA BC, MRSA/SA SSTI	1 hr	Blood*, Wound
Lightcycler MRSA	2 hrs	Nasal
Nanosphere Verigene	2.5 hrs	Blood*

*Blood Tests Detect: MSSA, MRSA, Coagulase-negative staphylococcus

Why all the Overuse?

Diagnostic Uncertainty

- Physicians often prescribe due to this
- Fail to think about the consequences
 - Individual and public health
- How to relieve uncertainty?
- What new tools may help?

Primary-care-based randomized placebo controlled trial of antibiotic treatment in acute maxillary sinusitis

Adults with suspected AMS were referred by GPs for Xrays of the maxillary sinus.

Those with radiographic abnormalities (n = 214) were randomly assigned treatment with amoxicillin (750 mg three times daily for 7 days; n = 108) or placebo (n = 106).

Clinical course was assessed after 1 week and 2 weeks, and reported relapses and complications were recorded during the following year.

- At 2 weeks, symptoms improved substantially or disappeared
- 83% AMOX and 77% placebo.
- No influence on the clinical course, frequency of relapses during the 1-year follow-up.
- Radiographs had no prognostic value
- Side-effects were recorded in 28% of patients given amox and in 9% of those taking placebo ($p < 0.01$). The occurrence of relapses was similar in both groups (21 vs 17%) during the follow-up year.

Rhinosinusitis

- One in 7 Americans, diagnosed each year
- In top 5 for Abx Rxs
- But...90-98% of these are viral
- When to prescribe....
 1. Symptoms >10 days w/o improvement
 2. Severe sx's with fever>102, nasal dc & facial pain>3 days
 3. Viral sinus sx's that worsen over 5-6 days and associated with new fever, headache, more nasal dc

What to treat ABRS with?

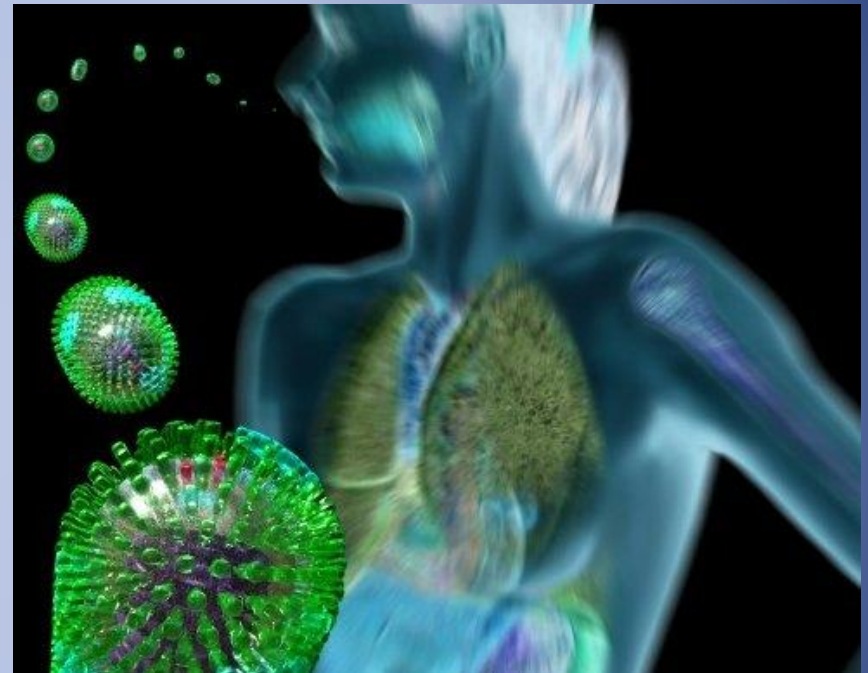
- Amox-Clav for 5-7 days in adults
- Nasal saline irrigation

Otitis Media – the evidence base

- 80% of acute OM resolves in 3 days without Rx
- ABX do not influence subsequent OM or deafness at 1 month
- May reduce no of children still in pain 2-7 days but for each 1 improved 3 will develop ABX related side effects
- Repeated courses may make recurrent infection more likely

Viral Infections don't require antibiotics

- Acute bronchitis
- Common colds
- Sinusitis with symptoms less than 7 days
- Pharyngitis not due to Group A *Streptococcus spp.*



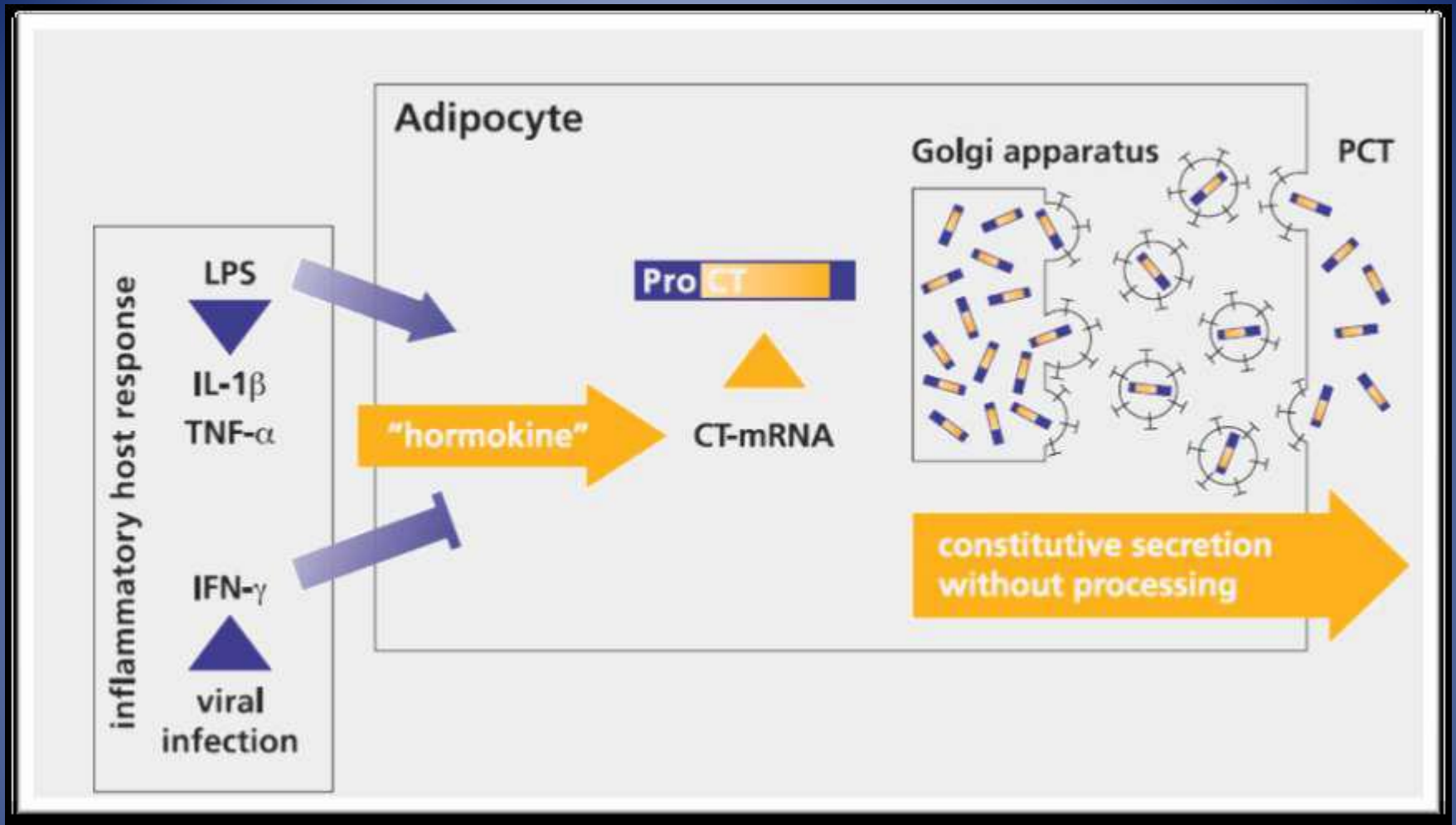
Gonzales R, et al. Annals of Intern Med 2001;134:479

Gonzales R, et al. Annals of Intern Med 2001;134:400

Gonzales R, et al. Annals of Intern Med 2001;134:521

URTIS – Improving Care

- Use Biomarkers
 - Procalcitonin
- Use Rapid Diagnostic tests – Multiplex PCR
- Patient education
- CDC Get Smart program
- Opportunity to Vaccinate
 - Influenza, Pertussis, Strep pneumoniae
- OMT?

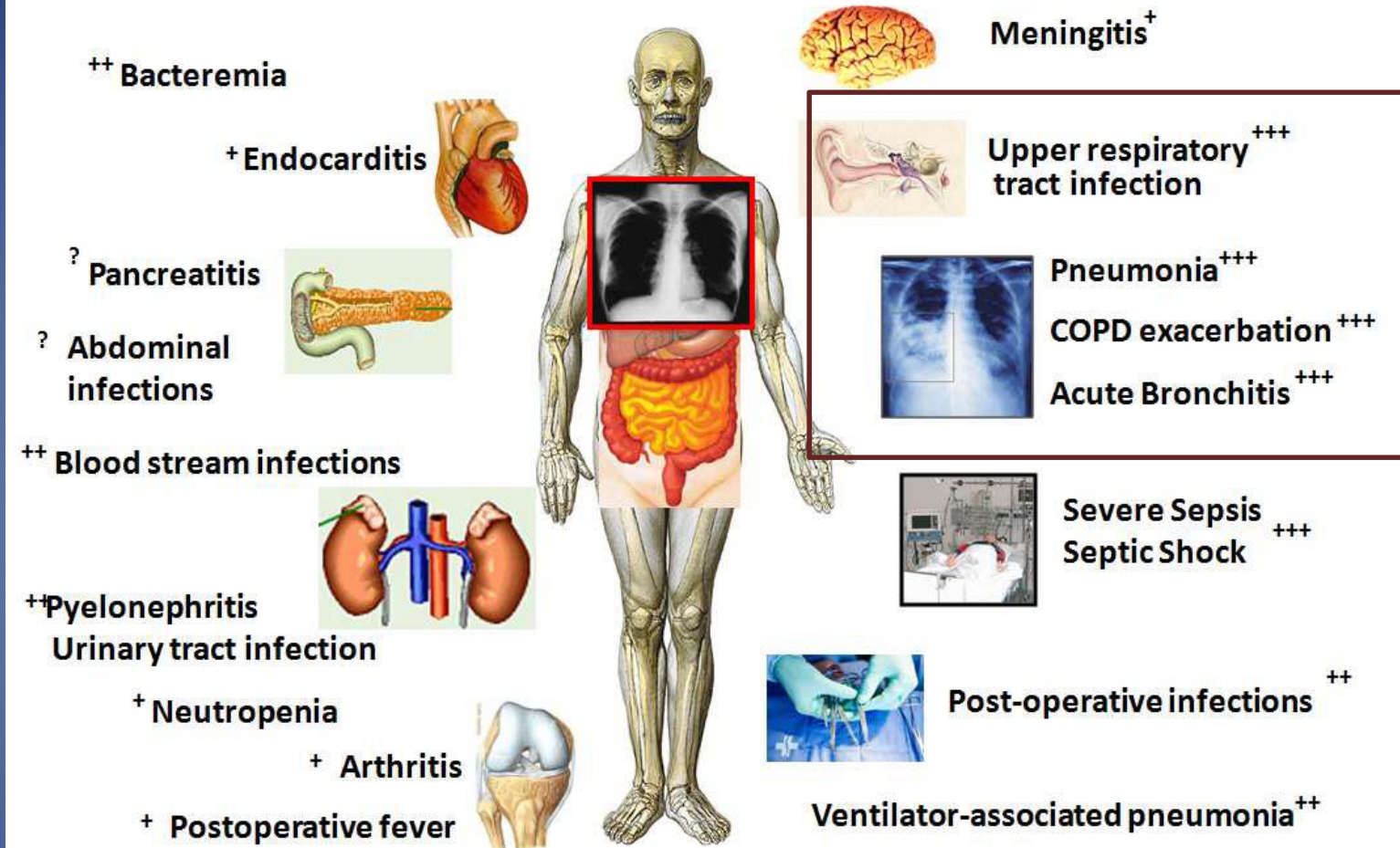


Bacterial infection and cytokines stimulate production of PCT in parenchymal tissues

- PCT is rapidly released into bloodstream
- Cytokines produced by viral infection inhibit this

Observational studies

Intervention studies



Evidence levels

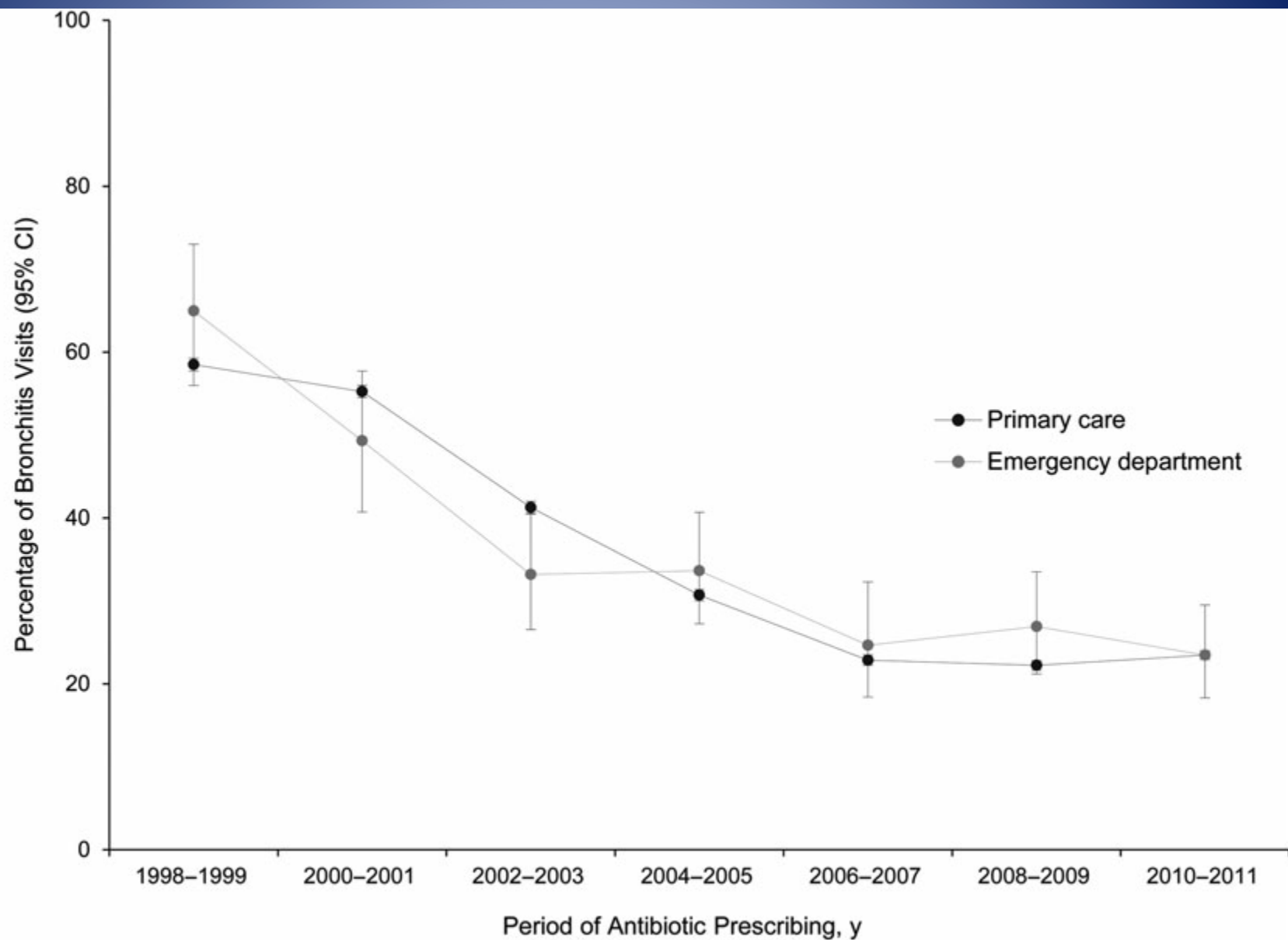
? Still undefined

+ Moderate

++ Good

+++ Strong

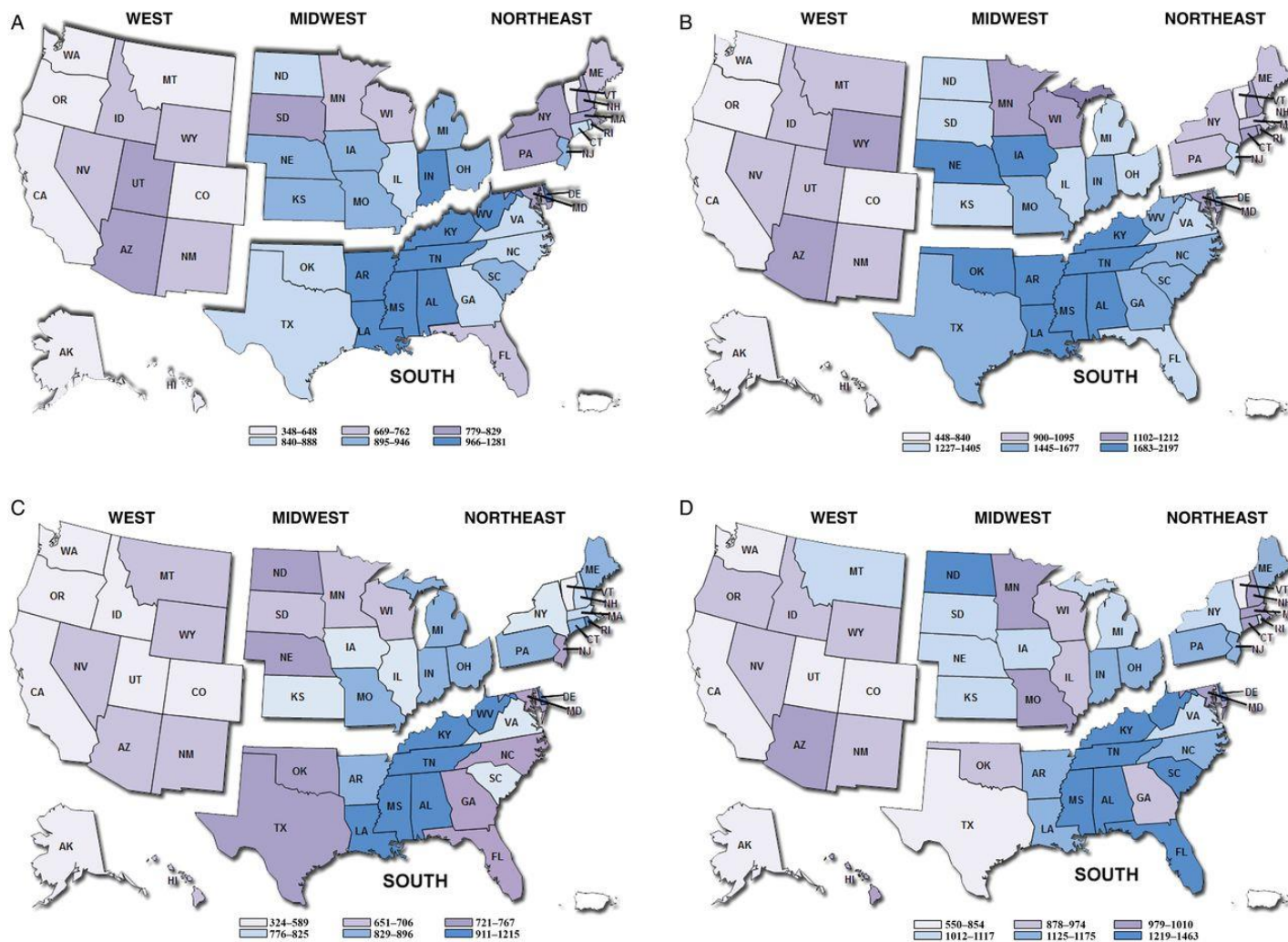
Procalcitonin data



No. of sample visits

Primary care	30 888	32 914	32 649	36 145	34 065	38 647	50 356
Emergency department	235	284	344	376	298	405	443

Antibiotic prescribing per 1000 persons by state (sextiles) in 2011 for all ages (A) and persons aged ≤ 2 (B), 3–64 (C), or ≥ 65 (D) years.



Lauri A. Hicks et al. Clin Infect Dis. 2015;60:1308-1316

Outpatient UTI Management

Uncomplicated Cystitis

- Women with at least 2 sx: dysuria, urgency, frequency and no vaginal discharge - >90% probability of acute cystitis
 - Studies found no benefit to doing testing

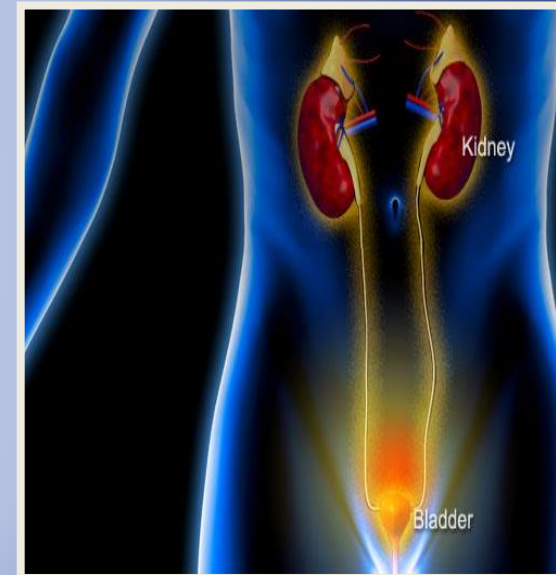
Women with relapse or recurrent UTI (>2/6m), complicated infections, Abx exposure or resistance should have a urine culture done

Treatment of Acute Cystitis

- Women
 - Nitrofurantoin 100 mg BID x 5 days
 - Fosfomycin 3g x 1 dose
 - TMP-SMX DS BID x 3 days (if resistance < 20%)
- Men
 - 7-14 days

Treat Bacterial Infection, not Colonization

- $\geq 10^5$ colony forming units is often used as a diagnostic criteria for a positive urine culture
- **It does NOT prove infection**; it is just implies the culture is unlikely due to contamination
- **Pyuria is not predictive** on its own
- Symptoms AND pyuria AND bacteruria denotes infection



Asymptomatic Bacteriuria is Common

<u>Age (years)</u>	<u>Women</u>	<u>Men</u>
20	1%	1%
70	20%	15%
>70 + long-term care	50%	40%
Spinal cord injury (with intermittent catheterization)	50%	50%
Chronic urinary catheter	100%	100%
Ileal loop conduit	100%	100%

Treatment of Asymptomatic Bacteriuria in the Elderly

Multiple prospective randomized clinical trials have shown no benefit

- No improvement in “mental status”
- No difference in the number of symptomatic UTIs
- No improvement in chronic urinary incontinence
- No improvement in survival



Inappropriate Abx Use in Asymptomatic Bacteriuria

- Dalen 2005 Ottawa 52%
 - Ghandi 2009 Michigan 33%
 - Cope 2009 Houston 32%
-
- 1/3-50% get antibiotics
despite evidence of no benefit

A Second Opportunity -UTIs

- Much of the antibiotic use here is not appropriate and avoidable.
- Wrong treatment, Wrong Drug, Wrong Duration are common
- **Resistance to Fluoroquinolones**
Trimethoprim-Sulfa
- Ensure the patient has a UTI not an alternate diagnosis
- When catheters in place - all are bacteriuric

What Causes the Pain in UTI

- Visceral pain is usually projected over the dermatome that shares common spinal innervation
- In murine models – strains which cause ASB elicit different responses than symptomatic UPEC strains – It is LPS which induces the pain through TLR4
- Inflammatory cells in urine are not the cause of pain and do not correlate with UTI in ASB
- New therapeutic approach? Probiotics with LPS

Biotherapeutics in UTI

- Vaginal application of *L. crispatus* reduces UTI
- ASB E. coli – bacterial interference
- Strain 83972 of E coli
- Use of these strains in mice prevents symptomatic infection
- Reduces pain more than ciprofloxacin
- Promotes clearance

Misuse in Skin and Soft Tissue Infections

Review 322 cases of SSTI @400 bed hospital in Denver 2007

- Positive cultures: 145/150 (97%) – *S. aureus* or streptococci

Treatment -70% got Abx for GNRs

- Imaging (151): Yield-1%
- Abx duration (median): 14 days



Every time antibiotics are prescribed:



Specific recommendations for common prescribing situations:



1. Order recommended cultures before antibiotics are given and start drugs promptly.



2. Make sure indication, dose, and expected duration are specified in the patient record.



3. Reassess within 48 hours and adjust Rx if necessary or stop Rx if indicated.



Rx for urinary tract infections

- Make sure that culture results represent true infection and not just colonization.
 - Assess patient for signs and symptoms of UTI.
 - Make sure that urinalysis is obtained with every urine culture.
- Treat for recommended length of time and ensure that planned post-discharge treatment takes into account the antibiotics given in the hospital.



Rx for pneumonia

- Make sure that symptoms truly represent pneumonia and not an alternate, non-infectious diagnosis.
- Treat for the recommended length of time and ensure that planned post-discharge treatment takes into account the antibiotics given in the hospital.



Rx for MRSA infections

- Verify that MRSA is growing in clinically relevant cultures. Do not use vancomycin to treat infections caused by methicillin-susceptible staph (and not MRSA).

SOURCE: CDC Vital Signs, 2014



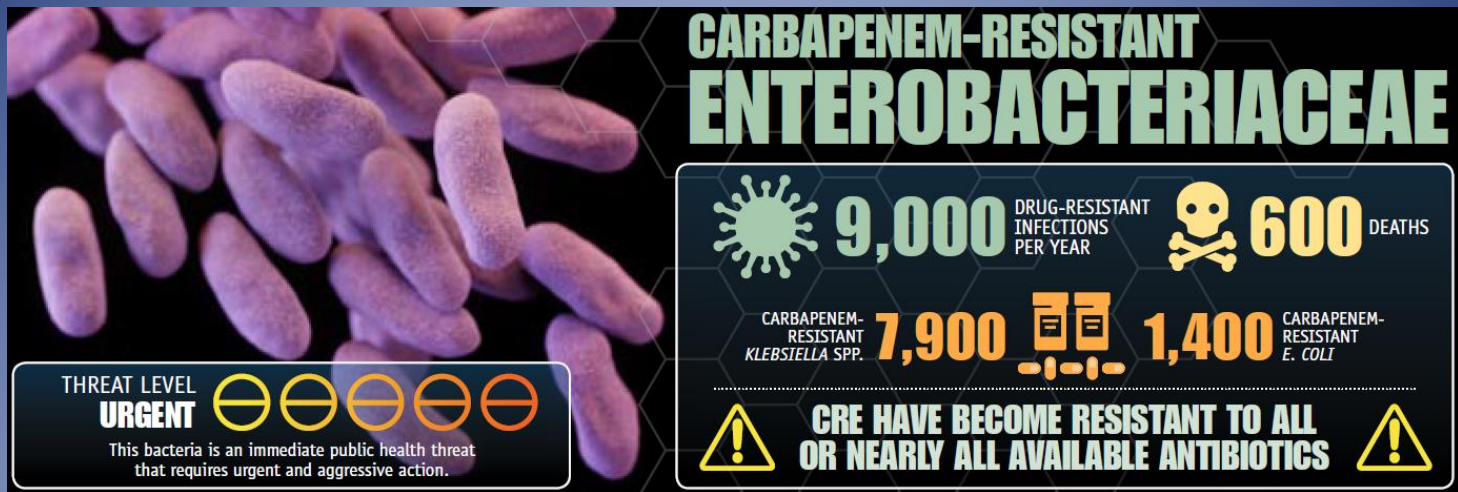
A Challenging UTI

- A 53 year old man with Parkinson's disease and a seizure disorder presents with his 4th urinary tract infection in the past year.
- He has back pain and dysuria. His current urinalysis shows pyuria and bacteriuria
- Urine culture is growing *Klebsiella pneumoniae*
Resistant to: Ciprofloxacin, Gentamicin, Trimethoprim-Sulfa, Pip-Tazo, Cefepime, Ertapenem, Imipenem, Meropenem
- What antibiotic is most likely to be effective for treatment of his *Klebsiella pneumoniae* infection?

Management of Carbapenem-resistant Enterobacteriaceae (CRE)

- Any Enterobacteriaceae isolate non-susceptible to all 3rd generation Ceph's and Imipenem, Doripenem or Meropenem
- **CALL FOR BACK-UP!!**





CRE GERMS KILL UP TO HALF OF PATIENTS WHO GET BLOODSTREAM INFECTIONS FROM THEM.

Vital^{CDC}**signs™**
www.cdc.gov/vitalsigns

The image shows a close-up of a petri dish held by a gloved hand, containing several bright pink, circular bacterial colonies on a clear agar surface. The background is a solid brown color.

New Drugs for MDROs

Ceftazidime-Avibactam (Avycaz)

- New non-beta-lactam beta-lactamase inhibitor added to Ceftazidime which enhances activity against some MDR GNRs including CRE
- Most KPCs, ESBL, AmpC
- *NOT Metallo-beta lactamases!*
- 2.5 g IV q 8h (over 2h)
 - 2 g Taz plus 500 mg Avibactam

Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013

- 87% from urine; 11% blood
- Device associated or hospitalized
- Fatal in 9%
- Higher rates in GA, MD, NY vs CO, NM, OR lower
- Median age 66
- Incidence 2.93/100k vs MRSA 25, CDI 147

New Cephalosporins for Resistant Gram Negatives

- **Ceftolozane/tazobactam (Zerbaxa)**
 - Similar to ceftazidime w/modified sidechain at position 3 - antiPseudomonal
 - Tazo protects the ceph from ESBLs
 - Better than Ceftaz vs *P. aeruginosa*
 - **Not active vs KPCs or MBLs**
 - Approved for IAI, UTI



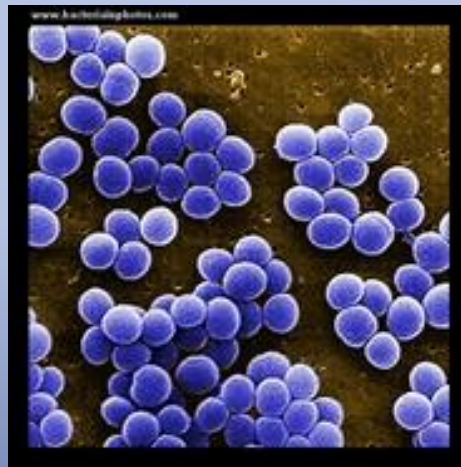
More MDROs

A 32 yo woman presents with severe dyspnea, hemoptysis and fever. She refused flu vaccination this year because it makes her sick.

8 days ago she had influenza A and was just beginning to improve when this struck.

Her past history is remarkable for recurrent skin boils and severe depression for which she takes Sertraline and Venlafaxine

Her CXR shows diffuse multilobar infiltrates and a sputum gram stain reveals the following :



Which antibiotic would you recommend to treat her pneumonia?

- A. Telavancin (Vibativ)
- B. Vancomycin
- C. Dalbavancin (Dalvance)
- D. Daptomycin (Cubicin)
- E. Tedizolid (Sivextro)



THE ANTI-MRSA BRIGADE

Vancomycin, Daptomycin, Telavancin, Linezolid, Tedizolid, Dalbavancin, Oritavancin, Clindamycin, Trimethoprim-Sulfa, Tigecycline, Minocycline, Ceftaroline, Quinupristin-dalfopristin

Telavancin (Vibativ)

- Lipoglycopeptide - daughter of Vancomycin
Longer half life (7.5h) – dosed 10 mg/kg q24h
over 1 hr **IV only**
- Approved for SSTI – MRSA \$\$\$
- Side effects – altered taste, nausea, foamy urine;
Red Person
- Prolongation of Qtc; interferes with INR
- Been used in HAP and VAP

Ceftaroline fosamil (Teflaro)

- “Ceph with enhanced gram positive activity
 - MRSA, VRE, VISA, hVISA, MDR-Strep; common gram negatives
 - Minimal activity vs *E. faecalis*
 - Not active vs *E. faecium*
- Lacks broad gram negative coverage – think RTI only!
- Approved for cSSTI, CAP (not MRSA) \$\$\$
 - 600 mg IV q12H IV
 - Similar to Vanco for SSTI; Ceftriaxone for RTI
 - Side effects of nausea, diarrhea

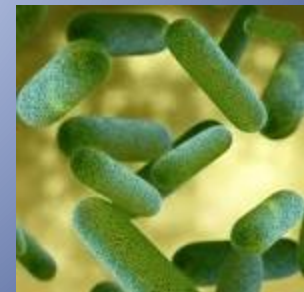
Tedizolid (Sivextro)

- Oxazolidinone similar to Linezolid
- Bacteriostatic
- 200 mg tab once daily orally for 6 days for SSTI

Dalbavancin (Dalvance)

Oritavancin (Orbactiv)

- These are long half-life lipoglycopeptides vs Gram positive infections – approved SSTI
- Redman syndrome like Vanco
- Allow once weekly dosing – IV only
 - Dalba 1g day 1, 500 mg day 8
 - Orita 1200 mg x 1 over 3 h
 - Increase PTT, PT for 48h
- \$\$\$\$\$



SSI Prevention

- A 68 year old woman presents with 3 weeks of left hip pain. She had a left THA 6 weeks ago at her local community orthopedic hospital for avascular necrosis.
- She was seen pre-operatively by an anesthesiologist who assessed her operative risk and okayed her for surgery. No special precautions were taken.
- Today an aspiration of the hip showed 45,000 WBC, 90% polys and gram stain showed numerous gram positive cocci in clusters.

Surgical Site Infections

- Most are due to Staph aureus
- Prevention
 - Screen with nasal swab 10-14 days pre-op or history of prior colonization
 - Decolonize carriers of Staph aureus
 - Mupirocin nasal ointment BID x 5 days
 - CHG wash daily for 5 days
 - If MRSA – use IV Vancomycin + Cefazolin px
 - If MSSA – Cefazolin – 1 dose

STOP-SSI Trial

- 43,087 operations
 - 28,593 before and 14,494 after
 - 90 day follow-up
 - 101 pre vs 29 after – OR 0.6

Still unclear whether all should be screened

Given that 400,000 cardiac and 1 million joint replacements done annually – the reduction in infections could have a huge impact

Duration of Antibiotics in Surgical Infections – Peritonitis STOP-IT Trial

- 500 pts – 23 US and Canadian sites
- 34% CRS 14% small bowel
- 11% Cancer 10% IBD 15% Diabetic
- Abx for 4days vs up to 10 days
 - 33% percutaneous drainage
 - 26% surgery
 - 21% surgical drainage
- No difference in SSI/recurrent intrabdominal infection or death in 30 days

Sawyer RG et al *N Engl J Med* 2015;372:1966

C. Difficile

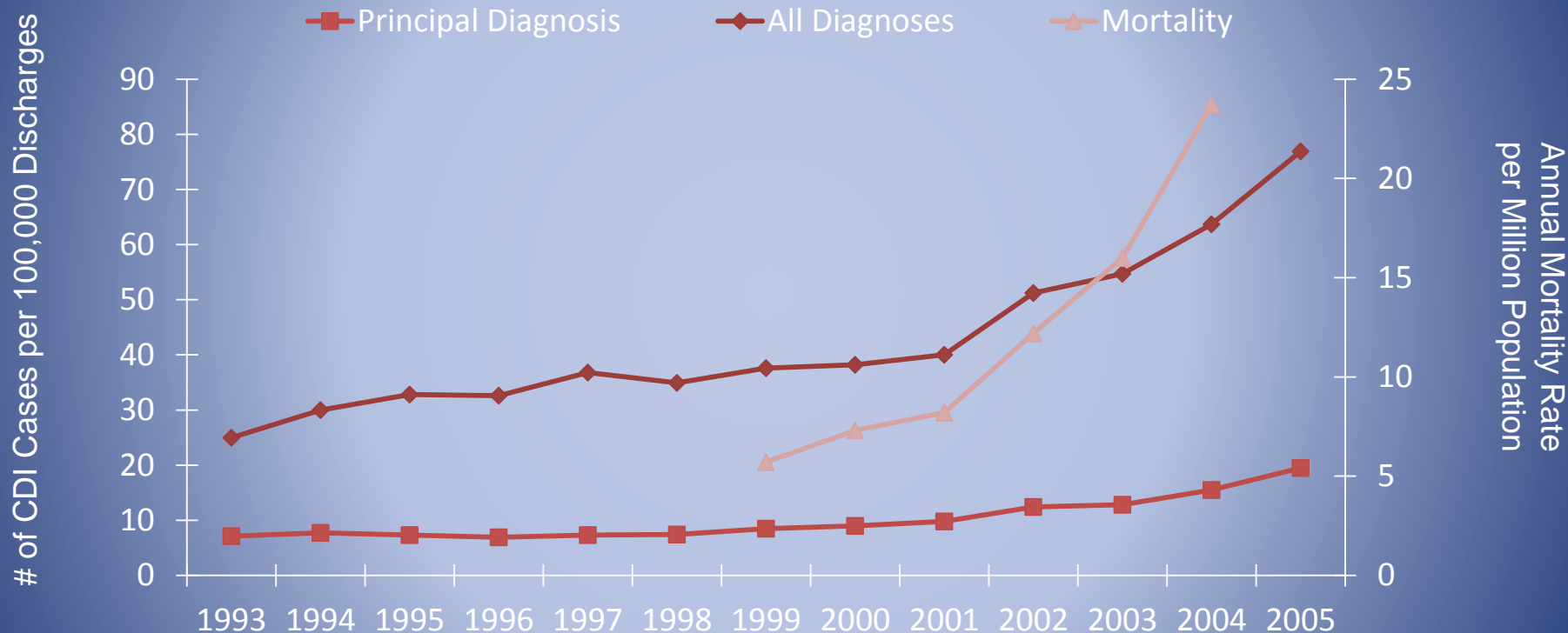
Another Outcome of Overuse

- Antibiotic exposure is the #1 risk factor for the development of *Clostridium difficile* infection (CDI).
 - Up to 85% of patients with CDI have antibiotic exposure in the 28 days before infection
- 20% of patients admitted to the ICU with CDI were receiving antibiotics without evidence of infection with an accompanying 28% in-hospital mortality

¹ *Infect Control Hosp Epidemiol* 2007; 28:926–931.

² *BMC Infect Dis* 2007; 7:42

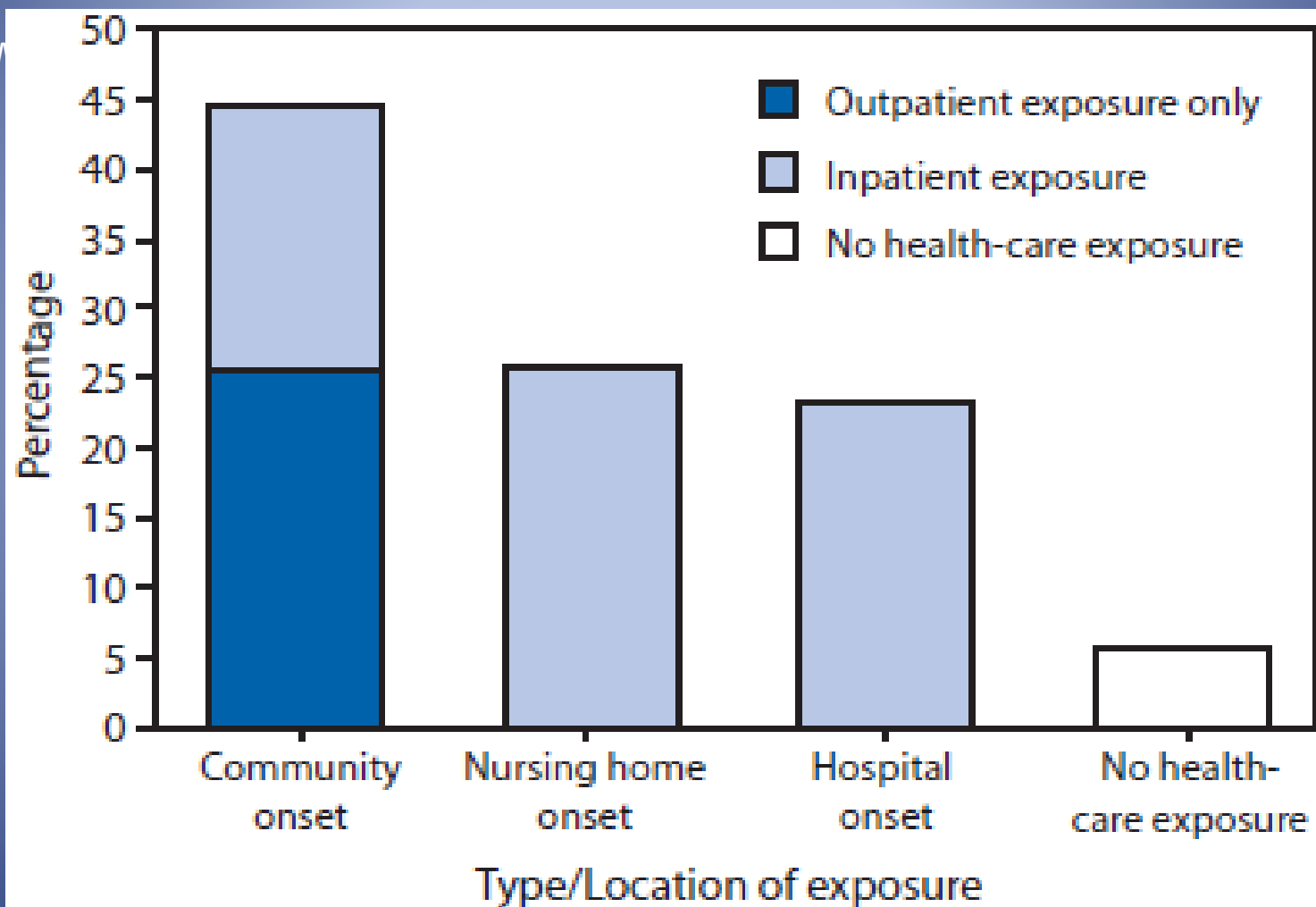
CDI: Incidence and Mortality are Increasing in US



1. Elixhauser A, et al. Healthcare Cost and Utilization Project: Statistical Brief #50. April 2008. Available at: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf>. Accessed March 10, 2010.
2. Redelings MD, et al. Emerg Infect Dis. 2007;13:1417-1419.

Its not just in hospitals - CDI

• MMWR



Control of *C. difficile* infection

- Appropriate use of antimicrobials
- Infection prevention measures
- New Monoclonal Ab vs CD toxin B (coming)
- *Microbiota replacement therapy*

Some Final Tips to Optimize Duration of Antibiotic Therapy

- **Avoid generic 10-14-day therapy**
 - Uncomplicated urinary tract infection: 3-5 days¹
 - Community-acquired pneumonia: 3-7 days²
 - Ventilator-associated pneumonia: 8 days³
 - CR-BSI Coagulase-negative staphylococci: 5-7 days⁴
 - Acute Hem Osteomyelitis in children-21 days⁵
 - Meningococcal meningitis-7 days⁶
 - Uncomplicated secondary peritonitis with source control: 4-7 days⁷
 - Uncomplicated SSTI⁸ 5 days

1. *Clin Infect Dis* 1999; 29:745-758

2. *Clin Infect Dis* 2007; 44:S27-72

3. *JAMA* 2003; 290:2588-2598

4. *Clin Infect Dis* 2009; 49:1-45

5. *Pediatr Infect Dis* 2010; 29:1123-1128

6. *N Engl J Med* 1997; 336:708-716

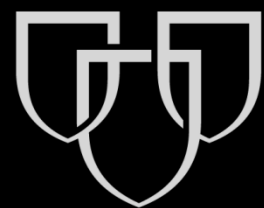
7. *Clin Infect Dis* 2010; 50:133-164

8. *Arch Intern Med* 2004; 164:1669-1674

Summary

To Control Antimicrobial Resistance





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