CRE in Illinois
A Situational Update

Michael Lin, MD MPH
Rush University Medical Center
Chicago CDC Prevention Epicenter
May 12, 2015

Disclosure

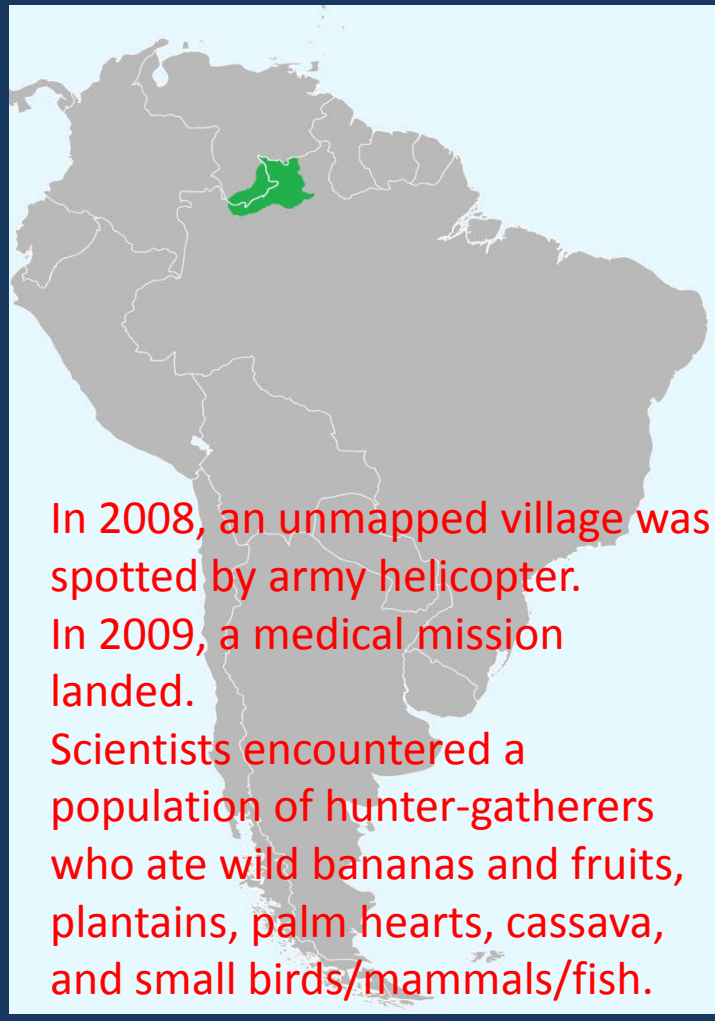
- I have nothing to disclose.

Overview

- How did we get here?
- The ABC's of CRE
- What's happening in Illinois
  - CRE trends (REALM project, XDRO registry)

High Orinoco area of Amazonas state in Venezuela

Yanomami tribe



In 2008, an unmapped village was spotted by army helicopter.
In 2009, a medical mission landed.
Scientists encountered a population of hunter-gatherers who ate wild bananas and fruits, plantains, palm hearts, cassava, and small birds/mammals/fish.

Science Advances April 2015

RESEARCH ARTICLE

MICROBIAL ECOLOGY

The microbiome of uncontacted Amerindians

Jose C. Clemente,[1,2]* Erica C. Pehrsson,[3]* Martin J. Blaser,[4,5] Kuldip Sandhu,[5†] Zhan Gao,[5] Bin Wang,[3] Magda Magris,[6] Glida Hidalgo,[6] Monica Contreras,[7] Óscar Noya-Alarcón,[6] Orlana Lander,[8] Jeremy McDonald,[9] Mike Cox,[9] Jens Walter,[10‡] Phaik Lyn Oh,[10] Jean F. Ruiz,[11] Selena Rodriguez,[11] Nan Shen,[1] Se Jin Song,[12] Jessica Metcalf,[12] Rob Knight,[12,13§] Gautam Dantas,[3,14] M. Gloria Dominguez-Bello[5,7,11¶]

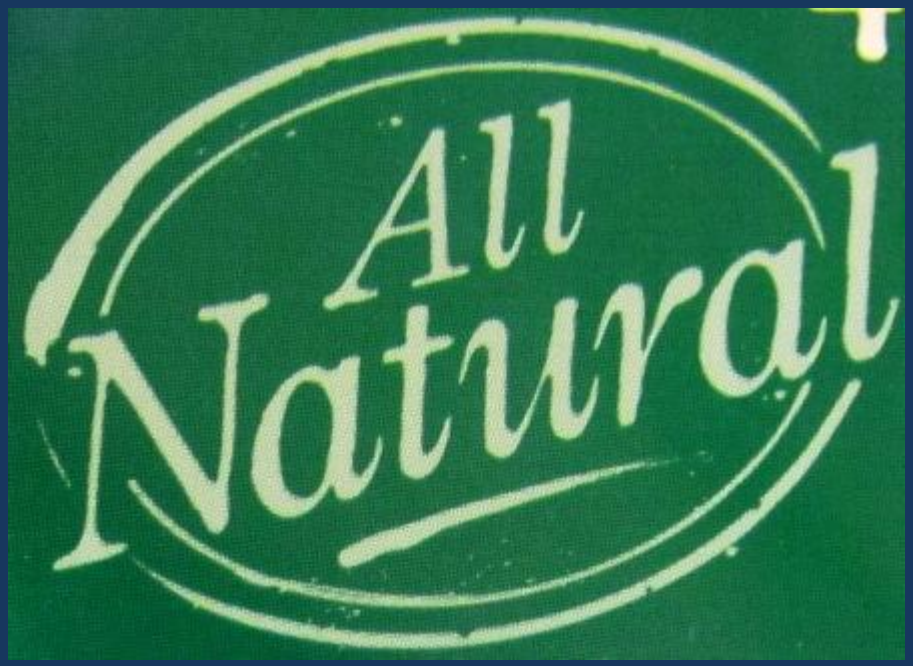
10.1126/sciadv.1500183

Most studies of the human microbiome have focused on westernized people with life-style practices that decrease microbial survival and transmission, or on traditional societies that are currently in transition to westernization. We characterize the fecal, oral, and skin bacterial microbiome and resistome of members of an isolated Yanomami Amerindian village with no documented previous contact with Western people. These Yanomami harbor a microbiome with the highest diversity of bacteria and genetic functions ever reported in a human group. Despite their isolation, presumably for >11,000 years since their ancestors arrived in South America, and no known exposure to antibiotics, they harbor bacteria that carry functional antibiotic resistance (AR) genes, including those that confer resistance to synthetic antibiotics and are syntenic with mobilization elements. These results suggest that westernization significantly affects human microbiome diversity and that functional AR genes appear to be a feature of the human microbiome even in the absence of exposure to commercial antibiotics. AR genes are likely poised for mobilization and enrichment upon exposure to pharmacological levels of antibiotics. Our findings emphasize the need

Key findings

- Highest diversity of microbiome ever found!
- Their *E. coli* were ancient, reflecting divergence 11,000 years ago (100 million bacterial generations)
- All *E. coli* were pan-susceptible
- Yet, the microbiome also carried 28 antibiotic resistance genes to man-made antibiotics, including ceftazidime, cefepime, aztreonam

Antibiotic resistance is a natural phenomenon…



An un-natural creation

BLOOD CULTURE (PERIPHERAL) (Abnormal):
PROCEDURE: BLOOD CULTURE (PERIPHERAL)
SOURCE: BLOOD
COLLECTED: [redacted]

---------- FINAL REPORT ----------

FINAL REPORT [redacted]
GROWTH OF GRAM NEGATIVE RODS
FINAL IDENTIFICATION: KLEBSIELLA PNEUMONIAE
This isolate demonstrates carbapenemase production.
Carbapenems, cephalosporins, and penicillins are
unlikely to be effective in treatment of serious
infections. Contact precautions required.

---------- SUSCEPTIBILITY TESTING ----------

	K PNEUMO			
	MIC mcg/ml	MIC INTERP	MIC mcg/ml	ET INTERP
TRIMETH/SULFA	>2/38	RESISTNT		
CEFAZOLIN	>16	RESISTNT		
TIGECYCLINE			1.00	SUSCEPT
LEVOFLOXACIN	>4	RESISTNT		
CEFOXITIN	16	INTERMED		
PIP/TAZOBACTAM	>64	RESISTNT		
TICARCIL/K CLAV	>64	RESISTNT		
CEFTRIAXONE	>32	RESISTNT		
GENTAMICIN	<=4	SUSCEPT		
TOBRAMYCIN	>8	RESISTNT		
AMIKACIN	16	SUSCEPT		
IMIPENEM	8	RESISTNT		
MEROPENEM	>8	RESISTNT		
CEFEPIME	16	RESISTNT		
COLISTIN			.38	SUSCEPT
A ERTAPENEM	>4	RESISTNT		

Antibiotic use: key driver

- In 2010 alone:
  - 73 billion units of antibiotics used in humans
    - 10 antibiotic units for every man, woman, and child on earth; 36% increase from 2000
    - India and China were largest consumers by country
      - Though had half of per-capita use compared to US (22 units/person)
  - 63,151 tons of antibiotics used in livestock

- Van Boeckel et al. The Lancet 2014
- Van Boeckel et al. PNAS 2015

The ABCs of CRE

Class	Enzyme
A	KPC
B (metallo-β-lactamases)	NDM-1, VIM, IMP
D	OXA

KPC – quick facts

- *"Klebsiella pneumoniae* carbapenemase"
- Origin: USA
- First identified: 1996
- Associated bacteria:
  - *Klebsiella pneumoniae >>> E. coli > Enterobacter*
- Primarily found in debilitated hospitalized patients. No significant community spread.

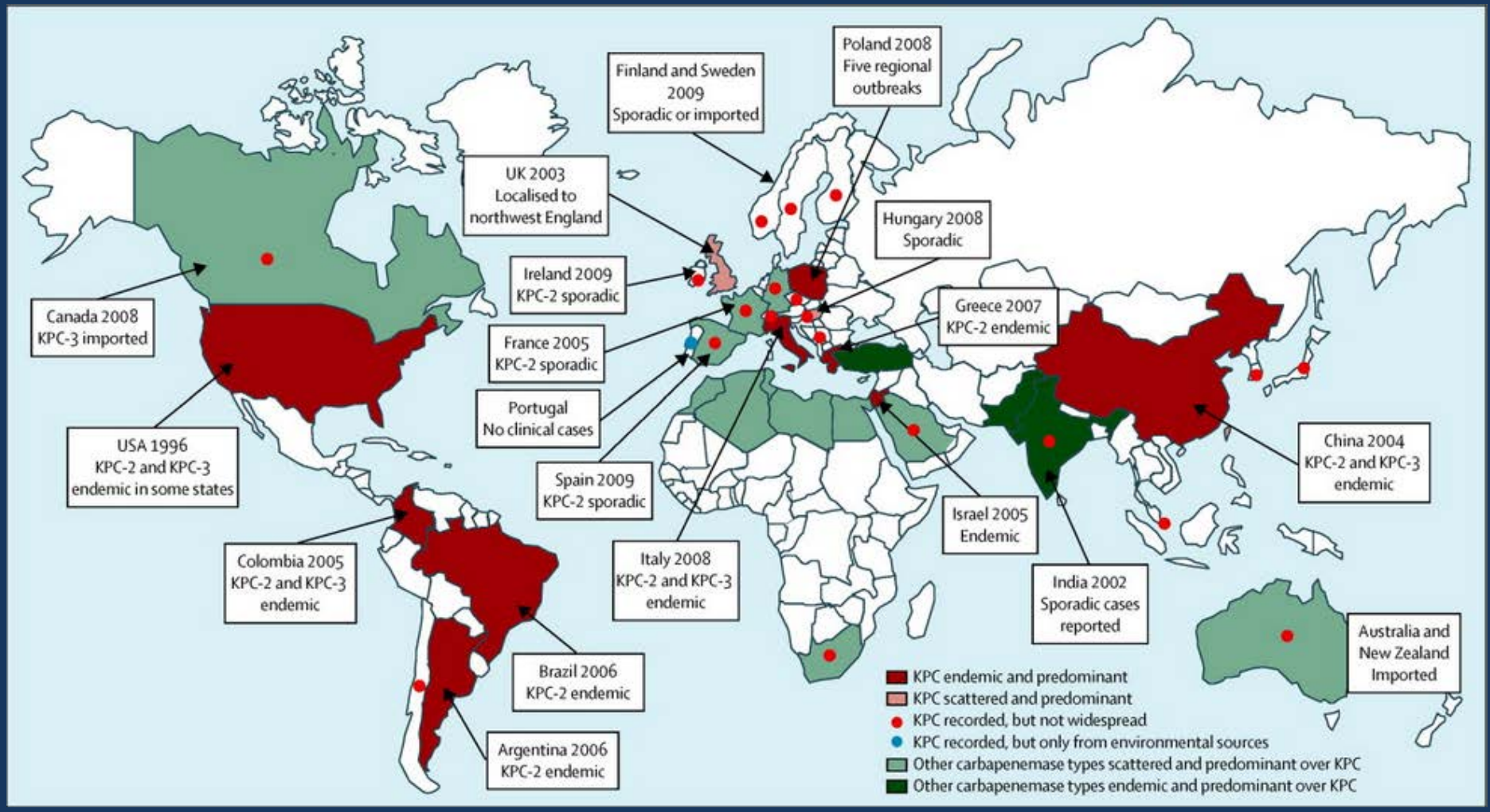
REVIEW ARTICLE

Country-to-Country Transfer of Patients and the Risk of Multi-Resistant Bacterial Infection

Benjamin A. Rogers,[1] Zohreh Aminzadeh,[1,2] Yoshiro Hayashi,[1,3] and David L. Paterson[1]

[1]University of Queensland Centre for Clinical Research, The University of Queensland, Herston, Brisbane, Australia; [2]Infectious Diseases Research Centre, Shaheed Beheshti University M. C., Tehran, Iran; [3]Department of Intensive Care Medicine, the Royal Brisbane & Women's Hospital, Herston, Brisbane, Australia

KPC global spread



Munoz-Price LS et al. Lancet ID. 2013

NDM – quick facts

- “New Delhi metallo-β-lactamase”
- Origin: South Asian continent
- First identified: 2008
- Species: *Klebsiella pneumoniae* = *E. coli*, others (*Enterobacter*, *Citrobacter*, *Proteus*, *Salmonella*, *Providentia*, *Acinetobacter*, *Pseudomonas*)
- Found in both in hospitalized pts and in the community

NDM global distribution

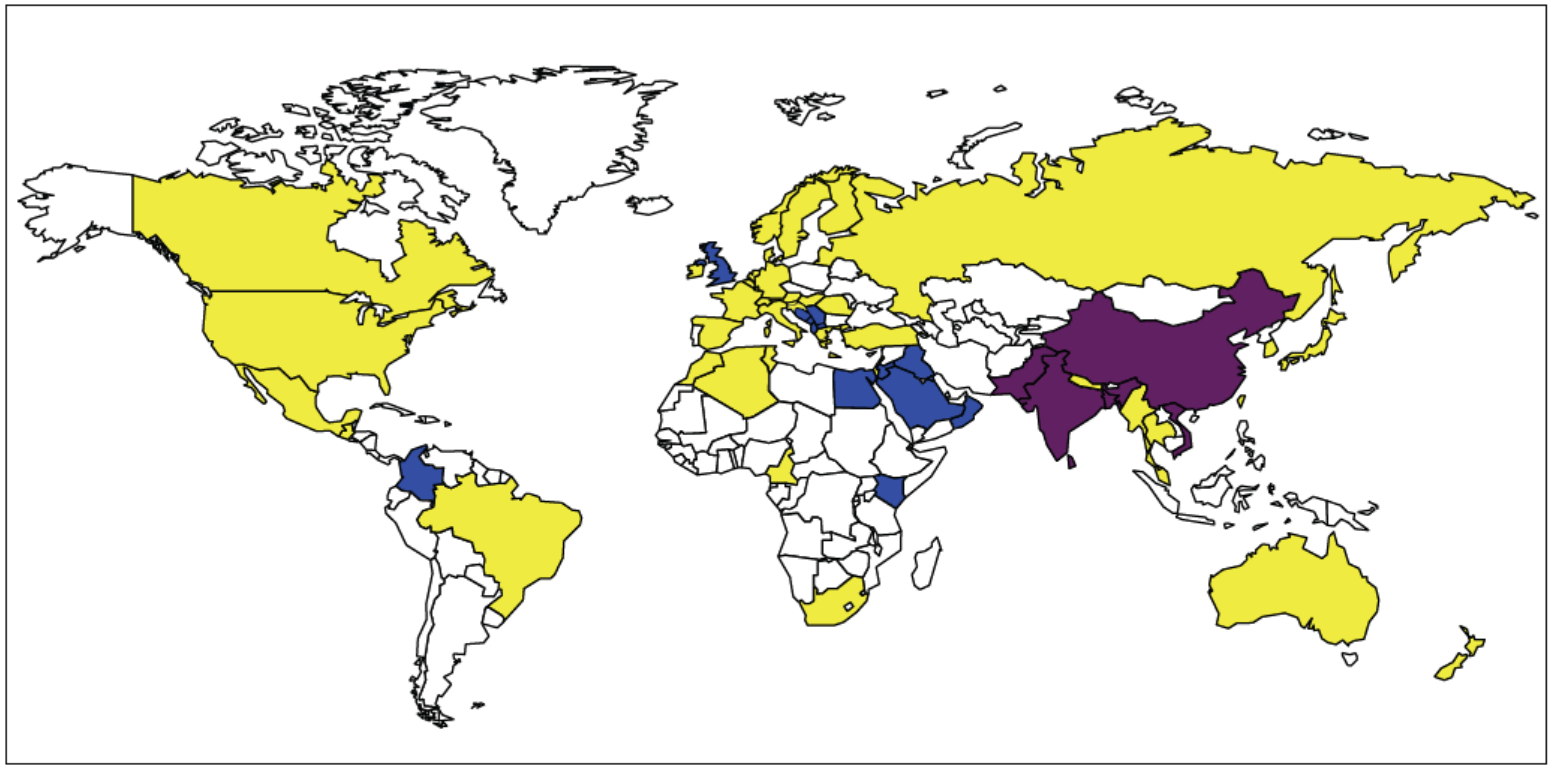


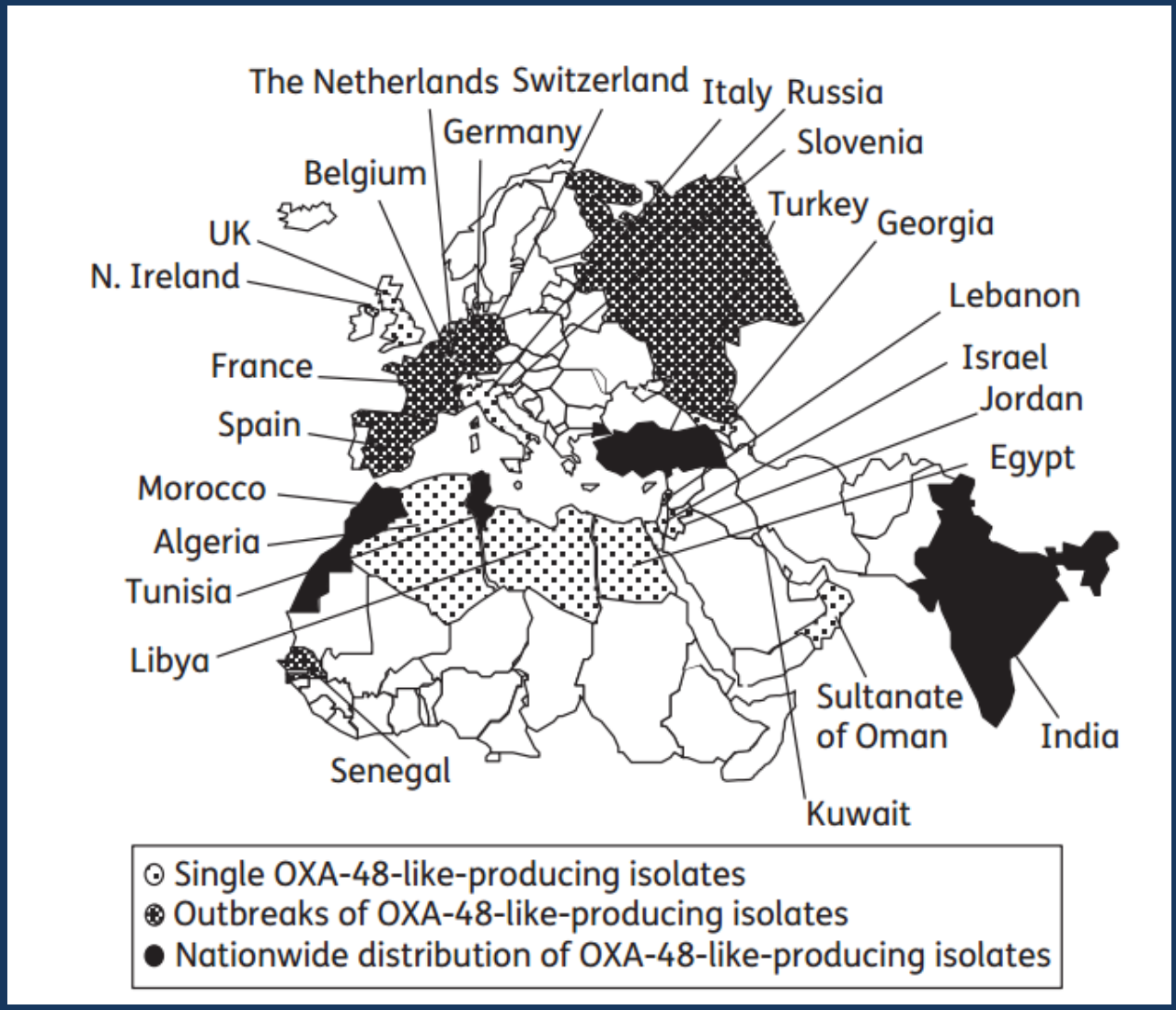
FIGURE 2: Geographical distribution of NDM producers.

Dortet et al. BioMed Res Int. 2014

OXA-48 quick facts

- OXA = “Oxacillinase”
- Origin: Turkey
- First identified: 2001
- Claim to fame: is a weak carbapenemase, and does not have cephalosporin resistance. (However, some OXA-48 have co-expressed ESBLs + outer membrane protein changes = high level resistance)
- Species: *Klebsiella pneumoniae* >>> *E. coli*, others

OXA-48 global



Poirel et al. J Antimicrob Chemo 2012; 67: 1597-1606

CRE: 3 important types for Illinois

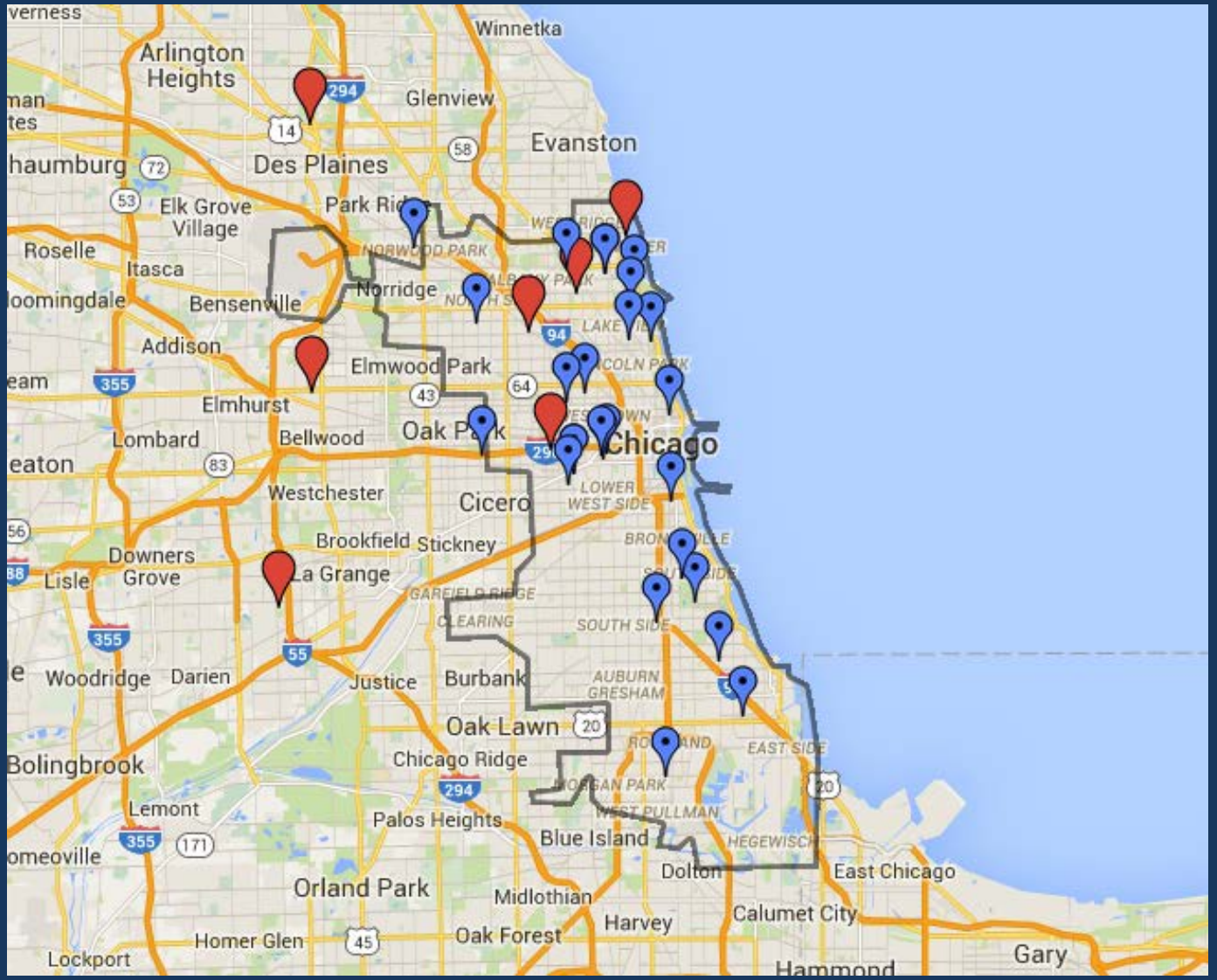
	KPC	NDM	OXA-48
Bacteria	*K. pneumo* > *E. coli*	*E. coli* = *K. pneumo*	*K. pneumo* > *E. coli*
Prevalence	Most common CRE	Rare but emerging	Rare but emerging
Take-home point	Most prevalent CRE in US	Most concerning CRE given propensity to spread among bacterial species and into community	A 'sneaky' CRE that can be difficult to recognize

What’s happening in Illinois?

REALM project

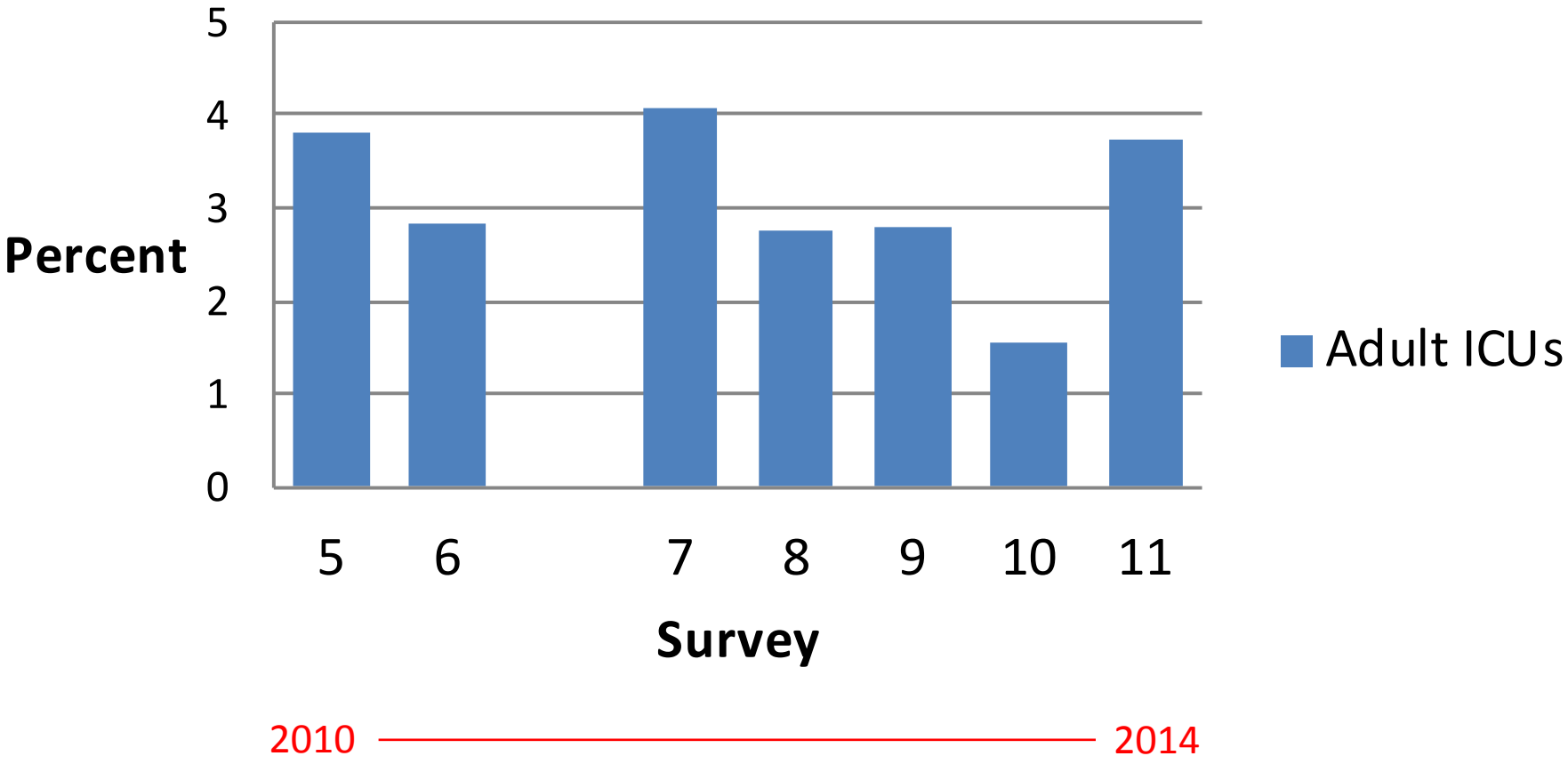
- Is a CDC-sponsored twice-yearly point prevalence survey for MDROs (CRE, since 2010)
  - Main advantage: tests for colonization

REALM project - KPC

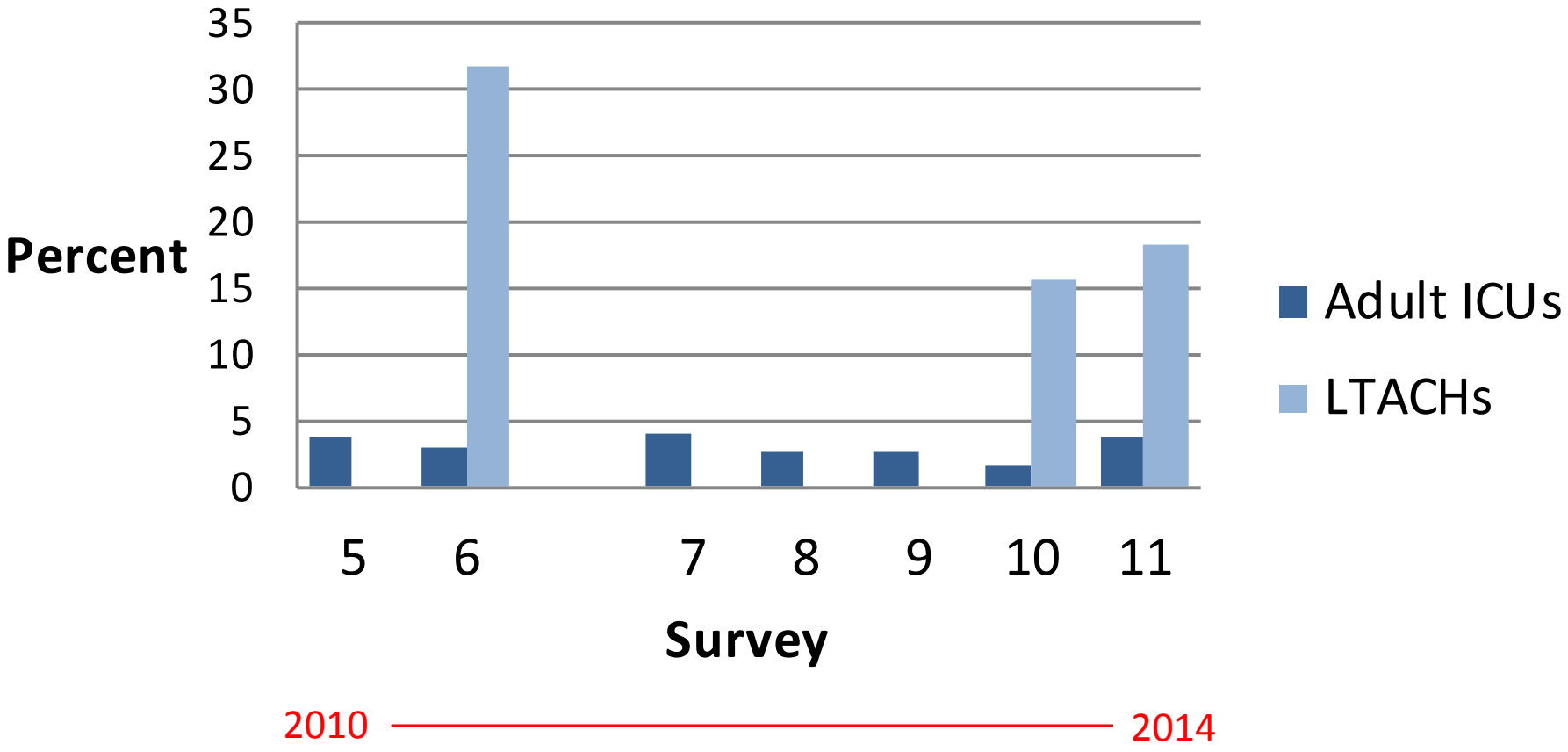


- Hospital ICUs (blue), LTACHs (red):

Prevalence of KPC colonization among adult ICU patients



Prevalence of KPC colonization among ICU vs. LTACH patients



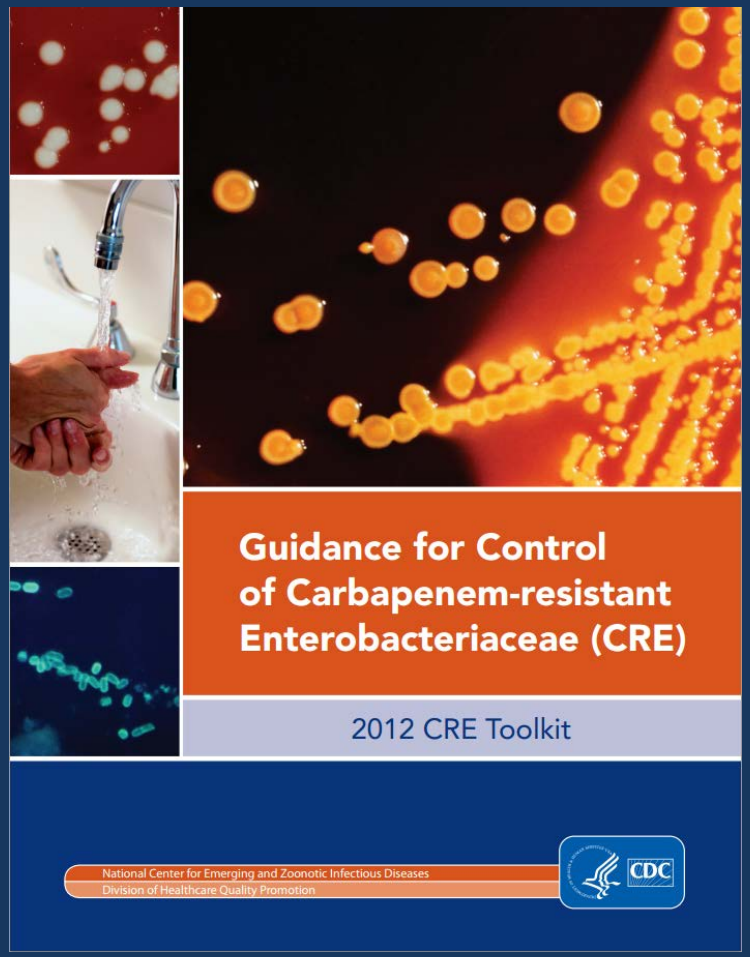
REALM project 2015 update

- Survey #12 is underway
  - We will now test for all 5 major carbapenemases (KPC, NDM, OXA-48, VIM, IMP)

Thank you to REALM hospitals for continued participation

Illinois' CRE Control efforts: Detect and Protect

“Detect and Protect”



- Detect: Identify all patients with CRE
- Protect: Maintain CRE-colonized patients in isolation precautions throughout the healthcare system

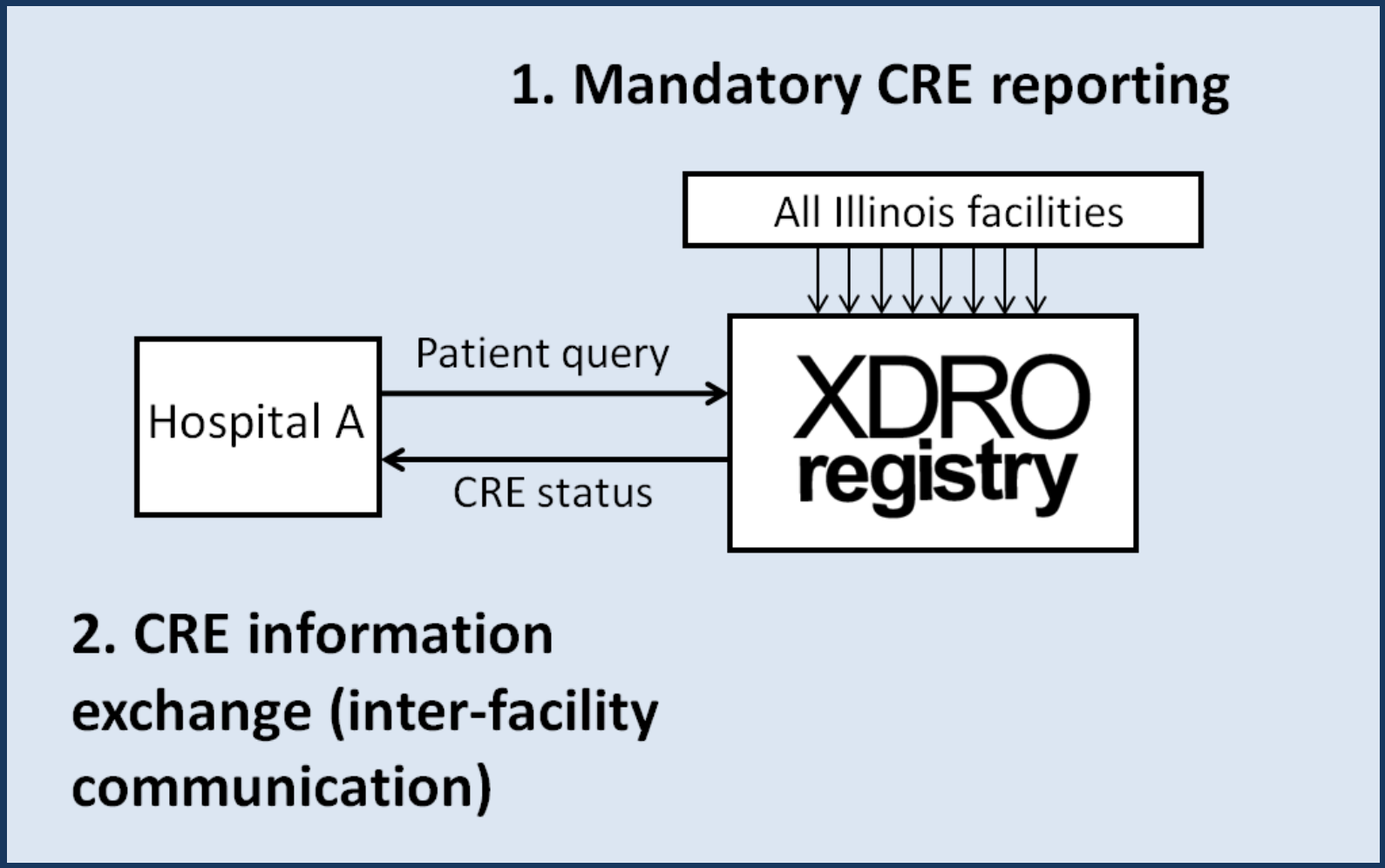
‘Detect & Protect‘ Challenges

- Laboratory identification of CRE can be tricky
- Patients move around a lot
  - During 1 year after ICU discharge, median 4 facility transitions (2/3 with re-admission)
    - Unroe, Annals Int Med, 2010; 153(3)
- Information can be lost at time of hospital transfer
- Many patients go home before going to another hospital

XDRO registry

- Public health infection control tool created to facilitate the Detect and Protect strategy
- Partnership
  - Illinois Department of Public Health
  - Chicago CDC Prevention Epicenter
  - Medical Research Analytics and Informatics Alliance (MRAIA)

XDRO registry overview



Participants: All Illinois hospitals, including LTACHs (142), nursing homes (784), laboratories

Illinois CRE definition: Enterobacteriaceae with one of the following test results:

1. Molecular test (e.g., PCR) specific for carbapenemase

OR

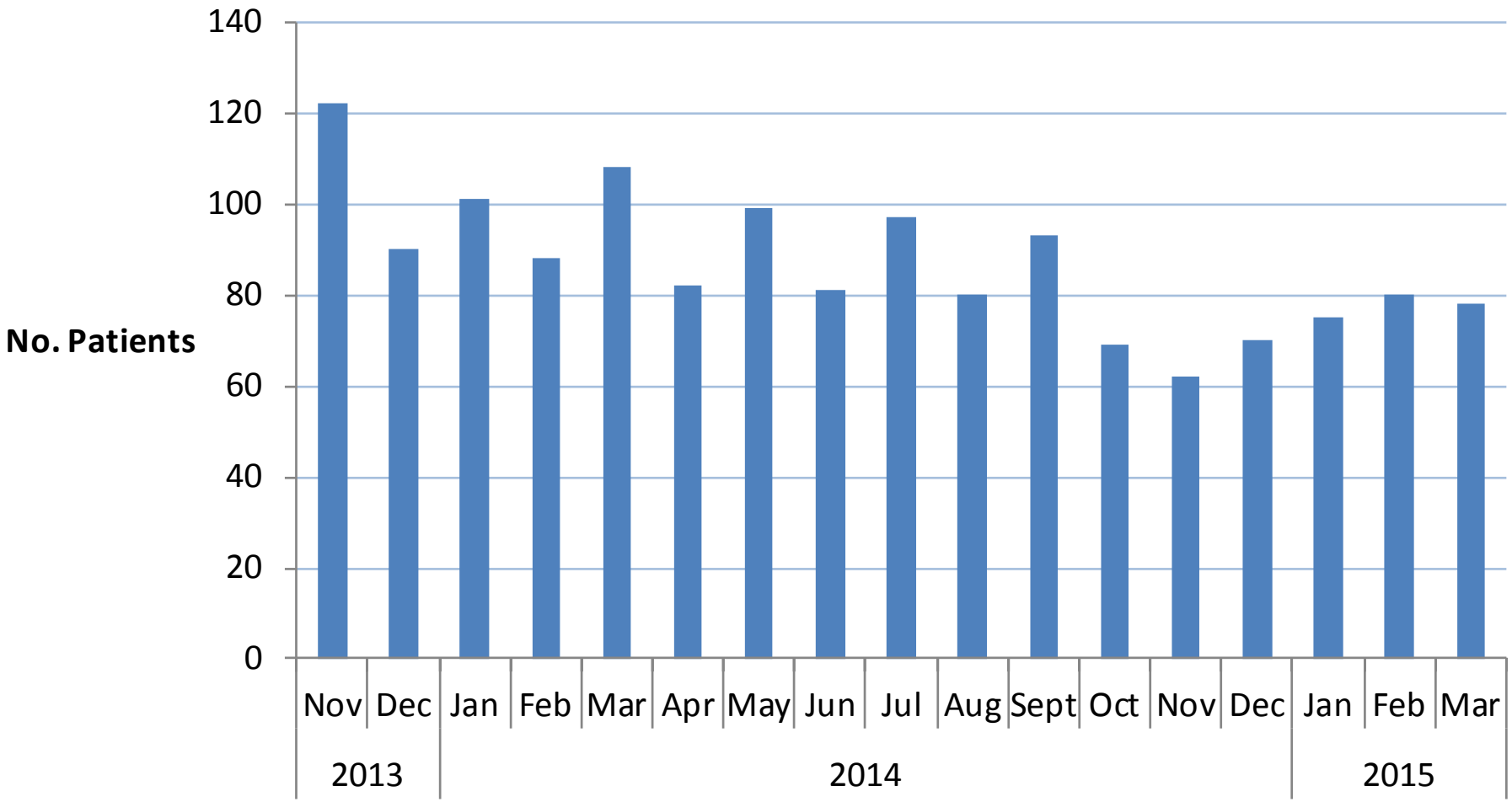
2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production

OR

3. For ***E. coli*** **and** ***Klebsiella*** species only: non-susceptible to ONE of the carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime).

Report 1st CRE event per patient per encounter

Unique patients reported to XDRO registry



Data courtesy of IDPH

XDRO registry, year 1

Reporting

- Unique reports: 1,557 reports
- Unique patients: 1,095
- Reporting facilities: 175

115	Acute hospitals
5	LTACHs
46	SNFs
7	reference labs
2	Outpatient clinics

Querying

- 30 unique facilities query the registry/month

XDRO registry summary, 2014

Characteristics of ALL submitted reports	N	%
Culture Type		
Clinical	1254	80
Screening	301	20
Organism		
Klebsiella spp.	1347	86
E. coli	103	7
Enterobacter spp.	77	5

Data and adapted slide from IDPH (A. Tang)

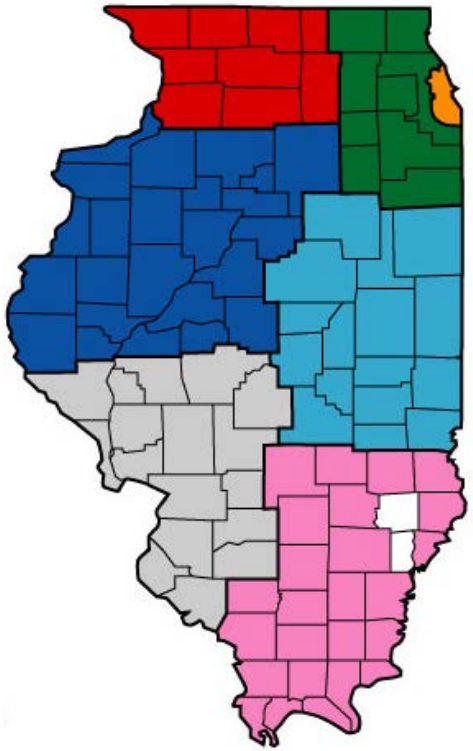
XDRO registry summary, 2014 (cont)

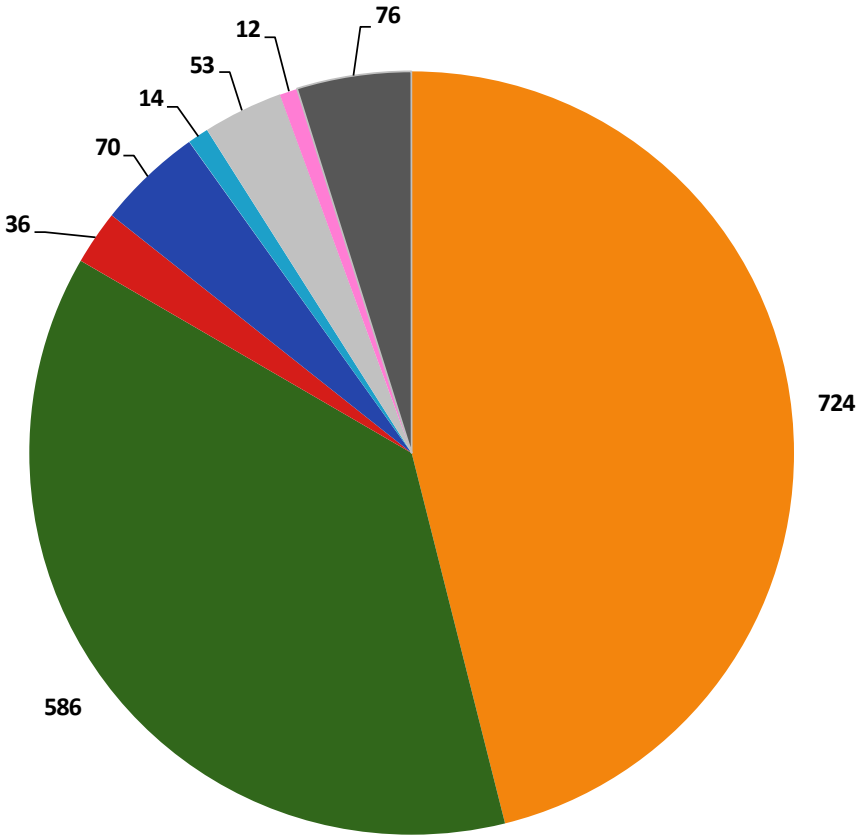
Characteristics of ALL submitted reports	N	%
Type of testing performed*		
1) Molecular test*	397	25
2) Phenotypic test*	751	48
3) Susceptibility test ONLY	449	29
Unknown	29	2
Mechanism of resistance (applies only to reports with molecular test)		
KPC	363	91
NDM	11	3
Other/Unknown	23	6

*≥1 response accepted per isolate

Data and adapted slide from IDPH (A. Tang)

All XDRO reports by region



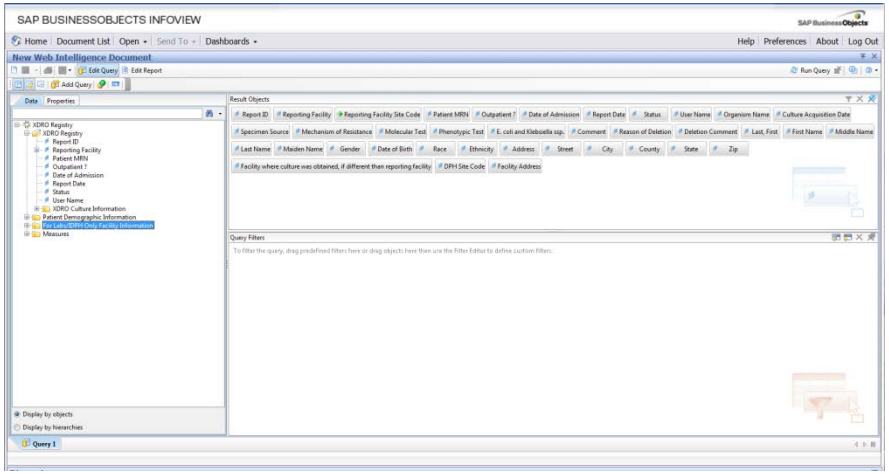


- City of Chicago
- West Chicago
- Rockford
- Peoria
- Champaign
- Edwardsville
- Marion
- Missing/Unknown

Data and adapted slide from IDPH (A. Tang)

XDRO data access for LHDs

- Local health departments can obtain access to XDRO data through I-NEDSS Business Objects
- Must fill out a user agreement form
- E-mail dph.xdroregistry@illinois.gov for the form or questions about XDRO data access



From IDPH (A. Tang)

XDRO registry: Future Directions

1. CRE validation
2. Automated CRE alerts
3. Cluster detection

Laboratory Validation

- First 5 consecutive CRE isolates from each lab should be sent to IDPH (Jan 1, 2015 -)
  - Identification to species
  - Antibiotic susceptibility testing
  - *bla*$_{KPC/NDM}$ PCR
  - Additional phenotypic and genotypic evaluation if necessary

Courtesy of M. Hayden

Validation preliminary results, 134 isolates (1/1/15 – 4/25/15)

- 115 (86%) Carbapenemase-producing *Enterobacteriaceae*
  - 111 (97%) KPC PCR+
  - 2 (2%) NDM PCR+
  - 2 (2%) OXA-48-like
- 10 (8%) carbapenem-resistant *Enterobacteriaceae*
  - 9 *Enterobacter* spp, 1 *E. coli*
- 3 (2%) carbapenem-resistant *Acinetobacter*/*Pseudomonas*
- 6 (5%) carbapenem-susceptible *E. coli*

Courtesy of M. Hayden

Lab validation – moving forward

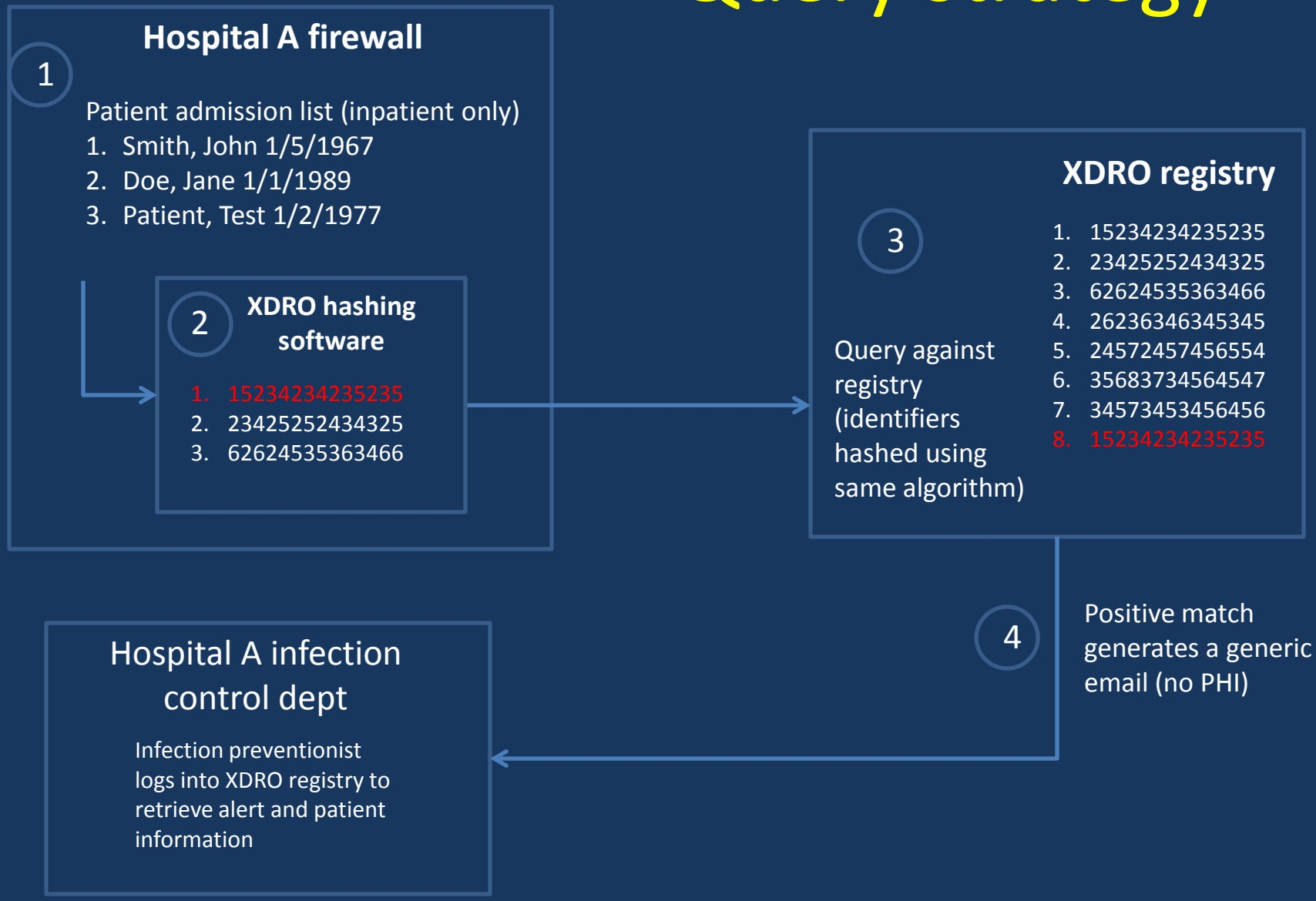
- Current protocol:
  - Labs should continue to send their first 5 consecutive CRE isolates of 2014 to IDPH until they meet their quota

- Proposed protocol for next year (contingent on CDC support)
  - Every lab sends 5 consecutive CRE isolates for 2015
  - For confusing CRE isolates, every lab can send an additional 5 CRE isolates

CRE automated alerts

In a REALM survey, 96% of hospitals indicated interest in receiving automated CRE alerts from the XDRO registry

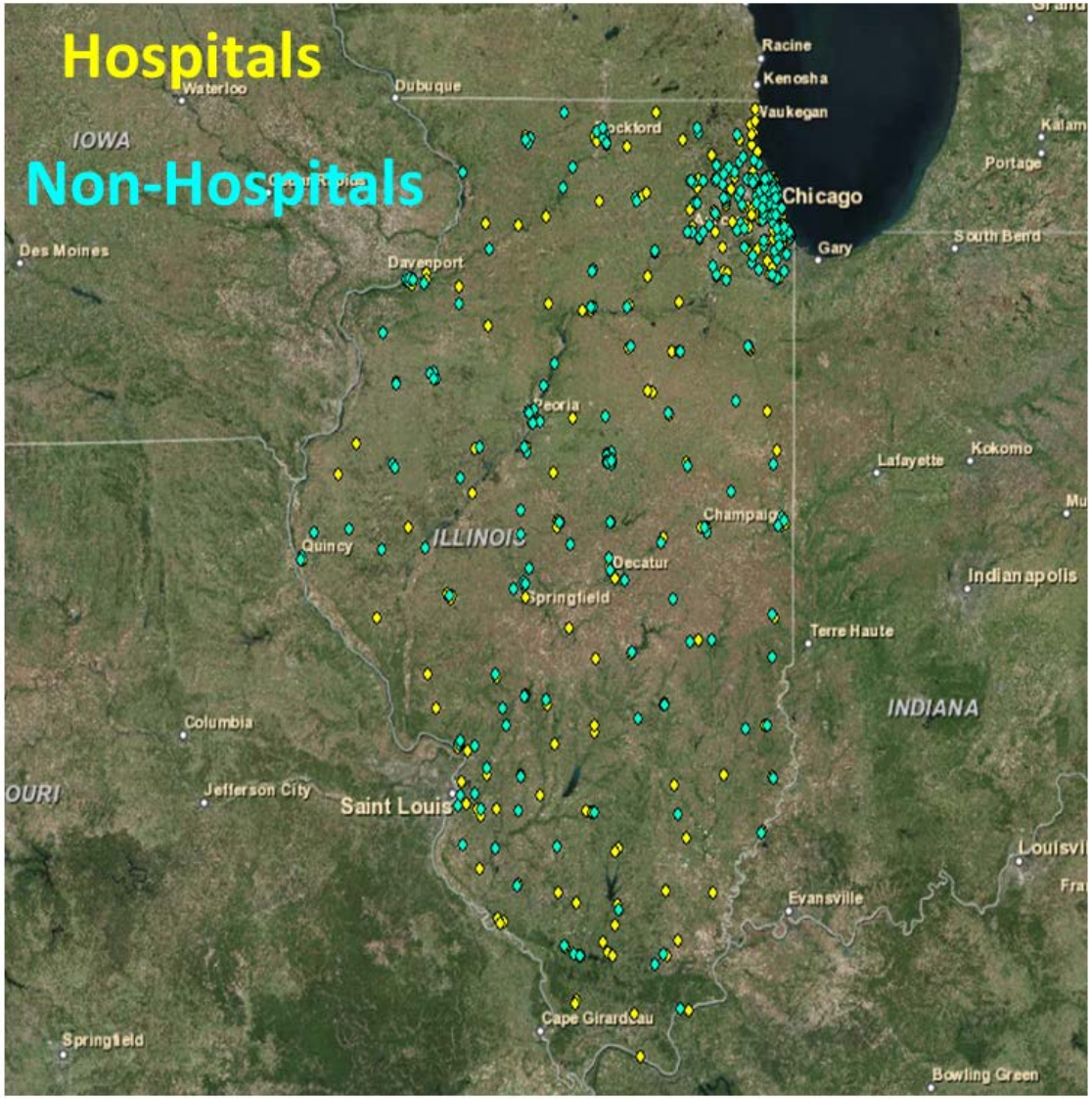
Query strategy



Piloting automated CRE alerts

- Pilot 1 (convenience sample)
  - 1 hospital (Stroger) active since Jan 2015
  - 2 hospitals (RUMC, ROPH) in next month
- Pilot 2 (MedMined hospitals)
  - Plan for 2 hospitals to trial alerts
  - MedMined represents 60+ Illinois hospitals (~42% of hospital beds in state)

Detection of CRE Clusters in Illinois



Cluster detection

- Only consider clinical cultures
- Run SaTScan software (www.satscan.org)
- Investigate clusters to determine if there are indications of a clonal outbreak
  - Same species/susceptibility pattern?
  - If isolates available, similar by whole genome sequencing?

Summary

- KPC is still most predominant in Illinois, but NDM, OXA-48 are emerging
- CRE prevalence is highest in Chicago region
- Overall CRE rates are stable but transmission is on-going
- We still need to improve CRE detection and inter-facility communication (XDRO registry). Antibiotic stewardship too!

Thank you

Illinois Dept. of Public Health	Chicago Dept. of Public Health
Allison Arwady	Stephanie Black
Craig Conover	Sarah Kemble
Mary Driscoll	
Mary Alice Lavin	UIC School of Public Health
Robynn Leidig	Michael Ray
Erica Runningdeer	
Angela Tang	CDC Prevention Epicenter
	Laura Bardowski
CDC	Mary Hayden
John Jernigan	William Trick
Alex Kallen	Robert Weinstein

Antimicrobial Stewardship at the Front Lines

David Schwartz, MD
Stroger Hospital of Cook County
May 12, 2015

Nothing to disclose

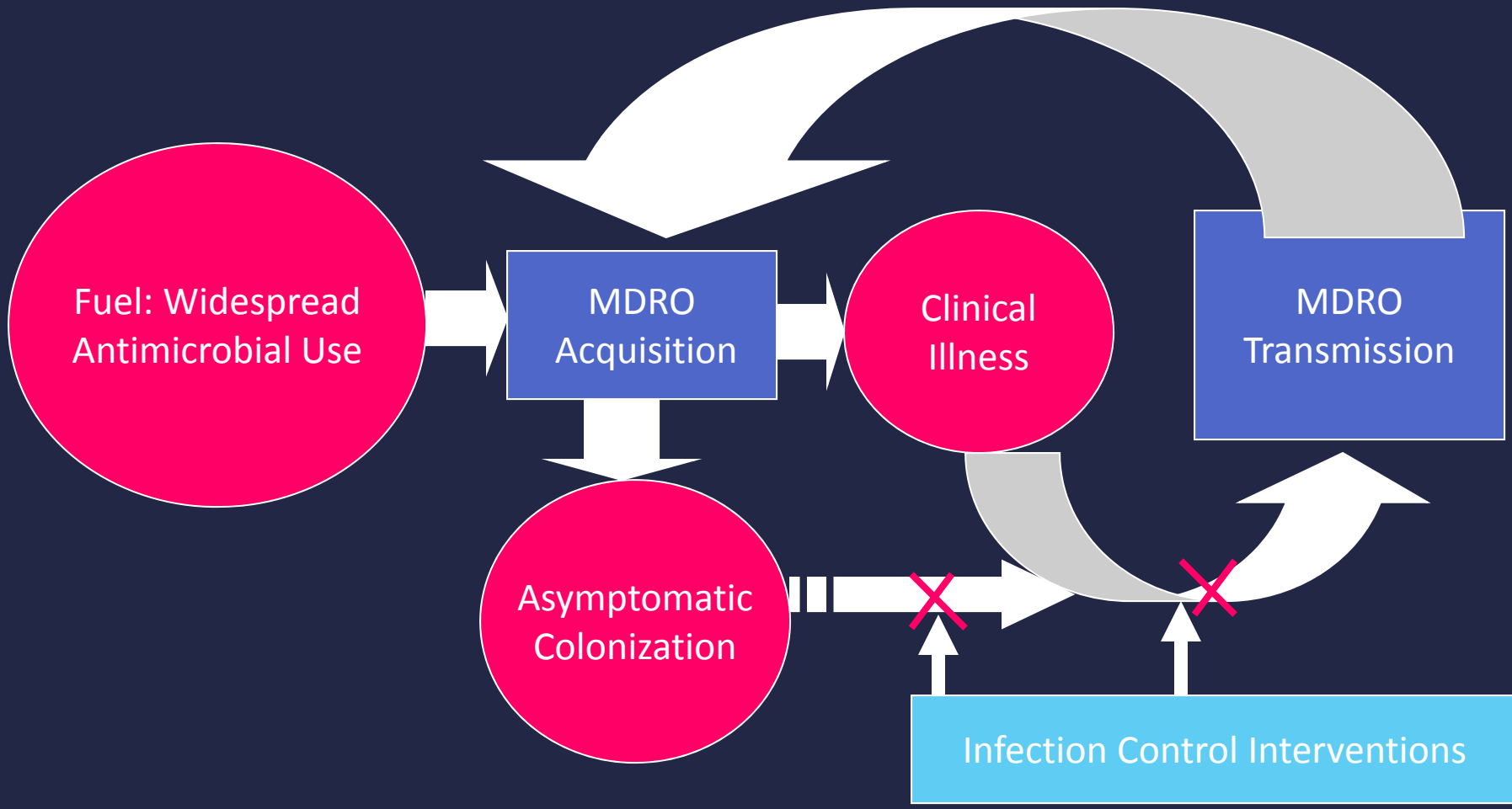
Outline

- Stewardship rationale
- Resources to/from stewardship
- Necessary procedural attributes
- Examples

The Primary Aim of Antimicrobial Stewardship Is…

A. To conserve the fuel driving antimicrobial resistance and other unintended consequences of antimicrobial use
B. To save money
C. To improve patient care and outcomes
D. **All of the above**

Fueling the Fire: MDRO Transmission Dynamics



Ingredients Necessary for Changing Behavior

- Compelling rationale
- Resources
- Procedures that are:
  - Comprehensive and comprehensible
  - Feasible given limits of workflow and competence

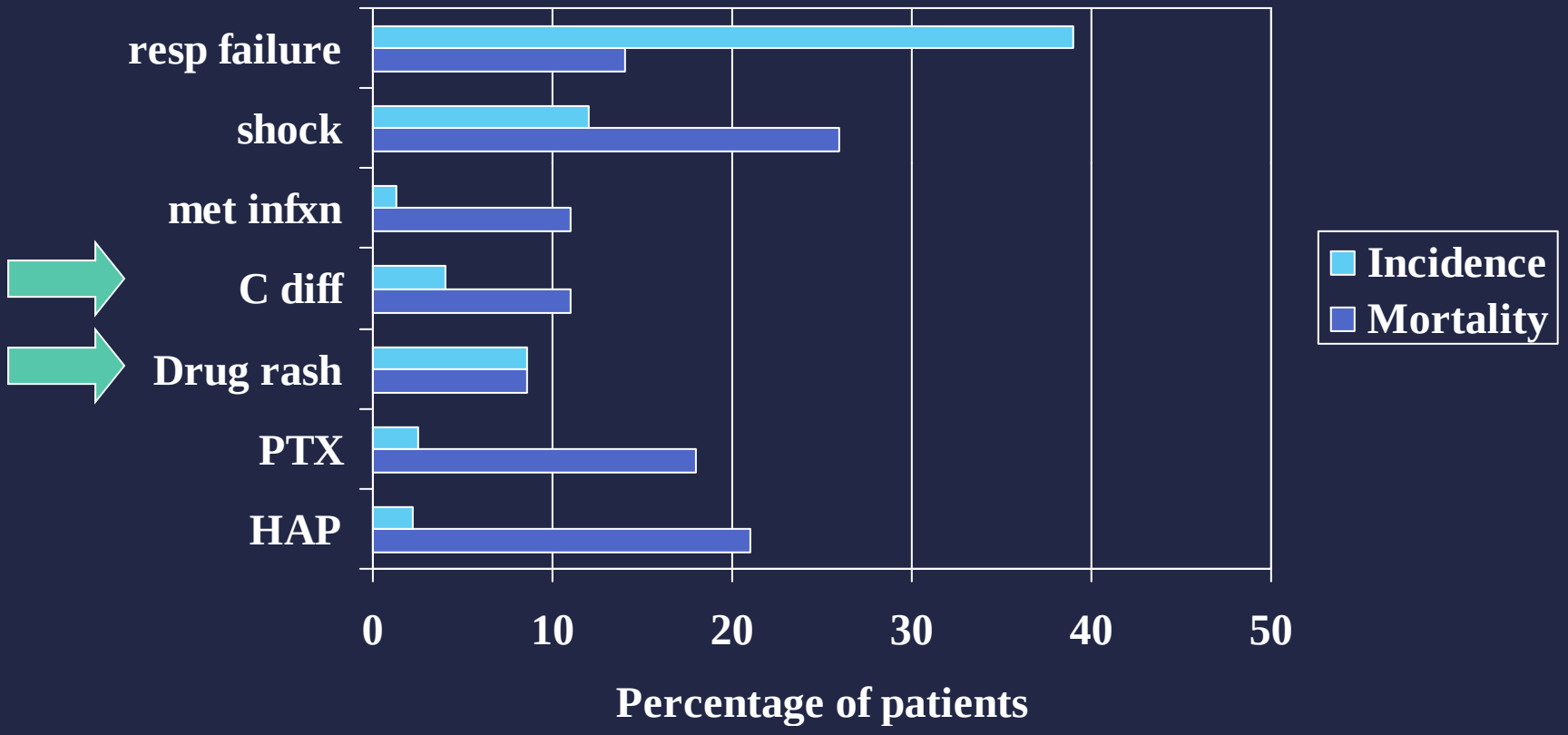
Antimicrobial Stewardship Rationale

- Antimicrobial use is unnatural:
  - Disrupts normal physiologic function
  - Characterizes other "restorative care" modalities:
    - Surgery
    - Cancer treatment
  - (Long-term intensive care: "beyond restorative" begets "beyond resistant"?)
- Antimicrobial exposure – breadth of spectrum, duration – should be limited to the extent possible

Antibiotic-Associated Adverse Drug Reactions

- "Allergic" reactions:
  - IgE-mediated
  - Fever, rash, hepatitis, nephritis, pneumonitis, etc.
- Dyspepsia, diarrhea
- Pill esophagitis
- Seizures, neuropathy
- Stevens-Johnson, TEN
- Bone marrow dyscrasias

Complications Among 1339 Inpatients with CAP



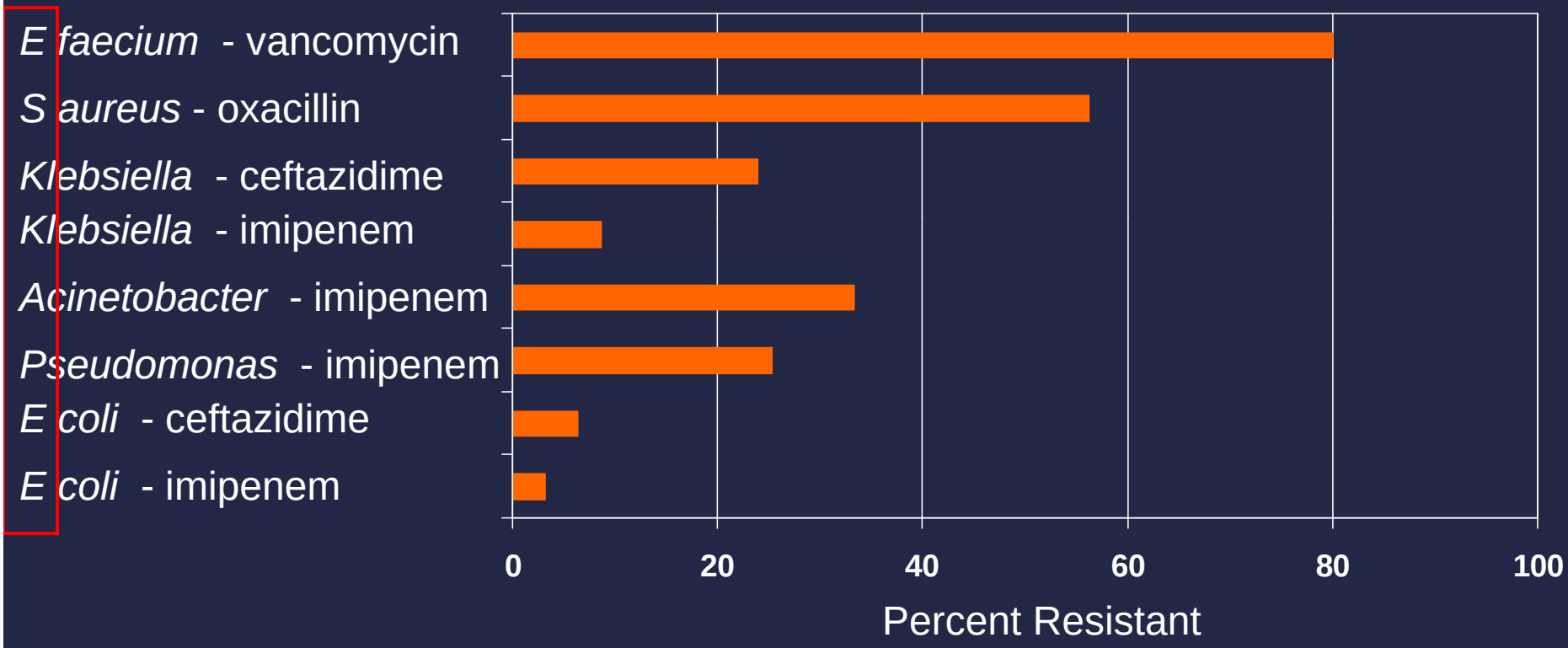
Arch Intern Med 1999;159:970-81

Antibiotic Use Begets Resistance in the Population and the Person

- Adjusted hazard ratios for development of specific resistance pattern after prior use:
  - Fluoroquinolones: 4.0
  - 3rd-generation cephalosporins: 3.5
  - Ampicillin-sulbactam: 2.3
  - Imipenem: 5.7

Harbarth et al. Clin Infect Dis 2001;33:1462-8

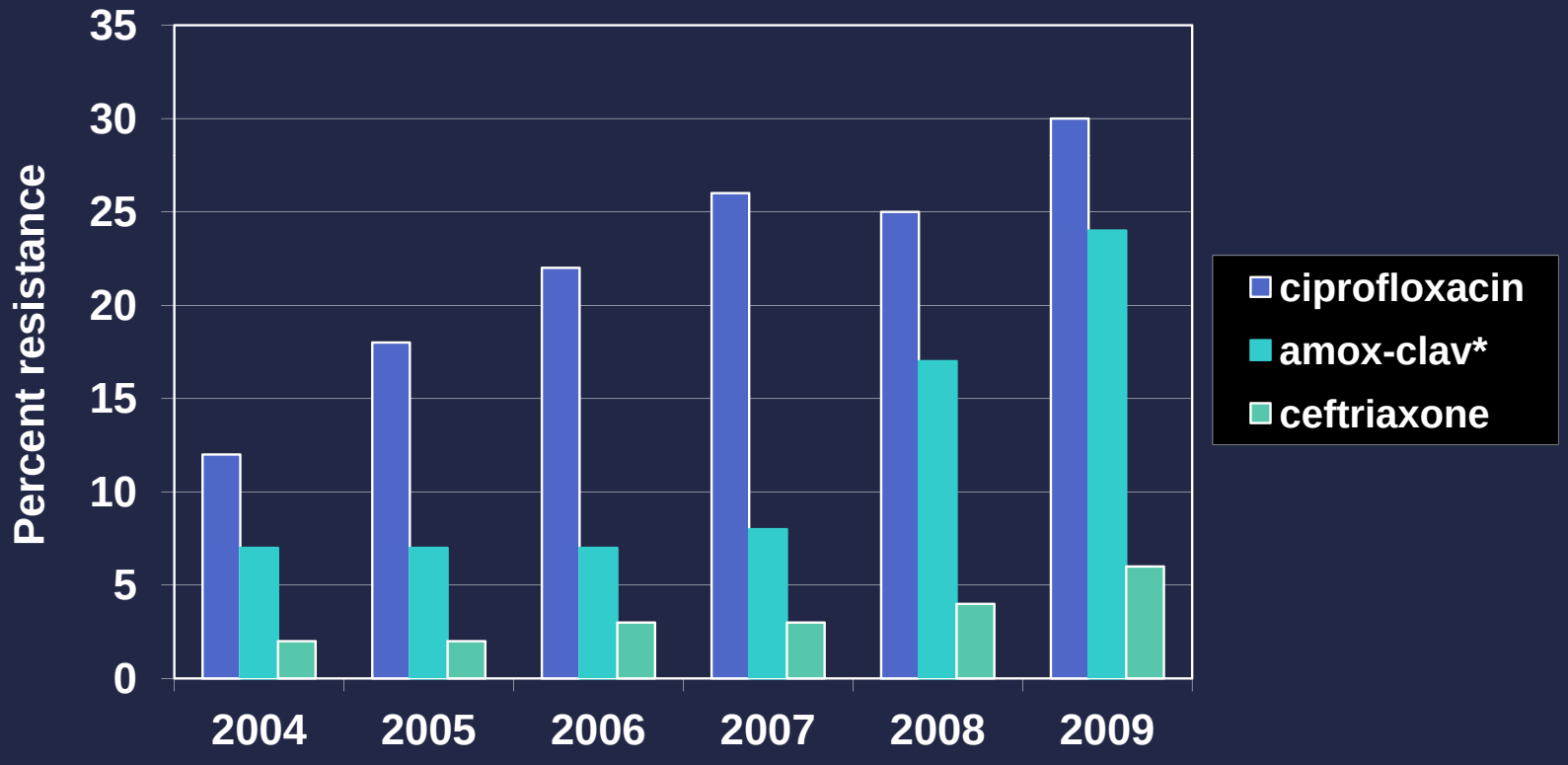
Antimicrobial Resistance Prevalence in Hospital-Acquired Infections*, NHSN-Reporting U.S Hospitals, 2006-7



*Central-line-associated bloodstream infections, catheter-associated urinary tract infections, ventilator-associated pneumonia only

Infect Control Hosp Epidemiol 2008;29:996-1011

Prevalence of Antibiotic Resistance Among Community-Onset Isolates of *E coli*, Stroger Hospital



* Percent intermediate or resistant

Schwartz DN, unpublished data

Resources for/from Antimicrobial Stewardship

- Resources needed:
  - Multidisciplinary staff:
    - MD/RN/PharmD
    - IT/IC/microbiology
  - Authority
    - Provider respect
    - Administrative support
  - Niche within QA infra-structure
  - Capacity for multimodal interventions
  - Process, outcome data
- Expected return:
  - Reduced medication acquisition costs
    - Big-ticket items
    - In aggregate
  - Reduced ancillary costs
    - Lab testing
    - Diapers
  - Better informed, more harmonious staff
  - Improved outcomes(?)

Antimicrobial Stewardship Procedures Must Be…

- Clearly (and repeatedly) communicated
- Easy for providers to access and understand
- Within provider and staff competence
- Minimally intrusive on established workflows
- More informative/persuasive than coercive
- Self-evidently promote improved patient care

Might he be infected? I'll give VANC & ZOSYN!

God, were the Bears awful – AGAIN?!!

I wonder what's on TV tonight?

The 6 Ds: Operational Goals of Antimicrobial Therapy and Stewardship

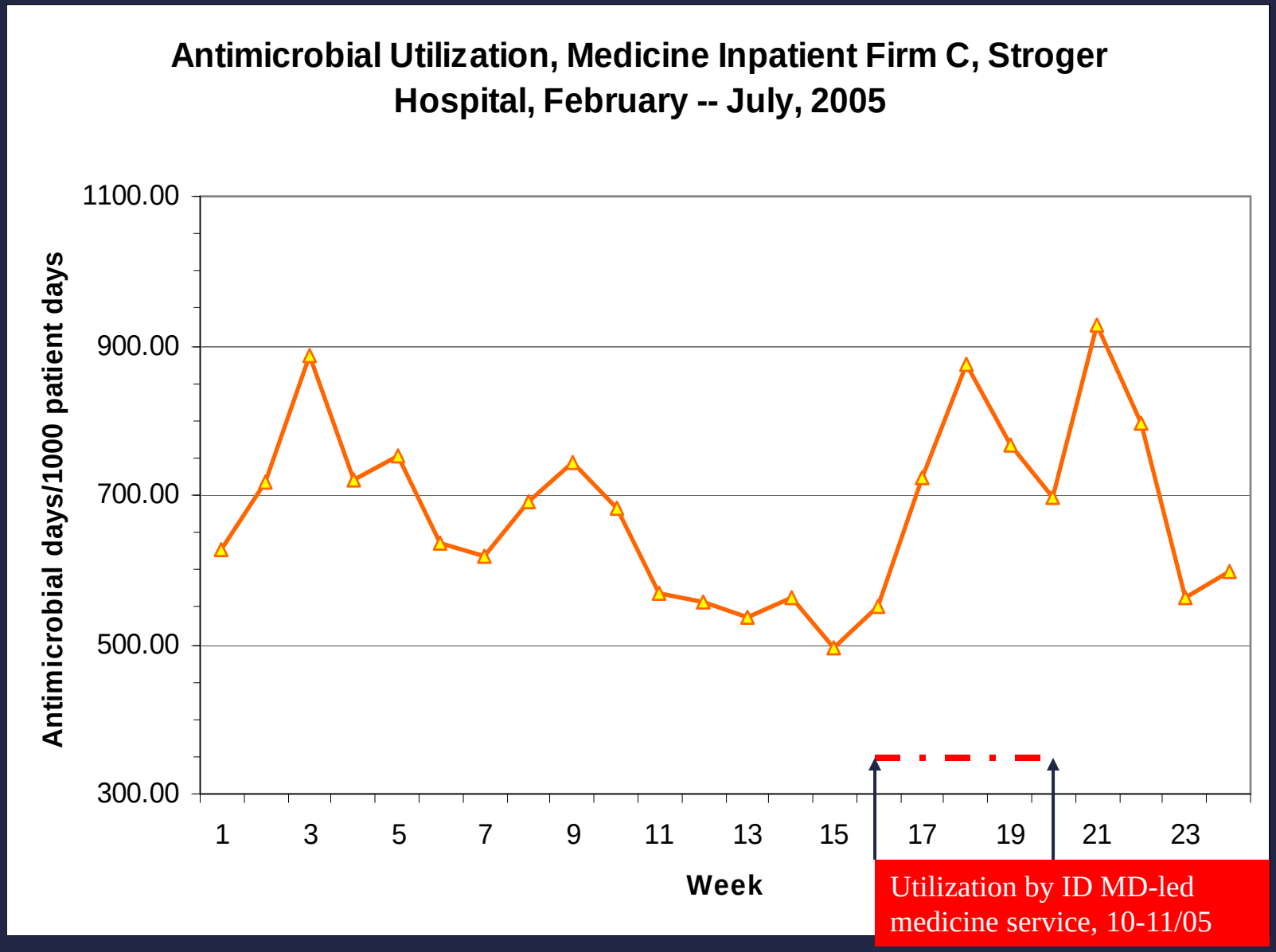
1. Right **D**iagnosis
   - What infection syndrome is being treated?
   - Is it responsive to antibiotics?
   - Have appropriate diagnostic tests been collected?
2. Right **D**rug(s)
   - Demonstrated effective
   - Safest
   - Narrowest spectrum
3. Right **D**ose

The 6 Ds: Operational Goals of Antimicrobial Therapy and Stewardship

4. Right **D**e-escalation: right Drug(s) redefined when:
   - Justified by culture results (positive or negative)
   - Clinical improvement (e.g., IV to PO switch)
5. Right **D**uration:
   - Minimum necessary
   - Defined infections requiring prolonged therapy
6. Right **D**ebridement or source control

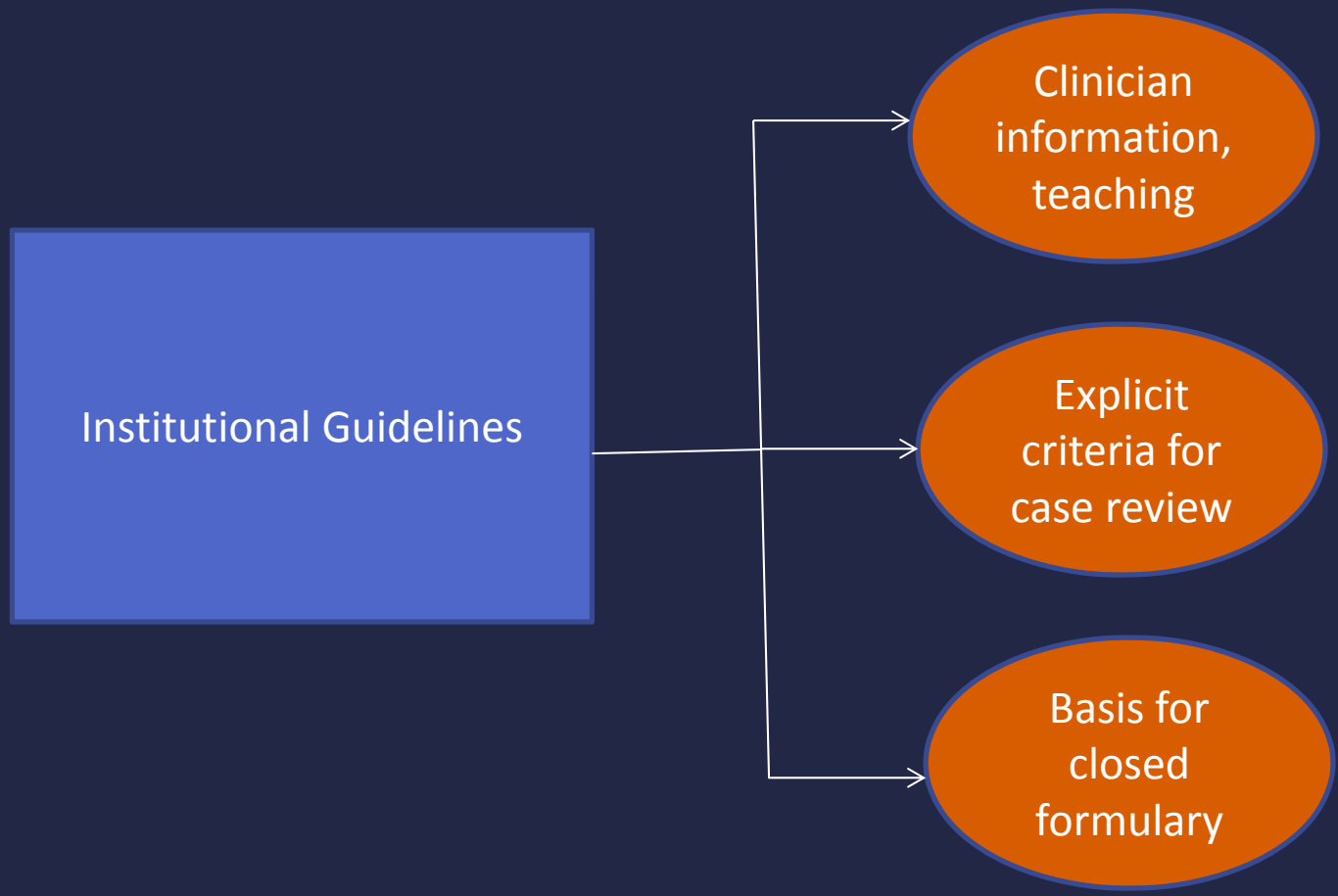
Antimicrobial Use Is Best When Thoughtful and Well Informed

- 40 syndromes, 40 drugs (antibacterials)
- How many bugs and resistance phenotypes?
- Variation by institution, over time
- “When will it get through to you ID guys that we need you to explain how we should treat common infections? Is that so hard to understand?”

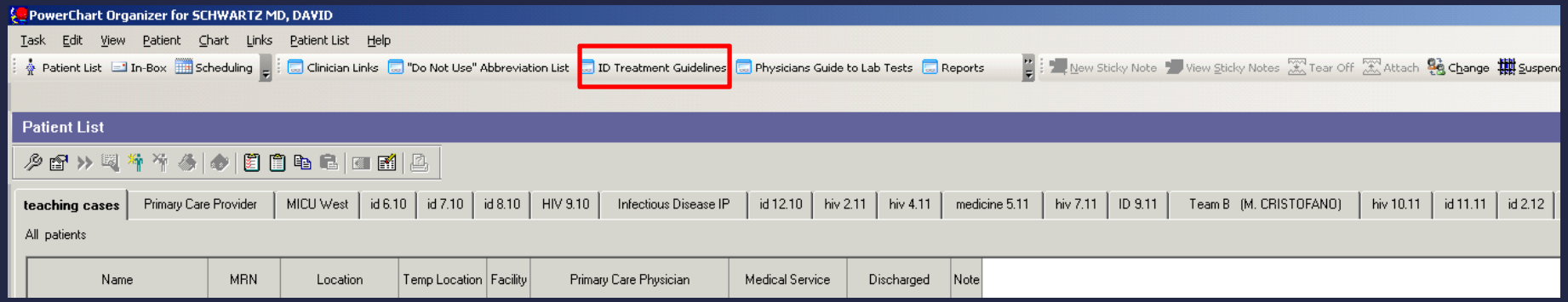


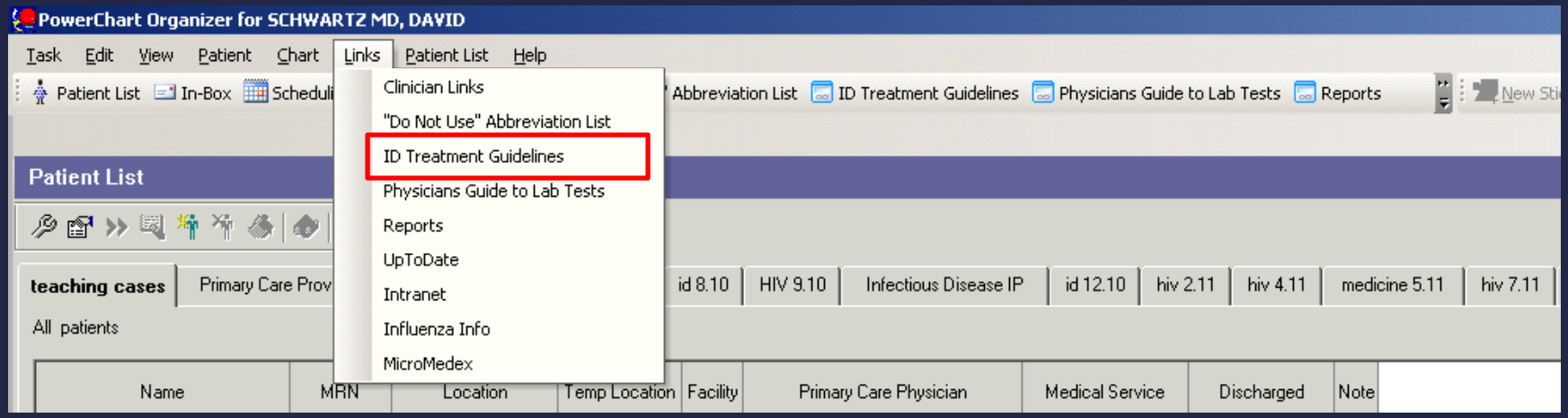
Hota B, et al. SHEA 2006, abstract 317; Schwartz DN, unpublished.

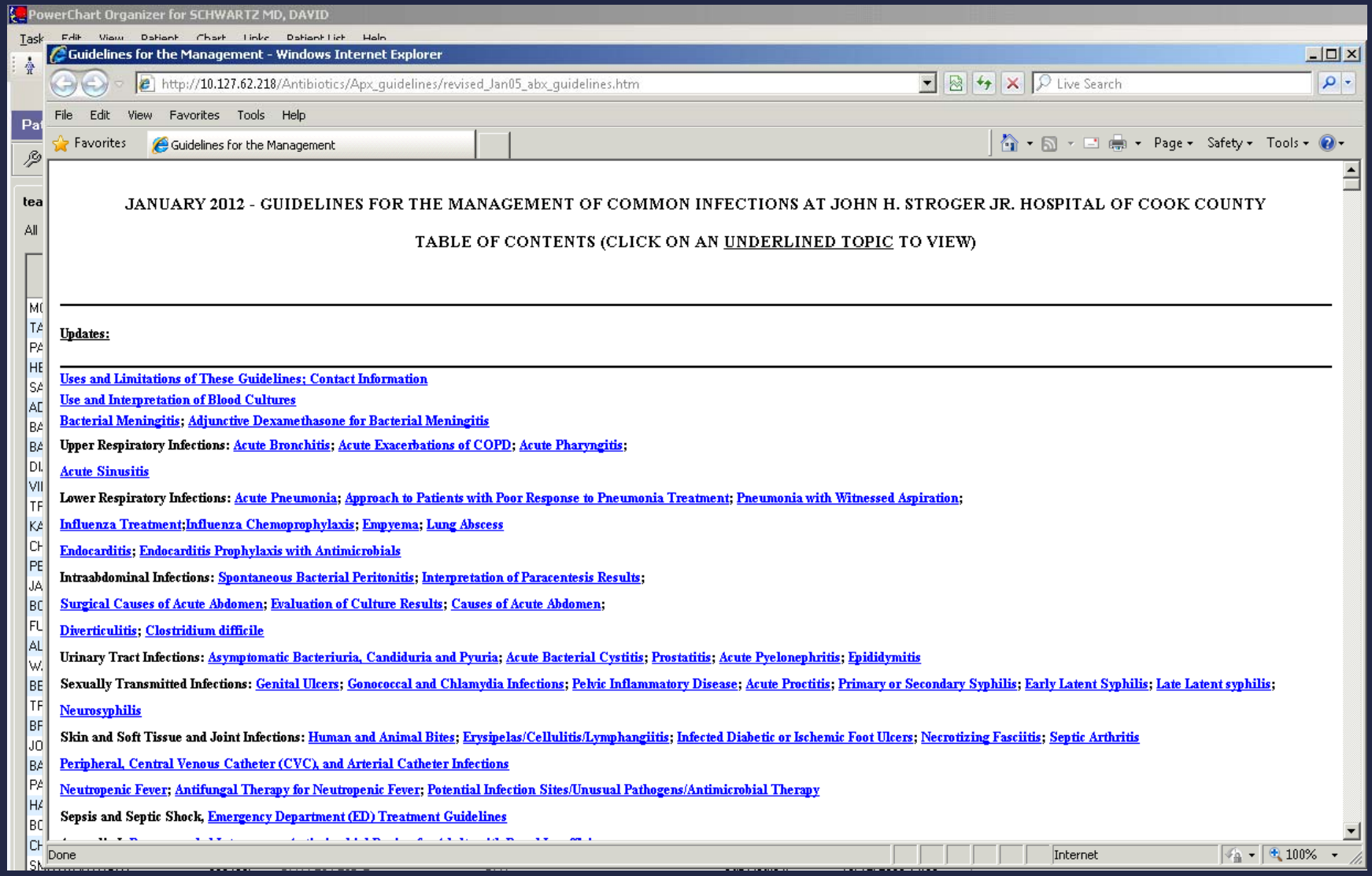
The Heart of the Matter



Stroger Hospital ID Treatment Guidelines



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Favorites
Guidelines for the Management
Page Safety Tools
JANUARY 2012 - GUIDELINES FOR THE MANAGEMENT OF COMMON INFECTIONS AT JOHN H. STROGER JR. HOSPITAL OF COOK COUNTY
TABLE OF CONTENTS (CLICK ON AN UNDERLINED TOPIC TO VIEW)
Updates:
Uses and Limitations of These Guidelines; Contact Information
Use and Interpretation of Blood Cultures
Bacterial Meningitis; Adjunctive Dexamethasone for Bacterial Meningitis
Upper Respiratory Infections: Acute Bronchitis; Acute Exacerbations of COPD; Acute Pharyngitis;
Acute Sinusitis
Lower Respiratory Infections: Acute Pneumonia; Approach to Patients with Poor Response to Pneumonia Treatment; Pneumonia with Witnessed Aspiration;
Influenza Treatment;Influenza Chemoprophylaxis; Empyema; Lung Abscess
Endocarditis; Endocarditis Prophylaxis with Antimicrobials
Intraabdominal Infections: Spontaneous Bacterial Peritonitis; Interpretation of Paracentesis Results;
Surgical Causes of Acute Abdomen; Evaluation of Culture Results; Causes of Acute Abdomen;
Diverticulitis; Clostridium difficile
Urinary Tract Infections: Asymptomatic Bacteriuria, Candiduria and Pyuria; Acute Bacterial Cystitis; Prostatitis; Acute Pyelonephritis; Epididymitis
Sexually Transmitted Infections: Genital Ulcers; Gonococcal and Chlamydia Infections; Pelvic Inflammatory Disease; Acute Proctitis; Primary or Secondary Syphilis; Early Latent Syphilis; Late Latent syphilis;
Neurosyphilis
Skin and Soft Tissue and Joint Infections: Human and Animal Bites; Erysipelas/Cellulitis/Lymphangiitis; Infected Diabetic or Ischemic Foot Ulcers; Necrotizing Fasciitis; Septic Arthritis
Peripheral, Central Venous Catheter (CVC), and Arterial Catheter Infections
Neutropenic Fever; Antifungal Therapy for Neutropenic Fever; Potential Infection Sites/Unusual Pathogens/Antimicrobial Therapy
Sepsis and Septic Shock, Emergency Department (ED) Treatment Guidelines
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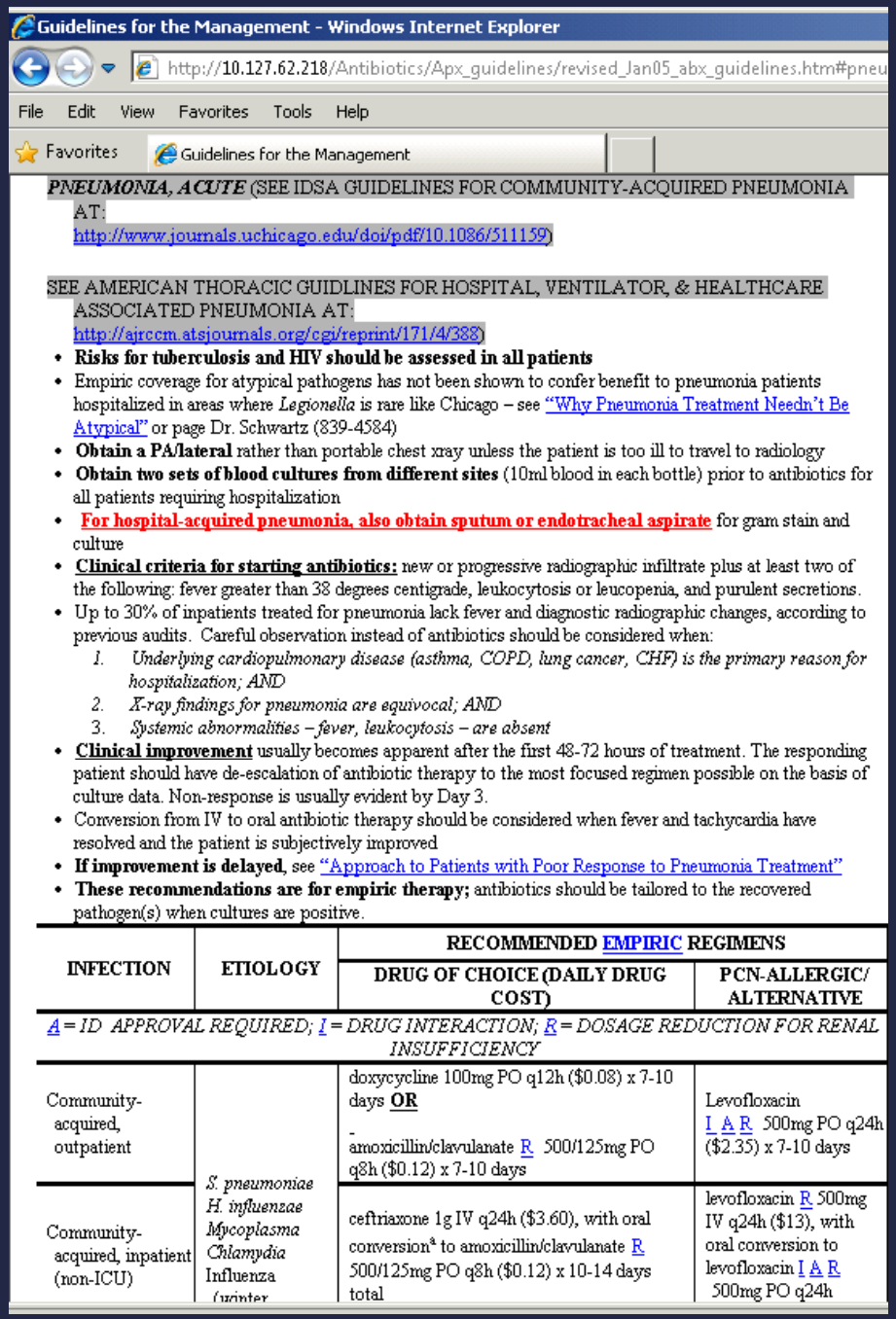

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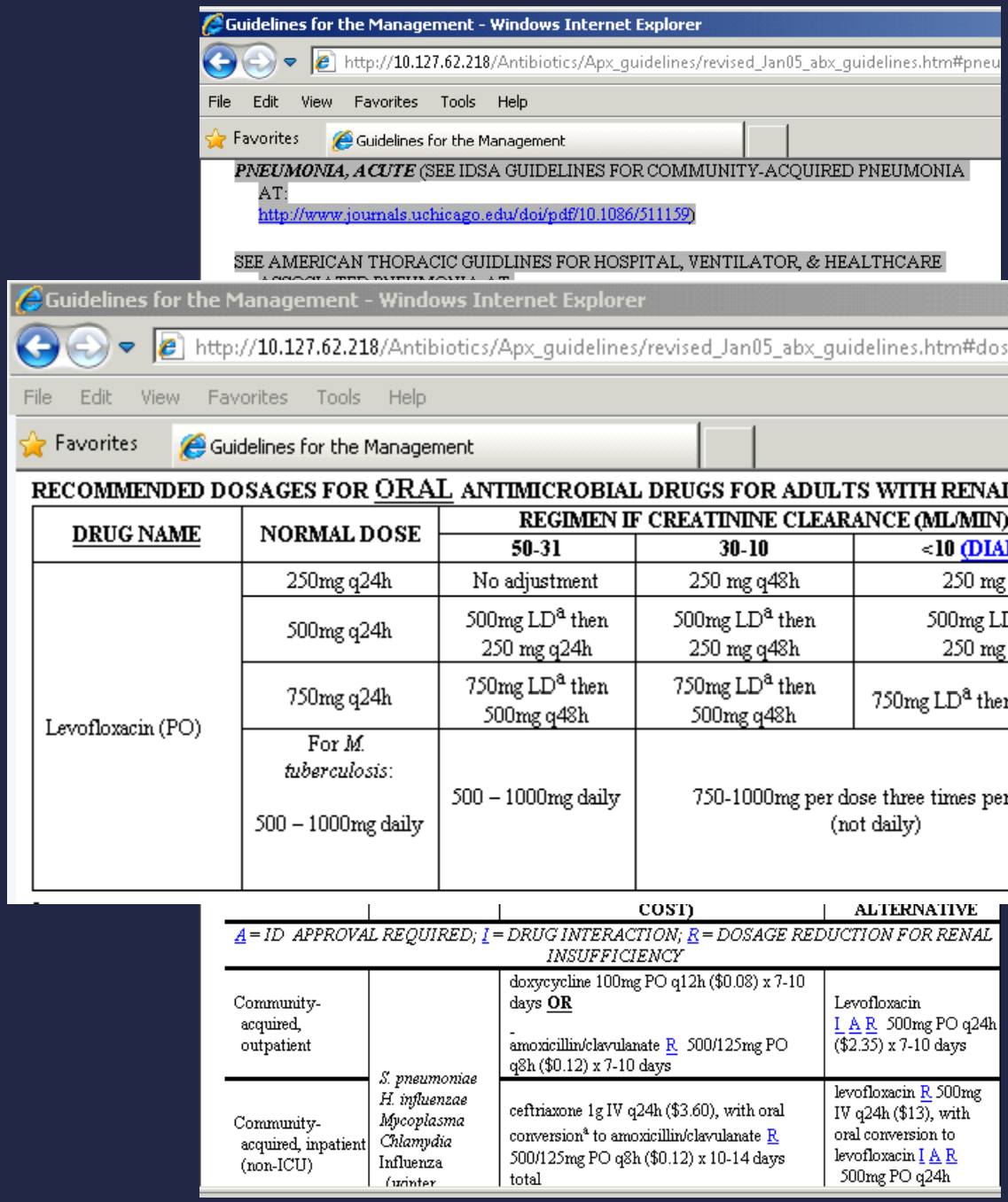
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Guidelines for the Management
RECOMMENDED DOSAGES FOR ORAL ANTIMICROBIAL DRUGS FOR ADULTS WITH RENAL INSUFFICIENCY
DRUG NAME
NORMAL DOSE
REGIMEN IF CREATININE CLEARANCE (ML/MIN)
50-31
30-10
<10 (DIALYSIS)
Levofloxacin (PO)
250mg q24h
No adjustment
250 mg q48h
250 mg q48h
500mg q24h
500mg LD[a] then 250 mg q24h
500mg LD[a] then 250 mg q48h
500mg LD[a] then 250 mg q48h
750mg q24h
750mg LD[a] then 500mg q48h
750mg LD[a] then 500mg q48h
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For M. tuberculosis:
500 – 1000mg daily
500 – 1000mg daily
750-1000mg per dose three times per week (not daily)
COST)
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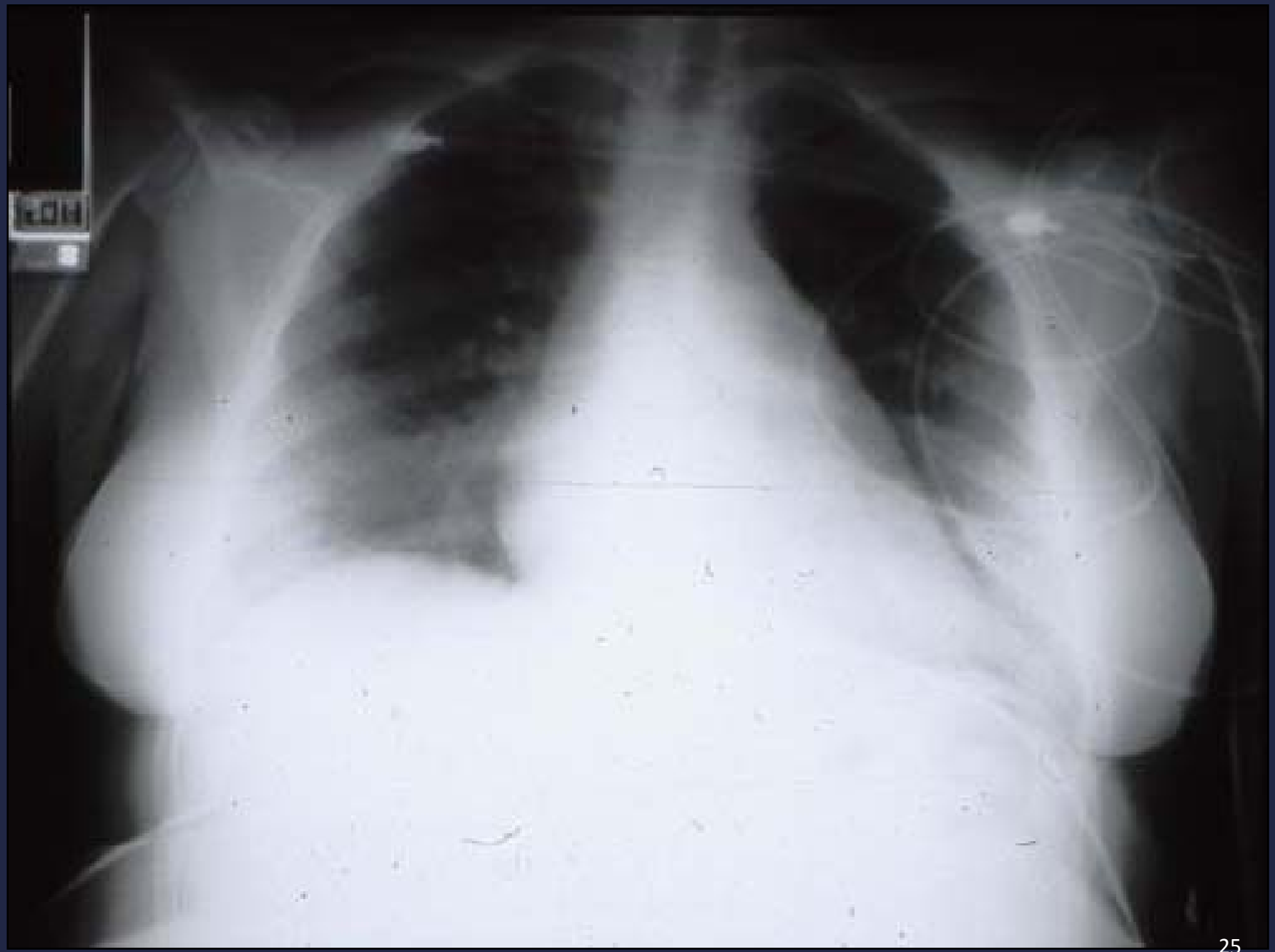
Case Report

- 29-year-old woman presents to the ER with a one-week h/o dyspnea, palpitations and anxiety; dysphagia for six months
- Denies cough, fever, chest pain
- Prior hyperthyroidism; stopped propylthiouricil 4 weeks ago after rash, now on no medications
- In no distress T 100.1 179/69 HR 138 RR 20; large goiter; otherwise normal exam



Case Report – continued

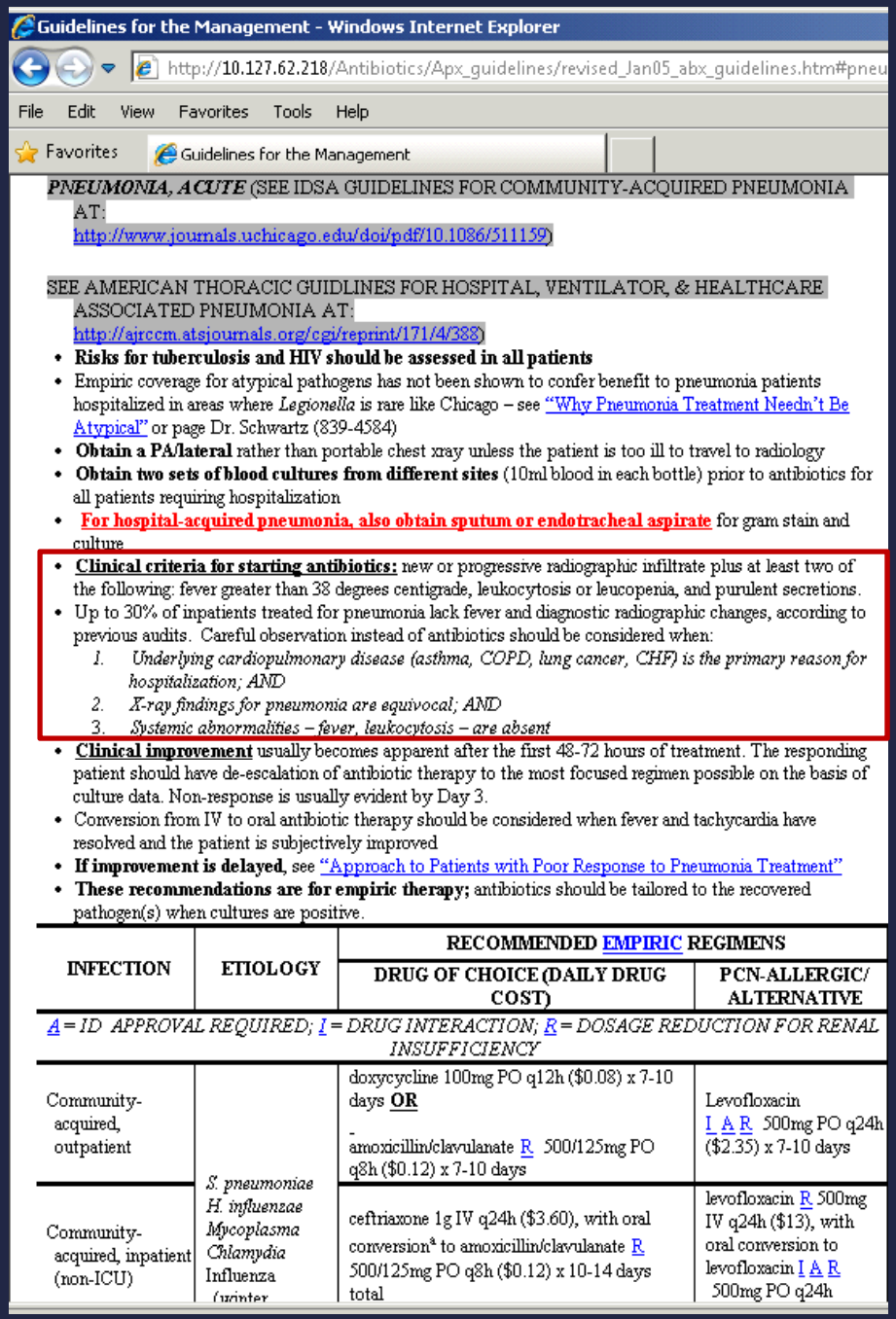
- Levofloxacin begun in the ER, continued by the admitting ward service

Case Report – continued

- Levofloxacin begun in the ER, continued by the admitting ward service
- Antibiotics were discontinued after the clinical and chest radiograph findings (normal breast shadowing) were reviewed
- The patient did well with management of her hyperthyroidism

How Did We Do That?

- Prospective audit and feedback implemented in patient's hospital ward
- Pharmacist reviewed charts of each antimicrobial recipient
- Guidelines served as reference standard
- Prescribing MD contacted when potential improvements were identified
- ID physician called to adjudicate clinical questions ("Does she have pneumonia?")



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Case Report

- 58-year-old man underwent right hemi-colectomy and ileal resection for obstructing cecal carcinoma
- Complex surgery; prolonged recovery
- PICC for post-operative TPN
- 8th post-operative day: fever (102.2° F)
- Single blood culture: *Enterococcus faecalis*

Case Report – continued

- Given 3 doses vancomycin on 9th and 10th post-operative days
- PICC removed
- Fever resolved
- Discharged on no antibiotics

Case Report – continued

- Readmitted 3 months later with fever, confusion
- Found to have aortic valvular endocarditis caused by *Enterococcus faecalis*
- Required mitral and aortic valve replacement
- Prolonged ICU course, then rehab, with IV antibiotics
- Died of recurrent cancer months later

Infectious Diseases Surveillance for Positive Blood Cultures

- Computer program identifies all newly positive blood culture gram stains
- ID fellow on consult service reviews chart:
  - Calls primary provider when opportunities for improvement detected
  - Reviews cases with ID attending

Clinician Training, Cohort Review/Feedback at Oak Forest Hospital

- 600-bed long-term/acute care hospital
- Bulk of care by 20 salaried internists
- Series of 2-hour trainings, guidelines issued
- Some of the lessons conveyed:
  - No abx for asymptomatic bacteriuria
  - Cultures, abx only useful for acutely ill patients
  - Avoid empiric levofloxacin (> 50% resistance)
- Cohorts reviewed, results given to clinicians

Schwartz DN, et al. J Amer Geriatr Soc 2007;55:1236-42

Fever Algorithm

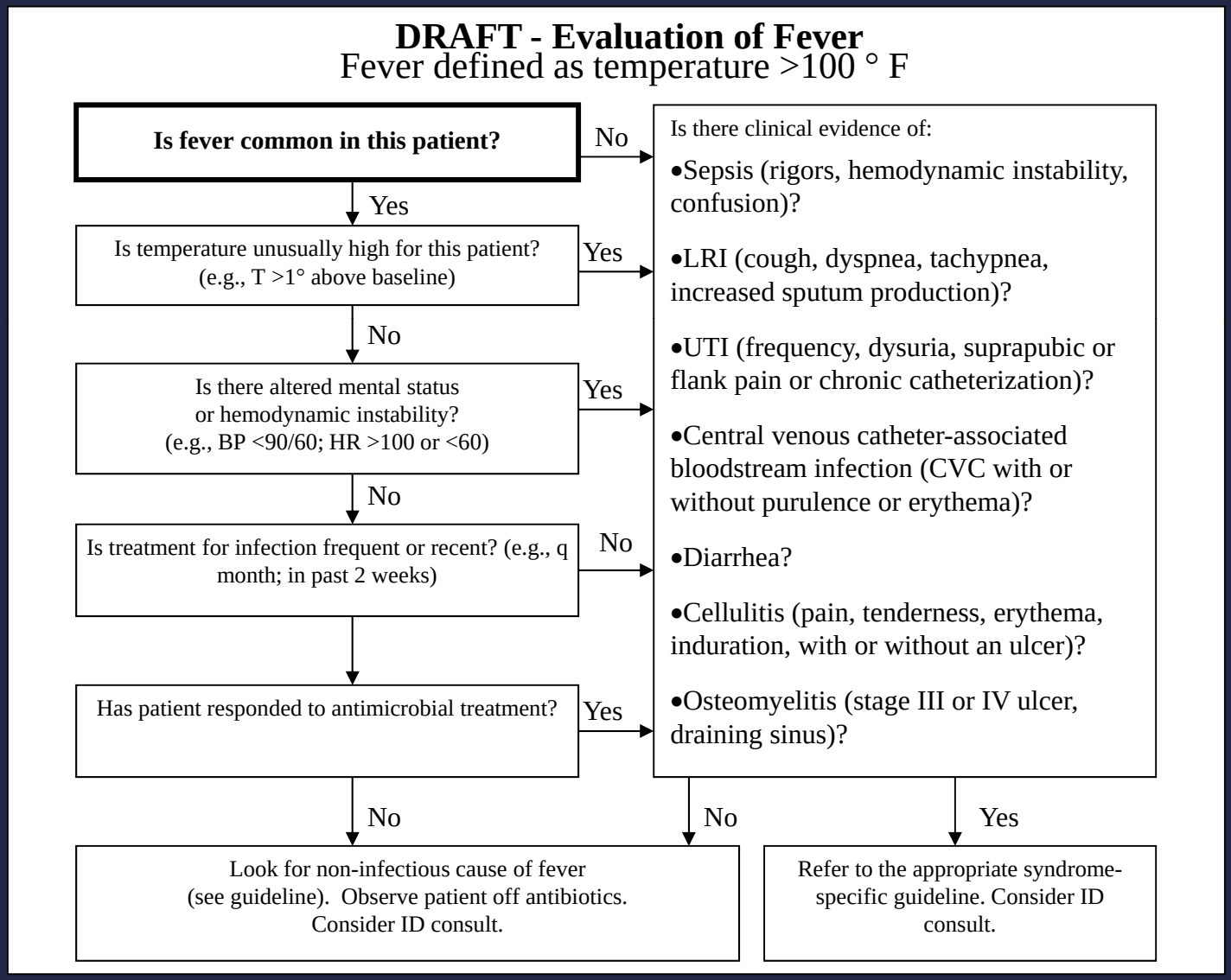
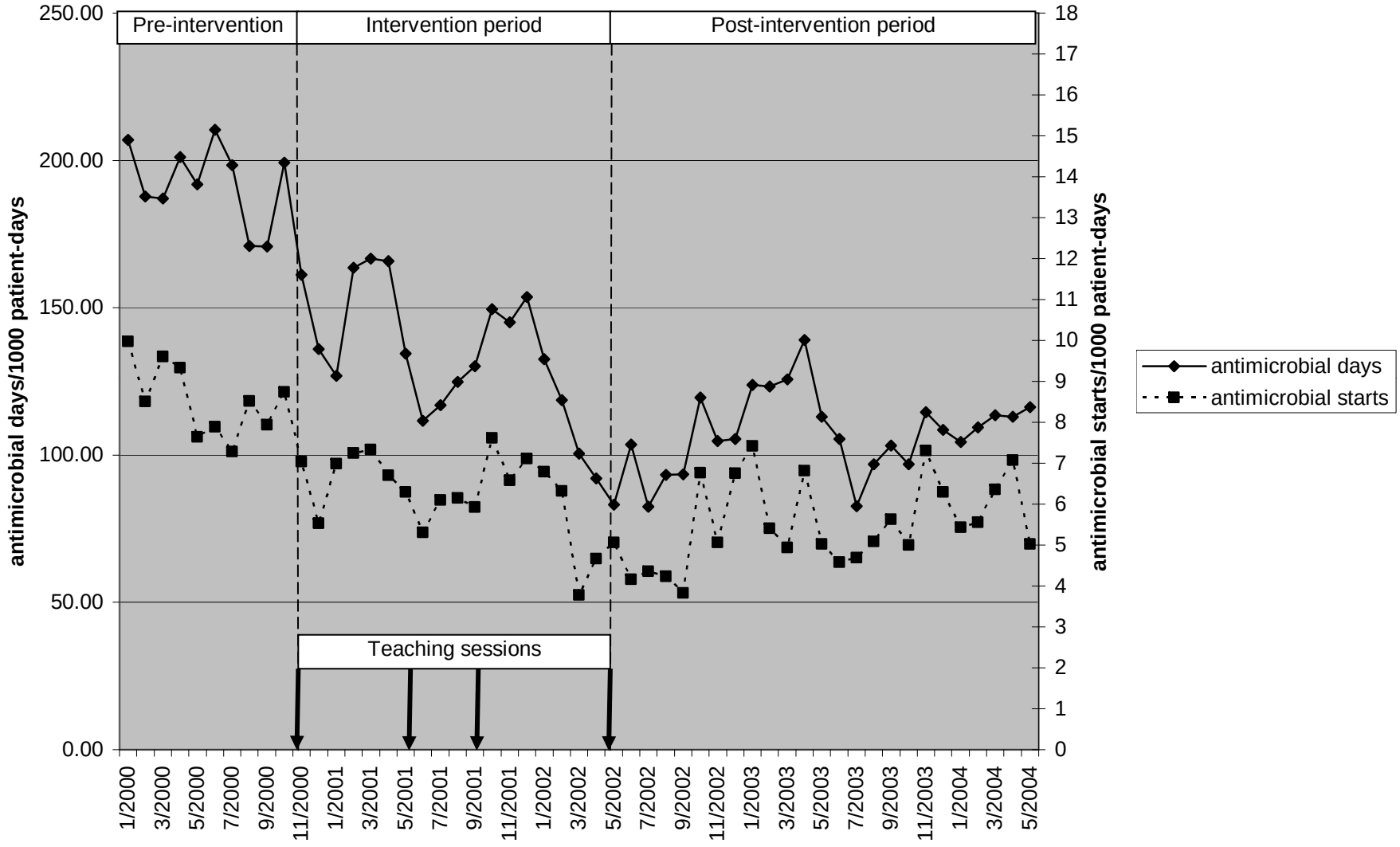


Figure 1a. LTC Antimicrobial Days and Starts per 1000 Patient-Days



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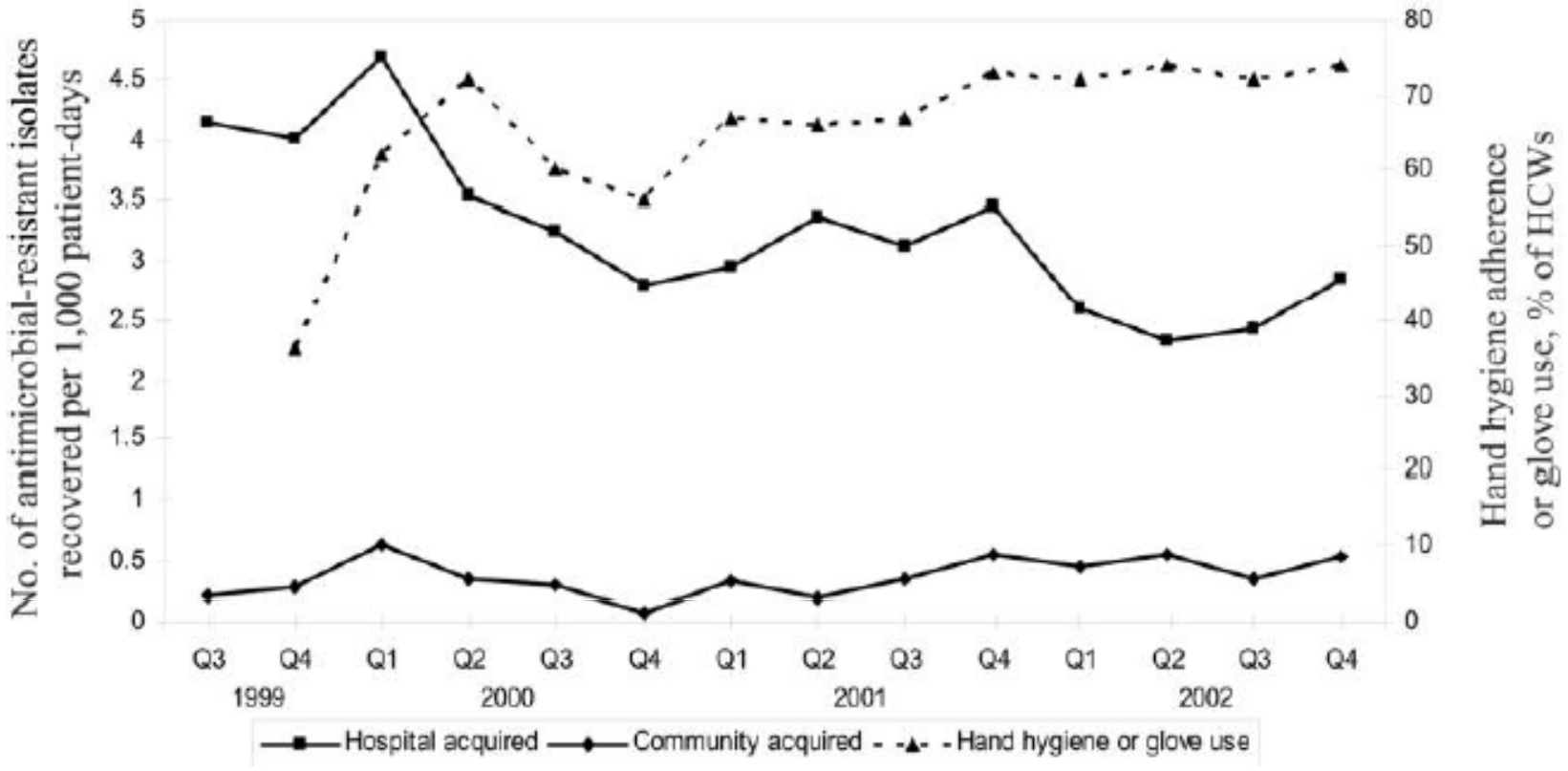

Trick WE, et al. Infect Control Hosp Epidemiol 2007;28:42-49

Additional Stewardship Strategies

- Surveillance and intervention for error-prone regimens:
  - Redundant antimicrobial spectra
  - Regimen-indication mismatch
  - Prolonged use with negative cultures
- Leverage computer support
  - Provider order entry
  - Decision support
- Optimize dosage regimens (e.g., piperacillin-tazobactam)
- Restriction with prior approval – <u>targeted only</u>

We Can Do This

- Stewardship is amenable to centralized resources, oversight, remote (computer-based) applications
- General goals, paradigm apply equally to other areas of medical care:
  - Analyses of surgical volume, procedures and outcomes
  - Procedural checklists
  - Patient-centered medical homes
  - Infection control

Questions?

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Northwestern Medicine®

CRE Surveillance and Prevention in Acute Care Hospitals

Maureen K. Bolon, MD, MS
Northwestern University Feinberg School of Medicine

Northern Illinois Infection Prevention and CRE Workshop

May 12, 2015

Objectives

- Demonstrate examples of ways to prevent CRE transmission
- Explain how to implement CRE surveillance in an acute-care facility
- List the steps involved in an outbreak investigation

*No Disclosures

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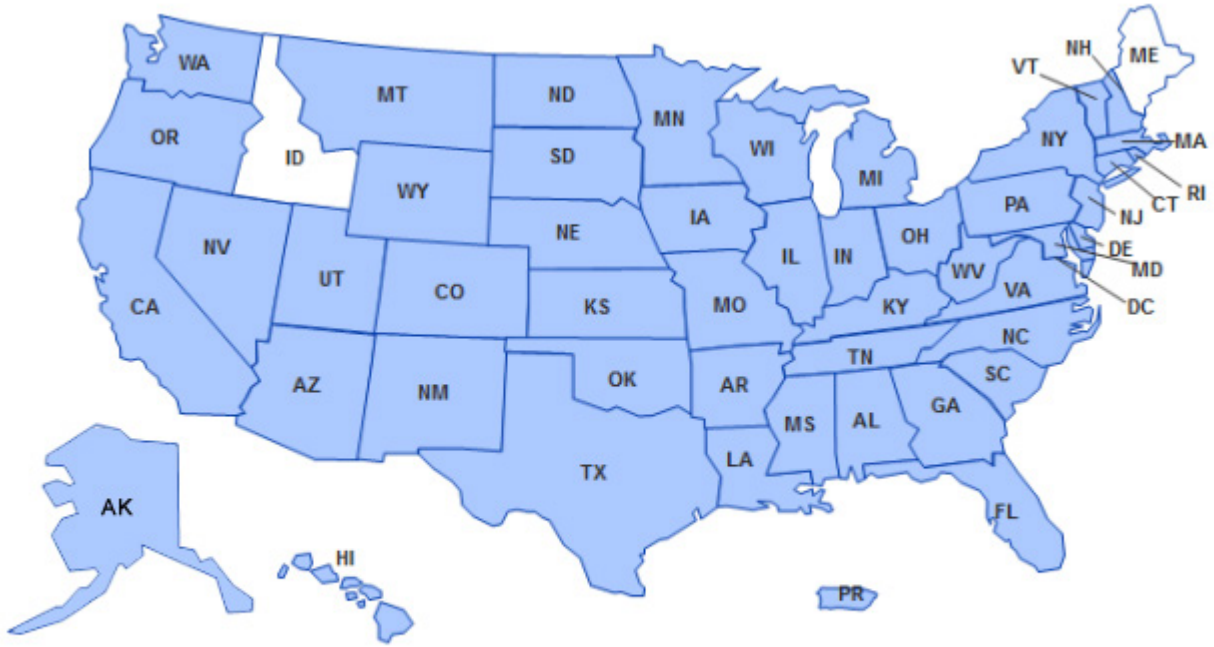
Carbapenemase-producing CRE in the United States, 2015



This map was last updated in February 2015

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CRE Prevention & Surveillance: 2011 IDPH/CDC Recommendations

- **None or Rarely Detected (e.g., 1 case per month or less)**
  - Review preceding 6-12 months of microbiology records to detect previously unrecognized CRE cases.
  - If review identifies previously unrecognized CRE cases, perform point prevalence survey (a single round of perirectal or rectal active surveillance cultures) in high-risk units to identify CRE cases (e.g., units where previously unrecognized cases were identified, ICU, and units with high antimicrobial utility).
  - Conduct perirectal or rectal surveillance testing of patients with epidemiologic links to previously unrecognized CRE cases (e.g., patients in same unit or who were provided care by same healthcare personnel).
- **Periodically Detected (e.g., 2-3 cases per month)**
  - Conduct perirectal or rectal surveillance testing of patients with epidemiologic links to previously unrecognized CRE cases.
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- **Endemic**

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  - Implement preemptive Contact Precautions for all patients admitted from settings/facilities with high prevalence of CRE or with risk factors for CRE until perirectal or rectal surveillance cultures are negative.
  - Conduct serial (e.g., weekly) unit-specific point prevalence culture surveys of CRE to assess efficacy of intensified control interventions.
  - Monitor cleaning performance to ensure consistent environmental cleaning and disinfection of surfaces frequently touched by patients and healthcare personnel (e.g., bedrails, tray table, etc.).

If CRE rates do not decrease, implement additional interventions as needed to reduce and eliminate transmission.

- **All hospitals should implement the following prevention measures regardless of their CRE prevalence:**
  - Place all CRE-colonized or –infected patients on Contact Precautions.
  - Place all CRE-colonized or –infected patients in single-patient rooms when possible.
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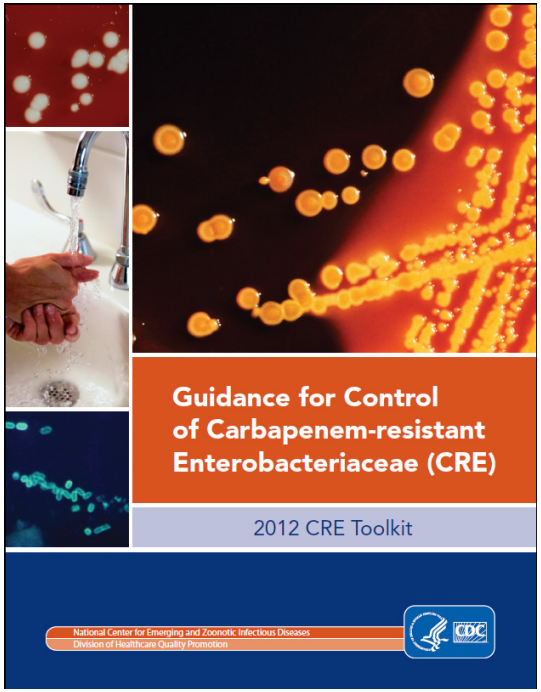


Core Measures for All Acute and Long-term Care Facilities

1. Hand hygiene

- Promote hand hygiene
- Monitor hand hygiene adherence and provide feedback
- Ensure access to hand hygiene stations

2. Contact Precautions

Acute care

- Place CRE colonized or infected patients on Contact Precautions (CP)
    - Preemptive CP might be used for patients transferred from high-risk settings
- Educate healthcare personnel about CP
- Monitor CP adherence and provide feedback
- No recommendation can be made for discontinuation of CP
- Develop lab protocols for notifying clinicians and IP about potential CRE

Long-term care

- Place CRE colonized or infected residents that are high-risk for transmission on CP (as described in text); for patients at lower risk for transmission use Standard Precautions for most situations

3. Patient and staff cohorting

- When available cohort CRE colonized or infected patients and the staff that care for them even if patients are housed in single rooms
- If the number of single patient rooms is limited, reserve these rooms for patients with highest risk for transmission (e.g., incontinence)

4. Minimize use of invasive devices

5. Promote antimicrobial stewardship

6. Screening

- Screen patient with epidemiologic links to unrecognized CRE colonized or infected patients and/or conduct point prevalence surveys of units containing unrecognized CRE patients

Supplemental Measures for Healthcare Facilities with CRE Transmission

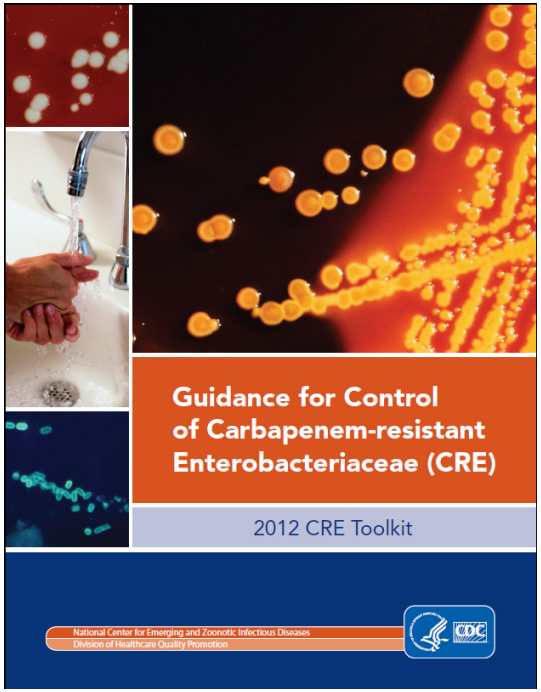
1. Conduct active surveillance testing

- Screen high-risk patients at admission or at admission and periodically during their facility stay for CRE. Preemptive CP can be used while results of admission surveillance testing are pending
- Consider screening patients transferred from facilities known to have CRE at admission

2. Chlorhexidine bathing

- Bathe patients with 2% chlorhexidine

General Approach to CRE Control in Facilities that Rarely or Have Not Identified CRE



New CRE-colonized or CRE-infected patient identified

- Notify appropriate personnel (i.e., clinical staff, infection prevention staff)
- Notify public health if indicated

- Place patient on Contact Precautions in single room (if available)
- Reinforce hand hygiene and use of Contact Precautions on affected ward/unit
- Educate healthcare personnel about preventing CRE transmission

- Screen epidemiologically-linked patient contacts (e.g., roommates) for CRE with at least stool, rectal, or peri-rectal cultures and/or consider point prevalence survey of affected unit
- Consider preemptive Contact Precautions of these patients pending results of screening cultures

- If screening cultures or further clinical cultures identify additional CRE-colonized or -infected patients, consider additional surveillance cultures of contacts or point prevalence surveys of affected units (if not already done)
- Consider cohorting patients and staff

- Ensure if patient transferred within the facility that precautions are continued
- Ensure if patient transferred to another facility CRE information is shared with accepting facility

Today's Talk: How is the Toolkit being Implemented?

- Review of recent publications regarding management of CRE in acute care hospitals
  - Both routine measures and outbreak control measures
- Most of Core Measures from Toolkit utilized
  - Limited discussion of stewardship
  - In depth discussion of screening

Survey: What are we doing for CRE?

- Survey of SHEA Research Network, Nov 2012-Feb 2013
- Infection control practices for MDROs
- 52% had encountered CRE
- Isolation practices for CRE:
  - 93.9% would use contact precautions
  - Duration of contact precautions (43.5% indefinitely; 29% until negative surveillance cx; 12.9% current hospitalization; 6.5% during active illness)
  - 72% would isolate on readmission
  - 21% perform active surveillance in at least one area of the hospital

Drees M et al. ICHE 2014; 35 (4): 362-66.

SHEA survey: CDC Toolkit implementation

- 37% use CHG bathing
- 24% conduct point prevalence surveys
- 39% use epidemiology-based screening
- 22% use active surveillance testing
- 61% had implemented updated CLSI breakpoints for GNB
- 61% performed modified Hodge test

Drees M et al. ICHE 2014; 35 (4): 362-66.

Contact Precautions & CRE

- Evaluation of gown & glove contamination following care of CRE patient
- 14% of HCW-patient interactions resulted in contamination of gloves or gowns
  - No difference between KPC and non-KPC-producers
- Activities most associated with HCW contamination
  - Wound care
  - Manipulating catheter or drain
  - Caring for patient with ETT or tracheostomy
- 3 “super-spreaders” identified who caused contamination of HCW or environment in 50% or more observations
  - All 3 were actively bacteremic and had sacral ulcers

Rock C et al. ICHE 2014; 35 (4): 426-9.

When to Discontinue Contact Precautions?

- Retrospective review of CRE surveillance program
  - Follow-up perirectal cultures obtained on CRE-colonized patients not on antibiotics and no sooner than 8 weeks after positive culture
- Evaluated for recurrence, defined as a positive culture following at least one negative perirectal culture

Results: Predictive Value of Negative Cultures

Previous Sequential Negative Cultures	Next Culture Negative/No. at Risk (%)
0 (first culture)	51 of 95 (54%)
1	24 of 31 (77%)
2	17 of 20 (85%)
≥ 3	6 of 8 (75%)

Lewis JD et al. ICHE epub Mar 2015.

Screening Epidemiologically-Linked Contacts: How productive is it?

- Comparison of two methods of identifying transmission to contacts of CRE-colonized or –infected patients.
- "Ring surveillance" vs. retrospectively identified CRE contacts
- 900 bed, academic institution in Chicago
- 3-4 new CRE patients identified/month

Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.
Image from youtube.com

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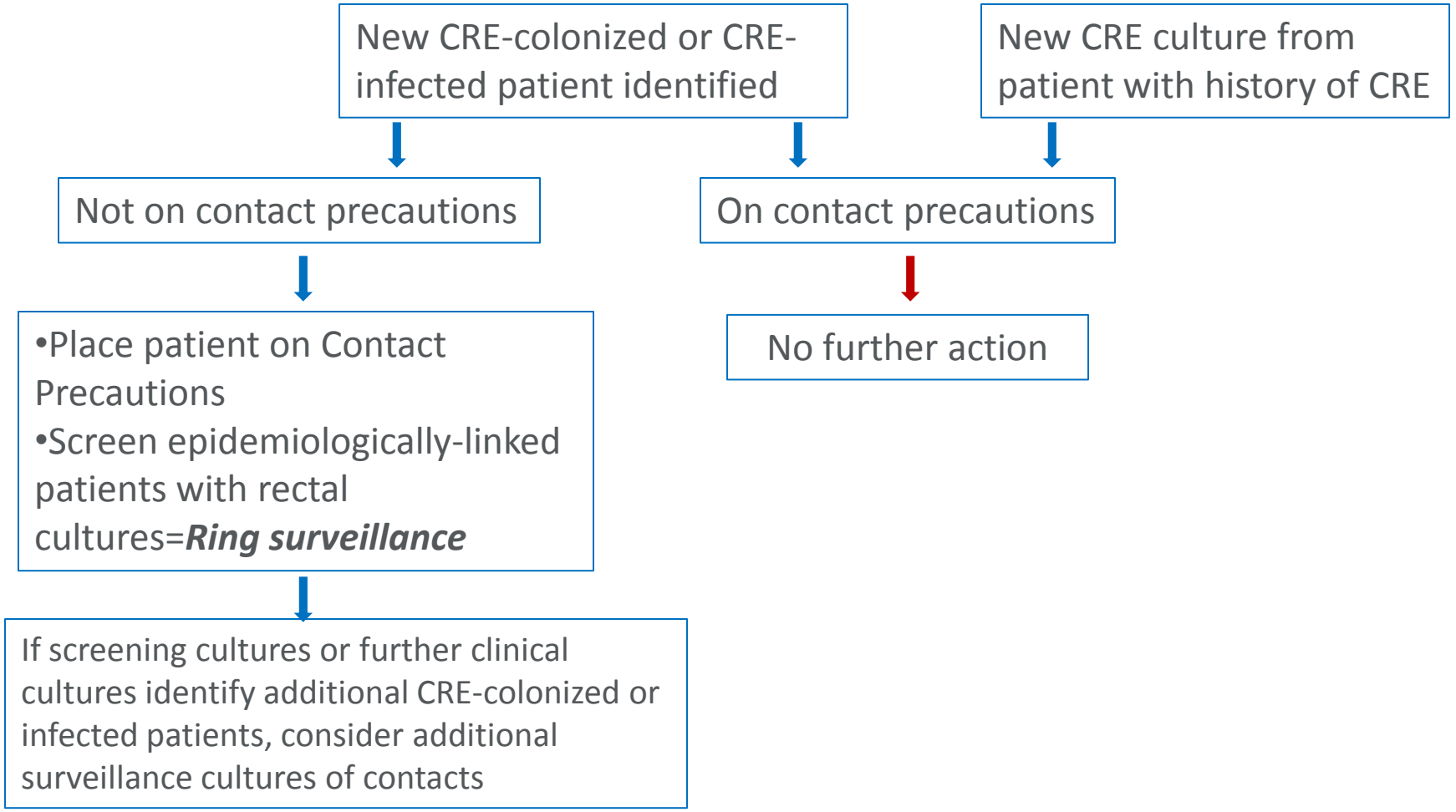
CRE Ring Surveillance Protocol



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Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.

CRE Ring Surveillance Findings

- 14 episodes of ring surveillance
  - September 2011 – January 2013
  - 173 patients had rectal cultures done for ring surveillance
  - Median 12 patients per episode (range 6-22)
  - 5 episodes (36%) in ICUs and 9 on general wards
    - [2 surgical, 3 medical, 4 heme/onc]

Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.

New CRE Identified by Ring Surveillance

- 3 patients identified as CRE-positive on ring surveillance
  - All colonization
  - All were colonized with different species than the source patient
  - One of patients was screened on day of admission and thus was felt to be pre-existing
  - None felt to represent transmission
- Duration between index culture obtained and ring surveillance initiated: median 5 days (range 3-7)

Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.

Looking for Transmission Under the Radar: Retrospectively-identified CRE Contacts

- Source = Any CRE-positive patient who spent at least 24 hours on a ward with the case patient prior to the case-patient's acquisition of CRE
- Possible transmission if case patient and source share a CRE with 0 to 3 band PFGE difference
- 7 potential transmissions identified involving 6 CRE-positive source patients

Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.

Summary of Possible CRE Transmissions

Culture Type of Source Patient	Shared Days	Source Patient in Isolation?	Case Patient in Isolation?
Blood	3	Yes	Yes
Wound	2	Yes	Yes
Respiratory	3	No	No
Urine	3	Yes	No
Respiratory	3	Yes	No
Urine	9	Yes	No
Respiratory	3	Yes	No

Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.

Ring Surveillance Conclusions

- Ring surveillance failed to identify transmissions
- Epidemiologic review and PFGE typing of retrospectively-identified source-case pairs did identify 7 transmissions in 17 month study period
- Flaws of ring surveillance
  - Ring surveillance done at single point in time, therefore limited in capturing transmissions
  - Time lag between obtaining CRE cultures and implementing RS allows patients to be missed d/t discharge, moving between wards
  - Decision to only perform ring surveillance for source patients not in contact isolation may have led to missed opportunities
- Regular point prevalence in high risk areas may be more fruitful

Fitzpatrick M et al. ICHE 2014; 35 (4): 419-22.

Risk-Based Screening for CRE: LTACH Patients

- Screened patients with a history of LTACH facility stay in the past year upon admission to hospital
- And screened patients upon admission to LTACH following discharge from hospital
- 48 new carriers identified in 2.5 years of study
  - 42% on admission to acute care and 58% on admission to LTAC
- Predictors of CRE colonization
  - High comorbidity score
  - Immunosuppression
  - Indwelling devices

Bhargava et al. ICHE 2014; 35 (4): 398-405.

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Risk-Based Screening for CRE: International Travel

- Questionnaire to guide CRE admission screening
- Administered by admitting clerk or nurse
- Infection Prevention reviewed questionnaires and ordered screening cultures for all patients with Out of Country Medical Care
- 48% of admissions completed questionnaires
- 3.1% had Out of Country Medical Care
  - 59% outpatient care; 18% inpatient care; 16% both
- 34% traveled to US; 23% to Asia; 15% to Europe; 11% to Central/South America
- 49% of those with Out of Country Medical Care were screened, **no positive results**

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Rajapakse et al. ICHE 2014; 35 (4): 450-1.

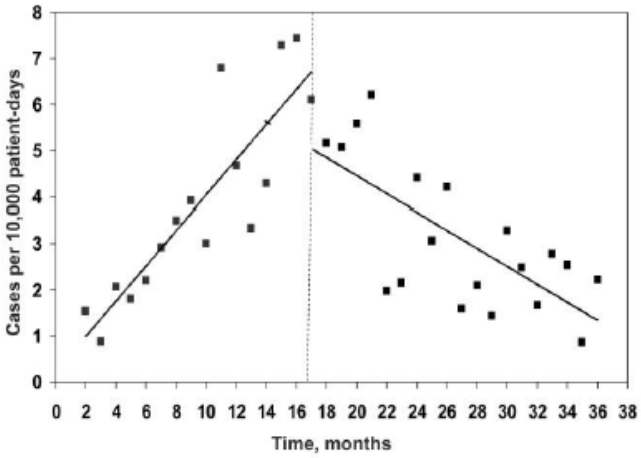
Effectiveness of Active Surveillance Testing for Uncovering Unidentified Carriers

- In Calfee study, admission & weekly screening introduced in ICUs
  - 2% of patients found to be colonized or infected
  - When screening fully implemented, 53% of patient were first identified by AST
  - Median time from admission to positive AST—18 days
  - 46% of patients positive by AST later had clinical culture
  - 21% of patients positive by AST later became bacteremic
  - AST prompted contact precautions and prevented 1396 days of unprotected patient & staff exposure
- In Swaminathan study, AST is done at admission and weekly in ICUs, med-surg units and acute rehab units
- 68% of CRE carriers would have gone undetected without active surveillance

Calfee et al. ICHE 2008; 29 (10): 966-8.
Swaminathan M et al. ICHE 2013; 34 (8): 809-17.

Active Surveillance Testing to Control a CRE Outbreak

Rates of CRE Infection



- AST culturing as an intervention during an outbreak of CRE
  - ICUs and step-down units
  - Admission & weekly
- 52% of patients identified by AST
  - 26% of these subsequently had clinical cultures
- Colonization detected a median of 9 days sooner
- 38% of days on contact precautions due to AST identification
- Clinical infections decreased 4.7 fold following intervention

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Ben-David et al. ICHE 2010; 31 (6): 620-6.

Chlorhexidine Bathing: Microbiologic and Pharmacologic Outcomes

- CHG bathing performed as part of a bundle of interventions at LTACHs
- Measured CHG concentrations on patient skin pre- and post-bath
- Also cultured skin for KPC
- CHG bathing reduced the proportion of patients colonized with KPC
  - 56% of patients pre-bath→ 32% of patients post-bath (p = 0.01)
- Also led to a 51% reduction in the skin sites colonized (p <0.001)

% KPC positive	Inguinal	Back	Antecubital	Axilla	Neck
Before bath	37	8	10	39	8
After bath	15	5	5	11	15

Lin MY et al. ICHE 2014; 35 (4): 440-2.

CHG bathing, continued

- Median concentration of CHG on skin higher after bathing
  - 312.5 vs. 78 mcg/mL; $p < 0.001$
- Inguinal and axillary sites had the highest concentrations
- Controlling for skin site, a CHG concentration of 128 mcg/mL or greater halved the risk of KPC colonization
- Other findings:
  - Diarrhea increased the risk of KPC colonization in the inguinal region
  - No patients without a tracheostomy had neck colonization

CHG concentration	Inguinal	Back	Antecubital	Axilla	Neck
Median pre-bath	312.5	19.5	58.6	156.3	14.7
Median post-bath	1250.0	234.4	312.5	625.0	78.0
≥ 128 mcg/mL pre-bath	81%	23%	27%	61%	6%
≥ 128 mcg/mL post-bath	97%	66%	77%	84%	47%

Lin MY et al. ICHE 2014; 35 (4): 440-2.

CRE in the Environment—Perhaps not a Major Concern

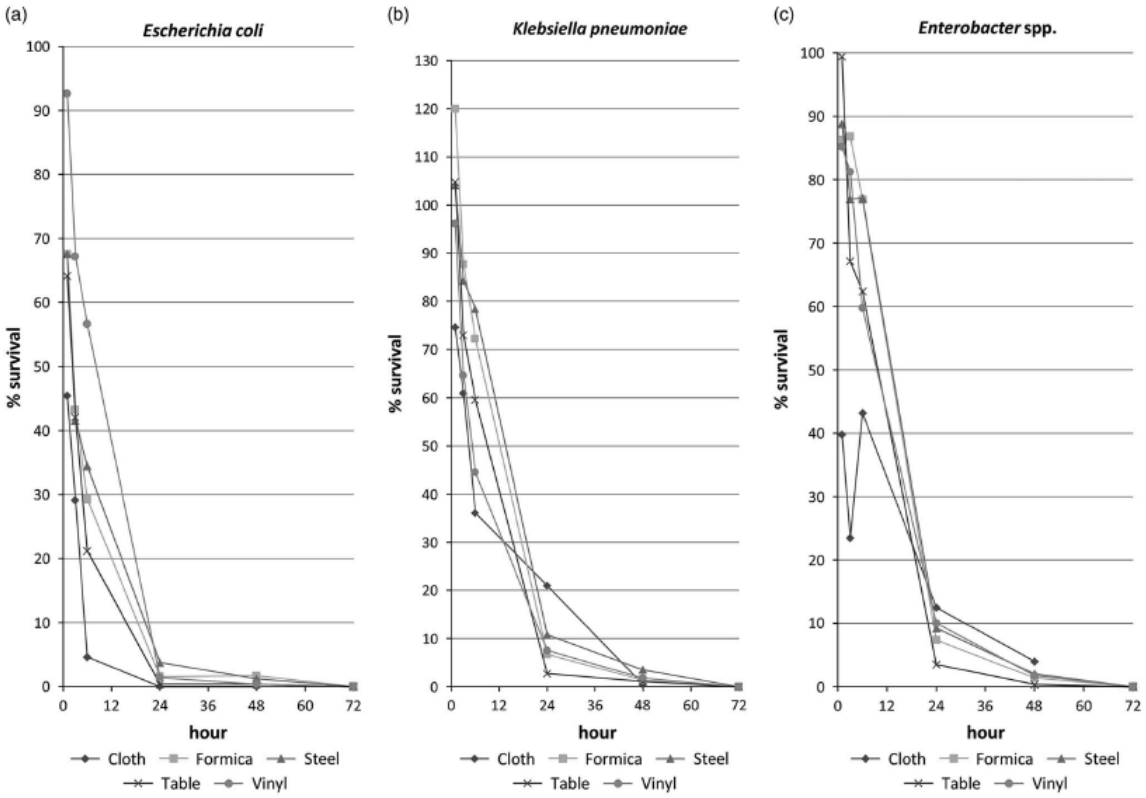
- Aim: describe the frequency & location of CRE contamination of hospital rooms and assess survival of CRE on surfaces

- Sampled surfaces in occupied CRE patient rooms
- 8.4% of surfaces are contaminated in occupied patient rooms
  - Sites more frequently contaminated: bed rail, sink, toilet

- Inoculated test surfaces: overbed table, vinyl, stainless steel, Formica, cloth
- Survival was < 15% at 24 hours; < 5% at 48 hours
  - No cultures positive at 72 hours

Weber DJ et al. ICHE 2015; 36 (5): 590-3.

Survival of CRE on Environmental Surfaces



Weber DJ et al. ICHE 2015; 36 (5): 590-3.

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Focus on Super-spreaders of CRE?

- Quantified environmental contamination from the vicinity of known CRE carriers
- 18% of carriers were responsible for 79% of environmental colonies detected
  - High rectal CRE concentrations
  - Admitted with respiratory disease

Lerner A et al. Clin Microbiol Infect 2014; epub.

NIH Outbreak

- Cluster of CRE infections at NIH
  - 18 patients acquired single strain over 15 month period
  - 7 died
- Interventions
  - Surveillance
    - Admission & twice weekly rectal, throat, inguinal swabs in ICU and neighboring medical wards
    - Monthly point prevalence hospital-wide
    - Rapid identification of organisms
      - Growth on KPC- CHROMager→ MALDI-TOF → PCR for KPC gene
  - Isolation Precautions
    - "Enhanced contact precautions": patients confined to room, visitors gown/glove, disposable dishes/trays, staff cannot touch pagers or phones
  - Geographic & Staff Cohorting

Palmore T et al. CID 2013; 57: 1593-9.

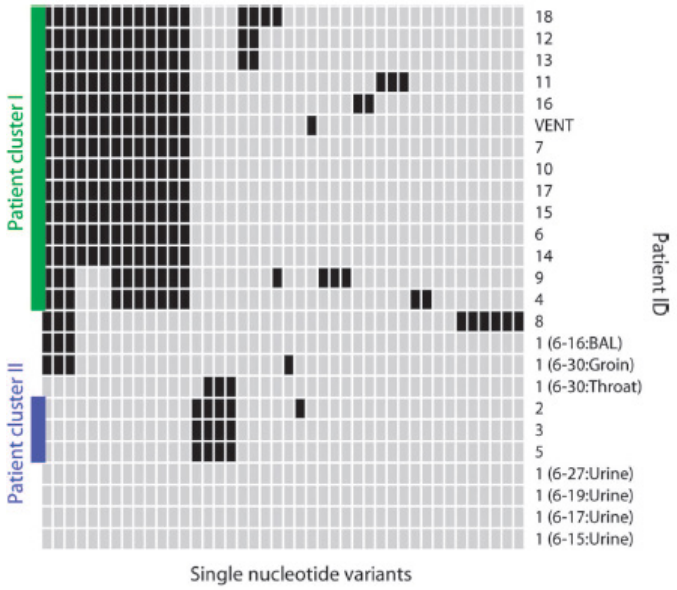
NIH Outbreak

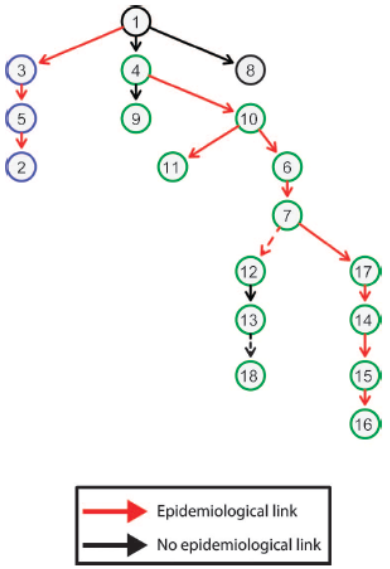
- Hand Hygiene
  - Improved from 80-85% to 100%
  - “Two pumps, 20 seconds”
  - Around the clock monitors, 3 positions: HH, contact precautions, and environmental disinfection
- Daily CHG Bathing
  - Improved adherence from <70% to > 90%
- Environmental Decontamination
  - For routine cleaning—double disinfection of high touch surfaces with bleach wipes
  - At discharge—double cleaning, disinfection with bleach, & decontamination with hydrogen peroxide vapor
  - Removal of sink drains for cleaning

Palmore T et al. CID 2013; 57: 1593-9.

NIH Outbreak

- Extensive communication, engagement of stakeholders, education
- Whole genome sequencing





Palmore T et al. CID 2013; 57: 1593-9.
Snitkin ES et al. Sci Transl Med 2012; 4 (148):

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CRE Surveillance & Prevention Conclusions

- Active surveillance testing is clearly useful
  - Also resource-intensive
  - Will depend upon institutional priorities
- Risk-based screening may allow focused use of resources
  - Will still need personnel and IT commitments
- Concept of super-spreader
  - Should interventions be tailored based on patient characteristics?
- Tried and true interventions still work for outbreak control
  - Primary benefit of new technologies may be speed

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  - Sharon Ward-Fore
- Teresa Zembower, MD, MS
- Margaret Fitzpatrick, MD, MSCI

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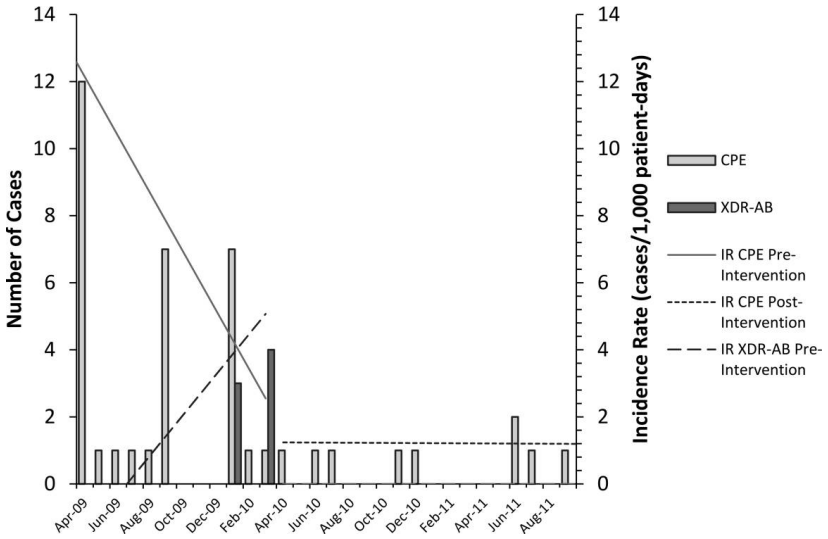
Questions?

Point Prevalence Screening Effective for Outbreak of CRE and XDR-Acinetobacter



- Weekly education and status update meetings
- Cohort patients, nursing and respiratory care staff
- HH monitoring
- Pre-emptive contact precautions
- Weekly point prevalence screening; increased to twice weekly
- Restricted carbapenems
- Daily CHG bathing (wipes)
- ATP testing to assess room cleaning

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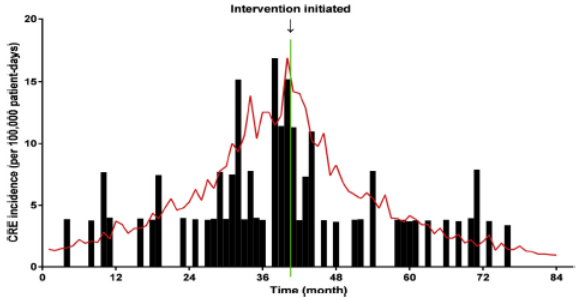
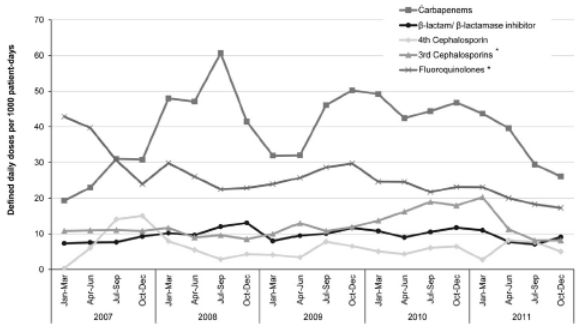
Enfield et al. ICHE 2014; 35 (7): 810-7.

CRE Control without Active Surveillance



ig 1. Monthly CRE incidence rates (per 100,000 patient days) during the study period. CRE, carbapenem-resistant *Enterobacteria*



- CRE incidence rose from 1.6 to 9.8 per 100,000 pt-days
- Returned to baseline following interventions
- Improvement of HH from 35% to 70%
- Enhanced antimicrobial stewardship of carbapenem

Kim N-H et al. AJIC 2014; 42: 1270-3.

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Infection Prevention in Nursing Homes

Dheeraj Mahajan, MD,CMD,CIC

Nothing to disclose.

TOPICS

- Effective infection control and prevention program in PA-LTC
- Barriers and challenges in our setting
- Isolation conundrum , medical care Vs. quality of life
- Safety Culture , Facility acquired and potentially preventable infections
- Anti-microbial Stewardship, our time has come

Burden of Infections

- Range 1-5 infections/1,000 resident days
  - Single day, point prevalence = 3-5%
    - 25% had devices; 10% of them with infection
  - Prospective study (MI):
    - No device: 5.7/1,000 days
    - Device: 9-11/1,000 device-days
- Nationwide estimates: 765K-2.8 million/year
- UTIs, pneumonia, skin and soft tissue, GI infections
  - 12%-30% treated for a UTI annually; more females than males

Consequences of Nursing Home Infections

- Leading cause of mortality and morbidity
- 150,000-300,000 hospital admissions each year
  - 26-50% of transfers due to infections
- Costliest of all adverse event related hospitalization

This means your resident might get sick, transfer to the hospital or even die of an HAI.

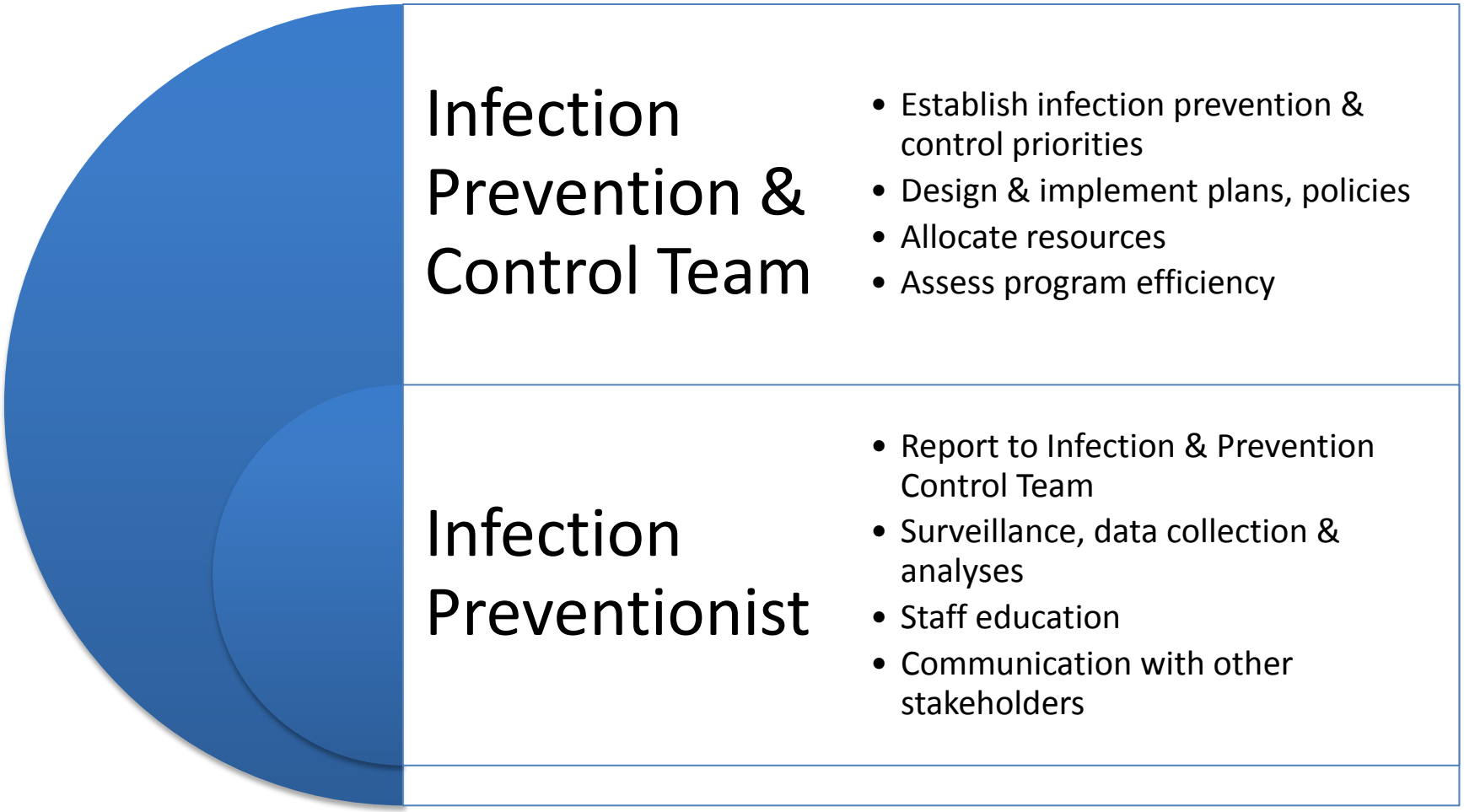
The goal of infection prevention is to prevent these infections from occurring and promote resident safety.

Aging health. 2011 December ; 7(6): 889–899. doi:10.2217/AHE.11.80.
Smith PW et al *ICHE* 2008.
Stone et al *ICHE* 2012.
Htwe. Infection in the elderly. *Infect Dis Clin N. Am*. 2007

Effective Infection Control and Prevention Program

- Establishing a core team , with IP at the center
- Ensuring person in IP role has optimum training and qualification
- Ensuring reasonable and fixed FTE is dedicated to IP activities
- Medical director as clinical resource , Infectious diseases specialist if needed.
- Integration into Laboratory , Pharmacy, Nutritional and Environmental services Work Flow

Suggested Team Structure



Barriers and challenges in our setting

- Lack of formal and structured program
- High staff turn over
- IP pulled in different directions
- IP lack of training and knowledge
- Lack of ownership and administration buy-in
- Fear of survey citations
- Poor medical director involvement
- Over all poor resource allocation, including IT

Isolation conundrum , medical care Vs. quality of life

- Long-term residents ‘live’ in nursing homes and deserve quality of life as if its their home
- Many residents are colonized and remain in prolonged contact isolation, further isolating them from social interactions
- Many facilities still follow arbitrary policies of repeated negative cultures prior to discontinuing isolation precautions (including but not limited to C-diff, MRSA, ESBL)

Safety Culture , Facility acquired and potentially preventable infections

- Resident safety culture is still not standard continued efforts on way (AHRQ,CMS)
- National action plan highlights the urgency of reducing HAIs
- Several national initiatives addressing HAIs (AHRQ-CUSP-CAUTI, QIN-QIO – NH Collaborative)
- Lack of robust hand hygiene programs

ANTIBIOTIC USE (ABUSE) in Nursing Homes

- Antimicrobials account for approximately 40% of all systemic drugs prescribed in LTCFs
- 50-70% of the residents will receive at least one course of a systemic antimicrobial agent during a one-year period.
- Studies estimate that 25-75% of systemic antibiotic use may be inappropriate in the long-term care setting

Anti-microbial Stewardship, our time has come

- Understanding AMS
- Getting leadership Buy-in
- Getting facility “antibiogram”
- Compiling a list of common infections and appropriate treatment guidelines
- Poor Man’s ATO
- Working with lab on timely microbiology reports
- Working with pharmacy on timely antibiotic reports

AMS Contd.

- “Choosing wisely” the UAs and other cultures
- IT/EMR integration for lab/MAR reporting
- Using minimum criteria for infection diagnosis
- Medical Director engagement for medical staff education
- Using data to identify any outliers for unnecessary testing or prescribing

DISCUSSION

LOYOLA UNIVERSITY CHICAGO

Northern Illinois Infection Prevention and CRE Workshop, Addison, IL

May 12, 2015

"What every Laboratory Should be Doing to Detect CRE's"

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Director, Clinical Microbiology Laboratory
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Financial Disclosures

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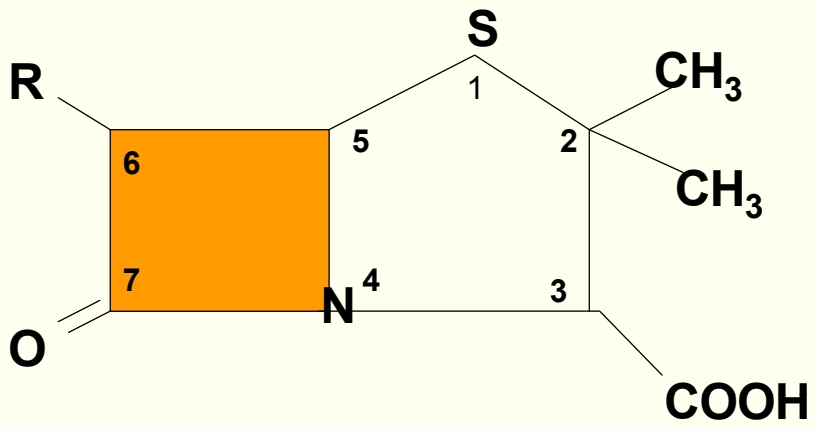
Independent contractor/Speaker's Bureau	Accelerate Dx., Beckman Coulter, bioMerieux, BioFire, Cepheid, Hardy Diagnostics, Merck, Thermo Fisher Scientific
Consultant/Advisory Committees	BioFire, Cepheid, GenMark, Quidel, Thermo Fisher Scientific, Theravance
Research Grants	Accelerate Dx, Becton-Dickinson, Beckman Coulter, BioFire, bioMerieux, Bruker, Cepheid,

Learning Objectives

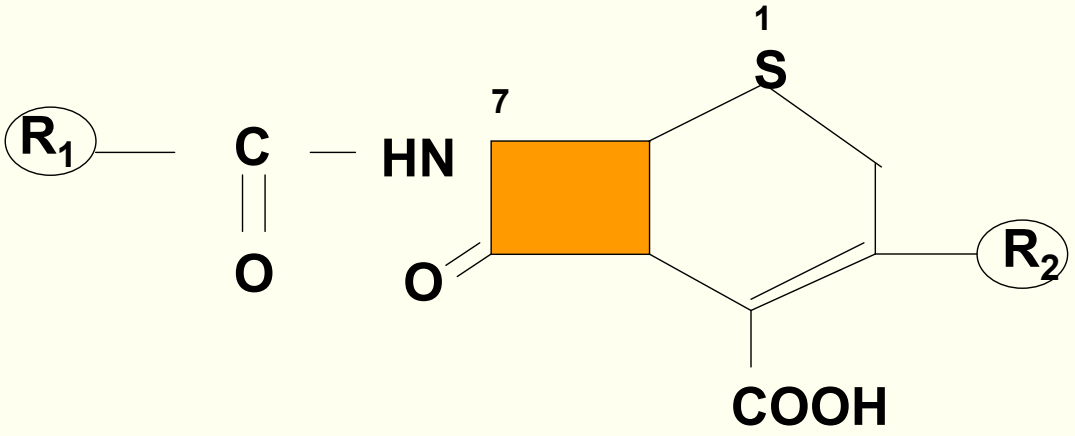
At the conclusion of this session, participants will be able to:

1. Describe the five major types of CRE
2. Review conventional and new approaches to detecting CRE
3. Explain the CSTE CRE definition proposal and its implications for labs
4. Evaluate their own laboratories readiness for detecting and reporting CRE

Penicillin nucleus



Cephalosporin nucleus



MODE OF ACTION OF BETA LACTAMS IN GRAM NEGATIVES

SUSCEPTIBLE	RESISTANT
β-Lactam Antibiotic	
↓	
Diffusion through Outer Membrane	← Porin Blocks Entry ← Efflux Pump
↓	
Diffusion through Peptidoglycan	← Beta-Lactamase Hydolyzes Beta-Lactam
↓	
Penicillin Binding Proteins	← Changes in PBP results in Failure to Bind to β-Lactam
↓	
Cell Death	

The β-lactam family of antibiotics

Penicillins	Cephalosporins	Cephamycins	Carbapenems	Monobactams
Benzyl-penicillin	Cephalothin 1st	Cefoxitin	Imipenem	Aztreonam
Methicillin	Cefamandole 2nd	Cefotetan	Meropenem	
Ampicillin	Cefuroxime 2nd	Cefmetazole	Ertapenem	
Carbenicillin	Cefotaxime 3rd		Doripenem	
Mezlocillin	Ceftazidime 3rd			
Ticarcillin	Ceftriaxone 3rd			
	Cefepime 4th			

The β-lactam family of antibiotics

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Mezlocillin	Ceftazidime 3rd			
Ticarcillin	Ceftriaxone 3rd			
	Cefepime 4th			

ESBLs hydrolyze all

Penicillins
Cephalosporins
Monobactams

The β-lactam family of antibiotics

Penicillins	Cephalosporins	Cephamycins	Carbapenems	Monobactams
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Carbenicillin	Cefotaxime 3rd		Doripenem	
Mezlocillin	Ceftazidime 3rd			
Ticarcillin	Ceftriaxone 3rd			

Cefepime 4th

ampCs hydrolyze all

Penicillins

1st, 2nd, 3rd Cephalosporins

Cephamycins

Monobactams

The β-lactam family of antibiotics

Penicillins	Cephalosporins	Cephamycins	Carbapenems	Monobactams
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Carbenicillin	Cefotaxime 3rd		Doripenem	
Mezlocillin	Ceftazidime 3rd			
Ticarcillin	Ceftriaxone 3rd			
	Cefepime 4th			

Metallo BL hydrolyze all

Penicillins
Cephalosporins
Cephamycins
Carbapenems

The β-lactam family of antibiotics

Penicillins	Cephalosporins	Cephamycins	Carbapenems	Monobactams
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Ampicillin	Cefuroxime 2nd	Cefmetazole	Ertapenem	
Carbenicillin	Cefotaxime 3rd		Doripenem	
Mezlocillin	Ceftazidime 3rd			
Ticarcillin	Ceftriaxone 3rd			
	Cefepime 4th			

KPCs hydrolyze all

Penicillins
Cephalosporins
Cephamycins
Carbapenems
Monobactams

Carbapenem-Resistance in Enterobacteriaceae

- Two mechanisms of resistance
  - Carbapenemase (β-lactamase that can hydrolyze carbapenems)
  - Cephalosporinase combined with porin loss
    - Some cephalosporinases (e.g., AmpC-type β-lactamases or certain ESBLs i.e. CTX-M) have a low-level carbapenemase activity
    - Porin loss limits entry of the carbapenem into the periplasmic space

Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Carbapenemase
  - Isolate likely to be resistant to all carbapenems and other β-lactam agents
  - May need to change susceptible reports to resistant for β-lactam drugs
  - Need to implement infection control measures such as contact precautions and possibly active surveillance testing
  - **These are an Infection Control Emergency**

Need to Distinguish Between Mechanisms of Carbapenem Resistance – Why?

- Cephalosporins combined with porin-loss
  - Class A ESBL's (CTX-M) + reduced permeability
  - Class C High AmpC + reduced permeability
- These hydrolyze ertapenem more than meropenem or imipenem
  - Not necessarily resistant to all carbapenems (i.e., would not need to change susceptible results to resistant reports for β-lactam drugs
- These isolates are clearly MDR and infection control measures are recommended. Healthcare institutions may reserve more aggressive measures for carbapenemase-producing isolates

5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac-teriaceae	Non-fermenters
A [1]	KPC[2]	+++	+
B (metallo)	NDM[3], IMP, VIM,	+++	+++
D	OXA-48-like	+++	+/-

[1]also includes SME; [2]most common in USA; [3]increasing in USA

….but several types within 5 groups and other types of carbapenemases

(slide courtesy Janet Hindler)

Strategy for Laboratory Detection of Carbapenemases

- Antibiogram – CDC approach: if any Enterobacteriaceae tests non-susceptible to any carbapenem call it CRE.
- Phenotypic testing
  - Modified Hodge Test
  - Boronic Acid Synergy Test
  - EDTA inhibition test (MBL Etest)
- Rapid Colorimetric
  - Carba NP
  - NEO-Rapid CARB Kit by Rosco Diagnostica (Hardy, Key Scientific)
  - RAPIDEC® CARBA NP (bioMerieux)
  - EPI-CRE® (Pilots Point, Sarasota, FL)
- MALDI-TOF MS
- Molecular - PCR

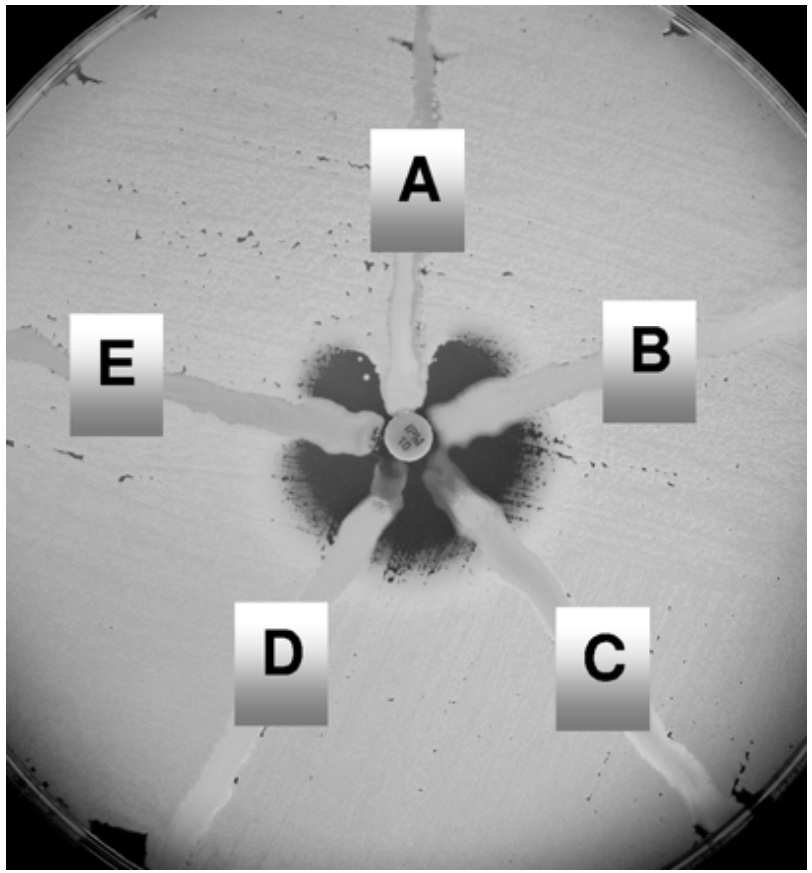
Strategy for Laboratory Detection of Carbapenemases

- CLSI Carbapenemase Screening Criteria (M100-S-25 Jan 2015 p.48)
  - "Laboratories should perform the modified Hodge test (MHT), the Carba NP test, and/or a molecular assay when isolates of *Enterobacteriaceae* are suspicious for carbapenemase production"

Strategy for Laboratory Detection of Carbapenemases

- CLSI Carbapenemase Screening Criteria (M100-S-25 Jan 2015 p.48)
  - Disk zone of < 22 mm for ertapenem or meropenem
  - MIC of >1 μg/ml for imipenem, ertapenem or meropenem
- Procedure Notes
  - Imipenem disk test is not a good screen
  - Imipenem MIC does not work as a screen for *Proteus/ Providencia/Morganella* due to slightly elevated MICs in this group by mechanisms other than carbapenemases

Modified Hodge Test



- Inoculate MH agar with a 1:10 dilution of a 0.5 McFarland suspension of *E. coli* ATCC 25922 and streak for confluent growth using a swab.
- Place 10-µg ertapenem or meropenem (best) disk in center
- Streak each test isolate from disk to edge of plate
- Isolate A is a KPC producer and positive by the modified Hodge test.

Anderson KF et al. JCM 2007 Aug;45(8):2723-5.

Modified Hodge Test

Neg Control

-

KPC

+

NDM

False -

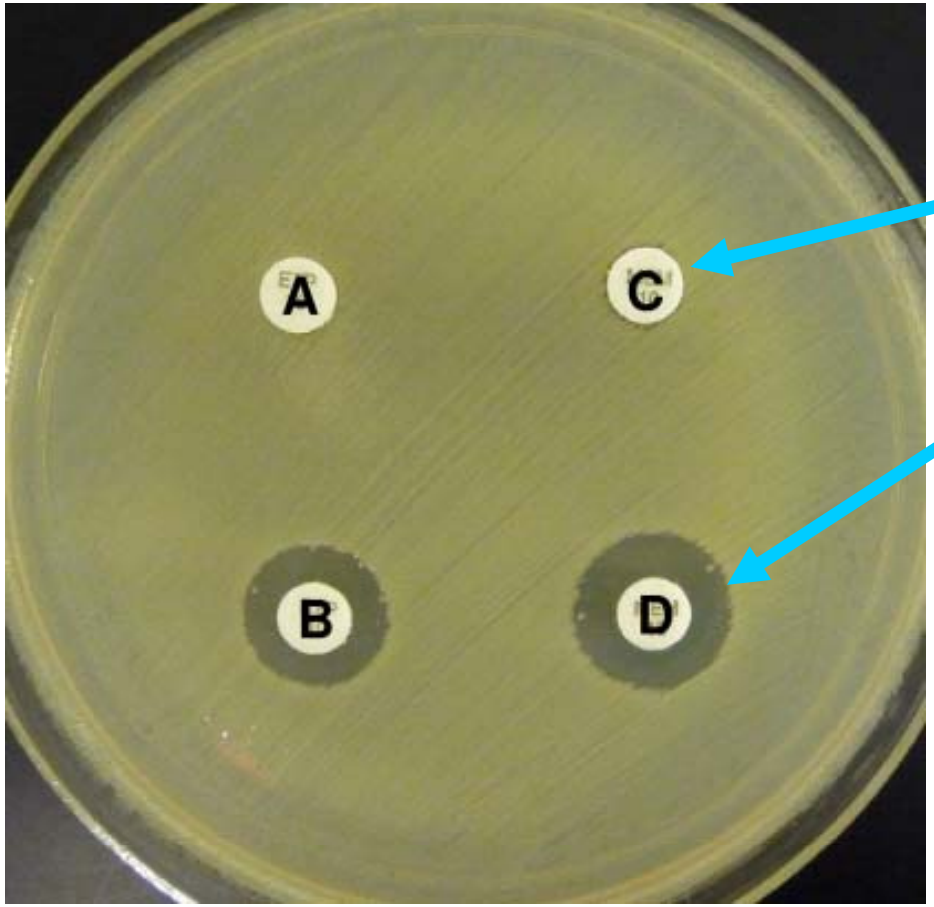
OXA 232

+

UCLA

(slide courtesy Janet Hindler)

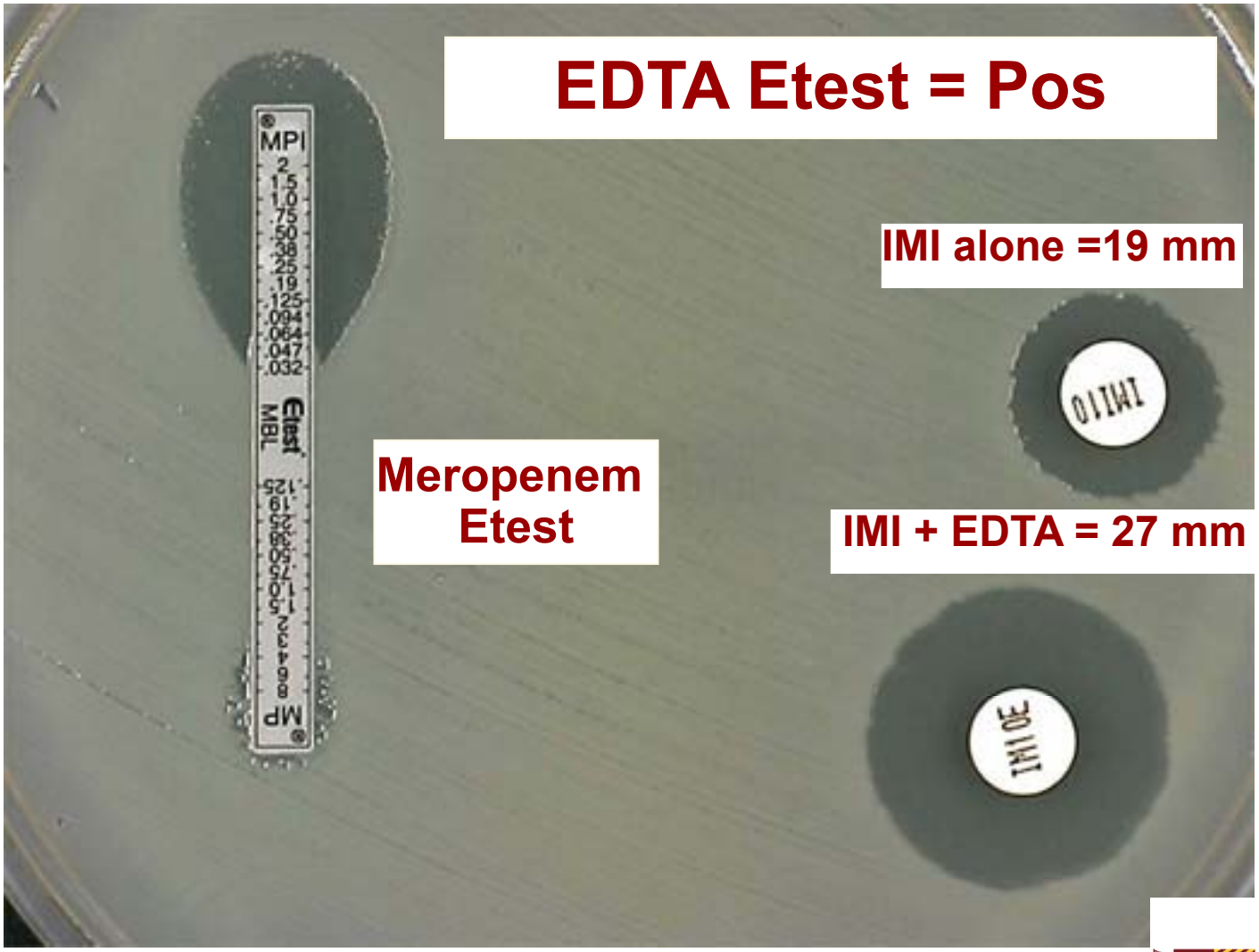
Boric Acid Synergy Test



Potentiation of carbapenems by APB in *K. pneumoniae* producing KPC-2. (A) Ertapenem (10 µg); (B) ertapenem plus APB (300 µg); (C) meropenem (10 µg); (D) meropenem plus APB (300 µg).

Doi Y et al. **J Clin Microbiol. 2008 Dec;46(12):4083-6.**

Rosco Diagnostica IMI/EDTA Disks
MBL Etest bioMerieux



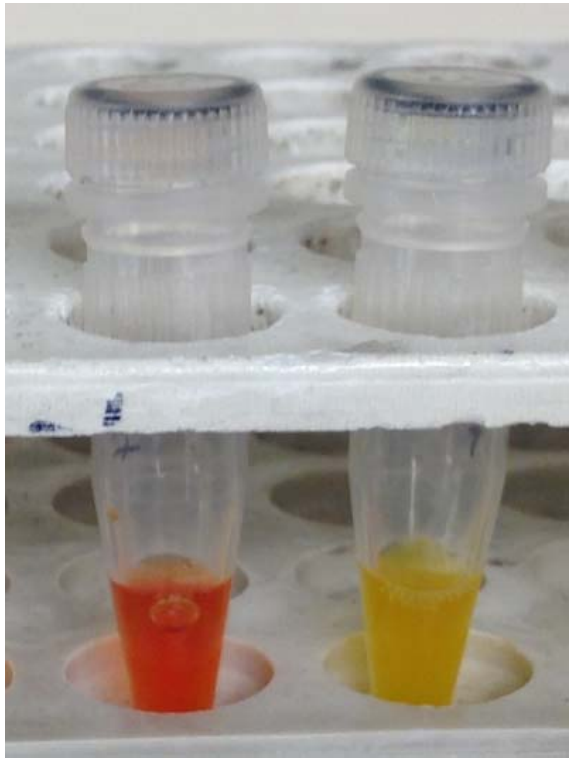
(Only Detects MBL's eg. NDM, IMP, VIM)

What is the Carba NP test?

- A **colorimetric test for carbapenemase** production by Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter*
  - Uses imipenem as the target substrate, phenol red as the pH indicator; positive hydrolysis turns yellow
  - Color usually turns fast, test ends at 2 hours
  - Good at detecting KPC, NDM, VIM, SPM, and SME, not so good at OXA
  - Will pick up carbapenem resistance if the MIC is 2 or 4 and you haven't changed your breakpoints

Carba NP Test for Carbapenemase Production

- Isolated colonies (lyse)
- Hydrolysis of imipenem
- Detected by change in pH of indicator (red to yellow/orange)
- Rapid <2h
- Microtube method



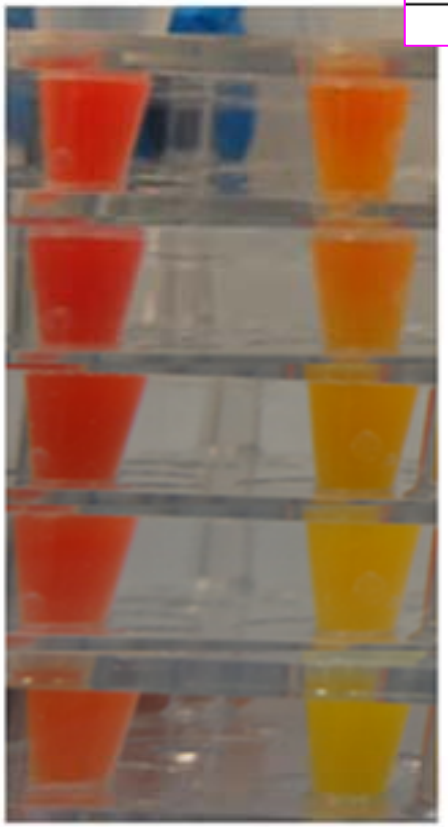
NO imipenem **+ imipenem**

Nordmann et al. 2012. Emerg Infect Dis. 18:1503.
Tijet et al. 2013. Antimicrob Agents Chemother. 57:4578.
Vasoo et al. 2013. J Clin Microbiol. 51:3092.
Dortet et al. 2014. J Med Microbiol. 63:772.
Dortet et al. 2014. Antimicrob Agents Chemother. 58:2441.

(slide courtesy Janet Hindler)

Results for Patient and QC Tubes		
Tube "a": Solution A (serves as internal control)	Tube "b": Solution B	Interpretation
Red or red-orange	Red or red-orange	Negative, no carbapenemase detected
Red or red-orange	Light-orange, dark yellow, or yellow	Positive, carbapenemase producer
Red or red-orange	Orange	Invalid
Orange, light-orange, dark yellow, or yellow	Any color	Invalid

Solution A

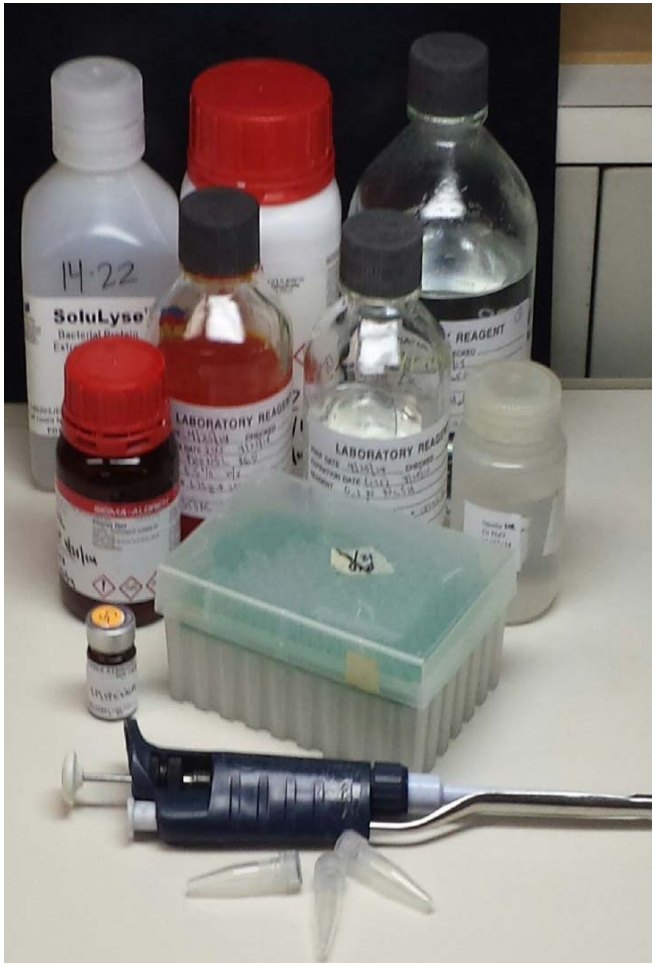


Red	Orange	Invalid
Red	Light Orange	+
Red	Dark Yellow	+
Red-orange	Yellow	+
Red-orange	Yellow	+

M100-S25. p.120-126.

(slide courtesy Janet Hindler)

Carba NP Test Materials/Reagents



- Testing simple
- Reagent Preparation takes time

Reagents Must be Prepared Fresh

10 mM Zinc sulfate heptahydrate

Phenol red solution

0.1 N NaOH

Carba NP Solution A

(phenol red + zinc solutions)

Carba NP Solution B

(Carba NP Solution A + imipenem)

(slide courtesy Janet Hindler)

Carba NP Test

UCLA

(slide courtesy Janet Hindler)

Commercial Test
Rapid CARB Screen Kit

- Commercial kit; similar to Carba NP
- Enterobacteriaceae and *P. aeruginosa*
- Tablets
  - Imipenem + indicator
  - Negative control
- ≤2 hours
- CLSI study isolates – UCLA results:
  - More difficult to read than Carba NP
  - Good agreement with Carba NP but more initial invalids that required repeating
  - Most problems with *Acinetobacter baumannii* – NDM (not indicated for this species)

www.rosco.dk **NOT FDA cleared**

Enterobacteriaceae Carbapenemase Detection

Study	N	Carba NP	Rapid CARB Screen Kit	MHT
1	235	97% sens 100% spec	98% sens 83% spec	-
2	92	91% sens 100% spec	73% sens 100% spec	-
3	150	-	98% sens 100% spec	75% sens 91% spec

1 Huang et al. 2014. J Clin Microbiol. 52:3060.
2 Yousef et al. 2014. Eur J Clin Microbiol Infect Dis. Jul 10 epub.
3 Simner et al. 2015. J Clin Microbiol. 53:105.

Rapid CARB Screen Kit discontinued !!!!
Reformatted Product is Neo-Rapid CARB Screen Kit

(slide courtesy Janet Hindler)

Commercial Test
RAPIDEC® CARBA NP

1) **Phenol red**: pH indicator

2) A **carbapenem**: imipenem (carbapenemase substrate) **+ Zinc**, required for the detection of metallodependent carbapenemase-producing strains

Detects (without distinction)
Class A, B and D Carbapenemases

bioMerieux

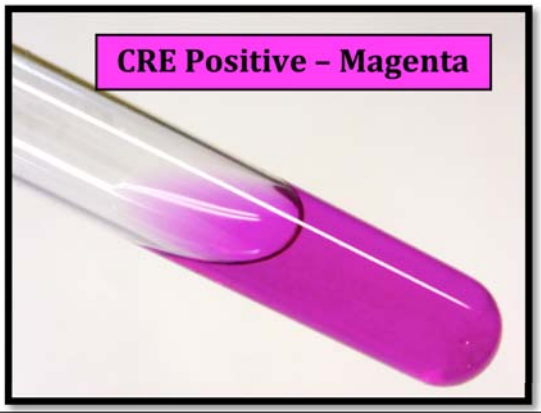
NOT FDA cleared

https://www.youtube.com/watch?v=3YXCBs34zyA

EPI-CRE®

Enterobacteriaceae (CRE)

It's Easy to See...



Specifications

Time to Results:	**Positive** – as soon as the sample changes from gold to magenta. **Negative** – after 24 hours if no color change from gold occurs.
Storage:	From 2 to 28 °C under dry conditions, EPI-CRE® is stable for 1 year from date of manufacture.
Sensitivity & Specificity:	EPI-CRE® detects ONLY living bacteria. It is 100% specific.
Regulatory:	CE/IVD approved.

Pilots Point, Sarasota, FL
www.pilotspoint.net

NOT FDA cleared

LOYOLA UNIVERSITY CHICAGO

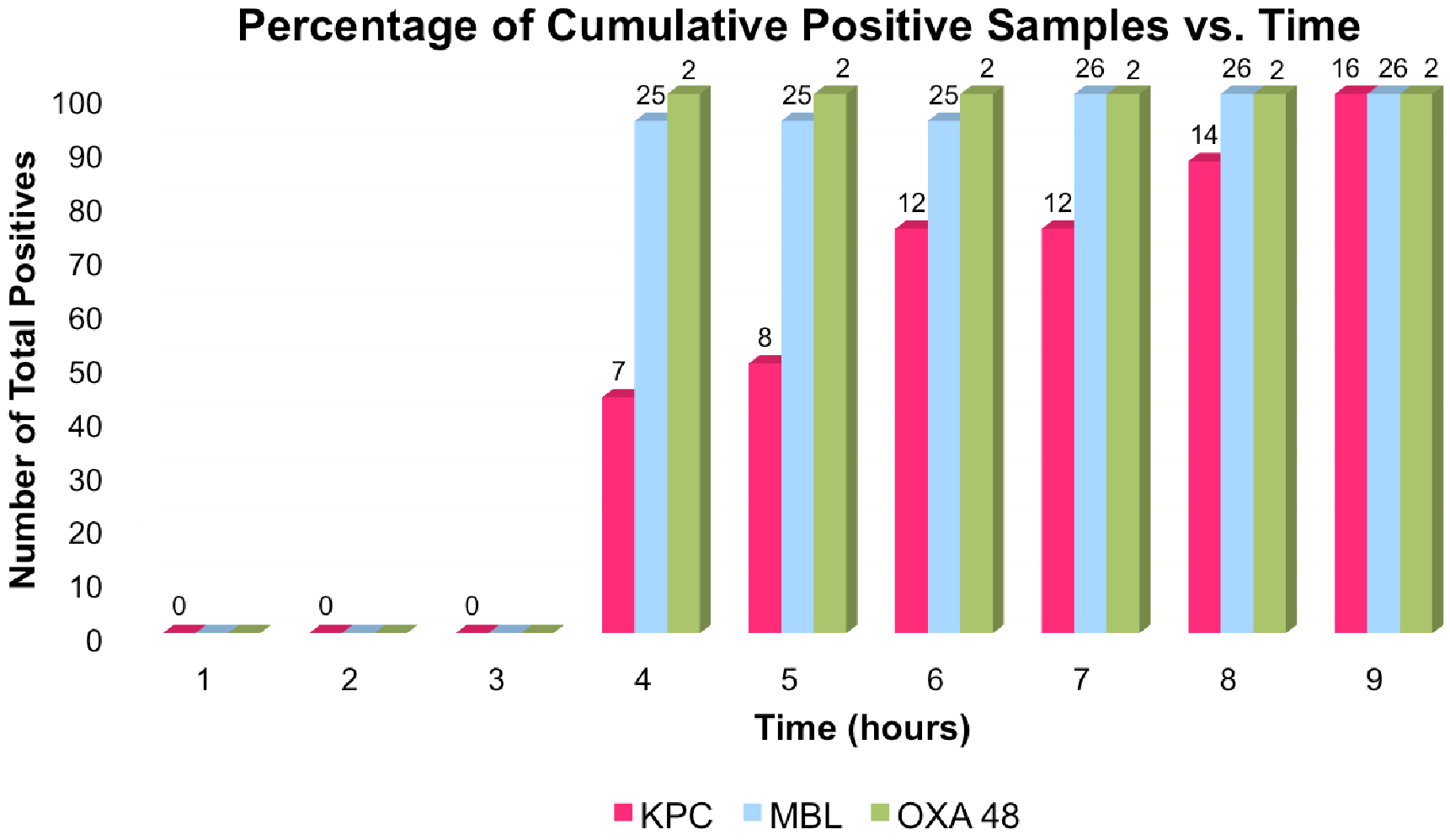
EPI-CRE®

	Carbapenemases					Cehpalosporinases			
Organism	KPC	MBL	OXA	Total	EPI-CRE Positive Results	ESBL	AmpC	Total	EPI-CRE Negative Results
C.freundii	0	0	0	0	0	0	2	2	2
E.aerogenes	2	0	0	2	2	0	5	5	5
E.cloacae	3	0	0	3	3	3	6	9	9
E.coli	2	24	1	27	27	12	0	12	12
K.oxytoca	0	0	0	0	0	1	0	1	1
K.pneumoniae	9	2	1	12	12	2	0	2	2
M.morganii	0	0	0	0	0	0	1	1	1
P.mirabilis	0	0	0	0	0	1	0	1	1
P.stuartii	0	0	0	0	0	1	1	2	2
S.marcesens	0	0	0	0	0	0	6	6	6
Total	16	26	2	44	44	20	20	40	40
				Sens-itivity	100%			Speci-ficity	100%

EPI-CRE inoculated with 50 µl 0.5 McFarland suspension

Slesar AJ, Schreckenberger PC. Evaluation of Modified EPI-CRE Tet for Rapid Carbapenemase Detection. Abstr. 115th Gen. Mtg. Am. Soc. Microbiol, New Orleans, LA, June 2, 2015.

EPI-CRE®



Slesar AJ, Schreckenberger PC. Evaluation of Modified EPI-CRE Tet for Rapid Carbapenemase Detection. Abstr. 115th Gen. Mtg. Am. Soc. Microbiol, New Orleans, LA, June 2, 2015.

LOYOLA UNIVERSITY CHICAGO

MALDI-TOF MS

Matrix Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry

Method	Sensitivity	Specificity
MALDI-TOF Assay	77%	100%
Carb NP Test	76%	100%
MALDI-TOF BIC Assay	98%	100%
BIC Assay includes addition of 50 mM NH_4HCO_3 to reaction buffer		

Both methods experienced problems with subset of 19 isolates producing OXA-48 carbapenemase

Papagiannitsis CC et al.
J Clin Microbiol. 2015 May;53:1731-5.

Molecular Tests for Carbapenemases

- Biofire *
  - KPC
- Nanosphere *
  - KPC, NDM, OXA, IMP, VIM
- BD Max
  - KPC, NDM, OXA-48
- Cepheid
  - KPC, NDM, OXA-48, IMP-1, VIM
- Check-Points
  - KPC, NDM, OXA-48, IMP, VIM
- Others?

* FDA cleared

(slide courtesy Janet Hindler)

Tests for Carbapenemases in *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp.

	MHT	Carba NP	Molecular
Use	Enterobacteriaceae	Enterobacteriaceae P. aeruginosa Acinetobacter	Enterobacteriaceae P. aeruginosa Acinetobacter
Strengths	Simple	Rapid	Determines type of carbapenemase
Limitation	Some false pos (eg, ESBL/ampC + porin) Some false neg (eg NDM) Enterobacteriaceae only	Special "fresh" reagents Some invalid results False neg for OXA-type carbapenemase	Special reagents Specific to targeted gene High Cost

(slide courtesy Janet Hindler) M100-S25. p. 112.

Why is Carbapenem Resistance a Public Health Problem?

- Significantly limits treatment options for life-threatening infections
- No new drugs for gram-negative bacilli
- Emerging resistance mechanisms, carbapenemases are mobile
- Detection of Carbapenem Producing Organisms (CPO's) and implementation of infection control practices are necessary to limit spread

Alphabet Soup: CRE, CPE, CPO

- **What is the difference between CPO, CPE and CRE?**
  - The differences depend on type of bacteria being included and the mechanisms of resistance to carbapenem antibiotics.
  - Carbapenem Resistant Enterobacteriaceae (CRE) refers to bacteria in the family of Enterobacteriaceae (e.g. *E.coli, Klebsiella*, etc) that are resistant to carbapenem antibiotics regardless of the method of resistance, as there are a number of different ways.

Alphabet Soup: CRE, CPE, CPO

- **What is the difference between CPO, CPE and CRE?**
  - Carbapenemase Producing Enterobacteriaceae (CPE) refers to bacteria in the family of Enterobacteriaceae (e.g. *E.coli, Klebsiella*, etc) that are resistant to carbapenem antibiotics by producing an enzyme to break down the carbapenem antibiotics. This is determined by testing for the genes that produce these enzymes, such as KPC and NDM.

Alphabet Soup: CRE, CPE, CPO

- **What is the difference between CPO, CPE and CRE?**
  - Carbapenemase Producing Organisms (CPO) refers to bacteria in the family of Enterobacteriaceae (e.g. *E.coli, Klebsiella*, etc) and those that do not belong to this family such as *Pseudomonas* and *Acinetobacter*, that are resistant to carbapenem antibiotics by producing an enzyme to break down the carbapenem antibiotics. This is determined by testing for the genes that produce these enzymes, such as KPC and NDM.

Alphabet Soup: CRE, CPE, CPO

- **Why are other countries using the term CPO?**
  - Genes for carbapenem resistance can be transferred to bacteria in the Enterobacteriaceae family and to bacteria not within this family
  - The term CPO includes the larger group of potentially affected bacteria. This is important for surveillance purposes so that we do not miss any groups of bacteria that may be carrying and spreading these antibiotic resistant genes.
  - CPO's are what laboratories should be looking for and what Infection Preventionists should be reporting.

CSTE Definition of CRE

- **The 2012 definition for CRE was:** *E. coli,* *Kl*ebsiella spp., and *Enterobacter* spp. nonsusceptible to imipenem, meropenem, or doripenem and resistant to all 3rd-generation cephalopsporins tested (e.g., ceftriaxone, cefotaxime, ceftazidime) Ertapenem was excluded.
- **Proposed 2015 definition for CRE is:** *E. coli,* *Klebsiella* spp., and *Enterobacter* spp. resistant to imipenem, meropenem, doripenem, or ertapenem or production of a carbapenemase (eg. KPC, NDM, VIM, OXA-48) demonstrated by a recognized test (e.g. PCR, MBL test, MHT, Carba NP

Problems with CSTE Definition

- MYSPACE Bugs (Morganella, Yersinia, Serratia, Providencia, Aeromonas, Citrobacter, Enterobacter, posses chromosomal AmpC beta-lactamase) may test ertapenem non-susceptible if also have porin mutation. These are not CPO's and are not an IC threat.
- At LUMC, 12% of *E. cloacae* test non-susceptible to ertapenem.
- In 2014, 40 patients would have been called CRE (that were not CPO's) and would have been placed in isolation and reported to XDRO registry

Problems with CSTE Definition

- Imipenem vs. Proteeae (i.e., *Morganella morganii, Proteus* spp., *Providencia* spp.)
- MIC_{90} of imipenem ≤ 1 ug/mL for most Enterobacteriaceae, but is 4-8 ug/mL for Proteeae and may test non-susceptible to imipenem using new CLSI/FDA BPs
- Some *P. mirabilis* are more resistant, with imipenem MICs ranging from 16 to 64 ug/mL
- Higher MICs seen with imipenem vs. *P. mirabilis* are not due to carbapenemases but rather diminished expression of penicillin-binding protein (PBP) 1a and reduced binding of imipenem by PBP2

Problems with CSTE Definition

- Proteeae that are non-susceptible to imipenem are not CPOs and are not an IC threat.
- These patients should not be placed in isolation and should not be reported to the XDRO registry
- *P. aeruginosa* and *Acinetobacter baumannii* have both been reported to have CPO's yet these are not reported using the CSTE definition.

Creation of XDRO Registry

- In response to the CRE public health threat, IDPH has amended the Control of Communicable Diseases Code (77 Ill. Adm. Code 690) Rules (see addendum) to require reporting of CREs to IDPH.
- All hospitals, hospital-affiliated clinical laboratories, independent or free-standing laboratories, longer-term care facilities, and long-term acute care hospitals in Illinois will be required to report CRE isolates that meet surveillance criteria to IDPH through a tool called the XDRO registry, effective **November 1, 2013.**

Report CRE Isolates to XDRO Registry with one of following test results:

1. Molecular test (e.g., PCR) specific for carbapenemase

OR

2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production

OR

3. For ***E. coli*** **and** ***Klebsiella*** species only: non-susceptible to ONE of the carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime).

Report 1st CRE event per patient per encounter

Why labs should continue to perform MHT and EDTA Inhibition Test on isolates that test Non-Susceptible to carbapenems

- Knowing the resistance mechanism is important
- The following cases demonstrate 4 different mechanisms of carbapenem resistance. Some require changes in antibiotic reporting, some require infection control notification, some require reporting to XDRO registry, and some require no action
- Can you tell the difference between them by MIC alone?

Patient History Case 1

- 58 y/o male, morbidly obese (>500 lbs)
- Presented to ER with episode of hypoxia and hypotension during dialysis
- PMH
  - Pt has trach for hypercapnea (COPD and OSA), vent dependent
  - Chronic foley catheter
  - Diabetes mellitus type 2
  - ESRD
- Exam:
  - Afebrile
  - Multiple decubitus ulcers (sacrum, spine, right leg)
  - Urine is grossly dirty
- Concerned that septic => Pan-cultures
  - Urine: *Klebsiella*…

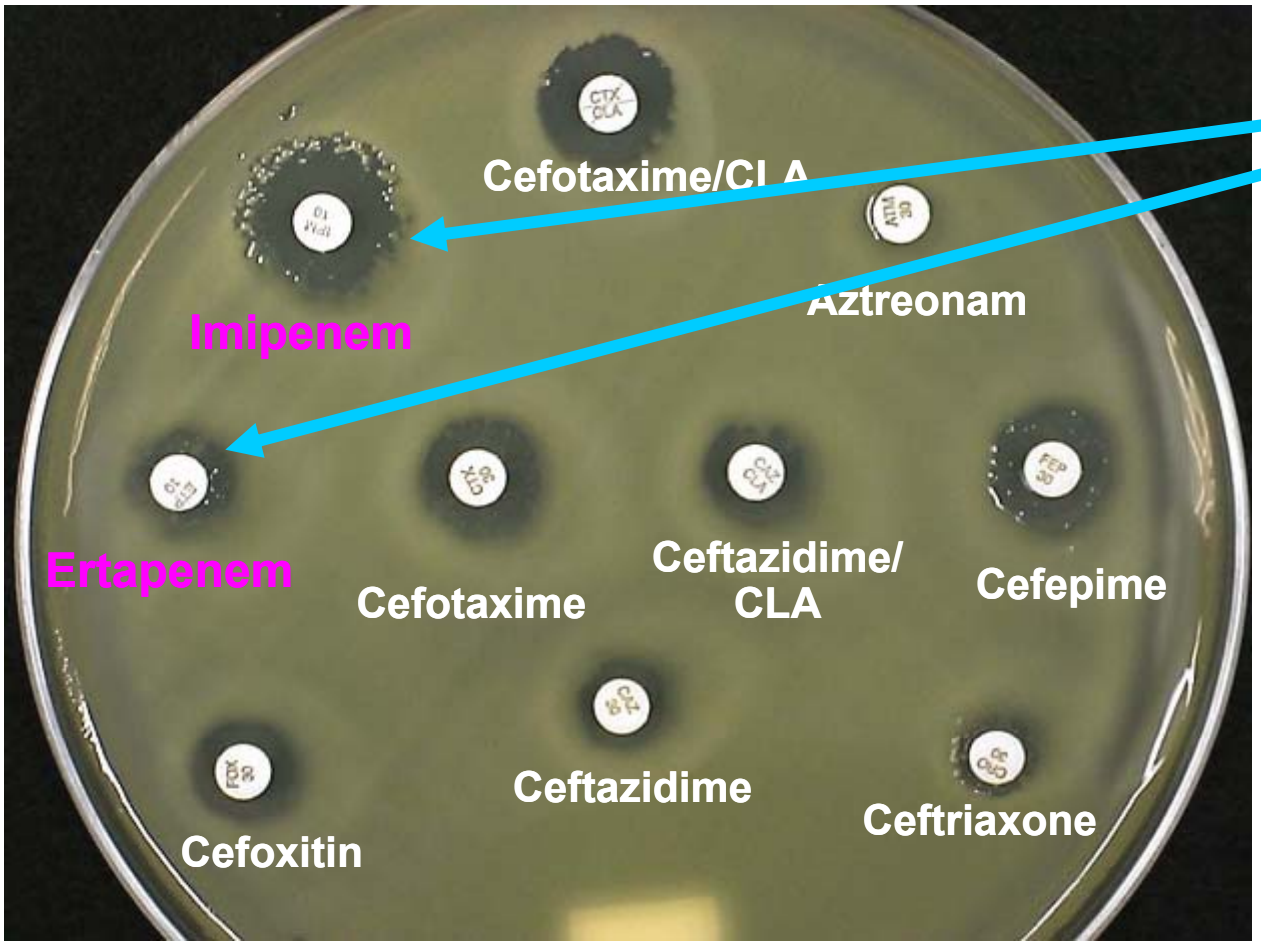
Vitek ID: [redacted] Oxidase -
Type: Gram Negative General Susceptibility 143 (GNS-143)
Status: Final
Elapsed Time: 13 hours
Organism: Klebsiella pneumoniae
Source: Manual
Demographics: [redacted]

	MIC	Instrument	Expert
Ampicillin	>=32	R	
Ampicillin/Sulbactam	>=32	R	
Piperacillin/Tazobactam	>=128	R	
Cefazolin	>=32	R	
Ceftriaxone	>=64	R	
Ceftazidime	>=32	R	
Cefepime	8	S	
Aztreonam	>=32	R	
Imipenem	<=4	S	
Gentamicin	4	S	
Tobramycin	>=16	R	
Ciprofloxacin	>=4	R	
Levofloxacin	>=8	R	
Trimeth-sulfa	>=320	R	
Nitrofurantoin	64	I	
ESBL		Negative	

MIC values in mcg/ml (M1) Wait for All
The presence of other Beta-lactamases (e.g. AmpC, IRT) may mask ESBL production.

49

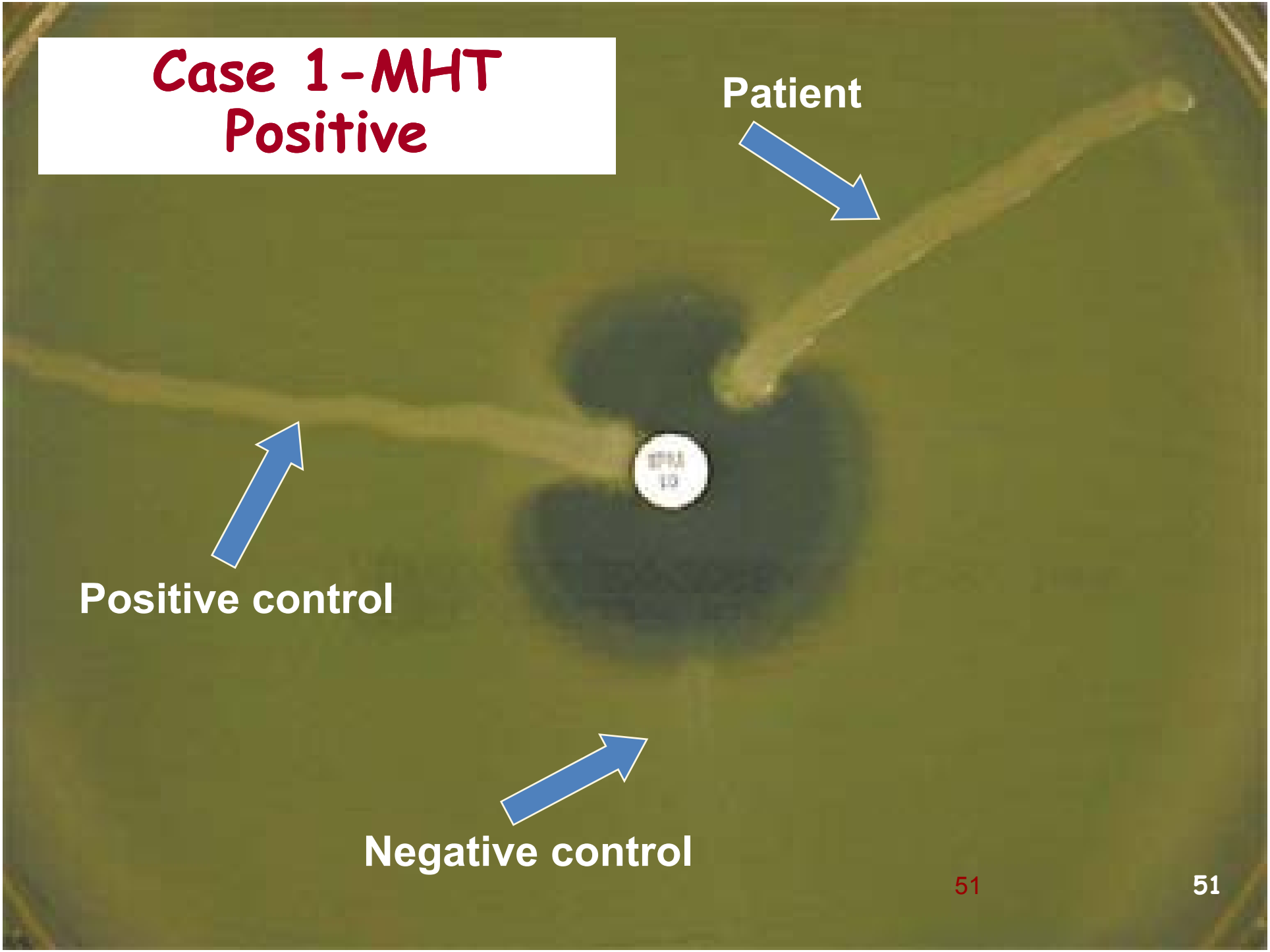
Double Disk Potentiation Method – Case 1



Imipenem - S
Ertapenem - R

Suggests possible KPC which should be confirmed with Hodge test or sent to reference lab for confirmation

Case 1-MHT Positive



51

And the Answer is …….

5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac-teriaceae	Non-fermenters
A [1]	KPC[2]	+++	+
B (metallo)	NDM[3], IMP, VIM,	+++	+++
D	OXA-48-like	+++	+/-

[1]also includes SME; [2]most common in USA; [3]increasing in USA

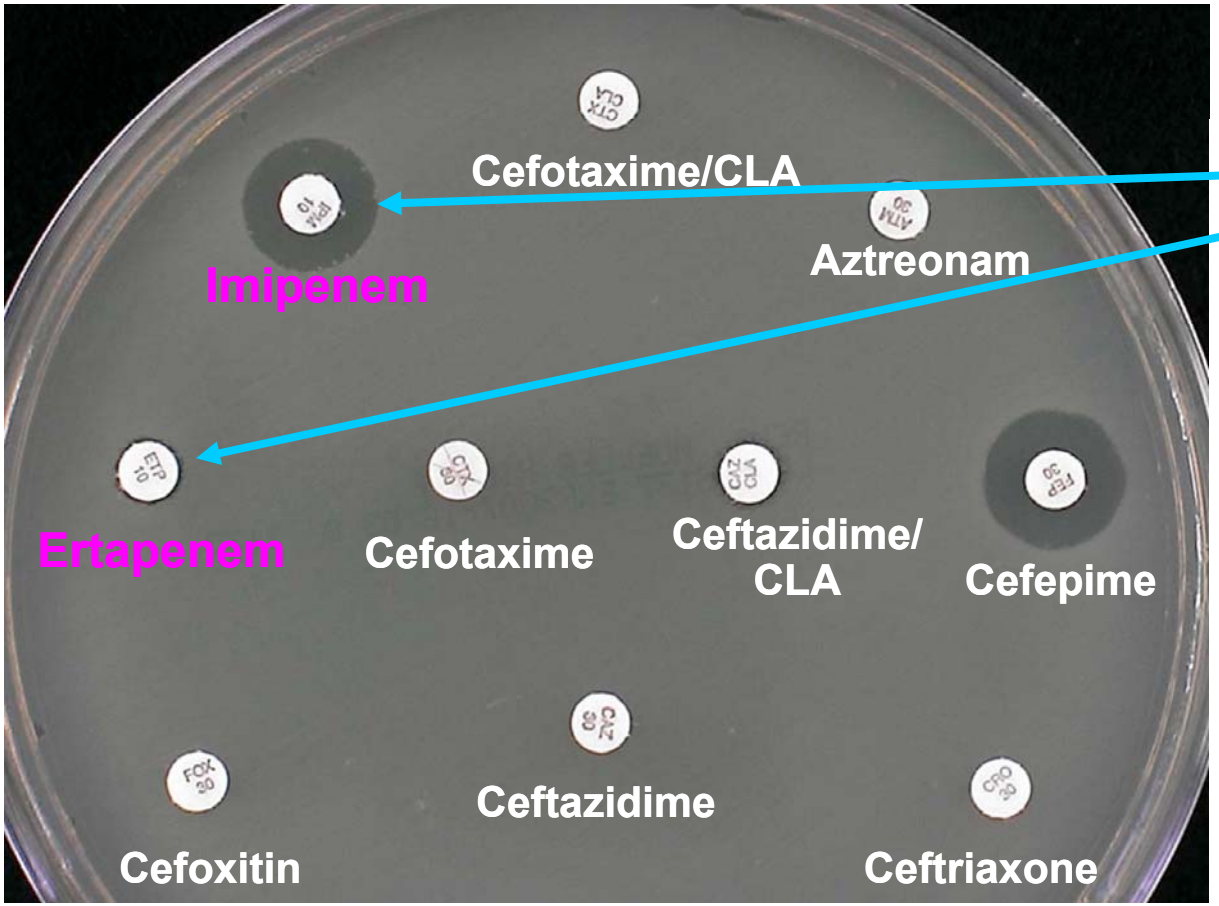
….but several types within 5 groups and other types of carbapenemases

(slide courtesy Janet Hindler)

Patient Report Case 1

- If using former CLSI/FDA breakpoints change all carbapenems to resistant
- If using new CLSI/FDA breakpoints report interpretations as tested
- Add following statement to report:
  "Carbapenem resistant *Enterobacteriaceae* (CRE) detected by Modified Hodge Test –probable KPC type. Implement infection control measures according to facility policy."
- REPORT TO XDRO REGISTRY

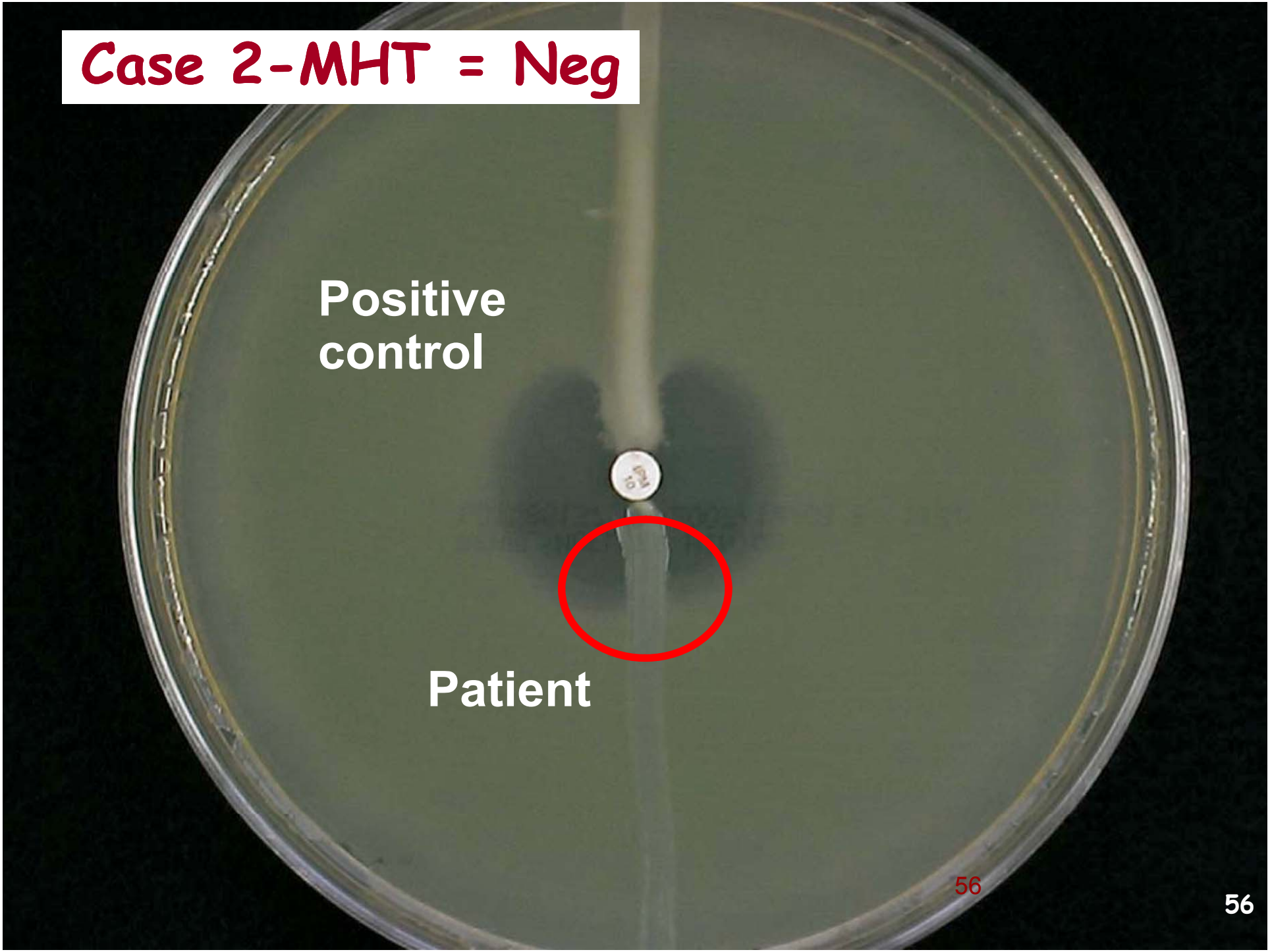
Double Disk Potentiation Method – Case 2
Blood Culture with *Enterobacter cloacae*



Imipenem - S
Ertapenem - R

Suggests possible KPC which should be confirmed with Hodge test or sent to reference lab for confirmation

Case 2-MHT = Neg



56

And the Answer is …….

And the Answer is …….

Chromosomal AmpC_(Derepressed mutant)_+ Porin mutation

Patient Report Case 2

- Susceptibility pattern in Case 2 is identical to susceptibility pattern in Case 1, except in Case 2 we have a chromosomal AmpC that is not MDRO, is not an infection control risk, and does not require modification of susceptibility report.
- Add following statement to report:
  "This organism is known to possess an inducible ß-lactamase. Isolates may become resistant to all cephalosporins after initiation of therapy. Avoid ß-lactam-inhibitor drugs"
- DO NOT REPORT TO XDRO REGISTRY

Case 3

- Patient is a 40 Y.O. male paraplegic who traveled to New Dehli India for a surgical procedure. 3-4 months after returning to the U.S. patient presents to outpatient center in Chicago with multiple decubitus ulcers and urinary tract infection. Urine collected from foley cath is submitted for culture.

MicroScan Report – Case 3

Panel Data

Biotype: 73115012

Organism Identification:

	Organism	% Probability	Footnotes	Special Characteristics
1	E. coli	99.99		

Biochemical Results: (Biochemicals that are bolded and underlined are atypical for the first choice organism)

GLU	+	RAF	-	INO	-	URE	-	LYS	+	TDA	-	CIT	-	CL4	-	ACE	-	K4	+	P4	+
SUC	+	RHA	+	ADO	-	H2S	-	ARG	-	ESC	-	MAL	-	CF8	+	CET	-	NIT	+	TAR	-
SOR	+	ARA	+	MEL	+	IND	+	ORN	+	VP	-	ONPG	+	OXI		FD64	-	OF/G	+	TO4	+

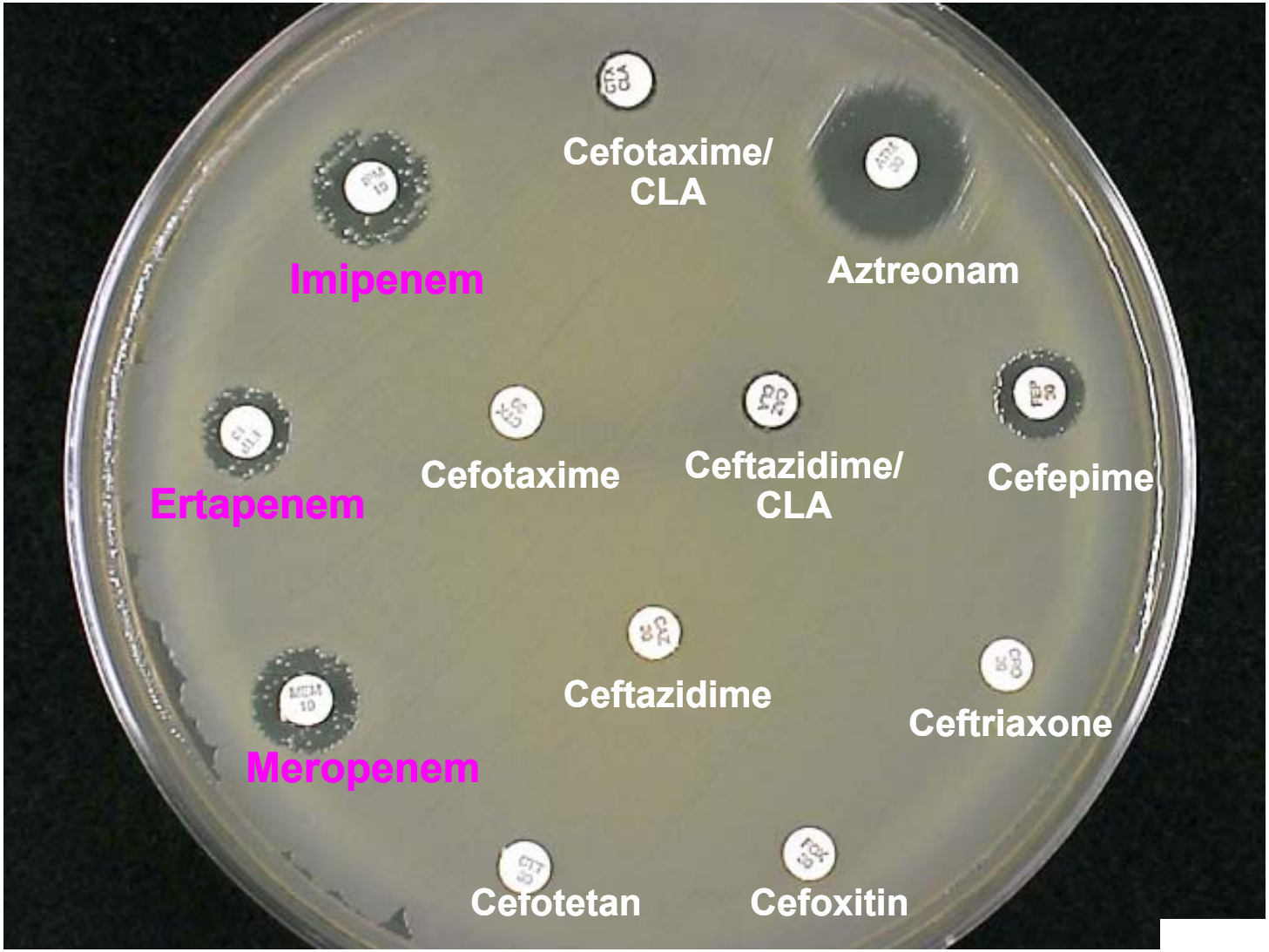
MIC Results: (Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

AM	A/S	P/T	CFZ	CAX	CAZ	CPE	MER	GM	Ø TE	TO	CP	T/S	Ø FD	AK
>16	>16/8	>64	>16	>32	>16	>16	>8	>8	>8	>8	>4	>2/38	<=32	>32
R	R	R	R	R	R	R	R	R	R	R	R	R		R

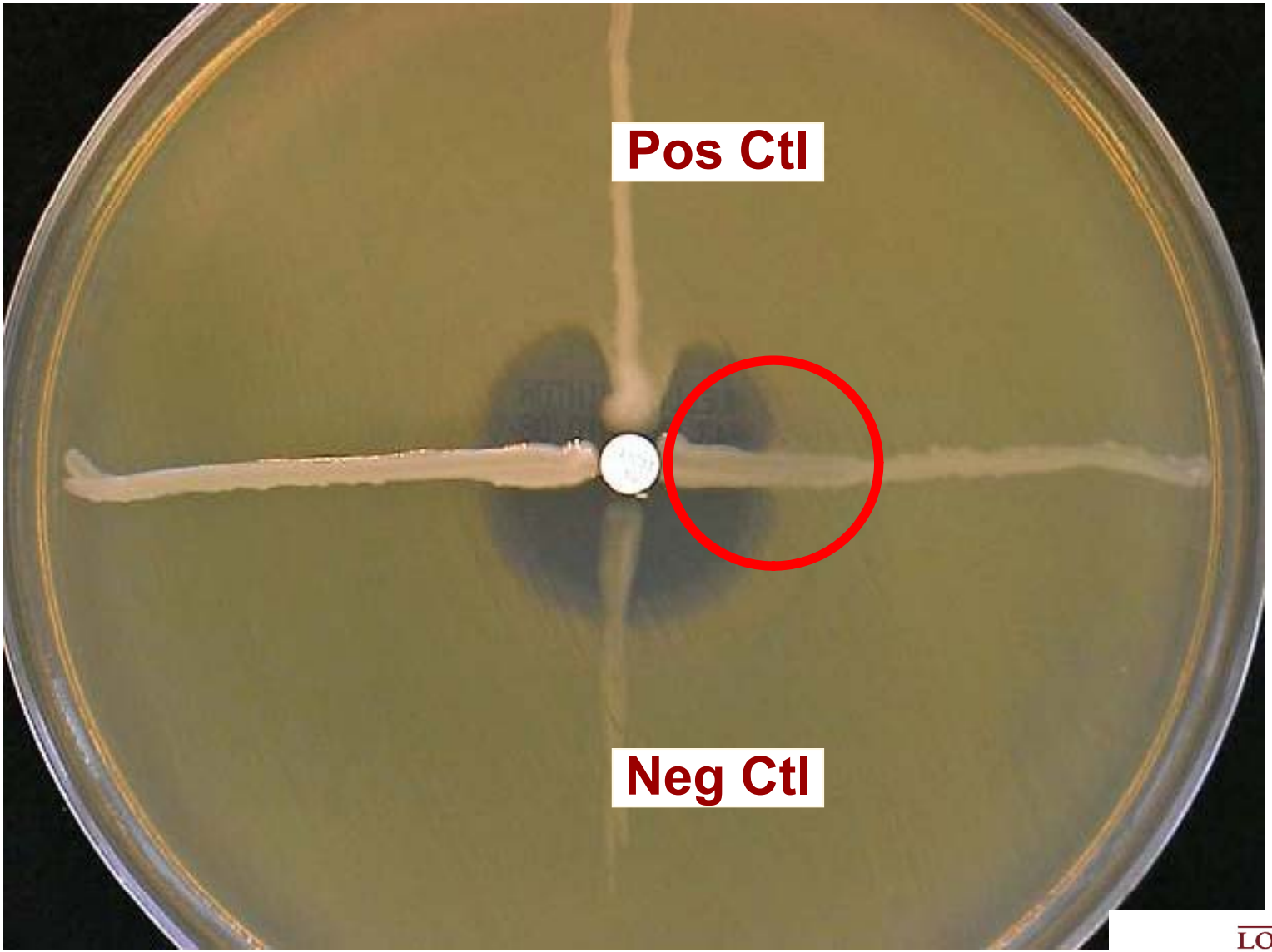
CAZ/CA	CFT	CFT/CA	ETP	IMP	Ø AUG	Ø CRM	Ø LVX	Ø MXF	Ø TIM
>2	>32	>4	>4	4	>16/8	>16	>4	>4	>64
	R		R	S	R	R	R	R	R

Extra Tests: ESBL -

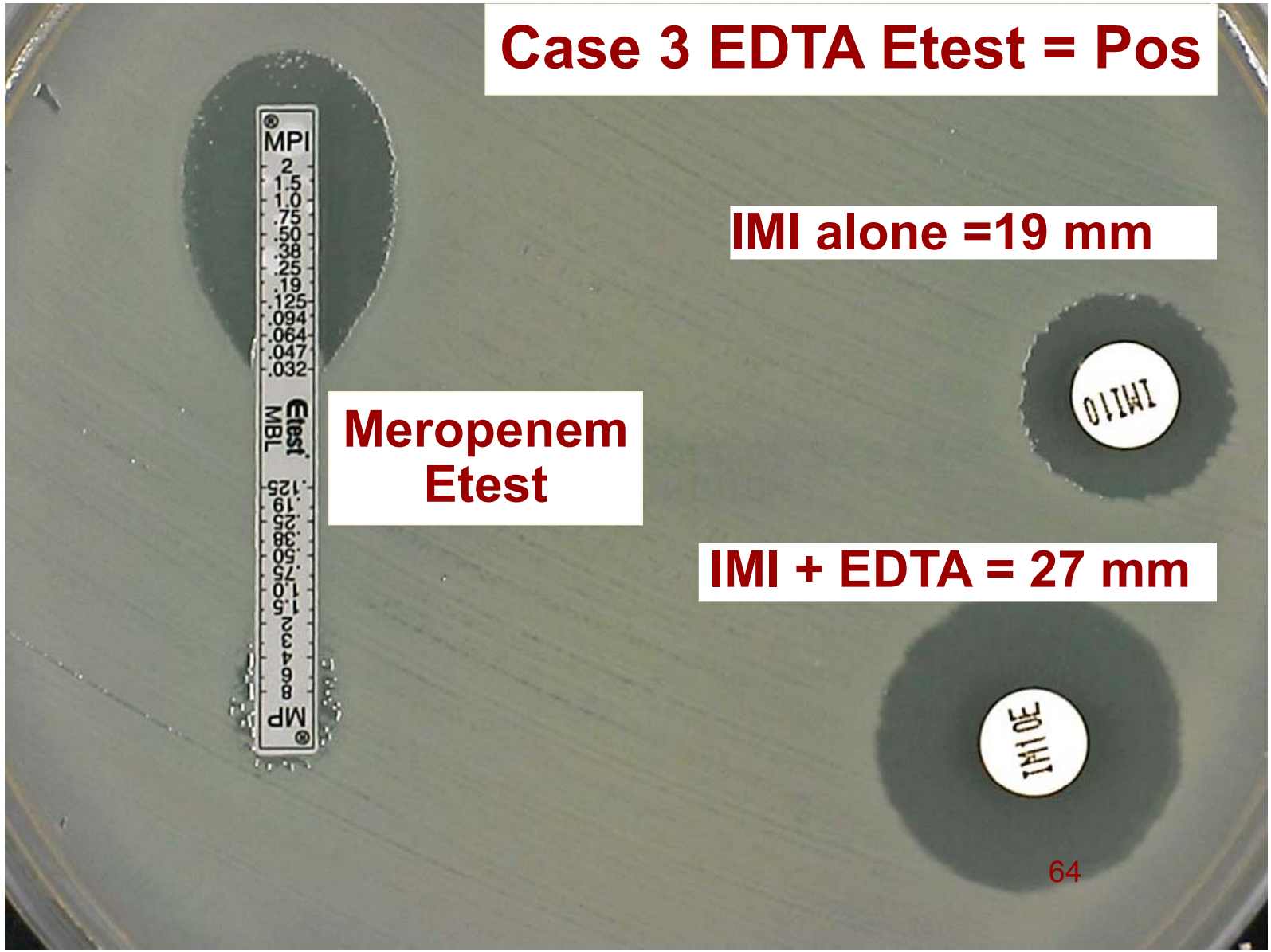
Case 3. 12 Disk



Case 3 - Modified Hodge Test



Rosco Diagnostica IMI/EDTA Disks
MBL Etest bioMerieux



And the Answer is …….

5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac-teriaceae	Non-fermenters
A [1]	KPC[2]	+++	+
B (metallo)	NDM[3], IMP, VIM,	+++	+++
D	OXA-48-like	+++	+/-

[1]also includes SME; [2]most common in USA; [3]increasing in USA

….but several types within 5 groups and other types of carbapenemases

(slide courtesy Janet Hindler)

MicroScan Report

Panel Data

Biotype: 73115012

Organism Identification:

	Organism	% Probability	Footnotes	Special Characteristics
1	E. coli	99.99		

Biochemical Results: (Biochemicals that are bolded and underlined are atypical for the first choice organism)

GLU	+	RAF	-	INO	-	URE	-	LYS	+	TDA	-	CIT	-	CL4	-	ACE	-	K4	+	P4	+
SUC	+	RHA	+	ADO	-	H2S	-	ARG	-	ESC	-	MAL	-	CF8	+	CET	-	NIT	+	TAR	-
SOR	+	ARA	+	MEL	+	IND	+	ORN	+	VP	-	ONPG	+	OXI		FD64	-	OF/G	+	TO4	+

MIC Results: (Antimicrobics marked with "Ø" are suppressed from Long and Short Format Patient Reports)

AM	A/S	P/T	CFZ	CAX	CAZ	CPE	MER	GM	Ø TE	TO	CP	T/S	Ø FD	AK
>16	>16/8	>64	>16	>32	>16	>16	>8	>8	>8	>8	>4	>2/38	<=32	>32
R	R	R	R	R	R	R	R	R	R	R	R	R		R

CAZ/CA	CFT	CFT/CA	ETP	IMP	Ø AUG	Ø CRM	Ø LVX	Ø MXF	Ø TIM
>2	>32	>4	>4	4	>16/8	>16	>4	>4	>64
	R		R	S	R	R	R	R	R

Extra Tests: ESBL -

Case 4

- Patient presenting with UTI grows *K. pneumoniae*. MHT, MBL Etest both negative.

5 Most Common Carbapenemases

Class	Carbapenemases	Enterobac-teriaceae	Non-fermenters
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D	OXA-48-like	+++	+/-

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….but several types within 5 groups and other types of carbapenemases

(slide courtesy Janet Hindler)

OXA-48 Carbapenemases

- Chromosomal gene from *Shewanella* spp. that moved via plasmid to Enterobacteriaceae (not yet to *Pseudomonas* or *Acinetobacter*)
- OXA-48 confers resistance or reduced susceptibility to carbapenems and penicillin-inhibitor combinations, but 3rd and 4th gen cephs remain susceptible unless have ESBL or AmpC
- Problem for detection by some automated systems that tend not to believe carbapenem-R, cephalosporin-S phenotypes
- Most reports from Turkey and North Africa. Only recently reported in US

OXA-48-Like* in Illinois

- On March 13, 2015, IDPH was notified two cases of OXA-48 like-producing CRE in suburban Chicago area.
- OXA-48 is an emerging mechanism for bacterial resistance to carbapenem antibiotics. These are the first CRE cases associated with OXA-48-like carbapenemases reported into Illinois XDRO Registry.

*** OXA-48-like refers to a family of similar OXA enzymes and includes: OXA-48, OXA-163, OXA-181, OXA-204, OXA-232, OXA-244**

OXA-48-Like in Illinois

- Both cases were detected from urine cultures; one was *Klebsiella pneumoniae* other was *Escherichia coli*.
- Patients had healthcare encounters at multiple facilities, including an acute care hospital, rehabilitation facility, assisted living, and skilled nursing facility. Neither patient had any known international travel or invasive medical procedures within the last six months.
- No epidemiological link between the cases

OXA-48-Like in Illinois

- Because these two patients had several transitions of care, they are examples of the importance of reporting CRE-positive patients into the XDRO Registry and indicating the mechanism of resistance (if available).
- The Registry data help inform the regional prevalence of CRE, identify the introduction of less common mechanisms of resistance, and enhance inter-facility communication.

CDC Lab Training Resources

- 5 e-learning courses in the basic curriculum–direct link: http://www.cdc.gov/labtraining/basic_courses.html
- Curriculum on antimicrobial susceptibility testing called MASTER – 3 e-learning courses offered: http://www.cdc.gov/labtraining/master_courses.html
- E-learning course on Packaging and Shipping Division 6.2 Materials. Relevant for facilities who need to send specimens to other labs for testing. Individuals who pass this course are eligible to be certified to pack and ship by their employer. http://www.cdc.gov/labtraining/course_listing/1043824.html

Antibiotic Resistance:
Darwin, Semelweis, & The Never Ending Story

Robert A. Weinstein, MD
May 12, 2015
Rush University Medical Center
Cook County Health & Hospitals System

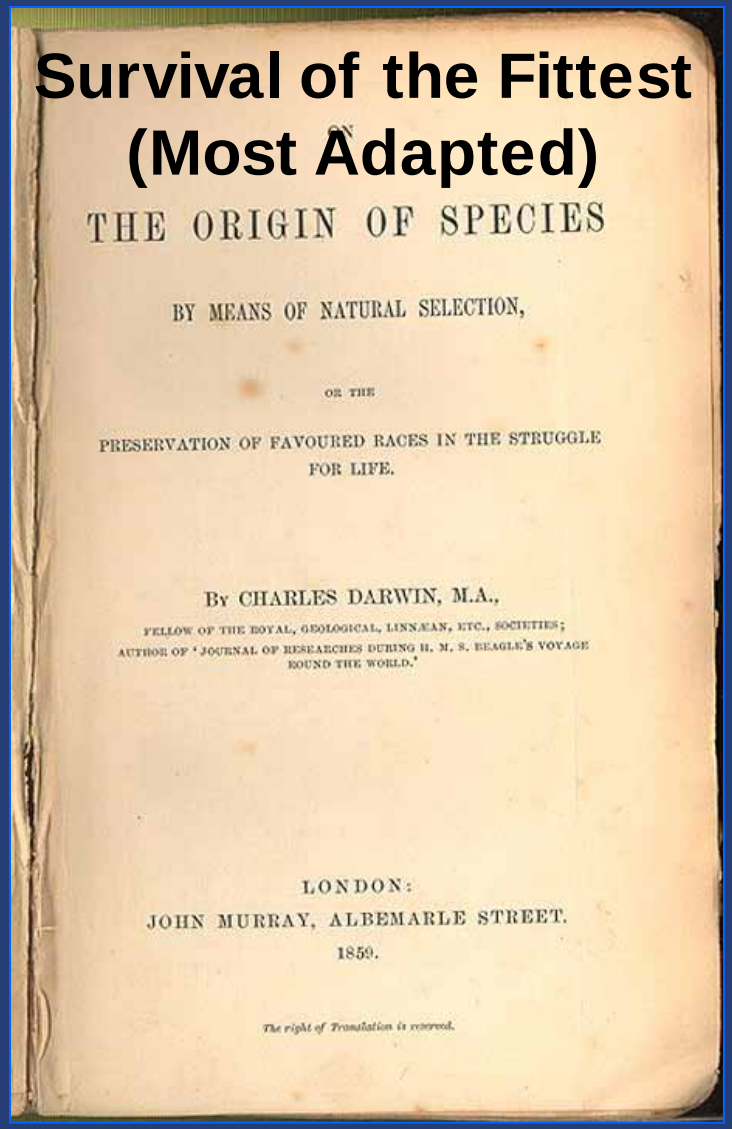
Disclosures: Sage Inc (Remote) & CDC (Current) Funding

Topics

- Background & Six Inconvenient Truths
- Trumping Low Hand Hygiene Rates
- Antibiotic Stewardship
- Microbiomes & Networks
- The National Action Plan

In the "Beginning"…

Survival of the Fittest (Most Adapted)



ON

THE ORIGIN OF SPECIES

BY MEANS OF NATURAL SELECTION,

OR THE

PRESERVATION OF FAVOURED RACES IN THE STRUGGLE FOR LIFE.

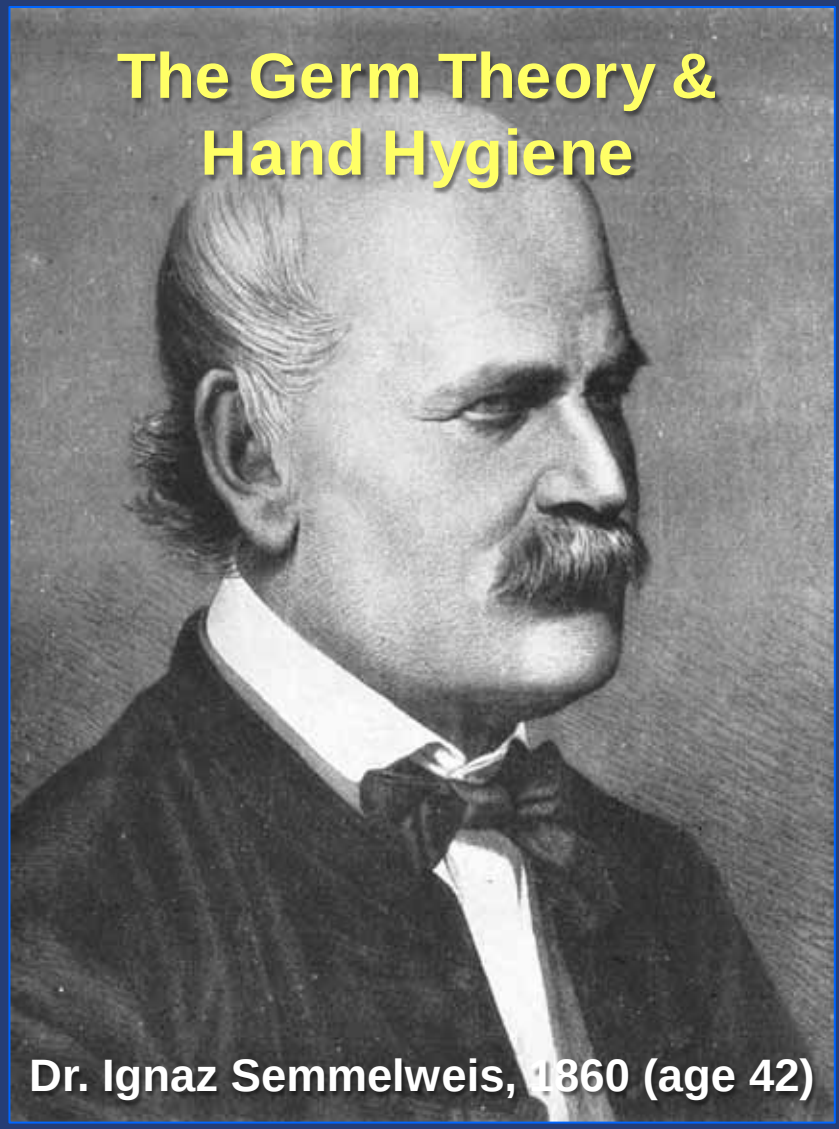
By CHARLES DARWIN, M.A.,

FELLOW OF THE ROYAL, GEOLOGICAL, LINNÆAN, ETC., SOCIETIES;
AUTHOR OF 'JOURNAL OF RESEARCHES DURING H. M. S. BEAGLE'S VOYAGE ROUND THE WORLD.'

LONDON:
JOHN MURRAY, ALBEMARLE STREET.
1859.

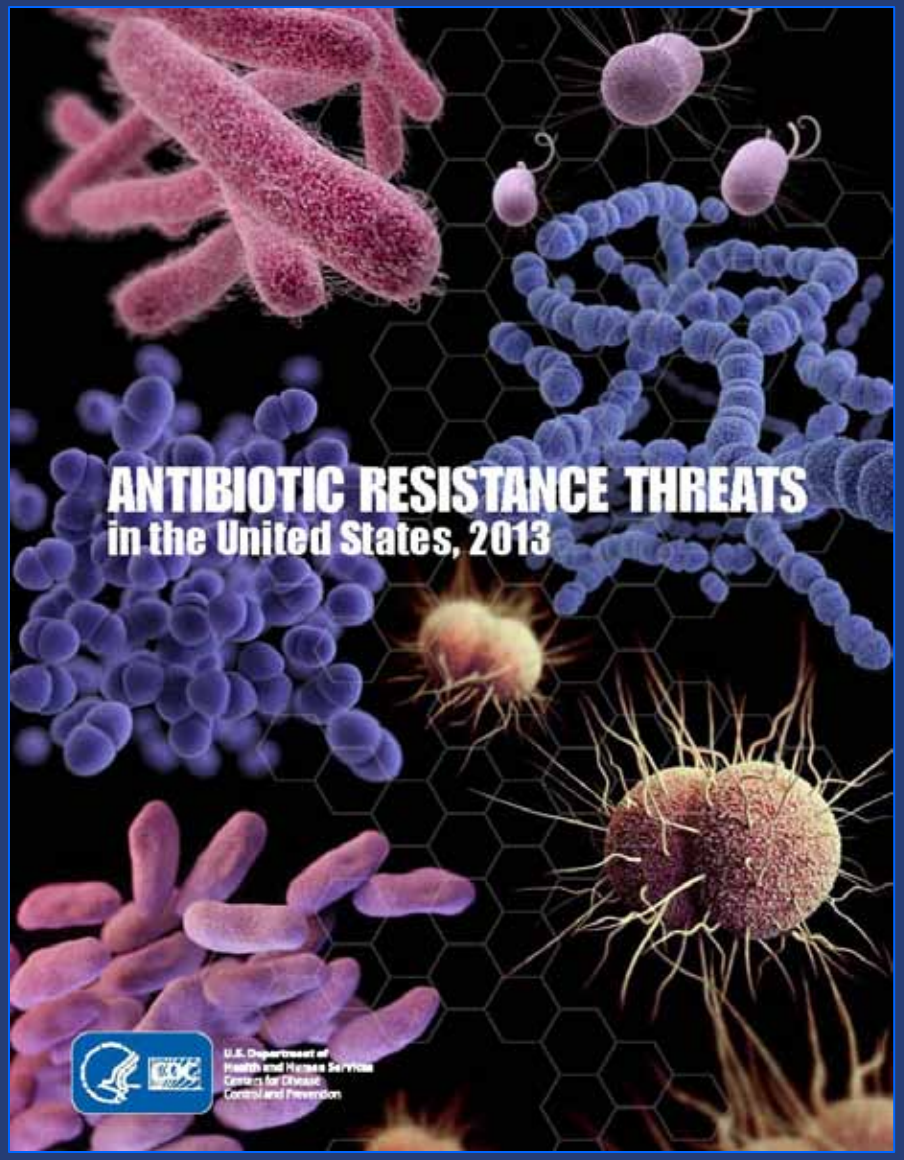
The right of Translation is reserved.

The Germ Theory & Hand Hygiene



Dr. Ignaz Semmelweis, 1860 (age 42)

… And Now



http://www.cdc.gov/drugresistance/threat-report-2013/

Urgent Threats

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

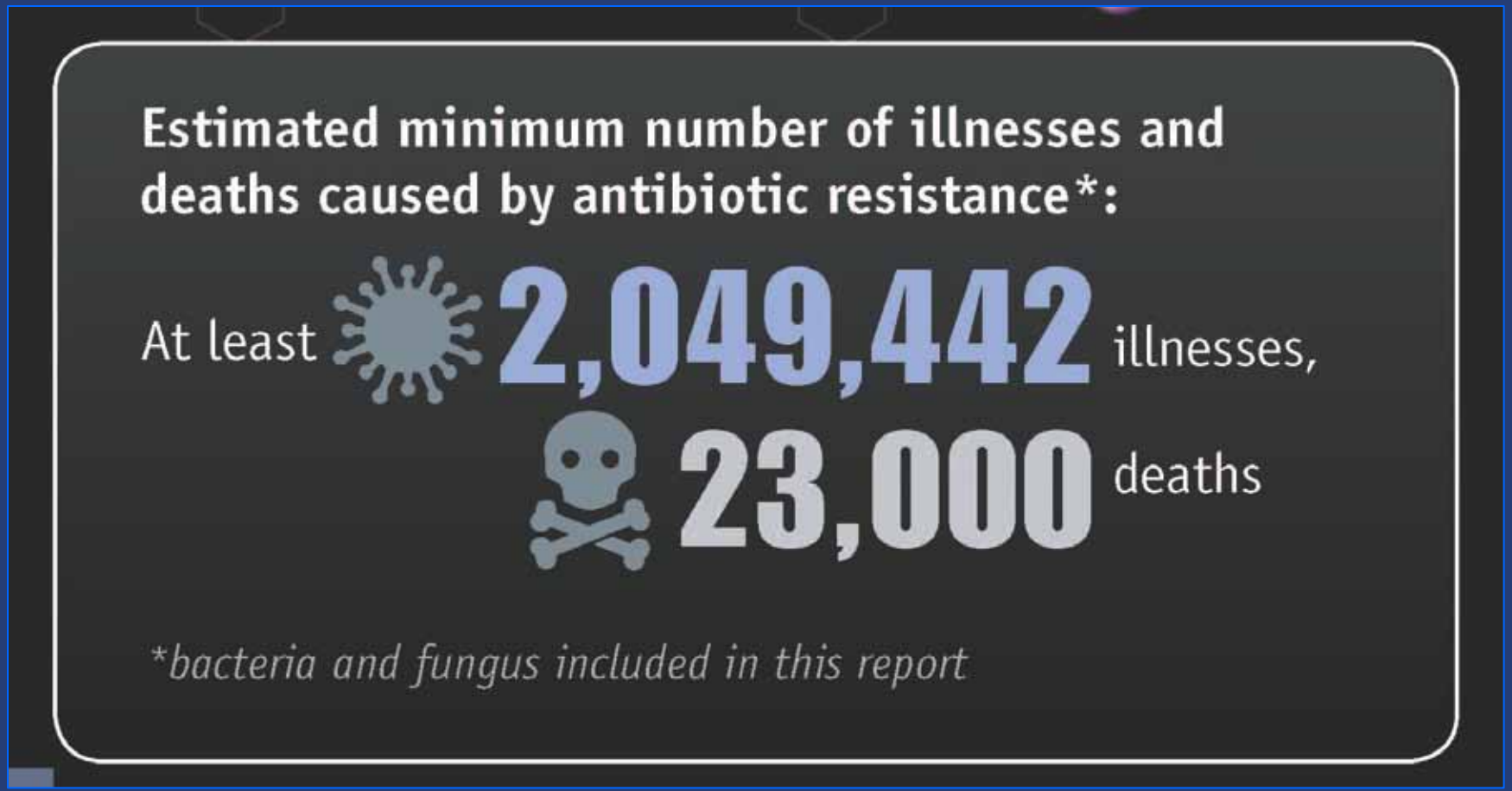
Serious Threats

- 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

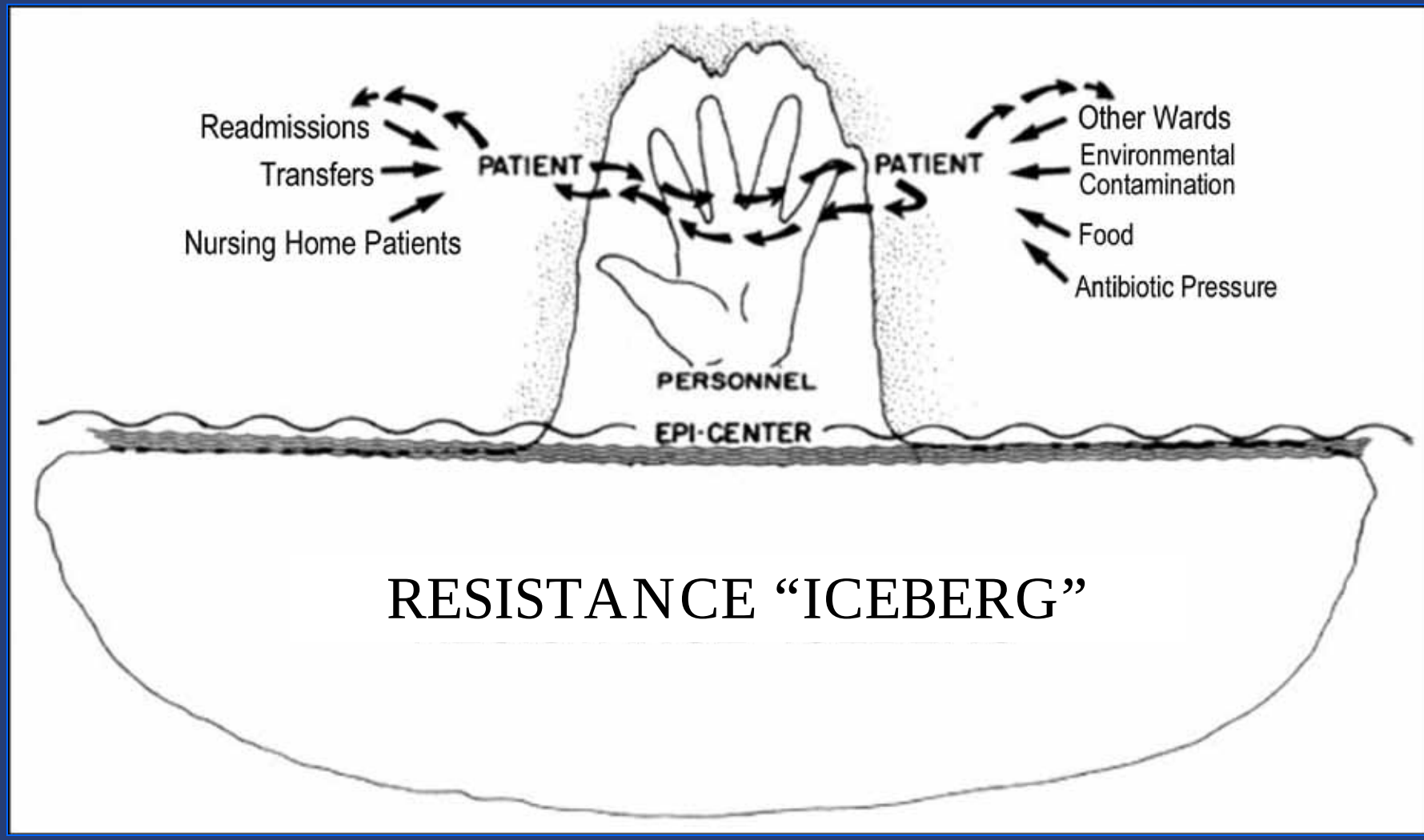
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

http://www.cdc.gov/drugresistance/threat-report-2013/



http://www.cdc.gov/drugresistance/threat-report-2013/

Resistance Bad — Control Measures Are Based on Epidemiology



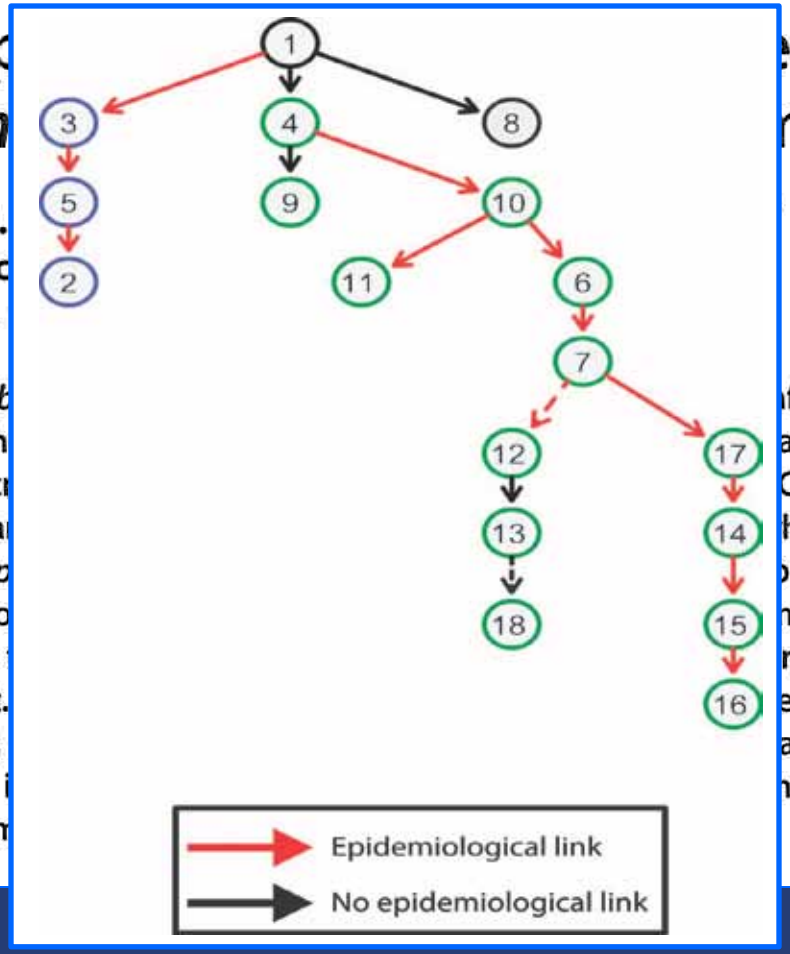
Adapted from Weinstein & Kabins, *Am J Med* 1981; 70:449-54

Putative map of *K. pneumoniae* Transmission During Outbreak

Tracking a Hosp … enem-Resistant *Klebsiella pneun* … ne Sequencing

Evan S. Snitkin,[1] Adrian M. … NISC Comparative Sequenc … Tara N. Palmore,[2]* Julia A. …

The Gram-negative bacteria *Kleb* … fections, primarily among immunocompromised patients. Th … as left few treatment options, making infection containment c… Clinical Center experienced an outbreak of carbapenem-resista… hom died. Whole-genome sequencing was performed on *K. p* … reak progressed despite early implementation of infection co… iological analysis traced the outbreak to three independent … rged 3 weeks before the next case became clinically apparent. … e for unexpected transmission routes, with subsequent mining … ations for these transmissions. Our analysis demonstrates that i… yield actionable insights and facilitate the control of nosocom…



Snitkin et al, *Sci Transl Med* 2012;
http://stm.sciencemag.org/content/4/148/148ra116.full.html

The Epidemiology of Healthcare-associated Infections is Generally Understood

Epidemiology of Endemic Nosocomial Resistance		
Factor leading to resistance	Relative contribution	
	Gram (-)	Gram (+)
Cross-infection via hands of hospital personnel	30-40%	60-80%
Antibiotic pressures	30-40%	10-20%
“Community” acquired	20-25%	10-50%
Other (contamination of environment, food, air: personnel carriers; unknown)	20+%	10-20+%

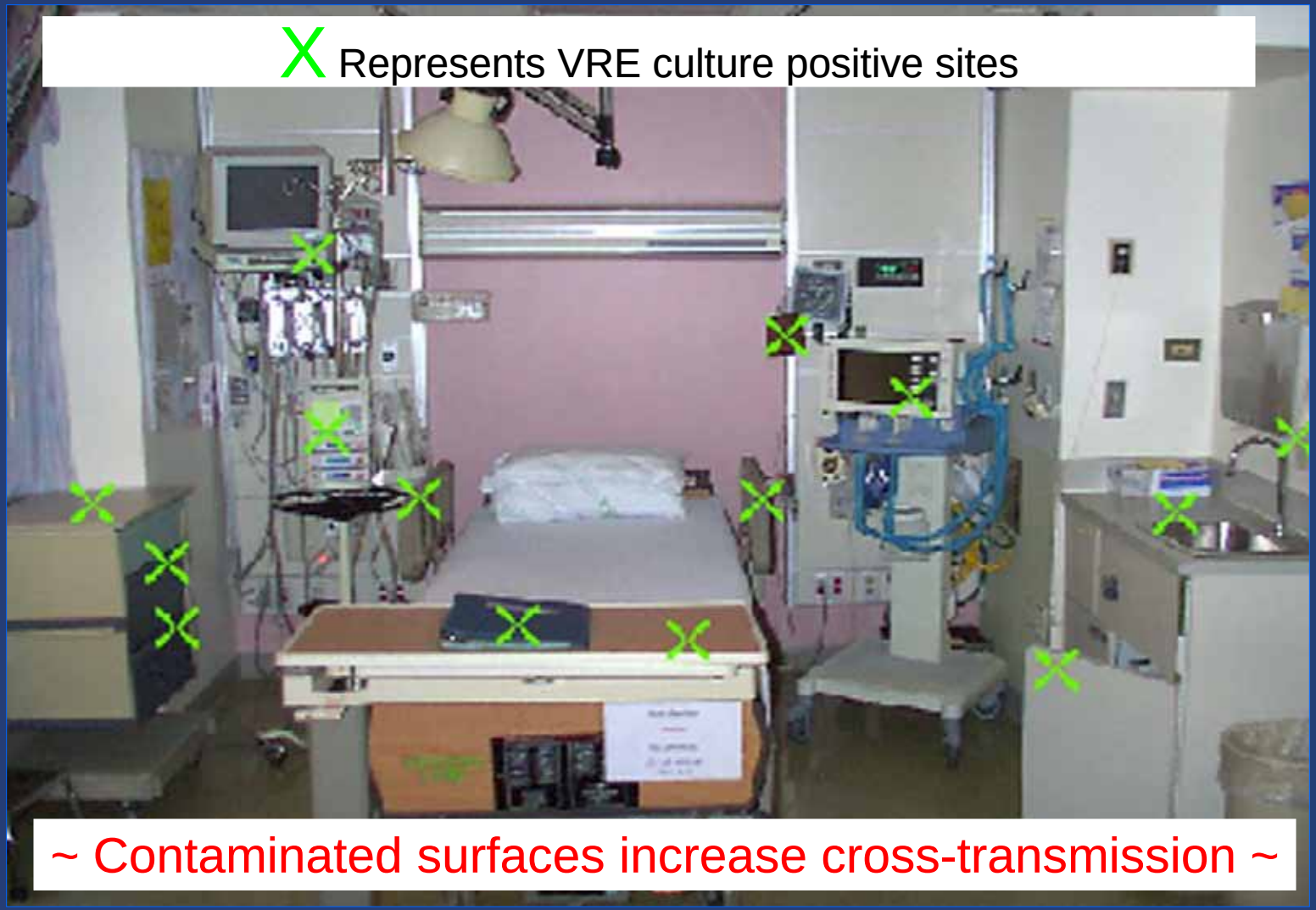
Six Inconvenient Truths About Antibiotic Resistance

- Hand hygiene often lacking
- Physicians believe antibiotic resistance is real but not in their hospital / practice
- Physicians view “antibiotic stewardship” as taking too much time and annoying patients
- Judicious antibiotic use in animal husbandry largely voluntary
- Bacterial “genetic barriers” to resistance vary greatly
- Repeated Federal Plans to control resistance

Attacking the Iceberg

Hand Hygiene – Appealing to Our Basic Instincts to Control Healthcare-associated Infections and Antibiotic Resistance

The Inanimate Environment Can Facilitate Transmission



Hota et al, *J Hosp Infect* 2009; 71:123-31

Source Control of MDROs — Remove the Fecal Patina

Chlorhexidine Gluconate to Cleanse Patients in a Medical Intensive Care Unit

The Effectiveness of Source Control to Reduce the Bioburden of Vancomycin-Resistant Enterococci

Michael O. Vernon, DrPH; Mary K. Hayden, MD; William E. Trick, MD; Robert A. Hayes, BSc; Donald W. Blom, RN; Robert A. Weinstein, MD; for the Chicago Antimicrobial Resistance Project (CARP)

Background: Historically, methods of interrupting pathogen transmission have focused on improving health care workers' adherence to recommended infection control practices. An adjunctive approach may be to use source control (eg, to decontaminate patients' skin).

Methods: We performed a prospective sequential-group single-arm clinical trial in a teaching hospital's medical intensive care unit from October 2002 to December 2003. We bathed or cleansed 1787 patients and assessed them for acquisition of vancomycin-resistant enterococci (VRE). We performed a nested study of 86 patients with VRE colonization and obtained culture specimens from 758 environmental surfaces and 529 health care workers' hands. All patients were cleansed daily with the procedure specific to the study period as follows: period 1, soap and water baths; period 2, cleansing with cloths saturated with 2% chlorhexidine gluconate; and period 3, cloth cleansing without chlorhexidine. We measured colonization of patient skin by VRE, health care worker hand or environmental surface contamination by VRE, and patient acquisition of VRE rectal colonization.

Results: Compared with soap and water baths, cleansing patients with chlorhexidine-saturated cloths resulted in 2.5 $\log_{10}$ less colonies of VRE on patients' skin and less VRE contamination of health care workers' hands (risk ratio [RR], 0.6; 95% confidence interval [CI], 0.4-0.8) and environmental surfaces (RR, 0.3; 95% CI, 0.2-0.5). The incidence of VRE acquisition decreased from 26 colonizations per 1000 patient-days to 9 per 1000 patient-days (RR, 0.4; 95% CI, 0.1-0.9). For all measures, effectiveness of cleansing with nonmedicated cloths was similar to that of soap and water baths.

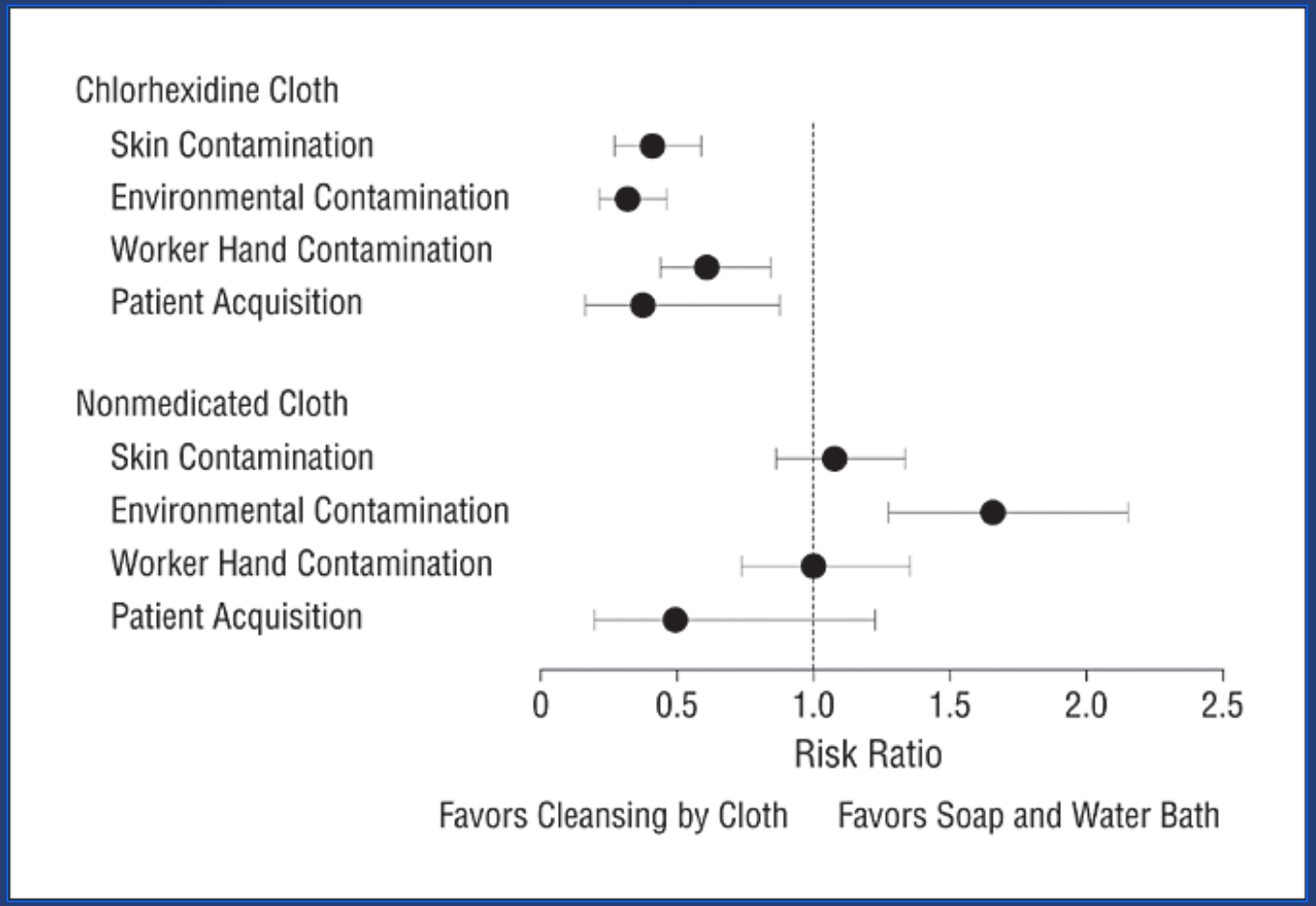
Conclusion: Cleansing patients with chlorhexidine-saturated cloths is a simple, effective strategy to reduce VRE contamination of patients' skin, the environment, and health care workers' hands and to decrease patient acquisition of VRE.

Arch Intern Med. 2006;166:306-312

MDRO, Multi-drug resistant organism

Vernon et al, *Arch Intern Med* 2006; 166:306-12

Risk Ratios for Skin Contamination and Environmental or Healthcare Worker Contamination by or Patient Acquisition of VRE



VRE, Vancomycin-resistant enterococci

Vernon et al, *Arch Intern Med* 2006; 166:306-12

Effectiveness of Chlorhexidine Bathing to Reduce Catheter-Associated Bloodstream Infections in Medical Intensive Care Unit Patients

Susan C. Bleasdale, MD; William E. Trick, MD; Ines M. Gonzalez, MD; Rosie D. Lyles, MD; Mary K. Hayden, MD; Robert A. Weinstein, MD

Objective: To determine whether patients bathed daily with chlorhexidine gluconate (CHG) have a lower incidence of primary bloodstream infections (BSIs) compared with patients bathed with soap and water.

Methods: The study design was a 52-week, 2-arm, crossover (ie, concurrent control group) clinical trial with intention-to-treat analysis. The study setting was the 22-bed medical intensive care unit (MICU), which comprises 2 geographically separate, similar 11-bed units, of the John H. Stroger Jr (Cook County) Hospital, a 464-bed public teaching hospital in Chicago, Illinois. The study population comprised 836 MICU patients. During the first of 2 study periods (28 weeks), 1 hospital unit was randomly selected to serve as the intervention unit in which patients were bathed daily with 2% CHG-impregnated washcloths (Sage 2% CHG cloths; Sage Products Inc, Cary, Illinois); patients in the concurrent control unit were bathed daily with soap and water. After a 2-week washout period at the end of the first period, cleansing methods were crossed over for 24 more weeks. Main outcome measures included incidences of primary BSIs and clinical (culture-negative) sepsis (primary outcomes) and incidences of other infections (secondary outcomes).

Results: Patients in the CHG intervention arm were significantly less likely to acquire a primary BSI (4.1 vs 10.4 infections per 1000 patient days; incidence difference, 6.3 [95% confidence interval, 1.2-11.0). The incidences of other infections, including clinical sepsis, were similar between the units. Protection against primary BSI by CHG cleansing was apparent after 5 or more days in the MICU.

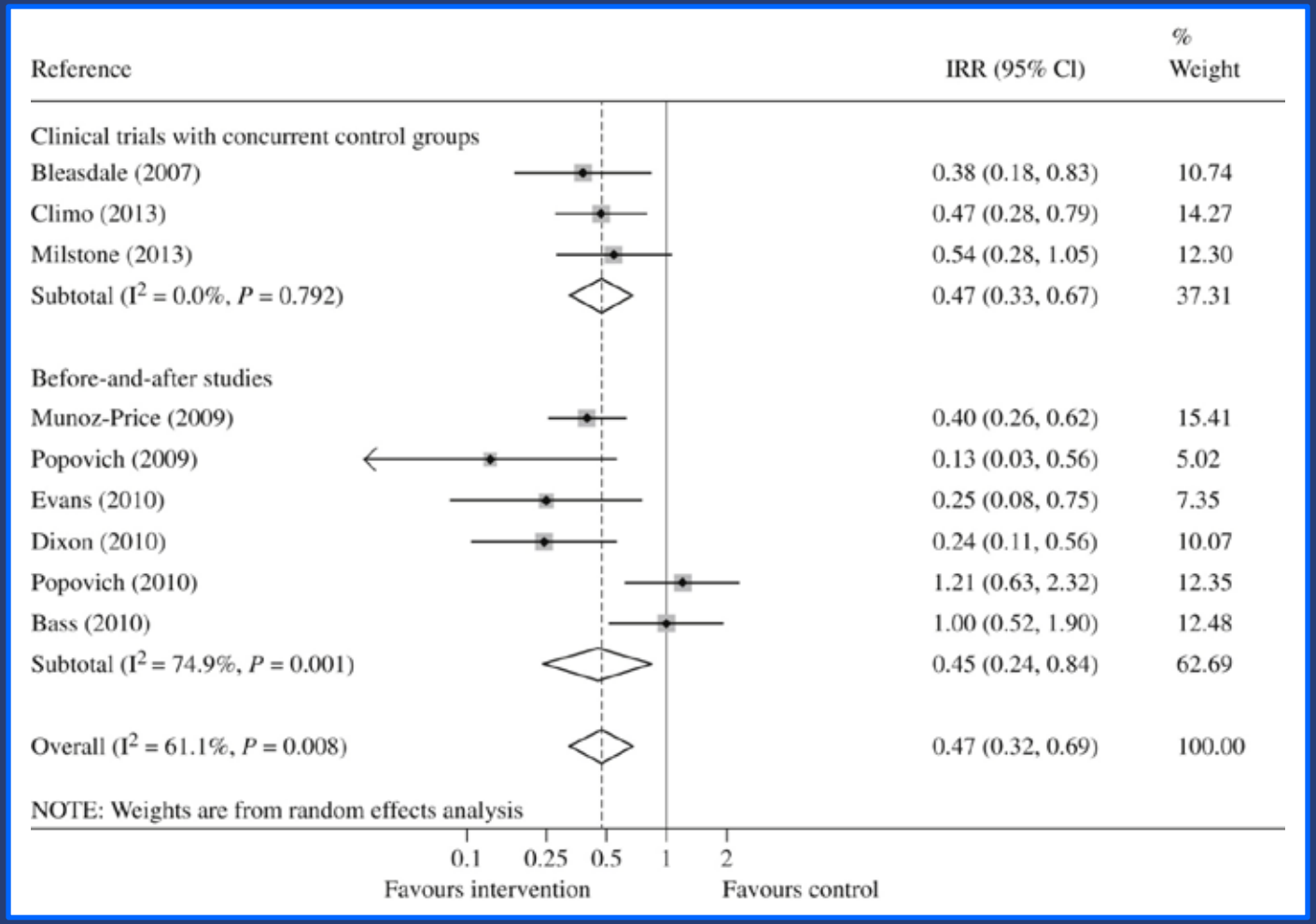
Conclusions: Daily cleansing of MICU patients with CHG-impregnated cloths is a simple, effective strategy to decrease the rate of primary BSIs.

Trial Registration: clinicaltrials.gov Identifier: NCT00130221

Arch Intern Med. 2007;167(19):2073-2079

Bleasdale et al, *Arch Intern Med* 2007; 167:2073-9

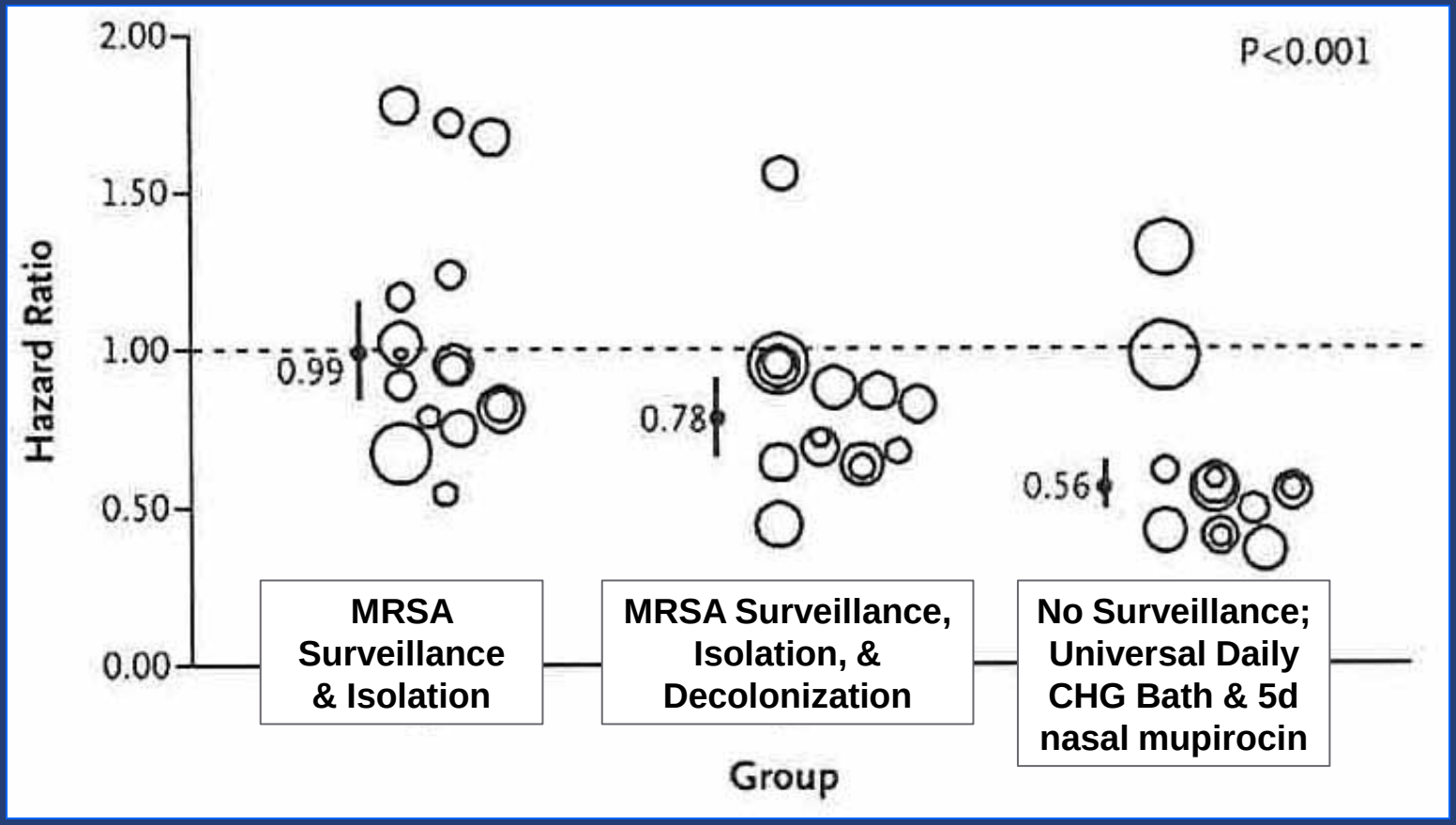
Effect of No-rinse 2% Chlorhexidine Washcloths on Reducing Incidence of Central-line Associated Bloodstream Infection



IRR, incidence rate ratio; CI, confidence interval

Karki and Cheng, *J Hosp Infect* 2012; 82:71-84; *J Hosp Infect* 2013; 84:266-7

Effect of Interventions on Bloodstream Infection from Any Pathogen



Shown are hazard ratios and 95% confidence intervals (vertical lines) for outcomes attributable to intensive care unit. Results based on unadjusted proportional-hazard models that accounted for clustering within hospitals. Bubble plots of hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to group effects are shown. Bubble size indicates relative number of patients contributing data to trial.

Huang et al, *N Engl J Med* 2013; 368(24):2255-65

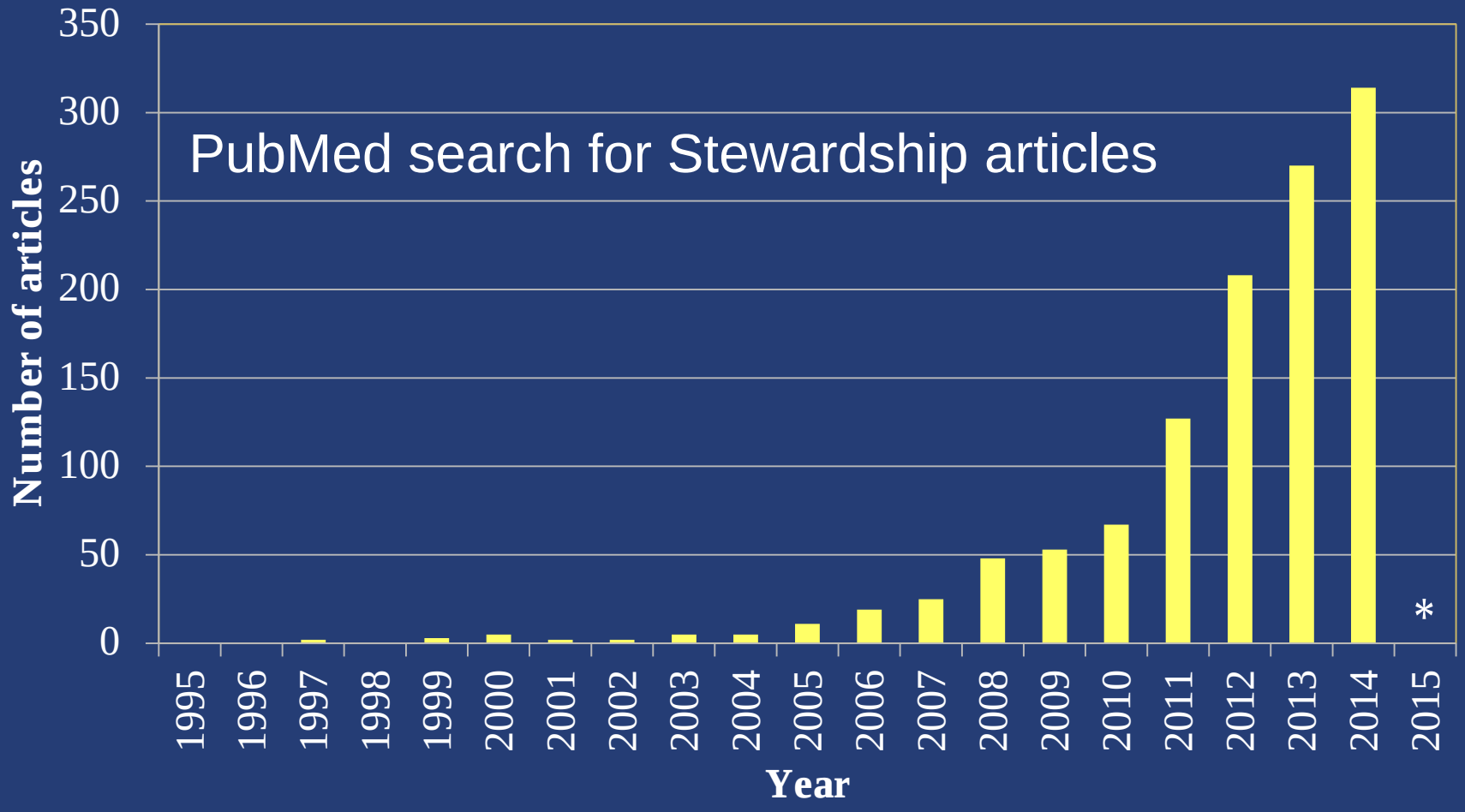
Screening Inpatients for MRSA — Case Closed

Michael B. Edmond, M.D., M.P.H., and Richard P. Wenzel, M.D.

"…..the folly of pursuing legislative mandates when evidence is lacking has been shown, and laws mandating MRSA screening should be repealed."

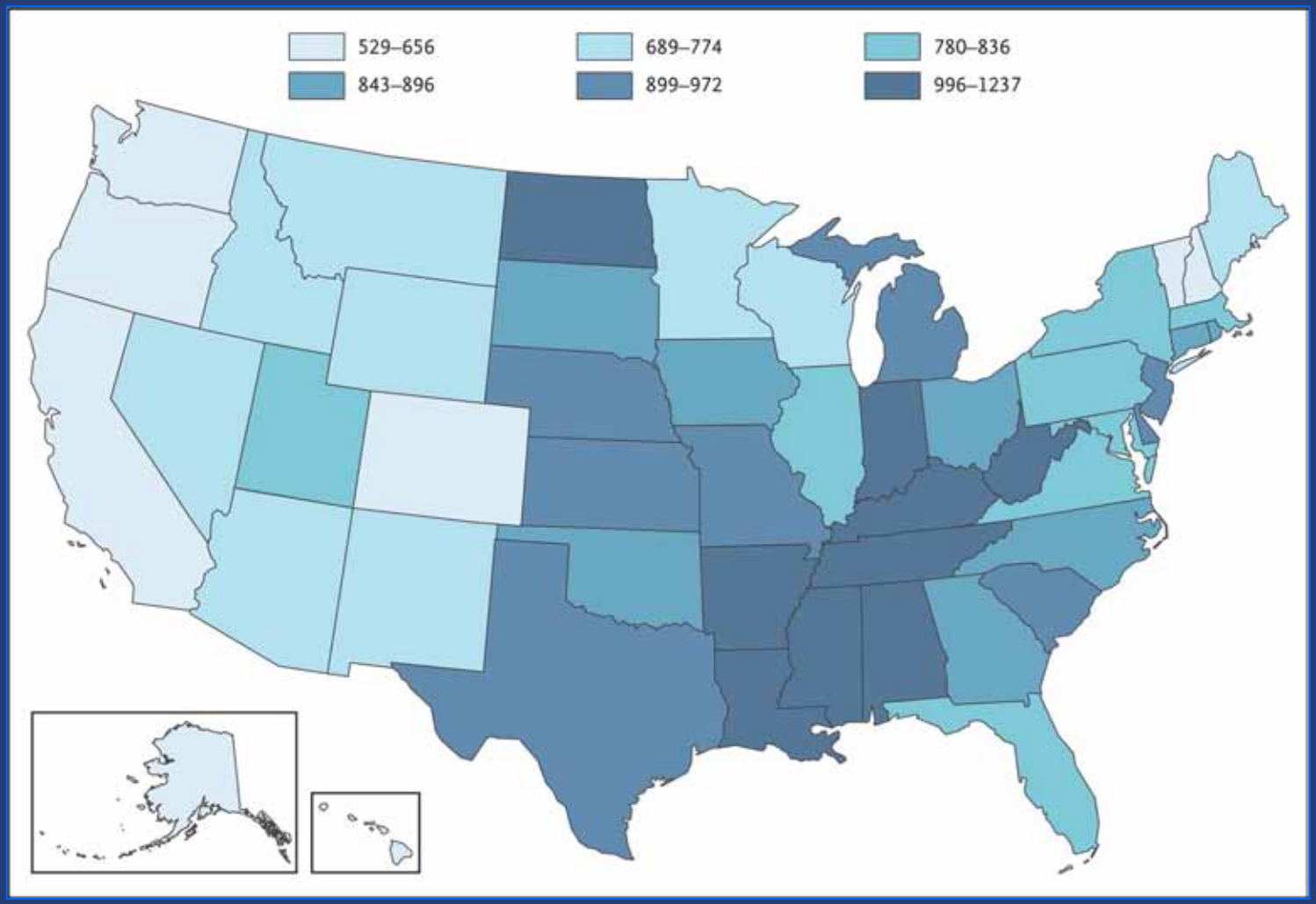
Edmond & Wenzel, *N Engl J Med* 2013; 368:2314-5

The 800 lb Gorilla
"Antimicrobial Stewardship"



*113 citations on PubMed as of April 14, 2015

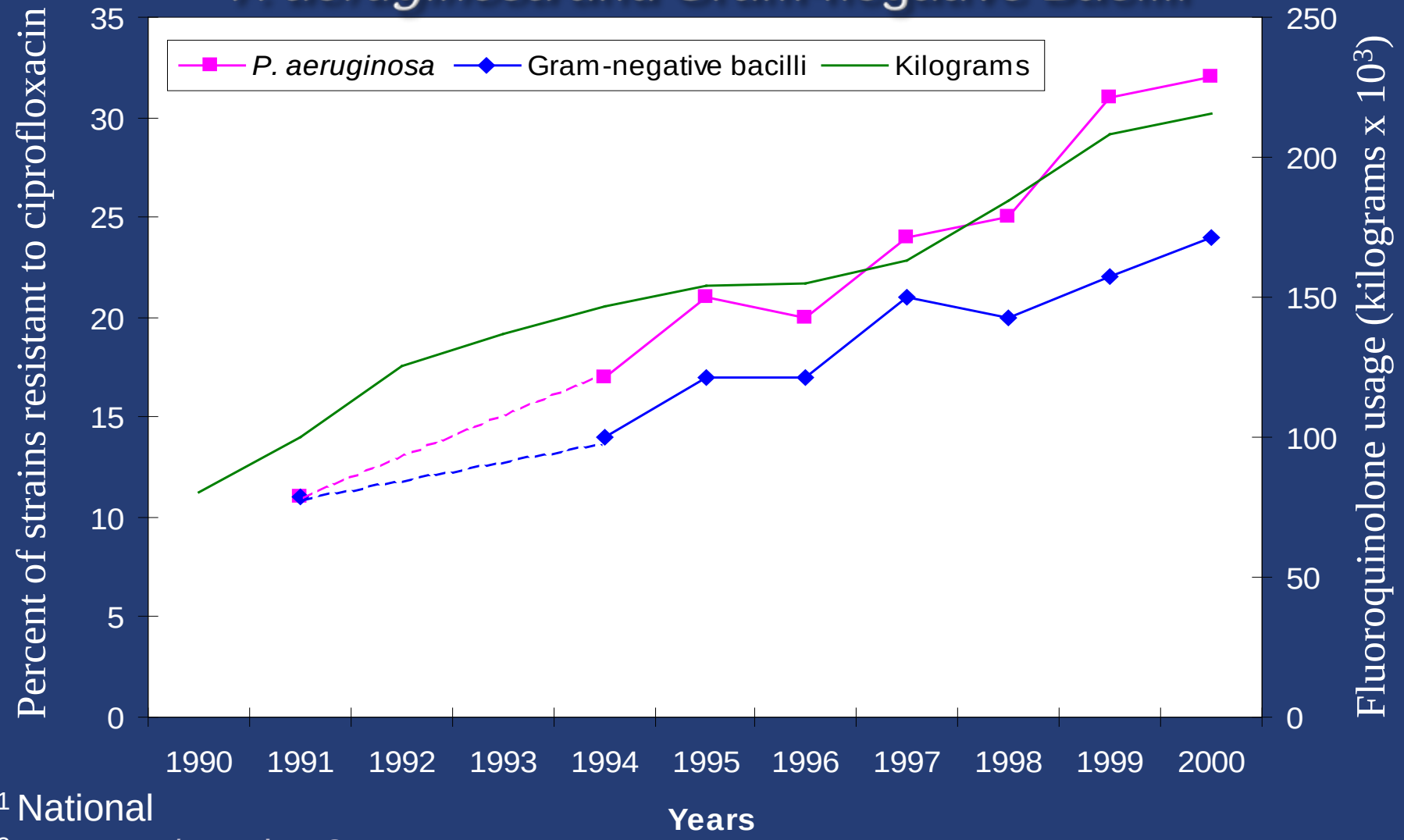
Profligate Antibacterial Use: Antibiotic Prescriptions per 1,000 Persons of All Ages According to State, 2010



Hicks et al, *N Engl J Med* 2013; 368:1461-2

Antimicrobial Use and Risk of Resistance

Fluoroquinolone Usage[1] and Resistance Rates in *P. aeruginosa* and Gram-negative Bacilli[2]

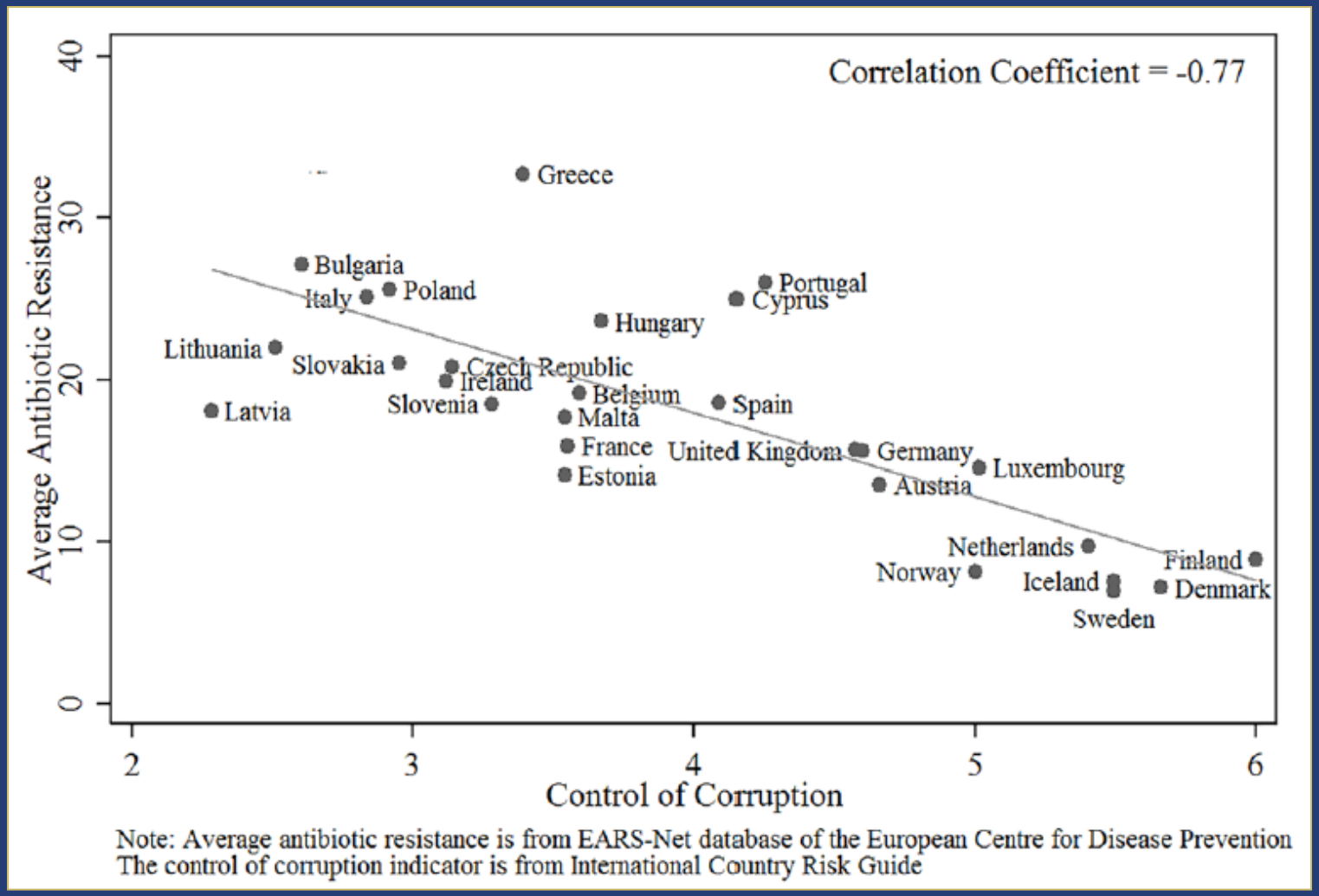


[1] National

[2] 77 to 117/year in 43 states.

Neuhauser et al, *JAMA* 2003; 289(7):885-8.

Average Microbial Resistance *vs* Control of Corruption



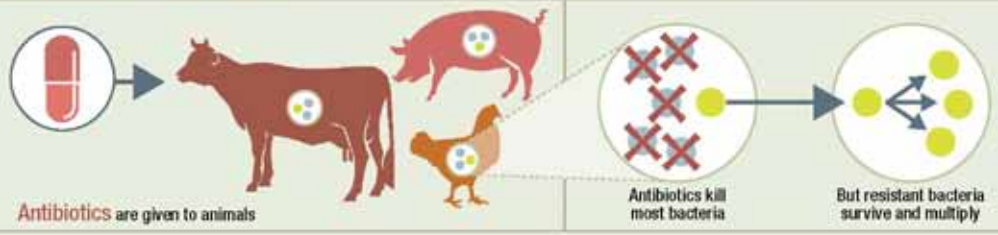
Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
The control of corruption indicator is from International Country Risk Guide

Collignon et al, PLoS One., 2015 Mar 18; 10(3):e0116746

ANTIBIOTIC RESISTANCE

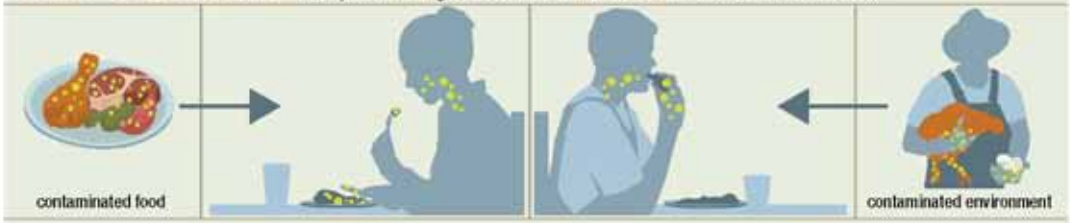
from the farm to the table

RESISTANCE All animals carry **bacteria** in their intestines



SPREAD Resistant bacteria can spread to...

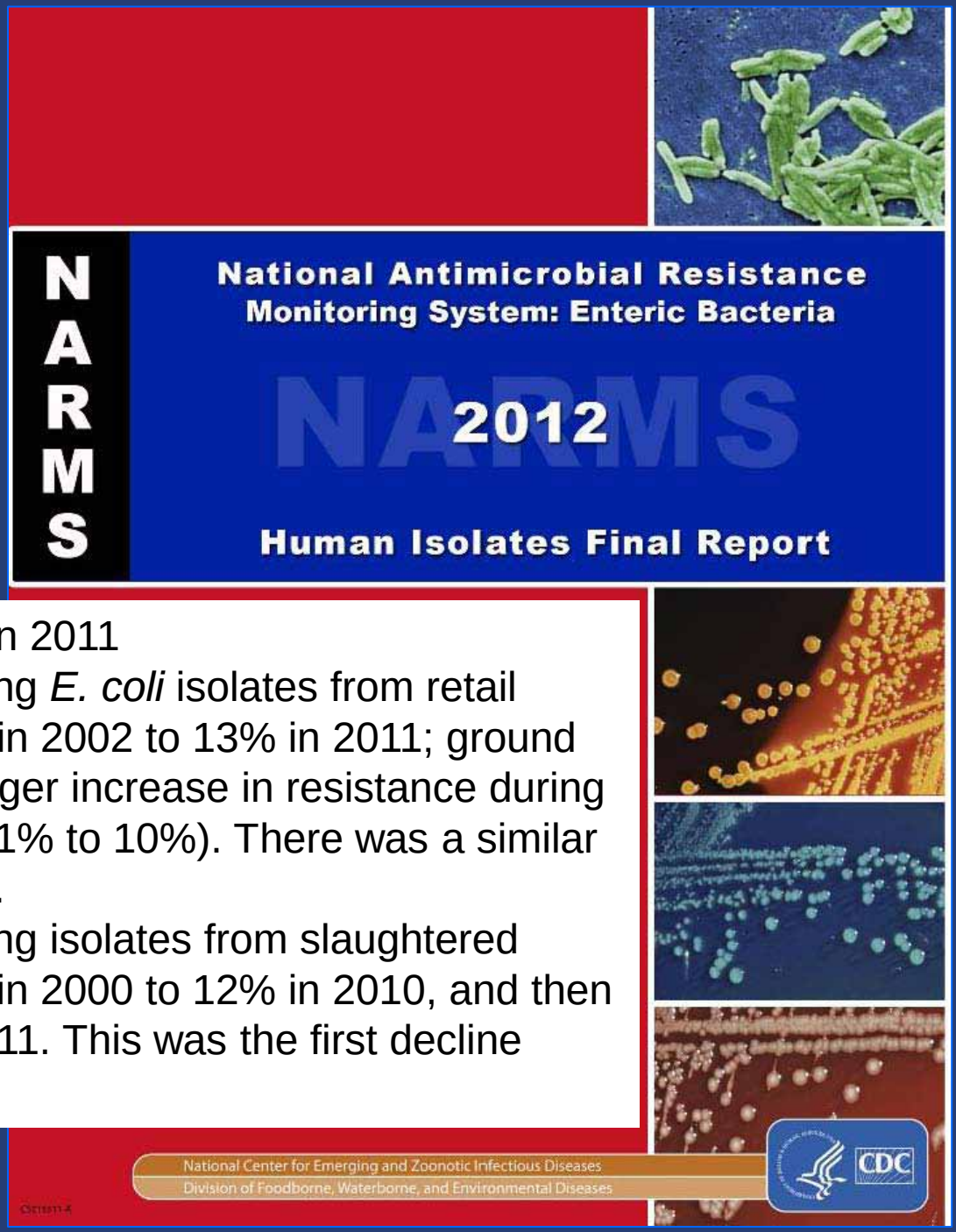
EXPOSURE People can get sick with resistant infections from...



IMPACT Some resistant infections cause...

CDC

Learn more about antibiotic resistance and food safety at **www.cdc.gov/foodsafety/antibiotic-resistance.html**



Important Resistance Trends in 2011

- Ceftriaxone resistance among *E. coli* isolates from retail chicken increased from 8% in 2002 to 13% in 2011; ground turkey isolates showed a larger increase in resistance during the same time period (from 1% to 10%). There was a similar trend in Salmonella isolates.
- Ceftriaxone resistance among isolates from slaughtered chicken increased from 6% in 2000 to 12% in 2010, and then dropped slightly to 9% in 2011. This was the first decline observed in the last 3 years

Seven Core Elements Critical to the Success of Hospital Antibiotic Stewardship Programs

- Leadership commitment: Dedicating necessary human, financial, and information technology resources
- Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs has shown that a physician leader is effective
- Drug expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use
- Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment need after a set period of initial treatment (i.e., "antibiotic time out" after 48 hours)
- Tracking: Monitoring antibiotic prescribing and resistance patterns
- Reporting: Regular reporting information on antibiotic use and resistance to doctors, nurses and relevant staff members
- Education: Educating clinicians about resistance and optimal prescribing

Source: CDC. Core elements of hospital antibiotic stewardship programs. Atlanta, GA: US Department of Health and Human Services, 2014. Available at http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html

AS — A CMS Condition of Participation (CoP)?

CMS

- In 2015 plans to propose AS as a CoP, with implementation in 2017
- Challenge – Permit flexibility based on size/resources (http://www.modernhealthcare.com/article/20141220/magazine/312209980)
- Making AS a CoP – "A Transformative Effect"?

States

- Only California mandates AS programs in hospitals

Do we need "**An antibiotic prenuptial agreement**"?

- Antibiotic prescribing licenses, consequences for prescriber non-adherence, antibiotic time-outs (and/or auto-stops), out-reach (to prescriber and public) (*Lancet Infect Dis* 2014; 14:1168-9)

AS, Antimicrobial Stewardship

Seeking the Holy Grail of Treatment

Procalcitonin to Guide Duration of Antimicrobial Therapy in Intensive Care Units: A Systematic Review

Rajender Agarwal[1] and David N. Schwartz[2,3]

Procalcitonin guidance of antimicrobial duration appears to decrease antimicrobial use in the ICU safely and significantly and may also decrease the length of stay in the ICU.

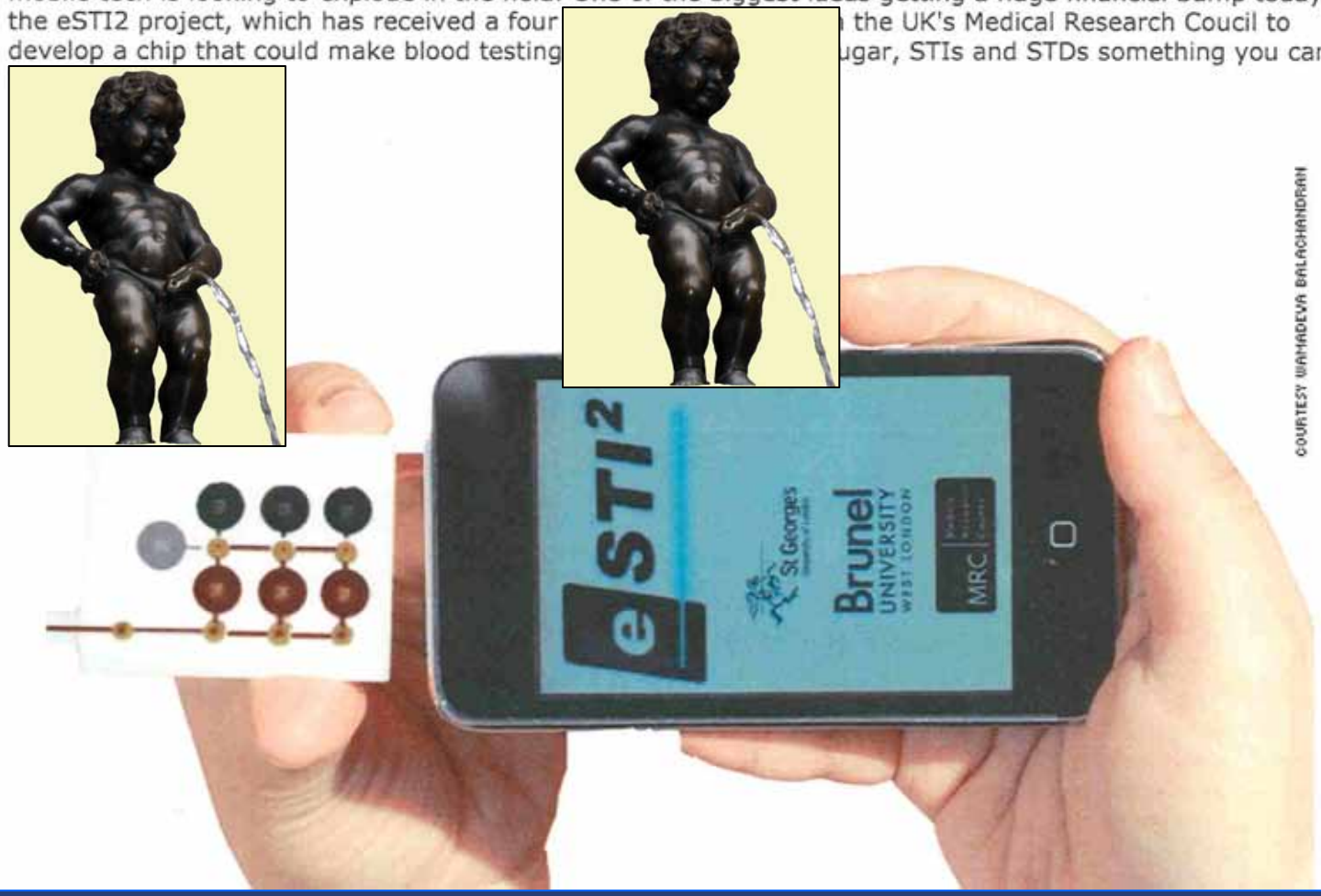
of ICU stay was significantly decreased in 2 studies but was unchanged in the others. Neither infection relapse nor mortality varied significantly in any of the studies. Procalcitonin guidance of antimicrobial duration appears to decrease antimicrobial use in the ICU safely and significantly and may also decrease the length of stay in the ICU.

Agarwal and Schwartz, *Clin Infect Dis* 2011; 53(4):379-87

NEEDED: Rapid Bedside Work-up — eDiagnosis

eSTI2 project looks to develop blood testing chip for mobile devices

The mobile industry is making its way into a ton of fields and one area that it is becoming more and more influential is the medical field. From tablet implementation in hospitals to scheduling appointments online, mobile tech is looking to explode in the field. One of the biggest ideas getting a huge financial bump today is the eSTI2 project, which has received a four [illegible] the UK's Medical Research Coucil to develop a chip that could make blood testing [illegible]ugar, STIs and STDs something you can



COURTESY WAHADEVA BALACHANDRAN

Bacterial Genetic Mechanism and Barriers for Resistance: Traditional Interventions

Mutations: Stewardship (& Infection Control)

Imipenem-S *P. aeruginosa* —Imipenem→ Imipenem-R *P. aeruginosa*

Gene Transfer: Infection control (& Stewardship)

Multi-S *E. coli* —NDM-containing Klebsiella→ NDM-containing *E. coli*

Clonal Dissemination: Infection Control (& Stewardship)

MSSA —Methicillin→ "NEVER" MRSA

MRSA → Clonal Dissemination

High Barrier: Fate?

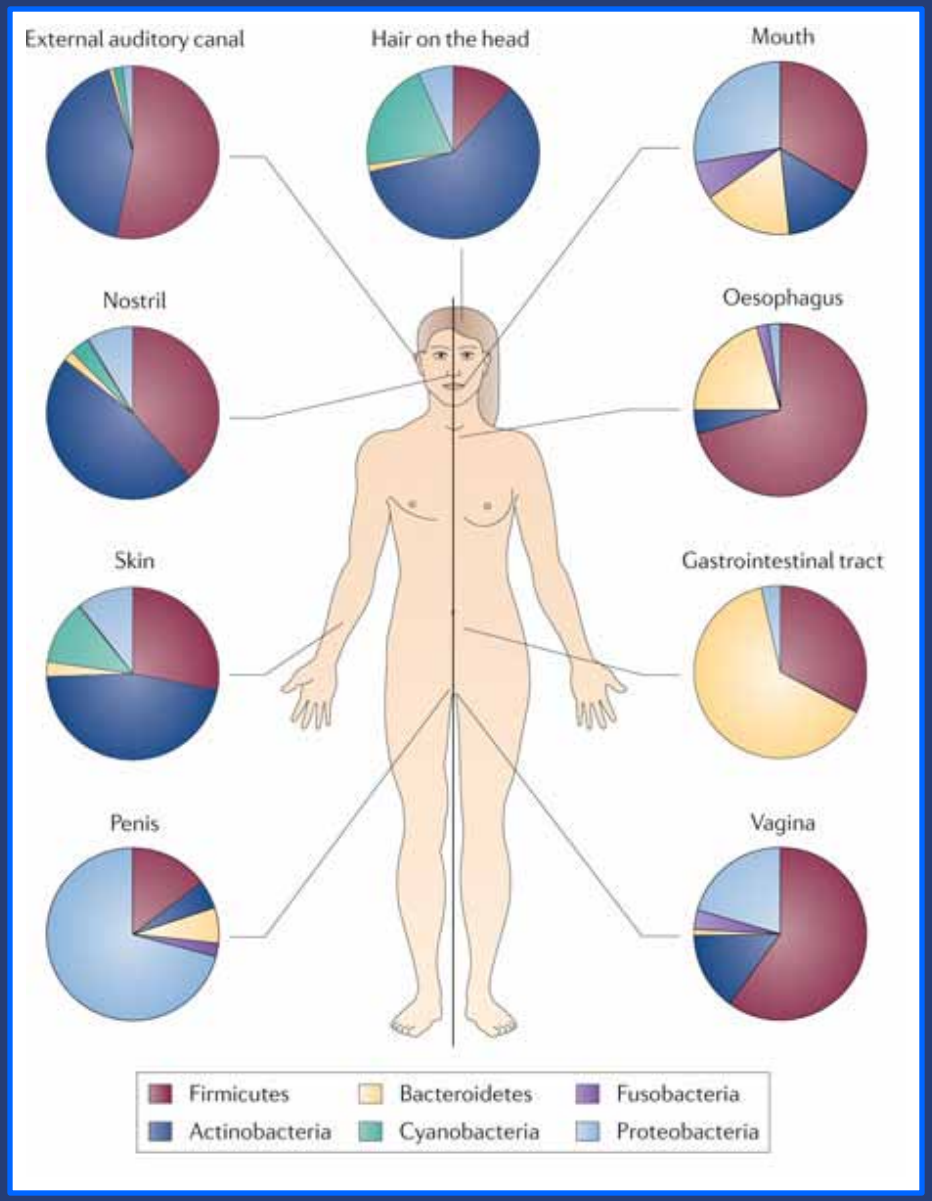
Grp A Strep —Penicillin→ No Pcn-R Grp A Strep (yet)

Antibiotic Treatment of Infections Due to Carbapenem-Resistant *Enterobacteriaceae*: Systematic Evaluation of the Available Evidence

- Twenty nonrandomized studies comprising 692 patients
- Almost all studies reported on *Klebsiella* spp. In 8 studies, majority of infections were bacteremias
- Clinical heterogeneity precluded meta-analysis
- Three studies (194 critically ill patients with bacteremia) showed lower mortality in the combination than in the monotherapy arms (mortality, ~50% to ~80%)
- Other studies showed no significant differences in mortality between the compared groups

Falagas et al, *Antimicrob Agents Chemother* 2014; 58(2):654-63

NIH Human Microbiome Project



WE ARE WHAT WE EAT?

- Gut Microbiomes of Malawian Twins Discordant for Kwashiorkor, *Science* 2013; 339:548-54
- Antibiotics Treat Malnutrition? *N Engl J Med* 2013; 368:425-35
- Intestinal Metabolism and Cardiac Risk, *N Engl J Med* 2013; 368:1575-84
- Gut Microbiota in Diabetes, *Nature* 2012; 490:55-60
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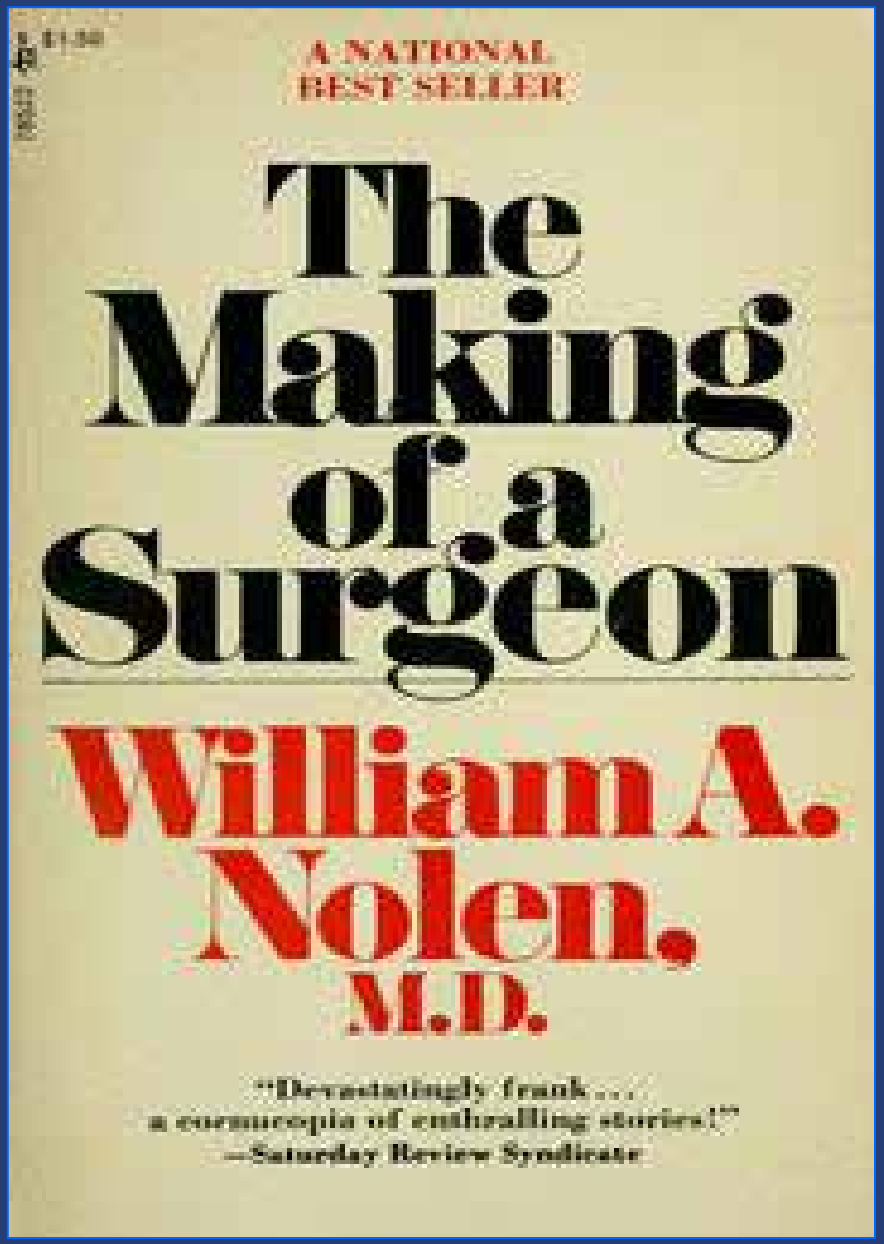
Spor, Koren, Ley, *Nature Rev Microbiol* 2011; 9:279

Microbiome Manipulation — Not New



Microbiome Manipulation to Control Resistance?

Intestinal Microbiota Containing *Barnesiella* Species Cures Vancomycin-Resistant *Enterococcus faecium* Colonization

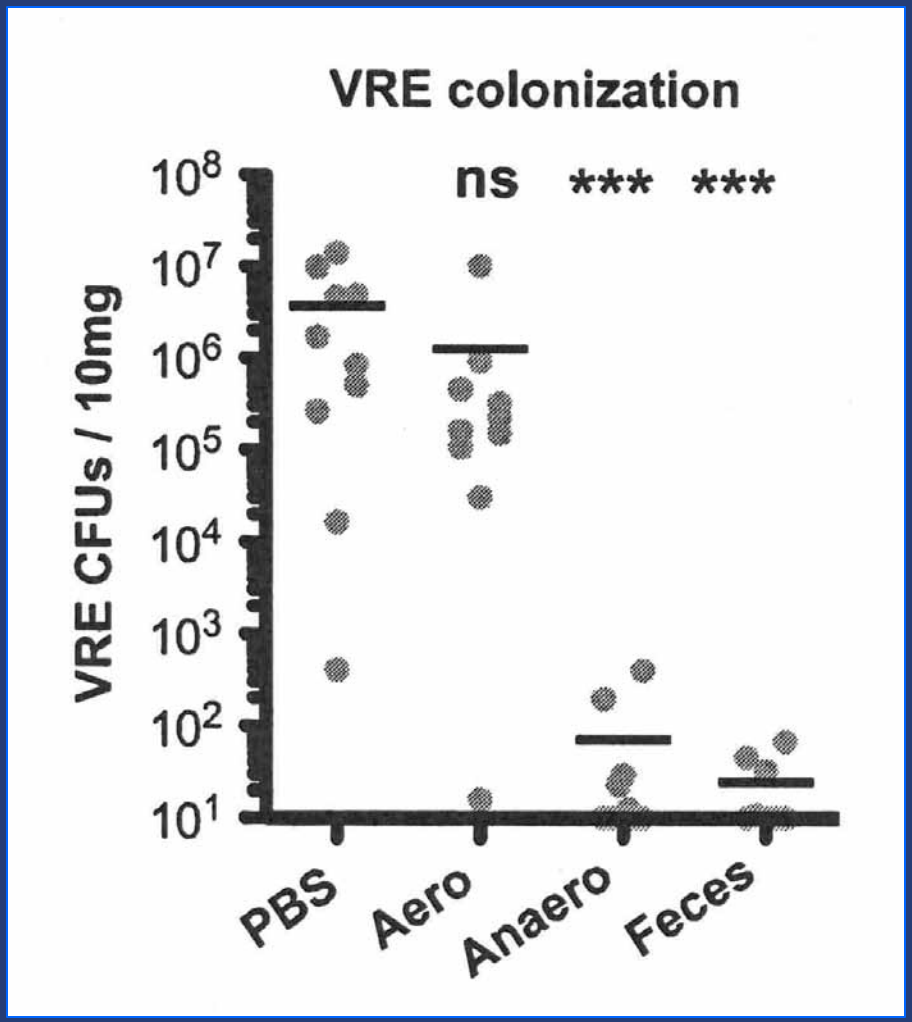
Carles Ubeda,[a,e,f] Vanni Bucci,[b] Silvia Caballero,[a,e] Ana Djukovic,[f] Nora C. Toussaint,[a,e] Michele Equinda,[a,e] Lauren Lipuma,[a,c,e] Lilan Ling,[a,e] Asia Gobourne,[a,c,e] Daniel No,[a,c,e] Ying Taur,[a,c] Robert R. Jenq,[d] Marcel R. M. van den Brink,[d] Joao B. Xavier,[b,c] Eric G. Pamer[a,c,e]

Infectious Diseases Service, Department of Medicine,[a] Computational Biology Center,[b] Lucille Castori Center for Microbes, Inflammation and Cancer,[c] and Bone Marrow Transplant Service, Department of Medicine,[d] Memorial Sloan-Kettering Cancer Center, New York, New York, USA; Immunology Program, Sloan-Kettering Institute, New York, New York, USA[e]; Departamento de Genómica y Salud, Centro Superior de Investigación en Salud Pública, Valencia, Spain[f]

Bacteria causing infections in hospitalized patients are increasingly antibiotic resistant. Classical infection control practices are only partially effective at preventing spread of antibiotic-resistant bacteria within hospitals. Because the density of intestinal colonization by the highly antibiotic-resistant bacterium vancomycin-resistant *Enterococcus* (VRE) can exceed 10^9 organisms per gram of feces, even optimally implemented hygiene protocols often fail. Decreasing the density of intestinal colonization, therefore, represents an important approach to limit VRE transmission. We demonstrate that reintroduction of a diverse intestinal microbiota to densely VRE-colonized mice eliminates VRE from the intestinal tract. While oxygen-tolerant members of the microbiota are ineffective at eliminating VRE, administration of obligate anaerobic commensal bacteria to mice results in a billionfold reduction in the density of intestinal VRE colonization. 16S rRNA gene sequence analysis of intestinal bacterial populations isolated from mice that cleared VRE following microbiota reconstitution revealed that recolonization with a microbiota that contains *Barnesiella* correlates with VRE elimination. Characterization of the fecal microbiota of patients undergoing allogeneic hematopoietic stem cell transplantation demonstrated that intestinal colonization with *Barnesiella* confers resistance to intestinal domination and bloodstream infection with VRE. Our studies indicate that obligate anaerobic bacteria belonging to the *Barnesiella* genus enable clearance of intestinal VRE colonization and may provide novel approaches to prevent the spread of highly antibiotic-resistant bacteria.

Ubeda et al, *Infect Immun* 2013; 81(3):965-73

Commensal Anaerobic Bacteria Suppress VRE Colonization in Antibiotic-treated Mice

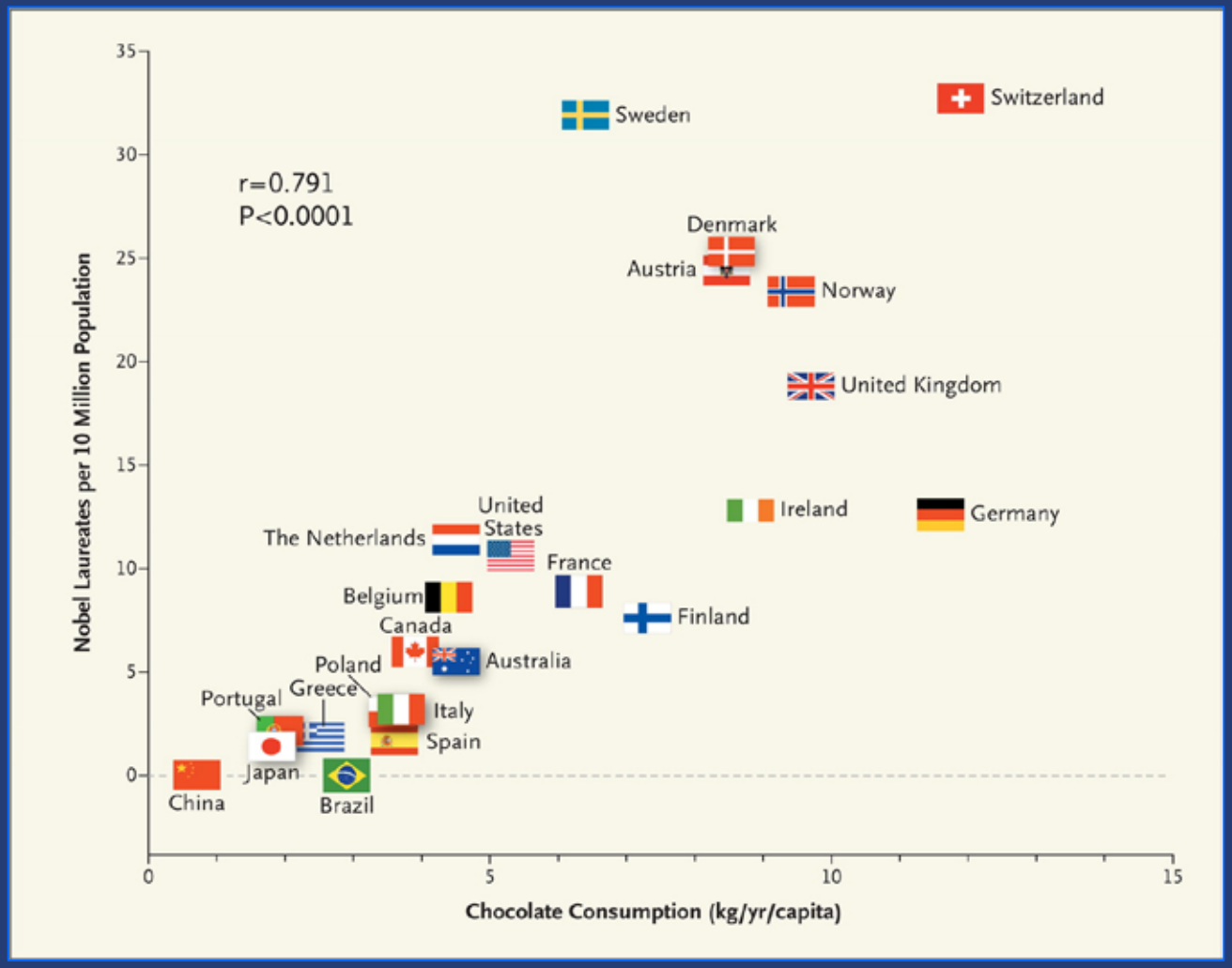


Mice were infected with 108 VRE CFU after 1 week of ampicillin treatment. One day after infection, ampicillin treatment was stopped. Mice were orally gavaged for 3 consecutive days, starting 1 day after antibiotic cessation, with PBS, a suspension of fecal pellets from untreated mice (feces), or an aerobic (aero) or anaerobic (anaero) culture of fecal microbiota from untreated mice. Numbers of VRE CFU in the fecal pellets of infected mice were analyzed 5 weeks after infection (*n* 8 to 10). Limit of detection, 10 CFU / 10 mg. ***, significantly different (P<0.001) from the PBS group; ns, not significant.

Ubeda et al, *Infect Immun* 2013; 81(3):965-73

Chocolate & Fecal Transplants – A "Ray Hogan Two-fer"

Correlation between Countries' Annual Per Capita Chocolate Consumption and the Number of Nobel Laureates Per 10 Million Population



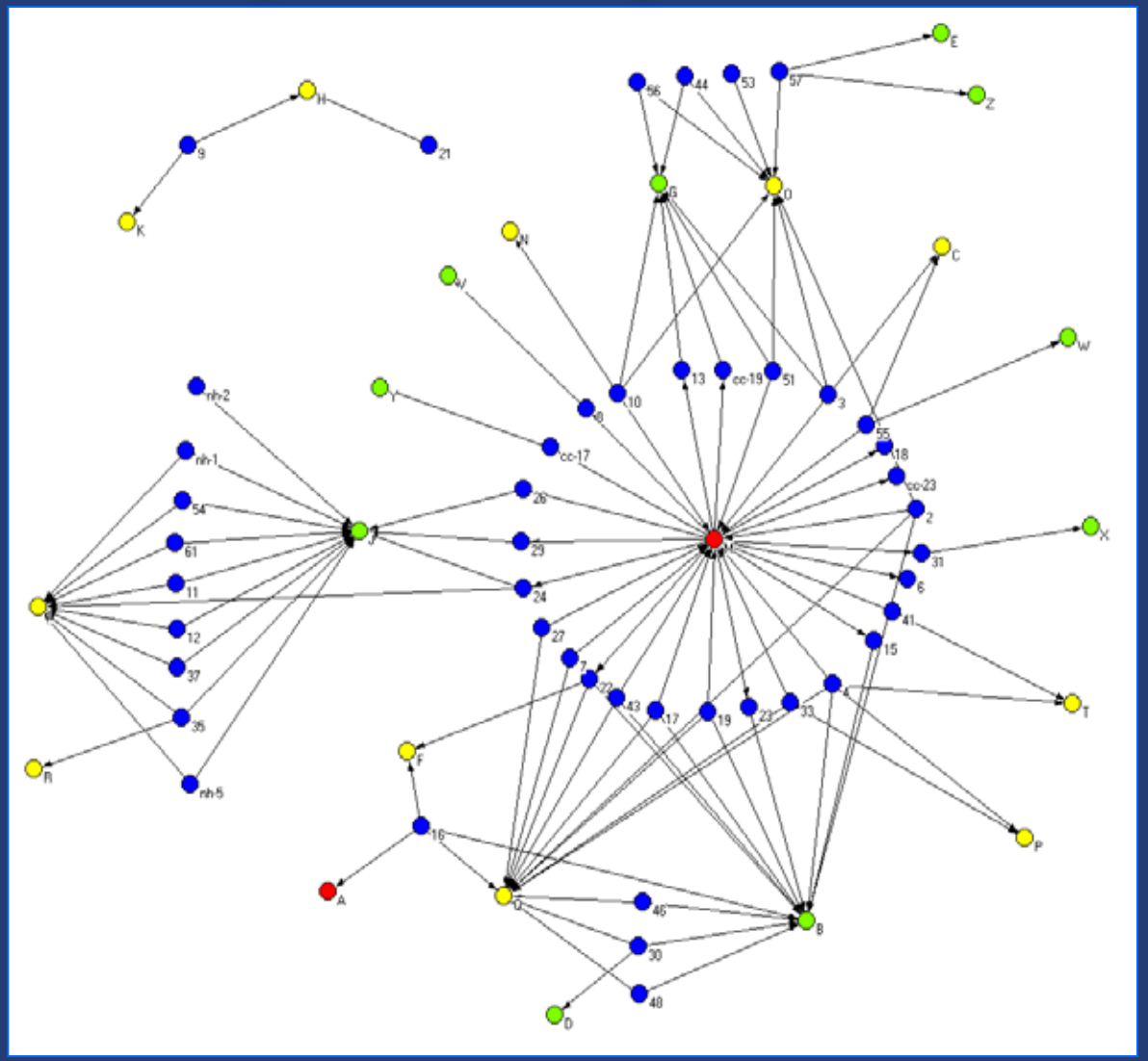
Messerli, *N Engl J Med* 2012; 367(16):1562-4

Social Network Analysis & Regional Control

Social Network depiction of LTACH, Nursing Home, & Hospital spread of KPC (Carbapenem-resistant *Klebsiella pneumoniae)*

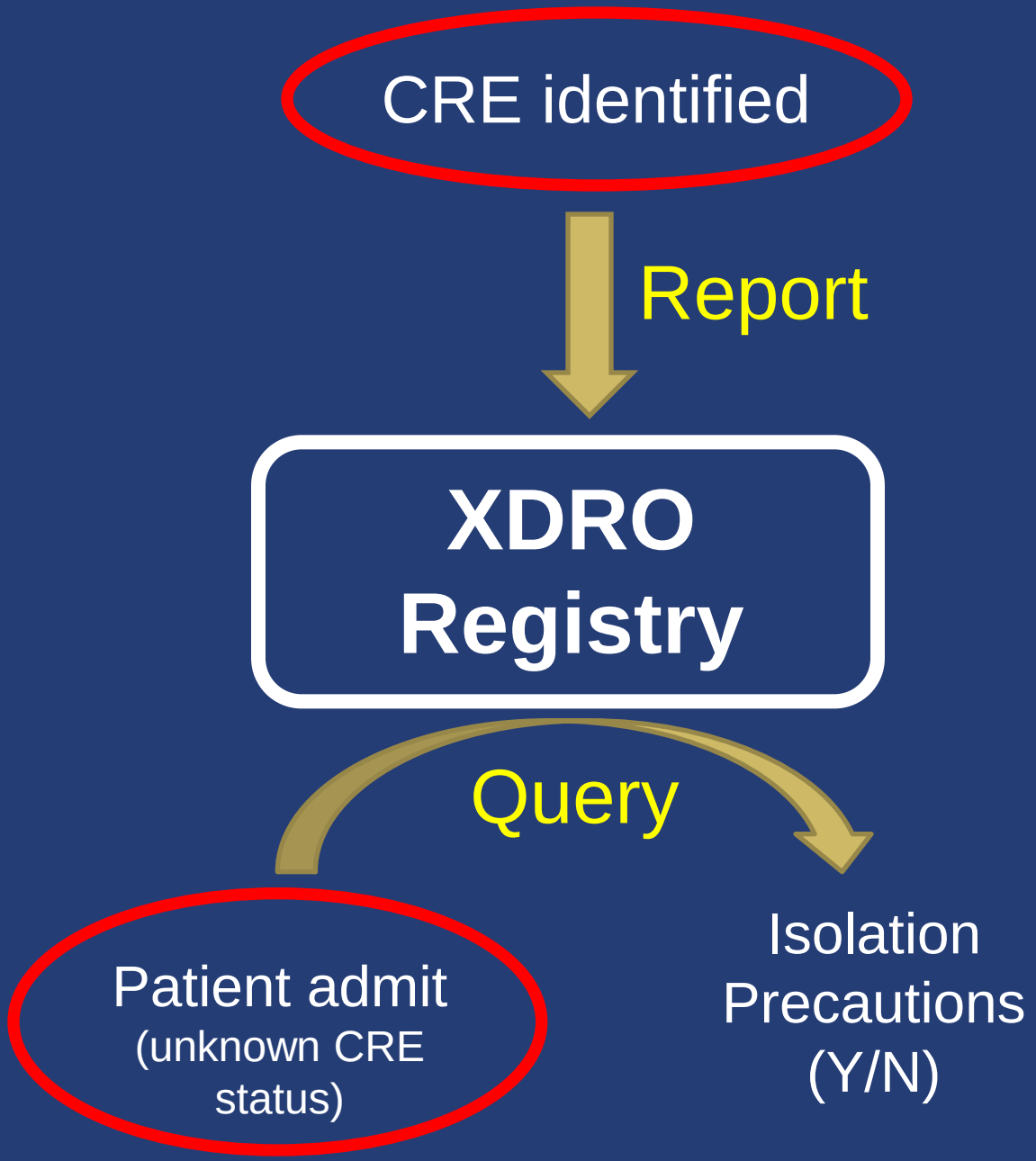
Legend

- LTACH
- Nursing Home
- Acute Hospital
- Patient



LTACH, Long term acute care hospital; MDRO, Multi-drug resistant organism.

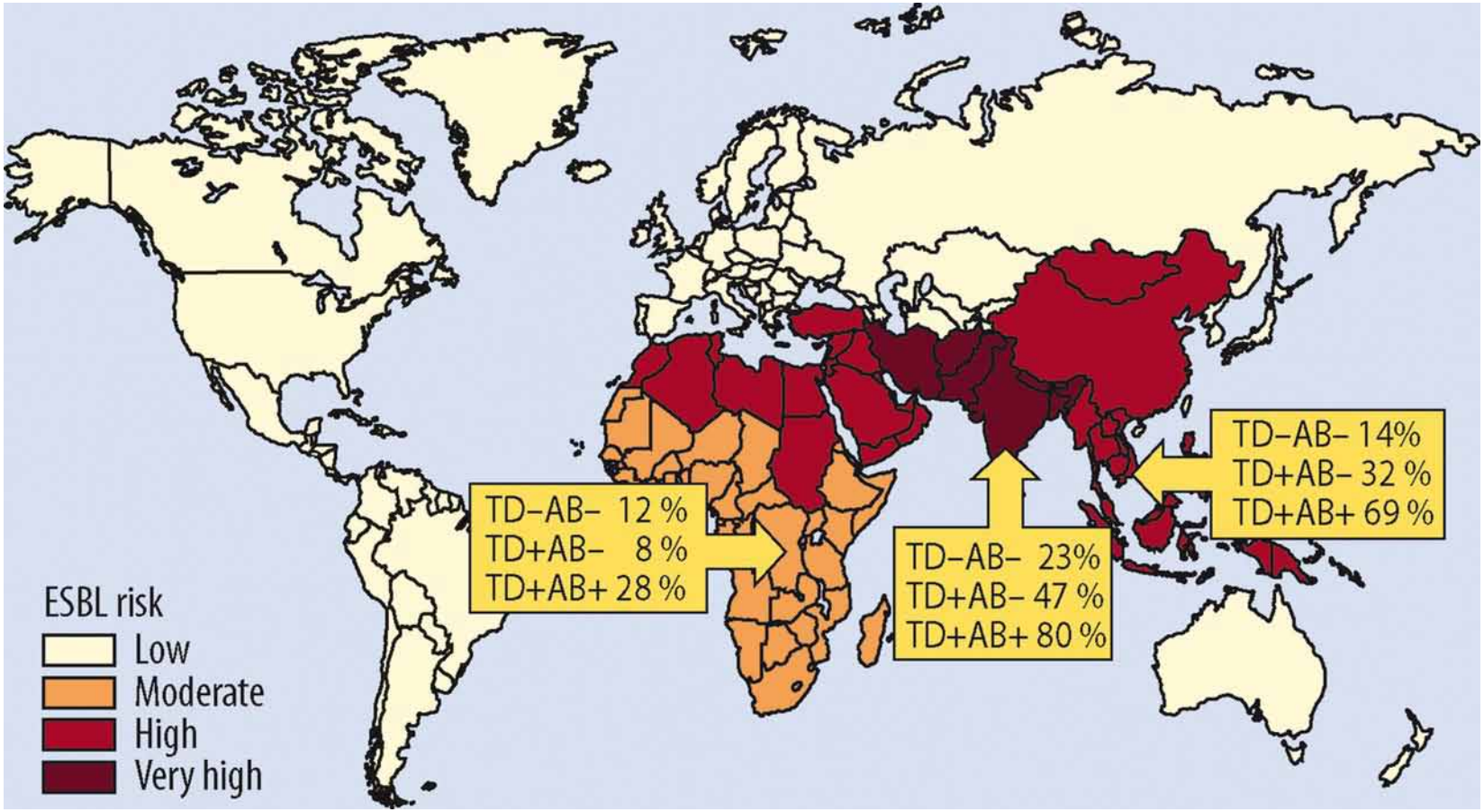
Won et al, *Clin Infect Dis* 2011; 53(6):532-40



Michael Y. Lin, MD, MPH, and William E. Trick, MD, Chicago Prevention & Intervention Epicenter & IL Dept of Public Health

Antimicrobials Increase Travelers' Risk of

Risk of Contracting ESBL-producing *Enterobacteriaceae*

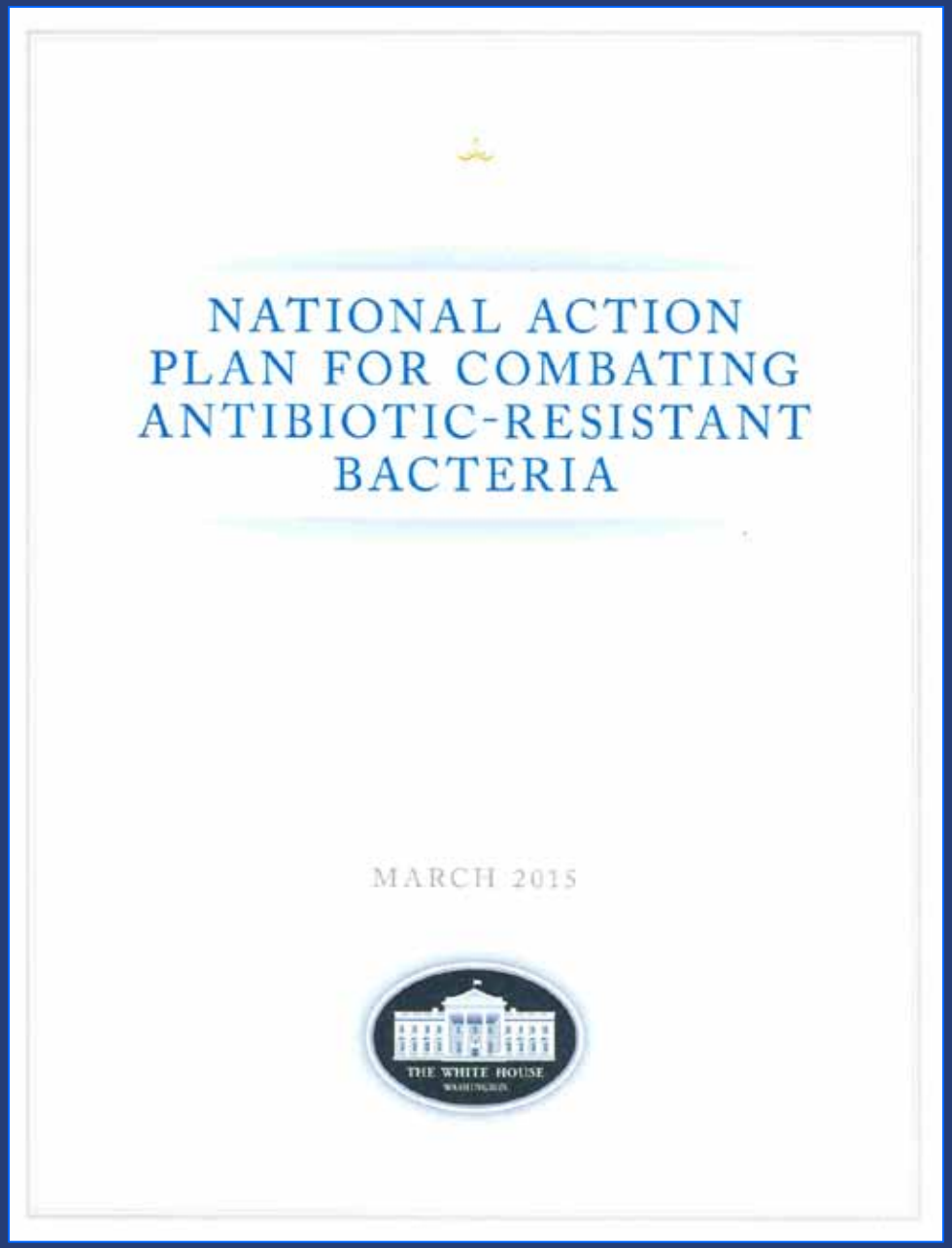


TD, traveler's diarrhea; AB, antimicrobials

Kantele et al, *Clin Infect Dis* 2015; 60:837-46

Way Forward & Take Home Messages

- Epidemiology of resistance and control — Much is known
- Problems
  - Motivating healthcare workers
  - Promoting judicious antibiotic use
  - Insuring regional and wider use of control measures
- Solutions
  - Continue to promote / monitor traditional and newer hospital control measures — And act Regionally
  - Federal mandates / support for in- and out-patient Antimicrobial Stewardship
  - Public Reporting; P4P & DRA / (carrot & stick)?
  - Better understanding and control of our microbiomes?
  - New National Action Plan

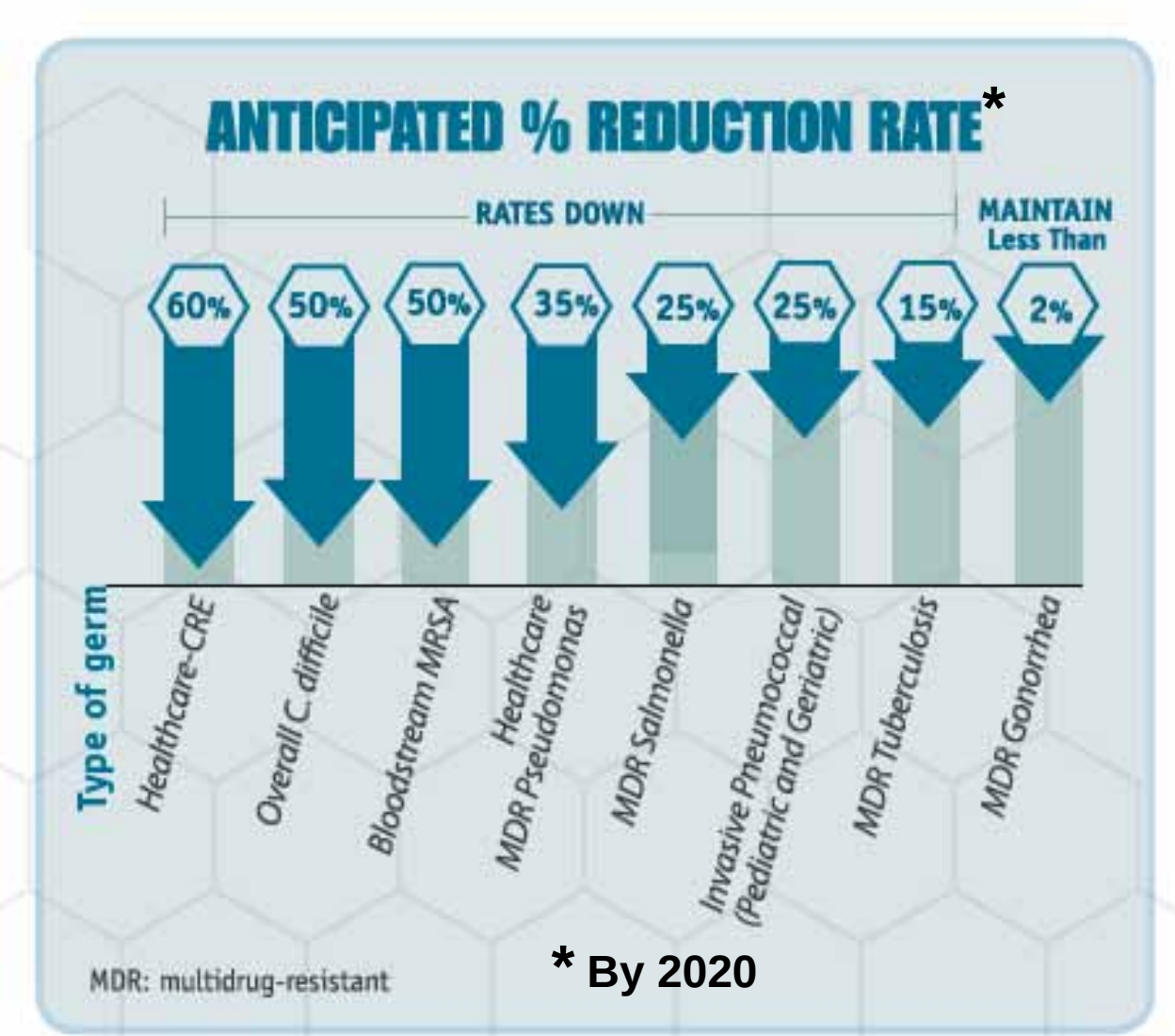


http://www.cdc.gov/drugresistance/solutions-initiative/

The National Strategy Identifies Five Core Actions:

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

http://www.cdc.gov/drugresistance/solutions-initiative/



http://www.cdc.gov/drugresistance/solutions-initiative/

Thank You
(and Ray Hogan)

Outbreak Management

it takes a village….

May 12, 2015

Linda Stein
Marge Gribogiannis

Advocate Health Care

Objectives

- Describe the steps in a CRE investigation.
- Explain the decision-making process for ERCP re-processing using a risk assessment/CDC/FDA guidelines
- Provide examples of CRE prevention strategies.

Disclosures

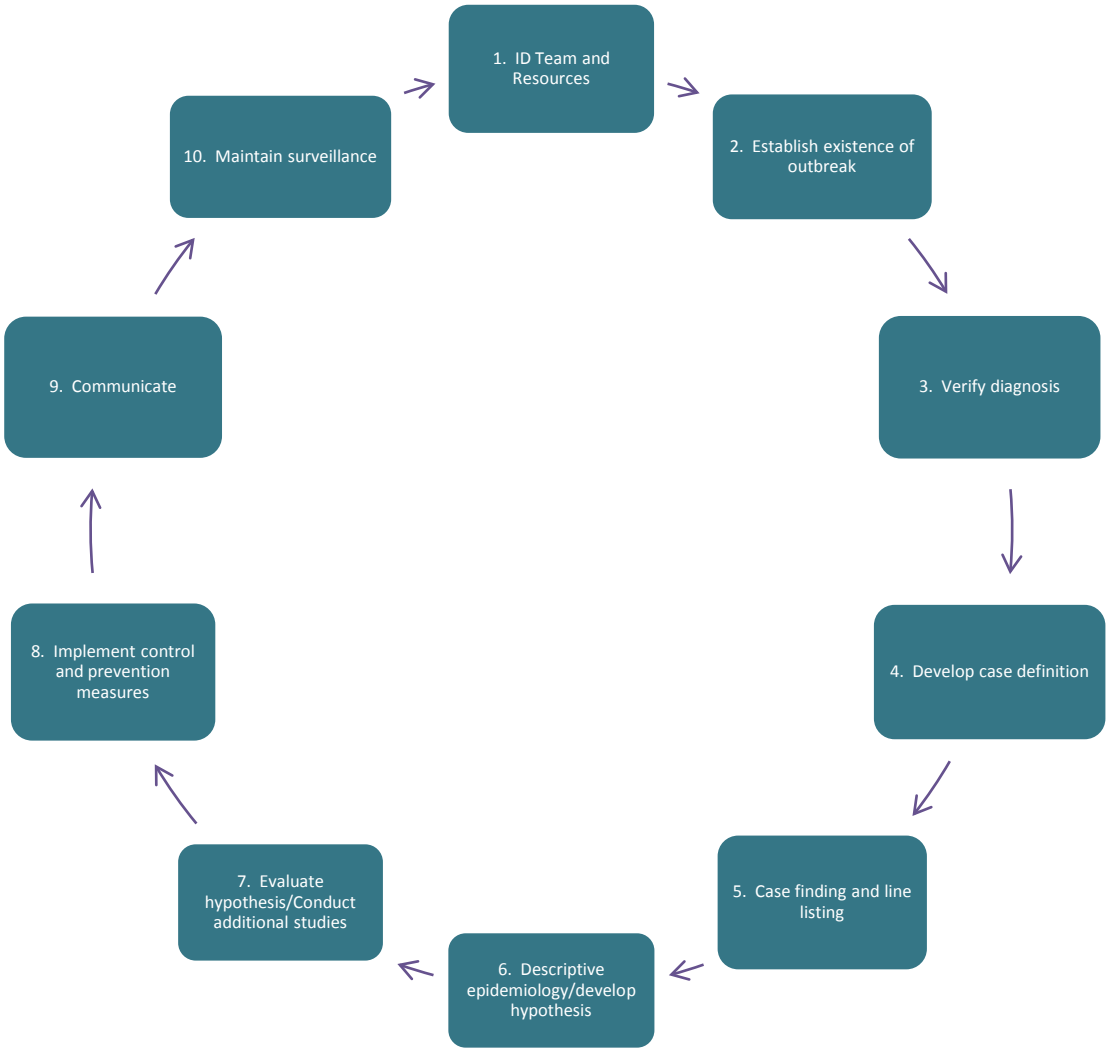
- Financial- No relevant financial relationship exists.
- Non financial- No relevant non-financial relationship exists.

Outbreak Investigation

Principles

- Be systematic
- Re-assess
- Coordinate with partners

Outbreak Management Cycle



Outbreak Investigations. The 10 Step Approach. Zack Moore.MD.
https://epi.publichealth.nc.gov/cd/lhds/manuals/cd/training/Module_1_1.6_ppt_OutbreakInvestigation.pdf

Advocate Health Care

Establish existence of outbreak

What made this an outbreak?

Over the course of one month:

- 3 readmissions with clinical CRE cultures
- Specimen source varied
- Organism metallo beta-lactamase positive
- Confirmed strain as NDM-1(Epidemiologically important pathogen)
- Eventually PFGE same

Verify the Diagnosis

- Background
  - Diagnosis
  - Not lab error
  - Commonality
    - Possible cause
    - Source spread of disease

Develop case definition

- Person, place & time
- Clinical information: characteristics, location, time

Case finding:

Any patient identified with specimens positive for Enterobacteriaceae metallo beta lactamase and/or a readmission history of GI procedure.

Case finding & line listing

- Identification, clinical info, time, demographics, location, risk factors, possible causes
  - Patient
  - Sex
  - Age
  - Admit diagnosis
  - Admit date
  - Patient location
  - Previous admissions and room locations
  - Medical history (surgery, immuno-compromised)
  - Risk Factors (e.g. prior nursing home stay, roommate of other CRE patient, procedure, equipment)
  - Culture and date of collection
  - Treatment
  - Discharge status

Descriptive epidemiology/ develop hypothesis

- Three patients were identified with specimens (e.g. ,urine, sputum,) positive for *E. coli*, New Delhi metallo beta-lactamase and history of GI lab procedure.
- Could this be related to specific procedure?
- ERCP/EUS?

Evaluating the hypothesis

Infection prevention measures:

- Review department policy & procedure
- Observation practice
  - ERCP procedure (pre & post)
  - High level disinfection
- Bring in equipment manufacturers
- Review & observe Environmental Services procedure
- Environmental surveillance (transmission source)
- Education
- Epi-linked surveillance (unit-based surveillance)

Epi-linked Active Surveillance Testing

- Develop “detect and protect” screening protocol
  - Engage your IP partners.(i.e. Nursing, IS, Physicians)-
  - Conduct bed-trace of patients
  - Provide education on CRE to both physicians and healthcare associates including specimen collection.
  - Provide patient education (SHEA MDRO FAQ)
  - Connect with Laboratory about testing
  - Follow up for any positive CRE screen results
  - Performed on various nursing units, & Epi-link ECF

Unit based AST

- Informing the patients/families/physicians
- Conducted over various time frames of the investigation:
  - March , April, May, July
  - All hospital epi-linked cultures were reported as negative for CRE.

Laboratory-Clinical Microbiology

- Follow Clinical and Laboratory Standards Institute guidelines for susceptibility testing.
- Establish a protocol for detection of carbapenemase production (e.g. modified Hodge test)
- Use e-swab for collection. Lab will place swab in TSB broth with ertapenem and plate onto chromagar with meropenem. This will identify any CRE. Additional identification required to determine if CRE isolates are NDM-1 strain.
- Establish system to ensure prompt notification of IP staff of all CREs.

CDC Vital Signs. Making Health Care Safer. Stop Infections from Lethal CRE Germs Now. March 2013.

Evaluate hypothesis & conduct additional studies

- Environmental culture found positive for *E.coli*,NDM-1 (ERCP Scope, specifically at the elevator platform)
- Epi-linked AST – negative (No unit based transmission)
- Additional studies identified “rugged” surface inside ERCP scope elevator platform.

Our initial Hypothesis

Situation: (4) NDM and (3) KPC patient cases were identified from varied specimens (e.g. blood, urine, sputum, wound) and readmission history of GI lab procedure, specifically same ERCP scope.

*Elevator section with possible platform defect.

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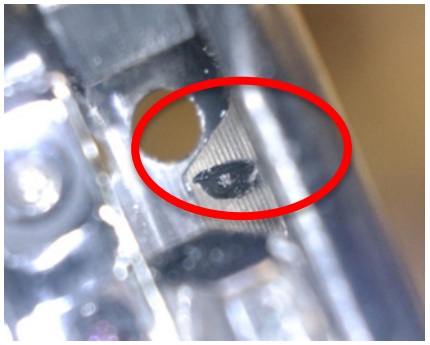
Additional studies



Inside elevator platform (Magnified 100X)

Actions taken:

✓Scope A removed from service
✓ALGH filed complaint with the FDA (SMDA)
✓CCDPH/IDPH initiated EPI-AID from the CDC arrival-August 2013
✓Scope manufacturer notified of potential “defect”
✓Scope A sent to CDC for investigation
✓CDC partnering with (FDA) for guidance &recommendation
✓Complete high level disinfection process reviewed.

Retrospective review and direct observation of endoscope reprocessing did not identify lapses in protocol.

Prevention steps taken: New scope purchased to replace scope A
Next steps: Continue investigation- how & why related to the scope

Implement control & prevention measures

- Re-reviewed department policies
  -ERCP procedure
  - High level disinfection
- Re-review manufacturer recommendations.
- Repeat audit of Environmental Services cleaning process
- Engage manufacturers to audit associates performing process.
- Additional environment culture (Clean room & Storage unit)
- Epi-linked AST
- Education

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CDC Partners

Initial CDC findings:

- PFGE results of Cluster : genetically related.
- Suggesting that Hospital 1 was the source of transmission for many of the patients, with subsequent transmission at ECF between two roommates.
- CDC to conduct further analysis of Scope A (Confirmed positive isolate for NDM)

ERCP Specimen Collection

NON-DESTRUCTIVE RECOVERY OF ENTERIC BACTERIA FROM DUODENOSCOPE

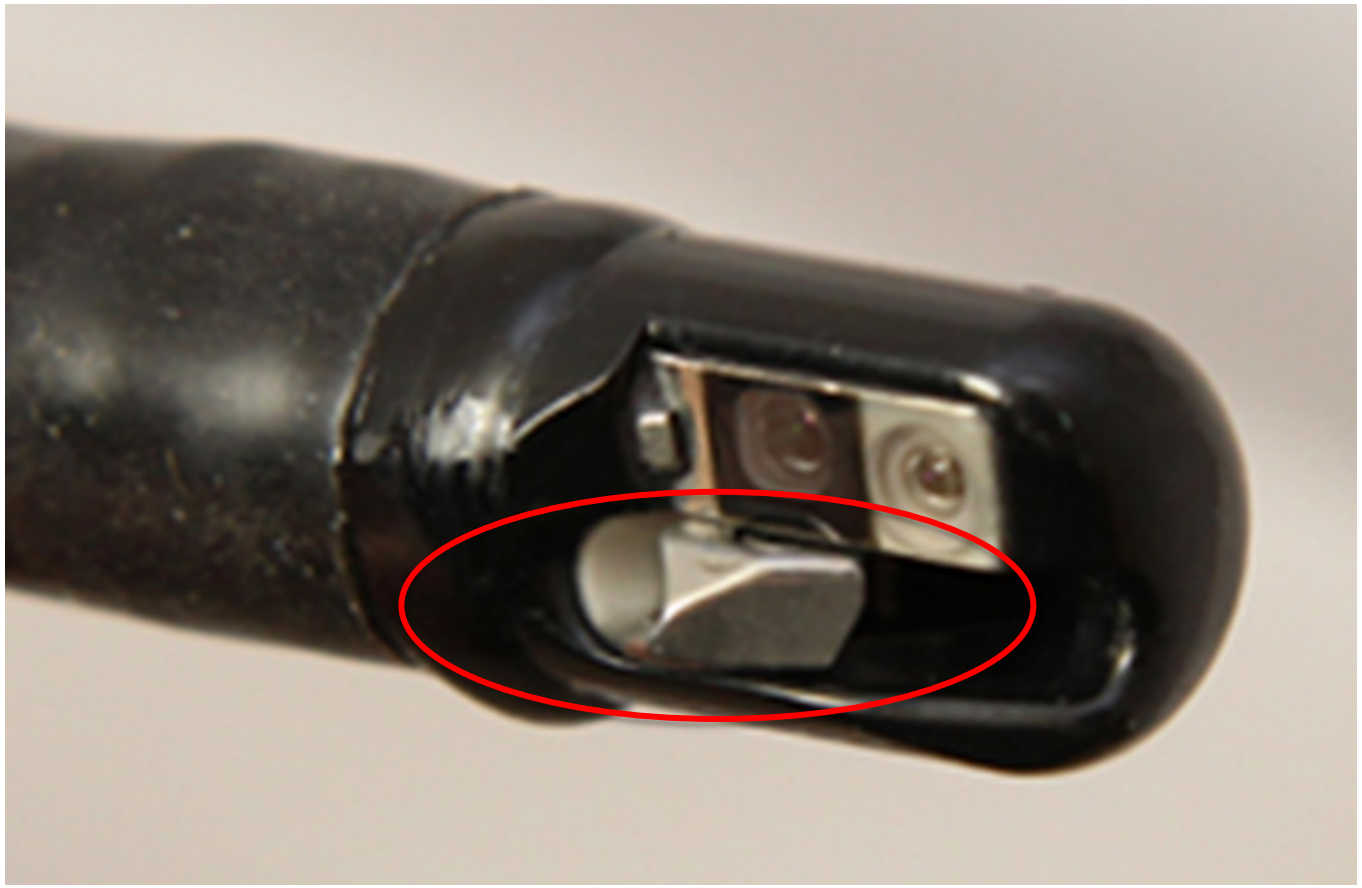
Equipment	**Materials and Reagents**
ERCP scope, post ETO sterilization	Sterile gloves
	E-swab (green top)
	Plastic specimen transport bag

Procedure:

Note: Due to the length of the device, it is recommended that this sampling procedure be performed by two persons, with one holding the endoscope steady while the other manipulates it.

- Don sterile gloves.
- Using the endoscope controls, manipulate the last 1.5-2 inches of the tip several times.
- Swab the endoscope channel tip, and the elevator channel repeatedly with the E-swab, moving back and forth 15 times.
- Place swab in E-swab container. Label container accordingly.
- Complete lab requisition.
- Transport in plastic bag to laboratory. Hand-off to Microbiology Tech.

Elevator mechanism - distal tip



Communication

- Patient Notification of all who had ERCP procedures with Scope A
- IP Resources: Administration, Risk Management, Public Relations, CCDPH,IDPH, CDC
  - Weekly conference calls
- Deliver consistent message to public
- Ensure any patients screened positive are informed, verbally and in writing.

Community Outreach

- Transparency
- Contacting patients/outreach to patients in ECFs
- IP resources included Post Acute Network, CCDPH to follow up on screening patients discharged to LTCFs.
- Additional mailings to patients who did not respond with first letter sent by certified mail.

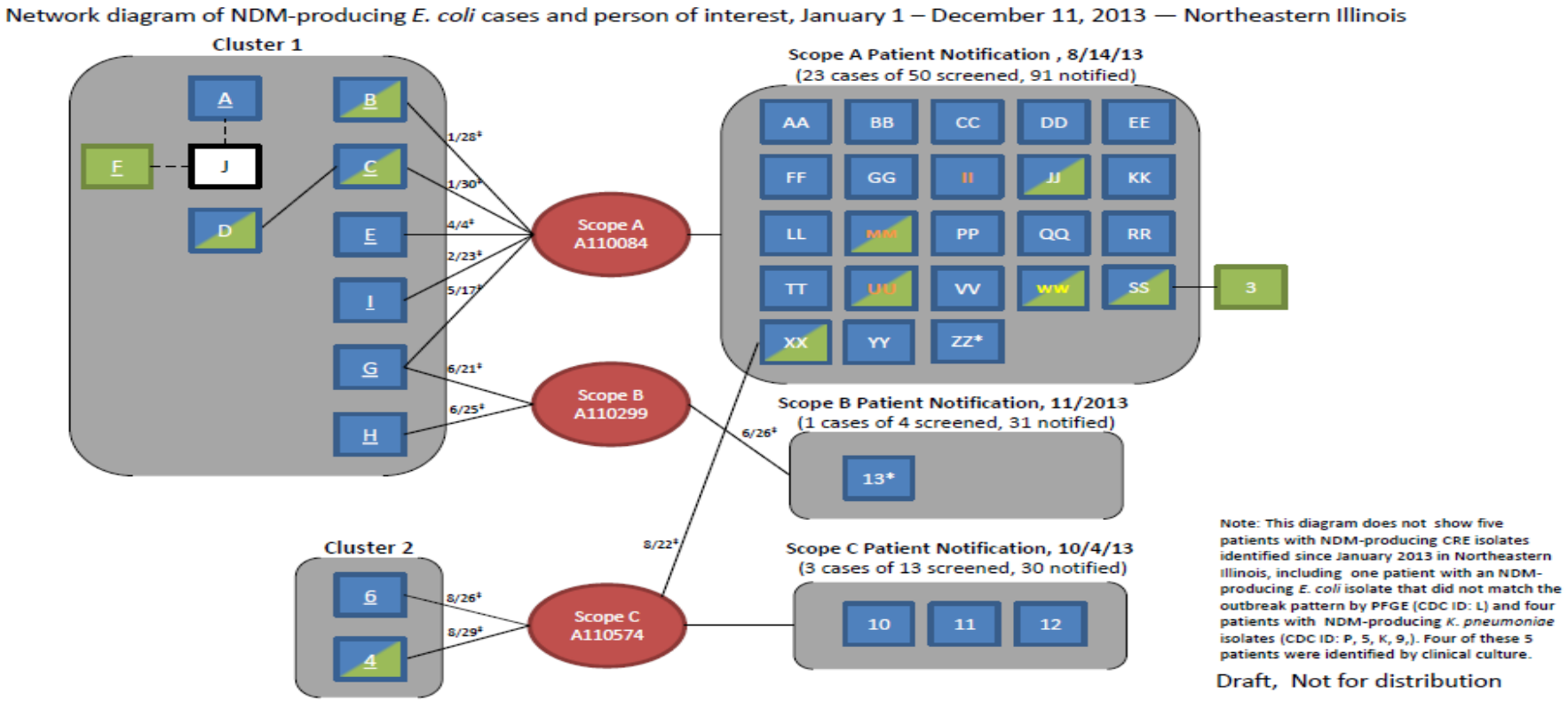
Evaluate hypothesis*

- A patient who had an ERCP with scope “C” had a positive culture for *E.coli MBL (metallo beta lactamase)*. This was the second case identified with the same source scope.
- There was a one month period of no discernible transmission between cluster 1 associated with scope “A” and cluster 2 associated with scope “B”.

* New Hypothesis:

  We have a repeated instance of another new scope associated with *E.coli MBL*, this would imply the source of the biofilm may be located within the integral components of the AER (automated endoscope reprocessor) which functions to wash and disinfect the scopes.

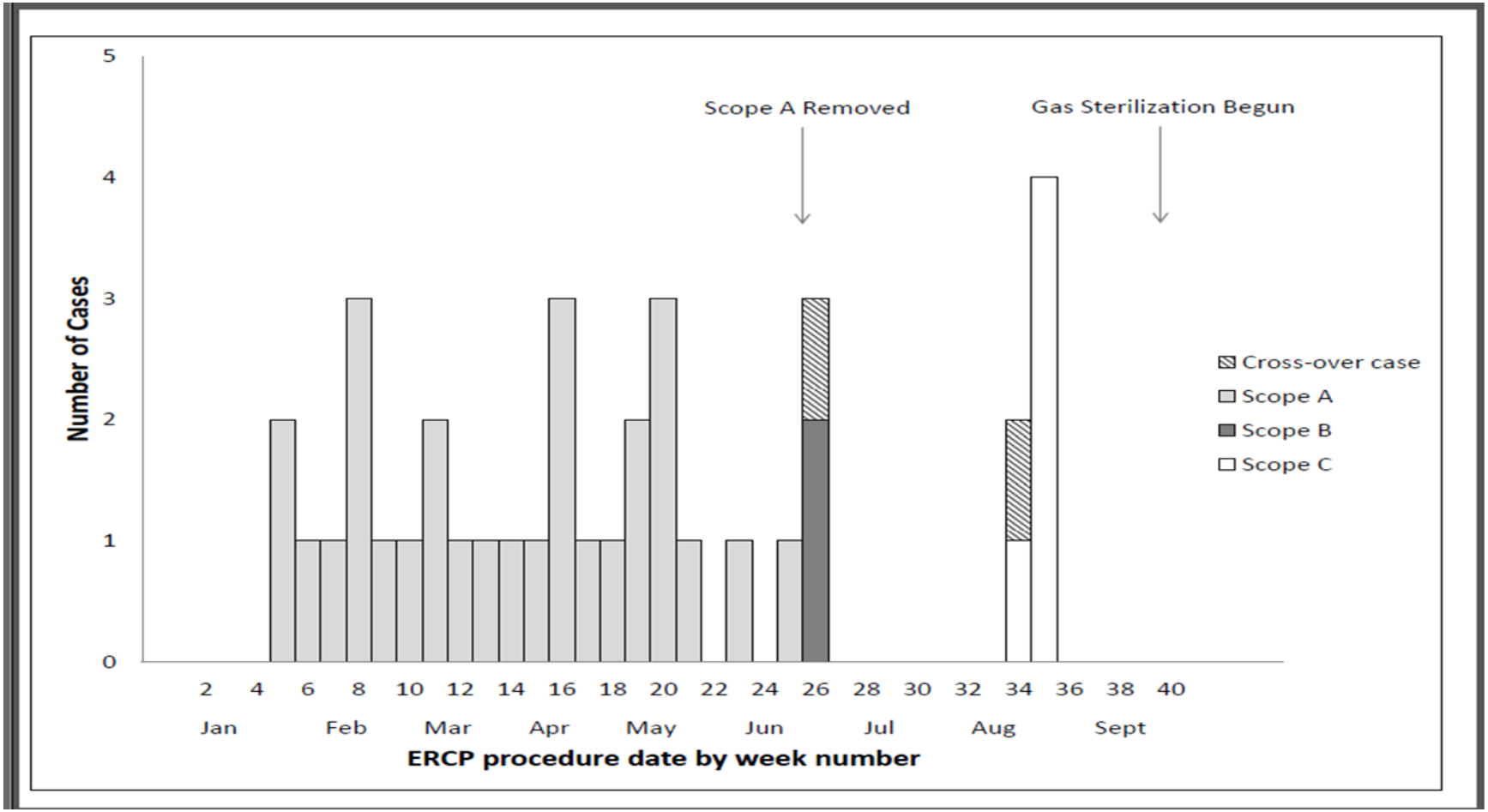
CRE Network Diagram



NewDelhi Metallo-β-Lactamase–Producing Carbapenem-Resistant *Escherichia coli* Associated With Exposure to Duodenoscopes. Lauren Epstein ,MD., et al. *JAMA. 2014;312(14):1447-1455*

Advocate Lutheran General Hospital
Inspiring medicine. Changing lives.

Epi Curve- Scopes



NewDelhi Metallo-β-Lactamase–Producing Carbapenem-Resistant *Escherichia coli* associated With Exposure to Duodenoscopes. Lauren Epstein ,MD., et al. *JAMA. 2014;312(14):1447-1455.*

Advocate Health Care

Infection Control Measures

- Manufacturer product evaluation of our AER equipment.
- Review manufactures recommendation of products (detergent, disinfectant)
- AER bay, detergent and alcohol lines bleached.
- Performed environmental surveillance cultures of AER reservoir holding tanks and filters.
- Patient notification
- Moved from HLD to sterilization with ETO (ethylene oxide).
- ERCP scopes post sterilization were cultured.
- Repeat audit of ERCP patient procedure (pre, during and post)
- Repeat audit of Environmental Services protocol.
- Prior to ERCP procedure, conduct AST CRE screening.

Final Hypothesis*

- Inability to effectively High Level Disinfect ERCP scopes.
- Challenges related to equipment design, impacting the cleaning and disinfection process. (i.e.) Service, maintenance, length of time device kept in service.
- Options for alternative methodologies to ensure equipment is safe for patients.

Over the past 6 months…

Los Angeles Times May 7, 2015

BUSINESS

FDA reveals 142 cases of tainted scopes

CHAD TERHUNE, Melody Petersen

May 7, 2015, 6:00 a.m.

Federal regulators shed … patients from a controv… reports of contaminate… since 2010.

The Food and Drug … received about half …

In the news: NFL Draft USAC Election

Scope manufacturer issued alerts in Europe two years before LA ou…

BY SARAH HAMBRO AND ALLISON ONG

Posted: April 23, 2015 12:33 am

…utbreak at the Ronald Reagan UCLA Medical Center had issued safety advisories about their scopes in Europ…

SHARE TWEET

'Superbug' outbreak reported at second Los Angeles hospital

THE ASSOCIATED PRESS / Thursday, March 5, 2015, 8:50 AM

Share Tweet Reddit COPY

More 'superbug' cases linked at Virginia Mason

Originally published April 28, 2015 at 9:20 pm Updated April 30, 2015 at 8:36 am

At least 39 people are included in an outbreak of multidrug-resistant infections spread by contaminated medical scopes at Virginia Mason. But health officials say the hospital has successfully halted the outbreak.

By JoNel Aleccia

Seattle Times health reporter

More cases of "superbug" infections tied to contaminated medical scopes have been detected at Seattle's Virginia Mason Medical Center, along with evidence of a separate cluster of potentially dangerous bacteria in other patients, newly released public records show.

At least 39 people are now included in the outbreak of … up from 32 acknowledged in January by officials at Pu…

…dition, four people not treated with those devices … released in response to a Seattle Times …

Thursday, May 7 … Disease Control an…

…another E. coli strain circu…

Superbug infection causes deadly bacterial outbreak at UCLA Ronald Reagan Medical Center

POSTED: 2:01 PM, Apr 13, 2015

UPDATED: 1:35 PM, Apr 16, 2015

HealthlineNews

Healthline → Healthline News → The Bacteria Will See You Now: How Little Bugs Create Big Problems in Hospitals

The Bacteria Will See You Now: How Little Bugs Create Big Problems in Hospitals

Advocate Health Care

Searching for a solution…

- FDA Safety Communication …Feb 19, 2015

  Design of Endoscopic Retrograde cholangiopancreatography (ERCP) duodenoscopes may impede effective cleaning.

- ECRI Institute: High Priority Hazard Report March 3

  #8 on ECRI's Top 10 Patient Safety Concerns for Healthcare Organizations 2015

- American Gastroenterological Association (AGA), FDA,CDC, ECRI and endoscope manufacturers meet on March 30, 2015

To test or not to test…..

- **CDC Interim Duodenoscope surveillance protocol, March 11, 2015**
  - Routine culturing of endoscopes is not part of current U.S. guidelines, recent outbreaks associated with duodenoscopes have led some facilities to consider regular monitoring to assess the adequacy of duodenoscope reprocessing
- **ASM, The Question of Culturing of Duodenoscopes, April 2015**
  - little to no data that document the performance of this culture method for either routine practice, or periodic validation of duodenoscope reprocessing practices
  - At this time, it seems clinical microbiology labs should not perform routine cultures of reprocessed duodenoscopes due to lack of data on utility of such culturing.
  - If culturing is deemed necessary as part of an outbreak investigation, consider sending to an appropriate reference lab.

Ongoing CRE Prevention Strategies

- **Surveillance:** CRE alert using data mining system
- **Reporting:** XDRO registry
- **Develop a comprehensive QC Program**
  - Visual inspection
  - Cleaning verification (ATP, Protein, bioburden)
  - On a monthly basis, each ERCP/EUS endoscope will be cultured specifically for CRE
  - Follow the method described in obtaining samples for culture using the E-swab.(1) swabs from each ERCP & EUS scope
    - Elevator up & down position
- **Patient Education & Consent**

CRE prevention strategies

Competency (Pre-cleaning, manual cleaning & HLD)

- Written standardize competency upon hire, change in process and annually.
- Observed competency(demonstration) upon hire, change in process and bi-annually.

Traceability

- Able to identify scope to patient for every procedure
- One hour time frame from end of procedure to reprocessing. If this cannot be met then scope should be flushed with enzymatic and soaked for one hour
- Ability to identify who cleaned & reprocessed scopes
- Infection Prevention will trace all new +CRE clinical cultures to determine if ERCP/EUS performed.

CRE prevention strategies

- Notification of positive culture
  - Notify site IP (Outbreak management plan)
  - Sequester scope Notify Risk Management
  - Positive culture will result in sequester scope (should not be returned to service until 2 negative cultures are obtained-this is a minimum of 4-6 days)
  - Complete SMDA (Safe Medical Devise Act)
  - Notify Manufacturer
  - Begin outbreak management process
- GI lab to maintain record of culture results
- Resource: http://www.cdc.gov/hai/outbreaks/index.html

Lessons Learned

- Keep a log/diary of investigation (timeline)
- Senior leadership is essential (resource allocation)
- Developing & performing a risk assessment is key
  - Standardization of products
  - Competency/education
  - Maintenance/inspection
  - Prevention strategies
- Renewed respect for associates dedicated to doing this job, every day.
- It truly does take a village……

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- http://www.cdc.gov/hai/outbreaks/outbreak-resources.html
- http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm434871.htm
- http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm439999.htm
- http://www.asge.org/uploadedFiles/Publications_and_Products/ASGE_InterimGuidance_CRE_03172015.pdf?zbrandid=439&zidType=CH&zid=9379886&zsubscriberId=93268278&zbdom=http://www.informz.net