

# Antimicrobial Stewardship and the Role of the Infection Preventionist

Zach Willis, MD, MPH

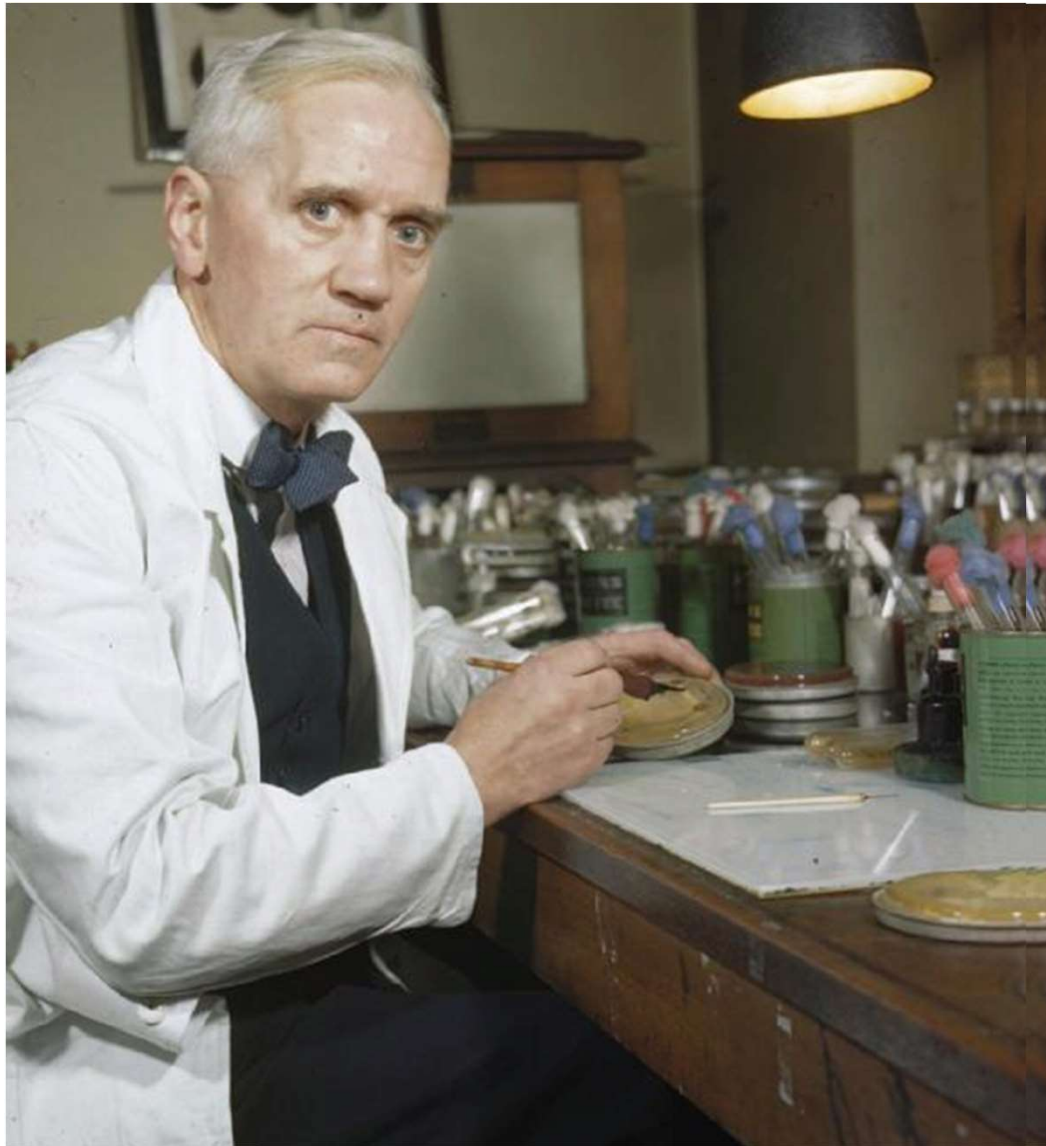
4/23/24

# Disclosures

I have the following financial relationships with the manufacturer(s) and/or provider(s) of commercial services discussed in this activity:

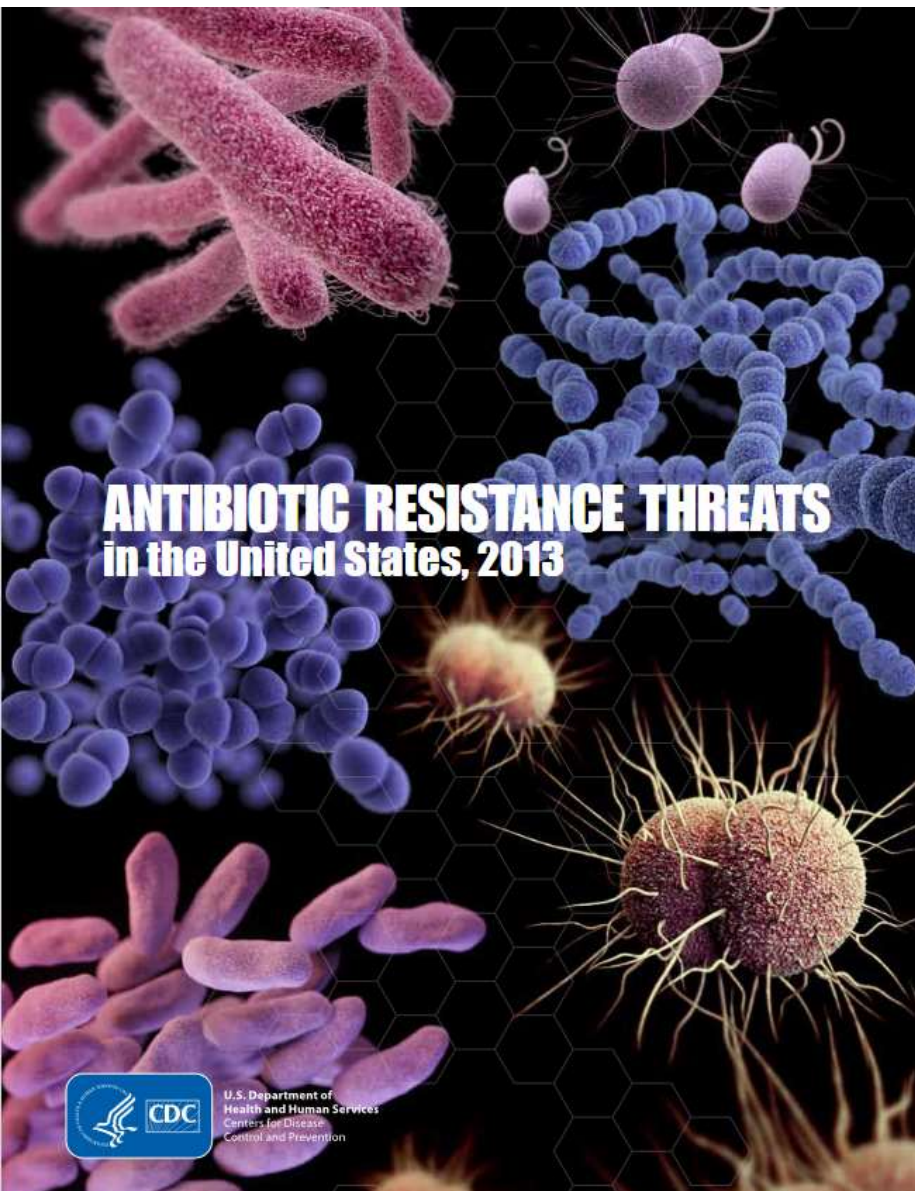
- Contracted research with:
  - Pfizer (pediatric nirmatrelvir-ritonavir)
  - Pfizer (maternal RSV vaccine)
  - Merck (monoclonal antibody for RSV prevention)

I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.



The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out.... In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism.

Sir Alexander Fleming,  
6/14/1945, *New York Times*





## ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention



Estimated minimum number of illnesses and deaths caused by antibiotic resistance\*:

At least  **2,049,442** illnesses,  
 **23,000** deaths

*\*bacteria and fungus included in this report*

+

Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least  **250,000** illnesses,  
 **14,000** deaths

<https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf>



# CDC's 2019 AR Threats Report: **PREVENTION WORKS.**

**↓ 18%** fewer deaths from antibiotic resistance overall since 2013 report

**↓ 28%** fewer deaths from antibiotic resistance in hospitals since 2013 report

## AND DECREASES IN INFECTIONS CAUSED BY:

**↓ 41%** Vancomycin-resistant *Enterococcus*

**↓ 33%** Carbapenem-resistant *Acinetobacter*

**↓ 29%** Multidrug-resistant *Pseudomonas aeruginosa*

**↓ 25%** Drug-resistant *Candida*

**↓ 21%** Methicillin-resistant *Staphylococcus aureus* (MRSA)

**STABLE** Carbapenem-resistant Enterobacteriaceae (CRE) & drug-resistant tuberculosis (TB disease cases)

# What Was Working?

- Infection Prevention
  - Known MDRO infections:
    - Screening, isolation
    - Information sharing between facilities
    - Surveillance
  - Reduction in Hospital-Acquired Infections
    - CLABSI, VAP, CAUTI
- Antimicrobial Stewardship



**2022  
SPECIAL  
REPORT**

# COVID-19

## U.S. IMPACT ON ANTIMICROBIAL RESISTANCE

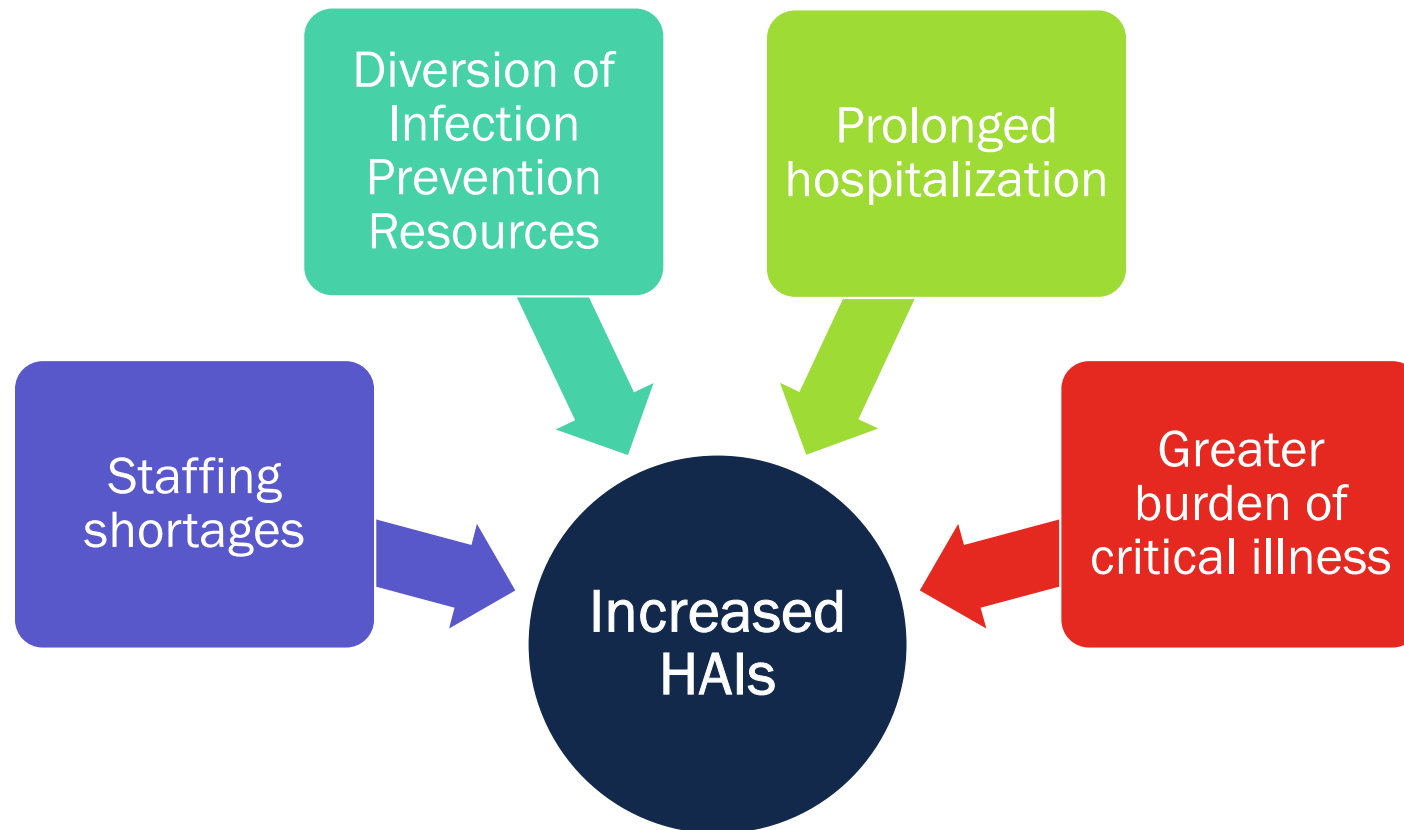
<https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf>



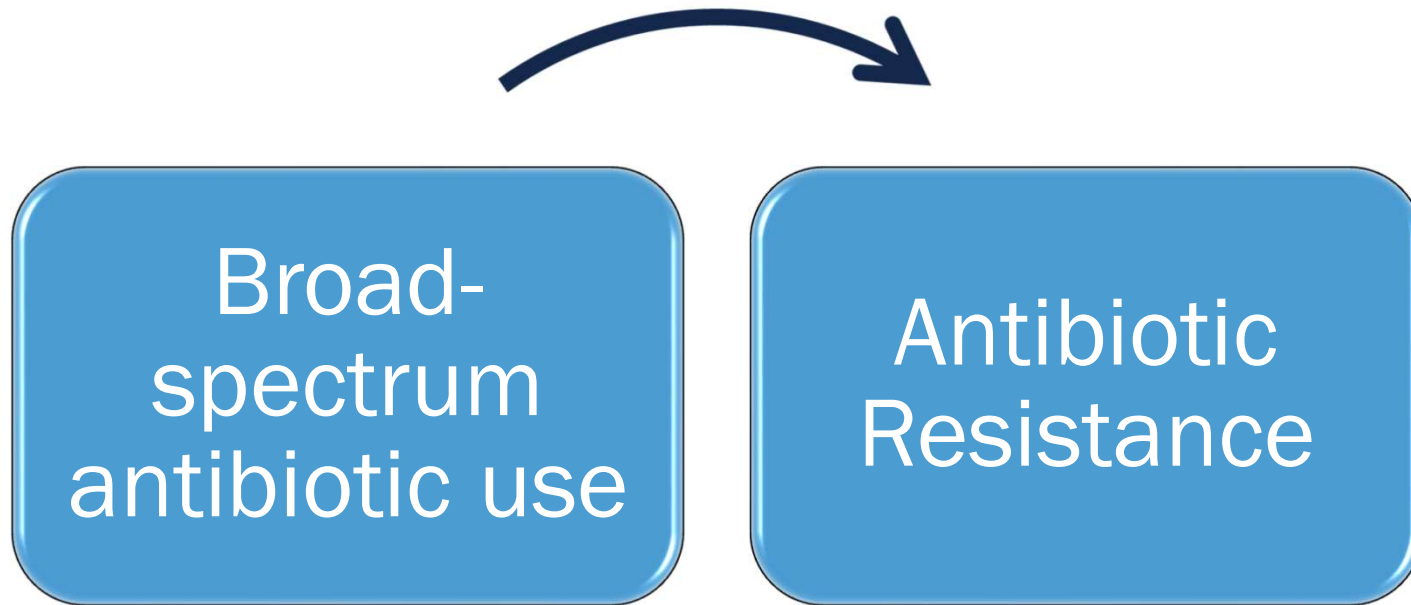
**Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.**

- Carbapenem-resistant *Acinetobacter* (+78%)
- Antifungal-resistant *Candida auris* (+60%)\*
- Carbapenem-resistant Enterobacterales (+35%)
- Antifungal-resistant *Candida* (+26%)
- ESBL-producing Enterobacterales (+32%)
- Vancomycin-resistant Enterococcus (+14%)
- Multidrug-resistant *P. aeruginosa* (+32%)
- Methicillin-resistant *Staphylococcus aureus* (+13%)

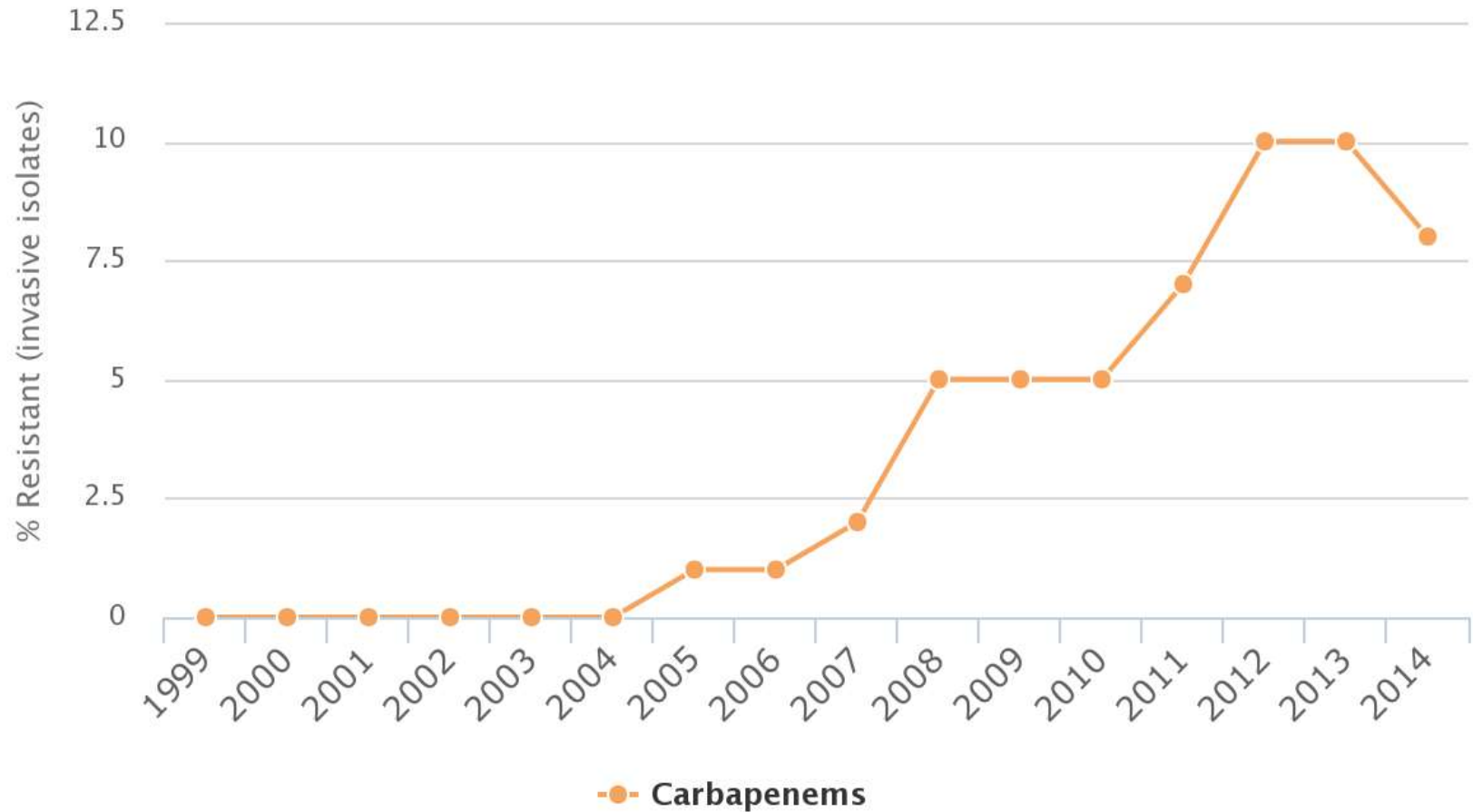
# Why Did Antimicrobial Resistance Get Worse in the Pandemic?





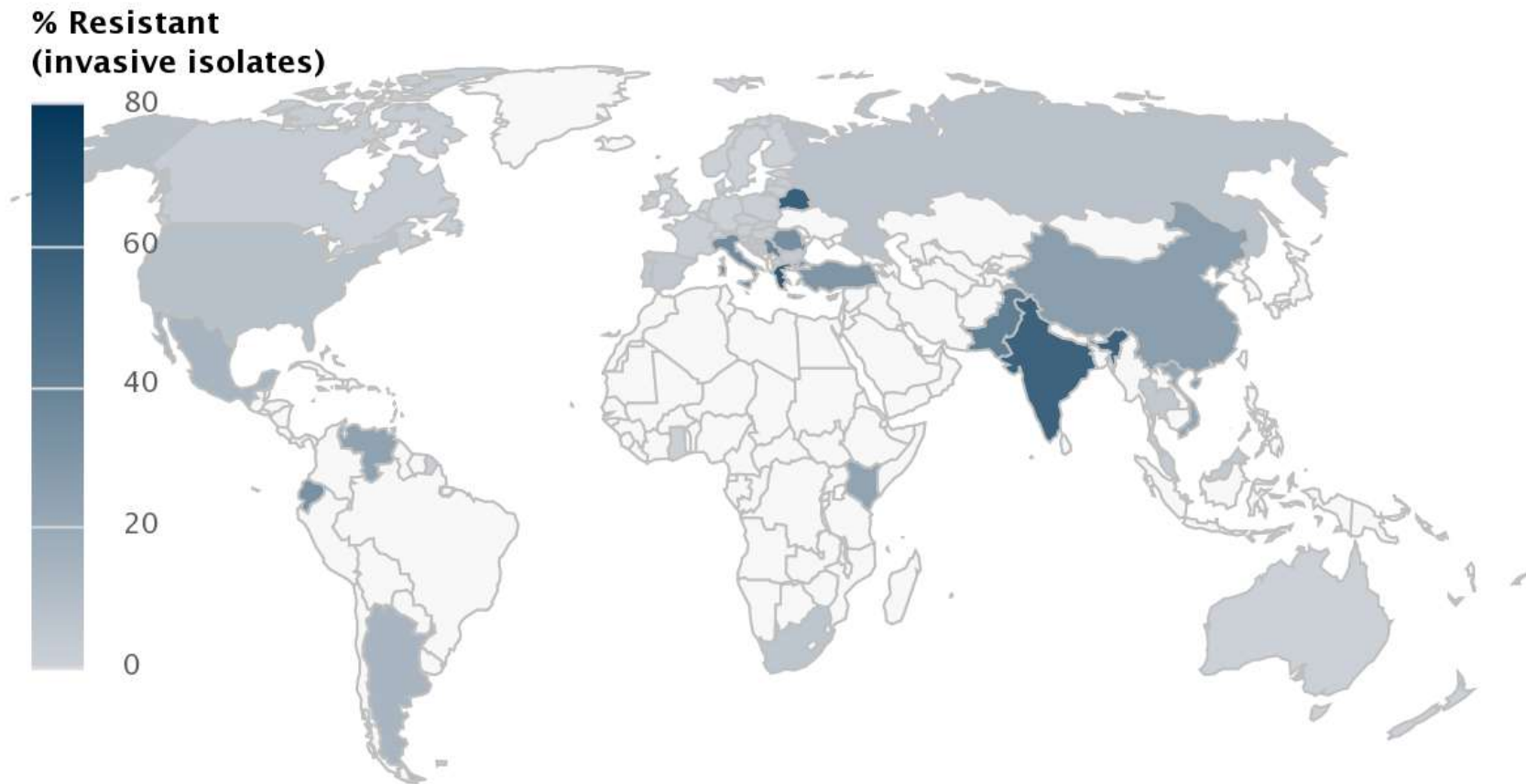


## Antibiotic Resistance of *Klebsiella pneumoniae* in United States



Center for Disease Dynamics, Economics & Policy (cddep.org)

## Resistance of *Klebsiella pneumoniae* to Carbapenems



# IP and AS Goal

Prevent  
antimicrobial  
resistant infections  
and C-diff

[Antibiotic Resistance Threats in the United States, 2019 \(cdc.gov\)](https://www.cdc.gov/antibiotic-resistance/threats-in-the-united-states-2019/)

Slide courtesy of Emily Sickbert-Bennett, PhD

## CDC strategies that work in healthcare:



Preventing device- and procedure-related infections, such as from urinary catheters or central lines



Stopping the spread of resistant germs within and between healthcare facilities



Containing emerging threats through early detection and aggressive response



Tracking and improving appropriate antibiotic use



Infection prevention and control in non-hospital settings, such as long-term care facilities

# AS: Core Elements

## Core Elements of Hospital Antibiotic Stewardship Programs



### Hospital Leadership Commitment

Dedicate necessary human, financial, and information technology resources.



### Accountability

Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes.



### Pharmacy Expertise (previously “Drug Expertise”):

Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antibiotic use.



### Action

Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use.



### Tracking

Monitor antibiotic prescribing, impact of interventions, and other important outcomes, like *C. difficile* infections and resistance patterns.



### Reporting

Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.



### Education

Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

4 of 7 have  
direct link to IP

<https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf>

Slide courtesy of Emily Sickbert-Bennett, PhD



# AS/IP Strategy Alignment

- MDRO epidemiology
- *C. difficile* prevention
- Diagnostic stewardship
  - CLABSI
  - HAP and VAP
  - CAUTI
  - *C. difficile*

# Key ASP Tactics

- Prospective Audit and Feedback
  - AKA “postprescription review”
- Prior authorization/Restriction
  - Preapproval required for certain antibiotics to be released
- Clinical Pathway/Guideline development
  - Incorporates diagnosis and management guidelines; good for standardization
- Provider education

# Additional ASP Tactics

- 48-hour antibiotic time-outs
- Handshake stewardship
  - ASP rounds
- Patient education
- Antimicrobial formulary management
- Medication use evaluations (MUE) and targeted education



# ASP: Tracking Data

- Antibiotic use in days of therapy/1000 patient-days (DOT/1000)
  - Can look at individual antibiotics, groups of antibiotics
  - Hospital-wide, specific units, groups of units...
- NHSN Antimicrobial Use (AU data)
  - Adds: reasonable(ish) antibiotic groupings
  - Benchmarks with similar(ish) units at other hospitals
  - SAAR  $\approx$  SIR
- Major limitation:
  - Don't know if the patient *should* be on antibiotics
  - Don't know if the antibiotic choices were optimal

# IP vs AS

	Infection Prevention	Antimicrobial Stewardship
#1 audience	Bedside staff esp. nursing	Ordering providers and pharmacists



# Stewardship: A Multidisciplinary Endeavor

Essential,  
"Core-Team"  
Personnel

- Lead Physician
- Lead Pharmacist
- Clinical Microbiologist
- Infection Preventionist
- Information Technologist

# Case

A surgical ICU has noticed an increase in the incidence of HA-CDI over the past six months, from 5 cases in the prior 4 quarters to 7 in the past 2 quarters. They have had no significant changes in staffing or patient population. What should they look at first?

- Adherence to isolation precautions
- Post-operative antibiotic prophylaxis
- Post-discharge deep cleaning
- Empiric antibiotic selection
- Handwashing practices

# Case

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- Empiric antibiotic selection
- Handwashing practices

# C-diff Prevention

## IP

- Handwashing
- Surveillance
- Isolation
- Unit layout
- Deep cleaning

## Both

- Diagnostic Stewardship!

## ASP

- Avoid highest-risk CDI antibiotics
- Basically everything we do

# C-diff: Don't blame me!

nature medicine



Article

<https://doi.org/10.1038/s41591-023-02549-4>

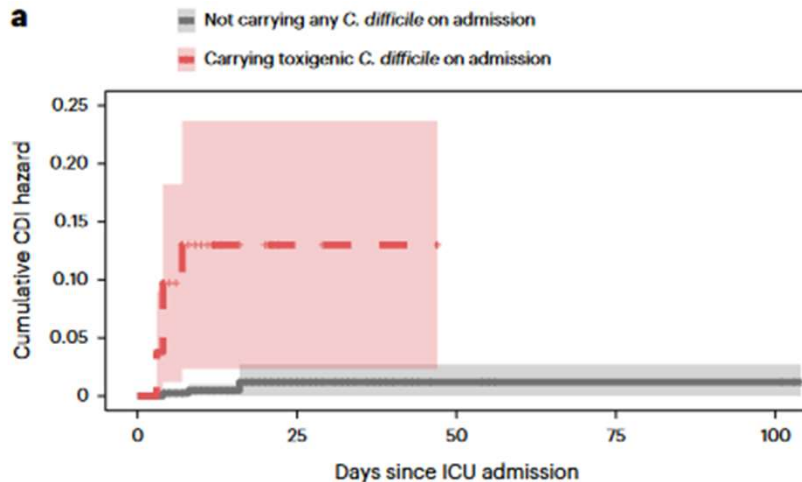
## Longitudinal genomic surveillance of carriage and transmission of *Clostridioides difficile* in an intensive care unit

Received: 2 August 2022

Accepted: 17 August 2023

Published online: 18 September 2023

Arianna Miles-Jay<sup>1</sup>, Evan S. Snitkin<sup>1,2</sup>, Michael Y. Lin<sup>3</sup>, Teppei Shimasaki<sup>3</sup>, Michael Schoeny<sup>3</sup>, Christine Fukuda<sup>3</sup>, Thelma Dangana<sup>3</sup>, Nicholas Moore<sup>3</sup>, Sarah E. Sansom<sup>3</sup>, Rachel D. Yelin<sup>3</sup>, Pamela Bell<sup>3</sup>, Krishna Rao<sup>2</sup>, Micah Keidan<sup>2</sup>, Alexandra Standke<sup>2</sup>, Christine Bassis<sup>2</sup>, Mary K. Hayden<sup>3</sup> & Vincent B. Young<sup>1,2</sup>



- Cultured almost 4,000 stools and rectal swabs from 1,289 ICU admissions
- Only 1% of eligible patients had acquisition of toxigenic *C. difficile* via cross-transmission
- Colonized with toxigenic *C. difficile* on admission: 24x greater risk of CDI



# Impact of AS programs *C.difficile*

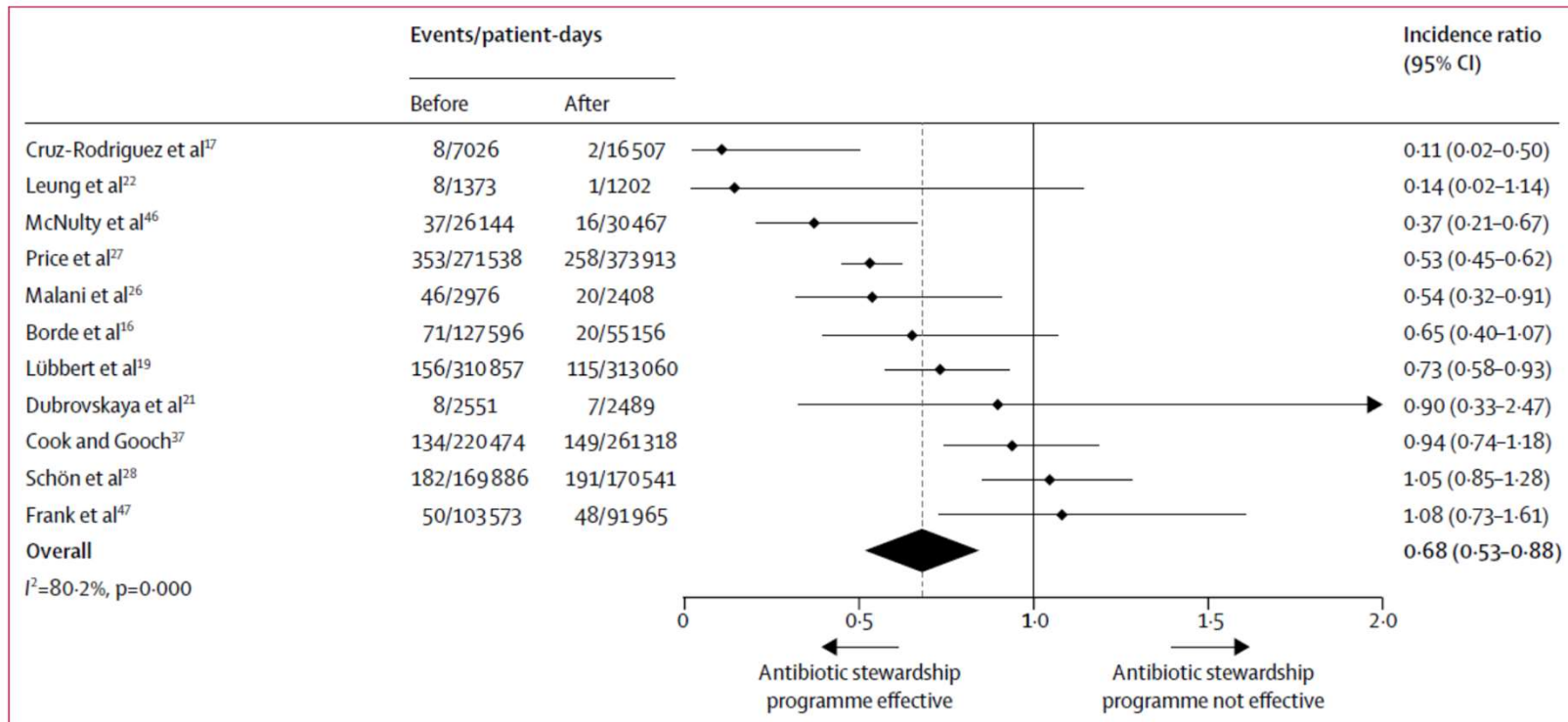



Figure 4: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections

Baur, Gladstone, Burkert, et al. *Lancet Infectious Diseases*; 17:9:990-1001, 2017

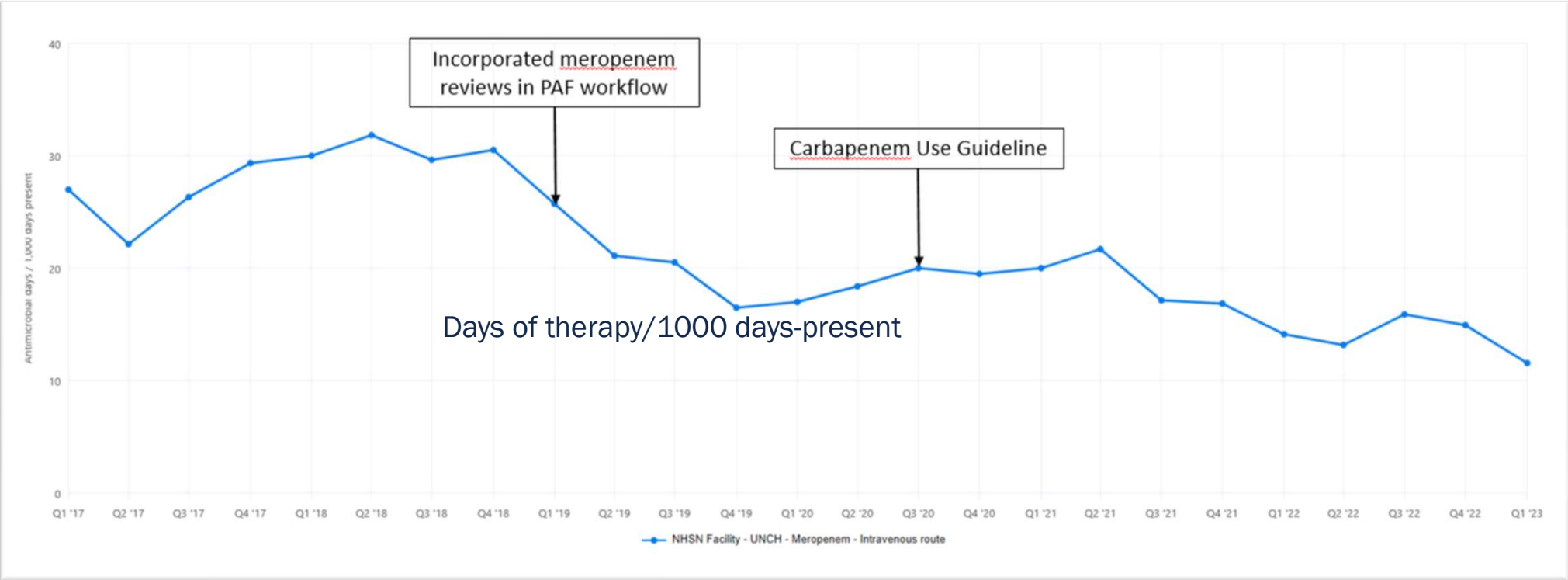
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**Antibiotics and healthcare facility-associated *Clostridioides difficile* infection: systematic review and meta-analysis 2020 update**

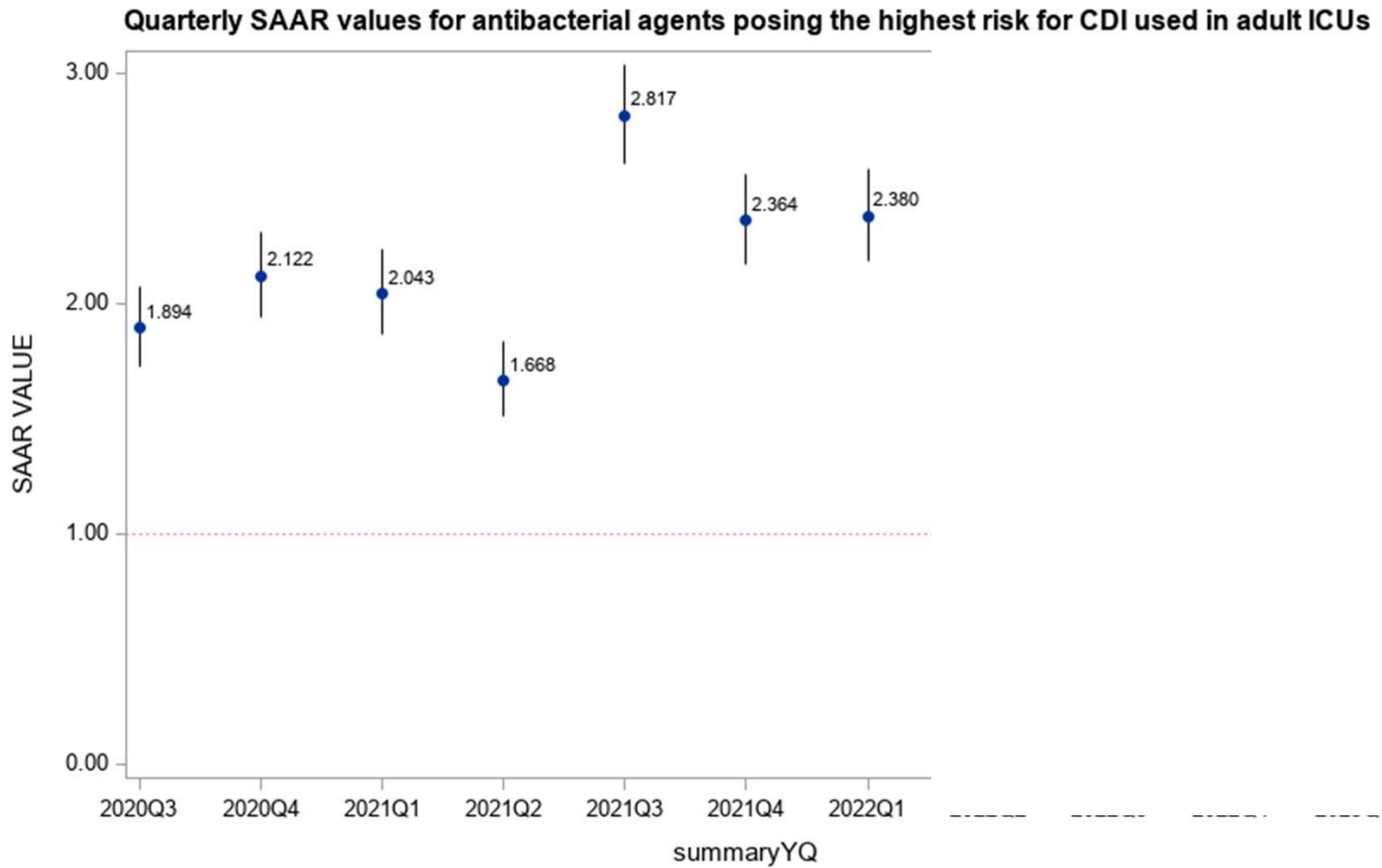
Claudia Slimings  <sup>1\*</sup> and Thomas V. Riley<sup>2,3</sup>

- Which antibiotics are most likely to cause CDI?
- Highest-risk classes (highest to lowest):
  - Carbapenems
  - 4<sup>th</sup>-gen and 3<sup>rd</sup>-gen cephalosporins
  - Vancomycin
  - Fluoroquinolones
  - Clindamycin
  - Piperacillin-tazobactam
  - No association: narrow penicillins, 1<sup>st</sup>-gen cephalosporins, TMP-SMX, tetracyclines
- Allows ASP to prioritize high-risk

# Meropenem Use 2017-2023



# Antibiotics with high risk for CDI in SICU



# Diagnostic Stewardship: Why?

- Most infectious diseases diagnostics have imperfect specificity and positive predictive value
  - Patients can have C-diff colonization, urinary tract colonization, ET tube or trach colonization, Group A Strep colonization, CVC colonization...
- False-positives:
  - Mask the patient's true problem
  - Cause unnecessary antibiotic exposure
  - Overcount HAIs
- Not the goal: missing HAIs, saving money

# Diagnostic Stewardship Principles

- Perform infectious diseases diagnostic testing *appropriately*
  - Examples:
    - Adequate blood culture volumes sent from fresh peripheral sticks
    - Reject formed stools sent for C-diff testing
- Only send testing when infection reasonably suspected
  - Avoid false-positives
  - Especially nonsterile sites

# Diagnostic Stewardship Stakeholders



Frontline staff

Obtain most samples for testing  
Often suggest testing to providers



Microbiology lab

Assess sample adequacy  
(rejecting formed stools, rejecting  
“sputum” that’s all spit)

Reporting algorithms:

- Urine culture with 3 organisms  
in low numbers vs “mixed  
urogenital flora”



Ordering providers and pharmacists

Order diagnostic tests and make  
treatment decisions



# *C. difficile* Diagnostic Stewardship

- *C. difficile* colonization is common
  - Nontoxigenic strains
  - Toxigenic strains not causing symptoms
- Diarrhea is common in the hospital
  - Laxatives, enteral feeds, withdrawal symptoms, most drugs, etc...
- Use high-specificity test algorithms
  - Avoid PCR-only CDI testing
- Avoid *C. difficile* testing if:
  - Not true diarrhea (<3 episodes/24 hours, formed stool)
  - Recent laxative exposure
  - Recent negative test

C. Difficile Assay ✓ Accept ✗ Cancel

**C. Diff Information**

**Laxatives**

Medication	Ordered Dose/Rate, Route, Frequency	Last Action
bisacodyl (DULCOLAX) EC tablet 5 mg	5 mg, Oral, Daily PRN	Given, 5 mg at 02/24 0905
docusate sodium (COLACE) capsule 100 mg	100 mg, Oral, Daily	Given, 100 mg at 07/24 1531

**C. Diff Results (Last 14 days)**  
No procedures found

Frequency:  Once STAT Tomorrow AM Daily

At:  Today Tomorrow

❗ Has the patient had >=3 liquid stools in the past 24 hour period?

❗ Is the patient on treatment for C. difficile?

❗ You MUST request infectious Diseases approval before signing this order. Did Infectious Diseases approve this order?

Specimen Type:

Specimen Source:

Add-on: No add-on specimen found

Comments: + Add Comments

Process Instructions: "Testing for C. difficile infection is appropriate in patients >= 2 years of age with >= 3 liquid stools in a 24 hour period. Do NOT test if patient: has received laxatives in the past 48 hours"; had a negative C. difficile test in the past 7 days with no NEW symptoms"; had a positive test in the past 14 days; is still on treatment for C. difficile; has finished treatment for C. difficile, in order to demonstrate a "cure".

Phase of Care:

## QUALITY IMPROVEMENT

# C. difficile test ordering: "hard stop"

✓ Accept ✗ Cancel

Frequency:  Once STAT Tomorrow AM Daily

At:  Today Tomorrow

❗ Has the patient had >=3 liquid stools in the past 24 hour period?

❗ Is the patient on treatment for C. difficile?

You MUST request infectious Diseases approval before signing this order. Did Infectious Diseases approve this order?

❗ Please indicate who approved this order and when:

Specimen Type:

Specimen Source:

Add-on: No add-on specimen found

Comments: + Add Comments

Process Instructions: "Testing for C. difficile infection is appropriate in patients >= 2 years of age with >= 3 liquid stools in a 24 hour period. Do NOT test if patient: has received laxatives in the past 48 hours"; had a negative C. difficile test in the past 7 days with no NEW symptoms"; had a positive test in the past 14 days; is still on treatment for C. difficile; has finished treatment for C. difficile, in order to demonstrate a "cure".

**⚠ You cannot sign these orders because information is missing or requires your attention:**

C. Diff testing is not currently indicated for this patient. If after review of the C Diff ordering guidelines, you still need to place the order, contact your designated approval point person and document the name and the date of contact in the C Diff order

Slide courtesy of  
Emily Sickbert-Bennett, PhD

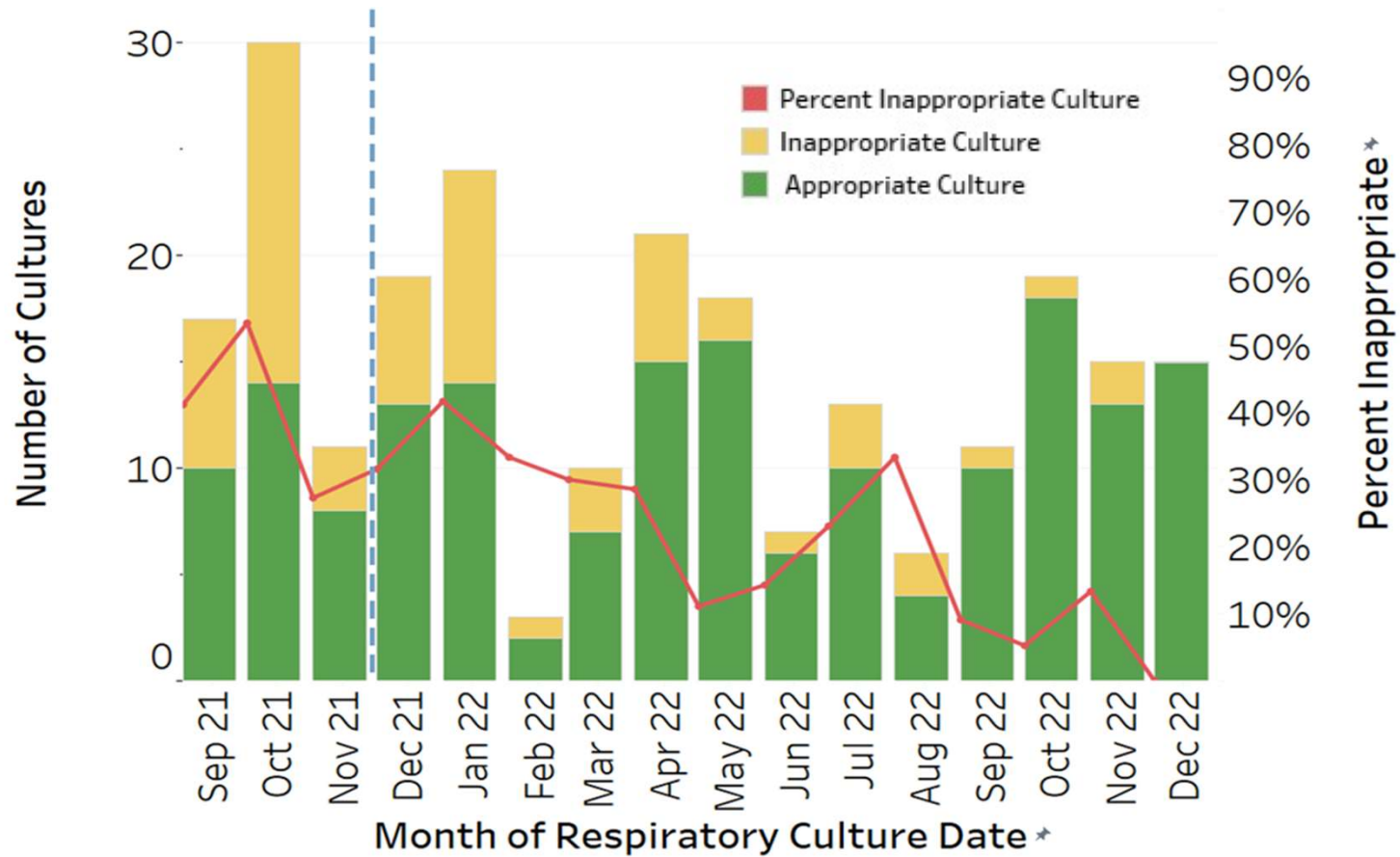
# HAP/VAP Diagnostic Stewardship

- Surveillance definition  $\neq$  Clinical definition
- Respiratory cultures from airway devices have very poor specificity and PPV
- False-positive cultures  $\rightarrow$  treatment courses
  - Often repetitively in one patient
  - Usually broad-spectrum

# Diagnostic Stewardship Project

- Education provided to PICU before launch
- Audited every respiratory culture sent from patients in PICU
  - 9/1/21-12/31/22 (15 months)
    - 3 months pre- and 12 months post-intervention.
  - Cultures assessed as guideline-concordant or –discordant
    - Systemic signs of illness (fever, leukocytosis, etc) PLUS respiratory symptoms (persistently increased PEEP/FiO<sub>2</sub>, CXR changes, purulent ETT output)
- Periodic feedback to PICU providers

# Proportion of Respiratory Cultures that were Guideline-Concordant

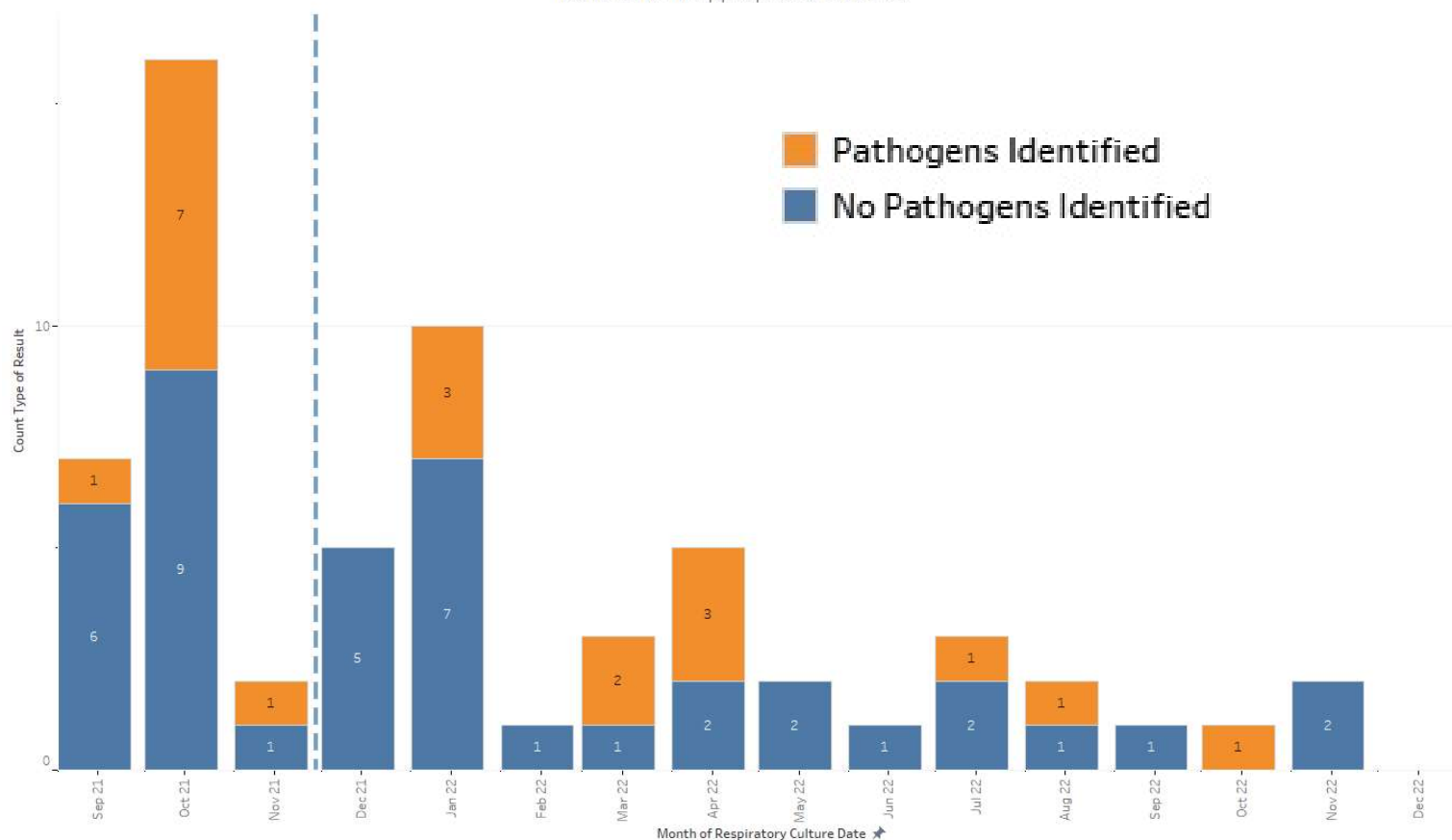


# Results of Guideline-Discordant Cultures

Orange:  
cultures  
that grew  
pathogens

Blue:  
cultures  
that did not  
grow

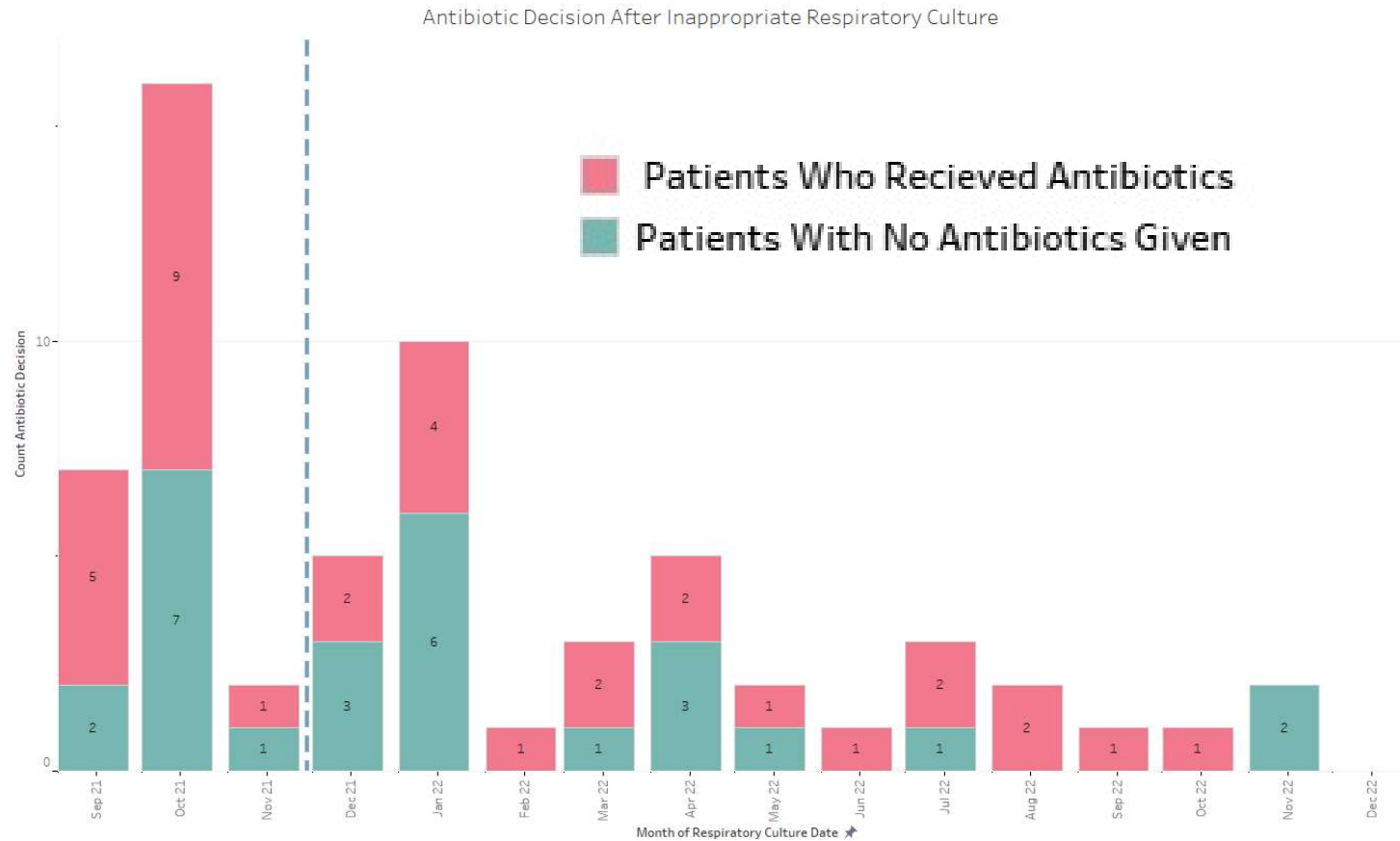
Results for Inappropriate Cultures



The plot of count of Combined Type of Resp Culture Result (copy 2) for Respiratory Culture Date Month. Color shows details about Combined Inappropriate Type of Resp Culture Result (copy). The marks are labeled by count of Combined Type of Resp Culture Result (copy 2). The data is filtered on Location, which keeps PCICU and PICU. The view is filtered on Combined Inappropriate Type of Resp Culture Result (copy), which excludes Null.

# Guideline-Discordant Cultures Treated with Antibiotics

Salmon: Number of guideline-discordant cultures treated with antibiotics



The plot of count of Were Antibiotics Given For Patients With Inappropriate Cultures? for Respiratory Culture Date Month. Color shows details about Were Antibiotics Given For Patients With Inappropriate Cultures?. The marks are labeled by count of Were Antibiotics Given For Patients With Inappropriate Cultures?. The data is filtered on Location, which keeps PCICU and PICU. The view is filtered on Were Antibiotics Given For Patients With Inappropriate Cultures?, which excludes Null.



# Blood Culture Diagnostic Stewardship

JAMA Pediatrics | [Original Investigation](#)

## Association of Diagnostic Stewardship for Blood Cultures in Critically Ill Children With Culture Rates, Antibiotic Use, and Patient Outcomes Results of the Bright STAR Collaborative

Charlotte Z. Woods-Hill, MD, MSHP; Elizabeth A. Colantuoni, PhD; Danielle W. Koontz, MA, MS; Annie Voskertchian, MPH; Anping Xie, PhD; Cary Thurm, PhD; Marlene R. Miller, MD, MSc; James C. Fackler, MD; Aaron M. Milstone, MD, MHS; and the Bright STAR Authorship Group

- Can we steward *blood cultures*? Should we?
- Logic: Fever → blood cultures → empiric antibiotics
- Would *CLABSIs go down??* Would septic shock go up?

# Blood Culture Diagnostic Stewardship

- 14 PICUs independently developed blood culture best practices
  - Reduce variability in blood culture decision, source, frequency of repeats
  - Studied 24 months pre- and 18 months post-implementation
- Results:
  - Blood cultures fell 33% (49 blood cultures/1000 patient-days fewer)
  - Broad-spectrum antibiotics use fell 13%
  - Unchanged: PICU mortality, LOS, readmission, sepsis, severe sepsis
  - CLABSIs fell 36% (1.79 → 1.14 CLABSI/1000 line-days)

# UTI Diagnostic Stewardship

- 2 major scenarios:
  - Inpatient with indwelling catheter (at risk for CAUTI)
  - Outpatients
- Asymptomatic bacteriuria is common
  - Older adults
  - Patients with indwelling catheters
- Overdiagnosis leads to:
  - Missed diagnoses
  - Antibiotic exposure (often repeatedly)
  - False-positive CAUTIs


# CAUTI Diagnosis Pitfalls

- Pyuria and asymptomatic bacteriuria are very common with long-dwelling urinary catheters
  - You can have ASB with or without pyuria, and pyuria may be sterile
  - You can NOT have a UTI without pyuria
    - Exception: neutropenia
- BUT ICU patients often unable to report symptoms
- Always get a UA BEFORE or at least with the urine culture
  - Use fresh catheter for culture whenever possible
- “Pan-culture” for febrile patients with an ETT and a Foley is likely to turn up a positive culture
  - Avoid this approach


# Asymptomatic bacteriuria

DO I REALLY NEED TO TREAT MY PATIENT FOR A UTI?


TREATING ASYMPTOMATIC BACTERIURIA HAS NO BENEFITS AND CAUSES HARM.  
IN FACT, IT LEADS TO AN INCREASE IN...




Healthcare costs




Length of stay



C. diff infections



Antibiotic resistance



Misclassification of CAUTI

---

**MY PATIENT IS SICK AND I SUSPECT A UTI SHOULD I TEST?**

UA is only helpful for predicting UTI among patients with appropriate urinary symptoms

<p><b>No UA Needed</b></p> <ul style="list-style-type: none"> <li>• Odor</li> <li>• Color</li> <li>• Altered mental status <b>alone</b></li> <li>• Fever or leukocytosis <b>without urinary symptoms</b></li> </ul>	<p><b>Send UA</b></p> <ul style="list-style-type: none"> <li>• Frequency</li> <li>• Burning</li> <li>• Pain</li> </ul>
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**WHAT IS THE BEST WAY TO TEST?**

- 1 Order a UA if symptomatic
- 2 Interpret UA
- 3 Order urine culture only if UA+
- 4 Treat based on culture results


Learn more at <https://uncmedicalcenter.intranet.unchealthcare.org/dept/Epidemiology/Pages/CAUTI-Prevention-Initiative.aspx>

## Adult UTI Guideline Update


4 New Algorithms




Diagnosis



Altered Mental Status



Treatment




Urine Culture Interpretation


**Reserve UTI diagnostic workup for those with UTI symptoms:**

- Painful urination
- New or worsening urinary frequency or urgency
- Suprapubic pain
- Flank pain or tenderness

**Inappropriate urine cultures pose harm to patients**




Unnecessary antibiotics



Misdiagnosis

**Bladder Infection or Cystitis**




UNC 1st line options:

- Nitrofurantoin
- Bactrim (SMX-TMP)

**!** Ciprofloxacin does NOT cover 1 in 3 E. coli isolates at UNCMC

**Pyelonephritis**



UNC 1st line empiric options:

- Ceftriaxone
- Gentamicin

**🎯** Target therapy to cultures & use shortest effective duration

# Case

The neonatal ICU has had three CLABSIs in the past four months with a similar pattern. The infections have occurred during the time period of days of life 3-7. The infants have all had umbilical venous catheters; all had had negative blood cultures at birth and received 48 hours of empiric antibiotics.

A NICU clinician notes that at their previous employer, it was common to continue the birth antibiotics until day of life 7, regardless of birth culture results.

# AS/IP: Are we ever at odds?

- Head in the sand approaches
  - No culture → No HAI!
- Antibiotic prophylaxis example:
  - Reduced incidence of VAP in neuro ICU patients who received a single dose of ceftriaxone



Can we start today?!

Umm, we need more data, maybe additional trials, then a Cochrane review and an update to IDSA guidelines





# Future Directions

- Diagnostic stewardship
  - Only scratched the surface
  - Requires IP/ASP collaboration and *many* stakeholders
- NHSN AR data
  - Becomes mandatory by next year
  - May give us *much* more data about AR patterns, relationships between AU and AR



**Questions?**

# References

CDC. The biggest antibiotic-resistant threats in the U.S. [Internet]. Centers for Disease Control and Prevention. 2022 [cited 2024 Mar 25]. Available from: <https://www.cdc.gov/drugresistance/biggest-threats.html>

Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013 [Internet]. 2013 p. 1–114. Available from: <http://www.cdc.gov/drugresistance/threat-report-2013/index.html>

Core Elements of Hospital Antibiotic Stewardship Programs | Antibiotic Use | CDC [Internet]. 2021 [cited 2021 Apr 28]. Available from: <https://www.cdc.gov/antibiotic-use/core-elements/hospital.html>

Miles-Jay A, Snitkin ES, Lin MY, Shimasaki T, Schoeny M, Fukuda C, Dangana T, Moore N, Sansom SE, Yelin RD, Bell P, Rao K, Keidan M, Standke A, Bassis C, Hayden MK, Young VB. Longitudinal genomic surveillance of carriage and transmission of *Clostridioides difficile* in an intensive care unit. *Nat Med*. Nature Publishing Group; 2023 Oct;29(10):2526–2534.

Slimings C, Riley TV. Antibiotics and healthcare facility-associated *Clostridioides difficile* infection: systematic review and meta-analysis 2020 update. *Journal of Antimicrobial Chemotherapy*. 2021 Jul 1;76(7):1676–1688.

Woods-Hill CZ, Colantuoni EA, Koontz DW, Voskertchian A, Xie A, Thurm C, Miller MR, Fackler JC, Milstone AM, Bright STAR Authorship Group. Association of Diagnostic Stewardship for Blood Cultures in Critically Ill Children With Culture Rates, Antibiotic Use, and Patient Outcomes: Results of the Bright STAR Collaborative. *JAMA Pediatrics* [Internet]. 2022 May 2 [cited 2022 Jun 7]; Available from: <https://doi.org/10.1001/jamapediatrics.2022.1024>

Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, Tacconelli E. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017 Sep;17(9):990–1001. PMID: 28629876