Antimicrobial Stewardship and the Role of the Infection Preventionist

Zach Willis, MD, MPH

4/23/24

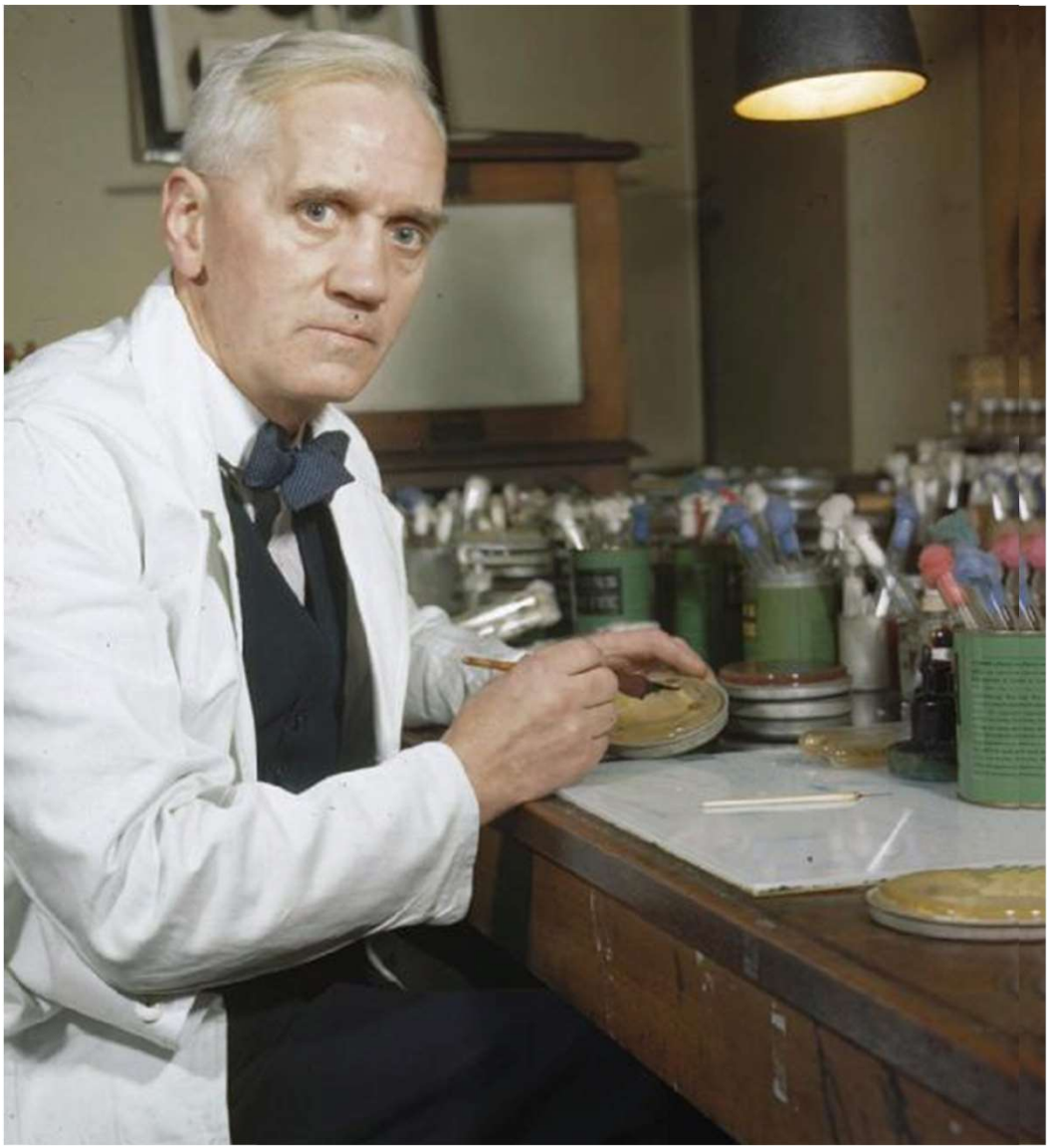
UNC SCHOOL OF MEDICINE

Disclosures

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

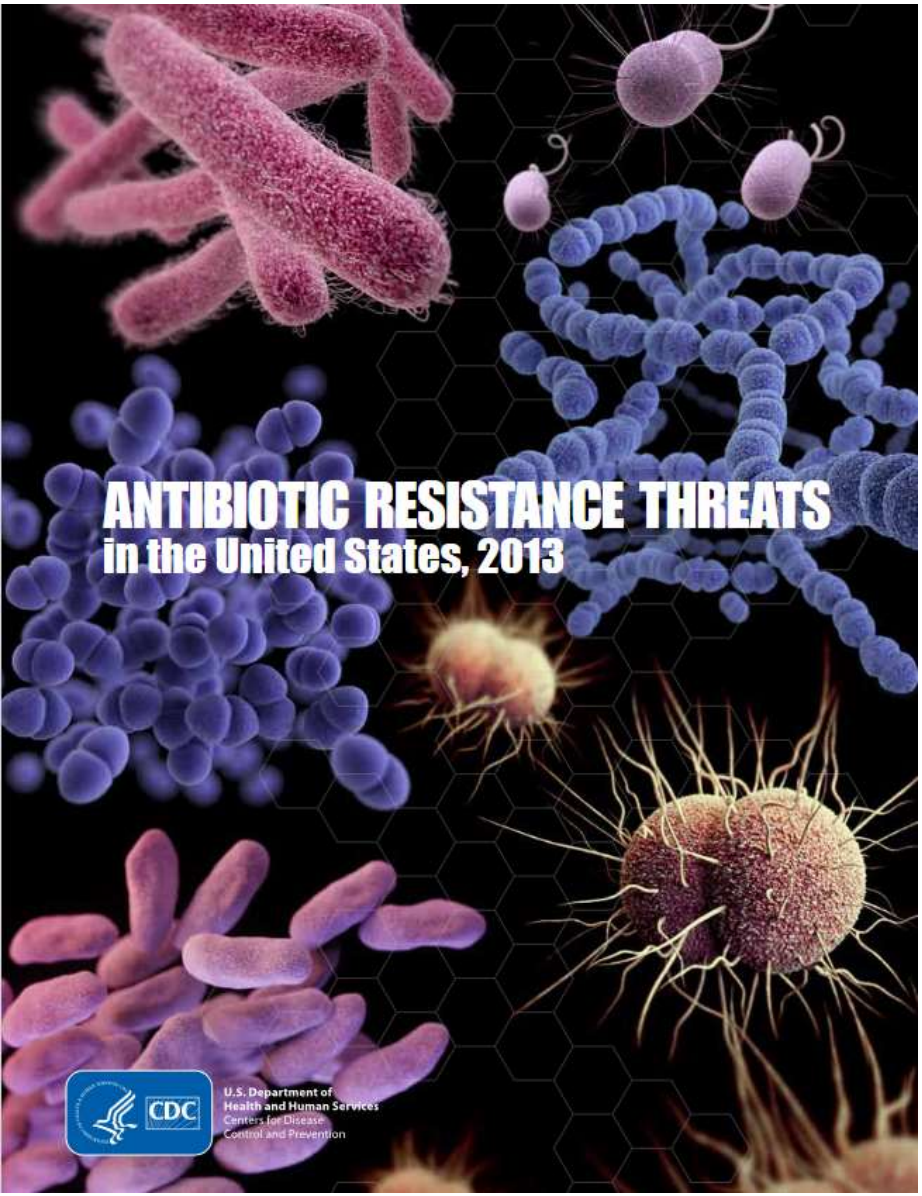
- Contracted research with:
  - Pfizer (pediatric nirmatrelvir-ritonavir)
  - Pfizer (maternal RSV vaccine)
  - Merck (monoclonal antibody for RSV prevention)

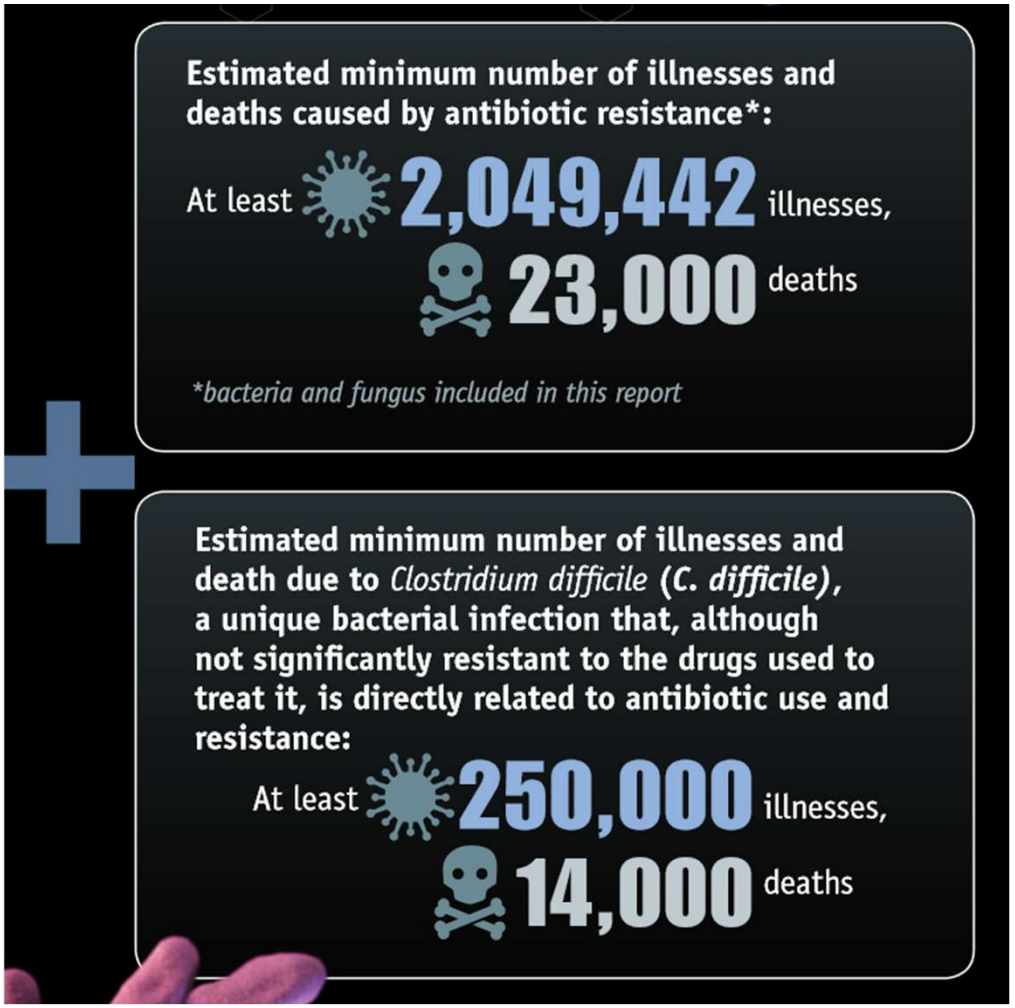
I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.



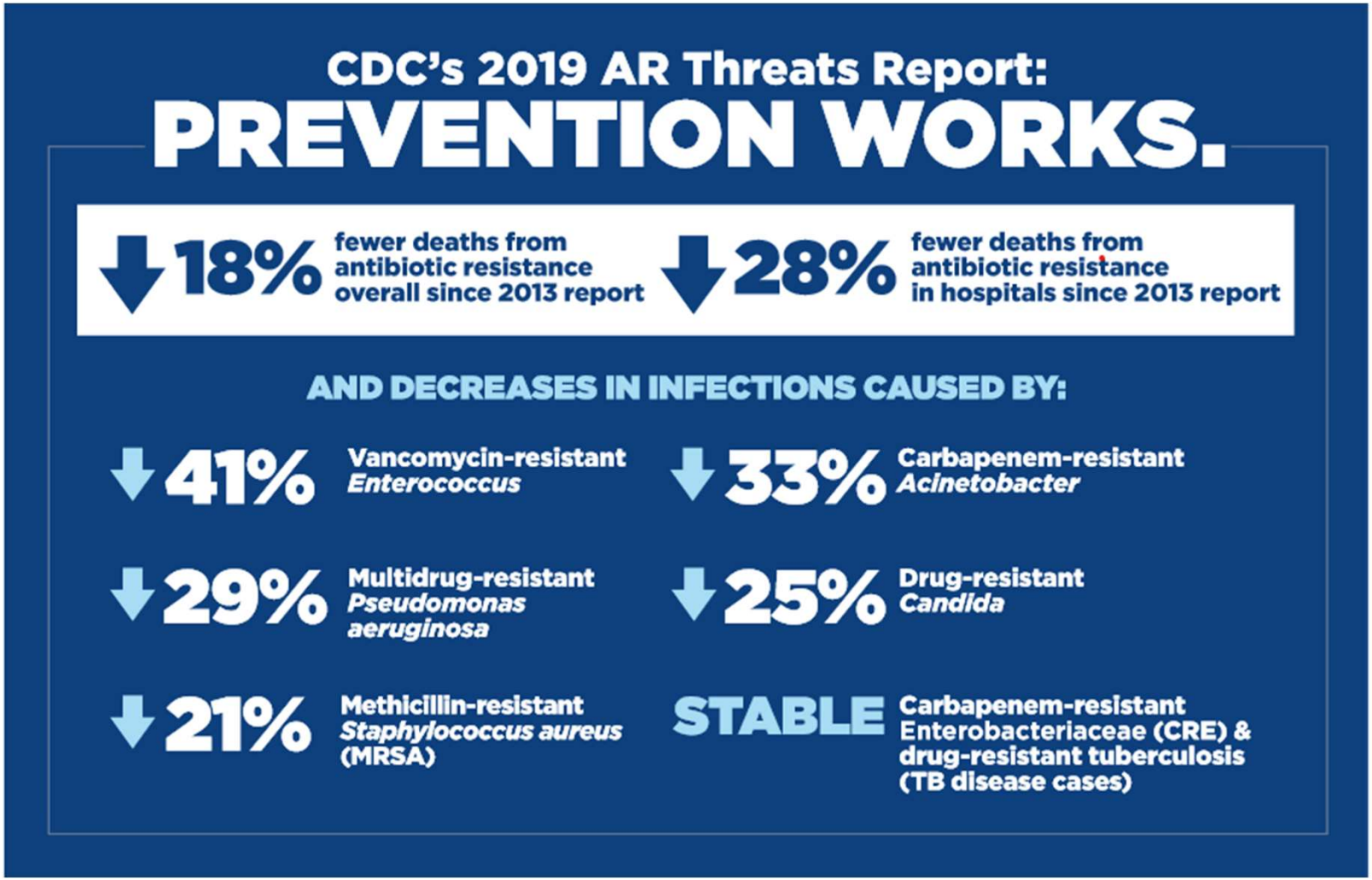
The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out.... In such cases the **thoughtless person playing with penicillin is morally responsible for the death** of the man who finally succumbs to infection with the penicillin-resistant organism.

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





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

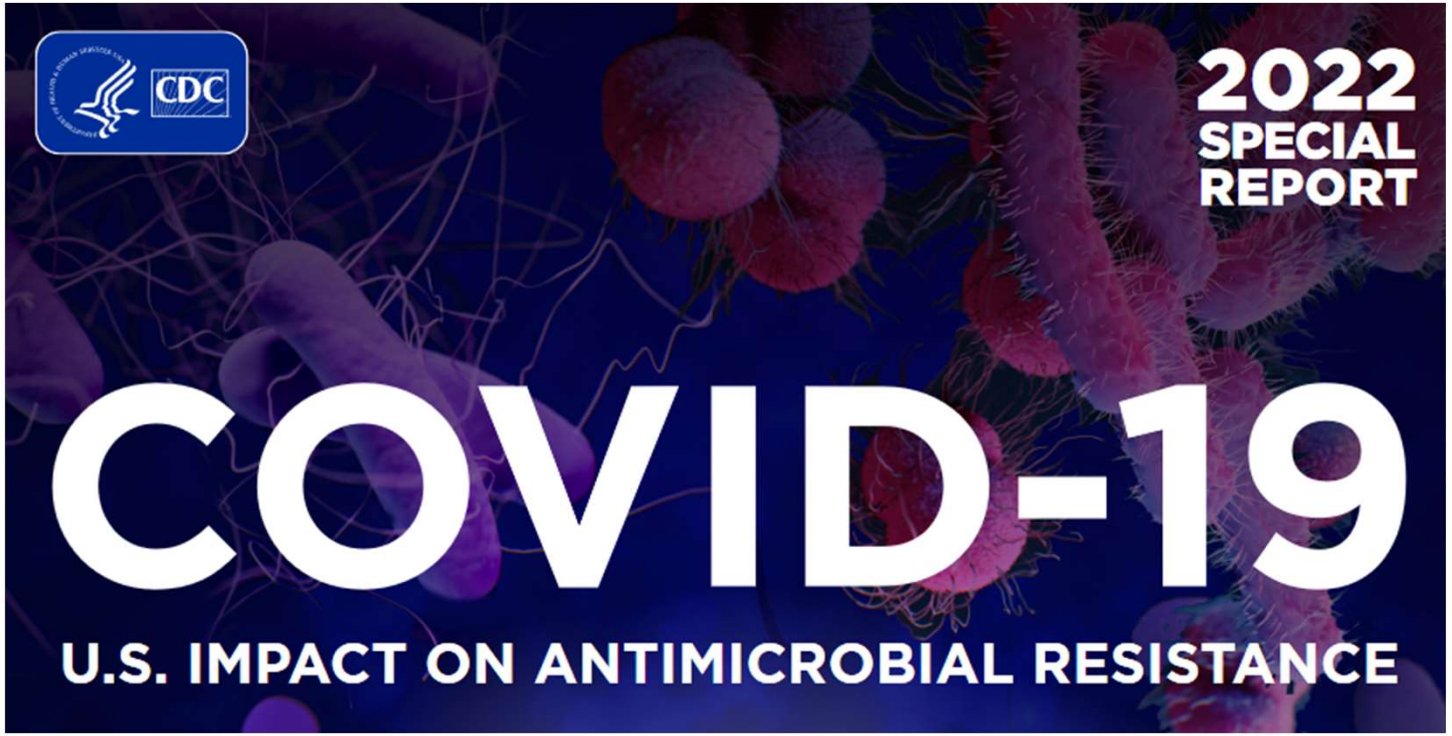


https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

What Was Working?

UNC SCHOOL OF MEDICINE

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



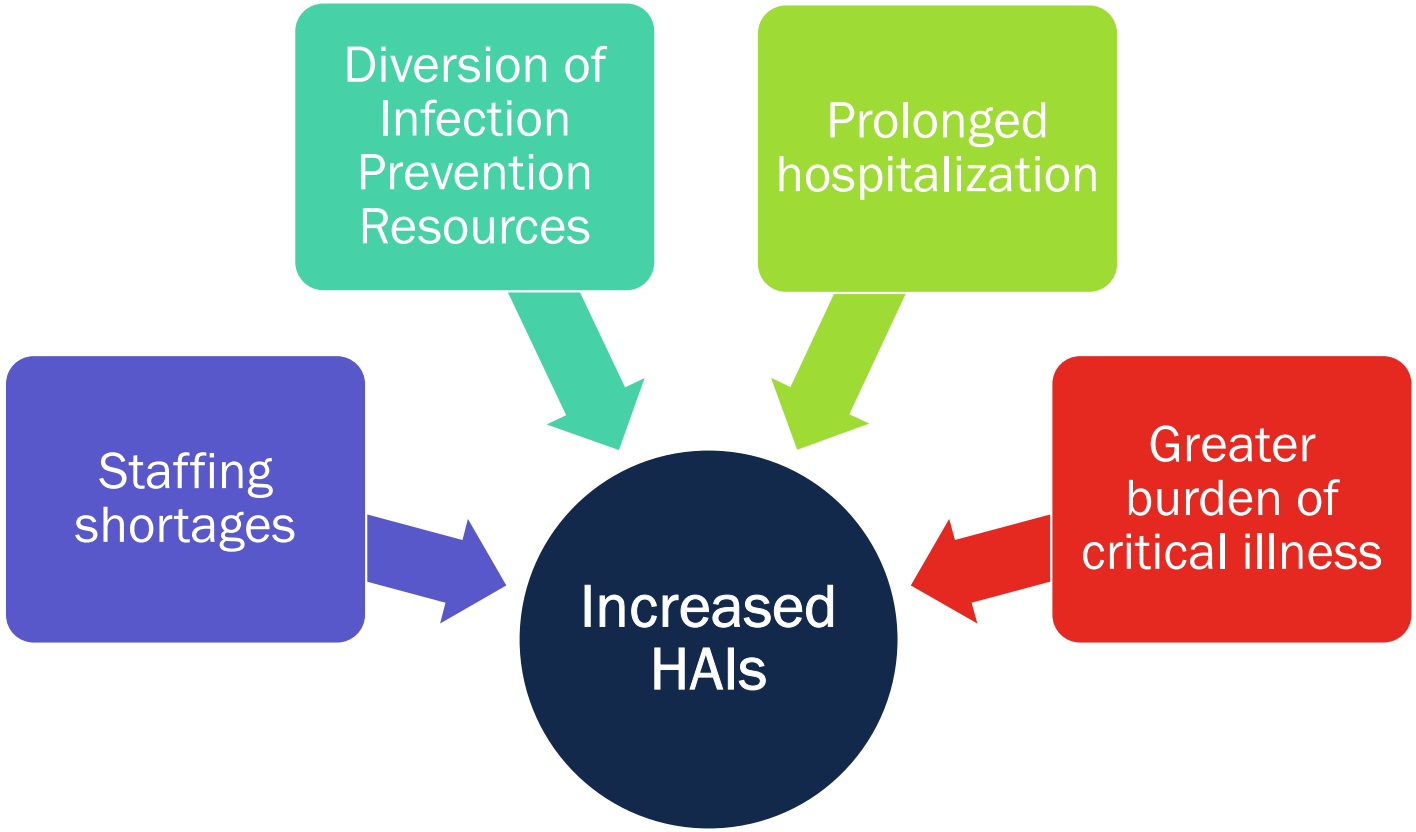
https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

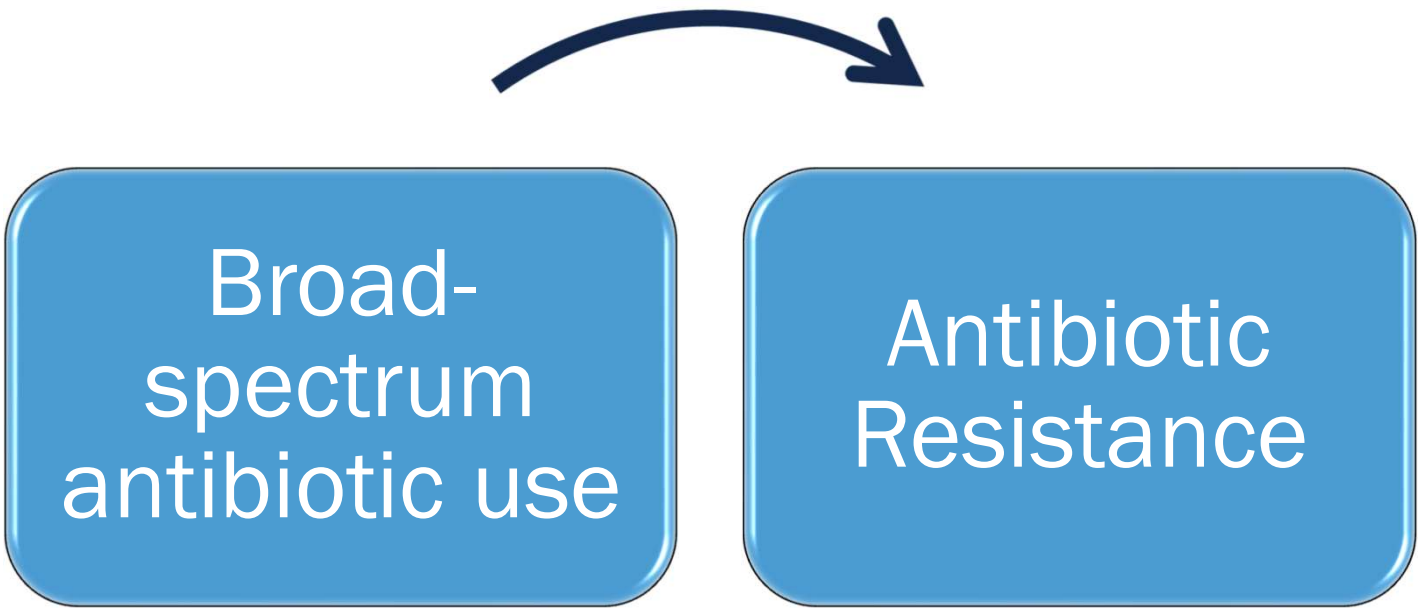
Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

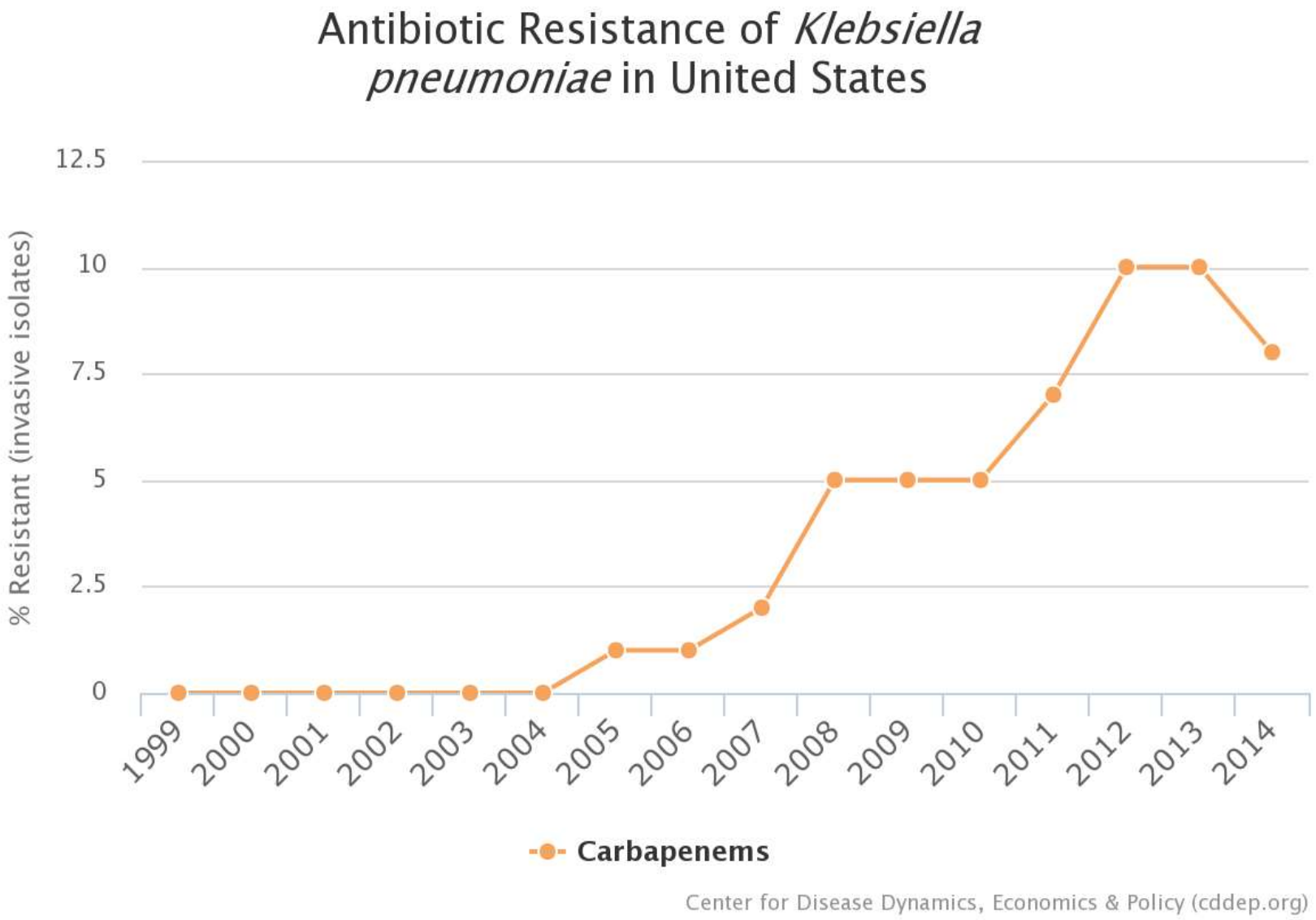
- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa*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

Why Did Antimicrobial Resistance Get Worse in the Pandemic?

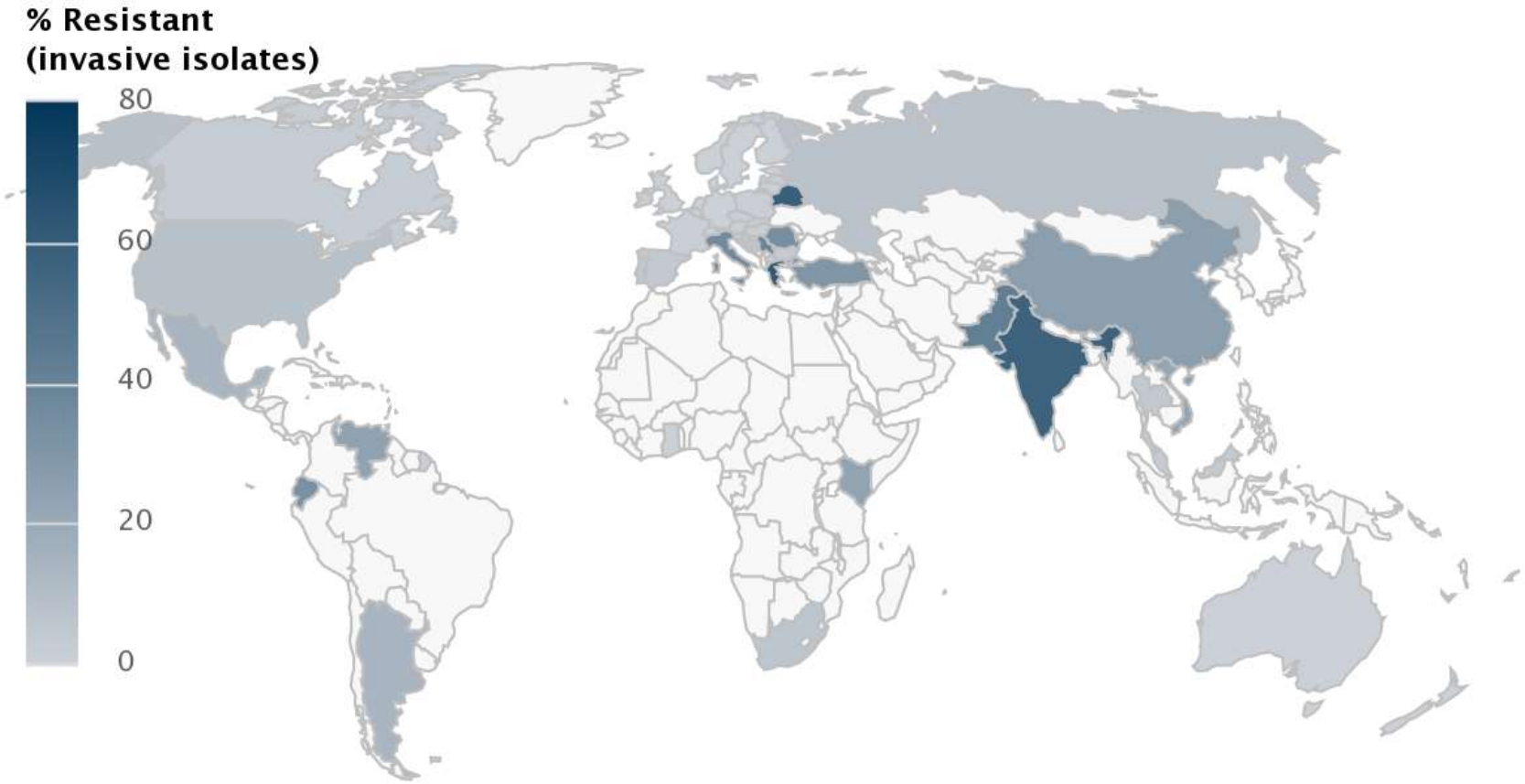
UNC SCHOOL OF MEDICINE




Broad-spectrum antibiotic use
Antibiotic Resistance


Antibiotic Resistance of *Klebsiella pneumoniae* in United States
% Resistant (invasive isolates)
12.5
10
7.5
5
2.5
0
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
Carbapenems
Center for Disease Dynamics, Economics & Policy (cddep.org)

Resistance of *Klebsiella pneumoniae* to Carbapenems



IP and AS Goal

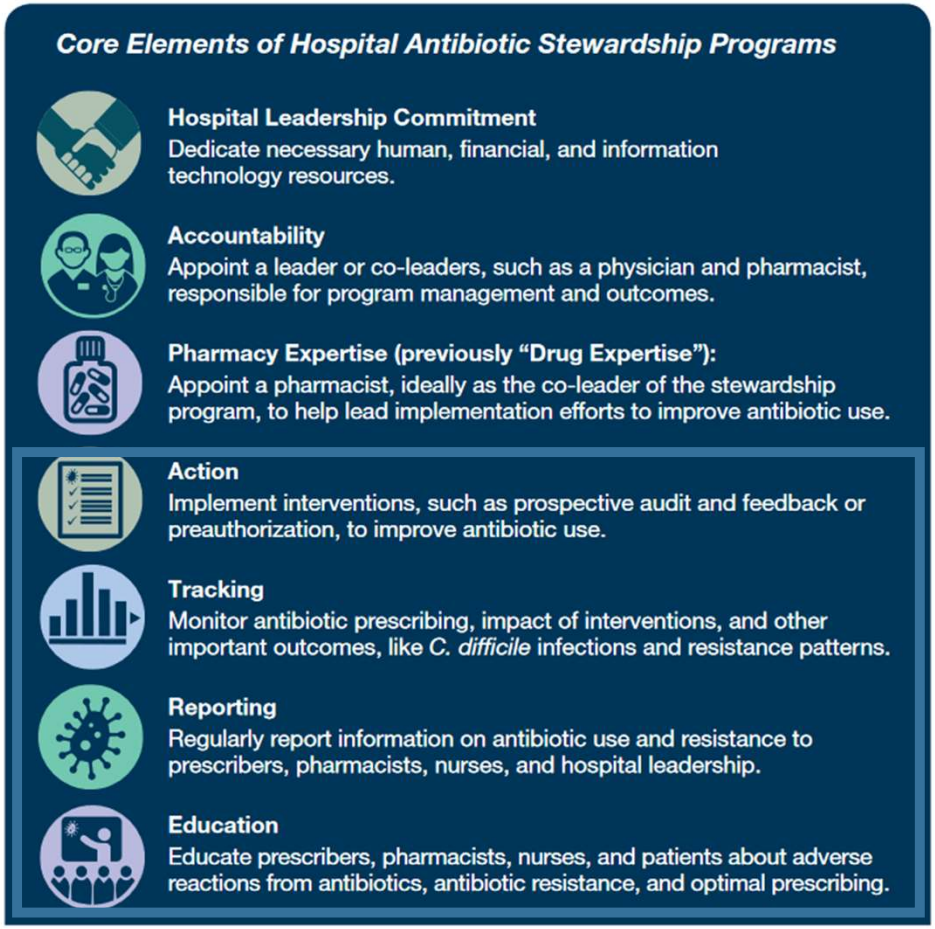
Prevent antimicrobial resistant infections and C-diff

[Antibiotic Resistance Threats in the United States, 2019 (cdc.gov)]

Slide courtesy of Emily Sickbert-Bennett, PhD

AS: Core Elements

UNC SCHOOL OF MEDICINE



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

UNC SCHOOL OF MEDICINE

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

Key ASP Tactics

UNC SCHOOL OF MEDICINE

- 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

UNC SCHOOL OF MEDICINE

- 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 ≈ 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

UNC SCHOOL OF MEDICINE

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

Stewardship: A Multidisciplinary Endeavor

UNC SCHOOL OF MEDICINE

Essential, "Core-Team" Personnel

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

Case

UNC SCHOOL OF MEDICINE

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

UNC SCHOOL OF MEDICINE

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

C-diff Prevention

UNC SCHOOL OF MEDICINE

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!

UNC SCHOOL OF MEDICINE

nature medicine

Article

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

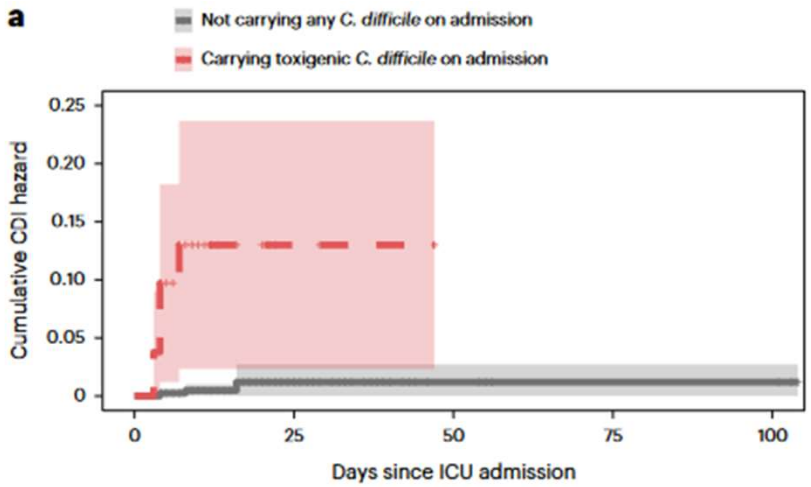
Longitudinal genomic surveillance of carriage and transmission of *Clostridioides difficile* in an intensive care unit

Received: 2 August 2022

Accepted: 17 August 2023

Published online: 18 September 2023

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



- 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*

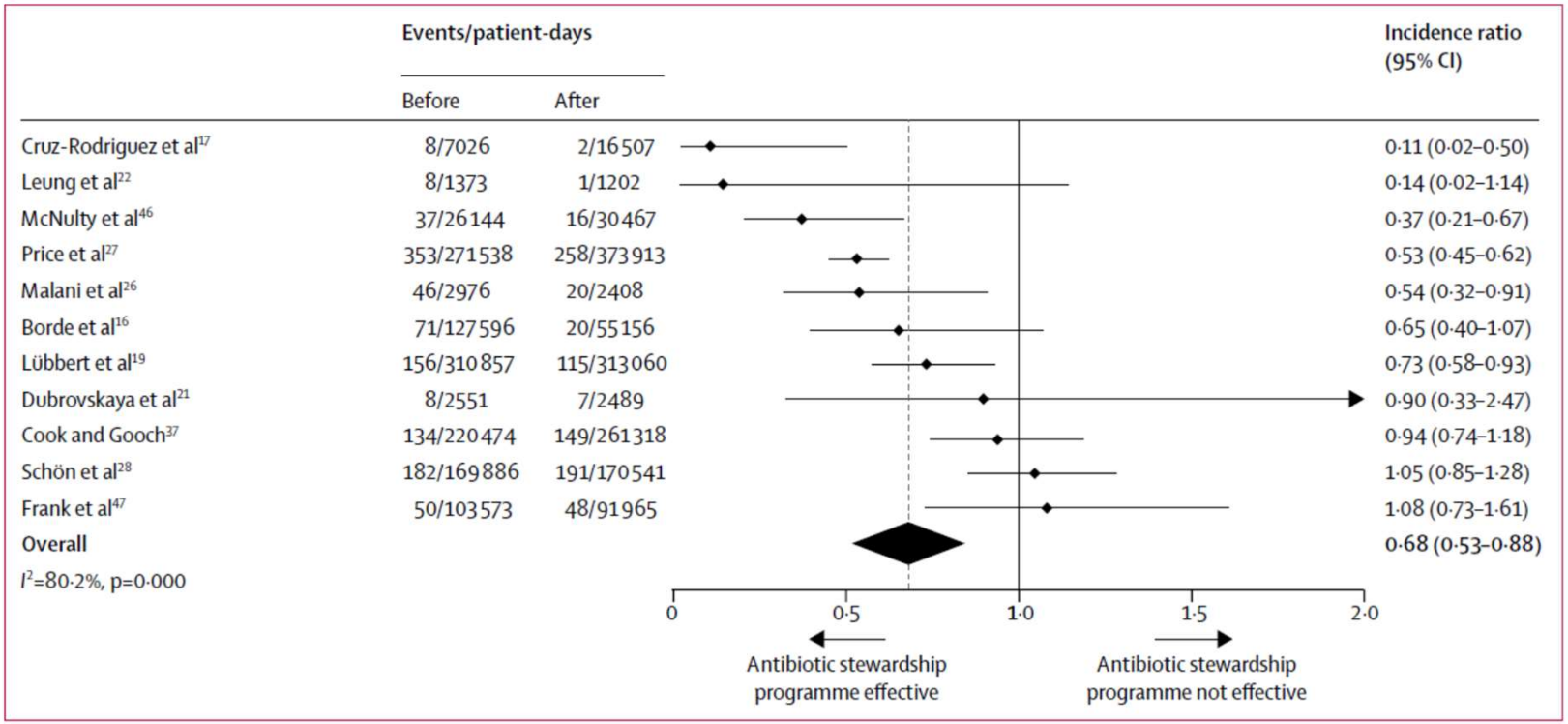


Figure 4: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections

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

J Antimicrob Chemother 2021; **76**: 1676–1688
doi:10.1093/jac/dkab091 Advance Access publication 31 March 2021

Journal of Antimicrobial Chemotherapy

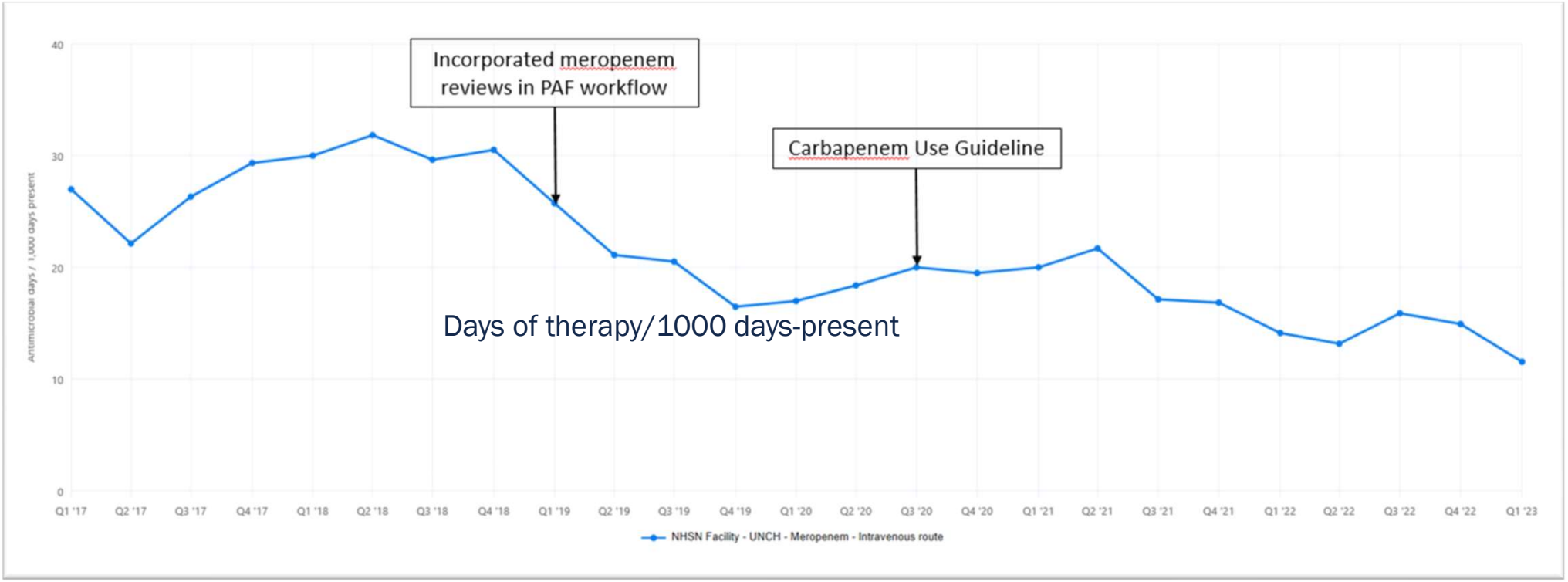
Antibiotics and healthcare facility-associated *Clostridioides difficile* infection: systematic review and meta-analysis 2020 update

Claudia Slimings [1]* and Thomas V. Riley[2,3]

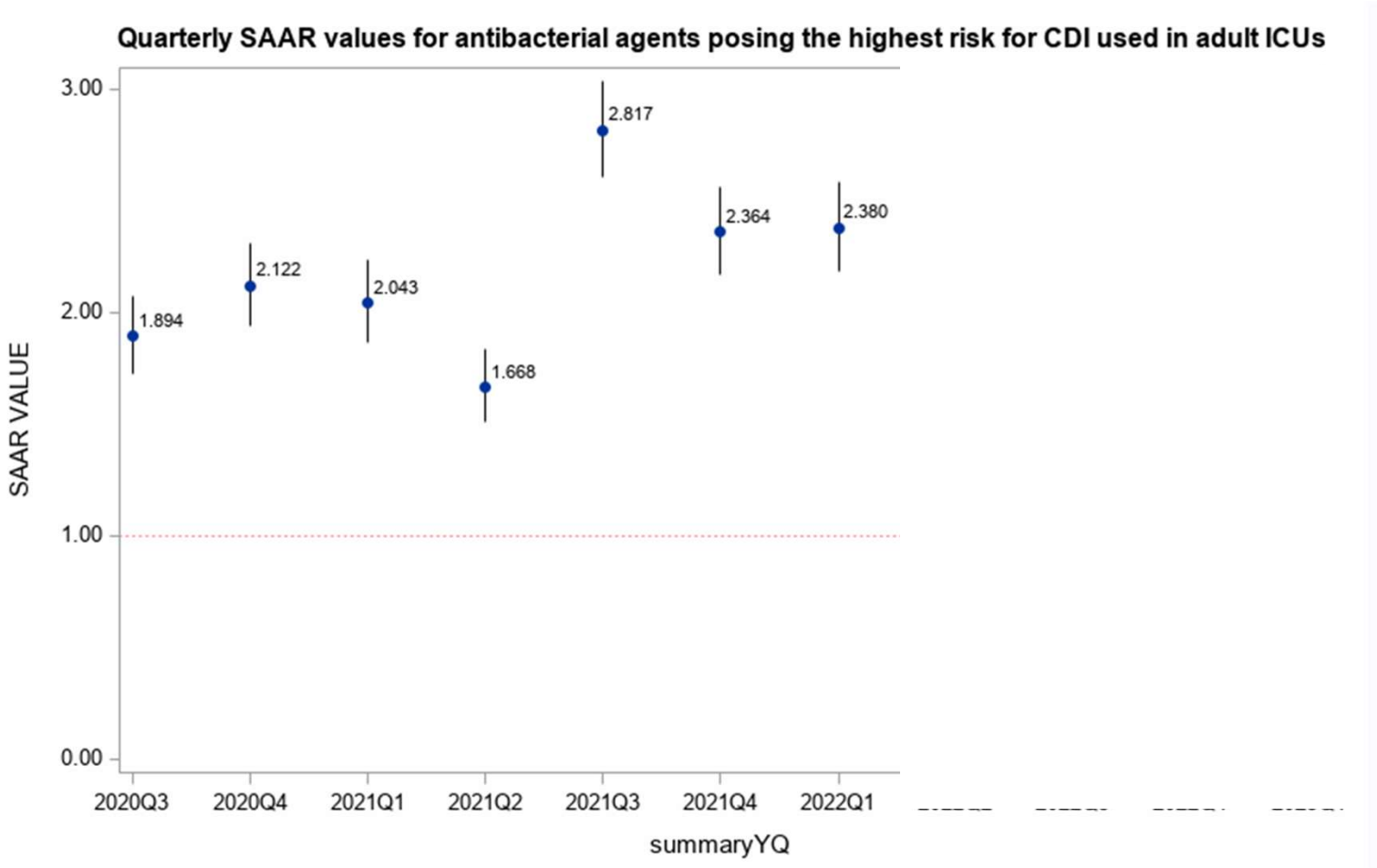
- Which antibiotics are most likely to cause CDI?
- Highest-risk classes (highest to lowest):
  - Carbapenems
  - 4th-gen and 3rd-gen cephalosporins
  - Vancomycin
  - Fluoroquinolones
  - Clindamycin
  - Piperacillin-tazobactam
  - No association: narrow penicillins, 1st-gen cephalosporins, TMP-SMX,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

Meropenem Use 2017-2023

UNC SCHOOL OF MEDICINE



Antibiotics with high risk for CDI in SICU



Diagnostic Stewardship: Why?

UNC SCHOOL OF MEDICINE

- 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

UNC SCHOOL OF MEDICINE

- 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

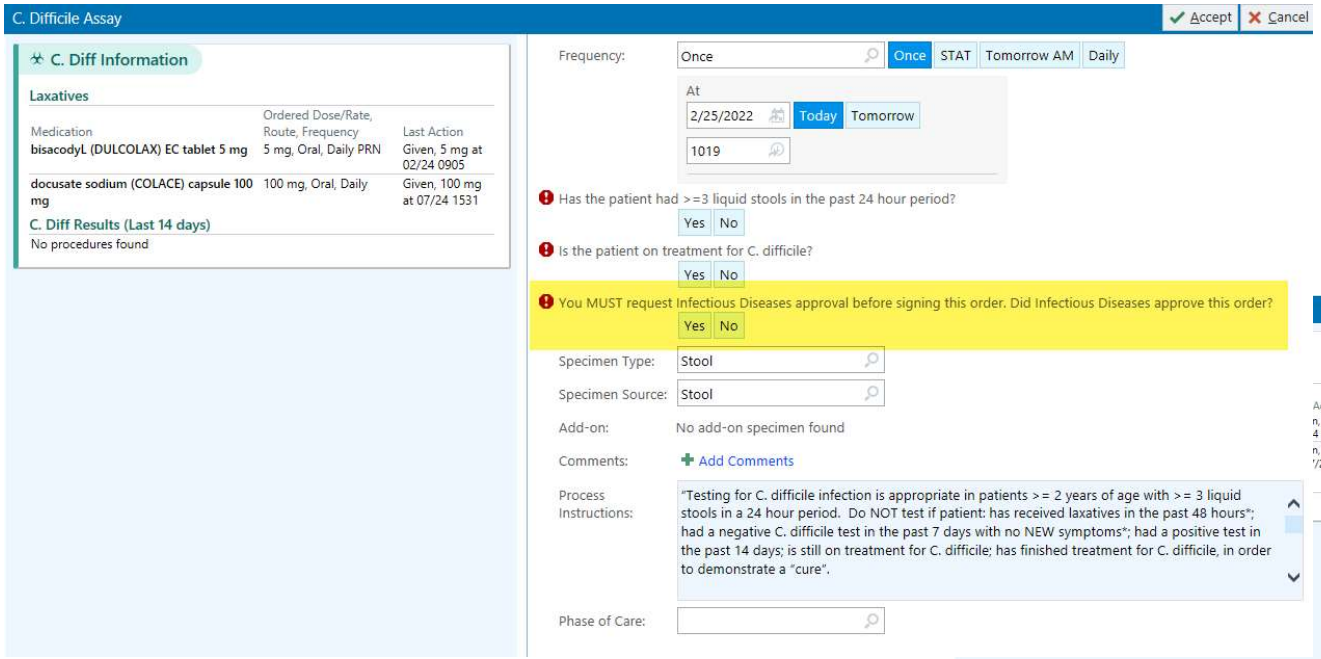
UNC SCHOOL OF MEDICINE

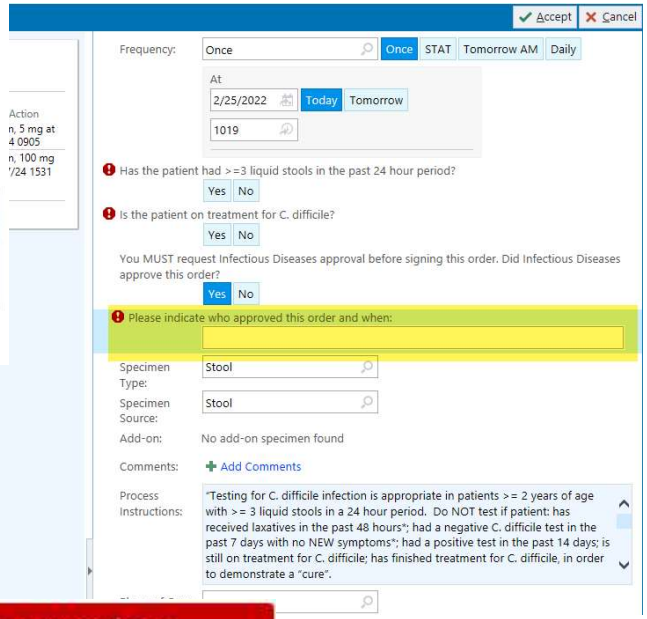
- *C. difficile* colonization is common
  - Nontoxigenic strains
  - Toxigenic strains not causing symptoms
- Diarrhea is common in the hospital
  - Laxatives, enteral feeds, withdrawal symptoms, most drugs, etc…

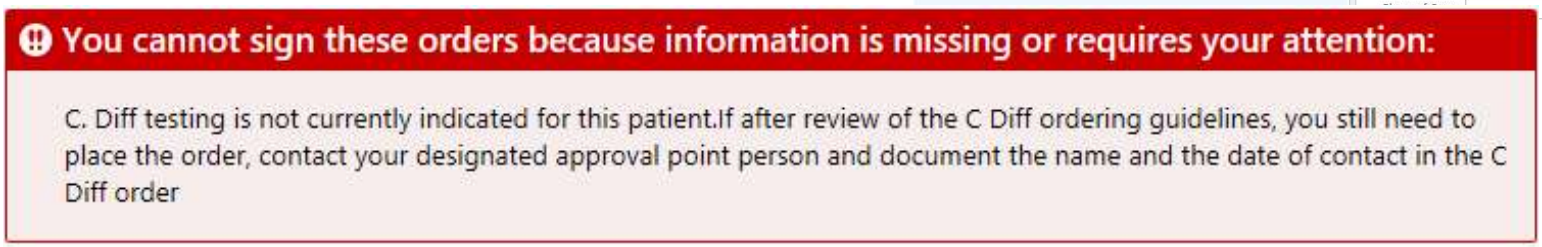
- Use high-specificity test algorithms
  - Avoid PCR-only CDI testing
- Avoid *C. difficile* testing if:
  - Not true diarrhea (<3 episodes/24 hours, formed stool)
  - Recent laxative exposure
  - Recent negative test

QUALITY IMPROVEMENT

C. difficile test ordering: "hard stop"







Slide courtesy of Emily Sickbert-Bennett, PhD

HAP/VAP Diagnostic Stewardship

UNC SCHOOL OF MEDICINE

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

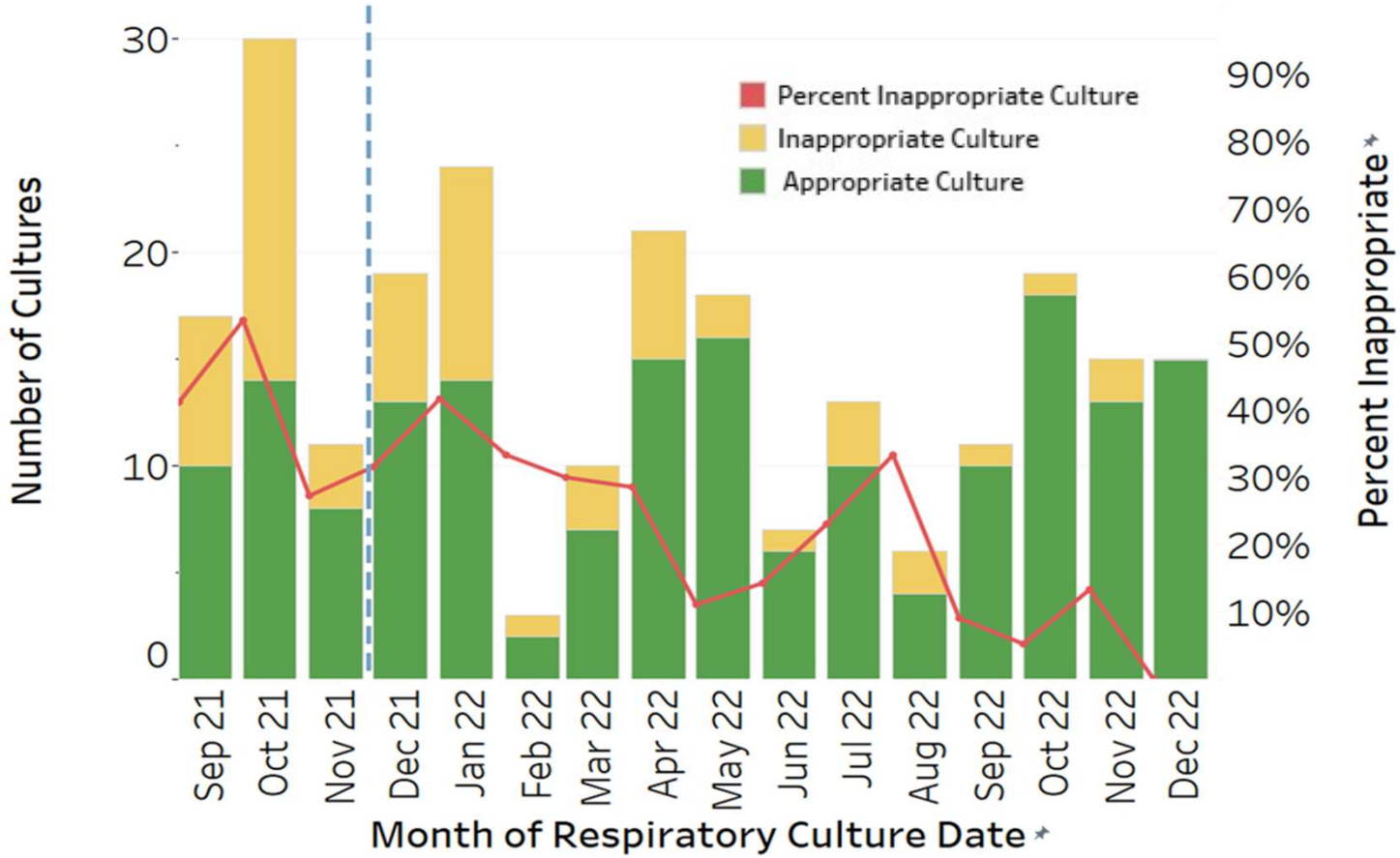
Diagnostic Stewardship Project

UNC SCHOOL OF MEDICINE

- 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/FiO2, CXR changes, purulent ETT output)
- Periodic feedback to PICU providers

Proportion of Respiratory Cultures that were Guideline-Concordant

UNC SCHOOL OF MEDICINE

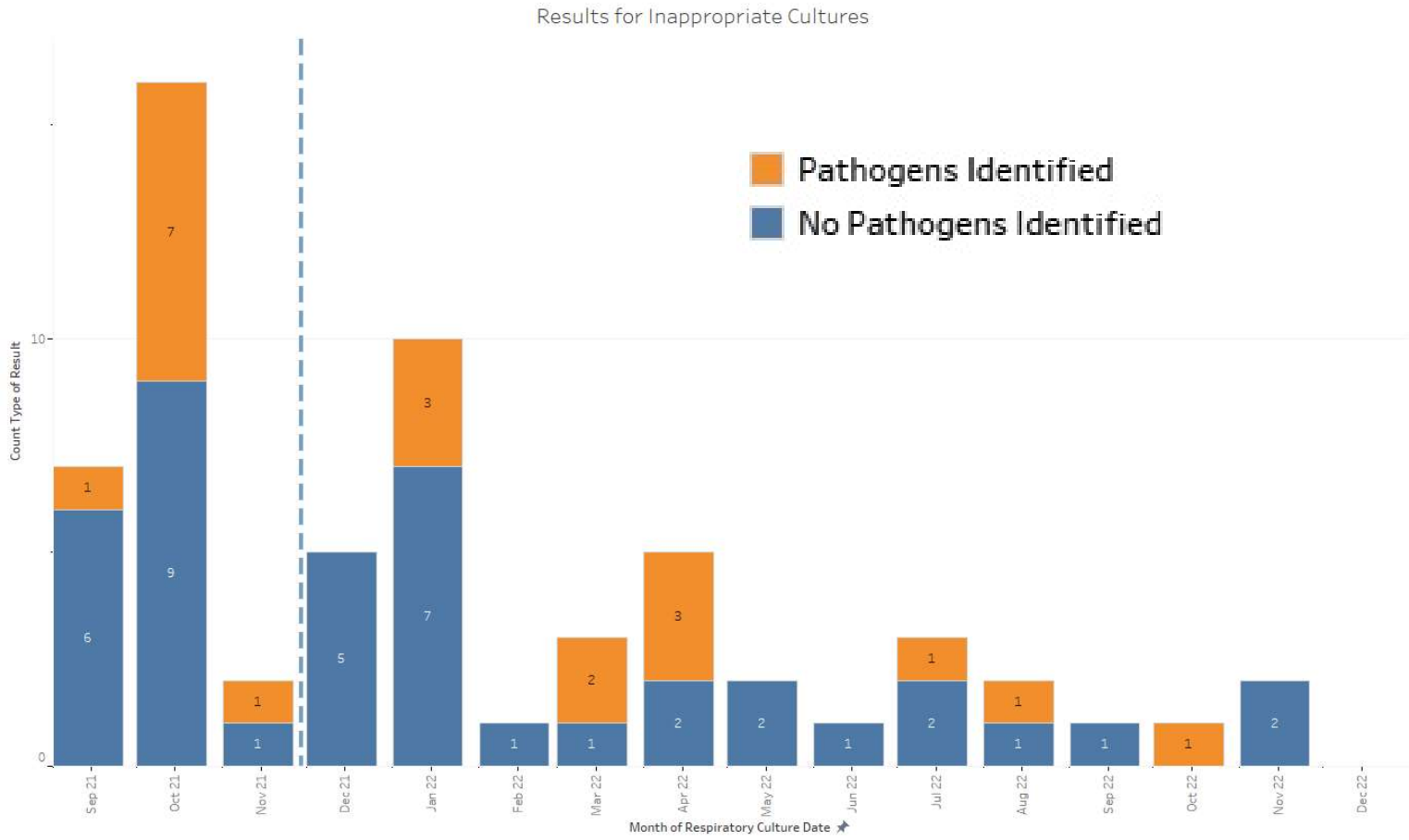


Results of Guideline-Discordant Cultures

UNC SCHOOL OF MEDICINE

Orange: cultures that grew pathogens

Blue: cultures that did not grow

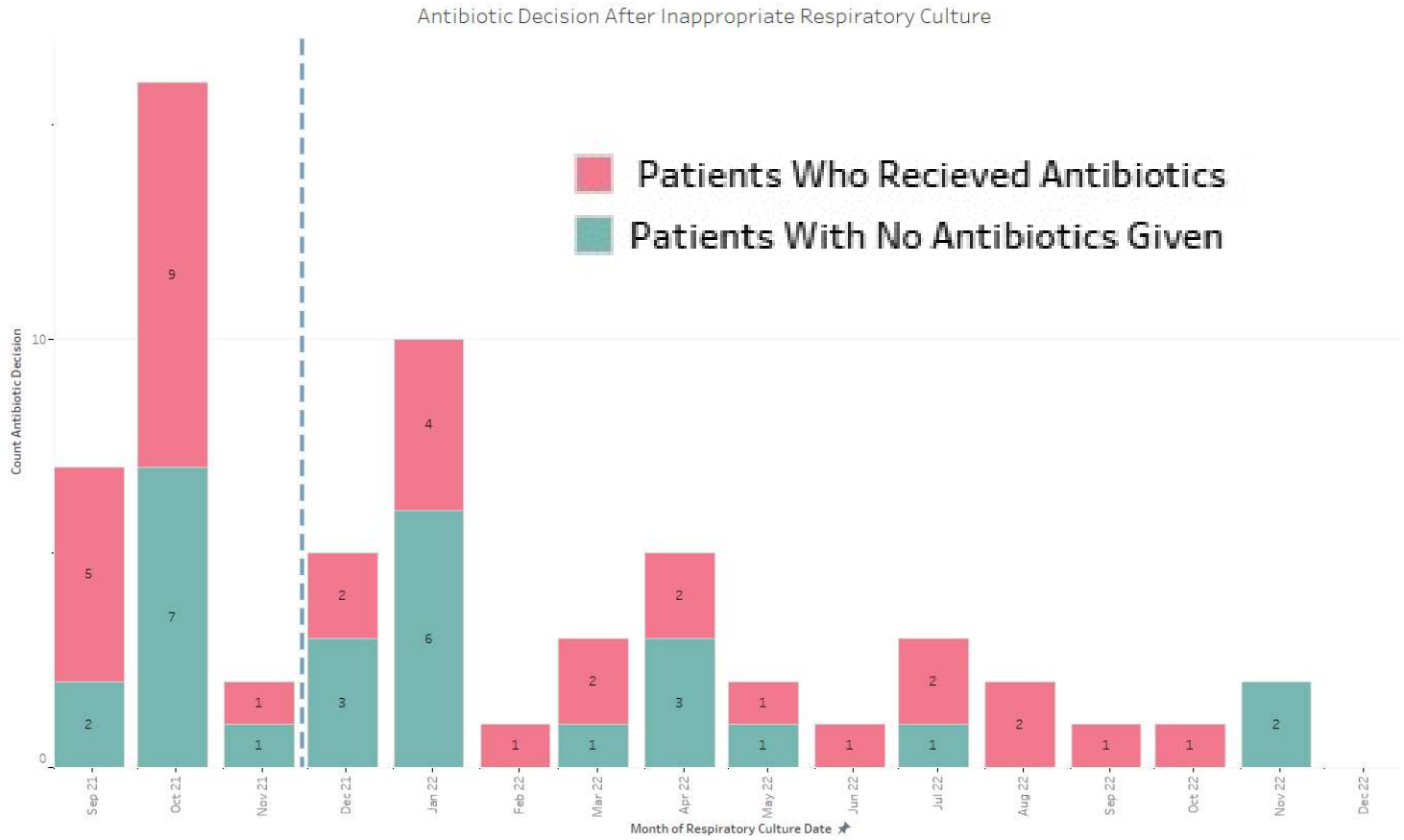


The plot of count of Combined Type of Resp Culture Result (copy 2) for Respiratory Culture Date Month. Color shows details about Combined Inappropriate Type of Resp Culture Result (copy). The marks are labeled by count of Combined Type of Resp Culture Result (copy 2). The data is filtered on Location,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

UNC SCHOOL OF MEDICINE

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

UNC SCHOOL OF MEDICINE

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

UNC SCHOOL OF MEDICINE

- 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

UNC SCHOOL OF MEDICINE

- 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

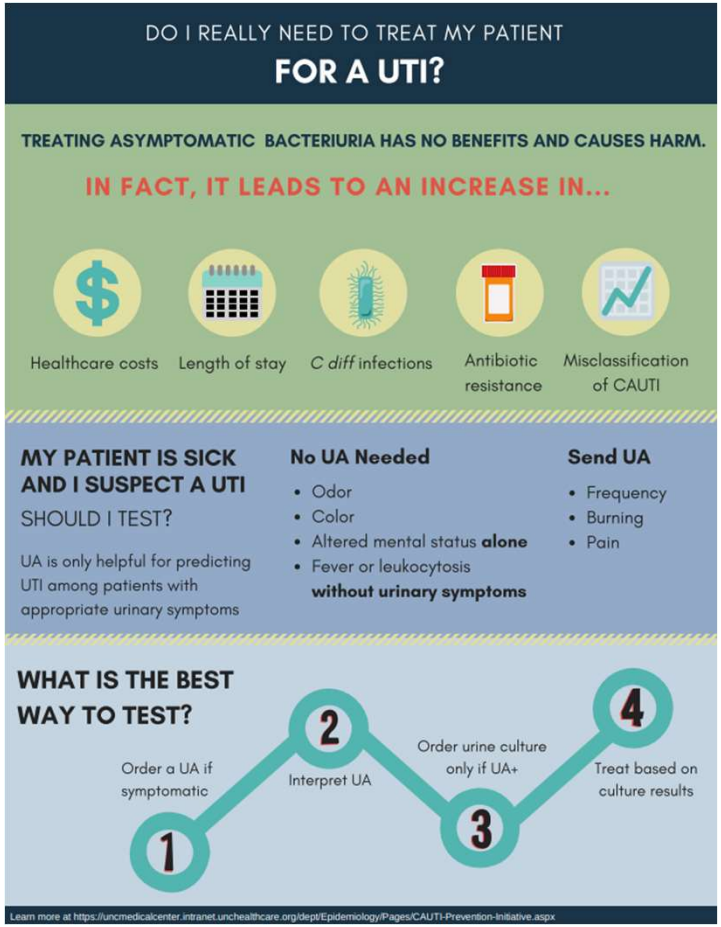
CAUTI Diagnosis Pitfalls

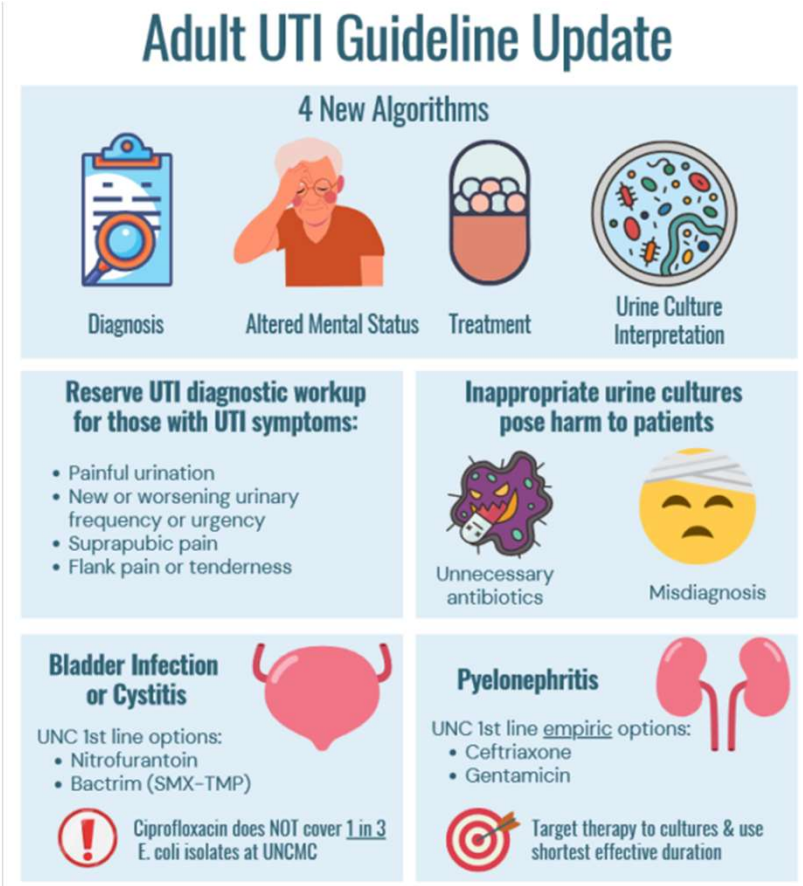
UNC SCHOOL OF MEDICINE

- 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

UNC SCHOOL OF MEDICINE





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?

UNC SCHOOL OF MEDICINE

- 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

Future Directions

UNC SCHOOL OF MEDICINE

- 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

UNC
SCHOOL OF MEDICINE

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