Epidemiology, Diagnosis, and Prevention of *Clostridium difficile* Infection

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Disclosures

- Consulting: Merck, Sanofi Pasteur, Rebiotix, Pfizer, Summitt, Daiichi
- Research: Merck, Rebiotix, Sanofi Pasteur

Learning Objectives

- Analyze the importance of *C. difficile* infection on patient outcomes
- Identify the advantages and disadvantages of *C. difficile* diagnostic assays
- Describe the role of the microbiology laboratory in the prevention of *C. difficile* infection

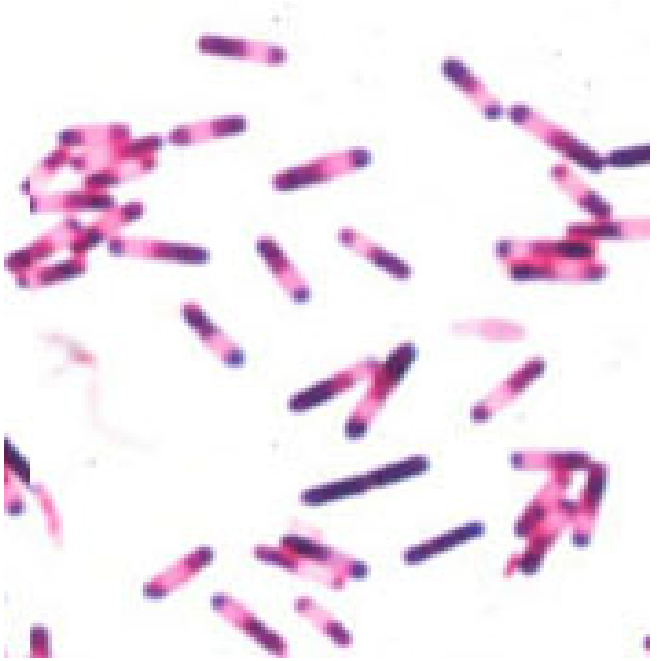
Historical Perspective

- 1935: *Bacillus difficilis* first described
- 1943 – 1978: antibiotic associated colitis (AAC) / pseudomembranous colitis (PMC)
- 1978: *Clostridium difficile* identified as causative agent of AAC/PMC
  - Cytotoxicity cell assay developed
- 1981: oral vancomycin FDA approved for treatment of *C. difficile* infection (CDI)
- 1982: oral metronidazole as effective as oral vancomycin
- 1984: Toxin EIAs approved

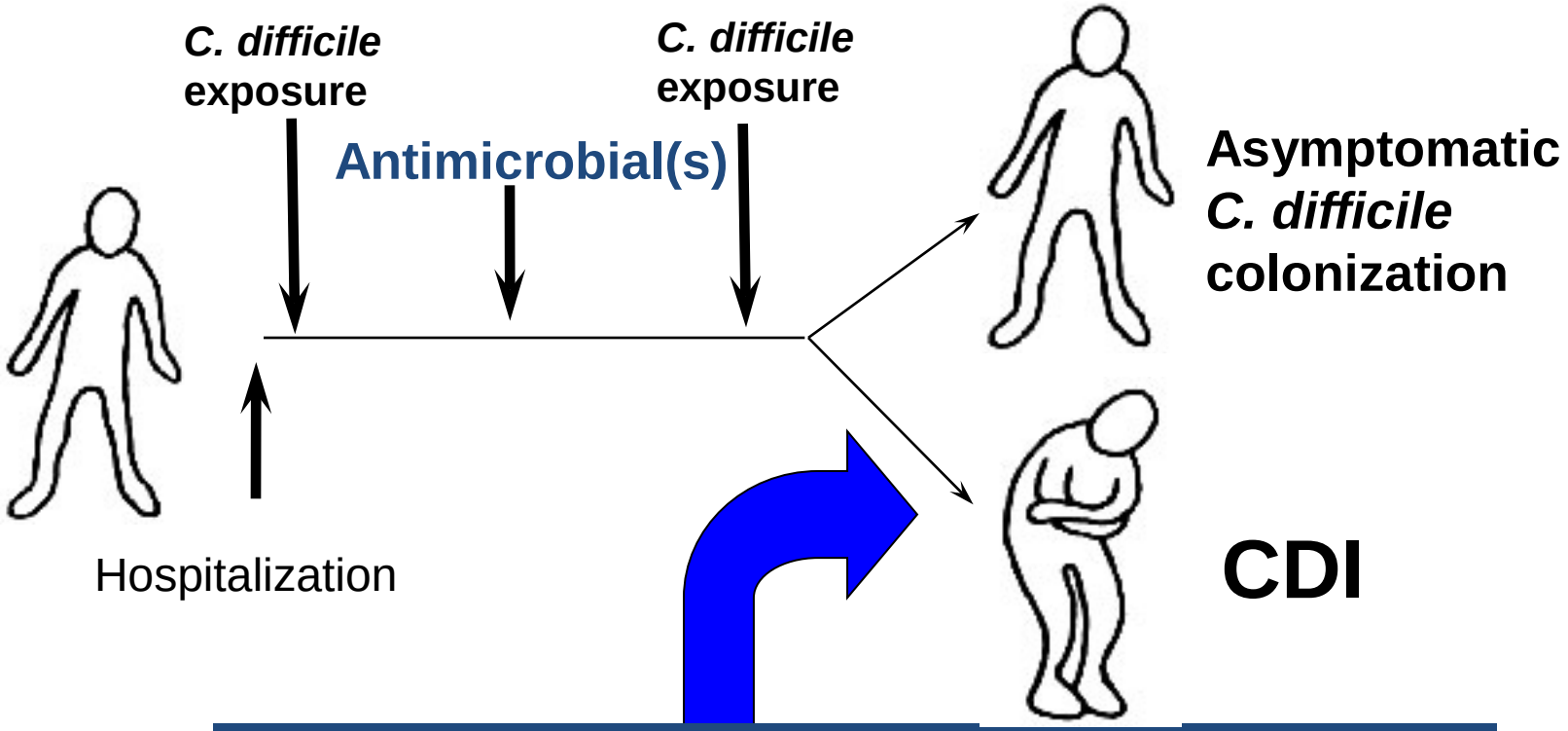
- 2000 – present: Increasing incidence and severity of CDI
- 2007: surveillance definitions developed
- 2007: First double blinded trial of CDI treatment published (Zar)
- 2009: Nucleic acid amplification tests approved
- 2011: Fidaxomicin FDA approved
- 2011: First diagnostic assay comparison where patients prospectively evaluated and included regardless of diarrhea severity

Clostridium difficile

- Gram positive, spore forming rod
- Obligate anaerobe
- Toxin A and Toxin B
  - Required to cause disease (toxigenic)
  - *C. difficile* infection (CDI, formerly CDAD)
    - Toxigenic *C. difficile* in stool ≠ CDI
- Ubiquitous
  - >50% infants culture positive, 3%-7% healthy adults
  - Cultured from food, water, pets, wild animals



Current Pathogenesis Model for *C. difficile* Infection (CDI)



Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic antibody response results in CDI.

Johnson S, Gerding DN. *Clin Infect Dis*. 1998;26:1027-1036.
Kyne L, et al. *N Engl J Med*. 2000;342:390-397.

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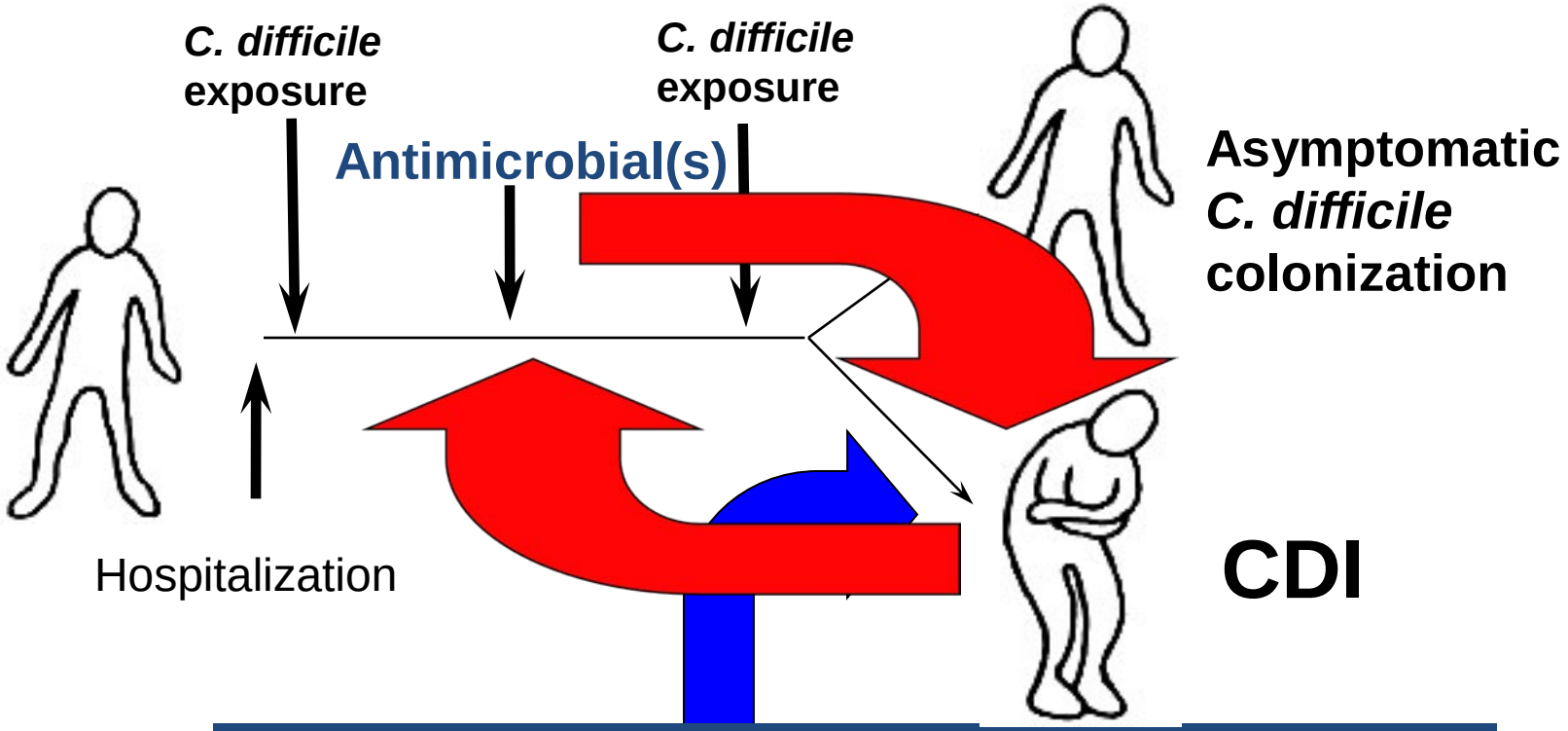

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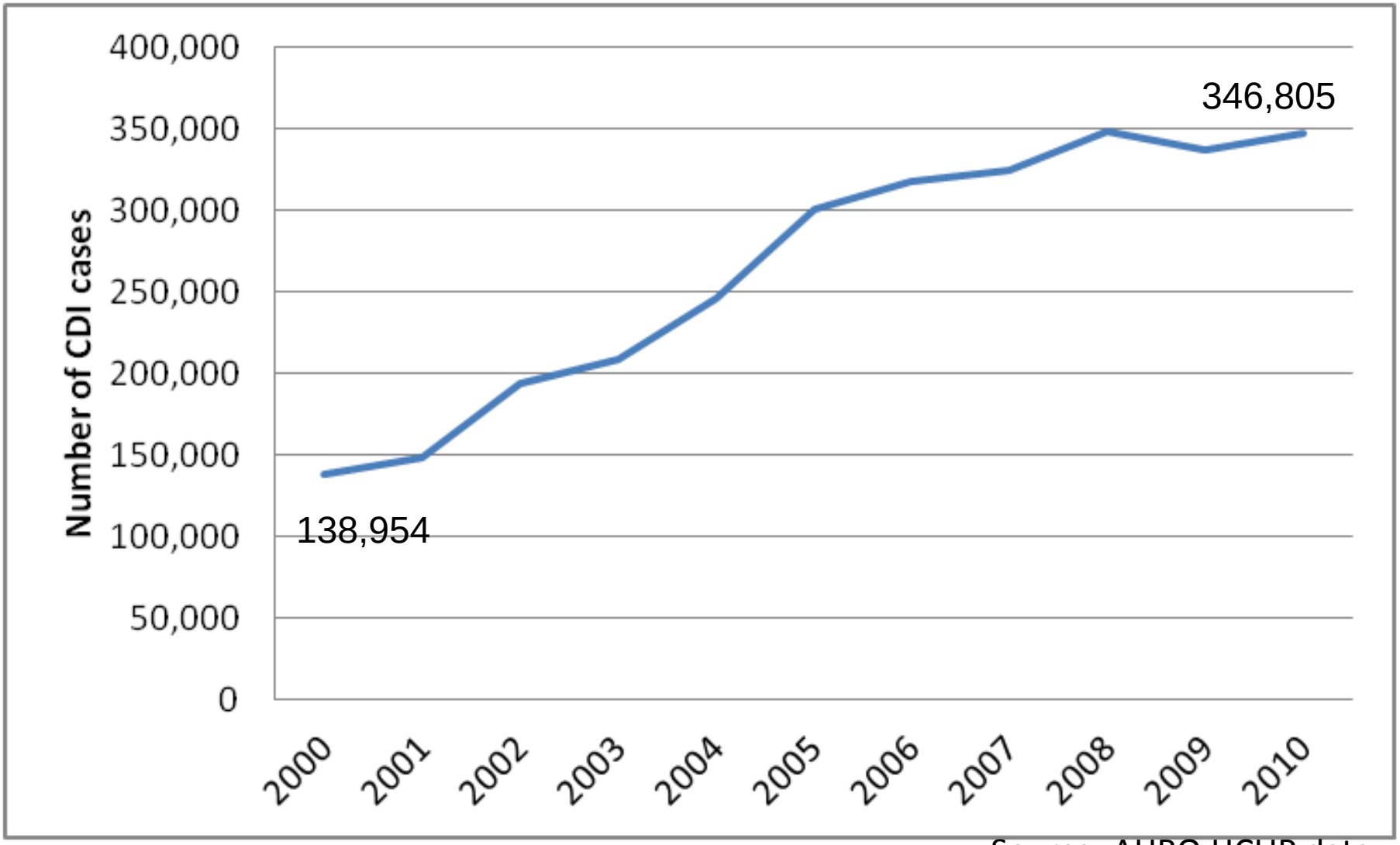
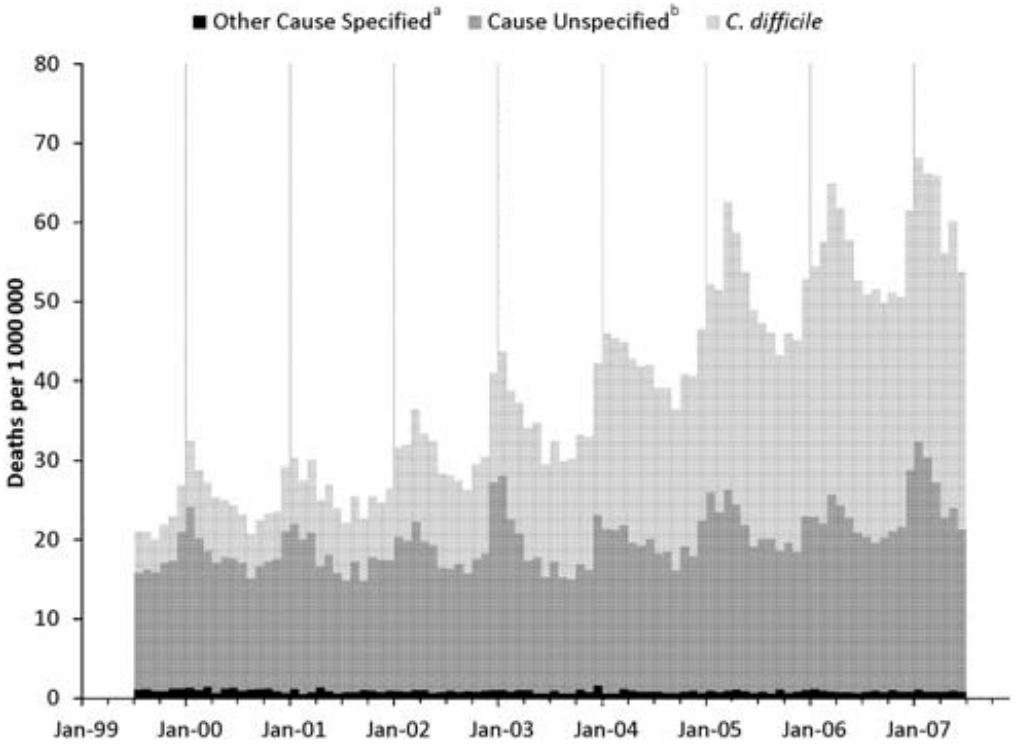
Total Number of Cases in U.S. Hospitals



Source: AHRQ HCUP data

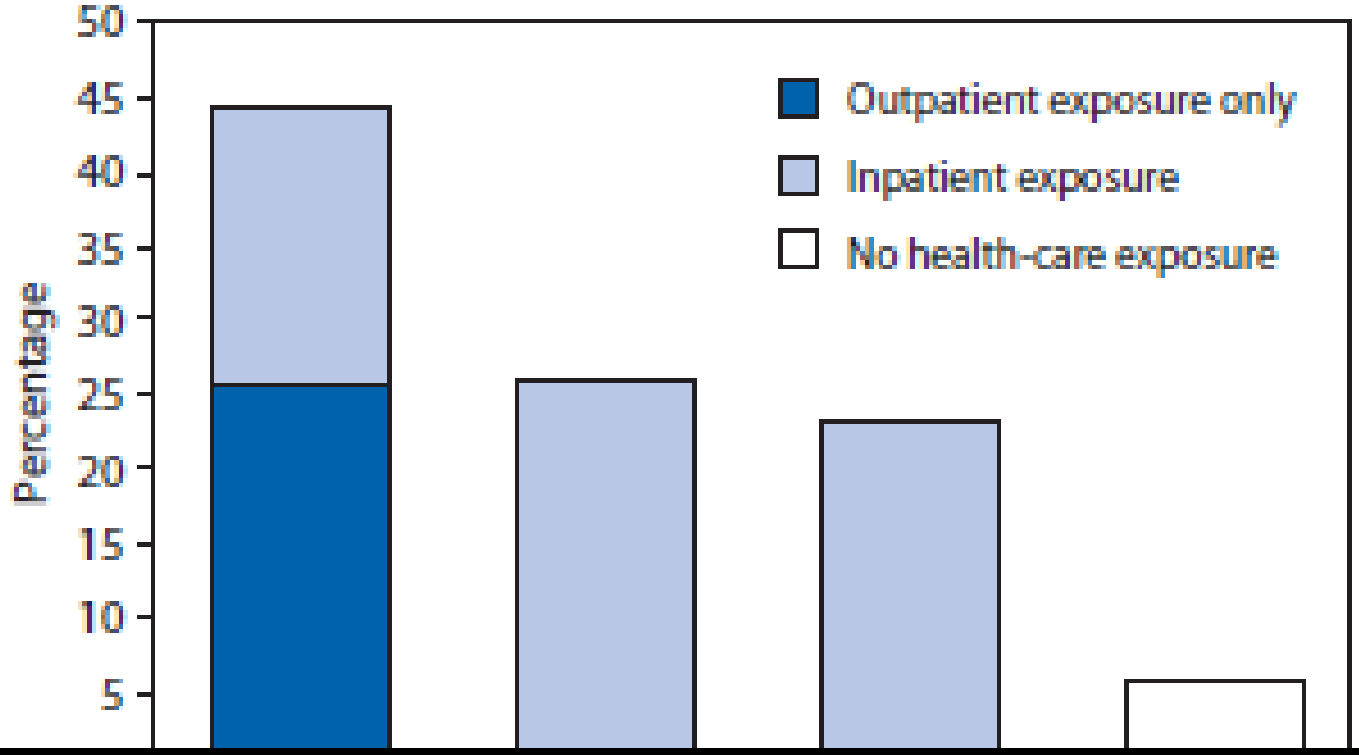
Increasing CDI Severity

- **Outbreaks of severe CDI in US, Canada, Ireland, England, Netherlands, France, Germany**
- **Sherbrooke, Quebec, Canada, outbreak, 2003**
  - **16.7% attributable mortality**
- **St. Louis, endemic, 2003**
  - **5.7% attributable mortality**
  - **2.2 times more likely readmitted**
  - **1.6 times more likely discharged to nursing home**



Pépin J, et al. Can Med Assoc J. 2005; Dubberke ER, et al. CID. 2008; Dubberke EID 2008; Hall. CID. 2012

CDI Onset in Nursing Homes and the Community

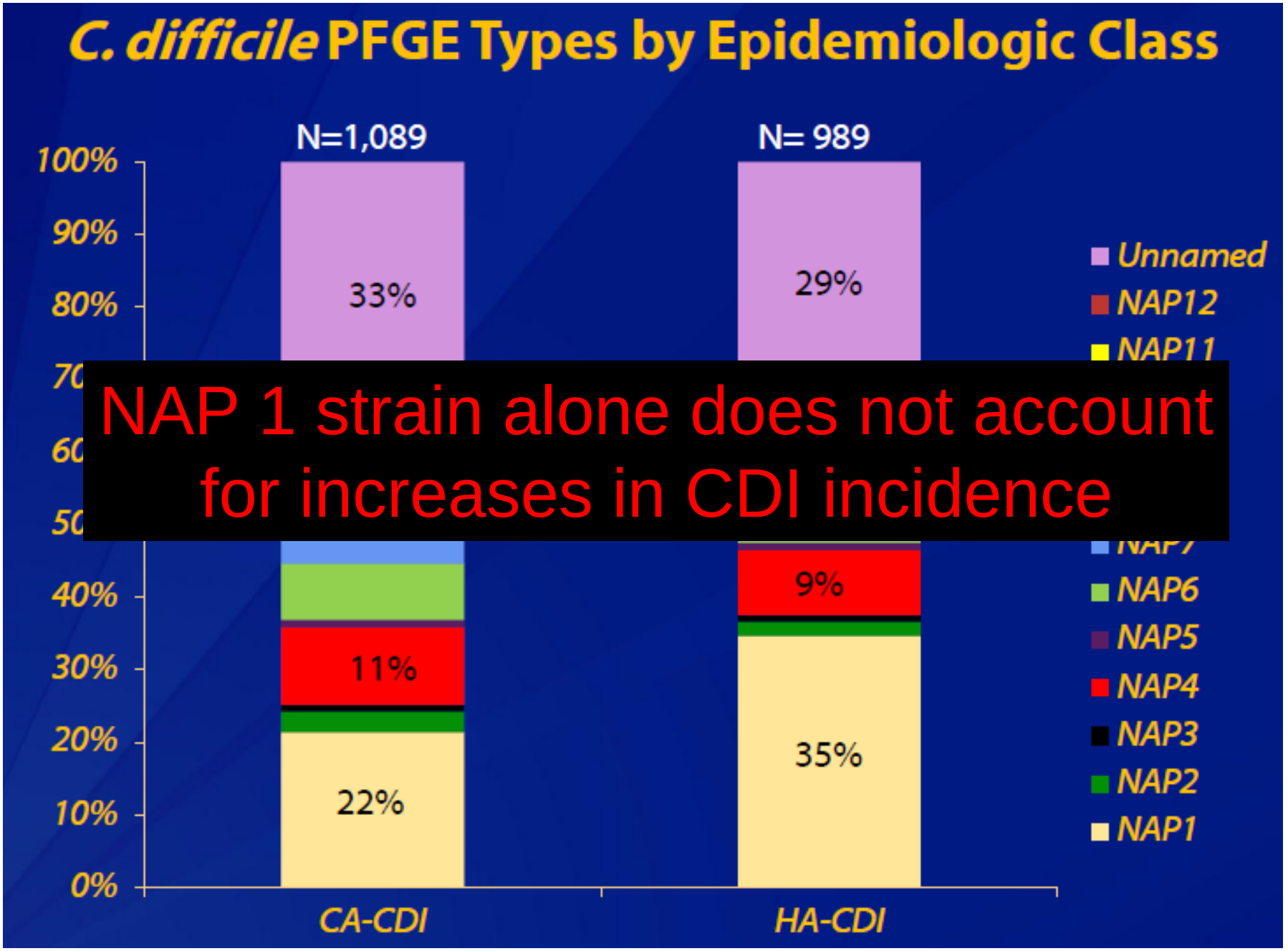


Including CDI diagnosed in hospitals, nursing homes, the community, and recurrent CDI: likely over 700,000 CDI cases in US in 2010

MMWR. Mar 6 2012

The “Epidemic” Strain

- Several methods of molecular typing
  - NAP1
  - BI
  - 027
- Virulence factors
  - tcdC mutation: more toxin A and B production
  - Binary toxin
- Fluoroquinolone resistance
  - New competitive advantage for old strain?


C. difficile PFGE Types by Epidemiologic Class
N=1,089
N= 989
100%
90%
80%
40%
30%
20%
10%
0%
33%
29%
11%
9%
22%
35%
CA-CDI
HA-CDI
Unnamed
NAP12
NAP11
NAP6
NAP5
NAP4
NAP3
NAP2
NAP1
NAP 1 strain alone does not account for increases in CDI incidence

CDC EIP data

C. difficile Diagnostics

- Critical role in:
  - *C. difficile* epidemiology
  - Treatment
  - Infection prevention and control
- Diagnostic test utilization also important
  - Patient selection

Diagnostics Available

Test	Advantage(s)	Disadvantage(s)
Toxin testing		
Toxin Enzyme immunoassay (EIA)	**Rapid, simple, inexpensive**	**Least sensitive method, assay variability**
Tissue culture cytotoxicity	**More sensitive than toxin EIA, associated with outcomes**	**Labor intensive; requires 24–48 hours for a final result, special equipment;**
Organism identification		
Glutamate dehydrogenase (GDH) EIA	**Rapid, sensitive,**	**Not specific, toxin testing required to verify diagnosis;**
Nucleic acid amplification tests (NAAT) / PCR	**Rapid, sensitive, detects presence of toxin gene**	**Cost, special equipment, may be “too” sensitive**
Stool culture	**Most sensitive test available when performed appropriately**	**Confirm toxin production; labor-intensive; requires 48–96 hours for results**

Flaws in Diagnostic Literature Interpretation

- Lack of clinical data
  - Detection of *C. difficile*, not diagnosis of CDI
    - Up to 15% of patients admitted to the hospital are colonized
    - Enhanced sensitivity for *C. difficile* detection may decrease specificity for CDI
- Focus on sensitivity and specificity
  - Not negative predictive value and positive predictive value

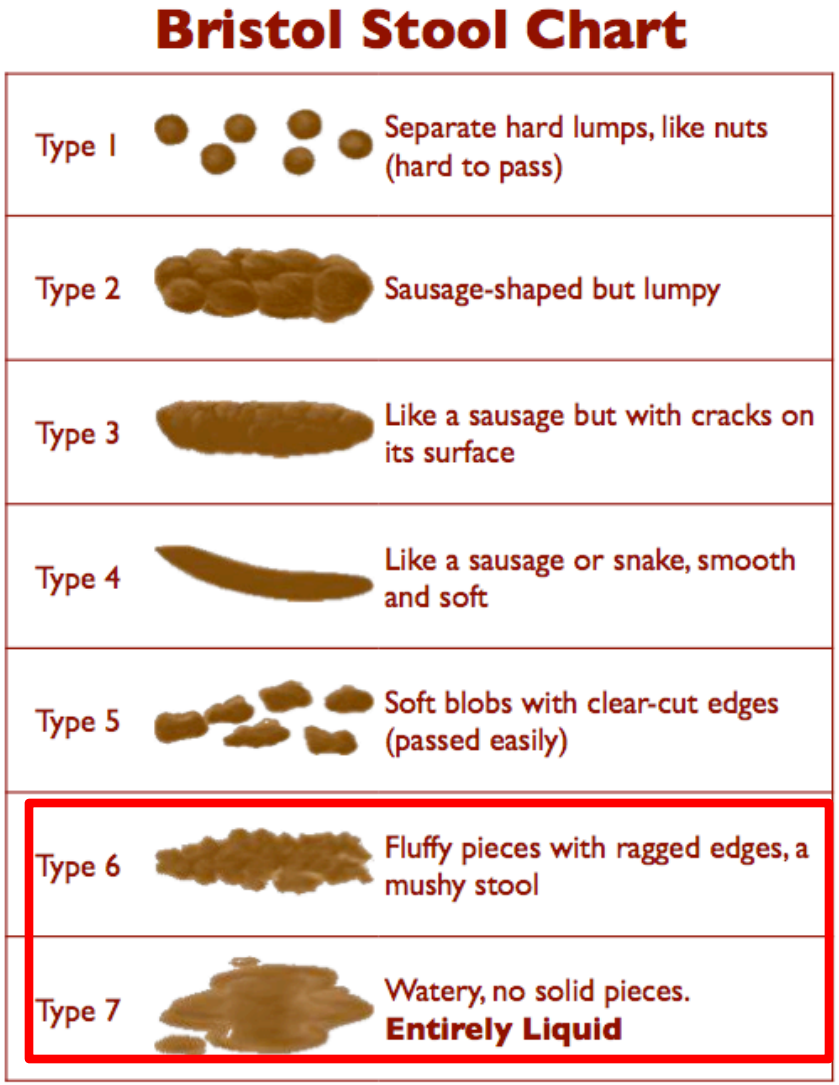
Dubberke. AAC. 2015; Peterson, CID. 2007

Types of False Positive Tests for CDI

- Toxigenic *C. difficile* present but no CDI
  - Concern of more sensitive tests
    - GDH
    - NAAT
    - Culture
- Assay result positive but toxigenic *C. difficile* not present
  - Tests that detect non-toxigenic *C. difficile*
    - GDH alone
    - Culture alone
  - Repeat testing
    - Decreasing prevalence leads to decreasing PPV

Enhanced Sensitivity May Decrease Specificity

- Including clinically significant diarrhea in gold standard:
  - No impact on sensitivity
  - Specificity of NAATs decreased from ~98% to ~89% ($p < 0.01$)
    - Positive predictive value decreased to **~60%** (25% drop)



Dubberke. JCM. 2011;

Largest Assay Comparison To Date

Variable	Cytotoxicity (CTX) +	CTX -/ NAAT +	-/-	(CTX+) vs. (CTX-/NAAT+)	(CTX+) vs. (-/-)	(CTX-/NAAT+) vs. (-/-)
Number	435	311	3943			
White blood count (SD)	12.4 (8.9)	9.9 (6.6)	10.0 (12.0)	<0.001	<0.001	0.863
Died	72 (16.6%)	30 (9.7%)	349 (8.9%)	0.004	<0.001	0.606

Planche. Lancet ID. 2013

More Data Indicating Poor Specificity of NAAT

Outcome	*C difficile* Positive		*C difficile* Negative	
	Tox+/PCR+ (n = 131)	Tox−/PCR+ (n = 162)	Tox−/PCR− (n = 1123)	*P* Value[a]
***C difficile*-Related Complication or Death Within 30 d, No. (%)**				
Complication[b]	10 (7.6)	0	3 (0.3)	<.001
Death[c]	11 (8.4)	1 (0.6)	0	<.001
Complication or death	18 (13.7)	1 (0.6)	3 (0.3)	<.001
Repeat *C difficile* Testing Within 14 d, No. (%)				
Retested	14 (10.7)	61 (37.7)	374 (33.3)	<.001
Positive toxin test result	3 (2.3)	13 (8.0)	17 (1.5)	<.001
Treatment Within 14 d				
Metronidazole or oral vancomycin, No. (%)[d]	131 (100)	66 (40.7)	361 (32.1)	<.001
Duration of metronidazole or oral vancomycin, if treated, median (IQR), d	14 (11-14)	6 (3-11)	5 (2-9)	<.001
Non-*C difficile* antibiotic, No. (%)	98 (74.8)	141 (87.0)	912 (81.2)	.03
Duration of non-*C difficile* antibiotic, if treated, median (IQR), d	11 (3-14)	10 (4-14)	10 (4-14)	.13

Polage. JAMA IM. 2015

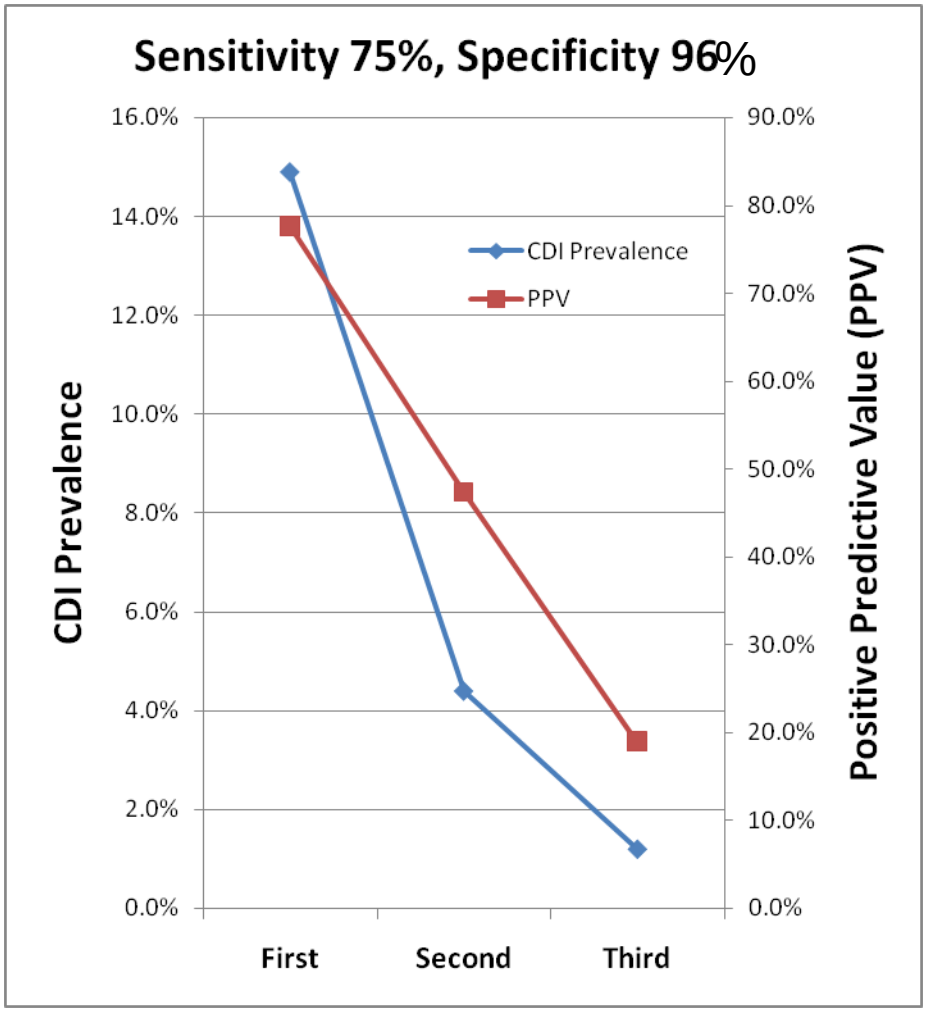
Pre-Test Probability for CDI

	Pre-test probability (n)		
Variable	Low (n=72)	Medium (n=34)	High (n=5)
Positive toxin EIA	0	3	1
Positive toxigenic culture	4	4	1
Negative EIA and empiric treatment	0	0	0
Negative EIA and CDI diagnosed in next 30 days	0	0	0
90-day mortality	0	1	0

Kwon J, et al. SHEA 2014, manuscript in progress

Automatic Repeat Testing: Poor Practice

- Prevalence of disease decreases with repeat testing
- Positive predictive value (PPV) plummets
- Negative predictive value of single toxin EIA >95%



Peterson. Ann Intern Med . 2009. 151:176-9; Litvin M. Infect Control Hosp Epidemiol. 2009. 30: 1166-71

C. difficile Testing Algorithms

- Original intent:
  - Cost containment: GDH -> NAAT
- Part of UK and Europe recommendations
  - GDH or NAAT screen
  - Toxin EIA if screen positive
  - Goal: decrease false positives

Algorithm Interpretation

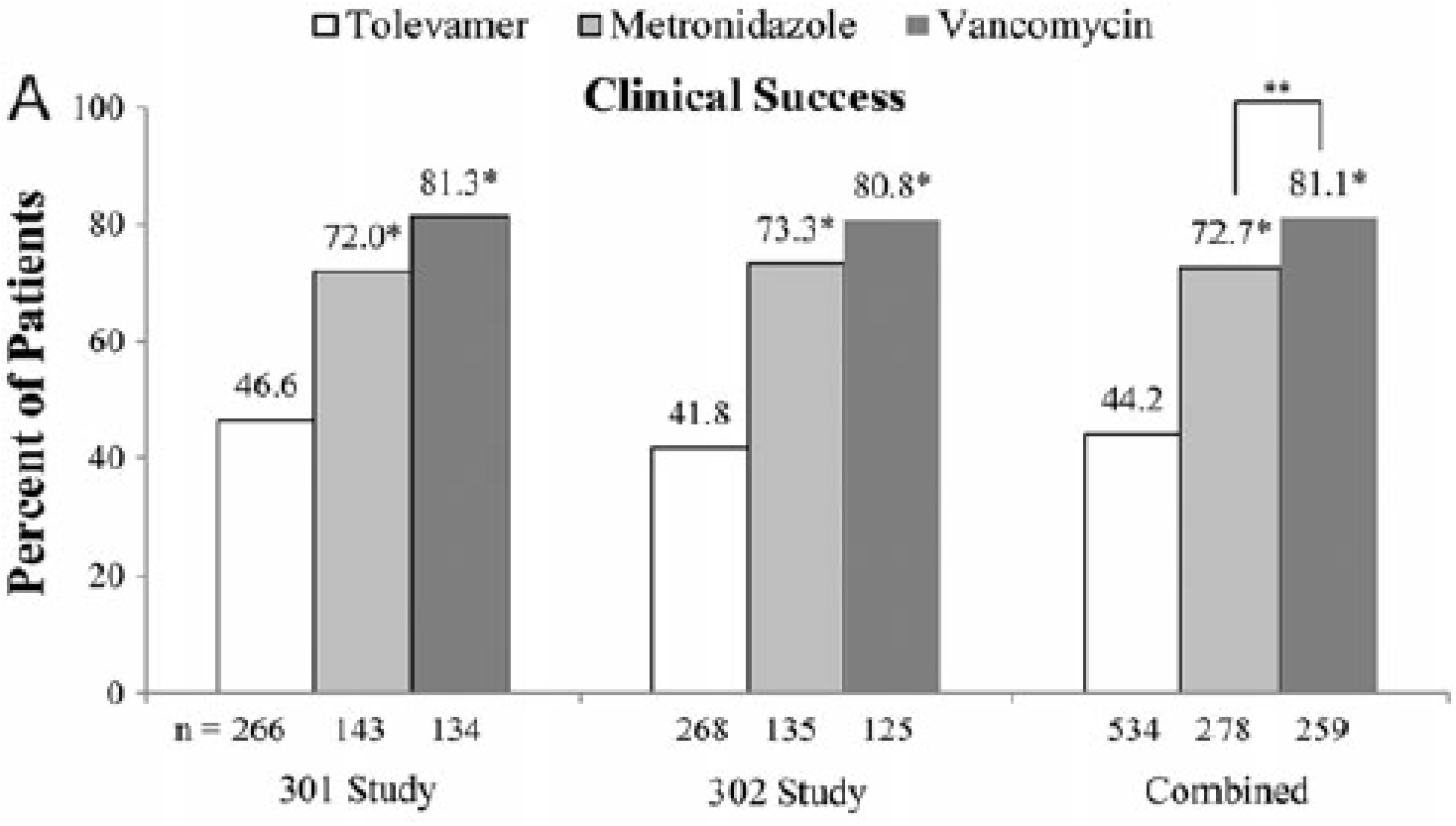
- GDH or NAAT –
  - Negative for *C. difficile* colonization
- GDH or NAAT + / Toxin –
  - Asymptomatic *C. difficile* carrier
- GDH or NAAT + / Toxin +
  - CDI

CDI Treatment Stratified by Severity: First CDI Episode

Clinical scenario	Supportive clinical data	Recommended treatment
Mild to moderate	Leukocytosis (WBC < 15,000 cells/uL) or SCr level < 1.5 times premorbid level	Metronidazole 500 mg 3 times per day PO for 10-14 days
Severe	Leukocytosis (WBC ≥ 15,000 cells/uL) or SCr level ≥ 1.5 times premorbid level	Vancomycin 125 mg 4 times per day PO for 10-14 days
Severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg 4 times per day PO or by nasogastric tube plus metronidazole 500 mg IV q 8 hrs

Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.

Metronidazole Also Inferior For Non-Severe CDI

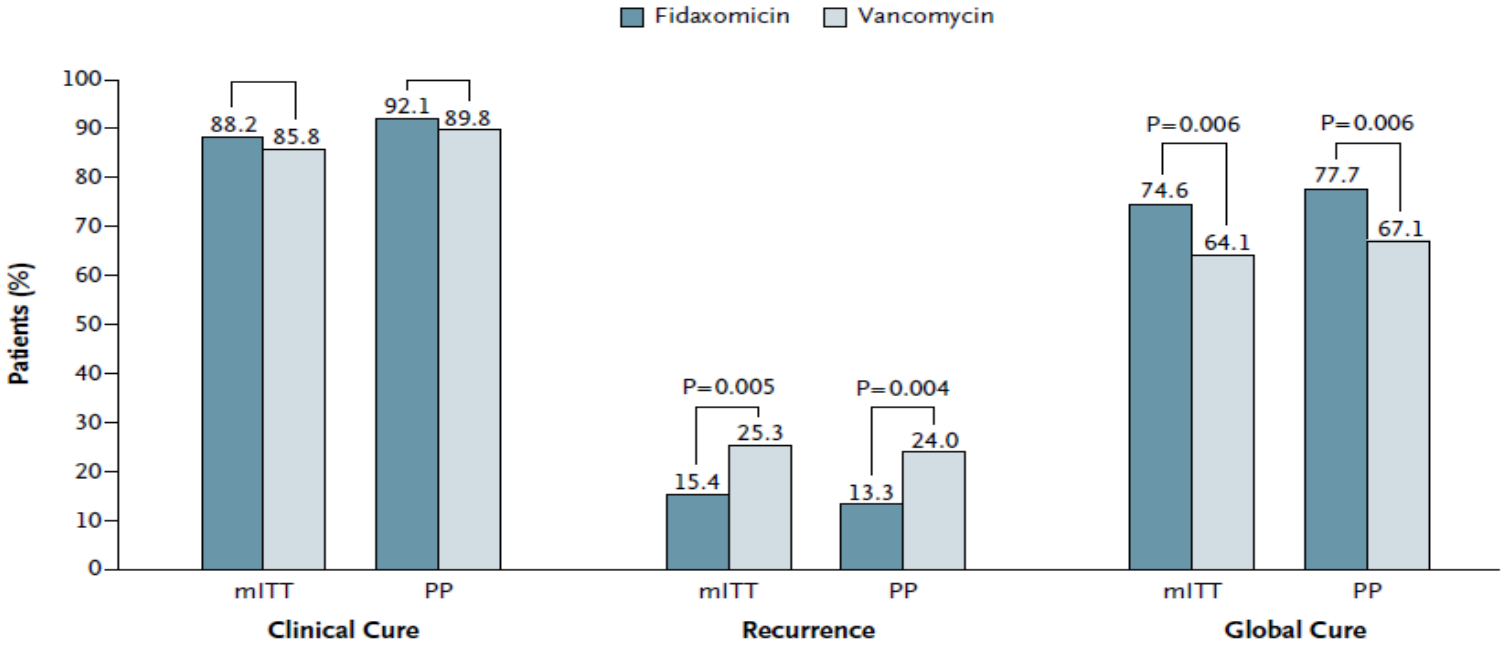


Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-354.

Fidaxomicin

- Novel antimicrobial: macrocyclic
- Narrow spectrum: No activity against Gram negatives
  - Sparing of *Bacteroides sp.*, bifidobacterium, clostridial clusters IV and XIV
- Decrease in recurrences
  - Patients with multiple recurrences were excluded



Louie TJ, et al. *N Engl J Med*. 2011

Management of Recurrent CDI

- CDI recurrence is a significant challenge

Clinical scenario	Recommended treatment
First recurrence	Treat as first episode according to disease severity
Second recurrence	Treat with oral vancomycin taper and/or pulse dosing

- Multiple recurrences
  - Alternate agents
  - Microbial approach

Cohen SH, et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.

Fecal Microbiota Transplant (FMT)

- Theory: Restoration of fecal microbiota and colonization resistance
- First report 1958
- Numerous reviews of published reports

Method	Resolution
Colonoscope	55/62 (88.7%)
Enema	105/110 (95.4%)
Gastric or duodenal tube	55/72 (76.4%)
Rectal catheter	44/46 (95.6%)
>1 method	19/21 (90.5%)
Not reported	6/6 (100%)

Gough. CID. 2011

Prospective Trials: Single Dose FMT Efficacy 60%-80%

Study	Single dose	Second dose
Youngster (n=20)	70%	90%
Hirsch (n=19)	68%	89%
Orenstein (n=35)	60%	88%
Youngster (n=14)	70%	90%
Van Nood (n=16)	81%	94%
Lee (PP n=178, mITT n=219)	62% / 51%	84% / 73%

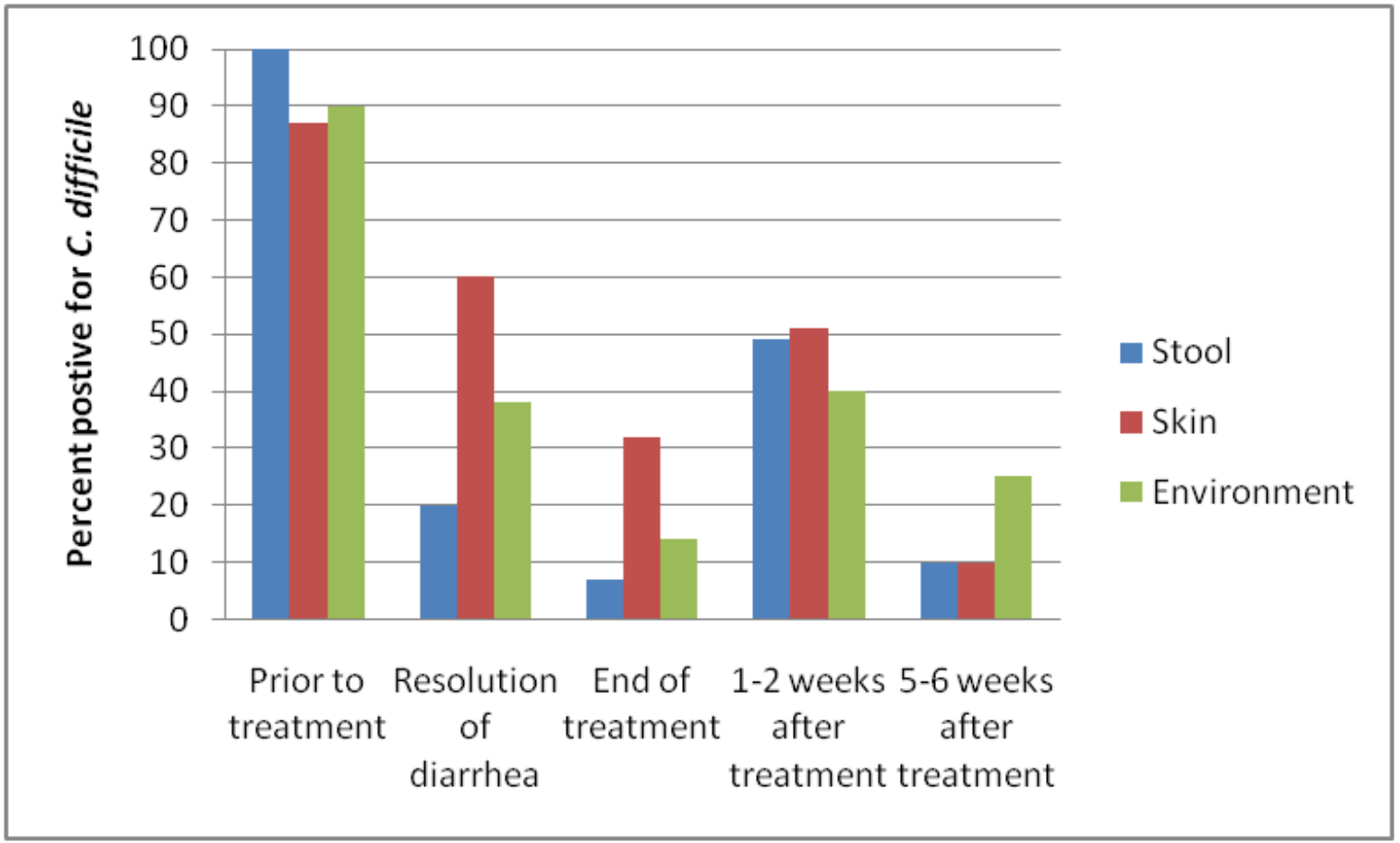
Youngster. CID. 2015, Hirsch. BMC ID. 2015, Orenstein CID. 2015, Youngster. JAMA. 2014, Van Nood. NEJM. 2013 , Lee. JAMA. 2016

Status of CDI Prevention Today

- Decrease risk of transmission
  - CDI: Contact precautions
    - Gloves/gowns
    - Dedicated patient equipment
  - Environment decontamination
- Decrease risk of CDI if transmission occurs
  - Antimicrobial stewardship

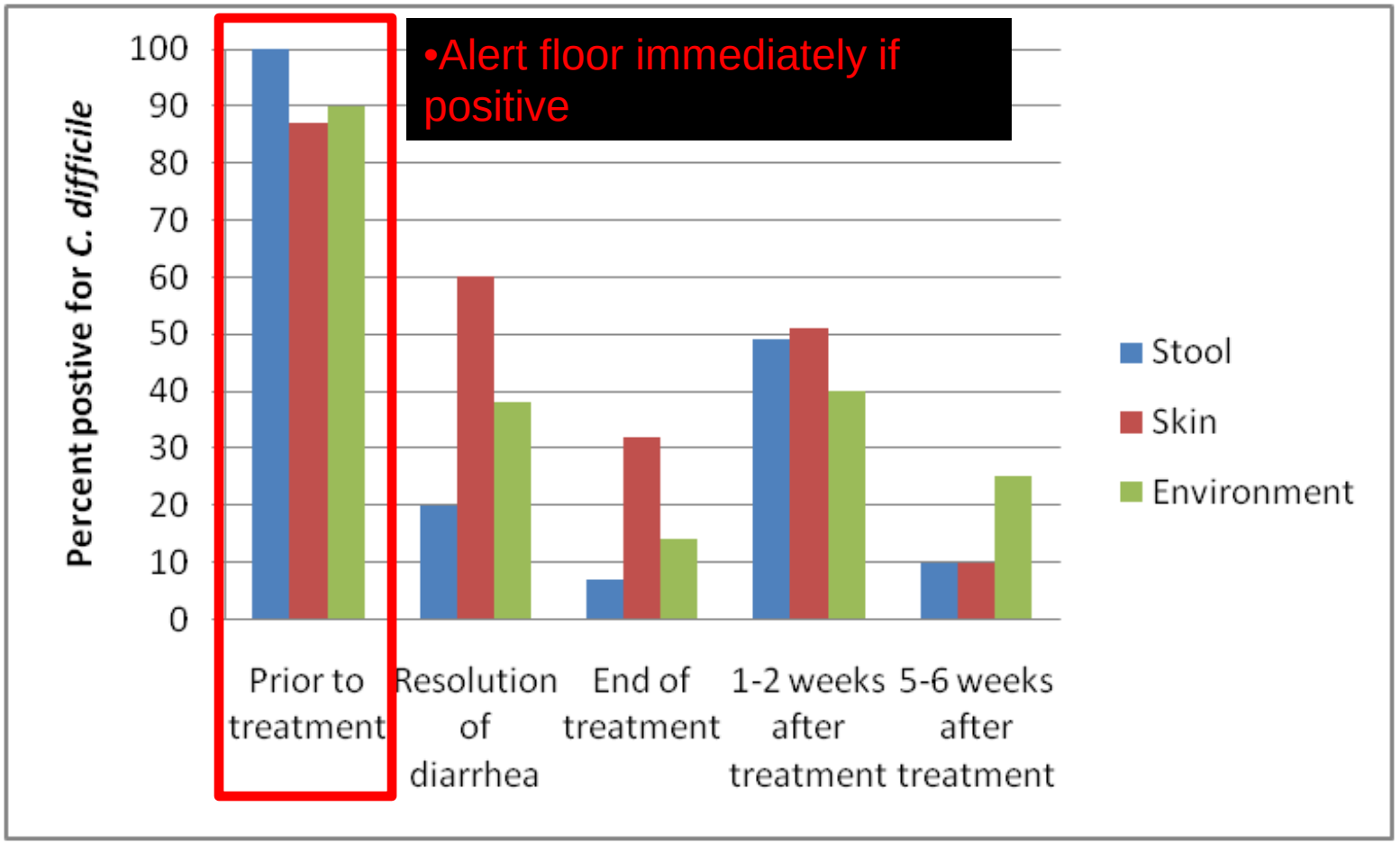
Dubberke. ICHE. 2014

Clinical Microbiology Laboratory and CDI Prevention



Sethi AJ, ICHE 2010;31:21-7

Clinical Microbiology Laboratory and CDI Prevention



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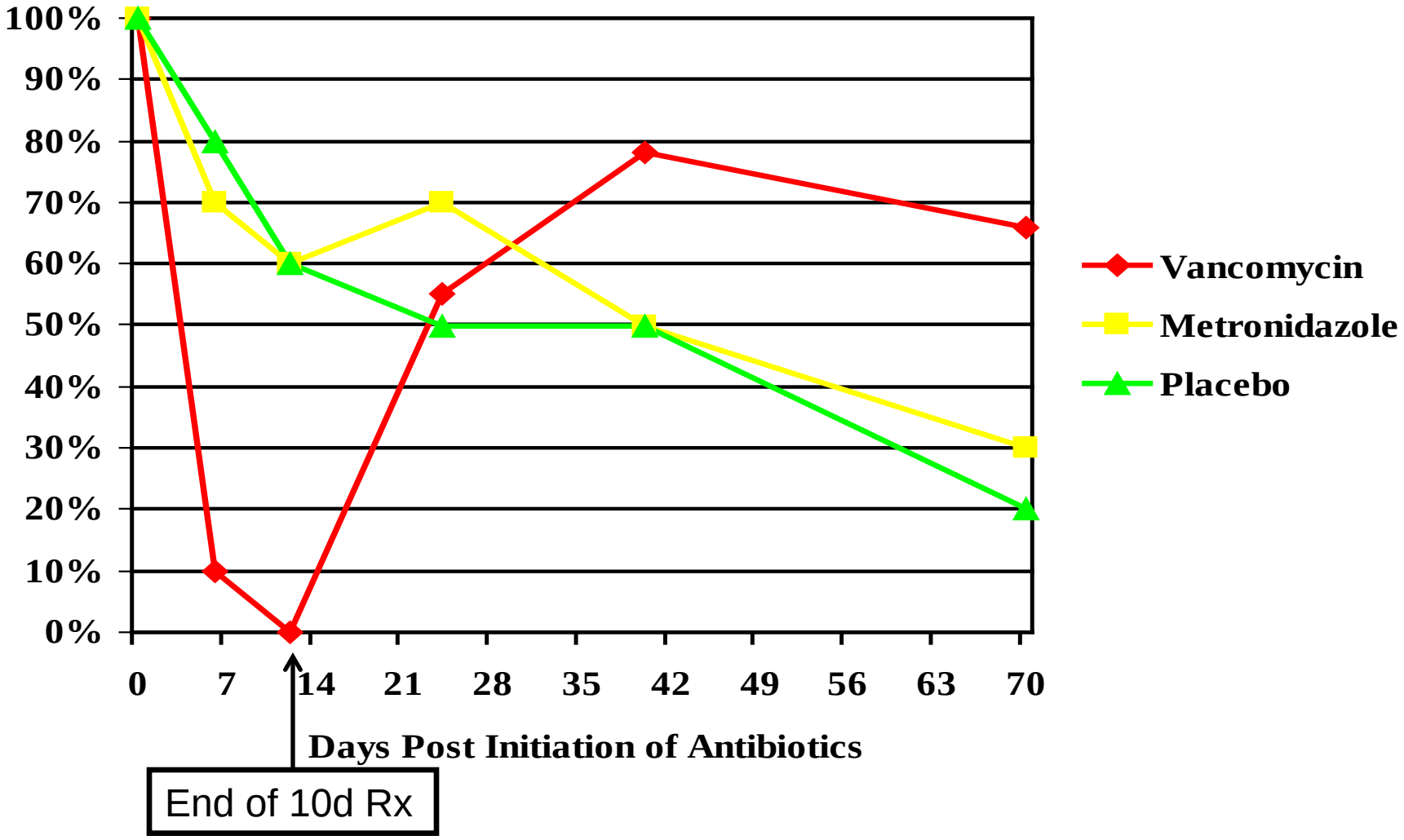
Minimize False Positives



Johnson S, et al. *AIM* 117: 297, 1992

Ways to Minimize False Positives

- DO NOT TEST FORMED STOOLS
  - No diarrhea = No CDI
- Do not allow automatic repeat testing
  - Require prior authorization
  - Quality improvement project: 90% reduction
- Decrease testing in patients without clinically significant diarrhea
  - Example: alert if recent laxative exposure
- Optimize testing

Different Testing Strategies and False Positives

- Hypothetical scenarios
  - Toxin EIA: sensitivity 85%, specificity 97%
  - NAAT: sensitivity 99%, specificity 89% (CDI)
  - Test 1,000 patients, 100 with CDI (10% prevalence)

Testing strategy	True positives	False positives
Toxin EIA	85	27
NAAT	99	99
NAAT + then Toxin EIA	84	3

Assist in Antimicrobial Stewardship

- Improve test utilization related to infections
  - Order of tests in drop down list
    - Most appropriate test first
  - Reflex urine cultures: >10 WBC / high power field
- Rapid diagnostics
  - MALDI
  - Rapid tests for resistance mechanisms
  - Respiratory multiplex PCRs

Barlam. CID. 2016; Sarg. ICHE. 2016; Subramony. J Pediatr. 2016

Additional Considerations When Selecting a *C. difficile* Assay

- Patient selection for testing
- Time from bowel movement to proper storage
- Number of specimens
- Frequency able to perform testing
- Not all assays equal
  - Membrane EIAs: ~10% drop sensitivity
  - *C. difficile* strain / toxin gene heterogeneity

Conclusions

- CDI = bad
- Diagnosis: patient first, test second
  - "CDI" assay does not exist
- Clinical microbiology laboratory plays an important role in CDI prevention
- One size does not fit all when selecting an assay