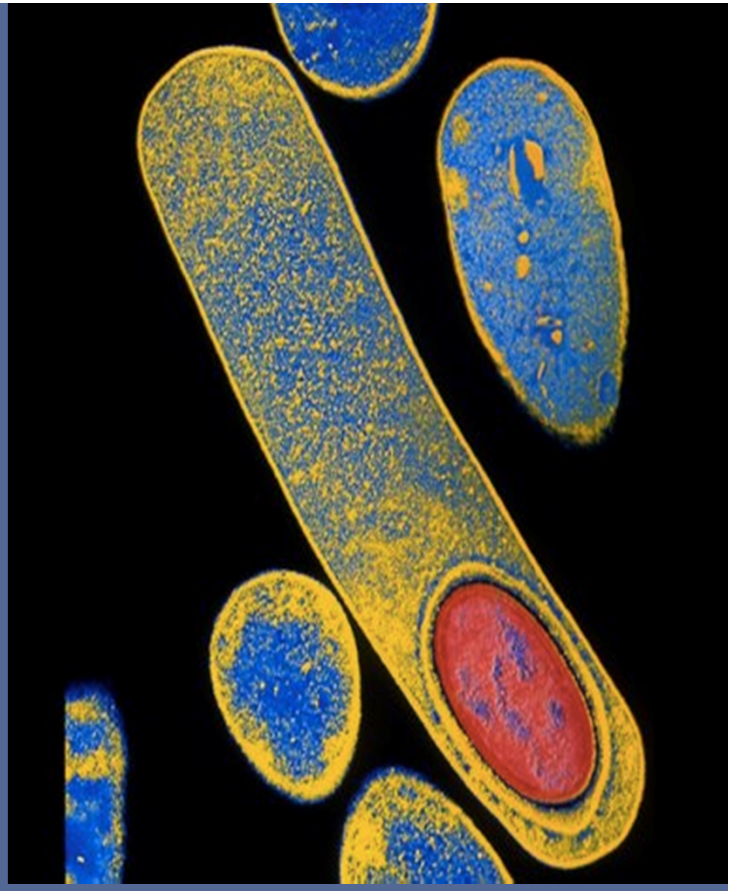
Clostridium difficile infection



December 16, 2014

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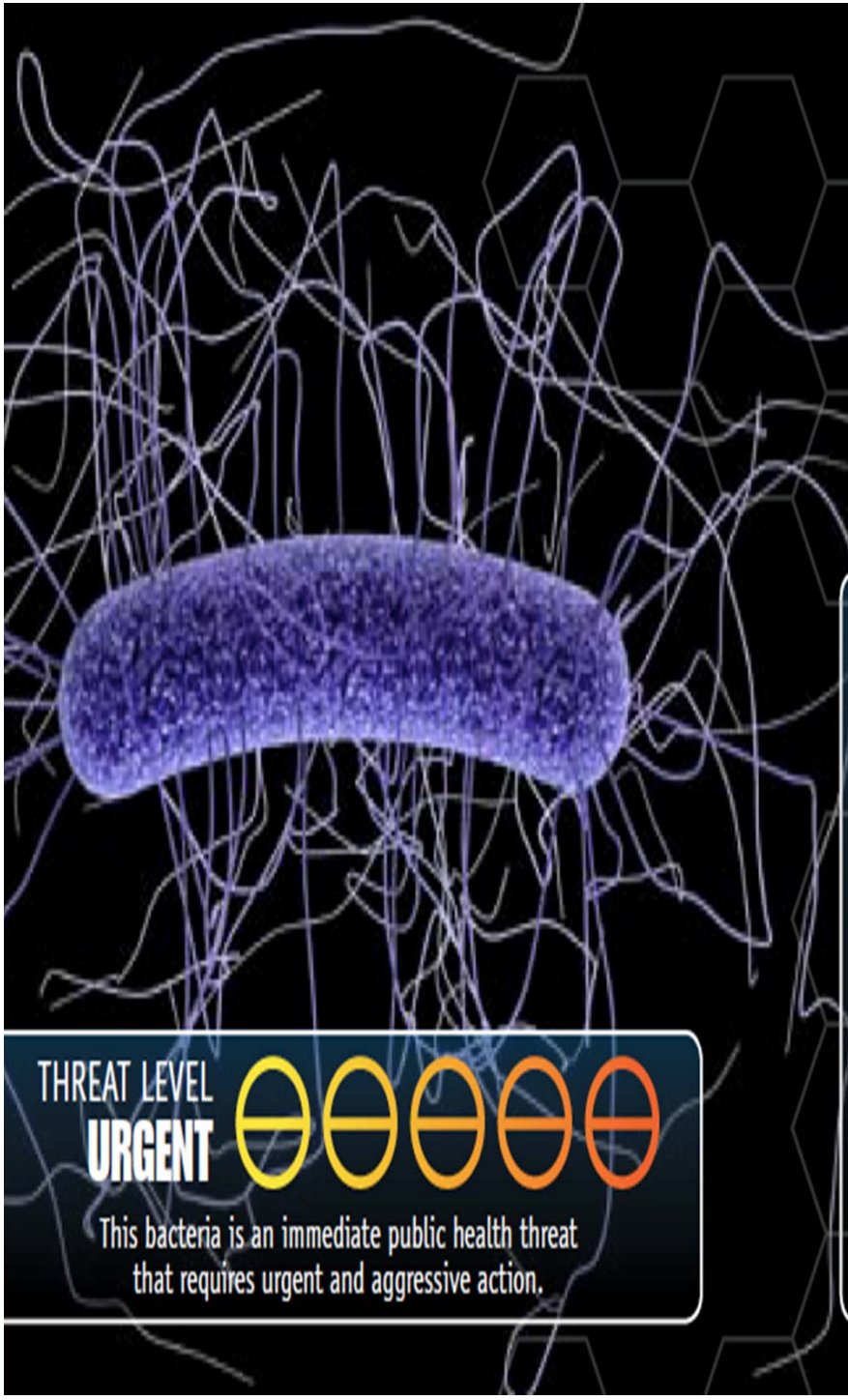
UCLA Health System

Objectives

- Review *C difficile* epidemiology and recent changes in trends
- Understand the pathophysiology and clinical spectrum of *C difficile*
- Summarize *C difficile* diagnostic testing and treatment options
- Review the infection prevention fundamentals of *C difficile*



CLOSTRIDIUM DIFFICILE

250,000
INFECTIONS PER YEAR

14,000
DEATHS

$1,000,000,000
IN EXCESS MEDICAL COSTS PER YEAR

THREAT LEVEL
URGENT

This bacteria is an immediate public health threat that requires urgent and aggressive action.

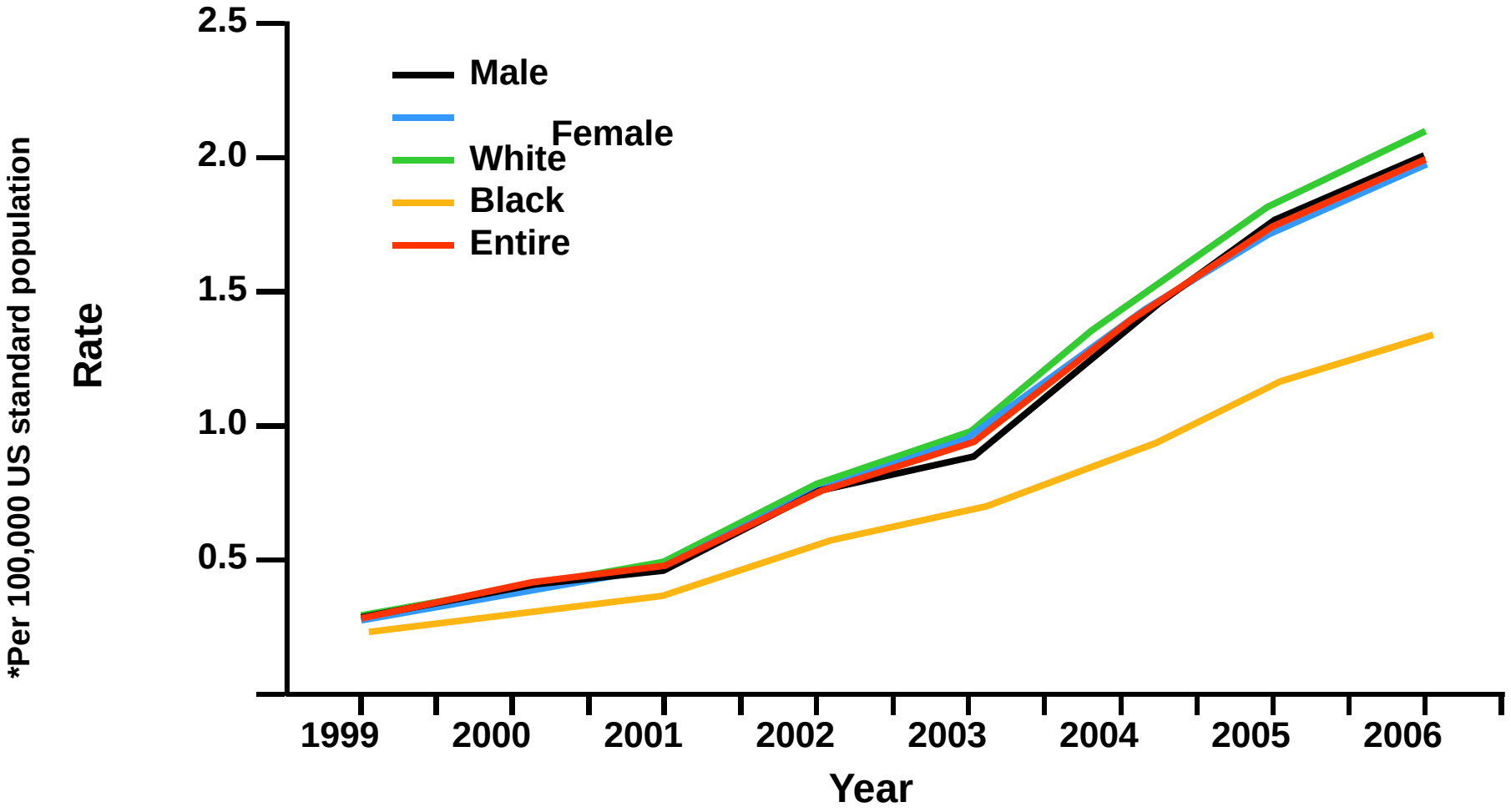
Los Angeles Times

BOOSTER SHOTS: Oddities, musings and news from the health world

Clostridium difficile infections increasing among children

January 03, 2011 | By Shari Roan, Los Angeles Times

Age-Adjusted Death Rate* for Enterocolitis Due to *C. difficile*, 1999–2006



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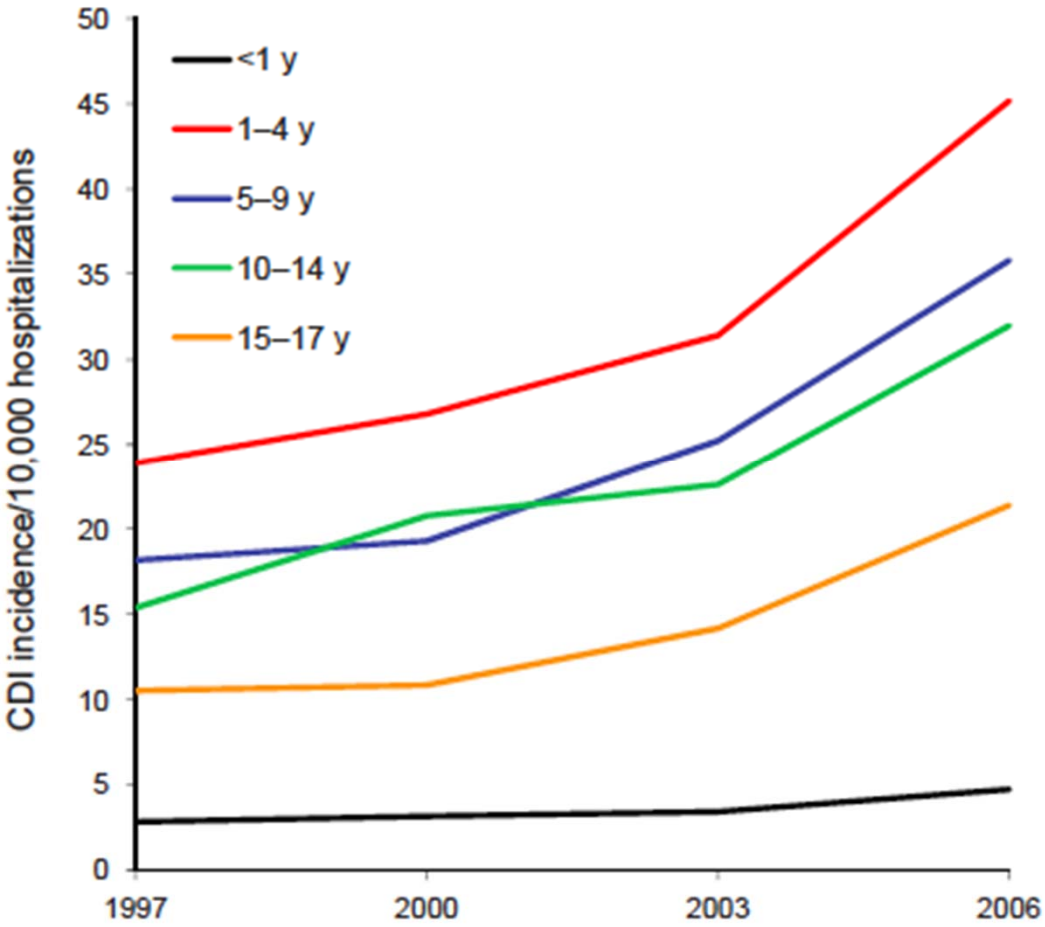
Heron et al. Natl Vital Stat Rep 2009;57(14).
Available at http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf

CDI Epidemiology

- 53% increase in infection rates 2001-2006
- Not associated with increase mortality or severe morbidity such as colectomy or toxic megacolon



Zilberger et al EID 2010; 16: 604; Sammons et al CID, 2013; 57: 1

CDI Differs by Age Group

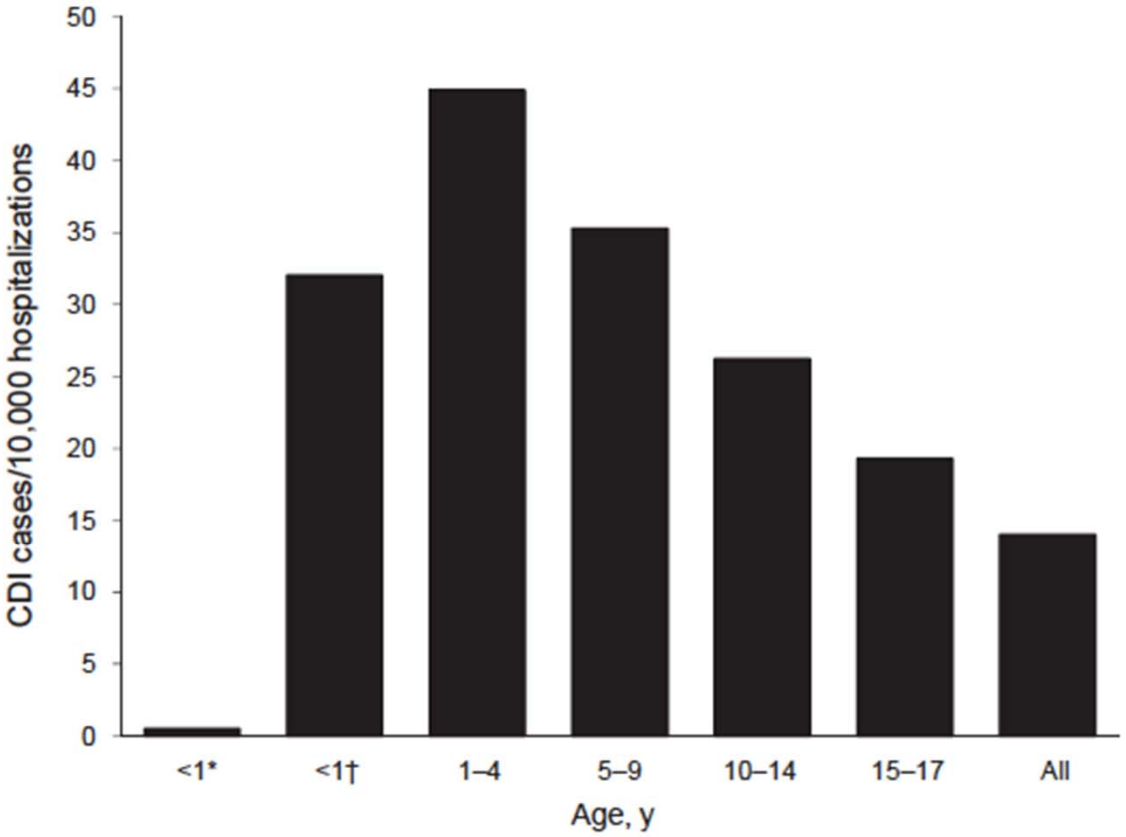
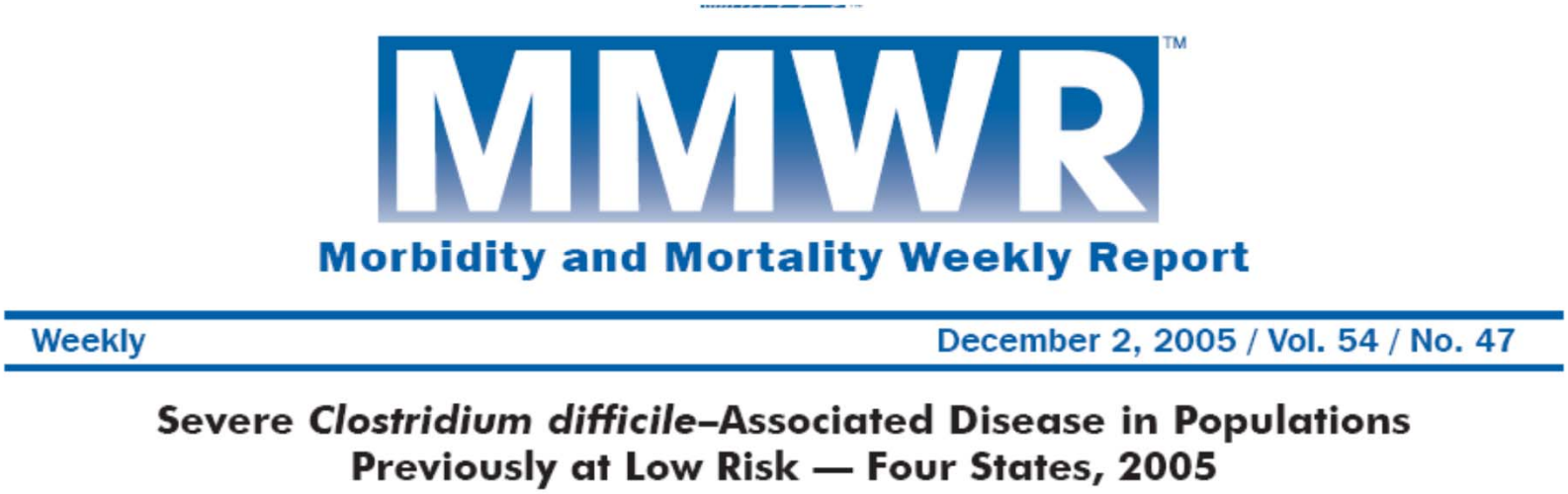


Figure 3. Age-specific incidence of *Clostridium difficile* infection (CDI) hospitalizations, National Hospital Discharge Survey, United States, 2006. *Newborn (i.e., during hospitalization for birth); †not newborn (i.e., during subsequent hospitalization).

Zilberg et al EID 2010; 16: 604

Why is CDI increasing?



- 10 cases of severe peripartum CDAD
- 23 cases of severe community-associated CDAD (CA-CDAD)
- 11 pediatric cases, all community-associated

- Approximately 1/3 without prior antimicrobial use

- Thought to be related to emergence of new strain, NAP1/027

Courtesy Romney Humphries, UCLA microbiology
MMWR Morbidity Mortality Wkly Rep 2005;54:1201–5.

NAP1/B1/027 Strain

- Hypervirulent *C difficile* strain
  - Seems to transmit more effectively
    - Associated with fluoroquinolone resistance
  - Possesses two standard toxins and an additional binary toxin
    - Hyperproduce toxin by more than a factor of 10
  - Represent 10-20% of toxigenic strains in children
    - Data inconclusive about association between NAP1 and more severe clinical presentations

Tolzis et al J Peds 2009; 154: 607
Kelly et al NEJM 2008; 359:18
Warny et al Lancet 2005; 366: 1079

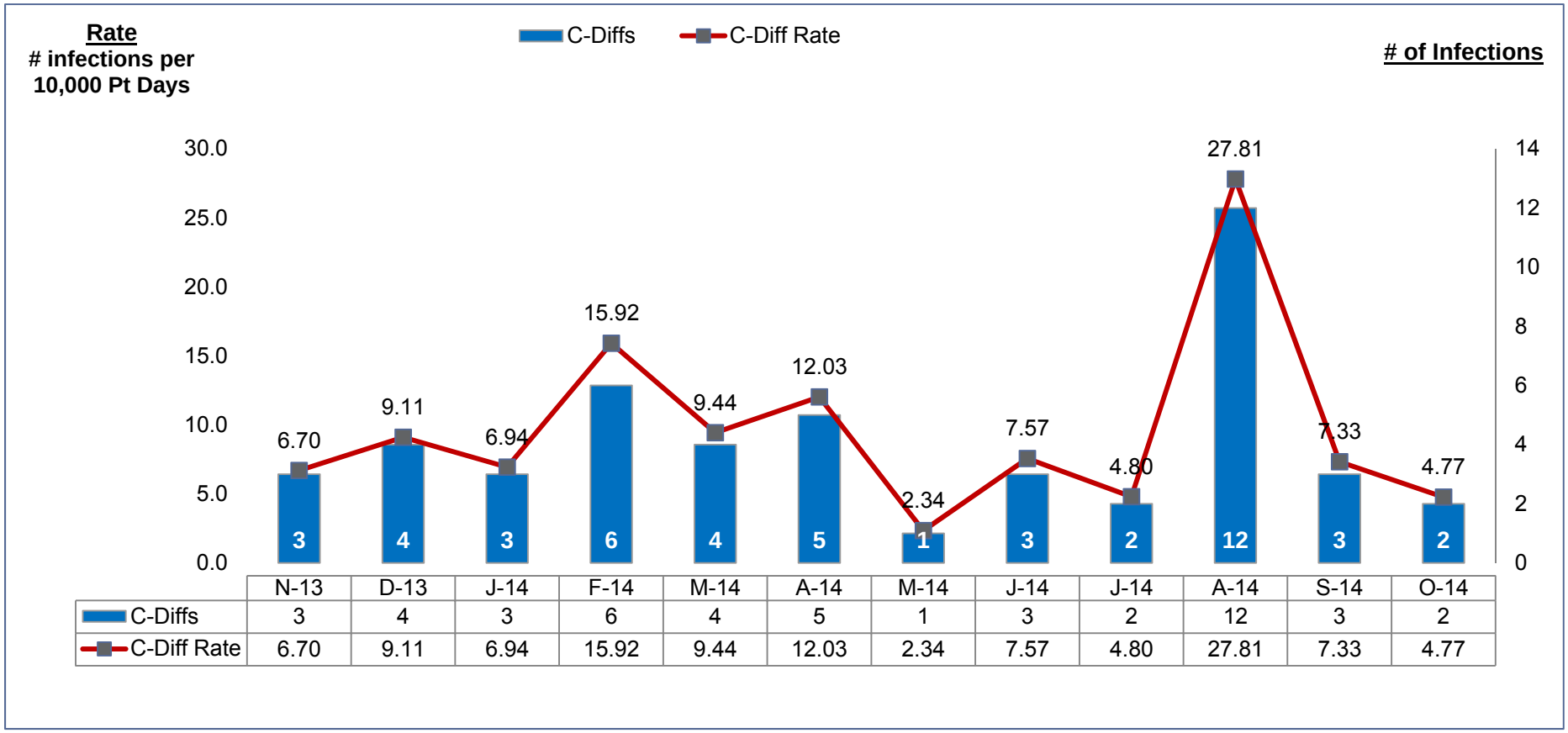
Lack of Antibiotic Exposure

- Number of pediatric studies highlight that a subset of children with CDI have no antibiotic exposure
  - 24-44%

- Limitations of published studies
  - How distinguish between colonization and infection?
  - How determine whether some patients seen in a different medical system?
  - How define antibiotic exposure? How determine if someone has received antibiotics?

Sandora et al, PIDJ 2011; 7: 580
Samady et al J Hosp Med 2013, epublished

Pooled CDI Rates[$], ICUs
RRUCMC, Nov 2013 - Oct 2014



	N-13	D-13	J-14	F-14	M-14	A-14	M-14	J-14	J-14	A-14	S-14	O-14
C-Diffs	3	4	3	6	4	5	1	3	2	12	3	2
C-Diff Rate	6.70	9.11	6.94	15.92	9.44	12.03	2.34	7.57	4.80	27.81	7.33	4.77

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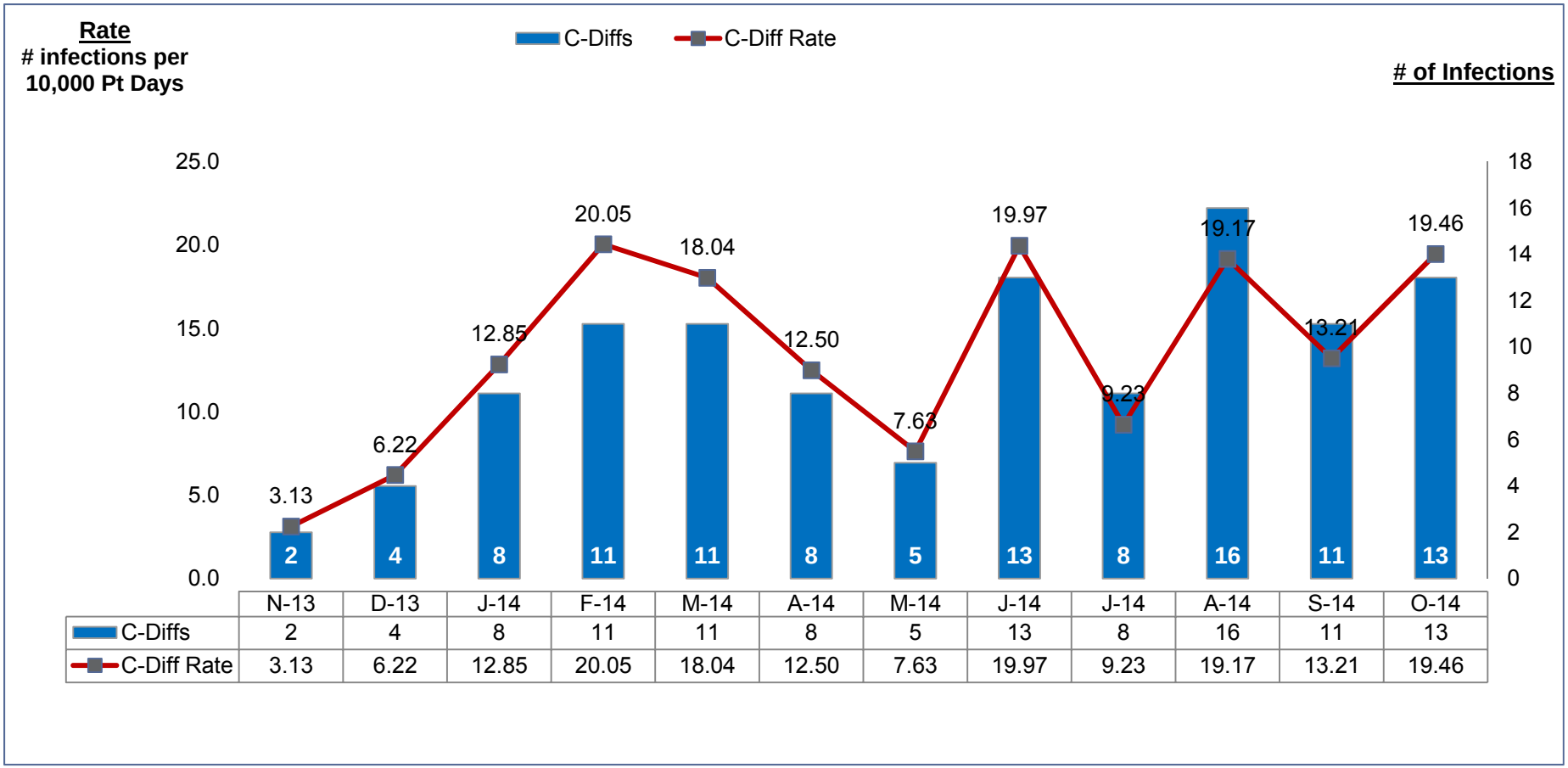
[$]All rates are CDI rate per 10,000 patient days

[1]CDPH Target Rate = 9.4/10,000, http://www.cdph.ca.gov/programs/hai/Documents

Pooled CDI Rates[$], ACUs
RRUCMC, Nov 2013 - Oct 2014



	N-13	D-13	J-14	F-14	M-14	A-14	M-14	J-14	J-14	A-14	S-14	O-14
C-Diffs	2	4	8	11	11	8	5	13	8	16	11	13
C-Diff Rate	3.13	6.22	12.85	20.05	18.04	12.50	7.63	19.97	9.23	19.17	13.21	19.46

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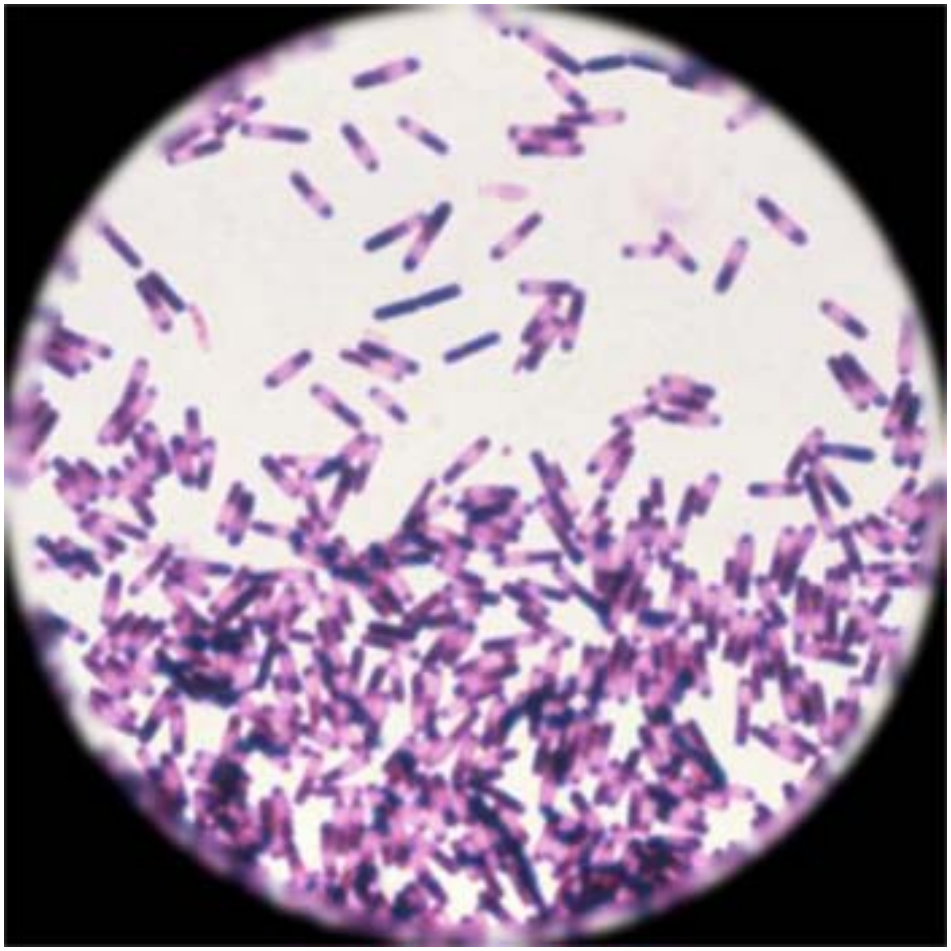
[$]All rates are CDI rate per 10,000 patient days
[1]CDPH Target Rate = 9.4/10,000, http://www.cdph.ca.gov/programs/hai/Documents

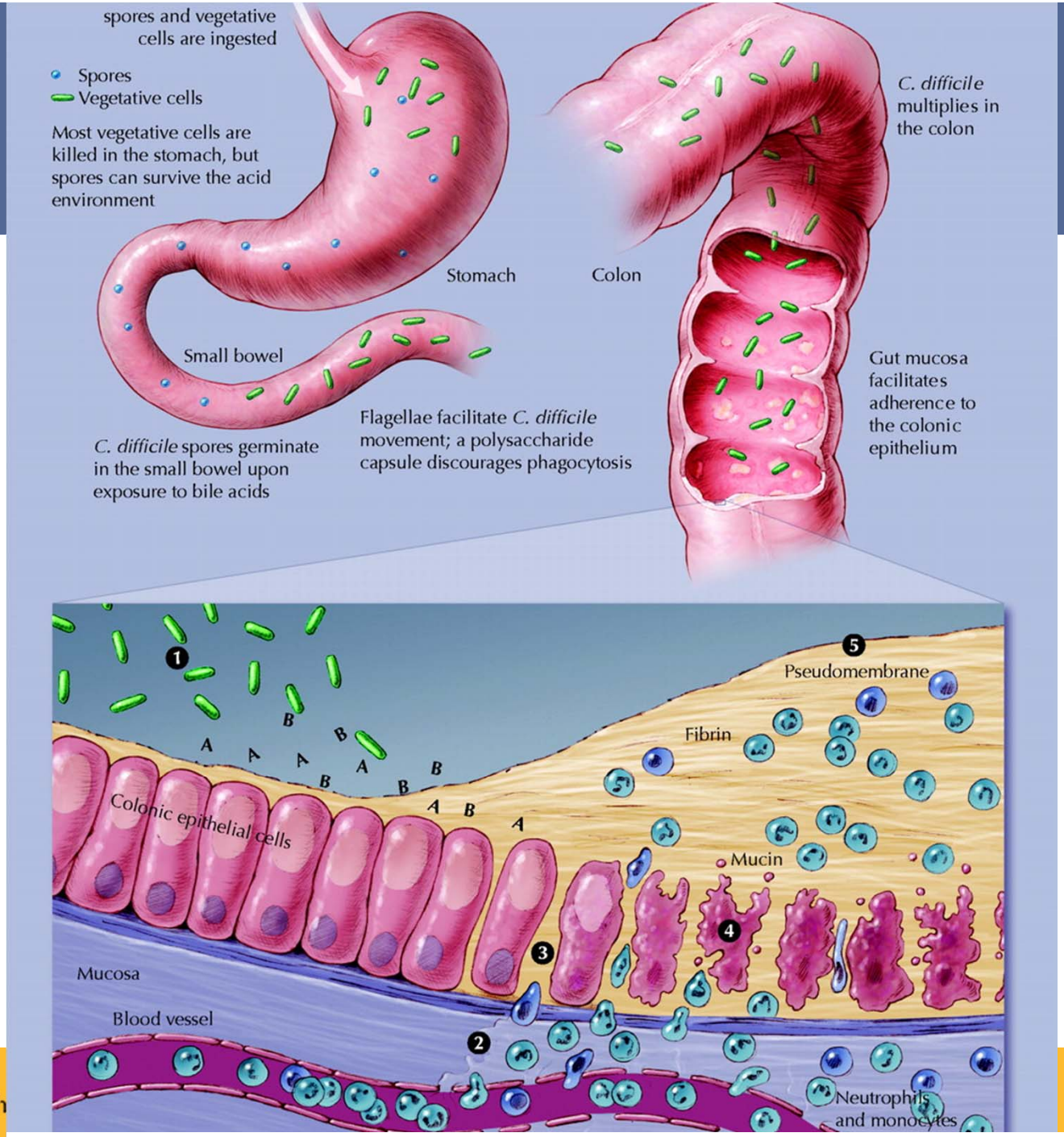
C difficile infection (CDI)



C difficile and microbiology

- Vegetative and spore forms
  - Spores can remain viable up to **5 months on hospital hard surfaces**
  - Resistant to cleaning and decontamination
- Fecal-oral
  - Inoculum can be as low as 10 spores
- Non-toxin and toxin-producing strains
  - Virulence factors are toxins A and B
  - Recent data suggests toxin B may be more potent that A
    - Strains that are toxin A-/B+ more likely to be associated with severe and recurrent disease

Tamma et al JPIDS 2012



http://www.cdiff-support.co.uk/images/cDiffLarge.jpeg

Spectrum of Disease

- 20% CDI carriage rates in hospitalized children/adults with diarrhea

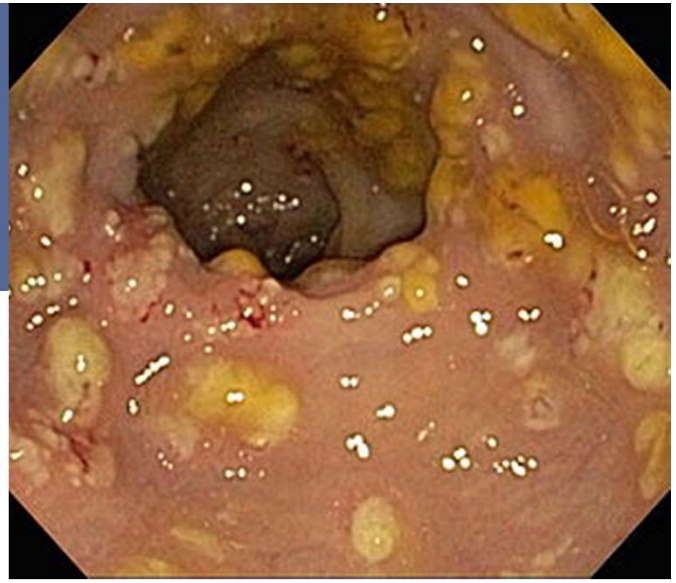
Sammons et al JAMA Pediatrics 2013

Clinical disease

Stool	>3 stools/24 hours Loose, watery (88%), bloody, mucous, fecal leukocytes
Clinical	Fever, dehydration, abdominal distension/pain, ileus, pseudomembranous colitis Severe (0-12%): sepsis, pleural effusion, toxic megacolon, perforation, ascites, pneumatosis, rectal prolapse, death
Laboratory	Leukocytosis, ↓ albumin ↑ creatinine

Samady et al J Hosp Med 2013, epublished;
Sammons et al JAMA Pediatrics 2013

Severe *C difficile* disease



- Pseudomembranous colitis
  - Endoscopic and histologic diagnosis
    - Associated with severe disease in adults
  - Rare in children
    - Few case reports in neonates and younger infants and children
- Severe CDI
  - One multicenter cohort evaluating CDI in hospitalized children
    - Colectomy rate of 1.3%, all cause mortality 4%
  - Another two center retrospective analysis
    - ICU admission within 2 days of diagnosis (17%)
    - 2% of the cohort had toxic megacolon, perforation, surgical intervention

Kim et al Peds 2008; 133: 1266
Kim et al PIDJ 2012 31: 134

Worse outcomes

- Retrospective nested case control study
  - Pediatric patients with CDI compared to matched hospitalized patients
    - Difference in length of stay higher
      - Community onset 5.6 days
      - Hospital onset 22 days
    - Mortality of hospital onset disease higher (OR 6.7 95% CI 3.8-12)
    - Higher cost
      - Community onset $19,000
      - Hospital onset $94,000

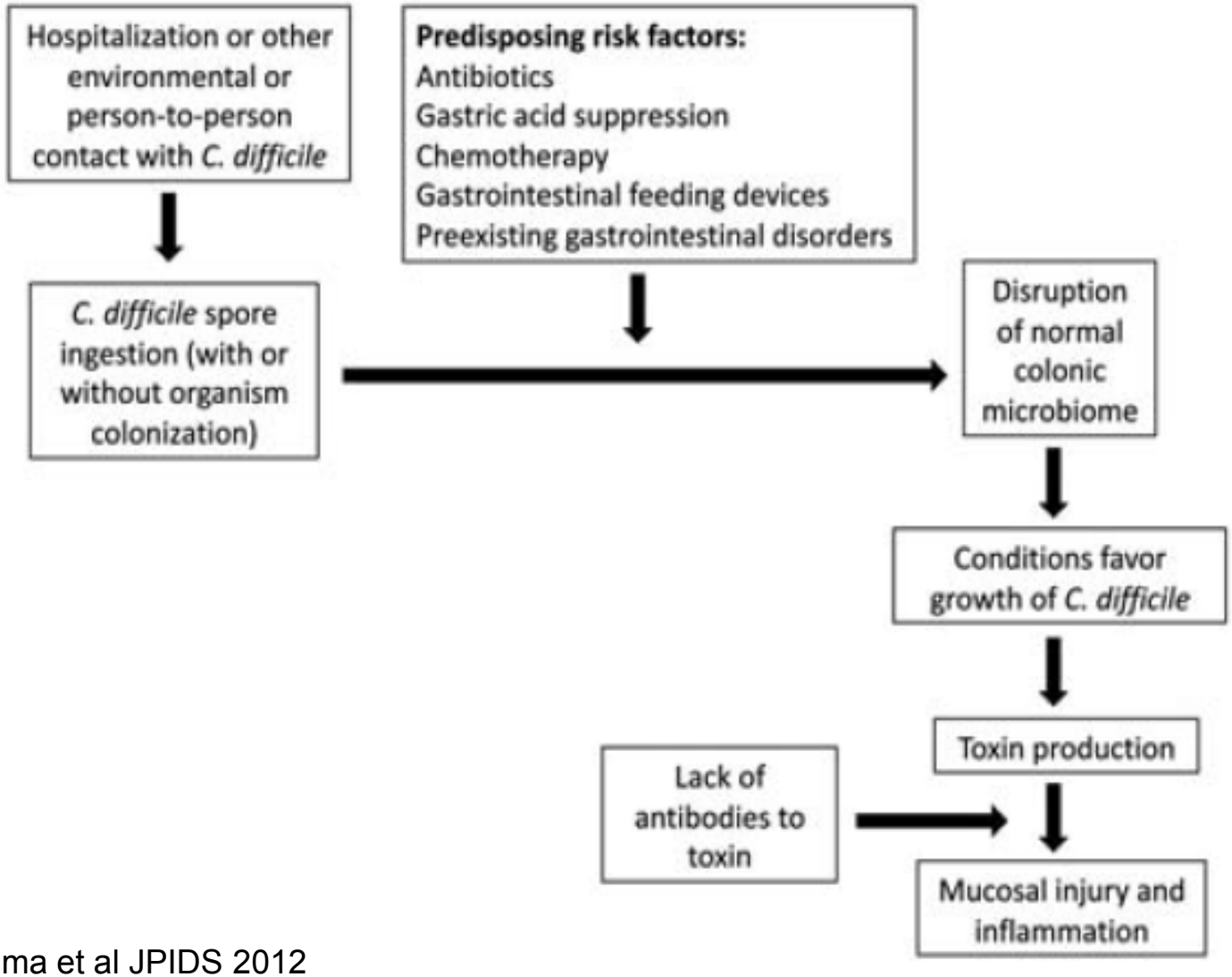
Sammons et al CID 2013: 51; 1

Rare Extraintestinal Manifestations

- Bacteremia
- Enteritis
- Peritonitis
- Appendicitis
- Wound infection, cellulitis, abscess
- Brain abscess
- Septic joints, osteomyelitis
- Reactive arthritis

Mattila et al, CID 2013

C difficile and pathogenesis



Tamma et al JPIDS 2012

Background: Epidemiology

Risk Factors

- Antimicrobial exposure
- Acquisition of *C. difficile*
- Advanced age
- Underlying illness
- Immunosuppression
- Tube feeds
- ? Gastric acid suppression

Main modifiable risk factors

Additional risk factors

- Risk factors
  - Proton pump inhibitors
  - Prolonged NG tube
  - Gastrostomy/jejunostomy tube
  - GI surgery
  - Repeated enemas
  - Use of diapers
- Underlying diagnoses
  - Underlying bowel disease, **inflammatory bowel disease**
  - Immunocompromised, impaired humoral immunity
  - Renal insufficiency

Tschudin-Sutter et al, CID 2013; 57: 1665
Sandora et al, PIDJ 2011; 7: 580
Samady et al J Hosp Med 2013, epublished

Which antibiotics are associated?

- **All antibiotics are associated with CDI**
  - 35-75% with CDI have antibiotic exposure
  - CDI usually occurs during or shortly after antibiotic exposure
    - Can occur as long as 2-3 months after antibiotic exposure
    - Colonization and infection can occur after single dose of antibiotics

Tamma et al JPIDS 2012; Privitera et al Anitmic Agents Chemotherap 1991; 35: 208; Carignan et al CID 2008; 46:1838

Not all antibiotics are the same

Antibiotic	Odd Ratio	95% CI
Penicillin combinations	1.5	1.1-2.0
Clindamycin	2.9	2.0-4.0
Cephalosporins		
3°	3.2	1.8-5.7
2°	2.2	1.5-3.4
4°	2.1	1.3-3.5
Carbapenems	1.8	1.3-2.4
Quinolones	1.7	1.2-2.4
Trimeth-sulfa	1.8	1.0-3.0

Adapted from Slimings et al J Antimic Chemother, 2013; epublished

Prevention Strategies

Prevention Strategies

- **Core Strategies**
  - High levels of scientific evidence
  - Demonstrated feasibility
- **Supplemental Strategies**
  - Some scientific evidence
  - Variable levels of feasibility

Prevention Strategies: Core

- Implement an antimicrobial stewardship program
- Contact Precautions for duration of diarrhea
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system for immediate notification of positive test results
- Educate about CDI: HCP, housekeeping, administration, patients, families

http://www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_HCP.html

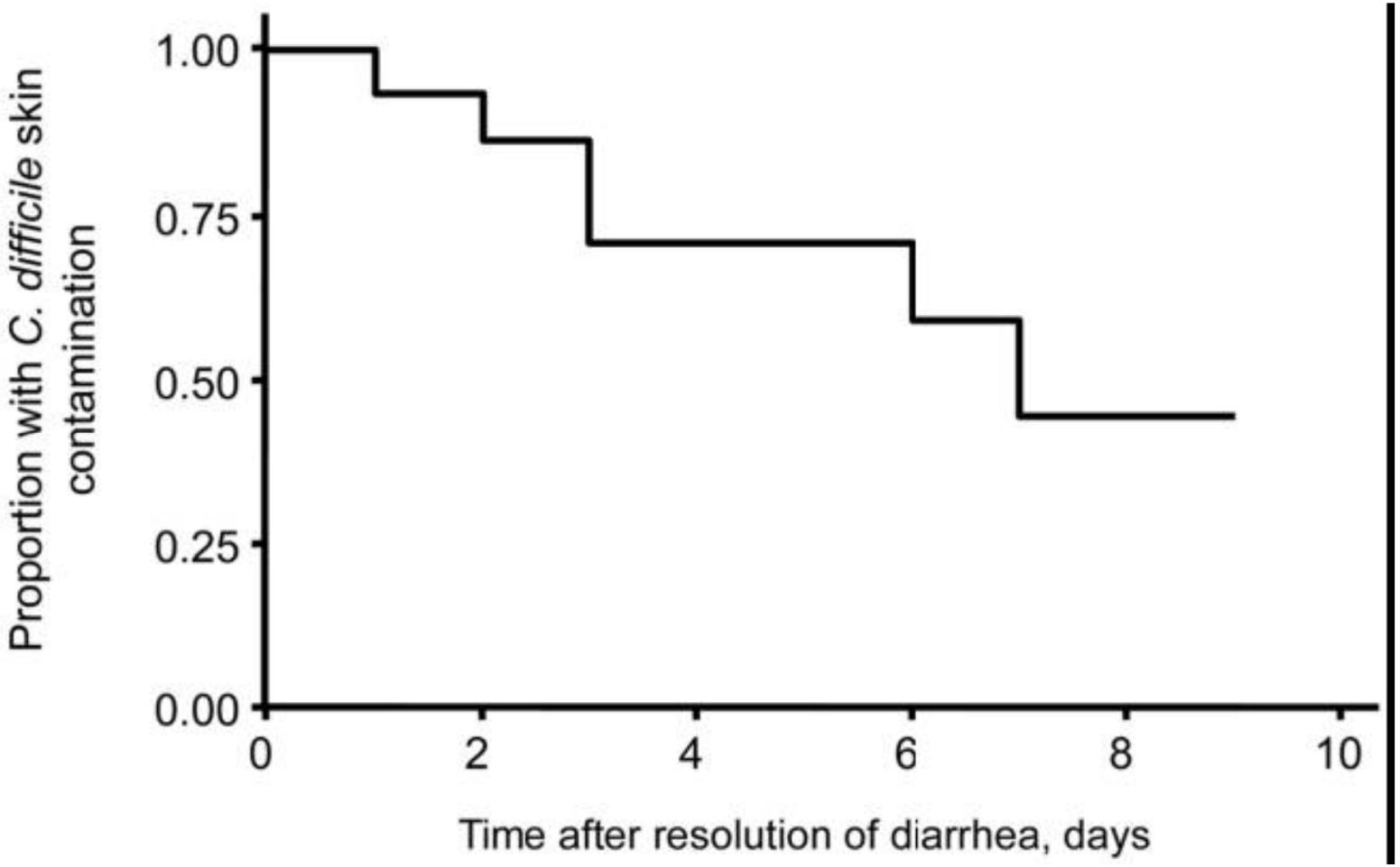
Dubberke et al. Infect Control Hosp Epidemiol 2008;29:S81-92.

Prevention Strategies: Supplemental

- Extend use of Contact Precautions beyond duration of diarrhea (e.g., 48 hours)*
- Presumptive isolation for symptomatic patients pending confirmation of CDI
- Evaluate and optimize testing for CDI
- Implement soap and water for hand hygiene before exiting room of a patient with CDI
- Implement universal glove use on units with high CDI rates*
- Use sodium hypochlorite (bleach) – containing agents for environmental cleaning

* Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions

Supplemental Prevention Strategies:
Rationale for considering extending isolation beyond duration of diarrhea



Bobulsky et al. Clin Infect Dis 2008;46:447-50.

Supplemental Prevention Strategies: Hand Hygiene – Soap vs. Alcohol gel

- Alcohol not effective in eradicating *C. difficile* spores
- However, one hospital study found that from 2000-2003, despite increasing use of alcohol hand rub, there was no concomitant increase in CDI rates
- Discouraging alcohol gel use may undermine overall hand hygiene program with untoward consequences for HAIs in general

Boyce et al. Infect Control Hosp Epidemiol 2006;27:479-83.

Supplemental Prevention Strategies:
Hand Washing: Product Comparison

Product	Log10 Reduction
Tap Water	0.76
4% CHG antimicrobial hand wash	0.77
Non-antimicrobial hand wash	0.78
Non-antimicrobial body wash	0.86
0.3% triclosan antimicrobial hand wash	0.99
Heavy duty hand cleaner used in manufacturing environments	1.21*

* Only value that was statistically better than others

Conclusion: Spores may be difficult to eradicate even with hand washing.

Edmonds, et al. Presented at: SHEA 2009; Abstract 43.

CDI and Infection Prevention

Johnson et al Am J Med 1990; 88: 137

Most important source of transmission of pathogens in the hospital setting

Healthcare worker hands

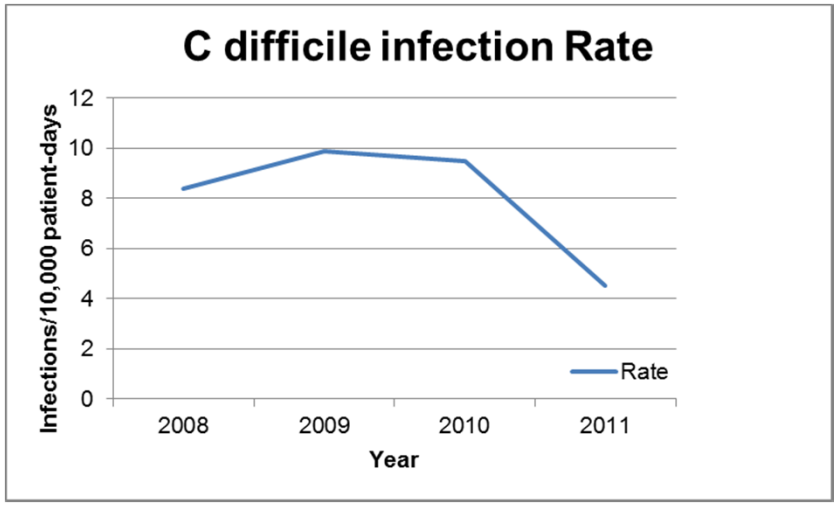
Glove up and wash your hands with soap and water after contact with CDI patient

C difficile and the Environment

- Spores resist desiccation and persist up to
  - 5 months on hard surfaces
    - Patients in room previously occupied by CDI patient at higher risk for acquisition
    - Room contamination
      - 49% in CDI rooms, 29% in asymptomatic carriers
    - Highest areas of contamination bedrails and floor
- Spores difficult to eradicate
    - Sodium hypochlorite kills spores → best cleaning agent
    - Spores resistant to alcohol and ammonium based products

UV Light Disinfection (Xenex System)

- UV light denatures DNA
- Active against C difficile
  Associated with decreased
  HAI CDI rates



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Levin et al Am J Infec Control 2013

Measurement: Process Measures

- **Core Measures:**
  - Measure compliance with CDC/WHO recommendations for hand hygiene and Contact Precautions
  - Assess adherence to protocols and adequacy of environmental cleaning
- **Supplemental Measures**:
  - Intensify assessment of compliance with process measures
  - Track use of antibiotics associated with CDI in a facility

Diagnosis

- Optimal testing algorithm for pediatric CDI unclear

- Diarrhea (≥3 stools/24 hours that take shape of container)

Table 2. The Brecher Guidelines

Observation	Response
Look at the stool specimen	If it ain't loose, it's of no use
Put a thin lab grade stick in the specimen	If the stick stands, the test is banned
	If the stick falls, test them all[a]

[a] Refers to a single stool specimen.

Brecher et al CID 2013; 57: 1175

The smell of *C difficile*: urban legend or truth?

Does the Nose Know? The Odiferous Diagnosis of *Clostridium difficile*–Associated Diarrhea

TO THE EDITOR—*Clostridium difficile*–as-

- Nurse surveyed n=138 at the time of stool collection
- Test characteristics of an odiferous diagnosis
  - Sensitivity 55%
  - Specificity 83%

Burdette and Bernstein, CID 2007; 44: 1142

Using a dog's superior olfactory sensitivity to identify *Clostridium difficile* in stools and patients: proof of principle study

- How do dogs compare?
- Diagnosis from stool samples
  - Sensitivity 100%
  - Specificity 100%
- Detection rounds on ward
  - Sensitivity 83%
  - Specificity 98%

Bomers et al, BMJ 2012; 345: e7396

C difficile testing

Test	Detects	Sensitivity	Specificity	Use for test of cure
ELISA for glutamate dehydrogenase	Organism only	>94%	60-70%	**No!**
Enzyme immunoassay	Toxin A and B	30-94%	75-100%	**No!** Toxin excretion 2wks 15-25% 4wks 5%
NAAT/PCR	Gene toxin A and/or B	85-95%	90-99%	**No!** Interval >4 weeks since last testing
GDH/EIA and PCR		68-100%	100%	**No!**

Brecher et al CID 2013; 57: 1175: 1209; Tamma et al JPIDS, 2012; 1: 230

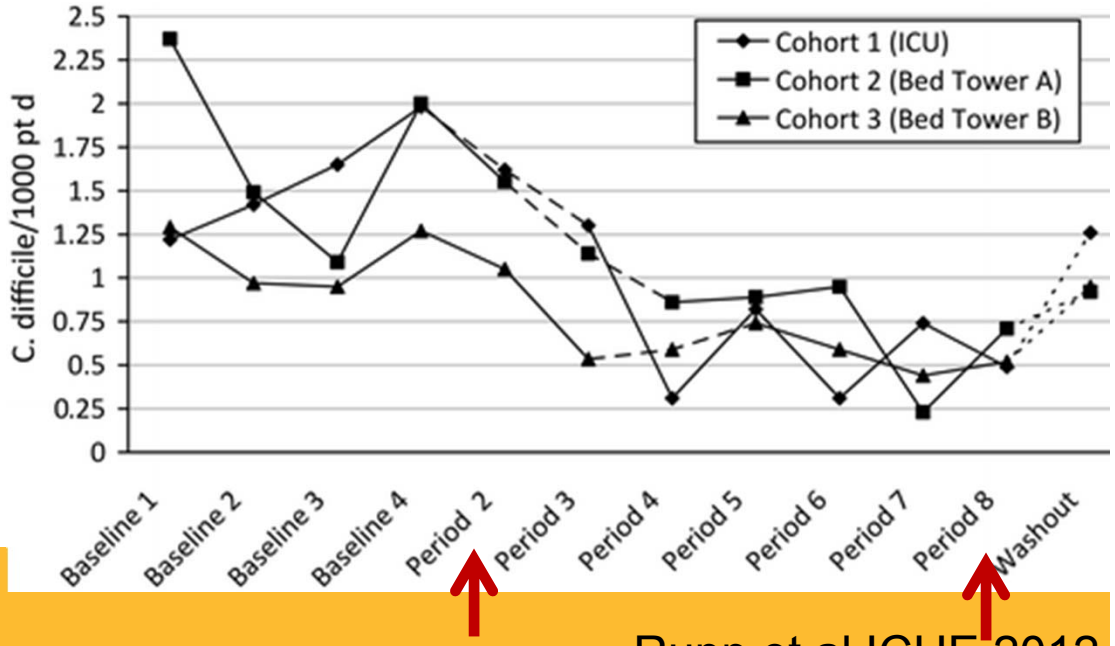
Surveillance Definition

- Recurrent CDI
  - >2 weeks and ≤8 weeks after most recent CDI
- Healthcare Facility
  - Stool collected >3 days after admission to the facility
- Community Onset
  - Stool collected from an outpatient ≤3 days after admission
- CO Healthcare Facility Associated
  - Meets community onset definition and discharged from facility ≤4 weeks prior to stool collection

http://www.cdc.gov/nhsn/acute-care-hospital/cdiff-mrsa/

C difficile and chlorhexidine gluconate (CHG)

- Chlorhexidine not sporicidal but active against vegetative cells and inhibits spore germination
  - Quasi experimental 19 mo study in academic center
  - Reported CDI RR 0.71 for 3x/week CHG and RR 0.41 for daily CHG compared to baseline



Rupp et al ICHE 2012

Summary

- *C difficile* infection is increasing in US
- Risk factors: antibiotics, hospital exposure
- Prevention strategies:
  - Identify early w >3 stools/24 hours
  - Soap & Water
  - Contact precautions for hospital stay
  - Bleach & UVC disinfection
  - CHG bathing
- Diagnosis:
  - PCR
  - Do not test for cure

Questions?

Treatment

- Differentiate asymptomatic carriage and infection
  - **Stop/narrow broad spectrum antibiotics if possible**
  - Stop antiperastaltic medications
- Pediatric treatment recommendations based on adult studies
  - Metronidazole (PO, IV)
  - Vancomycin (PO)
  - Additional agents
    - Rifaximin, nitazoxinide, fidaxomicin

Treatment

Episode	Categorization	Treatment	Adult max
Initial	Asymptomatic	Consider no therapy	
	Mild/moderate	Metronidazole 30mg/kg/day 10-14 days	500mg PO TID

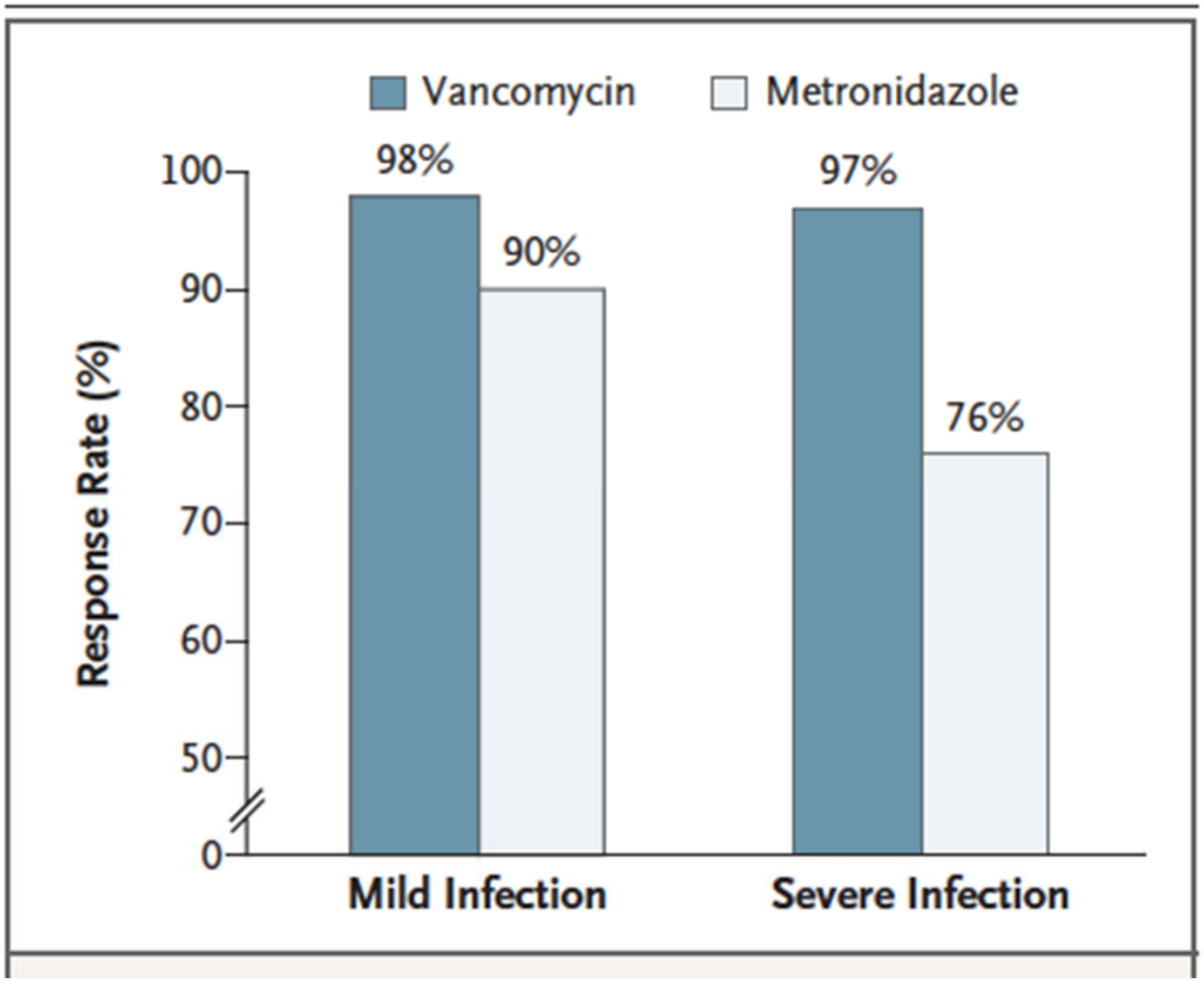
Adapted from Tamma et al JPIDS 2012

Treatment

Episode	Categorization	Treatment	Adult max
Initial	Severe: electrolyte disturbance, lab disturbance WBC >15 or <5, ↑Cr, pseudo-membranous colitis	Oral vancomycin 40mg/kg/day in 4 doses for 10-14 days	125mg q6hr
	Severe complicated (hypotension, toxic megacolon, perf, colectomy, ICU admit)	Oral vancomycin 40mg/kg/day in 4 doses for 10-14 days + metronidazole IV	Vanco PO 500mg q6hr Metro IV 500mg TID

Adapted from Tamma et al JPIDS 2012

Oral Metronidazole vs. oral vancomycin



Kelly et al NEJM, 2008; 350 adapting data by Zar et al CID 2007l 45: 302

Oral Metronidazole vs. oral vancomycin

Table 1. Treatment Failures and Recurrences of *C. difficile* Infection with Metronidazole and Vancomycin Therapy.*

Variable	No. of Studies	Treatment Failure	Recurrence
		no./total no. (%)	
Metronidazole			
Year 2000 or before	4	18/718 (2.5)	48/715 (6.7)
After 2000	5	275/1508 (18.2)	332/1162 (28.6)
Combined periods	9	293/2226 (13.2)	380/1877 (20.2)
Vancomycin			
Year 2000 or before	11	22/637 (3.5)	112/624 (17.9)
After 2000	2	2/71 (2.8)	36/181 (19.9)
Combined periods	13	24/708 (3.4)	148/805 (18.4)

* Data are from Aslam et al.[21] and Zar et al.[24]

Kelly et al NEJM 2008; 359:18

Additional CDI treatment considerations

- Probiotics
  - Inconclusive evidence
- IVIG
  - Anecdotal evidence for severe, recalcitrant cases
- Fecal transplants
  - Promising experience with fecal transplants

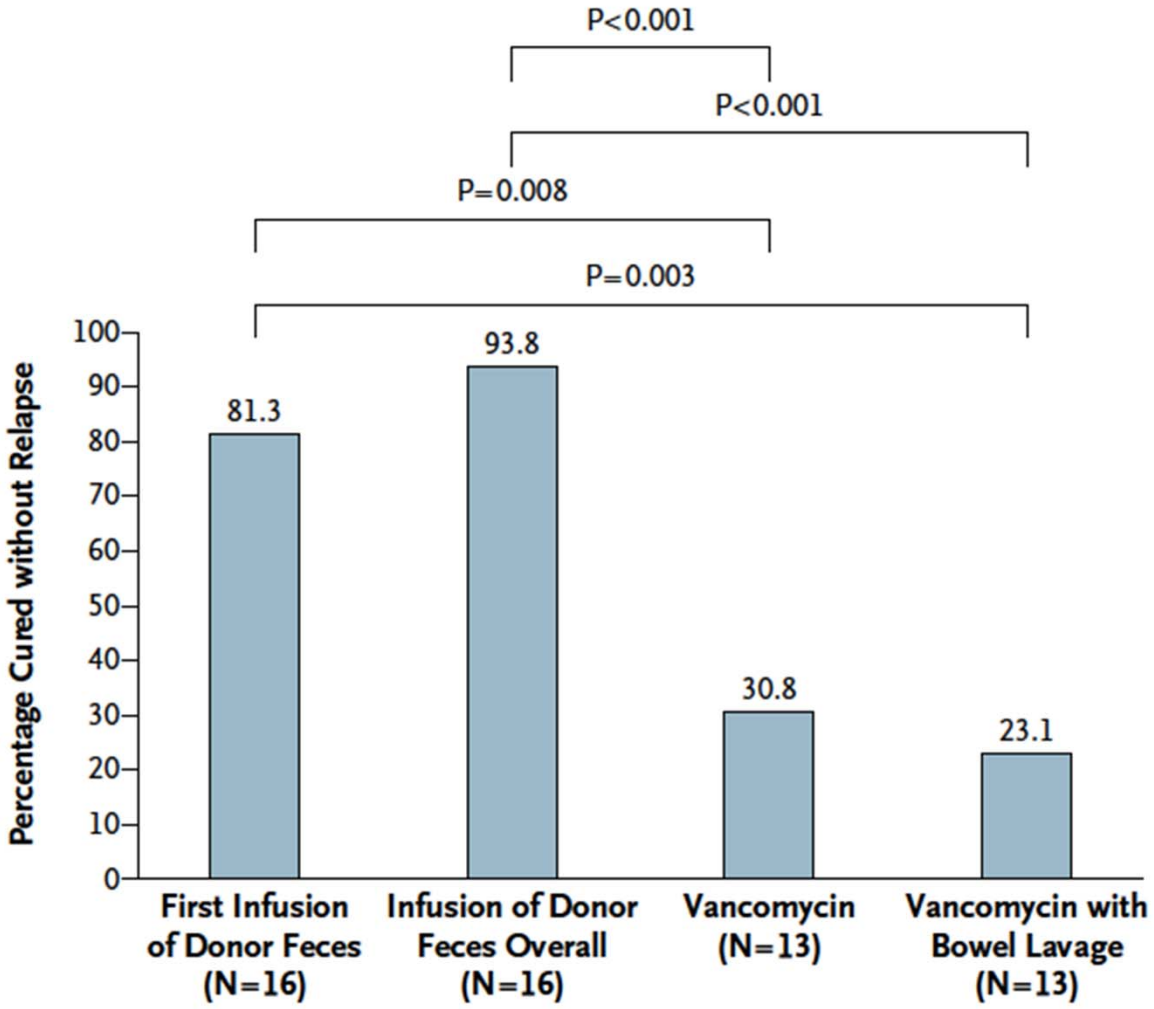


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile*

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van Nood et al NEJM, 2013; 368: 408

CDI Recurrence

- Recurrence occurs within 8 weeks after the prior episode, if symptoms resolve in the interim
  - Up to 25-30% of children develop a recurrence
  - Occurs due to relapse of original strain vs exposure new strain
- Retrospective pediatric study n=175 patients
  - Recurrence rate 12%
  - Mean time to recurrence 34 days (range 11-58 days)
  - Risk factors
    - On antibiotics during initial CDI treatment course
    - No association found between vancomycin vs metronidazole, nor NAP1 strain

Tschudin-Sutter et al PIDJ 2013, epublished

Treatment of CDI recurrence

- Optimal management not established in children nor adults
  - Options include
    - Initial recurrence
      - Repeat initial therapy for 10 days
      - If severe recurrence: Go from metronidazole to oral vancomycin
    - Second recurrence
      - Taper or pulse oral vancomycin regimens

Additional treatment considerations: CDI recurrence

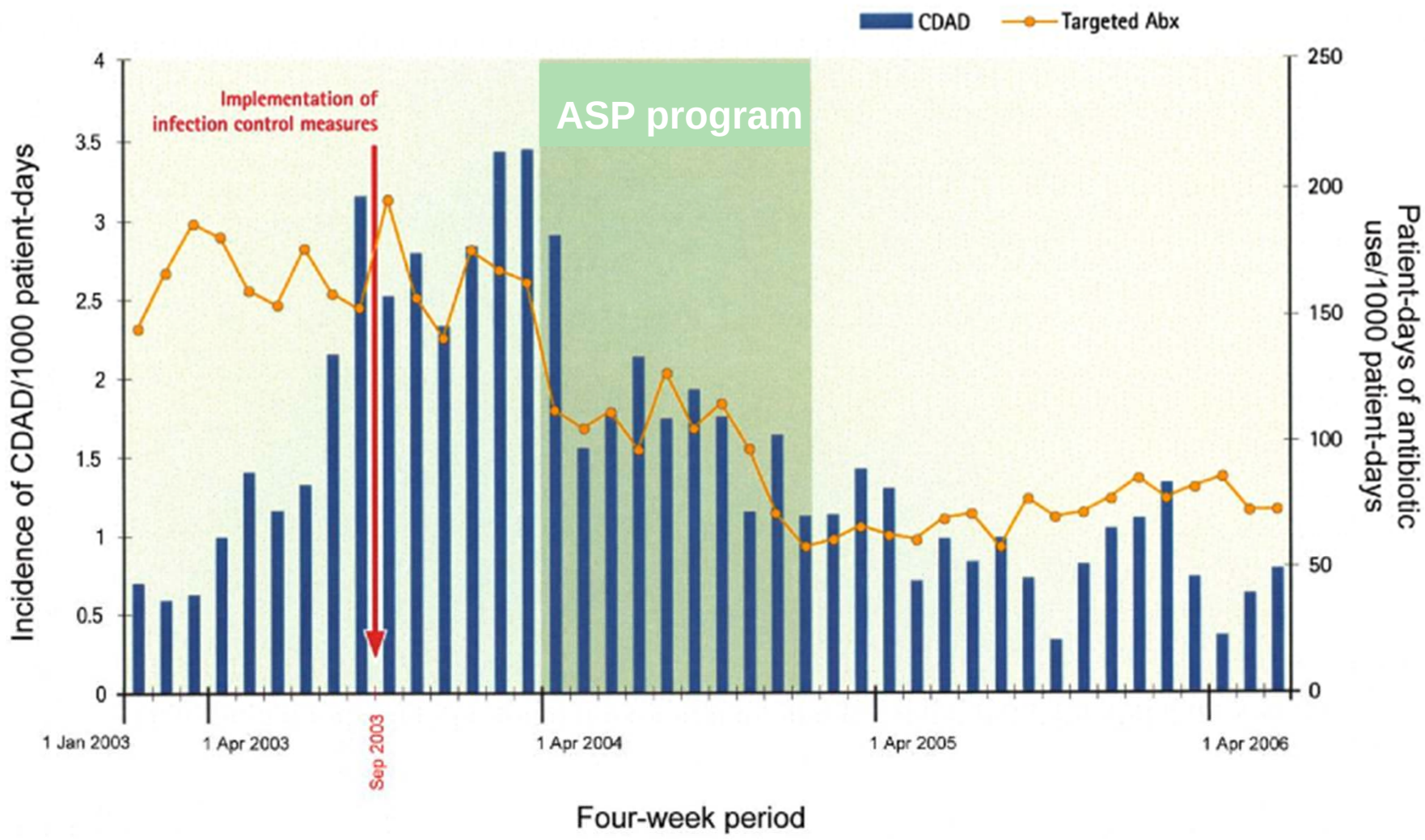
- Rifaximin
  - Nonabsorbed
  - Small case series in adults treated with rifaximin 20 days after completing standard therapy showed decrease recurrence (20% vs 50%)
  - Concern for development high level resistance
- Nitazoxanide
  - In adults produces cure and relapse rates similar to vanco/metronidazole
- Fidaxomicin
  - Approved in >18 yrs in May 2011
  - Noninferior to vancomycin, significant reduction CDI recurrence in non-NAP1 strains

Antibiotic	Mechanism of Action	Absorbed (Y/N)	Patients
Rifaximin	Rifamycin—inhibit transcription by bind to RNA polymerase Oral vancomycin followed by rifaximin may be effective for recurrent disease	No	Approved for children ≥12 years
Nitazoxanide	Possibly interferes with electron transfer chain through interference with pyruvate:ferredoxin oxidoreductase In adults produces cure and relapse rates similar to vanco/metro	Yes, converted into tizoxanide	Approved for children ≥1 year
Fidaxomicin	Macrocyclic antibiotic that inhibits RNA polymerase Minimally disrupts other GI flora, Noninferior to vancomycin, significant reduction CDI recurrence in non-NAP1 strains	No	Approved for patients ≥18 year

CDI and antimicrobial stewardship

- Critical to reduce CDI at the hospital level
  - CDI rate reduction shown with
    - Programs that restrict clindamycin
    - General antimicrobial stewardship programs
    - In outbreak settings

Carling et al. ICHE 2003;24:699-706
Climo et al. Ann Intern Med 1998;128:989-95
Khan et al. J Hosp Infect 2004;54:104-8
Pear et al. Ann Intern Med 1994;120:272-7
Bradley et al. J Antimicrob Chemother 1997;40:707-11



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Valiquette et al, CID 2007;45:S112

CDI and Infection Prevention

Johnson et al Am J Med 1990; 88: 137

Most important source of transmission of pathogens in the hospital setting

Healthcare worker hands

Glove up and wash your hands with soap and water after contact with CDI patient

What cleaning product is most efficacious against C difficile spores?

1) Quaternary ammonium wipes
2) Antibacterial soap and water
3) Sodium hypochlorite (bleach)

Thank you!

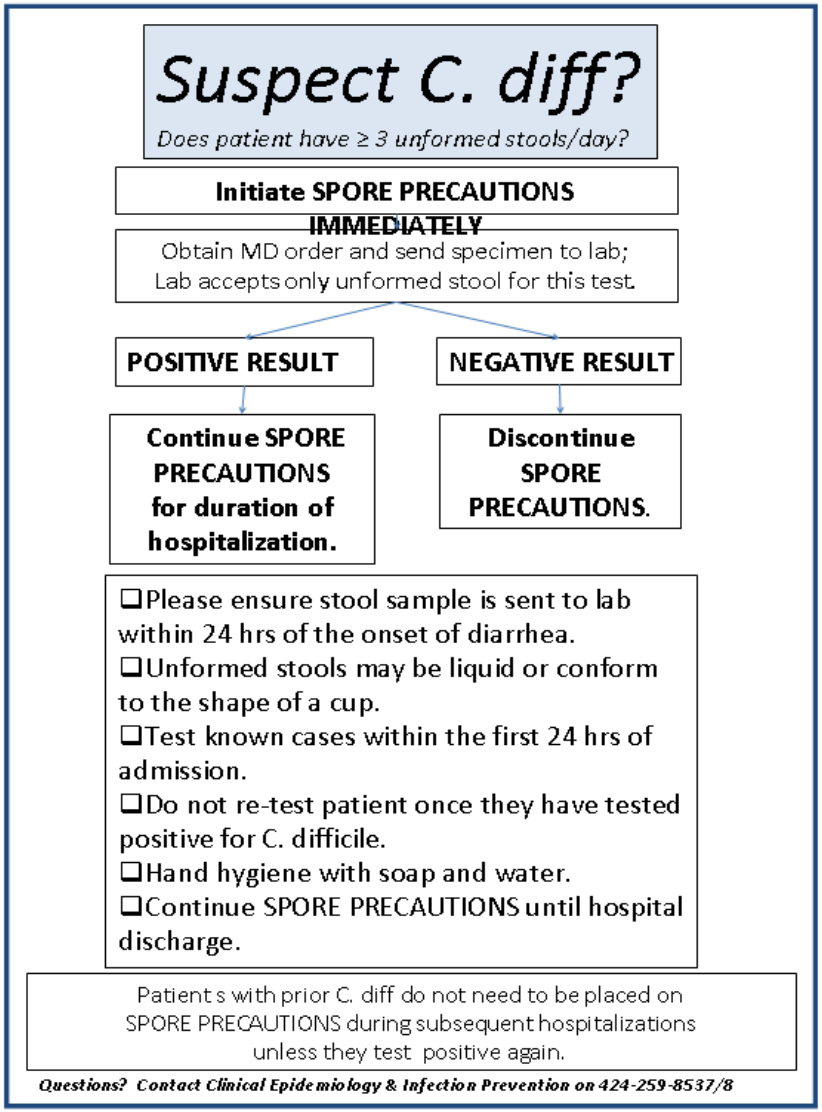
UCLA Health Syste

Ronald Reagan Medical Center

- Environment
  - Two Xenex machines
    - Rolled-out September, 2012
    - Used for *C difficile* discharge
    - From January 1-November 30, 2013
      - Total N= 5,882 uses
      - ICU specific: 1,029 (17%)
  - Black light room cleaning inspections

C difficile and Infection Prevention

- Nurse driven testing and isolation protocol
  - Identify high risk patients
    - Exposure to antibiotics, healthcare settings
    - Immunosuppressed
    - GI surgery, PPI exposure
  - Assess for signs
    - 3 or more unformed stools/24hr
    - Abdominal pain/discomfort
  - Place on isolation precautions & send test
    - Do not restest once positive
    - No test of cure



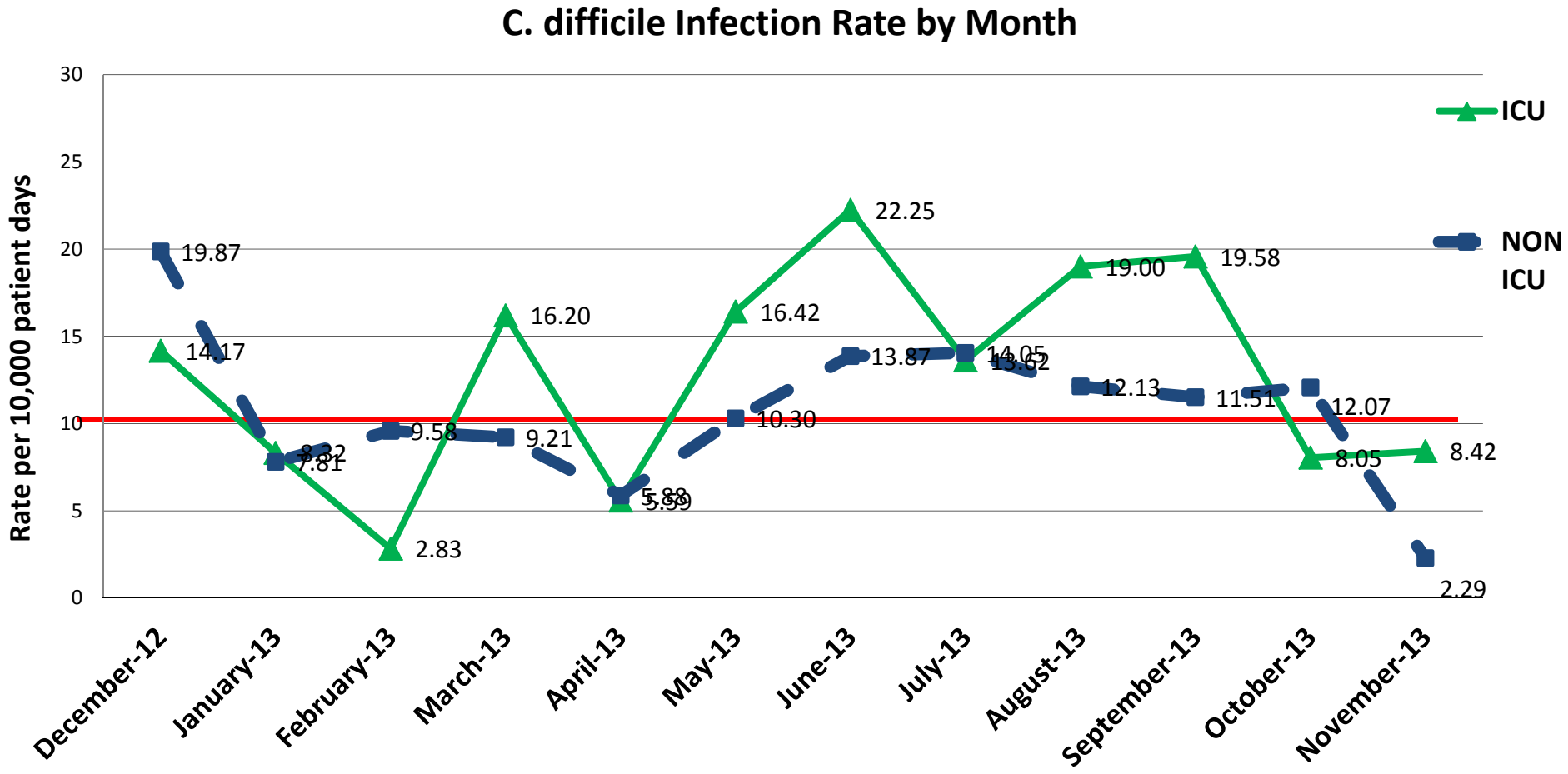
UCLA Health System

Ronald Reagan Medical Center

- Hand Hygiene
- Chlorhexidine treatment in all ICU patients >2 months
- Antimicrobial Stewardship Program (ASP)
  - Adult ASP since 2010
  - New pediatric ASP since March 2013

UCLA Health System

Pooled CDI Rates[$], ICUs and ACUs RRUCMC, 2012-2013



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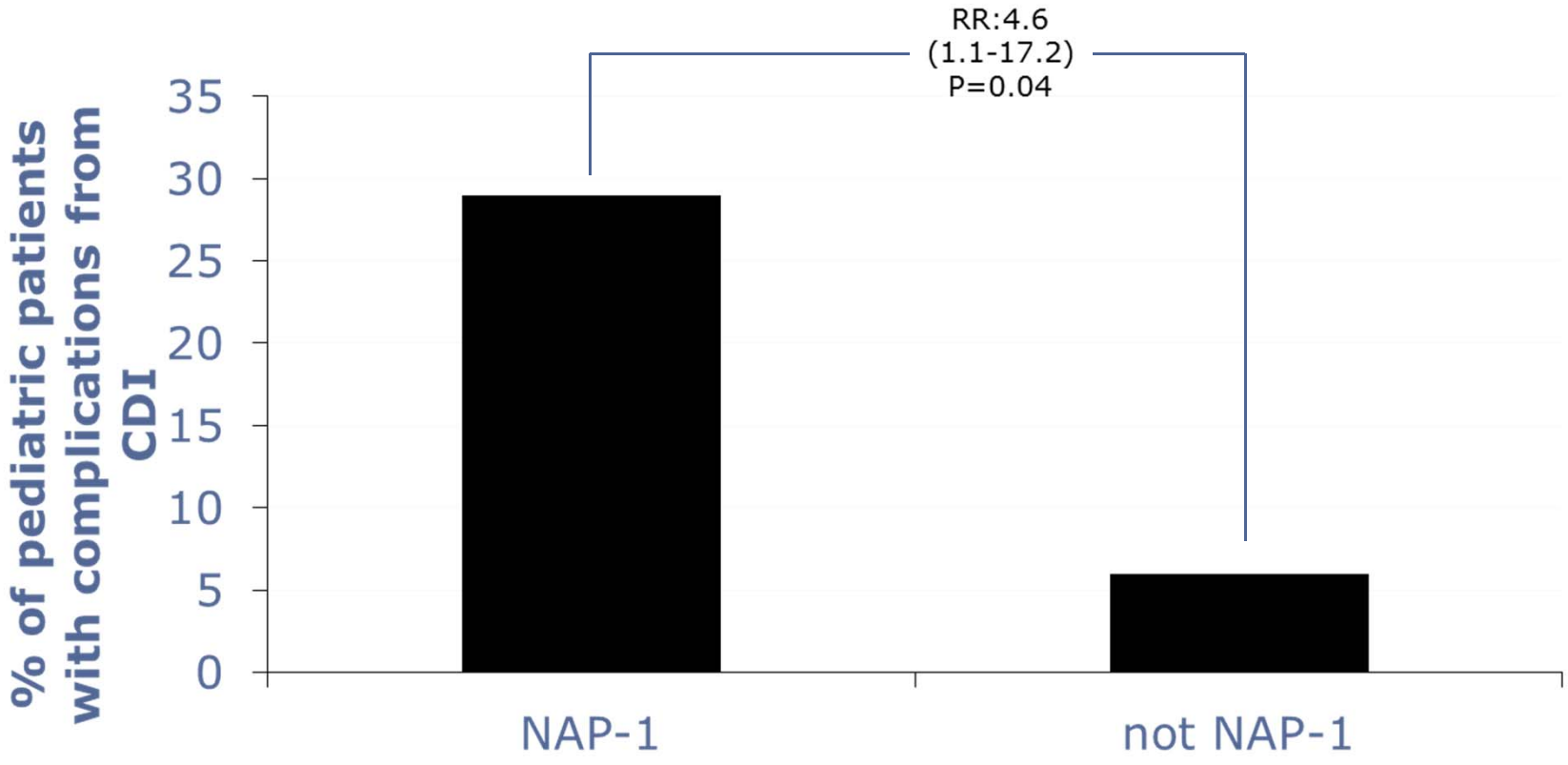
[$]All rates are CDI rate per 10,000 patient days

[1]CDPH Target Rate = 9.4/10,000, http://www.cdph.ca.gov/programs/hai/Documents

NAP1/B1/027 Strain and concern for worse outcomes



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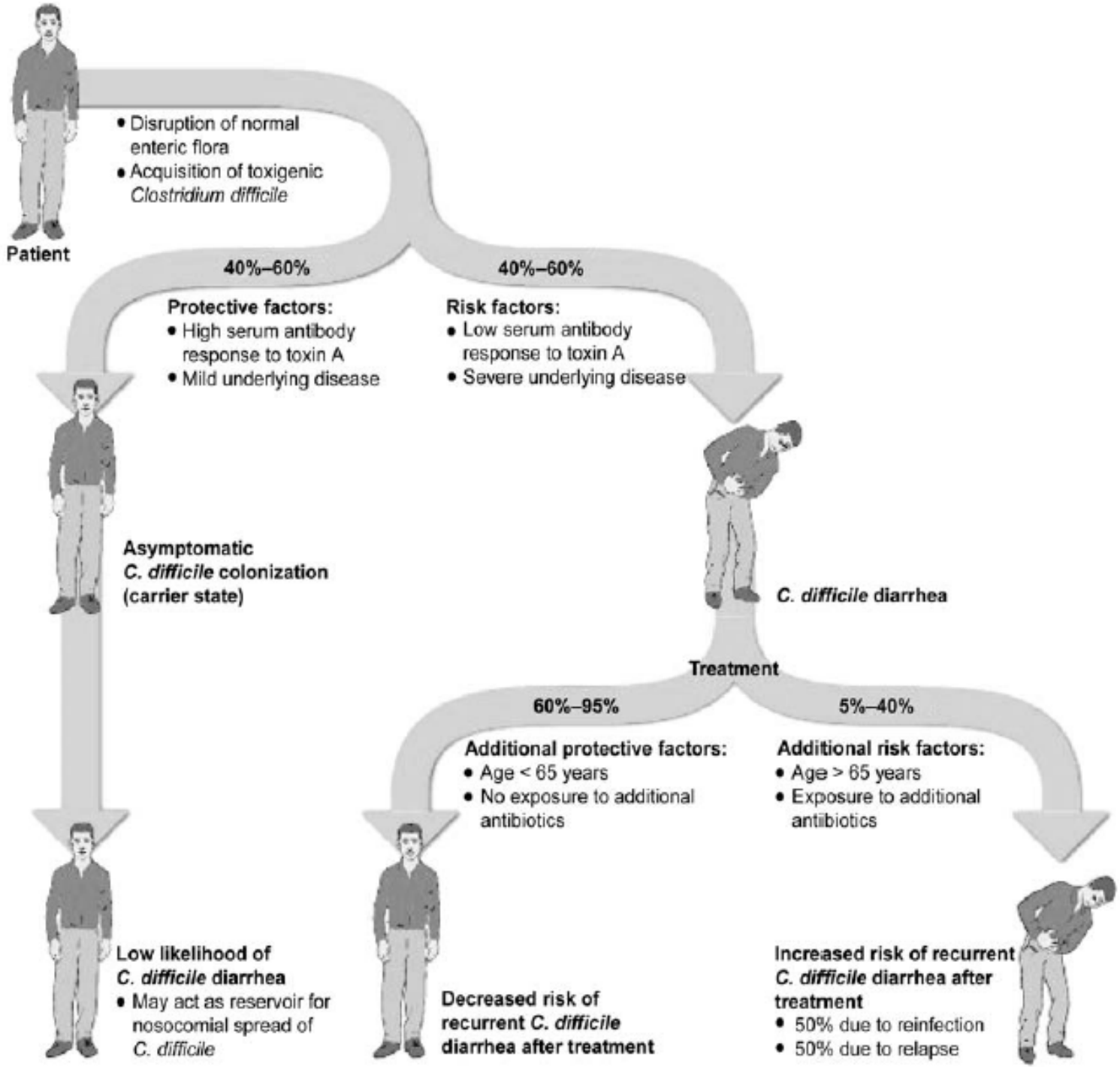
Suh et al. 2008 SHEA. Abstract 306

Courtesy Romney Humphries, UCLA microbiology

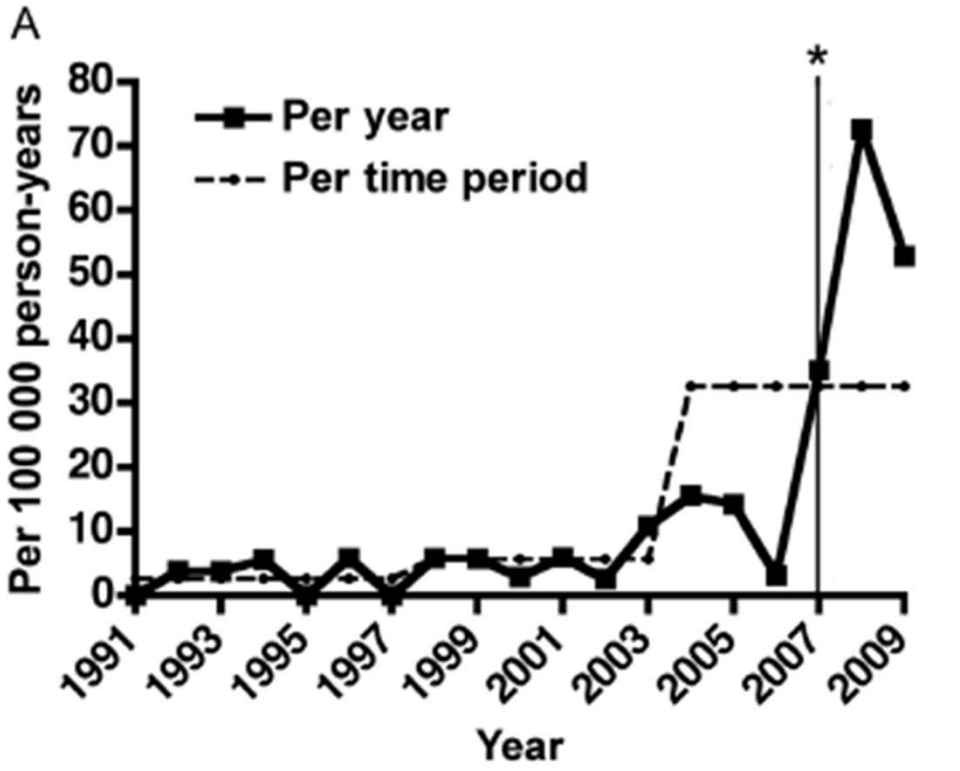

Patient
• Disruption of normal enteric flora
• Acquisition of toxigenic *Clostridium difficile*
40%–60%
Protective factors:
• High serum antibody response to toxin A
• Mild underlying disease
40%–60%
Risk factors:
• Low serum antibody response to toxin A
• Severe underlying disease
Asymptomatic *C. difficile* colonization (carrier state)
C. difficile diarrhea
Treatment
60%–95%
Additional protective factors:
• Age < 65 years
• No exposure to additional antibiotics
5%–40%
Additional risk factors:
• Age > 65 years
• Exposure to additional antibiotics
Low likelihood of *C. difficile* diarrhea
• May act as reservoir for nosocomial spread of *C. difficile*
Decreased risk of recurrent *C. difficile* diarrhea after treatment
Increased risk of recurrent *C. difficile* diarrhea after treatment
• 50% due to reinfection
• 50% due to relapse

Case, continued

- 8yo M with a history of ALL has been admitted for 7 days with fever and neutropenia when he develops copious diarrhea with abdominal pain. The stool is nonbloody. The child is on Day#7 of cefepime.
- The child has a positive *C difficile* testing and is started on metronidazole. 2 weeks later the child has recurrence of their diarrhea

- What is your differential diagnosis?
- What additional tests would you send?
- Would you start additional CDI-directed antibiotic treatment?

Change in test characteristics



*Stool test modality changed from EIA to PCR in July 2007

Khanna et al, CID 2013; 56: 1401

Proportion pediatric patients receiving vancomycin has increased

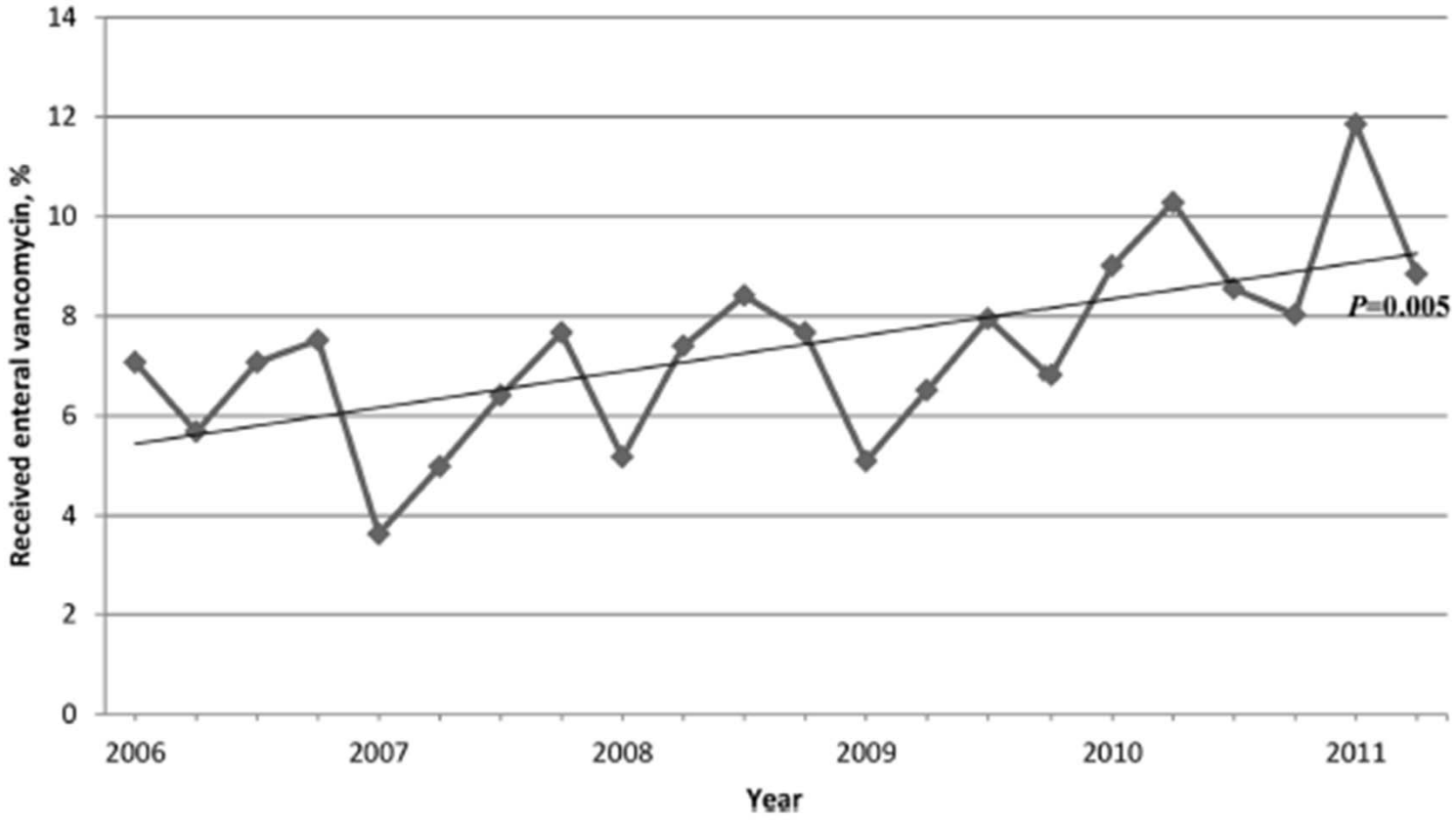


FIG 2 Proportion of children whose initial CDI regimen included enteral vancomycin, grouped by quarter (2006 to 2011).

Schwenk et al, Antimic Agents Chemo; 2013: 57: 4307