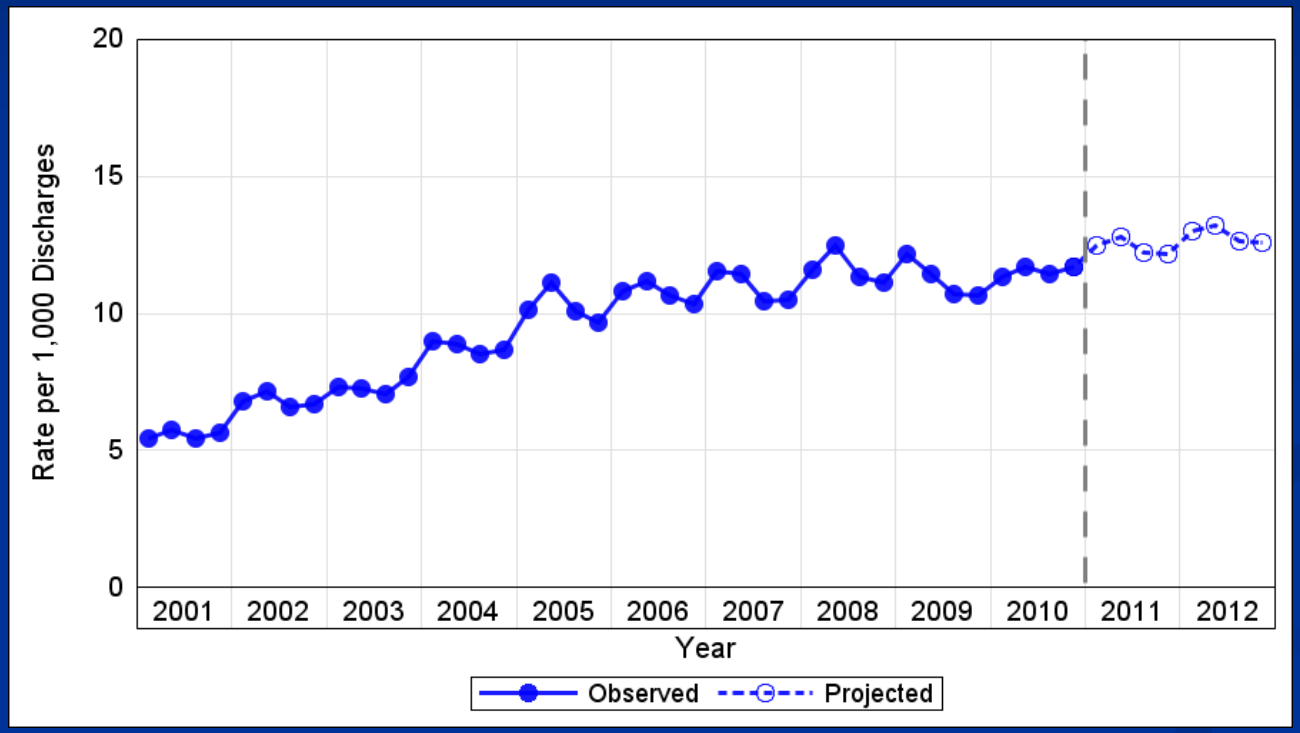
Can We Prevent All Healthcare-Associated *Clostridium difficile* infections in 10 Years?

Curtis Donskey, M.D.

Louis Stokes VA Medical Center
Cleveland, Ohio

Research support: Clorox, EcoLab, GOJO, Merck, AvidBiotics, Altapure
Advisory Board: 3M

Incidence of hospital-associated CDI in the US



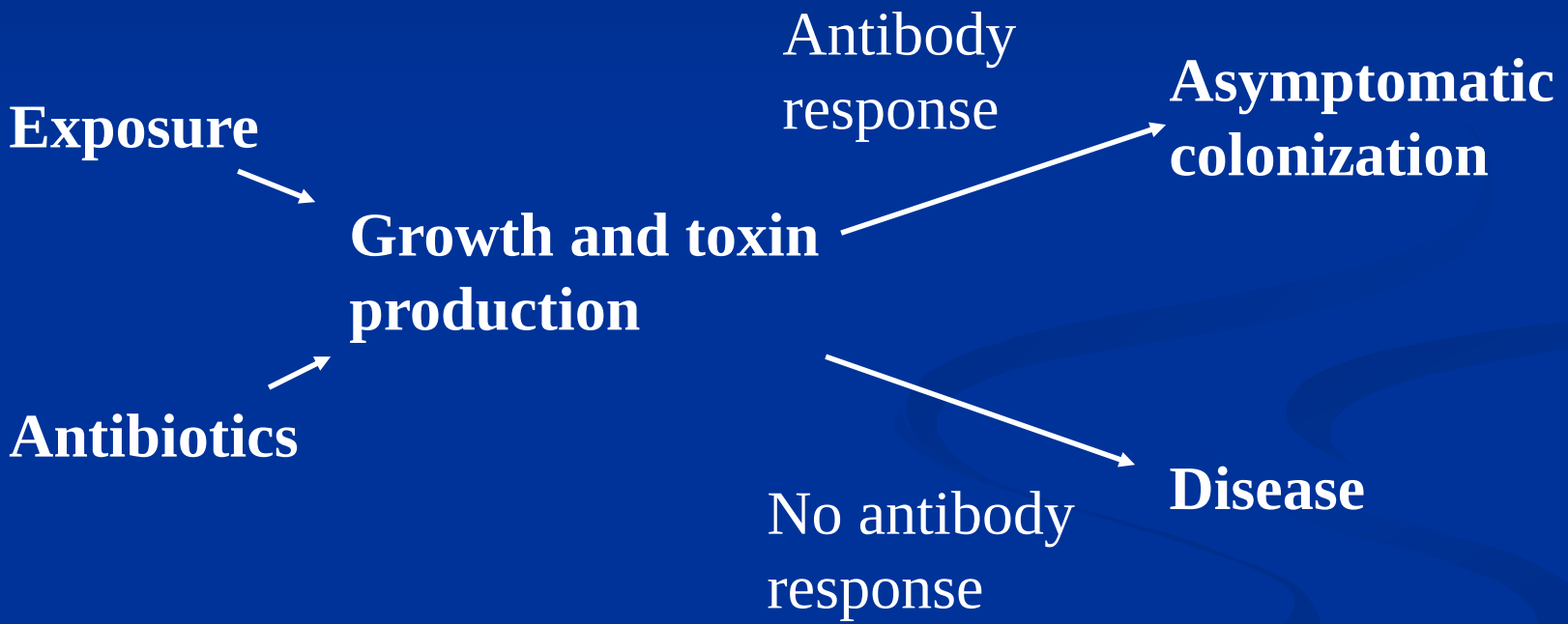
2011 – 453,000 incident cases and 29,300 deaths

Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project, CDI 2011 to 2012; Lessa FC, et al. NEJM 2015;372:825-33




23

Pathogenesis



Lancet 2001;357:189-93; NEJM 2000;342:390-7

C. difficile prevention

Environmental disinfection, contact precautions

Monoclonal antibody

Exposure

Growth and toxin production

Antibiotics

Antibody response

Asymptomatic colonization

No antibody response

Disease

Stewardship, Fecal transplant

Lancet 2001;357:189-93; NEJM 2000;342:390-7

Grey's Anatomy



Know your enemy and yourself and you can win one hundred battles

Sun Tzu, The Art of War

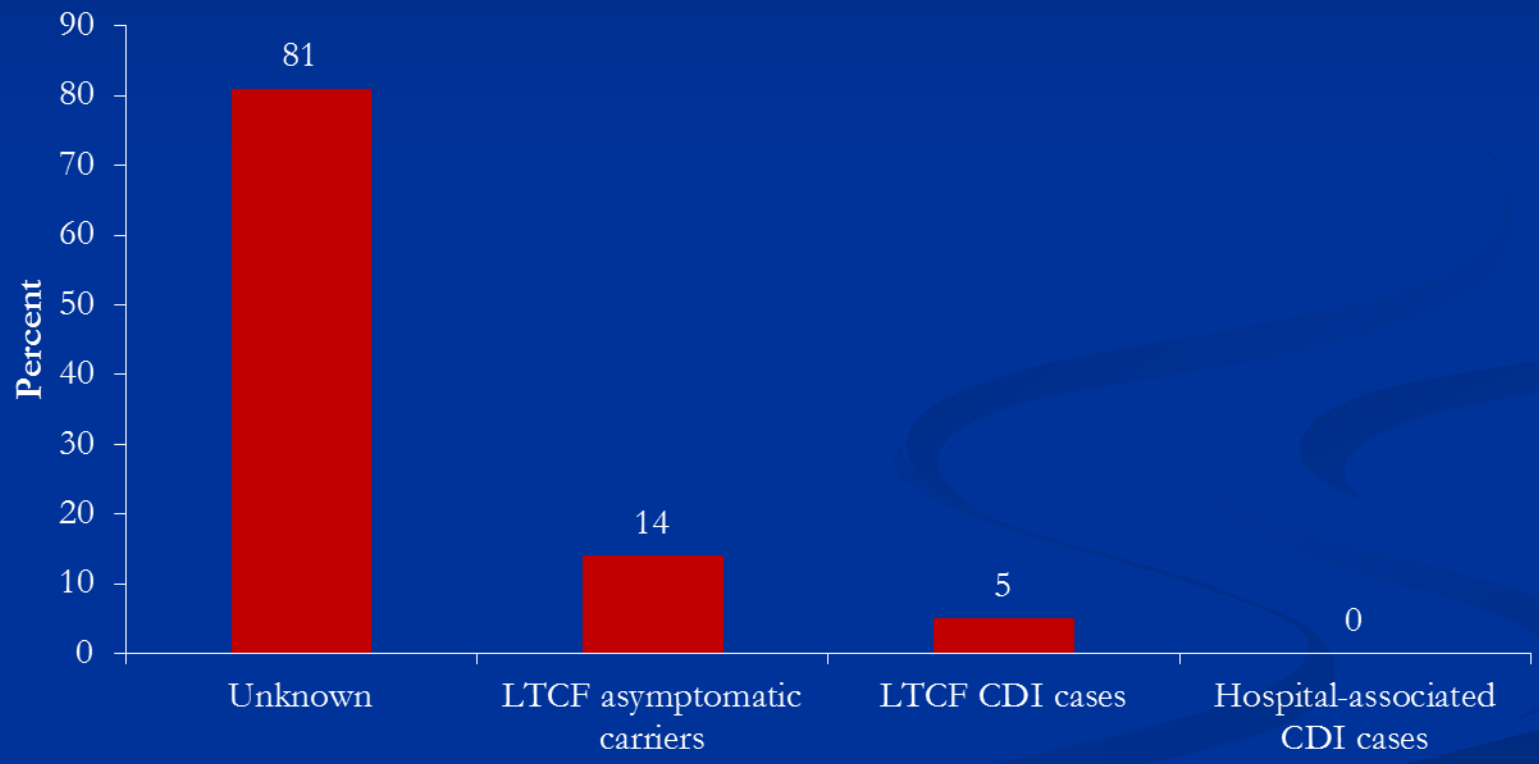
Know your pathogens and your personnel if you want to prevent healthcare-associated infections

The Art of Infection Control

What percentage of healthcare-associated CDI cases at the Cleveland VA Hospital are linked to other healthcare-associated cases?

- A. <5%
- B. 33%
- C. 66%
- D. >90%

Sources of healthcare-associated CDI cases based on whole genome sequencing



Donskey CJ, et al. Transmission of *C. difficile* by LTCF Residents with CDI or Asymptomatic Carriage of Toxigenic Strains. Manuscript submitted.

Top 10 questions we need to address to eliminate healthcare-associated CDI

10. Are many cases of healthcare-associated CDI acquired in non-healthcare settings?

- Lessa NEJM 2015 (US) [1]
  - 66% of CDI cases healthcare-associated
  - 82% of community-associated CDI cases have recent outpatient healthcare exposures



- Eyre NEJM 2013 (England) [2]
  - Diverse sources of acquisition
  - Only 35% of cases genetically linked to other cases



1. Lessa FC, et al. Burden of CDI in the U.S. NEJM 2015;372:825-33; 2. Eyre D, et al. Diverse sources of CDI identified on whole-genome sequencing. NEJM 2013;369:1195-1205; 3. Noren T, et al. Molecular Epidemiology of Hospital-Associated and Community-Acquired CDI in a Swedish County. J Clin Microbiol 2004;42:3635-43 (78% of primary episodes hospital associated but only 17-27% hospital acquisition based on ribotyping)

Potential sources of *C. difficile* in the community

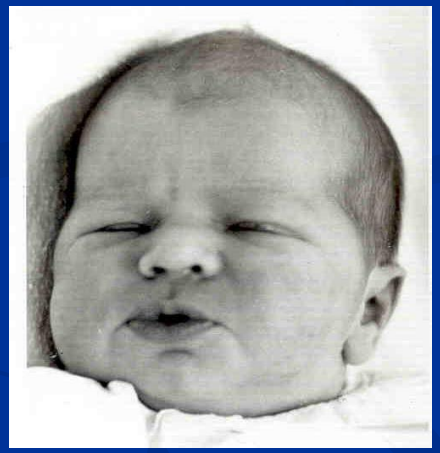












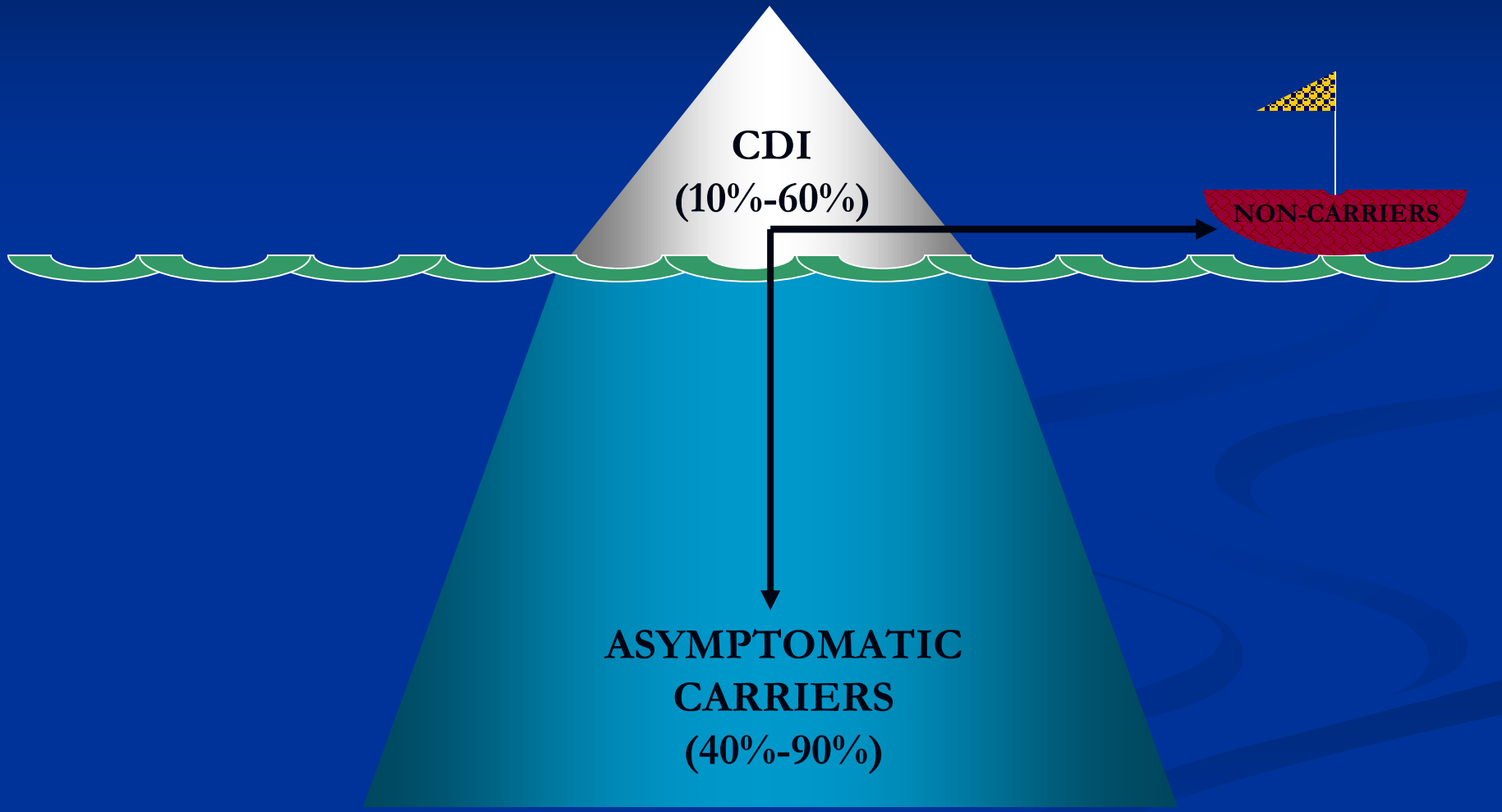
Wilcox MH, et a. J Antimicrob Chemother 2008;62:388-96; Kutty PK, et al. ICHE 2008;29:197-202; Kutty PK, et al. Emerg Infect Dis 2010;16:197-204; Lambert PJ, et al. ICHE 2009;30:445-51; Naggie S, et al. Am J Med 2011;124:276 e1-7; Dial S, et al. JAMA 2005;294:2989-2995; Weese JS, et al. Appl Environ Microbiol 2009;75:5009-11; Songer JG, et al. Emerg Infect Dis 2009;15:819-21; Rupnik M. Clin Microbiol Infect 2007;13:457-9; Weese JS. Clin Microbiol Infect 2010;16:3-10; Bakker D, et al. J Clin Microbiol 2010;48:3744-9; Goorhuis A, et al. Clin Infect Dis 2008;47:1162-70; Debast SB, et al. Environ Microbiol 2009;11:505-11; Jhung MA, et al. Emerg Infect Dis 2008;14:1039-45; Jury LA, et al. PLoS One. 2013 Jul 24;8(7):e70175.

Downton Anatomy



https://youtu.be/-d4bhZRdzD0

9. Are asymptomatic carriers a major source of transmission?



McFarland LV. NEJM 1989;320:204-10; Clabots CR. J Infect Dis 1992;166:561-7; Samore MH. Clin Infect Dis 1994;18:181-7; Kyne L. NEJM 2000;342;390-7; Loo VG. NEJM 2011;365:1693-1703; Hung YP. PLoS One 2012;7:e42415.

Asymptomatic carriers are a major source of transmission

Yes

- Pittsburgh - 29% of hospital-associated CDI cases linked to carriers (MLVA typing) [1]
- Montreal - Screening for and isolating carriers reduced healthcare-associated CDI by 63% [2]
- Denmark – exposure to carriers increased CDI risk [3]

No

- Boston - Only 1% of cases linked to asymptomatic carriers (roommates and adjacent rooms) (PFGE/REA typing) [4]
- UK – 18 carriers: no links to subsequent CDI cases (Whole genome sequencing)[5]

1. Curry SR. Clin Infect Dis 2013; 2. Longtin Y. JAMA Int Med 2016;Apr 25; 3. Blixt T. Gastroenterol 2017;152:1031-41; 4. Samore MH. Am J Med 1996;100:32-40; 5. Eyre DW. PLOS One 2013;8:e78445; 5. 4

8. Can we develop horizontal approaches to prevent transmission?

- Vertical approaches
  - Directed at specific pathogens
  - Example: Screening patients and isolating carriers
- Horizontal approaches
  - Broad approaches that may impact multiple pathogens and that are applied to all patients
  - Example: hand hygiene

Wenzel RP, Edmond MB. Infection Control: the case for horizontal rather than vertical interventional programs. Int J Infect Dis 2010;14 Suppl 4:14:S3-S5; McDonald LC. Looking to the future: vertical vs horizontal prevention of CDI. Clin Infect Dis 2013;57:1103-5

Sources of pathogen transmission

Infected patient

Asymptomatic carrier



Previously infected patient

Asymptomatic carrier

Newly infected patient not yet recognized

Asymptomatic carrier

Horizontal infection control practices versus MRSA

Chlorhexidine bathing

Hand hygiene (alcohol)

Colonized or Infected Patient



Susceptible Patient

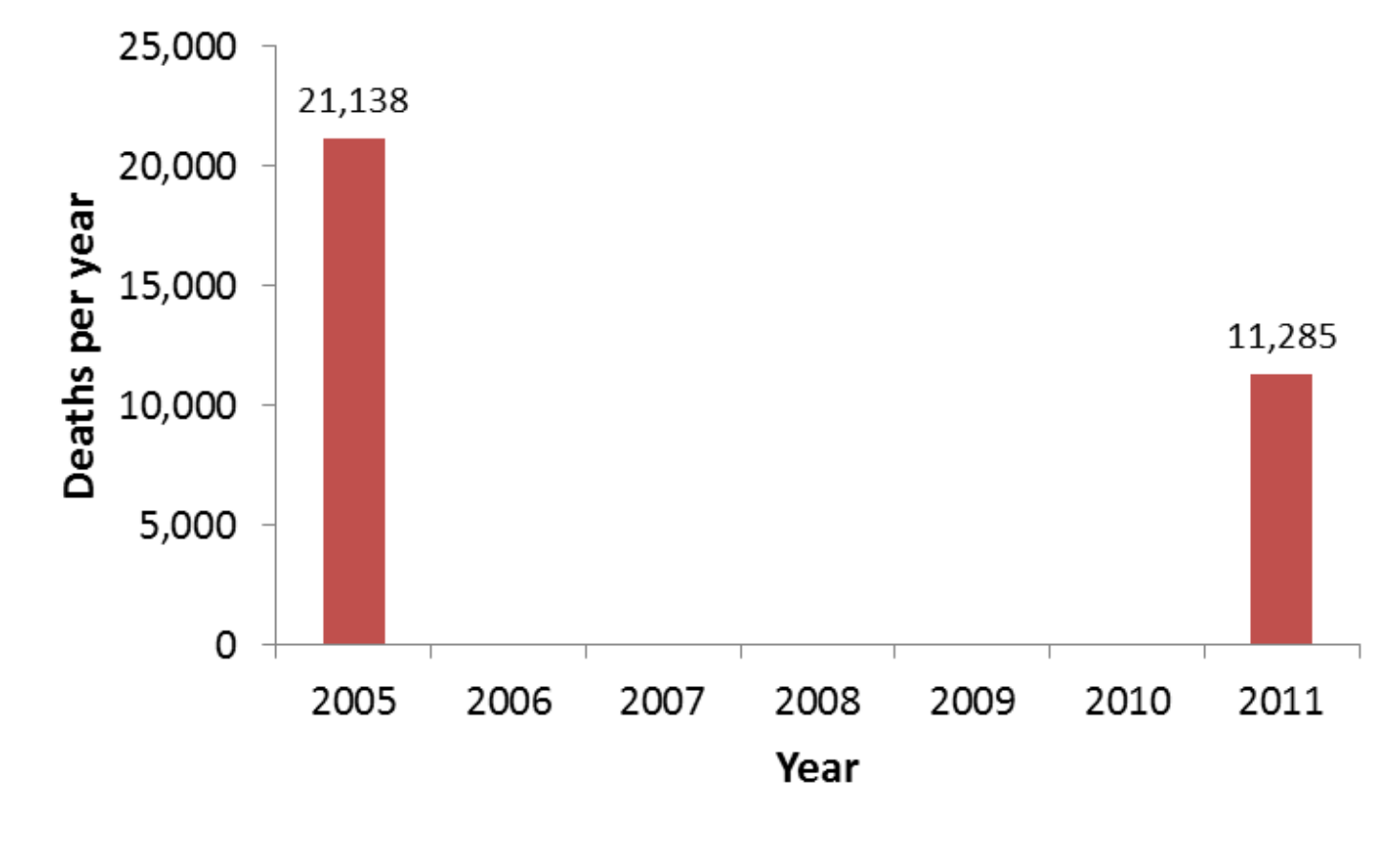
Decolonization

Environment

Environmental Cleaning

Huang SS, et al. Targeted versus universal decolonization to prevent ICU infection. NEJM 2013;368:2255-65; Septimus E, et al. Closing the Translation Gap: Toolkit Based Implementation of Universal Decolonization in Adult ICUs Reduces CLABSIs in 95 Community Hospitals. Clin Infect Dis 2016; May 3

Deaths due to MRSA infection in the U.S.



Dantes R, et al. JAMA Intern Med 2013;173:1970-8
Magill SS, et al. NEJM 2014;370:1198-208

Horizontal infection control practices versus *C. difficile*

Chlorhexidine bathing ✗

Hand hygiene (alcohol) ✗



Infected Patient → Susceptible Patient

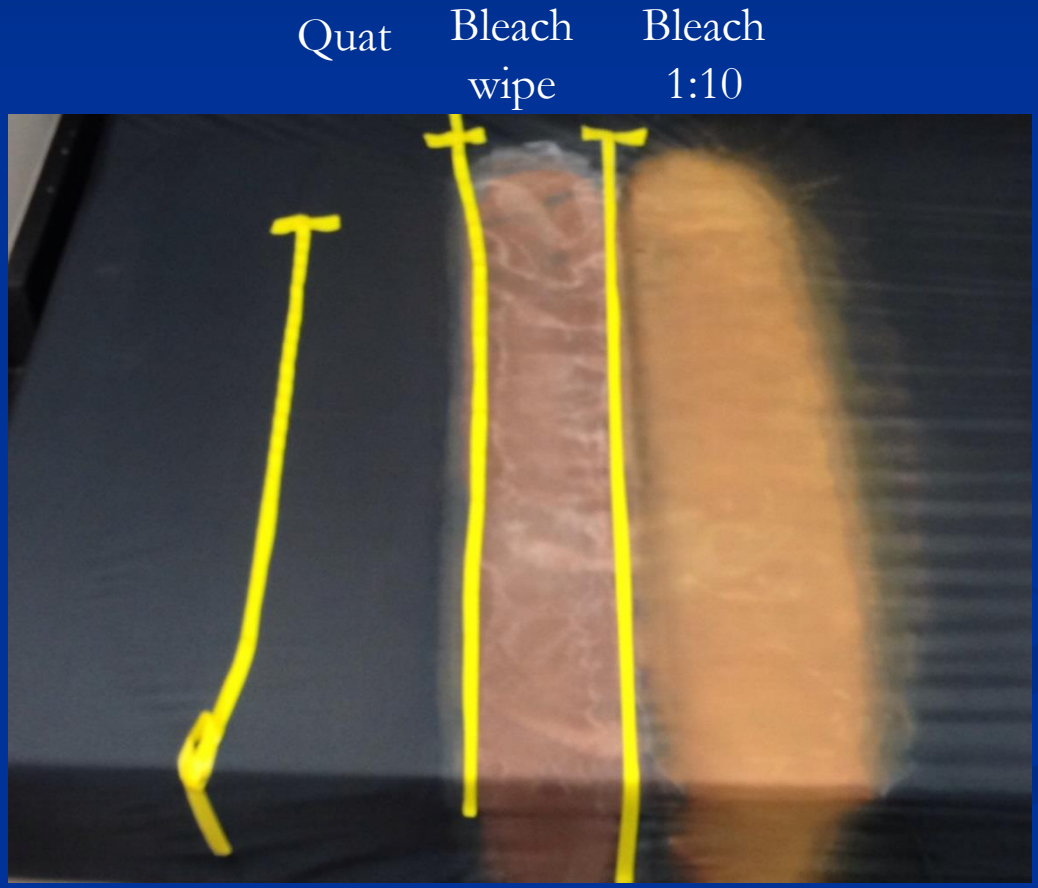
Infected Patient → Environment → Susceptible Patient

Decolonization ✗

Environmental Cleaning ✗

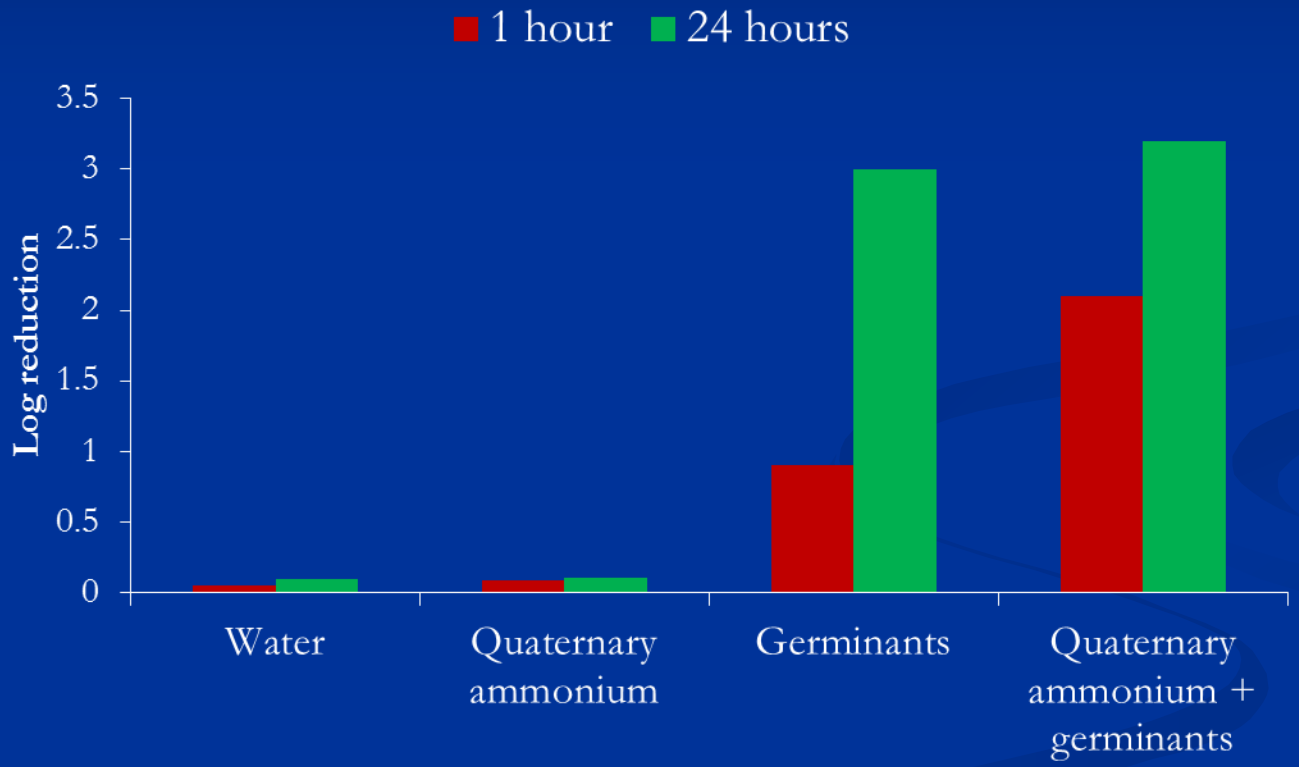
Use more bleach

Mattress exposed to bleach versus quaternary ammonium disinfectant



Cadnum JL, et al. SHEA 2017

Modify existing products: Germinate to Exterminate



Nerandzic M, et al. A Quaternary Ammonium Disinfectant Containing Germinants Reduces *C. difficile* Spores on Surfaces by Inducing Susceptibility to Environmental Stressors. Open Forum Inf Dis 2016;3:ofw196.

7. Are many patients with "healthcare-associated" CDI colonized on admission?

- Asymptomatic carriage of toxigenic *C. difficile* is common on hospital admission (4 to 15%) [1]
- A significant proportion of patients diagnosed with CDI are colonized on admission:
  - 25% of ICU patients [2]
  - 42% of stem cell transplant patients [3]
  - 21% of hospitalized patients [4]

1. Donskey CJ. Colonization versus carriage of *C. difficile*. Inf Dis Clin N Amer 2015; 2. Tschudin-Sutter S. Impact of toxigenic *C. difficile* colonization on the risk of subsequent CDI in ICU patients. ICHE 2015;36:1324-9; 3. Kamboj M. Transmission of *C. difficile* During Hospitalization for Allogeneic Stem Cell Transplant. ICHE 2016;37:37:8-15; 4. Blixt T. Asymptomatic carriers contribute to nosocomial CDI: A cohort study of 4508 patients. Gastroenterol 2017;152:1031-41

False-positive diagnosis of CDI in an asymptomatic carrier



6. What is the optimal strategy for diagnosis of CDI?

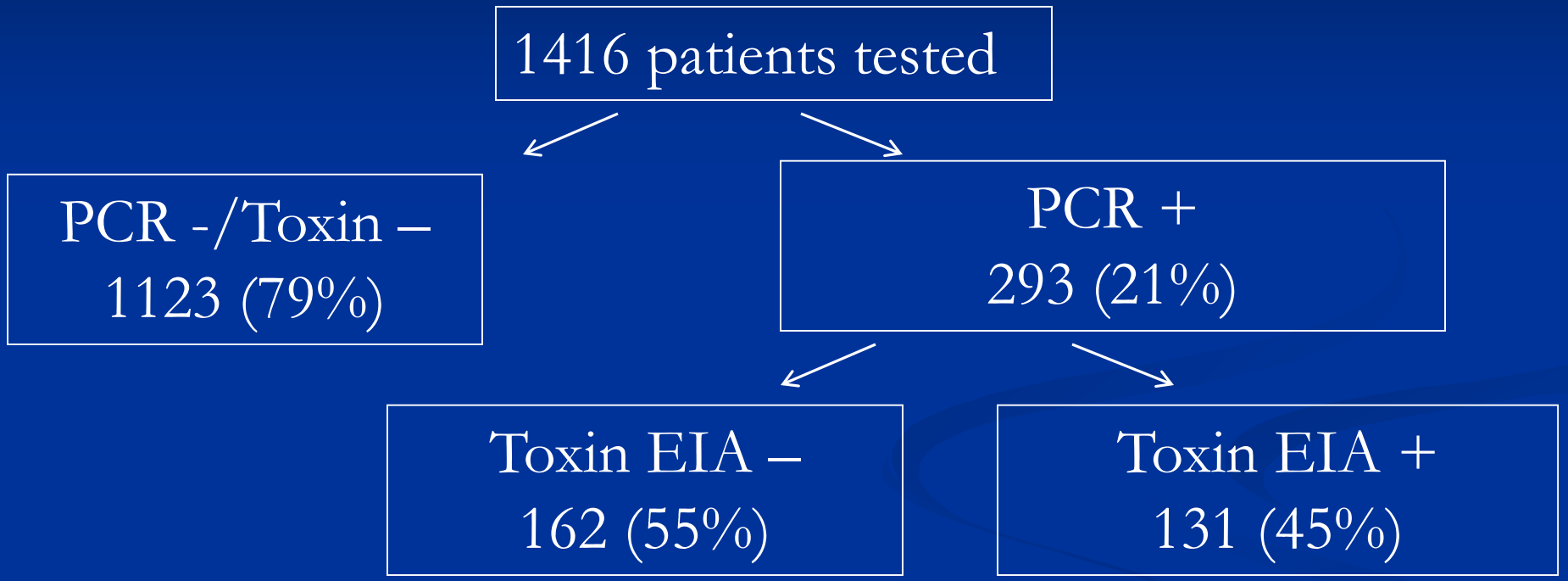




	UK - 2 or 3-stage algorithm	US - NAAT
Reject formed stool	Yes	Yes
# loose stools to trigger testing	≥1	≥3
Test unformed stools even if no CDI order	Yes	No
Avoid diagnosis of carriers as CDI	Toxin negative = carrier	Avoid inappropriate testing

Health Protection Agency, Dept of Health, CDI: how to deal with the problem. London: Dept of Health; 2008; Underdiagnosis of *C. difficile* across Europe. Lancet Infect Dis 2014;14:1208-19; Planche T, Wilcox MH. Diagnostic pitfalls in CDI. Infect Dis Clin N Am 2015;29:63-82

Over-diagnosis of CDI in the molecular test era[1]



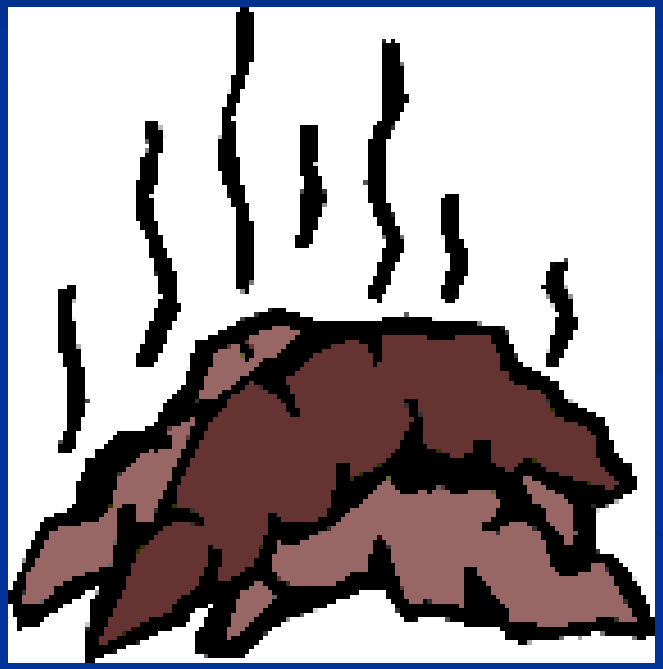
1. Polage CR. JAMA Intern Med 2015;175:1792; 2. Planche TD. Lancet Inf Dis 2013;13:936 (toxigenic culture +/toxin - patients did not differ from culture negative patients in mortality); 3. Longtin Y. Clin Inf Dis 2013;56:67-73 (cases detected by PCR had less complications than PCR +/toxin + cases); 4. de Jong E. Eur J Clin Microbiol Infect Dis 2012;31:2219-25 (PCR +/toxin - cases less likely to have wbc >15,000 than PCR +/EIA+ cases); 5. Polage CR. Diagnost Microbiol Infect Dis 2012;24:369-73; 6. Baker I. J Hosp Infect 2013;84:311-15 (positive EIA predicted death and prolonged diarrhea)

5. Can we apply the revolution in omics to control of *C. difficile*?

- Genomics
- Proteomics
- Metabolomics

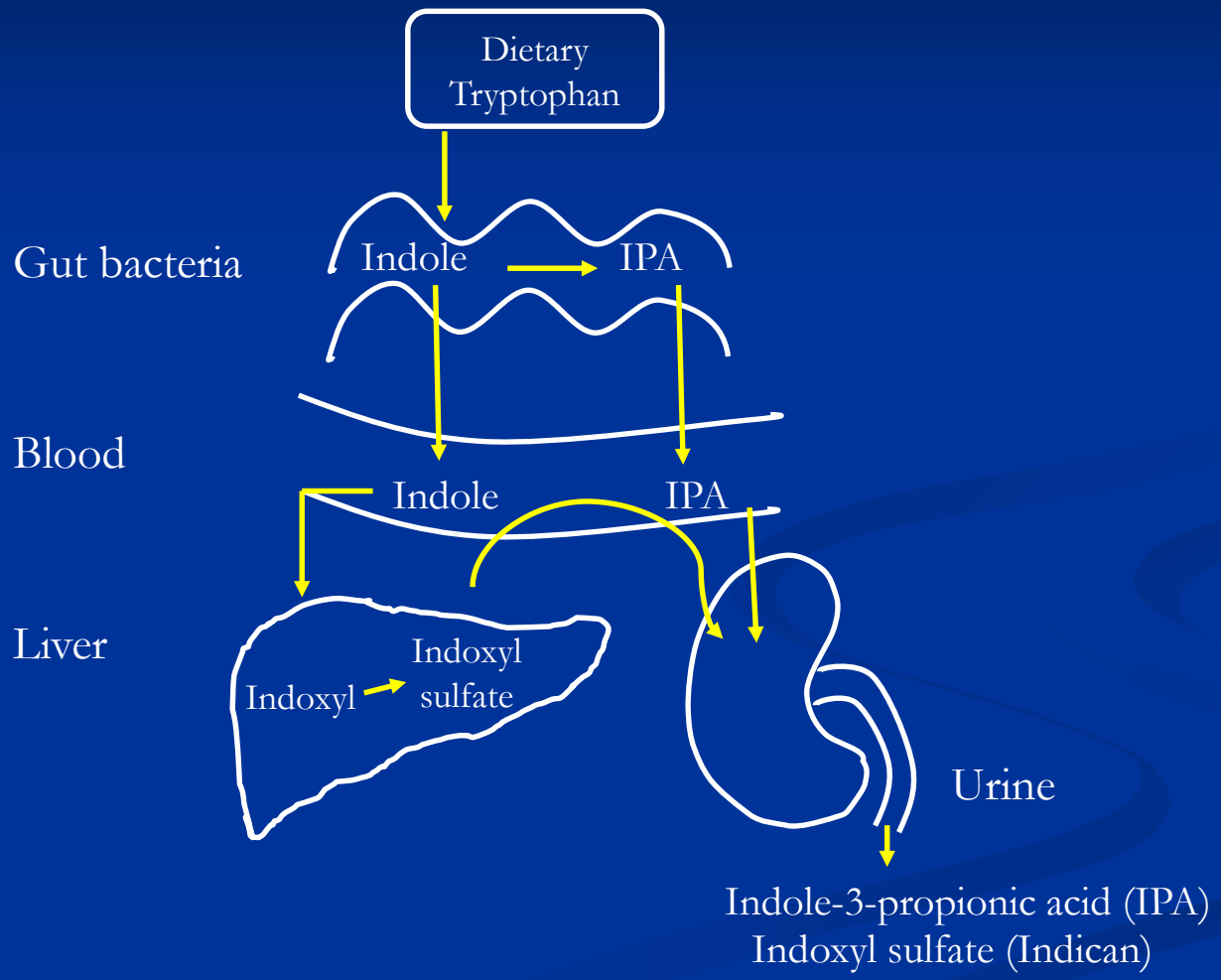
Kumar N, et al. Genome-Based Infection Tracking Reveals Dynamics of *C. difficile* Transmission and Disease Recurrence. Clin Infect Dis 2016;62:746-52; MacAogain M, et al. Whole-genome sequencing improves discrimination of relapse from reinfection and identifies transmission events among patients with recurrent *C. difficile* infections. J Hosp Infect 2015;90:108-16; Jump RLP, et al. Metabolomics analysis identifies intestinal microbiota-derived biomarkers of colonization resistance in clindamycin-treated mice. PLoS One 2014;9:e101267; Thieriot CM, et al. Antibiotic-induced shifts in the mouse gut microbiome and metabolome increase susceptibility to *C. difficile* infection. Nat Commun 2014;5:3114; Lichtman JS, et al. Host-Microbiota Interactions in the Pathogenesis of Antibiotic-Associated Diseases. Cell Reports 2016;14:1049-61

The problem



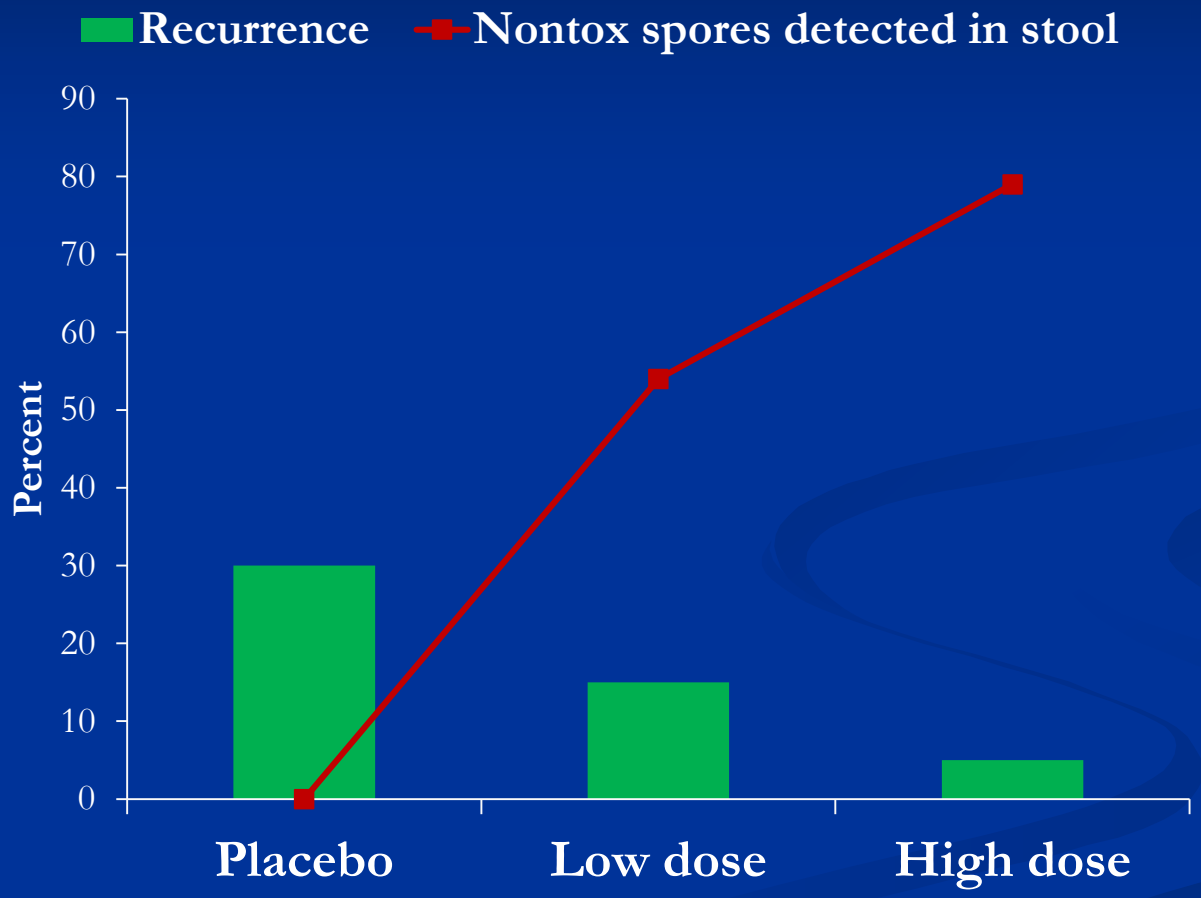
Jump RLP, et al. PLOS One 2014;9:e101267; Thieriot CM, et al. Nat Commun 2014;5:3114; Ng KM, et al. Nature 2013;502:96-9; Midtvedt T. Appl Environ Microbiol 1987;53:2866-71; Macfarlane GT. J AOAC Int 2012;95:50-60

Urine or serum biomarkers derived from intestinal microbiota



Obrenovich M, et al. A Targeted Metabolomics Analysis Identifies Intestinal Microbiota-Derived Urinary Biomarkers of Colonization Resistance in Mice. Antimicrob Agents Chemother in revision

Targeted bacteriotherapy: oral non-toxigenic *Clostridium difficile* spores



Gerding DN, et al. Administration of Spores of Nontoxigenic *C. difficile* Strain M3 for Prevention of Recurrent CDI: A Randomized Clinical Trial. JAMA 2015;313:1719-27.

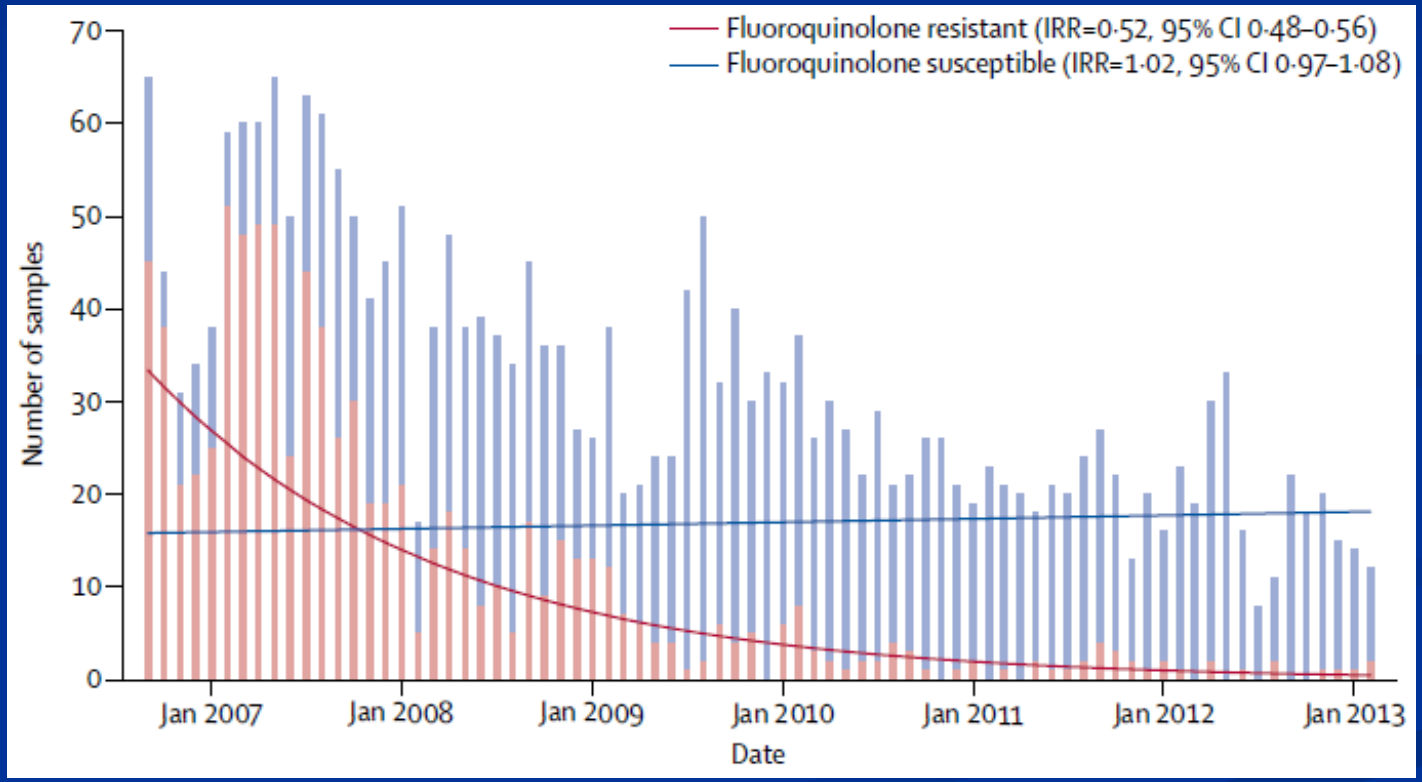
Chicago Anatomy, 2020



https://youtu.be/PNj35rNOlZY

4. Can we target stewardship interventions to control epidemic strains?

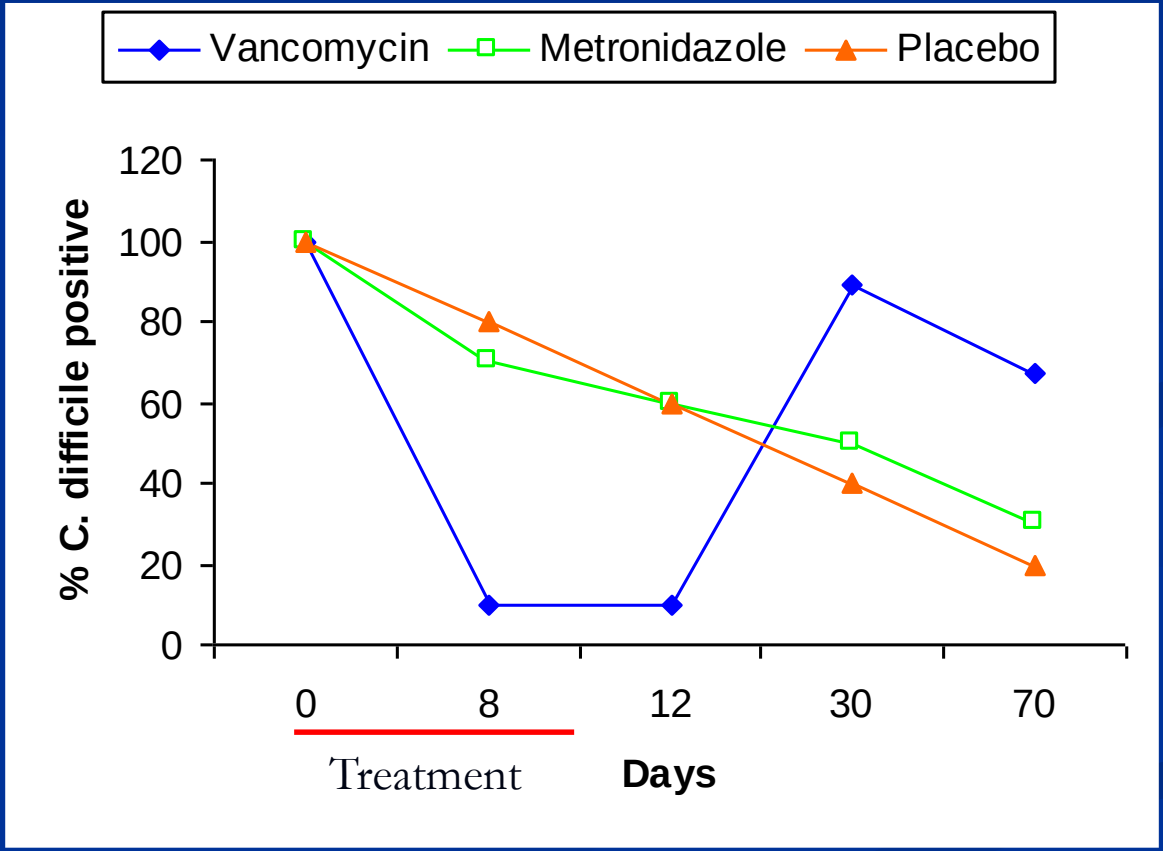
Fluoroquinolone restriction controlled fluoroquinolone-resistant *C. difficile*



Dingle K, et al. Effects of control interventions on CDI in England: an observational study. Lancet Infect Dis 2017;17:411-21; Donskey CJ. Fluoroquinolone restriction to control fluoroquinolone-resistant *C. difficile*. Lancet Infect Dis 2017;17

3. Can we develop improved methods to decolonize carriers?

Treatment of carriers with metronidazole vs vancomycin



Johnson S. Ann Intern Med 1992;117:297-302; Gebhart D. A modified bacteriocin specifically targeting *C difficile* prevents colonization of mice without affecting gut microbiota diversity. mBio 2015;6.pii: e02368-14

2. Can we continue to develop high-quality evidence to direct control efforts?

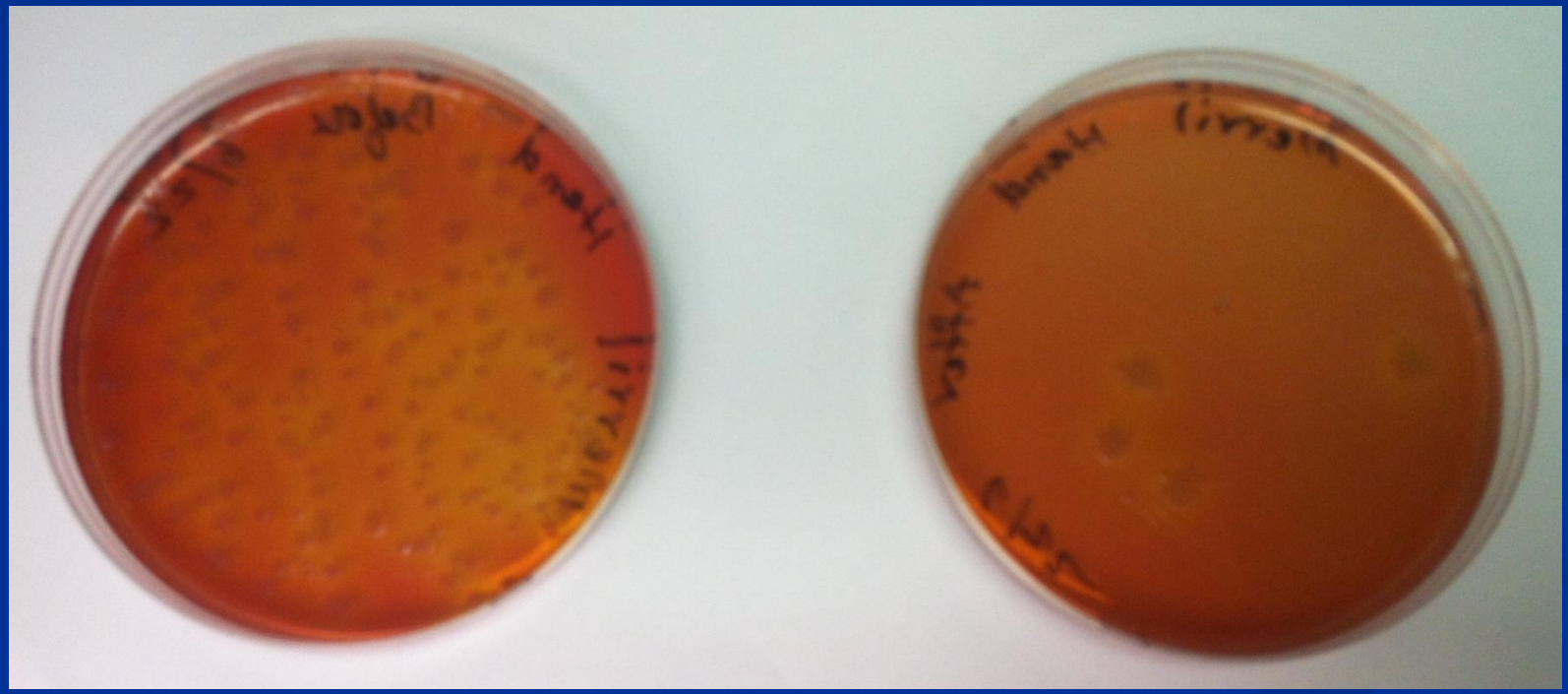
- Quasi-experimental studies
  - Multiple studies report reduced CDI with UV-C[1-7]
- Randomized trials
  - Cluster randomized, multicenter, crossover study[8]
    - No decrease in CDI with bleach + UV versus bleach alone
  - 16 hospital multicenter randomized trial[9]
    - Improved room disinfection but no decrease in CDI

1. Miller R. AJIC 2015;43:1350-3; 2. Levin J. AJIC 2013;41:746-8; 3. Nagaraja A. AJIC. 4. Vianna PG. AJIC 2016;44:299-303; 5. Haas JP. AJIC 2014;42:586-90; 6. Nagaraja A. AJIC 2015, July 6; 7. Pegues DA. ICHE 2017;38:39-44; 8. Anderson D, et al. Lancet 2017;389:805-17; 9. Ray AJ, et al. ICHE in press.

1. Can we find ways to involve patients in prevention efforts?

Patient hand washing to reduce spore contamination

Before hand wash **After hand wash**



Kundrapu S, et al. A Randomized Trial of Soap and Water Hand Wash Versus Alcohol Hand Rub for Removal of *C. difficile* Spores from Hands of Patients. ICHE 2014;35:204-6; Jury LA, et al. Effectiveness of routine patient bathing to reduce the burden of spores on skin of patients with CDI. ICHE 2011;32:181-4

Fear of failure: Engaging patients in stewardship after fecal transplant for CDI

- Of 73 patients receiving FMT, 25 (34%) consulted their FMT physicians regarding 43 antibiotic prescriptions
  - 26 (60%) deemed unnecessary
  - 7 (16%) necessary but alternative suggested
  - 10 (23%) necessary and appropriate
- 95% of recommendations followed

Hecker MT, et al. Fear of failure: Engaging patients in antimicrobial stewardship after fecal microbiota transplantation for recurrent CDI. ICHE 2017;38:127-129

Summary

- Current measures used to prevent healthcare-associated CDI are failing
- Eliminating healthcare-associated CDI will be difficult, but not impossible
- Beware of unintended consequences of trying to "get to zero"



https://youtu.be/oFcEZwLfHIc