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Clostridium difficile

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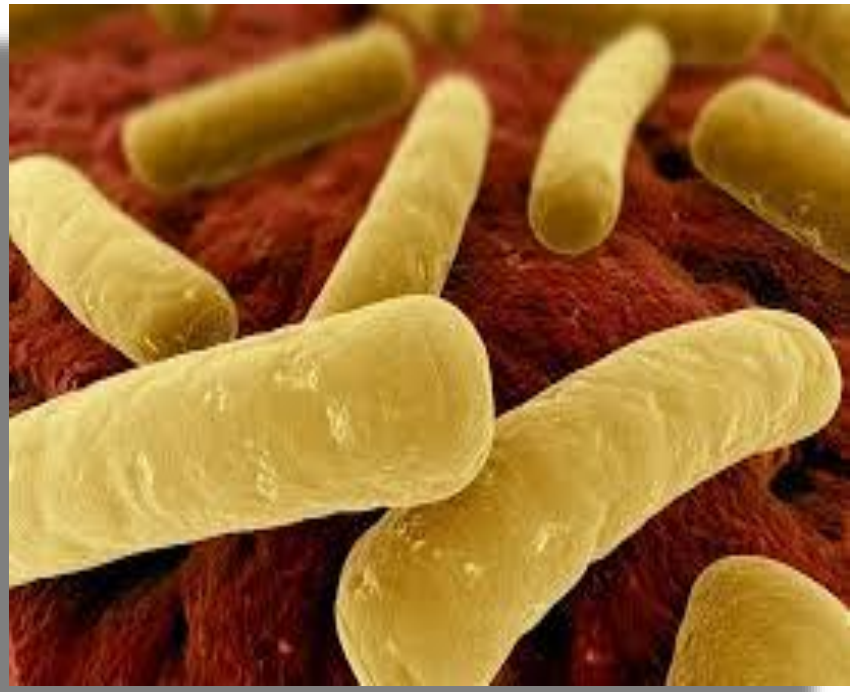
Disclosures

- Pesquisador Titular e Chefe do Laboratório de Epidemiologia e Bioestatística da Fundação Oswaldo Cruz - Bahia
- Coordenador do Centro de Pesquisas Clínicas da Fundação Irmã Dulce
- Investigador de protocolos de pesquisa clínica: MSD, Sanofi-Aventis, Pfizer, BMS, GSK, Takeda, Novartis e outras
- Consultor científico de comitês: Sanofi-Aventis, Pfizer e MSD
- Responsável por projetos de pesquisa financiados pelo CNPq e FAPESB
- Não possuo ações nem interesses comerciais em nenhuma empresa farmacêutica

Clostridium difficile: Summary

- ✓ **Biology**
- ✓ **Epidemiology**
- ✓ **Diagnosis and Treatment**
- ✓ **Control and Prevention**
- ✓ **Concluding Remarks**

Clostridium difficile:
Biology

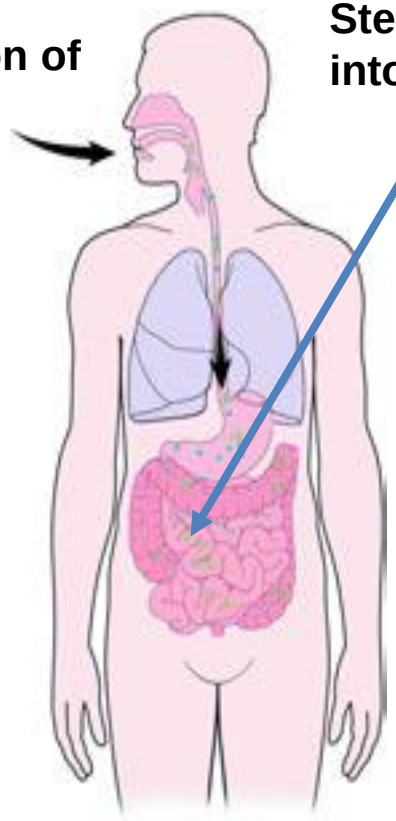


- Gram positive, toxin-producing, spore-forming anaerobic bacterium
- Opportunistic organism
- Patients with an alteration in intestinal microbiota
- Transmission via fecal-oral route

CDI: transmission through spores

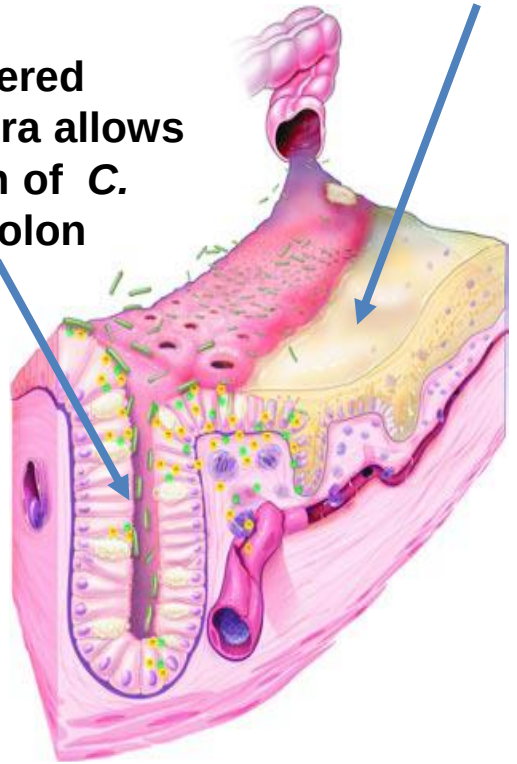
Step 1- Ingestion of spores

Step 2- Germination into vegetative cells



Step 3 - Altered intestine flora allows proliferation of *C. difficile* in colon

Step 4 . Toxin production leads to colon damage +/- pseudomembrane



What does *C. difficile* do to the gut?

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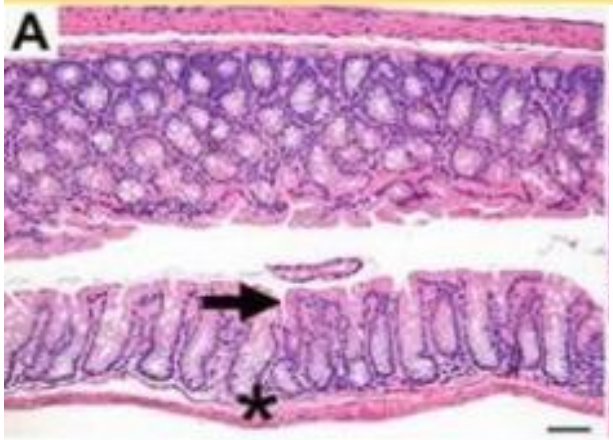
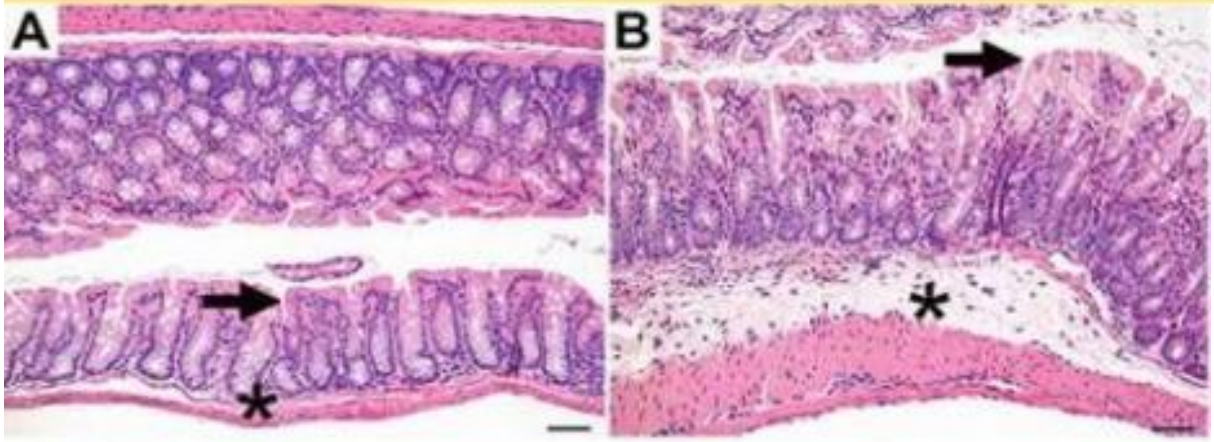


24 hours after exposure:
Cells of colon lining are normal

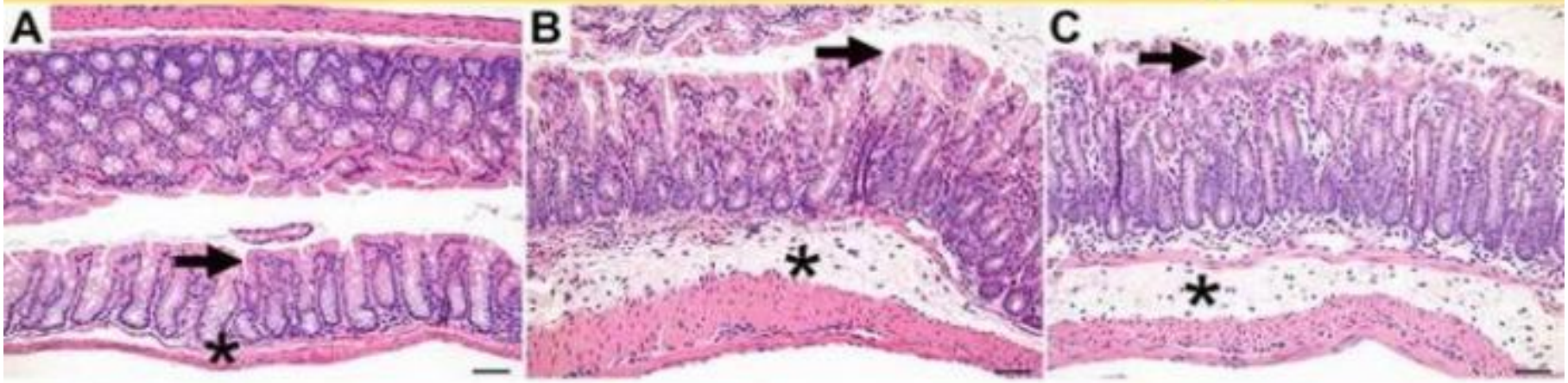
What does *C. difficile* do to the gut?



24 hours after exposure:
Cells of colon lining are normal

30 hours after exposure:
C. difficile toxin has started to damage cells, triggering inflammation & fluid buildup

What does *C. difficile* do to the gut?



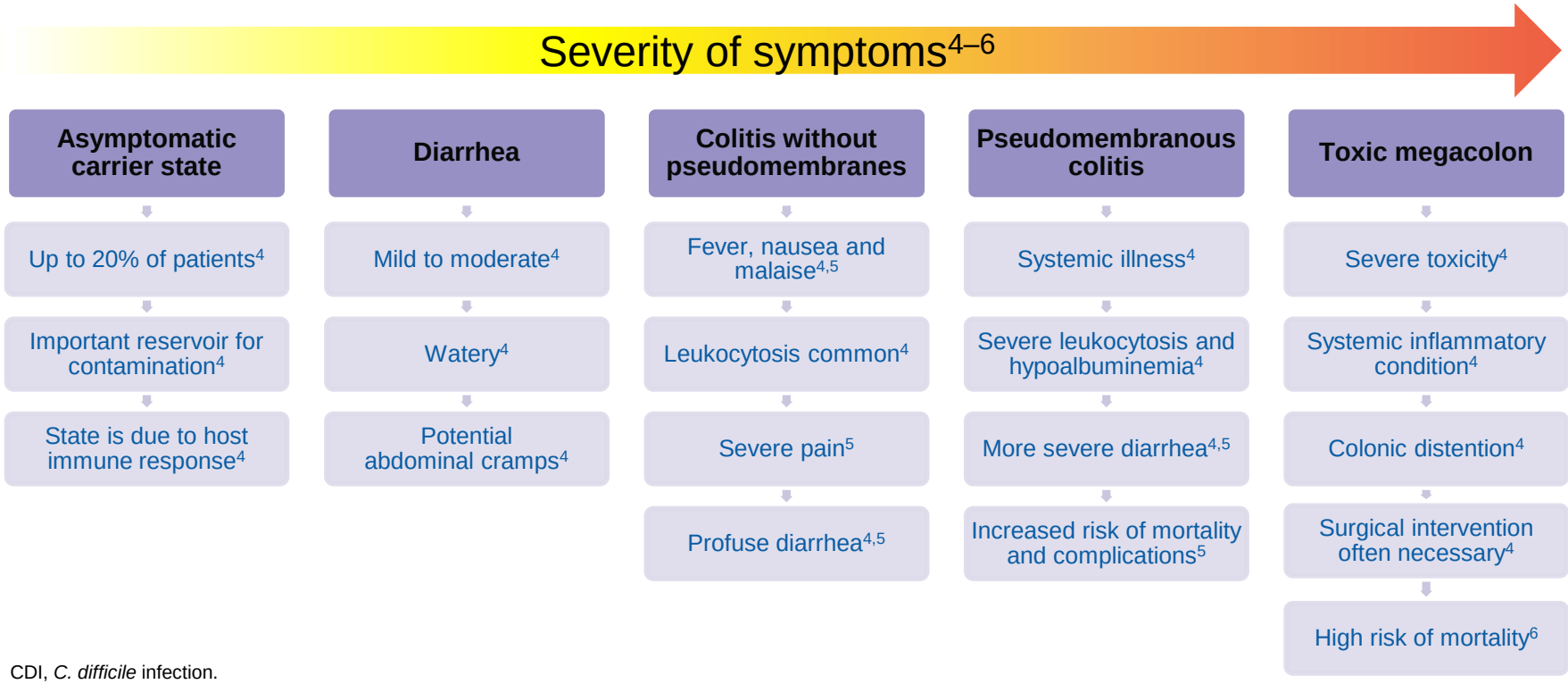
24 hours after exposure:
Cells of colon lining are normal

30 hours after exposure:
C. difficile toxin has started to damage cells, triggering inflammation & fluid buildup

36 hours after exposure:
Inflamed cells burst & die. *C. difficile* spores leave colon via diarrhea & await next host.

Clostridium difficile: Clinical Features

- *C. difficile* toxins cause the release of proinflammatory cytokines[1–3]
- This results in fluid secretion, inflammation, diarrhea and tissue damage

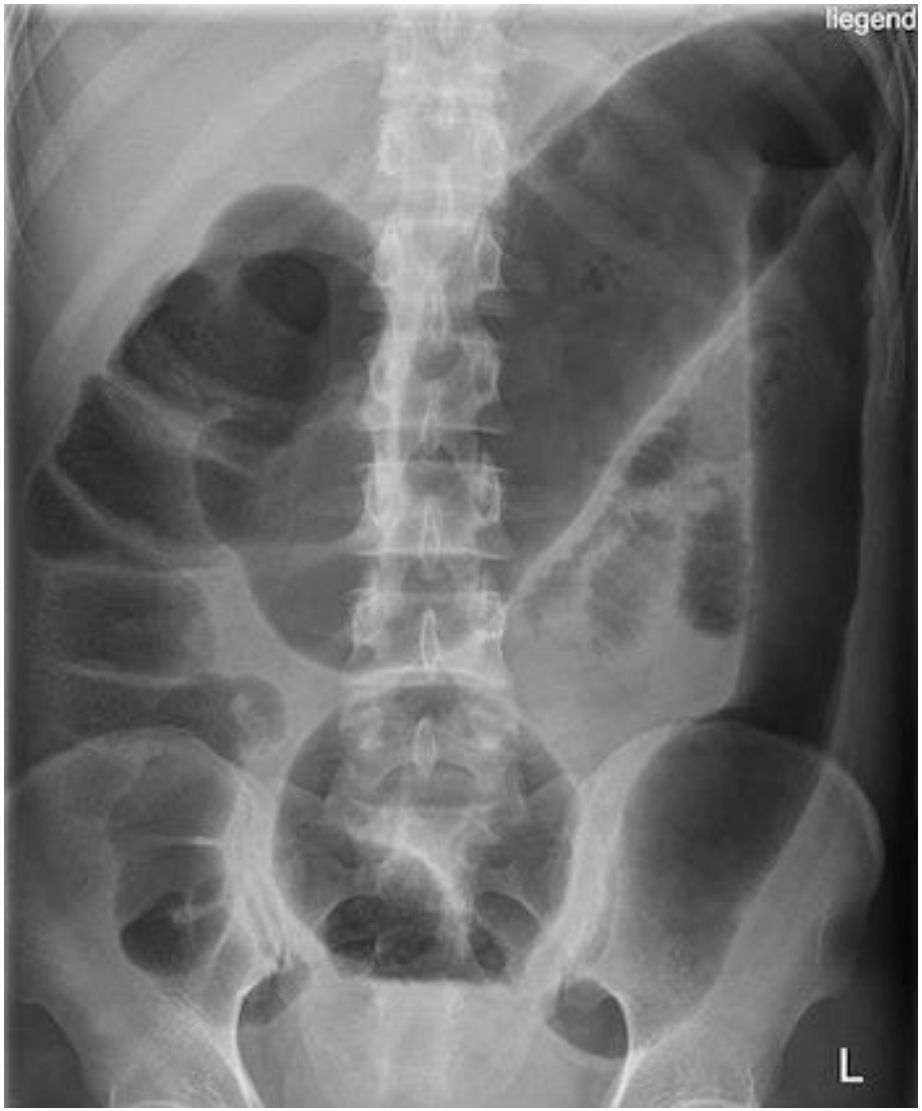


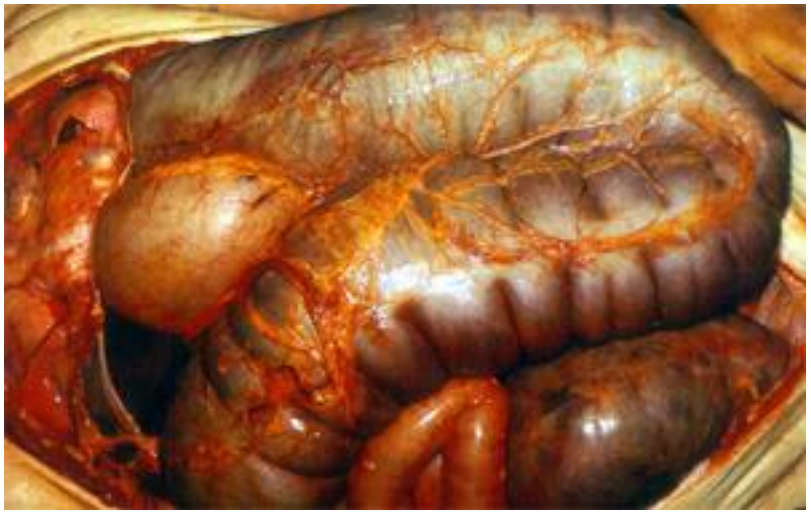
CDI, *C. difficile* infection.

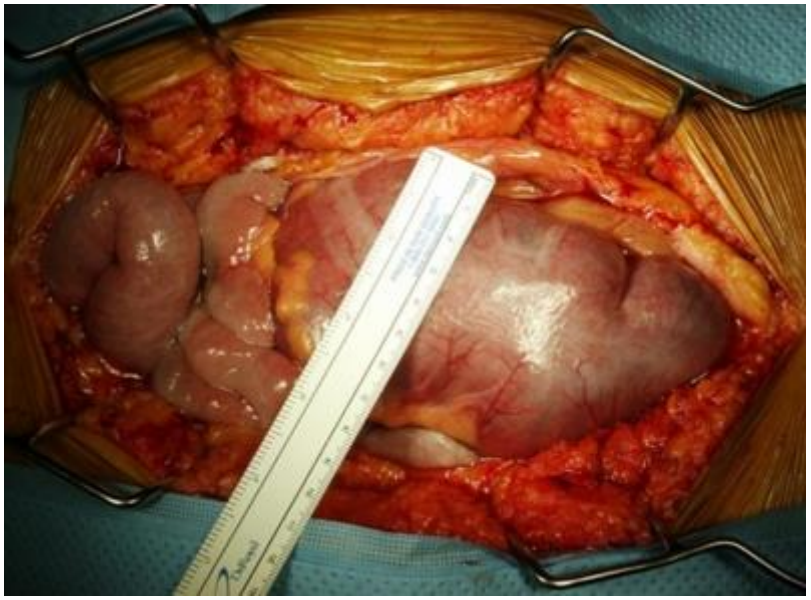
1. Pothoulakis C. Ann N Y Acad Sci 2000;915:347–56. 2. Mahida YR, et al. Gut 1996;38:337–47. 3. Voth DE & Ballard JD. Clin Microbiol Rev 2005;18:247–63. 4. Karmali S, et al. Can J Surg 2013;56:367–71. 5. Kelly CP, et al. N Engl J Med 1994;330:257–62. 6. Poutanen SM & Simor AE. CMAJ 2004;171:51–8.

Pseudomembranous colitis

Clostridium difficile







Clostridium difficile: Epidemiology

- Burden of CDI affect the patient and society alike
- > 300,000 hospitalizations/year
- $1.0 to $4.9 billion per year to the US health care system
- Large portion of this cost due to true increase in CDI incidence
- Some of the cost attributed to over-diagnosis of CDI

THE IMPACT OF *C. difficile* Infection (CDI)

CDI IS SERIOUS, DEADLY, AND EXPENSIVE

29,000
US deaths/year
within 30 days of diagnosis

1 in 5 (83,000)
recurrences
within 2 months

CDI adds up to:
12 days in the hospital
and
$27,160
per case
in direct costs

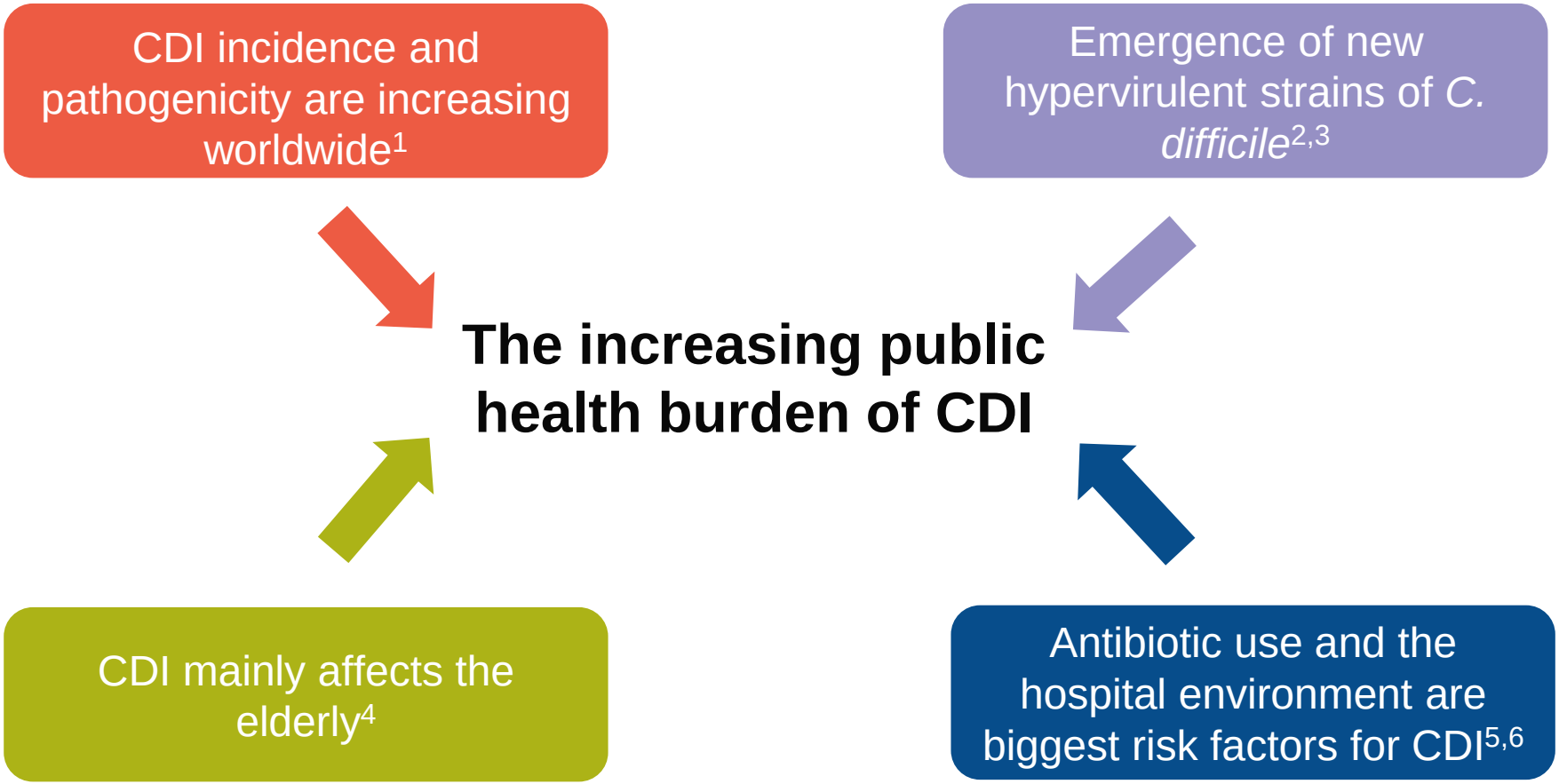
MORE THAN 1/3 OF CDI CASES ARE NOT ASSOCIATED WITH INPATIENT STAY

65%
at least one overnight, **INPATIENT** hospital stay

29%
OUTPATIENT healthcare exposures including doctor and dentist offices

6%
NOT HEALTHCARE-ASSOCIATED

CDI is a considerable public health burden



CDI, *C. difficile* infection.

1. Burke K & Lamont JT. Gut Liver 2014;8:1–6. 2. McDonald L, et al. NEJM 2005;353;2433–41. 3. Akerlund T, et al. J Clin Microbiol 2008;46:1530–3. 4. Lessa FC, et al. N Engl J Med 2015;372:825–35. 5. Shaughnessy MK, et al. Infect Control Hosp Epidemiol 2011;32:201–6. 6. Stevens V, et al. Clin Infect Dis 2011;53:42–8.

National and international bodies recognize CDI as an urgent priority

…an immediate public health threat that requires urgent and aggressive action[1]

C. difficile remains the most important cause of healthcare-associated diarrhea and is increasingly important as a community pathogen[2]

…overuse of antibiotics is contributing to the growing challenges posed by *Clostridium difficile* and other antibiotic-resistant bacteria in many hospitals[3]

CDI, *C. difficile* infection.

1. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. Available from: http://www.cdc.gov/drugresistance/threat-report-2013. Accessed Aug 2015. 2. Cohen SH, et al. Infect Control Hosp Epidemiol 2010;31:431–55. 3. European Centre for Disease Control and Prevention. Recommendations for future collaboration between the US and EU. Available from: http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf. Accessed Aug 2015.

Clostridium difficile
Most Common Risk Factor

- Patients currently receiving antibiotics (ABs) or who have received ABs in the past eight weeks
- Almost all ABs can increase the risk of CDI, frequently reported ABs include: 3rd gen. cephalosp., clindamycin, amoxicillin, fluoroquinolones

Antibiotic use is the greatest risk factor for CDI

Exposure to antibiotics increases risk of CDI

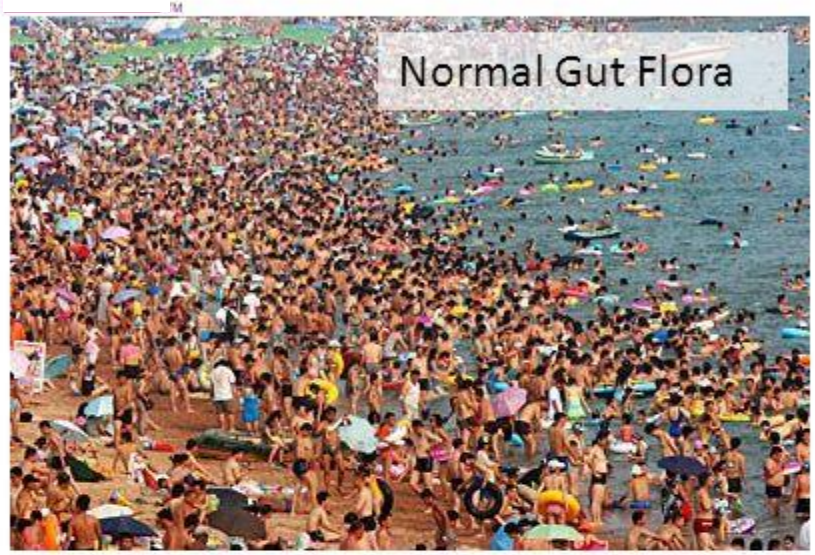
Antibiotic-associated CDI risk depends on:

- Number of antibiotics used[2]
- Days of exposure[2]
- Dose[2]
- Type of antibiotic[3]

CDI, *C. difficile* infection.

1. Shaughnessy MK, et al. Infect Control Hosp Epidemiol 2011;32:201–6. 2. Stevens V, et al. Clin Infect Dis 2011;53:42–8. 3. Aldeyab MA, et al. J Antimic Chemother 2012;67:2988–96.

Antibiotic-Associated Diarrhea:
Life's a Beach with *C. difficile*



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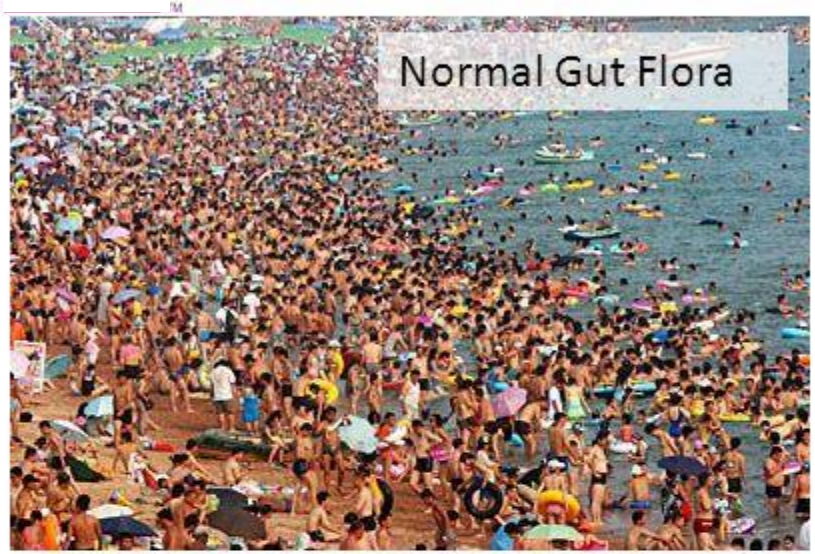

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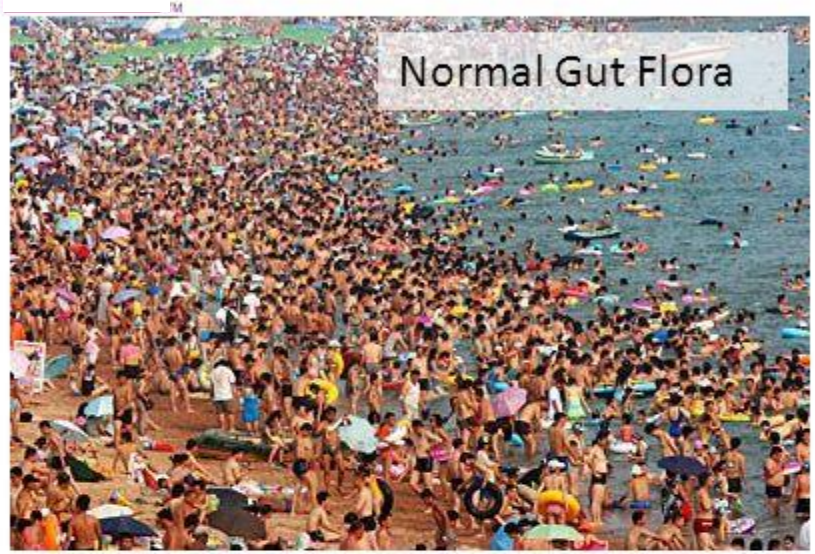

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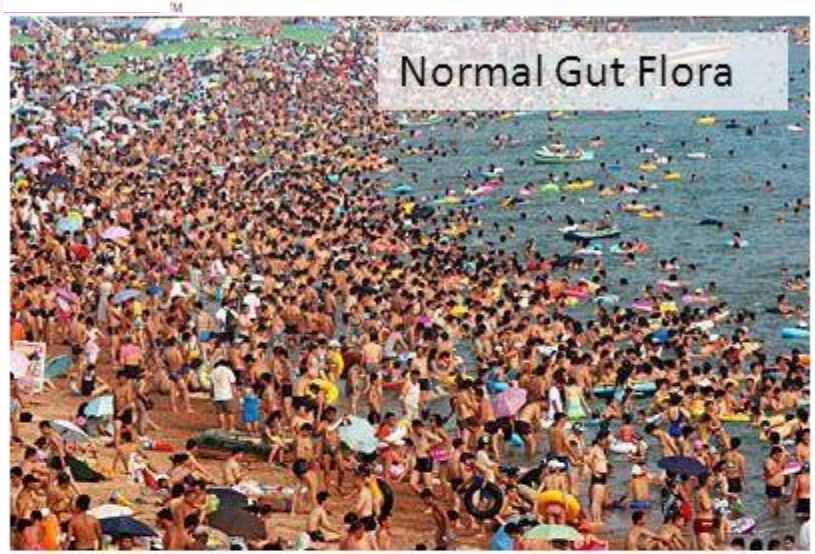


Clostridium difficile

Other Risk Factors

- Age >65 yrs
- Hospitalized or recently hospitalized
- Living in long-term care facilities

How to best diagnose CDI in a cost-effective manner?

Clostridium difficile: Diagnosis

- To treat CDI effectively diagnosis should be made rapidly
  - Based on CLINICAL + LABORATORY evidence of infection
- Testing only if patients have:
  - Clinical risk factors
  - Signs + Symptoms (most commonly diarrhea)

Clostridium difficile

Lab Testing

- Only on symptomatic patients
- Only on diarrheal stool

Clostridium difficile:
Lab Testing

COMMON CARRIERS	RATE
Healthy Adults	1 – 3%
People with recent healthcare exposure	15 – 25%
Residents of Long Term Care Facilities	20 - 51%
Newborn Infants	50 - 70%

- Treating carriers is ineffective
  - Contributes to antibiotic overuse
  - Puts individual patient at risk of contracting CDI
- Identification important for infection prevention

Clostridium difficile:
Lab Testing

1. Enzyme Immunoassay (EIA) for toxin A/B
2. Glutamate Dehydrogenase (GDH)
3. Nucleic Acid Amplification Tests (NAATs)
4. Toxigenic Culture (TC)
5. Cytotoxicin Neutralization (CTN) test

Clostridium difficile:
Enzyme Immunoassay (EIA) for toxin A/B

- Detection of CD toxins A and B by a solid-phase EIA
- Rapid turnaround (hours)
- Widely available and inexpensive
- Poor sensitivity: 45% to 60%
- High positive predicitve value: 90% to 100%
- No longer recommended as a stand-alone test

Clostridium difficile: Glutamate Dehydrogenase (GDH)

- Detects CD cell-wall-associated antigen
- Reported sensitivity: ~100%
- High negative predicitve value: ~100%
- Positive predicitve value: only 59%
- Rapid turnaround (hours)
- Widely available and affordable
- Recommended as a screening test for CDI diagnosis

Clostridium difficile:
Nucleic Acid Amplification Tests (NAATs)

- Detection of toxigenic CD strains based on DNA extraction
- Most target gene responsible for coding toxin B
- Sensitivity: 80% to 100% and Specificity: 87% to 99%
- Rapid turnaround (hours)
- Earlier detection of CDI than GDH and EIA
- Criticized for being overly sensitive (↑ incidence of CDI)
- False poditives can occur (detects gene not active toxin)

Clostridium difficile:
Best Standard Lab Test for Diagnosis of CDI

- There is no optimal test for *C. difficile*
- Each method has advantages & drawbacks

Method	Advantage	Drawback
GDH	Sensitive detection, shows bacteria are present	Doesn't say if *C. difficile* strain can produce toxin
Toxin A/B	Indicates active disease, Most clinically relevant	Will not identify carriers, may not detect all positive patients
Molecular	Sensitive detection of toxigenic bacteria	Doesn't say if toxin is present, does not differentiate active disease

Clostridium difficile: Treatment

- First step: stop the offending AB (when possible)
- Medical treatment of CDI varies based on:
  - Graded severity scale
  - Whether it is the first occurrence or recurrence of the disease
- Guidelines recommend the use of:
  - Metronidazole 500mg orally 3x/day for 10-14 days (mild to moderate disease)
  - Vancomycin 125mg orally 4x/day for 10-14 days (initial severe disease)

Which antibiotics are used to treat CDI?

Antibiotic	How long has it been used for?	Oral dose[1]	Absorption	Alternative dosing route
Metronidazole 	> 30 years	500 mg, 3 times daily	Well absorbed, but then thought to be secreted into colon through inflamed colonic mucosa, with secretion lessening as infection resolves[2]	Intravenous[2]
Vancomycin 	> 30 years	125 mg, 4 times daily	Minimally absorbed in most patients[3] → high concentration in gut	Rectal[4]
Fidaxomicin 	Since 2011	200 mg, 2 times daily	Minimally absorbed[5] → high concentration in gut Prolonged postantibiotic effect facilitates twice daily dosing[6]	—

Other antibiotics are sometimes used to treat CDI, including rifaximin, tigecycline, nitazoxanide, ramoplanin, teicoplanin, bacitracin and fusidic acid. Limited data are available to support the use of these antibiotics and they are not recommended in US or EU guidelines.[6]

CDI, *C. difficile* infection.

1. Debast SB, et al. Clin Microbiol Infect 2014;20:1–26. 2. Bolton RP, Culshaw, MA. Gut 1986;27:1169–72. 3. Vancomycin Summary of Product Characteristics. 4. Surawicz CM, et al. Am J Gastroenterol 2013;108:478–98. 5. Fidaxomicin Summary of Product Characteristics. 6. Mullane K. Ther Adv Chronic Dis 2014;5:69–84. Summaries of Product Characteristics available from: http://www.ema.europa.eu/ema/. Accessed Jan 2016.

Clostridium difficile:
Treatment of Recurrences

- High risk of recurrence: 25-30%
- Despite appropriate treatment
- Recurrences comprises both relapses and reinfection
- Difficult to distinguish
- Treatment of first recurrence is usually with the same AB
- However, Tx should also be guided by severity

Clostridium difficile: Treatment of Recurrences - Bacteriotherapy

- Bacteriotherapy with fecal microbiota transplantation (FMT)
- Has been shown to be an effective tx for recurrent CDI
- Stool from a healthy donor in the form of a liquid suspension is transplanted into patient's GI tract
  - Via nasogastric tube, nasojejunal tube, upper endoscopy, colonoscopy or enema, with similar success rates
- FMT rationale is to restore a healthier intestinal microbiota in patients with recurrent CDI
- It used to be considered a therapy of last resort for CDI, but it is becoming more widely practiced

Clostridium difficile - Treatment of Recurrences

Fecal Microbiota Transplantation (FMT)

Clostridium difficile - Treatment of Recurrences

Fecal Microbiota Transplantation (FMT)

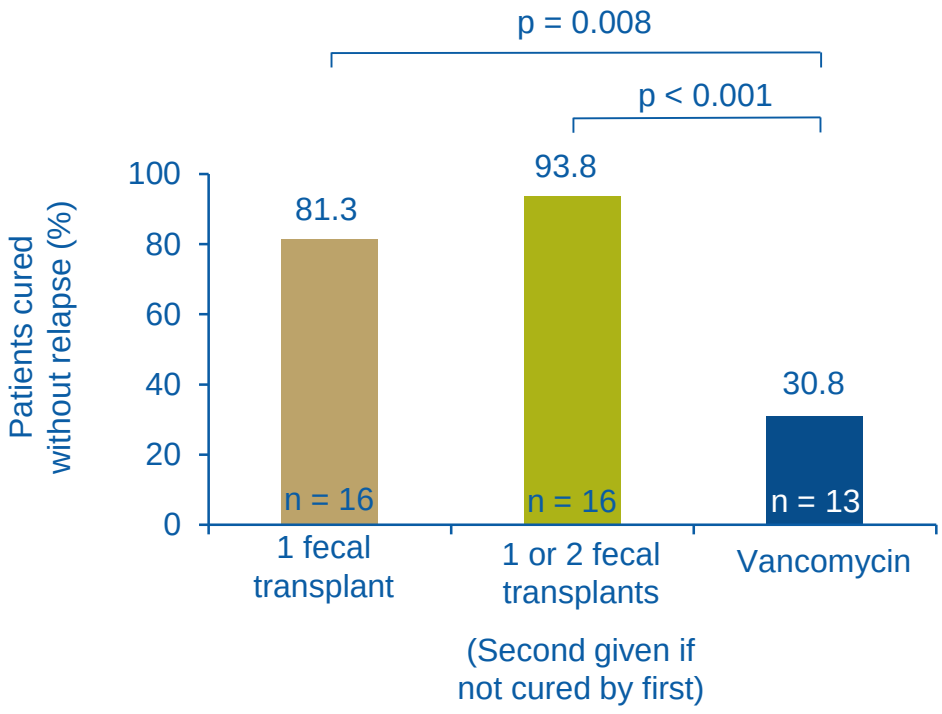
FMT aims to restore colonic microbiome and prevent recurrence

European guidelines
Consider FMT plus oral antibiotic treatment for multiple recurrent CDI[1]

US guidelines
Consider FMT at third recurrence, after trying a pulsed vancomycin regimen[2]

Data from FMT studies are encouraging but…

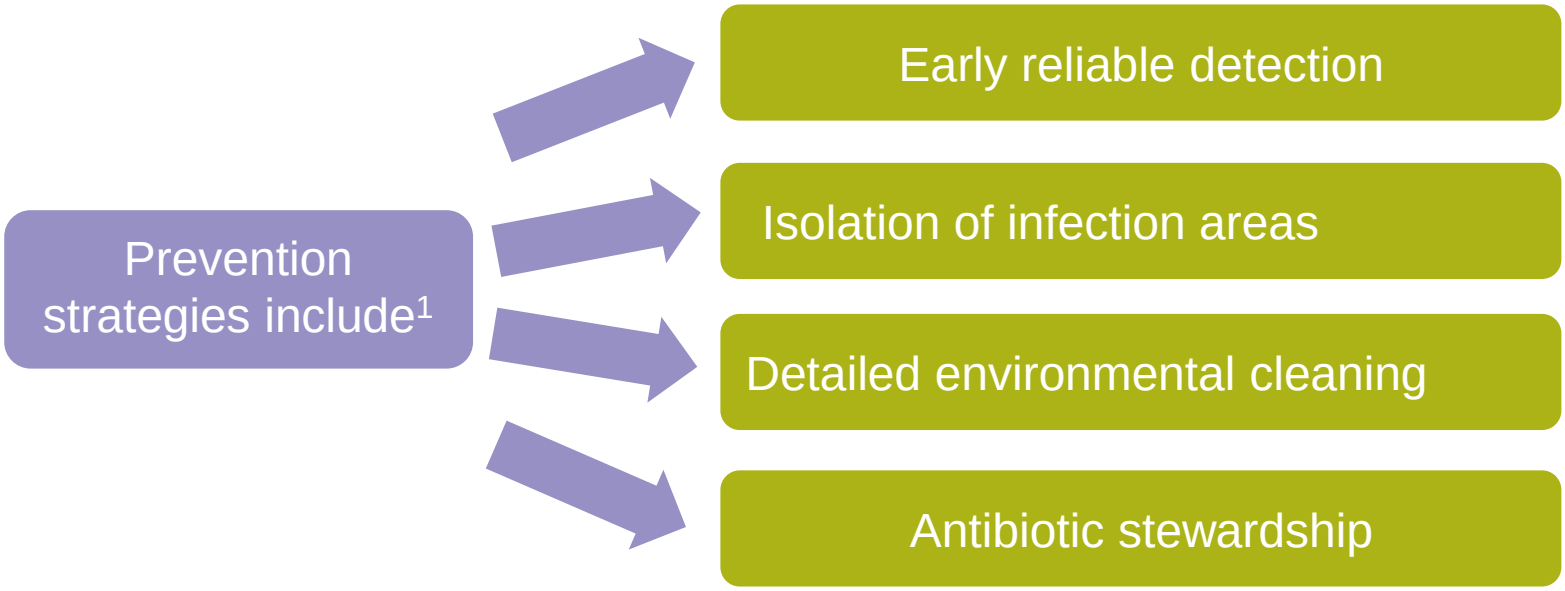
- Evidence mainly from uncontrolled case series[3]
- High proportion of patients achieve resolution of diarrhea
  - 90% in case series (N = 867)[4]
  - 81–94% in two small randomized, controlled trials (vs 26–31% with vancomycin)[5,6]



CDI, *C. difficile* infection; FMT, fecal microbiota transplant.

1. Debast SB, et al. Clin Microbiol Infect 2014;20:1–26. 2. Surawicz CM, et al. Am J Gastroenterol 2013;108:478–98. 3. Drekonja D, et al. Fecal microbiota transplantation for clostridium difficile infection: a systematic review of the evidence. Available from: http://www.hsrd.research.va.gov/publications/esp/FecalMicrobiota.pdf. Accessed Jan 2016. 4. Rossen NG, et al. World J Gastroenterol 2015;21:5359–71. 5. van Nood E, et al. N Engl J Med 2013;368:407–15. 6. Cammarota G, et al. Aliment Pharmacol Ther 2015;41:835–43.

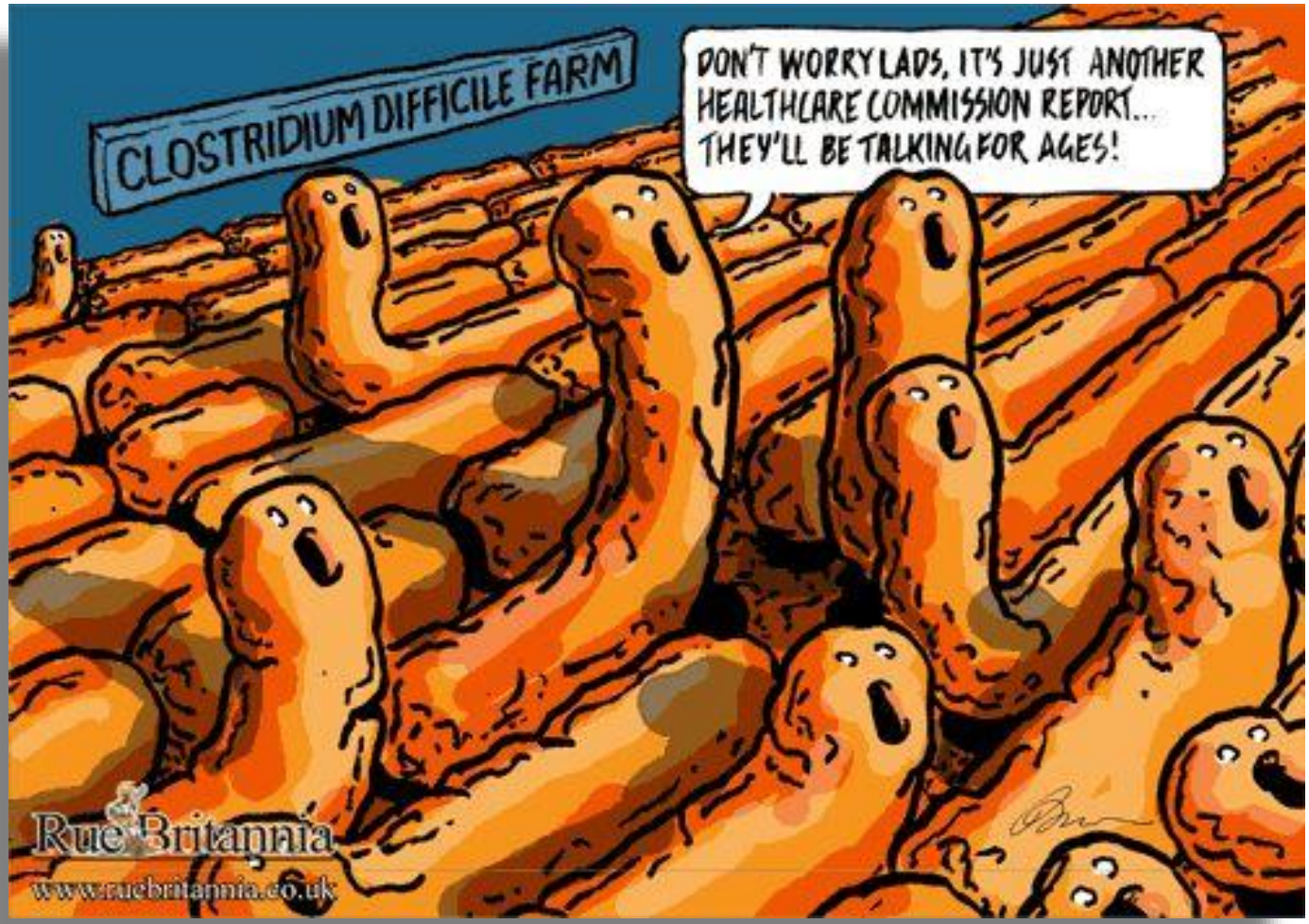
Preventing patients from contracting CDI is fundamental to effective infection management



- Infection control strategies have successfully decreased CDI rates by 20% in participating hospitals in the US[2]
- However, even the best infection control in hospitals cannot prevent CDI acquired outside hospitals, which may account for 50% of cases[2]

CDI, *C. difficile* infection.

1. Dubberke ER, et al. Infect Control Hosp Epidemiol 2014;35:628–45. 2. Centers for Disease Control and Prevention. Vital signs: preventing *Clostridium difficile* infections. Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6109a3.htm. Accessed Jan 2016.


CLOSTRIDIUM DIFFICILE FARM
DON'T WORRY LADS, IT'S JUST ANOTHER HEALTHCARE COMMISSION REPORT... THEY'LL BE TALKING FOR AGES!
Rue Britannia
www.ruebritannia.co.uk

No vaccine against CDI is currently licensed

"*C. difficile* vaccination could be cost-effective over a wide range of *C. difficile* risk, especially when being used post-CDI treatment to prevent recurrent disease."

Lee et al., Vaccine, 2010 Jul 19;28(32):5245-53

The potential value of *Clostridium difficile* vaccine: An economic computer simulation model.

30 October 2015 | News | By BioSpectrum Bureau

Global Clostridium difficile infections market to soar to $1.5 bn by 2024

Updated on 30 October 2015

The company's latest report states that this increase will be driven by the modest uptake of patent-protected, CDI-specific antibiotics and the arrival of novel non-antibiotic approaches to treat and prevent recurrent CDI

Bangalore: The global therapeutics and prophylactics market for Clostridium difficile infections (CDIs) will expand more than fourfold from $356.3 million in 2014 to over $1.5 billion by 2024, representing an impressive Compound Annual Growth Rate (CAGR) of 15.8%, according to research and consulting firm GlobalData.

The company's latest report states that this increase, which will occur across the seven major markets (7MM) of the US, France, Germany, Italy, Spain, the UK and Japan, will be driven by the modest uptake of patent-protected, CDI-

Clostridium difficile

Vaccines currently in clinical development for CDI

Vaccine product	Antigen	Formulation and schedule	Target population	Clinical status (ClinicalTrials.gov identifier)
Sanofi Pasteur *C. difficile* toxoid vaccine	Formalin-inactivated toxins A and B from VPI 10463	Intramuscular injection days 0, 7 and 30 Placebo comparator	Age >50 years	Phase III NCT01887912
Valneva Austria GmbH VLA84 *C. difficile* vaccine	Recombinant fusion protein of toxin A and B binding regions	+/– Aluminium adjuvant, intramuscular injection days 0, 7 and 28 Placebo comparator	Age 50–64 years Age >65 years	Phase II NCT02316470
Pfizer 3-dose *C. difficile* vaccine	Genetically modified and chemically treated recombinant vaccine	+/– Adjuvant, intramuscular injection days 1, 8 and 30 Placebo comparator	Age 50–85 years	Phase II NCT02117570 and NCT02561195

Kociolek, L. K. & Gerding, D. N. (2016) Breakthroughs in the treatment and prevention of *Clostridium difficile* infection *Nat. Rev. Gastroenterol. Hepatol.* doi:10.1038/nrgastro.2015.220

Obrigado!