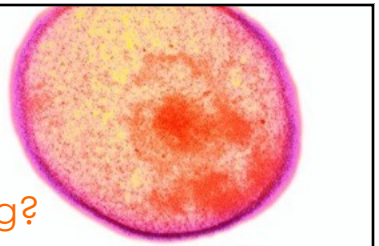
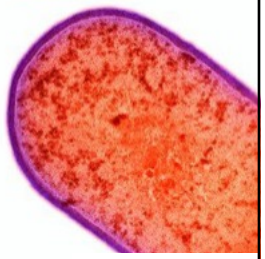
Clostridium difficile Asymptomatic Carriers – The Hidden Part of the Iceberg?
Dr. Yves Longtin, McGill University, Montreal
A Webber Training Teleclass

Clostridium difficile Asymptomatic Carriers – The Hidden Part of the Iceberg?





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Hosted by Paul Webber
paul@webbertraining.com

Disclosures

- Research Funding
  - Merck Canada, BD Diagnostics, AMD Medical, Canadian Institute for Health Research
- Speaker's Bureau for
  - Merck Canada, Pfizer
- Salary Support from the *Fonds de Recherche en Santé du Québec*

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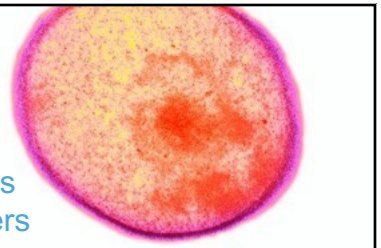
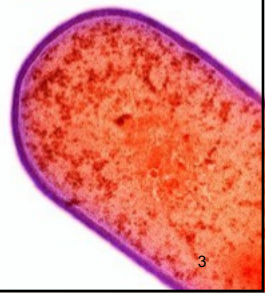
OBJECTIVES

① Review the epidemiology of C. difficile infections with emphasis on the role of asymptomatic carriers

② Explore novel avenues to prevent C. difficile infections and their potential impact on hospital burden

③ Provide additional insight





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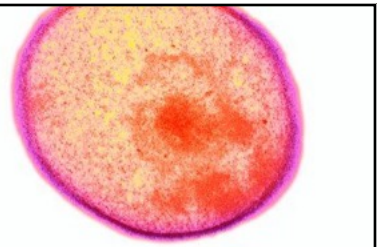
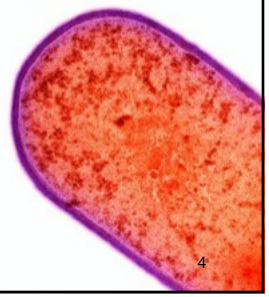
3

BACKGROUND





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4

Background

- *C. difficile* infections have become the most frequent cause of healthcare-associated infection in the USA[1-3]
- 500,000 cases per year[2]
- 29,000 deaths[2]
- $4.8 billion in excess medical costs[2]
- One of only 3 microorganisms designated as an "Urgent threat" to the population by CDC[3]

1. Leffler DA et al. N Engl J Med 2015;372:1539-48.
2. Lessa FC, et al. N Engl J Med 2015;372:825-34.
3. CDC ARO report Sept. 16, 2013.

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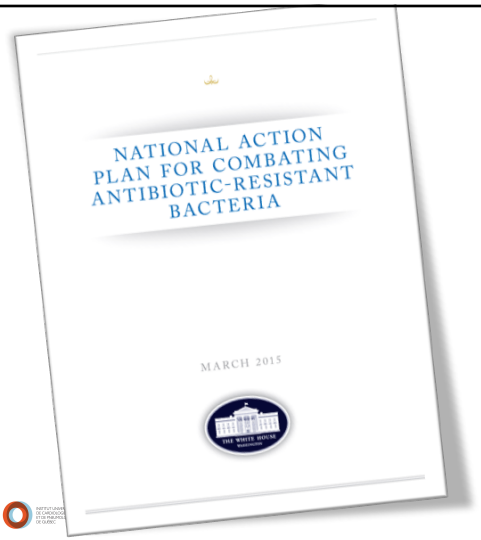

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NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria
By 2020, the United States will:
For CDC Recognized Urgent Threats:
Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.
Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.

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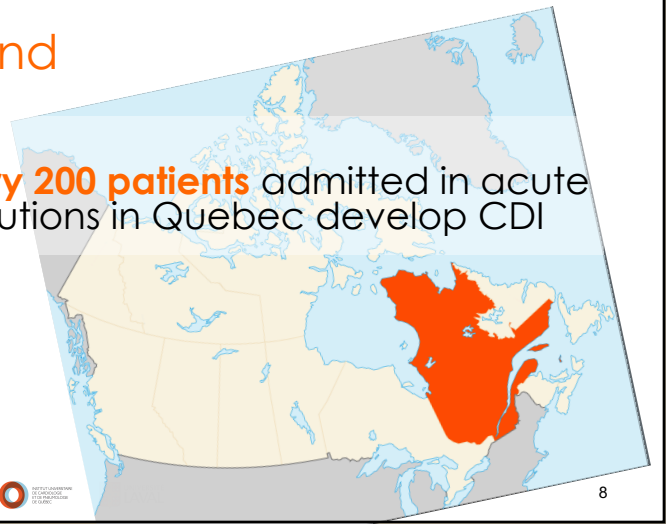
7

Background

1 out of every 200 patients admitted in acute care institutions in Quebec develop CDI



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Prevention of CDI

- Current recommendations relatively unchanged for more than 20 years[1,2]
  - i.e. prior to the onset of the NAP1 epidemic

1. Dubberke ER, et al. Strategies to prevent Clostridium difficile infections: 2014 update. Infect Control Hosp Epidemiol 2014;35 Suppl 2:S48-65.
2. Vonberg RP, et al. Infection control measures to limit the spread of Clostridium difficile. Clin Microbiol Infect 2008;14 Suppl 5:2-20.

Guidelines

- Measures recommended to prevent CDI
  - **Contact Precautions** for symptomatic patients
    - Only for duration of diarrhea
  - **Hand hygiene**
    - Hand washing in outbreak setting
  - **Environmental cleaning** with chlorine-based agent
  - **Optimization of antimicrobial use**
    - Minimize duration
    - Avoid high-risk drugs

Cohen, S.H., et al., Infect Control Hosp Epidemiol, 2010. **31**(5): p. 431-55.

Background

- Current preventive recommendations focus mainly on patients with CDI, but are insufficient to interrupt the dissemination of this microorganism in healthcare settings[1,2]

1. Dubberke ER, et al. Strategies to prevent Clostridium difficile infections: 2014 update. Infect Control Hosp Epidemiol 2014;35 Suppl 2:S48-65.
2. Vonberg RP, et al. Infection control measures to limit the spread of Clostridium difficile. Clin Microbiol Infect 2008;14 Suppl 5:2-20.

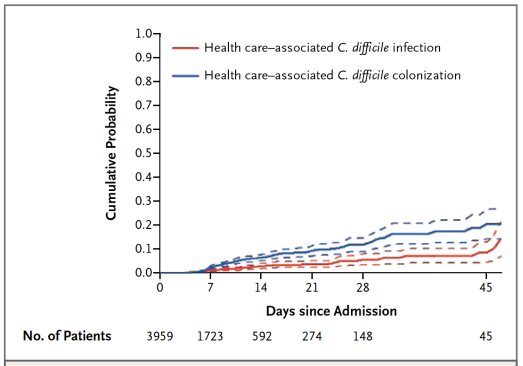
Cross-transmission in Acute Care

Asymptomatic colonization is frequent
during hospitalization in acute care settings

- **9.4%** (54/569) of patients during their hospital stay[1]
- **17%** acquired *C.difficile* during their hospitalization[2]
- **12%** of patients admitted on a geriatric unit[3]
- **8%** (6/76) during their hospital stay[4]
- **21%** (83/399) acquired *C. difficile* during their stay. A third progressed to CDI[5]
- Approximately **10%** after 21 days of hospitalisation[6]

1. Clabots CR. J Infect Dis 1992;166:561-7.
2. Kyne L. N Engl J Med 2000;342:390-7.
3. Rudensky B. Postgrad Med J 1993;69:45-7.
4. Bliss DZ. Ann Intern Med 1998;129:1012-9
5. McFarland LV. N Engl J Med 1989;320:204-10.
6. Loo V et al. N Engl J Med 365;18: 1693-1703

Ongoing Transmission in Quebec Hospitals



Loo V et al. N Engl J Med. 2011 Nov 3;365(18):1693-703.

Figure 2. Times to Health Care–Associated *Clostridium difficile* Infection and Colonization during Hospitalization.
Analyses of the cumulative probability of *C. difficile* infection or colonization excluded the 184 patients with *C. difficile* colonization on admission. The dashed lines indicate 95% confidence intervals.

Ongoing transmission DESPITE isolation of patients with CDI

Source of residual transmission?

1. CDI "breakthrough" transmission?
2. CD carriers?
3. Healthcare workers?
4. Food?

13

INFECTION CONTROL & HOSPITAL EPIDEMIOLOGY DECEMBER 2016, VOL. 37, NO. 12

ORIGINAL ARTICLE

An Evaluation of Food as a Potential Source for *Clostridium dif* Acquisition in Hospitalized Patients

Jennie H. Kwon, MSCI;[1] Cristina Lanzas, DVM, PhD;[2] Kimberly A. Reske, MPH;[1] Tiffany Hink, BS;[1] Sondra M. Sc
Kerry M. Bommarito, PhD;[1] Carey-Ann D. Burnham, PhD;[3] Erik R. Dubberke, MD, MSPH[1]

STOCHASTIC MODELING: FOOD WOULD BE RESPONSIBLE FOR < 1 NEWLY COLONIZED PATIENT /1,000 ADMS.

TABLE 3. Types of Food Positive for *Clostridium difficile*, by Food Type, for 910 Meals

Food item	Total	*C. difficile*, n (%)
Meat	308	0
Poultry	142	0
Fruit	179	0
Vegetables	455	1 (<1)[a]
Nuts	1	0
Dairy/eggs	210	0
Bread/grains	376	1 (<1)[a]
Other[b]	200	1 (1)[c]

NOT
tha
san
[a]Th
con
[b]Fo
[c]Ge

2 patients had food + for CD
1 of 2 patients tested for CD at d/c and found negative

Kwon JH et al. Infect Control Hosp Epidemiol 2016;37:1401–1407

14

Asymptomatic Carriers

SHEA The Society for Healthcare Epidemiology of America

Asymptomatically colonized patients who have not had CDI can shed *C. difficile* spores, but the number of spores and degree of contamination is not as great as for patients with active CDI

Dubberke ER, et al. Strategies to prevent Clostridium difficile infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35 Suppl 2:S48-65.

IDSA

There are insufficient data to recommend screening for asymptomatic carriage and placing asymptomatic carriers on contact precautions (no recommendation).

McDonald LC et al. Clin Infect Dis. 2018 Feb 15. doi: 10.1093/cid/cix1085.

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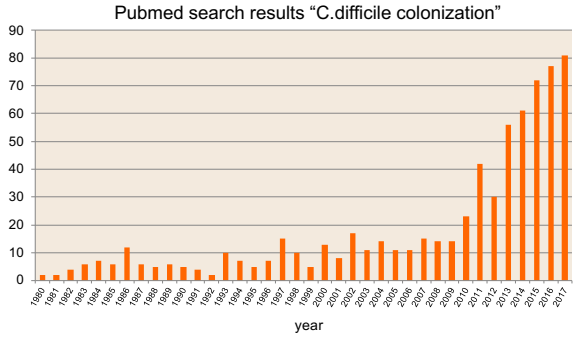
15

INCREASING INTEREST ON C. *DIFFICILE* COLONIZATION



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16

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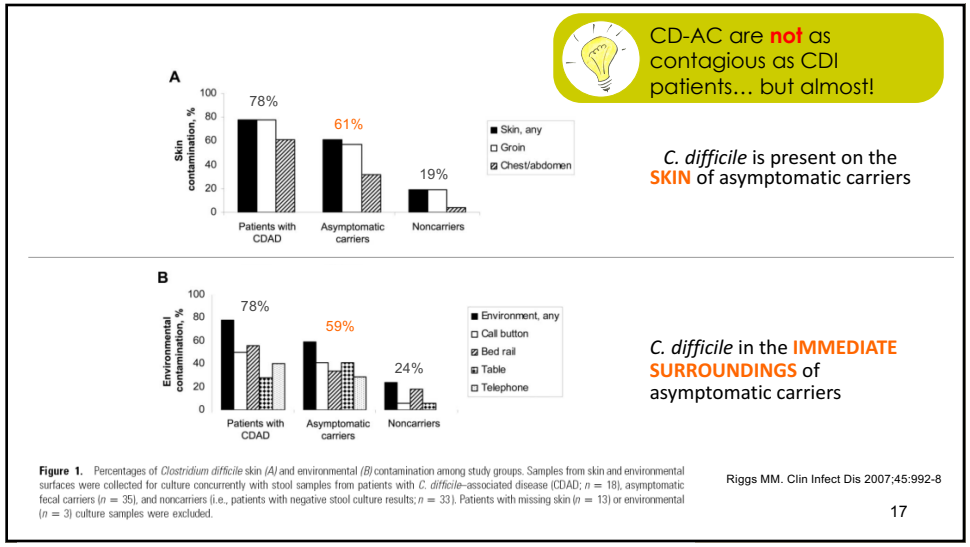

Figure 1. Percentages of *Clostridium difficile* skin *(A)* and environmental *(B)* contamination among study groups. Samples from skin and environmental surfaces were collected for culture concurrently with stool samples from patients with *C. difficile*–associated disease (CDAD; $n = 18$), asymptomatic fecal carriers ($n = 35$), and noncarriers (i.e., patients with negative stool culture results; $n = 33$). Patients with missing skin ($n = 13$) or environmental ($n = 3$) culture samples were excluded.

Riggs MM. Clin Infect Dis 2007;45:992-8

17

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How numerous are CD-AC?

- A point-prevalence of patients hospitalized in a LTCF during an epidemic showed a very high prevalence (35/73) of asymptomatic carriers and CDAD patients (5/73) (A:S ratio: 7:1)[1]
- A prevalence study of patients hospit. for >7days in a gen. hospital 9 were symptomatic and 51 were asymptomatic (A:S ratio 5:1)[2]
- In a large multicentric study in Quebec, there were 192 CDI cases (75 on admission and 117 after admission) and 307 CD-AC (184 on admission and 123 after admission) (A:S ratio: 1.5:1)[3]

1. Riggs MM, Clin Infect Dis 2007;45:992-8.
2. Johnson S et al. Lancet 1990;336:97-100.
3. Loo V et al. N Engl J Med. 2011 Nov 3;365(18):1693-703

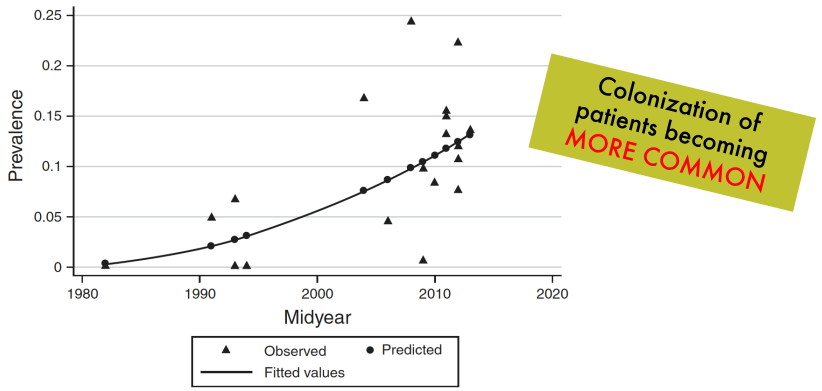
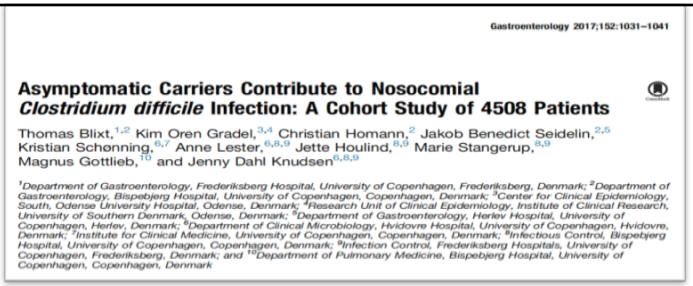


Figure 2. Toxinogenic *C. difficile* colonization trends over time. Observed (triangles) and fitted (circles) prevalence estimates, by study midyear.

Zacharioudakis IM, et al. Am J Gastroenterol **2015**; 110(3): 381-90



Gastroenterology 2017;152:1031–1041

Asymptomatic Carriers Contribute to Nosocomial *Clostridium difficile* Infection: A Cohort Study of 4508 Patients

Thomas Blixt,[1,2] Kim Oren Gradel,[3,4] Christian Homann,[2] Jakob Benedict Seidelin,[2,5] Kristian Schønning,[6,7] Anne Lester,[6,8,9] Jette Houlind,[8,9] Marie Stangerup,[8,9] Magnus Gottlieb,[10] and Jenny Dahl Knudsen[6,8,9]

[1]Department of Gastroenterology, Frederiksberg Hospital, University of Copenhagen, Frederiksberg, Denmark; [2]Department of Gastroenterology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark; [3]Center for Clinical Epidemiology, South, Odense University Hospital, Odense, Denmark; [4]Research Unit of Clinical Epidemiology, Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [5]Department of Gastroenterology, Herlev Hospital, University of Copenhagen, Herlev, Denmark; [6]Department of Clinical Microbiology, Hvidovre Hospital, University of Copenhagen, Hvidovre, Denmark; [7]Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [8]Infectious Control, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark; [9]Infection Control, Frederiksberg Hospitals, University of Copenhagen, Frederiksberg, Denmark; and [10]Department of Pulmonary Medicine, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

C. difficile carriers can cause CDI in other patients

Blixt T et al. Gastroenterology. 2017 Apr;152(5):1031-1041.

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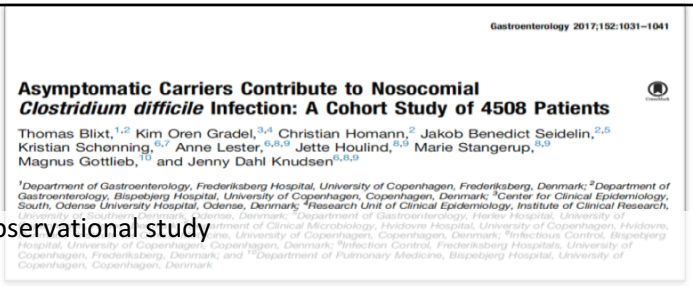
21



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- Observational study
- 8 wards in 2 hospitals in Copenhagen
- CDI incidence 2-2.5 per 1,000 patient-days
- Private rooms rare

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Blixt T et al. Gastroenterology. 2017 Apr;152(5):1031-1041.

22

Gastroenterology 2017;152:1031–1041

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- ✓ Exposure to a CD carrier doubled risk of CDI
  - OR 2.10 (95% CI, 0.97-4.53)
- ✓ Association between level of exposure and risk of CDI (no. of carriers and/or Length of stay)

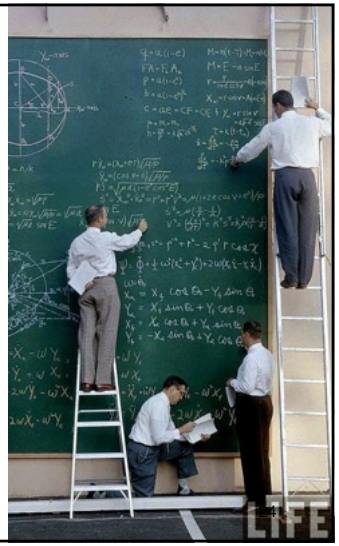
NNTH: 71 (ward level) and 50 (room level)

Blixt T et al. Gastroenterology. 2017 Apr;152(5):1031-1041.

23

Modeling Studies

- Asymptomatic carriers play a role in the dissemination of *C. difficile*, according to modeling experiments
  - Transmission of *C. difficile cannot* be explained solely by symptomatic patients[1]



1. Lanzas C et al. Infect Control Hosp Epidemiol 2011

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Maghdoori and Moghadas *BMC Infectious Diseases* (2017) 17:384
DOI 10.1186/s12879-017-2494-6

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Assessing the effect of patient screening and isolation on curtailing *Clostridium difficile* infection in hospital settings

Sara Maghdoori* and Seyed M. Moghadas

Rapid detection of colonized patients can significantly affect the prevalence of CDI and its control, especially in the context of asymptomatic carriers and in-ward transmission.

Maghdoori, Mohandas. BMC Infect Dis. 2017 Jun 2;17(1):384.

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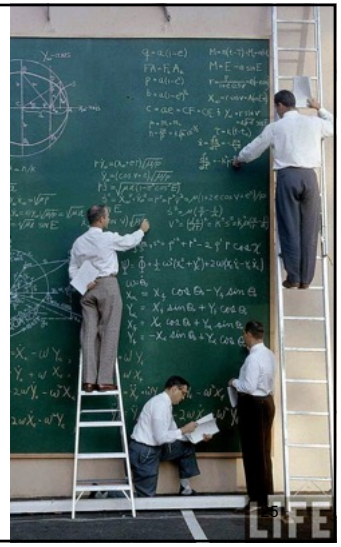

RESEARCH

Quantifying Transmission of *Clostridium difficile* within and outside Healthcare Settings

David P. Durham, Margaret A. Olsen, Erik R. Dubberke, Alison P. Galvani, Jeffrey P. Townsend

Despite lower transmission rates for asymptomatic carriers, this transmission route has a substantial effect on hospital-onset CDI because of the larger reservoir of hospitalized carriers

Durham DP et al. Emerg Infect Dis. 2016 Apr;22(4):608-16.

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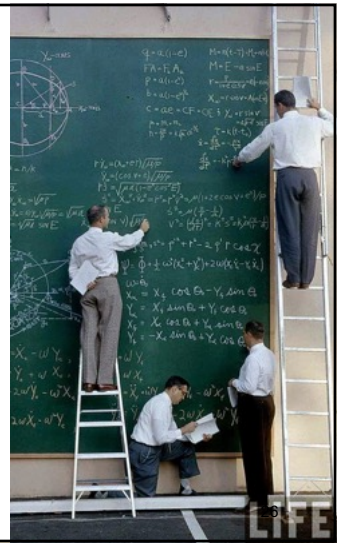

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RESEARCH ARTICLE

Isolation of *C. difficile* Carriers Alone and as Part of a Bundle Approach for the Prevention of *Clostridium difficile* Infection (CDI): A Mathematical Model Based on Clinical Study Data

Christos A. Grigoras[1,2], Fainareti N. Zervou[1], Ioannis M. Zacharioudakis[1], Constantinos I. Siettos[2], Eleftherios Mylonakis[1]*

From a baseline CDI incidence of 6.18 per 1,000 admissions, screening of patients at the time of hospital admission with PCR and isolation of those colonized, as a single additive policy to the standard practice, reduced CDI incidence to 4.99 per 1,000 admissions (95% CI, 4.59– 5.42; RR = 19.1%). Applying this policy as part of a bundle approach combined with an antimicrobial stewardship program had effectiveness in reducing CDI incidence. Specifically, CDI incidence reduced to 2.35 per 1,000 admissions (95% CI, 2.07– 2.65; RR = 61.88%) with the addition of an antimicrobial stewardship program.

Grigoras CA. PLoS ONE 11(6): e0156577.

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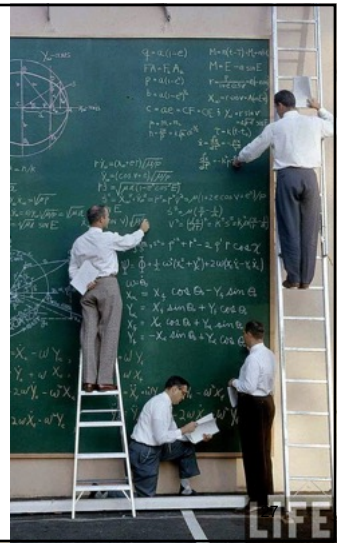

Bull Math Biol (2017) 79:2242–2257
DOI 10.1007/s11538-017-0328-8

Society for Mathematical Biology · CrossMark

ORIGINAL ARTICLE

Healthcare-Associated *Clostridium difficile* Infections are Sustained by Disease from the Community

Angus McLure[1] · Archie C. A. Clements[1] · Martyn Kirk[1] · Kathryn Glass[1]

Within-hospital transmission alone is insufficient to sustain endemic conditions in hospitals without the constant importation of colonised individuals. Improved hygiene practices to reduce transmission from symptomatic and asymptomatic individuals and reduced length of stay are most likely to reduce within-hospital transmission and infections;

McLure A. et al. Bull Math Biol. 2017 Aug 3. doi: 10.1007/s11538-017-0328-8.

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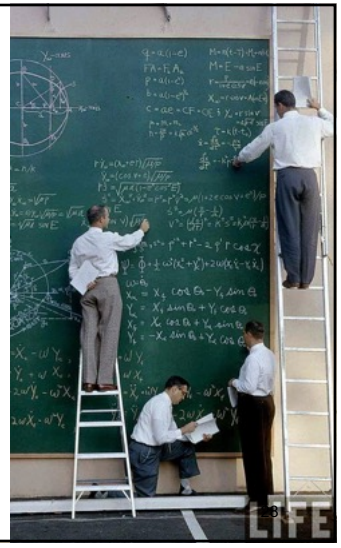

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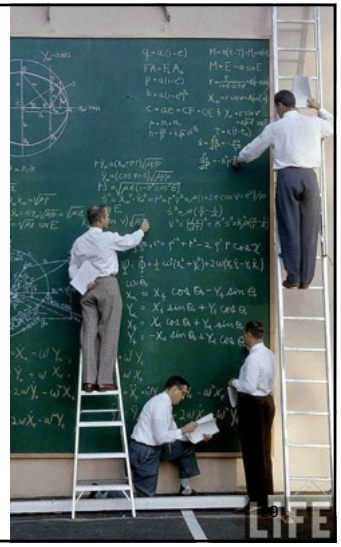
INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY AUGUST 2014, VOL. 35, NO. 8

ORIGINAL ARTICLE

Effectiveness of Screening Hospital Admissions to Detect Asymptomatic Carriers of *Clostridium difficile*: A Modeling Evaluation

Cristina Lanzas, PhD;[1] Erik R. Dubberke, MD[2]

On average, testing for asymptomatic carriers reduced the number of new colonizations and HO-CDI cases by 40%-50% and 10%-25%, respectively, compared with the baseline scenario.



Typing Studies

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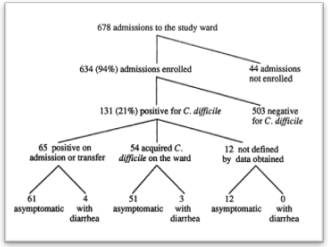
Acquisition of *Clostridium difficile* by Hospitalized Patients: Evidence for Colonized New Admissions as a Source of Infection

Connie R. Clabots, Stuart Johnson, Mary M. Olson, Lance R. Peterson,* and Dale N. Gerding

Infectious Disease Section, Department of Medicine; Microbiology Section, Department of Laboratory Medicine and Pathology; and Department of Surgery, VA Medical Center and University of Minnesota Medical School, Minneapolis



Nosocomial acquisition of a C. difficile strain was preceded by a documented introduction of that strain to the ward by another asymptomatic ward admission in 16 (84%) of 19 instances,

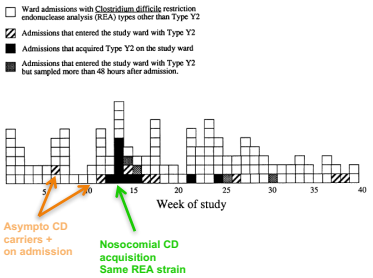


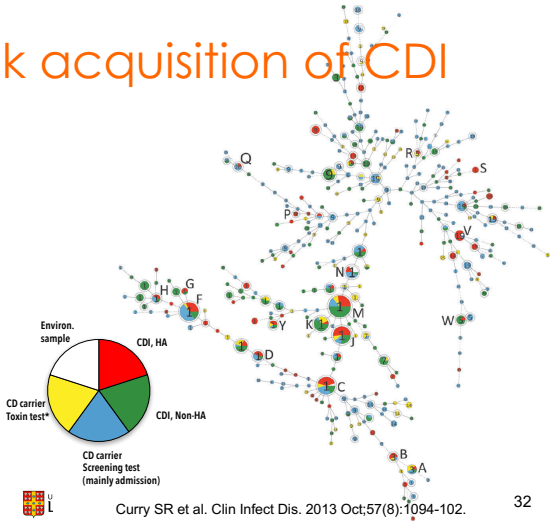
Figure 3. Epidemic curve for *C. difficile* restriction endonuclease analysis type Y2 culture-positive patients on study ward.

Clabots CR et al. J Infect Dis 1992; **166**: 561-567.

31

MLVA to track acquisition of CDI

- CD carriage detection using VRE swabs
- 5 months N=3006 screened patients
- 226 (7.5%) CD carriers
- 56 HA-CDI cases
  - 17 (30%) associated with CDI
  - 16 (29%) associated with CD carriers

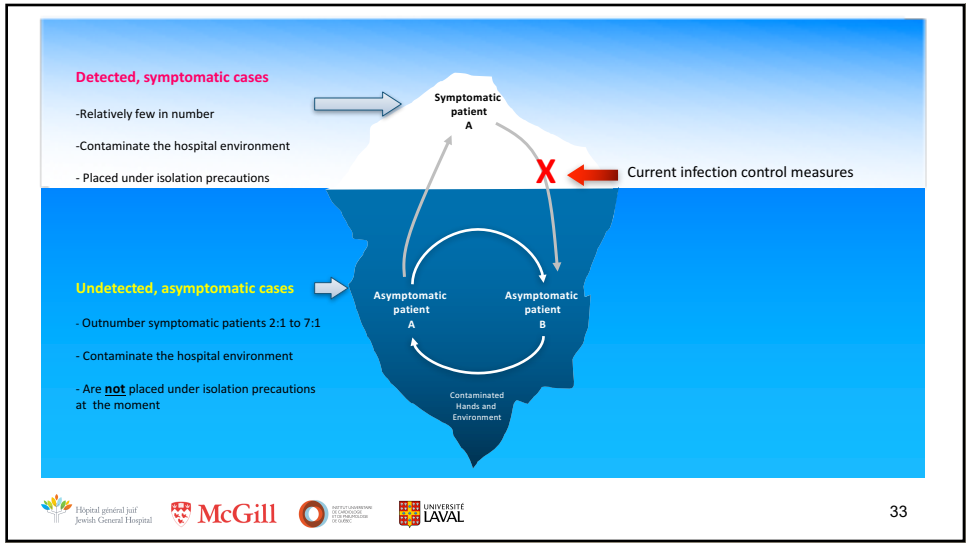


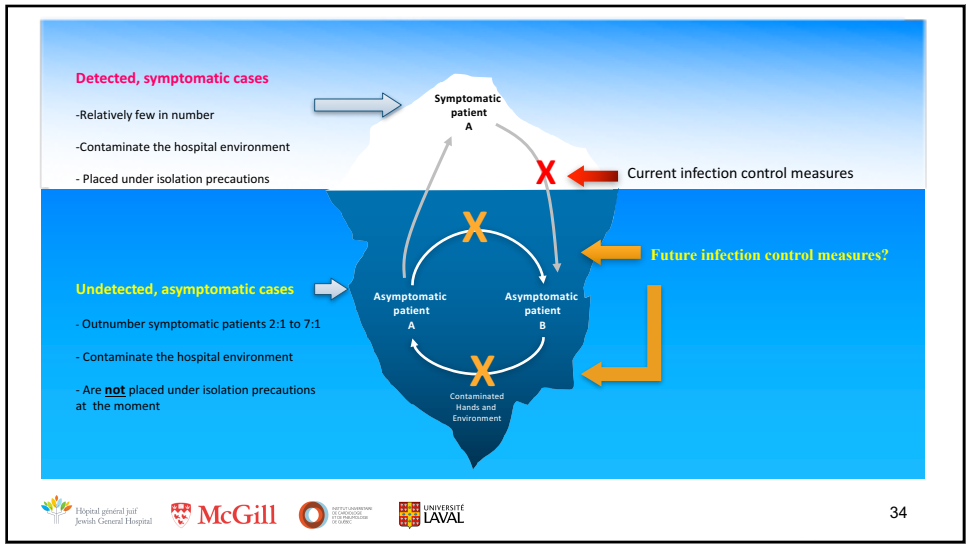
*CDI test + (CCNA) but symptoms do not fulfill criteria for CDI

Curry SR et al. Clin Infect Dis. 2013 Oct;57(8):1094-102.

32

Clostridium difficile Asymptomatic Carriers – The Hidden Part of the Iceberg?
Dr. Yves Longtin, McGill University, Montreal
A Webber Training Teleclass





Hosted by Paul Webber
www.webbertraining.com

Institut Universitaire de Cardiologie et Pneumologie de Québec

- 354-beds Canadian tertiary institution
- Endemic for CDI

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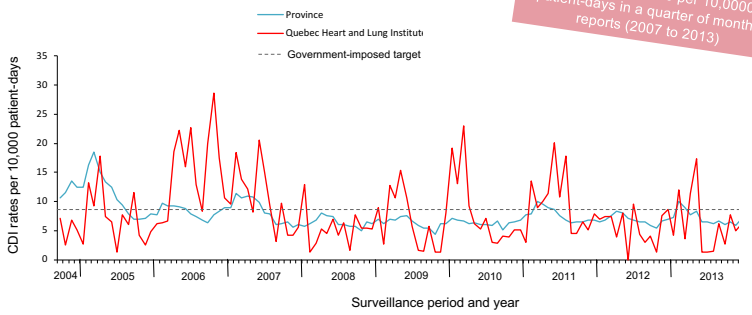
35

HA-CDI rates, 2004-2013

HA-CDI rates > 9.0 per 10,0000 patient-days in a quarter of monthly reports (2007 to 2013)



Incidence of healthcare-associated *Clostridium difficile* infection (CDI) per 4-week period at the Quebec Heart and Lung Institute and all institutions participating in the provincial CDI surveillance program (n=94).

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36

Control of CDI

Significant proportion of HA-CDI felt to be attributable to *C. difficile* asymptomatic carriers (CD-AC) given their high prevalence in Quebec (4.4% on admission)[1]

1. Loo VG, et al. N Engl J Med 2011;365:1693-703.

37

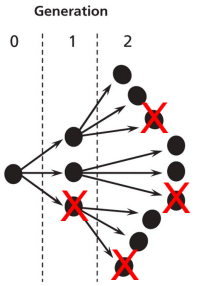
Control of CDI

October 2013

- Review of the literature on the potential role of CD carriers in CDI
- Request from executive committee to implement a strategy to detect and isolate CD-AC
- Creation of a new set of infection control measures for CD carriers

38

CD-AC measures



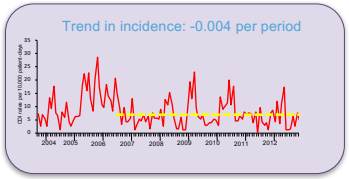
Initial phase of epidemic (R_0 = 3)

Fisman D. CMAJ August 4, 2009 vol. 181 no. 3-4

Goal: decrease basic reproductive number...

… Not necessarily interrupt!

A pragmatic decision



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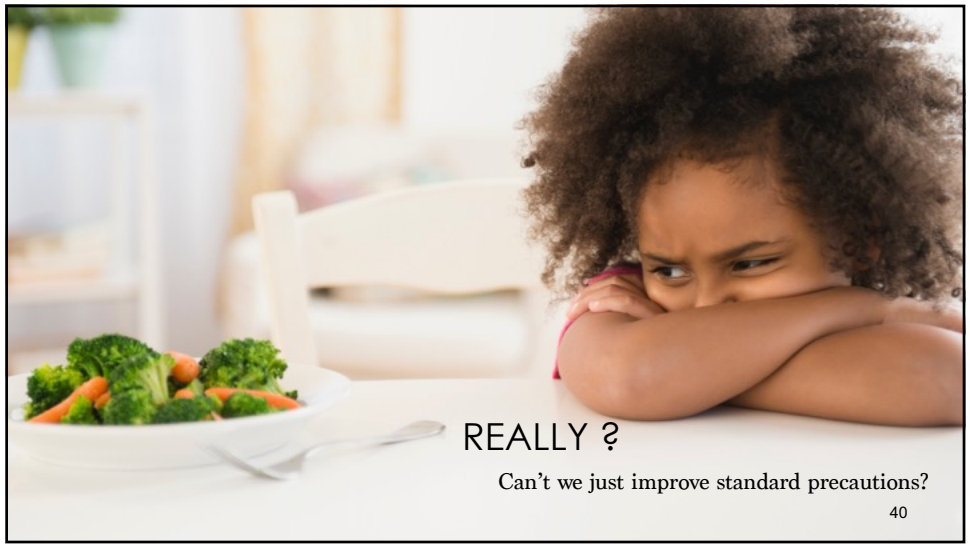
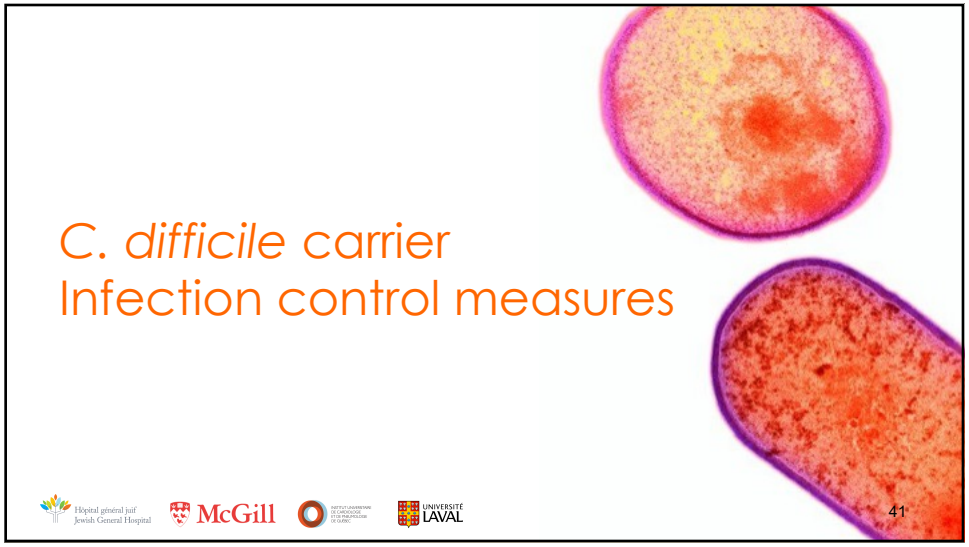
39




C. difficile carrier
Infection control measures
Hôpital général juif
Jewish General Hospital
McGill
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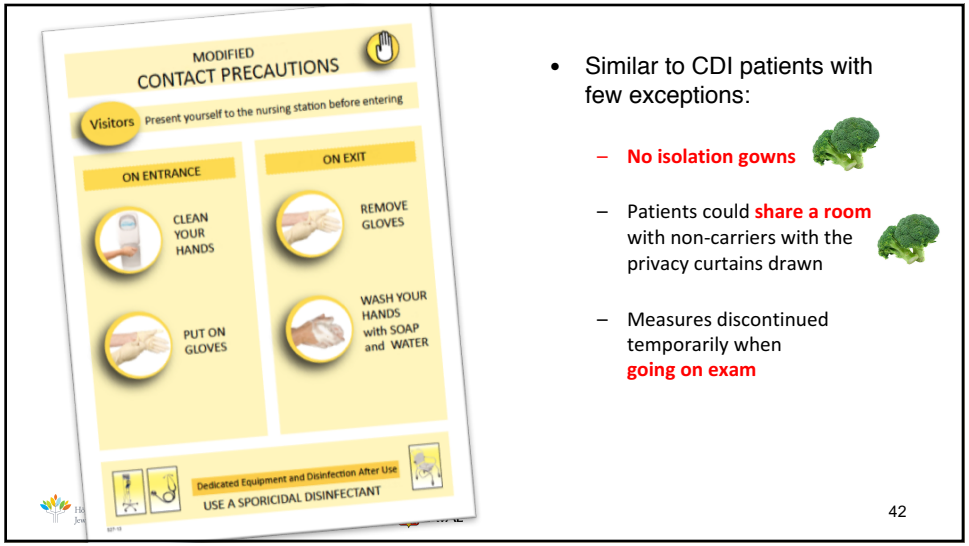
41


MODIFIED
CONTACT PRECAUTIONS
Visitors
Present yourself to the nursing station before entering
ON ENTRANCE
CLEAN YOUR HANDS
PUT ON GLOVES
ON EXIT
REMOVE GLOVES
WASH YOUR HANDS with SOAP and WATER
Dedicated Equipment and Disinfection After Use
USE A SPORICIDAL DISINFECTANT
• Similar to CDI patients with few exceptions:
– No isolation gowns
– Patients could share a room with non-carriers with the privacy curtains drawn
– Measures discontinued temporarily when going on exam
42


Why gloves?
Why not only soap and water ?
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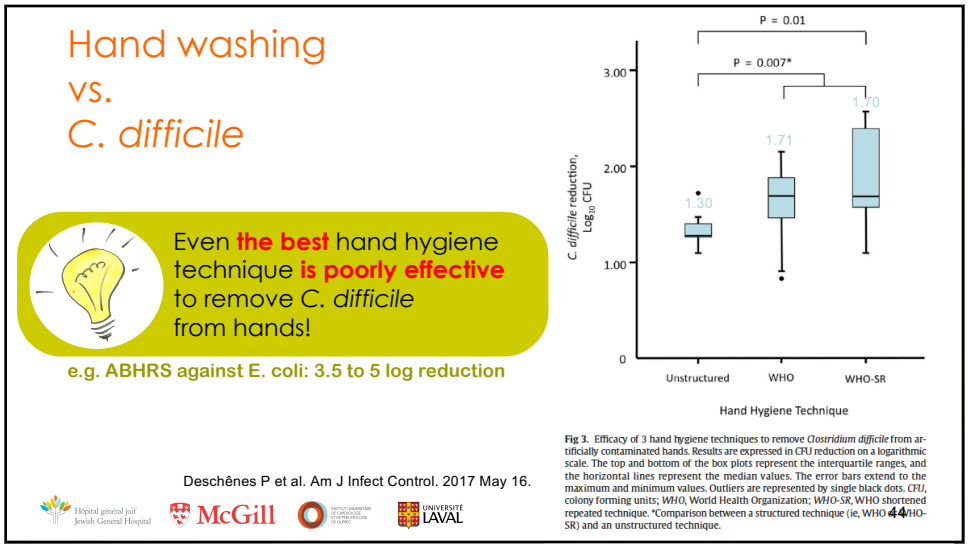
43


Hand washing
vs.
C. difficile
Even the best hand hygiene technique is poorly effective to remove C. difficile from hands!
e.g. ABHRS against E. coli: 3.5 to 5 log reduction
Deschênes P et al. Am J Infect Control. 2017 May 16.
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P = 0.01
P = 0.007*
3.00
2.00
1.00
0
1.30
1.71
1.70
C. difficile reduction, Log10 CFU
Unstructured
WHO
WHO-SR
Hand Hygiene Technique
Fig 3. Efficacy of 3 hand hygiene techniques to remove Clostridium difficile from artificially contaminated hands. Results are expressed in CFU reduction on a logarithmic scale. The top and bottom of the box plots represent the interquartile ranges, and the horizontal lines represent the median values. The error bars extend to the maximum and minimum values. Outliers are represented by single black dots. CFU, colony forming units; WHO, World Health Organization; WHO-SR, WHO shortened repeated technique. *Comparison between a structured technique (ie, WHO or WHO-SR) and an unstructured technique.
44

Efficacy of gloves

Summary of Events in Which Concordant Organisms Were Recovered From the Glove Exterior and Health Care Worker's Hand

Event No.	Patient Contact Site	Glove Type	Leak-Test Result (Did Glove Leak?)	Use Time, min	Microorganism	Colony Count on Gloves, cfu*	Colony Count on Hands, cfu*
1	Oral	Vinyl	Yes	10	*Enterobacter cloacae*	2.0×10^5	1.0×10^1
2	Oral	Vinyl	Yes	11	*Acinetobacter calcoaceticus*	1.2×10^5	4.0×10^1
3	Oral	Vinyl	Yes	17	*A calcoaceticus*	6.5×10^2	5.0×10^0
4	Oral	Vinyl	No	11	*A calcoaceticus*	3.0×10^5	2.5×10^2
5	Oral	Vinyl	Yes	6	*A calcoaceticus*	4.2×10^4	1.0×10^1
6	Oral	Vinyl	Yes	7	*A calcoaceticus, Enterobacter aerogenes*	. . .†	. . .†
7	Oral	Vinyl	Yes	16	*A calcoaceticus*	5.2×10^3	9.0×10^1
8	Oral	Vinyl	No	15	*Pseudomonas aeruginosa*	2.1×10^3	2.0×10^1
9	Rectal	Vinyl	No	2	*Escherichia coli*	2.0×10^6	2.0×10^1
10	Rectal	Vinyl	No	1	*P aeruginosa*	1.3×10^4	2.0×10^1
11	Oral	Latex	No	6	*A calcoaceticus*	1.5×10^4	1.0×10^1

*cfu indicates colony-forming units.
†Ellipses indicate data not available.

2-4 log reduction

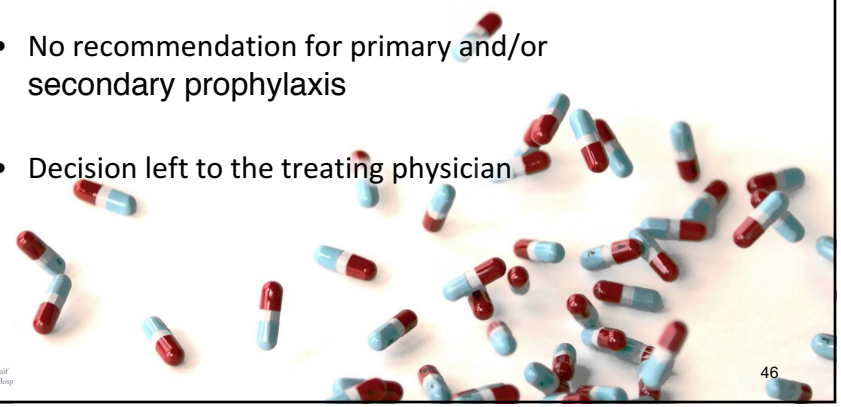
99% to 99.99% protective!

Olsen RJ et al. JAMA. 1993 Jul 21;270(3):350-3.

45

Prophylaxis for C. *difficile* carriers?

- No recommendation for primary and/or secondary prophylaxis
- Decision left to the treating physician



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Jewish General Hosp

46

Detection of carriers

- Rectal sampling with a sterile swab (Liquid Stuart aerobic transport media, Copan Italia, Brescia, Italia)
  - Visibly soiled swab only
- Swabs tested for presence of *tcdB* by PCR (BD GeneOhm Cdiff) once daily, 7 days a week
- Results available within 24 h and documented in the patients' charts

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47

Detection of carriers

- Only patients admitted through the emergency department were screened
- Direct admissions to the wards were not screened
  - E.g. electropysiology, elective surgeries, cath lab

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48

Detection of carriers

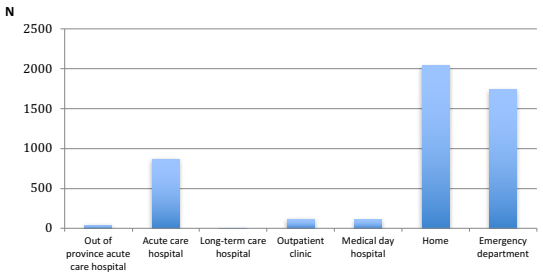

Figure 4. Origin of 4,953 consecutive admissions at the QHLI between Nov. 2014 and March 2015

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49

Detection of carriers

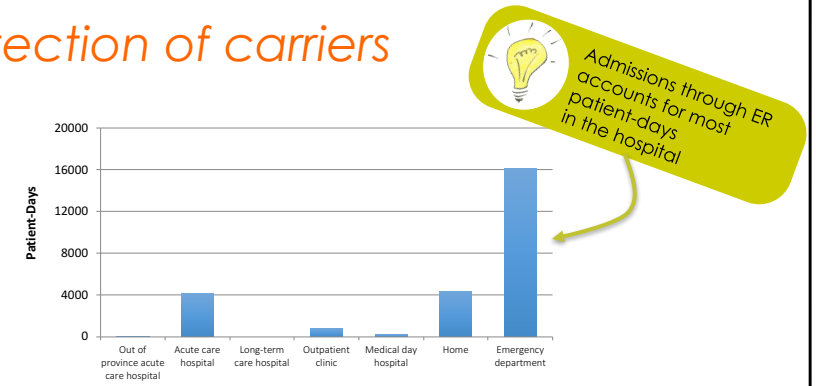

Figure 5. Total number of "at risk" patient-days per origin of patient admission. Excludes patients admitted to the electrophysiology lab, cath lab, polysomnography lab and bariatric surgery who are at low risk of disseminating *C. difficile*, Nov. 2014 - March 2015.

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50

Detection of carriers

- Sensitivity of PCR on a rectal swab?
  - At the time unclear
  - Was probably sufficiently sensitive to achieve our goal of decreasing transmission from CD carriers

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51

Detection of carriers

- Sensitivity of PCR on a rectal swab?
  - At the time unclear
  - Was probably sufficiently sensitive to achieve our goal of decreasing transmission from CD carriers

Nasal swabbing for MRSA detection
80-93% sensitivity

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52

Detection of carriers

Variables	
Level of Detection Assay	125 copies per sample
Quantity of stool on a rectal swab	50 ± 25 mg (local data)
C. difficile load among carriers	3.6 log10 CFU/g (SD, 1.3 log10)[1]
No. copies on a rectal swab	318 ± 159 copies

1. Riggs MM. *et al.*, Clin Infect Dis 2007;45:992-8

53

Detection of carriers

Journal of Clinical Microbiology

Detection of *Clostridium difficile* in Feces of Asymptomatic Patients Admitted to the Hospital

Elisabeth M. Terveer,[a] Monique J. T. Crobach,[a] Ingrid M. J. G. Sanders,[a] Margreet C. Vos,[b] Cees M. Verduin,[c] Ed J. Kuijper[a]
Department of Medical Microbiology, Leiden University Medical Center, Leiden, the Netherlands[a]; Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center, Rotterdam, the Netherlands[b]; Department of Microbiology and Infection Prevention, Amphia Hospital, Breda, the Netherlands[c]

ABSTRACT Recent evidence shows that patients asymptomatically colonized with *Clostridium difficile* may contribute to the transmission of *C. difficile* in health care facilities. Additionally, these patients may have a higher risk of developing *C. difficile* infection. The aim of this study was to compare a commercially available PCR directed to both toxin A and B (*artus C. difficile* QS-RGQ kit CE; Qiagen), an enzyme-linked fluorescent assay to glutamate dehydrogenase (GDH ELFA) (Vidas, bioMérieux), and an in-house-developed PCR to *tcdB*, with (toxigenic) culture of *C. difficile* as the gold standard to detect asymptomatic colonization. Test performances were evaluated in a collection of 765 stool samples obtained from asymptomatic patients at admission to the hospital. The *C. difficile* prevalence in this collection was 5.1%, and 3.1% contained toxigenic *C. difficile*. Compared to *C. difficile* culture, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the *C. difficile* GDH ELFA were 87.2%, 91.2%, 34.7%, and 99.3%, respectively. Compared with results of toxigenic culture, the sensitivity, specificity, PPV, and NPV of the commercially available PCR and the in-house PCR were 95.8%, 93.4%, 31.9%, 99.9%, and 87.5%, 98.8%, 70%, and 99.6%, respectively. We conclude that in a low-prevalence setting of asymptomatically colonized patients, both GDH ELFA and a nucleic acid amplification test can be applied as a first screening test, as they both display a high NPV. However, the low PPV of the tests hinders the use of these assays as stand-alone tests.

54

Terveer EM et al. J Clin Microbiol. 2017 Feb;55(2):403-411.

Detection of carriers

Journal of Clinical Microbiology

Detection of *Clostridium difficile* in Feces
ents Admitted to

Ingrid M. J. G. Sanders,[a]

TABLE 1 Comparison of various *C. difficile* detection assays in comparison with culture of toxigenic and nontoxigenic *C. difficile* as gold standards

Assay result	No. with toxigenic culture result[a]: Pos	Neg	Sensitivity (% [95% CI])	Specificity (% [95% CI])	PPV (%)	NPV (%)
GDH positive	34	64[b]	87.2 (72.6–95.7)	91.2 (88.9–93.1)	34.7	99.3
GDH negative	5	662				
artus positive	23	49[b]	95.8 (78.9–99.9)	93.4 (91.3–95.1)	31.9	99.9
artus negative	1	691				
In-house positive	21	9[b]	87.5 (67.6–97.3)	98.8 (97.7–99.4)	70	99.6
In-house negative	3	732				

GDH →
PCR →

[a]GDH ELFA was compared with *C. difficile* culture, and *artus* PCR and in-house PCR were compared with toxigenic culture. Pos, positive; Neg, negative.
[b]Four of the false-negative samples were positive in all tests (GDH, *artus*, and in-house PCR).

ents asymptomatically colonized with
smission of *C. difficile* in health care fa-
a higher risk of developing *C. difficile*
pare a commercially available PCR di-
e QS-RGQ kit CE; Qiagen), an enzyme-
rogenase (GDH ELFA) (Vidas, bioMéri-
with (toxigenic) culture of *C. difficile* as
colonization. Test performances were
obtained from asymptomatic patients
prevalence in this collection was 5.1%,
pared to *C. difficile* culture, the sensitiv-
and negative predictive value (NPV) of
34.7%, and 99.3%, respectively. Com-
sensitivity, specificity, PPV, and NPV of
house PCR were 95.8%, 93.4%, 31.9%,
spectively. We conclude that in a low-
nized patients, both GDH ELFA and a
as a first screening test, as they both
display a high NPV. However, the low PPV of the tests hinders the use of these as-
says as stand-alone tests.

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55

Terveer EM et al. J Clin Microbiol. 2017 Feb;55(2):403-411.

False +?

- Detection of ACDC in ICU patients by detection of tcdB gene by homebrew PCR
  - 396 tested; 16 ACDC detected
  - 100% (16/16) grew C. difficile by culture (true +)

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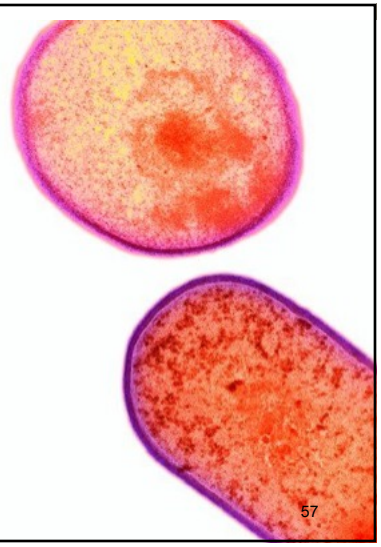
Zhang X et al. BMC Infect Dis. 2016 Aug 9;16:397

56

ANALYSIS



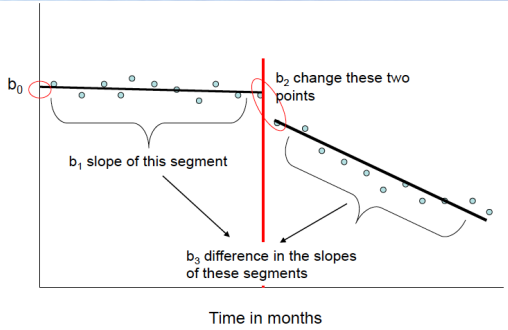
57

Outcomes

Primary outcome: Changes in HA-CDI incidence rate per 10,000 patient-days following implementation, defined as a change in level and/or trend compared with the pre-intervention period

58

$$Y_t = b_o + b_1T + b_2D + b_3P$$



Center for Health Research

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59

External control

Data from Quebec CDI surveillance program

- 95 institutions
- 3453 CDI annually (2015)
- 5 million patient-days (2015)
- Global incidence 6.8 per 10,000 patient-days

https://www.inspq.qc.ca/en/nosocomial-infections/spin-cdad/surveillance-results-2014-2015

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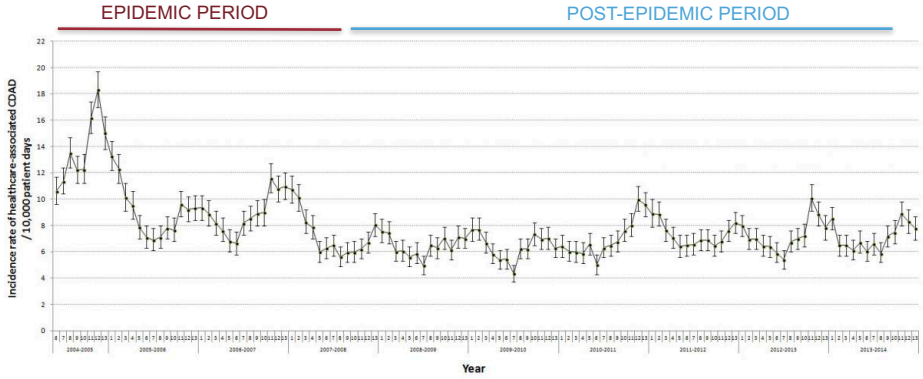
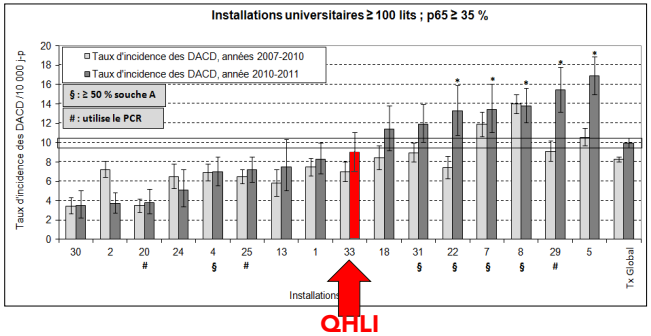
60



Healthcare-Associated CDI Incidence rate in Quebec, 2004-2014

61

Incidence rate among university hospitals, 2011-2012



Institut National de Santé Publique du Québec

62

Analyses

3 complementary statistical methods

① **Aggregated data**
- Intervention period vs. pre-intervention period

② **Interrupted time series analysis**
- Poisson regression (accounts for seasonality)

③ **ARIMA modeling**
- To assess the impact
- To evaluate the number of averted cases

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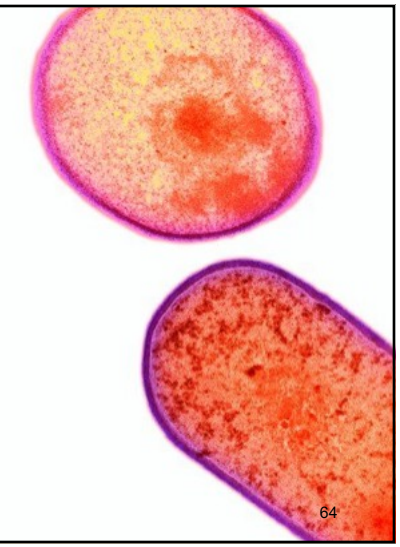
63

RESULTS



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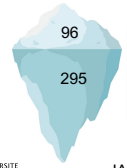
64

Table 1. Study Characteristics, *Clostridium difficile* Infections, and Complications by Study Period

Variable	Preintervention Period: Epidemic Period From August 22, 2004, to July 21, 2007	Preintervention Period: Postepidemic Period From July 22, 2007, to November 18, 2013	Intervention Period From November 19, 2013, to March 7, 2015	*P* Value[a]
Study periods				
Cumulative duration, mo	35	76	15	NA
4-wk Periods, No.	38	82	17	NA
Admissions, No.	43 783	83 314	18 382	NA
Patient-days, No.	276 072	600 358	127 883	NA
Screening for *C difficile* asymptomatic carriers, No./total No. (%)				
Screened patients[b]	NA	NA	7599/8218 (92.5)	NA
Asymptomatic carriers	NA	NA	368/7599 (4.8)	NA



Every Year
Approx. 295 carriers admitted
Approx. 96 patients with CDI
Ratio 3:1

JAMA Intern Med. 2016 Jun 1;176(6):796-804 65

Carriage rate on admission

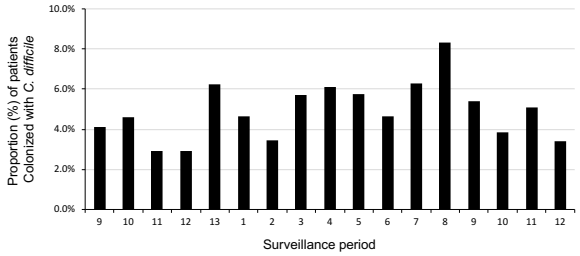


Figure. Proportion (%) of patients colonized with *Clostridium difficile* on admission per 4-week period, November 2013- March 2015, Quebec Heart and Lung Institute, Quebec City, Canada.

66

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Incidence (95% CI) of HA-CDIs per 10 000 patient-days	11.1 (9.9-12.4)	6.9 (6.3-7.6)	3.0 (2.1-4.0)	<.001
Periods above government-imposed target, No./total No. (%)[c]	20/138 (52.6)	20/82 (24.4)	0/17 (0)	.02
Incidence (95% CI) of CDIs associated with ambulatory care per 1000 admissions	0.27 (0.14-0.45)	0.35 (0.23-0.49)	0.54 (0.26-0.93)	.25
Incidence (95% CI) of hospitalized community-acquired CDIs per 1000 admissions	0.75 (0.52-1.03)	0.59 (0.44-0.77)	0.49 (0.22-0.86)	.60

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67

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Incidence (95% CI) of CDIs associated with ambulatory care per 1000 admissions	0.27 (0.14-0.45)	0.35 (0.23-0.49)	0.54 (0.26-0.93)	.25
Incidence (95% CI) of hospitalized community-acquired CDIs per 1000 admissions	0.75 (0.52-1.03)	0.59 (0.44-0.77)	0.49 (0.22-0.86)	.60

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68

Table 1. Study Characteristics, *Clostridium difficile* Infections, and Complications by Study Period

Variable	Preintervention Period: Epidemic Period From August 22, 2004, to July 21, 2007	Preintervention Period: Postepidemic Period From July 22, 2007, to November 18, 2013	Intervention Period From November 19, 2013, to March 7, 2015	*P* Value[a]
Complications, No./total No. (%)				
10-d All-cause mortality[d]	NA	31/383 (8.1)	3/38 (7.9)	.99
30-d All-cause mortality[d]	NA	56/383 (14.6)	7/38 (18.4)	.48
Admission to intensive care unit	6/306 (2.0)	7/416 (1.7)	0/38 (0.0)	.99
Colectomy	2/306 (0.7)	3/416 (0.7)	1/38 (2.6)	.30
Readmission for CDI recurrence	17/306 (5.6)	3/416 (7.5)	0/38 (0.0)	.10

NO CHANGE IN % MORTALITY

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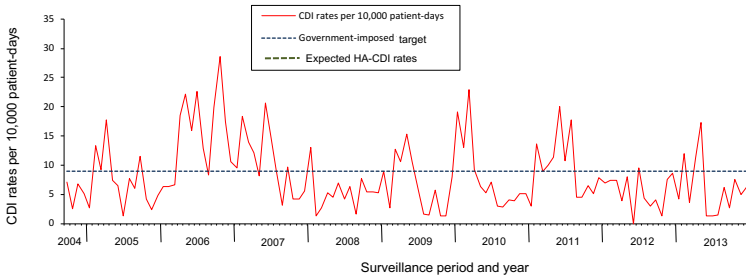

Figure 1. Incidence of healthcare-associated *Clostridium difficile* infection (CDI) per 4-week period according to standardized surveillance definitions, August 2004 - March 2015, Quebec Heart and Lung Institute, Quebec City, Canada. An intervention consisting of screening and isolation of *Clostridium difficile* asymptomatic carriers was introduced on November 19, 2013. The institution is subjected to a government-imposed threshold of 9.0 per 10 000 patient-days (blue dashed line). The expected HA-CDI rate during the intervention using an ARIMA prediction model is presented (dashed green line).

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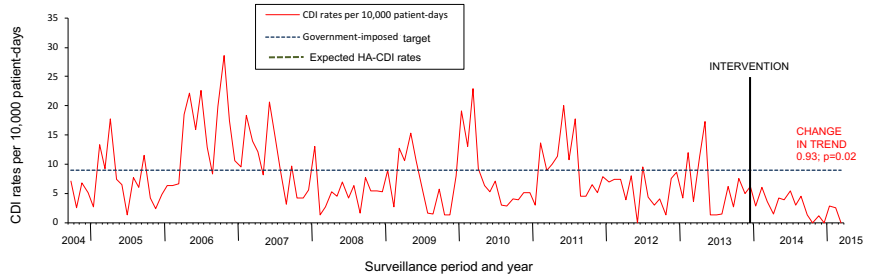

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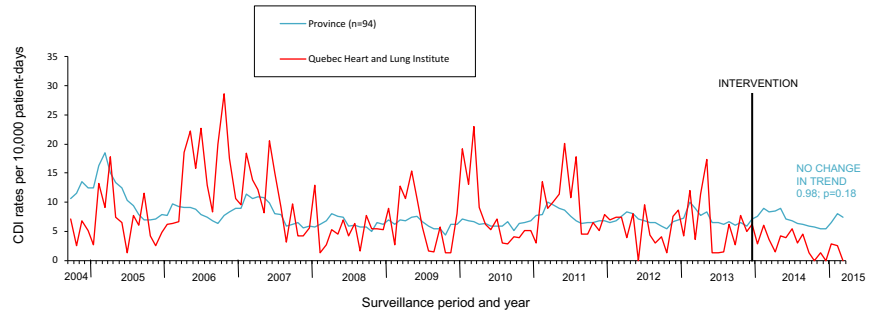

Figure 2. Incidence of healthcare-associated *Clostridium difficile* infection (CDI) per 4-week period at the Quebec Heart and Lung Institute and in 3 control groups: other institutions in Quebec City (n=6); matching academic institutions (n=15); and all institutions participating in the provincial CDI surveillance program (n=94).

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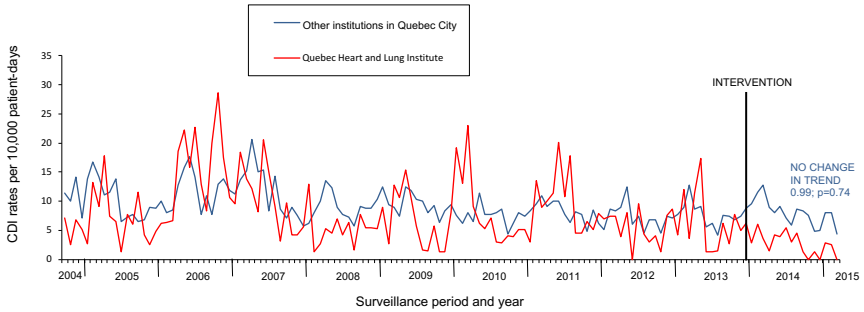
72



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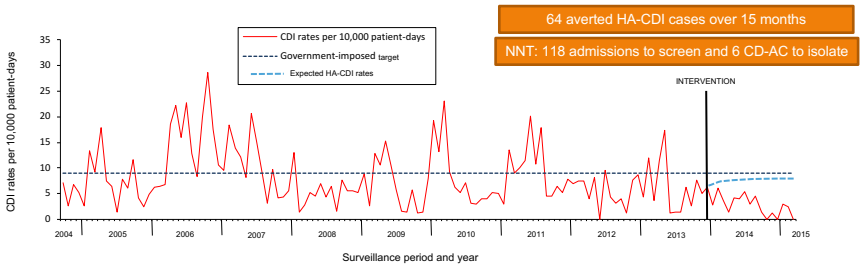
73

ARIMA modeling



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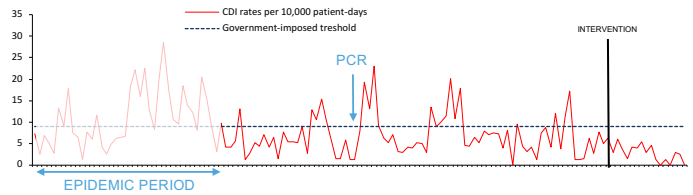
74

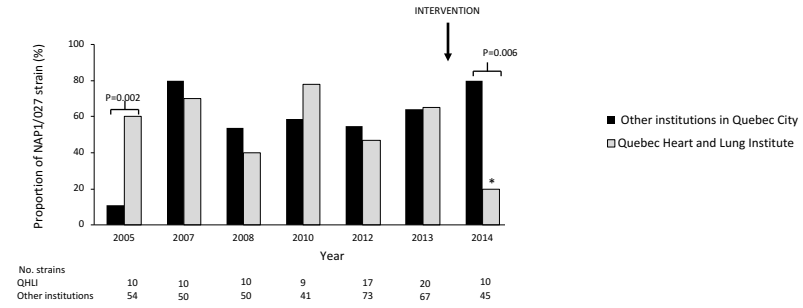
Sensitivity analyses

- Analyses repeated while excluding
  - Epidemic period
  - Controlling for switch in CDI assay (EIA/CCNA to PCR)
- Association remained significant by Poisson and ARIMA ($p<0.05$)



75

Strain Analysis

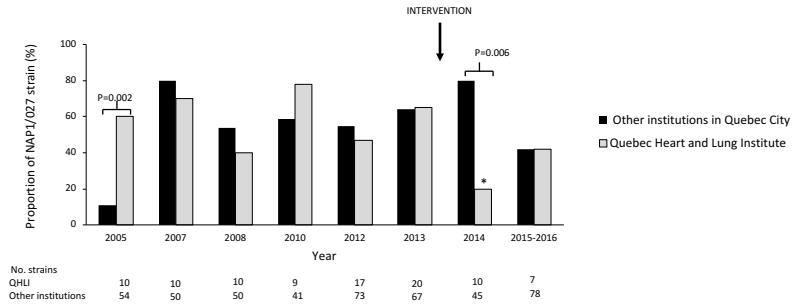


No. strains							
QHLI	10	10	10	9	17	20	10
Other institutions	54	50	50	41	73	67	45

Figure S1. Proportion (%) of NAP1/B1/027 strain recovered from patients with *Clostridium difficile* infections from Quebec Heart and Lung Institute (QHLI) and from other hospitals in Quebec City, 2005-2014.
* p=0.049 compared with 2005-2013 institutional global prevalence

76

Strain Analysis



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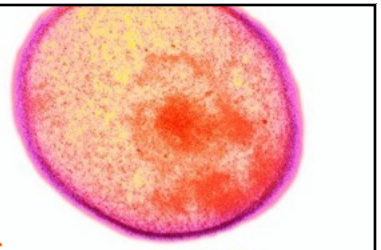
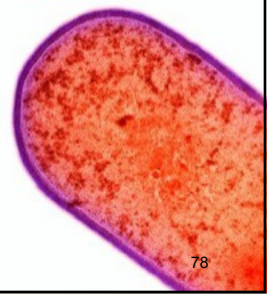
* p=0.049 compared with 2005-2013 institutional global prevalence

77

Potential Confounders





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78

Potential Confounders

- Hand hygiene compliance
  - Increased from 37% to 50% during intervention (p<0.001)
- Concomitant changes in infection control policies
  - KPC-producing Enterobacteriaceae outbreak on 2 wards December 2014-January 2015

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79

Antimicrobial and PPI use

Table 3. Analysis of Changes in the Level and Trend in Antimicrobial and Proton Pump Inhibitor Use After Implementation of the Intervention[a]

Variable	RR (95% CI) Preintervention Period From December 4, 2011, to November 18, 2013 (n = 192 188 Patient-days) Overall Trend Before the Intervention[b]	*P* Value	Intervention Period From November 19, 2013, to March 7, 2015 (n = 121 402 Patient-days) Immediate Change After the Start of the Intervention[c]	*P* Value	Change in Trend After the Start of the Intervention[d]	*P* Value
Total antimicrobials[e]	1.001 (1.000-1.002)	.20	1.025 (1.004-1.047)	.02	1.004 (1.002-1.006)	<.001
Proton pump inhibitors	1.001 (1.001-1.002)	<.001	0.94 (0.92-0.96)	<.001	1.005 (1.004-1.006)	<.001

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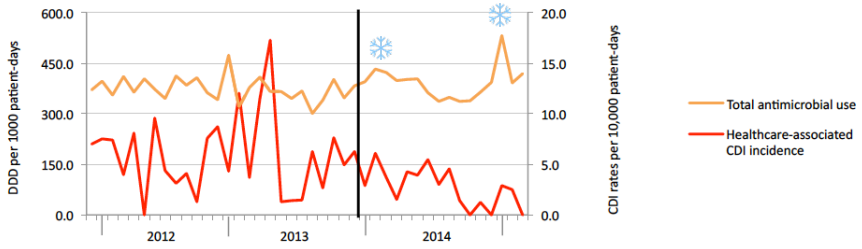
80

Antimicrobial use



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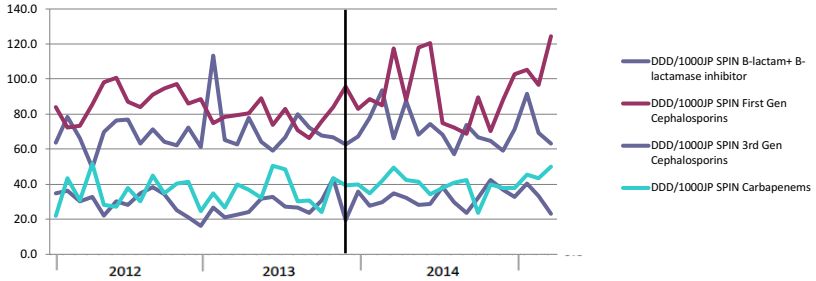
81

Antimicrobial use



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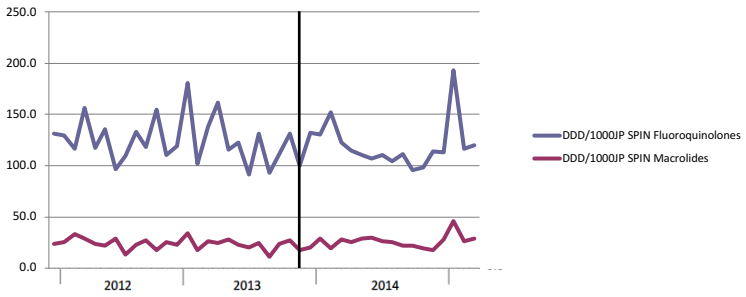
82

Antimicrobial use



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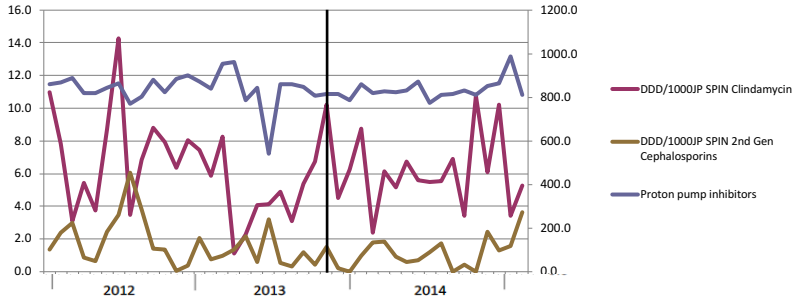
83

Antimicrobial and PPI use



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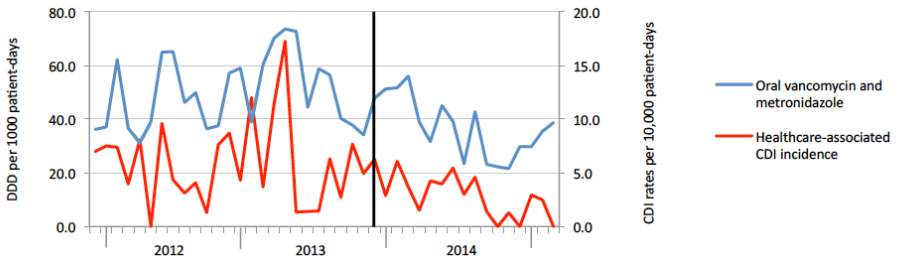
84

Anti-CDI antimicrobials



Change in trend: 0.97; p<0.001

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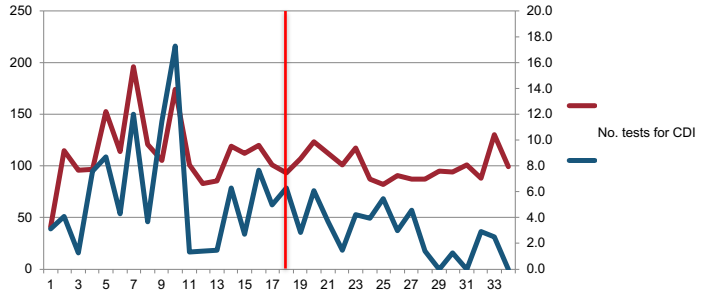
85

Intensity of CDI testing



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% of negative CDI tests

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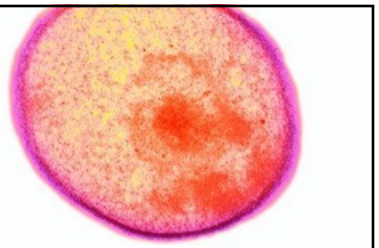
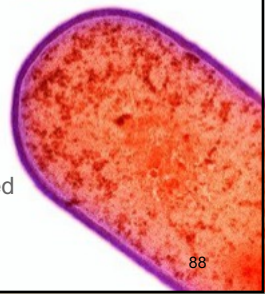
87

LONG-TERM Follow-up





…The intervention never stopped

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88

Long-term Impact

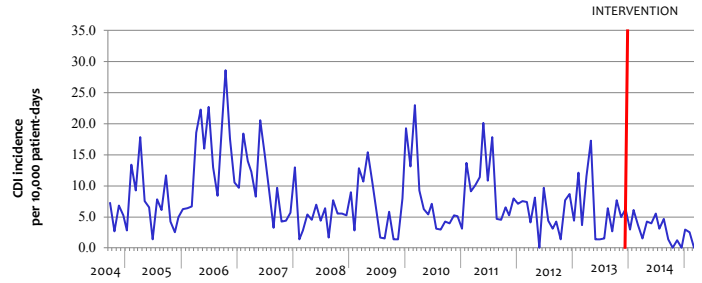

Figure 1. Healthcare-associated CDI incidence, Quebec Hearth and Lung Institute, 2004-2016

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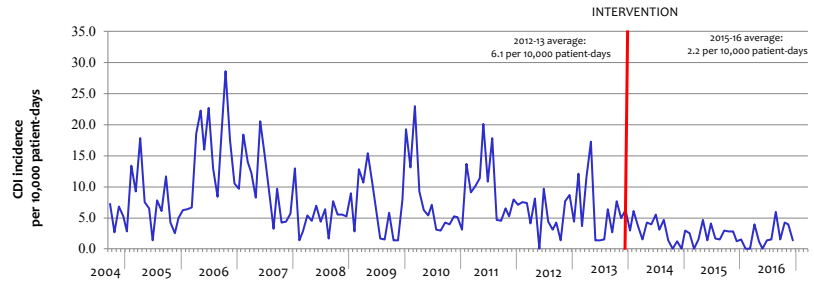
89

Long-term Impact



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90

Long-term follow-up

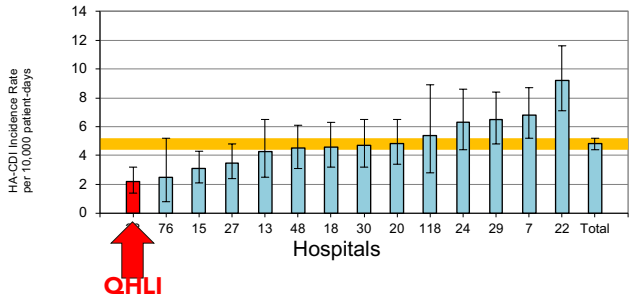

Figure 3. HA-CDI rates of University Hospitals in Quebec, 2015-2016. Red bar represents the HA-CDI incidence rate at the QHLI. Yellow Bar represents the 95% Confidence Interval for the stratum

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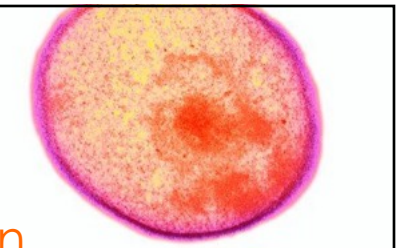
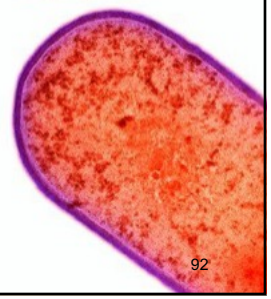
91

Impact of the Isolation Precaution Burden





… Can we isolate that many patients?

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92

Clostridium difficile Asymptomatic Carriers – The Hidden Part of the Iceberg?
Dr. Yves Longtin, McGill University, Montreal
A Webber Training Teleclass

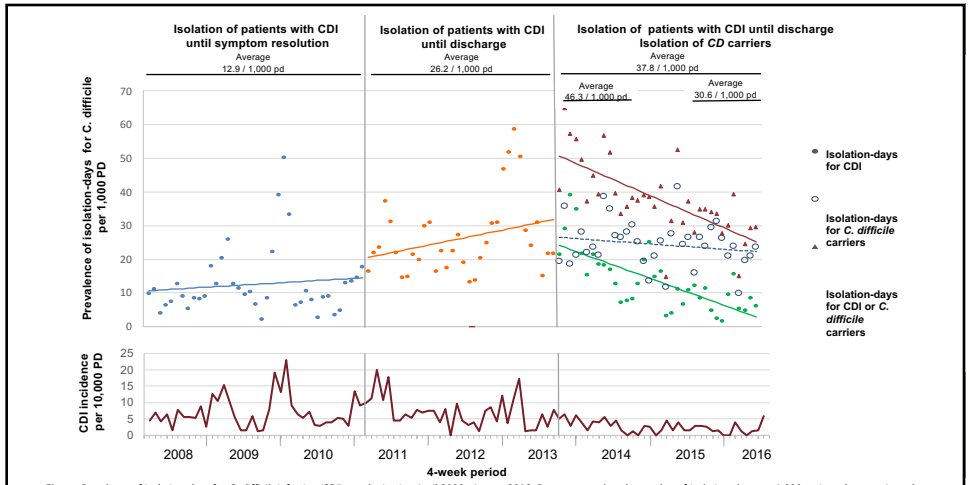
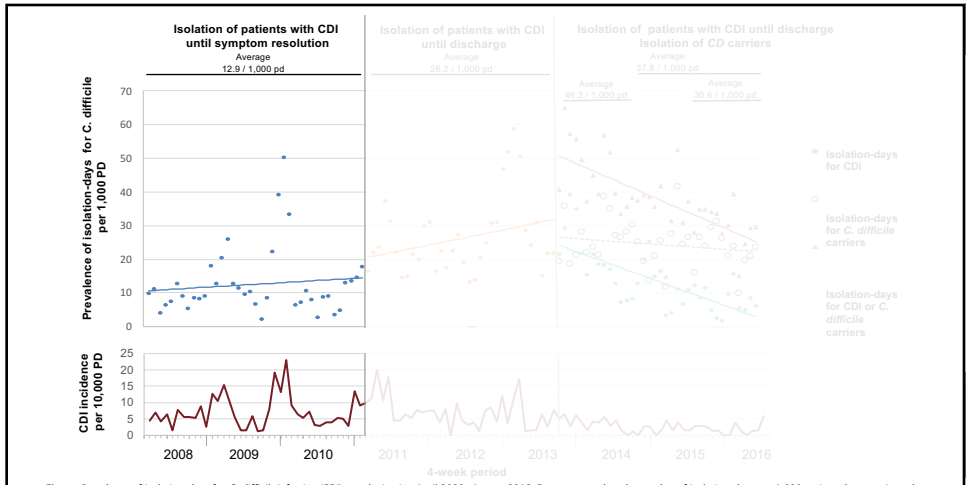


Figure. Prevalence of isolation-days for *C. difficile* infection (CDI) or colonization April 2008- August 2016. Data presented as the number of isolation-days per 1,000 patient-days per 4-week period. Averages represent the average isolation prevalence for C. difficile for the entire periods and for the first and last 12 months of the last period. Healthcare-associated CDI incidence rates during each study period are presented on the lower panel.
Abbreviations: CDI: *Clostridium difficile* infection; pd: patient-days

93



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94

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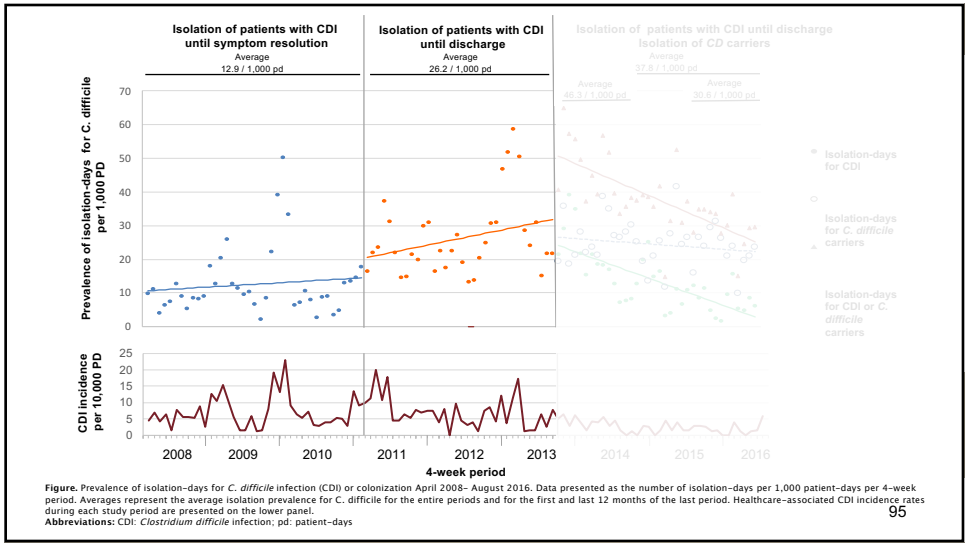

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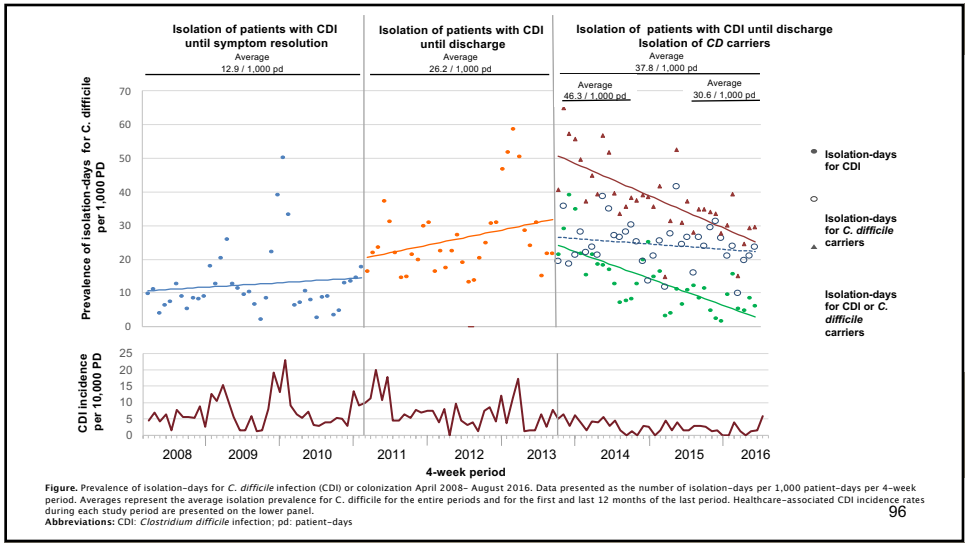
95



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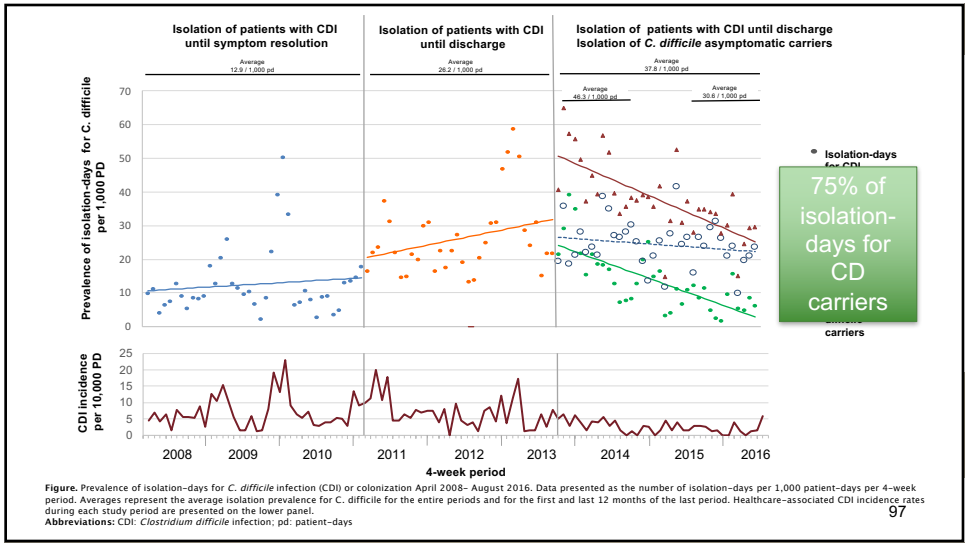

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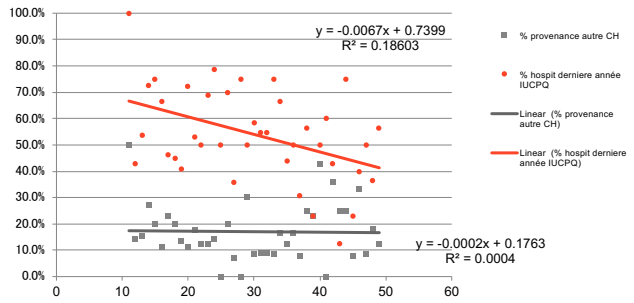
97

Proportion of Carriers with Recent Hospitalization at the QHLI



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Cost-Benefit Estimate

Potential Economic Value

Incremental cost effectiveness ratio (ICER, $/QALY) for C. difficile screening compared to no screening

C. difficile Colonization on Admission (%)	Contact Isolation Compliance (%)		
	25	50	75
Hospital Perspective			
Probability of Infection after Colonization = 5.88%			
0.5	256	241	208
1	122	105	94
5	5	3	1
10.3	Screen	Screen	Screen
15	Screen	Screen	Screen
20	Screen	Screen	Screen

Bartsch SM et al. Eur J Clin Microbiol Infect Dis. 2012 Nov;31(11):3163-71.
100

Cost-benefit analysis

- Preliminary estimates suggest that the intervention may be cost-beneficial

- Cost intervention: USD $130,000 for 15 months
- Number averted cases: 64
- Cost of 1 HA-CDI: $3,427 to $9,960
- Savings in averted CDI: USD $219,000 to $637,000
- Would be greater if prevention of recurrences taken into account

Cost-benefit analysis

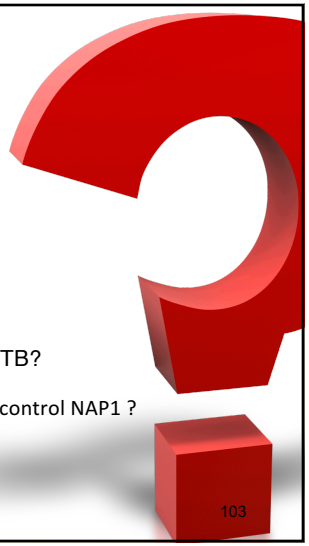
- Risk of recurrence among patients with CDI: 15-25%
- No. Recurrences averted: 9-15
- Cost per recurrence: $13,655 to $18,067 [1]
- Averted cost of recurrences: $122,895 to $271,000

Total savings (incl. recurrences):
$342,000 to >$800,000

1. Ghantoji SS et al. J Hosp Infect. 2010 Apr;74(4):309-18

Unknowns and Research Agenda

- Generalizability?
  - Very pro-infection control hospital
- Why did we "beat the forecasts"?
  - Modeling studies predict 20-30% decrease in HA-CDI
- Population-level analysis
  - Patient-level analysis of carriers under way
- Management of *C. difficile* carriers who must receive ATB?
- Where does it fit in relationship with ATB stewardship to control NAP1 ?



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103

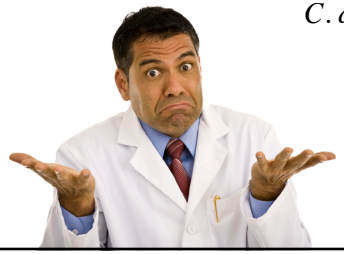
Clinical Infectious Diseases
MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association

Contribution to *Clostridium Difficile* Transmission of Symptomatic Patients With Toxigenic Strains Who Are Fecal Toxin Negative

Damian P. C. Mawer,[1,a] David W. Eyre,[2,3,a] David Griffiths,[2,3] Warren N. Fawley,[1,4] Jessica S. H. Martin,[5] T. Phuong Quan,[2,3] Timothy E. A. Peto,[2,3] Derrick W. Crook,[2,3,5] A. Sarah Walker,[2,3] and Mark H. Wilcox[1,3]

[1]Department of Microbiology, Leeds Teaching Hospitals NHS Trust; [2]Nuffield Department of Medicine, University of Oxford; [3]National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford; [4]Leeds Regional Microbiology Laboratory, Public Health England; [5]Leeds Institute of Biomedical and Clinical Sciences, University of Leeds; and [6]Public Health England, Colindale, United Kingdom

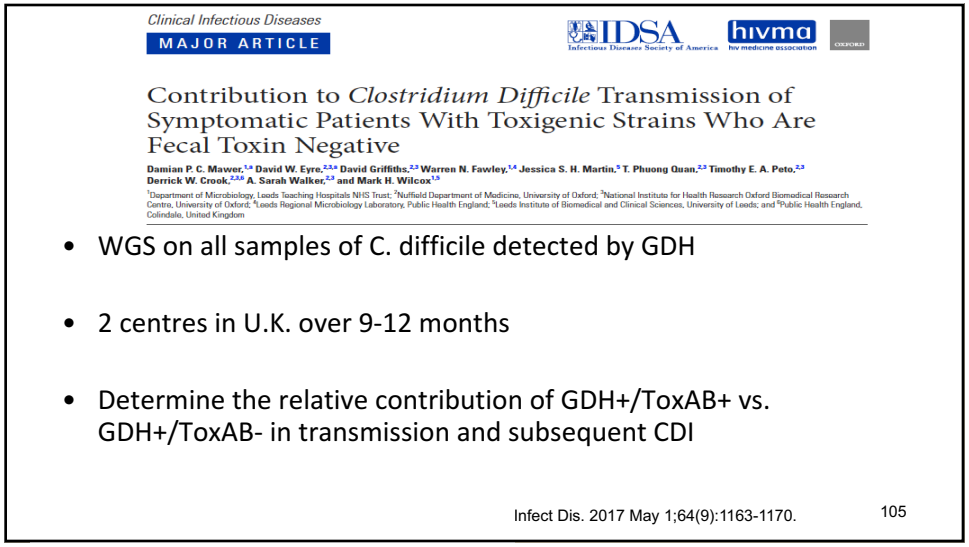


Patients with diarrhea who are carriers of toxigenic *C. difficile* but without detectable toxin levels : are they contagious?

GDH + but ToxAB -

Mawer DPC et al Clin Infect Dis. 2017 May 1;64(9):1163-1170.

104



Clinical Infectious Diseases
MAJOR ARTICLE

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Contribution to *Clostridium Difficile* Transmission of Symptomatic Patients With Toxigenic Strains Who Are Fecal Toxin Negative

Damian P. C. Mawer,[1,a] David W. Eyre,[2,3,a] David Griffiths,[2,3] Warren N. Fawley,[1,4] Jessica S. H. Martin,[5] T. Phuong Quan,[2,3] Timothy E. A. Peto,[2,3] Derrick W. Crook,[2,3,b] A. Sarah Walker,[2,3] and Mark H. Wilcox[1,b]

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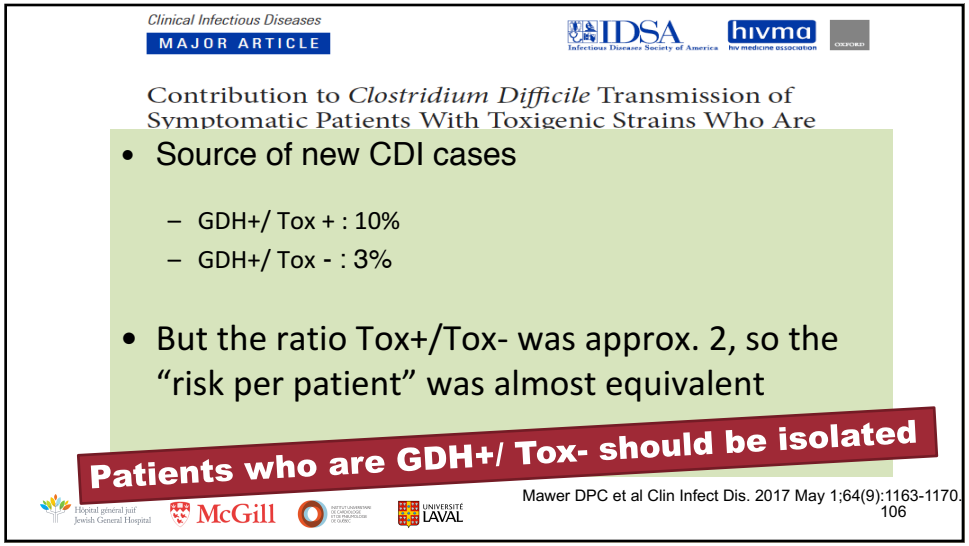
- WGS on all samples of C. difficile detected by GDH
- 2 centres in U.K. over 9-12 months
- Determine the relative contribution of GDH+/ToxAB+ vs. GDH+/ToxAB- in transmission and subsequent CDI

Infect Dis. 2017 May 1;64(9):1163-1170. 105



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Contribution to *Clostridium Difficile* Transmission of Symptomatic Patients With Toxigenic Strains Who Are

- Source of new CDI cases
  - GDH+/ Tox + : 10%
  - GDH+/ Tox - : 3%
- But the ratio Tox+/Tox- was approx. 2, so the "risk per patient" was almost equivalent

Patients who are GDH+/ Tox- should be isolated

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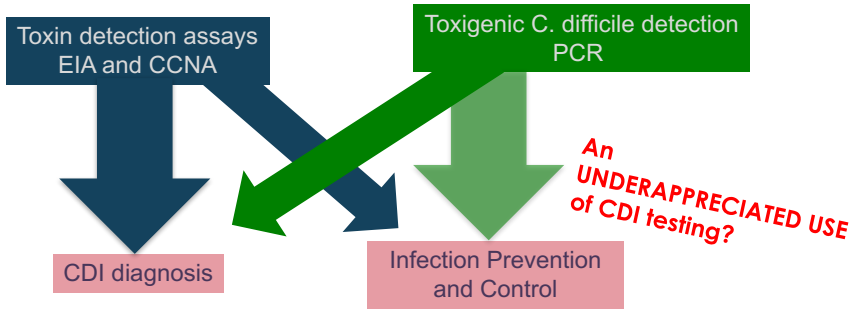
C. difficile testing – many tests, many potential uses



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107

Potential use of CD carrier isolation during outbreaks?

- No published data yet
- Preliminary data from 2 healthcare centers (n=4 outbreaks)

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108

Clostridium difficile Asymptomatic Carriers – The Hidden Part of the Iceberg?
Dr. Yves Longtin, McGill University, Montreal
A Webber Training Teleclass

Out-break num-ber	Hospital and specialty	Number of beds	No. HA-CDI so far upon screening	No. patients screened for *C. difficile* carriage	Number of CD-AC detected (%)	CD carrier Outbreak containment measures	Outcome of outbreak
1	QHLI; Cardiac surgery 3e PC	Total 39 7 private 24 semi-private 8 multi-patient	4	32	0 (0%)	Not applicable	3 additional CDI cases in patients admitted to ward after unit-wide screening
2	QHLI; General surgery 2e ND	Total 20 6 private 14 semi-private	3	17	1 (6%)	None; CD carrier was discharged from ward on the day of diagnosis	No additional CDI case
3	QHLI; Pneumology 5ePC	Total 48 6 private 42 semi-private	7	42	10 (24%)	Modified Contact Precautions for CD carriers	1 CD carrier progressed to CDI 3 additional cases of CDI in patients who tested negative during the unit-wide screening
4	JGH; General medicine 6W	Total 33 0 private 22 semi-private 11 multi-patient	7	21	1 (5%)	Modified Contact Precautions for CD carrier	1 CD carrier progressed to CDI 5 additional cases of CDI in patients admitted to ward after unit-wide screening
Total		**140**	**18**	**112**	**12 (11%)**		

Table. Description of *Clostridium difficile* infection outbreaks in which patients were tested for *C. difficile* asymptomatic carriage

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109

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CDI outbreaks are not created equal

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110

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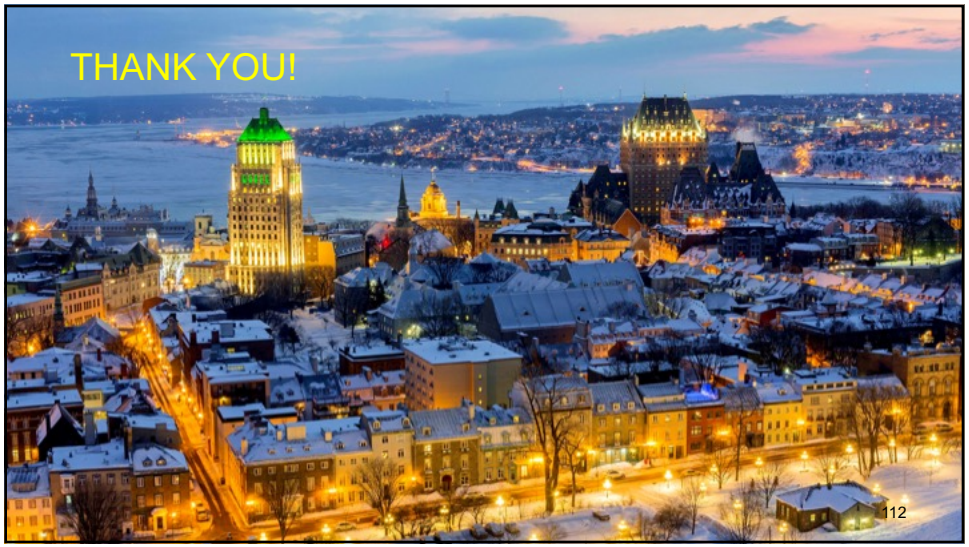
  - Simon Levesque PhD
  - Jean Longtin MD

111



112

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