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

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Hosted by Paul Webber
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Disclosures

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• Speaker’s Bureau for
  – Merck Canada, Pfizer

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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

BACKGROUND
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\(^3\)

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Background

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

- **Current recommendations relatively unchanged** for more than 20 years\(^1,2\)
  - i.e. prior to the onset of the NAP1 epidemic

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


Background

- Current preventive recommendations focus mainly on patients with CDI, but are insufficient to interrupt the dissemination of this microorganism in healthcare settings.\(^1,2\)

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 \(C\). \(d\) \(i\) \(f\) \(i\) \(c\) \(i\) \(l\) \(e\) 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 \(C\). \(d\) \(i\) \(f\) \(i\) \(c\) \(i\) \(l\) \(e\) during their stay. A third progressed to CDI\(^5\)
- Approximately \(10\%\) after 21 days of hospitalisation\(^6\)
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Ongoing Transmission in Quebec Hospitals

Table 2. Type of Food Positive for Clostridium difficile, by Food Type, for 930 Meals

<table>
<thead>
<tr>
<th>Food Item</th>
<th>Total</th>
<th>C. difficile, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meat</td>
<td>308</td>
<td>0</td>
</tr>
<tr>
<td>Pudding</td>
<td>142</td>
<td>0</td>
</tr>
<tr>
<td>Fruit</td>
<td>1879</td>
<td>0</td>
</tr>
<tr>
<td>Vegetables</td>
<td>455</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nuts</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dalysiges</td>
<td>210</td>
<td>0</td>
</tr>
<tr>
<td>Bread/grain</td>
<td>2576</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>200</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Stochastic modeling: Food would be responsible for < 1 newly colonized patient / 1,000 adms.


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**Asymptomatic Carriers**

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.

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


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CD-AC are not as contagious as CDI patients... but almost!

*Clostridium difficile* is present on the **skin** of asymptomatic carriers

*C. difficile* in the **IMMEDIATE SURROUNDINGS** of asymptomatic carriers

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*C. difficile* present on skin of asymptomatic carriers can be transferred to HCWs’ hands 30-60% of the time

Bobulsky GS. et al., Clin Infect Dis. 2008; 46(3):447-50

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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 >7 days 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)\(^3\)

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

Thomas Blixt,1,2 Kim Chen Graapel,3 Christian Homann,4 Jakob Banadet Saadalin,4,5 Kristian Schnanning,6,7 Anne Lester,4,8 Jette Houlind,4,9 Marie Stangerup,4,9

1Department of Gastroenterology, Frederiksborg Hospital, University of Copenhagen, Frederiksborg, Denmark; 2Department of Medicine, University of Copenhagen, Copenhagen, Denmark; 3Department of Infectious Diseases, Copenhagen University Hospital, Copenhagen, Denmark; 4Department of Epidemiology, University of Southern Denmark, Odense, Denmark; 5Department of Gastroenterology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; 6Department of Gastroenterology, Hvidovre Hospital, University of Copenhagen, Copenhagen, Denmark; 7Department of Clinical Microbiology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; 8Department of Gastroenterology, Glostrup Hospital, University of Copenhagen, Copenhagen, Denmark; and 9Department of Pulmonary Medicine, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark

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C. difficile carriers can cause CDI in other patients

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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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✓ 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)

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 patients¹

¹ Lanzas C et al. Infect Control Hosp Epidemiol 2011

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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.


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.

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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.


Within-hospital transmission alone is insufficient to sustain endemic conditions in hospitals without the constant importation of colonized 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.


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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.
**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

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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

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Detected, symptomatic cases
- Relatively few in number
- Contaminate the hospital environment
- Placed under isolation precautions

Undetected, asymptomatic cases
- Outnumber symptomatic patients 2:1 to 7:1
- Contaminate the hospital environment
- Are not placed under isolation precautions at the moment

Current infection control measures

Future infection control measures?
Institut Universitaire de Cardiologie et Pneumologie de Québec

- 354-beds Canadian tertiary institution
- Endemic for CDI

HA-CDI rates, 2004-2013

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).
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)\(^1\)


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

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**CD-AC measures**

Goal: decrease basic reproductive number...

... Not necessarily interrupt!

A pragmatic decision

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**REALLY?**

Can’t we just improve standard precautions?

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C. difficile carrier
Infection control measures

- 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
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Why gloves?
Why not only soap and water?

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


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Efficacy of gloves

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

<table>
<thead>
<tr>
<th>Event No.</th>
<th>Patient Contact Site</th>
<th>Glove Type</th>
<th>Leak-Test Result (Did Glove Leak?)</th>
<th>Use Time, min</th>
<th>Microorganism</th>
<th>Colony Count on Gloves, cfu*</th>
<th>Colony Count on Hands, cfu*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oral</td>
<td>Vinyl</td>
<td>Yes</td>
<td>10</td>
<td>Enterobacter cloacae</td>
<td>2.0×10⁵</td>
<td>1.0×10⁴</td>
</tr>
<tr>
<td>2</td>
<td>Oral</td>
<td>Vinyl</td>
<td>Yes</td>
<td>11</td>
<td>Acinetobacter calcoaceticus</td>
<td>1.2×10⁵</td>
<td>4.0×10⁴</td>
</tr>
<tr>
<td>3</td>
<td>Oral</td>
<td>Vinyl</td>
<td>Yes</td>
<td>17</td>
<td>A. calcoaceticus</td>
<td>6.0×10⁵</td>
<td>4.0×10⁴</td>
</tr>
<tr>
<td>4</td>
<td>Oral</td>
<td>Vinyl</td>
<td>No</td>
<td>11</td>
<td>A. calcoaceticus</td>
<td>2.0×10⁵</td>
<td>2.0×10⁴</td>
</tr>
<tr>
<td>5</td>
<td>Oral</td>
<td>Vinyl</td>
<td>Yes</td>
<td>6</td>
<td>A. calcoaceticus</td>
<td>4.0×10⁵</td>
<td>1.0×10⁴</td>
</tr>
<tr>
<td>6</td>
<td>Oral</td>
<td>Vinyl</td>
<td>Yes</td>
<td>7</td>
<td>A. calcoaceticus</td>
<td>[Ellipses]</td>
<td>[Ellipses]</td>
</tr>
<tr>
<td>7</td>
<td>Oral</td>
<td>Vinyl</td>
<td>Yes</td>
<td>16</td>
<td>A. calcoaceticus</td>
<td>[Ellipses]</td>
<td>[Ellipses]</td>
</tr>
<tr>
<td>8</td>
<td>Oral</td>
<td>Vinyl</td>
<td>No</td>
<td>15</td>
<td>Pseudomonas aeruginosa</td>
<td>2.0×10⁵</td>
<td>2.0×10⁴</td>
</tr>
<tr>
<td>9</td>
<td>Rectal</td>
<td>Vinyl</td>
<td>No</td>
<td>2</td>
<td>Escherichia coli</td>
<td>2.0×10⁵</td>
<td>2.0×10⁴</td>
</tr>
<tr>
<td>10</td>
<td>Rectal</td>
<td>Vinyl</td>
<td>No</td>
<td>1</td>
<td>P. aeruginosa</td>
<td>1.0×10⁵</td>
<td>2.0×10⁴</td>
</tr>
<tr>
<td>11</td>
<td>Oral</td>
<td>Latex</td>
<td>No</td>
<td>6</td>
<td>A. calcoaceticus</td>
<td>1.0×10⁵</td>
<td>1.0×10⁴</td>
</tr>
</tbody>
</table>

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


2-4 log reduction
99% to 99.99% protective!

Prophylaxis for C. difficile carriers?

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

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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 \textit{tcdB} by PCR (BD GeneOhm Cdiff) once daily, 7 days a week

- Results available within 24 h and documented in the patients’ charts

Detection of carriers

- Only patients admitted \textit{through the emergency department} were screened

- Direct admissions to the wards were \textit{not} screened
  - E.g. electropysiology, elective surgeries, cath lab
Detection of carriers

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

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.
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
Detection of carriers

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Detection Assay</td>
<td>125 copies per sample</td>
</tr>
<tr>
<td>Quantity of stool on a rectal swab</td>
<td>50 ± 25 mg (local data)</td>
</tr>
<tr>
<td>C. difficile load among carriers</td>
<td>3.6 log10 CFU/g (SD, 1.3 log10)</td>
</tr>
<tr>
<td>No. copies on a rectal swab</td>
<td>318 ± 159 copies</td>
</tr>
</tbody>
</table>


Detection of carriers

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

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Detection of carriers

Detection of Clostridium difficile in Feces of Patients Admitted to the ICU.

<table>
<thead>
<tr>
<th>GDH Positive</th>
<th>GDH Negative</th>
<th>PCR Positive</th>
<th>PCR Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>TcdB Positive</td>
<td>TcdB Negative</td>
<td>TcdB Positive</td>
<td>TcdB Negative</td>
</tr>
<tr>
<td>99% (95% CI)</td>
<td>99% (95% CI)</td>
<td>100% (16/16)</td>
<td>0% (0/0)</td>
</tr>
</tbody>
</table>


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 +)

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

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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.
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


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

Incidence rate among university hospitals, 2011-2012

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preintervention Period</th>
<th>Postepidemic Period</th>
<th>Intervention Period</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study periods</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative duration, mo</td>
<td>35</td>
<td>76</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>4-wk Periods, No.</td>
<td>38</td>
<td>38</td>
<td>17</td>
<td>NA</td>
</tr>
<tr>
<td>Admissions, No.</td>
<td>43 783</td>
<td>83 314</td>
<td>18 382</td>
<td>NA</td>
</tr>
<tr>
<td>Patient-days, No.</td>
<td>276 072</td>
<td>600 358</td>
<td>127 883</td>
<td>NA</td>
</tr>
<tr>
<td>Screening for C difficile asymptomatic carriers, No./Hct No. (%)</td>
<td>NA</td>
<td>NA</td>
<td>75/99/8218 (92.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Screened patients</td>
<td>NA</td>
<td>NA</td>
<td>368/75/99 (4.1B)</td>
<td>NA</td>
</tr>
<tr>
<td>Asymptomatic carriers</td>
<td>NA</td>
<td>NA</td>
<td>66</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (95% CI) of HA-CDIs per 10,000 patient-days</td>
<td>11.1 (9.9-12.4)</td>
<td>6.9 (6.3-7.6)</td>
<td>3.0 (2.1-4.0)</td>
</tr>
<tr>
<td>Periods above government-imposed target, No. per 10,000 admissions</td>
<td>20 (52.6)</td>
<td>20/82 (24.4)</td>
<td>6 (17.0)</td>
</tr>
<tr>
<td>Incidence (95% CI) of CDIs associated with ambulatory care settings per 10,000 admissions</td>
<td>0.27 (0.14-0.45)</td>
<td>0.35 (0.23-0.49)</td>
<td>0.54 (0.26-0.93)</td>
</tr>
<tr>
<td>Incidence (95% CI) of hospital-acquired community-acquired CDIs per 1000 admissions</td>
<td>0.75 (0.52-1.03)</td>
<td>0.59 (0.44-0.77)</td>
<td>0.49 (0.22-0.86)</td>
</tr>
</tbody>
</table>
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<th>Variable</th>
<th>Preintervention Period</th>
<th>Postepidemic Period</th>
<th>Intervention Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications, No./total No. (%)</td>
<td>NA</td>
<td>31/383 (8.1)</td>
<td>3/38 (7.9)</td>
</tr>
<tr>
<td>10-d all-cause mortality</td>
<td>NA</td>
<td>5/383 (1.3)</td>
<td>7/38 (18.4)</td>
</tr>
<tr>
<td>Admission to intensive care unit</td>
<td>6/306 (2.0)</td>
<td>7/346 (2.0)</td>
<td>0/38 (0.0)</td>
</tr>
<tr>
<td>Colorectomy</td>
<td>2/306 (0.7)</td>
<td>3/346 (0.7)</td>
<td>1/38 (2.6)</td>
</tr>
<tr>
<td>Readmission for C. difficile recurrence</td>
<td>17/306 (5.6)</td>
<td>3/346 (0.7)</td>
<td>0/38 (0.0)</td>
</tr>
<tr>
<td>P Value*</td>
<td>.99</td>
<td>.48</td>
<td>.99</td>
</tr>
</tbody>
</table>

Figure 1. Incidence of healthcare-associated C. 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 C. 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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**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).

**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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ARIMA modeling

64 averted HA-CDI cases over 15 months
NNT: 118 admissions to screen and 6 CD-AC to isolate

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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)

![Graph showing sensitivity analyses](image)

Strain Analysis

![Graph showing strain analysis](image)

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<0.05 compared with 2005-2013 institutional global prevalence

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**Strain Analysis**

![Graph showing the proportion of NAP1/027 strain from 2005-2016](image)

**Figure S1.** Proportion (%) of NAP1/027 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

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**Potential Confounders**

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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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Intervention Period From December 8, 2011, to November 18, 2013 (n = 722)</th>
<th>Intervention Period From November 18, 2013, to March 7, 2015 (n = 121)</th>
<th>P Value</th>
<th>Immediate Change After the Start of the Intervention</th>
<th>Change in Trend After the Start of the Intervention</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total antimicrobials</td>
<td>1.001 (1.000-1.002)</td>
<td>.20</td>
<td>1.015 (1.004-1.027)</td>
<td>.02</td>
<td>1.004 (1.002-1.006)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>1.001 (1.001-1.002)</td>
<td>&lt;.001</td>
<td>0.94 (0.92-0.96)</td>
<td>&lt;.001</td>
<td>1.005 (1.004-1.006)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
Antimicrobial use

Total antimicrobial use

Healthcare-associated CDI incidence

Antimicrobial use

DDD/1000 patient-days

CDI rates per 10,000 patient-days

2012 2013 2014

DDD/1000JP SPIN B-lactam+ B-lactamase inhibitor
DDD/1000JP SPIN First Gen Cephalosporins
DDD/1000JP SPIN 3rd Gen Cephalosporins
DDD/1000JP SPIN Carbapenems

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Antimicrobial use

Antimicrobial and PPI use

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**Anti-CDI antimicrobials**

Change in trend: 0.97; p<0.001

**Intensity of CDI testing**

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% of negative CDI tests

LONG-TERM Follow-up

…The intervention never stopped
**Long-term Impact**

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

2015-16 average: 2.2 per 10,000 patient-days

2012-13 average: 6.1 per 10,000 patient-days

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Long-term follow-up

Figure 1. 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.

Impact of the Isolation Precaution Burden

… Can we isolate that many patients?
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Isolation of patients with CDI until symptom resolution
Average
ID_CDI_per 1000 PD

Isolation of patients with CDI until discharge
Average
ID_CDAC_per 1000 PD

Isolation of CDI carriers
Average
ID_total_per 1000 PD

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 6 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

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Isolation of patients with CDI until symptom resolution

Average

Isolation of patients with CDI until discharge

Average

Isolation of CDI carriers

Average

CDI incidence per 10,000 PD

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.

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**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

<table>
<thead>
<tr>
<th>C. difficile Colonization on Admission (%)</th>
<th>Contact Isolation Compliance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>25 50 75</td>
</tr>
</tbody>
</table>


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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-CID: $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
- Averted cost of recurrences: $122,895 to $271,000

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

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

GDH + but ToxAB -

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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


• 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

C. difficile testing – many tests, many potential uses

- Toxin detection assays: EIA and CCNA
- Toxigenic C. difficile detection: PCR

CDI diagnosis: Infection Prevention and Control

An UNDERAPPRECIATED USE of CDI testing?

Potential use of CD carrier isolation during outbreaks?

- No published data yet
- Preliminary data from 2 healthcare centers (n=4 outbreaks)
### Clostridium difficile Asymptomatic Carriers – The Hidden Part of the Iceberg?

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<table>
<thead>
<tr>
<th>Outbreak number</th>
<th>Hospital and specialty</th>
<th>Number of beds</th>
<th>No. HA CDI as far as screening</th>
<th>No. patients screened for C. difficile carriage</th>
<th>No. of CD-AC detected (%)</th>
<th>CD carrier containment measures</th>
<th>Outcome of outbreak</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>JHIL Cardiac surgery</td>
<td>Total 39</td>
<td>7 private</td>
<td>26 semi-private 8 multi-patient</td>
<td>4</td>
<td>32</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>2e PC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Not applicable</td>
<td>1 additional CDI case admitted to ward after unit-wide screening</td>
</tr>
<tr>
<td>2</td>
<td>JHIL General surgery</td>
<td>Total 20</td>
<td>6 private</td>
<td>14 semi-private</td>
<td>3</td>
<td>17</td>
<td>1 (0%)</td>
</tr>
<tr>
<td></td>
<td>2a ND</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>None CD carrier was discharged from ward on the day of diagnostic</td>
<td>No additional CDI case</td>
</tr>
<tr>
<td>3</td>
<td>JHIL Pneumology</td>
<td>Total 48</td>
<td>6 private</td>
<td>42 semi-private</td>
<td>7</td>
<td>42</td>
<td>16 (24%)</td>
</tr>
<tr>
<td></td>
<td>SpA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Modified Contact Precautions for CD carrier</td>
<td>1 CD carrier progressed to CDI 1 additional cases of CDI in patients who tested negative during the unit-wide screening</td>
</tr>
<tr>
<td>4</td>
<td>JHIL General medicine</td>
<td>Total 33</td>
<td>0 private</td>
<td>22 semi-private 11 multi-patient</td>
<td>7</td>
<td>21</td>
<td>1 (3%)</td>
</tr>
<tr>
<td></td>
<td>6W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Modified Contact Precautions for CD carrier</td>
<td>1 CD carrier progressed to CDI 5 additional cases of CDI in patients admitted to ward after unit-wide screening</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>44</strong></td>
<td><strong>18</strong></td>
<td><strong>112</strong></td>
<td></td>
<td></td>
<td><strong>12 (11%)</strong></td>
</tr>
</tbody>
</table>

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

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*CDI outbreaks are not created equal*

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  - Jean Longtin MD
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