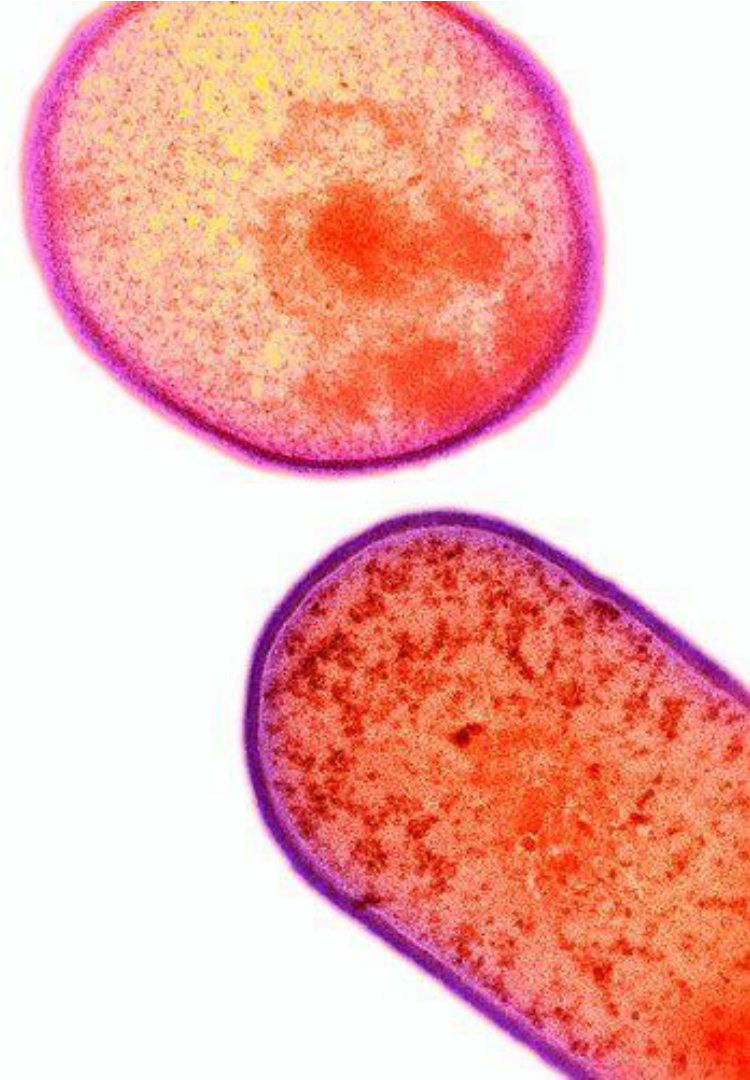


Isolating *C. difficile* Asymptomatic Carriers – Containing what Lies under the Waterline



Yves Longtin, MD

Chair, Infection Prevention and Control Unit

Jewish General Hospital

Associate professor of Medicine, McGill University

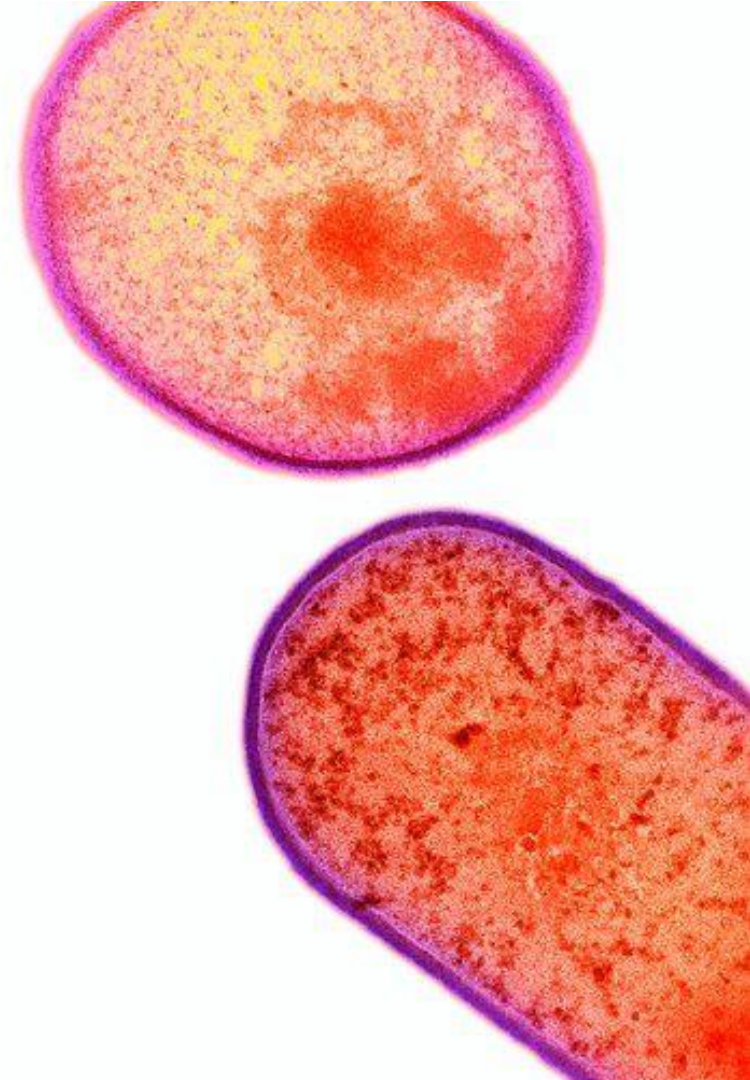
Yves.Longtin@McGill.ca

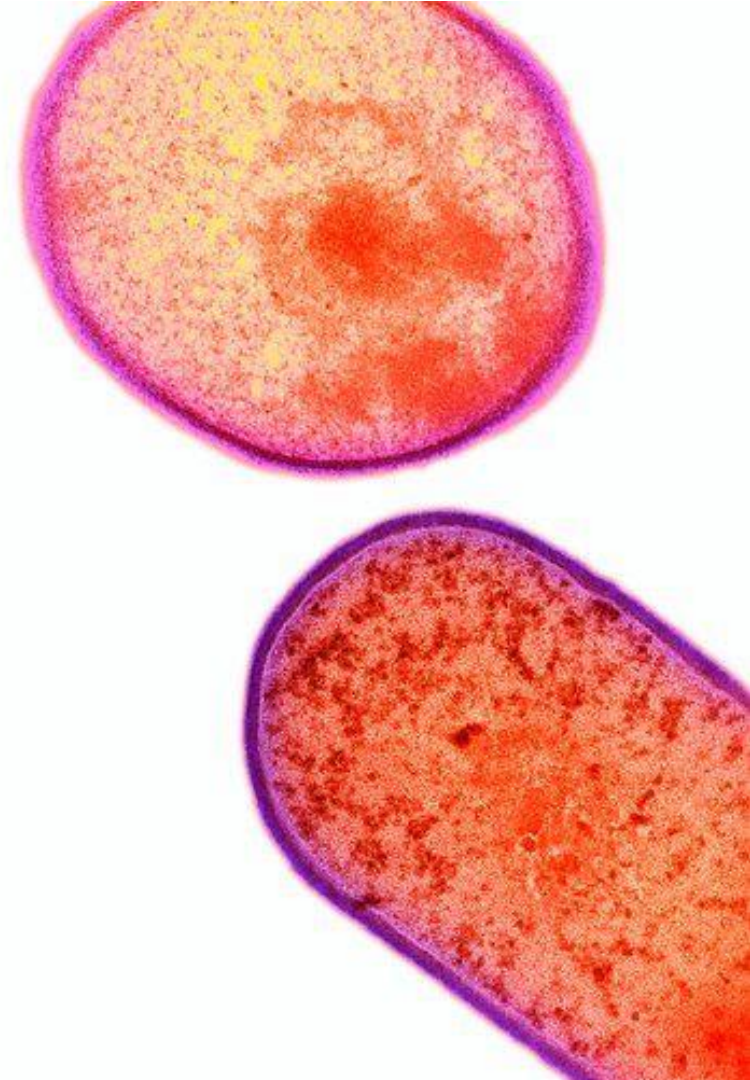
Disclosures

- 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*

OBJECTIVES

- ① Review literature
- ② Summarize our findings
- ③ Provide additional insight





BACKGROUND

Background

- *C. difficile* infections have become the **most frequent** cause of healthcare-associated infection in the USA¹⁻³
- **500,000 cases** per year²
- **29,000 deaths**²
- **\$4.8 billion** in excess medical costs²
- One of only 3 microorganisms designated as an “**Urgent threat**” to the population by CDC³

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.



NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015





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.

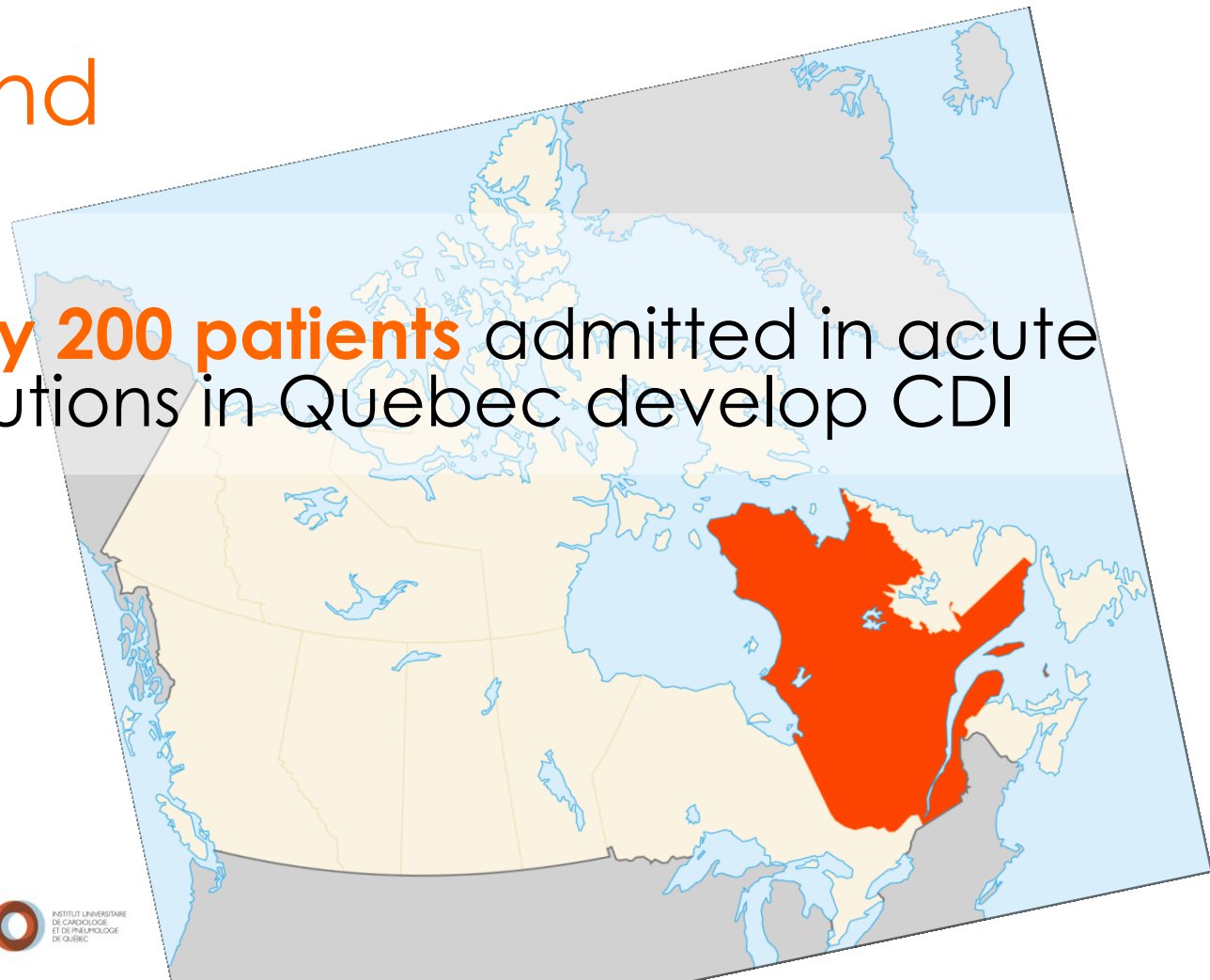
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.

Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.



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

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

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.

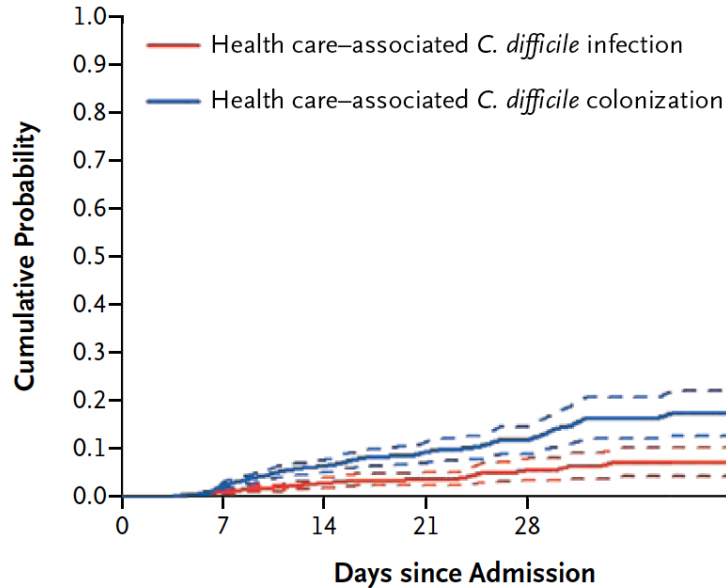
Cross-transmission in Acute Care

Asymptomatic colonization is frequent during hospitalization in acute care settings

- **9.4%** (54/569) of patients during their hospital stay¹
- **17%** acquired *C.difficile* during their hospitalization²
- **12%** of patients admitted on a geriatric unit³
- **8%** (6/76) during their hospital stay⁴
- **21%** (83/399) acquired *C. difficile* during their stay. A third progressed to CDI⁵
- Approximately **10%** after 21 days of hospitalisation⁶

Ongoing Transmission in Quebec Hospitals

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

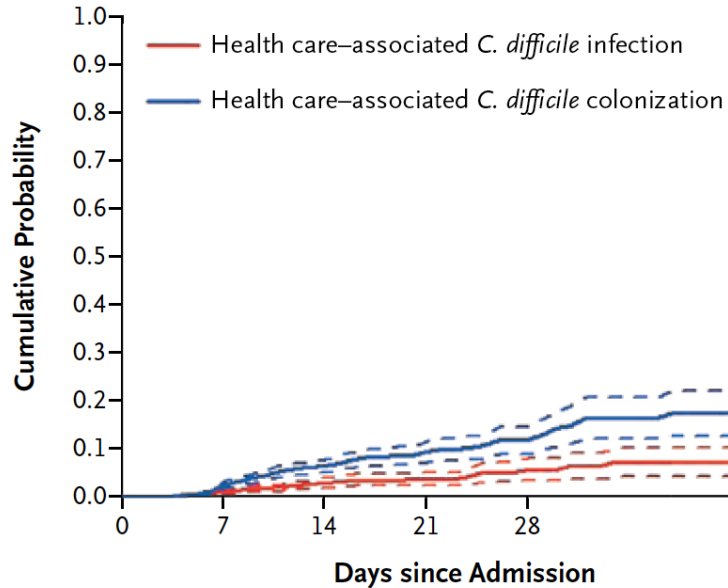


No. of Patients	3959	1723	592	274	148	45
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Figure 2. Times to Health Care–Associated *Clostridium difficile* Infection and Colonization during Hospitalization.

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 in Quebec Hospitals



No. of Patients 3959 1723 592 274 148 45

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?

Hospital food and C.difficile

Infect Control Hosp Epidemiol. 2016 Dec;37(12):1401-1407. Epub 2016 Oct 3.

An Evaluation of Food as a Potential Source for Clostridium difficile Acquisition in Hospitalized Patients.

Kwon JH1, Lanzas C2, Reske KA1, Hink T1, Seiler SM1, Bommarito KM1, Burnham CD3, Dubberke ER1.

Author information

Abstract

OBJECTIVE To determine whether Clostridium difficile is present in the food of hospitalized patients and to estimate the risk of subsequent colonization associated with C. difficile in food. **METHODS** This was a prospective cohort study of inpatients at a university-affiliated tertiary care center, May 9, 2011-July 12, 2012. Enrolled patients submitted a portion of food from each meal. Patient stool specimens and/or rectal swabs were collected at enrollment, every 3 days thereafter, and at discharge, and were cultured for C. difficile. Clinical data were reviewed for evidence of infection due to C. difficile. A stochastic, discrete event model was developed to predict exposure to C. difficile from food, and the estimated number of new colonization events from food exposures per 1,000 admissions was determined. **RESULTS** A total of 149 patients were enrolled and 910 food specimens were obtained. Two food specimens from 2 patients were positive for C. difficile (0.2% of food samples; 1.3% of patients). Neither of the 2 patients was colonized at baseline with C. difficile. Discharge colonization status was available for 1 of the 2 patients and was negative. Neither was diagnosed with C. difficile infection while hospitalized or during the year before or after study enrollment. Stochastic modeling indicated contaminated hospital food would be responsible for less than 1 newly colonized patient per 1,000 hospital admissions. **CONCLUSIONS** The recovery of C. difficile from the food of hospitalized patients was rare. Modeling suggests hospital food is unlikely to be a source of C. difficile acquisition. Infect Control Hosp Epidemiol 2016;1401-1407.

Asymptomatic Carriers

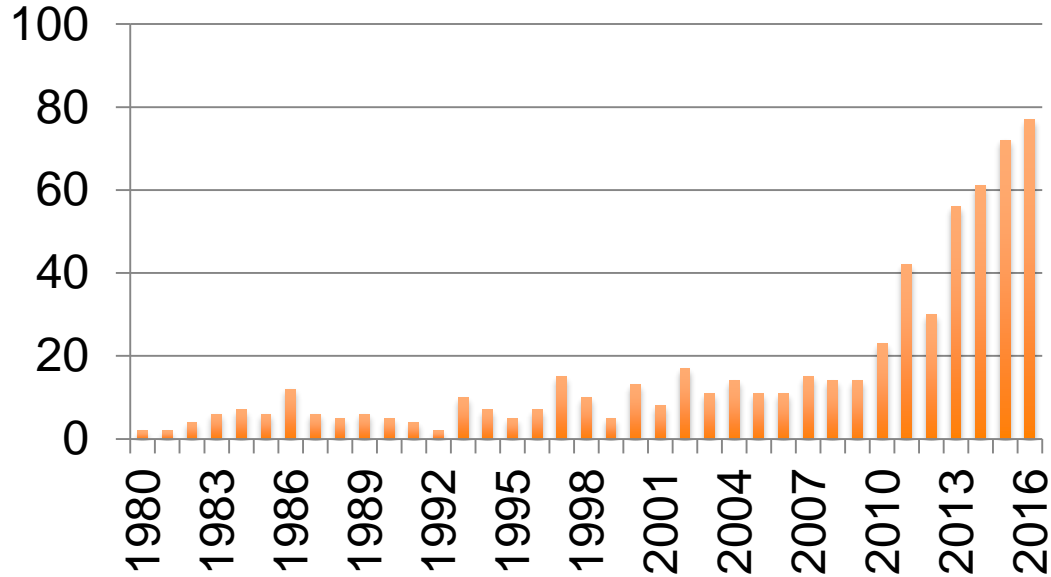


Asymptomatically colonized patients who have not had CDI can shed *C. difficile* spores, but the number of spores and degree of **contamination is not as great** as for patients with active CDI



There are currently **no data to support** detection or isolation of these asymptomatic patients. ***Area of controversy.***

Publications on CD colonization, 1980-2016



Barriers to isolation of carriers

- Lack of evidence rather than proof of lack of efficacy

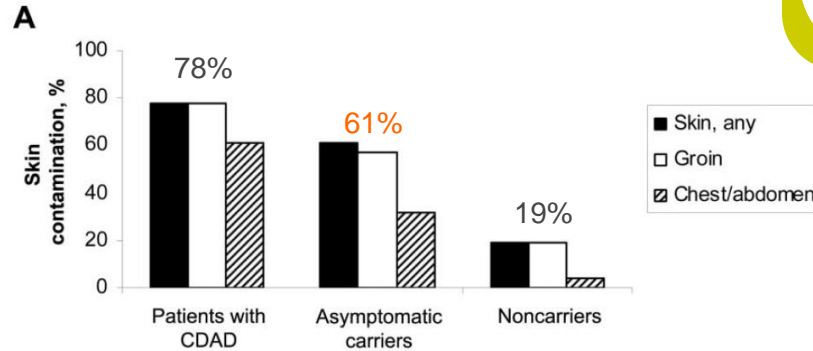
combined with

- Lack of feasibility
 - Need an assay that is rapid, sensitive and low-cost
 - Burden of isolation precautions

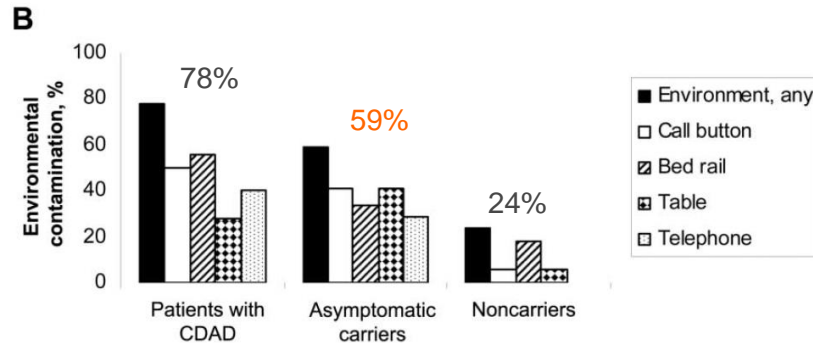




CD-AC are **not** as contagious as CDI patients... but almost!



C. difficile is present on the **SKIN** of asymptomatic carriers



C. difficile in the **immediate surroundings** of asymptomatic carriers

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.



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

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

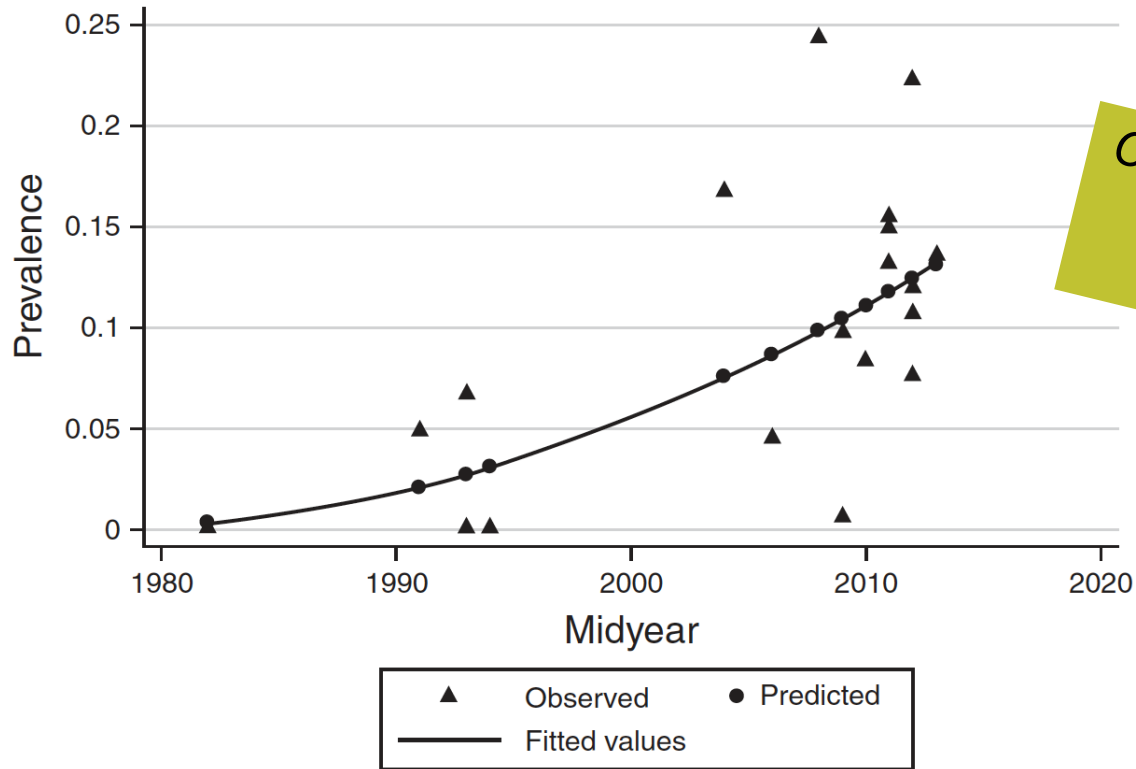


Figure 2. Toxinogenic *C. difficile* colonization trends over time. Observed (triangles) and fitted (circles) prevalence estimates, by study midyear.

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 Schönning,^{6,7} Anne Lester,^{6,8,9} Jette Houliind,^{8,9} Marie Stangerup,^{8,9} Magnus Gottlieb,¹⁰ and Jenny Dahl Knudsen^{6,8,9}

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

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

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 Schönning,^{6,7} Anne Lester,^{6,8,9} Jette Houliind,^{8,9} Marie Stangerup,^{8,9} Magnus Gottlieb,¹⁰ and Jenny Dahl Knudsen¹⁰

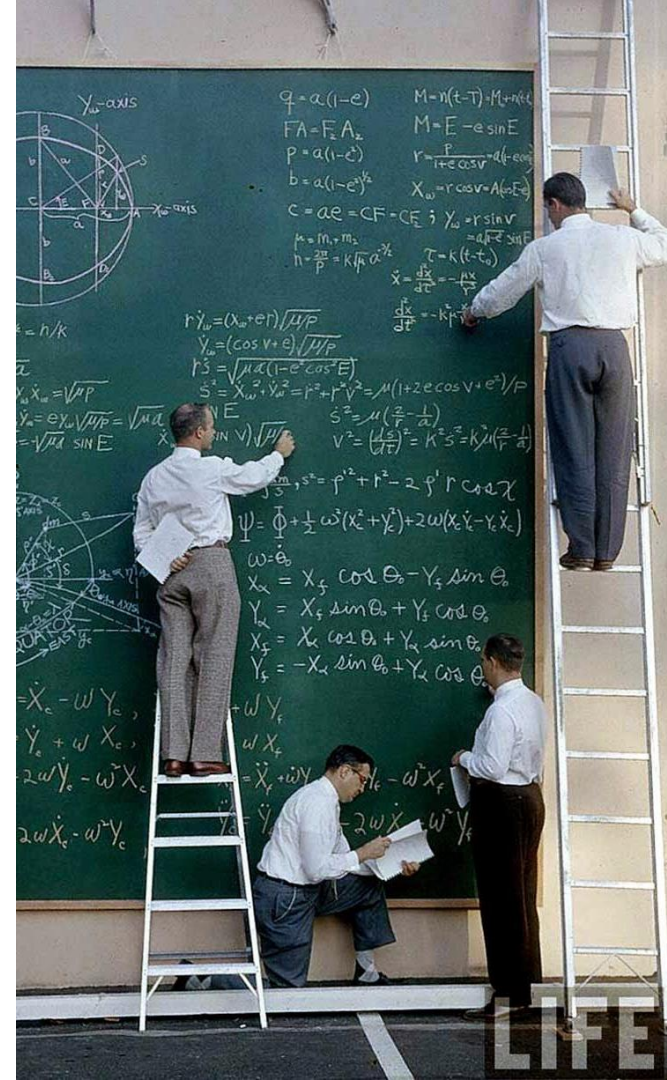
✓ Exposure to a CD carrier **doubled risk of CDI**
– OR 2.10 (95% CI, 0.97-4.53)

✓ Association between level of exposure and risk of CDI (no. carriers and LOS)

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



RESEARCH ARTICLE

Open Access

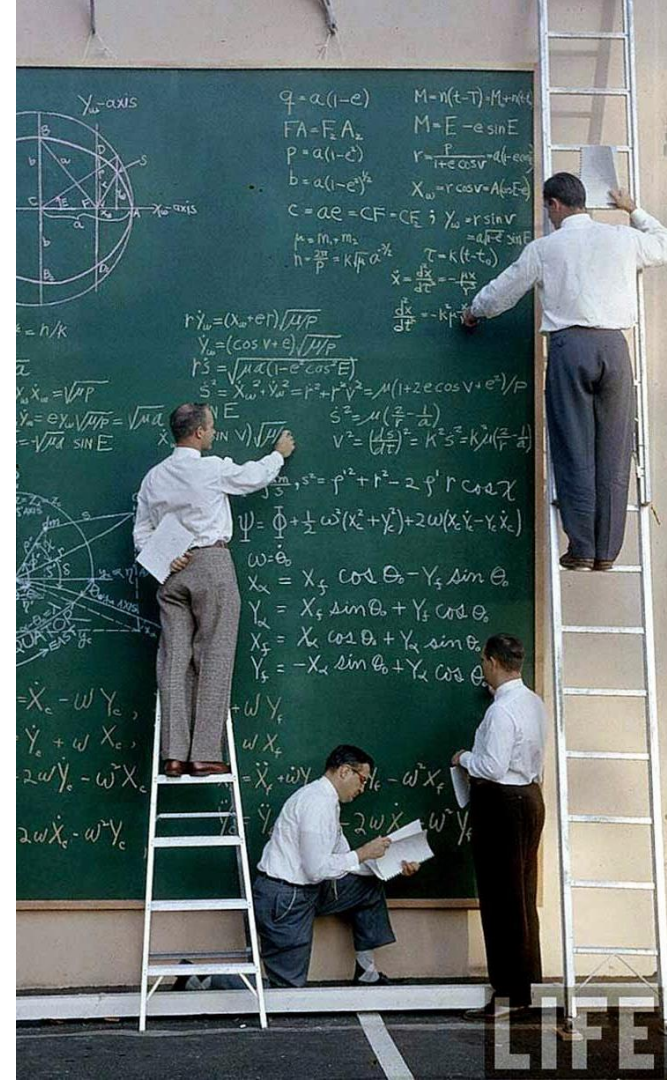


Assessing the effect of patient screening and isolation on curtailing *Clostridium difficile* infection in hospital settings

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.



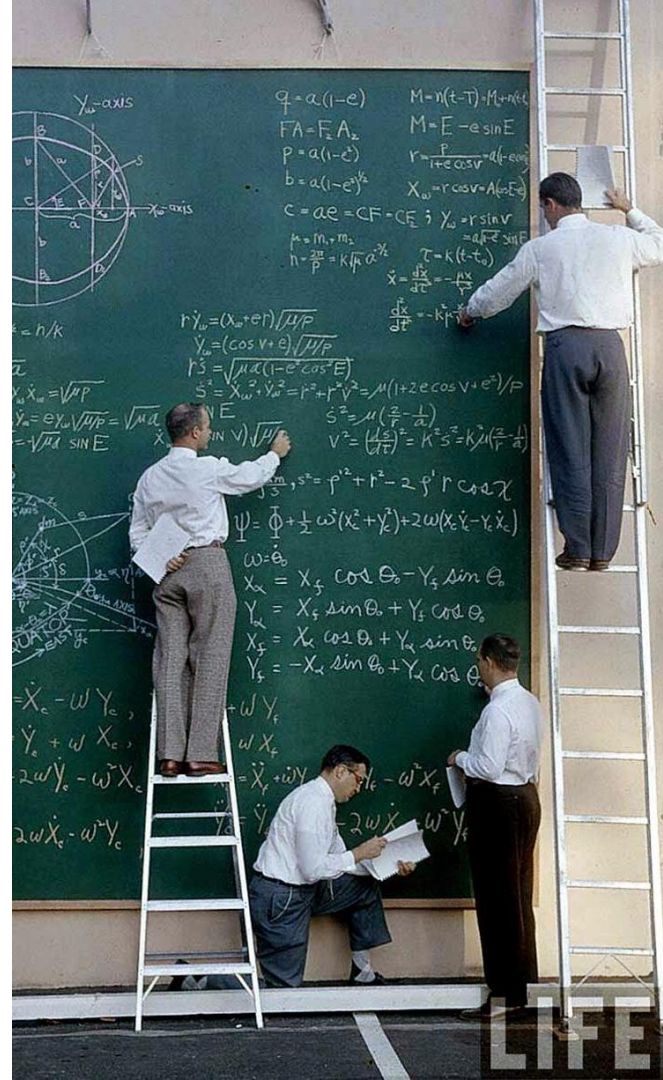
RESEARCH

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.



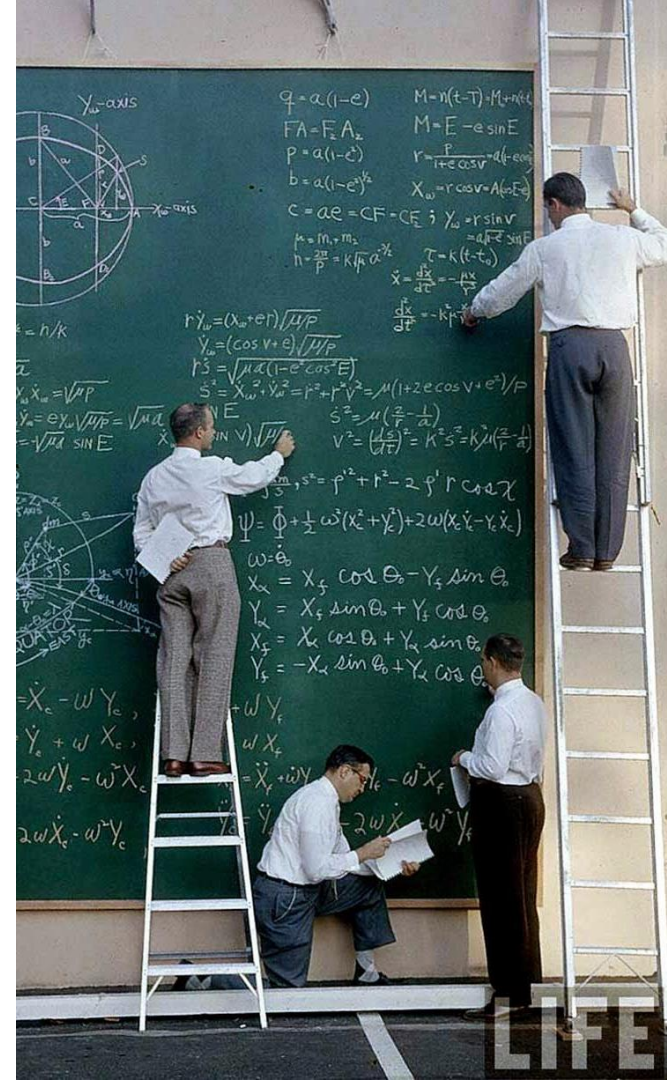
Isolation of *C. difficile* Carriers Alone and as Part of a Bundle Approach for the Prevention of *Clostridium difficile* Infection (CDI): A Mathematical Model Based on Clinical Study Data

Christos A. Grigoras^{1,2}, Fainareti N. Zervou¹, Ioannis M. Zacharioudakis¹, Constantinos I. Siettos², 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.

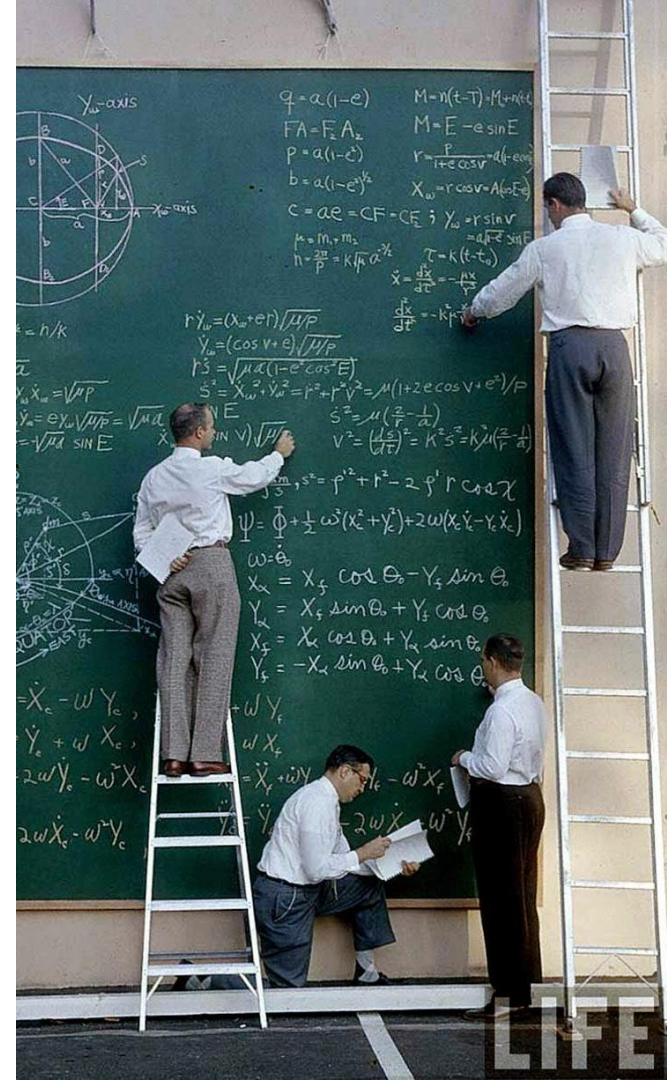


Healthcare-Associated *Clostridium difficile* Infections are Sustained by Disease from the Community

Angus McLure¹  · Archie C. A. Clements¹ ·
Marty Kirk¹ · Kathryn Glass¹

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.

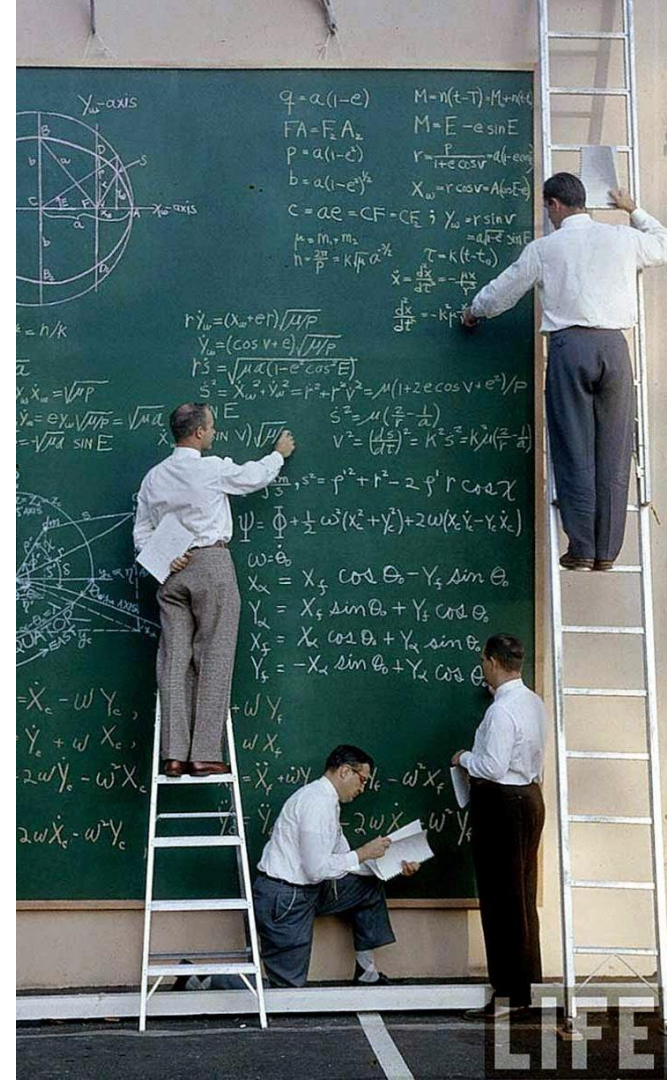


ORIGINAL ARTICLE

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

Cristina Lanzas, PhD;¹ Erik R. Dubberke, MD²

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.

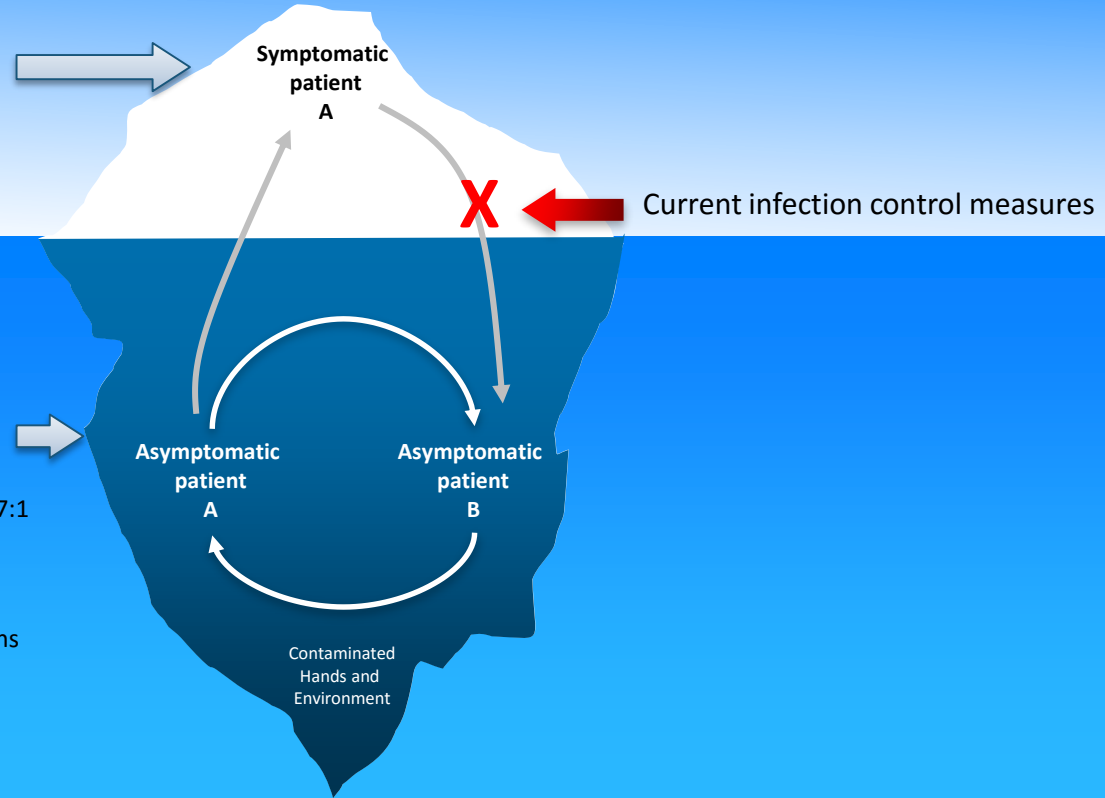


Detected, symptomatic cases

- 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

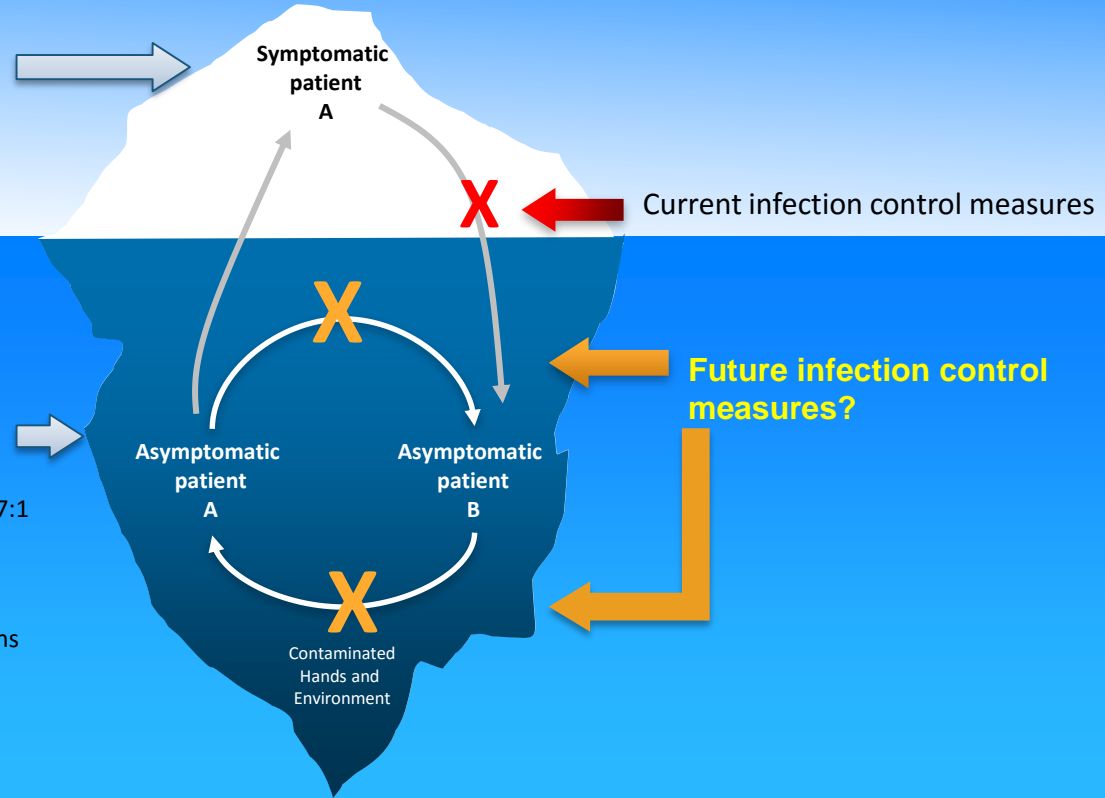


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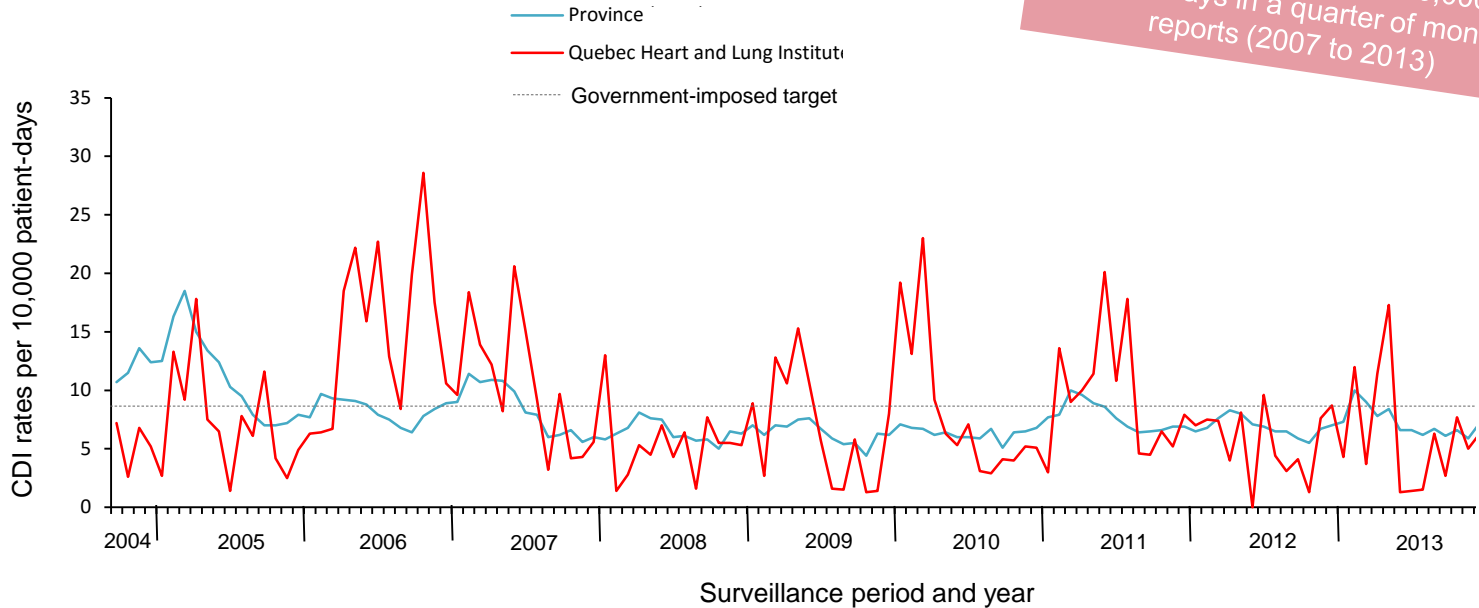
Institut Universitaire de Cardiologie et Pneumologie de Québec

- 354-beds Canadian tertiary institution
- Endemic for CDI



HA-CDI rates, 2004-2013

HA-CDI rates > 9.0 per 10,000 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).

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

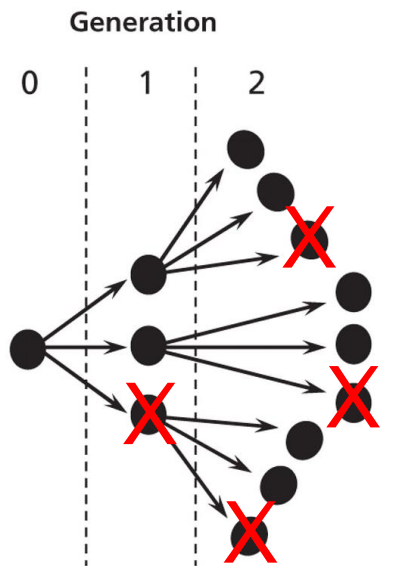
Control of CDI

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



CD-AC measures

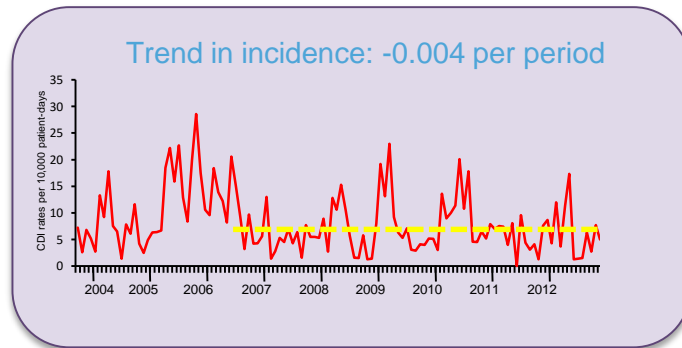


Initial phase of epidemic ($R_0 = 3$)

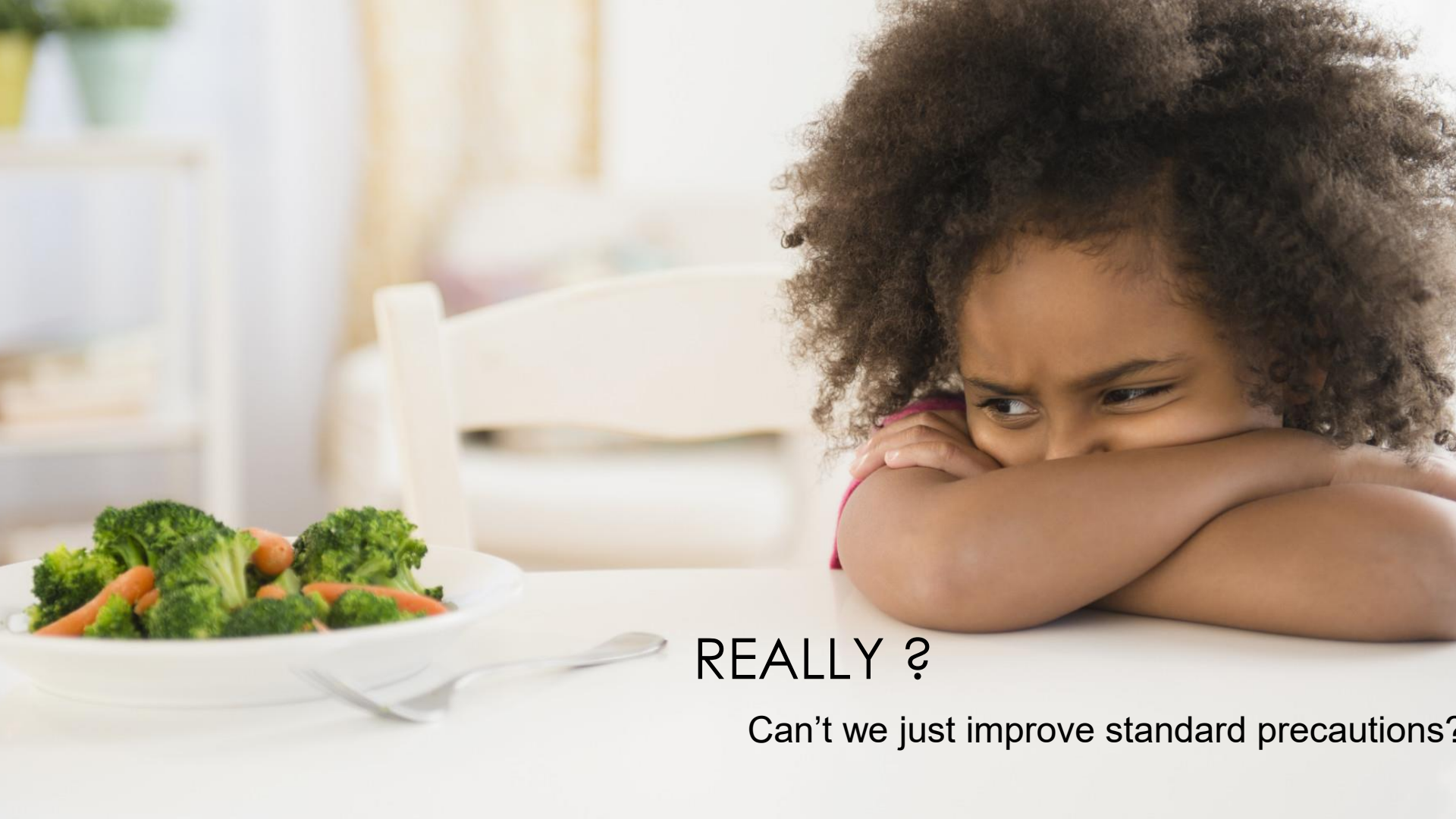
Goal: decrease basic reproductive number...

... Not necessarily interrupt!

A pragmatic decision



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

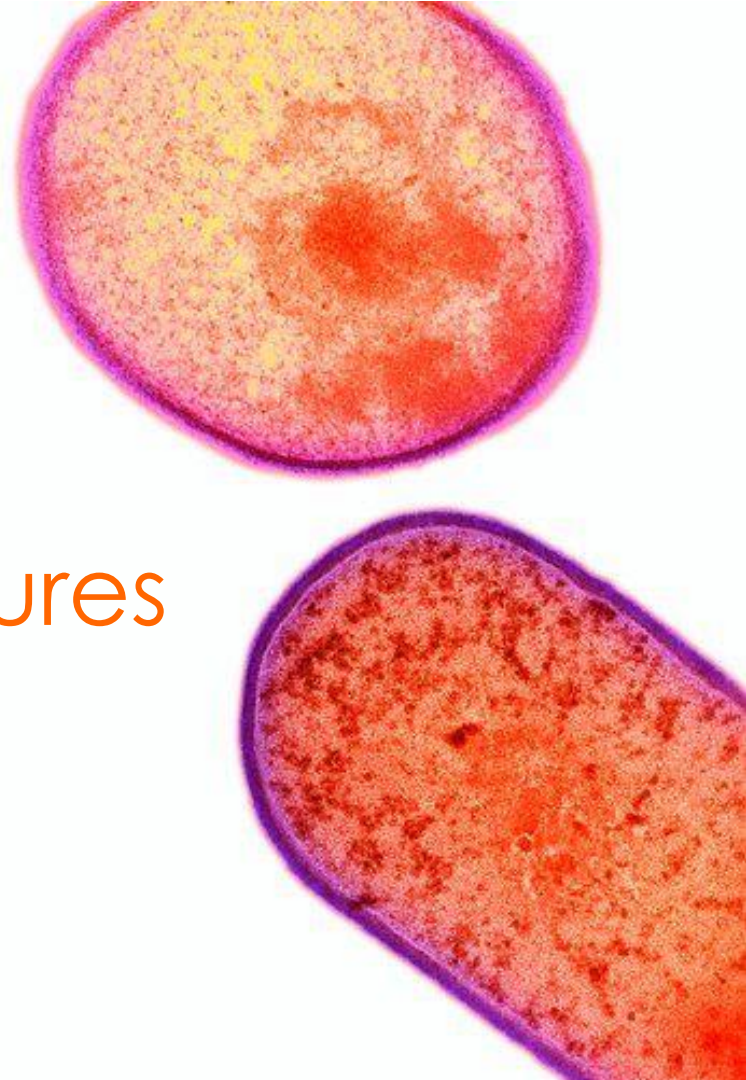


REALLY ?

Can't we just improve standard precautions?

C. difficile carrier

Infection control measures



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**

Infection Control Measures Recommended

Isolation Precautions

- Respect isolation precautions as described on isolation sign;
- Use regular (non-sterile) gloves when caring for the patient or before touching surfaces in the vicinity of the patient;
- Wash your hands with soap and water after contact with patient or his/her environment;
- Dedicate medical equipment to the patient (thermometer, sphygmomanometer, etc.);
- Dedicate the toilet or commode.

Patient Placement

- Flagged isolation in multi-patient room allowed (privacy curtain drawn and visible sign present at entrance of patient zone);
- Cohorting of patients with similar condition allowed
- Private room not required

Environmental Control

- Daily environmental disinfection with chlorine-based product;
- Disinfection of equipment leaving patient zone with chlorine-based product

Duration of precautions

- Until discharge; No pre-emptive isolation on readmission
- Measures can be temporarily suspended if patient leaves the room (e.g. going on examination)

Diagnosis and treatment of CDI

- In case of diarrhea compatible with infection, repeat testing for *C. difficile* infection on stool sample.
- If positive and presence of symptoms compatible with *C. difficile* infection, treat according to published guidelines

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

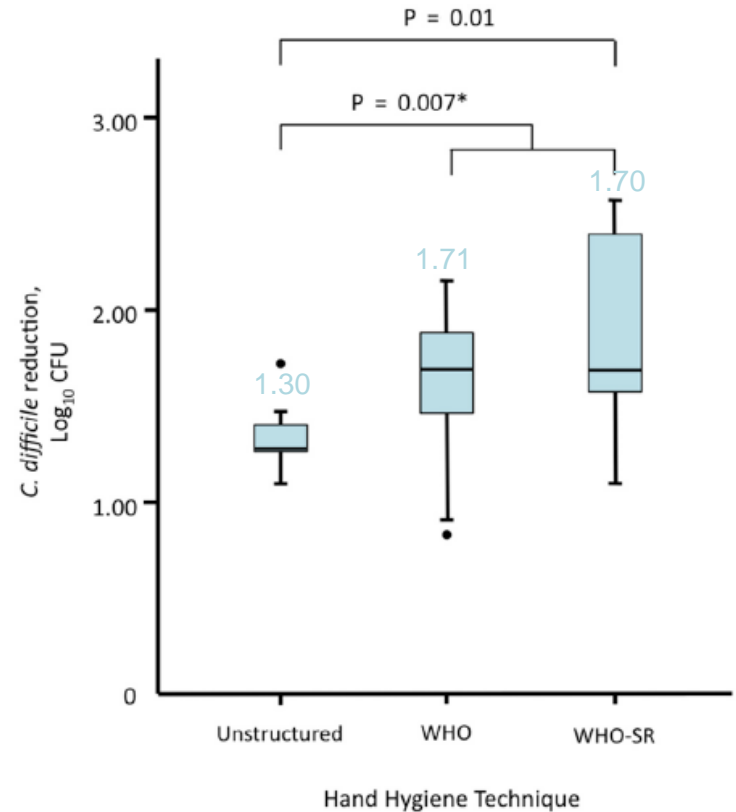


Fig 3. Efficacy of 3 hand hygiene techniques to remove *Clostridium difficile* from artificially contaminated hands. Results are expressed in CFU reduction on a logarithmic scale. The top and bottom of the box plots represent the interquartile ranges, and the horizontal lines represent the median values. 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.

Deschênes P et al. Am J Infect Control. 2017 May 16.

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	<i>Enterobacter cloacae</i>	2.0×10^5	1.0×10^1
2	Oral	Vinyl	Yes	11	<i>Acinetobacter calcoaceticus</i>	1.2×10^5	4.0×10^1
3	Oral	Vinyl	Yes	17	<i>A calcoaceticus</i>	6.5×10^2	5.0×10^0
4	Oral	Vinyl	No	11	<i>A calcoaceticus</i>	3.0×10^5	2.5×10^2
5	Oral	Vinyl	Yes	6	<i>A calcoaceticus</i>	4.2×10^4	1.0×10^1
6	Oral	Vinyl	Yes	7	<i>A calcoaceticus</i> , <i>Enterobacter aerogenes</i>	...†	...†
7	Oral	Vinyl	Yes	16	<i>A calcoaceticus</i>	5.2×10^3	9.0×10^1
8	Oral	Vinyl	No	15	<i>Pseudomonas aeruginosa</i>	2.1×10^3	2.0×10^1
9	Rectal	Vinyl	No	2	<i>Escherichia coli</i>	2.0×10^6	2.0×10^1
10	Rectal	Vinyl	No	1	<i>P aeruginosa</i>	1.3×10^4	2.0×10^1
11	Oral	Latex	No	6	<i>A calcoaceticus</i>	1.5×10^4	1.0×10^1

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

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

Prophylaxis for *C. difficile* carriers?

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

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

Detection of carriers

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

Detection of carriers

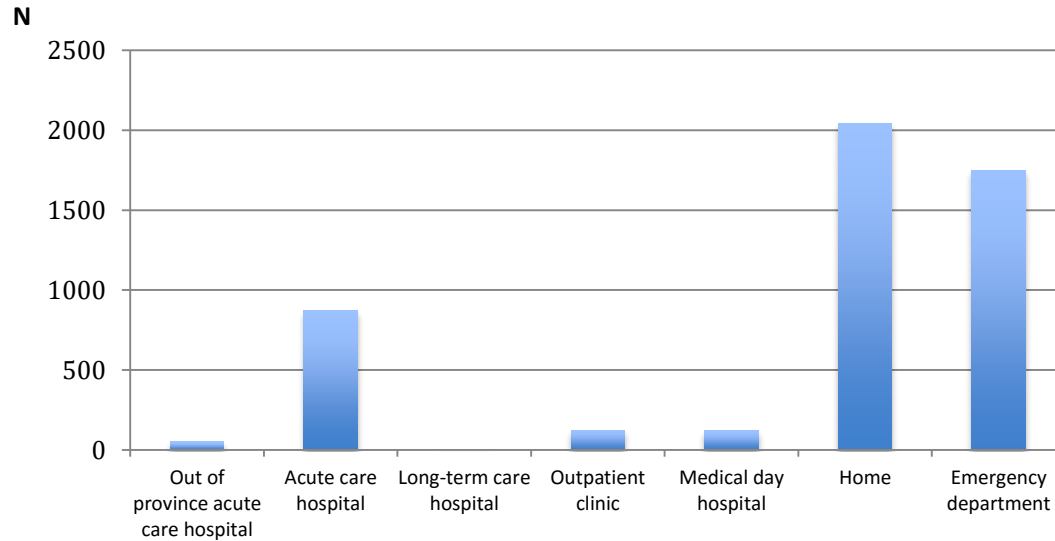
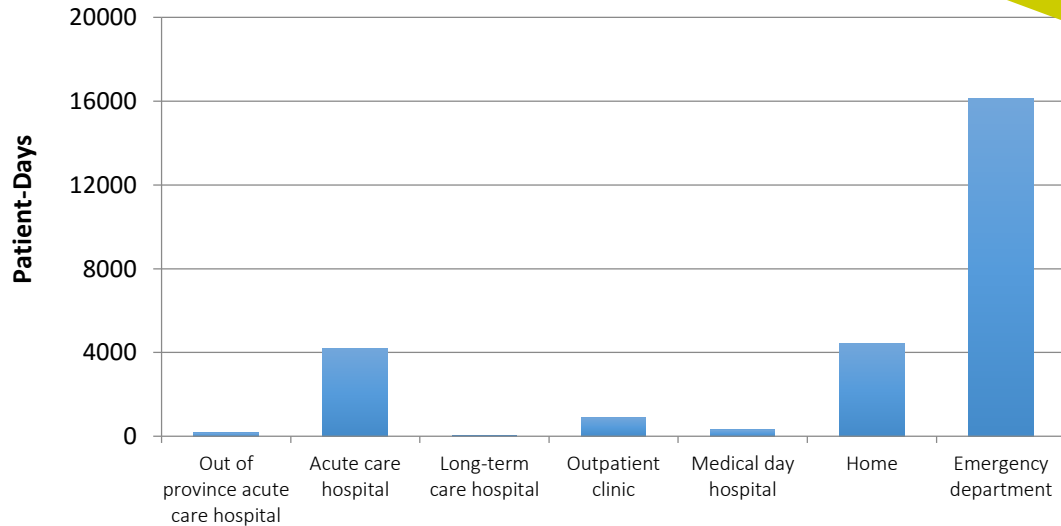


Figure 4. Origin of 4,953 consecutive admissions at the QHLI between Nov. 2014 and March 2015

Detection of carriers




 Admissions through ER accounts for most patient-days in the hospital

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

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

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 log ₁₀ CFU/g (SD, 1.3 log ₁₀) ¹
No. copies on a rectal swab	318 ± 159 copies

Detection of carriers

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

Elsabeth 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.

Detection of carriers

Detection of *Clostridium difficile* in Feces of Patients Admitted to

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 :		Sensitivity (% [95% CI])	Specificity (% [95% CI])	PPV (%)	NPV (%)
	Pos	Neg				
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 →

^aGDH ELFA was compared with *C. difficile* culture, and artus PCR and in-house PCR were compared with toxigenic culture. Pos, positive; Neg, negative.

^bFour of the false-negative samples were positive in all tests (GDH, artus, and in-house PCR).

Ingrid M. J. G. Sanders,^a
Tijper^a

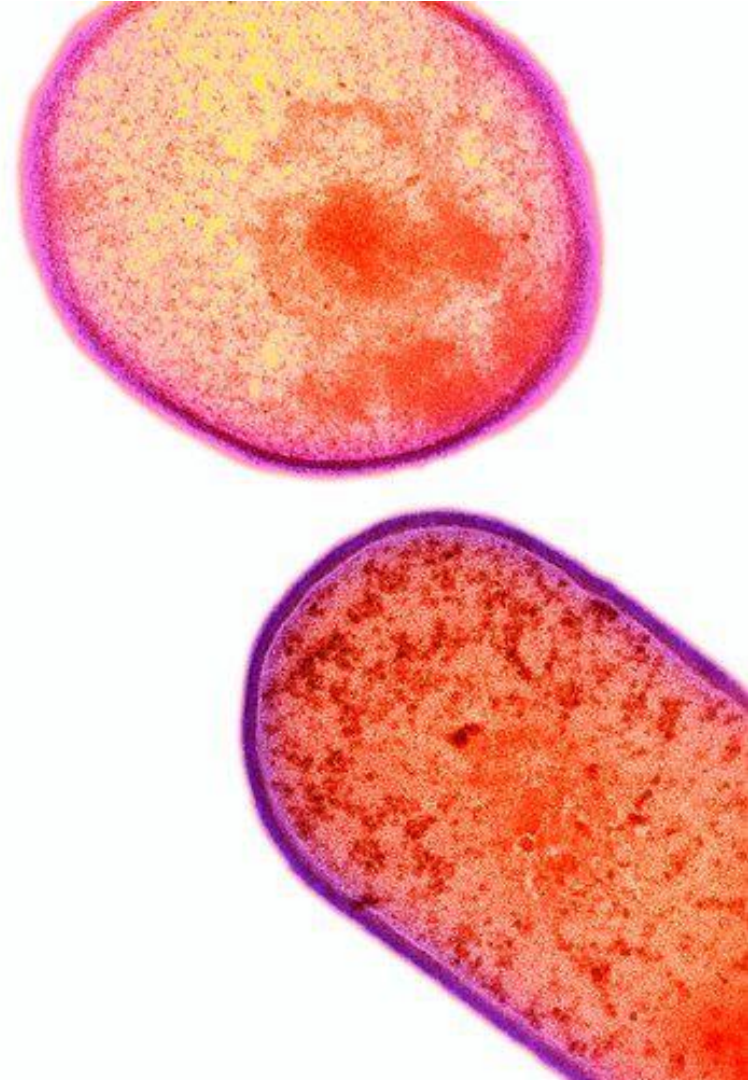
Medical Center, Leiden, the Netherlands; Department of Infectious Diseases, Radboud University Medical Center, Rotterdam, the Netherlands; and Department of Microbiology, Amphia Hospital, Breda, the Netherlands

Patients were asymptotically colonized with *C. difficile* in health care facilities, which is a higher risk of developing *C. difficile* infection. We compared a commercially available PCR detection assay (artus QS-RGQ kit CE; Qiagen), an enzyme immunoassay (GDH ELFA) (Vidas, bioMérieux), and a culture with (toxigenic) culture of *C. difficile* as gold standard for colonization. Test performances were compared with those obtained from asymptomatic patients. The prevalence in this collection was 5.1%. Compared to *C. difficile* culture, the sensitivity and negative predictive value (NPV) of the artus PCR, GDH ELFA, and in-house PCR were 95.8%, 93.4%, 31.9%, 99.9%, 34.7%, and 99.3%, respectively. Consistency, specificity, PPV, and NPV of the artus PCR were 95.8%, 93.4%, 31.9%, and 99.9%, respectively. We conclude that in a low-risk patient population, both GDH ELFA and artus PCR can be used 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.

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 +)

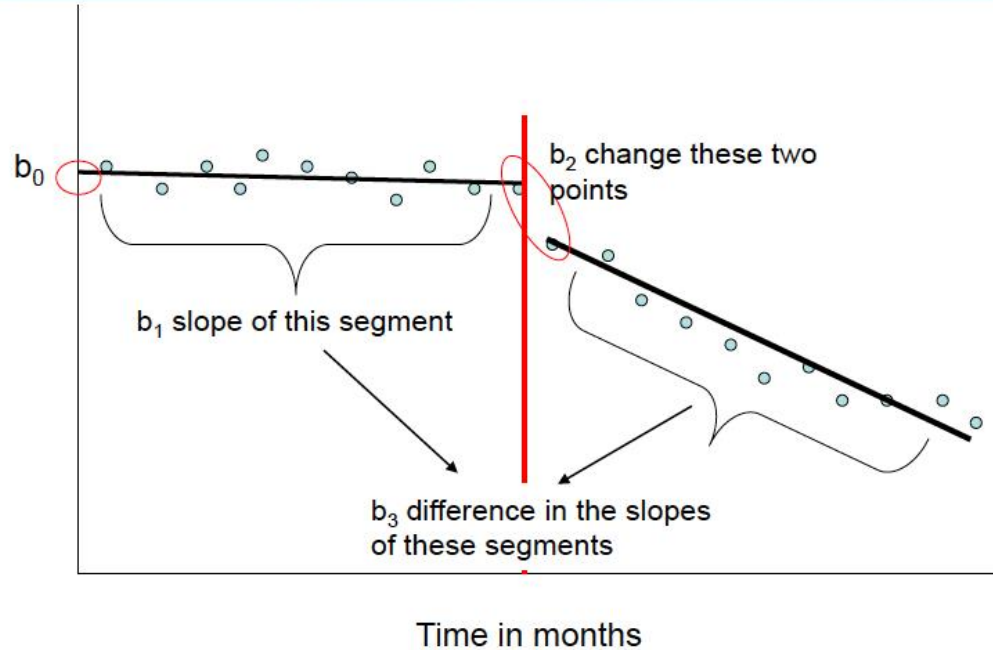


ANALYSIS

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

$$Y_t = b_0 + b_1T + b_2D + b_3P$$



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Center for
Health
Research

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>

INSPQ Centre d'expertise et de référence en santé publique
Publié sur INSPQ - Institut national de santé publique du Québec (<https://www.inspq.qc.ca>)

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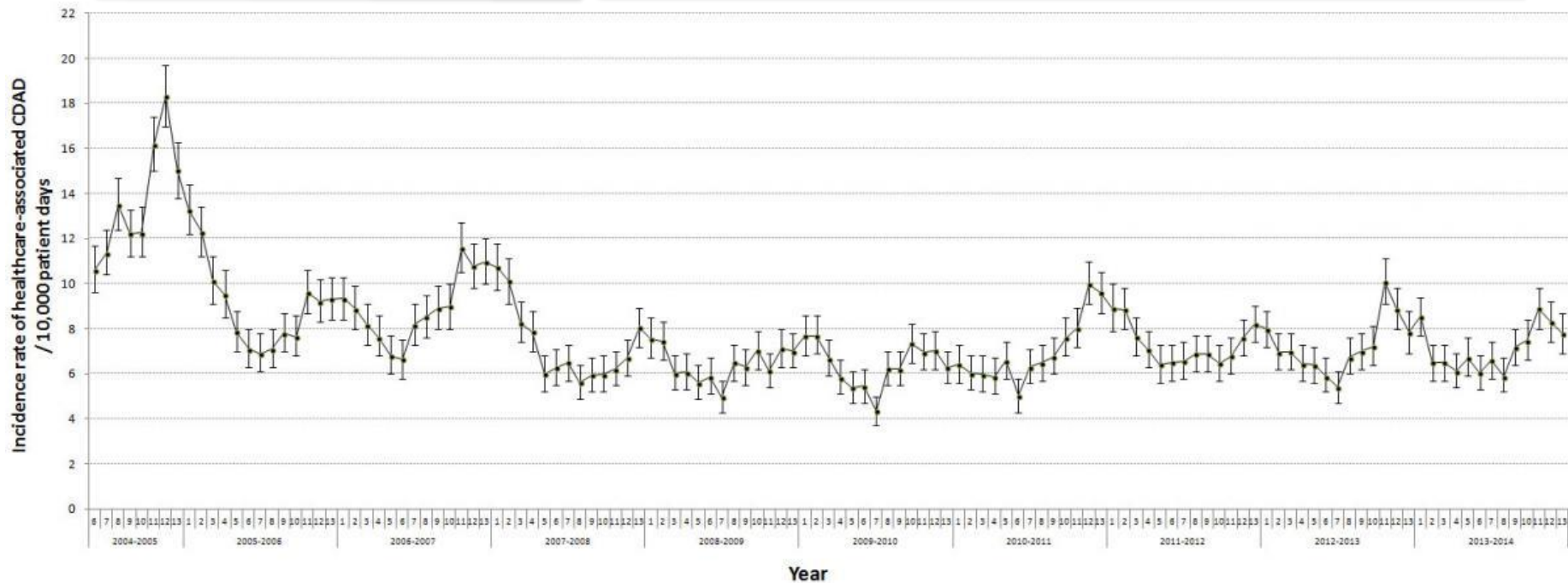
Clostridium difficile Diarrhées associées au
Résultats de surveillance 2014-2015

Entre le 1er avril 2014 et le 31 mars 2015, 95 installations ont participé à la surveillance des diarrhées à Clostridium difficile (DACD), pour un cumul de 5 076 655 jours-présence (tableau 1). Ces installations ont rapporté 3 453 DACD nosocomiales. Le taux d'incidence des DACD nosocomiales était de 6,8 par 10 000 jours-présence. Ce taux d'incidence des DACD significativement en baisse par rapport à celui de 2013-2014. La proportion de décès à 10 jours a été de 9,8 % (n = 285) et celle à 30 jours, de 18,6 % (n = 543). Au total, 36 (1,2 %) colectomies ont été déclarées. Les données ont été extraites le 20 mai 2015 et mises à jour le 1er juin 2015 pour les complications.

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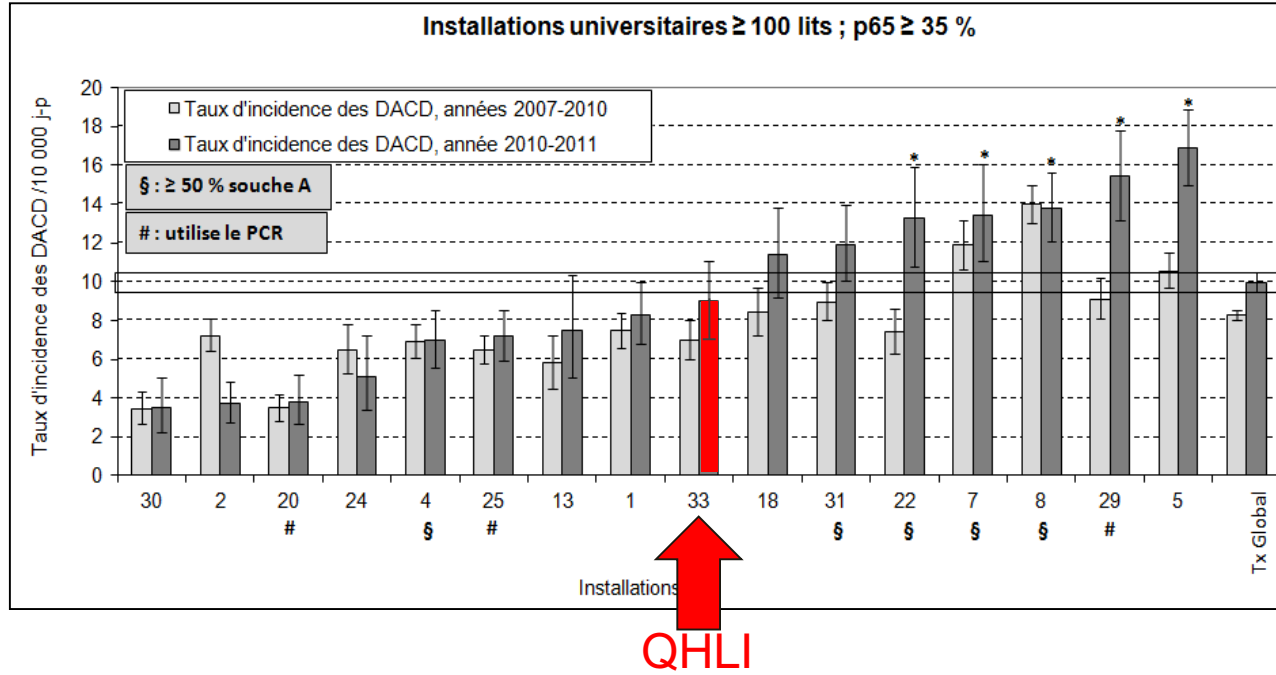
EPIDEMIC PERIOD

POST-EPIDEMIC PERIOD



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

Incidence rate among university hospitals, 2011-2012



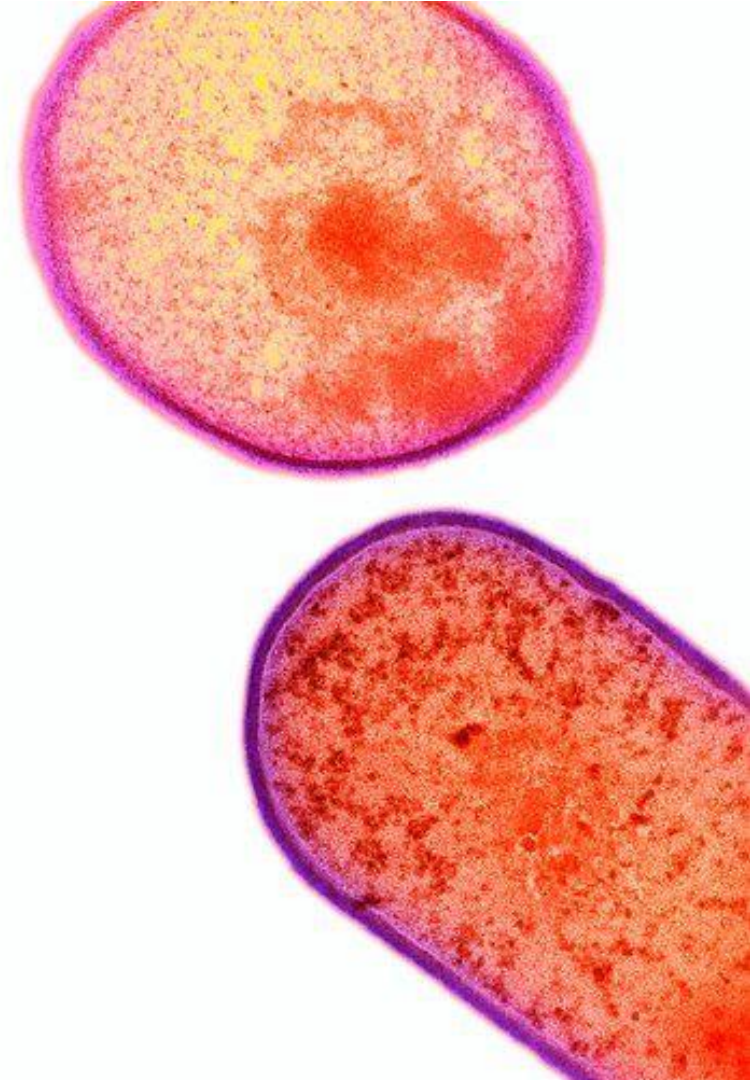
Analyses

3 complementary statistical methods

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

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

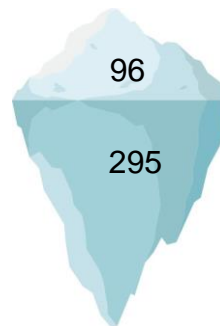
- ③ **ARIMA modeling**
 - To assess the impact
 - To evaluate the number of averted cases



RESULTS

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

Variable	Preintervention Period			P Value ^a
	Epidemic Period From August 22, 2004, to July 21, 2007	Postepidemic Period From July 22, 2007, to November 18, 2013	Intervention Period From November 19, 2013, to March 7, 2015	
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 <i>C difficile</i> 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

Carriage rate on admission

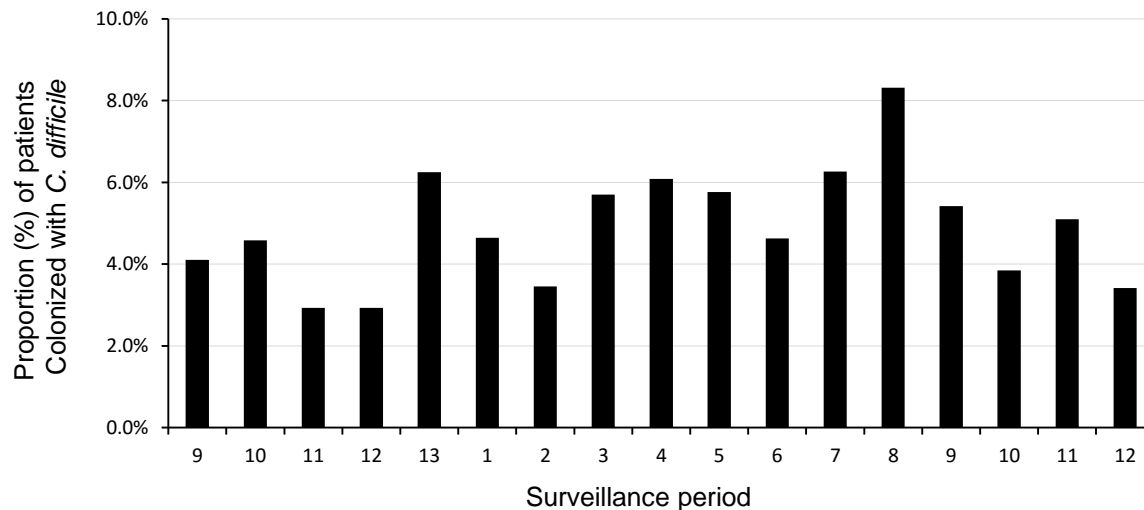


Figure. Proportion (%) of patients colonized with *Clostridium difficile* on admission per 4-week period, November 2013- March 2015, Quebec Heart and Lung Institute, Quebec City, Canada.

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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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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

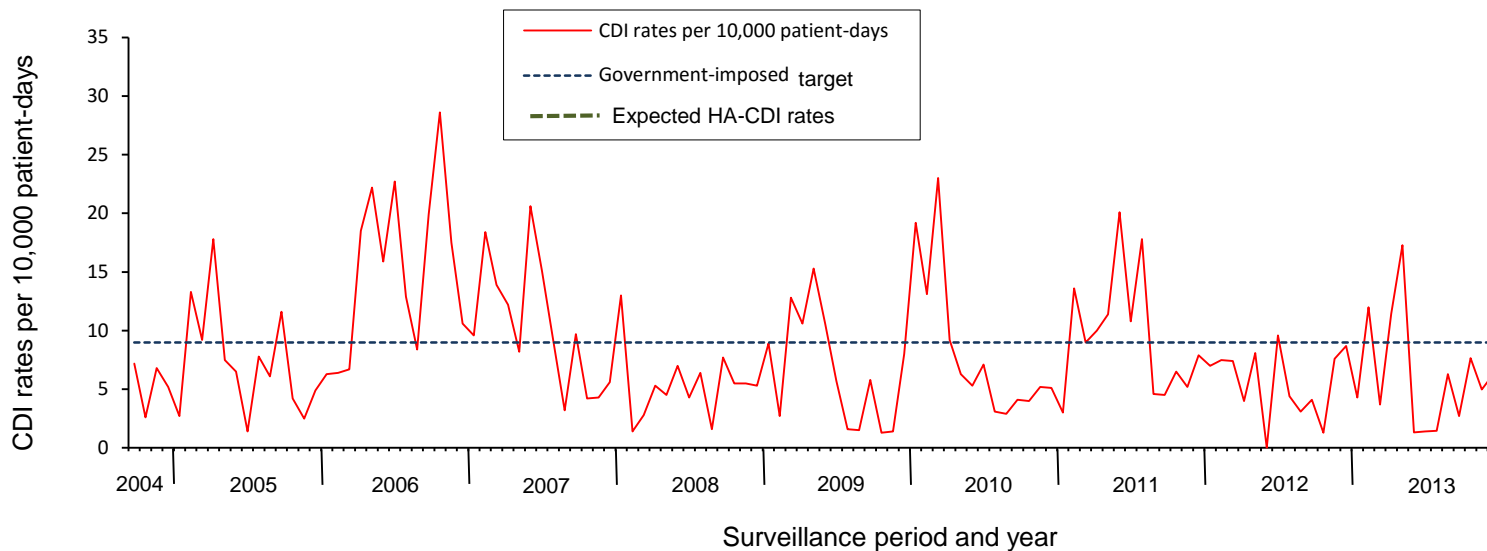


Figure 1. Incidence of healthcare-associated *Clostridium difficile* infection (CDI) per 4-week period according to standardized surveillance definitions, August 2004 - March 2015, Quebec Heart and Lung Institute, Quebec City, Canada. An intervention consisting of screening and isolation of *Clostridium 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).

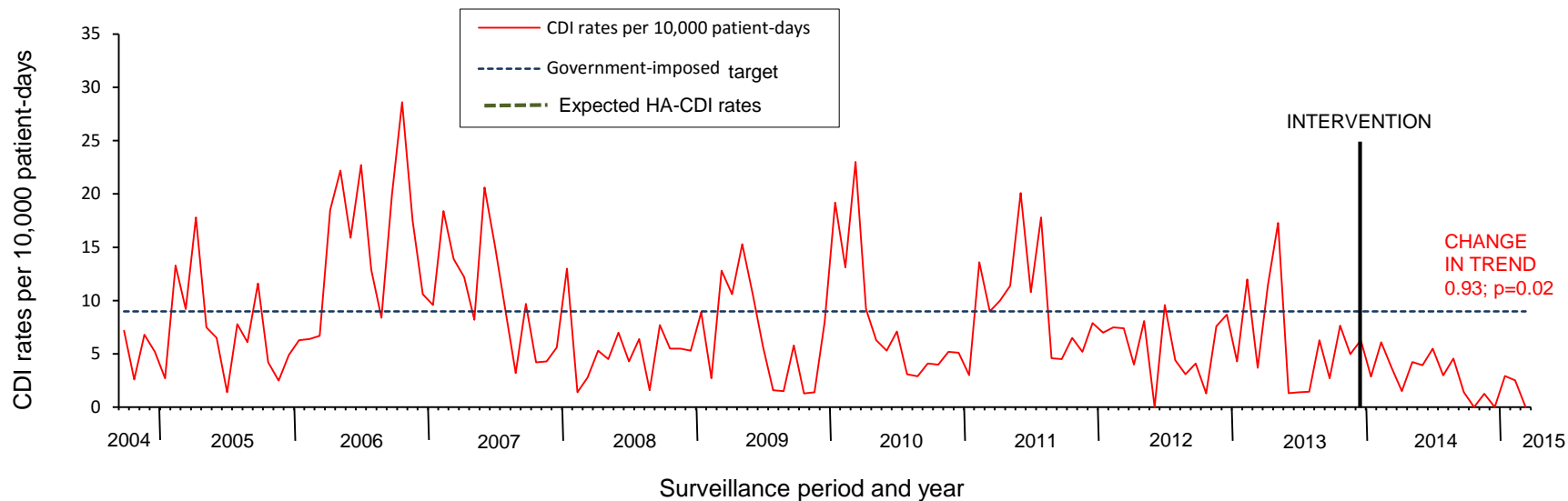


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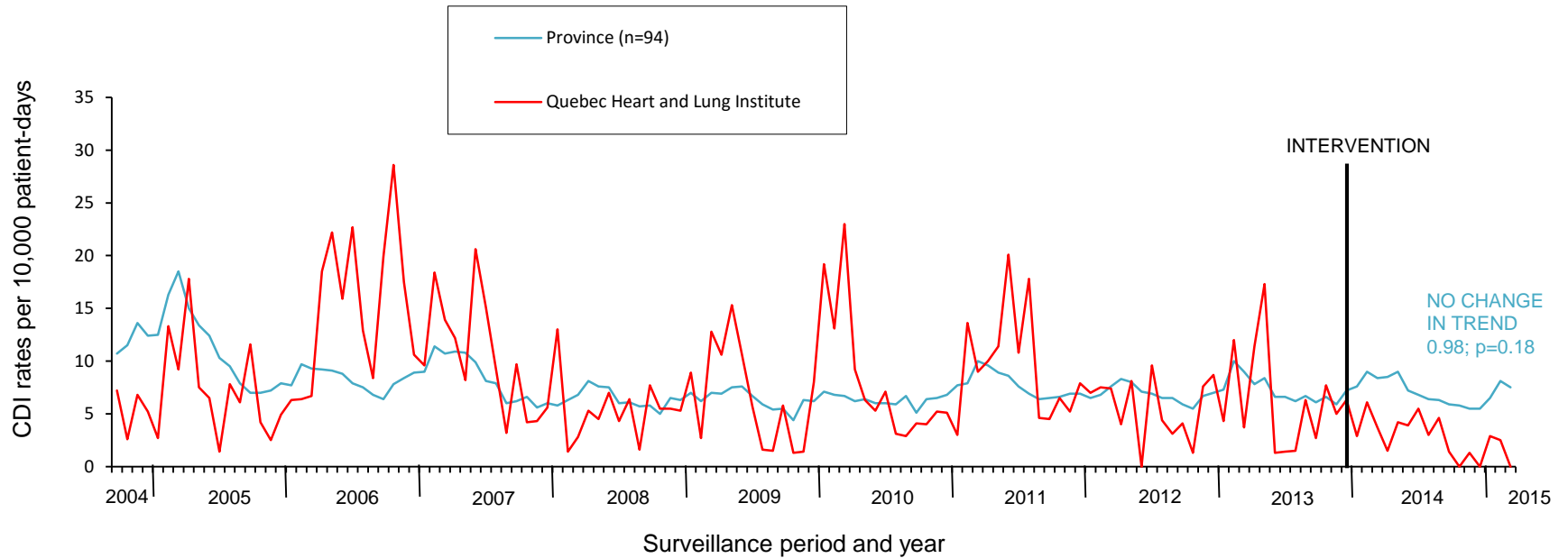


Figure 2. Incidence of healthcare-associated *Clostridium difficile* infection (CDI) per 4-week period at the Quebec Heart and Lung Institute and in 3 control groups: other institutions in Quebec City (n=6); matching academic institutions (n=15); and all institutions participating in the provincial CDI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

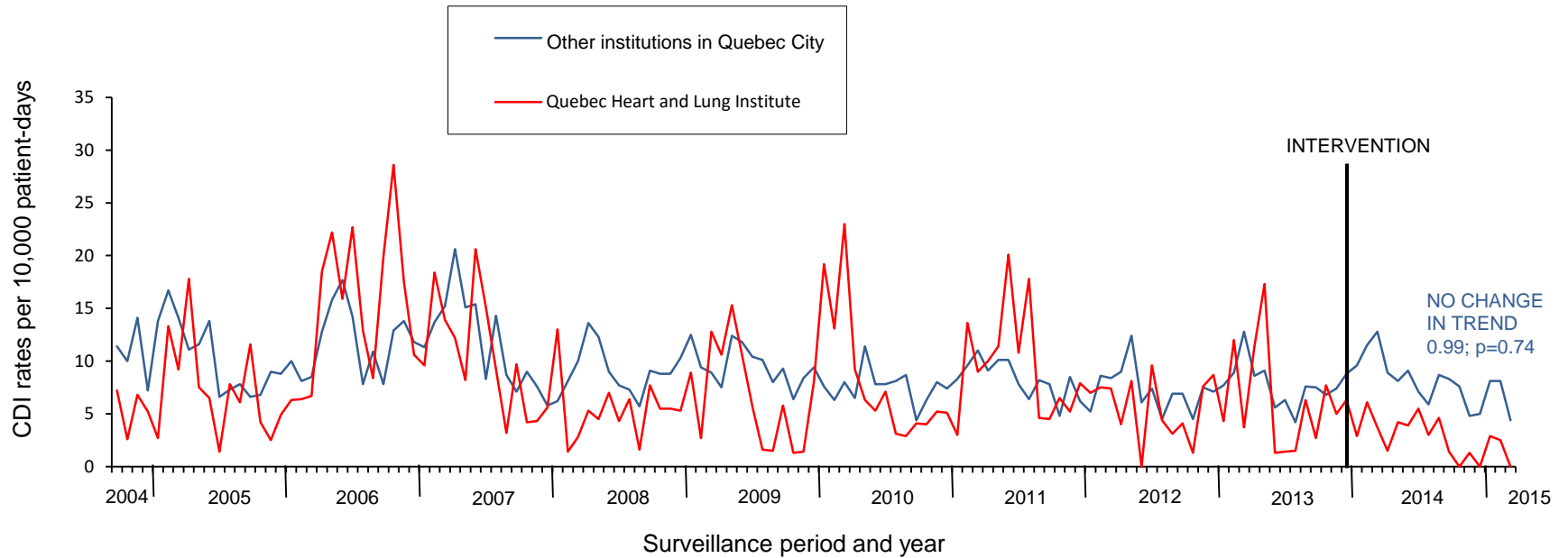


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ARIMA modeling

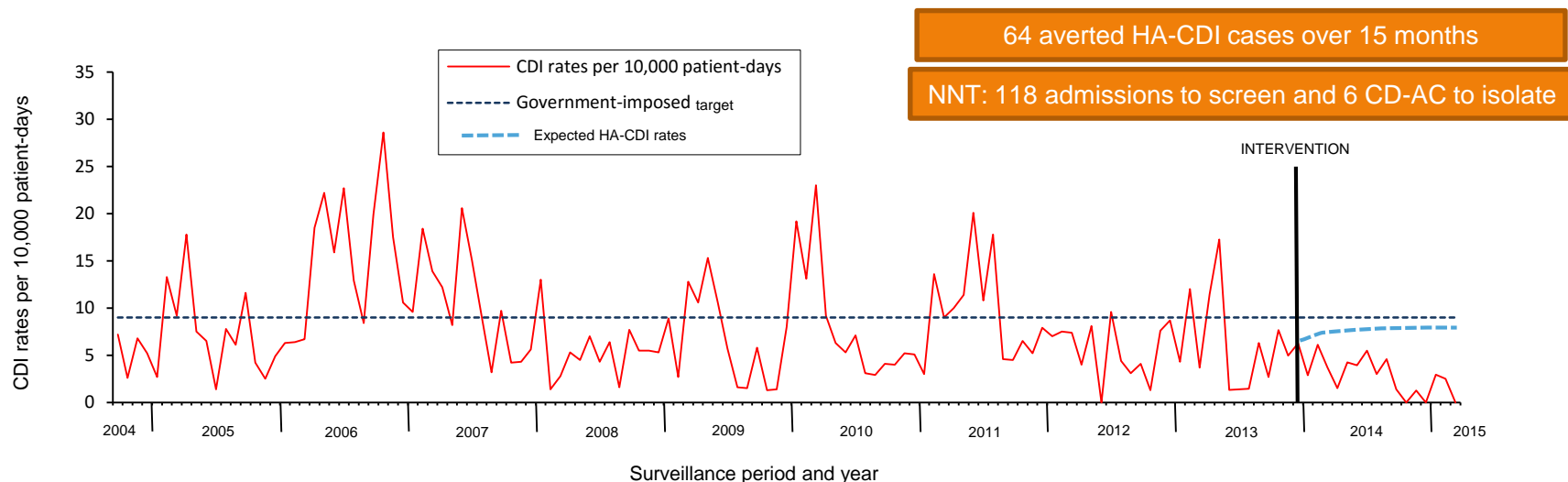
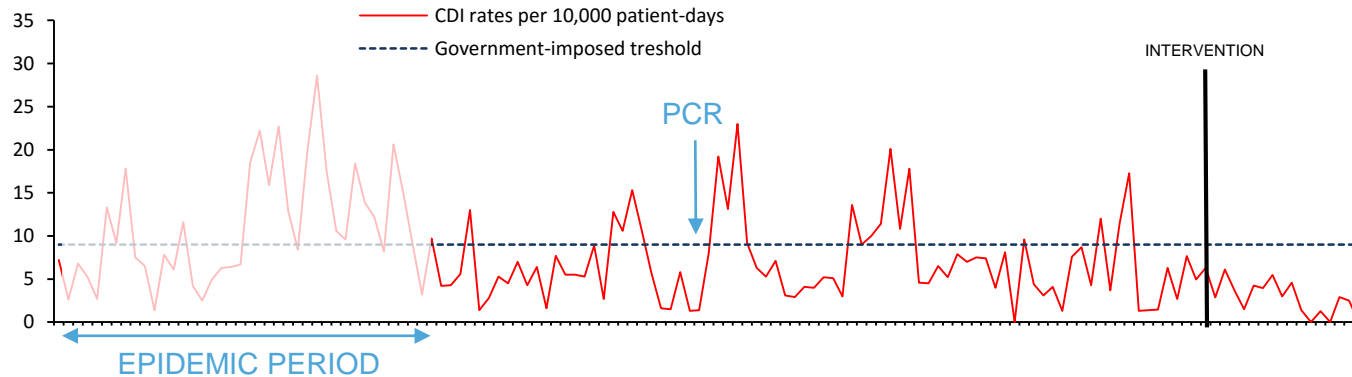


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Sensitivity analyses

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



Strain Analysis

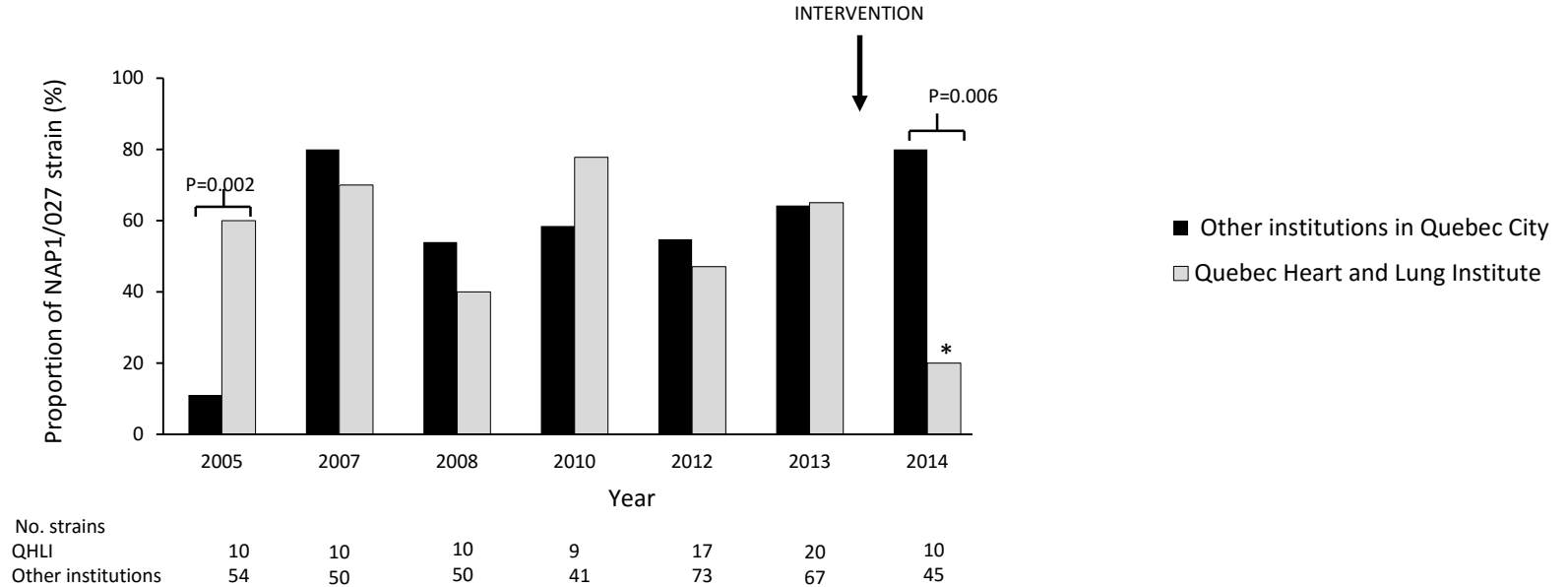


Figure S1. Proportion (%) of NAP1/B1/027 strain recovered from patients with *Clostridium difficile* infections from Quebec Heart and Lung Institute (QHLI) and from other hospitals in Quebec City, 2005-2014.
 * p=0.049 compared with 2005-2013 institutional global prevalence

Strain Analysis

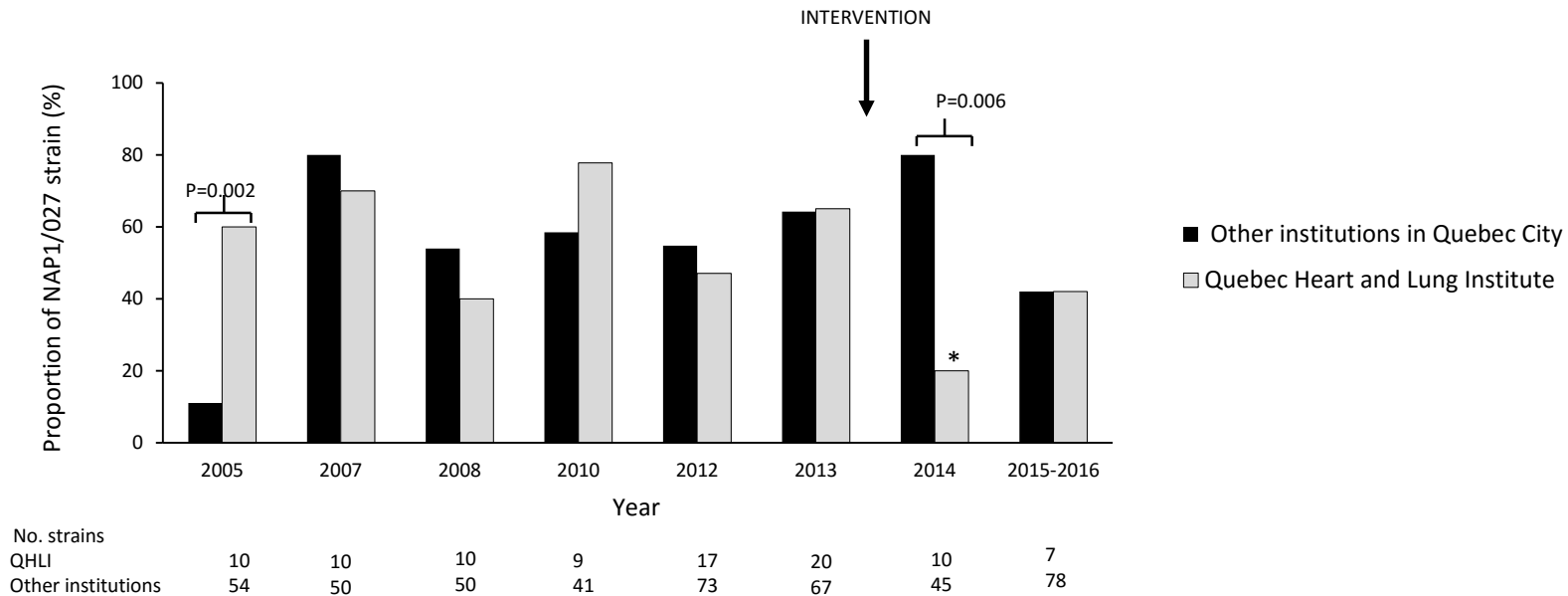
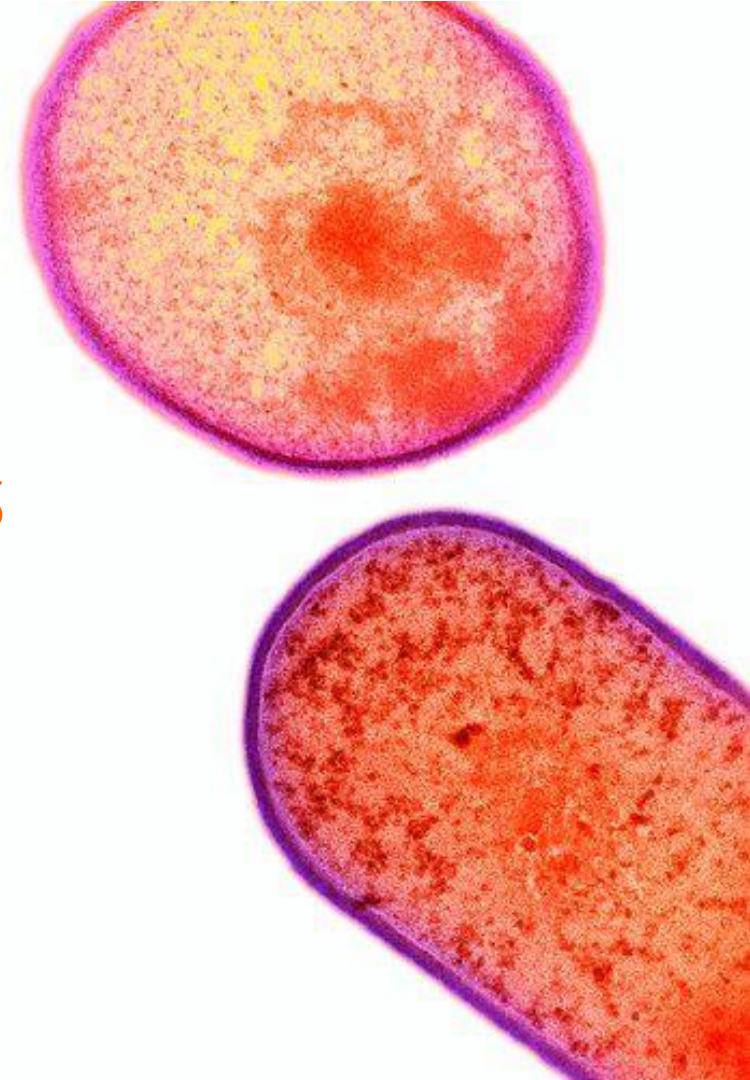


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Potential Confounders

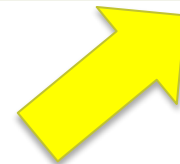
Potential Confounders

- 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

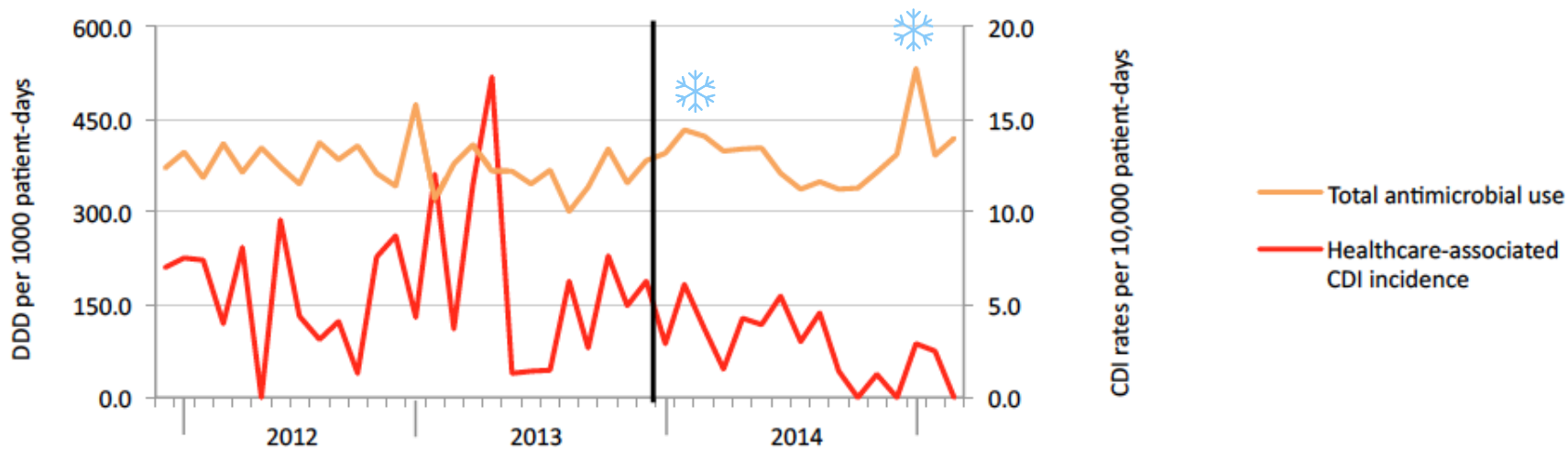
Antimicrobial and PPI use

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

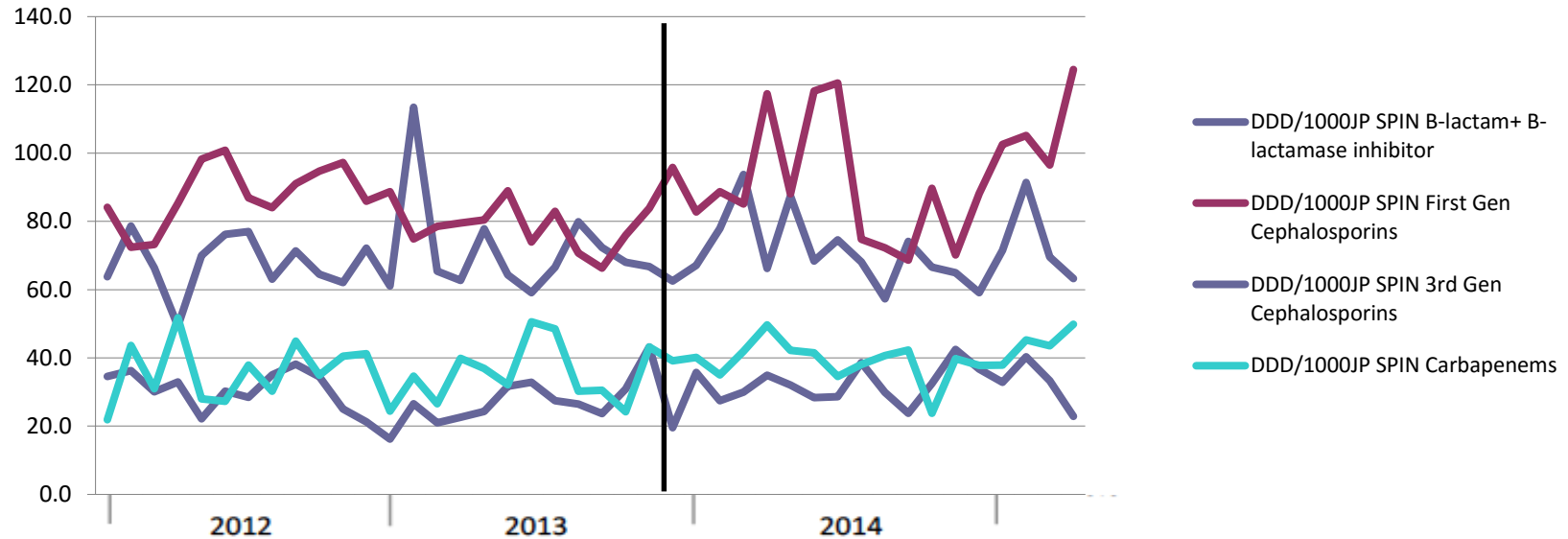
Variable	RR (95% CI)		Intervention Period From November 19, 2013, to March 7, 2015 (n = 121 402 Patient-days)			
	Overall Trend Before the Intervention ^b	P Value	Immediate Change After the Start of the Intervention ^c	P Value	Change in Trend After the Start of the Intervention ^d	P Value
Total antimicrobials ^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



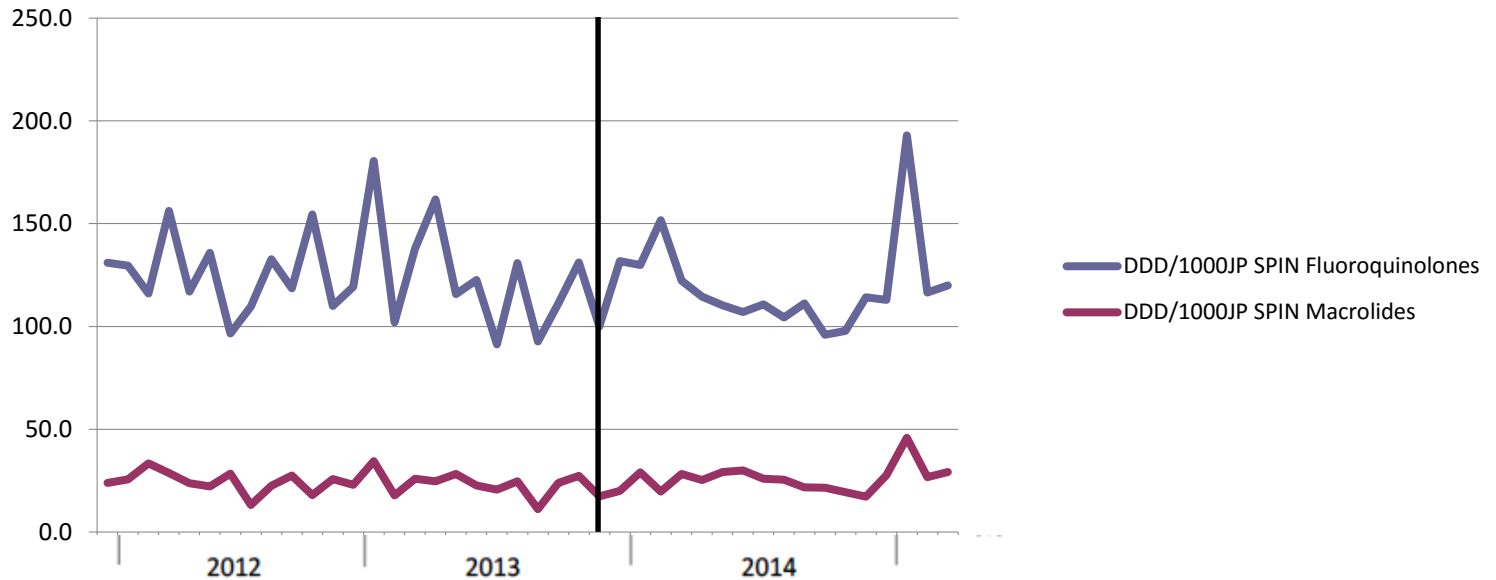
Antimicrobial use



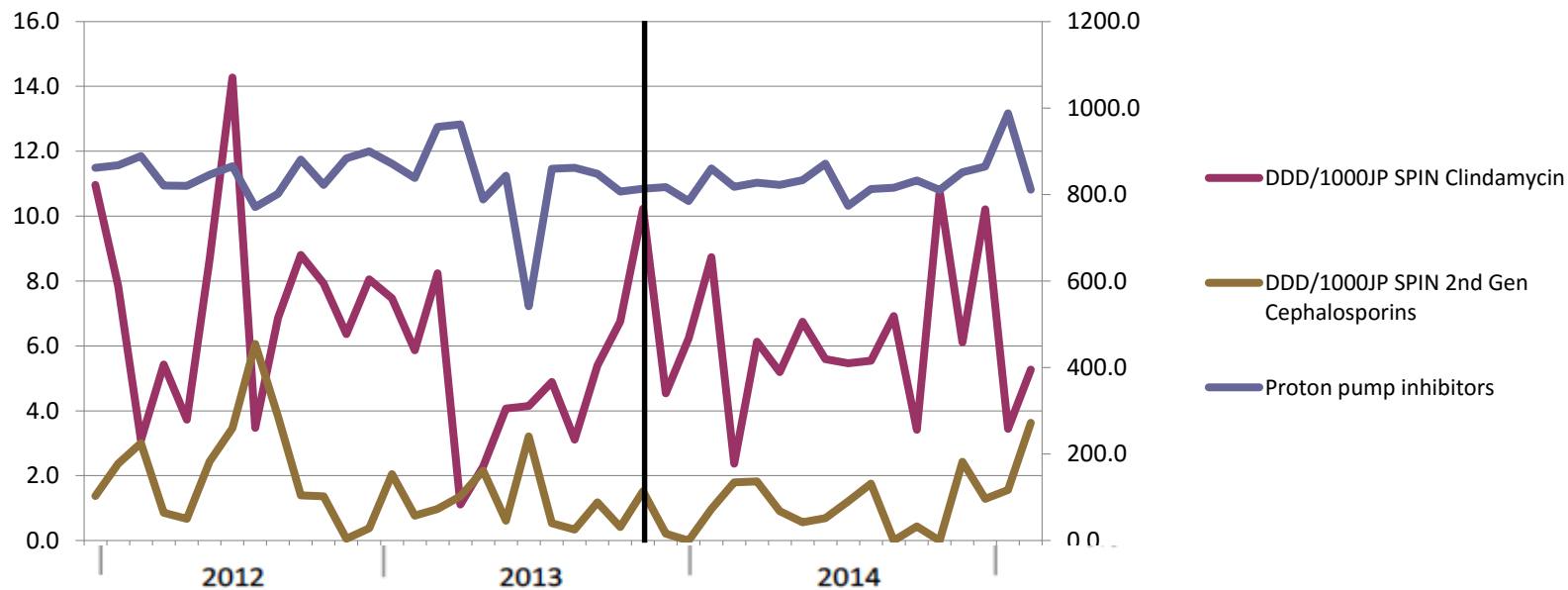
Antimicrobial use



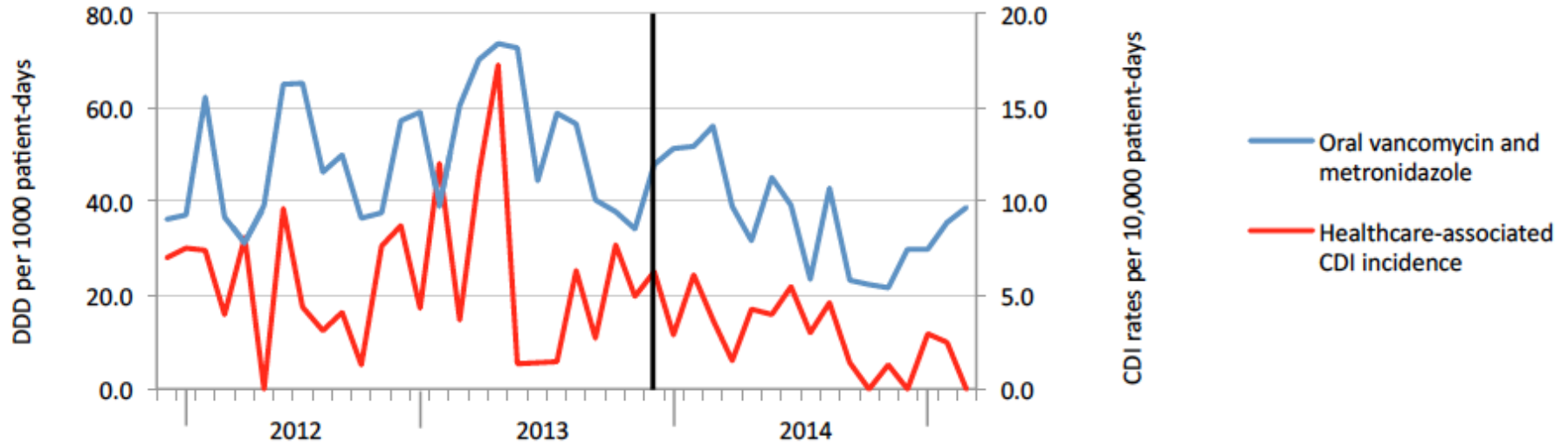
Antimicrobial use



Antimicrobial and PPI use

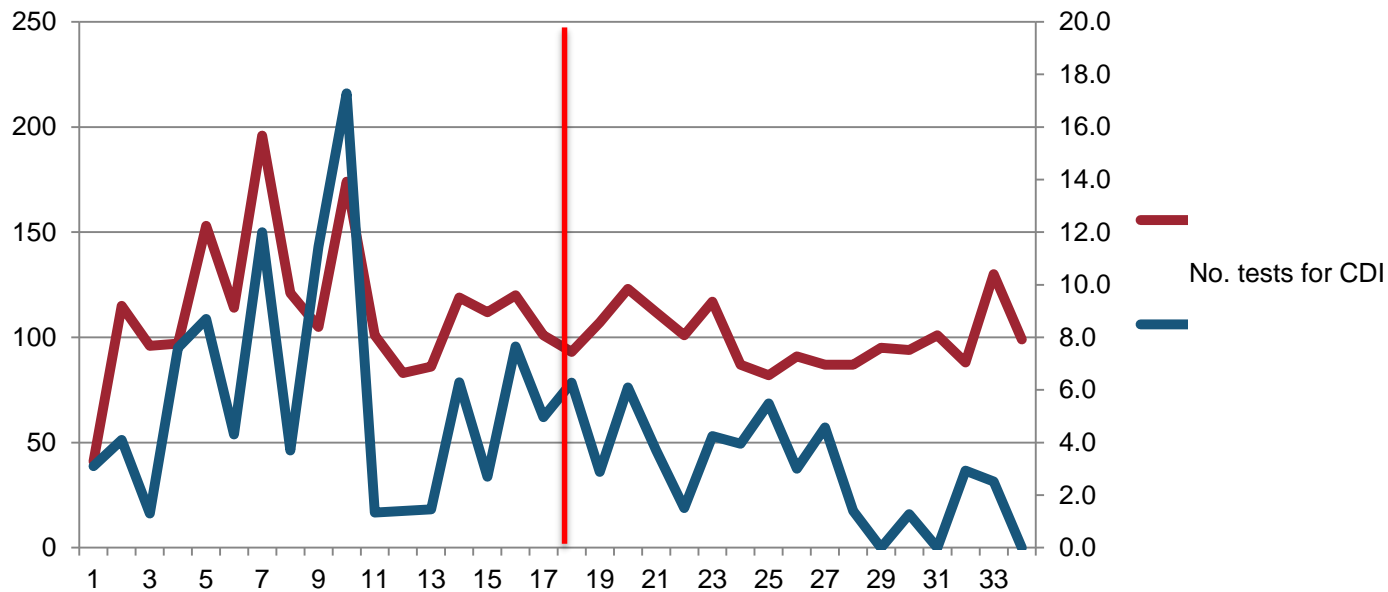


Anti-CDI antimicrobials



Change in trend: 0.97; $p < 0.001$

Intensity of CDI testing

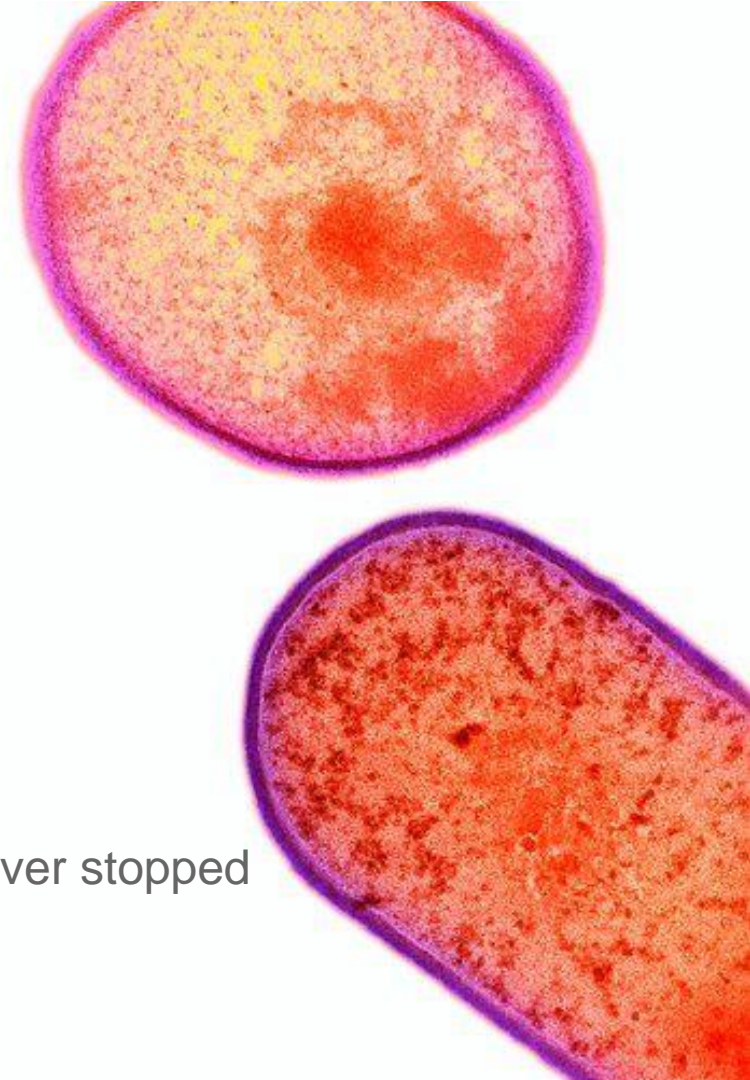


% of negative CDI tests



Stringency of definition application

- No. excluded cases 15 months prior to intervention: 135
- No. cases excluded during intervention: 110
- Main reasons for exclusion:
 - Insufficient number of soft stools per 24 hours (n=37);
 - duration of symptoms lasting less than 24 hours (n=25);
 - presence of an alternative medical condition explaining the symptoms (n=13);
 - recurrence of symptoms within 8 weeks of previous episodes (n=30);
 - use of laxatives (n=2).



LONG-TERM Follow-up

...The intervention never stopped

Long-term Impact

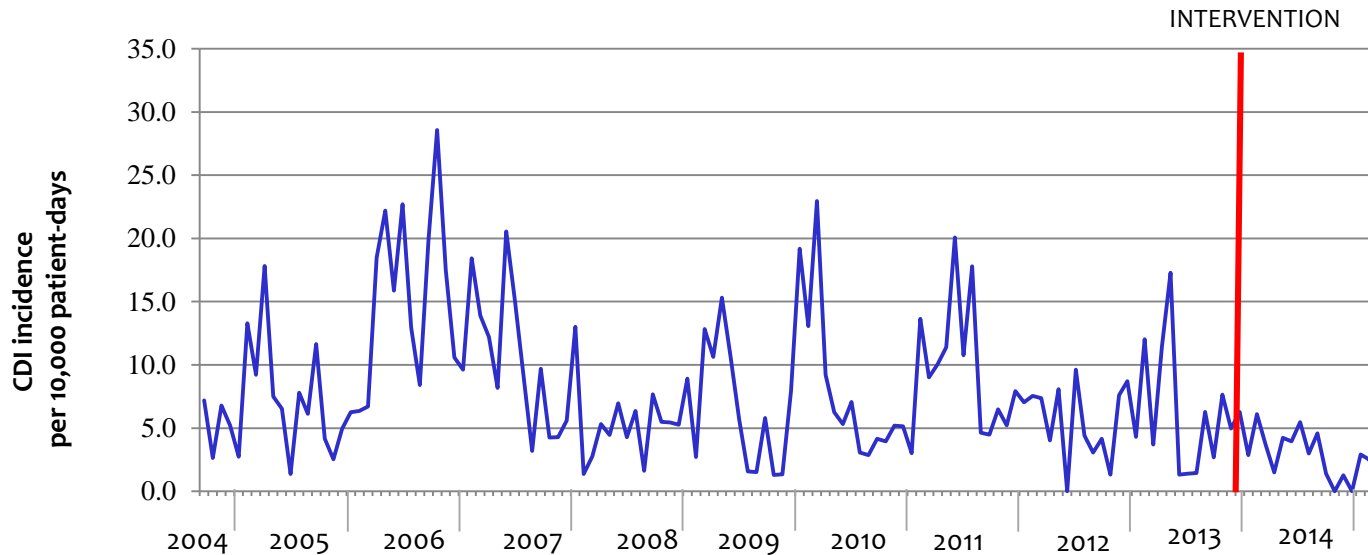


Figure 1. Healthcare-associated CDI incidence, Quebec Health and Lung Institute, 2004-2016

Long-term Impact

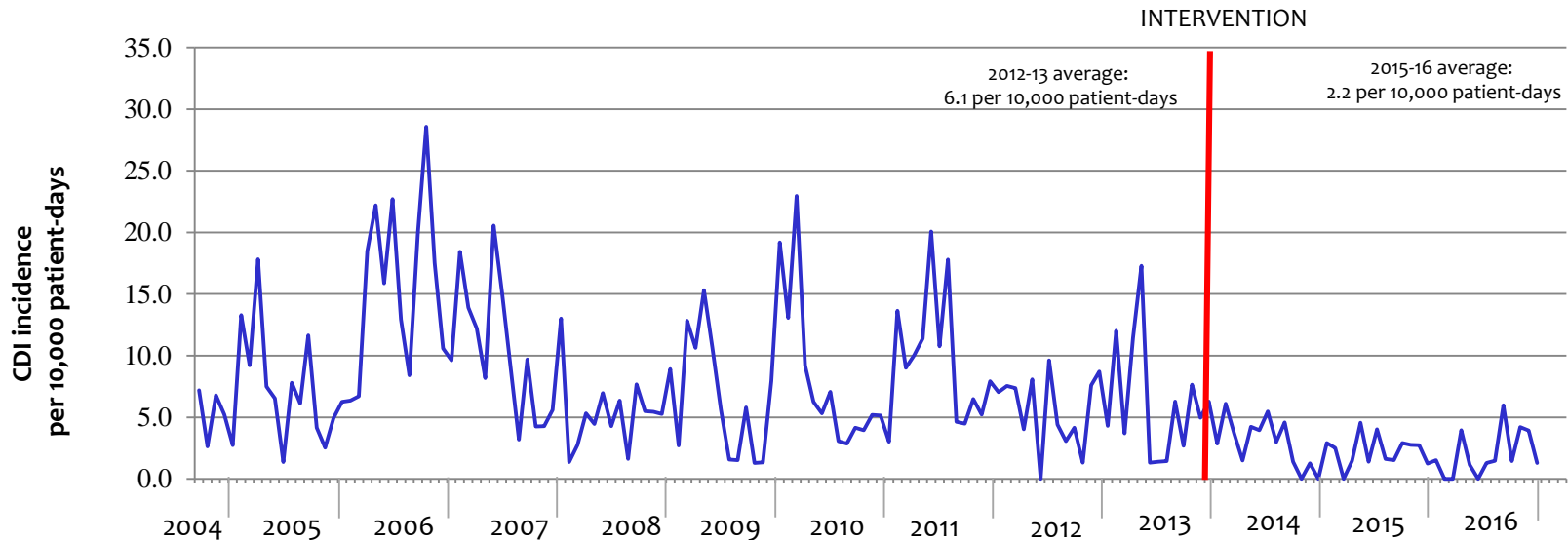


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Long-term follow-up

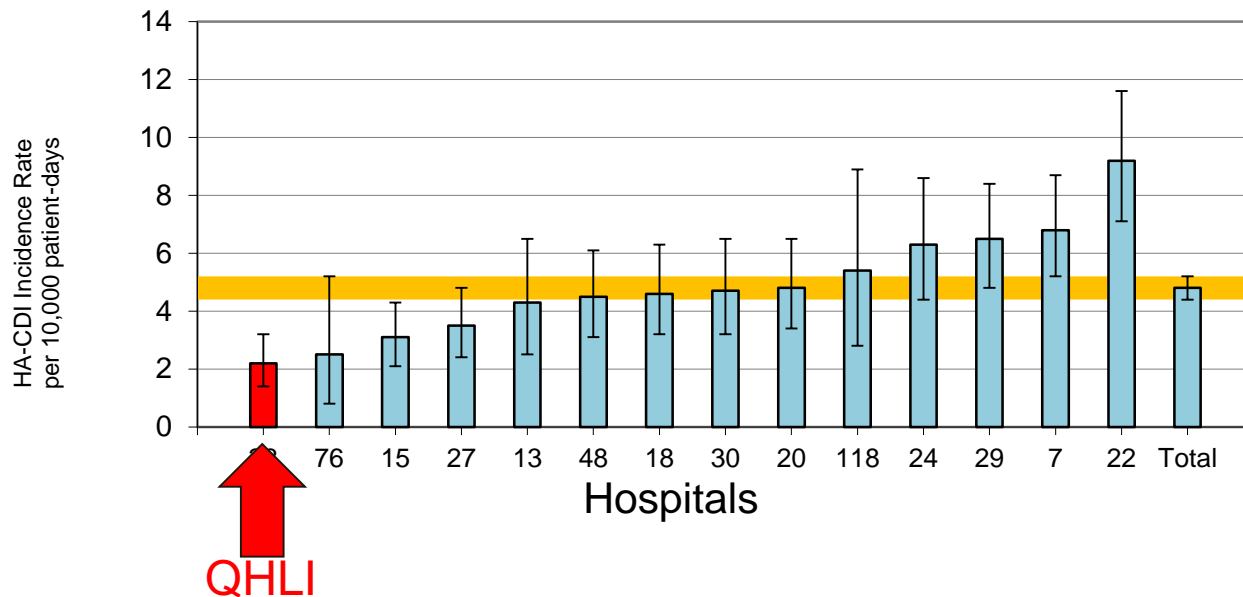
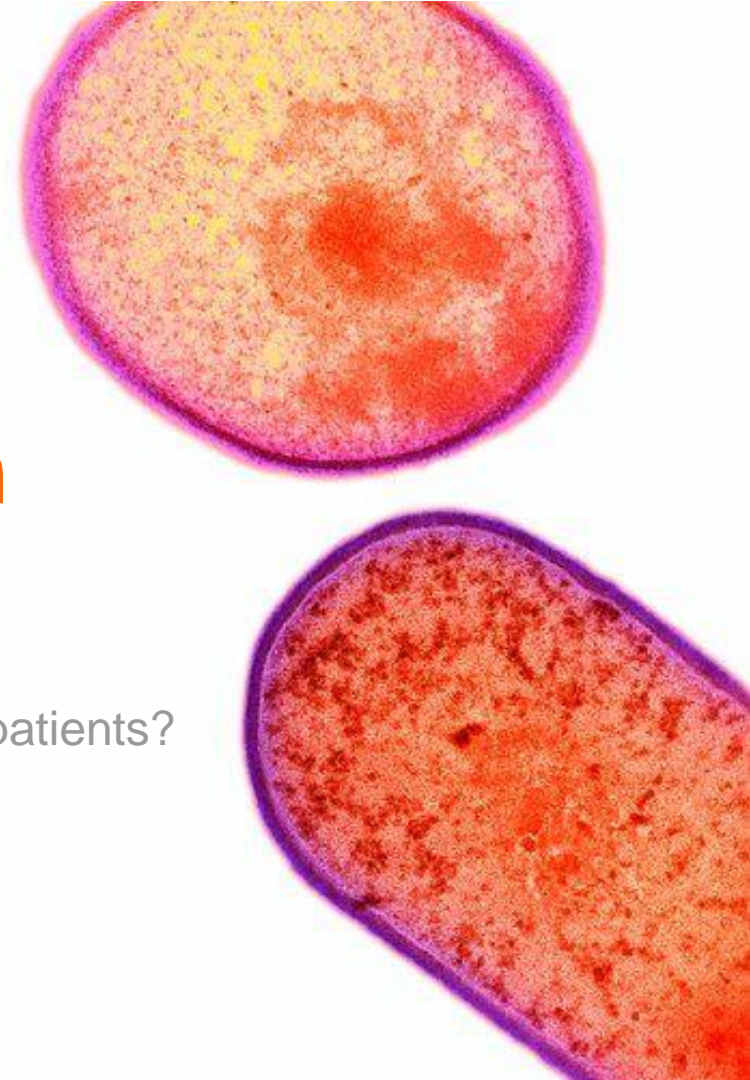


Figure 3. HA-CDI rates of University Hospitals in Quebec, 2015-2016. Red bar represents the HA-CDI incidence rate at the QHLI. Yellow Bar represents the 95% Confidence Interval for the stratum



Impact of the Isolation Precaution Burden

... Can we isolate that many patients?

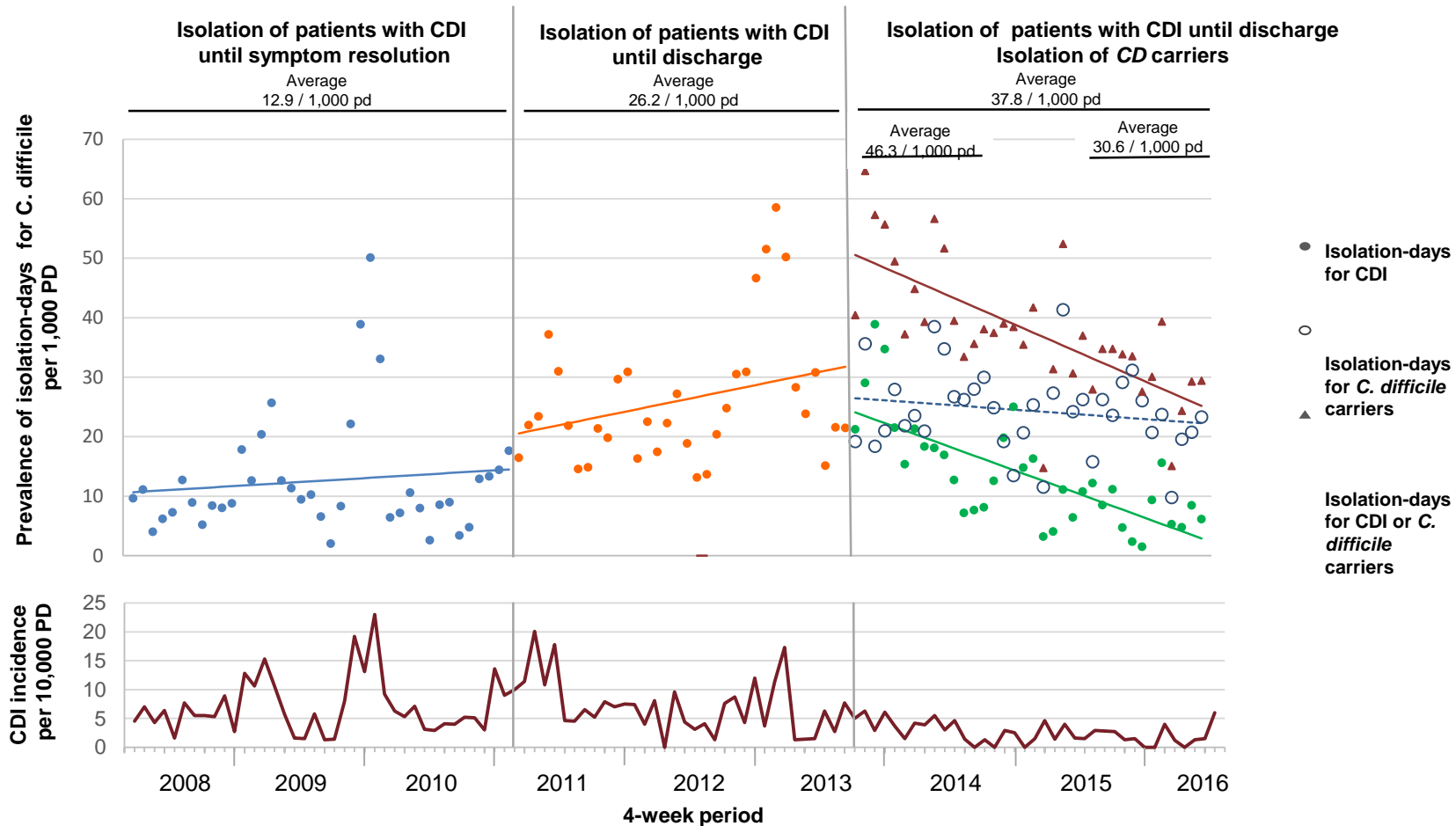


Figure. Prevalence of isolation-days for *C. difficile* infection (CDI) or colonization April 2008- August 2016. Data presented as the number of isolation-days per 1,000 patient-days per 4-week period. Averages represent the average isolation prevalence for *C. difficile* for the entire periods and for 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

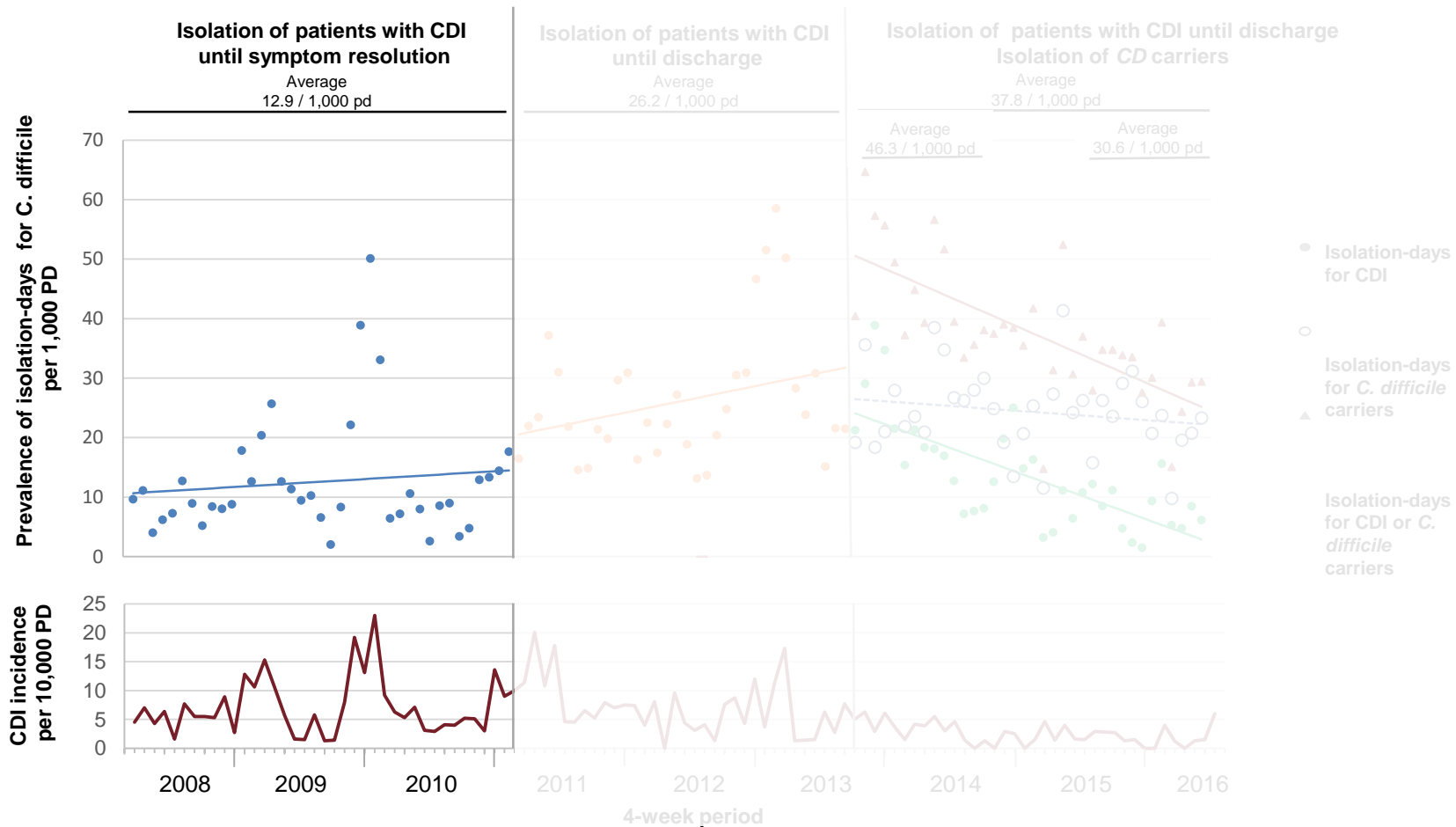


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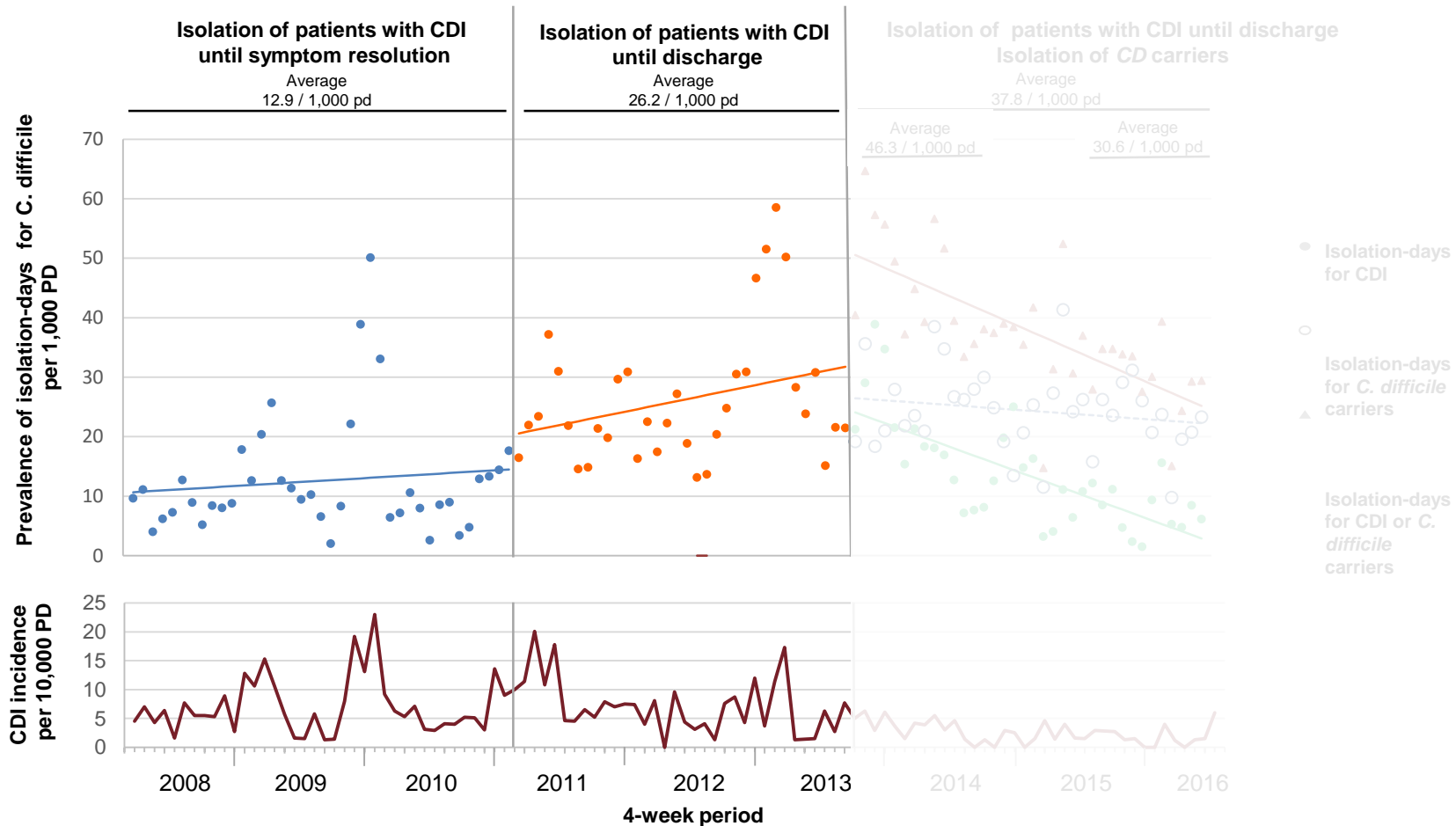


Figure. Prevalence of isolation-days for *C. difficile* infection (CDI) or colonization April 2008- August 2016. Data presented as the number of isolation-days per 1,000 patient-days per 4-week period. Averages represent the average isolation prevalence for *C. difficile* for the entire periods and for 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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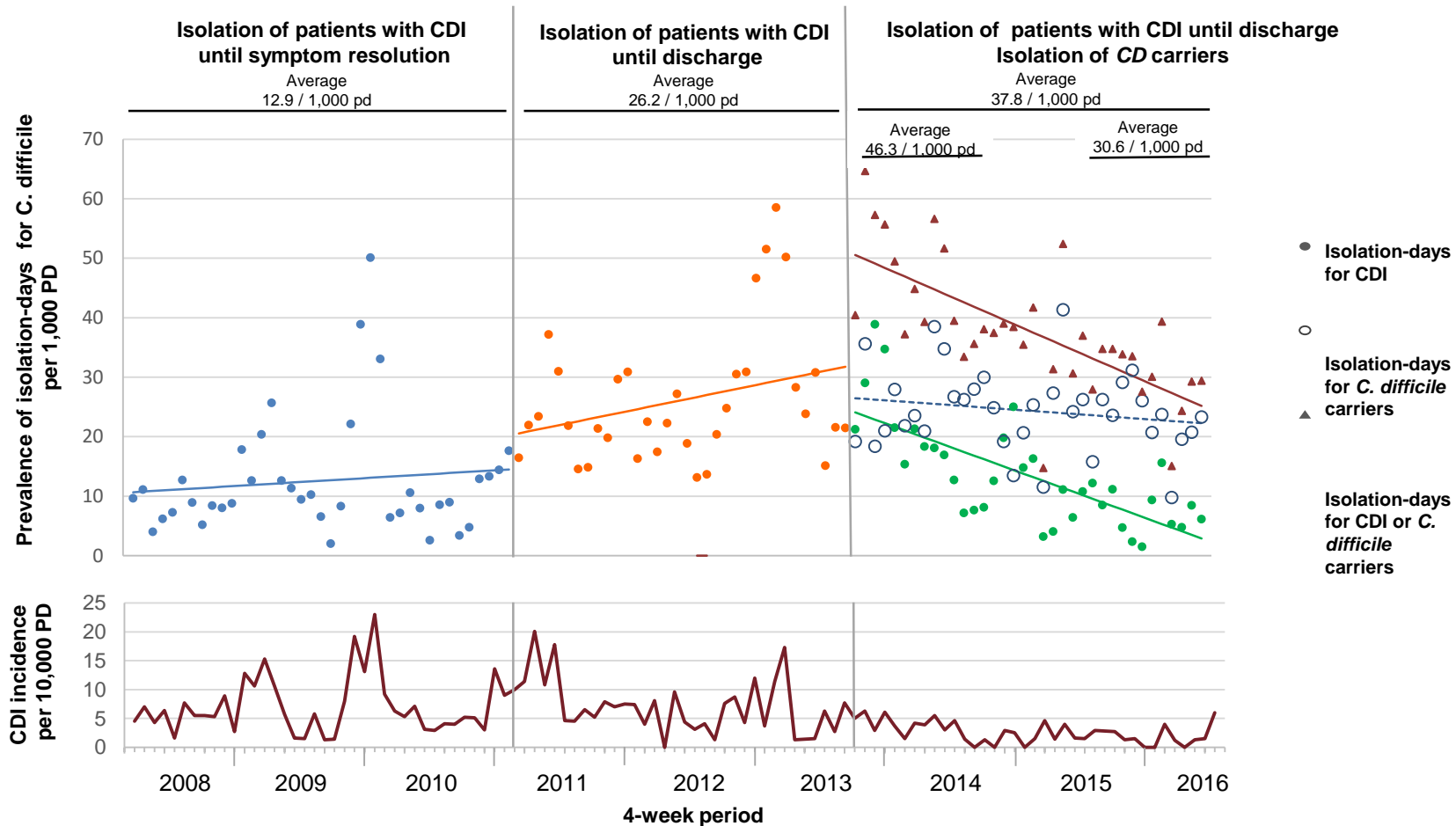


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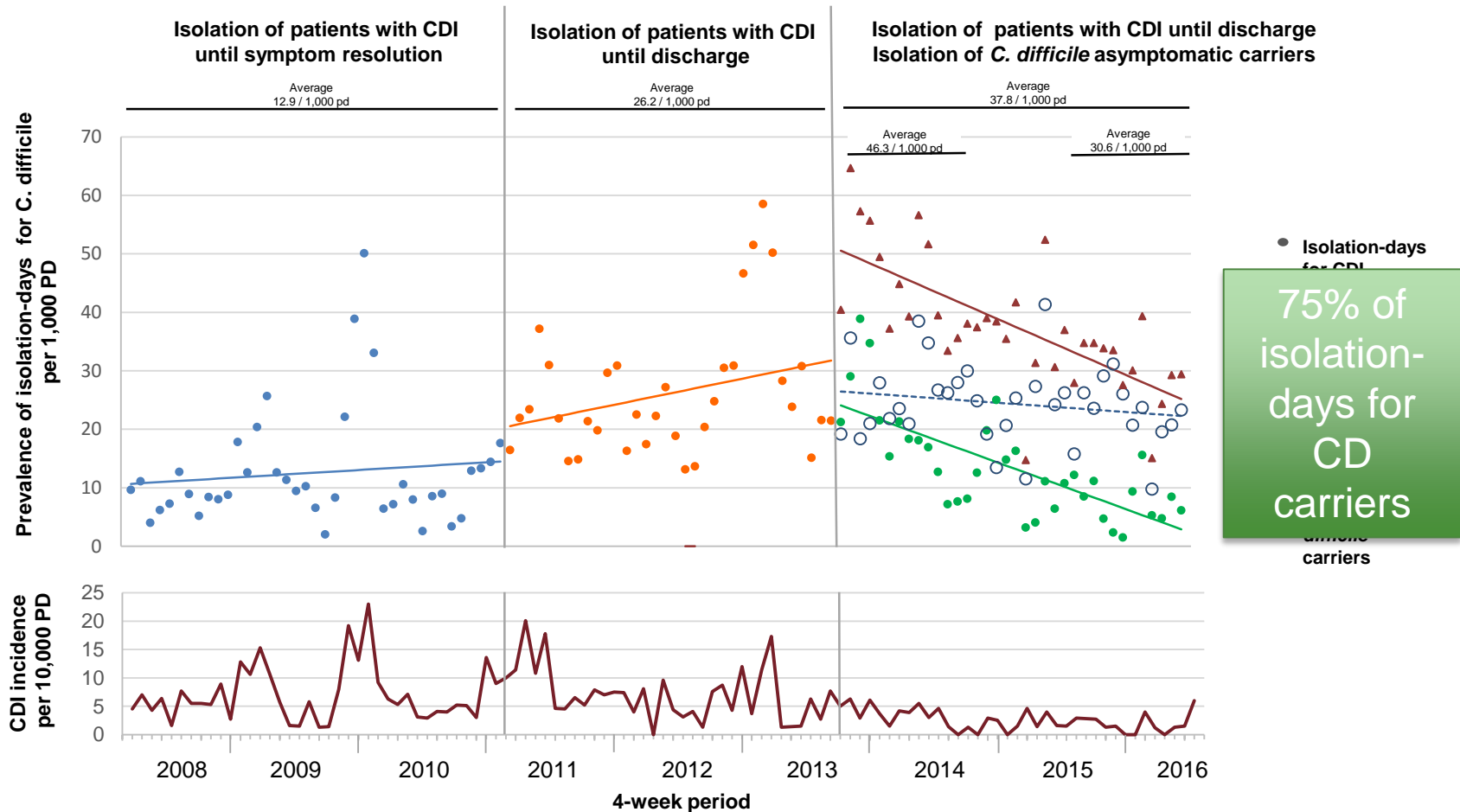
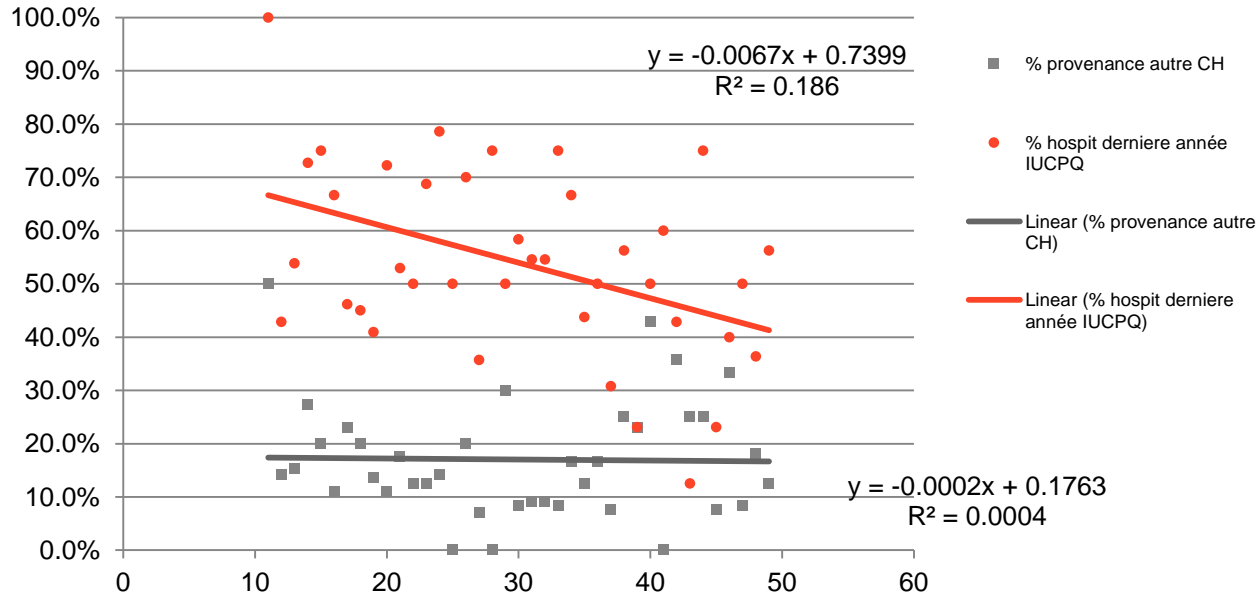


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Abbreviations: CDI: *Clostridium difficile* infection; pd: patient-days

	Period 1 Isolation of CDI until symptom resolution		Period 2 Isolation of CDI until discharge				Period 3 Isolation of CDI and CD carriers					
	Overall Trend Pre- intervention ^a RR (95% CI)	P	Immediate Change After the Start of the Intervention ^b	P		Change in Trend After the Start of the Intervention ^c	P		Immediate Change After the Start of the Intervention ^d	P	Change in Trend After the Start of the Intervention	P
Global isolation- days for <i>C. difficile</i>^f	1.005	0.19	1.456	<0.001		1.007	0.19		1.662	<0.001	0.970	<0.001
Isolation- days for <i>C. difficile</i> infections	Same as above ^g		Same as above ^g			Same as above ^g			0.891	0.25	0.944	<0.001
Isolation- days, <i>C. difficile</i> carriers^h	n/a		n/a			n/a			n/a	n/a	0.996	0.21

Proportion of Carriers with Recent Hospitalization at the QHLI



Cost-Benefit Estimate



Potential Economic Value



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

<i>C. difficile</i> Colonization on Admission (%)	<u>Contact Isolation Compliance (%)</u>		
	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

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

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 ?



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

Damian P. C. Mawer,^{1,4} David W. Eyre,^{2,3,4} 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,^{2,3,6} A. Sarah Walker,^{2,3} and Mark H. Wilcox^{1,5}

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



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

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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

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



Effect of a national 4C antibiotic stewardship intervention on the clinical and molecular epidemiology of *Clostridium difficile* infections in a region of Scotland: a non-linear time-series analysis

Timothy Lawes, José-María Lopez-Lozano, Cesar A Nebot, Gillian Macartney, Rashmi Subbarao-Sharma, Karen D Wares, Carolyn Sinclair, Ian M Gould

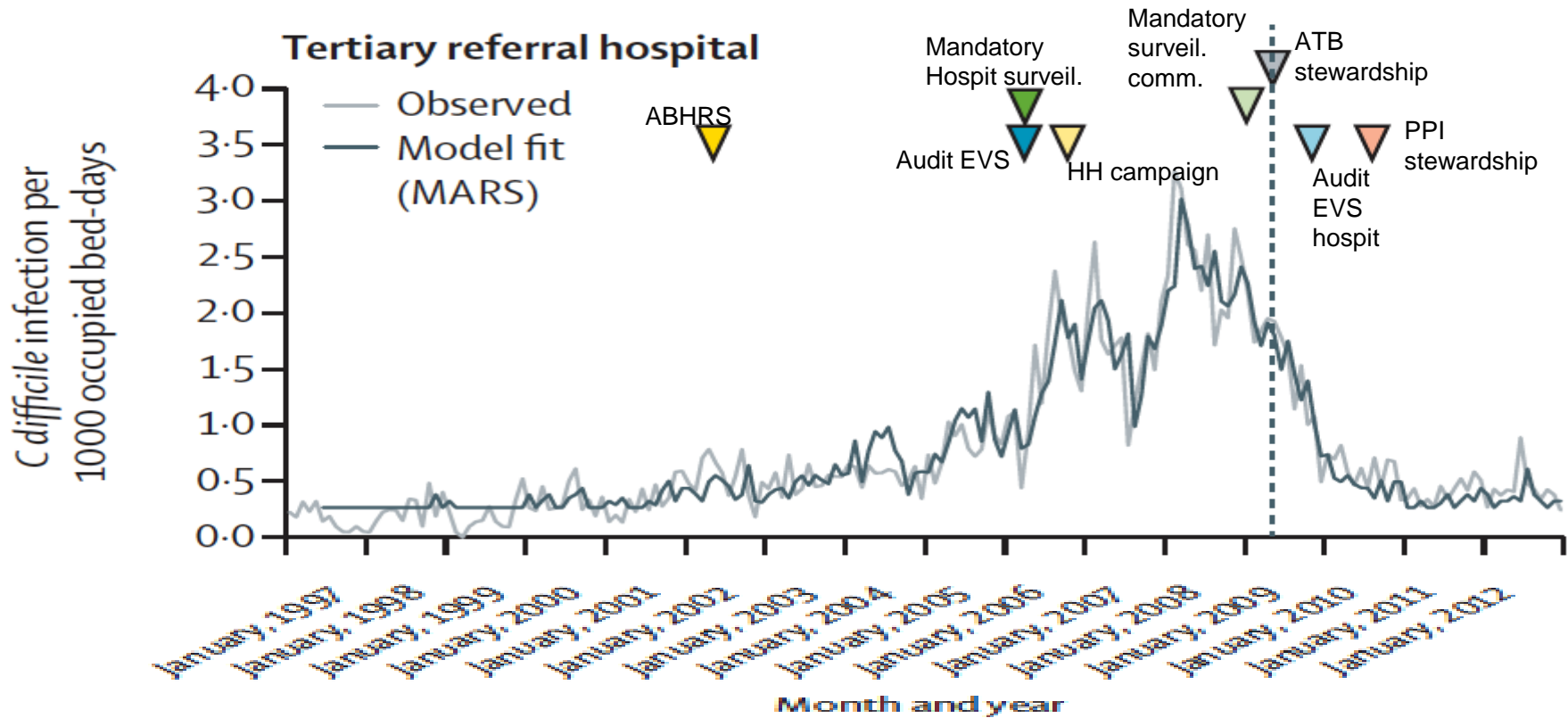
- National campaign of ATB restriction (4Cs 1997 – 2012)

- FluoroCinolones
- Cephalosporins
- Clindamycin
- Clavulin

50% ↓



- Hospital and in the community



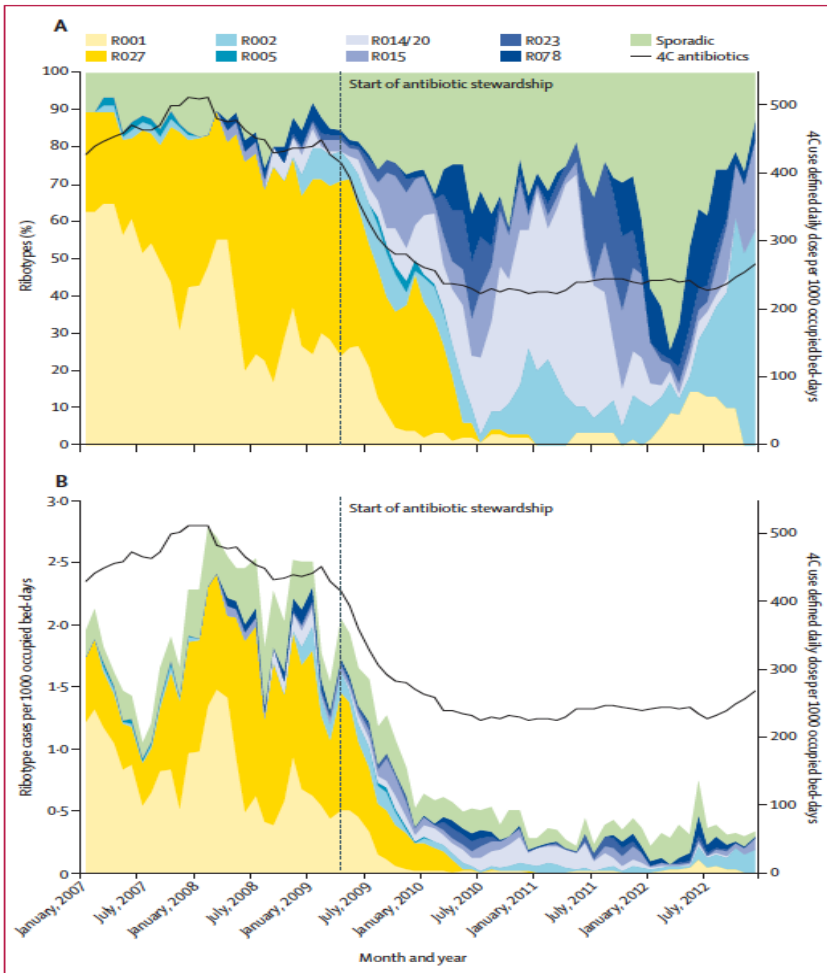


Figure 2: Ribotype distribution (A) and cumulative ribotype prevalence densities (B) with corresponding 4C antibiotic use
 Emergent ribotypes included R002, 005, 014/20, 015, 023, and 078. Sporadic ribotypes included those appearing for only 1–2 years during the study period and included R011, 12, 13, 17, 18, 24, 26, 42, 50, 54, 56, 64, 70, 103, 126, 137, 220, 228, 275, and 304.

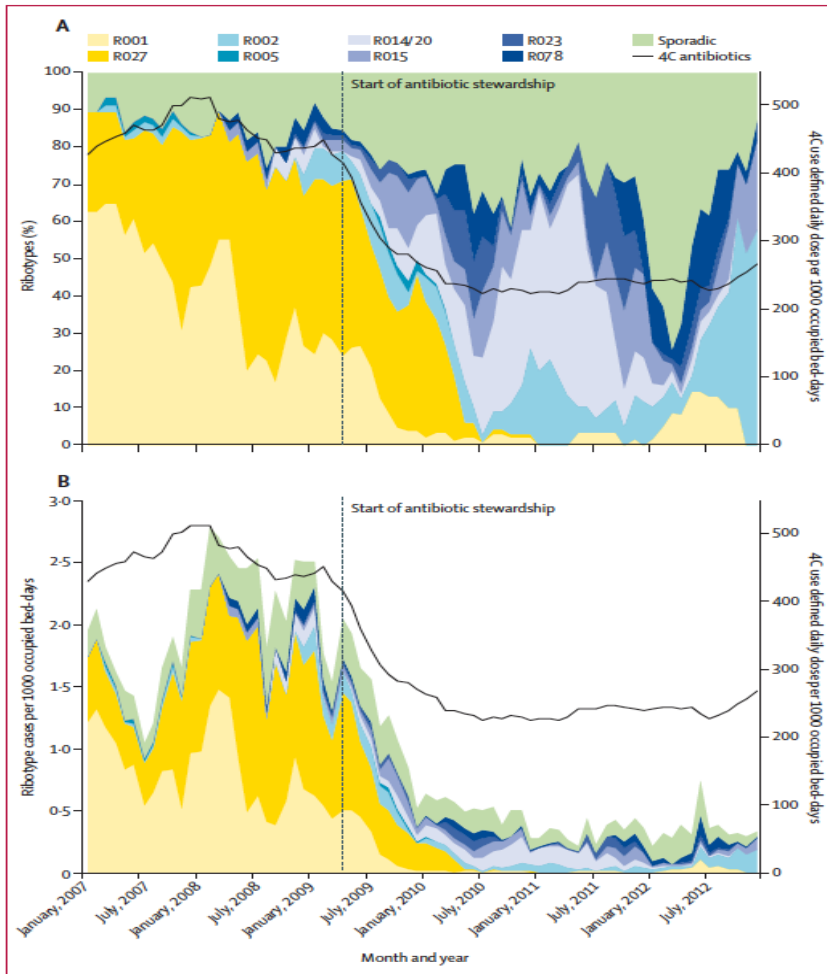
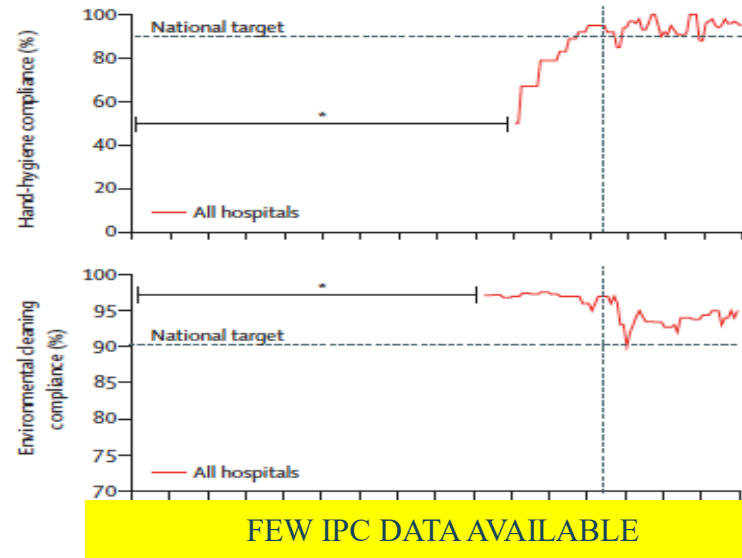


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Stewardship program led to 68% decrease in incidence

Effects of control interventions on *Clostridium difficile* infection in England: an observational study



Kate E Dingle, Xavier Didelot, T Phuong Quan, David W Eyre, Nicole Stoesser, Tanya Golubchik, Rosalind M Harding, Daniel J Wilson, David Griffiths, Alison Vaughan, John M Finney, David H Wyllie, Sarah J Oakley, Warren N Fawley, Jane Freeman, Kirsti Morris, Jessica Martin, Philip Howard, Sherwood Gorbach, Ellie J C Goldstein, Diane M Citron, Susan Hopkins, Russell Hope, Alan P Johnson, Mark H Wilcox, Timothy E A Peto, A Sarah Walker, Derrick W Crook, the Modernising Medical Microbiology Informatics Group*



What caused the >80% decrease in CDI since 2006?



ATB Stewardship?

??

IPAC?



CDI INCIDENCE

Strongly correlated with use
of quinolones and
cephalosporins

NOT correlated with global
ATB use

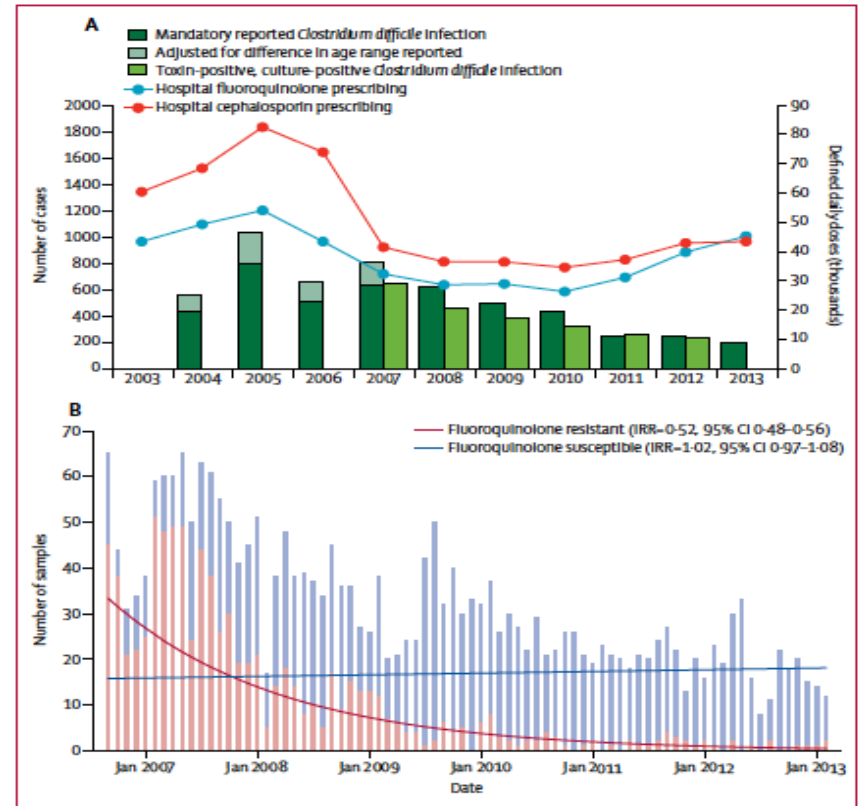
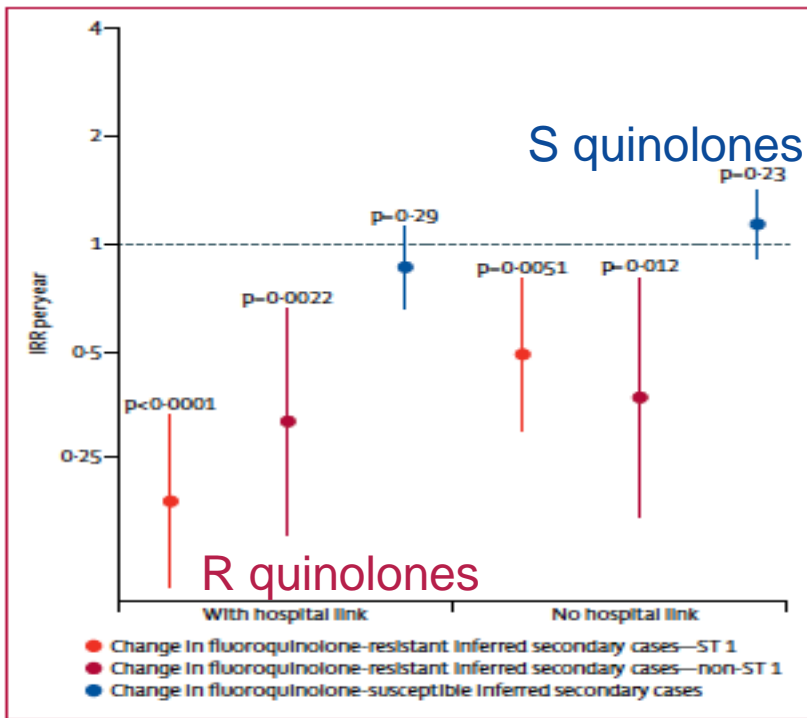


Figure 2: Incidence of *Clostridium difficile* infections together with fluoroquinolone and cephalosporin prescribing for Oxfordshire (A) and incidence of *C difficile* infections by fluoroquinolone susceptibility for Oxfordshire (B)

(A) Mandatory incidence of *C difficile* infections corresponds to all cases reported for individuals older than 2 years (from 2004 to 2007, cases were only reported for individuals older than 65 years, and are upweighted to provide similar estimates in individuals older than 2 years; appendix). Only toxin-positive culture-positive samples were used in the genotype-specific and phylogenetic analyses. (B) *C difficile* is inherently resistant to most cephalosporins.⁴ IRR—annual incidence rate ratio.



↓ of % CDI 2nd to quinolone R from 67% to 3% (IRR 0.52)

NO ↓ in CDI due to quinolone S strains (IRR 1.02)

INTERPRETATION

IPAC measures should have had the same impact regardless of quinolone sensitivity



ATB stewardship should be a central component of IPAC of CDI



Correspondence

Clostridium difficile in England: can we stop washing our hands?

“ANY STRAIN that has an advantage in disseminating will be disproportionately affected by any intervention, regardless of the IPAC measure”

Correspondence

Clostridium difficile in England: can we reduce incidence by washing our hands?

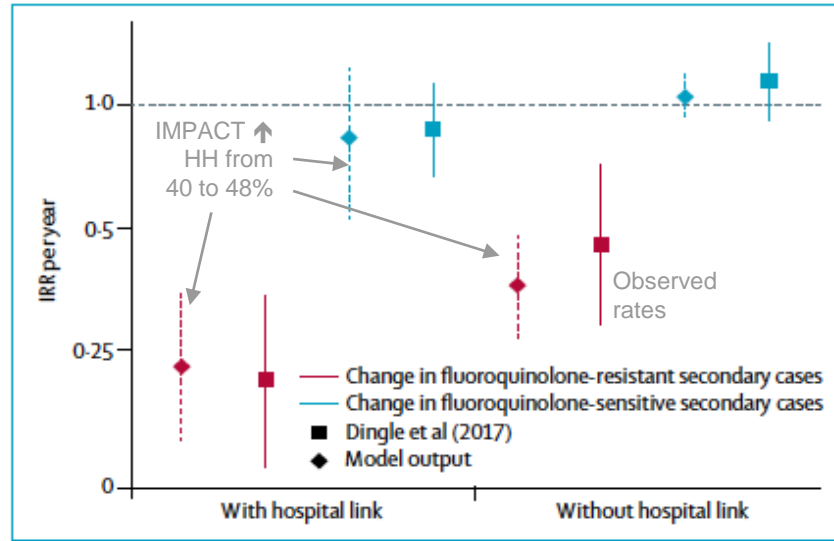


Figure 1: Model output—incidence trends of secondary *Clostridium difficile* cases
Predicted changes in new acquisitions of fluoroquinolone-resistant and fluoroquinolone-sensitive *C difficile* following a 7.5% improvement in hand hygiene compliance (as an example of improved hospital infection control) from a baseline of 40%. Individuals were assumed to be colonised with fluoroquinolone-resistant *C difficile* (symptomatically or asymptotically), colonised with fluoroquinolone-sensitive *C difficile*, or uncolonised and susceptible to both. Health-care workers were modelled explicitly with hand hygiene having an equal effect on resistant and susceptible strains. Before the introduction of enhanced infection control, 35% of transmission events occurred with resistant strains and 5% with susceptible strains in hospital (18% overall). Incidence rate ratios (IRRs) were calculated with the use of simulated data for 1 year before and after the intervention, where observed infections followed a negative binomial distribution with a mean given by the deterministic model. Dots represent medians and lines represent the 5th and 95th percentiles. An IRR of 1 corresponds to no change (dotted line).

Potential use of CD carrier isolation during outbreaks?

- No published data yet

Out-break number	Hospital and specialty	Number of beds	No. HA-CDI so far upon screening	No. patients screened for <i>C. difficile</i> carriage	Number of CD-AC detected (%)	CD carrier Outbreak containment measures	Outcome of outbreak
1	QHLL; 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	QHLL; 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	QHLL; 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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CDI outbreaks are not created equal

Acknowledgements

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THANK YOU!

