# Validation and characterization of community-acquired *Clostridium difficile* infections from the Quebec *Clostridium difficile* Infection Surveillance Program (QCISP)

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## Background

Community-acquired *Clostridium difficile* infections (CA-CDI) are under a mandatory reporting program starting in August 2004 across 95 health care institutions from the QCISP. There has been a slow and continuous increase in the incidence rate of hospitalized CA-CDI since 2007 (**Poster #477**) without any known obvious explanation. The first part is a retrospective study that aims to characterize CA-CDI reported to the mandatory QCISP and to test variations in a broad range of demographic, clinical and laboratory variables at the patient level. The second part is a trend study that aims to evaluate the possible association between variations in the incidence rate of CA-CDI and the use of various diagnostic approaches at the institutional level.

## Objectives

1) Validate and characterize CA-CDI cases reported to the mandatory QCISP.
2) Investigate the potential causes responsible for the increase in the incidence rate of CA-CDI.
3) Investigate trends in the incidence of CA-CDI and HA-CDI in hospitals using different diagnostic approaches.

## Methods

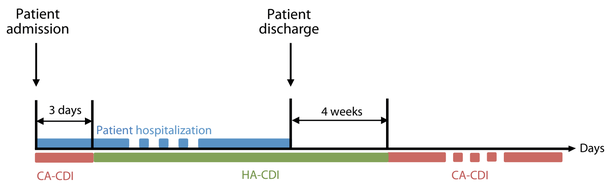
***The mandatory QCISP:*** The mandatory QCISP was implemented in August 2004 with the principal aims to follow the healthcare-associated CDI (HA-CDI) incidence rate and investigate the principal causes and risk factors of CDI(1). Similar to HA-CDI cases, CA-CDI cases are reported in an aggregated manner via a web-based system, however, patient-level clinical information is not reported(2). Surveillance is conducted prospectively by infection control practitioners.

***CA-CDI and HA-CDI definitions:*** CDI is defined as (1) diarrhea (≥ 3 unformed or liquid stools in < 24 hours) lasting at least 24 hours without any other known etiology, combined with a positive assay for toxigenic *C difficile*; (2) visualization of pseudomembranes by colonoscopy; or (3) a histopathologic diagnosis.

Cases in which the patient developed symptoms within 72 hours of admission, but with no history of hospitalization or ambulatory care visit in the previous 4 weeks are community-associated (CA-CDI). Cases are considered healthcare-associated (HA-CDI) if they occur >3 days after hospital admission and up to 4 weeks after discharge (Figure 1).

**Figure 1**

**Chronological criteria to determine the origin of CDI cases**




***Retrospective study:*** A retrospective study was carried out using a survey sent to eligible healthcare institutions. Hospitals participating in QCISP that reported ≥ 3 cases of CA-CDI from April 1st, 2016 to March 31st, 2017 (2016-2017) were invited to participate and were asked to provide clinical information regarding up to 3 consecutive cases of CA-CDI from April 1st, 2011 to March 31st, 2012 (2011-2012) and up to 3 cases in 2016-2017.

***Variables at the patient level:*** To characterize each CA-CDI case, a broad range of demographic, clinical and laboratory variables were collected including medical history, history of contact with primary and secondary health care institutions, previous antibiotics use as well as laboratory diagnostic test.

***Trend study for incidence rate of CA-CDI and laboratory diagnostic test approaches at the institutional level:*** To evaluate the possible association between variations in the incidence of CA-CDI, and the use of various diagnostic approaches, we extracted from the QCISP the incidence rates of HA-CDI and CA-CDI and laboratory diagnostic test approaches used in 2010-2011 and 2016-2017 for each of the 49 healthcare facilities that responded to the survey.

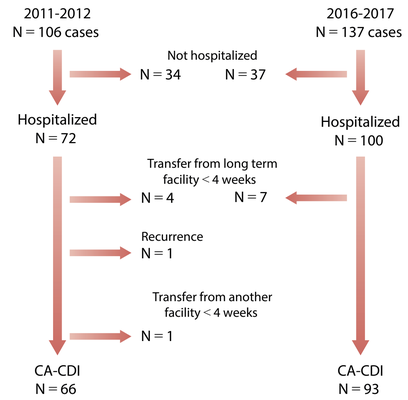
***Data analysis:*** $Chi^2$ and T-tests have been respectively used to compare year differences in indicator distributions and in means using statistical software (SAS, version 9.4; SAS Institute Inc). P-value < 0.05 was considered statistically significant. Homogeneity comparison of Kaplan Meier curves have been tested using log-rank test. Fisher exact test has been used to compare incidence rates.

## Results

A total of 49 healthcare facilities provided data on 243 cases of CA-CDI for which 71 of them were not hospitalized (29.2%) resulting in 172 hospitalized CA-CDI. After the exclusion of non-hospitalized cases, 92.4% (n=159) meet the QCISP CA-CDI criteria definition.

**Figure 2**

**Inclusion and exclusion diagram for reported CA-CDI in 2011-2012 and 2016-2017**




***Clinical characteristics of CA-CDI cases:*** Most patients (67.3%) were female and average age was 66.7±20.5 years old (Table1). A total of 15.9% and 26.4% of CA-CDI reported vomiting and rectorrhagia symptoms at patient admission, respectively. Among the 159 CA-CDI, 74% had received antibiotics in the year preceding the diagnosis, and type of antibiotic was known for 70% of them (Table 2). The proportion of cases visiting healthcare facilities and ambulatory healthcare settings during the year previous to patient admission was of 31.2% and 65.4%, respectively. Finally, the proportion of CA-CDI diagnosed by laboratory Nucleic acid amplification test (NAAT) was scarce in 2011-2012 (7.6%) as compared to 2016-2017 (54.8%).

**Table 1**

**Demographic description of reported CA-CDI in 2011-2012 and 2016-2017**

| | 2011-2012 | | 2016-2017 | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Number of healthcare facility** | 34 | | 44 | | |
| Non-teaching facility | 23 | 67.6% | 27 | 61.4% | |
| Teaching facility | 8 | 23.5% | 13 | 29.5% | |
| **Number of CA-CDI** | 66 | | 93 | | |
| **Healthcare facility type origins of CA-CDI** | | | | | |
| Non-teaching facility | 46 | 69.7% | 59 | 63.4% | |
| Teaching facility | 20 | 30.3% | 34 | 36.6% | 0.41 |
| **Patient age mean (SE)** | 64.2 (2.7) | | 68.4 (2.0) | | 0.18 |
| **Sexe** | | | | | |
| Men | 23 | 34.8% | 29 | 31.2% | |
| Women | 43 | 65.2% | 64 | 68.8% | 0.63 |

**Table 2**

**Frequency of antibiotic prescriptions during the year preceding the diagnosis in 2011-2012 and 2016-2017**

| | 2011-2012 | | 2016-2017 | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Penicillin** | | | | | |
| Yes | 21 | 31.8% | 20 | 21.5% | |
| No | 45 | 68.2% | 73 | 78.5% | 0.14 |
| **Cephalosporin** | | | | | |
| Yes | 15 | 22.7% | 14 | 15.1% | |
| No | 51 | 77.3% | 79 | 84.9% | 0.27 |
| **Macrolide** | | | | | |
| Yes | 10 | 15.2% | 16 | 17.2% | |
| No | 56 | 84.8% | 77 | 82.8% | 0.73 |
| **Quinolone** | | | | | |
| Yes | 18 | 27.3% | 23 | 24.7% | |
| No | 48 | 72.7% | 70 | 75.3% | 0.72 |
| **Vancomycine or Flagyl** | | | | | |
| Yes | 5 | 7.6% | 10 | 10.8% | |
| No | 61 | 92.4% | 83 | 89.2% | 0.50 |
| **Other** | | | | | |
| Yes | 8 | 12.1% | 12 | 12.9% | |
| No | 58 | 87.9% | 81 | 87.1% | 0.88 |
| **Number of antibiotics** | | | | | |
| 1 antibiotic | 25 | 37.9% | 41 | 44.1% | |
| 2 antibiotics | 12 | 18.2% | 20 | 21.5% | |
| 3 and + antibiotics | 9 | 13.6% | 4 | 4.3% | 0.10 |

***Variations in clinical characteristics, 2011-2012 and 2016-2017:*** Between the two survey periods, there was no significant change in the socio-demographic and clinical variables of CA-CDI cases (Table 1). No difference was observed in the proportion of cases with rectorrhagia (15.2% in 2011-2012; 15.1% in 2016-2017; p=0.88), vomiting (25.8% in 2011-2012; 26.9% in 2016-2017; p=0.83), inflammatory bowel disease (15.2% in 2011-2012; 11.8% in 2016-2017; p=0.39), immunosuppressive disease (7.6% in 2011-2012; 5.4% in 2016-2017; p=0.39), immunosuppressive drugs (9.1% in 2011-2012; 11.8% in 2016-2017; p=0.86), radiotherapy/chemotherapy (4.5% in 2011-2012; 3.2% in 2016-2017; p=0.16), CDI recurrence (10.6% in 2011-2012; 7.5% in 2016-2017; p=0.98) and abdominal surgery (4.5% in 2011-2012; 2.2% in 2016-2017; p=0.52).

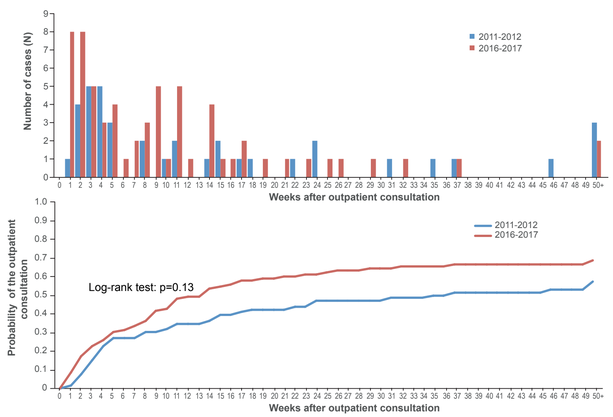
No difference was observed in the proportion of cases who received various classes of antibiotics (Table 2).

No difference was observed regarding the proportion of patients receiving immunosuppressive drugs (1.5% in 2011-2012; 3.2% in 2016-2017; p=0.37) and proton pump inhibitors (42.4% in 2011-2012; 46.2% in 2016-2017; p=0.86) at the time of diagnosis.

There was no difference in the proportion of patients with a history of hospitalization (log-rank, p=0.20) or in the proportion of patients with a history of outpatient consultation (log-rank, p=0.13) (Figure 3) within the previous 12 months.

**Figure 3**

**Evolution of the time period frequencies between outpatient consultation and sampling date in 2011-2012 and 2016-2017**




No difference was observed regarding hospitalization in an acute care facility (47.0% in 2011-2012; 35.5% in 2016-2017; p=0.11), hospitalization in the same healthcare facility (43.9% in 2011-2012; 36.6% in 2016-2017; p=0.29), accommodation in a residence or long-term healthcare facility (1.5% in 2011-2012; 1.1% in 2016-2017; p=0.11), accommodation in a rehabilitation healthcare facility (1.5% in 2011-2012; 2.2% in 2016-2017; p=0.35), outpatient consultation or external clinical contact (60.6% in 2011-2012; 68.8% in 2016-2017; p=0.18) during the year preceding the diagnosis.

***Variations in laboratory diagnostic tests, 2011-2012 and 2016-2017 (patient level):*** The most striking result was a significant increase in the proportion of CA-CDI diagnosed by laboratory Nucleic acid amplification test (NAAT) (from 7.6% in 2011-2012 to 54.8% in 2016-2017; p<0.0001) (Table 3).

**Table 3**

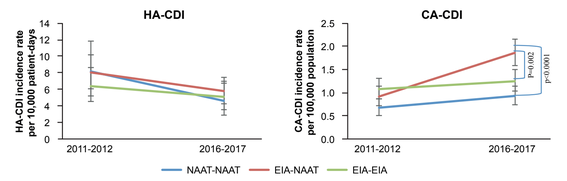
**Frequency of types of CDI laboratory diagnostic tests at time of CA-CDI diagnosis in 2011-2012 and 2016-2017**

| | 2011-2012 | | 2016-2017 | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| **Laboratory diagnostic tests** | | | | | |
| NAAT | 5 | 7.6% | 51 | 54.8% | |
| EIA | 54 | 81.8% | 41 | 44.1% | < 0,0001 |
| Unknown | 7 | 10.6% | 1 | 1.1% | |

***Variations in incidence rates according to laboratory diagnostic tests approaches, 2011-2012 and 2016-2017 (institutional level):*** The trends in the CDI incidence rates of healthcare facilities that used nucleic acid amplification tests (NAATs) for toxin B gene during both study periods (2011-2012 and 2016-2017), of facilities that used EIAs for toxin A and B during both study periods, and of facilities that switched from EIAs to NAAT between the study periods are presented in Figure 4 (3,4). Healthcare facilities that switched from EIAs in 2011-2012 to NAAT in 2016-2017 exhibited a significant increase in the CA-CDI incidence rate per 10,000 population as compared with facilities that used NAAT-NAAT (p<0.0001) and EIA-EIA (p = 0.002) (Figure 4). By contrast, the incidence rate of HA-CDI was globally decreasing at the same rate in all three groups of facilities.

**Figure 4**

**Evolution trends in HA-CDI and CA-CDI incidence rates according to laboratory diagnostic tests approaches used in healthcare facilities in 2011-2012 and 2016-2017**




## Conclusion

This study provides important insight regarding CA-CDI cases. Overall, CA-CDI cases are often misclassified, and the high frequency of reported vomiting and rectorrhagia suggests that some of these cases may not represent true CDI cases. Moreover, the majority of CA-CDI cases seem to have had previous contact with the healthcare settings. The increase in CA-CDI was strongly associated with increasing use of PCR to diagnose CDI, both at the patient level and the institutional level.

## References

1. Comité de surveillance provinciale des infections nosocomiales (SPIN), Garenc C, Longtin Y, Moisan D, Ngenda-Muadi M, Rocher I, et al. Clostridium difficile–Associated Diarrhea (CDAD) - Surveillance Results: 2016-2017 [Internet]. INSPQ; 2017 p. 15. Disponible sur: https://www.inspq.qc.ca/en/nosocomial-infections/spin-cdad/surveillance-results-2016-2017.
2. Comité de surveillance provinciale des infections nosocomiales (SPIN-CD), Longtin Y, Tremblay C, Moisan D, Frenette C, Garenc C, et al. Surveillance provinciale des diarrhées associées au Clostridium difficile au Québec - Protocole [Internet]. INSPQ; 2018 p. 42. Disponible sur: https://www.inspq.qc.ca/sites/default/files/documents/infectionsnosocomiales/protocole_dacd_2018.pdf.
3. Longtin Y, Trottier S, Brochu G, Paquet-Bolduc B, Garenc C, Loungnarath V, et al. Impact of the type of diagnostic assay on Clostridium difficile infection and complication rates in a mandatory reporting program. Clin Infect Dis Off Publ Infect Dis Soc Am. janv 2013;56(1):67-73.
4. Bogaty C, Lévesque S, Garenc C, Frenette C, Bolduc D, Galarneau L-A, et al. Trends in the use of laboratory tests for the diagnosis of Clostridium difficile infection and association with incidence rates in Quebec, Canada, 2010-2014. Am J Infect Control. 23 mai 2017.