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# Antibiotic Prescribing Choices and Their Comparative *C. Difficile* Infection Risks: A Longitudinal Case-Cohort Study

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***Background.*** Antibiotic use is the strongest modifiable risk factor for the development of *Clostridioides difficile* infection, but prescribers lack quantitative information on comparative risks of specific antibiotic courses. Our objective was to estimate risks of *C. difficile* infection associated with receipt of specific antibiotic courses.

***Methods.*** We conducted a longitudinal case-cohort analysis representing over 90% of Ontario nursing home residents, between 2012 and 2017. Our primary exposure was days of antibiotic receipt in the prior 90 days. Adjustment covariates included: age, sex, prior emergency department or acute care stay, Charlson comorbidity index, prior *C. difficile* infection, acid suppressant use, device use, and functional status. We examined incident *C. difficile* infection, including cases identified within the nursing home, and those identified during subsequent hospital admissions. Adjusted and unadjusted regression models were used to measure risk associated with 5- to 14-day courses of 18 different antibiotics.

***Results.*** We identified 1708 cases of *C. difficile* infection (1.27 per 100 000 resident-days). Longer antibiotic duration was associated with increased risk: 10- and 14-day courses incurred 12% (adjusted relative risk [ARR] = 1.12, 95% confidence interval [CI]: 1.09, 1.14) and 27% (ARR = 1.27, 95% CI: 1.21,1.30) more risk compared to 7-day courses. Among 7-day courses with similar indications: moxifloxacin resulted in 121% more risk than amoxicillin (ARR = 2.21, 95% CI: 1.67, 3.08), ciprofloxacin engendered 89% more risk than nitrofurantoin (ARR = 1.89, 95% CI: 1.45, 2.68), and clindamycin resulted in 112% (ARR = 2.12, 95% CI: 1.32, 3.78) more risk than cloxacillin.

***Conclusions.*** *C. difficile* infection risk increases with antibiotic duration, and there are wide disparities in risks associated with antibiotic courses used for similar indications.

**Keywords.** *Clostridioides difficile* infection; CDI; cohort study; antibiotics; comparative effectiveness.

Antibiotic use is the most important modifiable risk factor for the development of *Clostridioides difficile* infection. Antibiotic-associated *C. difficile* infection risk is driven by the duration of antimicrobial exposure, as well as the class of antimicrobial agent received [1–4]. Several meta-analyses have found that 2nd and 3rd generation cephalosporins, fluoroquinolones, and clindamycin have particularly strong tendencies to precipitate *C. difficile* infection [5, 6], but few studies have examined differences between specific agents within each class [7, 8]. The time elapsed since receipt is also an important qualifier of antibiotic risk; risk is concentrated in the first 90 days after antibiotic exposure [4]. No studies have examined the incremental impact of duration on risk for specific antibiotics, or compared risks associated with alternative prescribing options for common indications.

Physician prescribing choices may strongly impact patient *C. difficile* infection risk. Variability in initiation, duration, and specific agent prescribed is driven by physician choice more than patient factors [9, 10]. Potential adverse effects do not figure strongly in clinician antibiotic prescribing decisions [11], and clinicians often overestimate benefits and underestimate harms of treatments [12]. In the case of antibiotics, this could be driven by a lack of readily available, comparative information on antibiotic harms.

Our objective was to compare the incremental risk of *C. difficile* infection that exposure to a given antibiotic, for a given amount of time, confers on a patient, using a representative cohort of long-term care residents, a group at high risk for antibiotic related harms. The resulting granular estimates of *C. difficile* infection risk could be used by clinicians to better weigh the harms and benefits of different antibiotic prescribing choices, minimize *C. difficile* infection risk, and maximize the health and well-being of patients.

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## METHODS

### Data Sources

This study was made possible by comprehensive, individual-level and Ontario-wide, medico-administrative datasets, held at the ICES (formerly the Institute for Clinical Evaluative Sciences) in Toronto, Canada. These datasets were linked using unique encoded identifiers and analyzed at ICES. We included data sets corresponding to: mandated quarterly nursing home assessments from the Continuing Care Reporting System [13], physician billing claims to the Ontario Health Insurance Program, *International Classification of Diseases* version 10 coded discharge abstracts corresponding to ambulatory care, same day surgeries, and hospital admissions [14], and demographics from Ontario's population registry. Information on antibiotic prescribing was ascertained by the Ontario Drug Benefit database, which covers nonhospital antibiotic dispensing only for Ontarians 65 years and older, and which has been shown to be over 99% accurate [15].

### Study Design

This study employed a longitudinal case-cohort design. The study was longitudinal in that the unit of analysis was a resident-day, to ensure that the timing of *C. difficile* infection relative to antibiotic exposures could be captured accurately. Days on which residents developed *C. difficile* infection were case-days, and days on which residents did not develop *C. difficile* infection were control-days [2]. As such, a single resident could contribute both case- and control-days. Time-varying exposures, including antibiotics, were measured for each day [16]. The study used a case-cohort design in that controls were randomly sampled with a known probability of selection, and unlike a nested case-control study, controls were not matched to cases [17]. Because we anticipated over 150 million resident-day records and lacked the computing power for this size of data set, we selected 100% of *C. difficile* infection case-days and a 0.1% simple random sample of control-days. This design allowed us to analyze a data set that was almost 1000 times smaller than the full cohort, while obtaining results that case-cohort theory suggests should be indistinguishable from the full cohort analysis, because there were 80 controls per case (exceeding the 10:1 rule of thumb) [18].

### Population

We identified residents of nursing homes in Ontario, Canada, between 2012 and 2017. We included only residents aged 66 years of age or older in order to ensure 1 year of baseline prescribing information in the included cohort. We then selected 100% of case-days and 0.1% of control-days. After the case-cohort selection, we excluded resident-days with: (1) multiple antibiotics within a 90-day retrospective window to enable attribution of *C. difficile* risk to individual agents, (2) a hospitalization, rehabilitation, or continuing care stay in the prior 1–30 days, since antibiotic exposures in these centers are not captured in the Ontario Drug Benefit database (note that the day of admission itself was not excluded to enable detection of inpatient *C. difficile* infection), (3) a history of *C. difficile* infection in the prior 60 days, and (4) receipt of *C. difficile* treatment agents in the prior 90 days (oral vancomycin, metronidazole, and fidaxomicin) that did not meet the case definition, to ensure only incident *C. difficile* infections were included, and not the postinfection period, recurrent cases, or prolonged *C. difficile* infection treatment.

### Case Definition

The primary outcome was incident *C. difficile* infection, as identified in nursing homes and hospitals. In nursing homes, *C. difficile* infection was identified by either a physician visit billing corresponding to diarrhea (ICD-9 code 009) or a resident assessment with *C. difficile* infection, combined with initiation of a *C. difficile* infection treatment agent. Treatment agents were defined as metronidazole, oral vancomycin, or fidaxomicin. Among residents transferred to a hospital, *C. difficile* infection was identified as an emergency unit or hospital admission with diagnosis code corresponding to *C. difficile* infection (ICD-10 code A04.7), which has been shown to have good concordance with laboratory identified infection ($\kappa = 0.64$) and neither over- nor underestimates incidence [19]. The date of incident infection was defined as the date of treatment agent initiation (nursing homes) or the day of emergency unit or hospital admission (hospitals).

### Antibiotic Risk Factors

Antibiotics dispensed were assessed via the Ontario Drug Benefit database. Only antibiotics with a systemic route of administration (oral or parenteral) were included. For each resident-day, we measured the following, within a 90-day retrospective window: (1) the type of antibiotic received, if any, (2) days of antibiotic therapy, and (3) days elapsed since most recent antibiotic receipt.

### Other Risk Factors

We captured 14 resident-level covariates that could potentially confound an association between antibiotic receipt and *C. difficile* infection, including: age (66–75, 76–85, ≥86) and sex from the population registry, days of emergency department or acute care stay in the prior 31–90 days (0, 1–7, ≥8 days), Charlson comorbidity index (0, 1, 2–3, ≥4) [20] and history of *C. difficile* infection in the prior 2 years, 2 variables related to acid suppressant use in the prior 90 days (proton pump or H2 antagonist receipt), 5 variables related to functional status (requiring assistance with transferring, dressing, eating, hygiene, and toileting), and 2 variables related to device use in the prior 30 days (dialysis, feeding tube) from quarterly nursing home assessments [13].

### Statistical Analysis

Due to the case-cohort study design used in this study, we incorporated sampling weights to reflect the source population when calculating the cohort size, the prevalence of risk factors, and the incidence of *C. difficile* infection [18]. Sampling weights were 1 for case-days and 1000 for control-days, corresponding to the inverse of the selection probability.

We used logistic random-effects models to measure the probability of incident *C. difficile* infection on a given resident-day. In order to simultaneously account for both duration effects and waning effects after cessation, important qualifiers of antibiotic-associated risk [1, 4, 16], we developed 2 antibiotic exposure metrics. The "no waning" antibiotic metric was measured as the days having receipt of the antibiotic in the prior 90 days transformed using the log2(X + 1) transformation in order to account for the logarithmic relationship between antibiotic days and *C. difficile* infection risk. The "linear waning" antibiotic metric multiplied the "no waning" antibiotic metric by antibiotic recency which varied between 0 (no receipt in prior 90 days) and 1 (current receipt). Specifically, recency was measured as 1-X/90, where X was the number of days since a resident's most recent antibiotic. Linear combinations of the no waning and linear waning metrics could simultaneously capture both cumulative exposure in terms of days of therapy and waning effects.

Unadjusted models included both antibiotic metrics, which were allowed to vary according to the type of antibiotic received, parameterized as a random-effect interaction [21]. Adjusted models included the same variables as the unadjusted model, with the addition of the 14 individual-level covariates.

We predicted resident *C. difficile* infection risk for each of the 18 antibiotics for durations between 5 and 14 days [22] using the unadjusted and adjusted models developed above. For unadjusted 90-day incidence, we extracted predicted probabilities over a 90-day period, with day 1 defined as the day of antibiotic initiation and then summed these probabilities to obtain the cumulative 90-day probability of *C. difficile* infection. In total, there were 180 risk estimates (18 × 10) for patients with a history of antibiotic use and 1 risk estimate for patients without antibiotic use, for a total of 181 risk estimates. Adjusted 90-day incidence was measured analogously but using the prediction at the means approach [23].

We compared different risk estimates using the risk ratio measure: (1) initiating a 7-day antibiotic course compared to no antibiotic exposure, (2) a longer duration of the same antibiotic versus a shorter duration, or (3) substituting an antibiotic (same 7-day duration but for different agents). We presented clinically important comparisons within urinary infective agents: ciprofloxacin or trimethoprim-sulfomethoxazole (co-trimoxazole) versus nitrofurantoin; and respiratory infective agents: moxifloxacin, levofloxacin or amoxicillin-clavulanate versus amoxicillin; clindamycin or cephalexin versus cloxacillin.

We estimated 95% confidence intervals (CIs) for risk estimates and risk ratios by iteratively bootstrapping the model and then recalculating the risk estimates and risk ratios 1000 times [24].

### Sensitivity Analyses

We reran our prediction models on the following subsets: (1) residents without any hospital exposure in the prior 90 days, (2) residents without a prior history of *C. difficile,* and (3) using just a single, randomly selected, observation per resident.

## RESULTS

### Population

The source longitudinal cohort included 146.9 million days of follow-up, which was reduced to 149 917 days after the initial 0.1% selection of control resident-days (Figure 1). In sum, 9.4% of the remaining resident-days were excluded based on

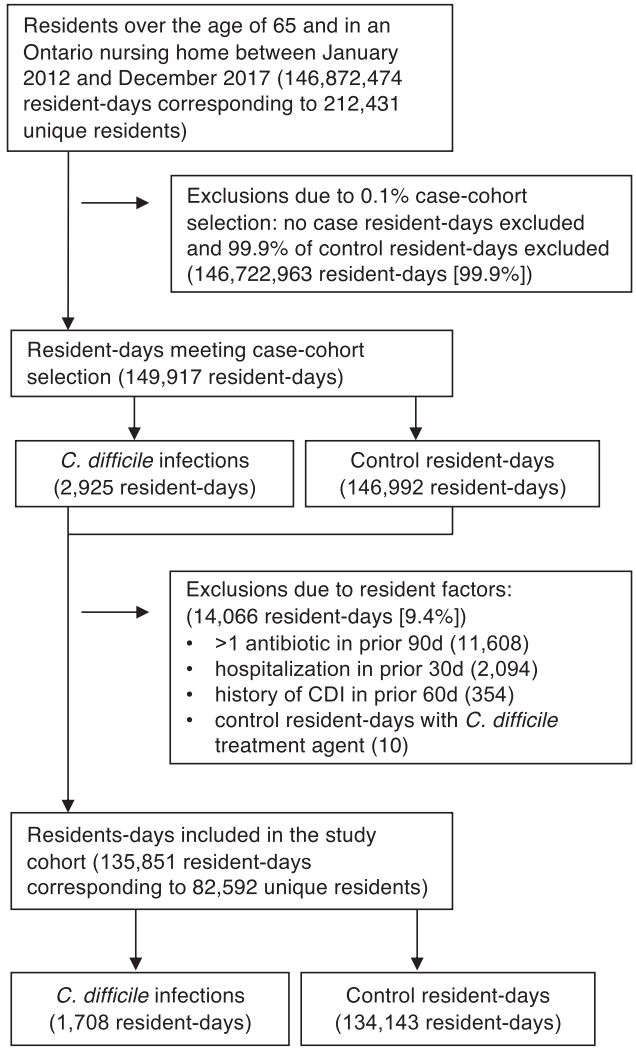


**Figure 1.** Study flow diagram. Abbreviation: CDI, *Clostridium difficile* infection.

resident-level exclusion criteria, of which receipt of > 1 antibiotic in the prior 90 days was the most significant, leaving 135 851 resident-days among 82 592 unique residents in the final cohort (mean of 1.6 days of observation per resident).

### C. *difficile* Infection Incidence

Of these 135 851 resident-days, we identified 1708 cases of *C. difficile* infection and 134 143 control resident-days for a case-control ratio of 80:1. Accounting for sampling weights [18], the incidence of *C. difficile* infection was 1.27 per 100 000 resident-days. Of the 1708 cases, 680 were identified as outpatients, whereas 1028 were identified in-hospital.

### Cohort Characteristics

The majority (54.7%) of residents were 86 or over, and 71.4% of residents were female (Table 1). A high proportion of residents had received a proton pump inhibitor in the prior 90 days (39.4%).

### Cohort Antibiotic Exposures

One fifth (20.4%) of residents in the cohort had exposure to antibiotics in the prior 90 days (Table 2). The 6 most common antibiotics were cephalexin, ciprofloxacin, amoxicillin, cotrimoxazole, nitrofurantoin, and moxifloxacin, which together accounted for 67.2% of antibiotic exposures in the cohort. The next 6 most common antibiotics included levofloxacin, amoxicillin-clavulanate, azithromycin, cefuroxime, norfloxacin, and clarithromycin, which together accounted for an additional 22.1% of antibiotic exposures. The next 6 most common antibiotics included clindamycin, cloxacillin, cefprozil, tetracycline, cefixime, and trimethoprim, accounting for just 8.7% of antibiotic exposures. Seven antibiotics, of which penicillin V and ceftriaxone were the most common, were rarely dispensed and accounted for the remaining 2% of antibiotic exposures.

### Comparative *C. difficile* Infection Risks of Antibiotic Courses

The 90-day risk of *C. difficile* infection among residents without antibiotics was 0.81 per 1000 residents (Table 3), compared to

**Table 1. Nursing Home Resident Cohort Characteristics and Exposures, 2012–2017**

| Variable | Cohort resident-days (000s)[a] | *C. difficile* infection (N) | Incidence Rate per 100 000 resident-days (95% CI) |
|---|---|---|---|
| Total | 134 145 (100%) | 1708 (100%) | 1.27 (1.21, 1.34) |
| Age | | | |
| 66 to 75 | 16 144 (12.0%) | 223 (13.1%) | 1.38 (1.21, 1.58) |
| 76 to 85 | 44 666 (33.3%) | 617 (36.1%) | 1.38 (1.27, 1.49) |
| ≥86 | 73 335 (54.7%) | 868 (50.8%) | 1.18 (1.11, 1.27) |
| Female | 95 782 (71.4%) | 1119 (65.5%) | 1.17 (1.10, 1.24) |
| Hospital visit in prior 31–90 d[b] | | | |
| None | 120 950 (90.2%) | 972 (56.9%) | .80 (.75, .86) |
| Any | 13 195 (9.8%) | 736 (43.1%) | 5.58 (5.18, 6.00) |
| 1 to 7 d | 10 006 (7.5%) | 489 (28.6%) | 4.89 (4.46, 5.34) |
| ≥8 d | 3140 (2.3%) | 247 (14.5%) | 7.87 (6.92, 8.91) |
| Charlson comorbidities | | | |
| 0 | 90 962 (67.8%) | 662 (38.8%) | .73 (.67, .79) |
| 1 | 18 381 (13.7%) | 291 (17%) | 1.58 (1.41, 1.78) |
| 2 to 3 | 17 721 (13.2%) | 478 (28%) | 2.70 (2.46, 2.95) |
| ≥4 | 7080 (5.3%) | 277 (16.2%) | 3.91 (3.47, 4.40) |
| History of *C. difficile* infection | 1989 (1.5%) | 312 (18.3%) | 15.7 (14.0, 17.5) |
| Acid suppressants in prior 90 d | | | |
| Proton pump inhibitor | 52 915 (39.4%) | 933 (54.6%) | 1.76 (1.65, 1.88) |
| H2 antagonist | 4732 (3.5%) | 91 (5.3%) | 1.92 (1.55, 2.36) |
| Device use in prior 30 d | | | |
| Feeding tube | 958 (0.7%) | 80 (4.7%) | 8.35 (6.62, 10.4) |
| Dialysis | 654 (0.5%) | 58 (3.4%) | 8.87 (6.73, 11.5) |
| Functional status, requires assistance … | | | |
| Transferring | 99 413 (74.1%) | 1402 (82.1%) | 1.41 (1.34, 1.49) |
| Dressing | 118 575 (88.4%) | 1576 (92.3%) | 1.33 (1.26, 1.40) |
| Eating | 48 959 (36.5%) | 628 (36.8%) | 1.28 (1.18, 1.39) |
| With hygiene | 112 334 (83.7%) | 1519 (88.9%) | 1.35 (1.29, 1.42) |
| Toileting | 118 800 (88.6%) | 1548 (90.6%) | 1.30 (1.24, 1.37) |

Abbreviation: CI, confidence interval.

[a]Weighted to reflect the source population (case weight = 1, control weight = 1000).

[b]Note that residents with a hospital visit in the prior 30 d were excluded from the cohort.

**Table 2. Prevalence of Antibiotic Exposures in the Nursing Home Resident Cohort**

| Variable | Cohort resident-days (000s)[a] | Mean Days of Antibiotic in Prior 90 d[a] | *C. difficile* Infection (N, %) | Incidence Rate per 100 000 resident-days (95% CI) |
|---|---|---|---|---|
| Antibiotic exposure in prior 90 d | | | | |
| None | 106 766 (79.6%) | 0 | 883 (51.7%) | 0.83 (.77, .88) |
| Any | 27 379 (20.4%) | 11.6 | 825 (48.3%) | 3.01 (2.81, 3.23) |
| Type of antibiotic | | | | |
| Cephalexin | 3641 (2.7%) | 11.0 | 123 (7.2%) | 3.38 (2.81, 4.03) |
| Ciprofloxacin | 3405 (2.5%) | 9.6 | 123 (7.2%) | 3.61 (3.00, 4.31) |
| Amoxicillin | 3409 (2.5%) | 9.6 | 57 (3.3%) | 1.67 (1.27, 2.17) |
| Cotrimoxazole | 2932 (2.2%) | 15.7 | 65 (3.8%) | 2.22 (1.71, 2.83) |
| Nitrofurantoin | 2667 (2.0%) | 19.7 | 35 (2.0%) | 1.31 (.91, 1.83) |
| Moxifloxacin | 2343 (1.7%) | 8.4 | 140 (8.2%) | 5.98 (5.03, 7.05) |
| Levofloxacin | 1814 (1.4%) | 8.2 | 42 (2.5%) | 2.32 (1.67, 3.13) |
| Amoxicillin-clavulanate | 1508 (1.1%) | 9.3 | 67 (3.9%) | 4.44 (3.44, 5.64) |
| Azithromycin | 1140 (0.8%) | 8.8 | 34 (2.0%) | 2.98 (2.07, 4.17) |
| Cefuroxime | 848 (0.6%) | 8.6 | 36 (2.1%) | 4.25 (2.97, 5.88) |
| Norfloxacin | 742 (0.6%) | 13.0 | 8 (0.5%) | 1.08 (.47, 2.12) |
| Clarithromycin | 602 (0.4%) | 8.6 | 8 (0.5%) | 1.33 (.57, 2.62) |
| Clindamycin | 526 (0.4%) | 8.6 | 32 (1.9%) | 6.08 (4.16, 8.59) |
| Cloxacillin | 440 (0.3%) | 10.8 | 13 (0.8%) | 2.95 (1.57, 5.05) |
| Cefprozil | 352 (0.3%) | 9.3 | 11 (0.6%) | 3.13 (1.56, 5.59) |
| Tetracycline | 174 (0.1%) | 45.6 | 0 (0%) | 0.00 (.00, 2.12) |
| Cefixime | 144 (0.1%) | 8.6 | 14 (0.8%) | 9.72 (5.32, 16.3) |
| Trimethoprim | 152 (0.1%) | 72.0 | 1–5 (0.0–0.3%)[b] | NA |
| Other [c] | 539 (0.4%) | 14.6 | 15 (0.9%) | 2.78 (1.56, 4.59) |

Abbreviation: CI, confidence interval; NA, not applicable.

[a] Weighted to reflect the source population (case weight = 1, control weight = 1000).

[b] Exact value suppressed.

[c] Includes penicillin V, ceftriaxone, and other less frequently prescribed antibiotics.

1.90 among those with a 7-day course of antibiotics. A 7-day course of antibiotics was associated with a 1.80-fold increase in *C. difficile* infection risk (ARR = 1.80 for 7-day course versus no antibiotics, 95% CI: 1.55, 1.97).

Antibiotic risks were heterogeneous. When examining 7-day courses of antibiotics, agents conferring the highest risks (Figure 2) were cefixime (ARR = 4.26, 95% CI: 2.41, 7.42), clindamycin (ARR = 4.04, 95% CI: 2.74, 5.72), moxifloxacin (ARR = 3.39, 95% CI: 2.83, 4.03), and amoxicillin-clavulanate (ARR = 2.43, 95% CI: 1.89, 3.08).

We compared 7-day courses of antibiotics with similar indications: ciprofloxacin engendered 89% more risk than nitrofurantoin (ARR = 1.89, 95% CI: 1.45, 2.68), moxifloxacin resulted in 121% more risk than amoxicillin (ARR = 2.21, 95% CI: 1.67, 3.08), and clindamycin resulted in 112% (ARR = 2.12, 95% CI: 1.32, 3.78) more risk than cloxacillin. Among fluoroquinolones, a 7-day course of moxifloxacin conferred significantly more *C. difficile* infection risk compared to the same duration of either ciprofloxacin (ARR = 1.79, 95% CI: 1.40, 2.30) or levofloxacin (ARR = 2.20, 95% CI: 1.62, 3.11).

Longer antibiotic durations were associated with greater *C. difficile* infection risk. On average, compared to a 7-day course, a 14-day course was associated with 27% more risk (ARR = 1.27, 95% CI: 1.21, 1.30), while a 5-day course was associated with 9% less risk (ARR = 0.91, 95% CI: .90, .93). However, the strength of the duration-risk association was heterogeneous; longer durations of low-risk agents (nitrofurantoin) did not increase risk substantially, while longer durations of high-risk agents (moxifloxacin) were particularly harmful (Figure 3).

To enable prescribers to compare the relative risks of alternative specific antibiotic courses, we developed a searchable table (https://rebrand.ly/cdiffrisk) to allow the comparison of 90-day *C. difficile* infection risk between 2 antibiotic courses defined by antibiotic type (among the 18 antibiotics included in this study) and duration (5–14 days), for a total of over 32 000 potential comparisons. For example, the searchable table can be used to show that a 5-day ciprofloxacin course is associated with substantially higher risk than a 7-day nitrofurantoin course (ARR = 1.72, 95% CI: 1.29, 2.49).

### Sensitivity Analyses

We used linear regression (Supplementary Data—Figure) to compare the ARRs for the 18 antibiotics in the main analysis versus the same analysis: (1) excluding patients with a recent

**Table 3. 90-day Incidence of *C. difficile* Infection for Antibiotic Courses**

| | Unadjusted 90-day Incidence (per 1000) | Unadjusted Relative Risk (95% CI) | Adjusted [a] 90-day Incidence (per 1000) | Adjusted [a] Relative Risk (95% CI) |
|---|---|---|---|---|
| Initiation (7 d) | | | | |
| No antibiotic | 0.81 | Reference | 0.57 | Reference |
| Any antibiotic | 1.90 | 2.34 (2.01, 2.53) | 1.02 | 1.80 (1.55, 1.97) |
| Clindamycin | 4.12 | 5.08 (3.55, 6.97) | 2.29 | 4.04 (2.74, 5.72) |
| Fluoroquinolones | | | | |
| Moxifloxacin | 3.66 | 4.50 (3.77, 5.24) | 1.92 | 3.39 (2.83, 4.03) |
| Ciprofloxacin | 2.38 | 2.93 (2.49, 3.45) | 1.07 | 1.90 (1.57, 2.25) |
| Levofloxacin | 1.78 | 2.20 (1.66, 2.74) | 0.87 | 1.55 (1.11, 1.98) |
| Norfloxacin | 0.92 | 1.14 (.62, 1.57) | 0.61 | 1.09 (.65, 1.50) |
| Cephalosporins | | | | |
| Cefixime | 4.74 | 5.83 (3.51, 9.66) | 2.41 | 4.26 (2.41, 7.42) |
| Cefuroxime | 2.66 | 3.28 (2.42, 4.29) | 1.39 | 2.46 (1.61, 3.45) |
| Cefprozil | 2.12 | 2.61 (1.49, 3.89) | 1.07 | 1.89 (1.13, 3.02) |
| Cephalexin | 1.96 | 2.41 (2.01, 2.80) | 1.05 | 1.85 (1.54, 2.15) |
| Macrolides | | | | |
| Azithromycin | 2.23 | 2.75 (1.91, 3.69) | 1.22 | 2.15 (1.53, 2.95) |
| clarithromycin | 1.20 | 1.48 (.82, 2.06) | 0.74 | 1.32 (.73, 1.85) |
| Penicillins | | | | |
| Amoxicillin-clavulanate | 2.89 | 3.55 (2.82, 4.34) | 1.37 | 2.43 (1.89, 3.08) |
| Cloxacillin | 1.90 | 2.35 (1.53, 3.28) | 1.08 | 1.90 (1.21, 2.79) |
| Amoxicillin | 1.39 | 1.71 (1.28, 2.11) | 0.87 | 1.53 (1.15, 1.92) |
| Sulfonamides and Trimethoprim | | | | |
| Cotrimoxazole | 1.56 | 1.92 (1.52, 2.34) | 0.85 | 1.50 (1.19, 1.83) |
| Trimethoprim | 1.28 | 1.58 (.73, 3.48) | 0.73 | 1.29 (.73, 2.95) |
| Nitrofurantoin | 1.08 | 1.33 (.95, 1.70) | 0.57 | 1.00 (.72, 1.25) |
| Tetracycline | 0.86 | 1.06 (.65, 1.23) | 0.53 | 0.94 (.65, 1.11) |
| Duration | | | | |
| 7 d | 1.90 | Reference | 1.02 | Reference |
| vs 5 d | 1.68 | 0.88 (.87, .90) | 0.93 | 0.91 (.90, .93) |
| vs 10 d | 2.19 | 1.15 (1.13, 1.17) | 1.14 | 1.12 (1.09, 1.14) |
| vs 14 d | 2.53 | 1.33 (1.27, 1.36) | 1.29 | 1.27 (1.21, 1.30) |
| Selection (7 d) | | | | |
| Nitrofurantoin | 1.08 | Reference | 0.57 | Reference |
| vs cotrimoxazole | 1.56 | 1.45 (1.05, 2.10) | 0.85 | 1.50 (1.10, 2.21) |
| vs ciprofloxacin | 2.38 | 2.21 (1.65, 3.24) | 1.07 | 1.89 (1.45, 2.68) |
| Amoxicillin | 1.39 | Reference | 0.87 | Reference |
| vs levofloxacin | 1.78 | 1.28 (.91, 1.86) | 0.87 | 1.01 (.70, 1.45) |
| vs amoxicillin-clavulanate | 2.89 | 2.08 (1.53, 2.96) | 1.37 | 1.58 (1.15, 2.28) |
| vs moxifloxacin | 3.66 | 2.63 (2.03, 3.55) | 1.92 | 2.21 (1.67, 3.08) |
| Cloxacillin | 1.90 | Reference | 1.08 | Reference |
| vs cephalexin | 1.96 | 1.03 (.71, 1.59) | 1.05 | .97 (.65, 1.56) |
| vs clindamycin | 4.12 | 2.17 (1.35, 3.85) | 2.29 | 2.12 (1.32, 3.78) |

Abbreviation: CI, confidence interval.

[a]Adjusted for 14 resident-level covariates: age, sex, days of emergency department or acute care stay in the prior 31–90 days, Charlson comorbidity index, and history of *C. difficile* infection in the prior 2 years, acid suppressant use in the prior 90 days, functional status, and device use in the prior 30 days.

hospitalization in the prior 90 days ($R^2 = 0.93$), (2) excluding patients with first-time *C. difficile* infection ($R^2 = 0.98$), and (3) including only a single observation per resident ($R^2 = 0.99$).

## CONCLUSIONS

Our study has shown that antibiotic prescribing choices lead to differences in *C. difficile* infection risk, with risk being a function of the decision to initiate, the duration dispensed, and the type of antibiotic selected. We have quantified these differential risks using a real-world population-based cohort of nursing home residents with comprehensive antibiotic exposure information.

Antibiotics are frequently prescribed for longer than necessary, driven by prescriber training and habit [9, 10]. We found that each additional day of antibiotic exposure was associated

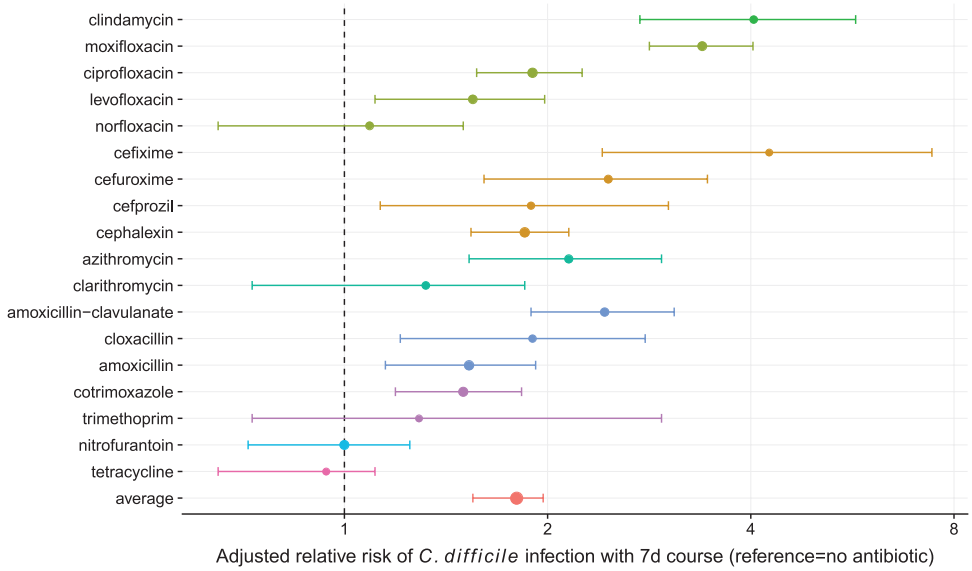


**Figure 2.** Forest plot of adjusted relative risks and 95% confidence intervals for 90-day *C. difficile* infection incidence associated with different 7-day antibiotic courses. The reference is the incidence in residents with no antibiotic receipt in the prior 90 days.

with increased *C. difficile* infection risk. Relative to a 7-day course, a 14-day course was associated with 27% more risk, whereas a shorter 5-day course was associated with 9% less risk. Shorter courses of 5–7 days have similar clinical efficacy compared to longer courses for uncomplicated urinary tract infections, pneumonia, and cellulitis [25]. When antibiotics are necessary, prescribers can use this information to select the shortest effective duration and minimize patient risk.

Consistent with previous meta-analyses [5, 6, 26], we showed that clindamycin, fluoroquinolones, and cephalosporins were the highest risk classes and that tetracyclines were a low risk class [27, 28]. We also identified important within-class

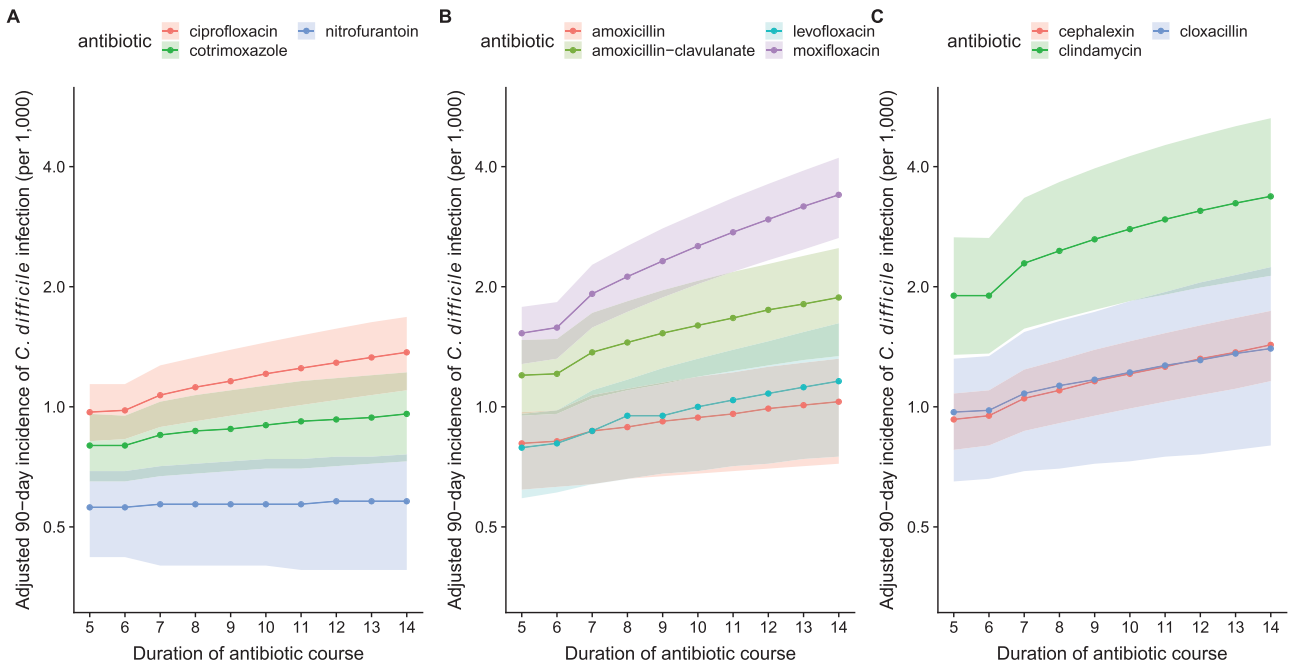


**Figure 3.** Adjusted 90-day incidence of *C. difficile* infection (per 1000 residents) for (*A*) ciprofloxacin, cotrimoxazole, nitrofurantoin, (*B*) amoxicillin, amoxicillin-clavulanate, levofloxacin, moxifloxacin, and (*C*) cephalexin, clindamycin, cloxacillin, for durations of 5 to 14 days. Shaded regions represent 95% confidence intervals.

differences in risk which prior studies were not powered to investigate. First, we showed that amoxicillin-clavulanate [6] conferred high risk, providing further evidence that penicillin-beta-lactamase combinations should be considered apart from other penicillins and prescribed with caution [29]. Second, we showed that moxifloxacin, a respiratory fluoroquinolone with extended anaerobic coverage, caused greater risk than ciprofloxacin and levofloxacin. A prior study, using Ontario outpatient data from the early 2000s, found that moxifloxacin had 37% higher risk than levofloxacin and ciprofloxacin, but this finding was not statistically significant [7]. This study, using a longitudinal model capturing detailed antibiotic exposures, has enabled better measurement of antibiotic risks.

Our study quantified the comparative risks of real-world prescribing choices. For example, prescribing a 7-day course of nitrofurantoin (an agent with good clinical efficacy for treatment of cystitis) [30], rather than ciprofloxacin, would lead to 47% less *C. difficile* risk. Similarly, for suspected or proven pneumococcal community-acquired pneumonia, amoxicillin is equally effective as the broader spectrum moxifloxacin [31]; however, this study found that a 7-day course of amoxicillin would lead to 55% less *C. difficile* infection risk compared to the same duration of moxifloxacin. These quantitative comparisons provide information for prescribers and patients to make informed choices [32] and minimize *C. difficile* risk.

Our study had certain limitations. Our dispensing data, although highly comprehensive for all Ontarians over 65 years of age, did not capture antibiotics administered during hospitalizations. We addressed this by excluding patients with a recent hospitalization in the prior 30 days from the main analysis. Furthermore, a sensitivity analysis excluding all residents with a hospitalization in the prior 90 days was also conducted and showed similar antibiotic risks ($R^2 = 0.93$). Some have highlighted confounding due to multiple antibiotic exposures as a common weakness of *C. difficile* risk studies [7]. We have eliminated this weakness by examining only residents receiving a single antibiotic type in the prior 90 days. However, this meant that we were unable to consider the impacts of antibiotic combinations. Although a strength of this study was the comprehensive exposure information in the nursing home cohort, we cannot be certain how well these findings generalize to younger patients and community dwelling elderly. Finally, our study only delineates the comparative risks of *C. difficile* and ignores other differences in antibiotic harms (allergy, organ toxicity, drug-drug interactions, and selection for antimicrobial resistance) and benefits (spectrum of coverage, potency, tissue penetration). Despite these limitations, this study provides much needed information on antibiotic risks that in the past could not be easily quantified.

*C. difficile* infection is an important antibiotic associated harm, and harms related to antibiotic prescribing may not be sufficiently considered when clinicians make prescribing decisions [11, 12]. We measured the relative risks across a wide range of antibiotic prescribing choices and found wide disparities in risks. The results of this study can be used by clinicians to weigh the potential harms of antibiotic prescribing choices to prevent *C. difficile* infection and improve patient outcomes.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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