Inter-facility patient sharing and *Clostridioides difficile* infection incidence in the Ontario hospital system: a 13-year cohort study

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Summary

In this ecologic study of 120 Ontario acute care facilities over 13 years, both receipt of patients from other high *C. difficile* incidence hospitals and receipt of patients with a recent history of *C. difficile* infection were associated with higher facility *C. difficile* incidence

Abstract

Objective: Inter-facility patient movement plays an important role in the dissemination of antimicrobial resistant organisms throughout healthcare systems. We evaluated how 3 alternative measures of inter-facility patient sharing were associated with *C. difficile* infection incidence in Ontario acute care facilities.

Design: The cohort included Ontario adult acute care facility stays of 3 or more days, between April 2003 and March 2016. We measured 3 facility-level metrics of patient sharing: 'general patient importation', 'incidence-weighted patient importation', and 'C. difficile case importation'. Each of the 3 patient-sharing metrics were examined against the incidence of *C. difficile* infection in the facility per 1,000 stays, using Poisson regression models.

Results: The analyzed cohort included 6.70 million stays at risk of *C. difficile* infection across 120 facilities. Over the 13-year period, we observed 62,189 new cases of healthcare-associated CDI (incidence = 9.3 per 1,000 stays). After adjustment for facility characteristics, general importation was not strongly associated with *C. difficile* infection incidence (RR per doubling=1.10, 95%CI=0.97 to 1.24, PCV=-2.0%), while incidence-weighted (RR per doubling=1.18, 95%CI=1.06 to 1.30, PCV=-8.4%) and *C. difficile* case importation (RR per doubling=1.43, 95%CI=1.29 to 1.58, PCV=-30.1%) were.

Conclusions: In this 13-year study of Ontario acute care facilities, inter-facility variation in *C. difficile* infection incidence was associated with importation of patients from other high incidence acute care facilities or specifically of patients with a recent history of *C. difficile* infection. Regional infection control strategies should consider the potential impact of importation of patients at high risk of *C. difficile* shedding from outside facilities.

Introduction

Clostridioides (formerly *Clostridium) difficile* infection (CDI) continues to be a highly prevalent healthcare-associated infection that causes substantial morbidity and mortality in hospitals across the globe.[1] While patient-level predictors of CDI are well established, less is known about the facility-level drivers of infection rates, especially among acute care facilities.[2] Studies considering facility-level antibiotic use and C. difficile incidence have diverged,[2–4] while studies considering reported infection prevention practices have not identified strong associations with CDI incidence,[5] suggesting that more research on the identification and measurement of factors driving facility-level rates is needed.

Several empirical studies have shown that inter-facility patient movement plays an important role in the dissemination of antimicrobial resistant organisms and CDI throughout healthcare systems, including acute care facilities.[6–8] Inter-facility patient sharing,[9,10] including both "direct" same-day patient transfers and "indirect" inter-facility patient movement with intervening non-hospital stays, may contribute to transmission between hospitals. The regional structures of most healthcare systems means that the majority of patient sharing occurs within healthcare regions[11] and genetic similarities of antibiotic resistant organisms reflect regional transfer patterns.[12] Patient sharing can be measured in terms of the movement of all patients, or in terms of the movement of subsets of patients more likely to be colonized or infected with an antimicrobial resistant organism.[13] Skin contamination and environment contamination with *C. difficile* spores persists during treatment and for over 6 weeks post-treatment.[14] The relative importance of these different patient sharing metrics for predicting CDI incidence is not known.

Information on patient sharing can be used to inform regional approaches to the control of antibiotic resistant organisms.[15,16] More predictive patient sharing measures could be used for better risk adjustment, to enable fair inter-hospital comparisons, or to design optimal strategies to slow the inter-facility spread of emergent strains of *C. difficile* or of other antimicrobial resistant organisms.

As such, we evaluated 3 different measures of inter-facility patient sharing, including general patient importation, CDI incidence-weighted patient importation, and *C. difficile* case importation, and their association with CDI incidence in Ontario acute care facilities. We hypothesized that each measure of importation would be positively associated with facility CDI incidence.

Methods

Data

This study relied on comprehensive medico-administrative data covering all inpatients in Ontario, Canada, housed at ICES, a not-for-profit research institute based in Toronto. Ontario has a universal publicly funded healthcare system and ICES databases include virtually the entire population (excluding recent migrants within 3 months, those residing on aboriginal reserves, and military personnel). To identify hospital stays, we used the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD) and the National Ambulatory Care Reporting System (NACRS), which together include information on all hospital stays in Ontario (whether inpatient admissions, same day surgery, or emergency department visits), in addition to diagnoses which are coded using the International Classification of Diseases 10th edition (ICD-10) discharge code. In addition, we used the Registered Persons Database (RPDB) in order to identify patient age, sex, and deaths, and an ICES-maintained healthcare institutions dataset (INST) that provides information on facility teaching status.

Population

We defined a full cohort of hospital stays between April 1, 2003 and March 31, 2016. A hospital stay was defined as the contiguous days spent at an emergency department, in day surgery, or as an inpatient in the same facility. We refer to hospital corporations as facilities since the large majority of hospital corporations consisted of stand-alone facilities. The full cohort was used to define hospital characteristics and patient sharing metrics.

In order to measure hospital incidence of *C. difficile* infection, we also defined a subset of the full cohort at risk of hospital onset infection. These were patients that had stays of 3 or more days, did not have a history of CDI in the prior 90 days, and were >=18 years of age. We excluded stays of 2 days or less, or with a history of CDI in the prior 90 days, as they were not at-risk of incident healthcare-facility onset CDI.[17] We excluded patients <18 years of age since these patients were at lower risk of CDI. We only included larger facilities that had at least than 5,000 at-risk stays and had 10 or more incident *C. difficile* cases, in order to ensure reliable measurement of *C. difficile* incidence rates.

Outcomes

Case patients with a first diagnosis of hospital-associated CDI in the prior 90 days were identified from the at-risk cohort of hospitalized patients using the ICD-10 discharge code (A04.7). The ICD code for CDI has both a high sensitivity (88%) and a high specificity (99.7%).[18,19] The primary outcome was the facility incidence of CDI per 1,000 at-risk stays during the study period.

Patient sharing metrics

We measured 3 facility-level metrics of patient sharing that could be associated with facility CDI incidence (Table 1).

First, 'general patient importation' – the number of patient stays with a discharge from any external facility in the prior 90-days, as a proportion of the total number of stays in the facility. This measure includes both directly transferred patients and patients with intervening nonhospital stays. General patient importation is a basic measure of inter-facility patient movement, and could be associated with facility CDI incidence since healthcare exposure is associated with increased risk of CDI and

colonization.[20,21] A conservative 90-day retrospective window was chosen since most studies show that CDI and colonization risk is elevated for extended periods after the time of discharge.[20,21]

Second, 'incidence-weighted patient importation' – the weighted sum of general importation from an *origin* facility multiplied by the incidence of CDI in that facility, across all *origin* facilities. This measure would better reflect the risk of importing either patients asymptomatically shedding *C. difficile* or identified *C. difficile* cases.

Third, '*C. difficile* case importation' – the proportion of patient stays in a facility with a history of *C. difficile* identified, based on the ICD-10 discharge code (A04.7), in any external facility in the prior 90-days. This represents the importation of the subset of patients with perhaps the highest risk of shedding *C. difficile* spores – patients that have been recently diagnosed with CDI, who are known to shed spores for at least 6 weeks after the end of treatment.[14] Once again, a conservative 90-day retrospective window was chosen to ensure complete capture of the post-treatment shedding period.

For the calculation of these 3 patient-sharing metrics, the full cohort, that included all stays in the study period, was used since all patients visiting a hospital could have contributed to transmission, and hence to a facility's CDI incidence.

Covariates

We measured the following 7 facility-level adjustment covariates: (1) mean age, (2) proportion female, (3) mean Charlson comorbidity index based on hospital admissions in the prior year, (4) mean length of stay (CIHI-DAD), (5) the percentage of admissions to medical-surgical, psychiatry, and other services (CIHI-DAD), (6) mean daily number of patients admitted (1 to 5, 6 to 25, 26 or more admissions per day), (7) teaching status of the facility (defined as facilities that give instruction to medical students, or give postgraduate education leading to certification or fellowship). As for the patient sharing metrics, the full cohort that included all stays in the study period was used for calculating each covariate. Note that we also measured the hospital administrative region (N=14) as a variable in descriptive analyses of patient sharing between and within regions.[22]

Statistical analysis

We described interfacility variation with the interdecile range, which is equal to the 90th percentile divided by the 10th percentile. In order to depict linkages between specific origin and destination facilities geographically, we broke down general importation for a given destination facility into the components from each origin facility. We then visually displayed linkages between facilities where the number of patients in a given destination facility with a discharge from an origin facility in the prior 90-days amounted to a least 1% of total stays to the destination facility

Poisson regression models with the outcome equal to the count of CDI cases in the facility and an offset corresponding to the number of stays were used to model the incidence rate of CDI in each hospital. Facility-level random effects were used to account for over-disperson.[23] For each patient sharing measure, an unadjusted and adjusted model was developed, for a total of 6 models.

Unadjusted models for each patient sharing measure included no additional covariates while adjusted models included all 7 covariates.

We communicated the impact of each covariate using risk ratios (RR) and 95% confidence intervals (CI). In order to make the estimated RRs comparable, all 3 patient sharing metrics were log2 transformed before being entered into models, so the RRs represented risk increases associated with a doubling in the patient sharing metrics. The 3 metrics were not included in a single model to guard against multicollinearity, which may have arisen due to the strong correlation between the 3 metrics.

We also measured covariate impact using the proportional change in variance (PCV) [24]. The PCV for a given covariate is measured by fitting and measuring the facility variance for two models, one without (σ^2_0) and one with (σ^2_1) the given covariate, and then measuring the proportional change in facility variance from σ^2_0 to σ^2_1 [24]. The PCV is similar to an R^2 statistic in that it can be interpreted as the percent of the facility-level variance that is explained by the covariate.

Results

The initial cohort hospital consisted of 29.86 million hospital stays in 168 hospitals over the 13-year period. After removal of small facilities with very few stays of patients at-risk of *C. difficile* infection (n=48), 29.32 million stays in 120 facilities were included. This was the full cohort, which was used for the purposes of measuring facility-level patient sharing metrics and hospital covariates.

Because not all stays were at risk of incident *C. difficile* infection, in order to measure facility-level *C. difficile* infection incidence, we applied certain exclusions to the initial cohort. These included stays of < 3 days (19.35 million), age ≤ 18 years (3.61 million), and a history of *C. difficile* in the prior 90 days (N=0.03 million). The at-risk cohort included 6.70 million stays across the same 120 facilities (Figure 1).

Facility covariates

The median length of stay was 3.3 days (Table 2) and 16 (13.4%) of the included facilities had teaching status.

C. difficile infection incidence

Over the 13-year period, we observed 62,189 new cases of healthcare-associated CDI (incidence = 9.3 per 1,000 stays). CDI incidence varied substantially across facilities (median=8.5 per 1,000 stays, 10th percentile [p10]=4.6, p90=13.1, IDR [inter-decile range]=2.8-fold).

Facility-level patient sharing metrics

We examined general importation which showed that a substantial portion of patients had visited another acute care facility in the prior 90 days (median=20.7%, p10=14.1, p90=33.4, IDR=2.4-fold). Note that this measure included both directly transferred patients and patients with intervening nonhospital stays.

When we examined importation from specific facilities (Figure 2), on average, 63% of general importation originated from facilities within the same healthcare region (N=14) as a given destination facility.

When general importation was weighted by incidence of CDI in the facility, the overall variation was slightly larger (median=18.6 per 10,000, p10=11.4, p90=31.5, IDR=2.8-fold) and this measure was strongly correlated with general importation (*r*=0.93).

Importation of patients with a history of CDI was much less common (median=5.5 per 10,000) and variation was substantially greater between facilities (p10=3.0, p90=12.7, IDR=4.2-fold) when compared to general patient importation (4.2/2.4=1.75). Importation of patients with *C. difficile* was only moderately correlated with general patient importation (*r*=0.51) and with incidence-weighted importation (*r*=0.52).

Prediction of facility CDI incidence

Levels of admission to medical-surgical services were positively associated with CDI incidence while admissions to psychiatry were negatively associated with incidence. Increasing average length of stay was positively associated with the incidence of CDI. Facility size and facility teaching status were not associated with CDI incidence.

In unadjusted models, the 3 importation measures were related to CDI incidence (Figure 3, Table 3). Each doubling of general patient importation was associated with a 17% increase in the facility incidence of CDI (RR=1.17, 95%CI: 1.04 to 1.32). This measure explained 5.7% of variation in CDI incidence (PCV=-5.7%). Each doubling of weighted patient importation was associated with a 24% increase in CDI incidence (95%CI: 1.12 to 1.37) and explained 14.1% of variation in CDI incidence. Each doubling of *C. difficile* case importation was associated with a 24% increase in incidence (95%CI: 1.15 to 1.34) and explained 22.4% of variation in CDI incidence (PCV=-22.4%). This PCV value for *C. difficile* case importation was larger than for the 7 other adjustment covariates examined.

After adjustment for 7 facility covariates, the strength of the association, in terms of both the risk ratio per doubling and in terms of the PCV, for general patient importation and weighted patient importation, were reduced. Specifically, each doubling of general importation was associated with a 10% increase in CDI incidence (95%CI: 0.97 to 1.24). Each doubling of weighted patient importation was associated with an 18% increase in CDI incidence (95%CI: 1.06 to 1.30) and explained 8.4% of variation in CDI incidence. However, the association for CDI case importation was not reduced. For CDI case importation, each doubling was associated with a 43% increase in CDI incidence (95%CI: 1.29 to 1.58) and this variable explained 30.1% of variation in CDI incidence.

Discussion

In this 13-year study of CDI in Ontario, we observed substantial variation in incidence that was associated with patient sharing with other acute care facilities. Measures that were made specific to *C.*

difficile, whether by weighting origin facilities by CDI incidence, or by only counting the importation of patients with a history of *C. difficile*, were more strongly associated with incidence.

We examined 3 alternative measures of patient sharing: general patient importation, incidence-weighted patient importation, and *C. difficile* case importation. Nekkab et al. examined interfacility patient movement in the French hospital system and found that both disease-agnostic and disease-specific patient sharing networks for hospital acquired infection reflected the French administrative structure.[13] Similarly, we found that importation networks in Ontario did reflect health administrative regions, with the majority of importation originating from facilities within the same administrative region. However, we found that *C. difficile* case importation was not strongly associated with general patient importation and varied 75% more than general importation.

We found that importation was associated with *C. difficile* infection incidence, and that this was particularly strong for disease-specific importation measures that incorporated information on CDI incidence in origin facilities or CDI among the imported patients. Prior studies have shown that importation measures are important for *C. difficile* infection incidence. Specifically, Simmering et al. showed that disease-agnostic measures of patient inflow (which they termed 'hospital indegree' and 'hospital weighted indegree')[6] were associated with infection incidence in California. We showed that disease-specific measures were associated in both nursing homes[20] and in acute care facilities[2] in the Veteran's Health Administration of the United States. This paper examined the relative performance of such measures of importation, suggesting that disease-specific importation metrics are more predictive of incidence than disease-agnostic importation metrics. These findings may be important in the design of interventions aiming to identify *C. difficile* colonization at admission.[25] Further decision analysis models will be needed to explore the cost-effectiveness of screening programs for patients with recent hospital admissions versus more targeted screening focusing on patients from high incidence hospitals or patients with a recent history of *C. difficile* infection.

Our study has a number of limitations. First, we had no measurement of testing practices including the frequency and method of *C. difficile* testing at the facility, which may have been associated with rates of over- and under-diagnosis of infection.[26,27] Second, we did not measure potentially important covariates including facility antibiotic utilization within facilities or infection control practices, though past studies looking at these factors have shown no association with CDI incidence among acute care facilities.[2,3,5] Third, our study examined the cross-sectional association between importation and CDI incidence across a 13-year period; because disease-specific importation for a specific hospital is likely highly variable throughout time, we would expect that the predictiveness of disease-specific importation to be higher in a longitudinal study design. Fourth, we did not consider importation from nursing homes to acute care facilities, which meant that importation, and its effects, were likely underestimated. A prior study of importation across a hospital system that included both acute care hospitals and nursing homes showed the predominance of importation in the opposite direction, that is, into nursing homes from acute care facilities.[2]

In this 13-year study of Ontario acute care facilities, we found that the incidence of *C. difficile* was associated with importation from other acute care facilities, especially of patients with a recent history of CDI in another facility. These findings complement recent findings from other jurisdictions,[2,6] and

suggest that regional infection control strategies should consider the potential impact of importation of patients at high risk of *C. difficile* shedding from outside facilities.

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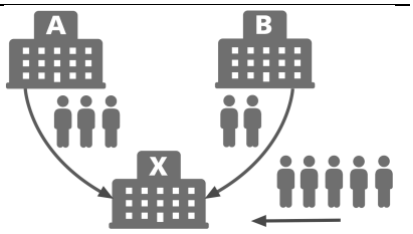
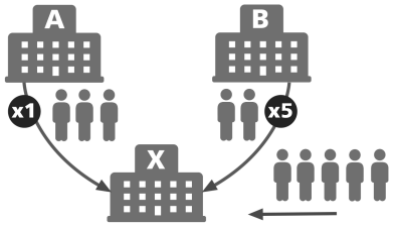
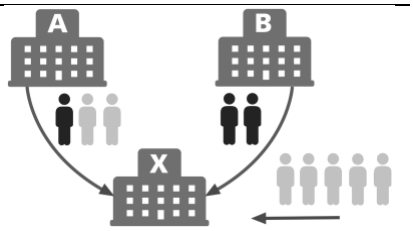
Tables

Table 1. Facility-level patient-sharing metrics

Metric	Example	Illustration
General Importation	Hospital X has 10 admissions. 3 patients admitted to hospital X had a recent stay* in hospital A, while 2 had a recent stay* in hospital B, and 5 had no recent hospital admissions. *Importation at hospital X* (2+3)/10 = 0.5	
Incidence-Weighted Importation	Suppose that hospital A has a CDI incidence of 1 per 10,000 admissions, while hospital B has an incidence of 5 per 10,000 admissions. *Importation at hospital X* (1*3+5*2)/10= 13/10 = 1.3	
Case Importation	Now suppose that of the 3 patients with a recent stay in hospital A, 1 was diagnosed with CDI, while both of the patients from hospital B were diagnosed. *Importation at hospital X* (2+1)/10 = 0.3	

* Includes both directly transferred patients and patients with intervening nonhospital stays within the prior 90-days.

Table 2. Acute care facility characteristics (N=120 facilities)

Characteristic	**N (%) median (p10, p90)**
Mean patient age	65.8 (60.5, 72.4)
Proportion female (%)	56.3 (52.9, 61.5)
Mean Charlson comorbidity index	0.8 (0.6, 1.0)
Mean length of stay (d)	3.3 (2.6, 4.6)
Proportion by admission type (%)	
Medical-surgical	90.2 (82.4, 96.4)
Medical	22.4 (3.4, 39.4)
Surgical	65.3 (50.0, 91.7)
Psychiatry	3.2 (1.5, 5.1)
Other	6.3 (0.1, 14.3)
Mean daily number of admissions (N, %)	
1 to 5	65 (54.2%)
6 to 25	47 (39.2%)
26 or more	8 (6.7%)
Teaching facility	17 (14.2%)
Patient sharing measures	
Importation (per 100 stays)	21.2 (14.2, 34.6)
Incidence-weighted importation (per 10,000)	19.2 (11.6, 33.5)
Case importation (per 10,000 stays)	5.6 (3.1, 12.5)

p10: 10^{th} percentile; p90: 90^{th} percentile

Table 3. Unadjusted and adjusted association between facility-level characteristics and *C. difficile* infection incidence (N=120 facilities).

	Unadjusted		Adjusted	
	RR	PCV (%)	RR	PCV (%)
Mean age	1.30 (1.13 to 1.50)	-10.7	1.67 (1.21 to 2.30)	-8.6
Proportion female	0.78 (0.67 to 0.90)	-9.3	0.88 (0.64 to 1.21)	-0.8
Mean Charlson comorbidity index	1.95 (1.30 to 2.94)	-9.0	1.88 (1.10 to 3.22)	-5.0
Admission type (%)				
Medical-Surgical	1.23 (1.12 to 1.36)		0.82 (0.59 to 1.13)	
Psychiatry	0.67 (0.45 to 0.98)	-16.3	0.60 (0.38 to 0.94)	-4.4
Other	Reference		Reference	
Mean length of stay (d)	1.05 (0.96 to 1.16)	-1.3	1.05 (0.95 to 1.16)	-0.9
Mean daily number of admissions				
1 to 5	0.84 (0.72 to 0.97)		0.67 (0.57 to 0.80)	
6 to 25	1.19 (0.88 to 1.61)	-6.1	0.73 (0.53 to 1.01)	-15.8
26 or more	Reference		Reference	
Teaching facility	1.00 (0.81 to 1.23)	0.0	0.99 (0.78 to 1.27)	0.0
Patient sharing measures*				
General importation	1.17 (1.04 to 1.32)	-5.7	1.10 (0.97 to 1.24)	-2.0
Incidence-weighted importation	1.24 (1.12 to 1.37)	-14.1	1.18 (1.06 to 1.30)	-8.4
Case importation	1.24 (1.15 to 1.34)	-22.4	1.43 (1.29 to 1.58)	-30.1

PCV: proportional change in facility-level variance; RR: relative risk

* For all patient sharing measures, the RRs are presented per doubling in the measure

Figures

Figure 1. Hospital stays excluded and included in the cohort.

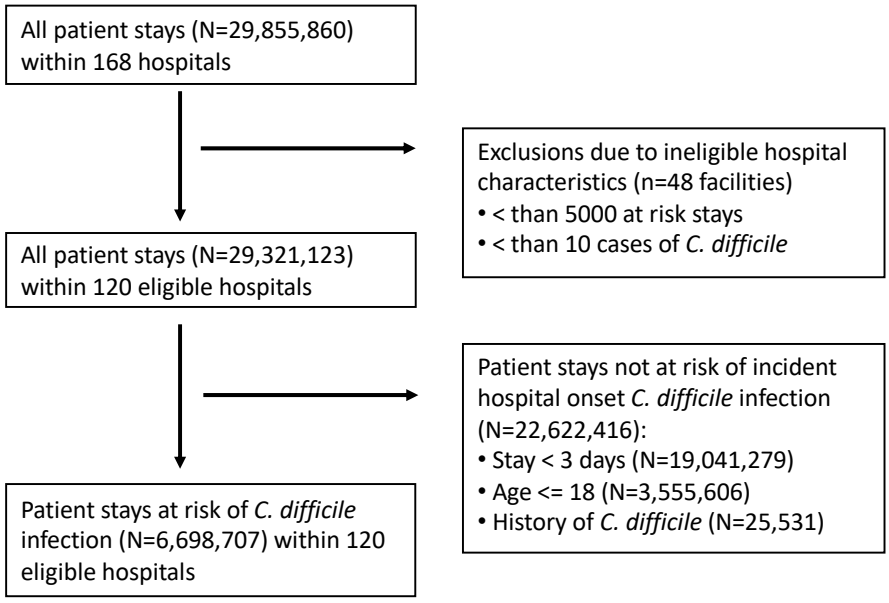
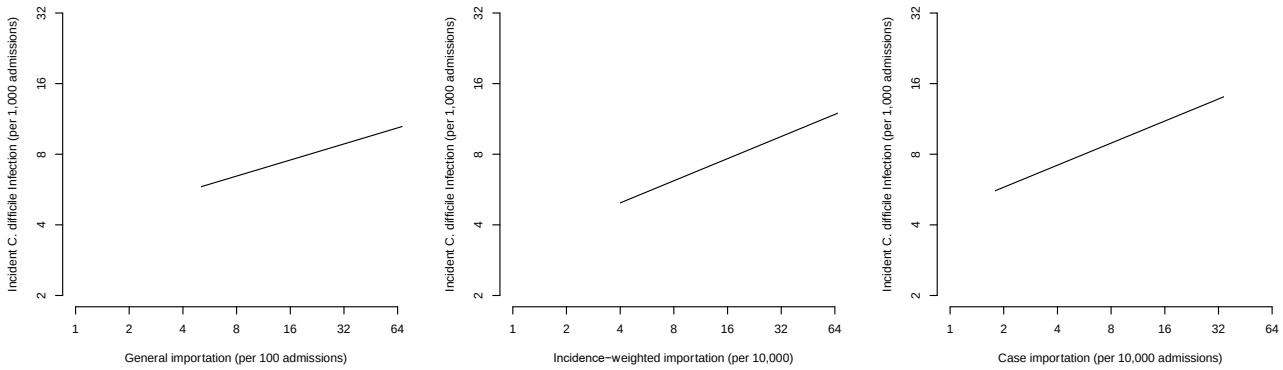


Figure 2. Geographic display of the proportion of patients with a stay in another acute care facility in the prior 90 days (N=120 facilities). Note that only destination facilities for whom at least 1% of admissions had stayed at a given origin facility are connected in the graph, and line weight is proportional to the strength of the connection.

Figure 3. The facility-level association between patient sharing measures (general importation, incidence weighted importation, and case importation) and *C. difficile* infection (N=120 facilities). Each bubble represents an individual facility, with size proportional to number of admissions.



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