

Presumably hospital-transmitted *Clostridium difficile* infections based on epidemiological linkage

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Abstract

OBJECTIVES: Given the traditionally low CDAD (*Clostridium difficile* associated diarrhoea) prevalence in Switzerland, CDAD patients are not routinely contact-isolated in our institution. In light of the globally changing *C. difficile* epidemiology, we sought to determine our institutional CDAD rate and to detect possible hospital transmission by means of epidemiological linkage.

METHODS: We included every CDAD patient hospitalised in our institution, a tertiary-care hospital in eastern Switzerland, in 2009/2010. Patients with healthcare facility associated (HCFA) CDAD were grouped into cases with and without exposure to an infectious CDAD patient. Exposure was defined as sharing the room/ward with an infectious patient before symptom onset, either at the same time or within 30 days after discharge of the infectious patient. Molecular strain typing was not performed.

RESULTS: We registered 141 CDAD episodes. Among them 108 were HCFA (associated with our institution), corresponding to an incidence of 2.3/10,000 patient days. Fifty-six percent (60/108) were exposed to an infectious CDAD patient, suggesting hospital transmission. The number of patients without exposure remained relatively stable, whereas presumably transmitted cases – often occurring within spatiotemporal clusters – showed high variability over time. Presumably transmitted cases were significantly older ($p = 0.032$) and more likely to have a Charlson score >1 ($p = 0.001$).

Abbreviations

CA	community associated
CO	community onset
CCNA	cell culture cytotoxicity neutralisation assay
CDAD	<i>Clostridium difficile</i> associated diarrhoea
HCFA	healthcare facility associated
HO	healthcare onset
HIV	human immunodeficiency virus
MLST	multilocus sequence typing
PCR	polymerase chain reaction
PFGE	pulsed field gel electrophoresis
PPI	proton-pump inhibitor

CONCLUSION: In our setting, 56% of healthcare associated CDAD cases have been exposed to an infectious CDAD patient. In view of the clustering of these presumed hospital transmissions, we consider an intensification of our current infection control measures, mainly on wards with elderly and comorbid patients which are particularly prone to *C. difficile* transmission.

Key words: *Clostridium difficile*; nosocomial; diarrhoea, transmission; infection control

Introduction

Clostridium difficile associated diarrhoea (CDAD) is among the most common causes of nosocomial diarrhoea and is associated with increased morbidity and mortality in infected patients [1]. In the past decade, the emergence of a novel *C. difficile* strain (NAP1/BI/027) has caused a substantial rise in CDAD rates and disease severity, not only in North America [2], but also in many European countries including Switzerland [3].

Risk factors for developing CDAD are disruption of the gut flora after antimicrobial exposure and other conditions leading to increased host susceptibility, mainly gastrointestinal surgery, immunodeficiency, older age and high comorbidity [4]. Exposure to infectious CDAD patients (and presumptive pathogen acquisition) has been identified as another risk factor for CDAD [5, 6], whereas primarily symptomless colonisation by *C. difficile* seems to be a protective factor against CDAD [7].

Current guidelines concerning infection control measures against *C. difficile* recommend contact precautions for all CDAD patients, including the use of gloves and gowns by healthcare workers and visitors [8]. However, these guidelines lack high-grade evidence and are often not universally implemented [9]. In settings with high CDAD prevalence and well implemented infection control measures, hospital-transmitted CDAD cases based on epidemiological and microbiological criteria (multilocus sequence typing, MLST) have been shown to account for only a maximum of 25% of CDAD cases [10].

In our setting, with assumed low *C. difficile* prevalence, infection control measures do not include routine contact-isolation for CDAD patients. In light of the changing *C. difficile* epidemiology, we aimed to determine the number of healthcare facility associated (HCFA) CDAD cases in our institution and to detect presumable *C. difficile* transmissions, thereby evaluating our current infection control strategy against *C. difficile*.

Methods

Setting

In our institution, a tertiary-care hospital with 700 beds in Eastern Switzerland, CDAD patients are not contact isolated except for those with stool incontinence and/or poor personal hygiene due to dementia or non-compliance. The alcohol-based hand rub used in our institution and the agents used for environmental cleaning are not effective against the spores of *C. difficile*. Hand washing with water and soap is not explicitly recommended after contact with CDAD patients.

Data collection

For the general quantitative surveillance, we included all hospitalised patients diagnosed with CDAD in our institution from January 2009 to December 2010, based on active laboratory reporting. In order to detect exposure to other CDAD patients, we additionally evaluated CDAD patients hospitalised in November and December 2008 as possible index cases, assuming an incubation period of a maximum of 60 days [11]. Hospitalisation was registered both before and after symptom onset. Between admission and discharge, all patient transfers within the hospital (ward and room changes) were recorded with the date, as documented in the institutional patient administration system.

The patient age and the Charlson comorbidity index [12] were assessed for each patient at the time of diagnosis. The Charlson comorbidity index is determined by calculating the sum of 19 different disease category points, each value reflecting the 10-year mortality risk in the corresponding category [12]. Data on previous antibiotic therapy, proton-pump inhibitor (PPI) use and immunodeficiency (in each case within 30 days before CDAD diagnosis) were collected retrospectively by reviewing patient charts. Immunodeficiency was defined as human immunodeficiency virus (HIV) positivity, aplasia, high-dose chemotherapy, steroid therapy (≥ 0.5 mg/kg bodyweight/day for at least 10 days) or other immunosuppressive medication. Furthermore, laboratory data at the time of diagnosis (or, if not available, within 7 days after diagnosis) as well as data on therapy for CDAD, and the patient outcome within 30 days after diagnosis were gathered. Patients were considered to have a complicated course of the disease if they had been diagnosed with pseudomembranous colitis (by colonoscopy), if they needed intensive care or surgical intervention because of CDAD, or if they died of CDAD (all within 30 days after diagnosis).

CDAD diagnosis

The decision to test a patient for *C. difficile* was up to the treating physician and based on his or her clinical judgement. For lack of consequences, the institutional recommendation is not to obtain samples routinely, but to test symptomatic patients with diarrhoea only (no specific definition). In our institution, laboratory diagnosis of CDAD is based on a positive cell culture cytotoxicity neutralisation assay (CCNA), which is regarded as the reference standard for the detection of *C. difficile* toxin [13]. PCR ribotyping of *C. difficile* is not performed in our institution.

Definitions

The day of symptom onset was defined as the first day of diarrhoea before diagnosis, as documented in the patient chart. According to the onset of symptoms, patients were grouped into different CDAD classes as described by McDonald et al. [14]. Cases with disease onset between 48 hours after hospital admission and 4 weeks after hospital discharge were classified as healthcare facility associated (HCFA). HCFA cases were further divided into patients with hospital onset (HO) and community onset (CO) CDAD. If the patient was not hospitalised during the 12 weeks preceding disease onset, the episode was classified as community associated (CA). Episodes meeting the criteria neither for HCFA nor for CA were classified as "other". CDAD incidence was calculated as the number of HCFA CDAD cases (with our institution being the related healthcare facility) per 10,000 patient days, as recommended by McDonald et al. [14].

CDAD recurrence was defined as a second episode of diarrhoea in combination with toxin detection in the faeces between 2 and 8 weeks after onset of the first episode [14]. If the second CDAD episode started more than 8 weeks after diagnosis of the first episode, the two events were considered as separate cases. Patients with CDAD recurrence were allowed to represent potential sources of infection, but only the first episode was included in the analysis regarding previous exposure to another CDAD patient.

Patients with HCFA CDAD (both hospital onset and community onset) were investigated for exposure to infectious CDAD patients before symptom onset. Patients were considered infectious for a 14-day period after symptom onset, based on data of Walker et al. [10] that demonstrated an infectious period of 0–14 days (interquartile range) for the most plausible potential *C. difficile* transmissions found in their study. Patients with recurrent disease were considered as constantly infectious until 14 days after the last positive CCNA.

In accordance with a study of Shaughnessy et al. [5], exposure was defined as sharing the room or the ward with an infectious patient, either at the same time or within 30 days after discharge of the infectious patient. Patients with more than one possible source of infection were classified in the category with the closest spatial and temporal proximity (same room closer than same ward, same time closer than within 30 days after discharge of the index patient). Based on a study of Palmore et al. [11], which found CDAD occurring up to 60 days after hospital discharge, the allowed time period from presumed *C. difficile* transmis-

sion to symptom onset (i.e. incubation time) was limited to a maximum of 60 days.

A CDAD cluster was defined as occurrence of at least two presumable *C. difficile* transmissions on the same ward within 3 months.

Statistical analysis

A nonmatched case-control design was used to identify risk factors for presumably hospital-transmitted cases of HCFA CDAD (case: HCFA CDAD patient with exposure to an infectious CDAD patient, control: HCFA CDAD patient without exposure to an infectious CDAD patient). Statistical analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at a two-sided p-value <0.05. For dichotomous variables, two-by-two tables (chi-square test or Fisher-exact, as appropriate) were applied. Parametric continuous variables were analysed with the Student-t test, nonparametric variables with the Mann-Whitney U-test.

Ethical aspects

No formal informed consent was obtained because the study was strictly observational and part of the institutional quality control activities.

Results

We registered 141 CDAD episodes from 138 different patients hospitalised in our institution in the observed 2-year period (in three patients, a second episode of CDAD occurred more than 8 weeks after the first and did therefore not meet the criteria for recurrence). Twenty-two (16%) of the 138 patients experienced CDAD recurrence. Median age was 68.6 years and 52% of patients were female. In 91% of episodes, there was previous antibiotic exposure with a mean duration of antibiotic therapy of 10 days. Mean Charlson score was 3.3, 32% of patients were immunocompromised and 64% were under PPI therapy at

time of diagnosis. None of the patients were contact-isolated during the observed time period. At least in 131/141 CDAD episodes (93%), patients received antibiotic therapy for CDAD (missing data for seven episodes, three episodes not treated for unknown reason). A total of 119/131 (91%) were treated with metronidazole alone, 3 (2%) with vancomycin alone and 9 (7%) with a combination of these two drugs. Four patients (2.8%) showed a complicated course (two classified as HCFA), of whom two died of CDAD, corresponding to a fatality rate of 1.4%.

Of the 122 HCFA CDAD episodes, 14 were related to other institutions. The remaining 108 HCFA CDAD episodes (in 108 different patients) related to our institution corresponds to an incidence of 2.3/10,000 patient days. Thereof, 56% (60/108) exhibited an epidemiological link to another CDAD patient before symptom onset, according to the criteria mentioned above. CDAD patients with exposure to infectious CDAD patients were significantly older (median age 71.0 vs 62.8 years, $p = 0.032$), were more likely to be hospitalised on a medical ward (68% vs 42%, $p = 0.005$) and to have a Charlson Score greater than 1 (92% vs 67%, $p = 0.001$), as compared with patients without any CDAD exposure before symptom onset. The two HCFA patients with a complicated course were in the group with presumably transmitted disease (table 1).

Per 3-month period, the number of presumably nontransmitted HCFA CDAD cases remained relatively stable over time (four to nine patients), whereas the number of presumably transmitted cases showed clear variability, ranging from 1 to 15 patients (figure 1). Of the 27 observed wards, 17 showed cases with presumable *C. difficile* transmissions. However, only four wards (nephrology, haematology, oncology, medical intensive care) accounted for 48% (29/60) of presumably transmitted cases (table).

We found a total of 13 CDAD clusters in the defined period (range: two to four patients per cluster). Temporal and spatial accumulation of clusters could be observed. Between April and June 2010, for instance, we found three clusters on wards A, B and C, which are all located on the same floor (figure 1). Regarding the mode of transmission, being hospitalised on the same ward at the same time with an infectious CDAD patient was the most frequently observed association (50% of presumably transmitted cases). Hospitalisation on the same ward within 30 days after discharge of the index patient was observed in 37% of cases. Direct patient contact (same room at the same time) was the presumed way of transmission in 8% and being hospitalised in the same room within 30 days after discharge of the index patient was found in 5%.

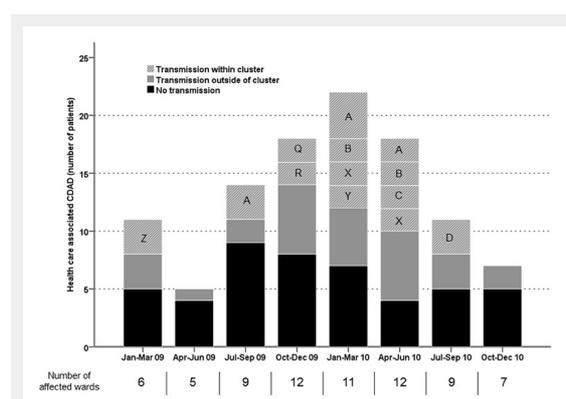


Figure 1

Number of healthcare facility associated CDAD (*Clostridium difficile* associated diarrhoea) patients per 3-month period (2009 and 2010), grouped into cases with and without presumably transmitted infections ($n = 106$, two patients with presumable transmission in 2008). Presumable transmissions are further differentiated into cases occurring within and outside clusters (≥ 2 presumable transmissions per 3 months per ward). Capital letters represent wards affected by clusters. Spatial relationship between wards A, B, C and D, wards Q and R as well as wards X, Y and Z.

Discussion

CDAD rate and presumable hospital transmissions

We found an overall healthcare facility associated CDAD rate of 2.3/10,000 patient days, which is similar to the CDAD rate in other hospitals in Switzerland [15], but clearly below the European average of 4.1 [16]. The absolute number of CDAD cases without previous exposure to an infectious CDAD patient remained relatively stable over time. However, clusters of presumably transmitted *C. dif-*

ficile cases suggest the occurrence of nosocomial CDAD outbreaks in our institution.

56% of HCFA CDAD patients showed an epidemiological link to another CDAD patient, suggesting hospital transmission. According to the study of Walker et al. which included molecular strain typing, only about 25% of CDAD patients acquire their infecting *C. difficile* strain during their hospital stay [10]. This difference can partially be explained by overestimating transmitted cases with solely epidemiological linkage without molecular strain typing. Possibly more important, the infection control measures in the setting described by Walker were stricter than ours, with all symptomatic patients being contact-isolated [10]. Anyhow, both in the study of Walker and in our study,

a substantial proportion of CDAD cases do not seem to have acquired *C. difficile* from other hospitalised CDAD patients. These findings suggest an important *C. difficile* reservoir, which either is healthcare associated (asymptomatic carriers among patients/healthcare workers, contaminated surfaces/equipment) or community associated (asymptomatic carriers, food, animals), as discussed in the study of Walker et al. [10].

Risk factors for presumable hospital transmissions

Forty-eight percent of the presumable hospital transmissions occurred on the nephrological and the oncological wards as well as on the medical intensive care unit. The infection control measures applied to CDAD patients on

Table 1: Healthcare facility associated CDAD cases (n = 108) grouped into patients without and with exposure to an infectious CDAD patient before symptom onset (exposure = sharing the same room/ward with an infectious CDAD patient, either at the same time or within 30 days after discharge of the infectious patient).

Characteristic	No Exposure		Exposure		p-value
	n = 48		n = 60		
	n or median	% or IQR	n or median	% or IQR	
Hospital ward¹					
Medicine (11 wards)	20	41.7	41	68.3	0.005
Nephrology (1 ward)	2	4.2	10	16.7	0.040
Oncology/haemato-oncology (2 wards)	8	16.7	12	20.0	0.658
Medical intensive care (1 ward)	1	2.1	7	11.7	0.120
Other medical wards (7 wards)	9	18.8	12	20.0	0.870
Surgery/orthopaedics (8 wards)	21	43.8	19	31.7	0.197
Surgical intensive care (1 ward)	3	6.3	3	5.0	>0.999
Others (4 wards)	7	14.6	0	0.0	0.009
Community onset	8	16.7	4	6.7	0.100
Length of stay in days	24.0	13–46	28.0	18–42	0.582
Days from admission to symptom onset	11.0	3–21	13.0	9–22	0.124
Days from presumed transmission to symptom onset	–	–	10.0	6–18	NA
Days from symptom onset to diagnosis	1.0	0–2	1.0	0–2	0.536
Female	24	50.0	34	56.7	0.490
Risk factors					
Age	62.8	53.0–75.9	71.0	61.6–80.0	0.032
Antibiotic therapy ²	46	95.8	57	95.0	1.000
Duration in days	11.0	8–17	10.0	7–16	0.262
Charlson score ³ (mean ± SD)	3.1	± 2.5	3.7	± 2.1	0.135
Charlson score ≥2 points	32	66.7	55	91.7	0.001
Immunodeficiency ⁴	14	29.2	22	36.7	0.411
PPI ²	34	70.8	43	71.7	0.924
Abdominal surgery ²	12	25.0	15	25.0	1.000
Clinical parameters at time of diagnosis⁵					
Body temperature max. (°C)	37.6	37.0–38.5	37.8	37.3–38.6	0.299
Systolic blood pressure min. (mm Hg)	107.0	96–117	107	98–120	0.770
Leucocyte count max. (G/l)	9.3	6.5–12.9	10.2	6.8–14.3	0.571
Creatinin max. (µmol/l)	72.0	59–142	86.0	61–126	0.611
Albumin min. (g/l)	21.2	18.2–30.5	21.3	17.8–24.7	0.474
Outcome					
Recurrence	6	12.5	8	13.3	0.898
Complicated course ⁶	0	0.0	2	3.4	NA
Pseudomembranous colitis	0	0.0	1	1.7	NA
Intensive care	0	0.0	1	1.7	NA
Death associated with CDAD	0	0.0	1	1.7	NA

CDAD = *Clostridium difficile* associated diarrhoea; IQR = interquartile range; SD = standard deviation; PPI = proton-pump inhibitor; NA = not applicable¹ For patients without exposure: ward at time of symptom onset (for hospital onset CDAD) or ward at time of discharge (for community onset CDAD). For patients with exposure: ward at time of presumed transmission.

² Within 30 days before CDAD diagnosis.

³ At time of diagnosis.

⁴ HIV, aplasia, high dose chemotherapy, steroids, other immunosuppressive therapy (within 30 days before diagnosis).

⁵ For the leucocyte count, creatinine and albumin, data were only available within 7 days after diagnosis in four, four and seven patients respectively.

⁶ Within 30 days after CDAD diagnosis (the same patient hospitalised on the intensive care unit died of CDAD).

these wards do not differ from the other wards, with CDAD patients not being contact-isolated unless they are faecally incontinent or in the case of poor personal hygiene due to dementia or noncompliance. However, the total number of patients with CDAD hospitalised on these particular wards is higher (either owing to actually higher prevalence/incidence or owing to increased testing) and, consequently, the probability of exposure is increased.

Nonetheless, like our study, the study of Walker et al. [10] showed the highest percentage of CDAD cases with supposed *C. difficile* transmission to occur on the renal/transplant and the haematology/oncology units. A study published by Khanna et al. [17], comparing patients with CA and HCFA CDAD, found older age, high comorbidity, male sex and acid-suppressive therapy to be associated with HCFA CDAD. In addition, older age and acid suppression have recently been shown to be the most important risk factors for the development of severe CDAD disease [18]. This risk pattern is similar to that of the presumably transmitted cases in our study. Moreover, the two HCFA patients with complicated course were presumably transmitted cases.

We therefore assume two different forms of CDAD development in hospitalised patients: if susceptibility to *C. difficile* is increased owing to old age and comorbidity, transmission of *C. difficile* will more readily lead to an active and often more severe infection. Time from transmission to disease onset (incubation time) will be relatively short and the event of transmission more easily detectable. In cases without detected exposure to other CDAD patients (often younger and healthier subjects, similarly to most of the community-acquired cases), time from *C. difficile* acquisition to disease onset would be longer and more variable (depending on when antibiotic therapy is begun). Alternatively, this patient group could be considered as primarily colonised with *C. difficile* without exhibiting any symptoms until endogenous activation of *C. difficile* (i.e. germination of spores) upon antibiotic exposure. Consistent with this concept, the incubation time in CDAD is a matter of debate and the disease has been shown to occur within days after exposure in some studies [11], whereas other studies report an increased risk for CDAD during several weeks after hospitalization (and possible *C. difficile* acquisition) [19]. However, besides old age and comorbidity we could not identify any further differences regarding immunological impairment in the two patient groups. This might be explained by the rather broad definition of immunodeficiency in our study (any immunosuppressive condition or medication within 30 days prior to diagnosis). Similarly, there was no difference in the use of PPIs, possibly due to the frequent use of PPIs in our patients (around 70%).

Mode of presumed *C. difficile* transmission

In 50% of presumably transmitted cases, patients were hospitalised on the same ward simultaneously with an infectious CDAD patient. This suggests spore transmission by healthcare workers between different rooms on the same ward. Indeed, transient hand carriage of *C. difficile* spores by healthcare workers is thought to be an important way of disease transmission [19]. In 37% of transmitted cases, pa-

tients were hospitalised on the same ward within 30 days after discharge of the index patient, suggesting environmental contamination with *C. difficile* spores. However, due to the extended time-period of 30 days, the number of CDAD patients exposed to another CDAD patient meeting by chance (without true transmission) might be particularly high in this category. Transmission within the same patient room – either at the same time (8%) or within 30 days after discharge of the index patient (5%) – was comparatively rare.

In our institution, hand hygiene adherence of both nurses and doctors, measured according to World Health Organisation recommendations [20], is relatively high at 80%. However, the alcohol-based hand rub and agents used for environmental cleaning are both not sporicidal. Together with CDAD patients not routinely being isolated, there is room for further improvement in hygiene measures against transmission of *C. difficile* spores.

Limitations

A major limitation of our study is that suspected nosocomial transmissions were not confirmed by molecular biological methods (PCR ribotyping or pulsed field gel electrophoresis, PFGE). This might have led to an overestimation of the putative *C. difficile* transmissions. Nevertheless, the constant number of CDAD cases without epidemiologically suspected transmission, as well as the changing number and clustering of presumably transmitted cases over time support our interpretation of the results.

Since we did not perform a multivariable analysis, we could not determine whether medical ward, older age and higher Charlson comorbidity index are independent risk factors for CDAD acquisition. However, for clinical practice this is of minor relevance.

The possibility of interward transmission of *C. difficile*, either through transportation of patients or through other potential vectors of transmission (equipment or healthcare workers), has not been considered in our analysis. Along with a potentially significant pool of undiagnosed patients with *C. difficile*, this might underestimate the number of transmitted cases. In addition, diagnosis of CDAD with only cell culture neutralisation assay (as done in our laboratory) might likewise underestimate the number of transmitted cases by not detecting all of the infected patients. However, CCNA is still regarded as reference standard, and sensitivity is comparable with other recommended detection algorithms (sensitivity of CCNA ranging from 67% to 100%) [8].

In our analysis, we allowed a maximum infectious period of 14 days after symptom onset, which might overestimate the real number of transmissions. Nevertheless, 10% of the most plausible putative transmissions in the study of Walker et al. [10] occurred even up to 8 weeks after symptom onset of the index patient.

Similarly, we assumed a maximum incubation time of 60 days, which is relatively long and might again have led to an overestimation of presumable transmissions. However, the median incubation time was only 10 days in patients with presumed transmission (interquartile range 6–18). Furthermore, there is great uncertainty in the literature concerning the incubation time of CDAD, as mentioned above.

Conclusion

In our setting (low *C. difficile* prevalence, no contact-isolation, no systematic hand washing with water and soap, no sporicidal agents for environmental cleaning), 56% of HCFA CDAD cases show an epidemiological link to another CDAD patient before symptom onset. In view of the spatiotemporal clustering of these presumable transmissions, we consider a targeted intensification of our current infection control measures against *C. difficile*, primarily on the most affected wards with their elderly and comorbid patients who are particularly prone to *C. difficile* acquisition.

All four authors have seen and approved the manuscript and have significantly contributed to the work.

The manuscript has not been published and is not being considered for publication elsewhere. Part of the data has previously been presented at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2012 in London and at the Annual Meeting of the Swiss Society for Infectious Diseases 2012 in St. Gallen as a poster presentation.

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Figures (large format)

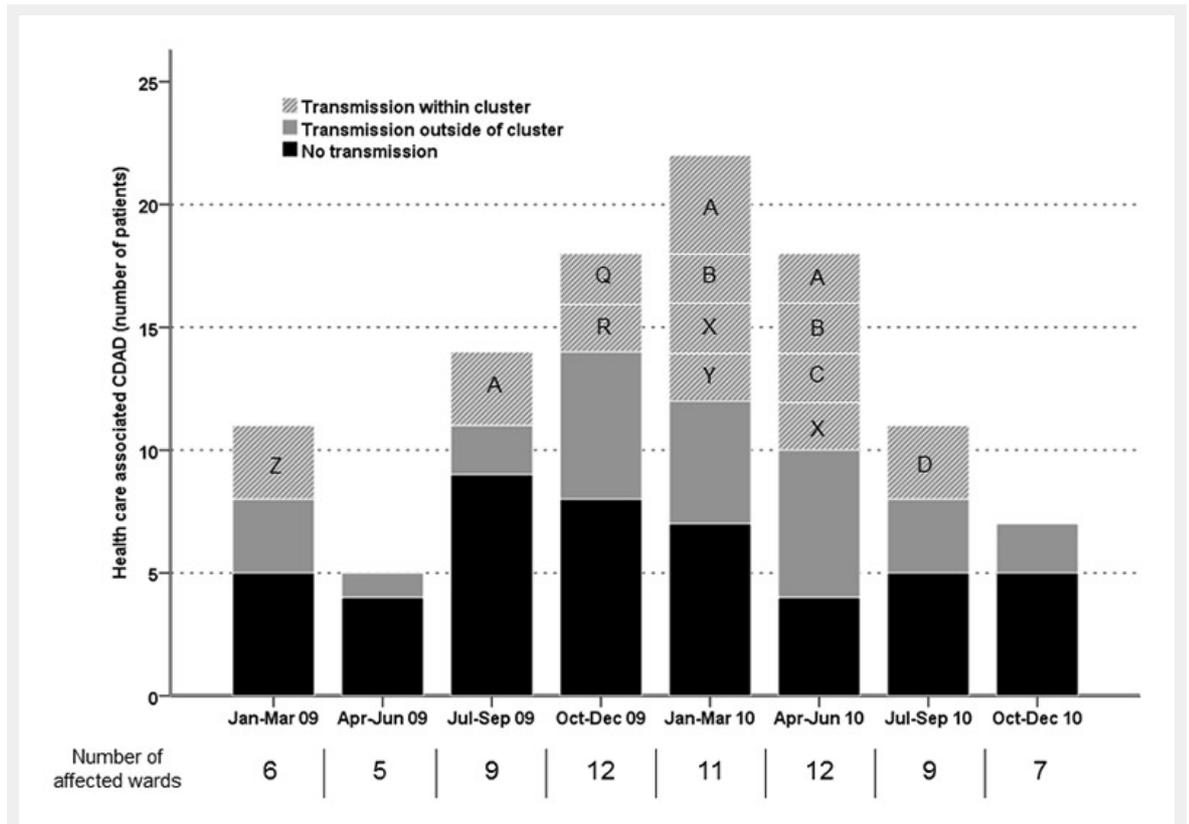


Figure 1

Number of healthcare facility associated CDAD (*Clostridium difficile* associated diarrhoea) patients per 3-month period (2009 and 2010), grouped into cases with and without presumably transmitted infections (n = 106, two patients with presumable transmission in 2008). Presumable transmissions are further differentiated into cases occurring within and outside clusters (≥2 presumable transmissions per 3 months per ward). Capital letters represent wards affected by clusters. Spatial relationship between wards A, B, C and D, wards Q and R as well as wards X, Y and Z.