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ARTICLE

Containment of *Clostridium difficile* infection without reduction in antimicrobial use in Hong Kong

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Abstract *Clostridium difficile* ribotype 002 with hypersporulating capacity has been increasingly identified in Hong Kong. Proactive infection control measures are important to prevent the establishment of endemicity of *C. difficile* ribotype 002. A total of 329 patients with healthcare-associated *C. difficile* infection (CDI) were recruited in our healthcare network between 1 January 2008 and 30 June 2012 in this study. The incidence rates of healthcare-associated CDI per 10,000 admissions and 10,000 patient-days increased significantly by 15.3 and 17.0 %, respectively, per quarter ($p<0.001$) from 2008 1Q to 2010 1Q by segmented Poisson regression. With the full implementation of enhanced infection control interventions, there was an immediate significant reduction in both healthcare-associated CDI rates per 10,000 admissions and per 10,000 patient-days by 47 % ($p<0.001$) in 2010 2Q, followed by a further decline of CDI per 10,000 admissions and CDI per 10,000 patient-days by −19.4 and −19.8 % from 2010 2Q to 2012 2Q, respectively ($p<0.001$), despite a replacement of hand washing with soap and water by alcohol-based hand rub in the healthcare network. The proportion of *C. difficile* ribotype 002 was not statistically different (34/177, 19.2 % vs. 25/152, 16.4 %, $p=0.515$), and the consumption of broad-spectrum antibiotics presented as divided daily dose per 1,000 acute bed-day occupancy per quarter remained unchanged (140.9 vs. 152.3) before and after infection control interventions. Our results suggested that the reduction of healthcare-associated CDI was attributable to infection control interventions instead of replacement of ribotypes or reduction in antimicrobial selective pressure.

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Introduction

The emergence of hypervirulent clone of *Clostridium difficile* ribotype 027 in North America and European countries in the 2000s has caused numerous outbreaks in the healthcare setting. Enhanced infection control measures, including education, active surveillance, contact precautions with single room isolation, hand hygiene practice, environmental decontamination, and antibiotic stewardship programs, have been proposed to control the endemicity of *C. difficile* [1]. Early studies demonstrated a 61 and 71 % reduction in the rate of *C. difficile* infection (CDI) after the implementation of multiple prolonged intervention strategy and bundle approach in North America, respectively [2, 3].

C. difficile ribotype 027 was first detected in Hong Kong in 2008 [4]. However, the molecular epidemiological study of all *C. difficile* isolates revealed that ribotype 002 was the predominant toxigenic *C. difficile* in 2009 and caused hospital outbreaks in Hong Kong [5, 6]. Proactive infection control measures are important to prevent the establishment of endemicity of *C. difficile* ribotype 002. Here, we reported our enhanced infection control interventions to combat *C. difficile* infection in Hong Kong.

Materials

Setting

This study was conducted in a university-affiliated acute hospital and three extended-care hospitals with a total of 3,200 beds in a healthcare network in Hong Kong. Diarrheal patients with stool samples positive for both *C. difficile* culture and cytotoxin between 1 January 2008 and 30 June 2012 were retrospectively retrieved for analysis. Healthcare-associated CDI was defined as patients with diarrhea symptoms onset more than 48 h after admission [7]. The healthcare-associated CDI rate was calculated on a quarterly basis, which was presented as the total number of newly diagnosed CDI per 10,000 admissions and per 10,000 patient-days.

Laboratory diagnosis of *C. difficile*

The conventional culture of *C. difficile* and cytotoxin were performed by a cell culture cytotoxicity neutralization assay (CCCNA), as previously described [5]. In addition to the direct detection of cytotoxin from stool filtrates, CCCNA was also performed on the stationary phase culture supernatant of each *C. difficile* isolate [4]. Capillary gel electrophoresis-based polymerase chain reaction (PCR) ribotyping was performed according to the method described by Indra et al. [8].

Infection control for CDI

Patients with CDI were nursed as a cohort with contact precautions. In view of the increasing trend of CDI, infection control interventions against CDI were fully enhanced in 2010 2Q. Strict contact precautions with glove and gown were worn during patient care practice preferably in single room and dedicated medical equipment and items such as bedpans, and commodes were used. Hand washing with soap and water was the preferred method of hand hygiene after caring for patients with CDI. The patient's room was cleaned at least twice daily with sodium hypochlorite 1,000 ppm. Cleaning staff was trained for 20 min with specific emphasis on the meticulous disinfection of high-touch areas, such as bedrail, bedside table, and locker. Terminal cleansing of the patient's room for 30 min and change of curtains were carried out when these patients were discharged or transferred. Education health talks were given to infection control linked persons and ward staff four times a year. The compliance of hand hygiene of healthcare workers was monitored as previously described [9]. An investigation was conducted for hospital outbreaks when

Table 1 Epidemiological characteristics of patients with healthcare-associated *Clostridium difficile* infection (CDI) before and after the implementation of infection control interventions

	Pre-intervention (2008–2010 1Q) (n=177)	Post-intervention (2010 2Q–2012 2Q) (n=152)	p-Value
Age (mean age±SD)	64.4±24.6	61.3±27.7	0.277
Female sex	81 (45.8 %)	75 (49.3 %)	0.517
Resident of elderly home[a]	33 (18.6 %)	28 (18.4 %)	0.959
Medical specialty	116 (65.5 %)	94 (61.8 %)	0.487
Presence of indwelling device			
Tracheostomy tube (%)	12 (6.8 %)	19 (12.5 %)	0.077
Chronic wound or ulcer (%)	26 (14.7 %)	27 (17.8 %)	0.450
Urinary catheter (%)	65 (36.7 %)	48 (31.6 %)	0.327
Drain (%)	8 (4.5 %)	9 (5.9 %)	0.567
Underlying diseases			
Chronic cerebral conditions	25 (14.1 %)	17 (11.2 %)	0.426
Chronic cardiopulmonary conditions	47 (26.6 %)	49 (32.2 %)	0.258
Chronic renal failure	19 (10.7 %)	16 (10.5 %)	0.951
Liver cirrhosis	9 (5.1 %)	8 (5.3 %)	0.942
Diabetes mellitus	17 (9.6 %)	15 (9.9 %)	0.936
Malignancies	50 (28.2 %)	59 (38.8 %)	0.042
Crude mortality at 30 days after CDI	41 (23.2 %)	25 (16.4 %)	0.129
Crude mortality at 60 days after CDI	58 (32.8 %)	40 (26.3 %)	0.202
Crude mortality at 90 days after CDI	68 (38.4 %)	49 (32.2 %)	0.243
Crude mortality at 180 days after CDI	84 (47.5 %)	58 (38.2 %)	0.090

[a] Persons living in long-term care facilities for elderly people in Hong Kong

three or more CDI patients epidemiologically linked to the same ward were identified. An antibiotic stewardship program was maintained throughout the study period as previously described [10]. The consumption of broad-spectrum antibiotics was monitored.

Statistical analysis

Patterns of changes in the incidence rates of healthcare-associated CDI (per 10,000 patient admissions and per 10,000 patient-days) before and after implementation of the infection control interventions were analyzed using segmented Poisson regression [11]. SPSS version 20 was used for the analysis and a significance level of 0.05 was adopted.

Results

Between 1 January 2008 and 30 June 2012, 329 patients had healthcare-associated CDI. There were 173 (52.6 %) males, with a median age of 72 years (range, 1–100). These episodes of CDIs occurred in 63 wards within four hospitals in our healthcare network, and 199 (60.5 %) of the 329 patients were diagnosed in the acute hospital. Sixty-four percent (210/329) of the CDI patients were diagnosed in the medical units, while 19 % (63 cases) and 5 % (18 cases) were diagnosed in the surgery and intensive care units, respectively. The median time from admission to diagnosis of CDI was 15 days (range, 3–315 days). There was no epidemiological evidence of nosocomial outbreaks involving three or more patients with CDI diagnosed in the same ward simultaneously.

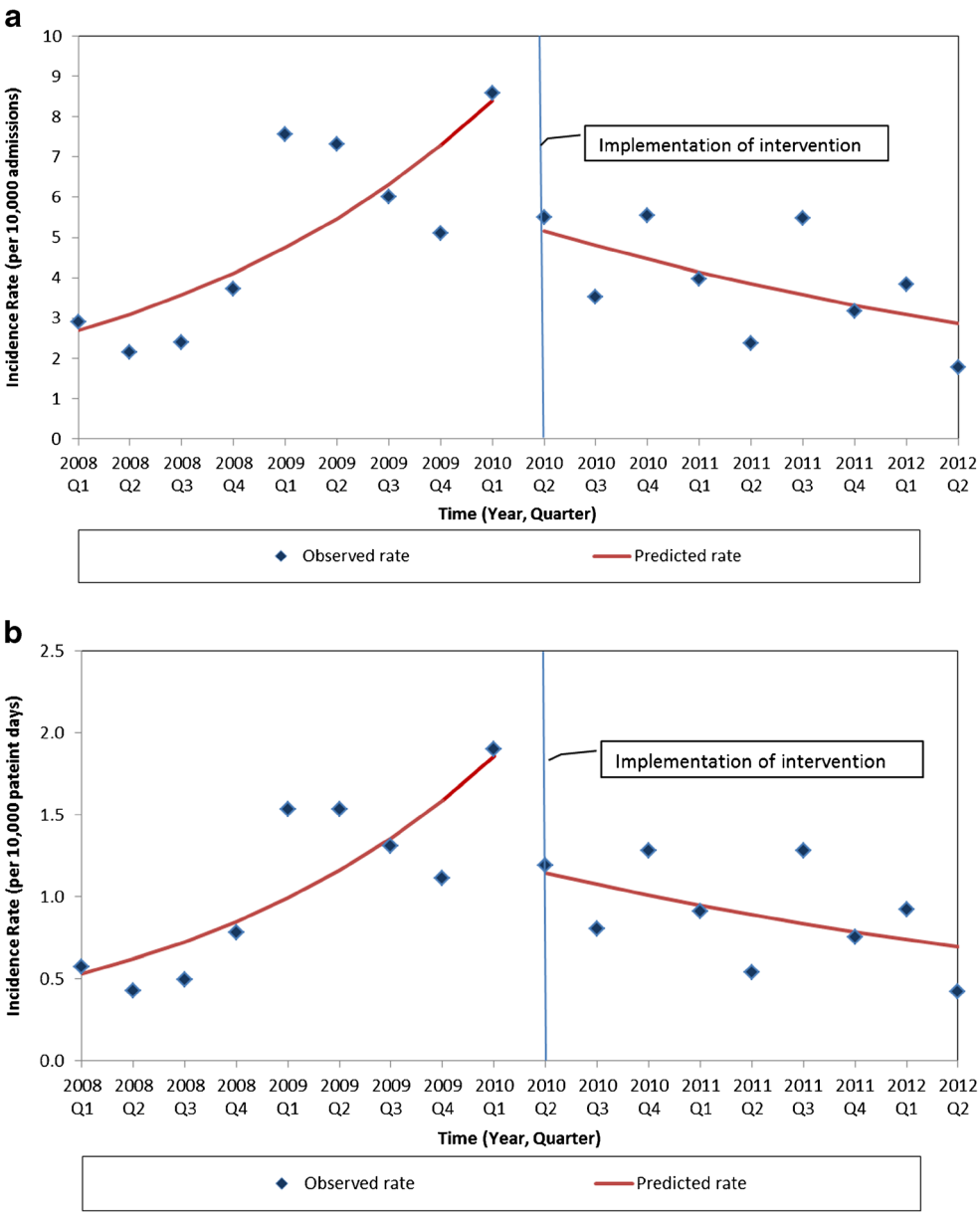

Fig. 1 **a** Observed and predicted incidence rate of healthcare-associated *Clostridium difficile* infection (CDI) per 10,000 admissions before and after infection control interventions. **b** Observed and predicted incidence rate of healthcare-associated CDI per 10,000 patient-days before and after infection control interventions

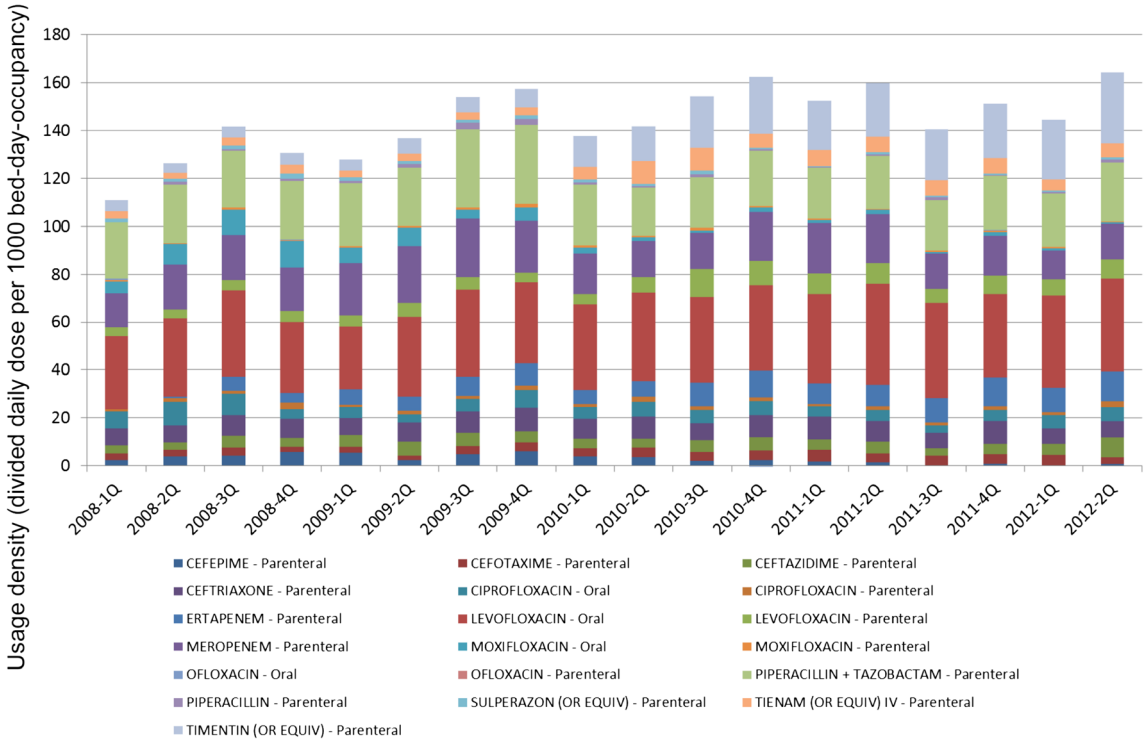

Fig. 2 Consumption of broad-spectrum antibiotics with potential for selecting *Clostridium difficile* in Intensive Care unit, Medicine, Surgery, Orthopedic, and Oncology in our healthcare network (2008–2012 2Q) Note: broad-spectrum antibiotics include cefepime, cefotaxime, ceftazidime, ceftriaxone, cefoperazone/sulbactam (Sulperazon), piperacillin/tazobactam, piperacillin, ticarcillin/clavulanate (Timentin), meropenem, imipenem/cilastatin (Tienam), ertapenem, ciprofloxacin (iv/po), levofloxacin (iv/po), moxifloxacin (iv/po), and ofloxacin (iv/po)

Enhanced infection control measures were fully implemented since 2010 2Q. There was no significant difference in terms of the epidemiological characteristics of patients with healthcare-associated CDI before and after infection control interventions, except for more patients with malignancy in the post-intervention period (Table 1). *C. difficile* ribotype 002 was the most predominant ribotype during our study period, which constituted 17.9 % (59/329) of patients with CDI. The proportion of *C. difficile* ribotype 002 was not significantly different before and after infection control interventions (34/177, 19.2 % vs. 25/152, 16.4 %, p=0.515).

Before the implementation of infection control interventions, the incidence rates of healthcare-associated CDI per 10,000 admissions and per 10,000 patient-days increased significantly by 15.3 and 17.0 %, respectively, per quarter (p<0.001) from 2008 1Q to 2010 1Q. Both healthcare-associated CDI rates per 10,000 admissions and per 10,000 patient-days declined significantly by 47 % (p<0.001) after the implementation of interventions in 2010 2Q. There was also a significant change of trend after the implementation of interventions (p<0.001) by −19.4 % for CDI per 10,000 admissions and −19.8 % for CDI per 10,000 patient-days, resulting in a decline of 7.1 % and 6.1 % in each quarter, respectively, during the period after 2010 2Q (Fig. 1a, b).

With the promotion of hand hygiene using alcohol-based hand rub, the overall compliance of hand hygiene increased from 57.8 % (2008) to 78.6 % (2012), while the proportion of hand washing using soap and water gradually reduced from 19.0 % (2008) to 13.3 % (2012). The consumption of broad-spectrum antibiotics presented as divided daily dose per 1,000 acute bed-day occupancy was 140.9 and 152.3 per quarter before and after infection control interventions, respectively (Fig. 2).

Discussion

With the implementation of enhanced infection control interventions, we have successfully contained the transmission of healthcare-associated CDI in our healthcare network, without a replacement by other *C. difficile* ribotypes. Unlike most of the CDI outbreak control where appropriate antimicrobial stewardship with reduced use of cephalosporins and fluoroquinolones played an important role [12, 13], the consumption of broad-spectrum antibiotics increased slightly throughout our study period, and our CDI patients may have received multiple courses of antibiotics before symptomatic diarrhea. In fact, a significant reduction of CDI could be achieved without restriction of antibiotic use in a medical intensive care unit [14]. In view of the increasing prevalence of multiple drug-resistant organisms in our locality [15, 16], it would be more difficult to reduce antibiotic consumption by

an antimicrobial stewardship program [10]. Infection control programs alone will be the most important armamentarium to control the outbreak of CDI [2, 17].

Isolation of patients with CDI in single room with contact precautions was the cornerstone measure to prevent the spread of this infection [18]. With the implementation of a hospital-wide hand hygiene campaign where patients with methicillin-resistant *Staphylococcus aureus* colonization were allowed to be cared for in an open cubicle [11], CDI patients could be more likely cared for in a single room, where strict contact precautions and meticulous environmental cleaning could be enforced.

Asymptomatic carriers were considered to be a potential source for the transmission of epidemic and non-epidemic *C. difficile* strains [19]. Patients' isolation requirements were expanded from the duration of illness to the duration of hospitalization as a part of the infection control bundle to manage a CDI outbreak, which had a peak incidence of 72 cases per 10,000 patient discharges [3]. However, such a measure was not possible in settings with a limited number of isolation rooms. Our timely implementation of infection control measures has reduced our peak incidence of healthcare-associated CDI from 8.6 per 10,000 patient admissions, which was eight times lower than that of the previous study. Therefore, we have successfully circumvented the difficulty associated with the lack single rooms needed when the peak incidence is eight times higher [3].

Hand hygiene with alcohol-based hand rub has been actively promoted in Hong Kong since 2007 [20], and has become a key component to control epidemiologically important viruses and multiple drug-resistant organisms [11, 21–26]. The proportion of hand hygiene practice using soap and water gradually reduced from 19.0 % (2008) to 13.3 % (2012) in our healthcare setting. Although alcohol-based hand rub was shown to be ineffective in removing bacterial spores of *C. difficile* [27], there was a lack of association between the increased incidence of CDI and the increasing use of alcohol-based hand rub [28].

There are limitations in this study. Conventional laboratory culture and cell culture cytotoxicity neutralization assay for toxin detection were used as the diagnosis for CDI without using enzyme immunoassay and PCR tests. Our findings may not be representative for laboratories using different diagnostic methods. Although our combination of tests is highly specific for the identification of toxigenic *C. difficile*, this confirmation takes an average of 4 days. This time lag may increase the risk of nosocomial transmission. It may also miss patients with milder infections. In addition, we did not use hydrogen peroxide or ultraviolet light for environmental disinfection. However, regular education for infection control linked persons and frontline staff to maintain a high level of alertness to identify patients with nosocomial diarrhea and to perform early microbiological investigation would minimize the negative impact associated with the time lag and test sensitivity.

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Conflict of interest None declared.

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