衞生防護中心
Centre for Health Protection

Scientific Committee on Enteric Infections and Foodborne Diseases

Epidemiology, prevention and control of *Clostridium difficile* associated outbreaks in Hong Kong

Purpose

This paper reviews the latest global and local epidemiology of *Clostridium difficile* (*C. difficile*) associated acute gastroenteritis outbreaks and, examines the public health measures for prevention and control of the diseases.

Bacteriology and pathogenesis

2. *C. difficile* is an obligate anaerobic, gram positive, spore forming, toxin-producing bacillus of which, the toxigenic strains can produce two exotoxins: toxin A (enterotoxin) and toxin B (cytotoxin) that are both cytotoxic to a number of different cell types (1, 2). These toxins cause increased vascular permeability by opening tight junctions between cells, and cause hemorrhage. They also induce the production of tumour necrosis factor-alpha and proinflammatory interleukins, which contribute to the associated inflammatory response and pseudomembrane formation (2).

3. *C. difficile* can cause intestinal disease varying from mild diarrheal illness to severe colitis. It is recognized as the primary pathogen responsible for antibiotic-associated colitis and nosocomial diarrhea (1). There have been reports of epidemics of *C. difficile* associated diarrhoea in hospitals and long-term care facilities all over the world (3-8).

Mode of transmission

4. Transmission of *C. difficile* occurs mainly through faecal-oral route. The spore form is considered to be the main transmissible form of the organism (9, 10). They are resistant to exposure to air, drying, heat, acid, antibiotics and can survive in the environment for months (9, 11). *C. difficile* is shed in feces and patients infected with *C. difficile* may excrete up to 10^9 organisms per gram of faeces (11). Any surface, device, or material (e.g., commodes, bathing tub, and electronic rectal thermometers) that becomes contaminated with feces may serve as a reservoir for the *C. difficile* spores (12). At hospital setting, they can be found on bedding, furniture, medical equipment, on the skin and jewelry of caregivers, as well as the hands of health care workers treating patients infected with *C. difficile*. Once ingested, the spores pass through the upper digestive tract into the intestines where they can germinate into vegetative bacteria and colonize the colon. Healthy individuals are usually protected from *C. difficile* infection by the normal bacterial flora of the gut, which resists *C. difficile*ôs colonization and growth. However, alteration of the normal lower intestinal microbiota by exposure to antibiotics provides an environment that allows *C. difficile* to multiply, flourish, and produce toxins that cause diarrhoea and colitis (13).

Clinical Presentations

5. The incubation period is not known for certain (10). Symptoms of *C. difficile* infection (CDI) usually begin soon after colonisation (with a median of 2-3 days) (10). However, the time from antibiotic exposure to onset of symptoms may range from 1 day to 6 weeks (2).

6. The most common risk factor of contracting CDI is exposure to antibiotics, especially those with broad-spectrum activity such as expanded-spectrum penicillins, cephalosporins, clindamycin and fluoroquinolones (2, 10, 14). Advanced age, prolonged hospitalisation, severe underlying illness, cancer chemotherapy and manipulation of the gastrointestinal tract (e.g. by surgery or tube feeding) are also associated with increased risk of CDI (2, 10).

7. Clinical features of CDI range from symptomless carriage to fulminant pseudomembranous colitis with sepsis, toxic megacolon, organ failure, and death (9). *C. difficile* can be present in the gut of up to 3% of healthy adults and 66% of infants. Asymptomatic carriage can occur in up to 50% of hospitalised patients with *C. difficile* (10). In long term care facilities, the prevalence of colonisation is lower, ranging from 5% to 7% (2).

8. Symptomatic patients commonly present with fever, abdominal cramps and watery diarrhoea, which may be associated with the passage of mucus or blood (10). Colonic ileus or toxic megacolon can occur in severe cases. The disease may also have severe complications such as colonic perforation, peritonitis, sepsis and death (10, 12). The mortality associated with toxic megacolon is reported to be 24-38% while the overall estimated case fatality rate of *C. difficile* infection is greater than 2% (9).

9. Recurrent *C. difficile* associated diarrhoea is especially difficult to manage. It occurs in 5-40% of treated patients (2). Recurrence has been postulated due to persistence of *C. difficile* spores in the gut or re-infection by organism.

Laboratory diagnosis (12, 15)

10. Diagnosis is made by laboratory investigation of stool specimens for *C. difficile* and / or its toxins. Testing for *C. difficile* or its toxins should only be performed on unformed, diarrheal stool (i.e. loose or watery stool).

11. Stool culture for *C. difficile* is one of the most sensitive test (10) but it is labour intensive, culture environment demanding for the growth of anaerobic microorganisms and has a slow turn-around time. Besides, it may associate with false-positive results due to the presence of non-toxigenic *C. difficile* strains. This can be overcome by testing isolates for toxin production, i.e. ñtoxigenic cultureò which has been employed as a gold-standard for comparison of laboratory tests.

12. Molecular tests, such as certain polymerase chain reaction (PCR) assays which test for the gene encoding toxin B, are highly sensitive and specific for the presence of a toxin-producing *C. difficile* organism.

13. Antigen test for *C. difficile* is rapid to detect the presence of *C. difficile* antigen by latex agglutination or immunochromatographic assays. Since the results of antigen testing alone are non-specific, antigen assays have been employed in combination with tests for toxin detection, PCR or toxigenic culture.

Clinical management (1, 9, 12)

14. For patients infected with *C. difficile*, the immediate goal of therapy is to alleviate the active symptoms of diarrhea and colitis. The ultimate goal of treatment is the restoration of the normal bacterial flora of the gut and elimination of the infection. The ideal treatment will not require the use of antibiotics but to stop all unnecessary antibiotics for patients who have acute infection of *C. difficile*. Treatment of CDI includes general measures such as supportive care with attention to correction of fluid losses and electrolyte imbalances. The initial therapy is to discontinue all antibiotics and monitor the patientôs progress. About 20% of patients with *C difficile* infection will resolve within 2-3 days of discontinuing the antibiotic to which the patient was previously exposed. If mild infection persists, or under situations that other antibiotics cannot be discontinued or the patients are frail, appropriate antibiotics such as metronidazole, vancomycin, or the recently approved fidaxomicin, is often used.

15. Metronidazole is considered as first-line therapy for patients with mild to moderately severe CDI. Oral vancomycin has been reserved for patients who do not respond to or tolerate metronidazole and for patients with multiple recurrences of CDI or severe disease.

16. In addition to the increasing prevalence of *C. difficile* infection and frequent relapse in patients, there is also growing concern with the difficulty in management with standard therapy. *C. difficile* colitis patients who are refractory to standard treatments has been reported (16). There is a need to identify alternative effective approaches for the treatment of *C. difficile* infection. Other agents such as human monoclonal antibodies against *C. difficile* toxins A (CDA1) and B (CDB1) (17), intravenous immunoglobulins (18, 19), rifaximin (16, 20), probiotics (21, 22), or fecal transplantation have been reported to be useful in studies. However, further researches for the evidence in efficacy, effectiveness, safety and their use in clinical practices are required.

Prevention and control of outbreaks (9, 15)

17. *C. difficile* is easily transmitted within healthcare settings causing outbreaks of acute gastroenteritis in hospitals and long-term care facilities. A number of infection control measures should be implemented to prevent or limit of the transmission of the organism. They include:-

- **Contact precautions** which should be implemented for both the suspected and confirmed cases until the diarrhea is resolved or its cause is determined not to be infectious;
- **Hand hygiene**;
- **Environmental cleaning and disinfection** by using chlorine-containing disinfectant or other sporicidal agents; and
- **Visitor management** including restriction on the number of visitors and educating them on the precautionary actions.

18. There should be system to keep monitoring and surveillance to detect early sign of outbreak. In case of outbreak, prompt investigation is required to be initiated and the infection control measures may need to be reviewed and stepped up to prevent its propagation.

19. In addition, there should be engineering and administrative measures to ensure that physical and cultural environments are conducive to the implementation of infection control measures. For examples, set up of single rooms with in-room private toilets, easily accessible hand-washing facilities for both resident and staff starting from the design stage of healthcare facilities; using surfaces that are constructed of materials that can be easily and effectively cleaned at the point of use; putting in place policies, guidelines and procedures on the implementation of infection control measures, related educational programmes, monitoring and audit activities, and prudent use of antibiotics, etc.

Global Situation

20. The burden of *C. difficile* infection has increased in both North America and Europe over the past decades (5, 7, 23-25). Nosocomial acquisition and transmission of *C. difficile* have been well documented (26), with incidence ranging from 1:100-1:1000 hospitalised patients (1). *C. difficile* infection is now the most common cause of diarrhea in the acute care setting, responsible

for up to 30% of all cases and accounts for more than 300,000 newly diagnosed cases per year (27). Besides, it is now recognized to be responsible for 20%-30% of cases of antibiotic associated diarrhea and 50%-75% of cases of antibiotic associated colitis (1). Furthermore, outbreaks of *C. difficile*-associated diarrhea at various hospital wards and long-term care facilities have been reported worldwide (6-8, 23-25).

21. In recent years, the rate of CDI in hospitals is increasing in the United States (US), Canada, Korea and Singapore (3, 28-30). Besides, CDI has also been reported in hospitals in China (31). Reil *et al* also reported that a seasonality pattern of CDI with a higher number of affected patients was observed in the winter months in Germany (32).

22. In US, the rates of hospital discharges with CDI listed as any diagnosis increased from 3.82 per 1,000 discharges in 2000 to 8.75 per 1,000 discharges in 2008 and 8.53 per 1,000 discharges in 2009 (3). Outbreaks at hospitals and other healthcare facilities were also reported. McDonald et al. reported that *C. difficile* associated outbreaks occurred in eight health care facilities in six states (Georgia, Illinois, Maine, New Jersey, Oregon, and Pennsylvania) of US with a total of 187 *C. difficile* isolates detected between 2000 and 2003 (24).

23. In Canada, mandatory reporting of nosocomial CDI began in public hospitals in Ontario in late 2008. The rates of CDI increased by 13% from 0.30 per 1,000 patient days in 2009 to 0.34 per 1,000 patient days in 2011 and a total of 71 confirmed hospital outbreaks caused by *C. difficile* had been reported in Ontario from 2009 to 2011 (28). Nosocomial epidemics or outbreaks have been reported over various areas of Canada. There was report of an epidemic of *C. difficile* spreading to many hospitals and caused significant mortality in Quebec since 2002 (7). From January to June, 2004, a prospective study at 12 hospitals in Quebec found that a total of 1,703 patients were identified during the nosocomial outbreaks (25).

24. *C. difficile* associated outbreaks at healthcare facilities were also reported in European countries. In England, a study reported that *C. difficile* caused an outbreak affecting over 300 elderly who had been treated with antibiotics in a hospital between 2003 to 2005 (23). There were also large outbreaks of CDI that had affected 318 patients in three acute care hospitals in Northern Ireland between June 2007 and August 2008 (33). In other parts of Europe, outbreaks

of CDI in hospitals were also reported in Vienna of Austria from 2008-2009 (8). Large outbreaks of CDI were reported in northern France and a total of 281 laboratory confirmed CDI were notified from thirty eight healthcare facilities (including long-term care hospitals and nursing homes) near the border between France and Belgium over a 22-month period from 2006 to 2007 (6).

25. The increase in number of *C. difficile* associated outbreaks in North America and Europe may attribute to the emergence of a hypervirulent epidemic strain (BI/NAP1/027) of *C. difficile*. Several characteristics found in BI/NAP1/027 may contribute to its hypervirulence and rapid spread. First, the epidemic strain has a mutation in a negative regulator of toxin production, tcdC, leading to higher toxin production compared to other strains (34). Second, there is the presence of a third toxin called binary toxin (24). The role of binary toxin is not completely understood yet. However, it is postulated that the binary toxin acts together with toxin A and B causing more severe disease (35). Third, resistance to the fluoroquinolone class of antibiotics likely contributes to the successful spread of this strain in healthcare settings (24).

26. In Asian countries, *C difficile* associated outbreaks were also reported. In 2001, Japan reported outbreaks at three hospitals located in diverse areas of Japan (36).

Local Situation

27. In Hong Kong, *C. difficile* infection is not a statutory notifiable disease under Prevention and Control of Disease Ordinance (Cap 599). The Centre for Health Protection (CHP) of the Department of Health (DH) encourages institutions to report outbreaks of acute gastroenteritis (AGE) including those related to *C. difficile*.

28. From 2004 to 2013, there were a total of 1,746 AGE outbreaks reported to DH. Among the 1,746 outbreaks, 829 and 163 occurred in residential care homes for elderly (RCHE) and hospitals respectively (Table 1).

	Residential care homes for elderly (RCHE)	Hospitals	Others	Total
2004	72	11	126	209
2005	34	7	53	94
2006	218	60	77	355
2007	92	15	50	157
2008	58	11	69	138
2009	125	10	88	223
2010	65	8	62	135
2011	32	14	72	118
2012	115	18	98	231
2013	18	9	59	86
Total	829	163	754	1746

Table 1 Number of AGE outbreaks reported to DH, 2004 to 2013

29. Among the reported AGE outbreaks, there were 16 outbreaks affecting 93 persons, confirmed to be associated with *C. difficile,* of which all occurred in hospitals. To facilitate outbreak investigation, *C. difficile* associated AGE outbreak is defined as follows:

- Any in-patients / residents or staff who presented with watery stool or loose stool; AND
- Positive laboratory result for *C. difficile*

30. The first *C. difficile* associated AGE outbreak, which affected 10 persons, was recorded in May 2006. There was no further case recorded until June 2011 when the second outbreak of CDI was reported. Since then, four to six outbreaks were recorded annually (Figure 1).

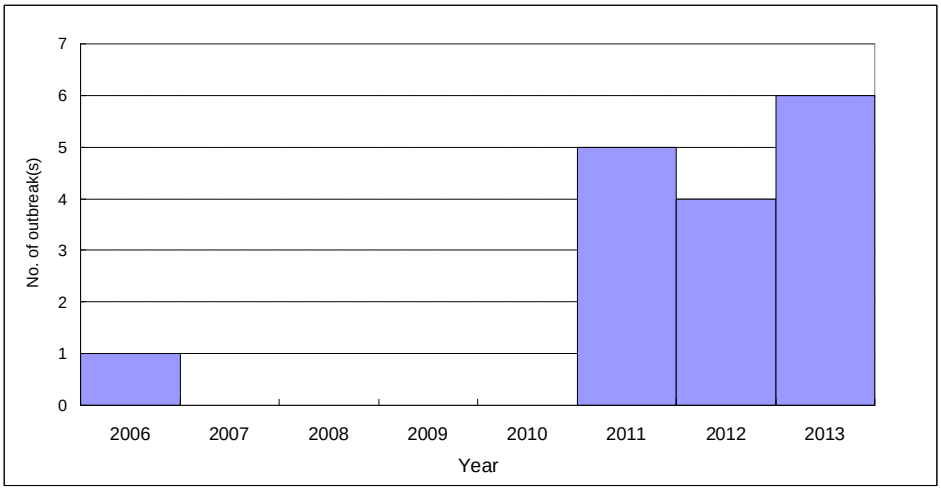

Figure 1 Number of AGE outbreaks associated with *C. difficile*, 2006 to 2013

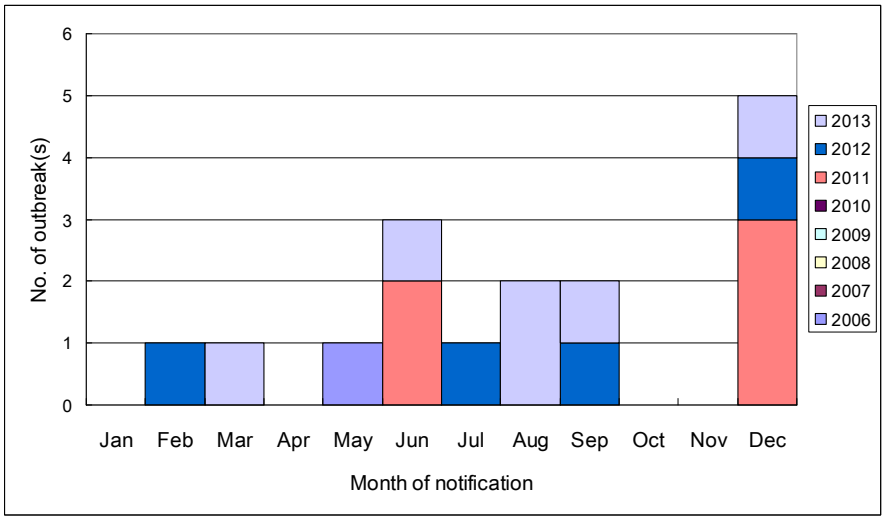

Figure 2 Number of AGE outbreaks associated with *C. difficile* by month of notification

31. The outbreaks occurred throughout the year but more outbreaks were reported in December (Figure 2). All reported outbreaks occurred in public hospitals. Six (37.5%) outbreaks occurred in Hospital A, six (37.5%) in Hospital B, two (12.5%) in Hospital C, one (6.3%) in Hospital E and one (6.3%) in Hospital F.

32. Five (31.2%) outbreaks occurred in Medical and Geriatric Ward, four (25%) in Extended Care Ward, four (25%) in Tuberculosis Ward and three (18.8%) in Convalescence Ward. The duration of outbreaks ranged from 1 to 37 days (Median: 11.5 days).

33. Among the 16 reported outbreaks, thirteen (81.3%) were confirmed by PCR, two (12.5%) by culture and one (6.2%) by detection of cytotoxin.

34. The number of persons affected in each outbreak ranged from 4 to 10 (Median: 5 persons). These outbreaks mainly affected elderly in hospitals. The median age of each outbreak ranged from 68 to 88.5 years. The male-to-female ratio was 1:0.8. No complications and fatal case due to CDI was reported.

35. Information on the predisposing risk factors among the 93 patients from the 16 outbreaks was analysed. Seventy-one patients (76.3%) were bed-bound/chair-bound, 56 patients (60.2%) required nasogastric tube feeding, 70 patients (75.3%) had napkin use and 79 (84.9%) patients had received antibiotics before onset of diarrhea (Annex 1).

36. Investigation of the outbreaks revealed that there was a ward without washing basin. It was advised that staff should use the nearest basin without touching surrounding areas and all staff were reinforced to wash hands after taking care for the cases and contacts. Non-compliance with hand hygiene after taking care of patients was also found in an outbreak. Prompt actions had been taken in all cases including compliance with hand hygiene and review of hospital policy in stepping up the supervision and monitoring of hand hygiene practice among staff and visitors. All outbreaks were contained finally with durations ranged from 1 to 37 days (Median: 11.5 days).

Prevention and Control Measures in Hong Kong

37. In Hong Kong, strategies on prevention and control of *C. difficile* infection and its associated diarrhoeal outbreaks are in place.

Surveillance and outbreak investigation and management

38. Currently, institutions including healthcare facilities are encouraged to report AGE outbreaks to CHP through Central Notification Office (CENO). Upon receipt of an outbreak, CHP will immediately initiate investigation and implement control measures.

39. For hospital outbreak, joint investigation through the Hospital Outbreak Control Team (HOCT) with members from the hospital, the Epidemiology and Surveillance Branch and the Infection Control Branch of CHP will be conducted. Based on the risks being identified, a series of control measures will be implemented accordingly.

40. Patients with CDI will be isolated or cohorted. Ward contacts will be kept under medical surveillance for 21 days. The hospital ward concerned is responsible for maintaining medical surveillance of in-patient contacts. For those who have been discharged home, the healthcare workers of the hospital

will educate the contacts to seek medical advice and inform the attending doctor of their exposure history if they develop symptoms during the surveillance period. In case the contacts are discharged to Residential Care Homes for Elderly (RCHE), hospital staff will remind the respective RCHE to alert CHP if the contacts become symptomatic during the surveillance period. The outbreak can be declared over if no new cases occur over the surveillance period.

Hospital policies and guidelines on infection control

41. Infection Control Branch of CHP, in conjunction with the Hospital Authority, has developed guidelines on the infection control measures for communicable diseases in hospital wards and other institutions (37). Those guidelines are available publicly on the CHP website. There are also hospital guidelines stipulating the infection control measures specific for preventing transmission of *C. difficile* in public hospitals under the Hospital Authority, which covers areas such as inpatient management and isolation, use of personal protective equipment, hand hygiene, use of patient care equipment, environmental disinfection and appropriate use of antibiotics.

42. Private hospitals are also required to have designated infection control officer to take charge of the infection control unit. Private hospitals are required to develop appropriate infection control guidelines, provide staff training, promulgate and monitor the implementation of infection control guidelines. The CHP has also set up a regular communication platform known as the Working Group of Collaboration between CHP and Private Hospitals on Safe Use of Antibiotics and Infection Control.

Health promotion

(a) Prudent use of antibiotics

43. To echo the global initiative led by World Health Organization (WHO) of promoting appropriate use of antibiotics to combat antibiotic resistance, DH has launched series of activities to promote prudent use of antibiotics. Antibiotic Awareness Day is one of public health initiatives to raise awareness about the threat of antibiotic resistance and the importance of prudent antibiotic use. In public hospitals, antibiotic stewardship programmes have been

implemented in public hospitals since 2005 to promote appropriate use of antibiotics in hospitals. Besides, CHP, in association with the Hospital Authority, two local universities and the Hong Kong Medical Association have developed the ñInterhospital Multi-disciplinary Programme on Antimicrobial ChemoTherapy (IMPACT) Guidelinesò to provide a reference tool for medical and healthcare professionals in reinforcing the appropriate use of antimicrobial drugs. It also identified the potential barriers to reaching the goals and recommended the corresponding countermeasures and improvement strategies (Table 2) (38).

Barrier	**Countermeasures and improvement strategies**
Ownership and accountability	
1. Lack of ownership and accountability for recognizing and reporting trends. 2. Failure to integrate work of laboratory, infection control, medical, nursing, and intensive care-unit staff.	1. Designate responsibility and accountability for the process. 2. Set up a multi-disciplinary team to develop a collaborative system and monitor results.
Staff knowledge and practice	
1. Lack of time for the laboratory and/or infection control staff to generate and analyze data. 2. Lack of time for healthcare providers to examine and discuss data and inconsistent or erroneous interpretation of data by staff.	1. Ensure adequacy of laboratory and infection-control staffing and prioritize activities of staff so that data can be generated and analyzed. 2. Report data in an easy-to-read/interpret format and, when appropriate, include data interpretation in the report.
Physician attitudes	
1. Lack of trust in the hospital administration.	1. Use a data-driven approach to cultivate trust; e.g. communicate regularly with physicians about trends in antimicrobial usage, cost, and resistance; feedback to individual physicians their performance results.

Expertise	
1. Lack of expertise in biostatistics (e.g. presenting trends and analyzing data).	1. Ensure availability of consultants, especially when designing analytic strategy and interpreting trend data.

Table 2 Potential barriers to reaching the strategic goals

(b) Hand hygiene

44. Hand hygiene practice is of prime importance in preventing *C. difficile* infection. Hand washing using soap and water after contact with the patient and the environment is effective in preventing the spread of *C. difficile* but, alcohol-based hand sanitizers is not effective to kill *C. difficile* spores (10, 12, 39). Use of gloves is also recommended to minimize the level of contamination of spores on the hands when caring the patients or in contact with the contaminated environment (10, 40). As early as 2005, Hong Kong has pledged to support WHOôs First Global Patient Safety Challenge: Clean Care is Safer Care initiative by active promotion of hand hygiene. Since 2010, Hand Hygiene Awareness Day has been marked annually on May 5 to arouse awareness on the importance of hand hygiene in infection prevention and control as a highlight of the WHOôs SAVE LIVES: Clean Your Hands global initiative. In celebration of the Hand Hygiene Awareness Day and to sustain the hand hygiene practices, the Infection Control Branch of CHP has developed a series of activities and promotional materials to remind colleagues in public, private medical sectors and long term care facilities of the importance of hand hygieneIn addition, hand hygiene practice in public hospitals is constantly monitored. The overall hand hygiene compliance rate among the Hong Kong East cluster in 2012 was 78.6% (41). A more update audit results showed that the hand hygiene compliance rates among the medical and surgical wards of public hospitals in late 2013 were generally below 80% (42).

(c) Other health education initiatives

45. Health education materials and guidelines are available in CHP website to provide infection control standards to RCHE to guard against communicable diseases. There are ñGuideline on Prevention of Communicable Diseases in Residential Care Homes for the Elderlyò and ñGuidelines on Prevention of Communicable Diseases in Residential Care Homes for Persons with

Disabilitiesò that contains practical information and control measures on prevention of communicable diseases (43).

Recommendations

Prudent use of antibiotics

46. Though there are policies and guidelines in place, cases of CDI after use of antibiotics are reported. Multiple approaches have been employed to enforce hospital policies to limit or control antimicrobial use. It is recommended to follow the improvement strategies suggested by the IMPACT to address the potential barriers of reaching the goals of prudent use of antibiotics.

Infection Control Measures for patients infected with *C. difficile*

47. Non-compliance with hand hygiene among healthcare worker has been identified during an investigation of *C. difficile* associated outbreak in a hospital. Hand hygiene compliance monitoring at public hospitals also reflects that the compliance in medical and surgical wards were generally below 80%. It is recommended to further enhance the promotion of hand hygiene including its awareness and practice (42) as well as the ineffectiveness of killing spores of *C. difficile* by alchohol-based hand rubs which should be replaced by handwashing after care of symptomatic patients. When managing patients with *C. difficile*, other infection control measures as mentioned in paragraph 17 above should also be strengthened. These include contact precautions including the donning of gloves and gowns, proper environmental cleaning and disinfection and, patients isolation and visitor management.

Surveillance of nosocomial AGE outbreak

48. Unlike the North American and European countries, the annual number of reported nosocomial *C. difficile* associated outbreaks in Hong Kong is relatively stable and low. It may be true that the local burden of the disease is low or may be due to under-reporting. To have a better estimation of the disease burden, CHP is recommended to keep close collaboration with hospitals and encourage them to report AGE outbreaks.

New approaches to treatment of CDI

49. To address the growing public health concern with the increasing prevalence of CDI and the difficulty in management with standard therapy, it is also recommended to keep latest abreast of the development of alternative approaches for the treatment and prevention of CDI.

Conclusion

50. The reported number of *C. difficile* associated AGE outbreaks in Hong Kong was low and all these outbreaks occurred in hospitals. There was no case reported to have severe complication and no fatal case arising from the infection was recorded. In Hong Kong, systems and measures are in place for prevention and control of the transmission of *C. difficile* in healthcare settings. There are recommended strategies to address the potential barriers to prudent use of antibiotics. It is also recommended to reinforce the awareness and compliance with hand hygiene and encourage hospitals to report nosocomial AGE outbreaks.

Centre for Health Protection
August 2014

Annex 1 Line listing of AGE outbreaks associated with *C. difficile*, 2006-2013

No.	Year	No. of persons affected	Age range (Median age) (Years)	Sex ratio (Male: Female)	Duration of outbreak (Days)	No. of bed-bound/ chair-bound patients	No. of patients required nasogastric tube feeding	No. of patients with napkin use	No. of patients with history of antibiotics use before diarrhoea
1	2006	10	51-89 (80)	7:3	8	8	5	4	8
2	2011	9	73-87 (80)	9:0	16	9	9	9	9
3	2011	4	75-99 (83)	4:0	9	4	3	4	4
4	2011	7	58-88 (84.5)	5:2	31	0	0	0	7
5	2011	5	71-94 (79)	0:5	9	5	5	5	4
6	2011	4	79-88 (81.5)	4:0	1	4	4	4	2
7	2012	6	34-78 (68)	2:4	26	3	2	3	2
8	2012	5	63-96 (86)	0:5	6	5	5	5	4
9	2012	7	69-86 (79)	7:0	14	7	5	7	4
10	2012	4	76-97 (87.5)	0:4	11	4	4	4	4
11	2013	6	75-91 (82)	3:3	20	6	6	6	6
12	2013	5	75-94 (83)	0:5	10	5	2	5	5
13	2013	4	79-85 (82.5)	4:0	12	4	1	4	3
14	2013	4	85-96 (88.5)	0:4	7	4	2	4	4
15	2013	8	55-87 (81.5)	6:2	37	3	2	3	8
16	2013	5	48-92 (80)	1:4	22	0	1	3	5

References

1. Nitzan O, Elias M, Chazan B, Raz R, Saliba W. Clostridium difficile and inflammatory bowel disease: role in pathogenesis and implications in treatment. World J Gastroenterol. 2013;19(43):7577-85.
2. Poutanen SM, Simor AE. Clostridium difficile-associated diarrhea in adults. CMAJ. 2004;171(1):51-8.
3. Lessa FC, Gould CV, McDonald LC. Current status of Clostridium difficile infection epidemiology. Clin Infect Dis. 2012;55 Suppl 2:S65-70.
4. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. N Engl J Med. 1989;320(4):204-10.
5. McDonald LC, Owings M, Jernigan DB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996-2003. Emerg Infect Dis. 2006;12(3):409-15.
6. Birgand G, Blanckaert K, Carbonne A, Coignard B, Barbut F, Eckert C, et al. Investigation of a large outbreak of Clostridium difficile PCR-ribotype 027 infections in northern France, 2006-2007 and associated clusters in 2008-2009. Euro Surveill. 2010;15(25).
7. Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ. 2005;173(9):1037-42.
8. Indra A, Huhulescu S, Fiedler A, Kernbichler S, Blaschitz M, Allerberger F. Outbreak of Clostridium difficile 027 infection in Vienna, Austria 2008-2009. Euro Surveill. 2009;14(17).
9. Martinez FJ, Leffler DA, Kelly CP. Clostridium difficile outbreaks: prevention and treatment strategies. Risk Manag Healthc Policy. 2012;5:55-64.
10. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55.
11. Department of Health/Public Health Laboratory Service Joint Working Group. Clostridium Difficile Infection Prevention and Management. In: Department of Health UK, editor. 1994.
12. Centers for Disease Control and Prevention U. Frequently Asked Questions about Clostridium difficile for Healthcare Providers 2012 [cited 2014 10 Febuary 2014]. Available from: http://www.cdc.gov/HAI/organisms/cdiff/Cdiff_faqs_HCP.html.

13. Gould CV, McDonald LC. Bench-to-bedside review: Clostridium difficile colitis. Crit Care. 2008;12(1):203.
14. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med. 2002;346(5):334-9.
15. Public Health Agency of Canada. Clostridium Difficile Infection Infection. Prevention and Control Guidance for Management in Long-term Care Facilities 2013 [cited 2014 12 March 2014]. Available from: http://www.phac-aspc.gc.ca/nois-sinp/guide/c-dif-ltc-sld/index-eng.php#a5.
16. Lao D, 2nd, Chiang T, Gomez E. Refractory Clostridium difficile Infection Successfully Treated with Tigecycline, Rifaximin, and Vancomycin. Case Rep Med. 2012;2012:702910.
17. Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. N Engl J Med. 2010;362(3):197-205.
18. O'Horo J, Safdar N. The role of immunoglobulin for the treatment of Clostridium difficile infection: a systematic review. Int J Infect Dis. 2009;13(6):663-7.
19. Salcedo J, Keates S, Pothoulakis C, Warny M, Castagliuolo I, LaMont JT, et al. Intravenous immunoglobulin therapy for severe Clostridium difficile colitis. Gut. 1997;41(3):366-70.
20. Lichtenstein GR. Rifaximin: recent advances in gastroenterology and hepatology. Gastroenterol Hepatol (N Y). 2007;3(6):474-83.
21. Hickson M. Probiotics in the prevention of antibiotic-associated diarrhoea and Clostridium difficile infection. Therap Adv Gastroenterol. 2011;4(3):185-97.
22. Fitzpatrick LR. Probiotics for the treatment of Clostridium difficile associated disease. World J Gastrointest Pathophysiol. 2013;4(3):47-52.
23. Smith A. Outbreak of Clostridium difficile infection in an English hospital linked to hypertoxin-producing strains in Canada and the US. Euro Surveill. 2005;10(6):E050630 2.
24. McDonald LC, Killgore GE, Thompson A, Owens RC, Jr., Kazakova SV, Sambol SP, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. N Engl J Med. 2005;353(23):2433-41.
25. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353(23):2442-9.
26. Alfa MJ, Du T, Beda G. Survey of incidence of Clostridium difficile infection in Canadian hospitals and diagnostic approaches. J Clin Microbiol. 1998;36(7):2076-80.
27. Stanley JD, Bartlett JG, Dart BWt, Ashcraft JH. Clostridium difficile infection. Curr Probl Surg. 2013;50(7):302-37.

28. Ontario Agency for Health Protection and Promotion (Public Health Ontario) PIDAC. Annex C ï testing, surveillance and management of Clostridium difficile. Annexed to: routine practices and additional precautions in all health care settings.: Toronto, ON: Queen's Printer for Ontario; 2013.
29. Kim YS, Han DS, Kim YH, Kim WH, Kim JS, Kim HS, et al. Incidence and clinical features of Clostridium difficile infection in Korea: a nationwide study. Epidemiol Infect. 2013;141(1):189-94.
30. Lim PL, Barkham TM, Ling LM, Dimatatac F, Alfred T, Ang B. Increasing incidence of Clostridium difficile-associated disease, Singapore. Emerg Infect Dis. 2008;14(9):1487-9.
31. Han XH, Du CX, Zhang CL, Zheng CL, Wang L, Li D, et al. Clostridium difficile infection in hospitalized cancer patients in Beijing, China is facilitated by receipt of cancer chemotherapy. Anaerobe. 2013;24:82-4.
32. Reil M, Hensgens MP, Kuijper EJ, Jakobiak T, Gruber H, Kist M, et al. Seasonality of Clostridium difficile infections in Southern Germany. Epidemiol Infect. 2012;140(10):1787-93.
33. Aldeyab MA, Devine MJ, Flanagan P, Mannion M, Craig A, Scott MG, et al. Multihospital outbreak of Clostridium difficile ribotype 027 infection: epidemiology and analysis of control measures. Infect Control Hosp Epidemiol. 2011;32(3):210-9.
34. Carter GP, Douce GR, Govind R, Howarth PM, Mackin KE, Spencer J, et al. The anti-sigma factor TcdC modulates hypervirulence in an epidemic BI/NAP1/027 clinical isolate of Clostridium difficile. PLoS Pathog. 2011;7(10):e1002317.
35. Barbut F, Decre D, Lalande V, Burghoffer B, Noussair L, Gigandon A, et al. Clinical features of Clostridium difficile-associated diarrhoea due to binary toxin (actin-specific ADP-ribosyltransferase)-producing strains. J Med Microbiol. 2005;54(Pt 2):181-5.
36. Kato H, Kato N, Watanabe K, Yamamoto T, Suzuki K, Ishigo S, et al. Analysis of Clostridium difficile isolates from nosocomial outbreaks at three hospitals in diverse areas of Japan. J Clin Microbiol. 2001;39(4):1391-5.
37. Centre for Health Protection Department of Health. ICB Infection Control Guidelines 2010 [cited 2014 13/3/2014]. Available from: http://www.chp.gov.hk/en/guideline1/346/365.html.
38. Ho PL, Wong SY. Reducing bacterial resistance with IMPACT. In: Centre for Health Protection Department of Health, editor. 4th Edition ed2012.
39. Oughton MT, Loo VG, Dendukuri N, Fenn S, Libman MD. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of Clostridium difficile. Infect Control Hosp Epidemiol. 2009;30(10):939-44.
40. Centre for Healthcare Related Infection Surveillance and Prevention Q.

GUIDELINE. Clostridium difficile Infection (CDI). Queensland 2014 [updated 2014]. Available from: http://www.health.qld.gov.au/qhpolicy/docs/gdl/qh-gdl-408.pdf.

41. Hospital Authority. Hospital authority quality and risk management annual report, 2011 -2012 2013 [cited 2014 17/3/2014]. Available from: http://www.ha.org.hk/haho/ho/psrm/EcopyQRMReport.pdf.

42. Hospital Authority. CICO Biweekly Update 2013 [cited 2014 17 March 2014]. No. 4:[Available from: http://www.ha.org.hk/haho/ho/cico/cicobiweeklyspecialedno4txt.pdf.

43. Centre for Health Protection Department of Health. Guidelines on Prevention of Communicable Diseases in Residential Care Homes for the Elderly 2007 [cited 2014 13/3/2014]. Available from: http://www.chp.gov.hk/en/guideline/478/35.html.