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Focus: *Clostridium difficile*

FEATURE ARTICLES

3 [Introduction to this issue](#)

Joanne Wong and Bonnie Marshall (APUA News Staff)

4 [C. difficile: an update](#)

Deirdre O'Brien, (Consultant Microbiologist, Aberdeen Royal Infirmary, UK)

7 [A risk-stratified algorithm for treating CDI](#)

Kirthana Raman, PharmD (Tufts Medical Center)

10 [A case study for cleaning, disinfection, and process compliance](#)

Timothy Wiemken, PhD, MPH, CIC (University of Louisville School of Medicine)

13 [Diagnosis of C. diff: the relevance of testing and clinical outcomes](#)

Glenn S. Tillotson, PhD, FIDSA, FCCP, FISC (Transcrip Partners & Public Health Research Institute)

16 [Programs to prevent CDI: a multiple strategy approach in Massachusetts](#)

Susanne Salem-Schatz, Sc.D. (MA Coalition for the Prevention of Medical Errors)

19 *Clostridium difficile*-related news

20 Elements of an infection control program

21 APUA headquarters in action

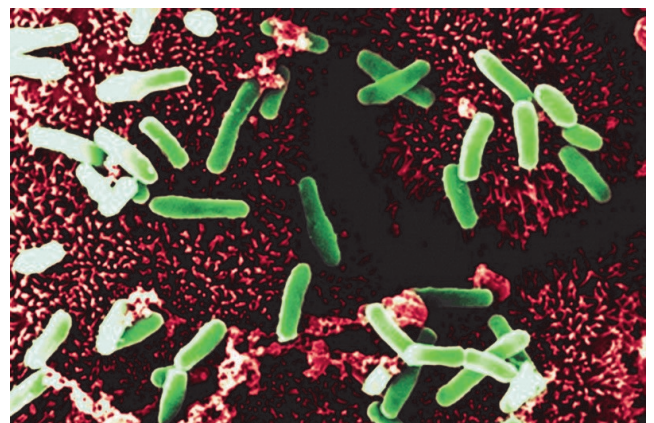
22 2013 APUA Leadership Award nomination

23 Policy updates

24 News & publications of note

25 APUA chapter research & reports

26 Upcoming events



Color-enhanced scanning electron micrograph of rod-shaped *Clostridium difficile* clinging to the microvilli of the human gut.

Source: [Med. Mic. Sciences Cardiff Uni](#), Wellcome Images



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***APUA welcomes letters to the Editor. Please send us your thoughts and questions. Names will be published but not addresses. All letters may be edited for style and length.**

Introduction to this issue

by Joanne Wong & Bonnie Marshall (APUA staff)

Clostridium difficile infection (CDI) is the most common cause of hospital-acquired infectious diarrhea [1], and generally occurs when patients have been treated with large doses of antibiotics. In recent years, CDI has re-emerged with higher incidence rates and caused more severe complications in patients, especially among seniors. While the majority of reported CDIs stem from hospital settings in the developed world [2], community-acquired CDI and CDI in the developing world are on the rise.

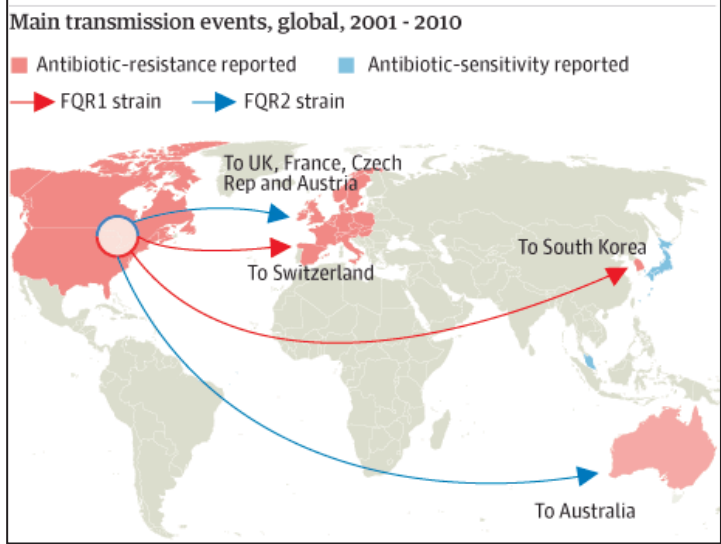
Geography: Genomic data show how *C. diff* strains spread around the world, and how interconnected our global healthcare system is. Two separate fluoroquinolone resistant lineages (FQR1 and FQR2, both derived from the NAP1/BI/027 ribotype) first emerged in North America and then disseminated rapidly to Europe, Australia and Asia (Figure 1). From DNA sequence tracking, scientists calculated that the highly virulent form of *C. diff*, which produces up to 20 times more toxin, caused major hospital outbreaks in five U.S. states before crossing the Atlantic. Since 2007, the drug-resistant bacteria have also been reported in South Korea, Australia, and Costa Rica [3].

CDI surveillance data from the developing countries are extremely limited. While *C. diff* infections are reported from the major city hospitals, detection of the epidemic 027 ribotype is rare or non-existent [3,5,9]. Testing is generally constrained in the developing world by limited capacity, perceptions of low prevalence and cost. Treatment guidelines are urgently needed, especially in endemic areas such as Nigeria where CDI is prevalent among HIV patients [4].

Community-acquired CDI: Although CDI is widely viewed as a hospital-acquired infection, research has shown that half of patients who have *C. diff* are already infected before they arrive at the hospital. CDI has been increasingly found in non-hospital based healthcare facilities, such as nursing homes and outpatient settings. Groups that were once considered to be at low risk, such as pregnant women and younger individuals lacking recent hospitalization, have now been shown to be at risk from exposure to infections associated with *C. diff* [5, 6].

Epidemiology: CDI spares no age group, but is particularly prevalent in the senior population. About 25% of *C. diff* infections appear first in hospital patients, while 75% first emerge in nursing homes or in persons recently treated in outpatient offices and clinics. Two thirds of people with *C. diff* are over 65 years of age and > 90% of the annual 14,000 *C. diff*-associated deaths occur in this age group [7]. Between 2010

Figure 1. Spread of epidemic *C. difficile*



Source: Adapted by The Guardian from the Sanger Institute [8]
FQR = fluoroquinolone-resistant

and 2030, this age group is projected to increase dramatically .

This issue provides an up-to-date overview of the nature of CDI—its prevention, treatment, and control. It presents the rationale for a new diagnostics category that will screen out false positives and explains why standard environmental hygiene is not always working for this infection. In addition to best practices for infection control and environmental hygiene, we provide antibiotic stewardship models that can minimize emergence of this infection and highlight the importance of data collection to measure intervention efficacy.

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Clostridium difficile: an update

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Since its discovery by Hall and O'Toole in 1935 *Clostridium difficile* has remained true to its name, “the difficult pathogen” [1]. *C. difficile* is an anaerobic gram-positive, spore forming bacillus that causes diarrhea via the production of two large molecular weight toxins, toxin A and toxin B [2]. Binding of these toxins to the colonic epithelial cell leads to disruption of vital cell signaling pathways. The resulting damage varies in severity, leading to a range of symptoms from diarrhea to toxic megacolon, colonic perforation and death. *C. difficile* infection (CDI) most commonly occurs following disruption of the normal gastrointestinal microbiota with antibiotic treatment.

The association between CDI and prior antibiotic use was first described in 1978, when it was proven to be the causative agent of antibiotic-associated pseudomembranous colitis, with clindamycin and lincomycin being the antibiotics most involved [3-5].

The incidence of CDI remained fairly stable throughout most of the 1990s until the emergence of the NAP1/BI/027 ribotype in North America in the early 2000s. The 2003 outbreak in Quebec, Canada showed a fourfold increase in the incidence of CDI (22.2 cases per 100,000 population in 1991 to 92.2 cases per 100,000 in 2003). This outbreak was associated not only with an increase in the frequency of disease encountered, but also with a greater severity of disease symptoms and significantly elevated mortality rates. The poorest outcomes were seen in those over 65 years of age [6]. Similar increases in CDI incidence and severity were noted contemporaneously worldwide and were subsequently shown to be due to the 027 ribotype [7]. The 027 ribotype is considered a hypervirulent strain due to its increased production of toxins A and B, resistance to fluoroquinolone, and the production of a newly

discovered toxin, designated binary toxin [8]. High recurrence rates and treatment failures with metronidazole and vancomycin are commonly encountered.

The massive burden of illness caused by these outbreaks led to intensive efforts by healthcare personnel to contain the spread of CDI. These involved a multi-faceted approach combining prudent antibiotic use (in particular, limiting the non-judicious prescribing of the most commonly implicated antibiotics), and careful attention to infection prevention and control precautions (including prompt isolation of patients with diarrhea and increased attention to hand hygiene and environmental cleaning).

Changing epidemiology

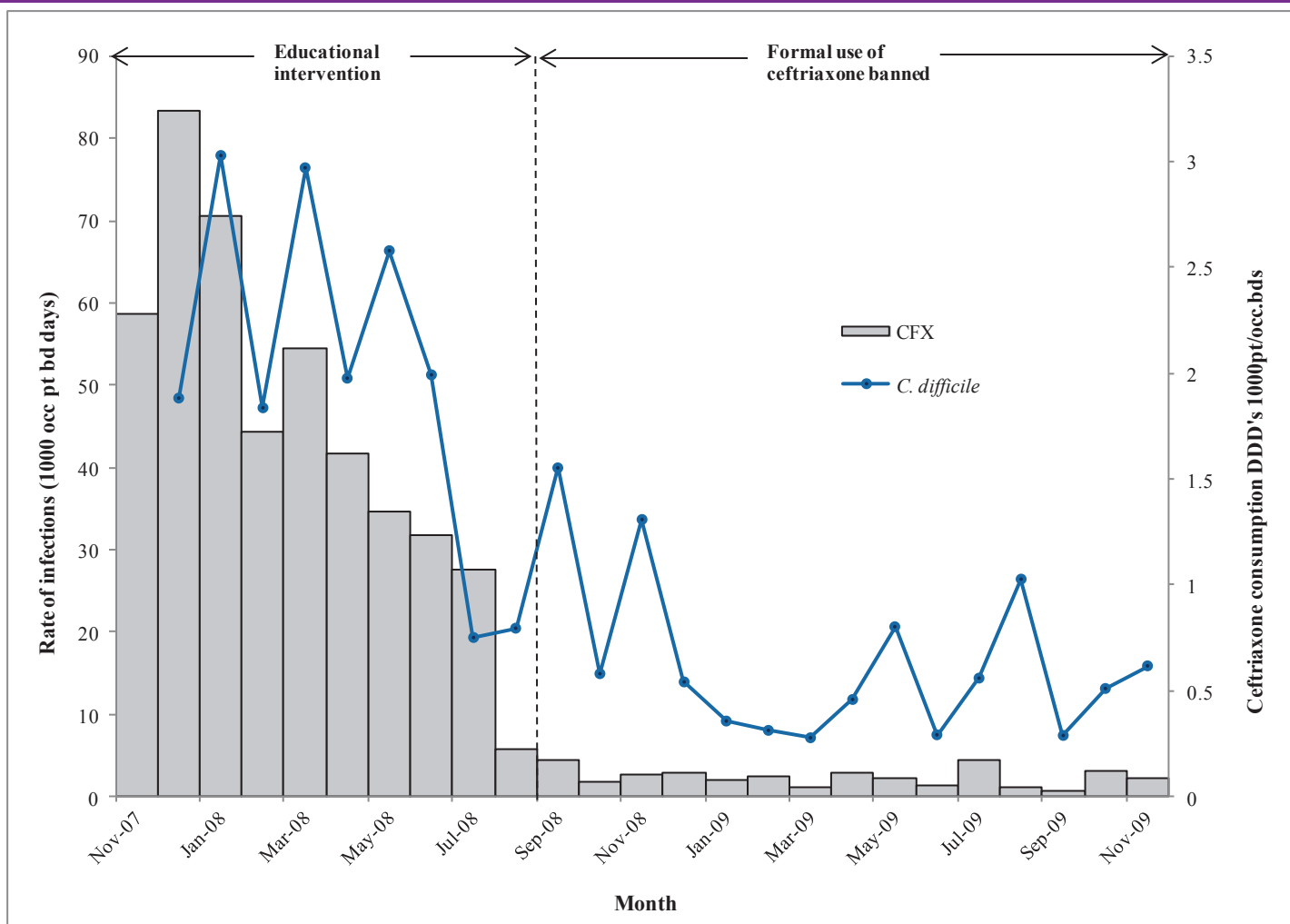
CDI has long been regarded as a consequence of hospitalization, but this view can no longer be upheld. Increasing evidence of community-onset CDI is emerging, with some reports showing that up to 40% of CDI is occurring in low risk populations (i.e. younger and fewer co-morbidities) without hospital exposure. These community onset cases differ in their epidemiology and presentation, with less severe infection being a prominent feature [9-11]. Nonetheless the proportion of CDI attributable to this cohort is significant and merits further investigation. Whether these cases represent a “spill-over” of infection from the hospital, or whether the reservoir is the community itself, remains to be elucidated. *C. difficile* and its spores are ubiquitous in the environment and carriage among many animals (both domestic and wild) has been demonstrated [12-15].

Utility of antimicrobial stewardship programs

Prudent antimicrobial prescribing has been shown to be an essential element in reducing CDI [16-18]. Most emphasis has been on the restricted use of the antibiotics most frequently

“Restrictive antibiotic policies limiting the use of ciprofloxacin and ceftriaxone, in conjunction with educational campaigns, have been proven to be successful at reducing-hospital acquired CDI.”

Figure 1. Reduction of *C. difficile* infection as a result of antibiotic stewardship intervention



Source: Adapted from Dancer, et al. [20]

implicated in CDI, such as the fluoroquinolones, clindamycin and cephalosporins. Examples of such initiatives include the “4C” campaign of the Scottish Antimicrobial Prescribing Group, which specifies restricted prescribing of the “4C” antibiotics, i.e., cephalosporins (esp. third generation), co-amoxiclav, ciprofloxacin (and other quinolones) and clindamycin [19]. Restrictive antibiotic policies limiting the use of ciprofloxacin and ceftriaxone, in conjunction with educational campaigns, have been proven to be successful at reducing-hospital acquired CDI [20]. In order to achieve a sustained reduction of CDI, it is imperative that antimicrobial stewardship programs encompass both community as well as hospital patients.

New treatment options

The mainstay of *Clostridium difficile*-associated diarrhea (CDAD) treatment has been either oral metronidazole or oral

vancomycin. Treatment failures and recurrences of up to 30% have been described with the use of both of these agents, and concerns exist regarding the emergence of vancomycin-resistant enterococci as a consequence of oral vancomycin therapy. A newly licensed agent showing promise, especially in the management of recurrent CDI, is fidaxomicin. It is a novel macrocyclic antibiotic which has little effect on normal bowel flora. Following first recurrence of CDI, fidaxomicin has been shown to be superior to vancomycin in preventing a second recurrence for up to 28 days, while achieving similar initial clinical response rates [21].

Fecal transplant is another modality that aims to restore the normal fecal flora by administering a sample of healthy donor stool. While unpalatable, it has a reported success rate of 91% [22] and may be especially useful in treating recurrent cases. Immunoglobulin therapy is still occasionally used, but there are currently no randomised controlled trials to support its use.

Conclusion

In summary, tackling CDI still remains a challenge, but can no longer be viewed as a problem confined to the acute health care sector and hospital environment. The increase of community-onset disease highlights the necessity for antimicrobial stewardship programs to involve primary care. Newer treatments such as fidaxomicin show promise, but the mainstay of CDI management remains the old adage “prevention is better than cure”. This is best achieved through prudent antimicrobial prescribing, in particular, judicious use of antibiotics known to be especially associated with CDI and careful adherence to infection prevention and control guidelines when cases arise.

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A risk-stratified algorithm for treating CDI

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Clostridium difficile infection (CDI) is a common hospital-acquired infection that has a significant morbidity, mortality, and financial burden on our healthcare system [1,3]. Epidemiologic surveillance suggests that 0.5-1.5% of hospitalized patients develop CDI; however these estimates are conservative, as the estimates are almost a decade old and the incidence of CDI is on the rise. Furthermore, this disease only became a reportable condition as of 2013, and historical surveillance studies may be subject to under-reporting bias [3,4]. The burden of CDI exists not only in its incidence as approximately 20% of initial cases will experience a recurrence [5, 7]. As the Centers for Medicare and Medicaid Services begin to withhold payment readmissions, readmission for CDI (primary or recurrent) can have significant financial implications to hospitals, depending on the index admission diagnosis. To mitigate the clinical and financial risks associated with this condition and its recurrences, a risk-stratified CDI treatment algorithm was developed at Tufts Medical Center (Figure 1).

The Tufts Medical Center CDI Treatment Algorithm was developed by a multidisciplinary group of physicians, pharmacists, and microbiologists. There were representatives from various medical and surgical disciplines, including infectious diseases, hematology / oncology, and critical care. This team incorporated consensus guidelines, published literature, clinical expertise, and internal research data to substantiate their recommendations [1, 2, 8].

The development of this algorithm has met with several barriers. Although consensus guidelines have been published recently, the recommendations within them are based on antiquated data [1, 9, 10]. Given the frequency with which CDI occurs and the evolving nature of this condition, there is a paucity of contemporary prospective, randomized, controlled data, with a heavy dependence on expert opinion. The decision

to utilize vancomycin over metronidazole for severe disease is based on recent reliable evidence[11]. However, treatment options for other clinical scenarios like toxic megacolon, ileus, or hemodynamic instability have only been assessed retrospectively and published in case reports [12, 13].

Assimilating new approaches

Financial constraints have impacted the decision to use new high-cost agents, like fidaxomicin. With fidaxomicin's potential to reduce the risk of recurrence and the looming financial penalty of readmission, the algorithm prudently incorporated this agent in the population at highest risk for recurrence [6]. Given its cost, the use of this agent will be closely monitored with prospective authorizations and retrospective evaluations to avoid misuse.

Stool transplantation is an innovative therapeutic option, and prospective data to support the beneficial outcomes of this procedure were recently published [14]. There are, however, some legal, clinical, and operational hurdles that must be overcome prior to successfully transplanting stool. In light of the new

data supporting this procedure, its role at our institution will be assessed for future iterations of the Tufts CDI Treatment Algorithm.

Given the heterogeneity of CDI presentations, medical centers are encouraged to develop treatment algorithms for their practitioners that incorporate various patient-specific factors. There are multiple treatment modalities for CDI and unique clinical situations when each of those therapies may be most appropriate. Consideration should be provided to both medical and surgical options, as well as novel drugs (fidaxomicin tablets), delivery methods (vancomycin rectally), and biologics (stool transplant). Providing institutional guidance via a hospital algorithm may improve the quality of care consistently and systematically.

“Consideration should be provided to both medical and surgical options, as well as novel drugs... delivery methods...and biologics...”



CLOSTRIDIUM DIFFICILE TREATMENT ALGORITHM

SEND STOOL FOR TOXIN IF CLINICAL CRITERIA FOR C. difficile INFECTION EXIST

- >3 loose stools in past 24 hours **OR** ileus **AND** other causes of diarrhea were ruled out (stool softeners, recent oral contrast)

STEP 1: CONTAIN AND PREVENT COMPLICATIONS

- **Initiate modified contact precautions**
- **Discontinue anti-motility agents**
- **Discontinue unnecessary concomitant antibiotics**

STEP 2: START EMPIRIC TREATMENT WHEN INDICATED

- Severely ill (hemodynamic instability **OR** ileus **OR** toxic megacolon)
Oral vancomycin 500 mg every 6 hours with IV metronidazole 500 mg every 8 hours
- Signs of ileus (decreasing stool output, absence of bowel sounds, ileus on imaging):
Add vancomycin PR 500 mg in 100 mL NS every 6 hours as a retention enema
- Toxic megacolon **OR** hemodynamic instability:
Obtain urgent surgical consultation for consideration of colectomy
- Not severely ill but C. difficile infection is **HIGHLY SUSPECTED**
 - C. difficile infection in past 12 months, age ≥70 years, **OR** creatinine clearance ≤60 mL/min: **Start oral fidaxomicin 200 mg every 12 hours (Call AMT for fidaxomicin approval)**
 - No history of C. difficile infection, acute onset of diarrhea in the hospital, **AND** WBC > 20,000 cells/μL or immunocompromise:
Start oral vancomycin 125 mg every 6 hours
- **IN ALL OTHERS: DO NOT START EMPIRIC THERAPY UNTIL TOXIN RESULTS ARE KNOWN**

STEP 3: **TOXIN NEGATIVE: DO NOT TREAT AND STOP EMPIRIC THERAPY**

TOXIN POSITIVE: TREAT BASED ON SEVERITY AND RISK OF RECURRENCE

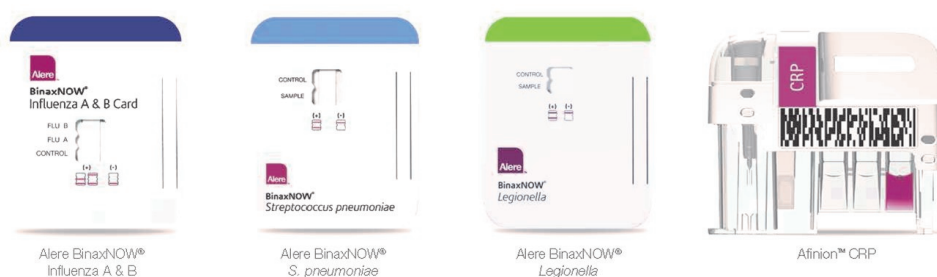
- If severely ill (hemodynamic instability **OR** ileus **OR** toxic megacolon)
Continue oral vancomycin 500 mg every 6 hours with IV metronidazole 500 mg every 8 hours
- Signs of ileus (decreasing stool output, absence of bowel sounds, ileus on imaging):
Add vancomycin PR 500 mg in 100 mL NS every 6 hours as a retention enema
- Toxic megacolon **OR** hemodynamic instability:
Obtain urgent surgical consultation for consideration of colectomy
- C. difficile infection in past 12 months, age ≥70 years, **OR** creatinine clearance ≤60 mL/min:
Start oral fidaxomicin 200 mg every 12 hours (Call AMT for fidaxomicin approval)
- If no C. difficile infection in past 3 months and minimally symptomatic (diarrhea <5 episodes in past 24 hours **AND** minimal cramps **AND** WBC < 10,000 cells/μL):
Start oral metronidazole 500 mg every 8 hours
- In all other patients:
Start oral vancomycin 125 mg every 6 hours

IF HISTORY OF >2 EPISODES OF C. difficile INFECTION IN THE PAST 3 MONTHS OR IF THE PATIENT DETERIORATES DESPITE APPROPRIATE THERAPY: CONSULT INFECTIOUS DISEASES

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A case study for cleaning, disinfection, and process compliance: reducing transmission of *C. difficile* in the healthcare environment

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Organisms in the genus *Clostridium* are anaerobic, gram-positive, spore-forming bacilli. There are over 90 known species, and approximately 30 are associated with human disease. *Clostridium* species have two main life stages, an actively growing vegetative form and a dormant spore form. Human diseases associated with these organisms are primarily toxin-mediated. Vegetative forms of the organism produce toxins during growth. The spore form is of particular importance due to its protection of the organism, conferring extreme longevity in the inanimate environment, and resistance to many disinfectants [1, 2].

Clostridium difficile is the most important of the clostridia associated with health-care-acquired infections. *Clostridium difficile* infection (CDI) is produced when the spore form of the organism germinates into the vegetative form and produces toxins. The importance of CDI in the USA is underscored by the 14,000 deaths and over \$1 billion in excess healthcare costs each year [3].

The pathway for a person to get CDI is complicated. Many risk factors for acquisition of CDI have been reported, including antimicrobial use (particularly with broad-spectrum antibiotics), advanced age, gastric acid inhibitors, and prolonged hospitalizations [4]. The first step in CDI is for a person to become colonized with the organism. This occurs when the person comes into contact and ingests the organism (typically the spore form). Next, the organism must be able to establish residence in the colon, which is often due to a reduction in the normal gastrointestinal bacteria (e.g., via antibiotic use). Finally, the spore must germinate into the vegetative form and produce toxins. These toxins attack the colonic epithelial cells, producing diarrhea, colonic pseudomembranes, toxic megacolon, and sometimes death.

Interventions for preventing CDI are critical, particularly in the

healthcare environment where the organism can be transmitted to other patients. Some of our research has investigated methods to limit the bioburden of spores in the healthcare environment. *C. difficile* spores can survive for extremely long periods of time outside of a host, thus presenting ample opportunity for transmission to any patient entering the facility, as well as to healthcare staff and visitors. For example, *C. difficile* has been identified on various surfaces in rooms of patients with CDI, in rooms of patients colonized (asymptomatic) with the organism, and in rooms where the previous patient had CDI. [5] Once the environment has been contaminated with this organism, transmission can readily occur.

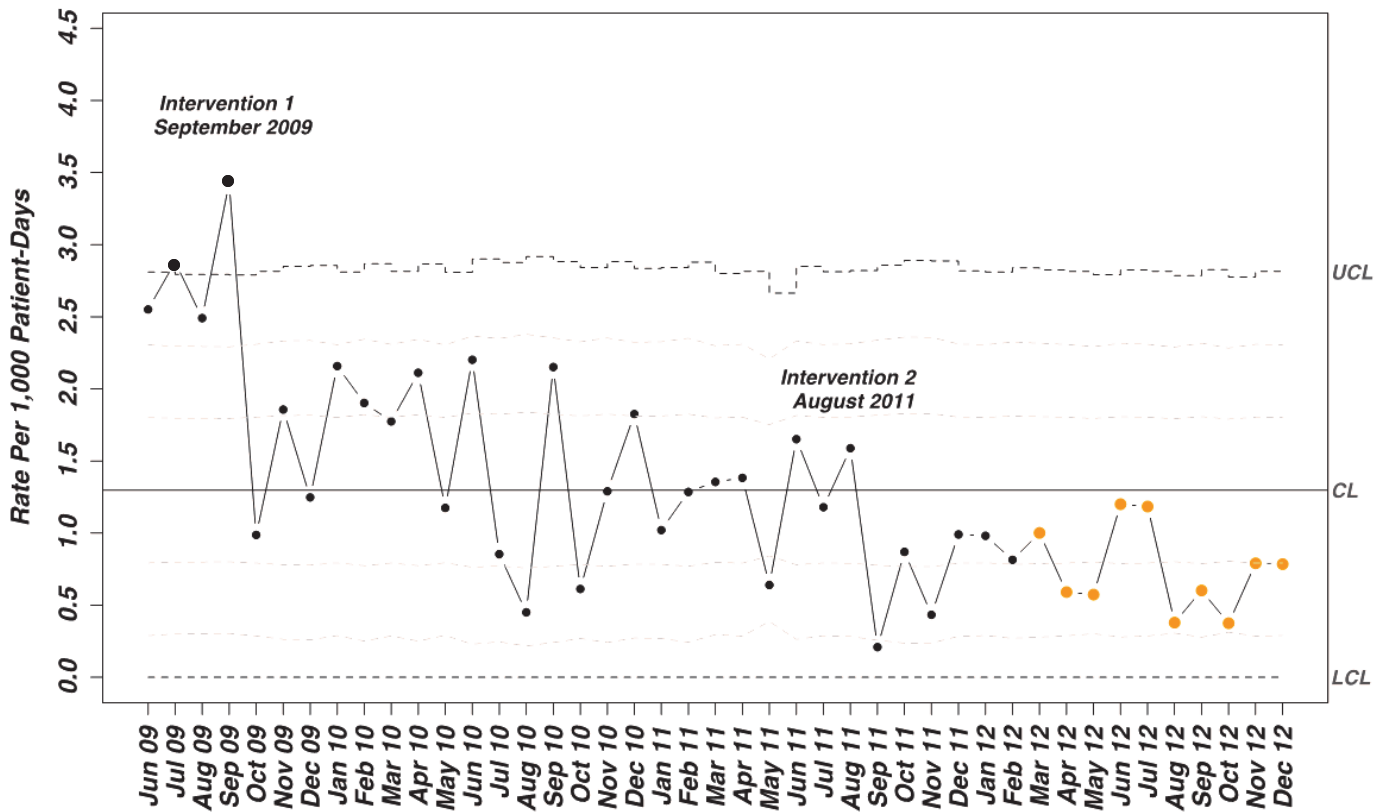
“The importance of CDI in the USA is underscored by the 14,000 deaths and over \$1 billion in excess health-care costs each year.”

Although many disinfectants are capable of killing the vegetative form of the organism, there are currently very few disinfectants capable of killing *C. difficile* spores. The Centers for Disease Control and Prevention recommend using 10% sodium hypochlorite (bleach) solutions

[5]. However this practice can be difficult to implement in healthcare. The major difficulties are: 1) dilution must be highly regulated, ensuring a 1:10 dilution, 2) once mixed, the diluted solution becomes inactivated in 24 hours, requiring tight control of dilution, and 3) areas must be cleaned with a detergent prior to disinfection with sodium hypochlorite, as it is inactivated by organic materials. Recently, novel “one-step” products containing detergents and disinfectants have been produced that eliminate the need to dilute the product, increase the longevity of the solution, and simultaneously, clean and disinfect in only one step. These products may be a better choice than household bleach when hypochlorite cleaning and disinfection is needed.

Our group experienced an outbreak of CDI in one of our local hospitals during the summer of 2009, and quickly began to experiment with different mechanisms of environmental disinfection. Initially, a quaternary ammonium product was

Figure 1. C. difficile management with disinfection interventions



Intervention 1 = daily and terminal disinfection of *C. difficile*-positive rooms with sodium hypochlorite; **Intervention 2** = replacement with a one-step sodium hypochlorite cleaner/disinfectant. Gray dots denote ≥ 8 points below the mean; UCL and LCL = upper and lower control limits, respectively.

used for disinfection in the facility. Since this disinfectant does not have activity against *C. difficile* spores, we instituted daily and terminal disinfection with sodium hypochlorite in all rooms of patients with CDI (Figure 1, Intervention 1). Environmental services staff were notified that the room required hypochlorite disinfection by placing a large, laminated letter “C” on the door by the contact isolation sign. Only the environmental services worker was allowed to remove the “C”, and the sign was only taken down after terminal cleaning of the room. While we experienced some success in the months after institution of this protocol, we felt that the rates were still too high and we presented risk of spiraling into another outbreak.

In August of 2011 (Figure 1, Intervention 2), we identified a number of process issues related to the hypochlorite solution—namely, difficulty in maintaining control over proper dilution, and use of the product past 24 hours post-dilution. To combat these issues we instituted a one-step sodium hypochlorite cleaner/disinfectant that did not require dilution. Only after introducing the one-step undiluted product did we achieve

sustained reductions and limited variation in our rates. These reductions are indicated by the special-cause variation noted in Figure 1 (gray points, criteria ≥ 8 points below the mean). From October 2009 to July 2011, there were 79 cases of CDI and 48,694 patient-days at risk. From August 2011 to December 2012, there were 93 CDI cases and 83,631 patient-days at risk. This reduction was statistically significant ($P=0.014$, Mid-P exact test).

Our experience highlights the importance of not only the proper cleaning and disinfectant product, but choosing a product that enables proper “process compliance”. Process compliance, such as correct dilution, eliminating “double-dipping” of a cloth into a clean disinfectant bucket, choosing cloth or microfiber rags that are compatible with the disinfectant, appropriate cleaning prior to disinfection, and regularly switching rags during a cleaning process are absolutely critical steps in ensuring organisms are killed and not merely relocated to other areas of the facility via the process of cleaning and disinfection.

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Diagnosis of *C. diff*: the relevance of testing and clinical outcomes

Glenn S. Tillotson, PhD, FIDSA, FCCP, FISC

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Clostridium difficile (*C. difficile* or *C. diff*) causes approximately 25% of cases of antibiotic-associated diarrhea and most instances of pseudomembranous colitis [1]. *C. difficile* has been associated with many outbreaks of diarrheal disease in the healthcare setting, including nursing homes and other residential facilities. *C. difficile* infection (CDI) is a toxin-mediated intestinal disease. Clinical presentation can range from asymptomatic colonization, to mild diarrhea and more severe illnesses including abdominal pain, fever and leukocytosis. Severe complicated or fulminant CDI is characterized by pseudomembranes in the colon with possible complications including toxic megacolon, sepsis, bowel perforation, septic shock and death. *C. difficile* continues to be a challenging disease to diagnose and manage. The Infectious Diseases Society of America and the Society of Healthcare Epidemiology of America are currently reviewing their guidelines for the management of CDI that were published in 2010, and the UK Department of Health recently completed a large study focusing on diagnostic testing and clinical outcomes [2,3].

Testing criteria and methodology

Testing for *C. difficile* should only be conducted on unformed, diarrheal stool samples. A rare exception to this would be patients with severe infection manifesting as ileus when no stool is produced, but such cases must be tested in conjunction with a clinician. Equally important is not testing specimens for a “test of cure” in treated patients, as patients may be asymptomatic carriers, but not infected.

There are six broad categories of *C. difficile* testing methods (Table 1). Toxigenic culture and cell cytotoxin assays are considered the “best” methods. The toxigenic culture method has some benefits; however, the main issue with this test is that only toxigenic bacteria are isolated, not whether disease is actually present; whereas the cell cytotoxin assay demonstrates the presence of *C. difficile* toxins thus active disease. For the purposes of this article I will focus on three methods to discuss in more detail; glutamate dehydrogenase (GDH), toxin enzyme

immunoassays (EIA) and nucleic acid amplification tests (NAAT).

Table 1. *C. diff* testing methods

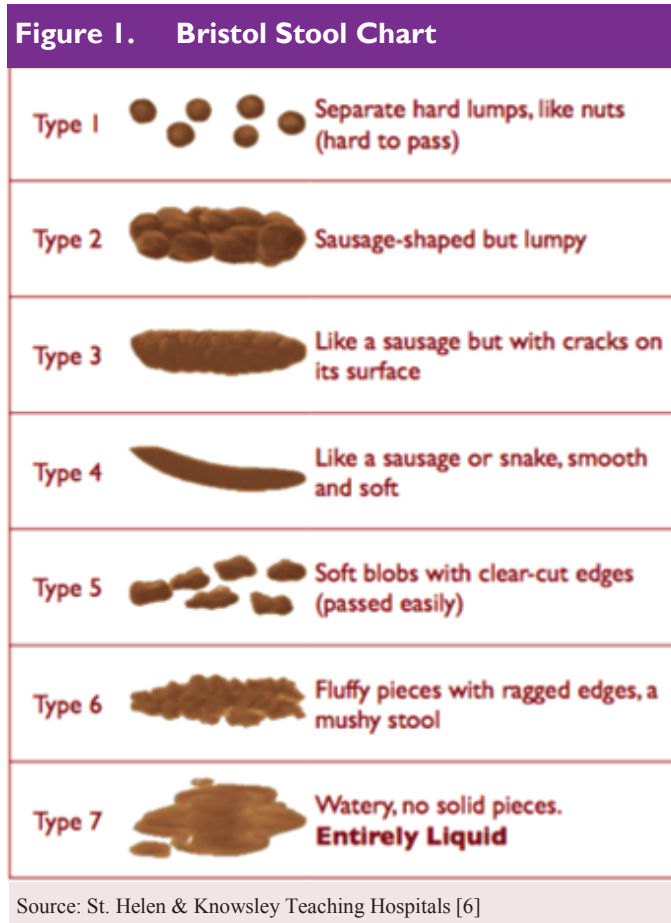
<i>Clostridium difficile</i> toxin	Cell cytotoxin assay (CTA) ¹
	Enzyme immunoassay (EIA)
<i>C. difficile</i> (organism only)	Bacterial culture
	GDH antigen detection
Toxigenic <i>C. difficile</i> (gene)	Cytotoxigenic culture
	Nucleic acid amplification test (NAAT) e.g., polymerase chain reaction (PCR)

¹ also known as the cell cytotoxicity assay (CTA)

GDH is an enzyme common to all *C. difficile* bacteria and is used as a marker in stool. The introduction of solid phase GDH tests yielded sensitivities and negative predictive values up to 100% versus toxigenic culture [4]. However, as the GDH assay detects both toxigenic and non-toxigenic strains of *C. difficile*, it is essential to combine this test with a toxin-specific assay. A key benefit for GDH is the ability to report *C. difficile*-negative stools immediately to clinicians. Enzyme immunoassays (EIAs) have been the basis for many microbiological and other antigen detection methods over the past 20 years—they are quick, convenient and easily interpreted; however, they have been shown in the case of *C. difficile* toxin EIA to lack some sensitivity, which can range from 60-81%, with a specificity of 91-99.4% [5]. Investigators have confirmed the limitations of use of EIA for toxin alone. Outcome data showed there were no CDI-related adverse events in patients who were reported as negative by Toxin A/B EIA, yet were positive by other assays [4].

NAAT, also known as molecular tests, are a group of assays that amplify a gene encoding for toxin, but do not detect toxin directly. Several assay systems are currently cleared by the FDA, including polymerase chain reaction (PCR) and isothermal methods. As these tests detect genes for Toxin B or

in some cases Toxin A, they have very high sensitivity for identifying the presence of *C. difficile*. However, the inability to detect toxin production limits their ability to differentiate active disease versus asymptomatic carriage and may present a misleading positive result, which could lead to inappropriate therapy and infection control measures.



Thus no method is perfect and all assays must be undertaken in accordance with clear clinical rules concerning diarrheal disease, i.e., the stool must match Bristol Stool Chart types 6-7 and conform to the shape of the container, and the patient must pass 3 or more unformed stools in a 24-hour period [7]* (Figure 1). These criteria are critical in understanding the reported results for *C. difficile*.

Evaluating methodologies—the UK study

So, how does one choose the best test for your institution, bearing in mind costs, personnel, clinical needs, etc.?

In 2012 the United Kingdom Department of Health published its updated guidance on the diagnosis and reporting of *C. difficile* [3]. Assays were selected to represent the three main *C.*

difficile detection choices in use in the UK, namely toxin EIA, toxin gene NAAT /PCR, and GDH EIA. Four laboratories were involved in the largest study of this type, with over 12,000 stool samples collected between October 2010-September 2011. Samples were examined by two reference methods (cell cytotoxicity assay [CTA] and cytotoxigenic culture [CC]) and compared with four commercially available tests: *C. difficile* toxin EIA (Premier Toxin A+B [Meridian Bioscience] and TOXIN A/B II [TechLab, Alere]), GDH detection by EIA (*C. DIFF CHEK-60* [TechLab, Alere]) and toxigenic *C. difficile* using PCR GenXpert *C. difficile* [Cepheid]. The authors conducted sensitivity and specificity as well as positive and negative predictive value analyses (PPV and NPV) and uniquely compared the results to individual clinical outcomes, thus putting the data into context [8].

From 10,691 patients, a total of 12,420 samples were examined. These yielded 7,853 results from 6,524 in-patients. Of these, 5,880 were negative by *both* CC and CTA tests. The overall results of the “standard tests” are shown in Table 2. Mortality was significantly higher in patients with toxin present (Group 1), compared with those having *C. difficile*, but no detectable toxin (Group 2) (17% vs. 10%, $p=0.02$) and also in Group 1 vs. Group 3 (*C. difficile* negative patients) (17% vs. 9%, $p<0.001$), but there was no difference between Groups 2 and 3. Interestingly, the key clinical marker of WCC $\geq 15 \times 10^9/L$ was 26%, 15% and 13% in the three respective groups [8].

Broadly speaking *C. difficile* Toxin A/B EIAs are not suitable as standalone tests for the detection or diagnosis of *C. difficile*. Thus the DoH recommends that a 2 stage approach be adopted which incorporates GDH EIA or NAAT/PCR to screen stool samples, followed by a sensitive toxin EIA or a cytotoxin assay (note this is a much slower test) [3]. If the screening test is negative, the second test is not required. Obviously there may be some GDH positive & Toxin A/B EIA negative results where a NAAT test could be used to follow up to confirm the presence of *C. difficile* from an infection control angle, but these patients are unlikely to experience a poor patient outcome. These patients have led to the suggestion of a new diagnostic category, potential *C difficile* excretor (i.e. carrier).

Over-reporting of *C. difficile* may contribute to overuse of antibiotics. Direct detection of the toxin drives clinical outcome as the UK study showed. Also it is important to remember the basic tenet of CDI—that antibiotics drive most infections, thus their cessation is important to reduce the microbial dysbiosis and allow the normal flora to be restored.

Table 2. Mortality of *C. diff* infection groups

Test	Result	Mortality
Cell cytotoxicity assay (CTA)	+	17%
Cytotoxigenic culture (CC)	+	10%
CTA & CC	-	9%

Summary guidelines

- It is critical to only request a lab test for *C. difficile* if the patient has had **≥3 unformed bowel movements*** in the previous 24 hours. The only exception would be severely ill patients who may have ileus. Clearly physician communication is critical in these patients.
- It is essential that samples are **not** taken to establish test of cure by testing post therapy specimens due to the possibility of asymptomatic carriage.
- The treatment of carriers with antibiotics must be avoided .
- Patients diagnosed with CDI should stop any concomitant antibiotics where possible other than those to treat the CDI
- GDH is a highly sensitive test for detecting the presence of *C. difficile* bacteria, but as these organisms vary in their ability to produce Toxins A or B, a specific test for the detection of these toxins is required. A negative GDH can be reported immediately to the clinician.
- Stool samples positive for both GDH and toxin can also be reported immediately (i.e., within an hour of receipt of the specimen) to the clinical staff.
- Molecular tests, known as nucleic acid amplification tests, detect the gene encoding for the toxin, not the actual toxin itself. It is possible to detect these genes when signs and symptoms have subsided.

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**Editor’s note: Authoritative non-USA sources differ on this point. See ref.3.*

Programs to prevent *C. difficile* infection: a multiple strategy approach in Massachusetts



Susanne Salem-Schatz, ScD

Massachusetts Coalition for the Prevention of Medical Errors
For the Massachusetts Infection Prevention Partnership

Since 2007, the Massachusetts Department of Public Health has sponsored programs to support healthcare-associated infection (HAI) prevention. Hospital-based efforts led to a 25% reduction in *C. difficile* infections (CDIs) among participating facilities. Current programs address the challenge of unnecessary antibiotic use in elderly long-term care residents, decreasing an important risk factor for CDI.

Clostridium difficile is a potentially life-threatening bacterium and the most commonly recognized cause of infectious diarrhea in hospitalized patients. In the past decade, the epidemiology of *Clostridium difficile* infection (CDI) has shifted, showing evidence of increased incidence and severity. Risk factors include advanced age, exposure to antimicrobials, and hospitalization, making residents of long-term care facilities particularly vulnerable. Between 2003 and 2009 the number of discharges from Massachusetts hospitals with a discharge diagnosis of CDI increased over 40%, as did the rate per 1,000 discharges.

The Department of Health and Human Services National Action Plan to reduce healthcare-associated infections (HAIs) calls for a 30% reduction in hospital-onset CDI by 2014. Guidelines exist for the prevention of CDI in healthcare settings, but are not universally followed. To support state-level efforts to reach HAI targets, the Centers for Disease Control has made funding available for HAI prevention.

The Massachusetts Department of Public Health (MDPH) has partnered with the Massachusetts Coalition for the Prevention of Medical Errors (the Coalition) on numerous initiatives to reduce hospital-acquired infections since 2007. A two-year hospital-focused CDI prevention initiative was launched in 2009, followed by collaborations with long-term care facilities (LTCFs) (2011-2012), and most recently, a focus on decreasing inappropriate antibiotic use. This article describes our early successes and ongoing efforts to support CDI prevention in Massachusetts healthcare facilities.

25% reduction in *C. difficile* infection

The *C. difficile* Prevention Collaborative (2009-2011) brought 27 hospitals together to implement strategies to prevent transmission of hospital-acquired *C. difficile* infection (HA-CDI). By program's end we achieved a 25% reduction in HA-CDI per 10,000 patient days among participating hospitals.

The Massachusetts CDI Prevention Collaborative provided support to these facilities using a core set of change principles and strategies (Table 1).

Participating hospital teams augmented the resources offered by the Collaborative with their own commitment and creative approaches to achieve an overall 25% decrease in the rate of CDI per 10,000 patient days. The work on *C. difficile* prevention in Massachusetts healthcare facilities continues and is currently supported by Masspro as part of the 10th scope of work.

Leveraging hospital knowledge to create cross-continuum collaborations and focus on antibiotic use

In 2011 the Massachusetts Infection Prevention Collaboration expanded to include the Massachusetts Senior Care Association. With this new partnership we extended our CDI prevention work to include the state's LTCFs. With traditionally fewer resources than their hospital counterparts, representatives of the long-term care community have actively and enthusiastically engaged in this work.

In initial work with LTCFs, the challenges of antibiotic stewardship came to the fore, since antibiotic use is an important risk factor for *C. difficile* infection in the elderly. These challenges are heightened when long-term care residents move back and forth between hospitals and their facilities.

With additional CDC funding, the current Massachusetts initiative (2012-2013) brings together improvement teams from 31 LTCFs and 10 hospital emergency departments. The focus

Table 1. Principles and strategies for reduction of CDI

Principle	Strategy
Lasting change is facilitated when a broad range of staff roles are included in the work from the beginning.	Encouraged creation of multidisciplinary improvement teams, including representatives from infection prevention, nursing, quality improvement, clinical leadership, microbiology, pharmacy and environmental services.
Sustainable change is enhanced through a combination of shared best practices and local modification	Provided a common set of practice and policy recommendations for surveillance, testing, isolation, hand hygiene, contact precautions, and environmental cleaning and disinfection
Quality improvement approaches should include a combination of shared learning and site-based learning through small tests of change	Programming included: three statewide full-day learning and sharing workshops, regional workshops featuring expert presentations and accomplishments of Collaborative participants, list serve access, and regular communication with team leaders, and coaching as needed.
Front-line staff engagement in identification of barriers and potential solutions enhances lasting change	In addition to traditional quality improvement training approaches that would include best practices in infection prevention and a framework and tools for quality improvement, specific strategies for engaging front-line staff in improvement work were offered.
Program support should be responsive to the needs of participants	Periodic one-one phone conversations and group coaching calls identified challenges. For example, an interest in antibiotic stewardship led to the creation of an informal workgroup and conference calls with a CDC expert.
Ongoing review of data is essential to quality improvement activities	Participants tracked rates of healthcare-acquired <i>C. difficile</i> infection, using the CDC’s NHSN definition. An Excel workbook was distributed for data entry that also created run charts showing progress over time that could be shared with facility teams.

of this work is to reduce inappropriate testing and treatment of urinary tract infection (UTI) in elderly LTCF residents.

The challenge

About one-third of antibiotic use in long term care residents is prescribed for the treatment of urinary tract infection; much of this may be unnecessary [1]. Up to half of elderly LTCF residents have asymptomatic bacteriuria [2], that is, bacteria in the urinary tract without an active infection. National medical specialty society guidelines recommend that a UTI be diagnosed, for most of the population, only when specific symptoms in addition to a positive culture are present [3].

A continued widespread misunderstanding exists among those who care for the elderly—that many non-specific symptoms, such as change in mental status, fatigue, or falls, are likely due to urinary tract infection. Consequently, the elderly with no specific symptoms of UTI are being treated on the basis of a positive culture. This practice persists, despite research that clearly demonstrates no benefit from treating residents with asymptomatic bacteriuria. The American Geriatric Society recently listed *giving antibiotics for asymptomatic bacteriuria* as one of the top five things clinicians and patients should question [4].

Our approach (Table 2)

Similar to the CDI prevention learning collaborative, we are encouraging participating facilities to:

- Create multidisciplinary teams
- Attend regional workshops, webinars and conference calls
- Engage leadership and include front-line staff in identifying barriers and developing solutions
- Use a quality improvement framework and tools
- Enhance communication within facilities, and encourage increased understanding, trust and communication between ED providers and staff in long-term care facilities
- Track core measures using interactive Excel workbooks

To address knowledge gaps and ongoing myths on this topic we have added the following features:

- Education for improvement teams on:
 - Increasing risks of antibiotic use, for individuals and the broader community
 - High prevalence of asymptomatic bacteriuria in

Table 2. Strategies for CDI prevention

Changes teams made to prevent CDI	How teams made change
<p>Most frequent areas for improvement included:</p> <ul style="list-style-type: none"> ● Cleaning and disinfection (71%) ● Timing and communication around lab test ordering (71%) ● Consistent use of contact precautions (57%) ● Hand hygiene (21%) ● Patient placement (14%) 	<p>Improvement approaches included:</p> <ul style="list-style-type: none"> ● Combining leadership support with front-line staff participation for a top-down/bottom-up approach ● Reinforcing training and education in infection prevention practices ● Improving communication on test results and contact precautions ● Enhancing culture of infection prevention through on-going conversation, review of data, and distinctive signage and videos.

- LTCF residents
 - Myths and facts regarding signs and symptoms of UTI in this population
- Development and distribution of materials and tools to support facility efforts
 - Graphic clinician education sheets (using an *Academic Detailing* approach) for both LTCF and ED prescribers and nurses
 - ◆ are based on social science principles of adult learning and behavior change
 - ◆ address common myths and facts
 - ◆ recommend alternatives to testing when appropriate
 - ◆ acknowledge both clinical and non-clinical influences on testing and treatment.
 - Educational pamphlets for LTCF residents/families, and ED visitors/families:
 - ◆ address importance of prudent antibiotics in the elderly
 - ◆ include a UTI-specific information sheet
 - UTI protocol for LCTFs
 - ◆ Provides decision support tool for urine testing and treatment
 - ◆ Enhances communication between nursing staff and prescribers

This program runs through July 2013. Practice support tools are available on the website of the Massachusetts Coalition for the Prevention of Medical Errors. <http://macoalition.org/evaluation-and-treatment-uti-in-elderly.shtml>

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APIC updates guidelines for preventing *C. diff*

The Association for Professionals in Infection Control (APIC) has released a [new implementation guide](#) for health practitioners—the Guide to Preventing *C. difficile* Infections. The Guide presents a variety of practical strategies to reduce CDI rates, including hand hygiene, contact and isolation procedures, and environmental infection prevention. In its chapter on antibiotic stewardship, APIC cautions against using antibiotics in ways that risk overly disrupting the normal flora, urging consideration of antibiotic spectrum, duration of use, colonic uptake, anaerobic capabilities, dosage, route of administration and excretion in the bile. A new section on fecal bacteriology similarly stresses the importance of maintaining normal flora in reducing rates of *C. diff*.

The updated guidelines are timely, as findings from the [Pace of Progress survey](#), presented at the recent [Clostridium difficile Educational and Consensus Conference](#), reveal that *C. diff* prevention efforts are not working. The nationwide survey conducted in January 2013 revealed that 70% of infection preventionists adopted additional interventions to address CDI since March 2010, but only 42% have seen a decline in CDI rates at their facilities over the past three years; 43% have seen no change. In addition, the survey noted inconsistencies between cleaning efforts and monitoring.

Fecal transplants offer alternative for fighting recurrent *C. diff*

Recurrent *C. diff* is a recalcitrant infection with high failure rates for antibiotic therapy. A recent clinical trial reports the promising use of fecal transplants as an alternative to conventional antibiotics. The trial compared a standard vancomycin regimen against a regimen with vancomycin (followed by bowel lavage) and a subsequent infusion of a solution of donor feces administered through a nasoduodenal tube. The trial was halted early due to the overwhelming success of the transplants. At least two other trials are now underway in Canada and in the [United States](#) (where transplants are done via colonoscopy). Leaders in gastroenterology are advocating to make fecal transplants mainstream, and also the primary treatment for *C. diff* and other gut disorders.

However, the use of human feces carries the risk of harmful pathogens, prompting Canadian microbiologists in Guelph, Canada to formulate a synthetic, ‘super-probiotic’ dubbed [RePOOPulate](#). Grown in ‘Robo-gut’ equipment at Dr. Allen-Vercoc’s lab from purified intestinal bacteria, the artificial feces mimic the kind made in human intestines, but offer a safer, more stable alternative.

Dedicated cleaning staff shown to reduce *C. diff* in hospitals

New research finds that a dedicated daily cleaning crew who clean and disinfect rooms contaminated by *C. difficile* reduces the risk of infection. Out of the three disinfecting intervention sequences including fluorescent markers and automated UV radiation, the implementation and use of an enhanced disinfection process and dedicated disinfecting team is shown to be the most effective. Disinfection was dramatically improved with the addition of enhanced standard disinfection process and supervisory assessment. The study is published in the May issue of *Infection Control and Hospital Epidemiology*, in a special edition focused on the role of the environment in infection prevention.

Canadian stewardship program reduces *C. diff* rate and drug costs

An antimicrobial [stewardship team](#) formed at Lakeridge Health Hospital in Ontario, Canada reports positive results from its program aimed at reducing antibiotic overprescription, *C. diff* rates, and drug costs. Started in the hospital’s critical care unit in November 2011, the program has since been introduced to two other medical units that previously had high *C. diff* rates. Results have shown a 30% decrease in antibiotic use, a 42% decrease in drug costs, and a 90% reduction in the *C. diff* infection rate hospital-wide.

CDI risk rises with antihistamine use

Mayo Clinic researchers have found that patients receiving antihistamines to suppress stomach acid are at greater risk for *C. diff*. The [study](#) highlights the need for the prudent use of antihistamines, and that reducing the use of these drugs could significantly reduce the risk of CDI. Although the study linked the drugs to a higher risk of CDI, it did not establish a cause-and-effect relationship.

Elements of an infection control program

Multidrug-resistant organism (MDRO) transmission

Dr. Stuart Levy, Bonnie Marshall (APUA)
M. Srikanth, MSc., SA Broaders, PhD (Clorox Services Co)

Implementation of, and adherence to, infection control practices are keys to preventing the transmission of infectious diseases caused by MDRO in all healthcare facilities.

Hand Hygiene – As part of hand hygiene precautions, the following procedures should be followed:

- Wash hands with soap and water when they are visibly dirty or soiled with blood or other body fluids. If hands are not visibly soiled, an alcohol-based hand sanitizer may be used.
- Avoid wearing artificial fingernails, and keep natural nail tips less than 1/4-inch long.
- Wear gloves when contact with blood, mucous membranes, non-intact skin, or other potentially infectious materials could occur.

Appropriate Antibiotic Use – The appropriate and prudent use of antibiotics is a key component in controlling MDRO. The CDC provides guidance for judicious use of antimicrobials and tools for implementation [1]. This effort focuses on effective antimicrobial treatment of infections, use of narrow-spectrum agents, avoiding excessive duration of therapy and restricting use of more potent antibiotics to the treatment of serious infections [2].

Environmental Measures – The CDC recommends cleaning and disinfecting surfaces and equipment that may be contaminated with pathogens, including those that are in close proximity to the patient and frequently touched surfaces in the patient care environment [3].

- Routine cleaning procedures should be reviewed along with assessment of the need for additional trained cleaning staff.
- Staff's adherence to routine cleaning procedures should be closely monitored, and best practices be reinforced to promote consistent and correct cleaning.
- Room cleaning of patients on contact precautions should be prioritized. Bath tubs, whirlpools, and hydrotherapy tubs should be cleaned and disinfected after each use.

EPA-registered disinfectants or detergents/disinfectants (such as sodium hypochlorite and quaternary ammonium chloride disinfectants) that best meet the overall needs of the healthcare facility for routine cleaning and disinfection should be selected [4, 5].

Standard Precautions/Transmission-Based Precautions – These require the use of work practice controls and protective apparel for all contact with blood and body substances, and airborne infection isolation, droplet, and contact precautions for patients with diseases known to be transmitted in whole or in part by those routes [6].

Administrative Measures – Interventions include providing the appropriate number and placement of hand washing sinks and hand sanitizer dispensers, maintaining appropriate staffing levels and enforcing adherence to recommended infection control practices.

Education – Patient care and environmental services staff should receive education and training regarding MDRO and the importance of transmission prevention.

Surveillance – Surveillance should include maintaining a confidential line listing of residents colonized and/or infected with targeted MDROs. Monitoring culture and antibiotic susceptibility data will help determine baseline rates for MDROs in a facility, indicate the occurrence of increased transmission, and monitor the effectiveness of outbreak control measures [7].

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APUA headquarters in action

USA Today features APUA in “Patient Safety” awareness campaign

APUA is pleased to be included in the patient safety awareness campaign launched by *USA Today*. On newsstands the weekend of March 29, the special insert section included information and articles that explain the challenges in patient safety, the different actors involved, and how consumers can acquire healthcare knowledge. APUA commented on bacterial evolution and prevention methods for combating drug-resistant bacteria. See the [full report](#), with special attention to the article “An evolutionary arms race: the ongoing cycle of drug development and bacterial evolution” on page 8:

http://doc.mediaplanet.com/all_projects/12027.pdf

APUA President Levy identifies unique antibiotic resistance mechanism in *E. coli*

Dr. Levy, in collaboration with a team of microbiologists in Boston and Beijing, has identified the unique resistance mechanisms of a clinical isolate of *E. coli* resistant to carbapenems. The study was published in the April issue of *Antimicrobial Agents and Chemotherapy*. “We knew that bacteria could resist carbapenems, but we had never before seen *E. coli* adapt so extensively to defeat an antibiotic,” says Dr. Levy. “Our research shows just how far bacteria will go with mutations in order to survive.”

According to the study results, *E. coli* genetically mutated four separate times in order to resist carbapenems. Specifically, the isolate removed two membrane proteins in order to prevent antibiotics from getting into the cell. The bacteria also carried a mutation of the regulatory protein *marR*, which controls how bacteria react in the presence of antibiotics. The isolate further achieved resistance by increasing expression of a multidrug efflux pump. Moreover, the researchers discovered that the *E. coli* was expressing a new protein, called *yedS*, which helped the drug enter the cell, but whose expression was curtailed by the *marR* mutation. *yedS* is a normally inactive protein acquired by some *E. coli* that affects how the drug enters the bacterial cell. It is generally expressed in bacteria through a mutation.

APUA participates in R&D conference

APUA Executive Director, Kathy Young, joined more than 500 participants in the “Lives in the Balance: Delivering Medical Innovations to Neglected Patients and Populations” conference

held in New York City on December 13-14, 2012. The event attracted key actors in global health and R&D from more than 20 countries. Discussion topics included progress and shortcomings of R&D initiatives, efforts to stimulate needs-driven R&D and how to improve medical innovation and ensure access to R&D for the most neglected patients, particularly those suffering from drug-resistant tuberculosis (DR-TB), deadly neglected tropical diseases such as Chagas disease, and many vaccine-preventable illnesses. For more information about the presentations and discussions, please visit the [Lives in the Balance website](#):

<http://www.doctorswithoutborders.org/events/symposiums/2012-lives-in-the-balance/>

APUA urges NIH to invest in antibiotic resistance research

APUA has responded to an open request from the National Institutes of Health for input on research areas that deserve expanded effort for the FY 2013-2018 Strategic Plan for the Office of Disease Prevention.

APUA recommends that antibiotic resistance—a public health problem neglected by many private health research funders—should receive expanded NIH investment. Antibiotic resistant infections are a threat to patient safety in hospitals and long-term care facilities. Antibiotic resistance has been identified by WHO, CDC and IDSA as one of the top five public health threats, with an estimated cost of \$56 billion in the US. Resistant bacterial infections, while not totally preventable, can be contained. The genetics and microbiology of resistance need to be better understood in order to inform interventions, and innovative diagnostics and new antibiotics must be developed. The field also requires further investigation into better promotion and uptake of known clinical and behavioral interventions.

APUA participates in CDC’s Twitter Chat on making healthcare safer

On March 25, CDC Director Dr. Tom Frieden hosted a live [Twitter chat](#) on making healthcare safer by protecting patients from life-threatening infections. APUA posed a variety of questions, ranging from the merits of antimicrobial stewardship to the financial incentives of new drug development. A number of healthcare organizations participated in the chat, and APUA was able to foster several new connections.

2013 APUA Leadership Award nomination

APUA is now accepting nominations for the **2013 APUA Leadership Award**

The annual APUA Leadership Award has traditionally recognized an individual or organization demonstrating extraordinary leadership in promoting the prudent use of antibiotics in order to contain antibiotic resistance. This year we would like to celebrate an **outstanding professional** who has demonstrated these achievements. Consideration will be given to the fields of basic science, public policy, and clinical practice.

Find the nomination form and read about past winners of the APUA Leadership Award on our website: www.apua.org.

We look forward to your nominations, and as always, thank you for all that you do.



Professor Roman S. Kozlov M.D., M. Sc., D.Sc., recipient of the 2012 APUA Leadership Award. Dr. Kozlov and APUA-Russia, of which he is president, were recognized for their sustained activities in containing antibiotic resistance in Russia and adjacent regions, and for the establishment of a network of sentinel laboratories that conduct continuous surveillance programs of both community and hospital-acquired pathogens.

Nominate today!

Past Recipients of the APUA Leadership Award

- | | |
|--|--|
| 2012: <i>Roman S. Kozlov M.D., M.Sc., D.Sc.</i> (Young Investigator Award)
APUA-Russia (Chapter Award, R. Kozlov, pres.) | 2006: <i>Dr. Anna Lönnroth</i> of the European Research Commission Program
<i>Dr. Herman Goossens</i> of The Laboratory of Medical Microbiology, University Hospital Antwerp |
| 2011: <i>Giuseppe Cornaglia, M.D., Ph.D.</i> of the European Society of Clinical Microbiology and Infectious Diseases
APUA-Nepal (Chapter Award, <i>Kumud K. Kafle, M.D., Ph.D.</i> , pres.) | 2005: <i>Dr. Richard Besser</i> of U.S. Centers for Disease Control & Prevention |
| 2010: <i>Otto Cars, M.D., Ph.D.</i> of the Swedish Institute of Infectious Disease Control
APUA-Mexico (Chapter Award, <i>Miguel Peredo López-Velarde, M.D., Ph.D.</i> , pres.) | 2004: <i>Dr. Gabriel Schmunis</i> of The Pan American Health Organization |
| 2009: <i>Martin Blaser, MD & Neil Fishman, MD</i> of IDSA | 2003: <i>Dr. Frank M. Aarestrup and Dr. Henrik C. Wegener</i> of the Danish Veterinary Institute
<i>Robert L. Langer</i> of McDonald's Corporation |
| 2008: <i>Dr. Inge C. Gyssens, Professor Jos W.M. Van Der Meer, Professor Henri S. Verbrugh, Professor John E. Degener</i> of SWAB
<i>Professor Christina M. Vandenbroucke – Grauls</i>
<i>Professor Peter J.M. Van Den Broek</i> of WIP | 2002: <i>Dr. David Bell</i> of the U.S. Centers for Disease Control and Prevention
<i>Dr. Marissa Miller</i> of the National Institute of Allergy and Infectious Diseases at the U.S. National Institutes of Health, and
<i>Dr. Murray Lumpkin</i> of the U.S. Food and Drug Administration |
| 2007: <i>Dr. Wasif Ali Kahn</i> of The International Center for Diarrheal Disease Research, Bangladesh
<i>Sabeena Ahmed, M.Sc.</i> of Clinical Research and Service Centre, Bangladesh | 2001: <i>Dr. Rosamund Williams</i> of the World Health Organization |

Policy updates

LPAD aimed at speeding approval of new antibacterials

As described by the Infectious Diseases Society of America (IDSA), [LPAD \(Limited Population Antimicrobial Drug\)](#) is an approval pathway through which a new drug's "safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials." The proposed LPAD legislation would facilitate faster approval of badly needed new antibacterials and provides the necessary incentives for drug developers to meet the challenge. Pew's *New Pathways* conference indicated that LPAD may offer smaller companies a break since they are more challenged by regulatory hurdles of early-stage clinical trials than larger companies. It is anticipated that the expensive price tag of LPAD drugs (\$15,000-\$30,000 per treatment course) will act as a deterrent to the potential overuse that could lead to the rapid emergence of drug resistance.

New guidance issued for pediatric ear infections

The American Academy of Pediatrics has issued [new guidance](#) to help health care providers with treating uncomplicated middle-ear infections in children. Middle-ear infection is the most common bacterial illness in children and the one most often treated with antibiotics. A key goal of the updated guidelines is to reduce the overuse of unnecessary antibiotics, which is the leading cause of antibiotic-resistant bacteria. Instead, pain relievers and observation may be the best treatment options. The guidelines recommend immediate antibiotic prescriptions for children with severe ear infections (significant pain or fever of 102.2 degrees or higher), ruptured ear drums with drainage, or infection in both ears for children age 2 or younger.

MN government bans antimicrobial soap

The Minnesota Pollution Control Agency has ordered all state agencies to [stop buying antimicrobial soap](#) and other products that contain triclosan, a microbe-killing chemical that converts

to environmental toxins, such as dioxin and other carcinogens. Following years of triclosan discharge from water-treatment plants, these toxins have been accumulating in the bottom of many lakes and rivers in the state.

Recent research has also shown that degradation products of triclosan may disrupt the natural food chain. In light of the Food and Drug Administration's finding in a 2010 study that products with triclosan are no more effective than regular soap and water, the Minnesota agency decided to move forward and join a number of other governments and organizations in banning antimicrobial soap. Japan has banned the sale of consumer products with the chemical. The Kaiser Permanente medical system has stopped using them in its hospitals, and the consumer product company Johnson & Johnson is phasing out its use.

A broader attempt at phasing out the use of triclosan in household personal care products was made at the state-level, but was defeated. Additional legislative progress on triclosan will most likely have to wait until future legislative sessions.

Updates on ADUFA & DATA Acts

In March, the Senate Health, Education, Labor and Pensions (HELP) Committee released its version of the Animal Drug User Fee Act (ADUFA) without the provisions that would have required the FDA's annual reporting of antibiotic sales for use in food animal production. Health and agriculture reform advocates who lobbied for greater reporting requirements were disappointed with the move. Advocates argued that more data would help the government track trends in usage and resistance.

The PEW Charitable Trusts has assembled a working group leading the reforms. APUA has signed on to several letters to USDA, FDA, and the HELP Committee urging them to strengthen data requirements. In addition, PEW will work with Senators Kirsten Gillibrand (D-NY) and Dianne Feinstein (D-CA) to get provisions, including elements of the [recently-introduced DATA Act](#) into the final version of the bill.

Condolences

APUA offers its deepest condolences and sympathies to the families and loved ones of all those killed and injured in the April 15 attacks in Boston. We salute all those who assisted in responding so quickly and professionally to this senseless tragedy: the first responders who ran into the chaos to save lives, exhausted runners who kept running to the nearest hospital to give blood, and ordinary citizens who stayed to tend to the wounded.

News and publications of note

CDC issues National Health Safety Network (NHSN) Data

The [NHSN report](#), published in the *American Journal of Infection Control*, provides a summary of Device-Associated Module data collected by hospitals participating in the network from January through December 2011. CDC's NHSN is the nation's most widely used healthcare-associated infection (HAI) tracking system. The goal of NHSN is to provide data needed to identify problem areas, measure progress of prevention efforts, and ultimately eliminate HAI.

Healthcare facilities using NHSN have real-time access to their data for local improvement strategies and efforts. The data presented in the report can be used to prioritize prevention efforts in those patient care areas that are shown to have the highest incidence of device-associated infections and/or high medical device utilization. Facilities may also use the percentile distributions provided in this report to set targets and strive for greater prevention success.

Pharma withdraws from antibiotic development

Major pharmaceutical companies are [reducing their investment in research and development](#) of new antimicrobials. AstraZeneca, one of the major companies still working on developing antibiotics, has recently announced its workforce restructuring to focus on three key therapy areas, and away from antibiotics. According to [Reuters](#), AstraZeneca joins Pfizer, Roche, Bristol-Myers Squibb and Eli Lilly, which all have reduced or eliminated their antibiotic research efforts. Behind this reluctance lies the following rationale: antibiotic drugs are expensive to research and develop, but the pathogens that the drugs aim to destroy eventually learn how to mutate and build up resistance. As a result, the drugs become ineffective, and the return on investment is low. Two drug giants, Merck & Co. and GlaxoSmithKline, however, are actively pursuing new antibiotic development.

Evolutionary consequences of antibiotic use exposed

The widespread use of antibiotics has evolutionary and ecological consequences that have been only minimally examined, according to Michael Gillings, professor of biological sciences at Macquarie University in Australia.

Antibiotics should be regarded as pollutants, since human production exceeds natural synthesis, and a large proportion enters the waste stream unmodified. Such antibiotic pollutants raise the general rates of mutation, recombination, and lateral gene transfer in the total microbiome. Their selective force results in the assemblage of complex, novel genetic elements that are now fixed at high frequency in diverse bacterial species. As such, these become “xenogenetic pollutants” that can replicate rather than degrade. Because these molecules act as drivers of bacterial evolution, the human use and release of antibiotics into the environment is having second-order effects on the microbial world.

'Nightmare bacteria' in the US & UK

England's Chief Medical Officer, Professor Dame Sally Davies, has called antibiotic resistance a “ticking time bomb”, while CDC director, Dr. Tom Frieden, has labelled CRE (carbapenemase-resistant enterobacteria) a “nightmare bacteria”.

The CDC released a new [Vital Signs report on CRE](#), and details the bacteria as a ‘triple threat’ because of its antibiotic-resistant nature, high risk of death in infected patients, and ease of spread. At the same time, the [UK Department of Health's annual report](#) provides a comprehensive overview of the threat of antimicrobial resistance and infectious diseases. Dame Sally Davies is urging that antimicrobial resistance be added to the national risk register and taken seriously by politicians at an international level, including the G8 and WHO. She is also advocating for improved surveillance and better hygiene measures.

Animated video about superbugs

CDDEP has produced a 3-minute animated video educating the public about the growing problem of antibiotic resistance. The video raises the issue from a natural resource perspective, and urges consumers, parents, and patients to limit the use of antibiotics. View the video here: <http://www.youtube.com/watch?v=rIfvLp1YHmE&feature=youtu.be>



APUA-Bulgaria

Molecular methods define epidemiology of *Clostridium difficile* in Bulgaria

R. Vatcheva –Dobrevska, E. Dobрева, I. Ivanov,
K. Ivanova, M. Marina, P. Petrov, T. Kantardjiev
National Centre For Infectious and Parasitic Diseases,

The prevalence and severity of *Clostridium difficile* infections (CDI) has been increasing worldwide. Bulgaria participates in the European Center for Disease Control (ECDC)-funded project to enhance laboratory capacity for CDI detection and surveillance in the European *Clostridium difficile* Infection Surveillance Network (ECDIS-Net). The *C. difficile* (CD) investigations are performed in the National Reference Laboratory for enteric pathogens and in the National HAI Reference Centre, NCIPD. Stool samples (n=120) were collected between 2008-2012 from 108 patients with mild to severe enterocolitis, diarrhea syndrome and history of previous antibiotic therapy. The CD culture isolation rate was 33.3% (40/120). Toxin A/B production was registered by immunoenzyme assay (EIA) in 82.5% (33/40) of the culture-positive stool samples. The glutamate dehydrogenase gene (*GluD*) was confirmed in only 80% (32/40). Duplex EvaGreen-based Real-time PCR assay was developed for rapid CD identification, including simultaneous detection of *gluD* and *tcdB* genes. The detection of toxin-encoding genes *tcdA* and *cdtA/cdtB* was performed by PCR and capillary electrophoresis. PCR-ribotyping and MLVA7 were applied for genotyping of 27 isolates using QiAxcel non-sequencer based capillary electrophoresis. Both *tcdA* and *tcdB* were detected in 90.6% (29/32) of the isolates; however, only 20 harbored the intact *tcdA* gene. The binary-toxin gene *cdtA/cdtB* was detected in three of the A+B+ strains. In general, four toxigenic variants were distinguished: A+B+CDT- (53.1%); A-B+CDT- (28.1%); A+B+CDT+ (9.4%); and A-B-CDT- (9.4%). Eight ribotypes were confirmed and the most prevalent was 017 (29.6%), followed by 014/020 (18.5%), then 001, 002, 012 (7.4% each) and 046, 070, 078 (3.7% each). Eighteen percent of CD (5/27) were non-typable and corresponded to non-reference PCR-ribotypes. A total of 17 MLVA7 genotypes were detected in our strains, distributed as follows: three for 017 ribotype; two for 014/020, 001, 002 each; and one each for ribotypes 046, 070

and 078. MLVA7 clustering showed significant correlation with ribotyping.

The results of our investigation should help support and improve the diagnostic and therapeutic preparedness of Bulgarian hospitals in the management of CDI.

APUA-India offers course on promoting rational drug use

APUA-India conducted a course on promoting rational use of drugs and prevention of antimicrobial resistance in the community at the Institute of Health Management Research in Jaipur, India from February 25 to March 5, 2013. It offered a condensed version adopted from the official two-week WHO course on 'Promoting Rational Drug Use in the Community'.

APUA-Cuba

In January, APUA-Cuba conducted a week-long course on tropical diseases, particularly Chagas disease, malaria, leishmaniasis, shistosomiasis, tuberculosis, dengue, filariasis, and onchocerciasis at the Manuel Fajardo Hospital in Havana. Pictured above are the attendees, interns, and residents from various Latin American and African countries. In February, APUA-Cuba (Villaclara Province Subchapter) conducted a two-day workshop on the risks of imprudent antibiotic use at the Arnaldo Milian Castro University Hospital. The workshop was attended by physicians, nurses, pharmacists and other stakeholders from Villaclara province.



Participants at the APUA-Cuba week-long course

Recently, APUA-Cuba President Dr. Moisés Morejón-García published two editorials (in Spanish) in successive issues of *Revista Cubana de Medicina*.

Upcoming events

April 27-30, 2013: European Congress on Clinical Microbiology and Infectious Diseases ([ECCMID 2013](#)), Berlin, Germany.

May 18-21, 2013: Annual Meeting of the American Society for Microbiology ([ASM 2013](#)), Denver, CO, USA.

May 28- June 1, 2013: API Chile hosts the [XVI Congreso de la Asociación Panamericana de Infectología](#) (Pan American Congress of Infectious Diseases), Santiago, Chile.

May 31- June 2, 2013: 11th Annual Conference of the Multidisciplinary Alliance Against Device-Related Infections ([MADRI 2013](#)), San Antonio, Texas.

June 5-8, 2013: International Congress of Chemotherapy and Infection ([ICC 2013](#)), Nishi-Ku, Japan.

June 8-10, 2013: Annual Conference of the Association for Professionals in Infection Control and Epidemiology ([APIC 2013](#)), Ft. Lauderdale, FL, USA.

June 25-28, 2013: International Conference on Prevention and Infection Control ([ICPIC 2013](#)), Geneva, Switzerland.

July 8-9, 2013: Annual Global Healthcare Conference ([GHC 2013](#)), Singapore, Malaysia.

August 2-3, 2013: Australasian Society for Infectious Diseases (ASID) ([Gram Negative 'Superbugs' Meeting](#)), Gold Coast, Australia.

August 31- September 1, 2013: Clinical Infectious Diseases Society Conference ([CIDSCON 2013](#)), Mumbai, India.

September 10-13, 2013: Interscience Conf. on Antimicrobial Agents and Chemotherapy ([ICAAC 2013](#)), Denver, CO, USA.

September 28, 2013: MRSA Survivors' Network hosts ([5th Annual World MRSA Day Kickoff Event and the Global MRSA & C. diff Summit](#)), Chjicago, IL, USA.

October 2-6, 2013: Infectious Diseases Society of America (IDSA), the Society for Healthcare Epidemiology of America (SHEA), the HIV Medicine Association (HIVMA), and the Pediatric Infectious Diseases Society (PIDS)'s [IDWeek 2013](#), San Francisco, CA.

November 19-22, 2013: International Conference on Infectious Disease Dynamics ([EPIDEMICS 2013](#)), Amsterdam, Netherlands.

About us

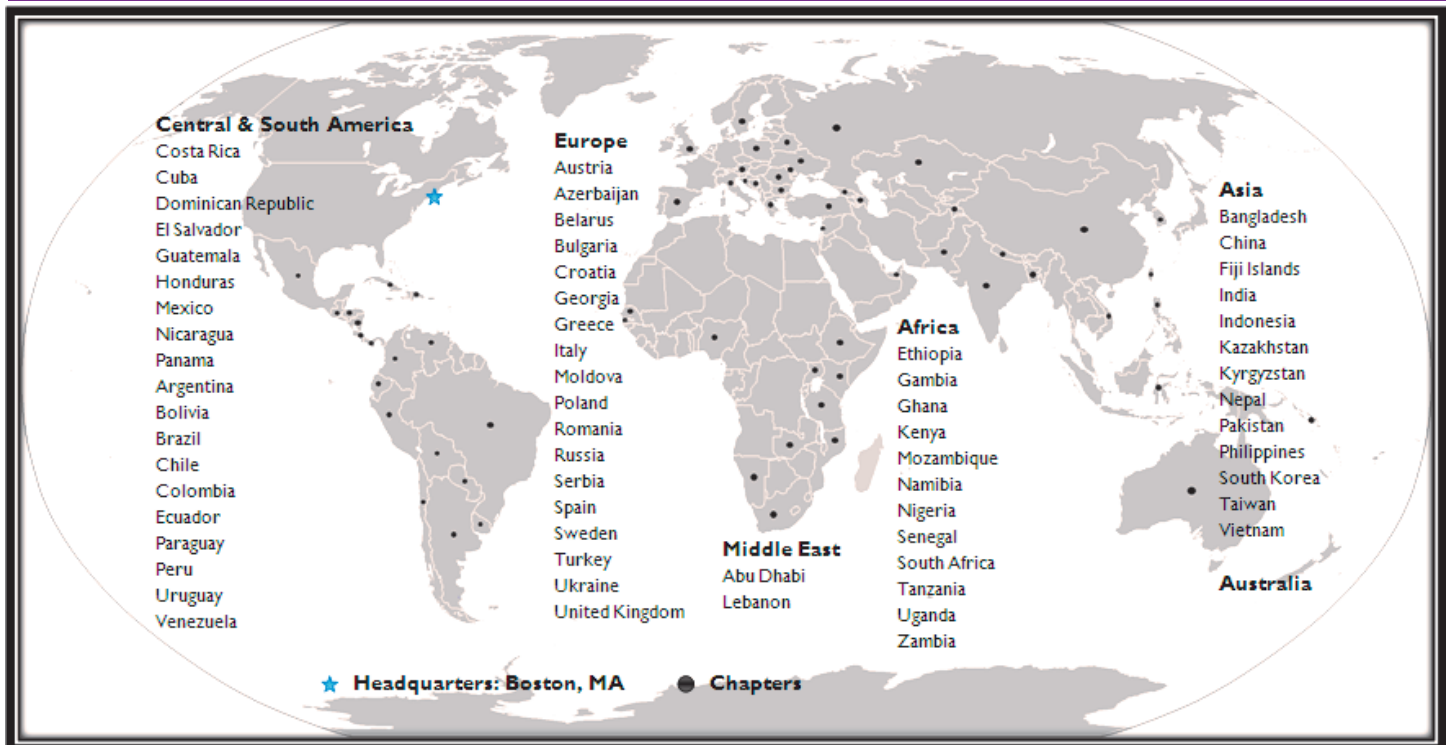
Antibiotics are humanity's key defense against disease-causing microbes. The growing prevalence of antibiotic resistance threatens a future where these drugs can no longer cure infections and killer epidemics run rampant. The Alliance for the Prudent Use of Antibiotics (APUA) has been the leading global non-governmental organization fighting to preserve the effectiveness of antimicrobial drugs since 1981. With affiliated chapters in more than 66 countries, including 33 in the developing world, we conduct research, education and advocacy programs to control antibiotic resistance and ensure access to effective antibiotics for current and future generations.

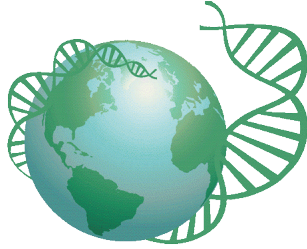
Our global network of infectious disease experts supports country-based activities to control and monitor antibiotic resistance tailored to local needs and customs. The APUA network facilitates the exchange of objective, up-to-date scientific and clinical information among scientists, health care providers, consumers and policy makers worldwide.

The APUA Clinical Newsletter has been published continuously three times per year since 1983.

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APUA global chapter network of local resources & expertise





APUA

ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

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