Prevalence of MRSA, VRE and *C. difficile* among Adults Hospitalized in Canadian Hospitals

Background

The emergence of antibiotic-resistant organisms is a major public health concern, particularly in hospitals and other healthcare settings (57, 61, 64). Antibiotic-resistant organisms appear to be biologically fit, and are capable of causing severe, life-threatening infections that may be more difficult to manage because treatment options are limited. Antimicrobial resistance may emerge in bacteria as a response to selective antibiotic pressure (16, 39), or a resistant organism may be spread from person-to-person within or between healthcare facilities (1, 29, 35, 53).

Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and *Clostridium difficile* represent antibiotic-resistant organisms that currently are of great clinical significance in hospitalized patients in Canada. Infections caused by each of these pathogens have been associated with excess morbidity and mortality (8, 9, 50, 55). These organisms have also been associated with transmission and cross-infection in healthcare facilities, leading to large outbreaks of infection (29, 33, 35, 38, 53, 60). A high prevalence of antibiotic-resistant pathogens may lead to increased lengths of hospital stay and bed-blocking in healthcare facilities. This, in turn, exacerbates hospital overcrowding, leading to a vicious cycle characterized by impeded access to care, diminished quality of care, and greater risk of infection prevention and control failures (6).

The treatment and prevention of these infections are associated with substantial increased direct and indirect costs to Canadian hospitals and society at-large. In the United States, cost estimates for managing antimicrobial resistance were estimated to be between $4 billion and $10 billion per year (US Office Technology, 1998). Seven years ago, a report commissioned by the Canadian Coordinating Committee on Antimicrobial Resistance noted that significant gaps existed in data addressing the issue of financial costs of antibiotic resistance, but

estimated that infections caused by antibiotic-resistant organisms increased direct hospital costs in Canada by $15-25 million annually (3). These estimates do not take into account indirect costs, or costs associated with infection prevention and control measures. Ironically, this increase in the incidence of drug-resistant pathogens is occurring at a time when the discovery and development of new anti-infective agents is decreasing (61).

Despite the concern about antimicrobial resistance, remarkably little is known about the epidemiology or burden of disease caused by antibiotic resistant organisms in Canada. The only national surveillance system, with linked epidemiologic and microbiologic data, tracking antimicrobial resistance in hospitalized patients is the Canadian Nosocomial Infection Surveillance Program (CNISP), currently involving 49 sentinel hospitals across the country working in collaboration with the Public Health Agency of Canada (19, 23, 41, 45, 52, 59, 60). Although the CNISP has provided valuable information, the surveillance involves a relatively small number of healthcare facilities, primarily tertiary-care teaching hospitals. Moreover, CNISP surveillance has provided important incidence data, but has done few prevalence surveys (the one prevalence survey for healthcare-associated infection conducted by the CNISP did not investigate antimicrobial resistant organisms) (19). Several provinces have now mandated public reporting of infections caused by these organisms, but these data are also limited in terms of the scope of infections reported, and by the little amount of information that is collected. An example is the province of Ontario where the only index reported for “MRSA infection” is the rate of MRSA bacteremia. This fails to capture the rates of colonization and other infections that do not cause the same amount of morbidity and mortality but are nonetheless just as important for infection control purposes.

Prevalence surveys have been used for a variety of evaluations including monitoring of infection control, trends in nosocomial infection rates, device utilization, patient acuity and costs of hospital infections (14, 15, 17, 56, 65). Despite lacking the accuracy of prospective data, prevalence surveys can provide baseline information and help establish priorities for efficient changes

(19). The aims of this point prevalence study are to generate baseline data about AROs in teaching and non-teaching, large and small, urban and rural hospitals in Canada. These data will assist in defining the burden of AROs in Canadian hospitals, and support the appropriate prioritization of prevention programs.

MRSA

Methicillin resistance in *S. aureus* is mediated by the presence of a genetic element called Staphylococcal Cassette Chromosome *mec* (SCC_{mec}) containing the *mecA* gene, which encodes the production of an altered penicillin-binding protein, called PBP2a (26). PBP2a does not effectively bind ß-lactam antibiotics, and as a result MRSA are multi-drug resistant, resistant to almost all currently available penicillins, cephalosporins, and carbapenems.

Although there is considerable variation in MRSA rates from country to country, and even from hospital to hospital within a country, MRSA is currently the most commonly identified antibiotic-resistant pathogen in hospitalized patients (20, 43). In North America, MRSA infection rates have increased in both American and Canadian hospitals, but are much higher in the United States (25, 43, 52, 59). In U.S. hospitals, the proportion of *S. aureus* isolates resistant to methicillin in intensive care units increased from 35.9% in 1992 to 64.4% in 2003, representing an increase of approximately 3% per year (31, 43). It was estimated that in 2005 there were approximately 278,203 MRSA-related hospitalizations in the U.S. (30). In a recent survey involving 21% of all U.S. healthcare facilities, the overall prevalence of MRSA was found to be 46 per 1,000 inpatients; the prevalence of MRSA infections was 34 per 1,000 inpatients (25). There are no comparable Canadian prevalence data, but the overall (colonization and infection) incidence of MRSA (newly identified cases) among hospitalized patients in hospitals participating in the CNISP in 2007 was 8.3 per 1,000 admissions and 11.6 per 10,000 patient-days. A little more than one-third of hospitalized patients with MRSA in Canada had an MRSA infection, for an infection rate of 2.9 per 1,000 admissions.

Until recently, MRSA was considered to be primarily a nosocomial pathogen, affecting older adults with comorbidities in hospital or nursing home settings. However, in the past decade, community-associated (CA-MRSA), involving a small number of unique clones, has emerged in many parts of the world, including Canada (10, 18, 42). Not surprisingly, CA-MRSA strains have been introduced into healthcare settings, and have been associated with hospital-acquired bloodstream infections, surgical site infections, and outbreaks in maternity units and hospital nurseries (48, 58).

The risk of adverse outcomes (mortality, increased length of hospital stay) in hospitalized patients with MRSA infection has generally been found to be higher than that in patients with infections due to susceptible strains of *S. aureus* (9, 54). Several studies have found that methicillin resistance is a significant and independent risk factor for mortality in patients with *S. aureus* bloodstream infections, even when logistic regression analysis was done to adjust for potential confounders of outcome (9, 40). In 2001, the mean attributable cost associated per patient with MRSA infection in a Canadian hospital was determined to be $14,360 (28). Increased costs associated with MRSA have been attributed to prolonged hospital stay, higher costs of antimicrobial therapy, and costs of isolation procedures (9, 28, 54).

VRE

Although generally less virulent than *S. aureus*, *Enterococcus* species (particularly *E. faecalis* and *E. faecium*) may also cause serious and life-threatening infections. Resistance to vancomycin in enterococci is due to the synthesis of modified cell wall precursors that do not bind glycopeptides. This occurs with the acquisition of a plasmid-associated gene cluster, most commonly the *vanA* or *vanB* genes (34). These genes are transferable and may spread from enterococci into MRSA (2). It is therefore noteworthy that 15% of Canadian inpatients with VRE were also found to be colonized or infected with MRSA (45).

In the U.S. in 2006-2007, 33% of enterococci causing medical device-associated infections were VRE (22). VRE rates in Canada, as determined by

the CNISP, are much lower, although they have been creeping up, from 0.4 per 1,000 admissions in 1999 to 1.2 per 1,000 admissions in 2007 (4, 45). Only a minority (6%) of VRE patients in Canada had a VRE infection. However, even patients with VRE colonization are investigated and put into an isolated room while in hospital, contributing to an incremental cost of approximately $6,700 per patient in Canadian hospitals (8). Several studies have documented that VRE infections are associated with attributable excess morbidity and mortality as compared to infections caused by susceptible strains of *Enterococcus* (11, 55).

Clostridium difficile

C. difficile may also be considered an antibiotic-resistant organism because it is typically resistant to the majority of available antimicrobial agents, and because *C. difficile*-associated disease is almost always triggered by exposure to antibiotics. *C. difficile* is the major cause of antibiotic-associated diarrhea, and is the most common infectious cause of nosocomial diarrhea (27, 51).

A devastating outbreak of *C. difficile* infection (CDI) occurred in many hospitals in Quebec beginning in 2002 (35, 49). Markedly increased rates (as high as 156 cases per 100,000 population) and severity of disease occurred, especially in the elderly (49, 50). The emergence of such severe disease is thought to have occurred because of the presence of a hypervirulent epidemic strain of *C. difficile* known as PCR ribotype 27, or North America pulso-type 1 (NAP1) (63). The same strain of *C. difficile* has caused extensive and severe disease in the U.S. and Europe (38). Importantly, the NAP1 strain has now been identified in most Canadian provinces, and has become the predominant strain in many Canadian hospitals, indicating the potential for the development of severe outbreaks in many parts of the country outside of Quebec (36).

The US Agency for Healthcare Research and Quality (AHRQ) tracked cases of CDI in U.S. hospitals, and found a 200% increase in the number of hospital patients infected with *C. difficile* from 2000 to 2005 (13). This study found that patients with CDI were hospitalized almost three times longer than

uninfected patients, and 10% died in hospital, compared with 2% of patients overall. In Canada, CDI rates were reported by CNISP hospitals to be 4.7 per 1,000 admissions and 7.3 per 10,000 patient –days in 2007 (5). Aggregate data for nosocomial *C. difficile* infections are now reportable in Ontario and Quebec. In the last quarter of 2008, nosocomial CDI rates in Ontario were reported to be approximately 4.0 per 10,000 patient-days (47). In Quebec the nosocomial CDI rate in 2007-2008 was 6.8 per 10,000 patient-days (24).

Similar to other antimicrobial resistant organisms, CDI also has a significant negative impact on patient illness and outcome, which persists even after hospital discharge. During the *C. difficile* epidemic in Quebec (2003-2004), patients with CDI had an excess attributable mortality one year following the infection of 16.7%; there was also an average excess length of stay in hospital of 10.7 days (50). In a non-outbreak setting in the U.S., Dubberke and colleagues found that CDI was associated with a 23% higher hazard of death within 180 days after hospital admission in a multivariable cohort analysis, and a 7.2% attributable mortality in a matched-pair analysis (12). This study also found that there was an excess length of stay of 2.8 days attributable to CDI, and an attributable readmission rate of 19.3%. Other studies have identified an attributable prolonged length of hospital stay of 3.0-3.6 days, with adjusted excess costs of $3,669-$13,675 (USD) per patient (32, 44).

The Need for Prevalence Data in Canada

The prevalence rate of an antibiotic resistant organism may be defined as the total number of patients with the organism (associated with either infection or colonization) in a specific population during a specified period of time. It may be possible to determine the prevalence per 100 patients admitted to hospital during the specified time period, or to determine a prevalence density to account for length of patient stay in the hospital (for prevalence density, the denominator would be the number of patient-days). Antimicrobial resistance surveillance that provides accurate prevalence data is critical for the development of strategies that may be used to limit the emergence and spread of antimicrobial resistant

organisms. Determining the prevalence of antibiotic resistance organisms has been recognized as an important metric for assessing the burden of disease associated with antimicrobial resistance, for identifying vulnerable patient populations, and for monitoring the effectiveness of various interventions (7).

Despite numerous calls for action (8, 21, 37), Canada does not currently have a comprehensive surveillance program for collecting and integrating accurate and representative national data on antimicrobial resistance (62). This significantly limits our ability to respond to the challenges posed to our healthcare system by antimicrobial resistant organisms. This study proposal focuses on the burden of illness associated with three major antibiotic-resistant pathogens: MRSA, VRE, and *C. difficile*. These organisms have been selected because they are of particular concern in Canadian healthcare facilities, because there continue to be significant gaps in our knowledge of the epidemiology of these organisms in Canadian hospitals, and because the majority of Canadian hospitals currently do active surveillance for these organisms, so that relevant data are likely to be available (46). Such information is essential in order to develop and evaluate the effectiveness of hospital and public health measures for the prevention of infections caused by these organisms.

References

1. Aires de Sousa M, Sanches IS, Ferro ML, Vaz MJ, Saraiva Z, Tendeiro T, et al. Intercontinental spread of a multidrug-resistant methicillin-resistant *Staphylococcus aureus* clone. J Clin Microbiol. 1998 Sep;36(9):2590-6.

2. Appelbaum PC. The emergence of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus*. Clin Microbiol Infect. 2006 Mar;12 Suppl 1:16-23.

3. Birnbaum D, Canadian Committee on Antibiotic Resistance. Antimicrobial resistance: A deadly burden no country can afford to ignore. Can Commun Dis Rep. 2003 Sep 15;29(18):157-64.

4. The Canadian Nosocomial Infection Surveillance Program- vancomycin resistant enterococci (VRE) surveillance [homepage on the Internet]. 2007. Available from: http://www.phac-aspc.gc.ca/nois-sinp/projects/vre-eng.php. (Accessed December 8, 2008)

5. Surveillance of *clostridium difficile* associated diarrhea prelimenary results from january 1st to april 30th, 2007 [homepage on the Internet]. Available from: http://www.phac-aspc.gc.ca/nois-sinp/projects/pdf/cdad_e.pdf. (Accessed Dec 8, 2008)

6. Clements A, Halton K, Graves N, Pettitt A, Morton A, Looke D, et al. Overcrowding and understaffing in modern health-care systems: Key determinants in meticillin-resistant *Staphylococcus aureus* transmission. Lancet Infect Dis. 2008 Jul;8(7):427-34.

7. Cohen AL, Calfee D, Fridkin SK, Huang SS, Jernigan JA, Lautenbach E, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. Infect Control Hosp Epidemiol. 2008 Oct;29(10):901-13.

8. Conly J. Antimicrobial resistance in Canada. CMAJ. 2002 Oct 15;167(8):885-91.

9. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: Mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol. 2005 Feb;26(2):166-74.

10. Deresinski S. Methicillin-resistant *Staphylococcus aureus*: An evolutionary, epidemiologic, and therapeutic odyssey. Clin Infect Dis. 2005 Feb 15;40(4):562-73.

11. DiazGranados CA, Zimmer SM, Klein M, Jernigan JA. Comparison of mortality associated with vancomycin-resistant and vancomycin-susceptible enterococcal bloodstream infections: A meta-analysis. Clin Infect Dis. 2005 Aug 1;41(3):327-33.

12. Dubberke ER, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, et al. Attributable outcomes of endemic *Clostridium difficile*-associated disease in nonsurgical patients. Emerg Infect Dis. 2008 Jul;14(7):1031-8.

13. *Clostridium difficile*-associated diarrhea in U.S. hospitals, 1993-2005. HCUP statistical brief #50 [homepage on the Internet]. Rockville, MD: Agency for Healthcare Research and Quality April 2008. Available from: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf. (Accessed December 8, 2008)

14. French GL, Cheng AF. Measurement of the costs of hospital infection by prevalence surveys. J Hosp Infect. 1991 Jun;18 Suppl A:65-72.

15. French GL, Cheng AF, Wong SL, Donnan S. Repeated prevalence surveys for monitoring effectiveness of hospital infection control. Lancet. 1989 Oct 28;2(8670):1021-3.

16. Gaynes R. Antibiotic resistance in ICUs: A multifaceted problem requiring a multifaceted solution. Infect Control Hosp Epidemiol. 1995 Jun;16(6):328-30.

17. Gikas A, Pediaditis I, Roumbelaki M, Troulakis G, Romanos J, Tselentis Y. Repeated multi-centre prevalence surveys of hospital-acquired infection in Greek hospitals. CICNet. Cretan infection control network. J Hosp Infect. 1999 Jan;41(1):11-8.

18. Gilbert M, MacDonald J, Gregson D, Siushansian J, Zhang K, Elsayed S, et al. Outbreak in Alberta of community-acquired (USA300) methicillin-resistant *Staphylococcus aureus* in people with a history of drug use, homelessness or incarceration. CMAJ. 2006 Jul 18;175(2):149-54.

19. Gravel D, Taylor G, Ofner M, Johnston L, Loeb M, Roth VR, et al. Point prevalence survey for healthcare-associated infections within Canadian adult acute-care hospitals. J Hosp Infect. 2007 Jul;66(3):243-8.

20. Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of meticillin-resistant *Staphylococcus aureus* as a public-health threat. Lancet. 2006 Sep 2;368(9538):874-85.

21. Health Canada and The Canadian Infectious Disease Society. Controlling antimicrobial resistance. An integrated action plan for Canadians. Can Commun Dis Rep. 1997 Nov;23 Suppl 7:i,iv, 1-32, i-iv, 1-32.

22. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. NHSN annual update: Antimicrobial-resistant pathogens associated with healthcare-associated infections: Annual summary of data reported to the national healthcare safety network at the centers for disease control and prevention, 2006-2007. Infect Control Hosp Epidemiol. 2008 Nov;29(11):996-1011.

23. Hyland M, Ofner-Agostini M, Miller M, Paton S, Gourdeau M, Ishak M, et al. N-CDAD in Canada: Results of the Canadian Nosocomial Infection Surveillance Program 1997 N-CDAD prevalence surveillance project. Can J Infect Dis. 2001 Mar;12(2):81-8.

24. Surveillance des diarrhées a *Clostridium difficile* au Québec bilan du 9 décembre 2007 au 31 mars 2008 [homepage on the Internet]. Available from: http://www.inspq.qc.ca/pdf/publications/851_Bilan_C_Difficile.pdf. (Accessed December 8, 2008)

25. Jarvis WR, Schlosser J, Chinn RY, Tweeten S, Jackson M. National prevalence of methicillin-resistant *Staphylococcus aureus* in inpatients at US health care facilities, 2006. Am J Infect Control. 2007 Dec;35(10):631-7.

26. Katayama Y, Ito T, Hiramatsu K. A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in *Staphylococcus aureus*. Antimicrob Agents Chemother. 2000 Jun;44(6):1549-55.

27. Kelly CP, LaMont JT. *Clostridium difficile*--more difficult than ever. N Engl J Med. 2008 Oct 30;359(18):1932-40.

28. Kim T, Oh PI, Simor AE. The economic impact of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals. Infect Control Hosp Epidemiol. 2001 Feb;22(2):99-104.

29. Kim WJ, Weinstein RA, Hayden MK. The changing molecular epidemiology and establishment of endemicity of vancomycin resistance in enterococci at one hospital over a 6-year period. J Infect Dis. 1999 Jan;179(1):163-71.

30. Klein E, Smith DL, Laxminarayan R. Hospitalizations and deaths caused by methicillin-resistant *Staphylococcus aureus*, United States, 1999-2005. Emerg Infect Dis. 2007 Dec;13(12):1840-6.

31. Klevens RM, Edwards JR, Tenover FC, McDonald LC, Horan T, Gaynes R, et al. Changes in the epidemiology of methicillin-resistant *Staphylococcus aureus* in intensive care units in US hospitals, 1992-2003. Clin Infect Dis. 2006 Feb 1;42(3):389-91.

32. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis. 2002 Feb 1;34(3):346-53.

33. Lai KK, Fontecchio SA, Kelley AL, Melvin ZS, Baker S. The epidemiology of fecal carriage of vancomycin-resistant enterococci. Infect Control Hosp Epidemiol. 1997 Nov;18(11):762-5.

34. Leclercq R, Courvalin P. Resistance to glycopeptides in enterococci. Clin Infect Dis. 1997 Apr;24(4):545,54; quiz 555-6.

35. 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 Dec 8;353(23):2442-9.

36. Martin H, Willey B, Low DE, Staempfli HR, McGeer A, Boerlin P, et al. Characterization of *Clostridium difficile* strains isolated from patients in Ontario, Canada, from 2004 to 2006. J Clin Microbiol. 2008 Sep;46(9):2999-3004.

37. Mazzuli T. Canadian patterns of antimicrobial resistance: Overview of current trends related to hospital pathogens. Can J Infect Dis. 2006;17(Suppl. B):3B-5B.

38. 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 Dec 8;353(23):2433-41.

39. McGowan JE,Jr. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. Rev Infect Dis. 1983 Nov-Dec;5(6):1033-48.

40. Melzer M, Eykyn SJ, Gransden WR, Chinn S. Is methicillin-resistant *Staphylococcus aureus* more virulent than methicillin-susceptible *S. aureus*? A comparative cohort study of British patients with nosocomial infection and bacteremia. Clin Infect Dis. 2003 Dec 1;37(11):1453-60.

41. Miller MA, Hyland M, Ofner-Agostini M, Gourdeau M, Ishak M, Canadian Hospital Epidemiology Committee. Canadian Nosocomial Infection Surveillance Program. Morbidity, mortality, and healthcare burden of nosocomial *Clostridium difficile*-associated diarrhea in Canadian hospitals. Infect Control Hosp Epidemiol. 2002 Mar;23(3):137-40.

42. Mulvey MR, MacDougall L, Cholin B, Horsman G, Fidyk M, Woods S, et al. Community-associated methicillin-resistant *Staphylococcus aureus*, Canada. Emerg Infect Dis. 2005 Jun;11(6):844-50.

43. National Nosocomial Infections Surveillance System. National nosocomial infections surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control. 2004 Dec;32(8):470-85.

44. O'Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of *Clostridium difficile*-associated disease in Massachusetts hospitals: Clinical and economic consequences. Infect Control Hosp Epidemiol. 2007 Nov;28(11):1219-27.

45. Ofner-Agostini M, Johnston BL, Simor AE, Embil J, Matlow A, Mulvey M, et al. Vancomycin-resistant enterococci in Canada: Results from the Canadian Nosocomial Infection Surveillance Program, 1999-2005. Infect Control Hosp Epidemiol. 2008 Mar;29(3):271-4.

46. Ofner-Agostini M, Varia M, Johnston L, Green K, Simor A, Amihod B, et al. Infection control and antimicrobial restriction practices for antimicrobial-resistant organisms in Canadian tertiary care hospitals. Am J Infect Control. 2007 Nov;35(9):563-8.

47. Patient safety [homepage on the Internet]. 2009. Available from: http://www.health.gov.on.ca/patient_safety/. (Accessed December 8, 2008)

48. Otter JA, French GL. Nosocomial transmission of community-associated methicillin-resistant *Staphylococcus aureus*: An emerging threat. Lancet Infect Dis. 2006 Dec;6(12):753-5.

49. Pepin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: A changing pattern of disease severity. CMAJ. 2004 Aug 31;171(5):466-72.

50. 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 Oct 25;173(9):1037-42.

51. Poutanen SM, Simor AE. *Clostridium difficile*-associated diarrhea in adults. CMAJ. 2004 Jul 6;171(1):51-8.

52. Public Health Agency of Canada. Surveillance for methicillin-resistant *Staphylococcus aureus* in Canadian hospitals--a report update from the Canadian Nosocomial Infection Surveillance Program. Can Commun Dis Rep. 2005 Feb 1;31(3):33-40.

53. Roberts RB, de Lencastre A, Eisner W, Severina EP, Shopsin B, Kreiswirth BN, et al. Molecular epidemiology of methicillin-resistant *Staphylococcus aureus* in 12 New York hospitals. MRSA collaborative study group. J Infect Dis. 1998 Jul;178(1):164-71.

54. Rubin RJ, Harrington CA, Poon A, Dietrich K, Greene JA, Moiduddin A. The economic impact of *Staphylococcus aureus* infection in New York City hospitals. Emerg Infect Dis. 1999 Jan-Feb;5(1):9-17.

55. Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: A meta-analysis. Infect Control Hosp Epidemiol. 2003 Sep;24(9):690-8.

56. Sax H, Hugonnet S, Harbarth S, Herrault P, Pittet D. Variation in nosocomial infection prevalence according to patient care setting: A hospital-wide survey. J Hosp Infect. 2001 May;48(1):27-32.

57. Schwartz B, Bell DM, Hughes JM. Preventing the emergence of antimicrobial resistance. A call for action by clinicians, public health officials, and patients. JAMA. 1997 Sep 17;278(11):944-5.

58. Seybold U, Kourbatova EV, Johnson JG, Halvosa SJ, Wang YF, King MD, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. Clin Infect Dis. 2006 Mar 1;42(5):647-56.

59. Simor AE, Ofner-Agostini M, Bryce E, Green K, McGeer A, Mulvey M, et al. The evolution of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: 5 years of national surveillance. CMAJ. 2001 Jul 10;165(1):21-6.

60. Simor AE, Ofner-Agostini M, Bryce E, McGeer A, Paton S, Mulvey MR, et al. Laboratory characterization of methicillin-resistant *Staphylococcus aureus* in Canadian hospitals: Results of 5 years of national surveillance, 1995-1999. J Infect Dis. 2002 Sep 1;186(5):652-60.

61. Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic-resistant infections: A call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis. 2008 Jan 15;46(2):155-64.

62. Stephen C, Parmley J, Dawson-Coates J, Fraser E, Conly J. Obstacles to developing a multinational report card on antimicrobial resistance for Canada: An evidence-based review. Microb Drug Resist. 2007 Winter;13(4):251-60.

63. Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet. 2005 Sep 24-30;366(9491):1079-84.

64. Webster PC. Alarm grows over management of antibiotic resistance file. CMAJ. 2010;182(2).

65. Weinstein JW, Mazon D, Pantelick E, Reagan-Cirincione P, Dembry LM, Hierholzer WJ,Jr. A decade of prevalence surveys in a tertiary-care center: Trends in nosocomial infection rates, device utilization, and patient acuity. Infect Control Hosp Epidemiol. 1999 Aug;20(8):543-8.

Primary Study Objectives

- To determine the prevalence of MRSA and VRE colonization and infection among adults hospitalized in Canadian hospitals
- To determine the prevalence of *C. difficile* infection among adults hospitalized in Canadian hospitals

Secondary Study Objectives

- To describe demographic and select clinical/epidemiologic features of patients with prevalent MRSA, VRE, and *C. difficile* infection in Canadian hospitals
- To determine institutional characteristics associated with MRSA, VRE, and *C. difficile* infection rates

Study Methods

Study population

All 406 acute-care hospitals in Canada with at least 50 inpatient beds will be approached to participate in this point-prevalence survey (hospitals identified from the Canadian Hospital Association [CHA] 2008 database, Volume 15.1). A letter inviting healthcare facilities to participate in the prevalence survey will be sent by e-mail to each facility's Infection Prevention & Control professional (ICP) (Appendix I). If there has been no response to this initial mailing, the ICP will be contacted a second time by e-mail, and if required, an attempt will also be made to contact the individual by telephone.

Eligible patients will include acute adult inpatients (usually ≥ 18 years of age) hospitalized in a participating hospital on the day of the survey (please note that hospitals may use their own cut-off age for identifying adult patients). Long-term care patients in these hospitals will be included if the long-term care beds are physically associated with a medical unit in the acute-care hospital, or if patients are awaiting transfer/placement to a long-term care facility. Other (free-standing) long-term care facilities, rehabilitation hospitals, complex care facilities

and psychiatric hospitals will not be included. It is anticipated that at least 250 (62%) hospitals will be willing and able to participate.

Study design

A one-day point-prevalence survey will be conducted in participating Canadian hospitals on a day chosen by each participating centre between November 8 to 21, 2010. On the selected day, eligible patients will be identified by the hospital census (usually defined at midnight or at 6am). Adult patients in hospital at that time will be included in the prevalence survey. Patients admitted after the census is defined will not be included. Identification of all patients known to be infected or colonized with MRSA or VRE on that day, and all those known to have *C. difficile* infection may be done at any time in the two weeks following this date. Patients with MRSA and VRE will be defined as those requiring isolation precautions for either of these two organisms (culture-confirmed at some prior point in time) on the day of the survey. Patients with MRSA or VRE infection must meet National Healthcare Safety Network (NHSN) criteria (2008) for infection, and must be on antimicrobial therapy for MRSA or VRE infection on the day of the survey. Patients with *C. difficile* infection will be identified as those receiving at least one dose of treatment for CDI with either metronidazole or oral vancomycin on the day of the survey for laboratory-confirmed (toxin-positive) *C. difficile* infection, or determined to have had pseudomembranous colitis on endoscopy within the previous 14 days. In addition, patients hospitalized on the day of the survey who have cultures or stool specimens obtained on that day that subsequently yield MRSA, VRE, or *C. difficile* toxin, will also be included. (See definitions in Appendix III)

Data to be collected for each patient with MRSA, VRE, and CDI include: (i) age; (ii) sex; (iii) hospital service on the day of the survey (medicine, surgery, obstetrics/gynecology, intensive care unit, etc.); (iv) for MRSA, whether the most recent isolate was obtained as a clinical specimen (to determine the presence of an infection), or as a screening/surveillance specimen (eg. nose swab); (v) whether the patient was thought to be infected (using standard definitions) or colonized; (vi) the anatomic site of the isolate (nose, skin, surgical site,

respiratory, blood, urine, etc); (vii) whether the organism was thought to be healthcare-associated (index facility or other healthcare facility) or community-acquired (using CNISP definitions); (viii) whether the organism was initially identified during the current admission or a previous admission; (ix) whether the organism was thought to have been acquired during this admission or a previous admission; (x) for *C. difficile* infection, whether this represented a first episode or recurrence (Appendix III).

Data will also be obtained to describe each participating hospital: (i) number of admitted inpatients in the hospital on the survey date (at midnight); (ii) total number of inpatient beds; (iii) number of ICU beds; (iv) hospital location (city, province, postal code); (v) type of facility (adults only, mixed adults-pediatrics); (vi) type of facility (teaching vs non-teaching hospital); (vii) scope of services provided (acute trauma, burns, oncology, stem-cell transplants, solid organ transplants, neurosurgery, cardiac surgery, dialysis, etc); (viii) number of FTE infection control professionals (ICPs) (Appendix II). All of the data are to be collected by a hospital Infection Control Professional (ICP) or appropriately trained delegate under the ICP's supervision.

Facilities will not be asked to obtain any additional cultures for the survey. Only data available in the chart or in infection prevention and control program records will be collected; no patient interviews will be expected or required.

Data analysis

The primary outcome measures will be the median and mean (with 95% Confidence Intervals) prevalence rates of MRSA, VRE, and *C. difficile* infection per 1,000 inpatients. The prevalence of MRSA and VRE infections will also be determined. Regional (or provincial) rates will be calculated, and the rates will also be determined based on: (i) hospital size (< 200 beds; 200-500 beds; > 500 beds); and (ii) hospital type (teaching vs non-teaching). Patients with MRSA, VRE, and *C. difficile* infection will be described by demographic information, and by hospital service.

Sample size calculation

To estimate the prevalence of carriage of MRSA, in Canada, within 0.5 cases per 1,000 inpatients, based on the estimated prevalence of 8.3 cases per 1,000 admissions, we estimate that 54,100 inpatients will need to be included in the surveillance. This would be accomplished if approximately 65% of hospitals with 50 or more beds (estimated total beds 94,538) agree to participate in the project. With a 65% hospital participation rate (dependant on the size of the hospitals), we would also be able to detect the prevalence of MRSA infection within 0.25 cases per 1,000; the prevalence of VRE infection within 0.25 cases per 1,000 inpatients; and the prevalence of *C. difficile* infection within 0.5 cases per 1,000 inpatients. See Table for sample size estimates.

Table: Estimated number of inpatients required to detect the prevalence of infection for MRSA, VRE, and *C. difficile,* in Canadian hospitals

Outcome	Estimated prevalence	Width of estimate		Number of inpatients
MRSA colonization	8.3 / 1,000	± 0.5	7.8-8.8 / 1,000	54,100
		± 1.0	7.3-9.3 / 1,000	23,695
MRSA infection	2.9 / 1,000	± 0.25	2.65-3.15 / 1,000	61,712
		± 0.5	2.4-3.4 / 1,000	30,226
		± 1.0	1.9-3.9 / 1,000	9,940
VRE infection	1.2 / 1,000	± 0.2	1.0-1.4 / 1,000	51,907
		0.25	0.95-1.45 / 1,000	41,404
C. difficile infection	4.7 / 1,000	± 1.0	3.7-5.7/ 1,000	15,100
		± 0.5	4.2-5.2 / 1,000	40,834

National Statistical Service, Sample size calculator (Australia)

Ethics

This point-prevalence survey is observational, without any change in patient care. Moreover, it will be considered to be within the scope of infection surveillance for many of the hospitals' Infection Prevention & Control programs. In order to maintain confidentiality, each hospital will be assigned a numeric code, and each patient will also be assigned a unique study number for entry into the database. No personal identifying data will be provided to the study investigators. Consequently, Review Ethics Board (REB) approval may not be required at all participating hospital sites. However, hospitals may submit the proposal to their local REB for approval if they wish.