Risk factors for and outcomes associated with clinical isolates of *Escherichia coli* and *Klebsiella* species resistant to extended-spectrum cephalosporins among patients admitted to Canadian hospitals

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M Ofner-Agostini, A Simor, M Mulvey, et al; Canadian Nosocomial Infection Surveillance Program (CNISP). Risk factors for and outcomes associated with clinical isolates of *Escherichia coli* and *Klebsiella* species resistant to extended-spectrum cephalosporins among patients admitted to Canadian hospitals. Can J Infect Dis Med Microbiol 2009;20(3):e43-e48.

BACKGROUND: Clinical features associated with Gram-negative bacterial isolates with extended-spectrum beta-lactamase (ESBL)- and AmpC-mediated resistance identified in Canadian hospitals is largely unknown. The objective of the present study was to determine the demographics, risk factors and outcomes of patients with ESBL- or AmpC-mediated resistant organisms in Canadian hospitals.

METHODS: Patients with clinical cultures of *Escherichia coli* or *Klebsiella* species were matched with patients with a similar organism but susceptible to third-generation cephalosporins. Molecular identification of the AmpC or ESBL was determined using a combination of polymerase chain reaction and sequence analysis. Univariate and multivariate logistic regression analysis was performed to identify variables associated with becoming a case.

RESULTS: Eight Canadian hospitals identified 106 cases (ESBL/AmpC) and 106 controls. All risk factors identified in the univariate analysis as a predictor of being an ESBL/AmpC cases at the 0.20 P-value were included in the multivariate analysis. No significant differences in outcomes were observed (unfavourable responses 17% versus 15% and mortality rates 13% versus 7%, P not significant). Multivariate logistic regression found an association of becoming an ESBL/AmpC case with: previous admission to a nursing home (OR 8.28, P=0.01) or acute care facility (OR 1.96, P=0.03), length of stay before infection (OR 3.05, P=0.004), and previous use of first-generation cephalosporins (OR 2.38, P=0.02) or third-generation cephalosporins (OR 4.52, P=0.01). Appropriate antibiotics were more likely to be given to controls (27.0% versus 13.3%, P=0.05) and number of days to appropriate antibiotics was longer for cases (median 2.8 days versus 1.2 days, P=0.05).

CONCLUSION: The importance of patient medical history, present admission and antibiotic use should be considered for all *E coli* or *Klebsiella* species patients pending susceptibility testing results.

Key Words: *AmpC resistance; Case-control; Extended-spectrum beta-lactamases; Outcomes; Risk factors*

Les facteurs de risque des isolats cliniques d'*Escherichia coli* et des espèces de *Klebsiella* résistants aux céphalosporines à large spectre et les issues s'y associant chez des patients admis dans des hôpitaux canadiens

HISTORIQUE : On ne connaît à peu près pas les caractéristiques cliniques liées aux isolats bactériens gram-négatifs médiateurs d'une résistance aux bêta-lactamases à large spectre (BLLS) et à l'AmpC dans les hôpitaux canadiens. La présente étude visait à déterminer la démographie, les facteurs de risque et les issues des patients ayant des organismes médiateurs d'une résistance aux BLLS et à l'AmpC dans des hôpitaux canadiens.

MÉTHODOLOGIE : On a jumelé des patients ayant des cultures cliniques d'*Escherichia coli* ou d'espèces de *Klebsiella* à des patients présentant des organismes similaires mais susceptibles aux céphalosporines de troisième génération. On a obtenu la détermination moléculaire de l'AmpC ou des BLLS au moyen d'une combinaison de réaction en chaîne de la polymérase et d'analyse des séquences. Une analyse de régression logistique univariée et multivariée a permis de repérer les variables associées au fait de devenir un cas.

RÉSULTATS : Huit hôpitaux canadiens ont repéré 106 cas (BLLS/AmpC) et 106 sujets témoins. Tous les facteurs de risque déterminés dans l'analyse univariée comme prédicteurs de cas BLLS/AmpC à une valeur P de 0,20 ont été inclus dans l'analyse multivariée. On n'a observé aucune différence significative d'issue (réponses défavorables de 17 % par rapport à 15 % et taux de mortalité de 13 % par rapport à 7 %, P non significatif). La régression logistique multivariée a permis d'établir une association entre devenir un cas BLLS/AmpC et une admission antérieure dans un centre d'hébergement et de soins de longue durée (RRR 8,28, P=0,01) ou un établissement de soins aigus (RRR 1,96, P=0,03), la durée du séjour avant l'infection (RRR 3,05, P=0,004) et l'utilisation antérieure de céphalosporines de première génération (RRR 2,38, P=0,02) ou de troisième génération (RRR 4,25, P=0,01). Des antibiotiques adéquats étaient plus susceptibles d'être administrés aux sujets témoins (27,0 % par rapport à 13,3 %, P=0,05) et le nombre de jours à prendre des antibiotiques adéquats était plus long pour les cas (médiane de 2,8 jours par rapport à 1,2 jour, P=0,05).

CONCLUSION : Il faut tenir compte des antécédents médicaux, de l'admission et de l'utilisation d'antibiotiques chez tous les patients infectés par l'*E coli* ou des espèces de *Klebsiella* en attendant les résultats des tests de susceptibilité.

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Gram-negative bacilli containing group 2bc extended spectrum beta-lactamases (ESBLs) and group 1 AmpC cephalosporinases not only produce enzymes that inactivate most beta-lactam antibiotics, but are frequently resistant to many other antimicrobial agents (1-3). Hospital outbreaks are well documented, generally affect the most critically ill patients and have been associated with substantial morbidity and mortality (4-6). Long-term care facilities may also act as reservoirs, potentially contributing to an increase in the burden of clinical disease as patients are transferred across the continuum of care (7). Current endemic areas now exist throughout the world, with ESBL types demonstrating geographic variation (8,9).

The clinical features and laboratory characteristics associated with ESBL- and AmpC-mediated resistance in Canadian hospitals is largely unknown. A Canadian survey conducted from 1999 to 2000 found 0.28% *Escherichia coli* (range 0% to 1.8%) and 0.8% *Klebsiella* species were confirmed as ESBL (range 0% to 3.25%) (10). In that survey, ESBL strains were isolated from Western Canada (39%; Manitoba to British Columbia), and the central region (61%; Ontario and Quebec), whereas no ESBLs were identified in the East (Atlantic provinces). ESBL strains were isolated from the urinary tract (64%), blood (11.5%), respiratory tract (11.5%) and wounds (5%). All strains were susceptible to imipenem; however, most displayed greater resistance to other classes of antibiotics including ciprofloxacin (35.6%), trimethoprim-sulfamethoxazole (68%), gentamicin (59%), tobramycin, (43%) and amikacin (5%) compared with non-ESBL isolates (11,12). Following this effort, a targeted surveillance program that included a matched case-control study was conducted in Canadian health care centres that participate in the Canadian Nosocomial Infection Surveillance Program (CNISP). The purpose of the present study was to determine the demographics, risk factors and outcomes of patients with ESBL- and/or AmpC-containing isolates of *E coli* and *Klebisella* species in tertiary care Canadian hospitals participating in CNISP.

METHODS

Design and definitions

The CNISP is a collaborative effort of the Canadian Hospital Epidemiology Committee, a subcommittee of the Association of Medical Microbiology and Infectious Disease Canada and the Public Health Agency of Canada. At the time of the present study, there were 40 university-affiliated hospitals in nine provinces that participated in the CNISP network. Of these, eight hospitals participated in the targeted surveillance for ESBL- and/or AmpC-containing isolates of *E coli* and *Klebisella* species. The study was designed as a case-control study to understand the risk factors and outcomes of the acquisition of group 2be ESBL and group 1 AmpC beta-lactamase-producing *E coli* or *Klebsiella* species. An ESBL case was defined as any patient with an *E coli* or *Klebsiella* species isolated from a clinical specimen that was confirmed as a group 2be ESBL-resistant organism according to National Committee for Clinical Laboratory Standards guidelines (13). AmpC-mediated resistance was considered to be present if the isolate was resistant to cefoxitin and to third-generation cephalosporins, and the resistance was not inhibited by clavulanic acid.

All patients admitted to a participating hospital in the year 2004 were eligible for enrolment, with restriction to first eligible episode of infection. Isolates from patients in emergency or outpatient departments were eligible for inclusion only if the patient was subsequently admitted directly to an inpatient ward. Patients known to the facility as previously harbouring these patterns of resistance were excluded.

Case patients were defined as unique patients with clinical isolates of *E coli* or *Klebsiella* species harbouring either ESBL or AmpC resistance. Control patients were those having the same clinical organism but susceptible to third-generation cephalosporins. Either could not have previously been identified with an *E coli* or *Klebsiella* species within the past year at that hospital. Matching was done 1:1 with the next available same organism, same specimen type (eg, blood to blood) and same setting (intensive care unit [ICU] versus non-ICU) identified within that institution. Blood culture, urine and respiratory isolates were matched exactly; however, 'other' isolates were matched with any other type of isolates except blood, urine or sputum. The case and corresponding control data collection form was completed by the infection control professional who followed the patients prospectively until time of discharge or eight weeks following the date of first positive culture. Data collected included patient demographics, risk factor information, including antimicrobial use (prior: four weeks before date of first culture; during: on or up to seven days after the date of culture), device information and organism information (site, colonization versus infection, reason for culture).

Patient outcomes were assessed via chart review at eight weeks after the first positive culture. Outcomes collected included: status of the patient (discharged, remained in hospital, deceased) and severity of illness, measured as: ICU transfer, hypotension (systolic blood pressure less than 90 mmHg or more than 30 mmHg less than the baseline value), use of vasopressors to maintain blood pressure, change in creatinine level (creatinine level greater than 200 μmol [greater than 2.0 mg/dL]), change in respiratory status (partial pressure of O_2 less than 60 mmHg, partial pressure of CO_2 greater than 50 mmHg or initiation of ventilator assistance) or change in level of consciousness, all 48 h pre- or postculture date. Response to antibiotic therapy was measured as favourable if substantial resolution of fever, leukocytosis and all signs of infection within seven days of starting antibiotics, or unfavourable if death was seen within seven days, persistence of the causative organism at four days or no substantial improvement of patient's condition at seven days was seen. Antibiotic type, date antibiotic given and antibiogram data were collected for patients and classified into two categories: appropriate treatment or inappropriate treatment. Time to appropriate antibiotic was calculated in days from first positive culture date to date of first appropriate antibiotic. Criteria for appropriate treatment included an antibiogram result for the antibiotic that was susceptible, or an antibiotic classified as 'appropriate' by an infectious disease physician for that type of infection and the specific organism.

Sample size and statistical analysis

Sample size calculations were based on the assumption that 15% of the controls would have had prior exposure to a risk factor known for acquiring ESBLs, with an alpha of 0.05 and power of 80%, and would detect an increased odds ratio of 2.75 or greater. A total of 101 cases and 101 controls were needed. Data were entered into Epi Info version 6.04c software (Centers

for Disease Control and Prevention, USA). Univariate analysis to determine the difference between ESBL cases and AmpC cases was performed for the purpose of ascertaining whether the cases could be aggregated together into one group of both ESBL and AmpC cases. Patient characteristics and outcome measures for cases and controls were compared using univariate analysis. Fisher's exact test or the χ^2 test, where appropriate, were used to compare categorical variables. Unpaired Student's *t* test was used for continuous data. Backward stepwise conditional logistic regression analysis was used to determine characteristics associated with acquisition of ESBLs or AmpC. Stepwise logistic regression models were used to determine significant variables and interactions. All tests were two-tailed, and P<0.05 was considered to be statistically significant. Multivariate analysis was performed using SPSS version 11.0 (SPSS Inc, USA).

RESULTS

Eight Canadian hospitals participating in CNISP prospectively identified 142 cases of *E coli* or *Klebsiella* species harbouring ESBL or AmpC beta-lactamases. Of these, 36 cases were excluded for not meeting the case definition or because incomplete data were submitted. A total of 106 cases of ESBL/AmpC *E coli* or *Klebsiella* species meeting the criteria for analysis were retained. Cultures from 80 cases grew *E coli* and 26 cases grew *Klebsiella* species with ESBL detected in 74 isolates (51 *E coli* and 23 *Klebsiella* species) and AmpC-mediated resistance was noted in 32 isolates (29 *E coli* and three *Klebsiella* species) There were no significant differences in the demographic or risk factor variables collected when comparing ESBL and AmpC cases and therefore the two groups were combined and classified as one, ESBL/AmpC, for the purposes of the present study. The majority of clinical specimens were urine (62%), followed by blood (17%), respiratory tract (10%), skin or soft tissue (7%), stool (6%) and other (14%). These specimens were not mutually exclusive and 22 patients had more than one positive clinical specimen, with the range of one to three positive cultures of *E coli* or *Klebsiella* species per patient.

Univariate analysis noted significant differences between cases and controls (Table 1). Those with P<0.20 were included in the multivariate analysis. Multivariate analysis (Table 2) found an association of becoming an ESBL/AmpC case with: prior admission to a nursing home (OR 8.28; 95% CI 1.70 to 40.26; P=0.01); prior admission to an acute care facility (OR 1.96; 95% CI 1.06 to 3.62; P=0.03), prior first- and third-generation cephalosporin use (OR 2.38; 95% CI 1.13 to 5.03; P=0.02 and OR 4.52; 95% CI 1.44 to 14.25; P=0.01) and length of stay before infection greater than 14 days (OR 3.05; 95% CI 1.44 to 6.49; P=0.004).

There were no significant differences between cases and controls in severity of illness as a result of the *E coli* or *Klebsiella* species (Table 3). A longer postinfection length of stay was found with cases (median 12 days versus seven days, P=0.03). Similarly there were no differences in 'unfavourable response', defined as death within seven days, persistence of the causative organism at 14 days or no improvement in condition at seven days (17% versus 15%, P=not significant). Mortality rate among cases was almost twice as high as controls (13% versus 7%, P=not significant); however, the difference was not statistically significant. In addition, the mortality rate for blood stream infection patients did not vary significantly between cases and controls at 25% versus 19% (P=not significant), respectively.

Information on appropriate antibiotic use was only available for 89 cases and 60 controls. Cases were 1.9 times more likely to not receive appropriate antibiotics compared with controls (27.0% versus 13.8%; P=0.05). Median length of time to receipt of appropriate antibiotics was 2.8 days for cases (range 0 to 27 days) and 1.2 days for control (range 0 to 7 days), P=0.05.

TABLE 1
Patient characteristics and antibiotic consumption before identification of *Escherichia coli* or *Klebsiella* species

	Cases, n=106	Controls, n=106	P
Age, years, median (range)	64.0 (0–96)	65.7 (0–92)	NS
Sex (female), n (%)	53 (45.3)	64 (54.7)	NS
Prior acute care facility stay (previous 6 months), n (%)	55 (52)	37 (35)	0.01
Prior nursing home stay (previous 6 months), n (%)	13 (12)	2 (2)	0.003
Prior intensive care unit stay (previous 30 days), n (%)	37 (35)	23 (22)	0.03
Prior antibiotic use (previous 4 weeks), n (%)	76 (72)	30 (28)	<0.001
Classification of antibiotic, n (%)			
Penicillins	23 (22)	13 (12)	NS
Carbapenems	4 (4)	2 (2)	NS
Aminoglycosides	13 (12)	8 (8)	NS
1st generation cephalosporins	30 (28)	16 (15)	0.03
2nd generation cephalosporins	4 (4)	1 (1)	NS
3rd generation cephalosporins	18 (17)	4 (4)	0.003
Macrolides	7 (6)	2 (2)	NS
Fluoroquinolones	33 (31)	13 (12)	0.002
Antibiotics used in the previous 4 weeks (mean)	2.1	0.9	<0.001
Concurrent MRSA, n (%)	9 (9)	2 (2)	0.03
Device in place seven days before acquiring organism, n (%)	81 (76.4)	63 (59.4)	0.01
Types of devices, n (%)			
Urinary catheter	62 (58)	49 (46)	0.09
Central venous catheter	40 (38)	26 (24)	0.05
Nasogastric or feeding tube	35 (33)	20 (19)	0.03
Tracheostomy	11 (10)	1 (1)	0.007
Length of stay before episode, median (range)	8 days (0–205)	2 days (1–182)	<0.001

MRSA Methicillin-resistant Staphylococcus aureas*; NS Not statistically significant*

TABLE 2
Multivariate analysis of risk factors for acquisition of extended-spectrum beta-lactamase/AmpC *Escherichia coli* or *Klebsiella* species

	OR	95% CI	P
Prior nursing home stay (previous 6 months)	8.28	1.70, 40.26	0.01
Prior 1st generation cephalosporin use	2.38	1.13, 5.03	0.02
Prior 3rd generation cephalosporin use	4.52	1.44, 14.25	0.01
Length of stay before infection >14 days	3.05	1.44, 6.49	0.004
Prior acute care facility stay (previous 6 months)	1.96	1.06, 3.62	0.03

TABLE 3
Outcome differences between extended-spectrum beta-lactamase/AmpC *Escherichia coli* or *Klebsiella* cases versus controls

	Cases	Controls	P
Mean length of stay post positive specimen (days)	12	7	0.3
Discharged at 8 weeks, n (%)	86 (84)	95 (94)	0.02
Not appropriate treatment given, n (%)	24 (27.0)	8 (13.3)	0.05
Median length of time in days to appropriate treatment (range)	2.8 (0–26)	1.2 (0–7)	0.004
Severity of Illness indicator* (infected cases only†), n (%)	69 (70)	59 (63)	NS
Unfavourable response‡ (infected cases only†), n (%)	17 (17)	14 (15)	NS
Death (infected cases only†), n (%)	13 (13)	7 (7)	NS

**Intensive care unit admission, hypotension, vasopressors used, creatinine level change, respiratory status change, decrease level of consciousness as a result of the infection. †Cases n=99; controls n=93; ‡Death within 7 days, persistence of the organism at 4 days, no improvement at 7 days. NS Not significant*

DISCUSSION

The clinical impact of ESBL or AmpC beta-lactamase-producing Gram-negative rods has been the subject of investigations in recent years and many factors have been associated with an increased risk for becoming colonized or infected with an ESBL or AmpC beta-lactamase-producing organism. These include prior antibiotic use, inadequate empirical antibiotic use, length of ICU stay, previous hospitalization, presence of an indwelling device, mechanical ventilation, and duration of hospitalization before identification of the isolate (4,12,14-23). However, many of these studies have been conducted during an outbreak or have focused on specific populations such as the ICU, those with blood stream infections, paediatric cases only or transplant wards. A one-year surveillance program of clinical isolates for ESBLs ending on September 30, 2000, at 12 teaching hospitals across Canada revealed that 0.28% (n=29,323) of *E coli* isolates and 0.8% (n=5156) of *Klebsiella* species were confirmed as having ESBL (10). Importantly, clonal dissemination of strains across large geographic areas was not noted and no predominant ESBL type was found. This trend continued throughout the course of the case-control study and it required 12 months to collect sufficient cases and controls to permit statistically significant analysis. Despite the length of time to complete the study, the multiple facility participation and the wide range of genotypes represented may better reflect the clinical situation in most acute care facilities.

A case-control analysis of 31 patients with ceftazidime-resistant *Klebsiella pneumoniae* or *E coli* bacteremia revealed no significant differences in length of stay after the bacteremic event, but a higher risk of dying in the case group if inappropriate treatment was received (24). Paterson et al (25) performed a prospective observational study of *K pneumoniae* bacteremias at 12 transplant units. Patients with ESBL-producing *K pneumoniae* had more breakthrough bacteremias and longer median length of stay compared to patients with non-ESBL-producing isolates. Kim et al (26), in an analysis of ESBL-producing *Klebsiella* bacteremia, documented higher initial treatment failures although cases did not have a higher mor tality than controls. Pena et al (23) found overall mortality rates for ESBL *E coli* of 25% versus non-ESBL *E coli* 11% (P=0.01), while Skippen et al (20) saw similar finding as this study with no differences in mortality between ESBL *E coli* and *Klebsiella* species cases and controls (P=0.2). In a matched case-control study of ESBL and AmpC beta-lactamase-producing *E coli* and *K pneumoniae*, Lautenbach et al (27) found that case patients received effective antibiotic treatment 72 h after the infection was suspected, significantly longer than control patients (11.5 h). Furthermore, infections with these organisms were associated with an increased length of hospitalization and cost (27).

The present study similarly demonstrated that cases on average took one day longer to receive appropriate antibiotic therapy and were associated with a longer postinfection length of stay. While there was no significant difference in persistence of the causative organism or lack of improvement in condition at seven days (likely because cases included nonbacteremia events), it should be noted that the mortality rate among cases was almost twice as high compared with controls, although the difference was not statistically significant. Differences may have reached statistical significance had there been sufficient number of serious infections (eg, sterile sites, bacteremias). One-third of the infections in the case group were considered to be significant infections (bacteremia, pneumonia, surgical site infection). The increased association with a concurrent antibiotic-resistant organism (ARO) is not surprising, and it can be speculated that the same antibiotic pressures that increase the risk of acquisition for *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococcus also select for ESBL or AmpC strains.

Limitations in the present study were that the populations examined were in major teaching hospitals and so likely not entirely representative of all hospitalized patients in Canada. Acuity of illness among hospitals was not evaluated and therefore findings cannot be generalized to the general patient population in Canada. The differences in the patient populations between the hospitals is likely insignificant given that these hospitals have successfully worked together in the past on a variety of surveillance projects and the patient case-mix has been found to be similar in those previous studies. However, as we did not evaluate the inter-reliability between hospitals, this remains a limitation to the study.

The main limitation is the choice of control patients being patients susceptible to third-generation cephalosporins. Because controls were not chosen from the base population of patients within these institutions estimates of risk may be biased. Prior exposure to first- and third-generation cephalosporins as a predictor of being a case may be overestimated because controls are less likely to be exposed to these antibiotics. The statistical strength of the specific 'risk of prior antibiotic' should be considered with this limitation in mind. Also, the matching of cases and controls did not factor in the 'place of acquisition' and therefore community-acquired patients admitted to hospital may have been matched with health care-acquired patients or vice versa where risk factors for acquisition would differ and alternatively affect results.

Despite these limitations, the data presented in this study are an important contribution to understanding the prevalence of ESBL and/or AmpC containing isolates of *E coli* and *Klebsiella* species in Canadian hospitals. The present study demonstrates that acute care facilities in Canada currently are

not important reservoirs for ESBL or AmpC bacteria and the presence of these AROs do not necessarily portend a poorer outcome when all clinical specimens are considered. Nevertheless, the association with other AROs, the higher risk of developing an infection if initially colonized with an ESBL or AmpC, and the prolonged postinfection stay compared with controls support previous recommendations for antimicrobial stewardship and a high index of suspicion in at-risk patient populations.

ACKNOWLEDGEMENTS: David Boyd, National Microbiology Laboratory, Public Health Agency of Canada; Elizabeth Bryce, Vancouver General Hospital, Vancouver, BC; John Conly, Foothills Medical Centre, Calgary, AB; Gordon Dow, The Moncton Hospital, Moncton, NB; John Embil, Health Sciences Centre, Winnipeg, MB; Joanne Embree, Health Sciences Centre, Winnipeg, MB; Charles Frenette, Hôpital Charles LeMoyne, Longueil, QC; Michael Gardam, University Health Network, Toronto, ON; Denise Gravel, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Elizabeth Henderson, Peter Lougheed Centre, Calgary, AB; James Hutchinson, Health Sciences Centre, St. John's, NL; Michael John, London Health Sciences Centre, London, ON; Lynn Johnston, Queen Elizabeth II Health Sciences Centre, Halifax, NS; Pamela Kibsey, Victoria General Hospital, Victoria, BC; Joanne Langley, IWK Health Science Centre, Halifax, NS; Mark Loeb, Hamilton Health Sciences Corporation, Hamilton, ON; Anne Matlow, Hospital for Sick Children, Toronto, ON; Allison McGeer, Mount Sinai Hospital, Toronto, ON; Sophie Michaud and Christian Sinave, CHUS-Hôpital Fleurimont, Sherbrooke, QC; Mark Miller, SMBD-Jewish General Hospital, Montreal, QC; Dorothy Moore, Montreal Children's Hospital, Montreal, QC; Michael Mulvey, National Microbiology Laboratory, Public Health Agency of Canada; Marianna Ofner-Agostini, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Shirley Paton, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Virginia Roth, The Ottawa Hospital, Ottawa, ON; Andrew Simor, Sunnybrook Health Sciences Centre, Toronto, ON; Jacob Stegenga, Centre for Infectious Disease Prevention and Control, Public Health Agency of Canada; Tammy Stuart, Canadian Field Epidemiology Program, Public Health Agency of Canada; Kathryn Suh, Children's Hospital of Eastern Ontario, Ottawa, ON; Geoffrey Taylor, University of Alberta Hospital, Edmonton, AB; Eva Thomas, Children's and Women's Health Center, Vancouver, BC; Nathalie Turgeon, Hôtel-Dieu de Québec du CHUQ, QC; Mary Vearncombe, Sunnybrook Health Sciences Centre, Toronto, ON; Joseph Vayalumkal, Canadian Field Epidemiology Program, Public Health Agency of Canada; Karl Weiss, Maisonneuve-Rosemont Hospital, Montreal, QC; Alice Wong, Royal University Hospital, Saskatoon, SK; Dick Zoutman, Kingston General Hospital, Kingston, ON.

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