Analysis of 1560 inpatient and outpatient *Escherichia coli* isolates from across Canada – Results from the CANWARD 2007 study

Philippe RS Lagacé-Wiens MD[1,3], Melanie R DeCorby MSc[1], Patricia J Baudry MSc[1], Daryl J Hoban PhD[1,2,3], James A Karlowsky PhD[1,2,3]; the Canadian Antimicrobial Resistance Alliance (CARA), George G Zhanel PhD[1,2]

PRS Lagacé-Wiens, MR DeCorby, PJ Baudry, et al. Analysis of 1560 inpatient and outpatient *Escherichia coli* isolates from across Canada – Results from the CANWARD 2007 study. Can J Infect Dis Med Microbiol 2009;20(Suppl A):49A-53A.

OBJECTIVES: *Escherichia coli* was the most common pathogen isolated in the Canadian Ward Surveillance Study (CANWARD 2007) and remains one of the most common pathogens isolated in all health care settings. An in-depth analysis of all *E coli* isolates was performed to determine the distribution and demographics associated with resistance to antimicrobials, presence of extended-spectrum beta-lactamases (ESBLs) and multidrug resistance (MDR; concurrent resistance to agents from three or more different antimicrobial classes).

METHODS: The CANWARD 2007 study characterized pathogens isolated from inpatient (surgical and medical wards, and intensive care units) and outpatient (emergency departments and clinics) areas of 12 Canadian hospitals between January and December 2007. *E coli* susceptibility to 12 antimicrobials was determined, ESBL production was determined, and a multivariate nominal logistic regression model was designed to determine if sex, isolation from a sterile site, inpatient versus outpatient status, and age were significantly associated with susceptibility to the tested antimicrobials, MDR or ESBL production.

RESULTS: In total, 1702 *E coli* isolates, representing 21.6% of all isolates collected in the CANWARD 2007 study, were investigated. Of these, 1560 isolates fell within the primary objective of the study and were included in the present analysis. Susceptibilities were greater than 90% for meropenem (100%), ertapenem (100%), tigecycline (99.9%), piperacillin-tazobactam (97.9%), cefepime (97.9%), ceftriaxone (95.4%), nitrofurantoin (95.2%), cefoxitin (94.8%), amoxicillin-clavulanate (92.9%) and gentamicin (91.4%). Cefazolin (89.4%), the fluoroquinolones (ciprofloxacin, 79.4%; levofloxacin, 79.9%) and trimethoprim-sulfamethoxazole (75.7%) were less active agents. In the multivariate model, invasive isolates were significantly associated with lower susceptibility rates for trimethoprim-sulfamethoxazole. Increasing age was associated with lower susceptibility to fluoroquinolones, ceftriaxone, cefepime, gentamicin and nitrofurantoin, as well as ESBL production. Sex was not associated with resistance to any antimicrobial or to ESBL production. Inpatient status was associated with higher resistance rates to amoxicillin-clavulanate, cefazolin, fluoroquinolones and trimethoprim-sulfamethoxazole. Isolation of an ESBL producer was only found to be independently associated with age, being more common in older patients. MDR was not found to be associated with any variable measured when ESBL producers were excluded from analysis.

CONCLUSIONS: *E coli* antimicrobial susceptibility varies according to patient factors. Age and inpatient status were the most important determinants in the present analysis and should be considered when prescribing empirical antimicrobial therapy. Fluoroquinolones and sulfonamides should be used cautiously and in consideration of local resistance patterns for infections caused by *E coli*, due to lower susceptibility rates. Independent factors associated with antimicrobial resistance were age, inpatient status and isolation from a sterile site. These factors should be considered when empirically treating infections likely caused by *E coli*. Local antimicrobial prescribing practices, in particular the liberal use of fluoroquinolones, and inadequate infection control practices may be reducing susceptibility rates.

Key Words: Escherichia coli; *Gram-negative; Infection; Resistance; Treatment*

L'analyse d'isolats d'*Escherichia coli* chez 1 560 patients hospitalisés et ambulatoires de partout au Canada – Les résultats de l'étude CANWARD 2007

OBJECTIFS : L'*Escherichia coli* était le pathogène le plus isolé dans l'étude CANWARD 2007 sur la surveillance des services aux hospitalisés canadiens et demeure l'un des pathogènes les plus isolés en milieu de santé. On a effectué une analyse approfondie de tous les isolats d'*E coli* pour déterminer la répartition et la démographie associées à la résistance aux antimicrobiens ainsi qu'à la présence de bêta-lactamases à large spectre (ESBL) et de multirésistance (résistance conjointe à au moins trois classes d'antimicrobiens).

MÉTHODOLOGIE : L'étude CANWARD 2007 caractérisait les pathogènes isolés de patients hospitalisés (service de chirurgie, service médical et unité de soins intensifs) et ambulatoires (urgence et cliniques) de 12 hôpitaux canadiens entre janvier et décembre 2007. On a déterminé la susceptibilité de l'*E coli* à 12 antimicrobiens ainsi que la production d'ESBL et conçu un modèle de régression logistique nominale multivariée pour déterminer si le sexe, l'isolement d'un foyer stérile, le statut de patient hospitalisé ou ambulatoire et l'âge s'associaient de manière significative à la susceptibilité aux antimicrobiens vérifiés, à la multirésistance ou à la production d'ESBL.

RÉSULTATS : Au total, on a évalué 1 072 isolats d'*E coli*, représentant 21,6 % de tous les isolats prélevés dans le cadre de l'étude CANWARD 2007. De ce nombre, 1 560 isolats respectaient l'objectif primaire de l'étude et ont été inclus dans la présente analyse. Les susceptibilités étaient supérieures à 90 % pour le méropénem (100 %), l'ertapénem (100 %), la tigécycline (99,9 %), la pipéracilline-tazobactam (97,9 %), la céfépime (97.9 %), la ceftriaxone (95,4 %), la nitrofurantoïne (95,2 %), la céfoxitine (94,8 %), l'amoxicilline-clavulanate (92,9 %) et la gentamicine (91,4 %). La céfazoline (89,4 %), les fluoroquinolones (ciprofloxacine, 79,4 %, lévofloxacine, 79,9 %) et le triméthoprim-sulfaméthoxazole (75,7 %) étaient moins actifs. Dans le modèle multivarié, les isolats envahissants étaient associés de manière marquée à des taux de susceptibilité plus faibles pour le triméthoprim-sulfaméthoxazole. Le vieillissement s'associait à une susceptibilité plus faible aux fluoroquinolones, à la ceftriaxone, à la

suite page suivante

[1]*Department of Medical Microbiology and Infectious Diseases, Faculty of Medicine, University of Manitoba;* [2]*Clinical Microbiology, Health Sciences Centre;* [3]*Clinical Microbiology, St Boniface General Hospital, Winnipeg, Manitoba*

Correspondence: Dr Philippe RS Lagacé-Wiens, Diagnostic Services Manitoba, St Boniface General Hospital, L4025-409 Taché Avenue, Winnipeg, Manitoba R2H 2A6. Telephone 204-237-2483, fax 204-237-6065, e-mail plagacewiens@sbgh.mb.ca

céfépime, à la gentamicine et à la nitrofurantoïne, ainsi qu'à la production d'ESBL. Le sexe ne s'associait pas à la résistance à un antimicrobien ou à la production d'ESBL. L'hospitalisation s'associait à des taux de résistance plus élevés à l'amoxicilline-clavulanate, à la céfazoline, aux fluoroquinolones et au triméthoprim-sulfaméthoxazole. L'isolement d'un producteur d'ESBL s'associait seulement de manière indépendante à l'âge, puisqu'il était plus courant chez les patients plus âgés. La multirésistance n'était pas reliée à une variable mesurée lorsque les producteurs d'ESBL étaient exclus de l'analyse.

CONCLUSIONS : La susceptibilité des antimicrobiens à l'*E coli* varie selon des facteurs propres au patient. Selon la présente analyse, l'âge et l'hospitalisation étaient les principaux déterminants, et il faudrait en tenir compte au moment de prescrire un traitement antimicrobien empirique. Les fluoroquinolones et les sulfamides doivent être utilisés avec prudence et compte tenu des profils de résistance locaux pour les infections causées par l'*E coli*, en raison de taux de susceptibilité plus faibles. Les facteurs indépendants liés à la résistance antimicrobienne étaient l'âge, l'hospitalisation et l'isolement d'un foyer stérile. Il faut tenir compte de ces facteurs lors du traitement empirique d'infections probablement causées par l'*E coli*. Les pratiques locales de prescription d'antimicrobiens, notamment l'utilisation libérale de fluoroquinolones et les pratiques inadéquates de contrôle de l'infection, pourraient réduire les taux de susceptibilité.

Escherichia coli is the most commonly isolated clinically relevant Gram-negative organism in most health care settings (1-3). Although most commonly associated with urinary tract infections, all body sites can be involved. Furthermore, resistance to multiple antimicrobials is increasing and multidrug resistant (MDR; concurrent resistance to agents from three or more different antimicrobial classes) isolates are common (1,4,5). Appropriate empirical antimicrobial choice must take into account local resistance patterns and other demographic variables such as patient age, site and severity of infection, sex, inpatient status as well as previous antimicrobial use, stay in hospitals or personal care homes, and colonization with antimicrobial resistant organisms (1,6). The purpose of the present study was to provide an in-depth analysis of patient factors associated with drug resistance in the most commonly isolated organism overall in Canadian hospitals.

METHODS

E coli isolates were obtained as part of the Canadian Ward Surveillance Study (CANWARD 2007), which collected isolates submitted to 12 clinical microbiology laboratories from tertiary care hospitals in seven provinces across Canada. Submitting sites and collection strategy are described elsewhere in the present supplement (2). Isolates had to be deemed clinically significant by the referring laboratory's current specimen work-up protocol. Demographic information collected with each isolate included patient age, sex, site of infection and the location of patient contact (surgical or medical ward, emergency room, intensive care unit [ICU] or hospital clinic). A minimum number of isolates from each hospital location and anatomical site was requested to provide more power to the study. The implication of this collection strategy is that the anatomical distribution of pathogen isolation and inpatient versus outpatient distribution does not reflect the true distribution in the population studied. Isolates were collected within both primary and secondary study objectives and only isolates collected within the primary objective were considered in this analysis. For statistical analysis, age was divided into four categories: 20 years and younger, 21 to 60 years, 61 to 80 years, and 81 years and older, and location of patient contact was divided into either inpatient (wards and ICUs) or outpatient (emergency room and clinics). Information on previous antimicrobial exposure, hospitalization duration and underlying medical conditions was not available. Antimicrobial susceptibility to amoxicillin-clavulanate, cefazolin, cefepime, ceftriaxone, ciprofloxacin, gentamicin, nitrofurantoin, levofloxacin, meropenem, ertapenem, piperacillin-tazobactam, tigecycline and trimethoprim-sulfamethoxazole was determined using broth dilution as described elsewhere in the present supplement (2). Screening for ESBL production was achieved using a 1 µg/mL or greater ceftriaxone breakpoint and confirmation was with the Clinical and Laboratory Standards Institute-recommended disk diffusion method (7). Univariate analysis using the χ^2 (or Fisher's exact test where required) was undertaken to identify relationships between susceptibility to each of the antimicrobials and ESBL production; and the following variables: sex, age group, inpatient/outpatient status and isolation from a sterile site (blood, cerebrospinal fluid, synovial fluid). Relationships where the $P<0.20$ in the univariate analysis were included in a multivariate nominal logistic regression model to determine independent explanatory variables. Initially, a full factorial multiple logistic regression analysis was performed using the potential explanatory variables identified in the univariate analysis for each antimicrobial, and then a backward selection so that all factors remaining in the model were statistically significant at a 5% level ($P<0.05$). Statistical analysis was undertaken using JMP software version 7.0 (SAS Institute Inc, USA).

RESULTS

Of 7881 total organisms, 1702 *E coli* (21.6%) were collected from the CANWARD 2007 study, making it the most common organism isolated from patients in Canadian hospitals overall. Of these, 1560 fell within the primary objective and the remaining 142 were submitted as putative ESBL producers for separate analysis and excluded from the present analysis. The mean age of patients infected with *E coli* was 56.9 years; 12.3% of *E coli* isolates were from patients younger than 21 years, 34.7% were 21 to 60 years of age, 33.9% were 61 to 80 years of age and 19.1% were older than 80 years of age. There were more samples from women (59.3%); with both sexes combined, 50.5% were invasive isolates (all bloodstream), and 40.7% were from urine, 6.4% from respiratory sources and 2.4% from wounds. Note that the sampling strategy was biased to include a surplus of bloodstream isolates to have greater numbers of these for analysis and this does not represent the true source distribution of *E coli* infections. The distribution among provinces was British Columbia, 9.7%; Alberta, 7.6%; Saskatchewan, 9.1%; Manitoba, 9.2%; Ontario, 28.3%; Quebec, 29.2% and Nova Scotia, 6.9%. Isolates were not obtained from Newfoundland, Nunavut, the Northwest Territories, Yukon, New Brunswick or Prince Edward Island.

Minimum inhibitory concentrations (MICs) required to inhibit 50% and 90% of organisms (MIC_{50}, MIC_{90}) and percentage of isolates susceptible to the antimicrobials are provided in Table 1. Susceptibilities were greater than 90% for meropenem (100%), ertapenem (100%), tigecycline (99.9%), piperacillin-tazobactam (97.9%), cefepime (97.9%), ceftriaxone

(95.4%), nitrofurantoin (95.2%), cefoxitin (94.8%), amoxicillin-clavulanate (92.9%) and gentamicin (91.4%). Cefazolin (89.4%), the fluoroquinolones (ciprofloxacin, 79.4%; levofloxacin, 79.9%) and trimethoprim-sulfamethoxazole (75.7%) were less active agents. One hundred twenty-seven (8.2%) of *E coli* isolates had an MDR phenotype and 53 (3.4%) of the isolates were phenotypically confirmed ESBL producers. The latter are discussed elsewhere in the present supplement.

Univariate statistical analysis revealed no relationship (P≥0.20) between any of the demographic variables and susceptibility to meropenem, ertapenem, tigecycline and cefoxitin. The multivariate model is illustrated in Table 2. Piperacillin-tazobactam is excluded from the table because no variables were associated with susceptibility to this antimicrobial in the multivariate model. Age was the strongest predictor of reduced susceptibility, being independently associated with reduced susceptibility to fluoroquinolones, ceftriaxone, cefepime, gentamicin and nitrofurantoin, ESBL production and MDR. Separate analysis of isolates that were MDR but not ESBL producers showed that the association between age and MDR isolated was largely driven by ESBL producers and no association existed between age and MDR isolates that were not ESBL producers (data not shown). Both stepwise regression analyses applied to age categories and linear regression applied to actual age (data not shown) confirmed that increasing age was associated with decreasing susceptibility to all agents and increased likelihood of ESBL production. Isolation from a sterile site was only independently associated with reduced susceptibility to trimethoprim-sulfamethoxazole. Inpatient status was associated with reduced susceptibility to amoxicillin-clavulanate, cefazolin, fluoroquinolones and trimethoprim-sulfamethoxazole. Sex was not independently associated with reduced susceptibility to any antimicrobials. Differences in susceptibility between sexes were driven by higher inpatient prevalence and higher mean and median age in men.

TABLE 1
Susceptibility and minimal inhibitory concentration (MIC) of 1560 *Escherichia coli* isolates in the CANWARD 2007 study

Antimicrobial	% S	% I	% R	MIC_{50}, µg/mL	MIC_{90}, µg/mL
Amoxicillin-clavulanate*	92.90	5.95	1.15	4	8
Cefazolin	89.40	3.53	13.49	2	16
Cefepime	97.94	1.22	0.83	≤1	≤1
Cefoxitin*	94.82	2.88	2.30	4	8
Ceftriaxone	95.44	1.41	3.15	≤1	≤1
Ciprofloxacin	79.38	0.32	20.30	≤0.06	>16
Gentamicin	91.22	0.45	8.17	≤0.5	2
Ertapenem	100	–	–	<0.06	<0.06
Levofloxacin	79.90	0.83	19.27	≤0.06	16
Meropenem	100	–	–	≤0.12	≤0.12
Nitrofurantoin*	95.20	2.50	2.30	16	32
Piperacillin-tazobactam	97.94	0.83	1.22	≤1	4
Tigecycline	99.87	0.13	–	0.25	0.5
Trimethoprim-sulfamethoxazole	75.72	–	24.34	≤0.12	>8

**521 isolates were tested against amoxicillin-clavulanate, cefoxitin and nitrofurantoin. I Intermediate; $MIC_{50/90}$ MICs required to inhibit 50%/90% of organisms; R Resistant; S Susceptible*

DISCUSSION

Low susceptibility of ICU *E coli* isolates to fluoroquinolones and trimethoprim-sulfamethoxazole was not unexpected given the wide use of these antimicrobials in both inpatients and outpatients. In particular, the dramatic increase in fluoroquinolone resistance has been observed in many settings (8-10). Our observations suggest that first-generation cephalosporins and amoxicillin-clavulanate are still useful agents for infections caused by *E coli* in that susceptibility rates remain near 90% overall. This is particularly true of outpatient isolates where susceptibility is greater than 90% for both these agents. On the contrary, low susceptibility to fluoroquinolones even in the outpatient setting (84%) begins to bring into question the use of these agents as first line for infections commonly caused by *E coli*, such as urinary tract infections. Trimethoprim-sulfamethoxazole susceptibility rates are below 80% in both inpatient and outpatient settings and should only be used for infections empirically in the context of supportive data from local antibiograms or definitive susceptibility data.

In our multivariate model, increasing age was independently associated with reduced susceptibility to fluoroquinolones, nitrofurantoin, ceftriaxone, cefepime, gentamicin and ESBL production. The association between age and fluoroquinolone susceptibility has been demonstrated previously and is likely due to increasing exposure to fluoroquinolones over time and avoidance of fluoroquinolone use in children (11-14). This suggests that fluoroquinolones as empirical therapy may be appropriate in younger patients if indicated. However, in routine pediatric practice, these drugs are best avoided because of concerns for toxicity. Age has also been described as a risk factor for infection with an ESBL-producing organism (15,16), and may be associated with increasing exposure to health care settings and antibiotics. Interestingly, exposure to fluoroquinolones has been described as a risk factor for acquisition of an ESBL producer, which may partially explain that age is associated with both resistance to fluoroquinolones and ESBL-producing *E coli* (16). The association between age and cefepime and ceftriaxone resistance is likely driven by the same factors responsible for the increase in infections caused by ESBL producers, because ESBL production correlates well with resistance to both cefepime and ceftriaxone. Because resistance to cefazolin was not associated with increasing age, it would appear that increasing age does not correlate with the acquisition of cephalosporinases capable of hydrolyzing on first-generation cephalosporins, but does correlate with acquisition of cephalosporinases with activity against advanced cephalosporins (ie, ESBLs). It is interesting that increasing age predicted resistance to gentamicin and nitrofurantoin. Age has been reported as a risk factor for resistance to several antimicrobials before and is likely related to an increased cumulative antimicrobial pressure (17). ESBL production has also been shown to be strongly associated with gentamicin resistance (18), as is the case in our data (gentamicin susceptibility in ESBL producers is 41.5% versus 93.2% in non-ESBL producers, P<0.001), which suggests that the increasing prevalence of ESBL producers with increasing age is playing a role in the increasing resistance to gentamicin.

TABLE 2
Percentage of *Escherichia coli* isolates susceptible to selected antimicrobials by explanatory variables significant in the multivariate nominal logistic regression model

Variable (number of isolates)	CLA (521)	CFZ (1560)	CRO (1560)	CPM (1560)	CIP (1560)	LVX (1560)	GM (1560)	SXT (1560)	NF (521)	MDR (127)	ESBL (53)
Age , years (n=1560)	NS	NS	P<0.001	P=0.048	P<0.001	P<0.001	P=0.012	NS	P<0.001	0.043	P<0.001
<21 (n=191)	90.2	90.0	100.0	100.0	94.2	94.2	95.8	80.1	98.0	4.2	0.0
21–60 (n=542)	92.9	90.4	96.3	98.5	81.1	81.7	92.0	75.0	98.2	8.2	2.2
61–80 (n=529)	94.1	87.9	92.8	96.6	74.8	75.8	88.6	72.5	96.0	10.2	6.1
>80 (n=298)	91.8	89.9	95.6	98.0	74.8	74.8	92.3	79.9	86.7	7.1	3.0
Sex (n=1560)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Male (n=636)	91.0	88.2	94.2	97.5	73.0	73.8	89.1	73.2	94.9	10.9	4.3
Female (n=924)	94.4	90.3	96.3	98.3	83.8	84.1	93.0	77.5	95.5	6.3	2.8
Sterile site isolate (n=1560)	NS	NS	NS	NS	NS	NS	NS	P<0.001	NS	NS	NS
Yes (n=788)	92.5	88.2	94.4	97.3	78.3	78.5	90.2	71.4	94.3	8.9	4.3
No (n=772)	95.7	90.7	96.5	98.6	80.5	81.3	92.6	80.1	95.3	7.4	2.5
Patient setting (n=1560)	P<0.001	P<0.001	NS	NS	P<0.001	P<0.001	NS	P<0.001	NS	NS	NS
Inpatient (n=693)	88.1	86.0	93.1	96.2	72.8	73.7	88.6	71.7	94.5	11.7	5.5
Outpatient (n=867)	96.4	92.1	97.3	99.3	84.6	84.9	93.6	79.0	95.7	5.3	1.7

CLA Amoxicillin-clavulanate; CFZ Cefazolin; CIP Ciprofloxacin; CPM Cefepime; CRO Ceftriaxone; ESBL Extended-spectrum beta-lactamase producers; GM Gentamicin; LVX Levofloxacin; MDR Resistant to three or more classes of antimicrobials tested; NF Nitrofurantoin; NS No statistically significant association between susceptibility to the antimicrobial and demographic variable at the 0.05 level in the multivariate model; SXT Trimethoprim-sulfamethoxazole

Isolation from a sterile site was significantly independently associated with resistance to trimethoprim-sulfamethoxazole. This observation was made in a previous study of ICU *E coli* isolates and was thought to be potentially associated with the unmeasured variable of length of stay (12). However, in the present study, this observation was independent of inpatient status, which suggests that another mechanism may be at play. Possible explanations include co-presence of virulence determinants and trimethoprim-sulfamethoxazole resistance genes on mobile elements (integrons) or data biased by widespread use of trimethoprim-sulfamethoxazole empirically in urinary tract infections caused by trimethoprim-sulfamethoxazole-resistant organisms that subsequently progress to bacteremia, thereby inflating the number of trimethoprim-sulfamethoxazole-resistant invasive isolates.

Predictably, inpatient isolates had lower susceptibility to several antibiotics, including amoxicillin-clavulanate, fluoroquinolones, cefazolin and trimethoprim-sulfamethoxazole. Interestingly, susceptibility to antimicrobials commonly used in the inpatient setting (ceftriaxone, cefepime, gentamicin, carbapenems and piperacillin-tazobactam) did not appear to be significantly affected by inpatient status. This is reassuring in that these antimicrobials maintain good activity overall in the hospital setting. The reason that antimicrobials commonly used in the community are most affected by inpatient status is not known, but may be due to general practitioners using these antimicrobials to treat outpatients and selection bias occurring because poor response due to antimicrobial resistance requires admission for parenteral antimicrobials.

Interestingly, sex was not a predictor of susceptibility to any of the antimicrobials tested after adjusting for other factors in the multivariate model. Although large differences were seen between susceptibility to fluoroquinolones, both inpatient status and age appeared to be confounding factors in the effect of sex on fluoroquinolone resistance. The absence of a sex effect contradicts the findings of others (16,17,19), but few of these studies adjusted both for inpatient status and age and other studies have demonstrated no association with sex (12,20).

Meropenem, ertapenem, piperacillin-tazobactam, tigecycline and cefoxitin were not significantly associated with any demographic variable in the multivariate model. Low overall resistance rates accounts for these observations.

Our study had some limitations. We could not collect patient information such as length of stay, previous antimicrobial exposure and underlying disease. Although of great interest for the prediction of antimicrobial resistance, the effect of these variables cannot be determined with our data. Also, our isolates reflect only information from the 12 centres studied and our data may not reflect the antimicrobial susceptibility patterns of all hospitals in Canada. However, this study does provide valuable information about the factors predicting antimicrobial susceptibility of *E coli* in one of the largest of inpatient and outpatient populations in Canada studied to date.

ACKNOWLEDGEMENTS: Funding for the CANWARD 2007 study was provided in part by the University of Manitoba, Health Sciences Center in Winnipeg, National Microbiology Laboratory-Health Canada, Abbott, Affinium Inc, Astellas, Bayer, Janssen Ortho Inc, Merck, Oryx, Pfizer Canada, TaiGen, Targanta and Wyeth Inc. Special thanks to Nancy Laing, Barb Weshnoweski, Ravi Vashisht, Franil Tailor, Lisa Bittner and Haley Butcher for technological assistance. The authors wish to thank M Tarka for expert secretarial assistance.

APPENDIX 1

The authors would like to thank the investigators and laboratory site staff at each medical centre that participated in the CANWARD 2007 study: Vancouver Hospital, Vancouver, British Columbia – Dr D Roscoe; University of Alberta Hospitals, Edmonton, Alberta – Dr R Rennie; Royal University Hospital, Saskatoon, Saskatchewan – Dr J Blondeau; Health Sciences Centre, Winnipeg, Manitoba – Drs D Hoban and

G Zhanel; Mount Sinai Hospital, Toronto, Ontario – Dr S Poutanen; Children's Hospital of Eastern Ontario, Ottawa, Ontario – Dr F Chan; London Health Sciences Centre, London, Ontario – Dr Z Hussain; St Joseph's Hospital, Hamilton, Ontario – Dr C Lee; Hopital Maisonneuve-Rosemont, Montreal, Quebec – Dr M Laverdiere; Montreal General Hospital, Montreal, Quebec – Dr V Loo; Royal Victoria Hospital, Montreal, Quebec – Dr V Loo; QEII Health Sciences Centre, Halifax, Nova Scotia – Drs K Forward and R Davidson. CANWARD data are also displayed at www.can-r.ca, the official Web site of the Canadian Antimicrobial Resistance Alliance (CARA)

REFERENCES

1. Anupurba S, Sen MR. Antimicrobial resistance profile of bacterial isolates from Intensive Care Unit: Changing trends. J Commun Dis 2005;37:58-65.
2. Zhanel GG, Karlowsky JA, DeCorby M, et al. Prevalence of antimicrobial-resistant pathogens in Canadian hospitals: Results of the Canadian Ward Surveillance Study (CANWARD 2007). Can J Infect Dis Med Microbiol 2009;20(Suppl A):9A-19A.
3. Singh AK, Sen MR, Anupurba S, Bhattacharya P. Antibiotic sensitivity pattern of the bacteria isolated from nosocomial infections in ICU. J Commun Dis 2002;34:257-63.
4. Rhomberg PR, Fritsche TR, Sader HS, Jones RN. Antimicrobial susceptibility pattern comparisons among intensive care unit and general ward Gram-negative isolates from the Meropenem Yearly Susceptibility Test Information Collection Program (USA). Diagn Microbiol Infect Dis 2006;56:57-62.
5. Richards MJ, Edwards JR, Culver DH, Gaynes RP. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. Crit Care Med 1999;27:887-92.
6. Mohammedi I, Ploin D, Duperret S, et al. Risk factors for piperacillin/tazobactam-resistant Escherichia coli in ICU patients: a clinical study. Intensive Care Med 2003;29:1164-8.
7. Clinical_and_Laboratory_Standards_Institute. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Seveth Edition: Approved Standard M7-A7. Wayne, PA, USA, 2006.
8. Hassoun A, Eiland E. Effectiveness of flouroquinolone therapy for gram-negative infections within the intensive care unit setting. Am J Med 2006;119:e7.
9. Levin PD, Fowler RA, Guest C, et al. Risk factors associated with resistance to ciprofloxacin in clinical bacterial isolates from intensive care unit patients. Infect Control Hosp Epidemiol 2007;28:331-6.
10. Paterson DL. Resistance in gram-negative bacteria: Enterobacteriaceae. Am J Infect Control 2006;34:S20-8;S64-73.
11. Kirby JT, Fritsche TR, Jones RN. Influence of patient age on the frequency of occurrence and antimicrobial resistance patterns of isolates from hematology/oncology patients: Report from the Chemotherapy Alliance for Neutropenics and the Control of Emerging Resistance Program (North America). Diagn Microbiol Infect Dis 2006;56:75-82.
12. Lagacé-Wiens PRS, DeCorby MR, Baudry PJ, et al. Differences in antimicrobial susceptibility in *Escherichia coli* from Canadian intensive care units based on regional and demographic variables. Can J Infect Dis Med Microbiol 2008;19:282-86.
13. Dromigny JA, Nabeth P, Juergens-Behr A, Perrier-Gros-Claude JD. Risk factors for antibiotic-resistant *Escherichia coli* isolated from community-acquired urinary tract infections in Dakar, Senegal. J Antimicrob Chemother 2005;56:236-9.
14. Kiffer CR, Mendes C, Oplustil CP, Sampaio JL. Antibiotic resistance and trend of urinary pathogens in general outpatients from a major urban city. Int Braz J Urol 2007;33:42-8.
15. Rodriguez-Bano J, Navarro MD. Extended-spectrum beta-lactamases in ambulatory care: a clinical perspective. Clin Microbiol Infect 2008;14(Suppl 1):104-10.
16. Colodner R, Rock W, Chazan B, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. Eur J Clin Microbiol Infect Dis 2004;23:163-7.
17. Gesu GP, Marchetti F. Increasing resistance according to patient's age and sex in *Escherichia coli* isolated from urine in Italy. J Chemother 2007;19:161-5.
18. Baudry PJ, Nichol K, DeCorby M, et al. Comparison of antimicrobial resistance profiles among extended-spectrum-beta-lactamase-producing and acquired AmpC beta-lactamase-producing *Escherichia coli* isolates from Canadian intensive care units. Antimicrob Agents Chemother 2008;52:1846-9.
19. Stelling JM, Travers K, Jones RN, et al. Integrating *Escherichia coli* antimicrobial susceptibility data from multiple surveillance programs. Emerg Infect Dis 2005;11:873-82.
20. Karlowsky JA, Kelly LJ, Thornsberry C, et al. Susceptibility to fluoroquinolones among commonly isolated Gram-negative bacilli in 2000: TRUST and TSN data for the United States. Tracking Resistance in the United States Today. The Surveillance Network. Int J Antimicrob Agents 2002;19:21-31.