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In Vitro Activity of Fosfomycin against *Escherichia coli* Isolated from Patients with Urinary Tract Infections in Canada as Part of the CANWARD Surveillance Study

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We tested 868 urinary isolates of *Escherichia coli* collected from 2010 to 2013 as part of the Canadian national surveillance study CANWARD against fosfomycin by using the Clinical and Laboratory Standards Institute (CLSI) agar dilution method with MIC interpretation in accordance with the CLSI M100-S23 (2013) criteria. The concentrations of fosfomycin inhibiting 50 and 90% of the isolates were ≤1 and 4 μg/ml; 99.4% of the isolates were susceptible to fosfomycin.

Escherichia coli is estimated to account for 75 to 90% of uncomplicated urinary tract infections and approximately 50 to 60% of the isolates from patients with recurrent or complicated infections (1). The currently recommended empirical antimicrobial regimen for treating acute uncomplicated bacterial cystitis in otherwise healthy adult nonpregnant females is a 5-day course of nitrofurantoin, a 3-day course of double-strength trimethoprim-sulfamethoxazole (SXT) in settings where the prevalence of SXT resistance is <10 to 20%, or a 3-g single dose of fosfomycin trometamine; fluoroquinolones and β-lactams, such as amoxicillin-clavulanate, are second-line therapies (2).

The most recently published national surveillance data describing antimicrobial resistance among urinary pathogens in the United States and Canada reported SXT, ciprofloxacin, amoxicillin-clavulanate, and nitrofurantoin resistance rates of 22 to 24%, 17 to 19%, 1 to 10%, and <2%, respectively (3, 4). Fosfomycin, an agent known for >40 years, has received renewed interest recently because of increasing resistance to traditionally used agents. However, there is a paucity of published Clinical and Laboratory Standards Institute (CLSI) reference method *in vitro* antimicrobial susceptibility testing data available for fosfomycin because of the complexities associated with the agar dilution method (5).

Midstream and catheter urinary isolates of *E. coli* ($n = 868$) collected from January 2010 to May 2013 as part of the ongoing annual Canadian national surveillance study CANWARD (6) were tested; 74.8% ($n = 649$) of these isolates originated from outpatients attending hospital clinics and emergency rooms, and 25.2% ($n = 219$) were from inpatients in medical and surgical wards and intensive care units. The 15 participant laboratories were located in 12 cities in 8 of the 10 Canadian provinces. All isolates were deemed clinically significant by algorithms in place in the participating laboratories. To better delineate the activity of fosfomycin against β-lactam-resistant isolates of *E. coli*, an additional 254 extended-spectrum-β-lactamase (ESBL)-producing *E. coli* isolates, 119 AmpC-producing *E. coli* isolates, and two carbapenem-resistant *E. coli* isolates collected by the CANWARD surveillance study from January 2007 to May 2013 were tested. These additional isolates were from blood, respiratory, and wound specimens collected from 2007 to 2013 and from urine specimens collected from 2007 to 2009 (urine specimens collected from 2010 to 2013 were excluded from this data set, so they were tested only once); 34.9% ($n = 131$) of these isolates originated from outpatients attending hospital clinics and emergency rooms, and 65.1% ($n = 244$) were from inpatients in medical and surgical wards and intensive care units.

Fosfomycin antimicrobial susceptibility testing was performed by the CLSI agar dilution method (MHA supplemented with 25 μg/ml of glucose-6-phosphate); all other antibacterial agents were tested with in-house-prepared 96-well broth microdilution panels in accordance with CLSI guidelines (5, 7). Fosfomycin was supplied by Triton Pharma Inc. (Concord, Ontario, Canada) and manufactured by ZaCh System SpA (Almisano di Lonigo, Italy). Quality control was performed in accordance with CLSI recommendations, and MICs were interpreted by using CLSI M100-S23 (2013) breakpoints (5). Every isolate identified as fosfomycin intermediate or resistant was retested to confirm its phenotype.

CLSI criteria were used to screen for potential ESBL-producing isolates of *E. coli* (5). ESBL confirmatory testing was done by the CLSI disk diffusion method with disks containing ceftazidime (30 μg), ceftazidime-clavulanic acid (30 μg/10 μg), cefotaxime (30 μg), and cefotaxime-clavulanic acid (30 μg/10 μg) (5) supplied by Mast Diagnostics (United Kingdom). Any putative ESBL-producing *E. coli* isolate that was negative by the ESBL confirmatory test and resistant to cefoxitin (MICs, ≥32 μg/ml) was identified as a putative AmpC producer. Carbapenem-resistant isolates were identified by using the current CLSI breakpoints (M100-S23) (5). Multidrug-resistant (MDR) isolates were those resistant to three or more agents in different antimicrobial classes (i.e., SXT, nitrofurantoin, ciprofloxacin, and amoxicillin-clavulanate).

Table 1 depicts the *in vitro* activities of fosfomycin and comparative orally administered antimicrobial agents against 868 urinary isolates of *E. coli* obtained by clinical laboratories across Canada from 2010 to 2013. Fosfomycin inhibited >99% of the isolates

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TABLE 1 *In vitro* activities of orally available antimicrobial agents against 868 urinary isolates of *E. coli* isolated by clinical laboratories across Canada from 2010 to 2013

E. coli isolate phenotype(s) (no. of isolates) and antimicrobial agent	MIC_{50}[e]	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
All (868)						
Fosfomycin	≤1	4	≤1–512	99.4	0.5	0.1
SXT	≤0.12	>8	≤0.12–>8	74.7		25.3
Nitrofurantoin	16	32	≤1–512	96.1	2.4	1.5
Ciprofloxacin	≤0.06	>16	≤0.06–>16	77.4	0.1	22.5
Amoxicillin-clavulanate	4	16	0.5–>32	81.3	13.0	5.7
Pansusceptible (481)[a]						
Fosfomycin	≤1	2	≤1–64	100	0	0
SXT	≤0.12	0.25	≤0.12–2	100		0
Nitrofurantoin	16	32	≤1–32	100	0	0
Ciprofloxacin	≤0.06	≤0.06	≤0.06–1	100	0	0
Amoxicillin-clavulanate	4	8	0.5–8	100	0	0
SXT susceptible (647)						
Fosfomycin	≤1	4	≤1–512	99.5	0.3	0.2
SXT	≤0.12	0.25	≤0.12–2	100		0
Nitrofurantoin	16	32	≤1–512	97.5	1.5	0.9
Ciprofloxacin	≤0.06	>16	≤0.06–>16	86.2	0	13.8
Amoxicillin-clavulanate	4	16	0.5–>32	86.1	8.5	5.4
SXT resistant (219)						
Fosfomycin	2	4	≤1–128	99.1	0.9	0
SXT	>8	>8	4–>8	0		100
Nitrofurantoin	16	32	≤1–256	91.8	5.0	3.2
Ciprofloxacin	1	>16	≤0.06–>16	51.6	0.5	47.9
Amoxicillin-clavulanate	8	16	1–>32	67.1	26.5	6.4
Ciprofloxacin susceptible (672)						
Fosfomycin	≤1	2	≤1–512	99.9	0	0.1
SXT	≤0.12	>8	≤0.12–>8	83.2		16.8
Nitrofurantoin	16	32	≤1–512	97.5	1.8	0.7
Ciprofloxacin	≤0.06	≤0.06	≤0.06–1	100	0	0
Amoxicillin-clavulanate	4	16	0.5–>32	85.7	8.9	5.4
Ciprofloxacin resistant (195)						
Fosfomycin	2	4	≤1–128	97.9	2.1	0
SXT	>8	>8	≤0.12–>8	45.9		54.1
Nitrofurantoin	16	32	≤1–256	91.3	4.6	4.1
Ciprofloxacin	>16	>16	4–>16	0	0	100
Amoxicillin-clavulanate	8	16	1–>32	66.0	27.3	6.7
Amoxicillin-clavulanate susceptible (704)						
Fosfomycin	≤1	2	≤1–128	99.6	0.4	0
SXT	≤0.12	>8	≤0.12–>8	79.1		20.9
Nitrofurantoin	16	32	≤1–256	96.7	2.3	1.0
Ciprofloxacin	≤0.06	>16	≤0.06–>16	81.7	0.1	18.2
Amoxicillin-clavulanate	4	8	0.5–8	100	0	0
Amoxicillin-clavulanate resistant (49)						
Fosfomycin	2	32	≤1–512	98.0	0	2.0
SXT	≤0.12	>8	≤0.12–>8	71.4		28.6
Nitrofurantoin	16	32	8–512	91.9	2.0	6.1
Ciprofloxacin	≤0.06	>16	≤0.06–>16	73.5	0	26.5
Amoxicillin-clavulanate	32	>32	32–>32	0	0	100
SXT and ciprofloxacin resistant (105)						
Fosfomycin	2	4	≤1–128	98.1	1.9	0
SXT	>8	>8	4–>8	0		100

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TABLE 1 (Continued)

E. coli isolate phenotype(s) (no. of isolates) and antimicrobial agent	MIC_{50}[e]	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
Nitrofurantoin	16	64	4–256	88.6	6.7	4.8
Ciprofloxacin	>16	>16	4–>16	0	0	100
Amoxicillin-clavulanate	8	16	2–>32	56.2	35.2	8.6
ESBL producing (42)[b]						
Fosfomycin	2	4	≤1–4	100	0	0
SXT	>8	>8	≤0.12–>8	35.7		64.3
Nitrofurantoin	16	64	≤1–256	83.3	11.9	4.8
Ciprofloxacin	>16	>16	≤0.06–>16	9.5	0	90.5
Amoxicillin-clavulanate	16	32	1–32	33.3	54.8	11.9
AmpC producing (16)[c]						
Fosfomycin	2	4	≤1–4	100	0	0
SXT	≤0.12	>8	≤0.12–>8	75.0		25.0
Nitrofurantoin	16	32	8–32	100	0	0
Ciprofloxacin	≤0.06	>16	≤0.06–>16	75.0	0	25.0
Amoxicillin-clavulanate	32	>32	8–>32	6.3	6.3	87.4
MDR (15)[d]						
Fosfomycin	2	4	≤1–4	100	0	0
SXT	>8	>8	≤0.12–>8	6.7		93.3
Nitrofurantoin	16	128	16–256	60.0	0	40.0
Ciprofloxacin	>16	>16	8–>16	0	0	100
Amoxicillin-clavulanate	32	>32	8–>32	13.3	20.0	66.7

[a] Pansusceptible is defined as susceptible to SXT, nitrofurantoin, ciprofloxacin, and amoxicillin-clavulanate.
[b] The ESBL positivity rate of *E. coli* was 4.8% (42/868).
[c] The AmpC positivity rate of *E. coli* was 1.8% (16/868).
[d] MDR isolates were defined as those that were resistant to three or more agents in different antimicrobial classes (SXT, nitrofurantoin, ciprofloxacin, and amoxicillin-clavulanate).
[e] MIC_{50}, concentration inhibiting 50% of the isolates; MIC_{90}, concentration inhibiting 90% of the isolates. MICs are reported in μg/ml.

tested and inhibited 100% of the ESBL-producing, AmpC-producing, and MDR isolates of *E. coli* from urine (Table 1); fosfomycin was slightly less active against ciprofloxacin-resistant (97.9% of the isolates susceptible), amoxicillin-clavulanate-resistant (98.0% of the isolates susceptible), and SXT- and ciprofloxacin-resistant (98.1% of the isolates susceptible) isolates. Only five isolates of *E. coli* that were nonsusceptible to fosfomycin were identified from 2010 to 2013. Each of these isolates was from a different medical center in four different provinces; four isolates were collected in 2010, and one was collected in 2011. Fosfomycin MIC distribution data for all of the isolates and the isolates with defined antimicrobial susceptibility and resistance phenotypes are shown in Table 2.

In the follow-up, larger set of ESBL-producing and AmpC-producing isolates of *E. coli*, fosfomycin inhibited 94.9% of the ESBL-producing and 96.6% of the AmpC-producing isolates (Table 3); 17 fosfomycin-nonsusceptible *E. coli* isolates were identified in this set of isolates (13/17 isolates were ESBL producers, and

TABLE 2 Distributions of fosfomycin MIC for 868 urinary isolates of *E. coli* isolated by clinical laboratories across Canada from 2010 to 2013 stratified by susceptibility or resistance phenotype

	Cumulative % of isolates inhibited at fosfomycin MIC (μg/ml)[a] of:									
E. coli isolate phenotype(s) (no. of isolates)	≤1	2	4	8	16	32	64	128	256	512
All (868)	52.3	89.2	96.2	97.1	97.7	98.6	99.4	99.9	99.9	100
Pansusceptible (481)[b]	56.8	92.3	97.5	98.5	98.8	99.4	100			
SXT susceptible (647)	53.5	88.9	95.8	97.1	97.7	98.8	99.5	99.8	99.8	100
SXT resistant (219)	48.9	90.0	97.3	97.3	97.7	98.2	99.1	100		
Ciprofloxacin susceptible (672)	56.1	90.5	96.7	97.6	98.1	99.0	99.9	99.9	99.9	100
Ciprofloxacin resistant (195)	39.0	84.6	94.4	95.4	96.4	97.4	97.9	100		
Amoxicillin-clavulanate susceptible (704)	54.8	91.3	96.3	97.4	98.2	98.9	99.6	100		
Amoxicillin-clavulanate resistant (49)	34.7	73.5	89.8	89.8	89.8	95.9	98.0	98.0	98.0	100
SXT and ciprofloxacin resistant (105)	36.2	85.7	96.2	96.2	96.2	97.1	98.1	100		
ESBL producing (42)[b]	42.9	83.3	100							
AmpC producing (16)[b]	31.3	62.5	100							
MDR (15)[b]	26.7	86.7	100							

[a] The fosfomycin-susceptible, -intermediate, and -resistant MIC breakpoints are ≤64, 128 (shaded), and ≥256 μg/ml, respectively (5).
[b] See footnotes to Table 1 for isolate phenotype descriptions.

TABLE 3 *In vitro* activity of fosfomycin against ESBL- and AmpC-producing *E. coli* isolates obtained by clinical laboratories across Canada from 2007 to 2013, excluding urinary isolates obtained from 2010 to 2013

Organism (no. of isolates tested)	MIC_{50}[c]	MIC_{90}	MIC range	% Susceptible	% Intermediate	% Resistant
ESBL-producing *E. coli* (254)[a]						
Fosfomycin	2	4	≤1–>512	94.9	3.9	1.2
SXT	>8	>8	≤0.12–>8	30.7		69.3
Nitrofurantoin	16	32	4–256	90.6	6.3	3.1
Ciprofloxacin	>16	>16	≤0.06–>16	11.4	0.8	87.8
Amoxicillin-clavulanate	8	16	2–>32	59.4	33.5	7.1
AmpC-producing *E. coli* (119)[b]						
Fosfomycin	2	16	≤1–>512	96.6	1.7	1.7
SXT	0.25	>8	≤0.12–>8	64.7		35.3
Nitrofurantoin	16	64	≤1–256	89.1	6.7	4.2
Ciprofloxacin	0.12	>16	≤0.06–>16	62.2	0.8	37.0
Amoxicillin-clavulanate	32	>32	1–>32	26.9	21.0	52.1

[a] The 254 ESBL-producing *E. coli* isolates included 151 isolates from blood (2007 to 2013), 52 isolates from urine (2007 to 2009), 40 isolates from respiratory sources (2007 to 2013), and 11 isolates from wound specimens (2007 to 2013).
[b] The 119 AmpC-producing *E. coli* isolates included 63 isolates from blood (2007 to 2013), 27 isolates from urine (2007 to 2009), 20 isolates from respiratory sources (2007 to 2013), and 9 isolates from wound specimens (2007 to 2013).
[c] MIC_{50}, concentration inhibiting 50% of the isolates; MIC_{90}, concentration inhibiting 90% of the isolates. MICs are reported in μg/ml. MICs are reported in μg/ml.

4 were AmpC producers). The 13 ESBL-producing, fosfomycin-nonsusceptible *E. coli* isolates were identified by 11 different laboratories in seven provinces; 3 isolates each were collected in 2007 and 2009, 2 isolates each were collected in 2008 and 2012, and 1 isolate each was collected in 2010, 2011, and 2013. The four AmpC-producing, fosfomycin-nonsusceptible *E. coli* isolates were identified in four different laboratories in four provinces. The four isolates were collected, one per year, in 2007 to 2010. Two carbapenem-resistant *E. coli* isolates were also identified. The MICs for these isolates were as follows: fosfomycin, 2 and 2 μg/ml; SXT, >8 and >8 μg/ml; nitrofurantoin, 8 and 16 μg/ml; ciprofloxacin, >16 and >16 μg/ml; amoxicillin-clavulanate, >32 and >32 μg/ml.

Fosfomycin is a phosphonic acid derivative that inactivates UDP-*N*-acetylglucosamine-3-enolpyruvyltransferase (MurA), the enzyme responsible for ligating phosphoenolpyruvate to the 3′-hydroxyl group of UDP-*N*-acetylglucosamine in the first step of peptidoglycan synthesis (8). Resistance to fosfomycin most commonly arises via mutations in the genes encoding the hexose phosphate transport (UhpT) and glycerol-3-phosphate transport (GlpT) pathways (9) but may also result from a myriad of other mechanisms, including modification, inactivation, or overexpression of the target site (MurA); fosfomycin kinases; or the presence of enzymes associated with fosfomycin inactivation (e.g., those encoded by *fosA*, *fosB*, and *fosX*) (8). Cross-resistance between fosfomycin and other antimicrobial agents is not widely anticipated, given fosfomycin's unique structure and distinct mechanism of action (8, 10).

Fosfomycin has been recommended by some investigators for the treatment of urinary tract infections caused by ESBL-producing *E. coli* (8, 10, 11). All of the ESBL-producing, AmpC-producing, and MDR isolates identified in our original study of 868 isolates of *E. coli* were susceptible to fosfomycin. However, in our supplementary data set, fosfomycin appeared slightly less active, with 94.9% of the ESBL-producing and 96.6% of the AmpC-producing isolates being susceptible to fosfomycin (Table 3). Studies by other investigators are limited but have generally reported that fosfomycin retains activity against ESBL-producing *E. coli* (12, 13). One contradictory study has been published by Spanish researchers who reported that an increase in the use of fosfomycin in the community correlated with an increase in resistance to fosfomycin in ESBL-producing *E. coli* and that rates of resistance to fosfomycin varied by the specific ESBL present in isolates (5.1, 5.6, and 15.3% of the SHV-12-positive, CTX-M-14-positive, and CTX-M-15-positive isolates were fosfomycin resistant, respectively) (14). This observation may also be important because the plasmid-mediated fosfomycin resistance gene *fosA3* has emerged in isolates harboring CTX-M type ESBLs (9) and CTX-M type ESBLs (specifically, CTX-M-15 and CTX-M-14) are frequently identified in *E. coli* and *Klebsiella pneumoniae* in Canada and worldwide (15).

In conclusion, rates of resistance to SXT and fluoroquinolones among urinary isolates of *E. coli* in Canada exceed limits that support their empirical use as therapies for the treatment of these infections (Table 1) (2). In this study, 99.4% of 868 recently (2010 to 2013) obtained urinary isolates of *E. coli* were susceptible to fosfomycin; fosfomycin also demonstrated marked activity against β-lactamase-producing isolates of *E. coli*, as 94.9 to 100% of the ESBL-producing and 96.6 to 100% of the AmpC-producing isolates were susceptible to fosfomycin, suggesting that it may be a reliable empirical therapeutic option for urinary tract infections caused by these organisms.

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REFERENCES

1. **Nicolle LE.** 2001. Epidemiology of urinary tract infections. Clin. Microbiol. Newsl. **24:**135–140. http://www.cmnewsletter.com/issues?issue_key=S0196-4399%2800%29X0302-9.
2. **Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE.** 2011. International clinical practice guidelines for the treatment of uncomplicated acute cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin. Infect. Dis. **52:**e103–e120. http://dx.doi.org/10.1093/cid/ciq257.
3. **Karlowsky JA, Lagacé-Wiens PR, Simner PJ, DeCorby MR, Adam HJ, Walkty A, Hoban DJ, Zhanel GG.** 2011. Antimicrobial resistance in urinary tract pathogens in Canada from 2007 to 2009: CANWARD surveillance study. Antimicrob. Agents Chemother. **55:**3169–3175. http://dx.doi.org/10.1128/AAC.00066-11.
4. **Sanchez GV, Master RN, Karlowsky JA, Bordon JM.** 2012. *In vitro* antimicrobial resistance of urinary *Escherichia coli* isolates among U.S. outpatients from 2000 to 2010. Antimicrob. Agents Chemother. 56:2181–2183. http://dx.doi.org/10.1128/AAC.06060-11.
5. **Clinical and Laboratory Standards Institute.** 2013. Performance standards for antimicrobial susceptibility testing; twenty-third informational supplement. M100-S23. Clinical and Laboratory Standards Institute, Wayne, PA.
6. **Zhanel GG, Adam H, Baxter MR, Fuller J, Nichol KA, Denisuik AJ, Lagacé-Wiens P, Walkty A, Karlowsky JA, Schweizer F, Hoban DJ.** 2013. Antimicrobial susceptibility of 22746 pathogens from Canadian hospitals: results of the CANWARD 2007-2011 study. J. Antimicrob. Chemother. **68**(Suppl 1)**:**i7–i22. http://dx.doi.org/10.1093/jac/dkt022.
7. **Clinical and Laboratory Standards Institute.** 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard—ninth edition. M07-A9. Clinical and Laboratory Standards Institute, Wayne, PA.
8. **Karageorgopoulos DE, Wang R, Xu-Hong Y, Falagas ME.** 2012. Fosfomycin: evaluation of the published evidence on the emergence of antimicrobial resistance in gram-negative pathogens. J. Antimicrob. Chemother. **67:**255–268. http://dx.doi.org/10.1093/jac/dkr466.
9. **Ho P-L, Chan J, Lo W-U, Lai EL, Cheung Y-Y, Lau TCK, Chow K-H.** 2013. Prevalence and molecular epidemiology of plasmid-mediated fosfomycin resistance genes among blood and urinary *Escherichia coli* isolates. J. Med. Microbiol. **62:**1707–1713. http://dx.doi.org/10.1099/jmm.0.062653-0.
10. **Raz R.** 2012. Fosfomycin: an old-new antibiotic. Clin. Microbiol. Infect. **18:**4–7. http://dx.doi.org/10.1111/j.1469-0691.2011.03636.x.
11. **Neuner EA, Sekeres J, Hall GS, van Duin D.** 2012. Experience with fosfomycin for treatment of urinary tract infections due to multidrug-resistant organisms. Antimicrob. Agents Chemother. **56:**5744–5748. http://dx.doi.org/10.1128/AAC.00402-12.
12. **Auer S, Wojna A, Hell M.** 2010. Oral treatment options for ambulatory patients with urinary tract infections caused by extended-spectrum-β-lactamase-producing *Escherichia coli*. Antimicrob. Agents Chemother. **54:**4006–4008. http://dx.doi.org/10.1128/AAC.01760-09.
13. **Liu H-Y, Lin H-C, Lin Y-C, Yu S-H, Wu W-H, Lee Y-J.** 2011. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* to fosfomycin and nitrofurantoin in a teaching hospital in Taiwan. J. Microbiol. Immunol. Infect. **44:**364–368. http://dx.doi.org/10.1016/j.jmii.2010.08.012.
14. **Oteo J, Bautista V, Lara N, Cuevas O, Arroya M, Fernández S, Lázaro E, de Abajo FJ, Campos J.** 2010. Parallel increase in community use of fosfomycin and resistance to fosfomycin in extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli*. J. Antimicrob. Chemother. **65:**2459–2463. http://dx.doi.org/10.1093/jac/dkq346.
15. **Denisuik AJ, Lagacé-Wiens PR, Pitout JD, Mulvey MR, Simner PJ, Tailor F, Karlowsky JA, Hoban DJ, Adam HJ, Zhanel GG.** 2013. Molecular epidemiology of extended-spectrum β-lactamase-, AmpC β-lactamase-, AmpC β-lactamase- and carbapenemase-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from Canadian hospitals over a 5 year period: CANWARD 2007-11. J. Antimicrob. Chemother. **68**(Suppl 1)**:**i57–i65. http://dx.doi.org/10.1093/jac/dkt027.