Nocardiosis in Quebec, Canada, 1988–2008

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Abstract

Nocardia is an uncommon pathogen, but immunosuppression, its main risk factor, is becoming more frequent. We aimed to evaluate changes in the annual incidence of nocardiosis and in the susceptibility profile of its aetiological agents. Demographic data were analysed for all isolates of *Nocardia* forwarded to the provincial public health laboratory of Quebec, Canada during the last two decades. Population incidence could be measured from 1997 onwards. Resistance patterns were analysed for those isolates selected for *in vitro* susceptibility testing. Throughout Quebec, 575 incident cases were identified between 1997 and 2008. The annual incidence of *Nocardia* infection/colonization increased from 0.33 (1997–1998) to 0.87 (2007–2008) per 100 000 inhabitants (p 0.001). In a small subset of patients for whom detailed clinical information was available, 59% of isolates corresponded to genuine infections. *Nocardia farcinica* predominated in specimens representing invasive infections (blood, brain, lung or pleural aspirates). Isolates were often non-susceptible to several antimicrobials, with the exception of amikacin and linezolid. Overall, 43% of 157 isolates were non-susceptible to trimethoprim–sulphamethoxazole. In conclusion, *Nocardia* infection/colonization remains rare. However, from 1997–1998, a progressive increase in incidence was noted in the province of Quebec. In regions such as ours, where a substantial proportion of invasive isolates are non-susceptible *in vitro* to trimethoprim–sulphamethoxazole, the latter may no longer be the empirical treatment of choice in immunosuppressed and severely ill patients with nocardiosis.

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Introduction

The Gram-positive aerobic actinomycete *Nocardia* is an uncommon human pathogen infecting the lungs, skin, central nervous system (CNS) or other organs. It can present as localized or disseminated infections [1–3]. Immunosuppression is the main risk factor for nocardiosis and/or for disseminated infection, especially those conditions that impair cell-mediated immunity [1–3]. Chronic diseases associated with nocardiosis include diabetes, alcoholism, cancer and alveolar proteinosis [1–3]. *Nocardia* spp. are ubiquitous and are found worldwide in soil and decaying organic plant matter [3,4]. The organism is acquired by inhalation or direct inoculation into the skin, and nosocomial transmission is rare [1]. Colonization or subclinical infection occurs, especially within the respiratory tract of patients with chronic obstructive pulmonary disease (COPD), malignancy, asthma or bronchiectasis [3].

Data on the incidence of nocardiosis are sparse, as it is generally not a reportable disease. Its incidence may be increasing because of a growing population of immunocompromised patients and the enhanced diagnostic capacity of microbiology laboratories [4–6]. Biochemical tests were inadequate for identification of species, especially the differentiation of *Nocardia asteroides* sensu stricto from the species within the *N. asteroides* complex (*Nocardia abscessus*, *Nocardia brevicatena*/*Nocardia paucivorans* complex, *Nocardia nova* complex, *Nocardia transvalensis* complex, *Nocardia farcinica*, and *Nocardia cyriacigeorgica*) [1]. Reference laboratories now rely on 16S rRNA gene sequencing, which is rapid, accurate and reproducible [1,7–10]. However, molecular approaches complicated the taxonomy: there are now 76 species of *Nocardia*, 25 of which can cause human disease [11,12]. Speciation guides initial empirical treatment, as *in vitro* susceptibility

testing is performed only in reference laboratories. Trimethoprim–sulphamethoxazole has been classically recommended [1–3].

We have noted in recent years a higher number of cases of *Nocardia* infections, often involving trimethoprim–sulphamethoxazole-resistant isolates. To improve our therapeutic strategies, we reviewed all cases of nocardiosis diagnosed in our region since 1991, for which detailed information was available, as well as the provincial public health laboratory database, which contains basic demographic and clinical information on a much larger number of isolates.

Materials and Methods

Patients seen at the Centre hospitalier universitaire de Sherbrooke (CHUS)

The Centre hospitalier universitaire de Sherbrooke (CHUS) is a 686-bed hospital that provides secondary care to the 304 702 inhabitants of the Estrie region in the Province of Quebec, Canada, and tertiary care to adjacent regions as well. Peripheral hospitals of the region usually forward their putative *Nocardia* isolates, and it is likely that all patients requiring treatment will be referred as well. Cases with a positive culture for *Nocardia* between January 1991 and December 2008 were identified from our computerized hospital records. Presumptive identification of *Nocardia* isolates was based on microscopic observation of branching Gram-positive bacilli, acid-fast by the modified Kinyoun stain, from a typical dry-chalky colony with aerial hyphae on Lowenstein–Jensen medium [11]. All isolates were sent to the Laboratoire de santé publique du Québec (LSPQ—provincial public health laboratory) for further confirmation and antimicrobial susceptibility testing. We sought to identify additional cases from the discharge diagnoses database, based on ICM-9 codes for nocardiosis. Permission to review these records was obtained from the CHUS institutional review board.

We collected socio-demographic data, past medical history and clinical, diagnostic, therapeutic and microbiology data concerning the episode of nocardiosis. A patient was considered to be infected with a *Nocardia* species if he or she presented with symptoms or signs compatible with a nocardial infection and no other pathogen was isolated or if the pathogen was isolated from a sterile site. Patients were considered to be colonized if a *Nocardia* species was isolated from a non-sterile site without compatible symptoms, signs or radiological signs, and no treatment was ordered by the medical team.

For determination of incidence rates, numerators included only partients living in the Estrie region. Denominators were obtained from the Institut de la statistique du Québec [13]. Rates were calculated only from 1997 onwards, after the four hospitals of Sherbrooke were merged, so it was very unlikely that cases could have been missed by our search methods. Annual incidences were calculated for 2-year periods to decrease random variations. To allow comparisons with the provincial data, we present data for infection and colonization combined.

Isolates characterized at the LSPQ

Nearly all suspected *Nocardia* isolates are submitted by the Quebec hospital laboratories to the LSPQ for further characterization. Its entire database of *Nocardia* isolates obtained between 1988 and 2008 was reviewed. In 1994, biochemical and chemotaxonomic tests were replaced with HPLC and selected traditional tests [14]. From mid-2006, identification was based solely on sequencing of the 16S rRNA gene, colonial morphology and microscopic examination [1,7–11,15]. When requested by the attending physician or if the specimen came from a sterile site, isolates were forwarded to the CDC for *in vitro* susceptibility testing by broth microdilution [16]. Information provided by the primary laboratory (age, sex, source of clinical specimen and, from 1997, region of residence) is kept in the LSPQ database. To avoid any bias from the repeated testing of colonized patients, we considered only the first isolate per patient for a given species, taking into account changes in taxonomy. A patient infected with two different species of *Nocardia* was tabulated as two events. We analysed secular changes in species and resistance patterns, keeping in mind the changes in taxonomy and identification methods.

For the determination of incidence, a patient with dual infections (two species in one or more specimens obtained within 1 year) and a patient with multiple isolates of the same species over a long period of time would be counted as a single episode occurring at the time of initial isolation. Annual infection/colonization incidence was calculated over 2-year periods, and only from 1997 onwards, when information on the region of residence became available for all isolates. To detect possible biases in the referral of specimens, incidence rates were calculated for the heavily populated Montreal metropolitan area (the island of Montreal and peripheral regions; the population in 2008 was 4 129 824) and the rest of Quebec (population of 3 620 680).

Data analysis

Proportions were compared with the chi-squared test or Fisher's test when appropriate. Continuous variables were compared with rank sum tests. Linear regression lines

were fitted to determine trends in nocardiosis rates, and the *t*-test was used to determine the significance of these trends.

Results

The CHUS patients—Estrie region

We identified 32 patients with at least one isolate of *Nocardia* processed at the CHUS. Their median age was 59 years (interquartile range 49.5–74.5) and 56% were male. Forty-seven per cent of the patients were immunosuppressed, and 56% had COPD. Nineteen patients (59%) had been considered by their attending physicians to be infected, and 13 were thought to be colonized (11 in respiratory secretions; two in skin swabs). These two groups did not differ significantly in their median age, sex distribution or past history of COPD (data not shown). Fifty-nine per cent of the infected patients and 31% of the colonized patients were immunosuppressed. *N. farcinica* was found in 32% of the infected patients and 15% of the colonized patients. All of these differences were non-significant. The only significant difference was in the use of long-term (≥30 days) corticosteroids: 59% among the infected patients and 15% among the colonized patients (p 0.04).

Three infected patients died with nocardiosis as a contributing factor, but treatment had been stopped because of the severity of their underlying conditions. Fifteen patients received trimethoprim–sulphamethoxazole at some point in their treatment. Eight of 11 (73%) infected patients for whom susceptibility testing was available were infected with an isolate resistant to trimethoprim–sulphamethoxazole. In four cases, treatment was modified when such results became available. In four other cases, trimethoprim–sulphamethoxazole was continued despite *in vitro* resistance, without clinical failure. No recurrence was documented.

The annual incidence rates of both infected and colonized individuals per 100 000 inhabitants for the Estrie region increased from 0 in 1997–1998 to 0.52 in 1999–2000, 0.51 in 2001–2002, 0.17 in 2003–2004, 1.00 in 2005–2006 and 1.32 in 2007–2008 (p 0.09).

Isolates characterized at the LSPQ

Table 1 displays the characteristics of the patients whose isolates (*n* = 718, obtained from 704 individuals) were submitted to the LSPQ by hospital laboratories across Quebec between 1988 and 2008; they are also presented in two periods according to the taxonomy changes. The median age of patients increased slightly. The preponderance of male patients decreased, and the proportion of patients living outside the Montreal metropolitan area increased. After improved differentiation of species, *N. nova*, *N. cyriacigeorgica* and *N. farcinica* were the three most frequently identified species. The proportion and number of isolates obtained from sputum or bronchoscopy specimens increased over time, whereas the proportion and number of those obtained from lung biopsy specimens, pleural aspirates, skin specimens and bone specimens decreased.

Table 2 shows the distribution of isolated species according to the source of specimens, stratified between 1988 and 2003, when speciation was only moderately adequate, and between 2004 and 2008, corresponding to the current taxonomy. During 1988–2003, species considered to be part of the *N. asteroides* complex predominated in most types of specimen. In skin and soft tissues, *Nocardia brasiliensis* and *Nocardia pseudobrasiliensis* were almost as important. Within

TABLE 1. Characteristics of 718 *Nocardia* spp. isolates, Quebec, 1988–2003 vs. 2004–2008

Characteristics	1988–2003 393 isolates	2004–2008 325 isolates	p-value
Age (years)			
Median	65.5	69	0.006
Interquartile range	52–75	57–77	
Sex, *N* (%)			
Female	131 (34)	138 (42)	0.02
Male	260 (66)	187 (58)	
Residence[a], *N* (%)			
Montreal metropolitan area	152 (59)	153 (47)	0.01
Rest of Quebec	105 (41)	172 (53)	
Species, *N* (%)			
Nocardia asteroides: sp. or complex	219 (56)	4 (1)	NR
Nocardia abscessus	1 (0)	14 (4)	
Nocardia brevicatena/Nocardia paucivorans complex	0	3 (1)	
Nocardia nova complex[b]	71 (18)	109 (34)	
Nocardia transvalensis complex[c]	2 (0)	4 (1)	
Nocardia farcinica	42 (11)	44 (14)	
Nocardia cyriacigeorgica	3 (0)	67 (21)	
Nocardia brasiliensis, *Nocardia pseudobrasiliensis*	28 (7)	13 (4)	
Nocardia otitidiscaviarum complex	17 (4)	4 (1)	
All others[d]	6 (2)	26 (8)	
Not speciated	4 (1)	37 (11)	
Type of specimen[e], *N* (%)			
Sputum	127 (35)	135 (42)	0.01
Bronchial secretions or lavage	107 (30)	125 (39)	0.002
Lung biopsy/pleural fluid	39 (11)	13 (4)	0.004
Soft tissue or bone	60 (17)	32 (10)	0.04
Blood	9 (2)	9 (3)	NS
Central nervous system	9 (2)	3 (1)	NS
All others[f]	12 (3)	7 (2)	NS

NR, not relevant because of taxonomy changes; NS, not significant.
[a]Incomplete before 1997.
[b]*N. nova* (120), *N. nova* complex (55), *Nocardia veterana* (three), *Nocardia elegans* (two) and *Nocardia kruczakiae* (one).
[c]*N. transvalensis* complex (two), *N. transvalensis* (two) *Nocardia wallacei* (two).
[d]*Nocardia arthritidis Nocardia asiatica* (six each), *Nocardia flavorosea* (three), *Nocardia takedensis*, *Nocardia puris*, *Nocardia higoensis*, *Nocardia carnea*, *Nocardia vinacea*, *Nocardia thailandica*, *Nocardia jiangxiensis*, *Nocardia beijingensis* (one each); *Nocardia autotrophica* (three isolates) and *Nocardia orientalis* (two isolates) were later reclassified as *Pseudonocardia autotrophica* and *Amycolatopsis orientalis*, respectively.
[e]Excluding 31 isolates for which the source was unknown.
[f]Urine (four), abdominal (12), eye (three), pericardium (one).

TABLE 2. Species of *Nocardia* isolated according to the source of specimens, Quebec, 1988–2003 vs. 2004–2008

Species	Sputum, *N* (%)		Bronchial, *N* (%)		Lung/pleural fluid, *N* (%)		Soft tissue/bone, *N* (%)		Blood, *N* (%)		CNS, *N* (%)		Others, *N* (%)	
	1988–2003	2004–2008	1988–2003	2004–2008	1988–2003	2004–2008	1988–2003	2004–2008	1988–2003	2004–2008	1988–2003	2004–2008	1988–2003	2004–2008
Nocardia asteroides: sp. or complex[a]	87 (69)	0	56 (52)	2 (2)	24 (62)	0	22 (37)	2 (6)	3 (33)	0	2 (22)	0	9 (75)	0
Nocardia abscessus	0	6 (4)	0	5 (4)	1 (3)	0	0	2 (6)	0	0	0	1 (33)	0	0
Nocardia brevicatena/ Nocardia paucivorans complex	0	2 (1)	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Nocardia nova complex	27 (21)	44 (33)	36 (34)	53 (42)	3 (8)	1 (8)	2 (3)	4 (12)	1 (11)	1 (10)	0	1 (33)	1 (8)	4 (57)
Nocardia transvalensis complex	0	2 (1)	1 (1)	2 (2)	0	0	0	0	0	0	1 (11)	0	0	0
Nocardia farcinica	7 (5)	15 (11)	6 (6)	14 (11)	8 (21)	4 (31)	6 (10)	5 (16)	4 (44)	5[b] (50)	5 (56)	0	1 (8)	2 (29)
Nocardia cyriacigeorgica	1 (1)	36 (27)	1 (1)	24 (19)	0	5 (38)	0	0	1 (11)	2[b] (20)	0	0	0	0
Nocardia brasiliensis/ Nocardia pseudobrasiliensis	0	0	1 (1)	0	1 (3)	1 (8)	23 (38)	11 (34)	0	1 (10)	0	0	1 (8)	0
Nocardia attidiscavarum complex	1 (1)	2 (1)	5 (5)	1 (1)	1 (3)	1 (8)	6 (10)	0	0	0	0	0	0	0
All others	1 (1)	13 (10)	1 (1)	7 (6)	0	0	1 (2)	4 (13)	0	0	1 (11)	1 (33)	0	1 (14)
Not speciated	3 (2)	15 (11)	0	16 (13)	1 (3)	1 (8)	0	4 (13)	0	1 (10)	0	0	0	0

CNS, central nervous system.
[a]The majority of these isolates are not *N. asteroides* sensu stricto but species of the *N. asteroides* complex when speciation was inadequate.
[b]A blood specimen grew *N. farcinica* and *N. cyriacigeorgica*.

the *N. asteroides* complex, and bearing in mind that in the first interval speciation was suboptimal, *N. farcinica* was much more important in specimens corresponding to an invasive infection (CNS specimens, blood, lung biopsy specimens or pleural aspirates) than in those that might have reflected colonization. The same observations were noted in 2004–2008, but the overwhelming majority of formerly *N. asteroides sp. N. asteroides* complex were by then newly named species. *N. nova* complex and *N. cyriacigeorgica* were found mostly in the respiratory tract.

Table 3 illustrates the prevalence of antimicrobial non-susceptibility among the most commonly isolated species in Quebec, based on 157 susceptibility tests performed at the CDC between 1997 and 2008. Our *Nocardia* isolates were often non-susceptible to several antimicrobials, with the exception of amikacin, with 97% susceptibility, and linezolid, with 100% susceptibility. Overall, 43% of the isolates were non-susceptible to trimethoprim–sulphamethoxazole, with *N. farcinica* being the most resistant species (85%), followed by *N. nova*.

A total of 575 incident cases were identified between 1997 and 2008. Fig. 1 shows the annual incidence of infection and colonization from 1997–1998. The incidence increased progressively, but more markedly outside the Montreal metropolitan area (p 0.001). For the whole province, the annual incidence increased 2.6-fold, from 0.33 to 0.87 per 100 000 inhabitants (p 0.001).

Discussion

Nocardia infection/colonization remained a rare event but, from 1997–1998, we noted a progressive increase in its incidence in our region and in the entire province of Quebec. We could not discriminate true infection from colonization, except for the CHUS patients, three-fifths of whom presented with genuine infections. Most instances of colonization were detected in COPD patients whose sputum was sent to the clinical laboratory for investigation. Similarities in the specimen sources of isolates and in secular changes in *Nocardia* incidence suggest that the proportion of true infections for the province was probably comparable to that for the Estrie region.

Few authors have measured the population incidence of nocardiosis. In Queensland, Australia, among 93 isolates obtained from 1983 to 1988, 74 were considered to represent true infections, giving an incidence of 0.4 per 100 000 inhabitants [17,18]. In a sub-area of Madrid, Spain, only six of 43 isolates were considered to represent colonization, giving incidences of *Nocardia* infection of 0.39 per 100 000

TABLE 3. **Numbers and percentages of *Nocardia* isolates non-susceptible to antimicrobials, Quebec, 1997–2008**[a]

Drug[a]	*Nocardia asteroides*[b], *N* = 30, no. (%)	*Nocardia abscessus*, *N* = 7, no. (%)	*Nocardia nova*, *N* = 31, no. (%)	*Nocardia farcinica*, *N* = 34, no. (%)	*Nocardia cyriacigeorgica*, *N* = 21, no. (%)	*Nocardia brasiliensis*, *N* = 13, no. (%)	Other species,[c] *N* = 21, no. (%)	Total, *N* = 157, no. (%)
Trimethoprim–sulphamethoxazole	5 (17)	0	19 (61)	29[d] (85)	4 (19)	4 (31)	7 (33)	68 (43)
Amikacin	0	0	0	2 (6)	0	0	3 (14)	5[e] (3)
Imipenem	9 (30)	4 (57)	2 (6)	14 (41)	11 (52)	11 (85)	12 (57)	63 (40)
Ceftriaxone	2 (7)	0	15 (48)	12/33 (94)	1 (5)	11 (85)	8 (38)	68/156 (44)
Amoxycillin–clavulanate	16 (53)	1 (14)	29 (94)	10 (29)	20 (95)	2 (15)	7 (33)	94 (60)
Minocycline	10 (33)	0	13 (42)	25 (74)	18 (86)	10 (77)	4 (19)	80[f] (51)
Ciprofloxacin	30 (100)	7 (100)	31 (100)	22 (65)	20 (95)	12 (92)	16 (76)	138 (88)
Clarithromycin	14/14 (100)	7 (100)	0	28/28 (100)	21 (100)	9/11 (82)	16 (76)	95/126 (75)
Linezolid	0/14	0	0	0/28	0	0	0	0/126 (0)

[a]Breakpoints for resistance are those of the CLSI [16].
[b]The majority of these isolates are not *N. asteroides* sensu stricto but species of the *N. asteroides* complex when speciation was inadequate.
[c]*Nocardia* spp. (six), *Nocardia otitidiscaviarum* (four), *Nocardia arthritidis* (two), *Nocardia puris* (two), *Nocardia transvalensis* complex (two), *Nocardia asiatica* (one), *Nocardia carnea* (one), *Nocardia higoensis* (one), *Nocardia pseudobrasiliensis* (one), *Nocardia vinacea* (one).
[d]Among the 29 *N. farcinica* isolates resistant to trimethoprim–sulphamethoxazole, five had MIC 4/76, five had MIC 8/152, and the other ten had MIC >8/152 mg/L.
[e]Both *N. farcinica* isolates had MIC 16 mg/L.
[f]Only seven isolates were resistant (MIC 8 mg/L), and the others were intermediate.

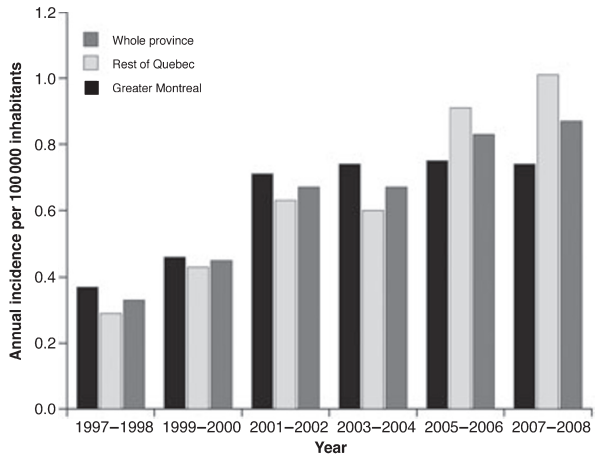

FIG. 1. Trends in the annual incidence of *Nocardia* infection/colonization per 100 000 inhabitants, Quebec, 1997–2008.

for 1995–1998 and 0.55 per 100 000 inhabitants for 2003–2006 [19]. Our estimate, based on 575 isolates, was much more robust, but gave incidence rates similar to those reported in Spain. On the assumption that, throughout Quebec, the proportion of isolates corresponding to genuine infections was the same as in the Estrie region, the incidence of *Nocardia* infection for the entire province can be estimated as 0.51 per 100 000 in 2007–2008. To our knowledge, this is the first study that is sufficiently powered to document an increasing incidence of *Nocardia* infection/colonization.

This increasing incidence throughout Quebec may be attributable to several factors. First, there might have been a more systematic referral of isolates to the LSPQ during recent years, especially from laboratories outside the Montreal metropolitan area, for which the increase in incidence was more marked. Second, hospital laboratories might have improved their proficiency in recovering and recognizing presumptive *Nocardia* spp. Automated systems utilizing enriched liquid media, first implemented only in larger laboratories for faster detection of mycobacteria, have been more widely used during the last decade. They have potentially improved the isolation rate for *Nocardia* isolates, as for the non-tuberculous mycobacteria. Third, nocardiosis is more common among older persons, and the ageing of our population might have played a role. Fourth, higher risks of nocardiosis have been reported among immunocompromised patients, whose numbers are increasing in Quebec, as elsewhere [4,5,17,20,21].

Another important finding of our study is the frequency of isolation of *N. farcinica* from specimens reflecting invasive disease, such as brain or lung biopsy specimens, pleural aspirates and blood. Its underestimated contribution in the earlier period, when speciation was less accurate, did not allow us to evaluate whether the distribution truly changed over time. In Belgium, where current molecular methods were used for 86 *Nocardia* isolates, *N. farcinica* was the most common species (44%), followed by *N. nova* (22%) and *N. cyriacigeorgica* (15%) [22]. *N. farcinica* was isolated mainly in blood and brain biopsy specimens, as in Europe and the USA [2,22,23]. Although many of the Quebec isolates of *N. cyriacigeorgica* were of uncertain clinical significance, we documented eight cases in which the species was clearly an invasive pathogen [24].

Trimethoprim–sulphamethoxazole is generally recommended for the empirical treatment of nocardiosis [1–3, 25,26]. Given the preponderance of invasive *N. farcinica* and the frequent non-susceptibility of our isolates to trimethoprim–sulphamethoxazole, this may no longer be appropriate

in Quebec. The susceptibility of *N. farcinica* to trimethoprim–sulphamethoxazole varies geographically, but the comparison is confounded by the use of different methodologies [23,25–29]. In regions such as ours, where non-susceptibility to trimethoprim–sulphamethoxazole is frequent, clinicians may want to consider other empirical treatments for patients for whom *Nocardia* spp. are isolated from CNS, blood, lung biopsy specimens or pleural aspirate, as well as for immunosuppressed patients. Even though *in vitro* antimicrobial non-susceptibility has not clearly been associated with clinical failures, treatment with a drug considered to be active on the basis of CLSI breakpoints would seem to be advisable. For non-CNS infections, empirical therapy with amikacin and/or linezolid might be considered. For CNS nocardiosis, linezolid, which crosses the blood–brain barrier and has an excellent bioavailability, is an attractive alternative. Although clinical experience is limited, linezolid seems, so far, to be quite effective [30,31].

In conclusion, although nocardiosis remains rare, its infection/colonization incidence more than doubled in Quebec from 1997 to 2008. *N. farcinica*, which was frequently recovered in CNS, blood, lung or pleural specimens, was often non-susceptible to trimethoprim–sulphamethoxazole. In regions such as ours, where non-susceptibility to trimethoprim–sulphamethoxazole is frequent, other drugs should be considered for the empirical treatment of nocardiosis, especially in severely ill and/or immunosuppressed patients. Future studies should attempt to correlate *in vitro* susceptibility with response to treatment.

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Transparency Declaration

L. Valiquette has been on the speakers' bureau for Wyeth, has served on advisory boards for Oryx, Iroko, Abbott and Wyeth, and has received compensation to conduct clinical trials involving antibacterials from Genzyme, Wyeth, Optimer and Arpida. J. Pépin has been on the speakers' bureau for Wyeth, and has served on advisory boards for Pfizer, Wyeth, Ortho, Merck, Acambis and The Medicines Company. The other authors have no competing interest to report.

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