# Outbreak of Invasive *Streptococcus pneumoniae* Serotype 12F Among a Marginalized Inner-City Population in Winnipeg, Canada, 2009–2011

**Erin Schillberg,[1,a] Michael Isaac,[2] Xianding Deng,[3] Gisele Peirano,[4,5] John L. Wylie,[6,7] Paul Van Caeseele,[6,7] Dylan R. Pillai,[4,5] Hasantha Sinnock,[2] and Salaheddin M. Mahmud[1,2,8]**

[1]Winnipeg Regional Health Authority, and [2]Vaccine and Drug Evaluation Centre, Department of Community Health Sciences, University of Manitoba, Winnipeg; [3]Department of Laboratory Medicine and Pathobiology, University of Toronto; [4]Department of Pathology and Laboratory Medicine, University of Calgary, and [5]Calgary Laboratory Services; [6]Cadham Provincial Laboratory, [7]Department of Medical Microbiology, and [8]Faculty of Pharmacy, University of Manitoba, Winnipeg, Canada

***Background.*** In 2010, Winnipeg, Canada, experienced a doubling of invasive pneumococcal disease (IPD) rates, with a significant increase in the number of cases due to *Streptococcus pneumoniae* serotype 12F, which previously had accounted for very few cases each year.

***Methods.*** All serotype 12F IPD cases reported between September 2009 and January 2011 were reviewed. Pulsed-field gel electrophoresis (PFGE) and multilocus variable number tandem repeat analysis (MLVA) were conducted on all isolates. PFGE and MLVA patterns identified several possible clusters. Additional interviews were conducted to obtain information on risk factors and outcomes.

***Results.*** Between September 2009 and January 2011, 169 cases of IPD were identified. The number of IPD cases due to 12F serotype increased sharply from about 3–4 cases per year (6% of IPD cases) in 2007–2009 to 28 (29%) in 2010. All 12F isolates belonged to a single sequence type (ST218), and they were generally susceptible to penicillin and fluoroquinolones but not to erythromycin. Compared with cases caused by other serotypes, patients with serotype 12F were more likely to be homeless, reside in low-income inner-city communities, and engage in substance abuse, including intravenous and crack cocaine use. Subclusters identified using MLVA had even higher rates of homelessness and substance use.

***Conclusions.*** An immunization campaign targeting high-risk groups was undertaken with pneumococcal polysaccharide vaccine, and subsequently rates of serotype 12F decreased. To our knowledge, this is the largest documented community outbreak of serotype 12F IPD and the first report of an outbreak of IPD serotype 12F in a marginalized urban population in Canada.

***Keywords.*** outbreak; invasive pneumococcal disease; surveillance; serotype 12F; homeless.

Invasive pneumococcal disease (IPD) has predominantly been limited to sporadic cases since the beginning of the antibiotic era. However, outbreaks have occurred in both institutional and community settings. *Streptococcus pneumoniae* serotype 12F has been identified as the cause of several outbreaks in both of these settings over the past 3 decades, despite the advent of effective antibiotics and a polysaccharide vaccine covering serotype 12F [1–5]. This serotype is reported to be hyperinvasive compared with other IPD strains [6], and reports suggest that it may be more likely to cause meningitis [7, 8].

In 2001, the Canadian province of Manitoba implemented a publicly funded pneumococcal polysaccharide vaccine (PPSV23) program for persons at high risk due to comorbidities and those aged ≥65 years. In 2004, a heptavalent pneumococcal conjugate vaccine

Received 23 December 2013; accepted 4 May 2014; electronically published 19 May 2014.

[a]Current affiliation: Médecins Sans Frontières, Port-au-Prince, Haiti.

Correspondence: Salaheddin M. Mahmud, MD, PhD, FRCPC, Vaccine and Drug Evaluation Centre, Department of Community Health Sciences, University of Manitoba, S111-750 Bannatyne Ave, Winnipeg, Manitoba, Canada R3E 0W3 (salah.mahmud@gmail.com).

**Clinical Infectious Diseases 2014;59(5):651–7**



DOI: 10.1093/cid/ciu366

was added to the publicly funded routine immunization program. In other jurisdictions, the implementation of such programs has resulted in significant decline in IPD rates in both children and adults [9, 10]. However, Manitoba's capital city, Winnipeg (population nearly 665 000), saw a doubling of IPD rates in 2010, with a significant increase in the number of cases due to serotype 12F, which previously had accounted for very few cases each year. In this report, we describe the results of laboratory and epidemiologic investigations of what is, to our knowledge, the largest documented community outbreak of serotype 12F IPD.

## METHODS

### Case Definition and Surveillance

A case of IPD was defined as isolation of *S. pneumoniae* from a normally sterile site including blood or cerebrospinal, synovial, or peritoneal fluids and bone tissue, but not from eye, middle ear, or pleural fluids [11]. All residents of Winnipeg who met the IPD case definition with an epidate between 1 September 2009 and 31 January 2011 were included in this analysis. The epidate was defined as the earliest of symptom onset date, specimen collection date, diagnosis date, and date reported to public health.

In Manitoba, all IPD cases are reportable to provincial public health officials, who then refer cases to the regional health authorities for investigation and management. IPD cases are investigated by public health nurses using a brief case form to gather demographic, clinical, and risk factor information, which is then entered into the electronic database of the regional Public Health Program. Data used in this investigation were obtained from that database. In addition, we obtained information on pneumococcal vaccination from the Manitoba Immunization Monitoring Registry, an electronic province-wide, population-based registry of immunization histories established in 1988.

Regardless of place of residence, all isolates of *S. pneumoniae* collected from IPD patients in Manitoba are forwarded to Cadham Provincial Laboratory, the provincial public health laboratory in Manitoba, and then to the National Microbiology Laboratory in Winnipeg for serotyping. Serotyping is performed by the Quellung reaction using pool, group, type, and factor commercial antisera (SSI Diagnostica, Statens Serum Institut, Copenhagen, Denmark) [12, 13].

For the purpose of this analysis, a hospitalized case was defined as an individual admitted for at least 24 hours; emergency room visits were not considered a hospitalization. Socioeconomic status was measured using the Socio-Economic Factor Index (SEFI) score, an area-based factor score derived from Canadian census data that reflects nonmedical social determinants of health including high school attendance, labor force participation, and employment levels [14]. Cases with a less favorable SEFI score were defined as those with SEFI scores in the bottom 2 quintiles. Any vaccine indication was defined as medical conditions for which pneumococcal vaccination is recommended as specified in the Canadian Immunization Guide (7th edition) [15].

### Molecular Typing of *S. pneumoniae* Isolates

Pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), and multilocus variable number tandem repeat analysis (MLVA) were conducted on all 12F isolates of cases diagnosed between January 2007 and January 2011. The PFGE procedure was conducted according to Louie et al [16]. MLST was performed according to the method of Enright and Spratt [17]. Polymerase chain reaction–based MLVA genotyping was performed and analyzed according to the scheme of Rakov et al and Koeck et al [6, 18]. In addition, antibiotic susceptibility testing was conducted according to guidelines established by the Clinical and Laboratory Standards Institute [19].

Based on PFGE and MLVA results, several possible clusters were identified, and all cases identified in clusters (n = 19) were investigated further. Face-to-face interviews using a standardized questionnaire were conducted to verify existing data and to obtain additional information on risk factors and outcomes including ethnicity, homelessness, preexisting medical conditions, and tobacco and substance abuse. Patients were located and interviewed by local public health nurses. For those who were deceased (n = 2) or could not be located (n = 1), medical and public health records were used.

### Statistical Analysis

We conducted a comparative descriptive analysis of sociodemographic and clinical factors as well as vaccination status of 12F cases and non-12F cases. Similar analyses were conducted to compare risk factors and outcomes of the clusters identified using MLVA. All analyses were completed using Stata software, version 11 (StataCorp, College Station, Texas).

## RESULTS

Between 1 September 2009 and 31 January 2011, 169 cases of IPD were identified (Figure 1). Rates of IPD were stable in Winnipeg from 2007 to 2009 at around 8.0 per 100 000 population (based on about 55 cases per year) but then rose to 14.1 per 100 000 population (n = 98) in 2010. The increase in IPD cases coincided with the "second wave" of the H1N1 pandemic in October–December 2009. However, most of the cases occurred much later in 2010 and early 2011. Numbers peaked in April and May 2010, declined over the summer months, and increased again at the end of 2010. The majority of IPD cases were male (58%), and the average age (range) was 42

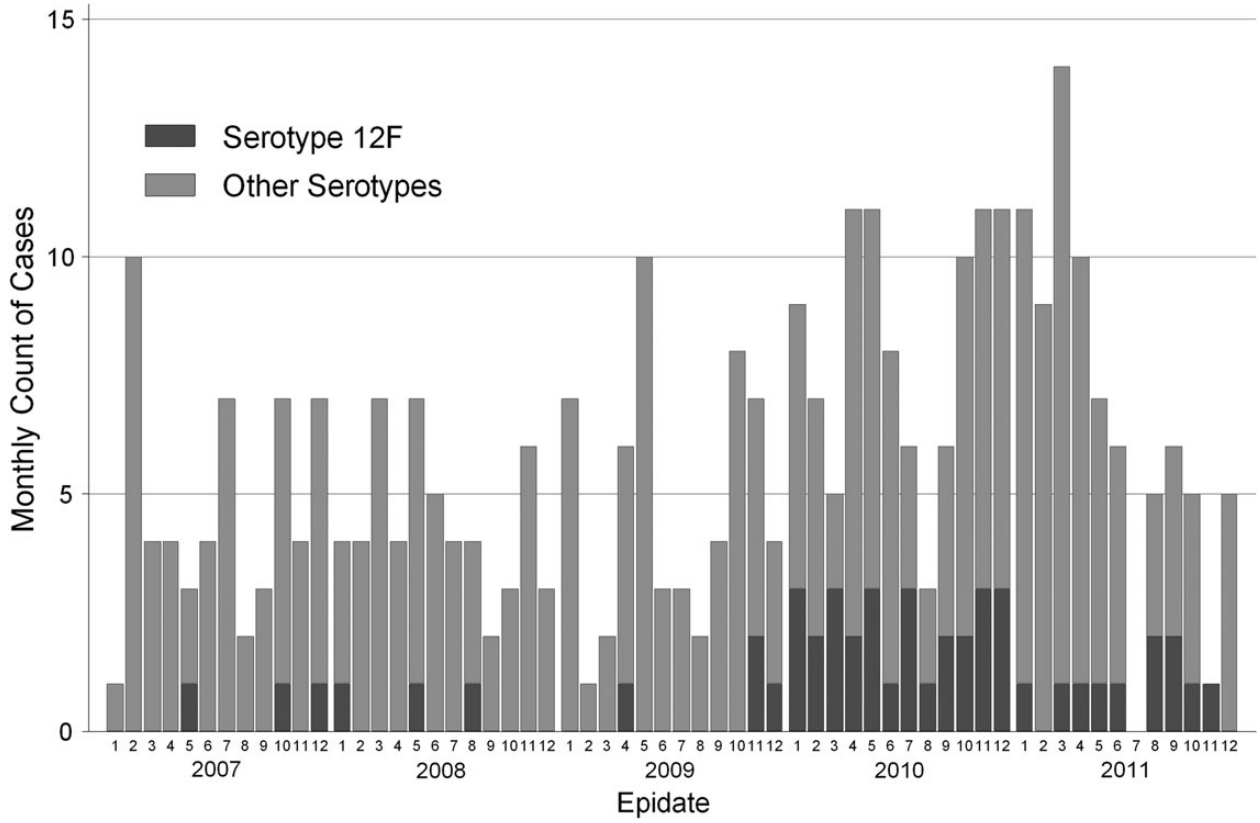


**Figure 1.** Monthly count of invasive pneumococcal disease cases by serotype and month and year of diagnosis, among Winnipeg residents, January 2009 to December 2011. Epidate is defined as the earliest of symptom onset date, specimen collection date, diagnosis date, and date reported to public health.

(0–94) years. Just less than half of all cases occurred in 2 neighboring inner-city communities that house <20% of Winnipeg's population. High proportions of homelessness (11.8%) and substance abuse (13.6%) were reported among these patients, and about 37% received a pneumococcal vaccine. Sixteen patients (10%) developed meningitis, and 124 (73%) were hospitalized. The case-fatality rate for all IPD cases during the study period was 10% (Table 1).

The number of IPD cases due to 12F serotype increased sharply from about 3–4 cases per year (2% of IPD cases) in 2007–2009 to 28 (29%) in 2010. Compared to other serotypes, 12F cases were more likely to be adults between the ages of 18 and 54 (odds ratio [OR], 3.7 [95% confidence interval {CI}, .8–17.3]) and were about 7 times as likely to reside in the above-mentioned inner-city communities (Table 1). Serotype 12F patients were more likely to report homelessness (OR, 12.7 [95% CI, 4.5–35.9]) or substance abuse (OR, 6.9 [95% CI, 2.7–17.7]) and less likely to report a preexisting chronic disease (OR, 0.5 [95% CI, .2–1.1]). Of the 32 serotype 12F cases reported between 1 September 2009 and 31 January 2011, 100% of isolates were penicillin susceptible, 97% were susceptible to levofloxacin, and only 6% were susceptible to erythromycin.

MLST typing determined that all 12F isolates belong to a single sequence type, ST218 (MLST allele profile: aroe 10, gdh 20, gki 14, recp 1, spi 6, xpt 1, and ddl 29). When MLVA was conducted, 12F isolates formed 2 clusters, with 1 cluster (cluster 1) representing 59% (n = 19) of the cases (Table 2). Although no obvious epidemiological links were found between cases in this cluster, compared with other 12F cases, these patients were more likely to be male (58%) and to be younger adults aged 18–54 years (79%). In addition, patients in this cluster were more likely to report homelessness (58%), alcohol abuse (53%), and substance abuse (53%) (Table 2). This cluster also contained a subcluster of 9 cases with an identical MLVA profile. These 9 patients showed even greater proportions of homelessness (n = 6), alcohol abuse (n = 5), and substance abuse (n = 6; mostly crack cocaine [n = 5] and intravenous drugs [n = 4]) (Table 2). The majority were of Aboriginal ethnicity (n = 8) and unemployed (n = 7), and 3 reported living in a shelter, group housing, or hotel. Two of these patients had human immunodeficiency virus/AIDS, and 4 had hepatitis C (Table 2).

**Table 1. Invasive Pneumococcal Disease Cases by Serotype, Demographic and Clinical Characteristics, and Risk Factors, Among Winnipeg Residents, 1 September 2009 to 31 January 2011**

| Characteristic | Serotype 12F (n = 32) | Non-12F Serotypes (n = 137) | Total (n = 169) | 12F vs Non-12F Cases, OR (95% CI)[a] | *P* Value |
|---|---|---|---|---|---|
| Age, y | | | | | |
| <18 | 2 (6.3) | 17 (12.4) | 19 (11.2) | Ref | . . . |
| 18–54 | 24 (75.0) | 55 (40.1) | 79 (46.7) | 3.7 (.8–17.3) | .096 |
| ≥55 | 6 (18.8) | 65 (47.4) | 71 (42.0) | 0.8 (.2–4.2) | .778 |
| Male sex | 18 (56.3) | 80 (58.4) | 98 (58.0) | 0.9 (.4–2.0) | .825 |
| Place of residence | | | | | |
| Other parts of the city | 6 (18.8) | 85 (62.0) | 91 (53.8) | Ref | . . . |
| Inner-city area 1 | 12 (37.5) | 23 (16.8) | 35 (20.7) | 7.4 (2.5–21.8) | <.001 |
| Inner-city area 2 | 14 (43.8) | 29 (21.2) | 43 (25.4) | 6.8 (2.4–19.5) | <.001 |
| Less favorable SEFI score[b] | 27 (84.4) | 85 (62.0) | 112 (66.3) | 3.3 (1.2–9.1) | .021 |
| Homeless | 13 (40.6) | 7 (5.1) | 20 (11.8) | 12.7 (4.5–35.9) | <.001 |
| Resides in a PCH/chronic care facility or attends daycare | 4 (12.5) | 13 (9.5) | 17 (10.1) | 1.4 (.4–4.5) | .510 |
| Alcohol abuse | 11 (34.4) | 28 (20.4) | 39 (23.1) | 2.0 (.9–4.7) | .096 |
| Tobacco use | 16 (50.0) | 34 (24.8) | 50 (29.6) | 3.0 (1.4–6.7) | .006 |
| Substance abuse | 12 (37.5) | 11 (8.0) | 23 (13.6) | 6.9 (2.7–17.7) | <.001 |
| Preexisting health condition | 13 (40.6) | 79 (57.7) | 92 (54.4) | 0.5 (.2–1.1) | .085 |
| Received PCV or PPSV | 9 (28.1) | 54 (39.4) | 63 (37.3) | 0.6 (.3–1.4) | .237 |
| Clinical outcomes | | | | | |
| Hospitalized | 19 (59.4) | 105 (76.6) | 124 (73.4) | 0.77 (.57–1.05)[c] | .044 |
| Septicemia | 28 (87.5) | 117 (85.4) | 145 (85.8) | 1.02 (.89–1.19)[c] | .762 |
| Meningitis | 1 (3.1) | 15 (10.9) | 16 (9.5) | 0.3 (.1–2.1)[c] | .170 |
| Deceased | 3 (9.4) | 14 (10.2) | 17 (10.1) | 0.9 (.3–3.0)[c] | .887 |

Data are presented as No. (%) unless otherwise specified.

Abbreviations: CI, confidence interval; OR, odds ratio; PCH, personal care home; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; SEFI, Socio-Economic Factor Index.

[a] From logistic regression models with 12F vs non-12F case status as the outcome and list characteristics as the exposure.

[b] Cases with a less favorable SEFI score were defined as those with SEFI scores in the bottom 2 quintiles.

[c] Values are risk ratios contrasting the risk of each clinical outcome among 12F cases with that among non 12F cases.

Cases in this subcluster showed very low immunization rates for IPD even compared with other IPD cases in Winnipeg, with only 1 patient being immunized. All 12F isolates within the subcluster were penicillin and levofloxacin susceptible, while being erythromycin resistant. Despite these similarities, obvious epidemiologic links (eg, sharing the same space) could not be identified between these cases.

## DISCUSSION

To our knowledge, this is the largest documented community outbreak of serotype 12F IPD and the first report of an outbreak of IPD serotype 12F in a marginalized urban population in Canada. It is not clear what caused the outbreak, but several possible explanations have been suggested including agent, host, and environmental factors.

This outbreak began just after the second wave of the H1N1 pandemic in the autumn of 2009. The hypothesis that increased blood culture testing during the pandemic may have led to increased detection of IPD cases was not supported by local laboratory data, which showed no significant increase in the number of blood cultures performed during this period compared with previous years. It has been suggested that susceptibility to bacterial infections may be increased after a viral respiratory infection such as influenza [20], but the majority of reported IPD cases occurred many months after the end of the pandemic during the mild 2010–2011 influenza season. Also, the H1N1 pandemic was most severe in northern Manitoba [21], yet no increase in IPD cases was noted in that region. Last, it is not clear why the pandemic would have specifically increased the incidence of 12F cases.

Serotype 12F is the most common cause of IPD in Japan and has been reported to be hyperinvasive [22, 23]. A study of IPD cases in Poland reported a significant increase in meningitis

**Table 2. Invasive Pneumococcal Disease Cases Caused by Serotype 12F by Multilocus Variable Number Tandem Repeat Analysis Cluster, Demographic and Clinical Characteristics, and Risk Factors, Among Winnipeg Residents, 1 September 2009 to 31 January 2011**

| Characteristic | Cluster 1 | | | Cluster 2 (n = 11) | Other (n = 2) | Total (n = 32) |
|---|---|---|---|---|---|---|
| | Subcluster A (n = 9) | Other (n = 10) | Total (n = 19) | | | |
| Age, y | | | | | | |
| <18 | 0 (0.0) | 1 (10.0) | 1 (5.26) | 0 (0.00) | 1 (50.0) | 2 (6.3) |
| 18–54 | 8 (88.9) | 7 (70.0) | 15 (78.9) | 8 (72.7) | 1 (50.0) | 24 (75.0) |
| ≥55 | 1 (11.1) | 2 (20.0) | 3 (15.8) | 3 (27.3) | 0 (0.0) | 6 (18.8) |
| Male sex | 3 (33.3) | 8 (80.0) | 11 (57.9) | 5 (45.5) | 2 (100.0) | 18 (56.3) |
| Place of residence | | | | | | |
| Other parts of the city | 1 (11.1) | 1 (10.0) | 2 (10.5) | 3 (27.3) | 1 (50.0) | 6 (18.8) |
| Inner-city area 1 | 4 (44.4) | 4 (40.0) | 8 (42.1) | 4 (36.4) | 0 (0.0) | 12 (37.5) |
| Inner-city area 2 | 4 (44.4) | 5 (50.0) | 9 (47.4) | 4 (36.4) | 1 (50.0) | 14 (43.8) |
| Less favorable SEFI score[a] | 8 (88.9) | 10 (100.0) | 18 (94.7) | 8 (72.7) | 1 (50.0) | 27 (84.4) |
| Homeless | 6 (66.7) | 5 (50.0) | 11 (57.9) | 2 (18.2) | 0 (0.0) | 13 (40.6) |
| Resides in a PCH/chronic care facility or attends daycare | 1 (11.1) | 1 (10.0) | 2 (10.5) | 2 (18.2) | 0 (0.0) | 4 (12.5) |
| Alcohol abuse | 5 (55.6) | 5 (50.0) | 10 (52.6) | 1 (9.1) | 0 (0.0) | 11 (34.4) |
| Tobacco use | 5 (55.6) | 4 (40.0) | 9 (47.4) | 6 (54.5) | 1 (50.0) | 16 (50.0) |
| Substance abuse | 6 (66.7) | 4 (40.0) | 10 (52.6) | 2 (18.2) | 0 (0.0) | 12 (37.5) |
| Any vaccine indication | 3 (33.3) | 7 (70.0) | 10 (52.6) | 3 (27.3) | 0 (0.0) | 12 (37.5) |
| Received PCV or PPSV | 1 (11.1) | 3 (30.0) | 4 (21.1) | 4 (36.4) | 1 (50.0) | 9 (28.1) |
| Clinical outcomes | | | | | | |
| Hospitalized | 3 (33.3) | 7 (70.0) | 10 (52.6) | 7 (63.6) | 2 (100.0) | 19 (59.4) |
| Septicemia | 9 (100.0) | 10 (100.0) | 19 (100.0) | 9 (81.8) | 0 (0.0) | 28 (87.5) |
| Meningitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (3.1) |
| Deceased | 1 (11.1) | 1 (10.0) | 2 (10.5) | 1 (9.1) | 0 (0.0) | 3 (9.4) |
| Antibiotic resistance | | | | | | |
| Penicillin | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Erythromycin | 9 (100.0) | 10 (100.0) | 19 (100.0) | 10 (9.1) | 1 (50.0) | 30 (93.8) |
| Levofloxacin | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Data are presented as No. (%).

Abbreviations: PCH, personal care home; PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; SEFI, Socio-Economic Factor Index.

[a] Cases with a less favorable SEFI score were defined as those with SEFI scores in the bottom 2 quintiles.

caused by serotype 12F over a several-year span; however, overall prevalence of 12F was increasing at the same time [8]. In addition, there are reports that 1 specific sequence type of serotype 12F, ST989, may have a propensity to cause meningitis [7]. However, all isolates in this outbreak were ST218, and our data did not show an increase in cases of meningitis, hospitalizations, or deaths among 12F cases when compared with non-12F cases. However, serotype 12F patients were 5 times less likely to have preexisting conditions or immunosuppression even after accounting for their younger age (75% of cases were between the ages of 18 and 54). This may point to increased virulence of this particular strain. Additional genetic studies of this strain will be essential to address the virulence question. Hypervirulent 12F strains are a major public health concern, as the 12F serotype is not included in any conjugate vaccine [24].

Macrolide resistance among *S. pneumoniae* in Canada has been well documented [25]. However, the 12F serotype seldom carries antibiotic resistance, as it is not considered a carriage strain that circulates constantly in the nasopharynx of healthy children and adults [26–29]. To our knowledge, this is the first time widespread macrolide resistance among 12F outbreak strains (93.8%) has been reported. It is possible that gaining macrolide resistance could have granted this 12F outbreak strain a survival advantage over other strains. Although high levels of resistance to penicillin [30] and fluoroquinolones [31] has been documented in Canada, the organisms in this outbreak were not resistant to these latter 2 classes of antibiotics.

Although we were not able to establish direct links between the reported cases, our analyses have consistently pointed to 3 interconnected risk factors that may have been responsible for this cluster: homelessness, substance abuse, and residence in 2 neighboring low-income inner-city communities.

Insecure housing, including homelessness, crowding, and homeless shelter use, has been implicated in IPD outbreaks of

both the 12F and non-12F IPD serotypes [2, 5, 32]. Crowding was not assessed in the Winnipeg outbreak; however, there was a significant association with homelessness, even compared with other (non-12F) IPD cases. Use of homeless shelters and other forms of insecure housing may have played a role in the genesis of the outbreak by facilitating exposure in close quarters between cases and contacts. Unfortunately, pinpointing a common location, such as a particular homeless shelter, was not possible due to poor recall and the frequent transitions from one place of residence to another.

One of the first documented outbreaks of serotype 12F was in a Texas jail in 1994 [2]. In that outbreak, the investigators found that intravenous drug use was strongly associated with IPD, which parallels the experience in Winnipeg with 44% of cases in one subcluster self-reporting intravenous drug use. Crack cocaine use has been previously associated with an outbreak of serotype 5 in Vancouver, Canada [5], and self-reported crack cocaine use was prevalent in one subcluster in the Winnipeg outbreak (56% of cases). The mechanism by which crack cocaine use leads to IPD is not clear. A common adulterant of street cocaine known as levamisole [33] has been increasingly detected in Canada [34, 35]. Because levamisole is known to cause agranulocytosis [35, 36], especially among populations with high prevalence of the *HLA-B27* allele [33] such as the First Nations community [37, 38] affected by this outbreak, further investigation into the connection between IPD cases in Winnipeg and crack cocaine use is warranted.

Cases were clustered geographically in 2 adjacent community areas in Winnipeg. A survey of individuals who use illicit drugs in Winnipeg found that a large percentage frequented several distinct geographic areas within the city [39]. Several of these locations match up with the communities within which this outbreak was found. These communities contain several homeless shelters, rooming houses, hotels, and outreach services for those who are homeless or use illicit drugs, which may partly explain the clustering.

Approximately 72% of patients with serotype 12F in this outbreak had not previously received the PPSV23 vaccine. A vaccination campaign using PPSV23 (which protects against serotype 12F) was undertaken targeting individuals at risk. Letters were sent to clinicians informing them of the outbreak and recommending the vaccination of unvaccinated individuals who were homeless or use illicit drugs. In addition, a total of 55 outreach clinics were conducted with >375 doses of PPSV23 administered by public health during February 2011. In the following months, the number of IPD cases due to serotype 12F decreased, although the overall case volume of IPD remained elevated. Ongoing enhanced surveillance has been implemented to further characterize future cases of IPD in Manitoba.

Our investigation was limited in the following aspects. Some IPD cases may have been missed, as the majority of data on case count was from routine passive surveillance, not active case finding. Although most information was gathered at the time of the outbreak, other questionnaire information was collected retrospectively up to 2 years after the outbreak, which may have affected recall accuracy.

This outbreak underscores the importance of continued monitoring of IPD incidence and *S. pneumoniae* serotype distribution following the introduction of several effective pneumococcal conjugate vaccines into routine childhood immunization programs. Further comparative genetic studies of the outbreak strains may offer insights into their virulence and connections with 12F strains implicated in previous 12F outbreaks in the United States and Canada, and nasopharyngeal carriage studies among high-risk populations may provide clues to the origin of this outbreak.

## Notes

***Author contributions.*** E. S. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. E. S. analyzed the data; E. S., M. I., and S. M. M. drafted the manuscript; G. P. and X. D. performed the molecular typing and susceptibility testing of 12F isolates; D. R. P., J. L. W., and P. V. C. supervised and coordinated laboratory investigations; and S. M. M. supervised the epidemiological analysis and coordinated the investigation. All authors contributed to the conception and design of the study and to the interpretation of the data. All authors critically revised the manuscript for intellectual content and approved the final draft for submission.

***Disclaimer.*** The interpretation and conclusions contained herein do not necessarily represent those of the Public Health Agency of Canada, Manitoba Health, or the Winnipeg Regional Health Authority.

***Financial support.*** S. M. M. was supported by an Establishment grant from the Manitoba Health Research Council. S. M. M. is a Canada Research Chair in Pharmaco-epidemiology and Vaccine Evaluation and The Great-West Life, London Life and a Canada Life Junior Investigator of the Canadian Cancer Society (grant number 2011-700644).

***Potential conflicts of interest.*** S. M. M. received unrestricted grant funding from GSK, Pfizer, and Sanofi Pasteur for unrelated studies. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

## References

1. Centers for Disease Control and Prevention. Outbreak of invasive pneumococcal disease—Alaska, 2003–2004. MMWR Morb Mortal Wkly Rep **2005**; 54:72–5.
2. Hoge CW, Reichler MR, Dominguez EA, et al. An epidemic of pneumococcal disease in an overcrowded, inadequately ventilated jail. N Engl J Med **1994**; 331:643–8.
3. Lee EH, Hosea S, Schulman E, et al. *Streptococcus pneumoniae* serotype 12F outbreak in a homeless population—California, 2004. In: 54th Annual Epidemic Intelligence Service (EIS) Conference, Atlanta, Georgia, April 11–15, 2005. Abstract p. 79.
4. Torzillo PJ, Morey F, Gratten M, Murphy D, Matters R, Dixon J. Changing epidemiology of invasive pneumococcal disease in central Australia prior to conjugate vaccine: a 16-year study. Vaccine **2007**; 25:2375–8.

5. Romney MG, Hull MW, Gustafson R, et al. Large community outbreak of *Streptococcus pneumoniae* serotype 5 invasive infection in an impoverished, urban population. Clin Infect Dis **2008**; 47:768–74.
6. Rakov AV, Ubukata K, Robinson DA. Population structure of hyperinvasive serotype 12F, clonal complex 218 *Streptococcus pneumoniae* revealed by multilocus boxB sequence typing. Infect Genet Evol **2011**; 11:1929–39.
7. Antonio M, Dada-Adegbola H, Biney E, et al. Molecular epidemiology of pneumococci obtained from Gambian children aged 2–29 months with invasive pneumococcal disease during a trial of a 9-valent pneumococcal conjugate vaccine. BMC Infect Dis **2008**; 8:81.
8. Skoczynska A, Sadowy E, Bojarska K, et al. The current status of invasive pneumococcal disease in Poland. Vaccine **2011**; 29:2199–205.
9. Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA **2005**; 294:2043–51.
10. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med **2003**; 348:1737–46.
11. Manitoba Health. Invasive pneumococcal disease (*Streptococcus pneumoniae*) (pneumococcus), **2011**. Available at: http://www.gov.mb.ca/health/publichealth/cdc/protocol/strep.pdf. Accessed 10 June 2013.
12. Austrian R. The Quellung reaction, a neglected microbiologic technique. Mt Sinai J Med **1976**; 43:699–709.
13. Lovgren M, Spika J, Talbot J. Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992–1995. Can Med Assoc J **1998**; 158:327–31.
14. Manitoba Centre for Health Policy. Constructing the SEFI (1996) score, **2001**. Available at: http://mchp-appserv.cpe.umanitoba.ca/concept/sefi_1996_additional.html. Accessed 10 June 2013.
15. Public Health Agency of Canada. Canadian immunization guide. 7th ed. **2006**. Available at: www.phac-aspc.gc.ca/publicat/ccdr-rmtc/08vol34. Accessed 25 February 2014.
16. Louie M, Louie L, Papia G, Talbot J, Lovgren M, Simor A. Molecular analysis of the genetic variation among penicillin-susceptible and penicillin-resistant *Streptococcus pneumoniae* serotypes in Canada. J Infect Dis **1999**; 179:892–900.
17. Enright MC, Spratt BG. A multilocus sequence typing scheme for *Streptococcus pneumoniae*: identification of clones associated with serious invasive disease. Microbiology **1998**; 144:3049–60.
18. Koeck JL, Njanpop-Lafourcade BM, Cade S, et al. Evaluation and selection of tandem repeat loci for *Streptococcus pneumoniae* MLVA strain typing. BMC Microbiol **2005**; 5:66.
19. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 23rd informational supplement. Wayne, PA: CLSI, **2013**.
20. Shrestha S, Foxman B, Weinberger DM, Steiner C, Viboud C, Rohani P. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med **2013**; 5:191ra84.
21. Mahmud SM, Becker M, Keynan Y, et al. Estimated cumulative incidence of pandemic (H1N1) influenza among pregnant women during the first wave of the 2009 pandemic. Can Med Assoc J **2010**; 182:1522.
22. Chiba N, Morozumi M, Sunaoshi K, et al. Serotype and antibiotic resistance of isolates from patients with invasive pneumococcal disease in Japan. Epidemiol Infect **2010**; 138:61–8.
23. Song JY, Nahm MH, Moseley MA. Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. J Korean Med Sci **2013**; 28:4–15.
24. Deng X, Church D, Vanderkooi OG, Low DE, Pillai DR. *Streptococcus pneumoniae* infection: a Canadian perspective. Expert Rev Anti Infect Ther **2013**; 11:781–91.
25. Wierzbowski AK, Karlowsky JA, Adam HJ, Nichol KA, Hoban DJ, Zhanel GG. Evolution and molecular characterization of macrolide-resistant *Streptococcus pneumoniae* in Canada between 1998 and 2008. J Antimicrob Chemother **2014**; 69:59–66.
26. Klein JO. The epidemiology of pneumococcal disease in infants and children. Rev Infect Dis **1981**; 3:246–53.
27. Lloyd-Evans N, O'Dempsey TJ, Baldeh I, et al. Nasopharyngeal carriage of pneumococci in Gambian children and in their families. Pediatr Infect Dis J **1996**; 15:866–71.
28. Loda FA, Collier AM, Glezen WP, Strangert K, Clyde WA Jr, Denny FW. Occurrence of *Diplococcus pneumoniae* in the upper respiratory tract of children. J Pediatr **1975**; 87(6 pt 2):1087–93.
29. Robinson DA, Turner JS, Facklam RR, et al. Molecular characterization of a globally distributed lineage of serotype 12F S*treptococcus pneumoniae* causing invasive disease. J Infect Dis **1999**; 179:414–22.
30. Bigham M, Patrick DM, Bryce E, et al. Epidemiology, antibiotic susceptibility, and serotype distribution of *Streptococcus pneumoniae* associated with invasive pneumococcal disease in British Columbia: a call to strengthen public health pneumococcal immunization programs. Can J Infect Dis **2003**; 14:261.
31. Adam HJ, Schurek KN, Nichol KA, et al. Molecular characterization of increasing fluoroquinolone resistance in *Streptococcus pneumoniae* isolates in Canada, 1997 to 2005. Antimicrob Agents Chemother **2007**; 51:198–207.
32. Mercat A, Nguyen J, Dautzenberg B. An outbreak of pneumococcal pneumonia in two men's shelters. Chest **1991**; 99:5.
33. Chang A, Osterloh J, Thomas J. Levamisole: a dangerous new cocaine adulterant. Clin Pharmacol Ther **2010**; 88:408–11.
34. Knowles L, Buxton JA, Skuridina N, et al. Levamisole tainted cocaine causing severe neutropenia in Alberta and British Columbia. Harm Reduct J **2009**; 6:30.
35. Wiens MO, Son WK, Ross C, Hayden M, Carleton B. Cases: cocaine adulterant linked to neutropenia. CMAJ **2010**; 182:57–9.
36. Larocque A, Hoffman RS. Levamisole in cocaine: unexpected news from an old acquaintance. Clin Toxicol (Phila) **2012**; 50:231–41.
37. Ferucci ED, Templin DW, Lanier AP. Rheumatoid arthritis in American Indians and Alaska Natives: a review of the literature. Semin Arthritis Rheum **2005**; 34:662–7.
38. Peschken CA, Esdaile JM. Rheumatic diseases in North America's indigenous peoples. Semin Arthritis Rheum **1999**; 28:368–91.
39. Wylie JL, Shah L, Jolly A. Incorporating geographic settings into a social network analysis of injection drug use and bloodborne pathogen prevalence. Health Place **2007**; 13:617–28.