Challenges to the Surveillance of Meningococcal Disease in an Era of Declining Incidence in Montréal, Québec

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ABSTRACT

OBJECTIVES: Though rare in Montréal, meningococcal disease continues to cause serious morbidity and mortality. In an era of declining incidence, our objective was to evaluate the sensitivity and the timeliness of case reporting and the capacity to statistically detect disease clusters.

METHODS: We used the public health department's reportable disease database (RDD) to calculate the timeliness of reporting by physicians and laboratories for the period 1995 to 2008. The sensitivity of case reporting was evaluated through capture-recapture estimation using the RDD and the hospitalization discharge database (MED-ECHO). To evaluate the detection of cases clustered by time and proximity, we applied scan statistics to the RDD with cases coded by time and geographic location for the period 1992 to 2008.

RESULTS: While the system sensitivity was judged to be high at 94%, physicians reported only 54% of cases. A total of 92.3% of cases were notified by physicians or laboratories within seven days, meaning that in theory, 13 cases were not notified in time to conduct thorough contact tracing and offer chemoprophylaxis to close contacts. In high-incidence years, scan statistics detected two statistically-significant clusters one to two weeks earlier than traditional detection through the manual monitoring of cumulative cases.

CONCLUSIONS: To improve system performance, we recommended increasing the emphasis of laboratory reporting, reinforcing early reporting by physicians and if incidence increases, using scan statistics to identify clusters that can add to a public health practitioner's initial "hunch" of an emerging outbreak.

KEY WORDS: Disease clustering; evaluation; *Neisseria meningitidis*; public health; surveillance

La traduction du résumé se trouve à la fin de l'article.

Can J Public Health 2013;104(4):e335-e339.

Invasive meningococcal disease (IMD) is a major cause of epidemic meningitis, and may be fulminant or lethal.¹ In Québec, the case fatality ratio from 1997 to 2011 was 15% for serogroup C and 5.7% for serogroup B.² Long-term sequelae, including loss of limbs, hearing and renal problems occur in 3-15% of cases.³ Decreases in the incidence of serogroup C disease were observed following serogroup C outbreaks in Québec and associated mass vaccination campaigns among persons 6 months to 20 years of age in 1993 and 2001.^{4,5} From 2001, the National Advisory Committee on Immunization (NACI) recommended routine and catch-up vaccination using the monovalent serogroup C vaccine for infants, children aged one to four years, adolescents and young adults up to 20 years of age.⁶ In Québec since 2002, one dose of serogroup C vaccine is administered to children at 12 months of age. Accordingly, vaccination coverage by 24 months is 96%.⁷ In parallel with these provincial and national estimations, the incidence in Montréal decreased by over 50%, from 1.6 to 0.5 cases per 100,000 in 1995 and 2008, respectively (Figure 1).

In Montréal, physicians and laboratories are mandated to promptly report to the local public health department by phone or fax probable and laboratory-confirmed cases based on a standardized case definition.⁸ This enables the department to conduct epidemiological investigation, post-exposure prophylaxis (PEP), vaccination for household contacts of a case infected by a vaccine-preventable serogroup, and surveillance to observe changes in incidence and serogroup predominance. A previous evaluation of IMD

surveillance in Montréal from 1993-1995 found that the sensitivity was high (94.8%) and the timeliness was reasonable (85.3% reported within six days).⁹ In an era of declining incidence, we were concerned about complete and timely reporting. We evaluated the sensitivity and timeliness of reporting and the capacity to statistically detect clusters; this could facilitate early identification of common characteristics or venues amenable to intervention. To produce results that are comparable with the previous sensitivity and timeliness evaluation conducted April 1, 1993 to March 31, 1995, we conducted these analyses for the period April 1, 1995 to December 31, 2008. We used a longer period to evaluate the statistical detection of clusters, January 1, 1992 to December 31, 2008, to include a period of high incidence in the early 1990s.

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Acknowledgements: We thank Jean Gratton and Maryse Lapierre of the Direction de santé publique for their help with file retrieval, and the Canadian Field Epidemiology Program and participants of its scientific writing workshop for their review of the initial report.

Conflict of Interest: None to declare.

Figure 1. Incidence of invasive meningococcal disease per 100,000 persons, Montréal, 1992 to 2008

METHODS

Case definitions

The case definitions used are those established by the Ministère de la Santé et des Services sociaux de Québec and correspond with those recommended by the Public Health Agency of Canada:^{8,10}

A confirmed case includes:

- Clinical evidence of invasive disease with laboratory confirmation of infection through isolation of *N. meningitidis* from a normally sterile site (blood, cerebrospinal fluid, joint, pleural or pericardial fluid)

A probable case includes:

- Clinical evidence of invasive disease including meningitis and/or septicaemia with purpura fulminans or petechiae, OR
- Clinical evidence of invasive disease AND detection of *N. meningitidis* antigen in the cerebrospinal fluid.

To be counted as a case in Montréal, patients must have been residents of and must have become ill in Montréal or have become ill elsewhere and have been transferred to Montréal.

To measure sensitivity, we compared data on confirmed and probable IMD cases among Montréal residents between April 1, 1995 and December 31, 2008 using two independent data sources: the reportable disease database (RDD) and the provincial hospitalization database (*Maintenance et exploitation des données pour l'étude de la clientèle hospitalière* or MED-ECHO). We extracted hospitalizations using ICD-9 (036.0-036.9; used 1995-2005) and ICD-10 (A39.0-39.9, used 2006-2008) codes associated with IMD. This assumed that all IMD cases are hospitalized. The sensitivity of case reporting was calculated using the cases reported to the RDD (R) divided by the total estimated cases by a capture-recapture calculation (N).¹¹ As MED-ECHO records are non-nominal, the datasets were linked manually by age, sex and a three-day window between the dates of reporting and dates of admission. For the unmatched

Table 1. Capture-recapture Estimates and Case Reporting Sensitivity for IMD Cases, Montréal, April 1, 1995 - December 31, 2008

Hospitalization Database	Public Health Registry		
	Cases Reported	Cases Not Reported	All Cases
Cases listed	133	8	141
	(C)	(N ₂)	(S)
Cases not listed	51	3.1*	54.1
	(N ₁)	(X)	
All cases	184	11.1	195.1†
	(R)		(N)

* Calculated: $X = (N_2 * N_1) / (C) = (8 * 51) / (133) = 3.07$

† Calculated: $N = C + N_1 + N_2 + X = (133) + (51) + (8) + (3.07) = 195.07$

Sensitivity = $R / N = 184 / 195.1 = 94.3\%$ [95% CI = 90.5-97.0]

MED-ECHO entries, an epidemiologist reviewed hospital and laboratory records against the case definition.

The timeliness for reporting by physicians and laboratories was calculated as the difference in days between the date of specimen collection (signifying physician contact) and the date of reporting. A 7-day limit was deemed to be a realistic period during which PEP can be administered within the 14-day period in which it is most effective, accounting for delays in reaching household contacts.¹²

The space-time scan statistic (STSS) was used to detect cluster signals for January 1, 1992 to December 31, 2008, as implemented by SaTScan™ version 9.0 [http://www.satscan.org/]. SaTScan examines the relative risk (RR) or ratio of observed numbers of cases inside and outside a cluster given the population density. Cases were assigned a time-code (date of specimen collection), geo-code (the Canada Post forward sortation area [FSA] of residence as a proxy for exposure to household contacts) and population at risk (census population by FSA). A Poisson distribution of numbers of cases per FSA was assumed. Likelihood ratio statistics and Monte-Carlo simulations produced a P-value for each cluster indicating its statisti-

Figure 2. Cumulative frequency of number of days to report IMD cases to the public health department, by source, n=168 cases with date of specimen sampling, Montréal, April 1, 1995 - December 31, 2008

cal significance of occurring not due to chance ($p < 0.05$). A cluster was defined as two or more serogroup B or C cases bound too tightly in time (≤ 40 days between the date of specimen collection for the first and last case, or four times the longest incubation period) and geographic location (cluster area included $\leq 50\%$ of the Montréal population) to be produced by chance. Cluster signals were tested retrospectively. When a cluster was detected retrospectively, we applied repeated prospective scans. Prospective scans simulated the addition of cases over time in order to evaluate the generation of early warning signals resulting from the addition of each successive case. The delay between the first early warning signal and the date of each subsequent case was calculated to estimate how early the cluster was detected. These results were compared with observations of clustering found in case files.

As a program evaluation, this protocol did not require ethical review.

RESULTS

The date of specimen collection was present for 168 (91.3%) of the 184 cases retrieved from the RDD (R) for 1995 to 2008. There were 147 hospitalizations retrieved from MED-ECHO (S) (Table 1). A total of 133 cases were found in both datasets (C), 51 in RDD only (N_1) and 14 in MED-ECHO only. Investigation of the 14 unmatched hospitalizations found 8 true cases (N_2) and 6 false-positive cases. Three of the eight true cases met the confirmed case definition and were supported by laboratory confirmation, and five of the eight could not be retrieved without a date of birth and were considered con-

firmed without laboratory confirmation. Of the six false-positive hospitalizations, three of the six were unrelated meningitis (not *N. meningitidis*), two of the six had a change in discharge diagnosis and one of the six had a coding error. Therefore, we adjusted the number of MED-ECHO hospitalizations from 147 to 141 (147 minus 6 false-positive cases). Capture-recapture estimated 195 total cases. The sensitivity was 94.3% [95% CI 90.5-97].

Of the 184 reported cases, 100 (54.3%) and 168 (91.3%) were reported by physicians and laboratories, respectively. Of the 168 cases with a date of specimen collection, 87 (51.8%) were reported within seven days by physicians (range 0 to 13 days) and 115 (68.5%) were reported within seven days by laboratories (range 0 to 39 days) (Figure 2). Overall, 155 (92.3%) cases were reported within seven days by the first reporting source. Physicians tended to report a higher proportion of cases within days zero to two (40.5%), which is reflected in two thirds of all cases being reported by the first reporter by day two (66.7%). From days three to seven, laboratories reported a consistently higher proportion of cases (50.6% to 68.5%) compared to physicians (45.8% to 51.8%).

For the 206 cases from 1992 to 2008, 2 of the 11 clusters detected were statistically significant. Four clustered serogroup C cases were reported between December 9, 1993 and January 5, 1994 ($RR=81.1$, $p < 0.04$). Although two deaths occurred in a short time span, the case files did not indicate that this cluster was detected or investigated in real time and no microbiological subtyping information was available to explore its plausibility. Prospective detection signalled the cluster when the second case was added on

December 22 and then again with each successive case. The detection time was reduced by 6 to 14 days. Five serogroup B cases were reported between September 21 and October 25, 1995 (RR=54.9, $p<0.02$). An overlapping cluster of five serogroup B cases with matching electrophoretic profiles (ET-5) between September 23 and October 20, 1995 was manually detected in 1995 and investigated; three of the five cases frequented raves, and links to a specific bar were also demonstrated.¹³ Prospective detection signalled the cluster when the second case was added on October 7, and again with each successive case, reducing detection time by 8-13 days. From the case files and the published outbreak report, we were unable to identify the date that the cluster was manually detected.

DISCUSSION

Case-reporting sensitivity remained high with 94.3% of cases reported to the surveillance system, similar to the 1993-1995 capture-recapture estimate for Montréal (94.8%).⁹ The overall timeliness of reporting was inadequate. The proportion (54%) of physician reports was low; 46% of cases were dependent on time-insensitive laboratory reporting, which tended to increase slowly after the first two days. To compare, physicians reported 70% of cases in Montréal in 1993-1995.⁹ The proportion of physicians reporting cases compares negatively to that of a comparably sized population in Thames Valley, UK (90%).¹⁴ This may affect the ability of the public health department to administer PEP and vaccination to contacts in the 14-day window. A total of 92.3% of cases were notified by physicians or laboratories within seven days, meaning that in theory, 13 cases were not notified in time to conduct thorough contact tracing and offer PEP when indicated. Correcting these avoidable delays may prevent such secondary cases as have been recently documented in the UK and the US.^{15,16}

Without specific mention of IMD, a previous survey on the knowledge of notifiable diseases reporting among emergency physicians in Canada showed substantial barriers concerning knowledge on which diseases to report to the public health department and the time and effort required to report.¹⁷ However, as a severe disease that affects children which can be notified on a clinical basis before any laboratory confirmation, it follows that physician reporting is likely to be more assured for IMD as compared to other reportable diseases.¹⁸ In this case, reporting appears to have shifted to laboratories. Therefore, ad-hoc reminders to physicians and the posting of reportable disease lists and guidelines for reporting procedures in emergency rooms may be useful.¹⁷ For laboratories, automated electronic reporting of results using an online system would be ideal for increasing speed. However, this will require accommodating the various types of software used in laboratories and hospitals, which is currently not feasible.

Space-time scan statistics detected cluster signals at the local level in 1994 and 1995. One cluster signal was shown to have evidence of being microbiologically-linked through identical microbiological profiles, and the prospective method identified an emerging outbreak linked to a risk group ("ravers").¹³ This provided early warning of a suspected cluster before the serotyping that traditionally confirms an outbreak after cumulative cases is undertaken. No cluster signals were generated after 1995. The decreased incidence since 2001 may have lowered the power to detect clustering, thus limiting usefulness in a low incidence period. As well, the proportion of fulminant cases to asymptomatic carriers involved in

clusters may be low. Only 4.4% (9/206) cases were found to be clustered. Similarly, only 4.2% of cases were found to be clustered using STSS with molecular typing in Germany.¹⁹ At the local level, STSS may be more effective in detecting clusters of high-incidence diseases such as shigellosis as compared to meningococcal disease.²⁰

There are several limitations to this evaluation. The data sources may not be completely independent because the public health department and hospitals may exchange information on cases; this may overestimate the reporting completeness.²¹ The under-reporting of the 51 cases found in the RDD but not listed in MED-ECHO could not be further investigated due to lack of identifying data in the MED-ECHO dataset, but may indicate several possibilities: that infection by *N. meningitidis* may have been coded as another bacterial or viral cause of meningitis in MED-ECHO; for fatal cases, that *N. meningitidis* may not have been isolated by the time of completion of the discharge form; and that some fulminant cases may have been reached by public health but not hospitalized due to rapid recovery or death.^{21,22} To fully explore these possibilities, registries that contain unique identifiers to perfectly match cases and hospitalizations would be optimal for routine evaluations, such as that used in Denmark.²³ Second, the true impact of the reduced physician reporting is dependent on whether physicians undertook preventive actions such as administering PEP and vaccinating contacts (who are often family members to whom they have access). Third, cluster detection sensitivity was decreased by the inability to incorporate asymptomatic carriers and geographic locators other than residence where transmission often occurs (i.e., day cares, workplaces).

Our findings suggest that vigilance towards IMD reporting has shifted from physicians to laboratories in this era of declining incidence in Montréal. This may be true for other jurisdictions in Canada. We recommended three improvements for the surveillance system: 1) reminding physicians to report probable and confirmed cases in order to provide simultaneous reporting by two sources, 2) restating the role of the public health department in more extensive contact tracing beyond family members, and 3) in the absence of automatic electronic reporting, monitoring and increasing the speed of laboratory reporting. When incidence is high, daily cluster analysis by serogroup may hasten the detection of outbreaks by one to two weeks, adding to a public health practitioner's initial "hunch" of an outbreak before serotyping is available. Such early warning systems require, as does routine surveillance, complete and timely reporting by clinicians.

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Received: November 13, 2012

Accepted: April 8, 2013

RÉSUMÉ

OBJECTIF : Bien qu'elles soient rares à Montréal, les infections invasives à méningocoques continuent de causer de la morbidité grave et de la mortalité. En période d'incidence décroissante, notre objectif était d'évaluer la sensibilité et la rapidité de la déclaration des cas et la capacité de détecter statistiquement les cas groupés de cette maladie.

MÉTHODE : Nous avons utilisé la base de données des maladies à déclaration obligatoire de la Direction de santé publique (« RDD ») pour calculer la rapidité de la déclaration des cas par les médecins et laboratoires pour la période de 1995 à 2008. La sensibilité de la déclaration des cas a été évaluée par la méthode capture-recapture en utilisant le « RDD » et la base de données des départs hospitaliers (« MED-ECHO »). Pour évaluer la détection des cas groupés dans le temps et l'espace, nous avons appliqué une statistique d'agrégation spatio-temporelle au « RDD » avec les cas codés pour la date et la localisation géographique, pour la période de 1992 à 2008.

RÉSULTATS : Bien que la sensibilité du système ait été considérée élevée, à 94 %, les médecins ont déclaré seulement 54 % des cas; 92,3 % des cas ont été déclarés par les médecins ou laboratoires en sept jours ou moins. Cela signifie que, en théorie, 13 cas n'ont pas été déclarés à temps pour faire l'enquête épidémiologique et offrir la chimioprophylaxie aux contacts étroits. Dans les années où l'incidence était élevée, les statistiques d'agrégation spatio-temporelle ont détecté deux agrégats significatifs de cas une à deux semaines plus tôt que la détection traditionnelle par la surveillance manuelle des cas accumulés.

CONCLUSION : Pour améliorer le fonctionnement du système, nous recommandons de mettre l'accent sur la déclaration par les laboratoires et le renforcement de la déclaration rapide par les médecins. Si l'incidence augmente, nous recommandons d'utiliser des statistiques d'agrégation spatio-temporelle pour identifier les cas groupés, ce qui peut constituer un système de détection précoce d'une épidémie émergente pour les praticiens de santé publique.

MOTS CLÉS : agrégation des maladies; évaluation; *Neisseria meningitidis*; santé publique; surveillance