

**EPIDEMIOLOGY OF A CLUSTER OF ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS
IN NORTHERN MANITOBA**

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Abstract

Background

Although recent studies have shown a high incidence of post-streptococcal glomerulonephritis (PSGN) in certain parts of Canada, not much is known about its epidemiology in Manitoba. In 2017, the Northern Region of Manitoba experienced an increase in cases of PSGN. A rapid syndromic surveillance system was instituted to further delineate the characteristics of the cluster and compare it to rates of PSGN in other jurisdictions.

Methods

PSGN cases were identified through voluntary reporting from physicians, as well as using laboratory surveillance. Descriptive epidemiology is included for cases from June 1, 2017 – April 1, 2018, and *emm* characterization was completed for available isolates.

Results

From June 1, 2017 – April 1, 2018 there were 14 confirmed and 15 probable cases of PSGN, with an apparent peak in cases from August – November 2017. There were 12 male cases and 17 females. The incidence rate for children < 15 years old was 77.0 confirmed cases / 100,000 person-years. *emm*-type 49 was identified in three cases. Close geographic clustering of cases was not observed.

Interpretation

The rate of PSGN in northern Manitoba is higher than expected for a developed country, and the rate of confirmed cases was comparable to that seen in developing countries, as well as other Canadian populations experiencing structural disadvantages. A rapid syndromic surveillance system was successfully instituted to further characterize the outbreak and identify a putative *emm* type. The high rate of PSGN in northern Manitoba is concerning due to both acute illness, as well as potentially increasing the likelihood of chronic kidney disease. This cluster further highlights existing inequities in health outcomes for those in Canada's mid-north.

Introduction

Post streptococcal glomerulonephritis (PSGN) is a non-suppurative sequelae of Group A streptococcus (GAS) infection that involves immune complex deposition in kidney glomeruli. Rates of PSGN have decreased in developed countries, however there continue to be geographical pockets with rates similar to those in developing countries(1)(2). This is well-documented in the Australian Indigenous population(3), and has also been observed in the First Nations population in Northwestern Ontario(4).

Northern Manitoba shares demographic, geographic and historical characteristics with Northwestern Ontario. Both have large Indigenous populations which often face challenges of overcrowding and inadequate sanitation. In Australia, these conditions have been documented to increase rates of infection, particularly with GAS(5)(6).

Acute PSGN has very low mortality rates, but evidence suggests higher incidence of chronic kidney disease following PSGN(7). northern Manitoba has a high baseline burden of chronic kidney disease(8), making PSGN particularly concerning in this area.

In June of 2017, pediatricians in northern Manitoba reported a higher than normal rate of PSGN and a surveillance system was put in place to track the cluster of cases. In this paper we describe the surveillance system, the epidemiology of the cluster, and the response taken.

Methods

Surveillance

The local Medical Officer of Health (MOH) was alerted by pediatricians to an increase in the number of PSGN cases seen in Thompson, Manitoba in June of 2017. PSGN is not a reportable disease under the Public Health Act in Manitoba and, due to this, a two-pronged surveillance system was implemented beginning in June 2017. Physicians were requested to notify the MOH when they diagnosed a PSGN case (clinical notification). In addition, the provincial public health lab (Cadhams Provincial Laboratory) informed the MOH when they tested a sample for Anti-Streptolysin O titre (ASOT, lab reporting). The patient's electronic medical record (EMR) was then reviewed for relevant lab data to determine whether the case met the PSGN case definition (**Box 1**). Rates per 100,000 pediatric population (<15 years of age) were calculated and compared to physician billing data which were used as a proxy for baseline rates of pediatric PSGN in each of the province's health regions from 2000 – 2018.

Box 1. PSGN case definition

Children from northern Manitoba
Symptom onset June 1, 2017 or later

Confirmed Case:

- 1) Laboratory evidence of proteinuria and hematuria
- 2) Positive throat or skin culture for group A streptococcus

Plus one of the following:

- a) Anti- DNase B (ADB) above cutoff (>375 U/ml)
- b) Anti-streptolysin O titre (ASOT) above cutoff (>200 IU/ml)
- c) Complement 3 (C3) level below cutoff (<0.76 g/L)

Probable Case:

- 1) Laboratory evidence of proteinuria and hematuria

Plus one of the following:

- d) Anti- DNase B (ADB) above cutoff (>375 U/ml)
- e) Anti-streptolysin O titre (ASOT) above cutoff (<200 IU/ml)
- f) Complement 3 (C3) level below cutoff (<0.76 g/L)

emm-typing

Where cultures were available bacterial *emm*-type was determined.

Results

Over the ten-month period from June 1, 2017 – April 1, 2018, 14 confirmed and 15 probable pediatric (< 15 years old) cases were identified in 16 different communities in northern Manitoba. There were 12 male cases and 17 female. Ages ranged from 1 – 14 years, with an average age of 6.9 years. Of the confirmed cases, 11/14 had a documented preceding GAS pharyngitis whereas, 3/14 had preceding GAS pyoderma within an 8 week period prior to PSGN diagnosis.

The number of confirmed and probable cases per community ranged from 1 to 6. Extensive clustering of cases was not seen with respect to time. The number of confirmed and probable cases peaked in August 2017, and then slowly decreased until March (Fig 1).

The rate of PSGN in the pediatric population of northern Manitoba from June 1, 2017 – April 1, 2018 was 77.0 confirmed cases / 100,000 person-years.

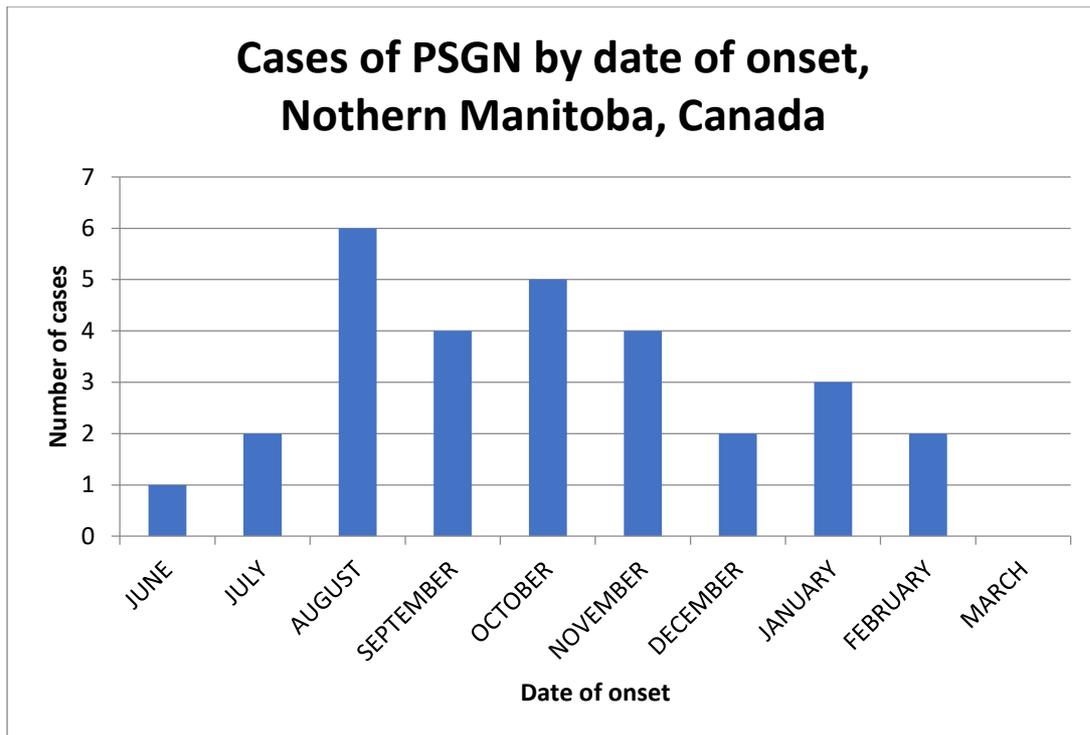


Figure 1. Number of confirmed and probable PSGN cases per month in the Northern Health Region from June 2017 – March 2018(9).

Billing data

From the years 2000 – 2017 the average rate of PSGN in northern Manitoba was 50.7/100,000 pediatric person years, 6.8 times higher than the average rates in the other health regions. However there was significant variation in the rate over time: from 2009 – 2015 the GN rate in the NHR decreased to levels similar to the other health regions but by 2017 it returned to pre-2009 levels (Figure 2). The rates of GN in the NHR ranged from 0 in 2011 to 96.3 cases/100,000 person years in 2001.

The majority of patients in the north diagnosed with GN did not have a documented strep throat or skin infection 8 weeks prior to GN diagnosis.

emm-typing

Three isolates were available for emm-typing. In all three, emm-type 49 was identified.

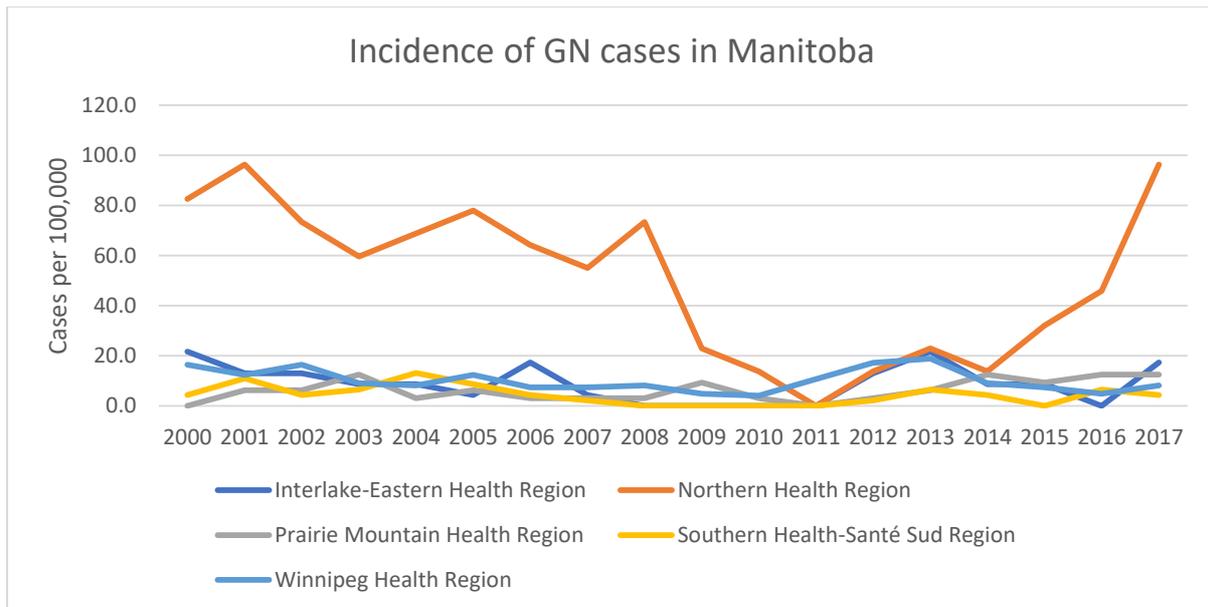


Figure 2. Incidence of pediatric PSGN per capita in each of Manitoba’s health regions from 2000 to 2017.

Interpretation

This study has described a cluster of pediatric PSGN cases in northern Manitoba from June 1, 2017 – April 1, 2018, which had a rate of 77.0 confirmed cases / 100,000 pediatric person-years. A surveillance system was first put in place when pediatricians in Thompson, Manitoba notified the MOH of a higher than usual number of PSGN cases. Initially doctors reported cases when they found them, but after some time doctors stopped reporting new cases. Ultimately the data provided by the lab was more effective for monitoring the cluster. Billing data over the period from 2000 – 2017 showed that northern Manitoba has a GN rate over 6 times higher than other health regions in the province. No community reached the definition of a PSGN outbreak. Healthcare workers in the worst affected community were educated on how to recognize PSGN and surveillance was continued.

There are no well-established guidelines for controlling a PSGN outbreak although administration of prophylactic penicillin has shown some effectiveness(10,11). A study in Australia which investigated prophylactic penicillin to stop PSGN outbreaks defined an outbreak as at least than 2 cases in a week or at least 3 cases in a month(11). No community in northern Manitoba fulfilled this outbreak definition when using only confirmed cases. Two communities came close: one community had three confirmed cases over 37 days and one community had one confirmed and one probable case in under a week.

Options for dealing with the high number of cases were discussed with the community that had 3 confirmed cases. The community chose to have the MOH and a pediatrician run a training session for nursing station staff on how to recognize PSGN, and to continue monitoring for cases of PSGN. No more cases were reported from the community and therefore no screening and prophylactic treatment program was implemented.

All three isolates that were available to be typed were *emm49*. *emm49* is one of the 20 most common *emm* types in high income countries, although it is not included in the current experimental 26-valent vaccination formulation(12). Studies in Ontario and Japan have found that *emm49* has a high invasive index(13,14). It has been associated with several GN outbreaks including the 1953 and 1966 in Red Lake Indian Reservation in northern Minnesota and an outbreak in 2000 in the Northern Territory of Australia(15,16). Several other *emm* sequences have been isolated from PSGN outbreaks in Australia, namely *emm19.7*, *emm3.22*, *emm70.0*, *emm85.0*, and *emm 55.0*(16). An outbreak of PSGN in China was postulated to be due to the strains *emm60.1* and *emm63.0*(17).

emm49 is documented as a nephritogenic strain(18). Nephritogenic strains more commonly infect the skin and PSGN cases peak in late summer, while rheumatogenic strains tend to infect the throat and cases peak in October(18,19). Climate also affects the site of GAS infection. Pharyngitis is more common in temperate climates while impetigo is more common in tropical climates(20). Furthermore, temperate climates show seasonal variation: impetigo is more likely to be seen in the summer(21). Interestingly, 11 of the 14 confirmed PSGN cases in our dataset were preceded by GAS pharyngitis. This is not surprising, given the subarctic climate of northern Manitoba. That *emm49*, a nephritogenic strain, was causing pharyngitis is not unsurprising given the climate of the study region and previous documentation of nephritogenic strains infecting the throat(19).

The rate of PSGN in northern Manitoba is more than 6 times higher than the other health regions in Manitoba, as seen in Figure X. Indeed, the rates seen in northern Manitoba are comparable to rates seen in developing countries and populations of disadvantaged minorities in developed countries, although the lack of a universally accepted case definition makes comparison across studies and regions difficult.

The average pediatric PSGN rate in developed countries is 6 / 100,000 pediatric person-years(22), similar to the rate in Manitoba when the Northern Health Region is excluded: 7.4 / 100,000 pediatric person-years. The median rate in developing countries or minority populations in developed countries is 24.3 / 100,000(22), similar to the rate of 20.8 per 100,000 pediatric person-years reported for Northwestern Ontario(4), a district comparable to northern Manitoba in terms of demographics, geography and history. Our rate of 77.0 confirmed cases per 100,000 pediatric person-years is higher than these rates, but lower than the rate in the Northern Territory of Australia of 94.3 cases / 100,000 pediatric person-years(16). The elevated rate of PSGN in northern Manitoba compared to the rates observed in the south of the province suggests that characteristics of the region contribute to the high rate of PSGN. Northern Manitoba has a largely remote population some of whom do not have access to basic necessities such as safe housing, clean drinking water, education and employment(23). In Australia, a study demonstrated that these determinants of health were linked to increased GAS infections and that improvement in these conditions decreased infection(5,6). In Chile, lower socioeconomic status and overcrowding were related to increased rates of PSGN(24). This complex interplay between the different social determinants of health suggests that a multifaceted approach is needed to facilitate infection control(25). If plans are put in place to control PSGN in northern Manitoba, it is crucial to address these underlying inequities that affect infection.

Limitations

There are several limitations in this study that need to be addressed. First, there is no universally accepted case definition for PSGN, limiting our ability to compare rates across jurisdictions. Importantly, the case definitions used in studies conducted in Australia and northwestern Ontario included both clinical and laboratory data(4)(16), while ours included only laboratory data. The decision to include only laboratory data was made because of the impracticality of accessing written medical records in communities only accessible by plane, and the presumed inconsistency in which symptoms doctors would report in their notes. The difference in case definitions may partially explain why our rate is much higher than the rate reported for northwestern Ontario.

The lack of clinical evidence in our definition could result in inaccuracies in the number of PSGN cases, although when the anti-streptolysin O titres (ASOT) and anti-deoxyribonuclease B (ADNaseB) lab tests are used in conjunction they have a sensitivity of 95.5%(26). This suggests we captured the majority of positive cases, though we may have false negatives in our dataset.

There is no unique billing code for PSGN and therefore the billing data may include some cases of GN that are not post-infectious, and may miss some cases that are. Therefore the billing data can only be used to get an idea of trends in GN over time, and cannot be interpreted as the exact number of cases each year.

A major limitation in interpreting the *emm*-type data was the limited number of samples available for typing, due to the fact that it is not a standard procedure and samples were often discarded before results came back that they were GAS-positive.

Conclusion

The rate of PSGN in northern Manitoba is much higher than expected for a developed country, and higher than rates in other parts of the province. The rate is more comparable to rates in developing countries and disadvantaged populations within developed countries. This is a concern due to the acute illness caused by PSGN but also because of its potential to increase the likelihood of chronic kidney disease which is already a concern in this region(8).

Continued monitoring for PSGN is needed and if another increase in cases is detected, the laboratory monitoring system can be re-implemented. If clusters continue to happen, discussion with affected communities about prophylactic treatment may be necessary as well as more rigorous tracking of circulating *emm*-types. Making PSGN a reportable disease may also be considered.

Ultimately, high rates of PSGN are found among disadvantaged populations with poor access to health care, water and sanitation. To treat the root cause of the high rates of PSGN, improvements need to be made to living conditions and health care access in northern Manitoba.

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