BMJ
open

Transmissibility of the 2009 H1N1 pandemic in remote and isolated Canadian communities

SCHOLARONE™
Manuscripts

Transmissibility of the 2009 H1N1 pandemic in remote and isolated Canadian communities

LC Mostaço-Guidolin,[1] CS Bowman,[2] AL Greer ,[3, 4] DN Fisman,[4] and SM Moghadas[1]

[1] Centre for Disease Modelling, York University, Toronto, Ontario, Canada

[2] Department of Mathematics, University of Manitoba, Winnipeg, Manitoba, Canada

[3] Public Health Agency of Canada, Ottawa, Ontario, Canada

[4] Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Running title: Transmissibility of the 2009 H1N1 pandemic

Abstract

Objectives: During the first wave of the 2009 influenza pH1N1, disease burden was distributed in a geographically heterogeneous fashion. It was particularly high in some remote and isolated Canadian communities when compared to urban centres. We sought to estimate the transmissibility (the basic reproduction number) of pH1N1 strain in some remote and isolated Canadian communities.

Design: A discrete time susceptible-exposed-infected (SIR) transmission model to was fit to infection curves simulated from laboratory-confirmed case counts for pH1N1 on each day. Sampling from Poisson distribution was used to estimated the basic reproduction number, R_0, of pH1N1 during the spring wave for five different communities in Manitoba and Nunavut,

1

Canada, where remote and isolated communities experienced a high incidence of infection, and high rates of hospitalization and intensive care unit (ICU) admission.

 Setting: Remote and isolated communities in Northern Manitoba, Nunavut, and the largest urban centre (Winnipeg) in the province of Manitoba, Canada.

Results: Using published values of the exposed and infectious periods specific to H1N1 infection, corresponding to the average generation time of 2.69 days, we estimated a mean value of 2.25 for R_0 (95% CI: 1.10–4.25) in a community located in northern Manitoba. Estimates of R_0 for other communities in Nunavut varied considerably with higher mean values of 4.38 (95% CI: 2.83–6.76); 2.23 (95% CI: 1.46–4.44); and 2.62 (95% CI: 1.65–4.02). We estimated a lower mean value of 1.62 (95% CI: 1.38-2.00) for R_0 in the Winnipeg health region, as the largest urban centre in Manitoba.

Conclusions: Influenza pH1N1 appears to have been far more transmissible in rural and isolated Canadian communities than other large urban areas. The differential severity of the pandemic in these regions may be explained partly by differential transmissibility, and suggests the need for more nuanced, targeted, or population specific control strategies in Canada.

2

Introduction

Early outbreaks of the 2009 H1N1 influenza pandemic displayed variable degrees of incidence, apparently higher attack rates, and more severe disease outcomes in several remote and isolated communities in Canada [1,2]. Epidemiological data collected during the first wave of H1N1 pandemic indicate disproportionately higher rates of hospitalization and intensive care unit (ICU) admission in these communities. For instance, hospitalization rates in Nunavut and northern Manitoba were 2.44 and 1.27 per 1,000 population, respectively, which are significantly higher than the corresponding rates for Winnipeg (0.13) or the province of Ontario (0.033). Similar differences are evident from data regarding ICU admission rates, which were higher for Nunavut (0.20) and northern Manitoba (0.16) than those for Winnipeg (0.032) and Ontario (0.0056), per 1,000 population. The differential prevalence of predisposing health conditions including diabetes, pregnancy and morbid obesity, has received considerable attention as explicators of severe outcomes of H1N1 pandemic in rural and urban communities in Canada [2]. The high rates of hospitalization and ICU admission within these remote regions, could be linked to both transmissibility of the disease and to the prevalence of factors predisposing to more severe outcomes in infected individuals.

An important index of transmissibility for a communicable disease is the basic reproduction number (R_0) that represents the number of secondary infections generated by a single infected case in an entirely susceptible population [3]. Early published literature for the transmissibility of pandemic H1N1 infection provides a range of 1.2–1.8 for R_0 [4,5,6,7], mainly in large urban settings, suggesting that the novel H1N1 strain was less transmissible than the

1918-1919 pandemic virus for which R_0 has been estimated in the range 1.8–3.0 [8]. However, early estimates may not apply in remote and isolated communities that have distinct demographic characteristics, as well as distinct environmental (built or natural) conditions. We sought to evaluate differential transmissibility of H1N1 in five distinct population settings in Canada: a remote/isolated community in the Burntwood health region of northern Manitoba, three remote/isolated communities in Nunavut, and compare them with the largest urban area (i.e., the Winnipeg health region) in Manitoba. Communities in Nunavut as well as several communities in northern Manitoba would be considered remote and/or isolated communities [9] and many of these geographic areas have predominantly Aboriginal populations (e.g., 85% of the Nunavut population and 76% of the northern Manitoba region self-identify as Aboriginal) [10].

Material and Methods

To estimate plausible ranges for R_0, we employed a discrete time epidemic model, and fitted to infection curves inferred from collected data for laboratory-confirmed cases of H1N1 infection during the first wave of the 2009 pandemic. Details of data and estimation procedure are described below.

Case Data

We obtained the daily number of laboratory-confirmed cases of pandemic H1N1 influenza (in which the cases were reported based on the earliest date of symptom onset, initial care, specimen collection, hospital admission, or ICU admission) for the period of May 3 to August 5, 2009, for each community under study. A laboratory-confirmed case was reported as

4

an individual with ILI or severe respiratory illness who tested positive for pandemic H1N1

influenza A virus by real-time reverse-transcriptase PCR (RT-PCR) or viral culture. These data

were collected and provided by Manitoba Health, and the Nunavut Department of Health and

Social Services (HSS).

The Model

We considered a homogeneous mixing structure for the model in which individuals are

identified by their epidemiological status as susceptible (S), exposed but not yet infectious

(E), Infectious (I), and recovered (R). Exposed state refers to the period of time following

transmission of infection during which the newly infected person cannot transmit the disease

and symptoms are absent before developing clinical disease. Assuming that the reduction in the

number of susceptibles is small during the early stages of the outbreak (i.e. $S(t)/S_0 \approx 1$, where

S_0 is the initial number of susceptibles) [11], the number of infections at time t is given by [12]

$$I(t) \approx I_0 e^{\frac{1}{2}\left[\sqrt{4(R_0-1)\sigma\gamma+(\sigma+\gamma)^2}-(\sigma+\gamma)\right]t} \tag{1}$$

where σ and γ are the average duration of exposed and infectious stages, I_0 is the initial

number of infectious cases, and R_0 is the basic reproduction number. The expression (1)

describes the exponential growth of epidemic spread following disease outset. We estimated

R_0 by fitting $I(t)$ to infection curves during the exponential phase of epidemic growth.

Model Parameters

The values of exposed and infectious periods were taken from estimated ranges in the

published literature specific to the 2009 pandemic, with a fixed exposed period of 1 day, and a

mean duration of infectiousness of 3.38 days [11,13]. Using a common heuristic, that the generation times can be estimated as the sum of the exposed period and half of the duration of infectiousness[14], leads to a mean generation times of 2.69 days, which lies in the estimated range for pandemic H1N1 [15,16,17] .

Sampling

To determine the variability in R_0 , we generated 1000 datasets for case counts on each day through sampling from a Poisson distribution, with reported cases on the corresponding day as the mean of distribution. To create an infection curve for each dataset, first we sampled an infectious period for each case from a log-normal distribution with the scale parameter $a = 1.192$ and shape parameter $b = 0.233$, with the 95% range of 2.13 – 5.1 days [11]. We assumed that the infectious period was initiated one day before the case was confirmed (reported date) [12]. This effectively means that every case was on the infection curve $I(t)$ for its sampled duration of infectiousness (Figures 1 and 2).

R₀ Estimation

Since the reproduction number only reflects the growth rate during the early stages of the epidemic, estimating R_0 is sensitive to the time period chosen for fitting the model to the data [18]. For a fit with very short timelines following the onset of the outbreak (establishment phase), the uncertainty in estimates of R_0 will be high. On the other hand, fitting the model using data that extend beyond the epidemic peak, will result in underestimating R_0 , through the influence of several factors, including widespread implementation of public health

measures and an increase in herd immunity, which may in turn invalidate the assumption

$S(t)/S_0 \approx 1$. In order to minimize these effects, we obtained the turning points of the

outbreaks following the initial exponential growth phase, and performed fitting from the date

at which the first laboratory confirmed case was identified, up to one day before the turning

point for each infection curve. Turning point for each dataset was obtained through fitting the

Richards model to cumulative number of daily counts in each infection curve [19,20]. Assuming

that K represents the cumulative number of daily cases for the infection curve $I(t)$ (generated

through sampling method), the first turning point t_m was obtained by solving the equation

$I(t_m) = K(1+c)^{1/c}$, where c is the deviation parameter estimated using the method of least

squares through curve-fitting [21]. We then estimated R_0 by fitting $I(t)$ in equation (1) to the

generated infection curves from the date of the first laboratory case until $t_m - 1$. The mean

values and 95% confidence intervals were obtained from the R_0 distributions.

Results

The infection curves and the corresponding posterior distributions for the ranges of R_0

are illustrated in Figures 1 and 2. The mean estimate of R_0 for a northern community in

Manitoba (Figure 1b) is 2.25 (95% CI: 1.10–4.25), which is higher than the estimate for

Winnipeg health region with the mean value of 1.62 (95% CI: 1.38-2.00). We obtained

considerably higher estimates for the mean values of R_0 for other communities in the territory

of Nunavut (Figures 1d,f,h): 4.37 (95% CI: 2.83 – 6.76); 2.23 (95% CI: 1.46 – 4.44); and 2.62 (95%

CI: 1.65 – 4.02). Mean values of R_0 stay above previous estimates for H1N1 transmission in

7

larger communities and urban centres [4,5,6,7]. While estimated R_0 ranges considerably overlap, outbreaks in Nunavut appear to have been driven by somewhat higher transmissibility that is comparable or higher than that of the 1918 pandemic [8]. We further estimated R_0 by creating a single dataset for northern communities in Manitoba and Nunavut. The mean value of R_0 was 2.27 (95% CI: 1.79-2.94), providing a significant difference (Wilcoxon signed-rank test: $p < 0.001$) when compared with R_0 estimates for the Winnipeg health region.

Discussion

Determining the variability in transmissibility of a novel disease in populations with different demographics (e.g. age structure, household age composition, and housing density) is crucial for identifying the within-community factors that have the greatest influence on disease spread and, (by changing the total number of infections), its severity. Our results suggest that more severe outcomes observed in the 2009 influenza A H1N1 pandemic in remote and isolated communities [2] may have been due to differential transmissibility of infection, resulting in more rapid epidemic spread and larger numbers of individuals affected at northern latitudes [22].

Estimates of transmissibility could play an important role in determining the most effective utilization of public health interventions, in particular when resources are scarce. It is important to note that R_0 is effectively an *exponent* that determines both epidemic growth properties, the final size of an epidemic, and the fraction of individuals who need to be vaccinated to achieve herd immunity. For example, the expected relative final size of an epidemic with an R_0 of 2.7 is 25% larger in the absence of intervention than an epidemic with

8

an R_0 of 1.8; and to attain an immune herd (i.e., critical vaccination level: 1-1/R_0), the absolute

fraction of the population vaccinated must be 19% higher in the population with the higher R_0.

This has important public health implications for vaccination programs and suggests that

transmissibility is an important consideration in prioritizing the allocation of limited health

resources.

The mechanisms underlying the differential transmissibility of a pathogen in these

Canadian communities are unclear, but could be related to the effectiveness of available

disease control programs, environmental factors including the prevalence of low quality

housing [23], exposure to indoor air pollutants, lack of access to clean water, and also to

differences in demographic characteristics, crowding, and mixing patterns. For example, the

average number of persons per household in the northern Manitoba region is 3.6, which is 44%

greater than the mean size of 2.5 persons per household in Winnipeg as the largest urban

centre in the same province [24,25]. The average number of people per household in Nunavut

is 3.8, which is higher than both northern Manitoba and Winnipeg [10]; this may therefore

account for a higher rate of secondary household transmission, which is known as a major

route for the spread of influenza infection in the wider community [26,27,28]. In addition, age

has been recognized as an important parameter for the spread of disease with higher rates of

infectious contacts among schoolchildren and younger adults. There are also differences in the

age profiles of the populations studied here with other urban centres. For example, the average

age in the northern Manitoba region is 24 and in Nunavut is 23 [10], which is approximately 15-

16 years younger than the average age (38.7) in Winnipeg [24,25]. In Nunavut, only 2.7% of the

population is greater than 65 years of age and 34% of the population is less than 15 years of age

9

[10]. Although older age has been associated with a higher risk of severe outcomes during seasonal influenza epidemics, pandemics (e.g., 1918, 1957) are generally characterized by high rates of morbidity and mortality among younger adults [29,30], as has also been documented for the 2009 H1N1 pandemic [31]. Moreover, serological studies have shown the existence of cross-reactive antibody responses for individuals older than 50 years of age due to prior exposure to similar viruses [32], which may reflect a reduced likelihood of H1N1 infection in older populations. As was observed in other geographic regions [33], in Manitoba the 2009 pandemic predominantly affected young adults and children in both spring and fall waves (Figure 3).

In populations with low mean age (such as Nunavut), the buffering effect of pre-existing immunity in older individuals is less pronounced, which may contribute to higher transmissibility of the virus. In remote and isolated communities in Canada, climate, healthcare capacity in the community, socioeconomic status, health status, presence of vulnerable groups (e.g. children < 5 years of age, immunocompromised, and pregnant women), limited numbers of healthcare workers in the community, equipment and facilities, medical transportation and other critical infrastructure such as housing also play a role in determining differential epidemic impact [34].

The model employed in this study is subject to limitations, including the simplifying assumption of homogeneity in the population interactions. Some of the limitations are imposed by the lack of specific data, which precludes the use of more complex models with network structure or age-stratified populations. The simple model structure does not elucidate the specific mechanisms driving increased transmissibility in these communities. However,

10

empirical evidence to support the observation of increased transmissibility in these

communities clearly demonstrates the need for ongoing research in order to identify the

specific mechanisms. Due to uncertainties in the level of pre-existing immunity and its

distribution in different age-segments of the population, we did not include the effect of

immune responses in our model. However, considering prior immunity [35] we would expect to

estimate greater values for R_0 compared to when the entire population is assumed to be

susceptible. Finally, our model considers these communities without considering travel or

interactions with other population settings in the same region. It is possible that some influenza

cases were undiagnosed and thus not captured in surveillance data; this would lead us to

underestimate the transmissibility of the virus, making our estimates "lower bound" estimates.

We would expect underreporting to be less likely in the first wave of the pandemic (the time

period that we examined) than the second wave, as individuals with influenza-like illness

symptoms were encouraged to seek medical care, especially in remote and isolated

communities. In the absence of data for the true burden of the disease, we used laboratory

confirmed case counts, which may be subject to biases due to differential rates of testing

between different age groups, different geographic regions, and over time. However, it is

difficult to assess the magnitude and direction of such biases. Data available for this study did

not provide any relevant information on other potential confounders that could be included in

our estimation model. Despite these limitations, our results suggest that there is indeed a

considerable difference between the reproduction numbers of H1N1 outbreaks in remote and

isolated communities and urban centers. Further investigation is required to explore the

underlying mechanistic reasons for this differential transmissibility, which could determine

11

population specific factors that should be integrated into the process of public health decision making for future planning, in the face of an emerging infectious disease.

Competing Interests:

The authors declare that they have no competing interests.

Authors' Contributions:

Conceived, designed the study, and collected data: SM. Developed the Model and Performed Inference: LG, CB. Wrote the paper: DF, AG, SM. Contributed reagents/materials/analysis tools: LG, CS, AG, DF, SM. All the authors have read the final version of the paper and approved it.

Ethics: Data use was approved by the Human Research Ethics Board of the University of Manitoba (H2009:339) and Health Information Privacy Committee of Manitoba (2009/2010-40), and the University of Toronto Research Ethics Board.

a) Community 1, Manitoba
b)
c) Community 2, Nunavut
d)
e) Community 3, Nunavut
f)
g) Community 4, Nunavut
h)

13
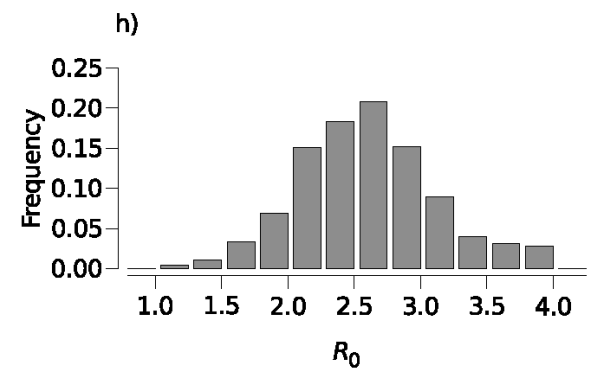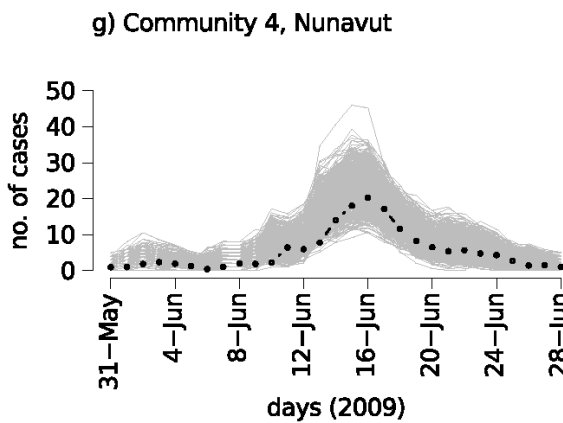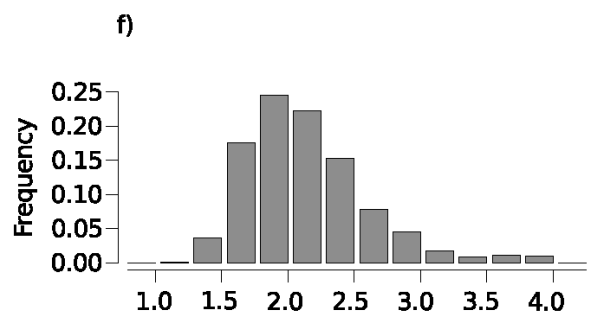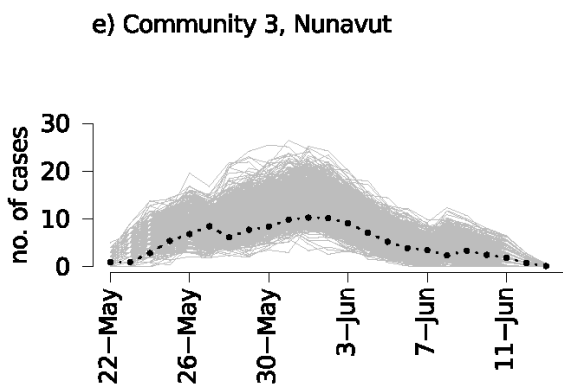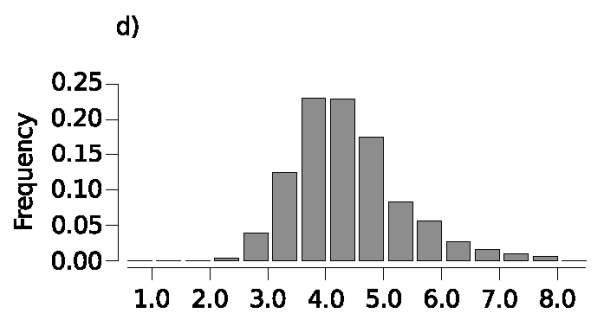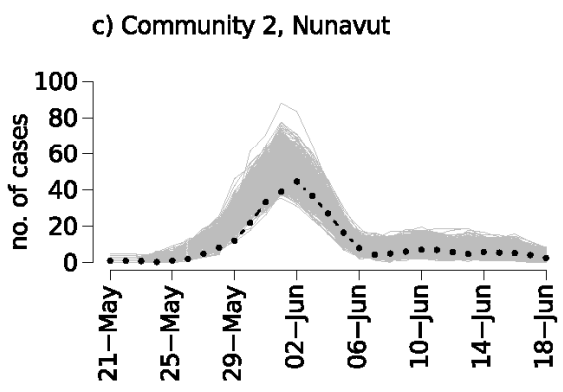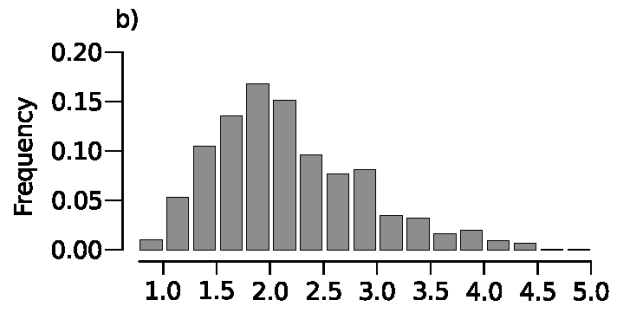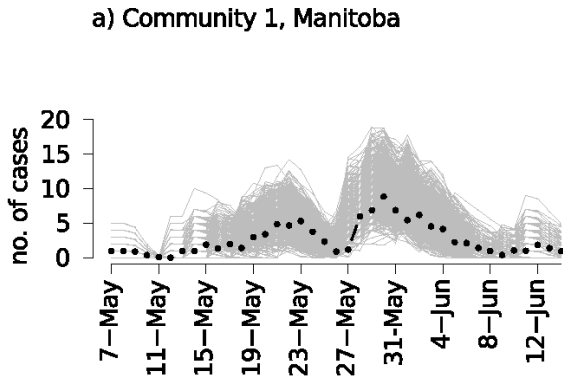
Figure 1. Infection curves for remote and isolated communities, generated through sampling procedure and posterior distributions of R_0 represented as probability, corresponding to the fraction of samples for each R_0 value obtained from fitting. The black circled-curves in the time courses correspond to the infection curves generated from the reported data, and grey curves are generated from sampled data.

a) Winnipeg, Manitoba

b)

no. of cases

days (2009)

Frequency

R_0
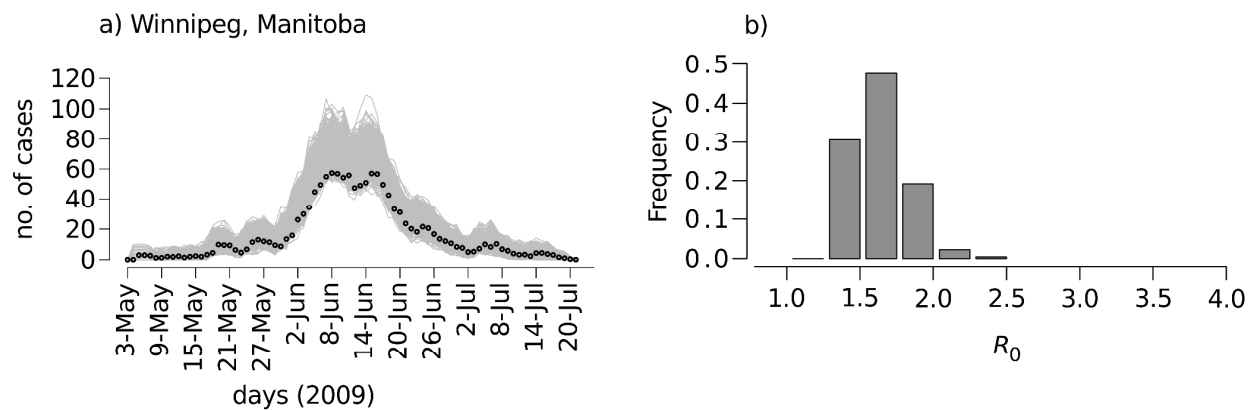
Figure 2. Infection curve for Winnipeg health region, generated through sampling procedure and posterior distributions of R_0 represented as probability, corresponding to the fraction of samples for each R_0 value obtained from fitting. The black circled-curves in the time courses correspond to the infection curves generated from the reported data, and grey curves are generated from sampled data.
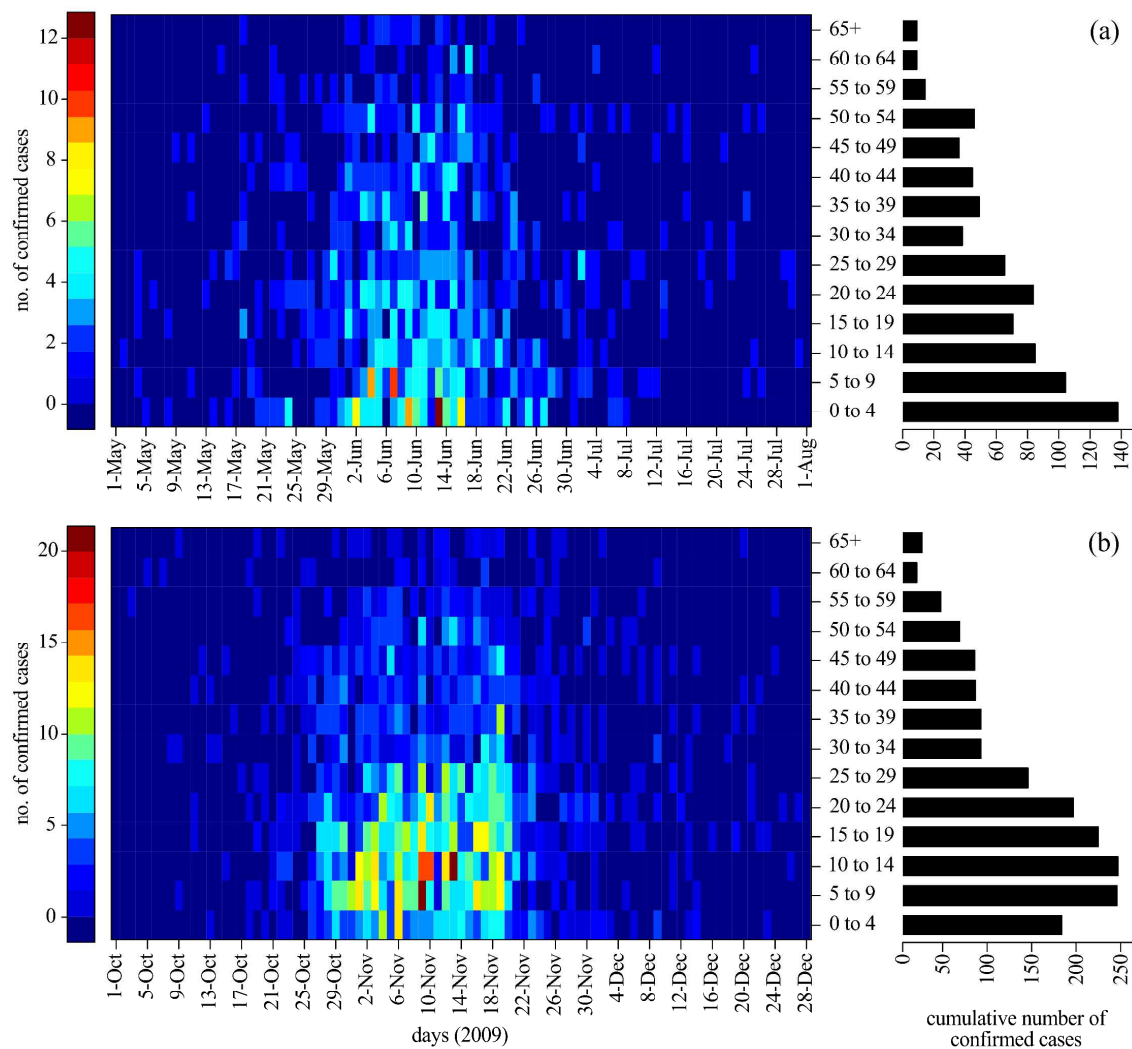
Figure 3. Heatmaps represent the daily number of laboratory confirmed cases of H1N1 infection for various age-groups during the first (a) and second (b) waves of the 2009 pandemic in the province of Manitoba. Barplots represent the cumulative number of laboratory confirmed cases for different age-groups during the first (a) and second (b) waves of the 2009 pandemic in the province of Manitoba.

15

References

1. Kumar A, Zarychanski R, Pinto R, et al., Critically ill patients with 2009 influenza A(H1N1) infection in Canada, JAMA 2009;**302**:1872-1879.

2. Zarychanski R, Stuart TL, Kumar A, et al., Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection, CMAJ 2010;**182**:257-264.

3. Diekmann O, Heesterbeek JAP, Mathematical Epidemiology of Infectious Diseases. John Wiley and Sons Ltd, 2000.

4. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science 2009;**324**:1557-1561.

5. Pourbohloul B, Ahued A, Davoudi B, et al. Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respiratory Viruses 2009;**3**:215-222.

6. White LF, Wallinga J, Finelli L, et al. Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. Influenza Other Respiratory Viruses 2009;**3**:267-276.

7. Yang Y, Sugimoto JD, Halloran ME, et al., The transmissibility and control of pandemic influenza A (H1N1) virus. Science 2009;**326**:729-733.

8. Mills CE, Robins JM, Lipsitch M, Transmissibility of 1918 pandemic influenza, Nature 2004;**432**:904-906.

9. Public Health Agency of Canada: Considerations for Definitions of "Remote" and "Isolated" in the Context of Pandemic (H1N1) 2009. http://www.phac-aspc.gc.ca/alert-

alerte/h1n1/guidance_lignesdirectrices/cdricp-cdeicp-eng.php#fn2 (accessed November 15, 2011).

10. Statistics Canada: Nunavut (Code 62, table), 2006 Community Profiles, 2006 Census, Catalogue no. 92-591-XWE. Ottawa, Released March 13, 2007 (accessed November 15, 2011).

11. Tuite AR, Greer AL, Whelan M, et al., Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza, CMAJ 2010;**182**:131-136.

12. Guidolin LC, Pizzi NJ, Moghadas SM, A classical approach for estimating the transmissibility of the 2009 H1N1 pandemic, Canad Appl Math Quart 2011;**19**:185-194.

13. Lessler J, Reich NG, Cummings DAT, et al. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. New Engl J Med 2009;**361**:2628-2636

14. Moghadas SM, Day T, Bauch C, et al., Modelling of pandemic influenza: a guide for the perplexed, CMAJ 2009;**181**:171-173.

15. Donnelly CA, Finelli L, Cauchemez S, et al. Serial Intervals and the Temporal Distribution of Secondary Infections within Households of 2009 Pandemic Influenza A (H1N1): Implications for Influenza Control Recommendations. Clin Infect Dis 2010;**52**:S123-S130.

16. McBryde E, Bergeri I, van Gemert C, et al., Early transmission characteristics of influenza A(H1N1)v in Australia: Victorian state, 16 May - 3 June 2009. Euro Surveill 2009;14(42).

17. Hahné S, Donker T, Meijer A, et al., Epidemiology and control of influenza A(H1N1)v in the Netherlands: the first 115 cases. Euro surveill 2009;**14**:1-4.

17

18. Nishiura H, Chowell G, Safan M, et al., Pros and cons of estimating the reproduction number from early epidemic growth rate of influenza A (H1N1) 2009. Theoret Biol Med Modell 2010;**7**:1.

19. Turner Jr. ME, Bradley Jr. EL, Kirk KA, et al., A theory of growth. Math Biosci 1976;**29**:367-373.

20. Hsieh Y-H, Fisman DN, Wu J. On epidemic modeling in real time: An application to the 2009 Novel A (H1N1) influenza outbreak in Canada. BMC Res Notes 2010;**3**:283.

21. Tsoularis A, Wallace J, Analysis of logistic growth models, Math Biosci 2001;**179**:21-55.

22. Greer AL, Tuite A, Fisman DN, Age, influenza pandemics and disease dynamics, Epidemiol Infect 2010;**138**:1542-1549.

23. Housing conditions that serve as risk factors for tuberculosis infection and disease, Canada Communicable Disease Report Volume 33: ACS-9, 1 October 2007. Available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-09/index-eng.php

24. Statistics Canada Catalogue no. 92-591-XWE. Ottawa. Released March 13 2007, http://www12.statcan.ca/census-recensement/2006/dp-pd/prof/92-591/details/page.cfm?Lang=E&Geo1=HR&Code1=4680&Geo2=PR&Code2=46&Data=Count&SearchText=burntwood&SearchType=Begins&SearchPR=46&B1=All&Custom=

25. Community Profile of the City of Winnipeg", Statistics Canada, 2006 Census of Population. 2007-09-30, http://www12.statcan.ca/census-recensement/2006/dp-pd/prof/92-591/details/page.cfm?Lang=E&Geo1=HR&Code1=4610&Geo2=PR&Code2=46&Data=Count&SearchText=winnipeg&SearchType=Begins&SearchPR=46&B1=All&Custom=

18

26. Cowling BJ, Chan KH, Fang VJ, et al., Comparative epidemiology of pandemic and seasonal influenza A in households, N Engl J Med 2010;**362**:2175-2184.

27. Cauchemez S, Donnelly CA, Reed C, et al., Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States, N Engl J Med 2009;**361**:2619-2627.

28. Laskowski M, Mostaço-Guidolin LC, Greer AL, et al., The impact of demographic variables on disease spread: influenza in remote communities, Sci Rep 2011;**1**:105.

29. Laver G, Garman E, Pandemic influenza: its origin and control. Microb Infect 2002;**4**:1309-1316.

30. Bush RM, Influenza evolution, Chapter 13 in Encyclopedia of Infectious Diseases: Modern Methodologies. Edt. Tibayrenc M, John Wiley & Sons, Inc., Hoboken, New Jersey, 2007.

31. Fisman DN, Savage R, Gubbay J, et al. Older age and a reduced likelihood of 2009 H1N1 virus infection, N Engl J Med 2009;**361**:2000-2001.

32. Hancock K, Veguilla V, Lu X, et al., Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N Engl J Med 2009;**361**:1945-1952.

33. Viboud C, Miller M, Olson D, et al., Preliminary estimates of mortality and years of life lost associated with the 2009 A/H1N1 pandemic in the US and comparison with past influenza seasons. PLoS Current Influenza. 2010

34. MacLeod MLP, Kulig JC, Stewart NJ, et al., The Nature of Nursing Practice in Rural and Remote Canada. September 2004: Available at http://www.chsrf.ca/final_research/ogc/pdf/macleod_final.pdf

19

35. Greenbaum JA, Kotturi MF, Kim Y, et al., Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population. Proc Natl Acad Sci USA 2009;**106**:20365-20370.

a) Community 1, Manitoba
b)
c) Community 2, Nunavut
d)
e) Community 3, Nunavut
f)
g) Community 4, Nunavut
h)

days (2009)

R_0

175x161mm (300 x 300 DPI)

BMJ
open

Transmissibility of the 2009 H1N1 pandemic in remote and isolated Canadian communities

SCHOLARONE™
Manuscripts

Transmissibility of the 2009 H1N1 pandemic in remote and isolated Canadian communities

LC Mostaço-Guidolin,[1] CS Bowman,[2] AL Greer ,[3, 4] DN Fisman,[4] and SM Moghadas[1]

[1] Centre for Disease Modelling, York University, Toronto, Ontario, Canada

[2] Department of Mathematics, University of Manitoba, Winnipeg, Manitoba, Canada

[3] Public Health Agency of Canada, Ottawa, Ontario, Canada

[4] Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

Running title: Transmissibility of the 2009 H1N1 pandemic

Abstract

Objectives: During the first wave of the 2009 influenza pH1N1, disease burden was distributed in a geographically heterogeneous fashion. It was particularly high in some remote and isolated Canadian communities when compared to urban centres. We sought to estimate the transmissibility (the basic reproduction number) of pH1N1 strain in some remote and isolated Canadian communities.

Design: A discrete time susceptible-exposed-infected (SIR) transmission model to was fit to infection curves simulated from laboratory-confirmed case counts for pH1N1 on each day. Sampling from Poisson distribution was used to estimated the basic reproduction number, R_0, of pH1N1 during the spring wave for five different communities in Manitoba and Nunavut,

1

Canada, where remote and isolated communities experienced a high incidence of infection, and

high rates of hospitalization and intensive care unit (ICU) admission.

Setting: Remote and isolated communities in Northern Manitoba, Nunavut, and the largest

urban centre (Winnipeg) in the province of Manitoba, Canada.

Results: Using published values of the exposed and infectious periods specific to H1N1

infection, corresponding to the average generation time of 2.78 days, we estimated a mean

value of 2.26 for R_0 (95% CI: 1.57–3.75) in a community located in northern Manitoba.

Estimates of R_0 for other communities in Nunavut varied considerably with higher mean values

of 3.91 (95% CI: 3.08–4.87); 2.03 (95% CI: 1.50–3.19); and 2.45 (95% CI: 1.68–3.44). We

estimated a lower mean value of 1.57 (95% CI: 1.35–1.87) for R_0 in the Winnipeg health region,

as the largest urban centre in Manitoba.

Conclusions: Influenza pH1N1 appears to have been far more transmissible in rural and isolated

Canadian communities than other large urban areas. The differential severity of the pandemic

in these regions may be explained partly by differential transmissibility, and suggests the need

for more nuanced, targeted, or population specific control strategies in Canada.

2

Introduction

Early outbreaks of the 2009 H1N1 influenza pandemic displayed variable degrees of incidence, apparently higher attack rates, and more severe disease outcomes in several remote and isolated communities in Canada [1,2]. Epidemiological data collected during the first wave of H1N1 pandemic indicate disproportionately higher rates of hospitalization and intensive care unit (ICU) admission in these communities. For instance, hospitalization rates in Nunavut and northern Manitoba were 2.44 and 1.27 per 1,000 population, respectively, which are significantly higher than the corresponding rates for Winnipeg (0.13) or the province of Ontario (0.033). Similar differences are evident from data regarding ICU admission rates, which were higher for Nunavut (0.20) and northern Manitoba (0.16) than those for Winnipeg (0.032) and Ontario (0.0056), per 1,000 population. The differential prevalence of predisposing health conditions including diabetes, pregnancy and morbid obesity, has received considerable attention as explicators of severe outcomes of H1N1 pandemic in rural and urban communities in Canada [2]. The high rates of hospitalization and ICU admission within these remote regions, could be linked to both transmissibility of the disease and to the prevalence of factors predisposing to more severe outcomes in infected individuals.

An important index of transmissibility for a communicable disease is the basic reproduction number (R_0) that represents the number of secondary infections generated by a single infected case in an entirely susceptible population [3]. Early published literature for the transmissibility of pandemic H1N1 infection provides a range of 1.2–1.8 for R_0 [4,5,6,7], mainly in large urban settings, suggesting that the novel H1N1 strain was less transmissible than the

3

1918-1919 pandemic virus for which R_0 has been estimated in the range 1.8–3.0 [8]. However, early estimates may not apply in remote and isolated communities that have distinct demographic characteristics, as well as distinct environmental (built or natural) conditions. We sought to evaluate differential transmissibility of H1N1 in five distinct population settings in Canada: a remote/isolated community in the Burntwood health region of northern Manitoba, three remote/isolated communities in Nunavut, and compare them with the largest urban area (i.e., the Winnipeg health region) in Manitoba. Communities in Nunavut as well as several communities in northern Manitoba would be considered remote and/or isolated communities [9] and many of these geographic areas have predominantly Aboriginal populations (e.g., 85% of the Nunavut population and 76% of the northern Manitoba region self-identify as Aboriginal) [10].

Material and Methods

To estimate plausible ranges for R_0, we employed a discrete time epidemic model, and fitted to infection curves inferred from collected data for laboratory-confirmed cases of H1N1 infection during the first wave of the 2009 pandemic. Details of data and estimation procedure are described below.

Case Data

We obtained the daily number of laboratory-confirmed cases of pandemic H1N1 influenza (in which the cases were reported based on the earliest date of symptom onset, initial care, specimen collection, hospital admission, or ICU admission) for the period of May 3 to August 5, 2009, for each community under study. A laboratory-confirmed case was reported as

4

an individual with ILI or severe respiratory illness who tested positive for pandemic H1N1 influenza A virus by real-time reverse-transcriptase PCR (RT-PCR) or viral culture. These data were collected and provided by Manitoba Health, and the Nunavut Department of Health and Social Services.

The Model

We considered a homogeneous mixing structure for the model in which individuals are identified by their epidemiological status as susceptible (S), exposed but not yet infectious (E), Infectious (I), and recovered (R). Exposed state refers to the period of time following transmission of infection during which the newly infected person cannot transmit the disease and symptoms are absent before developing clinical disease. Assuming that the reduction in the number of susceptibles is small during the early stages of the outbreak (i.e., $S(t)/S_0 \approx 1$, where S_0 is the initial number of susceptibles) [11], the number of infections at time t is given by [12]

$$I(t) \approx I_0 e^{\frac{1}{2}\left[\sqrt{4(R_0-1)\sigma\gamma + (\sigma+\gamma)^2} - (\sigma+\gamma)\right]t} \tag{1}$$

where σ and γ are the average duration of exposed and infectious stages, I_0 is the initial number of infectious cases (in this case, the number of cases in datasets generated through sampling described below), and R_0 is the basic reproduction number. The expression (1) describes the exponential growth of epidemic spread following disease outset. We estimated R_0 by fitting $I(t)$ to infection curves during the exponential phase of epidemic growth.

5

Model Parameters

The values of exposed and infectious periods were taken from estimated ranges in the published literature specific to the 2009 pandemic, with a fixed exposed period of 1 day [13]. We sampled the duration of infectiousness from a log-normal distribution with the mean of 3.38 days [11]. Using a common heuristic, that the generation times can be estimated as the sum of the exposed period and half of the duration of infectiousness [14], leads to a mean generation times of 2.69 days. Considering a size-biased sampling approach, where primary cases with many secondary cases are assigned a greater weight [15], the mean of generation times includes an additional term given by variance multiplied by half of the duration of infectious period. This gives a slightly higher mean generation times of 2.78 days which lies within the estimated range for pandemic H1N1 [16,17,18].

Sampling

To determine the variability in R_0, we generated 1000 datasets for case counts on each day through sampling from a Poisson distribution. We considered the absolute difference between the number of laboratory confirmed cases on day *j* and day *j*+1 as the mean of distribution. To generate new datasets, we added (subtracted if the difference was negative) the sampled value to the number of reported cases on day *j* to obtain new cases on day *j*+1. This sampling approach captures a higher variability in the number of observed cases during the epidemic course and a smaller variability at the onset or towards the end of epidemic [19]. To create an infection curve for each dataset, first we sampled an infectious period for each case from a log-normal distribution with the scale parameter $a = 1.192$ and shape parameter

$b = 0.05$ [11]. We assumed that the infectious period was initiated one day before the case was confirmed (reported date) [11,12]. This effectively means that every case was on the infection curve $I(t)$ for its sampled duration of infectiousness (Figures 1 and 2).

R_0 Estimation

Since the reproduction number only reflects the growth rate during the early stages of the epidemic, estimating R_0 is sensitive to the time period chosen for fitting the model to the data [20]. For a fit with very short timelines following the onset of the outbreak (establishment phase), the uncertainty in estimates of R_0 will be high. On the other hand, fitting the model using data that extend beyond the epidemic peak, will result in underestimating R_0, through the influence of several factors, including widespread implementation of public health measures and an increase in herd immunity, which may in turn invalidate the assumption $S(t)/S_0 \approx 1$. In order to minimize these effects, we obtained the turning points of the outbreaks following the initial exponential growth phase, beyond which the epidemic will no longer have exponential growth. We performed fitting from the date at which the first laboratory confirmed case was identified, up to one day before the turning point for each infection curve, to ensure that R_0 estimates reflect the initial growth phase of the outbreak. Turning point for each dataset was obtained through fitting the Richards model to the cumulative number of daily counts in each infection curve [21,22]. Assuming that K represents the cumulative number of daily cases for an infection curve $I(t)$ (generated through sampling method described above), the first turning point t_m was obtained by solving the equation $I(t_m) = K(1+c)^{1/c}$, where c is the deviation parameter estimated using the method of least

7

squares through curve-fitting [23]. This equation holds at the inflection point for the solution of the Richards model. We then estimated R_0 by fitting $I(t)$ in equation (1) to the generated infection curves from the date of the first laboratory case until $t_m - 1$. The mean values and 95% confidence intervals were obtained from the R_0 distributions generated through fitting procedure.

Results

The infection curves generated for fitting are illustrated in Figures 1 and 2. The mean estimate of R_0 for a northern community in Manitoba (Figure 1a) is 2.26 (95% CI: 1.57–3.75), which is higher than the estimate for Winnipeg health region with the mean value of 1.57 (95% CI: 1.35–1.87). We obtained considerably higher estimates for the mean values of R_0 for other communities in the territory of Nunavut (Figures 1b,c,d): 3.91 (95% CI: 3.08–4.87); 2.03 (95% CI: 1.50–3.19); and 2.45 (95% CI: 1.68–3.44). Mean values of R_0 stay above previous estimates for H1N1 transmission in larger communities and urban centres [4,5,6,7]. While estimated R_0 ranges considerably overlap, outbreaks in Nunavut appear to have been driven by somewhat higher transmissibility that is comparable or higher than that of the 1918 pandemic [8]. We further estimated R_0 by creating a single dataset for northern communities in Manitoba and Nunavut. The mean value of R_0 was 2.21 (95% CI: 1.98-2.50), providing a significant difference (Wilcoxon signed-rank test: $p < 0.001$) when compared with R_0 estimates for the Winnipeg health region.

8

Discussion

Determining the variability in transmissibility of a novel disease in populations with different demographics (e.g., age structure, household composition, and housing density) is crucial for identifying the within-community factors that have the greatest influence on disease spread and, (by changing the total number of infections), its severity. Our results suggest that more severe outcomes observed in the 2009 influenza A H1N1 pandemic in remote and isolated communities [2] may have been due to differential transmissibility of infection, resulting in more rapid epidemic spread and larger numbers of individuals affected at northern latitudes [24].

Estimates of transmissibility could play an important role in determining the most effective utilization of public health interventions, in particular when resources are scarce. It is important to note that R_0 is effectively an *exponent* that determines both epidemic growth properties at the early stage of disease outset, the final size of an epidemic in the absence of interventions, and the fraction of individuals who need to be vaccinated to achieve herd immunity [25]. For example, the expected relative final size of an epidemic with an R_0 of 2.7 is 25% larger in the absence of intervention than an epidemic with an R_0 of 1.8; and to attain an immune herd (i.e., critical vaccination level: $1-1/R_0$), the absolute fraction of the population vaccinated must be 19% higher in the population with the higher R_0. This has important public health implications for vaccination programs and suggests that transmissibility is an important consideration in prioritizing the allocation of limited health resources.

The mechanisms underlying the differential transmissibility of a pathogen in these Canadian communities are unclear, but could be related to the effectiveness of available disease control programs, environmental factors including the prevalence of low quality housing [26], exposure to indoor air pollutants, lack of access to clean water, and also to differences in demographic characteristics, crowding, and mixing patterns. For example, the average number of persons per household in the northern Manitoba region is 3.6, which is 44% greater than the mean size of 2.5 persons per household in Winnipeg as the largest urban centre in the same province [27,28]. The average number of people per household in Nunavut is 3.8, which is higher than both northern Manitoba and Winnipeg [10]; this may therefore account for a higher rate of secondary household transmission, which is known as a major route for the spread of influenza infection in the wider community [29,30,31]. In addition, age has been recognized as an important parameter for the spread of disease with higher rates of infectious contacts among schoolchildren and younger adults. There are also differences in the age profiles of the populations studied here with other urban centres. For example, the average age in the northern Manitoba region is 24 and in Nunavut is 23 [10], which is approximately 15-16 years younger than the average age (38.7) in Winnipeg [27,28]. In Nunavut, only 2.7% of the population is greater than 65 years of age and 34% of the population is less than 15 years of age [10]. Although older age has been associated with a higher risk of severe outcomes during seasonal influenza epidemics, pandemics (e.g., 1918, 1957) are generally characterized by high rates of morbidity and mortality among younger adults [32,33], as has also been documented for the 2009 H1N1 pandemic [34]. Moreover, serological studies have shown the existence of cross-reactive antibody responses for individuals older than 50 years of age due to prior

exposure to similar viruses [35], which may reflect a reduced likelihood of H1N1 infection in

older populations. As was observed in other geographic regions [36], in Manitoba the 2009

pandemic predominantly affected young adults and children in both spring and fall waves

(Figure 3).

In populations with low mean age (such as Nunavut), the buffering effect of pre-existing

immunity in older individuals is less pronounced, which may contribute to higher

transmissibility of the virus. In remote and isolated communities in Canada, climate, healthcare

capacity in the community, socioeconomic status, health status, presence of vulnerable groups

(e.g., children < 5 years of age, immunocompromised, and pregnant women), limited numbers

of healthcare workers in the community, equipment and facilities, medical transportation and

other critical infrastructure such as housing also play a role in determining differential epidemic

impact [37].

The model employed in this study is subject to limitations, including the simplifying

assumption of homogeneity in the population interactions. Some of the limitations are imposed

by the lack of specific data, which precludes the use of more complex models with network

structure or age-stratified populations. The simple model structure does not elucidate the

specific mechanisms driving increased transmissibility in these communities. However,

empirical evidence to support the observation of increased transmissibility in these

communities clearly demonstrates the need for ongoing research in order to identify the

specific mechanisms. Due to uncertainties in the level of pre-existing immunity and its

distribution in different age-segments of the population, we did not include the effect of

immune responses in our model. However, considering prior immunity [38] we would expect to

11

estimate greater values for R_0 compared to when the entire population is assumed to be susceptible. Finally, our model considers these communities without considering travel or interactions with other population settings in the same region. It is possible that some influenza cases were undiagnosed and thus not captured in surveillance data; this would lead us to underestimate the transmissibility of the virus, making our estimates "lower bound" estimates. We would expect underreporting to be less likely in the first wave of the pandemic (the time period that we examined) than the second wave, as individuals with influenza-like illness symptoms were encouraged to seek medical care, especially in remote and isolated communities. In the absence of data for the true burden of the disease, we used laboratory confirmed case counts, which may be subject to biases due to differential rates of testing between different age groups, different geographic regions, and over time. However, it is difficult to assess the magnitude and direction of such biases. Data available for this study did not provide any relevant information on other potential confounders that could be included in our estimation model. Despite these limitations, our results suggest that there is indeed a considerable difference between the reproduction numbers of H1N1 outbreaks in remote and isolated communities and urban centers. Further investigation is required to explore the underlying mechanistic reasons for this differential transmissibility, which could determine population specific factors that should be integrated into the process of public health decision making for future planning, in the face of an emerging infectious disease.

Authors' Contributions:

Conceived, designed the study, and collected data: SM. Developed the model and performed inference: LG, CB. Wrote the paper: DF, AG, SM. Contributed reagents/materials/analysis tools: LG, CS, AG, DF, SM. All the authors have read the final version of the paper and approved it.

Ethics: Data use was approved by the Human Research Ethics Board of the University of Manitoba (H2009:339), Health Information Privacy Committee of Manitoba (2009/2010-40), and the University of Toronto Research Ethics Board.

References

1. Kumar A, Zarychanski R, Pinto R, et al., Critically ill patients with 2009 influenza A(H1N1) infection in Canada, JAMA 2009;**302**:1872-1879.

2. Zarychanski R, Stuart TL, Kumar A, et al., Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection, CMAJ 2010;**182**:257-264.

3. Diekmann O, Heesterbeek JAP, Mathematical Epidemiology of Infectious Diseases. John Wiley and Sons Ltd, 2000.

4. Fraser C, Donnelly CA, Cauchemez S, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science 2009;**324**:1557-1561.

5. Pourbohloul B, Ahued A, Davoudi B, et al. Initial human transmission dynamics of the pandemic (H1N1) 2009 virus in North America. Influenza Other Respiratory Viruses 2009;**3**:215-222.

6. White LF, Wallinga J, Finelli L, et al. Estimation of the reproductive number and the serial interval in early phase of the 2009 influenza A/H1N1 pandemic in the USA. Influenza Other Respiratory Viruses 2009;**3**:267-276.

7. Yang Y, Sugimoto JD, Halloran ME, et al., The transmissibility and control of pandemic influenza A (H1N1) virus. Science 2009;**326**:729-733.

8. Mills CE, Robins JM, Lipsitch M, Transmissibility of 1918 pandemic influenza, Nature 2004;**432**:904-906.

9. Public Health Agency of Canada: Considerations for Definitions of "Remote" and "Isolated" in the Context of Pandemic (H1N1) 2009. http://www.phac-aspc.gc.ca/alert-

14

alerte/h1n1/guidance_lignesdirectrices/cdricp-cdeicp-eng.php#fn2 (accessed November 15, 2011).

10. Statistics Canada: Nunavut (Code 62, table), 2006 Community Profiles, 2006 Census, Catalogue no. 92-591-XWE. Ottawa, Released March 13, 2007 (accessed November 15, 2011).

11. Tuite AR, Greer AL, Whelan M, et al., Estimated epidemiologic parameters and morbidity associated with pandemic H1N1 influenza, CMAJ 2010;**182**:131-136.

12. Guidolin LC, Pizzi NJ, Moghadas SM, A classical approach for estimating the transmissibility of the 2009 H1N1 pandemic, Canad Appl Math Quart 2011;**19**:185-194.

13. Lessler J, Reich NG, Cummings DAT, et al. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. New Engl J Med 2009;**361**:2628-2636

14. Moghadas SM, Day T, Bauch C, et al., Modelling of pandemic influenza: a guide for the perplexed, CMAJ 2009;181:171-173.

15. Svensson Å, A note on generation times in epidemic models. Math Biosci 2007;208:300–311.

16. Donnelly CA, Finelli L, Cauchemez S, et al. Serial Intervals and the Temporal Distribution of Secondary Infections within Households of 2009 Pandemic Influenza A (H1N1): Implications for Influenza Control Recommendations. Clin Infect Dis 2010;**52**:S123-S130.

17. McBryde E, Bergeri I, van Gemert C, et al., Early transmission characteristics of influenza A(H1N1)v in Australia: Victorian state, 16 May - 3 June 2009. Euro Surveill 2009;14(42).

18. Hahné S, Donker T, Meijer A, et al., Epidemiology and control of influenza A(H1N1)v in the Netherlands: the first 115 cases. Euro surveill 2009;**14**:1-4.

19. Chowell G, Shim E, Brauer F, et al, Modelling the transmission dynamics of acute haemorrhagic conjunctivitis: application to the 2003 outbreak in Mexico, Stat Med 2006; 25:1840-1857.

20. Nishiura H, Chowell G, Safan M, et al., Pros and cons of estimating the reproduction number from early epidemic growth rate of influenza A (H1N1) 2009. Theoret Biol Med Modell 2010;**7**:1.

21. Turner Jr. ME, Bradley Jr. EL, Kirk KA, et al., A theory of growth. Math Biosci 1976;**29**:367-373.

22. Hsieh Y-H, Fisman DN, Wu J. On epidemic modeling in real time: An application to the 2009 Novel A (H1N1) influenza outbreak in Canada. BMC Res Notes 2010;**3**:283.

23. Tsoularis A, Wallace J, Analysis of logistic growth models, Math Biosci 2002;**179**:21-55.

24. Greer AL, Tuite A, Fisman DN, Age, influenza pandemics and disease dynamics, Epidemiol Infect 2010;**138**:1542-1549.

25. Keeling MJ, Rohani P, Modeling Infectious Diseases in Humans and Animals, Princeton University Press, 2007.

26. Housing conditions that serve as risk factors for tuberculosis infection and disease, Canada Communicable Disease Report Volume 33: ACS-9, 1 October 2007. Available at: http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/07vol33/acs-09/index-eng.php

16

27. Statistics Canada Catalogue no. 92-591-XWE. Ottawa. Released March 13 2007,

    http://www12.statcan.ca/census-recensement/2006/dp-pd/prof/92-

    591/details/page.cfm?Lang=E&Geo1=HR&Code1=4680&Geo2=PR&Code2=46&Data=Count

    &SearchText=burntwood&SearchType=Begins&SearchPR=46&B1=All&Custom=

28. Community Profile of the City of Winnipeg", Statistics Canada, 2006 Census of Population.

    2007-09-30, http://www12.statcan.ca/census-recensement/2006/dp-pd/prof/92-

    591/details/page.cfm?Lang=E&Geo1=HR&Code1=4610&Geo2=PR&Code2=46&Data=Count

    &SearchText=winnipeg&SearchType=Begins&SearchPR=46&B1=All&Custom=

29. Cowling BJ, Chan KH, Fang VJ, et al., Comparative epidemiology of pandemic and seasonal

    influenza A in households, N Engl J Med 2010;**362**:2175-2184.

30. Cauchemez S, Donnelly CA, Reed C, et al., Household transmission of 2009 pandemic

    influenza A (H1N1) virus in the United States, N Engl J Med 2009;**361**:2619-2627.

31. Laskowski M, Mostaço-Guidolin LC, Greer AL, et al., The impact of demographic variables

    on disease spread: influenza in remote communities, Sci Rep 2011;**1**:105.

32. Laver G, Garman E, Pandemic influenza: its origin and control. Microb Infect 2002;**4**:1309-

    1316.

33. Bush RM, Influenza evolution, Chapter 13 in Encyclopedia of Infectious Diseases: Modern

    Methodologies. Edt. Tibayrenc M, John Wiley & Sons, Inc., Hoboken, New Jersey, 2007.

34. Fisman DN, Savage R, Gubbay J, et al. Older age and a reduced likelihood of 2009 H1N1

    virus infection, N Engl J Med 2009;**361**:2000-2001.

35. Hancock K, Veguilla V, Lu X, et al., Cross-reactive antibody responses to the 2009 pandemic

    H1N1 influenza virus. N Engl J Med 2009;**361**:1945-1952.

17

36. Viboud C, Miller M, Olson D, et al., Preliminary estimates of mortality and years of life lost associated with the 2009 A/H1N1 pandemic in the US and comparison with past influenza seasons. PLoS Current Influenza. 2010

37. MacLeod MLP, Kulig JC, Stewart NJ, et al., The Nature of Nursing Practice in Rural and Remote Canada. September 2004: Available at

http://www.chsrf.ca/final_research/ogc/pdf/macleod_final.pdf

38. Greenbaum JA, Kotturi MF, Kim Y, et al., Pre-existing immunity against swine-origin H1N1 influenza viruses in the general human population. Proc Natl Acad Sci USA 2009;**106**:20365-20370.

a) Community 1, Manitoba
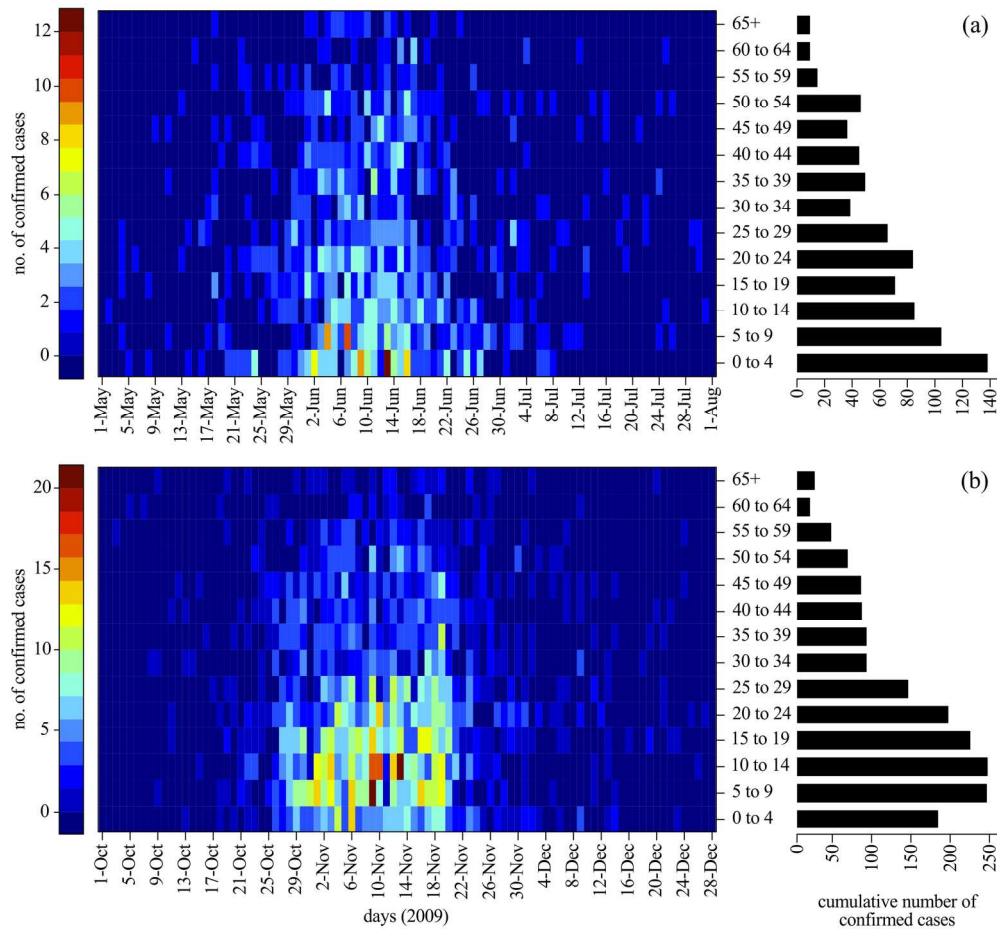
c) Community 2, Nunavut
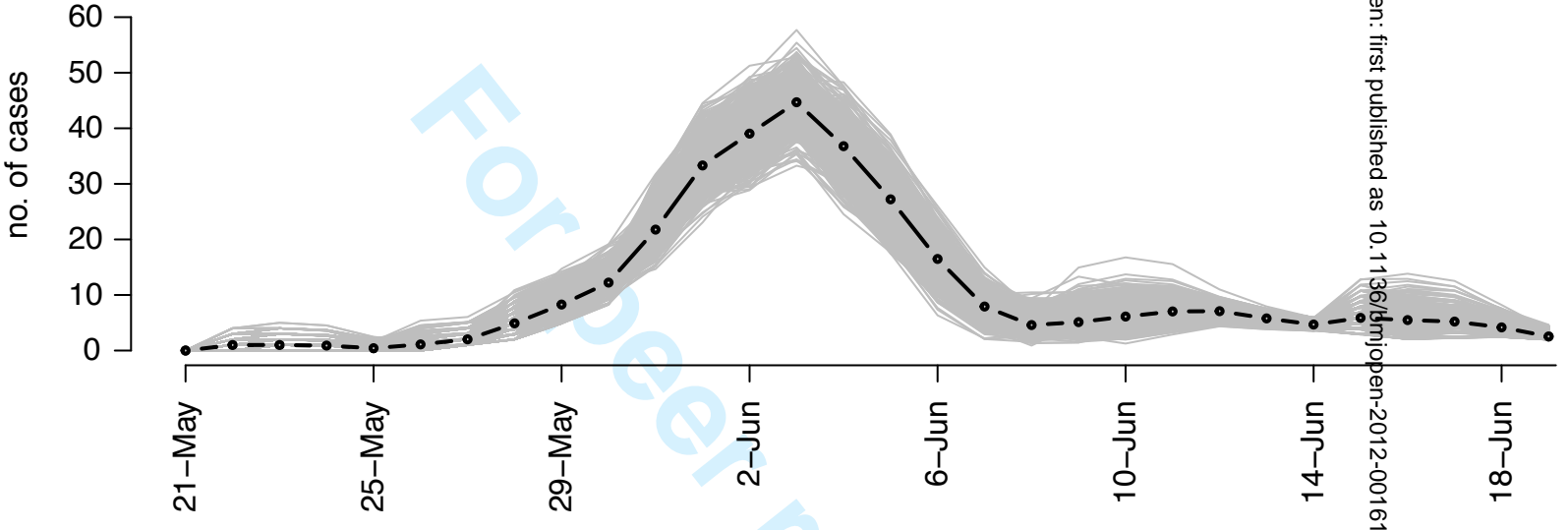
e) Community 3, Nunavut

g) Community 4, Nunavut

days (2009)

a) Winnipeg, Manitoba

days (2009)

175x161mm (300 x 300 DPI)