

Estimated impact of aggressive empirical antiviral treatment in containing an outbreak of pandemic influenza H1N1 in an isolated First Nations community

Yanyu Xiao,^a Zeenat Patel,^b Adam Fiddler,^c Lilian Yuan,^{b,d} Marie-Elaine Delvin,^b David N. Fisman^e

^aDepartment of Applied Mathematics, University of Western Ontario, London, ON, Canada. ^bFirst Nations and Inuit Health Branch, Health Canada, Toronto, ON, Canada. ^cSandy Lake First Nation, Sandy Lake, ON, Canada. ^dThe York Region Community and Health Services, Newmarket, ON, Canada. ^eThe Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada.

Correspondence: David N. Fisman, Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, 155 College Street, Room 547, Toronto, ON M5T 3M7, Canada. E-mail: david.fisman@utoronto.ca

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Background The 2009 influenza A (H1N1) pandemic was mild by historical standards, but was more severe in isolated Canadian Indigenous communities. Oseltamivir was used aggressively for outbreak control in an isolated northern Ontario First Nations community. We used mathematical modeling to quantify the impact of antiviral therapy on the course of this outbreak.

Methods We used both a Richards growth model and a compartmental model to evaluate the characteristics of the outbreak based on both respiratory visits and influenza-like illness counts. Estimates of best-fit model parameters, including basic reproductive number (R_0) and antiviral efficacy, and simulations, were used to estimate the impact of antiviral drugs compared to social distancing interventions alone.

Results Using both approaches, we found that a rapidly growing outbreak slowed markedly with aggressive antiviral therapy. Richards model turning points occurred within 24 hours of antiviral

implementation. Compartmental models estimated antiviral efficacy at 70–95%. Plausible estimates of R from both modeling approaches ranged from 4.0 to 15.8, higher than published estimates for southern Canada; utilization of aggressive antiviral therapy in this community prevented 962–1757 cases of symptomatic influenza and as many as 114 medical evacuations in this community.

Conclusion Although not advocated in other settings in Canada, aggressive antiviral therapy markedly reduced the impact of a pandemic-related influenza A (H1N1) outbreak in an isolated Canadian First Nations community in northern Ontario, Canada. The differential risk experienced by such communities makes tailored interventions that consider risk and lack of access to medical services, appropriate.

Keywords Epidemiology, Indigenous health, influenza, mathematical modeling, oseltamivir.

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Background

The year 2009 saw the occurrence of a pandemic of influenza A (H1N1),¹ which was remarkably mild when measured against the standard of earlier influenza pandemics.² However, the impact varied across populations, geographical regions, and ethnic groups. In particular, in high income countries such as Canada, the United States and Australia, Indigenous people suffered disproportionately from severe illness, and isolated communities experienced extremely high attack rates.³ In northern Ontario, Canada, many Indigenous (First Nations, Inuit, Métis, and other) communities have limited access to medical care facilities, are accessible only by air, and have a high proportion of residents with underlying health conditions (including diabetes) that have been asso-

ciated with worse outcomes related to influenza virus infection.^{3,4}

In June 2009, an outbreak of pH1N1 occurred in a remote First Nations reserve in northern Ontario, with rapid spread within the community. Because of concern related to the potential for severe illness in community members, the remote nature of medical care services, and uncertainty at that point in the pandemic regarding the severity of pH1N1 infection, implementation of initial, non-pharmacological disease mitigation interventions was followed by the intensive use of antiviral therapy with the neuraminidase inhibitor oseltamivir, which was administered to all individuals meeting criteria for “influenza-like illness.” Aggressive antiviral therapy was temporally associated with the apparent rapid cessation of disease transmission.

We sought to use the limited epidemiological data derived from this community outbreak to parameterize two simple epidemiological models: a growth model (the Richards model) and a more traditional compartmental model.⁵ Our objectives were (i) to attempt to derive estimates for the rate of growth of pH1N1 outbreaks in the context of a small, isolated First Nations reserve; (ii) to identify the possible impact of non-pharmacological interventions on disease transmission; and (iii) to project the likely final size of the outbreak that would have been expected in the absence of aggressive pharmacological intervention.

Data sources and methods

Community and outbreak description

Sandy Lake is a treaty-defined First Nations reserve in a heavily forested area of northwestern Ontario. It is effectively a closed community, accessible only by air, except for period of several weeks during the winter during which ice roads are used. The community had a population at the time of the outbreak of 2650; although the crude population density for the entire community area is 52 individuals per km², the actual area of the town site is much smaller and has a density of approximately 424 individuals per km². Average occupancy is 4–8 persons per dwelling, with 18.5% of households having more than one person per room. The community is young: 14% of residents are children under 5 years and 39% of the population is aged less than 15 (as compared to 27% for the province of Ontario as a whole). Only 4% of residents are aged over 64.⁶ The community has a nursing station but no hospital.

In the context of the 2009 influenza pandemic, individuals were considered to have “influenza-like illness” if they had acute onset of respiratory illness with fever ($>38^{\circ}\text{C}$) and new or worsening cough and one or more of the following: sore throat, arthralgia, myalgia, or prostration which could be due to the influenza virus. Gastrointestinal symptoms in children under five were also considered to be a symptom of influenza. Three initial index cases of influenza-like respiratory disease were identified on June 3 and 4, 2009; these were subsequently confirmed virologically to represent infection with the influenza A (H1N1)-2009 pandemic strain. 12 additional cases of influenza-like illness with virological confirmation were documented with symptom onset prior to June 15. The median age of virologically confirmed cases was 11 years (range 0–58) and 8 (57%) were male. Additional detail on age and gender of virologically confirmed cases is presented in Figure 1.

Additional cases of influenza-like illness were reported to the nursing station during the period until June 21, but these individuals did not undergo confirmatory virologic testing. In total, 177 cases of influenza-like illness were reported in the community until June 21, for a cumulative symptomatic

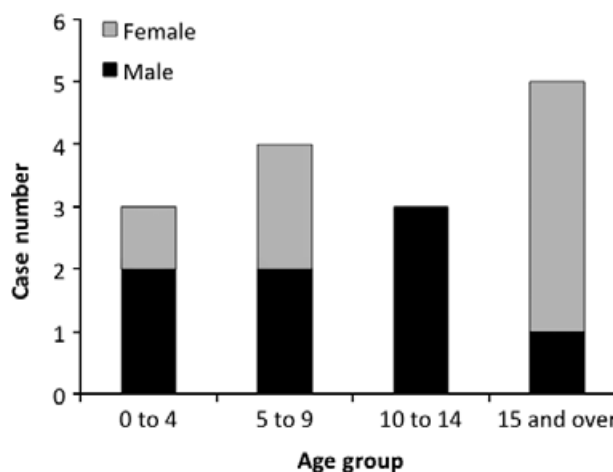


Figure 1. Demographic characteristics of 16 initial virologically confirmed cases of influenza A (H1N1)-2009 in Sandy Lake.

attack rate of 6.6%. Disease mitigation interventions initially focused on social distancing and cancellation of public gatherings; schools were closed on June 10; a Treaty Day gathering was cancelled on June 13; a community school graduation ceremony was cancelled on June 17, and a community-wide market was cancelled on June 20 and 21. Due to increasing case numbers in the face of these interventions and concern regarding possible severe illness, universal antiviral treatment of those meeting the ILI case definition was approved in the community on June 13 and was initiated on June 14. Oseltamivir was given at a standard dose of 75 mg po bid for adults, and based on weight in children, for a five-day course. By this time, antiviral therapy was approved, four individuals had been medically evacuated from the community to receive care elsewhere; a 5th medical evacuation occurred on June 14. Forty-four individuals had ILI prior to June 14, and an additional 47 ILI cases were identified on June 14. A total of 156 individuals received oseltamivir; of these individuals 122 met criteria for ILI and 34 did not. Antiviral therapy was provided a median of two days (range 1 to 10 days) after symptom onset.

Richards model: properties and application

The Richards growth model is a type of logistic model first described in the 1950s and intended for application to biological processes.⁷ Hsieh.^{8–11} The model is defined by a simple, single-variable differential equation and differs from compartmental models of infectious diseases in that it considers only the intrinsic rate of growth in the number of infectious individuals, without reference to susceptible or immune individuals in the population. This was desirable in the current scenario, where empirical information on immunity to influenza A (H1N1)-2009 in the community of interest was unavailable; a second desirable property of the Richards model relates to its description of “turning points”

potentially reflecting the impact of interventions. The characteristics and application of the Richards model are presented in detail in Appendix S1.

We assumed that A represented the upper bound fraction of infected individuals in the absence of intervention and calculated cases averted through intervention as A minus actual epidemic size. Efficacy of antiviral therapy was estimated as $1 - \text{relative risk (RR) of infection}$; RR was estimated as the ratio of observed symptomatic cases to cases expected based on final size calculations as described in Appendix S1.

Compartmental model

While the Richards model was attractive for the reasons described above, we evaluated the robustness of our findings using a more traditional compartmental susceptible–latent–infectious–recovered (SEIR) model as described elsewhere,^{12,13} which was parameterized under the assumption that 73% of the population was susceptible at baseline based on prior published estimates by our group for Canadian First Nations.¹⁴ We used a base case duration of infectivity of 3.5 days, and of latency of 2.5 days, based on our group's published estimates for the 2009 pH1N1 pandemic in the province of Ontario.¹

Three model parameters (basic reproductive number (R_0), efficacy of social distancing measures (SD) (in place from June 10 onwards), and efficacy of antiviral therapy (AV) (in place from June 14 onwards) were estimated by optimizing model fits, via minimization of sum-of-squared distance from the epidemic curve, to simulated epidemic curves that assumed Poisson distributed errors for influenza-like illness and total clinic visit counts as described elsewhere.¹ This model and the approach to parameterization are described in further detail in Appendix S1.

Results

Respiratory healthcare visits, and visits in individuals in individuals meeting age-specific definitions of ILI, are presented by date in Figure 2. Respiratory visits declined markedly within 48 hours of initiation of oseltamivir therapy. Fits for Richards models, against cumulative case counts (hollow circles), are presented in Figure 3. As shown in Figures 3(A, B), both fitting algorithms approximated the shape of the actual epidemic very well, whether applied to individuals with influenza-like illness only (Figure 3A) or to all individuals presenting with symptoms possibly compatible with influenza (Figure 3B). For all models, the turning point for the outbreak occurred around June 15 (14 days after the initial case or 24 hours after initial doses of antiviral drugs were administered). Estimated values for K (~175 for a July 9 end date) closely approximated observed cumulative ILI cases (177 cases); model-projected cases counts

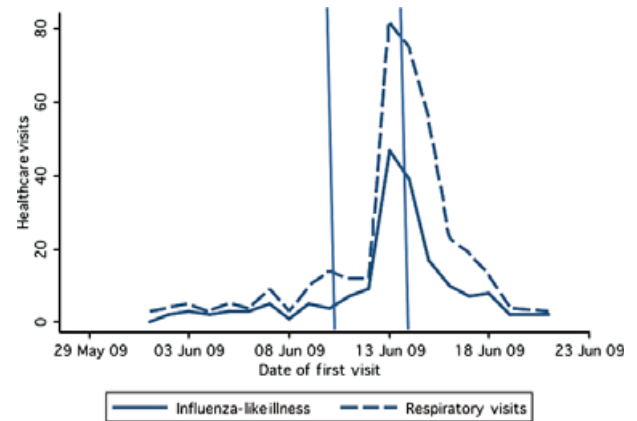


Figure 2. Epidemic curves for influenza A (H1N1)-2009 outbreak in Sandy Lake. Epidemic curves from June 1 to June 21, 2009. Solid curve denotes epidemic curve for all healthcare visits related to influenza-like illness; dashed curve represents visits meeting case definition for respiratory symptoms possibly compatible with influenza. The first vertical line denotes implementation of social distancing measures, while the second denotes actual implementation of aggressive antiviral treatment.

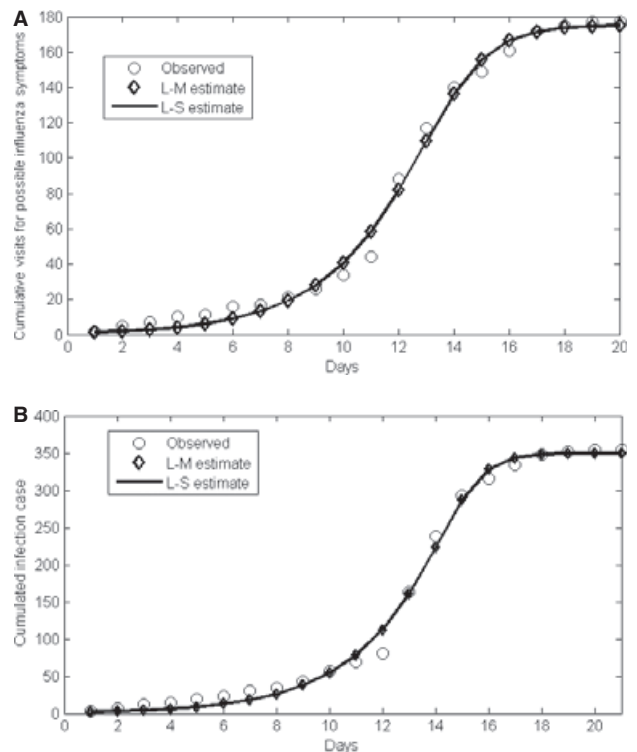


Figure 3. Actual and model-predicted cumulative case counts by day of outbreak. Data are represented by hollow circles; model projections are denoted by solid curves (for large-scale least squares, L-S) or diamonds (Levenberg–Marquardt (L-M)). Models fit well for time series restricted to individuals meeting influenza-like illness case definition (see text) (A) and for all individuals with symptomatology suggestive of possible influenza (B).

Table 1. Estimates of parameters for Richards model based on all healthcare visits for respiratory symptoms

End date 2009-6-21	Growth rate (r)	Exponent of deviation (a)	Turning point (days)	Maximum case number
L-M method	1.3805	3.7640	14.1244	349.9858
L-S method	1.3809 (0.4629, 2.2990)	3.7656 (0.6699, 6.8614)	14.1247 (13.4461, 14.8034)	349.9840 (337.5509, 362.4171)

Bracketed numbers represent 95% confidence limits; L-M, Levenberg–Marquardt method; L-S, large-scale least squares method. Based on time series from June 1 to June 21, 2009.

Table 2. Estimates of parameters for Richards model based on influenza-like illness counts in Sandy Lake

End date 2009-6-21	Growth rate (r)	Exponent of deviation (a)	Turning point (days)	Maximum case number
L-M method	0.9195	2.4114	13.8513	175.3128
L-S method	0.9201 (0.4274, 1.4128)	2.4134 (0.5647, 4.2621)	13.8521 (13.1430, 14.5612)	175.3093 (167.6665, 182.9521)

Bracketed numbers represent 95% confidence limits; L-M, Levenberg–Marquardt method; L-S, large-scale least squares method. Based on time series from June 1 to June 21, 2009.

($K = 344$) approximated total respiratory symptom visits ($N = 359$) equally well. The performance of L-S and L-M algorithms was similar (Tables 1 and 2).

Best-fit SEIR models that incorporated both social distancing effects and antiviral effects, and which assumed a partially immune population at baseline, also fit reasonably well with available data (Figure 4). Best-fit models identified far greater efficacy for antiviral drugs, than for social distancing interventions (Table 3).

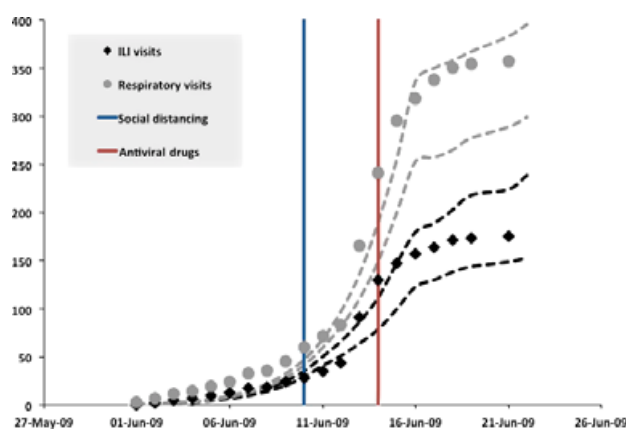


Figure 4. Compartmental model fits to Sandy Lake outbreak data. Ranges of model-projected cumulative case counts by date (dashed lines) plotted against observed case counts for influenza-like illness (black) and respiratory illness (gray). The blue vertical line denotes initiation of social distancing measures; the red vertical line denotes implementation of aggressive antiviral drug therapy.

Based on initial growth rates in Richards models, and under varying assumptions regarding the length of serial intervals of influenza in Sandy Lake, we derived estimates of R based on serial intervals of 1–5 days.^{1,15,16} It can be seen that extremely high values for R were derived using the Richards model (Figure 5). Even using serial interval estimates as short as 1.5–2 days, R estimates ranged from 4.0 to 6.3 when ILI time series were used and 7.9–15.8 when respiratory visits were used. Estimates of R_0 were derived using a longer serial interval (4.3 days) based on our empirical estimates from Southern Ontario;¹ again, best model fits produced extremely high values for R_0 based on both ILI time series and respiratory illness time series (Table 3).

Based on final size calculations, and assuming that 73% of residents were susceptible to influenza A (H1N1)-2009¹⁴ and R may have been as low as 1.5, it would be estimated that 42–73% of residents would have been infected in the absence of intervention. As such, it would be projected that the intervention prevented between 962–1757 cases of ILI in this community. Even assuming that symptomatic attack rates may have been as low as 50% during the 2009 influenza pandemic¹⁷ (meaning that twice as many infections occurred as we estimate here based on ILI and respiratory illness counts), we would estimate that between 211–790 symptomatic infections were prevented through antiviral use. Similarly, simulations using SEIR models suggested that the addition of antiviral drugs to social distancing measures prevented 1187–1436 cases of influenza-like illness or 1242–1434 cases of respiratory illness.

Table 3. Efficacy estimates for antiviral drugs and social distancing, and estimates of basic reproductive number (R_0) derived from Best-Fit SEIR models

Parameter estimates (Median, range)	Models fit to influenza-like illness time series	Models fit to respiratory illness time series
Antiviral efficacy	0.79 (0.72–0.89)	0.92 (0.86–0.95)
Social distancing efficacy	0.44 (0.17–0.47)	0.11 (0.02–0.27)
Basic reproductive number (R_0)	11.04 (10.07–11.43)	11.92 (11.61–12.52)

As noted above, of 177 individuals with ILI, 2.8% (0.9–6.5%) were medically evacuated to hospitals in larger centers. Applying this proportion to infections averted, we would estimate that aggressive antiviral use averted between 2 and 114 medical evacuations from this community alone.

Discussion

A long-recognized characteristic of influenza pandemics is their tendency to be highly variable and geographically specific in their severity. This was the case with the 2009 influenza A (H1N1) pandemic: in Canada, the pandemic was characterized as “mild” with reference to its case fatality rate in Canada, the United States, and Australia. However, severe illness was observed and appeared to be particularly common in Indigenous populations in these countries.^{3,4,14,18} The reasons for heterogeneity are unclear, but have been postulated to include crowding, poor nutritional status in

impoverished communities, a high rate of medical comorbidities (e.g. diabetes) associated with severe influenza outcomes and younger age distributions.^{3,4,14,18} The risk and costs of influenza outbreaks are further enhanced in the context of isolated Indigenous communities such as this one, which lacks inpatient medical facilities and was accessible only by air at the time of the outbreak; severe illness in this context is compounded by the delays, risks, and costs associated with evacuation by air ambulance.^{19,20}

In this context, the risk-benefit ratio associated with aggressive disease control interventions changes in isolated Indigenous communities, and it may be appropriate to utilize disease control programs in isolated Indigenous communities that would not be advocated elsewhere in Canada. We have described an outbreak in which joint action by community and government personnel, with aggressive use of the antiviral oseltamivir, was associated with a rapid reduction in the incidence of influenza-like illness and a small total outbreak size. A key question in this context is whether disease transmission was disrupted by antiviral use or whether antiviral initiation simply coincided with the waning of an outbreak that would have stopped regardless.

In the context of a public health urgency or emergency, clinical trials may be impossible or unethical.^{21,22} The primary obligation of public health and disease control professionals is to make the outbreak stop, or failing that, to minimize morbidity and mortality to the best of their ability, using tools at their disposal. In this context, it is impossible to know with certainty what the epidemiological “counterfactual” would have been in this case; that is, we cannot know what the contour of this outbreak would have been if aggressive antiviral drug use had not been initiated in this community. Mathematical models of infectious diseases, however, can provide a useful framework for data synthesis, and for exploring the impact of alternate disease management strategies based on the best available data, and based on current understanding of the epidemiology of the disease under study.⁵ We used two complementary modeling approaches (the Richards growth model, and a more typical compartmental model) to represent this event.^{5,8,9,11} The Richards model has the advantages both of being able to describe logistic growth processes (like epidemics) with relatively few parameters and limited data, but also of

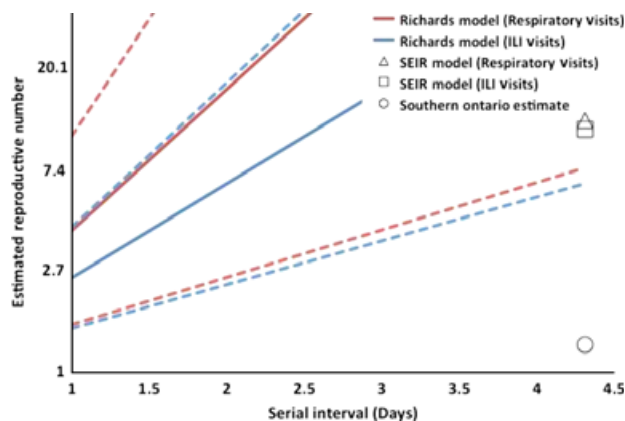


Figure 5. Model-based estimates of reproductive numbers plotted against generation times. Estimates generated using Richards models are plotted as solid lines with 95% confidence limits (dashed lines). Red lines represent late-scale least squares fit models for all respiratory symptoms; blue lines are based on cases meeting case definition for influenza-like illness (blue curves). Mean basic reproductive number estimates generated using compartmental SEIR models are presented as hollow triangle (respiratory visits) or hollow square (influenza-like illness). The estimated reproductive number and from southern Ontario, derived from Tuite *et al.*,¹ is shown as a hollow circle. Note that reproductive numbers are plotted on a natural log scale.

identifying “turning” points, at which an epidemic moves from accelerating to decelerating growth. This latter property was particularly attractive in the situation described above, as we wished to better quantify the temporal relationship between aggressive antiviral use in the community and attenuation of the epidemic. Our use of a compartmental model permitted both explicit estimation of the impact of social distancing and antiviral efficacy, but required explicit assumptions regarding random mixing and baseline levels of immunity to influenza A H1N1-2009 in the community.

Nonetheless, our use of two distinct modeling approaches provides a degree of cross-validation of our main findings, which were similar in both cases, and regardless of whether influenza-like illness counts, or respiratory illness visits more generally, were used for model fitting. While the Richards growth model, for a given generation time, produced a far higher estimate of the reproductive number for influenza in this community than was produced by fitting a compartmental model, both approaches produced estimates for reproductive numbers far higher than those reported elsewhere in Canada and echo prior reports suggesting higher reproductive numbers for influenza in Canadian First Nations.^{14,23} To approximate the reproductive number estimates derived in southern Canada, we would have to postulate serial intervals (time between successive generations of cases) that are shorter than those attributed to influenza,^{1,15} and certainly shorter than those estimated in southern Ontario during the 2009 influenza A H1N1 pandemic.¹ In either case, these model-based estimates derived using two very different approaches are compatible with a distinctive epidemiology for influenza in isolated Canadian Indigenous populations. Both the extent and speed of transmission could be enhanced by environmental factors that have previously been identified in these communities, including crowding and low-quality housing stock with poor ventilation,^{24,25} and perhaps by environmental transmission of influenza viruses.²⁶

Both modeling approaches suggest that, in this isolated Indigenous community, the impact of aggressive oseltamivir use was probably rapid and dramatic. A Richards growth model that reproduced observed trends almost perfectly implied that growth decelerated approximately 1 day after the antiviral drugs became available in the community; our compartmental model suggested that the efficacy of antiviral drugs in reducing transmission of influenza was 70–95%, a range consistent with published estimates of antiviral efficacy in reducing symptomatic infection in contacts when cases are treated.^{27,28} Of course, this could be coincidental (i.e. widespread use of oseltamivir was introduced just as the epidemic was ending for other, unclear, reasons), but the reproductive numbers we estimated using the same model suggest that in the absence of effective intervention, the outbreak would have continued until the majority of the population was infected. Even allowing for the fact that many

influenza infections are likely minimally symptomatic,¹⁷ our best-fit models suggest that swift action by community leaders and public health authorities likely reduced the total extent of this epidemic several-fold, and likely prevented adverse outcomes including hospitalization and medical evacuations, and may have prevented deaths.

After the apparent success of this intervention as described above, the same approach was employed in additional isolated communities, which experienced minimal illness, suggesting that the impact of this approach in preventing morbidity and mortality may have extended beyond the context described here. Of course, some will suggest that the low impact of influenza A H1N1-2009 was low in these communities despite rather than because of antiviral use, but in light of available data, randomized trials in this context would have been neither desirable nor ethical.

Prior modeling work on the use of aggressive antiviral therapy for influenza control in pandemic situations has generally suggested that these drugs could attenuate transmission of pandemic influenza strains and could reduce mortality in infected individuals.^{29–33} However, modeling projections have had limited predictive validity: Although models suggested that community transmission of influenza could be controlled via aggressive antiviral use if the R_0 of the emerging flu strain was low (i.e. <1.8),³⁰ such approaches were not successful in the recent pandemic. Modeling by Moghadas and colleagues that incorporates the emergence of antiviral resistance also raises concern that overly aggressive use of antiviral drugs in large populations could foster strain replacement, such that pandemics occur but are due to antiviral resistance strains.^{31–33} The applicability of such projections to the scenario described above is, however, unclear: the small size of the community and its isolated nature, attenuated both the likelihood, and the likely impact, of emergence of a resistant strain.

Like any mathematical model, the model we describe here is subject to limitations, including the relatively limited availability of high-quality input data on contact between cases, lack of virological confirmation on most cases, and assumptions necessary for construction of both the Richards and compartmental models. As we state above, we cannot attribute the sudden cessation of ILI cases in this community to use of antiviral drugs with certainty; however, the consistency of our findings, both with respect to the epidemiology of the underlying outbreak, and the impact of antiviral drugs, using two very different modeling approaches, may provide a degree of cross-validation for this work. While additional work is needed, our findings, in conjunction with the “precautionary principle” that dictates prudence in the face of a dire potential threat, suggest aggressive antiviral use may have an important role in mitigating the apparently severe impact of influenza outbreaks in isolated Indigenous communities.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Details of model fitting.