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Original Research

Clinical Guidelines

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these agents. The ACP recommends that clinicians prescribe an oral drug for patients diagnosed with type 2 diabetes when diet and exercise fail to adequately control hyperglycemia, use monotherapy with metformin as first-line oral therapy unless contraindications exist, and add a second drug to metformin therapy when monotherapy fails. The ACP found no strong evidence to support that one class of drug is better than another as a second drug.

Ideas and Opinions

D. Paschal

A physician working at the urgent care clinic at the New Orleans Veterans Administration Hospital after Hurricane Katrina observed that clinical evaluations that previously took weeks to complete in traditional outpatient settings could be accomplished in a few hours or days. The author proposes duplicating this experience in academic medical centers by affiliating an urgent care clinic with an ambulatory procedure unit and quick access to subspecialty consultants.

History of Medicine

P. Kazanjian

Frederick Novy was a U.S. physician, medical researcher, and microbiologist who devised culture techniques to visualize anaerobic bacteria, parasites, and spirochetes. This essay describes how Novy's research on the cause of unexplained deaths in his laboratory rats, begun in 1909, was halted in 1918 when study materials mysteriously vanished from his laboratory. Persistence, excellent laboratory notes, and new technological discoveries enabled Novy to return to his experiments in 1951 at age 88 when a box containing the missing test tubes was found. Novy identified that a virus rather than a bacterium had killed his laboratory rats.

Editorials

D.N. Fisman

Earn and colleagues' article in this issue demonstrates that school closure may be an effective strategy for reducing the spread of influenza during pandemics. The editorialist notes that decision makers will need to consider the virulence of future pandemics and weigh the benefits and costs of social distancing to limit the spread of influenza.

P.S. Douglas and L.H. Curtis

MacFadden and colleagues' study in this issue demonstrates similar ICD implantation rates among men and women after referral for electrophysiologic evaluation but higher rates of complications in women. The editorialists note that available research limits our ability to fully assess the value of ICDs in women and that a one-size-fits-all approach to ICDs may not be appropriate.

S.A. Fryhofer

In this issue, the ACIP presents the recommended Adult Immunization Schedule for 2012. The editorialist discusses the rationale behind key changes between this and previous ACIP recommendations.

On Being a Doctor

D.S. Tweedy

One of my first patients as a medical intern was an avowed racist. His body failing, he turned to our hospital for help only to find me, a black man, as one of the doctors entrusted to extend his life. The year was 2003, but for a time, it felt more like 1963.

Letters

Comments and Responses

In the Clinic

Cover photograph by Nicola Mumoli, MD

Effects of School Closure on Incidence of Pandemic Influenza in Alberta, Canada

Summaries for Patients are a service provided by *Annals* to help patients better understand the complicated and often mystifying language of modern medicine.

The full report is titled "Effects of School Closure on Incidence of Pandemic Influenza in Alberta, Canada." It is in the 7 February 2012 issue of *Annals of Internal Medicine* (volume 156, pages 173-181). The authors are D.J.D. Earn, D. He, M.B. Loeb, K. Fonseca, B.E. Lee, and J. Dushoff.

What is the problem and what is known about it so far?

Influenza ("the flu") is a virus that spreads from person to person through coughing and sneezing. Keeping infected persons away from others may slow an influenza epidemic or even prevent one from occurring. Influenza may start to spread in a community mainly through schoolchildren. Communities often close schools to try to lessen the effect of influenza, but it has been hard to prove that this technique really works.

Why did the researchers do this particular study?

In the spring of 2009, a new strain of influenza emerged. Because a large segment of the population did not have natural immunity (protection by their immune system), the virus spread rapidly around the world. This allowed scientists to study how this new strain of influenza spread and how the planned closing of schools for the summer break affected the spread of the virus.

How was the study done?

In Alberta, Canada, a province with 3.7 million people, patients with symptoms that suggested influenza who sought health care from April to October 2009—a much longer period of testing than that in the United States or other parts of Canada—were routinely tested for the new influenza virus (and other viruses that cause colds and flu-like illnesses) More than 35 000 samples were obtained during this time. Researchers recorded influenza test results by date, age, and location and looked at data on weather patterns. They also noted when schools closed for the summer and opened for the fall term in various parts of the province. These data were put into mathematical models to predict what factors affected influenza transmission.

What did the researchers find?

Closing schools for the summer break dramatically decreased the spread of influenza in the community. Changes in temperature also affected the number of cases of influenza that occurred, but to a much smaller degree.

What were the limitations of the study?

The results are based on mathematical models applied to natural observations; such results are less reliable than those based on controlled experiments.

What are the implications of the study?

Closing schools may reduce spread of influenza and the number of infected people. Well-planned school closure may therefore be an effective tool for communities to combat influenza. However, the benefits of school closure need to be weighed against the negative effects, such as disrupting educational programs and forcing some parents to miss work.

Getting Schooled: School Closure, Age Distribution, and Pandemic Mitigation

Despite the gains in antimicrobial therapy and vaccines that have come in the past 100 years (1), epidemics and pandemics (synchronized, global epidemics) remain an important source of morbidity, mortality, and costs in high-, middle-, and low-income countries. Epidemics can be thought of as self-perpetuating, exponential growth processes; because infections are communicable, the more cases you have, the more cases you will get, as long as the population contains susceptible persons to infect.

Epidemiologists refer to the key index of this type of growth as the *reproductive number* of an infectious disease—the number of new (incident) cases created by each old (prevalent) case before the prevalent case recovers (2). Reproductive numbers are the product of 3 core components: how infectious a person is, the duration of infectiousness of a person, and how many contacts that person has. Epidemic mitigation strategies that seek to reduce the latter component of the reproductive number (contact between infectious and susceptible persons) are often referred to as *social-distancing measures*.

Social-distancing measures may include closing schools, suspending religious services, and canceling large public gatherings. A famous study in contrasts with respect to the implementation of social distancing for influenza pandemic control occurred in St. Louis and Philadelphia during the severe influenza A(H1N1) pandemic in 1918 to 1919 (3). Authorities in Philadelphia declined to impose social-distancing measures (including, famously, not canceling a parade through the center of the city that drew large crowds) until the epidemic was severe. In contrast, St. Louis proactively and aggressively restricted religious and social gatherings and closed schools early in its epidemic, and the effect of influenza seems to have been greatly mitigated (3). Whether the divergent courses of St. Louis and Philadelphia were attributable to social-distancing measures or whether the willingness to implement such measures reflected fundamental differences in public health culture is not known. However, an analysis of more U.S. cities during the pandemic (4) suggests that the speed at which social distancing is implemented plays a role in reducing a pandemic's effect.

The 3 subsequent recognized influenza pandemics (in 1957, 1968, and 2009) have been far less severe than that of 1918 to 1919, with the 2009 pandemic being notably mild (5). However, social distancing was considered a component of pandemic response in both the United States and Canada in 2009. One particularly attractive means of social distancing is school closure, and numerous schools were closed because of concern about the spread of influenza, especially early in the 2009 pandemic (6).

The intuitive attractiveness of school closure relates to the particular epidemiology of younger persons in relation to influenza. Children and teenagers seem to play a key role in the propagation of seasonal influenza epidemics (7, 8), and such age effects are even more marked in pandemics (9, 10). The effect of the 1918 and 2009 pandemics was heavily skewed toward younger persons in the population (9, 10). In both seasonal influenza epidemics and influenza pandemics, interventions (such as immunization) aimed at younger persons seem to reduce attack rates in all persons in the population (11, 12). Natural experiments associated with holiday-related school closures (in France) and labor-related closures (in Israel) support the contention that school closure disrupts influenza transmission in children (13–15).

Regardless, school closure as a social-distancing strategy in pandemics remains controversial. The lack of trials or other experimental data on school closure may make available data on school closure seem less credible to decision makers. These individuals may be concerned that closure will simply redistribute children and teenagers to other venues (such as day care centers or shopping malls). Even if closing schools effectively reduces influenza transmission, questions would remain with regard to cost-effectiveness. The need for parents to leave work to provide child care would result in large societal costs and could disrupt the provision of other essential services, such as health care (14, 16). Furthermore, modeling studies (which assume effectiveness of school closure) note that if closure is triggered by incidence exceeding a predetermined threshold, schools would need to be repeatedly closed and reopened in the absence of a vaccine (17).

Several methodological difficulties are associated with studying the effect of school closure as a means of mitigating the spread of influenza. First, when virologically confirmed influenza is the outcome of interest, sampling intensity may change over time. For example, in Ontario, Canada, influenza virus testing was restricted in June 2009 (18), such that subsequent decreases in observed cases of influenza could have been attributed to school closure or to a decrease in testing. Second, school closure is likely to occur in concert with other disease-control measures, both formal (such as the use of prophylactic antiviral therapy) and informal (such as a tendency to avoid handshaking because of concern related to illness); isolating the effect of school closure from the effect of other contemporaneous changes could be difficult. Finally, in many temperate countries, reproductive numbers for influenza are likely to oscillate seasonally (19), such that the end of the school year in late spring or early summer may coincide with a nadir for the transmissibility of influenza.

Bearing these limitations in mind, the 2009 influenza pandemic has now produced at least 2 natural experiments that strongly support the efficacy of school closure as a means of mitigating pandemic influenza transmission. The first of these occurred in Mexico, where an early April spring break, the subsequent reopening of schools, and a late April emergency school closure order provided Chowell and colleagues (20) with an opportunity to evaluate the within-season effect of school closing and reopening on the dynamics of influenza transmission. These investigators found that the reproductive numbers declined to approximately 1 (which is associated with cessation of epidemic growth) when the schools closed and then increased again when the schools reopened. Consistent with school closures being the driver behind the decrease in transmissibility, the relative decrease in cases was concentrated in school-aged children (20).

The second natural experiment occurred in Alberta, Canada, and is the subject of a well-thought-out study by Earn and colleagues in this issue (21). Because virologic testing continued in Alberta through the first wave and much of the second wave of the 2009 influenza pandemic and because school dismissal dates in the province varied by age group in a manner that did not correlate with (and thus was not confounded by) the level of influenza activity within a given age group or region, Earn and colleagues saw an opportunity to evaluate the effect of school closure. Because the dates of dismissal were within 2 weeks of each other, differences in change in incidence between age groups are unlikely to be due to seasonally varying factors. Indeed, school closure as an exposure has effectively been randomized across age groups. The findings are striking: Incidence within a given age group fell sharply within 1 to 2 incubation periods of the dismissal of classes. A best-fit mathematical model included 2 factors: school dismissal and a temperature variable. The second wave of the pandemic was also easily simulated by using a model that considered school opening dates and decreases in temperature.

Although these studies make a strong case for the effectiveness of school closure as a means of mitigating influenza transmission in a pandemic, it is important to note that the timing of influenza waves has substantially varied in earlier pandemics (9). In the case of Alberta, it is less clear that a pandemic wave that occurred in the middle of the (rather cold) Alberta winter could be as easily mitigated via school closure, not only because the seasonal reproductive number would be higher (and may stay above 1 even with school closure, all other things being equal) but also because outdoor environmental conditions would require that children and teenagers continue to spend substantial time indoors, where transmission might still be enhanced by crowding.

The authors also note that the economic costs associated with school closure are likely to be substantial, but correctly indicate that the question of cost is distinct from that of effectiveness. In the face of a future pandemic, decision makers will probably need to perform cost–benefit calculations that carefully consider the virulence of the newly emerged influenza strain against the economic costs of social-distancing measures (16). In a mild pandemic, such as the one in 2009, the costs of school closure could outweigh the benefits (22); however, given the remarkable variability in clinical severity associated with influenza, this may not be the case in future pandemics. Earn and colleagues have demonstrated that school closure represents a practical and effective means to buy time in a future pandemic while vaccine against the newly emerged viral strain is developed and produced.

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Ann Intern Med. 2012;156:238-240.

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Annals of Internal Medicine | ORIGINAL RESEARCH

Effects of School Closure on Incidence of Pandemic Influenza in Alberta, Canada

David J.D. Earn, PhD; Daihai He, PhD; Mark B. Loeb, MD, MSc; Kevin Fonseca, PhD; Bonita E. Lee, MD, MSc; and Jonathan Dushoff, PhD

Background: Control of pandemic influenza by social-distancing measures, such as school closures, is a controversial aspect of pandemic planning. However, investigations of the extent to which these measures actually affect the progression of a pandemic have been limited.

Objective: To examine correlations between the incidence of pandemic H1N1 (pH1N1) influenza in Alberta, Canada, in 2009 and school closures or weather changes, and to estimate the effects of school closures and weather changes on pH1N1 transmission.

Design: Mathematical transmission models were fit to data that compared the pattern of confirmed pH1N1 cases with the school calendar and weather patterns.

Setting: Alberta, Canada, from 19 April 2009 to 2 January 2010.

Data Sources: 2009 virologic test results, 2006 census data, 2009 daily temperature and humidity data, and 2009 school calendars.

Measurements: Age-specific daily counts of positive results for pH1N1 from the complete database of 35 510 specimens submitted to the Alberta Provincial Laboratory for Public Health for virologic testing from 19 April 2009 to 2 January 2010.

Results: The ending and restarting of school terms had a major effect in attenuating the first wave and starting the second wave of pandemic influenza cases. Mathematical models suggested that school closure reduced transmission among school-age children by more than 50% and that this was a key factor in interrupting transmission. The models also indicated that seasonal changes in weather had a significant effect on the temporal pattern of the epidemic.

Limitations: Data probably represent a small sample of all viral infections. The mathematical models make simplifying assumptions in order to make simulations and analysis feasible.

Conclusion: Analysis of data from unrestricted virologic testing during an influenza pandemic provides compelling evidence that closing schools can have dramatic effects on transmission of pandemic influenza. School closure seems to be an effective strategy for slowing the spread of pandemic influenza in countries with social contact networks similar to those in Canada.

Primary Funding Source: Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Public Health Agency of Canada.

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For author affiliations, see end of text.

Social-distancing measures feature prominently in analyses of pandemic preparedness and management strategies (1), and school closure is one of the most frequently considered measures (2). Influenza incidence and mortality data do not typically show obvious effects of school closures, but several studies (2–4) have used mathematical models to infer that closing schools reduced transmission in various situations, including the first phase of the 2009 influenza pandemic in Hong Kong (5). Here, we present the effects of closing schools in Alberta, Canada, during the 2009 pandemic. The effects are visually apparent in the data and confirmed by transmission modeling.

The 2009 pandemic emerged first in Mexico in April 2009 (6). The subtype of the new virus (A/H1N1) was the same as the 1918 pandemic strain, descendants of which have circulated continuously since 1977 (7). However, the new pandemic H1N1 (pH1N1) virus was sufficiently antigenically novel in humans that preexisting immunity seemed to be weak or absent in most persons (8). The World Health Organization declared the outbreak to be a pandemic on 11 June 2009 (8). By the end of December 2009, more than 12 000 deaths and more than 600 000 laboratory-confirmed cases of pH1N1 had been reported worldwide (9, 10). The World Health Organization declared the pandemic to be over on 10 August 2010.

As the first wave of the pandemic grew in intensity, many public health laboratories were overwhelmed and implemented stringent eligibility restrictions for respiratory virus testing (11). In Alberta, a large Canadian province with a population of 3.7 million, no such restrictions were implemented until the middle of the second wave of the pandemic. As a result, from 20 April 2009 (when the first laboratory-confirmed pH1N1 sample was collected) to 30 October 2009 (when restricted testing commenced [12]), reported laboratory-confirmed cases of pH1N1 in Alberta were not biased by sampling restrictions.

Population-level analyses have indicated that pH1N1 has weak to moderate transmissibility (13–17), which makes it plausible that social-distancing measures had a

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Context

Whether schools should close during influenza epidemics is controversial. In 2009, testing for influenza A(H1N1) was performed for many months in Alberta, Canada. A mathematical model of H1N1 transmission was then constructed by using those virologic data, as well as census data, climate records, and school calendars.

Contribution

School closure was associated with reduced transmission among schoolchildren by more than 50%, attenuating the first wave of the H1N1 epidemic. The reopening of the schools probably initiated the second H1N1 influenza wave. Seasonal changes in weather also affected the epidemic pattern.

Caution

Mathematical models simplify reality.

Implication

Closing schools may slow the spread of influenza epidemics.

—The Editors

substantial effect on epidemic speed and spread, as is suggested to have occurred during the 1918 influenza pandemic (18–20). In North America, the school year ended in June 2009, during the first wave of the pandemic. We examine the incidence pattern of pH1N1 in Alberta together with the pattern of classes ending for the summer and investigate whether they are associated.

METHODS

Surveillance Data

The Alberta Provincial Laboratory for Public Health (ProvLab) tests for respiratory viruses at the request of hospitals, community physicians, and a sentinel physician network (The Alberta Recording and Research Network [TARRANT]) or in response to respiratory outbreaks monitored by public health. During the 2009 influenza pandemic, all samples submitted to regional laboratories for respiratory virus testing were referred to ProvLab for comprehensive molecular testing for influenza A; testing included an in-house validated reverse transcriptase real-time polymerase chain reaction test for influenza A and B or the xTAG Respiratory Virus Panel assay (Luminex Molecular Diagnostics, Toronto, Ontario, Canada) (21). We obtained testing data by using the Data Integration for Alberta Laboratories application (22), a Web-based, user-specific, secure platform that has automatic data extraction and interpretation processes for respiratory virus testing data at ProvLab (including testing results and patient sex, age, and geographic information).

During the pandemic, specimens were submitted to ProvLab from both community-based health providers (including general practitioners, family physicians, and pediatricians) and hospitals (emergency departments, hospital clinics, and patient care units). Health facilities in the province instituted strict infection-control practices at the beginning of the pandemic, which did not change during its course. Until 30 October 2009, all specimens submitted to ProvLab were tested. After 30 October 2009, respiratory virus testing was restricted to patients awaiting hospital admission; hospitalized patients; specimens from outbreak investigations, as requested by public health officials; and specimens noted by the TARRANT surveillance program (<5% of specimens).

Weather Data

We downloaded daily average air and hourly air temperatures and dew points from Environment Canada (www.weatheroffice.gc.ca/canada_e.html). We used the hourly data to calculate hourly absolute humidity (**Supplement**, available at www.annals.org) and averaged these values to obtain the daily average absolute humidity.

Transmission Model

We used a "susceptible–infectious–removed" model (23) with 2 age classes, persons aged 5 to 18 years (school-age children) and others. We allowed transmission within and between age classes to vary for up to 4 different transmission parameters, and we multiplied each transmission parameter by the same seasonal factor (either a sinusoid or a function of temperature or absolute humidity). We assumed that the epidemic corresponded to a stochastic realization of the individual-based version of this model, and that the observed case reports were generated by sampling from the epidemic. We used a negative binomial sampling distribution for reports, to account for possible clustering (24). The **Supplement** contains our model equations.

Parameter Estimation

We constructed maximum likelihood estimates for the model parameters and initial conditions by using the iterated filtering method of Ionides and colleagues (25), implemented in the POMP package, version 0.16-9 (http://pomp.r-forge.r-project.org), written for the R statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria). The **Table** provides parameter estimates. In our simple model, the mean infectious period is equivalent to the generation time of the disease. For dynamic purposes, this value should be compared with the observed generation time of the disease, not the observed infectious period (26). The **Supplement** discusses the initial conditions.

Role of the Funding Source

Our study was funded by the Canadian Institutes of Health Research, the Natural Sciences and Engineering Research Council of Canada, and the Public Health Agency of Canada. The funding sources played no role in the design, conduct, or analysis of our study or in the decision to submit the manuscript for publication.

Table. **Maximum Likelihood Estimates for Parameters of the Best-Fit, 2-Age-Class Transmission Model for the 2 Largest Cities in Alberta and the Province***

Parameter	Maximum Likelihood Estimate (95% CI)		
	Calgary	Edmonton	Alberta
R_{ss}†			
School terms	2.35 (2.10–2.68)	2.35 (2.06–2.51)	2.30 (2.06–2.40)
Summer	1.06 (0.78–1.22)	0.68 (0.11–0.70)	0.89 (0.00–0.89)
Proportional reduction	0.63 (0.43–0.84)	1.00 (0.69–1.00)	0.86 (0.70–1.00)
R_{oo}‡	0.95 (0.80–1.31)	1.05 (0.71–1.12)	1.09 (0.80–1.10)
R_0§	1.74 (1.52–1.97)	1.72 (1.29–1.82)	1.78 (1.52–1.80)
Seasonal amplitude	0.026 (0.018–0.029)	0.030 (0.028–0.042)	0.025 (0.023–0.029)
Reporting rate during intensive testing period	0.157 (0.071–0.527)	0.056 (0.006–0.187)	0.181 (0.096–0.369)
Weeks of intensive testing	2.220 (0.104–2.729)	3.770 (2.872–4.505)	2.210 (1.684–3.416)
Reporting rate after intensive testing period	0.009 (0.007–0.021)	0.016 (0.009–0.037)	0.018 (0.010–0.045)
Importation	0.59 (0.01–1.83)	3.00 (0.95–4.23)	0.81 (0.01–4.23)

* The seasonal amplitude determines the magnitude of the effect of temperature on transmission rate. In our best-fit model, the mean infectious period is fixed at 4.5 d, the drop date is fixed at the cohort-weighted mean school closing date (22 June 2009), and the rise date is fixed at the school opening date (27 August 2009 in Calgary and 31 August 2009 in Edmonton; we used the average of these, 29 August 2009, for Alberta). We also estimated the mean infectious period and the school closing and opening dates by refitting the model without fixing these parameters, as described in **Supplement Figure 2** (available at www.annals.org).
† A subgroup reproductive number that represents the expected number of new cases in school-age children (aged 5–18 y) per case caused by school-age children.
‡ A subgroup reproductive number that represents the expected number of new cases in others (persons not aged 5–18 y) per case caused by others.
§ The basic reproductive number; the lead eigenvalue of a 2 × 2 matrix of subgroup reproductive numbers. The R_0 reported in this table is based on a time average of the transmission matrix (Supplement, available at www.annals.org).

RESULTS

Patterns of Confirmed pH1N1 in Alberta

Between 19 April 2009 and 2 January 2010, ProvLab conducted respiratory virus tests on 35 510 specimens, of which 6745 (19%) were positive for pH1N1. The top panel of **Figure 1** shows the weekly numbers of specimens tested for respiratory virus, specimens positive for pH1N1, and specimens positive for any influenza virus. Restricted testing was implemented on 30 October 2009; although vaccination for pH1N1 was available to the general public beginning on 26 October 2009, this is unlikely to have substantially affected incidence before 30 October. The surge of testing in May (before substantial growth in cases of pH1N1) seems to have resulted from general public concern about pH1N1 induced by media attention and the coincident circulation of other viruses (such as rhinoviruses and coronaviruses) in April and May. This disparity between tests conducted and confirmed cases of pH1N1 highlights the various factors that drive influenza testing patterns in addition to influenza illness.

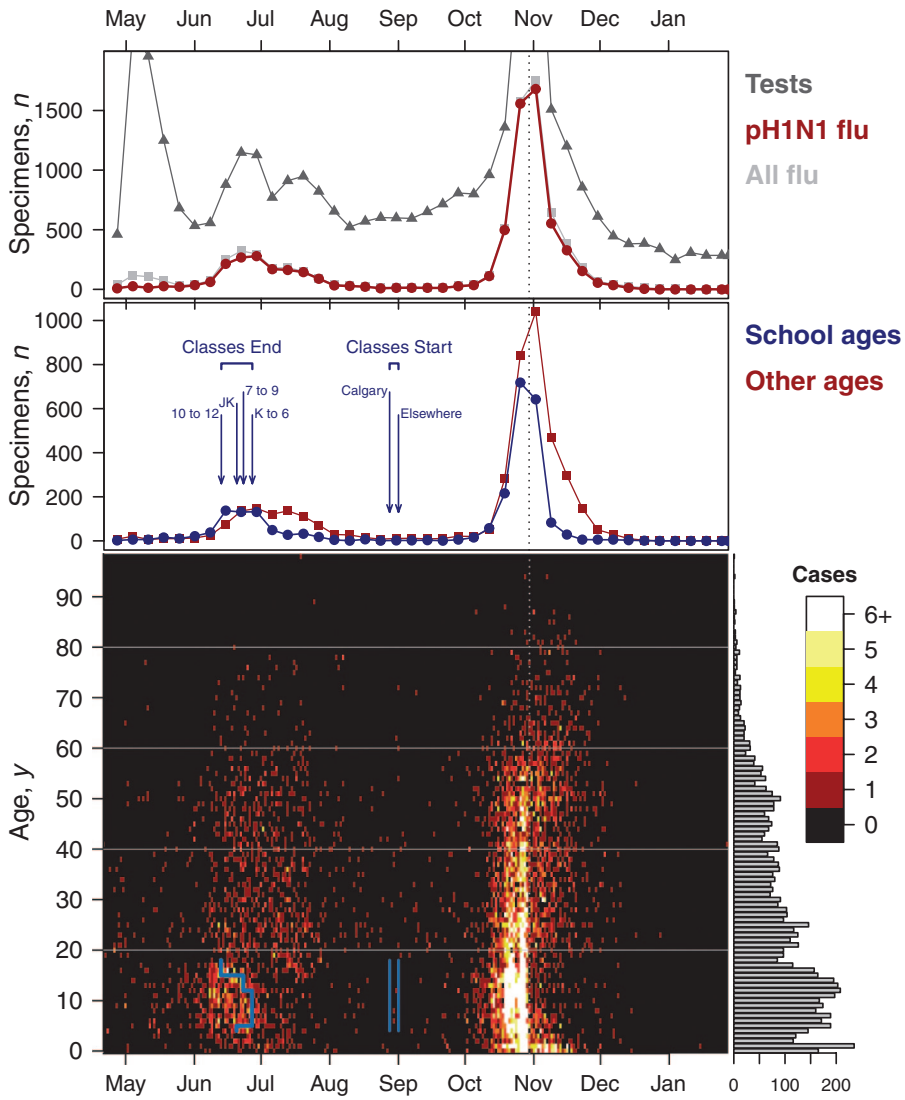
The middle panel of **Figure 1** shows weekly confirmed cases of pH1N1 in school-age children (aged 5 to 18 years) and in all other persons. Arrows indicate the dates on which classes ended in schools of various levels and the dates on which schools reopened (which were the same for all levels and the same in all locations except Calgary).

The bottom panel of **Figure 1** shows the daily pattern of pH1N1 case confirmations for each age; the bar plot on the right shows the cumulative age distribution of cases, which is consistent with age distributions inferred in other studies on the basis of hospitalizations (27) and serology (28). The dates on which classes ended are indicated as a function of age, which yields the blue boundary near the bottom left of the panel. Incidence dropped sharply when schools closed, which is consistent with the hypothesis that school closure reduces the level of contact among school-age children (and also with a short incubation period for pH1N1 [16, 29, 30]). This decrease could also be explained in part by changes in reporting.

The dates on which schools reopened preceded the observable growth of the second wave of cases by several weeks (**Figure 1**, *bottom*). As the second wave grew, the highest density of confirmed cases was in school-age children (indicated in **Figure 1** by the age structure during the first 2 weeks of October). In fact, school-age children had the highest density of confirmed cases except from late June to late September (and after the implementation of restricted testing).

Figure 2 summarizes the spatiotemporal structure of the epidemic, showing the distribution of confirmed cases across the province (**Figure 2**, *left*) and the temporal pattern of the epidemic (**Figure 2**, *right*) by latitude. Weekly time series for the 2 largest cities, Calgary and Edmonton, are shown above the latitudinal plot. The names and populations of major cities and towns are indicated at their latitudes, and their positions are highlighted on the map. By the third week of the epidemic in mid-May, cases had already been confirmed in large regions of the province; substantial growth had not yet occurred anywhere, so a spatially structured control strategy would probably not have prevented the spread of influenza throughout the province. Exponential growth of the first wave was evident first in Edmonton, from which some latitudinal spread is apparent (as it is from several other major population centers). The second wave became evident earliest in Calgary, perhaps because schools opened 4 days earlier in Calgary

Figure 1. **Age structure of laboratory-confirmed cases of pH1N1 in Alberta, Canada, in 2009.**



Dates when schools closed and opened are indicated in blue. Classes ended on different dates for different levels of school: high school (grades 10 to 12) on 12 June, middle school (grades 7 to 9) on 22 June, elementary school (kindergarten [*K*] to grade 6) on 26 June, and junior kindergarten (*JK*) on 19 June; classes began on 27 August 2009 in Calgary and on 31 August 2009 in the rest of the province (Field Services, Alberta Ministry of Education. Personal communication.). The dotted line in each panel indicates the start of restricted testing on 30 October 2009 (12). pH1N1 = pandemic H1N1 influenza. **Top.** Aggregate weekly total number of specimens tested, specimens positive for pH1N1 (*red*), and specimens positive for any type of influenza A or B, by date of specimen collection. The 2 highest peaks in the weekly totals, which are too high to be seen in the graph, are 2162 on 3 May 2009 and 3600 on 1 November 2009. **Middle.** Confirmed cases of pH1N1 broken into 2 age classes, school-age children (aged 5–18 y) and all others (children aged <5 y and adults aged >18 y). **Bottom.** Intensity plot of date of sample collection versus age of patient, with cumulative cases by age shown in the bar plot on the right.

than in the rest of the province; however, the long delay before substantial growth of the second wave makes this uncertain. Note that a sudden drop in incidence is expected if transmission is suddenly reduced in the middle of an epidemic, when incidence is high. In contrast, when incidence is low, a gradual change is expected after a change in transmission rate. When schools opened in late August 2009, incidence rates were extremely low; a sudden increase in transmission rate can start an exponential increase in cases, but this would take several weeks to be detectable at the population level.

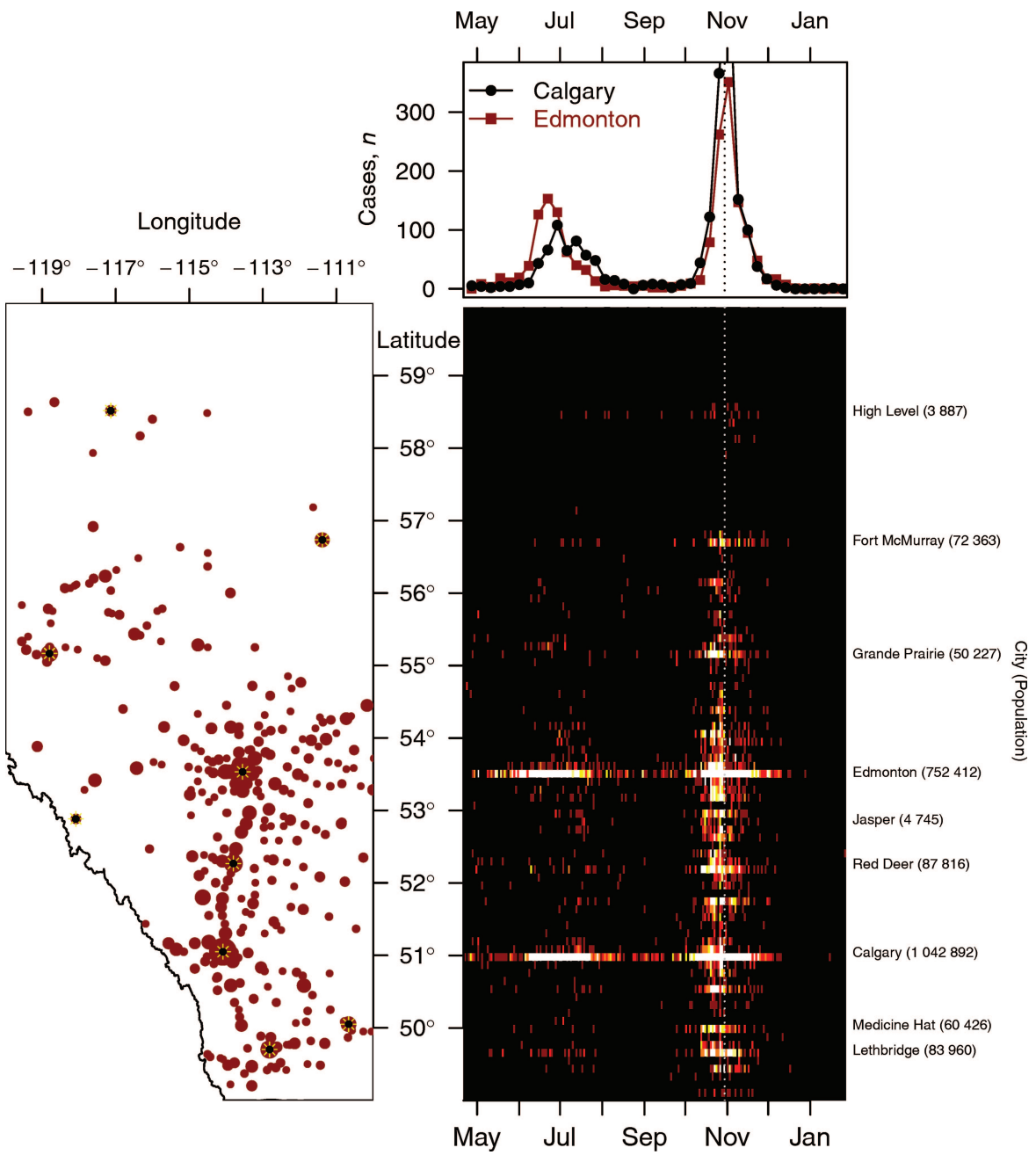
Modeling pH1N1 Transmission in Alberta

To examine how transmission rates (as opposed to incidence) changed over the course of the epidemic, we used a simple epidemiologic model with 2 age classes, school-age children (aged 5 to 18 years) and all others. We modeled seasonal changes in influenza transmission by using a

sinusoidal function (31) and a functional response to weather variables (temperature or absolute humidity [32–35]), and also considered the possibility of abrupt changes in transmission in either or both of the age classes. Because school-based public-health responses could have led to increased testing while school was in session, we also constructed models in which reporting rate was allowed to vary among age classes and change abruptly. We used a standard particle-filtering algorithm (24, 36, 37) to estimate 95% CIs for each model's parameters.

We fit our models to the data from the 2 largest cities, Calgary and Edmonton, and to the province, and conducted an extensive model selection analysis in each case on the basis of 20 model variants (**Supplement**). In all

Figure 2. **Spatial structure of laboratory-confirmed cases of pH1N1 in Alberta, Canada, in 2009.**



pH1N1 = pandemic H1N1 influenza. **Bottom left.** Cumulative incidence by location (larger disks indicate more confirmed cases). **Bottom right.** Epidemic progression, aggregated by latitude. The cities and towns labeled on the right (with their population sizes) are also highlighted at their exact position in the left panel. **Top right.** Weekly confirmed cases in Calgary and Edmonton.

cases, the best-fit model according to the sample size–corrected Akaike information criterion (AIC) (38) was found when we allowed transmission rate to be linked to temperature, with an abrupt change in incidence in school-age children (but not the other age class) on school opening and closing dates and an intensive testing period at the beginning of the epidemic. The **Table** lists maximum likelihood parameter estimates and 95% CIs. Models that used absolute humidity instead of temperature, or changes in reporting rate rather than (or in addition to) transmission rate, did not fit as well (change in AIC for Calgary >7 or >22, respectively). During the second wave of the epidemic, a large decrease in temperature obviously correlated with a large increase in cases of pH1N1 influenza (**Figure 1**), which suggests a substantial causative link; however, the exponential increase of the second wave began before the substantial change in temperature, which indicates that the opening of schools was probably a more important factor in seeding the second wave.

The **Table** indicates that the predicted magnitude of the reduction in transmission rate in school-age children was 63% (95% CI, 43% to 84%) in Calgary, 100% (CI, 69% to 100%) in Edmonton, and 86% (CI, 70% to 100%) in Alberta. Our estimates of the aggregate basic reproductive number are consistent with analyses of other pH1N1 data (13–16).

To study the link between the observed change in transmission and the school schedule, we refitted our model while allowing the dates of transmission change to be free parameters (**Supplement**). We found that the 95% CIs for the estimated dates on which the transmission rate decreased in school-age children are narrow and overlap (or nearly overlap, in the case of Edmonton) with the range of dates when schools actually closed (**Figure 2**). The 95% CIs for the estimated dates on which the transmission rate increased in this age class are much wider; much greater uncertainty is expected when estimating this date because stochastic variations are relatively more important at the start than in the middle of an outbreak. After Calgary and Edmonton, the next largest city in Alberta (Red Deer) is smaller by an order of magnitude, and the data during the first wave were very noisy (**Figure 2**), which makes it difficult to detect the beginning and end of the wave, as well as any relationships with the school calendar or weather patterns. We therefore restricted our analyses to the 2 largest cities and to the province.

Predicted Outcome If Schools Had Not Been Closed

Figure 3 compares simulation time series with the observed pH1N1 incidence data for Alberta as a whole; **Supplement Figures 1** and **2** (available at www.annals.org) compare these data for Calgary and Edmonton, respectively. In each figure, the simulations used for the top panels are based on the parameters estimated for our best-fit model (**Table**), whereas the bottom panels show what the same model predicts if schools had remained open all summer: The first wave would not have burnt out but would still have been moderated by temperature effects; more persons would have been infected before the vaccine became available; and a major second wave induced by temperature effects would still have occurred in the fall. The predicted factor by which the total number of cases would have been greater if schools had remained open is 1.38 (CI, 1.21 to 1.64) in Calgary, 1.54 (CI, 1.36 to 1.77) in Edmonton, and 2.1 (CI, 2.0 to 2.5) in the province. Of note, although our best-fit models include the effects of temperature, our conclusions do not depend specifically on including temperature. Including absolute humidity instead yields lower AICs but similar parameter estimates and results (in particular, a similar estimate for the effect of school closure on transmission and on the incidence pattern in the absence of school closure). Temperature variations could coincidentally yield the best AIC among the seasonal models; the key point with respect to seasonality is that we have strong evidence for a seasonal effect on transmission (with no seasonal forcing, change in AIC compared with the best-fit model was >14 for Calgary and >31 for Edmonton). Ignoring school closure also precludes a good fit (change in AIC >22 for Calgary and >23 for Edmonton).

Discussion

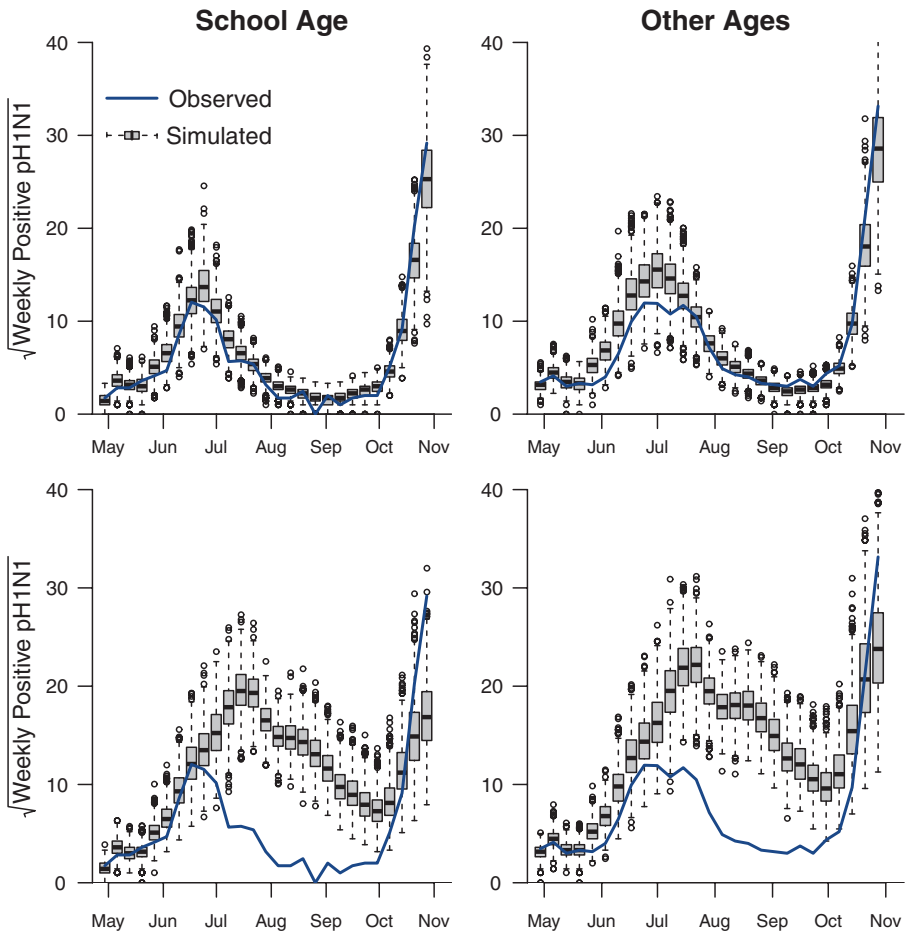
Much previous research (2–5, 18–20, 39, 40) has aimed to connect observed temporal patterns of influenza epidemics with unobserved changes in transmission rate and to connect inferred changes in transmission rate with observed or inferred changes in environmental conditions or human behavior. This previous work has shown that convincingly establishing such links is difficult at best.

Our findings strongly indicate a large reduction in influenza transmission resulting from schools closing for the summer. Although our models cannot include all relevant factors, we have shown that this result is robust to a wide range of assumptions and holds up whether we consider the whole province of Alberta or look separately at large cities. In particular, the result is robust even when we explore different assumptions about influenza reporting.

Given the correlation between the drop in incidence in school-age children and the dates when classes ended, as well as the abrupt associated change in transmission that our models identify, we infer that school closure vastly reduced transmission in school-age children, which substantially reduced the incidence of influenza (initially in school-age children and within a few weeks in the entire population). Our modeling also points to a dramatic increase in transmission among school-age children after schools opened.

Closing schools in Alberta was not undertaken as a control measure; the first wave of pH1N1 infection happened to occur when classes ended for the summer. However, our observations suggest that closing all schools could

Figure 3. **Comparison of pH1N1 data for the province of Alberta with simulations.**



Box plots are based on 1000 realizations of our best-fit model, as specified in the **Table**. Data and simulation results are shown for school-age children (aged 5–18 y) (*left panels*) and for the rest of the population (*right panels*). Data are compared with simulations of our best-fit model (**Table**) (*top panels*) and with predicted results if schools had been left open in Alberta throughout the summer (*bottom panels*). pH1N1 = pandemic H1N1 influenza.

affect the course of future epidemics, regardless of when they occur. Of course, policymakers would also need to consider the social disruption that would result from closing all schools in such a large area as Alberta during the normal school year.

The key inference of our study is that school-age children were fundamentally important drivers of pH1N1 transmission in 2009. Systematically reducing transmission in this age group could substantially mitigate the effects of future pandemics. We suggest that school closures (either local or regional) should be seriously considered if a pandemic occurs during the school year. Our findings also support targeting schoolchildren for interventions aimed at interrupting influenza transmission, including vaccination (41), hygiene (42, 43), and chemoprophylaxis.

Our modeling also indicated that seasonal changes in weather (such as changes in temperature or humidity) significantly affected influenza transmission in cities in Alberta. Although temperature fits these particular data substantially better than humidity, the fits yield similar parameter estimates, and we consider both measures as proxies for more complex seasonal and weather effects. In places where summer started earlier than in Alberta, it would not be surprising to find that the decline of the first wave of the 2009 H1N1 influenza pandemic began before schools closed for the summer.

Finally, our work shows the value of unrestricted virologic testing. Data like those we have analyzed greatly increase our power to discover the cause of sudden changes in incidence, whether they result from school closures or other factors. Our approach (comparing the performance of many simple models fitted to high-volume data) is generally underutilized in settings of infectious disease outbreaks. In the future, if data were made available in real time for this type of analysis, debates over the key drivers of incidence could be helpfully constrained.

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Reproducible Research Statement: *Study protocol*: Not available. *Statistical code*: Available from Dr. He (e-mail, daihai@math.mcmaster.ca). *Data set*: Available at the International Infectious Disease Data Archive (http://iidda.mcmaster.ca).

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Effects of school closure on pandemic influenza incidence in Alberta, Canada

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APPENDIX

Normalization of case data

The bottom right of Figure 1 shows a bar plot of the cumulative sum, for each age, of all laboratory-confirmed pH1N1 in 2009; it does not take the age structure of the population into account. We investigated the potential effects of age structure on the shape of the bar plot. Figure 5 compares the total incidence across age (panel a) with *per capita* incidence (panel b). The distributions of raw incidence and incidence per 100,000 population are very similar. Figure 5 also compares the age distributions of confirmed cases before and after testing restrictions were implemented (on 30 October 2009), emphasizing the sampling bias caused by testing restrictions.

Transmission model

We used a standard SIR framework (23) with two age classes: individuals aged 5–18 (s) and all others (o). We denote the numbers of schoolchildren (other individuals) in each disease compartment by S_s and I_s (S_o and I_o), and use N to denote the total population size, including immune individuals. The transmission rate matrix β has four entries, corresponding to transmission within and between each of the two age classes,

$$\beta(t) = \begin{pmatrix} \beta_{\mathrm{ss}}(t) & \beta_{\mathrm{os}}(t) \\ \beta_{\mathrm{so}}(t) & \beta_{\mathrm{oo}}(t) \end{pmatrix} . \tag{1}$$

We assume $\beta_{\mathrm{os}} = \beta_{\mathrm{so}}$. The time-dependence of the entries of this matrix are discussed in a separate section below. We denote the disease recovery rate by γ (so the mean infectious period is $1/\gamma$). We consider importation of cases from outside the focal region to occur at a constant rate ι (a proportion p_s of which are assumed occur in school-age children, where p_s is the actual proportion of the population comprised of individuals between the ages of 5 and 18).

The deterministic version of the model equations are

$$\dot{S}_\mathrm{s} = -S_\mathrm{s}(\beta_\mathrm{ss} I_\mathrm{s} + \beta_\mathrm{os} I_\mathrm{o})/N \tag{2a}$$

$$\dot{I}_\mathrm{s} = S_\mathrm{s}(\beta_\mathrm{ss} I_\mathrm{s} + \beta_\mathrm{os} I_\mathrm{o})/N - \gamma I_\mathrm{s} + \iota p_\mathrm{s} \tag{2b}$$

$$\dot{S}_\mathrm{o} = -S_\mathrm{o}(\beta_\mathrm{so} I_\mathrm{s} + \beta_\mathrm{oo} I_\mathrm{o})/N \tag{2c}$$

$$\dot{I}_\mathrm{o} = S_\mathrm{o}(\beta_\mathrm{so} I_\mathrm{s} + \beta_\mathrm{oo} I_\mathrm{o})/N - \gamma I_\mathrm{o} + \iota(1 - p_\mathrm{s}), \tag{2d}$$

where the dot indicates a derivative with respect to time. We simulated the fully stochastic model via the standard fixed-time-step binomial approximation (24; 37) of the exact Gillespie algorithm (44), using the above equations to specify the event rates (45). Laboratory-confirmed case data represent a sample of all cases; we refer to the mean of the sampling distribution as the report ratio, which we denote η.

Time-dependence of the transmission rate

In our models, each component of the transmission rate matrix (1) was the product of two (potentially) time-dependent factors, one associated with the contact pattern within the group in question (or between the two groups), and the other (identical in all four components) associated with seasonal variation in transmission caused by environmental factors. Thus, for example, the transmission rate among schoolchildren was

$$\beta_\mathrm{ss}(t) = \beta^\star_\mathrm{ss}(t) f(t)\,, \tag{3}$$

where $\beta^\star_\mathrm{ss}(t)$ is a step function that changes on dates when school closes or opens and $f(t)$ is the seasonal forcing factor (which is the same in all four entries of β).

In the case of sinusoidal seasonality,

$$f(t) = 1 + \alpha \cos 2\pi(t - t_0 - \phi)\,, \tag{4}$$

where α and ϕ (both to be fitted) are the amplitude and phase of seasonality, respectively, and t_0 is a convenient reference time (the beginning of January 2009).

In the case of seasonality induced by temperature changes,

$$f(t) = 1 - \alpha T(t)\,, \tag{5}$$

where $T(t)$ is the air temperature at time t and the seasonal amplitude α (to be fitted) determines the magnitude of the effect of temperature on influenza transmission.

We considered two possible functional responses of transmission rate to absolute humidity $\mathrm{AH}(t)$ (our calculation of $\mathrm{AH}(t)$ itself is detailed in the next section). The first form is motivated by recent indications (33; 34) that influenza survival is an exponential function of absolute humidity, suggesting

$$f(t) = 1 + a e^{-b\mathrm{AH}(t)}\,, \tag{6}$$

where a and b are parameters to be fitted. The second form attempts to be as simple as possible (and more similar to the other two forms of seasonality considered above), positing a linear relation between absolute humidity and seasonal forcing of transmission rate,

$$f(t) = 1 - \alpha \mathrm{AH}(t)\,. \tag{7}$$

Here, α is a parameter to be fitted.

Temperature

The top panel of Appendix Figure 1 shows the daily average temperature in Calgary and Edmonton in 2009 (the middle panel shows the daily time series of total confirmed pH1N1 cases for reference). When fitting models to all the case data (for the province as a whole) we used the daily average of the plotted temperatures in Calgary and Edmonton.

Calculation of absolute humidity

We estimated vapor pressure (v) from dewpoint temperature (T_{D}) using Teten's equation (46):

$$v = a10^{bT_{\mathrm{D}}/(c+T_{\mathrm{D}})}\,. \tag{8}$$

We obtained parameter values from Ref. (47): $a = 611\,\mathrm{Pa}$, $b = 7.5$, $c = 237.7\,^{\circ}\mathrm{C}$. We verified this estimate by calculating relative humidity (RH) as the ratio of vapor pressure to saturated vapor pressure (estimated by applying Teten's equation to the observed temperature) and comparing to the RH values published by Environment Canada.

Absolute humidity (AH) is the density of water vapor in moist air ($\mathrm{kg/m^3}$). It can be expressed as

$$\mathrm{AH} = \frac{v}{T \cdot R_{\mathrm{w}}}\,, \tag{9}$$

where v is the vapor pressure, T is the air temperature in degrees Kelvin and R_{w} is the gas constant for water vapor, $R_{\mathrm{w}} = 461.5\,\mathrm{JK/kg}$.

We used equation (9) to calculate hourly AH in Calgary and Edmonton from April to December 2009. From these hourly estimates we computed daily average AH in each city (shown in the bottom panel of Appendix Figure 1). We took the average of the AH and temperature in each of the two major cities to represent Alberta as a whole.

Parameter estimation

Table 1 reports point estimates and 95% confidence intervals for the parameters of our best-fit model. Our model formulation above is not expressed directly in terms of these parameters, so we comment here on the relationships between the model parameters in our formulation above and the (more easily interpretable) parameters that we chose to estimate.

If the recovery rate is γ then the mean infectious period is $1/\gamma$.

The subgroup reproductive number $\mathcal{R}_{xy}$ is the expected number of cases in subgroup y caused by an infectious individual in group x in a susceptible population. This is given by the product of the transmission rate β_{xy}, the mean infectious period $1/\gamma$ and the proportion of the population in group y, $p_y = N_y/N$. We estimated the proportion of school-age individuals (ages 5–18) to be $p_{\mathrm{s}} = 0.1876$ for all of the subpopulations we considered (48).

We estimate the (aggregate) basic reproductive number $\mathcal{R}_0$ by using the *time-averaged* (49) transmission matrix $\beta(t)$ [equation (1)] to calculate the matrix $\mathcal{R}_{xy}$, and then calculating the leading eigenvalue of this matrix.

All the parameter estimates we report are based on models with a time step of $\Delta t = 1$ day. We repeated fits with $\Delta t = 1/2$ day and $\Delta t = 1/4$ day and found only slight differences. For example, with our best-fit model, our point estimate and 95% confidence interval for the proportional reduction in transmission induced by closing schools was 0.63 [0.43, 0.84] with $\Delta t = 1$ day, 0.66 [0.46, 0.95] with $\Delta t = 1/2$ day, and 0.66 [0.45, 0.95] with $\Delta t = 1/4$ day.

Intensive testing during the initial phase

The number of specimens submitted to ProvLab during the first few weeks of the first wave of the pandemic was about four times as large as the number submitted during the equivalent period at the beginning of the second wave, and is not representative of confirmed cases (see top panel of Figure 1). To account for a period of intensive testing during the initial period of concern about the pandemic, we allowed the report ratio to be a step function,

$$\eta(t) = \begin{cases} \eta_0 & t < t_1 \\ \eta_1 & t \geq t_1 \end{cases} \tag{10}$$

Here, t_1 is the date on which intensive testing ceased, η_0 is the report ratio during the intensive testing period, and η_1 is the report ratio subsequently.

Comparison of models

We compared models using the sample-size corrected (second-order) Akaike Information Criterion (50; 38; 51) ($\mathrm{AIC_c}$), which can be written

$$\mathrm{AIC_c} = -2 \max_{\theta} \ell(\theta) + \frac{2 N_{\mathrm{par}} N_{\mathrm{samp}}}{N_{\mathrm{samp}} - N_{\mathrm{par}} - 1} \,. \tag{11}$$

Here, θ is the vector of parameters, ℓ refers to the log-likelihood function, N_{par} is the number of parameters (dimension of θ) and N_{samp} is the sample size. We used weekly bi-variate data over 27 weeks (weekly sums of reported cases in the two age classes), so our sample size was $N_{\mathrm{samp}} = 54$. $\mathrm{AIC_c}$ as defined above is always positive (likelihoods are probabilities, so $-\infty < \ell(\theta) \leq 0$, and $N_{\mathrm{samp}} > N_{\mathrm{par}} + 1$); lower values of $\mathrm{AIC_c}$ correspond to better models.

Initial conditions

Initial conditions (the initial numbers of susceptibles and infecteds in each age class) were treated as free parameters in our models and hence were included in the total number of free parameters when calculating $\mathrm{AIC_c}$. However, we assumed that the initial proportion susceptible was at least 90% in schoolchildren and at least 75% in others. This assumption is plausible given that pH1N1 is believed to have invaded the human population for the first time in 2009; in addition, it helps to address parameter identifiability issues, i.e., anticorrelation between estimates of basic reproductive number $\mathcal{R}_0$ and the initial number of suspectibles. Although this assumption may affect the *scale* of $\mathcal{R}_0$ and the reporting ratio, we do not expect it to affect the temporal changes that are the focus of this paper.

Sensitivity analyses

We investigated the robustness of our parameter estimates by examining 20 different model formulations. The parameter estimates listed in Table 1 correspond to the the best model according to $\mathrm{AIC_c}$ (which was the same model for each city and for the province as a whole), namely the model with

- specified mean infectious period of 4.5 days;
- specified dates on which the transmission rate among schoolchildren dropped (22 June 2009, the cohort-weighted mean date on which schools actually closed in Alberta) and

rose (27 or 31 August 2009, in Calgary and Edmonton, respectively; 29 Aug 2009 for the province as a whole);

- two fitted values of baseline transmission rate in schoolchildren (i.e., the same value of $\beta^\star$ as defined in equation (3) before and after the summer and another value of $\beta^\star$ during the summer holiday);
- seasonal variation in transmission rate induced by temperature changes (equation (5));
- no latent period (i.e., SIR rather than SEIR);
- out-of-city importation of cases into Edmonton, but not Calgary; out-of-province importatation of cases in Alberta as a whole;
- reporting rate high during the intensive testing period and low after that, and identical for both age classes.

In our best model, we fixed the mean infectious period and school closing/opening dates. We also challenged our model by fitting the mean infectious period and school closing/opening dates and the estimates are summarized in Appendix Figure 2. The estimated mean infectious period is close to the fixed value of 4.5 days. The estimated school closing/opening dates match the true values in Alberta as a whole and in Calgary; the mismatch in Edmonton is likely a consequence of the relatively larger effect of demographic stochasticity in this smaller population. With the exception of the model with unspecified mean infectious period, and the model with unspecified school dates, all our model formulations can be obtained from the best model by relaxing the above constraints in various ways (e.g., using a simple sinusoid or absolute humidity as the basis of seasonal forcing, as discussed above). Most of these models fit the data considerably worse than the model for which Table 1 reports parameter estimates, though some were only marginally worse (e.g., including a latent class). Each of the models we investigated is listed together with the associated AICc in Appendix Tables 1, 2 and 3.

Validation of parameter estimation methodology

The methodology we have used (e.g., the freely available R package POMP) has been extensively tested in previous work (25; 51; 24). In Appendix Figure 6, we validate our approach by applying it to 256 realizations of our best-fit model and checking that the distribution of estimates for each parameter is consistent with the correct value (marked with a red vertical line).

Appendix Table 1: Comparison of pH1N1 transmission models for Calgary. MLL refers to the maximum log likelihood. N_{par} is the number of free parameters in the model. AICc is Akaike's Information Criterion, corrected for small sample sizes. School indicates whether or not transmission is affected by school being in session (either with the dates of summer closure fixed at their known values or free to be fitted). Several types of seasonal forcing were considered, as described in the Methods section (functions of temperature T, absolute humidity AH, or a simple sinusoid). I.P. denotes the mean infectious period, which was either fixed at 4.5 days or free to be fitted in the SIR model (the SEIR model included a fixed mean latent period of 1.5 days and a fixed mean infectious period of 3 days). The fitted Reporting Rate was either identical for both age classes (same), distinct for each age class (different), or distinct for each age class and different in the summer for school-age children (diff summer). In models that allowed for intensive testing, the Reporting Rate was fitted separately before and after a (fitted) date on which intensive testing ceased. Importation, when included, involved a constant (fitted) rate of cases from elsewhere.

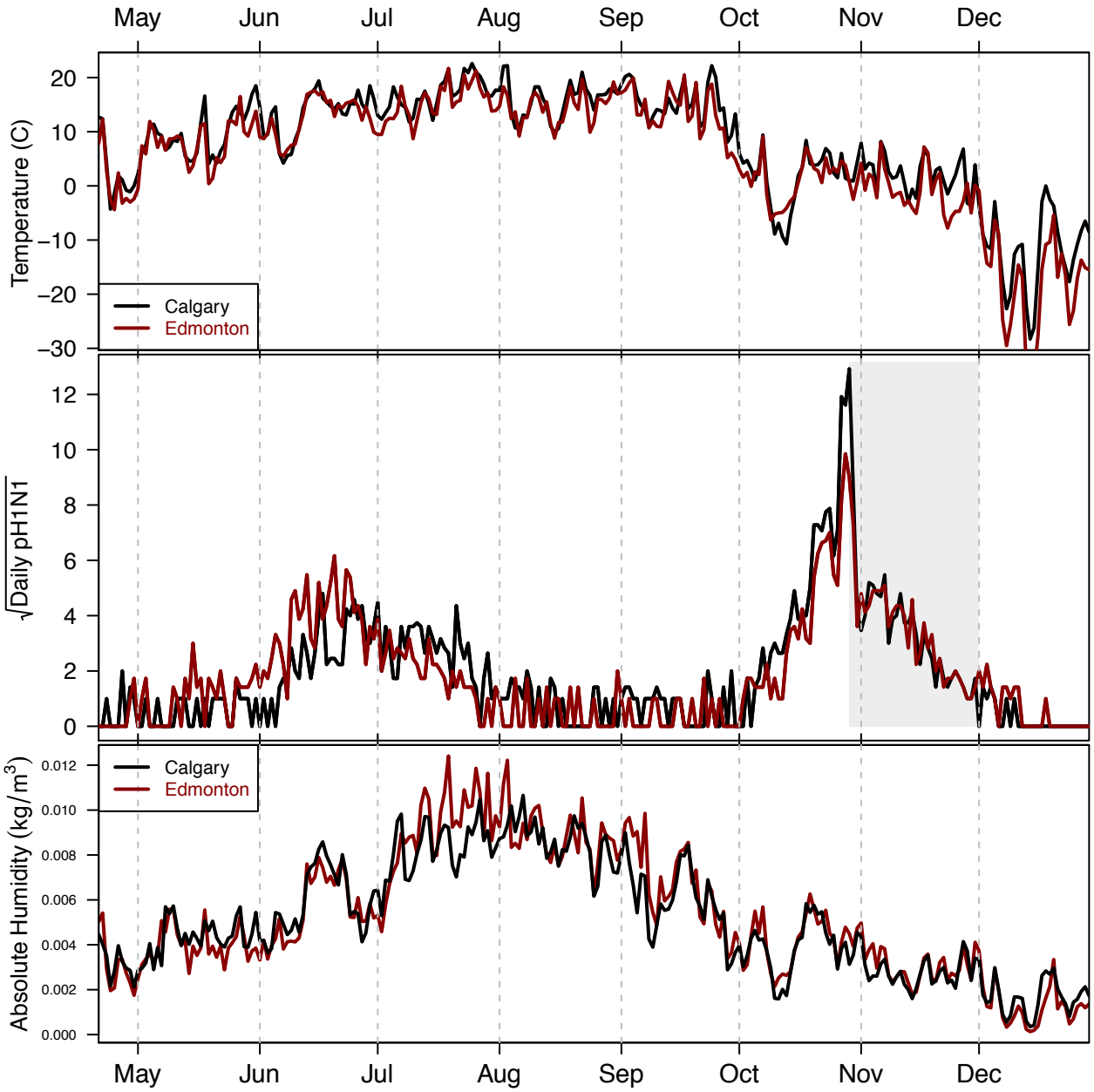
	Model	MLL	N_{par}	$\mathrm{AIC_c}$	School (date)	Seasonal forcing	I.P.	Reporting rate	Importation	Early intensive testing
1	SIR	-150.21	12	332.03	Yes(fixed)	1+a*T	fixed	same	No	Yes
2	SIR	-154.97	10	335.06	Yes(fixed)	1+a*T	fixed	same	No	No
3	SIR	-154.49	11	337.26	Yes(fixed)	1+a*T	fixed	same	Yes	No
4	SIR	-154.52	11	337.32	Yes(fixed)	1+a*T	free	same	No	No
5	SIR	-153.29	12	338.20	Yes(fixed)	1+a*T	fixed	diff summer	No	No
6	SIR	-153.32	12	338.24	Yes(free)	1+a*T	fixed	same	No	No
7	SIR	-155.10	11	338.48	Yes(fixed)	1+a*T	fixed	different	No	No
8	SIR	-149.86	14	338.49	Yes(fixed)	1+a*T	fixed	same	Yes	Yes
9	SEIR	-153.64	12	338.88	Yes(fixed)	1+a*T	fixed	same	No	No
10	SIR	-158.49	10	342.09	Yes(fixed)	1+a*AH	fixed	same	No	No
11	SIR	-158.24	11	344.76	Yes(fixed)	a*exp(-b*AH)	fixed	same	No	No
12	SIR	-158.42	11	345.12	Yes(fixed)	1+a*AH	fixed	same	Yes	No
13	SIR	-158.75	11	345.79	Yes(fixed)	1+a*sin(t-b)	fixed	same	No	No
14	SIR	-158.31	12	348.23	Yes(fixed)	1+a*sin(t-b)	fixed	same	Yes	No
15	SIR	-163.68	9	349.46	Yes(fixed)	Constant	fixed	same	No	No
16	SIR	-157.44	13	349.98	Yes(fixed)	1+a*AH	fixed	same	Yes	Yes
17	SIR	-158.45	13	352.01	Yes(fixed)	1+a*sin(t-b)	fixed	same	No	Yes
18	SIR	-164.97	11	358.22	No(fixed)	1+a*T	fixed	diff summer	No	No
19	SIR	-168.47	10	362.06	No(fixed)	1+a*T	fixed	different	No	No
20	SIR	-167.12	12	365.84	No(fixed)	1+a*T	fixed	same	Yes	Yes

Appendix Table 2: Comparison of pH1N1 transmission models for Edmonton. See caption to Appendix Table 1 for details.

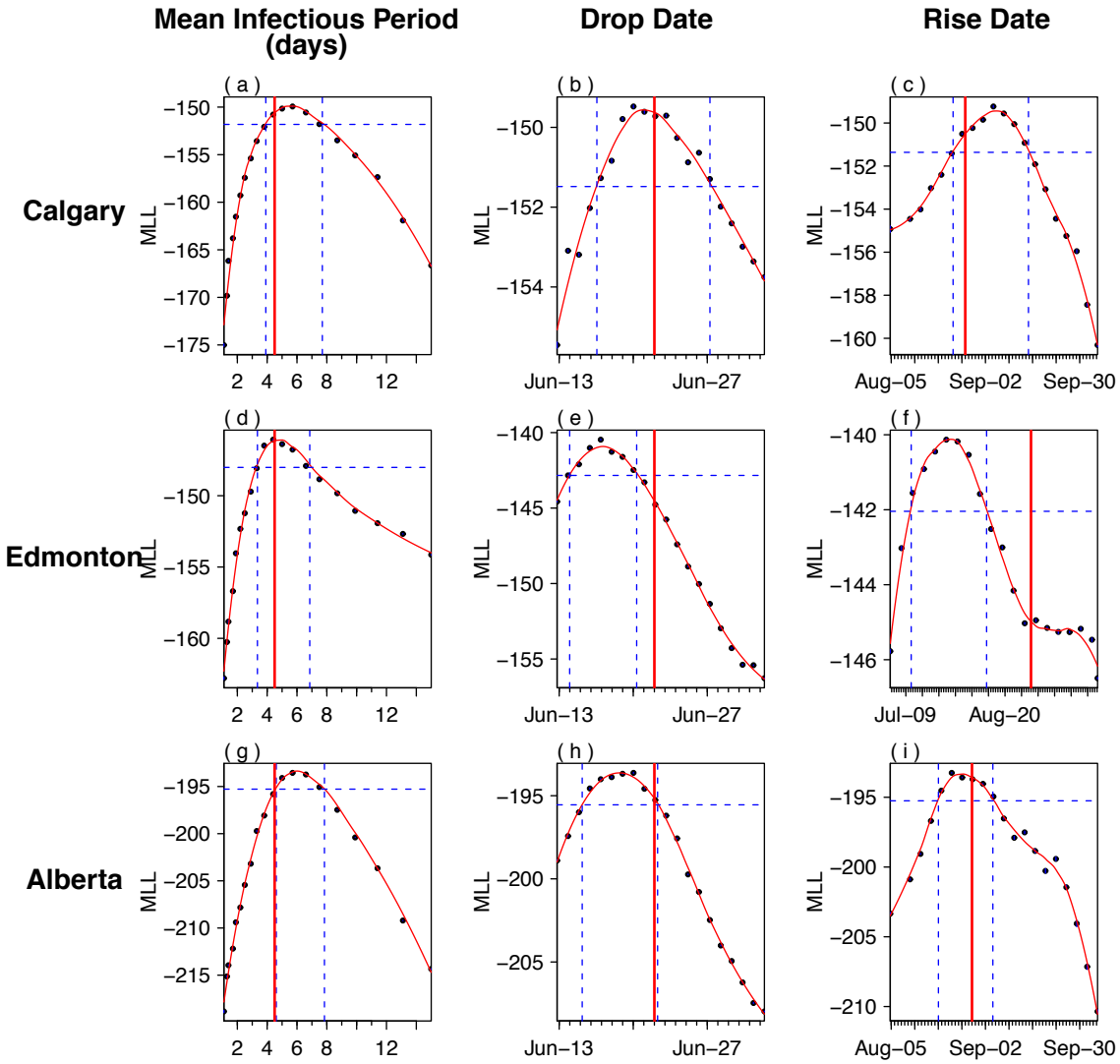
	Model	MLL	N_{par}	AIC_{c}	School (date)	Seasonal forcing	I.P.	Reporting rate	Importation	Early intensive testing
1	SIR	-145.34	13	325.79	Yes(fixed)	1+a*T	fixed	same	Yes	Yes
2	SIR	-150.17	11	328.63	Yes(fixed)	1+a*T	fixed	same	Yes	No
3	SIR	-147.09	13	329.27	Yes(fixed)	1+a*sin(t-b)	fixed	same	No	Yes
4	SIR	-149.69	12	331.00	Yes(fixed)	1+a*T	fixed	different	Yes	No
5	SEIR	-149.98	12	331.57	Yes(fixed)	1+a*T	fixed	same	Yes	No
6	SIR	-146.41	14	331.58	Yes(fixed)	1+a*T	fixed	different	Yes	Yes
7	SIR	-150.13	12	331.87	Yes(fixed)	1+a*T	free	same	Yes	No
8	SIR	-148.78	13	332.67	Yes(free)	1+a*T	fixed	same	Yes	No
9	SIR	-152.36	11	333.01	Yes(fixed)	1+a*sin(t-b)	fixed	same	No	No
10	SIR	-149.46	13	334.02	Yes(fixed)	1+a*T	fixed	diff summer	Yes	No
11	SIR	-155.28	10	335.68	Yes(fixed)	1+a*T	fixed	same	No	No
12	SIR	-152.32	12	336.25	Yes(fixed)	1+a*sin(t-b)	fixed	same	Yes	No
13	SIR	-158.69	11	345.67	Yes(fixed)	1+a*AH	fixed	same	Yes	No
14	SIR	-157.70	12	347.01	Yes(fixed)	a*exp(-b*AH)	fixed	same	Yes	No
15	SIR	-157.46	13	350.02	Yes(fixed)	1+a*AH	fixed	same	Yes	Yes
16	SIR	-160.39	12	352.39	No(fixed)	1+a*T	fixed	same	Yes	Yes
17	SIR	-163.82	10	352.75	Yes(fixed)	1+a*AH	fixed	same	No	No
18	SIR	-161.28	12	354.17	No(fixed)	1+a*T	fixed	diff summer	Yes	No
19	SIR	-159.94	13	354.99	No(fixed)	1+a*T	fixed	different	Yes	Yes
20	SIR	-167.75	10	360.62	Yes(fixed)	Constant	fixed	same	Yes	No

Appendix Table 3: Comparison of pH1N1 transmission models for Alberta as a whole. See caption to Appendix Table 1 for details.

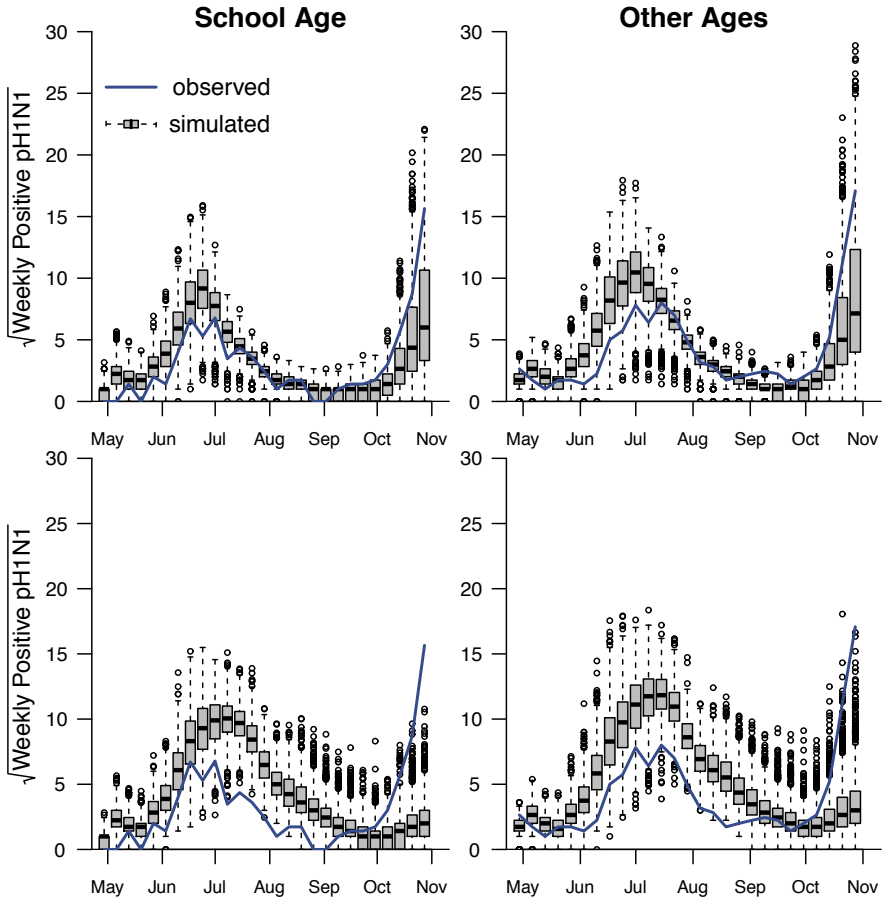
	Model	MLL	N_{par}	AIC_{c}	School (date)	Seasonal forcing	I.P.	Reporting rate	Importation	Early intensive testing
1	SIR	-193.89	13	422.88	Yes(fixed)	1+a*T	fixed	same	Yes	Yes
2	SIR	-193.25	14	425.27	Yes(free)	1+a*T	fixed	same	Yes	Yes
3	SIR	-193.55	14	425.88	Yes(fixed)	1+a*T	free	same	Yes	Yes
4	SIR	-199.31	11	426.91	Yes(fixed)	1+a*T	fixed	same	No	No
5	SIR	-201.35	14	441.47	Yes(fixed)	a*exp(-b*AH)	free	same	No	Yes
6	SIR	-204.00	13	443.11	Yes(fixed)	1+a*sin(t-b)	fixed	same	Yes	Yes
7	SIR	-204.28	14	447.33	Yes(fixed)	a*exp(-b*AH)	fixed	same	Yes	Yes
8	SIR	-210.14	13	455.39	Yes(fixed)	1+a*AH	fixed	same	Yes	Yes
9	SIR	-224.47	12	480.55	Yes(fixed)	constant	fixed	same	Yes	Yes
10	SIR	-225.97	12	483.54	No(fixed)	1+a*T	fixed	same	Yes	Yes



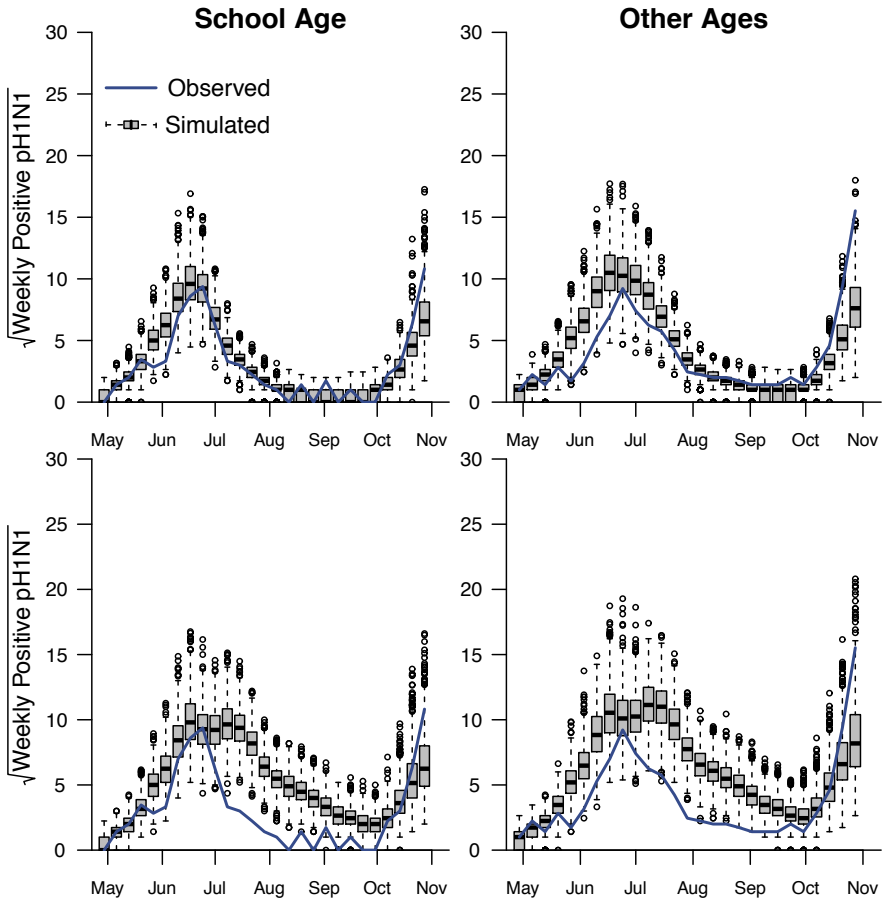
Appendix Figure 1: Daily average temperature (top panel), daily confirmed pH1N1 cases (middle panel) and daily absolute humidity (bottom panel) in Calgary and Edmonton in 2009. The grey shaded region in the middle panel highlights the time period when virological testing restrictions were in place. Models were fitted only to data that preceded the initiation of testing restrictions.



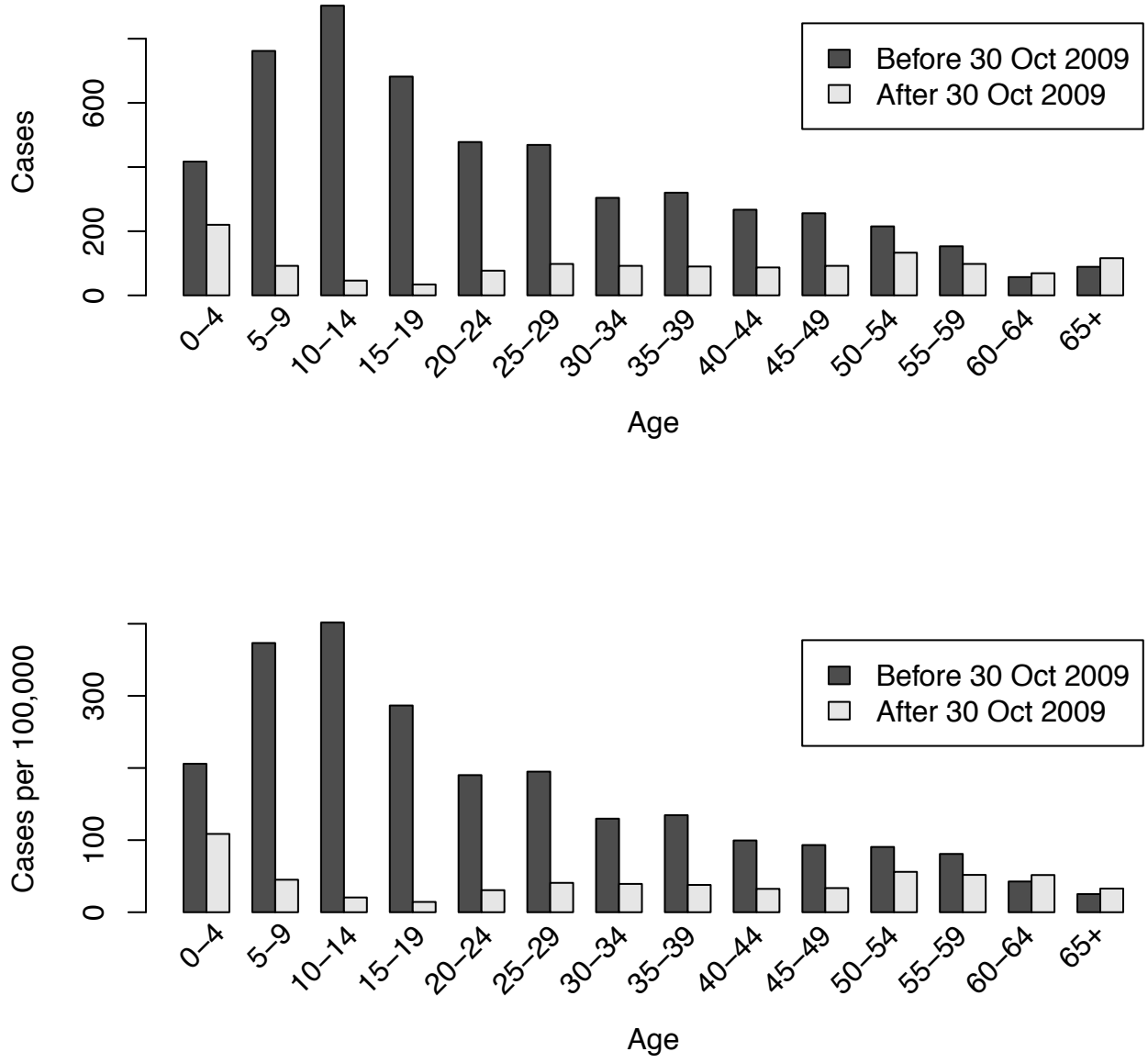
Appendix Figure 2: Comparison of fitted vs fixed value of the mean infectious period (column 1) and fitted vs known values of the dates on which the transmission rate dropped (column 2) and rose (column 3) as a result of schools closing for the summer in Calgary (row 1), Edmonton (row 2) and the province of Alberta as a whole (row 3). Panels (a,d,g) in column 1 show the likelihood profile for the mean infectious period, estimated using our best-fit model (Table 1), but allowing the mean infectious period to be fitted. The 95% confidence lies between the two dotted vertical blue lines, while the *a priori* fixed value of 4.5 days is indicated with a solid vertical red line. Similarly, columns 2 and 3 show likelihood profiles for fitted vs actual school closing and opening dates.



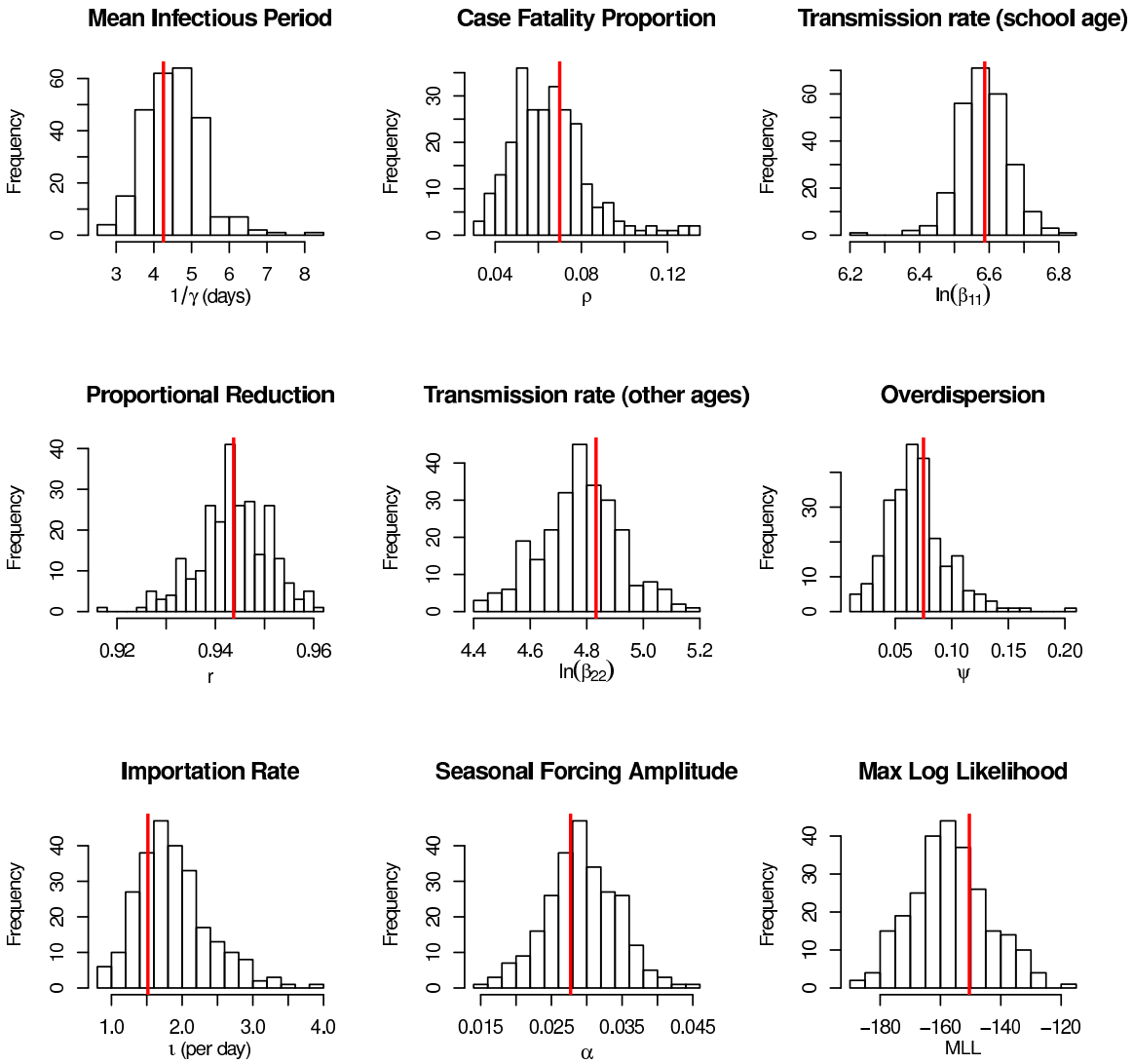
Appendix Figure 3: Comparison of pH1N1 data for Calgary (blue) with simulations (box plots are based on 1000 realizations of our best-fit model) as specified in Appendix Table 1. The left panels show data and simulation results for school-age children and the right panels show the corresponding data and simulations results for the rest of the population. The top panels compare the data with simulations of our best-fit model (Appendix Table 1). The bottom panels show what the model predicts if schools had been left open throughout the summer.



Appendix Figure 4: Comparison of pH1N1 data for the city of Edmonton (blue) with simulations (box plots). See caption to Appendix Figure 3 for details.



Appendix Figure 5: Age distribution of laboratory-confirmed cases of pH1N1 in Alberta in 2009. Top panel: Cases. Bottom panel: Case rates (per 100,000 population, based on data from Ref. (48)).



Appendix Figure 6: Validation of parameter estimation methodology. With parameters set to their MLE values, we generated 256 stochastic realizations of our best-fit model. Using POMP, we then refitted our model to each of these 256 simulations. For each parameter, a histogram shows the distribution of MLEs and a red vertical line shows the true value (which always lies close to the centre of the distribution of MLEs). The final (bottom right) panel shows the distribution of the maximum log likelihood (MLL) for each simulation compared with the MLL for the observed data (red vertical line). While the MLL is not a parameter and should not be directly compared for different data sets, the MLL associated with a given model fitted to observed data should be similar to the MLL obtained by fitting to simulations of the same model (as we find here).