A composite epidemic curve for seasonal influenza in Canada with an international comparison

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Background Empirical data on laboratory-confirmed seasonal influenza is limited by very low and possibly non-systematic case ascertainment as well as geographical variation.

Objective To provide a visual representation of an influenza epidemic at the community and regional level using empirical data and to describe the epidemic characteristics.

Methods Weekly influenza A confirmations were obtained from the Canadian FluWatch program and American FluView program for the 1997/1998–2006/2007 seasons; 1-year data were also available for Europe (FluNet, WHO). For seasons where at least 80% of the influenza A strains were antigenically similar, a composite epidemic curve was created by centring the local epidemics relative to their epidemic midpoint.

Results The range in timing of the regional peaks varied from 5 to 13 weeks. Once the epidemic curves were centred relative to their peak, the composite epidemic curves were similar for

Canada, the United States and Europe, and the epidemic growth rates were similar for most subgroups (city size; regions; H1N1 versus H3N2 seasons). During the exponential growth period, the number of cases increased by a factor of 1·5–2·0 per week, averaging 1·8. Exponential growth was evident approximately 10 weeks before the peak. Evidence of sustained transmission occurred from mid-September to early June.

Discussion The shape of the composite curve created in this study clearly demonstrates a consistency in the epidemic pattern across geographically disparate locales. Laboratory confirmation will likely play an increasing role in the development of better methods for early detection and summary measures of influenza activity.

Keywords Empirical epidemic curve, influenza, surveillance, transmission dynamics.

Introduction

Many developed countries now include laboratory-confirmed influenza tests as part of their national influenza surveillance programs, and this information is communicated through the Internet to the public health community on a weekly basis.[1,2] As influenza causes considerable mortality burden[3–5] over a short period of time, deaths because of an influenza-like illness have been used to study transmission rates associated with influenza epidemics and pandemics.[6] In temperate climates, the annual influenza epidemic typically peaks during the cooler, drier, winter months.[1,2,6,7] By contrast, semi-tropical regions such as Hong Kong often experience biannual epidemics,[8] with evidence of a latitude gradient from tropical to semi-tropical regions.[9]

The shape of the national epidemic curve for Canada (Figure 1) is irregular compared to a typical epidemic curve as described by epidemic models.[10] According to these epidemic models, once established, the epidemic proceeds through three distinct phases: a period of exponential growth, a period of peak activity, followed by epidemic decline. The apparent irregularity at the national level may be because of variation in the timing of the onset of the epidemic as it spreads from region to region.[1] While influenza is estimated to affect 5–10% of the population each year[11–13], laboratory testing to confirm the viral aetiology of persons presenting with an influenza-like illness is not routine in Canada[14,15], and only a small proportion of influenza infections are confirmed through laboratory testing. In this study, we created a composite epidemic curve by pooling laboratory-confirmed influenza A cases across

cities, regions and/or seasons after controlling for the regional differences in epidemic timing, and used the composite epidemic curves as a tool to assess various hypotheses proposed to explain the seasonality and transmissibility of influenza.[16] We expected to see different epidemic growth rates because of varying climatic conditions and latitude gradients across the countries examined.

It has been suggested that transmissibility of interpandemic influenza is highest when a new antigenic strain emerges and that it is higher in large cities compared to smaller towns.[17] We assessed these hypotheses and looked as well for seasonal differences in the transmission rates that might contribute to the seasonality of influenza.

Influenza testing and reporting varies across jurisdictions and over time, and so the number of laboratory-confirmed cases is not thought to reflect the number of cases at a population level. The construction of the composite epidemic curve was designed to control for geographical differences in testing procedures and asynchronous epidemics by centring each local epidemic relative to its midpoint. However, other systematic irregularities in testing and reporting procedures over a single season could occur and could not be controlled in this analysis (for example, limited laboratory capacity during peak periods or holiday periods). Hence, we compared composite epidemic curves across jurisdictions and by calendar time to assess whether there were systematic irregularities in testing over the influenza season.

Methods

Sources of data

Laboratory confirmations for influenza A by province and week from September 1997 to August 2007 were obtained from the Respiratory Virus Detection Surveillance System (RVDSS), Public Health Agency of Canada[1,18], which collects, collates and reports weekly laboratory results from participating laboratories. Specimens are submitted to laboratories by clinicians in the course of clinical care and by sentinel physicians participating in the national influenza surveillance program FluWatch.[1] As influenza testing procedures, reporting practices and the availability of diagnostic services vary by jurisdiction, the number of confirmed cases is not considered geographically representative. The number of respiratory specimens in which influenza A was detected is reported weekly for each of the 10 provinces. Most of the RVDSS participating laboratories also provided additional epidemiological information on a case-by-case basis. From the case-by-case database, city of residence was available for approximately 80% of the influenza-positive tests reported to the RVDSS[18], providing a finer geographical scale for analysis. The recorded city name was grouped into census metropolitan areas (CMA) or census agglomer-

ations (CA). A CMA/CA is an area consisting of one or more neighbouring municipalities situated around a major urban core. A CMA must have a total population of at least 100 000 of which 50 000 or more live in the urban core. A CA must have an urban core population of at least 10 000. As of the 2001 census, there were 33 CMAs and 111 CAs in Canada.[19] Census metropolitan areas and CAs reporting at least 50 influenza confirmations per season were included in the community-level analysis as separate geographical units.

In the United States, weekly reports of specimens tested for influenza in about 80 U.S. World Health Organization (WHO) laboratories and 70 laboratories of the National Respiratory and Enteric Virus Surveillance System (NREVSS) were provided by the US Centers for Disease Control and Prevention's (CDC) Influenza Division FluView program[2] for nine influenza surveillance regions. The weekly number of influenza A–positive specimens was obtained for each of the nine influenza surveillance regions in the United States for the 1997/1998 to 2006/2007 influenza seasons.

The WHO Global Influenza Surveillance Network (GISN) provides virological data to FluNet for dissemination through WHO's Communicable Disease Global Database.[20] This database was explored as a source for weekly reports of influenza A isolates at the international level. For the 2006/2007 season, 20 European countries provided weekly reports of at least 50 influenza A isolates to the GISN. The data were collected by the European Influenza Surveillance Scheme (EISS),[21] and provided to the European Influenza Surveillance Network (EISN)[22], which also participates in the GISN. WHO/Europe also provides reports on epidemiological and virological data from the 53 member states through its EuroFlu platform.[23] Although the international data available through GISN were limited, an analysis of the European data for the 2006/2007 season was included as a further international comparison.

The population of Canada used to estimate detection rates was obtained from Statistics Canada census and intercensus estimates.[24]

Statistical analysis

The epidemic midpoint, defined as the week when cumulative incidence reaches 50% of the cumulative total of the seasonal cases, was determined for each reporting geographical unit: Canadian province, Canadian CMA or CA for which at least 50 laboratory-confirmed cases of influenza A were reported, the US region and European countries. A composite epidemic curve was created by aligning the local epidemic curves relative to the week corresponding to the local epidemic midpoint and aggregating over various geographical units or seasons. Seasons were characterized by national year-end summary reports[1,2,21,25,26], and with the exception of the 2004/2005 and 2006/2007 sea-

Table 1. Strain characterization

(a) Summary of laboratory surveillance of influenza seasons

Region	Season	Predominant A strain	Sub-Type	Proportion antigenically similar to the predominant A strain*	Emerging strain	Vaccine match to dominant strain	Co-circulation of Influenza B (% of influenza specimens)
Canada	1997/1998	A/Sydney/05/97	H3N2	**82%**	New		0·2%
	1998/1999	A/Sydney/05/97	H3N2	**99%**		Match	29%
	1999/2000	A/Sydney/05/97	H3N2	**83%**		Match	7%
	2000/2001	A/New Caledonia/20/99	H1N1	**97%**	New	Match	51%
	2001/2002	A/Panama/2007/99	H3N2	**82%**	New	Match	26%
	2002/2003	A/New Caledonia/20/99	H1N1	79%		Match	23%
	2003/2004	A/Fujian/411/02	H3N2	**99·5%**	New		5%
	2004/2005	A/Fujian/411/02	H3N2	56%		Match	19%
	2005/2006	A/California/7/2004	H3N2	72%		Match	46%
	2006/2007	A/Wisconsin/67/2005	H3N2	59%		Match	12%
United States	1997/1998	A/Sydney/05/97	H3N2	**81%**	New		0·8%
	1998/1999	A/Sydney/05/97	H3N2	**90%**		Match	30%
	1999/2000	A/Sydney/05/97	H3N2	**84%**		Match	1%
	2000/2001	A/New Caledonia/20/99	H1N1	**85%**	New	Match	88%
	2001/2002	A/Panama/2007/99	H3N2	**93%**	New	Match	16%
	2002/2003	A/New Caledonia/20/99	H1N1	67%		Match	71%
	2003/2004	A/Fujian/411/2002	H3N2	**89%**	New		1%
	2004/2005	A/California/7/2004	H3N2	77%	New	Match	23%
	2005/2006	A/California/7/2004	H3N2	59%		Match	21%
	2006/2007	A/New Caledonia/20/99	H1N1	57%		Match	20%
Europe	2006/2007	A/Wisconsin/67/2005	H3N2	**93%**		Match	3%

(b) Vaccine component

Season	H3N2	H1N1
1997/1998	A/Wuhan/359/95	A/Johannesburg/82/96
1998/1999	A/Sydney/5/97	A/Beijing/262/95
1999/2000	A/Sydney/5/97	A/Beijing/262/95
2000/2001	A/Panama/2007/99	A/New Caledonia/20/99
2001/2002	A/Panama/2007/99	A/New Caledonia/20/99
2002/2003	A/Panama/2007/99	A/New Caledonia/20/99
2003/2004	A/Panama/2007/99	A/New Caledonia/20/99
2004/2005	A/Fujian/411/02	A/New Caledonia/20/99
2005/2006	A/California/7/04	A/New Caledonia/20/99
2006/2007	A/Wisconsin/67/2005	A/New Caledonia/20/99

*Sub-typing and strain identification was based on a sample of all influenza A–positive specimens. In seasons where at least 80% of the influenza A specimens characterized were antigenically similar, the season was labelled as a 'Dominant A Season', and the contribution of co-circulating strains to the influenza A epidemic curve were considered minimal. Dominant A seasons are shown in bold.

sons, the predominant strains circulating in Canada and the United States were similar (Table 1a). As we were unable to control for the co-circulation of multiple strains, we chose to focus on seasons where one antigenic strain dominated. Seasons where at least 80% of the influenza A strains were antigenically similar were defined in this study as dominant A seasons (1997/1998, 1998/1999, 1999/2000, 2000/2001, 2001/2002, and 2003/2004). Of the dominant A seasons, the predominant A strain was antigenically similar to the predominant strain that circulated in the previous season in 1998/1999 and 1999/2000, and the vaccine was poorly matched to the dominant strain in the 1997/1998 and 2003/2004 seasons (Table 1b). In the 2000/2001 and 2002/2003 seasons, H1N1 was the predominant subtype, though only the 2000/2001 season was considered a dominant A season.

To describe the duration and general shape of an epidemic curve corresponding to different geographical scales, the city-level and provincial-level composite epidemic curves were summarized by the inter-quartile (IQ) range, and the 90 and 98 percentile ranges. The IQ range corresponds to the minimum number of consecutive weeks during peak activity that account for 50% of all cases, and the 90 and 98 percentile ranges correspond to the number of consecutive weeks centred around the epidemic midpoint that account for 90% and 98% of all cases, respectively.

Simple epidemic models, or SEIR models named for compartmentalizing the population as Susceptible, Exposed, Infectious and Recovered persons, were developed to model infectious disease epidemics.[10] These models predict a period of exponential growth in the initial phase of the epidemic where the depletion of susceptibles is nearly negligible. We noted the approximate length of the exponential growth period and estimated the weekly epidemic growth rate, ρ, from a composite epidemic curve over the approximately log-linear portion of the epidemic (Poisson regression, PROC GENMOD, SAS[27]) by fitting a log-linear trend line. The weekly epidemic growth factor, r, was calculated as e^{ρ} (a weekly growth rate of 0·69 per week gives a growth factor of $e^{0·69}$ or 2, implying that the number of cases double every week).

As peak influenza activity usually occurs during the winter period in temperate climates, it has been suggested that influenza transmission rates are higher during the winter period. To assess the seasonality of transmission rates by calendar week, the weekly growth factor for calendar week w, r_w, was calculated as the ratio of the number of influenza A confirmations in calendar week w divided by the number of confirmations in week w-1, where a data pair (regional confirmations in week w and $w-1$) was included in the calculation of r_w if the regional epidemic peaked in week $w+2$ or later. The choice of week -2 as a cut-off likely biased the estimate the weekly growth factor downward; however, there were too few cases corresponding to earlier cut-offs to assess a calendar time trend, and this bias is unlikely to influence the trend.

There are various approaches to calculate R_0, the basic reproduction number or the average number of new infections generated from one infected case in a totally susceptible population. Whether one converts r to R_0,[28,29] or alternatively, estimates R_0 directly using an SEIR model[29], assumptions about the duration of the infectious and latency periods are still required.[28]

Results

The number of influenza A–positive tests reported to the RVDSS each year varied from 1000 to 11 000, even in recent years. Assuming that influenza virus infection affects 5–10% of the population each year[11–13], the case detection rate in Canada was likely less than a half of one per cent. From the 1997/1998 season through to the 2006/2007 season (10 seasons), the RVDSS collected an average of 6000 positive test reports per season. For the same period, the case-by-case database provided city of residence for an average of 4000 cases per season, of which 57% and 15% came from CMAs and CAs, respectively. As per the 2001 census, 64% of the population lived in a CMA and 15% in a CA.[19] The rest lived in rural areas (21%), of which over half lived in communities where at least 5% of the local labour force commuted to work in a nearby CMA or CA. The number of CMA/CAs reporting more than 50 laboratory-confirmed influenza A cases to the case-by-case database varied by the severity of the season, with 18 CMAs and 4 CAs reaching this threshold in the 2003/2004 season, and only Toronto and Montreal in the 2002/2003 season.

Viewed at the national level, the Canadian epidemic curves for each influenza season are seen to vary in intensity and timing of peak activity (Figure 1A). After aligning the national epidemic curves for each influenza season by the week of the epidemic midpoint and normalizing by the total number of laboratory-confirmed cases for each season, the irregular shape of the epidemic curve for Canada remains (Figure 1B). Community-level epidemics peaked from early November to mid-April, and even within a single season, the range in timing of the community-level peaks varied from 5 to 13 weeks across Canada. In contrast, aligning epidemic curves for each CMA before aggregating to the national level produced remarkably consistent composite epidemic curves for each dominant A season (Figure 1C). It is noted that the epidemic midpoint aligns with the epidemic peak. In the Canadian data, CMA-level and provincial-level composite epidemic curves were similar in shape (Figure 2A). As it was presumed that influenza would spread faster in large urban centres than across the broader rural areas, consisting of many smaller communities combined, the composite epidemic curve created for the rural areas (rest of the province) was expected to be much broader than the composite epidemic curve for CMAs only. However, as shown in Figure 2B, the composite epidemic curves for CMAs and CAs with at least 50 laboratory-confirmed cases over the season were similar to the provincial-level composite for the rest of the province. Figure 2C provides confirmation that transmission patterns can be similar for large urban centres and neighbouring rural areas during a single season. In this figure, the epidemic curves for the 2003/2004 A/Fujian/411/02 season for the two CMAs in the province of Alberta (Edmonton and Calgary) are compared with the epidemic curve for the rest of the province, showing both the level of synchronization as well as the similarity in shape. The composite epidemic pattern was also remarkably similar for Canada, the United States and Europe (Figure 2D).
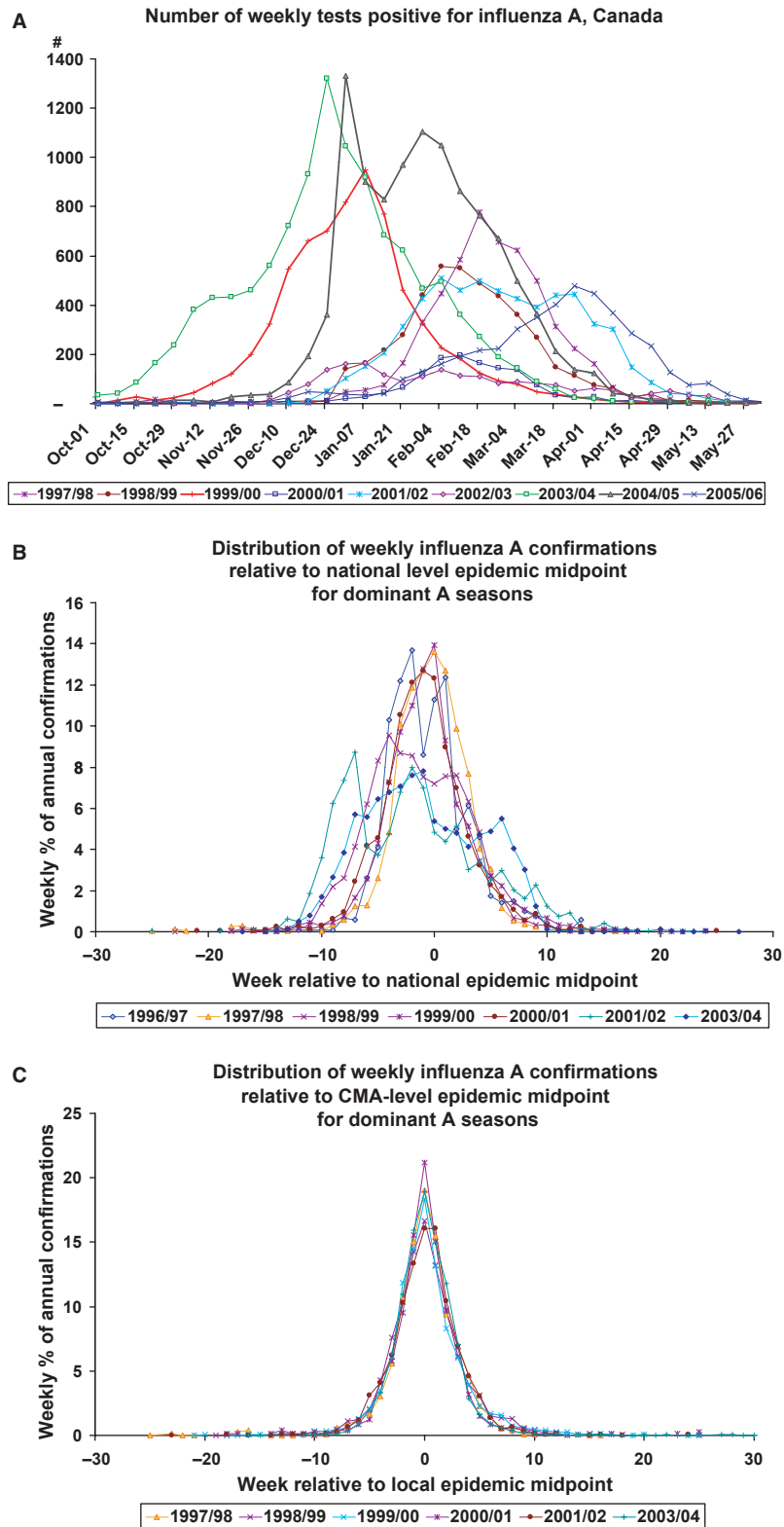
A

Number of weekly tests positive for influenza A, Canada

B

Distribution of weekly influenza A confirmations relative to national level epidemic midpoint for dominant A seasons

C

Distribution of weekly influenza A confirmations relative to CMA-level epidemic midpoint for dominant A seasons

Figure 1. (A) Number of Weekly Tests Positive for Influenza A, Canada. The variation in influenza epidemics and irregularity in influenza A epidemics at the national level is seen in this figure. (B) Distribution of weekly influenza A confirmations for Canada relative to the national-level epidemic midpoint, for seasons where at least 80% of influenza-positive specimens were antigenically similar. Variation in the shape of the national-level epidemics remains after centring the national-level epidemics by their midpoint. (C) Distribution of weekly influenza A confirmations relative to the census metropolitan area (CMA)–level epidemic midpoint for dominant A seasons. Epidemic curves for CMAs aligned by the CMA-level epidemic peak show remarkable consistency. Influenza epidemics, as viewed at the city level, follow a simple epidemic curve, the shape of which is remarkably consistent from year to year.

For large urban centres (CMAs) that reported more than 50 laboratory-confirmed cases of influenza A in a season where a single influenza A strain dominated, 50% of the confirmed cases occurred within a 4- to 5- week period centred around the epidemic midpoint; 90% within 9–13 weeks; and 98% within 12–22 weeks, where the given
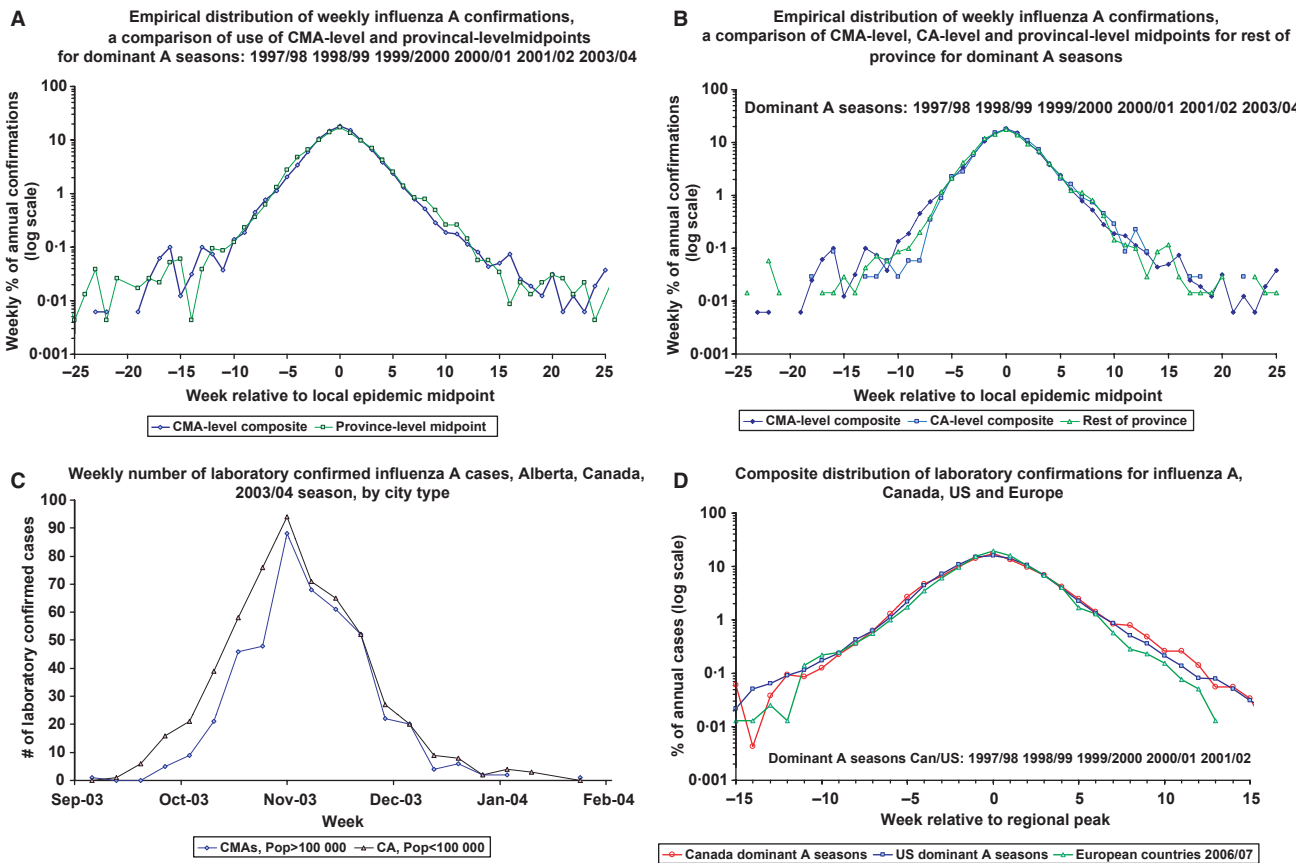
Figure 2. (A) Empirical distribution of weekly influenza A confirmations, a comparison of the use of census metropolitan area (CMA)–level and provincial-level midpoints. The composite epidemic curves constructed at two different geographical scales (CMA and province) were remarkably similar. Notice as well the long pre- and post-epidemic periods. (B) Empirical distribution of weekly influenza A confirmations, a comparison of the CMA-level, CA-level and provincial-level midpoints for the rest of the province. The composite epidemic curves for CMAs and CAs with at least 50 laboratory-confirmed cases over the season were similar to the provincial-level composite for the rest of the province, with epidemics growing slightly faster in communities with a population under 100 000 (CA) than for the larger CMAs (population over 100 000 persons). (C) Weekly number of laboratory confirmed influenza A cases, Alberta, Canada, 2003/2004 season, by city type. The epidemic curves, by calendar date, for the two CMAs in Alberta (Edmonton and Calgary) and the many smaller towns are remarkably similar. While for some of the smaller towns, the epidemic likely peaked weeks earlier or later than the provincial average, this figure for the 2003/2004 season in which most influenza A–positive specimens were antigenically similar to A/Fujian/411/02 (H3N2), illustrates that transmission rates can be similar for large urban centres and for regions consisting of smaller towns and rural areas. (D) Composite distribution of laboratory confirmations for influenza A, Canada, the United States and Europe. The composite epidemic curve for Canada is similar to the composite epidemic curve for the United States and Europe.

ranges correspond to the first and third quartile (for example, 90% of the confirmed cases for each season occurred within 9–13 weeks in 50% of the 139 CMA-level seasonal epidemics). For CAs, the epidemic period was slightly shorter at 3–4 weeks, 7–9 weeks, 9–13 weeks, respectively, whereas, when cases were combined at the provincial level, 50% of the confirmed cases occurred within 4–6 weeks; 90% within 10–14 weeks; and 98% within 15–24 weeks.

At the CMA level, the exponential growth phase extended from approximately week -10 to week -2 relative to the epidemic midpoint. New cases increased by a factor of 1·73 per week (95% CI 1·67, 1·78), or doubling every 8–9 days in seasons where at least 80% of the influenza A–positive specimens were antigenically similar (a growth

factor of $r = 1\cdot73$ means that the number of cases will increase by a factor of 1·73 each week during the exponential growth period. This is equivalent to a weekly growth rate of $\rho = \ln(r)$ or a rate of exponential growth rate of 0·55 cases per week). In smaller communities, the rate of growth was slightly higher, increasing by a factor of 1·9 (95% CI 1·5, 2·3) per week (corresponding to the composite epidemic curve illustrated in Figure 2B). As only a few CAs confirmed more than 50 cases in a season, laboratory-confirmed cases for the many small communities that had fewer than 50 cases each were combined into a 'rest of province' category. The resulting epidemic growth was similar at 1·9 (95% CI 1·8, 2·0) per week (Figure 2B).

Table 2. Sample epidemic progression for seasonal influenza A in a community of 1 million

Epidemic phase	Description	Week relative to peak	Approximate # of new infections	# of confirmed cases
Pre-epidemic	A number of imported cases, some clusters die out			
Epidemic start		−10	A couple hundred per week	(only in composite)
Epidemic detection	Early cases	−6 to −4	5000 per week	10 per week
Epidemic growth	Cases double nearly every week	−10 to −3		
Peak		−2 to 2	50% of infections	50% of confirmed cases
Epidemic decline	The number of new cases declines exponentially because of a depletion of the number of persons still susceptible	3 to 10		
Total infections		−10 to 10	100 000	200

1 Assuming a 10% clinical attack rate and that 2 out of 1000 infections are laboratory confirmed.

Given the stochastic nature of epidemics, we would expect considerable variability in the time from the first imported case to the epidemic peak and some uncertainty in identifying the actual epidemic start date. The composite epidemic curves suggest that the exponential growth starts approximately 10 weeks prior to peak in larger urban centres; though, the number of cases is still small at this point, perhaps a couple hundred cases per week per city of 1 million. Detection of influenza activity is more likely to occur around 5 weeks before the peak, at which point the number of cases has increased to approximately 5% of the epidemic total. This conversion of laboratory-confirmed cases into an estimate of the actual number of new infections per week based on the assumption of a 10% clinical attack rate in a city of 1 million people is presented in Table 2.

At the provincial level, the epidemic increased by a factor of 1·77 per week (95% CI 1·72, 1·80), ranging from 1·5 to 2·0 with statistically significant differences for seasons and regions (the Poisson regression model was adapted to include effects for season and region). For American regions, the corresponding growth factor was 1·82 (95% CI 1·8, 1·84) per week.

In the Canadian data, differences in the epidemic growth rate were most strongly associated with the month of the epidemic peak (P-value <0·0001). In the American data, the epidemic growth rate was not associated with the month of the epidemic peak (P-value 0·09) but was associated with the emergence of a new antigenic strain (growth factor of 2·1 per week in the first wave versus 1·6 per week for subsequent waves, Figure 3), and possibly sub-type, although the number of laboratory-confirmed cases during the H1N1 season were limited.

Displaying composite epidemic curves by the month of epidemic peak shows sustained transmission from mid-September through to early June, with epidemics peaking in November through to March. The number of laboratory-confirmed cases for April peaking epidemics was limited, resulting in an irregular epidemic curve for April (Figure 4). Transmission rates appeared slower in epidemics/regions that peaked later in the season with a significant trend primarily for Canada (Figure 5A). Transmission by calendar week shows a similar pattern (Figure 5B) in the Canadian and American data. The downward trend in transmission rates is statistically significant (P-value = 0·004); though, calendar week may not be the only factor influencing observed trend.

Discussion

We were able to combine laboratory-confirmed cases from different seasons or regions to illustrate that epidemics resulting from a single antigenic influenza A strain, follow a reasonably predictable period of epidemic growth, followed by a period of peak activity and then epidemic decline. The resulting composite epidemic curve showed that exponential growth occurred over a longer period of time than was identifiable using excess deaths or hospital admissions associated with pneumonia and influenza.[30] The composite epidemic curves for Canada, United States and European countries were remarkably similar. Further research is needed to elicit more subtle differences. The epidemic period for influenza A at the city level appears to last approximately 20 weeks with 50% of the cases occurring with a 4- to 5- week period of peak activity. Influenza seasonality is often identified by its period of peak activity (usually winter months of January and February in Canada and the United States); however, the composite epidemic curves suggest that influenza A epidemics start to build at least 10 weeks earlier. An epidemic that peaks in January
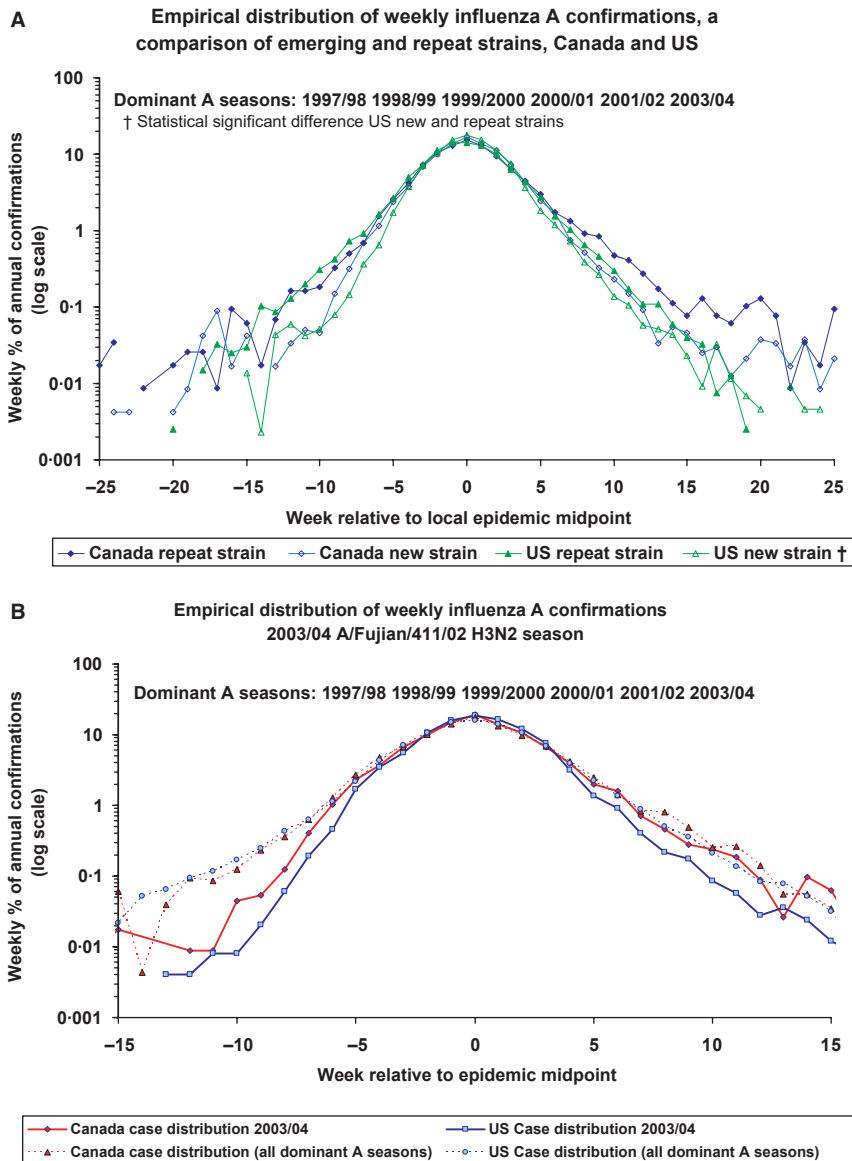
A

Empirical distribution of weekly influenza A confirmations, a comparison of emerging and repeat strains, Canada and US

Dominant A seasons: 1997/98 1998/99 1999/2000 2000/01 2001/02 2003/04
† Statistical significant difference US new and repeat strains

Weekly % of annual confirmations (log scale)

Week relative to local epidemic midpoint

→ Canada repeat strain   → Canada new strain   → US repeat strain   → US new strain †

B

Empirical distribution of weekly influenza A confirmations 2003/04 A/Fujian/411/02 H3N2 season

Dominant A seasons: 1997/98 1998/99 1999/2000 2000/01 2001/02 2003/04

Weekly % of annual confirmations (log scale)

Week relative to epidemic midpoint

→ Canada case distribution 2003/04   → US Case distribution 2003/04
→ Canada case distribution (all dominant A seasons)   → US Case distribution (all dominant A seasons)

Figure 3. (A) Empirical distribution of weekly influenza A confirmations, a comparison of emerging and repeat strains for Canada and the United States. The faster epidemic growth in the very early period of the epidemic growth phase shown to be associated with the emergence of a new antigenic strain in the US data may have been influenced by other confounding factors such as the presence of co-circulating strains during the period of early growth. (B) Empirical distribution of weekly influenza A confirmations, A/Fujian/411/02 2003/2004 H3N2 season. The faster epidemic growth was a characteristic of the A/Fujian/411/02 2003/2004 season.

would therefore have already been established by the end of October.

Epidemic peaks occurred from November through to April in Canada over the study period, providing evidence of sustained transmission (during the periods of epidemic growth or decline) from mid-September to early June. The seasonality of influenza epidemics in temperate climates has not been fully explained[16]; though, we saw some evidence that transmission rates may be slightly higher earlier in the season, which has been suggested as a possible explanation for the seasonality of influenza.[31] We explored trends in transmission rates by calendar time, and both testing and transmission rates appeared to be consistent through the Christmas holiday period when school is not in session and many people are away from work. Increased

surveillance activity early in the epidemic was not evident, though remains a possibility. Testing patterns at the community level seem to have been consistent throughout the season. While the provincial-level and city-level composite epidemic curves were similar, a lack of synchronization at the sub-provincial level has been observed, and surveillance at a finer geographical scale would be helpful to better assess the level of local influenza activity.

As antigenic drift is thought to be a result of immunological pressure, and vaccines may be mismatched in the first season of a new antigenic strain[16], it has been suggested that transmissibility would be highest in the first season of a new antigenic strain. This hypothesis is supported by the studies of the three 1918 pandemic waves in Europe which show a clear slowing of transmission rates

Composite epidemic curve by month of epidemic midpoint

Figure 4. Composite epidemic curve for Canadian provinces grouped by the month of epidemic midpoint. These composite epidemic curves by the month of epidemic midpoint show evidence of sustained transmission ranging from mid-September to the end of May. The number of confirmed cases for April peaking epidemics is limited, hence the irregular shape to the curve (random variation).
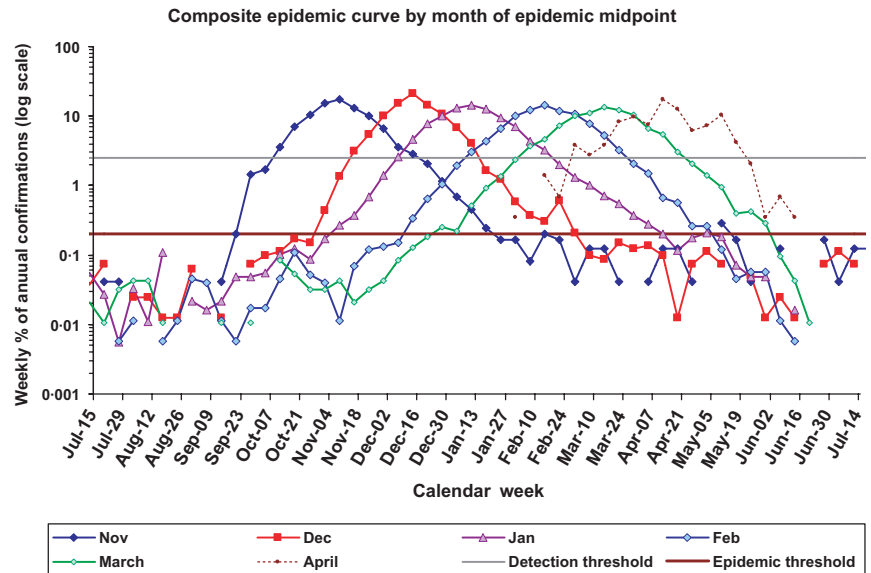
between the first and subsequent waves[32,33] and a study of illness from army camps that provides evidence that infection during the spring wave provided substantial cross-protection during the more severe fall wave.[34] Chowell and colleagues[30] using excess pneumonia and influenza (P&I) deaths in the United States, France and Australia as a proxy for influenza cases did not detect a difference in R_0 between first and subsequent waves of the same antigenic strain of seasonal influenza. From our data, the effect of the emergence of a new antigenic strain was small, with some evidence that transmission rates may be slightly higher when a new antigenic strain emerges.

The main limitation of the approach we used to study influenza epidemics is that various influenza A strains routinely co-circulate and strain characterization is not routine. In seasons with more than one A strain or subtype circulating, as the waves are unlikely to be synchronized, and because we could not identify cases resulting from the different A strains, it was not possible to properly align the epidemic curves. Particularly if the more dominant strain emerges later in the season, the apparent growth rate of the combined influenza A epidemic curve will be dampened once the epidemic resulting from the first strain starts to peak. Hence, an estimate of transmission rates associated with mixed seasons was not possible with this approach, limiting our analysis to six seasons where at least 80% of the influenza A–positive specimens characterized were antigenically similar. As a result, differences in epidemic growth rates, while statistically significant, may be a result of confounding factors or the influence of a particular season. For example, the epidemic growth rate was initially higher in the A/Fujian/411/02 2003/2004 season (Figure 3B) and it remains unclear whether the rapid increase

in the early growth period of the 2003/2004 A/Fujian/411/02 season can be attributed to the lack of other co-circulating influenza A strains, to the novelty of the antigenic strain (A/Fujian/411/02) or to the early emergence of this strain (the A/Fujian/411/02 strain was responsible for the November peaks).

The differences in the exponential growth rates seen in the Canadian data could suggest that transmission rates are higher in the fall than winter, but this seasonal trend is less evident in the US data. The US data suggest that the emergence of a new antigenic strain is more important; though, this observation is primarily a result of differences in the 1997/1998 A/Sydney/05097 season which emerged 5 weeks earlier in the United States than in Canada. We note, however, that these differences were small and translate into a small difference in susceptibility based on SEIR model calculations of R_0 (Yan's[28] C11 formula suggests that for a latent period of 1·4 days and infectious period of 4 days a difference in the susceptibility of 6% would account for a reduction in epidemic growth factor from 1·8 to 1·6, while a 20% reduction in susceptibility would drop the epidemic growth factor from 1·8 to 1·25.) The population is not homogeneous and other factors likely account for some of this difference. Clearly, we are not seeing large differences in susceptibility from season to season, at least not in seasons where one strain dominates. For comparison purposes, the epidemic growth factor for influenza B and respiratory syncytial virus (RSV) are noted, 1·6 (95%CI 1·53–1·65) and 1·27 (95% CI 1·26–1·28), respectively (based on a similar analysis of the RVDSS provincial-level data for these viruses).

The 2009 influenza A H1N1 pandemic drew the attention of public health to our current influenza surveillance
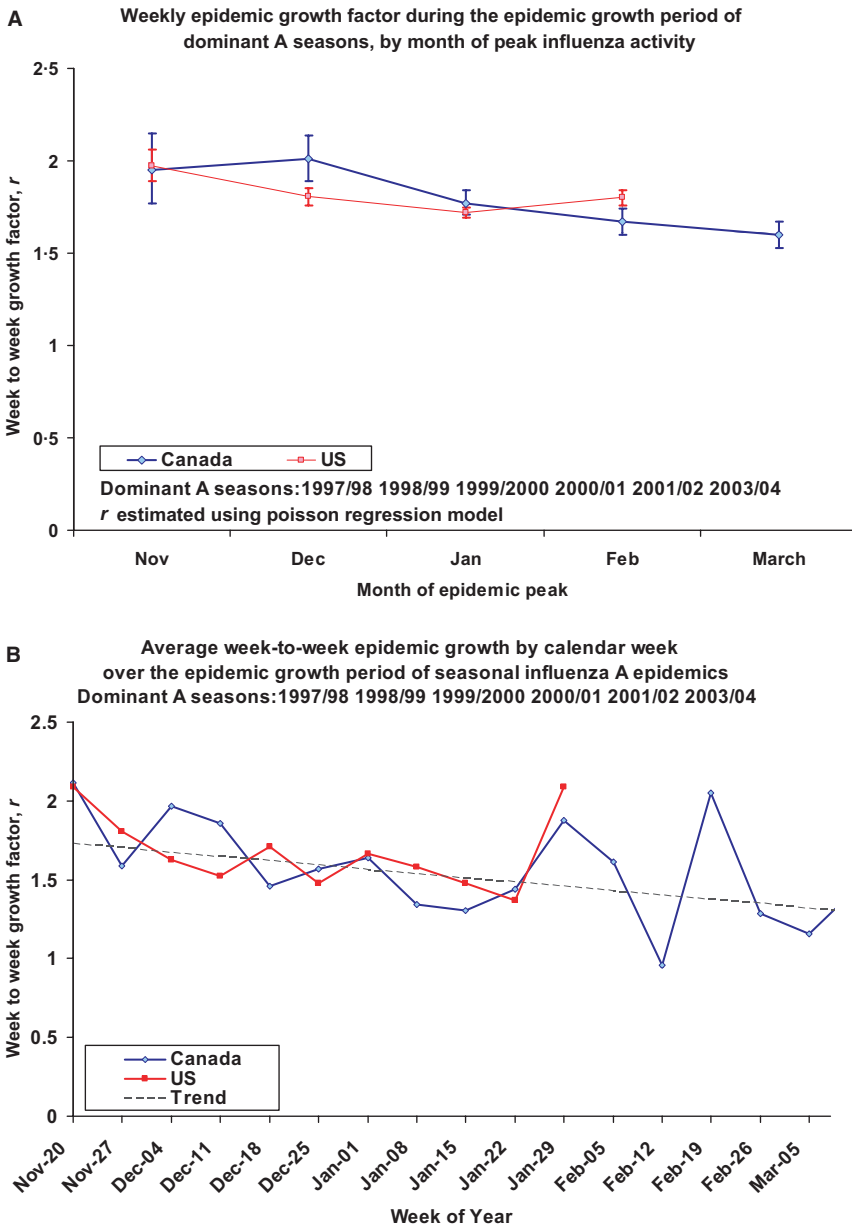
A

Weekly epidemic growth factor during the epidemic growth period of dominant A seasons, by month of peak influenza activity

B

Average week-to-week epidemic growth by calendar week over the epidemic growth period of seasonal influenza A epidemics
Dominant A seasons:1997/98 1998/99 1999/2000 2000/01 2001/02 2003/04

Figure 5. (A) Weekly epidemic growth factor during the epidemic growth period, by month of peak influenza activity. The weekly epidemic growth factor was estimated by fitting a log-linear trend to the epidemic growth period (weeks -8 to -3) of the composite epidemic curve corresponding to the month of peak activity. (B) Average Week-to-Week Epidemic Growth Factor over the Epidemic Growth Period of Seasonal Influenza A Epidemics. The weekly epidemic growth factor for this figure was calculated as the ratio of the number of laboratory-confirmed cases in week *w* over week *w*-1, where week *w* is at least 2 weeks before the regional peak. Only dominant A seasons were included. This figure shows little change in transmission over the two-week Christmas period when schools are closed, but children and adults socialized, and a slight decline from November to January.

system. Current indicators of influenza activity vary in their sensitivity and specificity to influenza, their timeliness, their geographical scale, detection rate and representativeness both spatially and temporally. As we move forward with a review of our influenza surveillance needs, all these issues will need to be considered. Approaches to surveillance and methods to summarize the level and extent of influenza activity vary internationally. Some of this methods may be suitable in the Canadian context. More systematic laboratory confirmation will likely play an increasing role in our understanding of influenza epidemics as well as in the further development of methods to summarize influenza activity. Validation of infectious disease models against the

empirical data should facilitate improved planning and better assessment of the effectiveness of interventions. As methods to estimate R_0 are still somewhat controversial, modellers would benefit from access to international data at an appropriate geographical scale and over many influenza seasons so that multiple epidemic waves could be studied using a single method. There is still a significant random or unexplained component to influenza waves. Had the composite epidemic curve had a significantly different shape, even estimation of the epidemic growth rate would have been questionable, perhaps suggesting the need for more complex agent-based models to account for non-homogeneous mixing, an approach that many modellers

use. Low detection rates have likely influenced our impressions of community-level activity as well. While influenza epidemics waves at the community level appear to behave in a manor consistent with theoretical models, the degree of asynchronization between communities within a geographical reporting unit may vary from season to season, and this geographical variation will still pose a challenge to the interpretation of surveillance data in real time.

The technique of aligning epidemics locally as part of the analytical process was essential to the analysis of the influenza surveillance data presented in this study. Based on the success of the alignment process used in this study, we will explore the geographical patterns at a fine spatial scale. Beyond the analysis presented here, the composite epidemic curve itself has been a helpful tool in identifying small age-specific differences in the timing of infections, and we continue to develop opportunities to assess the effects of interventions on the epidemic growth rate.

Acknowledgements

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