

Invasive bacterial infections following influenza: a time-series analysis in Montréal, Canada, 1996–2008

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Background Shared seasonal patterns, such as between influenza and some respiratory bacterial infections, can create associations between phenomena not causally related.

Objectives To estimate the association of influenza with subsequent bacterial infections after full adjustment for confounding by seasonal and long-term trends.

Methods Time series of weekly counts of notified cases of invasive infections with *Haemophilus influenzae*, *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Streptococcus pyogenes*, in Montréal, Canada, 1996–2008, were modelled by negative binomial regression, with terms representing seasonal and long-term trends and terms for numbers of positive laboratory tests for influenza A and B.

Results The associations of *S. pneumoniae*, *H. influenzae* and *N. meningitidis* with influenza disappeared after seasonal terms

were added to the model. However, the influenza B count remained associated with the *S. pyogenes* counts for the same week and the following week: *S. pyogenes* incidence rate ratios were 1.0376 (95% CI: 1.0009–1.0757) and 1.0354 (0.9958–1.0766), respectively, for each increase of 1 in the influenza count.

Conclusions Influenza B accounts for about 8% of the incidence of invasive *S. pyogenes* infections, over and above any effect associated with modellable seasonal and long-term trends. This association of influenza B with *S. pyogenes* infections can be attributed largely to the years 1997, 2001, 2007 and 2008, when late peaks in influenza B counts were followed by peaks in *S. pyogenes* notifications. This finding reinforces the case for universal immunization against influenza, as partial protection against the ‘flesh eating disease’.

Keywords Bacterial infections, incidence, influenza.

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At the time of the 1889 influenza pandemic, there was still much uncertainty about the disease being infectious¹ but after the discovery of *Haemophilus influenzae* by Pfeiffer in 1892, the belief in its bacterial aetiology became widespread.² However, invasive bacterial infections have been recognized as complications of influenza at least since the 1918 pandemic^{3,4} when some, like Goodpasture, believed the disease itself to be ‘caused by an unknown virus’.⁵ Bacteria were well confirmed as secondary invaders by the 1930s.⁶

The association between viral and subsequent bacterial infections result from a great variety of mechanisms, including the breakdown of physical barriers, increased bacterial adhesion, increased apoptosis of antibacterial immune cells and decreased phagocytosis by alveolar macrophages.⁷ Specifically, there is evidence that the hemagglutinin of the influenza virus promotes the internalization

Streptococcus pyogenes (group A beta-haemolytic streptococci)⁸ and that the neuraminidase promotes the adherence of *Streptococcus pneumoniae* to human respiratory cells.⁹

At a population level, over several decades and in various populations, strong and consistent associations have been found between influenza and secondary pneumonia caused by *Staphylococcus aureus*, *S. pneumoniae*, *Neisseria meningitidis*,¹⁰ *S. pyogenes* and *Hemophilus influenzae*,^{10,11} and also with mortality. This applies to seasonal^{16,12} and pandemic¹⁰ influenza A, including the 2009 pH1N1 strain,¹³ and to influenza B.⁶ About 95% of deaths associated with influenza are considered to be caused by secondary bacterial pneumonia, the susceptibility to which is thought to peak 1–2 weeks after exposure to influenza.^{11,14} However, the peak may be later for pneumococcal infections, up to 4 weeks in adults and 8 weeks in children.¹⁵

The seasonality of transmissible diseases may be due to the following factors: (i) changes in host susceptibility, possibly related to light–dark cycles or photoperiodicity^{12,16–19} and to melatonin production^{16,20}; (ii) latitude,^{16,19} solar radiation,²¹ humidity^{19,22} and temperature^{19,23}; (iii) air pollution²³; (iv) crowding of susceptible hosts^{16,23}; and (v) the circulation of other, predisposing or triggering, infectious agents.¹⁷ To what extent any of the above actually causes seasonal variations in the incidence of a given transmissible disease, or is merely a confounder,^{16,19,23,24} lies at the heart of the seasonality problem.

Seasonality has been studied mostly by (i) aggregating data by season,¹² (ii) by modelling time series of numbers of cases using regression or autoregression^{17,25} or Poisson models with terms representing seasonal and secular trends,²⁶ or (iii) by dynamic (compartmental, SEIR) modelling.^{19,24,27} Conformity of the observations to the seasonal pattern expected on the basis of such models tells us little about the processes behind the pattern, there being so many synchronous processes whose effects are jointly subsumed under the seasonal model terms. However, *non-systematic deviations* of the observations from the predicted pattern may be easier to associate with a particular cause.¹⁸

Our goal in the present study was therefore twofold. First, to model the reported incidence of four invasive bacterial infections, those caused by *S. pneumoniae*, *S. pyogenes*, *H. influenzae* and *N. meningitidis*, as functions of earlier numbers of positive tests for influenza A and B. Second, in doing so, to represent as fully as possible seasonality and long-term trends in the reported incidences of bacterial infections by means of dedicated model terms, leaving only the remaining variance to be explained by earlier numbers of positive influenza tests.

Methods

We studied all laboratory-confirmed cases of invasive *S. pneumoniae*, *S. pyogenes*, *H. influenzae* and *N. meningitidis* infection among residents of Montréal, Canada, notified to the Public Health Department of the Montréal Health and Social Services Agency between 1 January 1996 and 7 June 2008 (with the exception of *S. pneumoniae*, whose notification began on January 5, 1997). The notifications of each infection were aggregated into weekly case counts. Numbers of positive influenza A and B test results for residents of Montréal during the same period were provided by the Québec Public Health Laboratory from a sentinel laboratory surveillance network database and were similarly aggregated into weekly influenza A or B counts. The number of hospital laboratories in the sentinel network varied from six in 1996 to seven in 2008, with a stable core of five laboratories throughout the study period. Testing practices

changed after the introduction of commercial rapid tests in 1996 and after improvement in the access to antiviral drugs, contributing to an overall increase in the total number of positive results.

A binary indicator variable (short work week) was created to identify weeks that include fewer than five working days, when fewer notifications are to be expected, because non-emergency medical care is less accessible or notification is delayed. About 6 weeks per year include other holidays that were not taken into account because their dates vary from year to year and could not be recovered.

Descriptive analyses used frequency distribution histograms, correlation matrices and time series of counts. Modelling of the bacterial infection counts used multivariate negative binomial regression, rather than Poisson regression, because it does not require the variance of observations to be equal to their mean. The parameters β_i of the models are most easily understood after transformation into incidence rate ratios (IRR). The IRR for any predictor x_i is equal to e^{β_i} ; it represents the ratio of the expected value of the count when x_i is in the model over its expected value when x_i is not in the model. If x_i is an influenza count, the IRR is the ratio of the risk associated with a count of $x_i + 1$ compared to the risk for a count of x_i ; the IRR for a count of $x_i + n$ compared to x_i is IRR^n .

Overall trends in the time series of counts were accounted for by including in the model restricted cubic spline terms to remove long-term (secular) trends, and sine-cosine (periodic) terms to remove seasonal trends.²⁸ The restricted cubic spline function used had six knots²⁹ and therefore five parameters,³⁰ referred to as spline1–spline5. The small number of knots was chosen so that the spline terms would reflect only the long-time trends, while the periods for the sine-cosine terms were 1 year, plus the first five harmonics (1/2 year, 1/3, 1/4, 1/5, 1/6) to account for seasonality and any <1 year periodicities. Periodic terms had the forms $\sin(xt)$ and $\cos(xt)$, where $x = 1$ to 6 and $t = (2\pi \times \text{week number} \times 12.438)/649$; the week number ranged from 1 to 649, representing 12.438 years, the length of our time series of counts.

Comparisons of the overall closeness-of-fit of nested models (all the terms in the smaller model being included in the larger model) used the deviance ($-2 \times$ difference between log-likelihoods), tested by chi-square. The deviance served as an overall test of whether a model including a set of terms (for instance the influenza counts) is statistically superior to the same model without these terms.

As any effect of influenza on the risk of subsequent bacterial infections should occur within a few weeks,^{11,14,15} and relying on preliminary results, we decided to estimate the effects on the bacterial infection counts for any given week (called week 0) of influenza counts for the same week and for the five preceding weeks (called weeks -1 to -5).

All analyses were carried out with Stata 10.1 (Stata Corp., Cary, NC, USA). The data used are all publicly available aggregate surveillance results, and no ethical review was required.

Results

During the study period, there were 3027 positive tests for influenza A, with a mean weekly count of 4.664 (range 0–85) and 745 positive tests for influenza B (mean: 1.148, range 0–33). There were 107 infections caused by *H. influenzae* (mean: 0.165, variance: 0.212), 156 by *N. meningitidis* (mean: 0.240, var.: 0.248), 2920 by *S. pneumoniae* (over the last 596 weeks, mean: 4.899, var.: 11.190) and 667 by *S. pyogenes* (mean 1.028, var.: 1.292). Weekly bacterial infection counts were roughly Poisson distributed, but variances being consistently larger than means justified the choice of negative binomial regression.

The time series of influenza A and B counts (Figure 1) shows that type B varies proportionately more from year to year than type A and usually peaks some weeks later. The smoothed *N. meningitidis* and *H. influenzae* counts (Figure 2) show a seasonality that is irregular in period and amplitude; in addition, *H. influenzae* counts increased markedly between 2003 and 2004, when all invasive *H. influenzae* infections became reportable, not only those of type B. The smoothed *S. pneumoniae* and *S. pyogenes* counts (Figure 3) show yearly peaks that are particularly marked for *S. pneumoniae*; however, the peaks are not synchronous, those for *S. pyogenes* tending to occur later in the year.

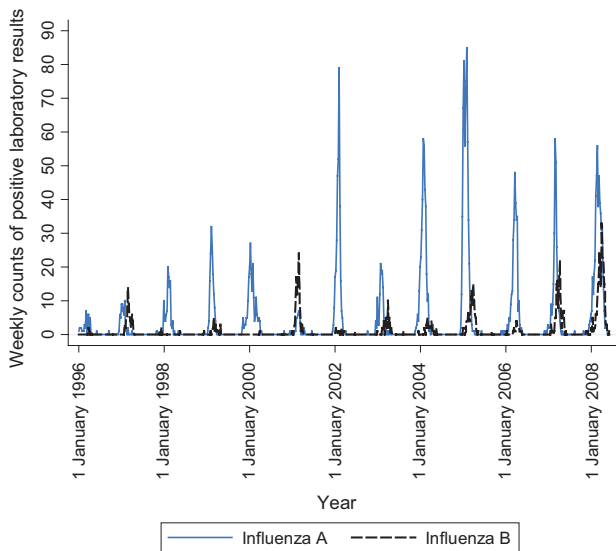


Figure 1. Time series of weekly numbers of positive tests for influenza A and B, Montréal, 1996–2008.

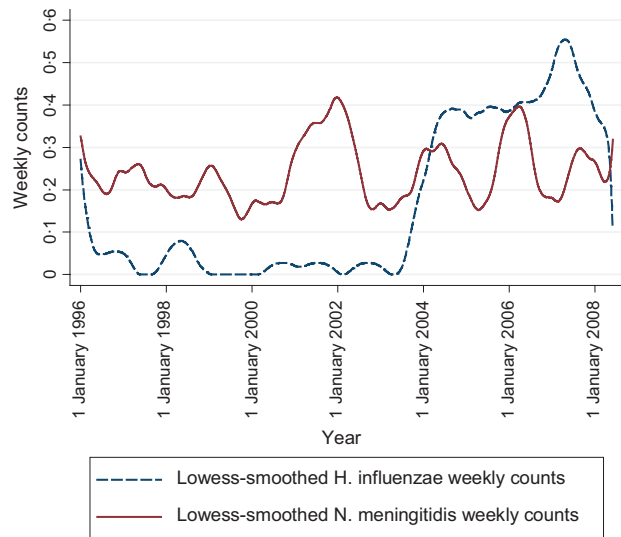


Figure 2. Time series of weekly numbers of notified cases of *Haemophilus influenzae* and *Neisseria meningitidis* infections, Montréal, 1996–2008.

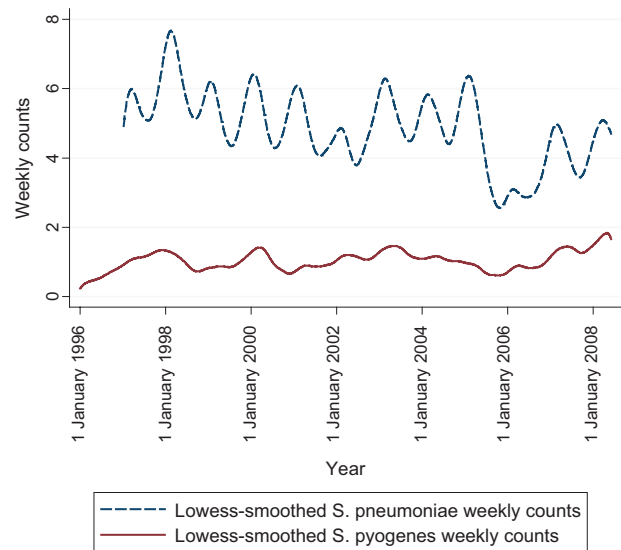


Figure 3. Time series of weekly numbers of notified cases of *Streptococcus pneumoniae* and *Streptococcus pyogenes* infections, Montréal, 1996–2008.

Correlations between weekly influenza counts and later bacterial counts were generally high, as expected (results not shown), but the corresponding IRR adjusted for short work weeks, long-term and seasonal trends, in Table 1, show much weaker associations. Only two IRR, between influenza B and subsequent *S. pyogenes* infections, approach significance.

The full model for influenza B and *S. pyogenes*, in Table 2, shows several effects, all adjusted for each other.

Table 1. Incidence rate ratios (IRR) between each of the bacterial infection counts for a given week (week 0) and the influenza A and B counts for weeks 0 to -5. Negative binomial models including influenza A and B counts, plus the short work week, long-term and seasonal terms (not shown)

Independent variables		Dependent variables			
Influenza type	Week	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pyogenes</i>	<i>Haemophilus influenzae</i>	<i>Neisseria meningitidis</i>
A	0	1.0052*	1.0114	0.9850	0.9937
	-1	0.9963	0.9882	1.0290	0.9994
	-2	1.0083	1.0068	0.9768	1.0039
	-3	0.9924	1.0118	0.9894	1.0053
	-4	1.0022	0.9836	1.0288	0.9782
	-5	1.0015	1.0075	0.9781	1.0006
B	0	1.0060	1.0376 ^a	0.9344	0.9660
	-1	1.0080	1.0354 ^b	1.0228	1.0195
	-2	1.0034	0.9753	1.0123	0.9726
	-3	1.0056	0.9808	1.0001	0.9069 ^c
	-4	0.9860	0.9875	1.0233	1.0908 ^d
	-5	1.0102	0.9998	0.9930	1.0143
Number of weeks		596	644	644	644

*The probability associated with the IRR is >0.05 unless indicated in a footnote. $n = 644$. The first 5 weeks are excluded from the analysis, as influenza counts for earlier weeks up to -5 are unavailable for them.

^a $P = 0.045$; ^b $P = 0.080$; ^c $P = 0.093$; ^d $P = 0.051$.

(i) Short work weeks are associated with a 27% decrease $[(1-0.7337)*100]$ in *S. pyogenes* notifications. (ii) The large coefficient for $\text{sin}t$ reflects the yearly notification peaks, but there is also a weaker six-monthly ($\text{cosine}2$) and two-monthly ($\text{cosine}6$) periodicity. (iii) All the long-term-trend terms are highly significant. (iv) Influenza B counts for a given week (week 0) are associated with increases in *S. pyogenes* notifications in the same week and in the following one (weeks 0 and +1), of about 3.8% $[(1.0376-1)*100]$ and 3.5% $[(1.0354-1)*100]$ per additional positive influenza B test, respectively. They are also associated, although not statistically significantly, with decreases in *S. pyogenes* notifications in weeks +2 to +5. These two phenomena together are suggestive of 'harvesting'^{31,32}: at least some of the *S. pyogenes* infections following influenza B would have occurred even without influenza, but a few weeks later, having merely been brought forward in time by influenza B. However, a model containing influenza B counts for all 6 weeks does not show a better fit than one containing only the counts for weeks 0 and -1 (deviance = 6.96, $P = 0.1381$), indicating that this apparent 'harvesting' of cases may well be in fact random variations in the parameters. (Note that the *N. meningitidis* terms marked c and d in Table 1, although large and almost significant, are in the wrong sequence for harvesting, which is why they are not reported as a finding.)

The comparison of observed and expected *S. pyogenes* counts before and after influenza counts are added to the

model (Figures 4 and 5) shows a visible improvement in fit. A comparison of the two dark lines shows that, with influenza B in the model, four transient increases in *S. pyogenes* infections are now modelled that were not before: those in 1997, 2001, 2007 and especially 2008. Looking back at the time series of influenza B counts (dark line in Figure 1), one notes that these were years with late, high peaks in the weekly numbers of influenza B-positive tests. An additional indication that this association may be causal is that the average age of known influenza B cases in these 4 years is significantly higher, 33.9 years, than in other years, 24.6 years ($P < 0.000$), and closer to the average ages of *S. pyogenes* cases, 45.9 years.

Comparisons of the closeness-of-fit of various nested models quantify rigorously the relative contributions of long-term trends, seasonal trends and influenza (Table 3). All infections except those caused by *N. meningitidis* display significant long-term trends (model 1), and both streptococcal infections also show significant seasonality (model 2). These findings confirm what has been observed in Figure 3. When long-term trends but not seasonality are controlled for (models 3 and 4), influenza A and B counts significantly improve the model fit for both streptococcal infections, but the improvement is greater for *S. pneumoniae* than for *S. pyogenes*. When seasonality is also controlled for by dedicated terms, however, the only effect remaining is that of influenza B counts on *S. pyogenes* counts, as mentioned earlier (models 5 and 6). This effect

Table 2. Full negative binomial regression model for the associations between *Streptococcus pyogenes* infection counts for a given week (week 0) and the influenza B counts for weeks 0 to -5*

Independent variable		Regression coefficient	95% CI of coefficient	IRR	95% CI of IRR
Short work week		–	–	0.7337	0.5547–0.9705
Seasonal trends					
	Sine1	0.3113	0.1758–0.4469	–	–
	Cosine1	–0.0646	–0.1824–0.0532	–	–
	Sine2	–0.0414	–0.1631–0.0804	–	–
	Cosine2	0.1464	0.0192–0.2736	–	–
	Sine3	0.0100	–0.1141–0.1341	–	–
	Cosine3	0.0546	–0.0618–0.1710	–	–
	Sine4	–0.0069	–0.1236–0.1098	–	–
	Cosine4	0.0223	–0.1039–0.1486	–	–
	Sine5	0.0340	–0.0820–0.1500	–	–
	Cosine5	0.0230	–0.0947–0.1407	–	–
	Sine6	–0.0166	–0.1297–0.0965	–	–
	Cosine6	0.1954	0.0758–0.3151	–	–
Long-term trends					
	Spline1	0.0071	0.0024–0.0117	–	–
	Spline2	–0.0654	–0.1064 to –0.0243	–	–
	Spline3	0.2113	0.0868–0.3359	–	–
	Spline4	–0.3157	–0.4843 to –0.1471	–	–
	Spline5	0.3303	0.1665–0.4941	–	–
Influenza B, week 0		–	–	1.0376	1.0009–1.0757
Influenza B, week -1		–	–	1.0354	0.9958–1.0766
Influenza B, week -2		–	–	0.9753	0.9346–1.0178
Influenza B, week -3		–	–	0.9808	0.9386–1.0249
Influenza B, week -4		–	–	0.9875	0.9440–1.0331
Influenza B, week -5		–	–	0.9998	0.9605–1.0408

*The regression coefficients and the bounds of their confidence intervals (CI) have been transformed into incidence rate ratios (IRR) when they are interpretable as such. $n = 644$. The first 5 weeks are excluded from the analysis, as influenza B counts for earlier weeks up to -5 are unavailable for them.

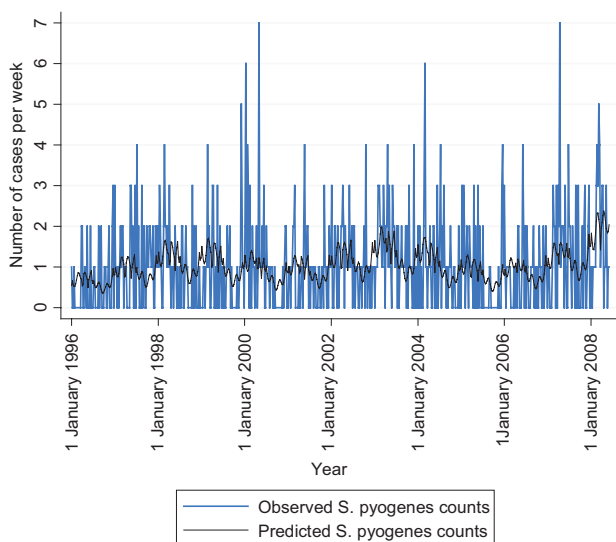


Figure 4. Time series of weekly *Streptococcus pyogenes* counts, observed and predicted by a binomial regression model including only short work week, seasonal and long-term trend terms, Montréal, 1996–2008.

remains essentially the same if one uses Poisson regression, includes earlier *S. pyogenes* counts in the model, splines with five or seven knots, or fewer harmonics for the periodic functions (results not shown).

Discussion

Associations between two phenomena that share a seasonal pattern are intrinsically difficult to interpret as causal because one can rarely exclude that they are both consequences of other phenomena displaying the same pattern (a form of confounding). Our analyses shows that such associations may well disappear once confounding by long-term or seasonal trends has been controlled. We submit that the associations that have resisted such control provide the clearest information about true effects, in the absence of data on specific confounders. This may be especially true if these associations can be attributed to particular deviations from the usual patterns, as observed in explaining the differences between Figures 4 and 5 by means of Figure 1. Our results illustrate that the opportunities provided by

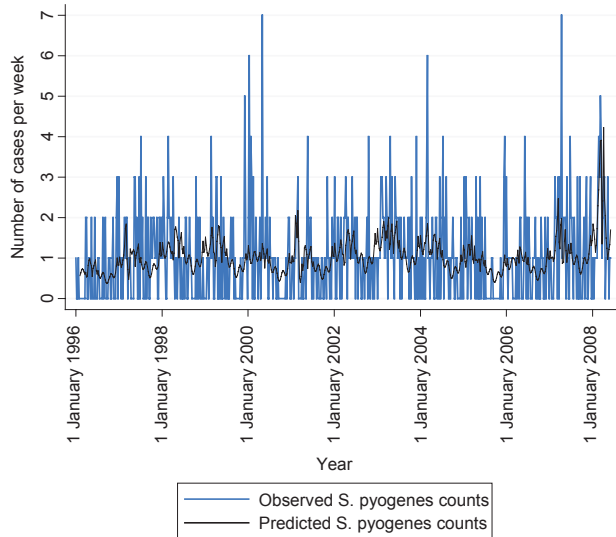


Figure 5. Time series of weekly *Streptococcus pyogenes* counts, observed and predicted from the full binomial regression model (as described in Table 2), Montréal, 1996–2008.

modelling aberrations are different from those provided by modelling regularities: in Table 2, had the observed seasonality of *S. pyogenes* always been that predicted by the seasonal trend terms, no IRR for influenza B would have emerged as significant.

The *S. pyogenes* count for any given week is multiplied by 1.0376 for each additional influenza B-positive test result that same week and by 1.0354 for the same increase

the preceding week (Table 1). The combined effect of both weeks is the product of these IRR, 1.0743. The average weekly influenza B count being 1.1479, its effect over these 2 weeks is to multiply the *S. pyogenes* case count by $1.0743^{1.1479} = 1.0858$, an 8.6% increase. With an average of 59 *S. pyogenes* cases per year in Montréal, this represents about five extra cases every year.

All the estimates in the previous paragraph are approximations, being valid only to the extent that numbers of positive influenza B tests are a constant proportion of all incident cases of the disease. The reported incidence of invasive bacterial infections better reflects their true incidence, especially for those caused by *N. meningitidis* and *S. pyogenes*, because of their severity and their requiring an urgent public health intervention.

Other limitations include delays in the measurement of the variables. Ideally, one would use time series of dates of acquisition of all infections under study. In reality, for influenza we had the dates when the specimens were taken, and for the bacterial infections the dates when notifications reached the public health department (as this is the only date we have for all notified cases). Thus, the effects observed over weeks 0 and -1 probably occurred after only a few days, because the median delay between onset of symptoms because of *S. pyogenes* infection and its notification is 6 days, in the 489 cases for which it is known.

Another limitation in estimating the effects of influenza is the lack of control for (i) confounding by other triggering factors for invasive *S. pyogenes* infections, such as varicella and respiratory syncytial virus infections, temperature

Table 3. Deviances between nested negative binomial models, with their probabilities*

Models	Deviance*, probability	Dependent variables			
		<i>Neisseria meningitidis</i>	<i>Haemophilus influenzae</i>	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pyogenes</i>
1 Long-term trends	From constant: pr =	6.16 0.4051	115.58 0	31.31 0.0000	18.28 0.0055
2 Long-term and seasonal trends	From model 1: pr =	9.90 0.6249	6.45 0.8905	230.91 0	41.19 0.0000
3 Long-term trends and influenza A	From model 1: pr =	0.72 0.9940	2.45 0.8739	49.57 0	17.72 0.0069
4 Long-term trends and influenza B	From model 1: pr =	6.64 0.3554	1.59 0.9536	26.35 0.001	19.83 0.0029
5 Long-term and seasonal trends and influenza A	From model 2: pr =	3.18 0.7863	3.60 0.7312	6.78 0.3412	7.01 0.3201
6 Long-term and seasonal trends and influenza B	From model 2: pr =	10.06 0.1221	2.39 0.8807	5.85 0.4405	13.56 0.0349

*Deviances were estimated using the last 596 weeks, when counts for all bacterial infections were available, including those due to *Streptococcus pneumoniae*. Those that are significant at the 0.05 level are in bold type.

or humidity levels, and (ii) the variations in predominant influenza B subtype or in vaccine formulation and uptake. Point ii) might explain why the 2005 influenza B peak was not followed by a *S. pyogenes* peak. Effect modification, especially by age, also remains to be investigated: because of our relatively small bacterial infection counts, an age-stratified analysis would have resulted in losing too much statistical power.

Finally, because we tried to model all trends, secular or periodic, as much as possible through dedicated terms, the absence of significant effects of influenza A, or of effects on other bacterial infections than those because of *S. pyogenes*, does not mean such effects do not exist. These effects may simply be so similar in strength and timing to the overall effects modelled by periodic and spline terms that their contributions are entirely subsumed by these terms.

Both types of influenza have been associated with secondary infections and an increased risk of mortality,³³ but the risk associated with type B has been less well documented than for type A. There are a few reports concerning the association of influenza B with unspecified or pneumococcal pneumonia, or other respiratory infections,^{34–38} fewer with *S. pyogenes* infections,^{39–41} and no attempt, to our knowledge, to quantify any of these associations.

The demonstration of a specific contribution of influenza B to the occurrence of invasive *S. pyogenes* infections, which include the widely feared ‘flesh eating disease’, reinforces the case for immunizing against influenza. There is already experimental evidence in mice that influenza A vaccine protects against *S. pyogenes* superinfection,⁴² and influenza immunization has been recommended as protection against bacterial superinfections in humans,¹⁴ including those caused by *S. pyogenes*.^{43,44} Our rough estimate of the proportion of *S. pyogenes* infections in the general population attributable to influenza B (8%) is understandably smaller than the 50–77% preventable by influenza immunization among army trainees,⁴⁵ among whom the infection pressure for both diseases is very high. Yet, its greater generalizability provides additional support for the recent recommendation to immunize all persons aged ≥ 6 months against influenza.⁴⁶ The ability of invasive *S. pyogenes* infections to cripple or kill previously healthy adults makes even partial protection against them an appreciable argument in the promotion of universal influenza vaccination.

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