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Predictions by early indicators of the time and height of yearly influenza outbreaks in Sweden

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Abstract

Aims: Methods for prediction of the peak of the influenza from early observations are suggested. These predictions can be used for planning purposes. *Methods*: In this study, new robust methods are described and applied on weekly Swedish data on influenza-like illness (ILI) and weekly laboratory diagnoses of influenza (LDI). Both simple and advanced rules for how to predict the time and height of the peak of LDI are suggested. The predictions are made using covariates calculated from data in early LDI reports. The simple rules are based on the observed LDI values while the advanced ones are based on smoothing by unimodal regression. The suggested predictors were evaluated by cross-validation and by application to the observed seasons. *Results:* The relation between ILI and LDI was investigated and it was found that the ILI variable is not a good proxy for the LDI variable. The advanced prediction rule regarding the time of the peak of LDI had a median error of 0.9 weeks, and the advanced prediction rule for the height of the peak had a median deviation of 28%. *Conclusions:* The statistical methods for predictions have practical usefulness.

Keywords **Prediction, Influenza, Outbreak**

Background

In this report we study how early observations from routine surveillance may be used for predicting characteristics of yearly influenza epidemics as measured by LDI. Surveillance of influenza is important since epidemics and pandemics may cause major problems both in health care and in society as a whole (1). To minimise the consequences of influenza activity, predictions that allow authorities to plan for adequate measures are of vital importance. Predictions of the time and height of the peak of an influenza outbreak are also useful for the possibility to forecast complications such as pneumonia and for planning how medical resources should be used. In one published study dealing with forecasting variables related to influenza incidence, the number of deaths due to pneumonia and influenza were predicted by univariate and multivariate ARIMA (autoregressive integrated moving averages) models (2). Time series techniques with long-range dependencies have also been used to estimate and forecast hospital admissions due to influenza in the UK (3). Despite these published studies, there is a present lack of useful epidemiological forecasts designed for public health authorities to predict the character of the current influenza season (4).

There is an obvious need to harmonise diagnostic procedures and surveillance systems in the European countries in order to get public health benefits and improve the validity and comparability of results (5). Harmonization can be done for example by sharing of reportable disease information and awareness of border-related epidemiology issues and by using similar definitions, reporting methods and methods of analysis. Influenza does not respect national borders, and early observations in one country may provide valuable information which could form the basis for action in others (5). Many international organisations and networks (for example the European Influenza Surveillance Scheme (EISS), European Groupes Régionaux d'Observation de la Grippe (EuroGROG), Flunet at the World Health Organization (WHO), Center for Disease Control (CDC) in Atlanta, and also commercially linked initiatives in the United States) have established influenza surveillance schemes. Normally these include the provision of weekly data on the percentage of patients with influenza-like illnesses (%ILI) and/or acute respiratory illness (ARI) seeking a general practitioner (GP) included in the sentinel system of the country in question (6, 7). Information on surveillance schemes is found at the respective web sites. Information on influenza surveillance in Sweden is found in the publications on the web site of the Swedish Institute for Infectious Disease Control (SMI) and has been described previously (www.smittskyddsinstitutet.se and (8)). The EISS is the European network where Sweden is included. According to its instructions, the sentinel physicians should be evenly spread over the country and the collection of patients treated by the sentinel physicians should include at least 1% of the population. The reports should be presented in relation to the total number of patients listed for the GP. The surveillance should also include laboratory data. Ideally, specimens should be analysed from a proportion of the patients seeking the sentinel physicians.

Sweden has had sentinel physicians since 1999 and established sentinel sampling in 2006. Since 1993, the laboratory monitoring of influenza has been based on reports from all Swedish laboratories providing laboratory diagnoses of influenza (LDI). Because of the structure of the health care system, which discourage

unnecessary visits, rather few patients in Sweden visit GPs (on average 1.3 visits to primary care per inhabitant in 2005, data not published), and the low frequency also applies to respiratory tract infections. The number of diagnoses reported by routine laboratories often exceeds the number of patients reported by sentinel physicians. The existing laboratory reporting in Sweden is thought of as providing reliable and useful information.

Aims

Predictions of the characteristics of the coming influenza season should be made as early as possible. In this study, the aim was to suggest both simple and advanced rules for how to predict the time and height of the peak of LDI by means of very early observations. The incidences of laboratory-diagnosed cases were compared to the sentinel reporting to explore their relation and the usefulness of these series for predicting the development of yearly outbreaks. Since Swedish LDI data are considered to be reliable, indicators that can provide early and reliable predictions of the LDI values are of great interest. We therefore investigated the relation between %ILI and LDI to see if %ILI could be used as a proxy for LDI. The suggested methods were evaluated by cross-validation and by application to the observed seasons.

Methods

Data collection

Data on influenza-like illness are reported to the SMI by sentinel physicians while laboratory verified infections are reported by microbiological laboratories. The reporting systems have been described in (8) and at www.smittskyddsinstitutet.se. In accordance with the EISS, influenza surveillance in Sweden formally starts in week 40 of the current year and extends to week 20 of the following year. A web-based system called Sentinet was developed in Sweden in 2003, to be used by both sentinel physicians and laboratories in order to facilitate the submission of data to SMI. While most of the sentinel physicians make use of this tool, there are still laboratories and a few sentinel physicians that prefer sending their information by fax. Both the sentinel physicians and the laboratories report the collected data for one week during the first days of the following week. A weekly report on all data from the previous week is published at the SMI web site every Thursday. At the end of the season, a yearly report in English summarises the data for the entire season, including analyses by sex and age group.

The sentinel physicians report the number of patients diagnosed as having ILI as well as their total number of patients during the week. For each ILI patient, the visit date, sex and age are stated. The majority of reports come from health units (i.e. several sentinel physicians working in the same practice), but some come from individual sentinel physicians. The sentinel physicians participate voluntarily, and

thus the number of active sentinel physicians and the area they cover vary from year to year and between weeks. In general, it is estimated that sentinel physicians covering at least 2% of the population report during the surveillance. No formal case definition has been demanded for ILI, but a description of the characteristics of influenza is provided in the recruitment letter that is sent to the sentinel physicians.

Influenza cases confirmed by laboratories are reported to SMI. During the 2000-2001 season 20 laboratories were active in the influenza surveillance, and during the following years the number increased to reach 24 during the 2005-2006 season. For each influenza case, the date when the sample was taken, the age and sex of the patient, and the type of influenza (A or B) are reported. Only positive results are reported, not the total number of samples tested, but it is continuously monitored that all laboratories are reporting. The laboratory-confirmed cases, LDI, are analysed as absolute figures, since no denominator is reported. In this report, %ILI denotes the percentage of patients attending the sentinel physicians and regarded as having influenza-like illness. For the analyses in this report, there were available data on %ILI for seven seasons, from the 1999-2000 season to the 2005-2006 season. Data on eight seasons were used for LDI (including also 1998-1999). LDI included influenza cases of both type A and type B.

To obtain a natural ordering of weeks, the timescale used in this report is the number of weeks after the start in week 40; thus week 40 equals t=0.

Statistical methods

The influenza incidence during each season was estimated as a unimodal regression on time. We used the methodology of nonparametric least squares under the order restriction of unimodality (9) but without other assumptions on the regression function. This technique produces consistent estimates of the time and the height of the peak. Computer programs for carrying out this analysis are available from the corresponding author.

The results from the unimodal regression estimates of influenza-season characteristics such as time of onset and early slope of the curve were used in the investigation of the relation between LDI and %ILI. The relation was investigated using simple and multiple regression analysis as well as correlation analysis.

The unimodal estimates were also used in the development of the prediction rules regarding the time and height of the peak. These analyses were performed by fitting a linear regression to the time of the peak with the estimated early characteristics as independent variables. A similar analysis was carried out for the height of the peak.

The recommended prediction functions were evaluated by applying the results to each season independently and by cross-validation (10). In the latter case, the prediction function was re-estimated with one season excluded, and the prediction error for the excluded season was calculated. This was repeated for all seasons.

A simple prediction rule for the time of the peak was derived by calculating the average of the time difference between the time of the peak, TP, and the time when the incidence exceeded 10, TO. The latter was used as an indicator of the time of the onset of the outbreak. A simple prediction of the height of the peak was determined by linear regression between the height and TO.

Results

Visits to the sentinel physicians and the yearly influenza activity

The total number of patients visiting the sentinel physicians varied considerably between weeks. The same pattern can be seen after subtracting the number of influenza patients. During the 2005-2006 season, for example, between 35 and 96 health units and individual sentinel physicians participated any given week. The number of influenza patients contributed only marginally to the variation in the number of patients. The decrease at Christmas can be seen every year. The time dependent number of patients reduces the usefulness of %ILI. Reporting systems have improved over the years, as demonstrated by the higher and more even curves of the later seasons (Figure 1).

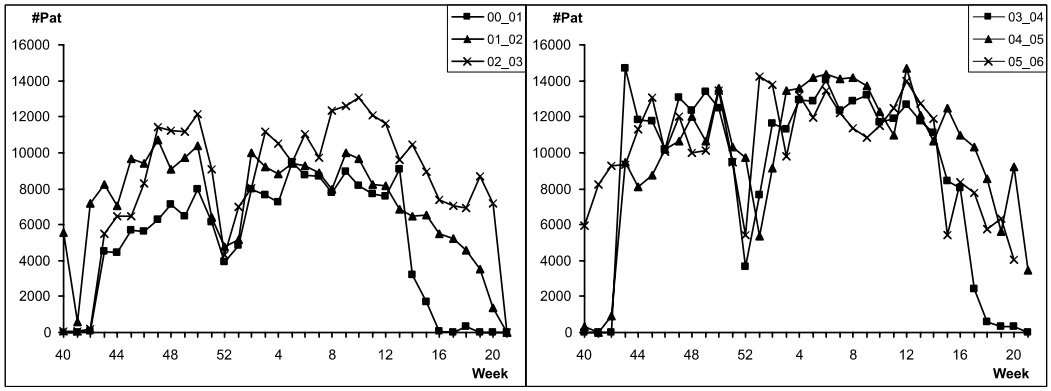

Figure 1. The number of patients reported seen by the sentinel physicians.

The epidemic curves in Sweden in terms of LDI are shown in Figure 2. The peaks occurred after calendar week 6 in 5 out of 8 seasons, for LDI and in 5 out of 7 for %ILI (data not shown). For both series, late peaks were of lesser magnitude than early ones.

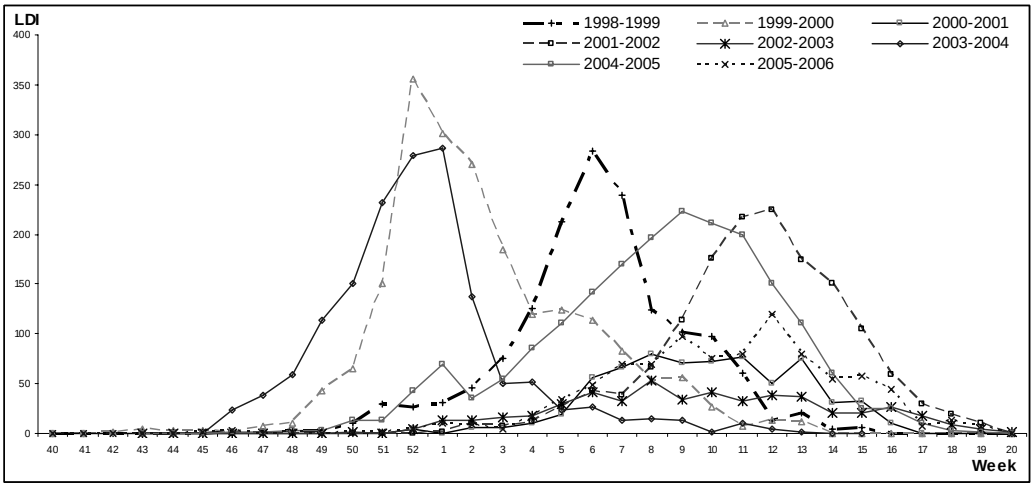

Figure 2. The number of laboratory-diagnosed influenza cases, LDI, for the seasons which were analysed. The cases for week 53 in 2004 were divided between week 52 and 1.

The relation between %ILI and LDI

In order to determine if %ILI can be used as a proxy for LDI, we first investigated the relationship between the estimated peak times for both variables. Estimates of the peaks were calculated by the unimodal regression technique (results in Table 1). If the peak of ILI always preceded that of LDI, then the observed time and height of %ILI could be used to predict the peak of LDI. However, as is seen in Table 1, this is not the case.

Table 1. The time (TPu) and height (HPu) of the peaks determined by unimodal regression. 1:

	%ILI		LDI	
Season	TPu	HPu	TPu	HPu
1998-1999	-	-	18	284
1999-2000	13	8.39	12	355
2000-2001	22	2.33	23	77
2001-2002	24	1.89	24	233
2002-2003	19	0.65	23	52
2003-2004	12	2.98	13	285
2004-2005	24	1.20	21	241
2005-2006	20	0.57	24	119

We further studied the relation between %ILI and LDI in Figure 3. The relation between LDI and %ILI was shown to be different before and after the peak. This is possibly related to the fact that the sentinel reporting vary with the seasonal epidemic (as is indicated in Figure 1) and hampers the possibilities to use %ILI as a proxy for LDI.

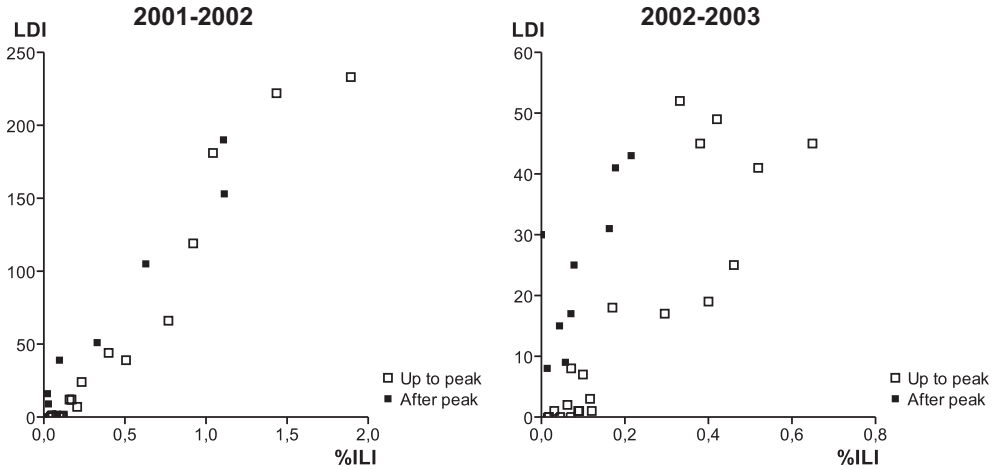

Figure 3. The number of laboratory-diagnosed influenza cases, LDI, and the percentage of influenza-like illness, %ILI, for the 2001-2002 and 2002-2003 seasons. Different markers indicate observations made before and after the peak of LDI.

The low numbers of patients at the onset of the epidemic makes the variance of %ILI large and indicates that early values of %ILI are not useful for predictions. We investigated whether the variable %ILI was a proxy of later values of LDI by studying the correlation between %ILI(t) and the time-shifted LDI(t+j) where the time shift j

was 0, 1, 2, 3. Generally, the correlation decreased with j. That meant that the %ILI variable, in its present form, was not a good estimate of later values of LDI.

In conclusion, %ILI was found not to be a good predictor for LDI, and further analyses were carried out based solely on LDI.

Prediction of the time of the peak

Data on LDI was used as the basis for the methods for prediction of the time and the height of the peak. Using correlation and linear regression, we examined how the time of the onset of the outbreak and the initial slope could give information on when a peak is to be expected. The time of the onset of the outbreak, TO, was represented by the first week when LDI indicated that the influenza had started. In the case of Sweden, it was chosen as the first week when LDI exceeded 10. The slope was represented by the time difference, TD, between the week when LDI exceeded 30 cases and the week when LDI exceeded 10 cases. To get better estimates of TO (time of onset of outbreak) and TD (initial slope), the unimodal estimate of the incidence curve was used instead of the raw data. For TD, in addition, the times when LDI exceeded the limits 10 and 30 were estimated by linear interpolation from the unimodal estimates. The estimates, based on the unimodal estimate, are denoted TOu and TDu respectively. A linear regression of the time of the peak, TPu, as a function of TOu and TDu was determined:

Recommended prediction rule for the time of the peak:
TPu = 5.62 + 0.96 TOu + 1.36 TDu

Table 2. Prediction of the time of the peak using recommended prediction rule. TO is the time of outbreak, the time difference TD indicates the slope at the outbreak and TPu is the time of the peak. Exact definitions given in the text.

Season	Early indicators		Time of peak		Prediction error	
	TO	TD	TP	TPu	Each season	Cross-validation
1998-1999	11	2	18	18.9	-0.9	-1.0
1999-2000	8	1	12	14.2	-2.2	-3.4
2000-2001	17	1	23	22.7	0.3	0.8
2001-2002	14	4	24	23.1	0.9	1.3
2002-2003	15	4	23	24.8	-1.8	-2.7
2003-2004	6	1	13	12.3	0.7	1.4
2004-2005	10	3	21	18.3	2.7	3.2
2005-2006	12	5	24	23.7	0.3	0.7

When the rule was applied to each individual season, the median of the absolute prediction errors was 0.9 weeks, i.e. less than 1 week. In the cross-validation, the median absolute prediction error was 1.35 weeks.

The correlation between TP and TO was 0.84. The strong linear relationship suggests a simple natural prediction rule based only on the observed values without any calculations. From Table 2 we find that the average time between onset and peak is 8 weeks, and thus follows:

Simple prediction rule for the time of the peak: "The peak will appear about 8 weeks after the week when the value of LDI exceeds 10 cases."

When applied to each individual season, this simple prediction rule had a median absolute prediction error of 2 weeks, with errors ranging from –4 to 4 weeks.

Prediction of the height of the peak

As with the time of the peak, we investigated the possibility of using TOu and TDu as predictors for the height of the peak (HPu) by fitting a linear regression.

Recommended prediction rule for the height of the peak:
HPu = 482 -18.6TOu – 27.6TDu

When the recommended rule was applied to each season, the median absolute prediction error was 58 cases; this was 28% of the average value of HP. The highest peak during the eight seasons was nearly 700% higher than the lowest one. In the cross-validation, the median absolute prediction error was 77 cases, corresponding to 37% of the average height.

A simpler rule using only observed TO was also possible to suggest, given the strong correlation of 0.73 between HP and TO (Figure 4). A linear regression was fitted to HP and TO data:

Simple prediction rule for the height of the peak:
"The predicted height of the peak is 500-25 TO."

This rule had a median absolute prediction error of 62 cases, representing 30% of the average HP. The values of the absolute error ranged from 1 to 84 cases.

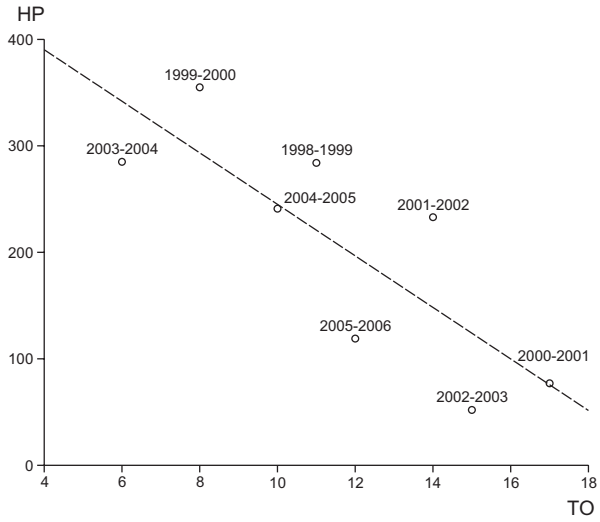

Figure 4. The relation between the height of the peak, HP, and the time of outbreak, TO. The time variable takes the value 0 at week 40. The straight line is the linear regression.

Discussion

The choice of data suitable for predicting the time and height of influenza peaks is critical. Many indicators could be considered. Data from other countries where the influenza often appears earlier than in Sweden are available on the web site of the European Influenza Surveillance Scheme www.eiss.org and could be useful. Sales of over-the-counter medicals have been suggested as early indicators of anthrax outbreaks and also as a leading indicator of influenza (11). French data on weekly health service-based indicators, such as emergency visits and absenteeism from work, collected by the Regional Influenza Surveillance Group (GROG) in France have been considered in and as leading indicators of influenza epidemics (defined by laboratory diagnoses) (12).

A relation was found between LDI and emergency department ambulance diversion in Toronto (13), and it has been suggested that the volume of ambulance dispatch calls be used in surveillance for outbreak detection (14). The number of deaths due to all causes and reported cases of ILI have also been used (15). However, ambulance dispatches or deaths are late occurrences during the yearly influenza outbreaks. In Sweden the use of suggested variables other than LDI and %ILI would require new procedures for systematic collection of data. Therefore, in this study we evaluate the usefulness of already existing reporting systems in Sweden for prediction purposes. The same analysis could be performed for other types of surveillance reporting in other countries, with this study as a model.

The reporting of laboratory data in Sweden is relatively stable due to the limited number of microbiological laboratories. In the case of Sweden, LDI was found to be a useful indicator, but specific structures in other countries may give other results. The available data on ILI are not good indicators of the LDI variable. One reason could be that the number of units reporting ILI varies substantially over time. The varying number of patients might reflect the physicians' motivation to send reports. Before influenza is laboratory verified, the sentinel physicians are not likely to believe that their patient is the first influenza case in Sweden. During certain weeks (for example after the peak of the influenza), some physicians may lose interest in sending reports, thereby lowering the reliability of the system. The ILI data should, consequently, be interpreted with care. A similar conclusion was made in a previous European study (12). In addition, the construction of the Swedish insurance and health care systems, discouraging visits regarding short-term infectious disease that can be handled without professional aid, hampers the effectiveness of the sentinel reporting in a surveillance system. We conclude that ILI data are presently not useful for a proxy for LDI in Sweden and that there may be similar problems in other countries.

The importance of timely indicators for surveillance systems has already been recognised (16). Both LDI and ILI are late indicators of the true influenza incidence, since they are not reported in real-time but as aggregated weekly data. Further, they only depict information available within the health care system and not the extent of the epidemic in the general population. With the rapid methods used today, laboratory confirmation of influenza seldom takes more than one day. Both LDI and %ILI could be reported on a daily basis, but this demands a higher motivation among the reporters than at present. Automatic draws from laboratory systems and patient data sets could be a substantial improvement in the future. Since indicators that can give early estimates of the LDI values or the true influenza incidence are of great interest to the general population and in health care planning, efforts should be invested in the

evaluation of surveillance systems as bases for predictions already at the planning stage.

Predictions of the time and the height of influenza peaks based on early observations are of interest in order to give an early alert about what is to be expected for the current season. The suggested simple rules based on routine LDI of influenza give rough predictions as early as about 8 weeks before the peak appears. Also more advanced prediction rules based on smoothing with unimodal regression giving higher precision have been suggested. By using estimated curves, we avoided the stochastic variation in the observed values of %ILI and LDI data. However, parametric estimation is hampered by the fact that the parameters would vary much between seasons (17). Moving averages and kernel smoothing are common methods which could be possible alternatives, but they have the disadvantage of not preserving the peak location (9). Since the peak is of great concern but other characteristics of the curve are uncertain, we decided to use unimodal regression (9). We thereby avoided the use of questionable parametrical models. Instead, we got consistent estimates of the time and the height of the peak. Also other characteristics of each influenza season were based on the unimodal regressions, for example the estimated time of onset of the outbreak for LDI and the estimated initial slope for LDI.

The recommended rule for predicting the time of the peak gave small prediction errors. The median of the absolute values of the prediction error for rule TPu was 0.9, i.e. less than 1 week on average. Since the prediction equation was fitted using all eight seasons, however, it gives a somewhat too favourable impression. The median of the absolute error when each season was excluded in the cross-validation was 1.35. This is a pessimistic value since each regression was fitted to only seven seasons. The optimistic evaluation thus gives a prediction error of slightly less than 1 week and the pessimistic one an error of slightly more than 1 week. Also a little more than 1 week must be regarded as a small prediction error. The very simple rule could also be satisfactory for many purposes. It has a median of the absolute error equal to 2 for the eight seasons, and the error ranges from -4 to 4. There are few comparable suggestions of prediction. However, similar regression models have been used for the prediction of the time of the peak of a pandemic influenza (18). Here, predictions of the time of the peak were made for the pandemics of 1918-1919, 1957 and 1968-1969. A difference in timing between -2 and +3 weeks was reported for forecasts that were made 5 weeks in advance of the peak to 1 week after the peak, thus closer to the peak than in our study.

Advanced parametric models have advantages for causal interpretation, but the situation is different when it comes to prediction. In this study we used nonparametric smoothing, which preserves the peak characteristics, and combined it with multivariate regression. The previously mentioned prediction (18) contains nine parameters, some of which should be re-estimated every week. The repeated re-estimation might be necessary in case of a new kind of infectious disease. However, it was shown here that prediction by a simple technique, made once and early during the season, may be useful for the yearly influenza outbreaks.

It has been described that influenza seasons that start early cause more severe epidemics compared to seasons that start late (19). The prediction rules for the height of the peak agree well with that concept. The relation between a low peak and a late start most likely reflects a slow and low-grade spread in a population with relatively high immunity in years when there is little change in the circulating influenza strain. The Christmas holidays and vacations may also delay the spread. The prediction errors of 28% and 30% of the average height of the peak for the advanced and simple

rules, respectively, can be considered satisfactory in view of the large variation between the seasons. The highest peak was 700% higher than the lowest of the eight peaks.

Conclusion

The current system for collecting information on %ILI precludes its use for predicting the influenza epidemic peak date and severity. Simple but carefully chosen regression models, based on easily derived covariates from early LDI reports, can be useful for public health response planning. The timing and height of the peak of the yearly influenza season can be reasonably well predicted using available early data and simple rules. Better predictions are achieved by using nonparametric regression. The correspondence of a late time for the influenza peak with a lower peak and thus a less disease burden is supported here.

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