Can syndromic thresholds provide early warning of national influenza outbreaks?

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ABSTRACT

Background Influenza incidence thresholds are used to help predict the likely impact of influenza and inform health professionals and the public of current activity. We evaluate the potential of syndromic data (calls to a UK health helpline NHS Direct) to provide early warning of national influenza outbreaks.

Methods Time series of NHS Direct calls concerning ‘cold/flu’ and fever syndromes for England and Wales were compared against influenza-like-illness clinical incidence data and laboratory reports of influenza. Poisson regression models were used to derive NHS Direct thresholds. The early warning potential of thresholds was evaluated retrospectively for 2002–06 and prospectively for winter 2006–07.

Results NHS Direct ‘cold/flu’ and fever calls generally rose and peaked at the same time as clinical and laboratory influenza data. We derived a national ‘cold/flu’ threshold of 1.2% of total calls and a fever (5–14 years) threshold of 9%. An initial lower fever threshold of 7.7% was discarded as it produced false alarms. Thresholds provided 2 weeks advanced warning of seasonal influenza activity during three of the four winters studied retrospectively, and 6 days advance warning during prospective evaluation.

Conclusion Syndromic thresholds based on NHS Direct data provide advance warning of influenza circulating in the community. We recommend that age-group specific thresholds be developed for other clinical influenza surveillance systems in the UK and elsewhere.

Keywords syndromic surveillance, influenza, surveillance, NHS Direct

Introduction

To help public health teams predict and respond to the likely impact of influenza, the concept of thresholds levels have been applied in a number of national surveillance programmes.¹–³ Statistical threshold levels provide a clear and consistent picture to public health practitioners, the public and the media about current influenza activity.⁴ In England and Wales, threshold levels have been estimated on the basis of the incidence rate of new episodes of influenza-like illness (ILI) recorded by the Royal College of General Practitioners (RCGPs) Weekly Returns Service (WRS). The RCGP WRS is a sentinel surveillance network currently comprised of 103 practices and ~500 general practitioners (GPs) monitoring an average weekly population of 900 000 patients.⁵ A weekly ILI incidence rate of <30 per 100 000 indicates ‘baseline’ activity, 30–200 per 100 000 ‘normal seasonal’ activity, and >200 per 100 000 ‘epidemic’ activity.¹ These thresholds are used by the UK Department of Health to determine the decision on when GPs are advised to use antiviral drugs for treating seasonal influenza (e.g. oseltamivir).⁶

In recent years, another source of clinical information has contributed to the UK influenza surveillance programme; syndromic calls to NHS Direct, a national nurse led telephone health line.⁷ NHS Direct calls are broadly representative of the population although there is a high proportion of calls about young children, and higher use by women.⁸ Previous work has shown that statistically significant rises in respiratory complaints to NHS Direct are timely indicators
of influenza circulating in the community. To better understand the value of syndromic data, we compared NHS Direct data against clinical and laboratory influenza data over multiple influenza seasons. We then used a statistical model of NHS Direct calls and GP consultations about ILI to define NHS Direct threshold levels for influenza surveillance. These threshold levels were evaluated retrospectively and prospectively to test whether they provided advanced warning of community rises in influenza.

Methods

Data sources

NHS Direct nurses use clinical decision support software [the NHS Clinical Assessment System (NHS CAS)] to handle callers reported health problems. We obtained data for England and Wales, for weekly counts of NHS Direct calls classified under the ‘cold/flu’ clinical algorithm (all ages 0–4, 5–14, 15–44, 45–64, 65+ years) and fever algorithm (0–4 and 5–14 years), and total algorithm calls, for weeks 40/02–20/06 inclusive. Weekly NHS Direct data were used, as opposed to daily data, to allow a direct comparison with weekly clinical and laboratory data. We obtained weekly ILI rates for England and Wales from the RCGP WRS for the same time period and age groups (from here on described as GP ILI). Weekly counts of the number (all ages combined) of positive influenza samples from community sources were collected from the Health Protection Agency, Centre for Infections virological surveillance scheme. This surveillance scheme collects 5–10 swabs per week from a network of 50 general practices in England and Wales. Data were compared using weekly time-series graphs.

Calculating NHS Direct thresholds

The relationship between weekly NHS Direct ‘cold/flu’ and fever calls, and GP ILI was explored using Poisson regression models, taking the total weekly number of ‘cold/flu’ or fever calls as the dependent variable, the logarithm of the total weekly number of calls as an offset, and GP ILI rate per 100 000 as the independent variable. Only weeks during the influenza season were used for the statistical models (weeks 40–20: October–May). Poisson regression is suitable for this analysis as the data of interest are events (NHS Direct calls) within specified time periods (weeks), and both numerator and denominator are reasonably high. The goodness of fit and validity of the models were tested using pseudo R² values, the Pearson χ² statistic and inspection of model residuals.

A predicted NHS Direct upper threshold value for baseline activity (the weekly percentage of calls for cold/flu or fever calls) was calculated from the fitted model for a GP rate of 30 per 100 000 (the current clinical threshold for baseline activity). Separate models were constructed for each age group and for cold/flu and fever calls separately. It is feasible that an NHS Direct threshold population rate, as well as a threshold percentage, may be useful for public health practice so separate models were also constructed using the logarithm of the total population of England and Wales as an offset. NHS Direct upper threshold rates per 100 000 for baseline activity were then calculated.

An NHS Direct threshold level for epidemic activity could not be estimated because there has not been ‘epidemic’ levels of GP ILI since winter 1999/2000 (before the NHS Direct national syndromic surveillance system was established).

Evaluating thresholds

The usefulness of NHS Direct thresholds (potential to provide early warning) was tested retrospectively for the study period (2002–06), and prospectively during the winter of 2006/07. For the retrospective evaluation we compared, for each age group, the week the derived NHS Direct threshold was exceeded (an NHS Direct alarm) against the week the existing GP ILI threshold of 30 per 100 000 was exceeded (GP alarm). NHS Direct alarms occurring in advance of any laboratory influenza detections were considered false alarms.

The derived NHS Direct threshold values were also used prospectively during winter 2006/07. For the prospective evaluation, we wanted to maximize the benefit of receiving and analysing daily NHS Direct data. Seven day rolling averages of the proportions of cold/flu and fever calls were calculated on a daily basis. An NHS Direct alarm was called if there were three consecutive daily alarms using the rolling averages. The date of the NHS Direct alarm was reported and was compared against the date that the first GP alarm was reported.

Results

During the study period, there were five influenza seasons (Table 1) of which 2003/04 had the highest rates of GP ILI (peak = 62 per 100 000), and 2005/06 the highest number of influenza reports (293 reports).

Comparison of data sources

The rise and peaks in the percentage of NHS Direct cold/flu calls and GP ILI occurred concurrently during
winters 2003/04 and 2004/05 (influenza A dominant seasons) (Fig. 1). There was a moderate peak in ‘cold/flu’ calls after relatively low peak in GP ILI during winter 2002/03, and generally low levels of ‘cold/flu’ calls during winter 2005/06. The timing of the rise and peaks in cold/flu calls for adults (15–64 years) was similar to total cold/flu calls (Fig. 2). The lowest level of cold/flu calls was for the ≥65 year age-group mirroring the pattern of total NHS Direct usage for this age group. For the 5–14 year age group, ‘cold/flu’ and fever calls peaked at the same time as laboratory reports of influenza, and within 1 week of the peak in GP ILI, during winters 2002/03, 2003/04 and 2005/06 (Fig. 3). There were, however, also regular peaks of fever calls (5–14 years) of between 8 and 9% during late

Table 1 Summary of influenza surveillance data from laboratories, general practitioners (GPs), and NHS Direct during the study period (2002–07)

<table>
<thead>
<tr>
<th>Winter</th>
<th>Laboratory: virological surveillance scheme</th>
<th>Clinical: GP ILI</th>
<th>NHS Direct cold/flu calls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dominant influenza subtype</td>
<td>Total number of positive reports</td>
<td>Peak week</td>
</tr>
<tr>
<td>2002/03</td>
<td>A (H3N2) and B co-circulation</td>
<td>101</td>
<td>2003/08</td>
</tr>
<tr>
<td>2003/04</td>
<td>A (H3N2)</td>
<td>258</td>
<td>2003/46</td>
</tr>
<tr>
<td>2004/05</td>
<td>A (H3N2)</td>
<td>143</td>
<td>2005/05</td>
</tr>
<tr>
<td>2005/06</td>
<td>B and A (H3N2) co-circulation</td>
<td>293</td>
<td>2006/05 and 06</td>
</tr>
<tr>
<td>2006/07</td>
<td>A (H3N2)</td>
<td>a</td>
<td></td>
</tr>
</tbody>
</table>

aData not yet available for the entire influenza season.

Fig. 1 Weekly RCGPs weekly consultation rate for ILI per 100 000 (all ages), percentage of NHS Direct ‘cold/flu’ calls (all ages), number of influenza reports (Cfi community scheme), and NHS Direct cold/flu threshold for baseline activity (2002–06).
Fig. 2 Weekly percentage of NHS Direct ‘cold/flu’ calls by adult age group (2002–06).

Fig. 3 Weekly RCGP ILI consultations per 100,000 (5–14 years), percentage of NHS Direct ‘cold/flu’ (5–14 years) and fever calls (5–14 years), number of influenza reports (Cfi community scheme) and NHS Direct thresholds for fever (5–14 years) calls (2002–06).
December and July. ‘Cold/flu’ (0–4 years) calls exhibited a secular downward trend and fever calls (0–4 years) peaked at the same time as other influenza data during a single season in November 2003 (data not shown).

**Threshold values**
The best fitting Poisson models were for the percentage of ‘cold/flu’ calls (all ages) \( (R^2 = 0.54) \), rate of cold/flu calls (all ages) \( (R^2 = 0.51) \), proportion of fever calls (5–14 years) \( (R^2 = 0.53) \), and rate of fever calls (5–14 years) \( (R^2 = 0.51) \) (Table 2). With a Poisson model the pseudo \( R^2 \) values provide an approximate measure of the explanatory power of the model, but not an exact measure of the proportion of variation explained by the model, as for linear regression models. High Pearson \( \chi^2 \) statistics for these same models revealed that the data did not conform to a standard Poisson distribution and was likely to be over-dispersed as previously demonstrated.\(^8\) Examination of the model residuals revealed that the cold/flu model over estimated the percentage of calls during winter 2005/06, and that the fever (5–14 years) model under estimated the percentage of calls during weeks 50–52, whilst over estimating during non-influenza periods (Fig. 4).

Through a combination of visually examining trends in the three data sources and using the best fitting Poisson models, three indicators—cold/flu calls (all ages), cold/flu calls (5–14 years) and fever calls (5–14 years)—appeared most suitable for testing the early warning potential of NHS Direct thresholds. These three indicators are now examined in more detail.

The models estimated an NHS Direct ‘cold/flu’ upper threshold for baseline activity of 1.2% of total calls or 1.5 calls per 100 000 (Table 2, Fig. 1), comparable to the GP ILI threshold of 30 per 100 000. The estimated cold/flu (5–14 years) threshold was 1.3% or 1.25 per 100 000, and fever (5–14 years) 7.7% or 7.6 per 100 000 (Table 2, Fig. 3). Owing to the regular December peaks in the proportion of fever calls (5–14 years), in excess of the 7.6% threshold, we decided to raise this threshold to 9% to avoid false alarms during periods when laboratory data indicated that influenza was not circulating. These numerical threshold values represent the transmission point from baseline to normal seasonal influenza activity.

**Evaluation**
**Retrospective—winters 2002–06**
Table 3 presents, for each influenza season, the time lag between the first exceedance of the NHS Direct threshold for baseline activity (termed an NHS Direct alarm) and the first exceedance of the GP ILI threshold for baseline activity.
During winter 2002/03 the NHS Direct cold/flu (all ages) alarm occurred four weeks after the GP alarm. The NHS Direct ‘cold/flu’ (5–14 years) alarm occurred three weeks prior to the GP alarm. This is considered a false alarm as laboratory data indicated no influenza activity during this week (Fig. 3). During winters 2003/04 and 2004/05, all three NHS Direct alarms occurred one to three weeks in advance of the GP alarm. During winter 2005/06 the raised NHS Direct fever (5–14 years) alarm occurred 2 weeks in advance of the GP alarm. The first NHS Direct fever (5–14 years) alarm occurred on the 31 January 2007 was reported to national influenza surveillance coordinators on the 1 February, and in a publicly available surveillance bulletin. The GP weekly alarm signalled during week 05/01 (30.2 consultations of ILI per 100 000) and was reported on 7 February. The NHS Direct cold/flu (all ages) and cold/flu (5–14 years) alarm did not signal during the winter of 2006/07, and the cold/flu (15–44 years) alarm signalled on the 9 February.

Table 3 Time lag (weeks) between the RCGP threshold being exceeded (GP alarm) and the NHS Direct threshold being exceeded (NHS Direct alarm) for the retrospective evaluation

<table>
<thead>
<tr>
<th>Winter</th>
<th>Influenza season</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week of the first GP ILI alarm</td>
<td>2002/03</td>
</tr>
<tr>
<td>Year/Week 2003/02</td>
<td>Year/Week 2003/44</td>
</tr>
<tr>
<td>Time lag between an NHS Direct cold/flu (all ages) alarm and a GP ILI alarm</td>
<td></td>
</tr>
<tr>
<td>NHS Direct cold/flu (5–14 years)</td>
<td>+4</td>
</tr>
<tr>
<td>Raising NHS Direct fever (5–14 years) threshold</td>
<td>−3</td>
</tr>
</tbody>
</table>

For example, a time lag of −2 indicates that the NHS Direct alarm occurred 2 weeks in advance of the GP alarm.
Discussion

Main findings

NHS Direct calls about ‘influenza-like-illness (ILI)’ generally rose and peaked at the same time as GP diagnosed ILI and laboratory reports of influenza. Influenza thresholds based on NHS Direct calls provided advance warning of influenza circulating in the community. We propose an overall ‘cold/flu’ threshold of 1.2% of total calls and fever threshold of 9% for the 5–14 years age group be used for influenza surveillance in England and Wales. In a retrospective evaluation these two thresholds provided 2 weeks advanced warning of seasonal influenza activity in three of four winters studied, with no false alarms. During prospective evaluation the NHS Direct fever threshold signalled 6 days earlier than an influenza surveillance system based on GP consultations. Timely information was given to influenza surveillance coordinators, local health protection teams and the public.

The use of age-group specific thresholds meant that the start of the influenza season was detected regardless of the influenza subtype and age groups predominantly affected. No single age-group threshold provided early warning during all winters. The threshold value for total ‘cold/flu’ calls was of particular value during a winter characterised by influenza activity early in the 2003/04 season of a new influenza A drift variant (A/Fujian/411/2002 (H3N2)-like virus). In addition, the threshold value for fever calls (5–14 years) provided a comparative advantage during a national influenza B outbreak during 2005/06. Variation in the amount of early warning provided by these thresholds (ranging from 0 to 2 weeks in our study) is likely to have been influenced by annual changes in the virulence of the circulating influenza sub-types and the main age-group affected, which in turn influence presenting patterns to NHS Direct and GP surgeries. We suggest that a range of age-group specific thresholds are required for timely warning of different subtypes of the influenza virus, and are recommended for surveillance systems based on telehealth data.

What is already known on this topic?

ILI is caused by infection or co-infection with a number of pathogens including influenza, respiratory syncytial virus (RSV), adenovirus and parainfluenza. In the UK, RSV regularly peaks in late December so confounds these results. For example, ‘NHS Direct fever peaks’ occurred during week 50 in all but the 2003/04 winter when it was submerged within the early peak caused by the new influenza drift variant. It is likely that the confounding effect of RSV and other pathogens is greater for NHS Direct calls than GP ILI as the NHS Direct baseline level is relatively higher during non-influenza periods (Fig. 1). Also NHS Direct nurses triage callers using a generic ‘cold/flu’ algorithm so specificity is likely to be lower than GP ILI where RSV infection is predominately diagnosed as acute bronchitis. Previous modelling work suggests RSV, influenza and pneumococcal are the main cause of respiratory complaints made to NHS Direct. A self-sampling study of NHS Direct callers previously resulted in 16% testing positive for influenza and 5% for RSV during winter. Despite the apparent ‘NHS Direct RSV peak’ these results suggest that the NHS Direct thresholds have sufficient specificity to minimize false alarms caused by circulation of other respiratory diseases.

Numerical influenza thresholds are used widely throughout Europe and in the USA to describe influenza activity. They provide a clear and consistent message of influenza levels, place current activity in the contact of previous winters and avoid confusion caused by different authorities describing influenza levels in different ways. Thresholds are also used to trigger action by GPs to prescribe antiviral medication, aid diagnoses, and encourage identification of high-risk patients and sampling for laboratory testing. Communications may also be made with hospitals forewarning them of the need to free bed space for an expected rise in respiratory admissions. The necessity for accurate influenza thresholds is such that the Health Protection Agency is currently recommending that a variety of surveillance systems (including NHS Direct) should be used to trigger antiviral prescribing for influenza, after the realisation that virus activity can occur before current thresholds levels are reached and after they have fallen back to baseline.

Various means of obtaining statistical thresholds such as ARIMA regression models and CUSUMS have been employed for syndromic surveillance purposes. These methods commonly use Emergency Department data and detect significant changes in daily visits from an expected level. Often initially designed for the detection of potential bio-terrorist events, these systems have been successful in detecting statistically significant rises in respiratory disease and the onset of the influenza season.

What this study adds

The syndromic thresholds derived here differ from other methods in that they are based on telehealth data in comparison with influenza data from other sources (clinical and laboratory). They are also designed solely for detecting the start of influenza seasons and not for surveillance of general respiratory disease. Work in the USA comparing telephone health line data against doctor diagnosed ILI and influenza...
isolates has shown concurrent peaks in data. In another study, numbers of medical centre outpatients with ‘fever’ correlated strongly with viral respiratory pathogens. Our work uses a different source of syndromic data (telehealth calls) but supports these conclusions, adding that a community rise in influenza may be predicted by a rise in fever calls. It is hoped that this work will be of relevance to evolving syndromic surveillance systems using telehealth data, for example in Canada, and within the newly established framework for ‘epidemic intelligence’ gathering in Europe.

Although the RCGP GP surveillance scheme, used as a reference point, represents less than 2% of the population of England and Wales we consider this the gold standard for GP ILI surveillance having reported ILI rates since the 1960s. We have shown age-group specific NHS Direct thresholds may complement this scheme. The fever calls threshold for school age children may be of particular use when the predominant circulating influenza strain does not initially cause significant levels of illness reported to general practitioners. For example, during January and February 2006 there were an unusually high number of school outbreaks (many confirmed as influenza B) in England and Wales, not initially reflected within the GP ILI rates. It may be argued that the NHS Direct fever threshold, which signalled 2 weeks earlier than GP ILI during winter 2005/06, was more sensitive in detecting this national influenza outbreak. In practice, NHS Direct data can be analysed and reported on each weekday. This extends the lead-time as weekly GP ILI data are generally reported 3 days after the end of the reporting week, and laboratory data from community virological schemes up to 10 days from specimen collection. Further work is needed to test whether prospective spatio-temporal analyses of NHS Direct data to a local level could identify the origin of national outbreaks, thus extending the lead-time further.

Limitations of this study
Systematic residual patterns suggest that a constant threshold value over an entire winter may not be justified and that an iterative approach, with daily or weekly changes in the threshold, is more suitable (e.g. ARIMA, CUSUMS). The NHS Direct surveillance system already employs a control chart methodology incorporating day of the week, seasonal and long term trend factors. These control charts flag significant rises in a variety of syndromes (e.g. cold/flu, fever, diarrhoea, vomiting). This study, however, has taken a pragmatic approach to produce constant threshold values designed specifically for influenza surveillance, derived directly from Poisson models and adjusted if necessary to improve specificity. It is hoped that these thresholds will complement the control charts already employed. Similarly, pragmatism has also driven derivation of the RCGP threshold for baseline ILI activity which was recently lowered from <50 to <30 per 100 000 following studies of 10 years incidence data.

By examining the model residuals along with the time lag between signals (Table 3) we were able to determine which age-group specific threshold was most useful in differing influenza seasons (e.g. influenza A or B).

Relatively low levels of influenza activity in the UK during the study period have made it difficult to derive thresholds for epidemic activity. For example, during winter 1999/2000 GP ILI peaked at 256 per 100 000, four times higher than the peak rate of 62 per 100 000 during our study period. A principle aim of this paper, however, is to establish thresholds for early warning (notification of the beginning of the influenza season) and not to predict extreme values. The secular downward trend in respiratory illness reported in the UK means there may not be the opportunity to test our syndromic surveillance system in epidemic conditions until novel influenza viruses [e.g. avian influenza A(H5N1)] with high human pathogenicity emerge.

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