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## Excess mortality monitoring in England and Wales during the influenza A(H1N1) 2009 pandemic

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P. HARDELID<sup>1\*</sup>, N. ANDREWS<sup>1</sup> AND R. PEBODY<sup>2</sup>

<sup>1</sup> *Statistics Unit, Health Protection Agency Centre for Infections, London, UK*

<sup>2</sup> *Immunisation, Hepatitis and Blood Safety and Respiratory Diseases Departments, Health Protection Agency Centre for Infections, London, UK*

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### SUMMARY

We present the results from a novel surveillance system for detecting excess all-cause mortality by age group in England and Wales developed during the pandemic influenza A(H1N1) 2009 period from April 2009 to March 2010. A Poisson regression model was fitted to age-specific mortality data from 1999 to 2008 and used to predict the expected number of weekly deaths in the absence of extreme health events. The system included adjustment for reporting delays. During the pandemic, excess all-cause mortality was seen in the 5–14 years age group, where mortality was flagged as being in excess for 1 week after the second peak in pandemic influenza activity; and in age groups >45 years during a period of very cold weather. This new system has utility for rapidly estimating excess mortality for other acute public health events such as extreme heat or cold weather.

**Key words:** Influenza A, statistics.

### INTRODUCTION

In April 2009, a novel reassorted pandemic influenza virus emerged from the Americas, followed by rapid global spread [1, 2]. To date, more than 18 000 individual laboratory-confirmed deaths with pandemic influenza A(H1N1) 2009 (pandemic influenza) have been reported worldwide by the World Health Organization [3] with higher population mortality rates observed in young adults. Excess mortality monitoring has been the traditional approach to estimate the population-level impact of influenza [4]. Using this method for the influenza A(H1N1) 2009 pandemic, some countries have documented a small excess in

pneumonia and influenza mortality [5], while others have reported a probable excess in all-cause mortality in older children [6].

In England and Wales, a long-standing excess mortality surveillance system has been operational using weekly death registration data from the Office for National Statistics (ONS) and used to monitor the impact of influenza each winter season. During the H1N1 2009 pandemic in England, surveillance of confirmed pandemic influenza deaths had indicated that children and young adults were disproportionately affected compared to the elderly [7]. A key question was whether any excess mortality had been observed in the age groups with the highest number of cases, namely school children and persons aged 15–44 years [8].

During 2009, a new online death registration system was introduced by the General Registry Office (GRO) in England and Wales. We present the results of an

\* Author for correspondence: Dr P. Hardelid, Dr Foster Unit at Imperial College, 12 Smithfield St, London EC1A 9LA, UK.  
(Email: p.hardelid@imperial.ac.uk)

analysis of this data stream to assess age-specific excess mortality during the H1N1 pandemic period; April 2009–March 2010.

## METHODS

To monitor weekly mortality, age-specific baseline models similar to that proposed by Serfling [4] were developed using historical mortality data from 1999 to 2008. This method allows prospective flagging of weekly death counts which are significantly higher than those expected for a particular week, having taken into account unexplained seasonal variation in the absence of mortality peaks. The expected counts could also be used at the end of the pandemic to assess overall excess mortality across the first and second pandemic waves.

### Method for estimating expected mortality

Baseline mortality was estimated using historical time-series of deaths registered between 1999 and 2008 by date of death, date of registration and age, made available by ONS. Death counts were aggregated to ISO weeks of death to estimate baseline weekly mortality. In the ISO date system, some years have 53 weeks; all weeks, including the weeks numbered 53 were included when estimating excess mortality. Baseline mortality was estimated for all ages, by seven age groups (<1, 1–4, 5–14, 15–24, 25–44, 45–64, ≥65 years). During the winter months, the ≥65 years age group was stratified more finely into deaths in individuals aged 65–74, 75–84 and ≥85 years.

Poisson regression models with cyclical terms [4] of the following form were fitted to weekly death counts:

$$\ln(y_i) = \beta_0 + \beta_1(\text{week}_i) + \beta_2 \left( \sin \frac{2\pi(\text{week}_i)}{52} \right) + \beta_3 \left( \cos \frac{2\pi(\text{week}_i)}{52} \right) + \varepsilon_i, \quad (1)$$

where  $y_i$  is the number of deaths occurring in week $_i$ , and week $_i$  is an ordered week variable so that  $1 \leq i \leq 520$  and week $_1 = 1 =$  week 1 (1999) and week $_{520} = 520 =$  week 51 (2008). The models were fitted using a quasi-likelihood method [9] which allows the variance to be scaled by a dispersion factor, in the presence of overdispersion. As suggested by Farrington *et al.* [10] standardized (Anscombe) residuals ( $r_{Ai}$ ) were obtained from this model and weights calculated as follows:

$$\text{weight}_i = \begin{cases} r_{Ai}^{-2} & \text{if } |r_{Ai}| > 1 \\ 1 & \text{otherwise} \end{cases}. \quad (2)$$

The model in equation (1) was then refitted with these weights. This process was repeated so that the original model was weighted and refitted twice to further reduce the influence of previous mortality peaks on baseline mortality. If the dispersion parameter estimated through the quasi-likelihood method was  $< 1$ , a model of the same form as equation (1) was fitted using maximum-likelihood with the dispersion parameter fixed at 1.

The parameters from the model were used to predict the expected number of weekly deaths until end of March 2010 (week 12), and were used as a comparison with the observed number of deaths. The choice of prediction limit for the expected number of deaths is important; by setting the limit too high, important aberrations in mortality will be missed, whereas setting the limit too low will generate frequent false alarms. We chose a 99.5% upper prediction limit, since every week all nine age groups as well as total mortality were being monitored. A higher limit was therefore deemed necessary in order to prevent the algorithm from being too sensitive and producing false-positive flags for excess mortality.

The 99.5% upper prediction limit  $U_i$  of the expected baseline deaths for week  $i$  for a particular age group can then be obtained by [10]:

$$U_i = \left( \hat{y}_i^{\frac{2}{3}} + z_{0.995} \left( \frac{4\hat{y}_i^{\frac{1}{3}}(\phi + \text{var}(\hat{y}_i)/\hat{y}_i)}{9} \right)^{\frac{1}{2}} \right)^{\frac{3}{2}}, \quad (3)$$

where  $\hat{y}_i$  is the baseline estimate of mortality obtained from the model described in equation (1) above, and  $\phi$  the dispersion parameter. The  $\frac{2}{3}$  power transformation is the transformation to symmetry for the Poisson distribution, and provides correction for skewness, which may be a problem for children, for whom there are only a small number of deaths every week.

### Characteristics of prospective weekly mortality data and adjustment for reporting delay

In England and Wales, deaths are reported by relatives or clinicians to one of 233 registry offices reporting to GRO. A new Registration Online (RON) system had been gradually rolled out to registry offices, prior to the pandemic with all registry offices reporting from 1 July 2009. The data is collated by the GRO and sent for coding by ONS. As part of monitoring the impact of pandemic influenza A(H1N1) 2009, death registrations by age, registration district, date of death and registration were sent daily with

only 1 day's delay by GRO to the Department of Health and the Health Protection Agency (HPA) (data on gender were not available). Cause-of-death information was not available through this system; cause-of-death data requires subsequent coding by ONS, and using it would have incurred considerable delays.

As the mortality monitoring system was based on the date of occurrence of deaths (rather than date of report), adjustment for reporting delays was required. In England and Wales, reporting delays result as deaths cannot be registered if a deceased person had not been in recent contact with health services. Such deaths, which occur without a known cause or in suspicious circumstances are referred to a coroner's office. This can introduce reporting delays of weeks to several months [11], particularly for deaths in younger people. For example, based on the data from 1999 to 2008, for persons aged 15–24 years, only 61 % of deaths had been registered after 26 weeks, compared to 99 % in persons aged  $\geq 65$  years. To create a weekly mortality reporting system based on date of death, each week reporting delays by age group were calculated based on the observed delay between occurrence and registration. To account for reporting delays, the observed number of deaths in a particular week was divided by the proportion of deaths expected to have been reported by that week from the observed delay distribution. All deaths were assumed to have been reported after 2 years. The upper limits of the prediction intervals were also adjusted by replacing the term  $\hat{y}_i$  in equation (3) with  $p_i \hat{y}_i$  where  $p_i$  is the proportion of deaths expected to have been reported by week  $i$ , based on the observed delay distribution; the resulting upper limit was then divided by  $p_i$ . Since only a proportion of registry offices were using RON before 1 July 2009, an adjustment to allow for this was also made to deaths registered before this date.

### Prospective monitoring

Mortality each week was assessed prospectively by plotting the delay-corrected observed mortality by date of occurrence against the expected baseline and upper limit. Any observed weekly death count above the 99.5 % upper prediction limit was deemed to indicate the presence of excess mortality. The estimate of the number of excess deaths in these 'flagged' weeks was calculated as the delay-corrected observed deaths minus the expected number of deaths. Estimates for previous weeks were constantly revised as more

deaths for those weeks were registered and a smaller correction for reporting delay was needed. The monitoring system was set up using Stata [12] for data management, and updated weekly reports were created using R version 2.10.1 [13] and Sweave [14].

### Cumulative sums (CUSUMs)

In order to also examine potentially smaller but also sustained shifts from expected mortality, the CUSUM of observed deaths minus the expected baseline mortality was also analysed, with monitoring starting from the beginning of each pandemic wave.

### Retrospective assessment of mortality during the pandemic waves

To assess whether observed mortality across the first and second wave was significantly higher than expected, the sum of the observed number of deaths across the weeks which contained about 90 % of estimated clinical cases of pandemic H1N1 [15], as well as 2 weeks after this period, was obtained. In a US study of confirmed paediatric H1N1 cases, the median time delay between onset and death was 6 days [16], whereas in hospitalized cases in Canada it was 12 days [17]. Allowing 2 weeks after the end of the period incorporating 90 % of cases was therefore deemed to be sufficient to allow for delay between onset and death, while still maintaining specificity.

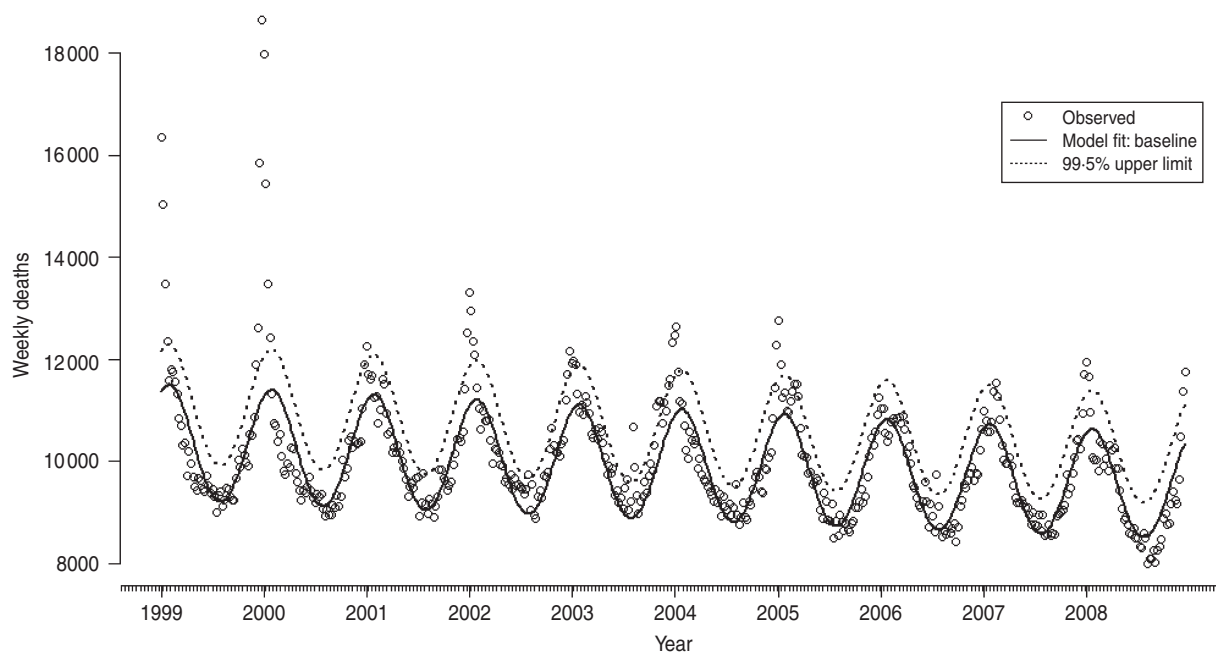
The observed number of deaths in this period was compared to the sum of the expected number of deaths in the same period. 95 % confidence intervals (CI) for the sum of deaths across weeks could then be obtained by the following expression:

$$95\% \text{ CI} = \left( \left( \sum \hat{y}_i \right)^{\frac{2}{3}} \pm z_{0.975} \left( \sum \frac{4\hat{y}_i^{\frac{1}{3}}(\phi + \text{var}(\hat{y}_i)/\hat{y}_i)}{9} \right)^{\frac{1}{3}} \right)^{\frac{3}{2}}. \quad (4)$$

These calculations (including determination of the weeks with  $\sim 90\%$  of estimated clinical pandemic H1N1 cases), were performed separately for each age group.

### Estimated number of clinical cases of H1N1

The estimated number of clinical cases of H1N1 was produced by the HPA throughout the H1N1 pandemic [15], and was based on the product of the age-specific influenza-like illness (ILI) consultation and



**Fig. 1.** Expected number of deaths from model fit (baseline mortality) and observed all-cause weekly mortality in England and Wales, 1999–2008.

swabbing positivity rates for persons attending either their GP or contacting the National Pandemic Flu Service, incorporating assumptions about the proportion of people with ILI who contacted health services.

### Meteorological data

Mean daily temperature data from Central England (CET) was obtained from the Meteorological Office [18].

## RESULTS

Figure 1 shows the observed all-age weekly mortality and expected mortality with the 99.5% upper limit; the weighted quasi-Poisson regression model with cyclical terms and linear trend provided a level of baseline mortality which was deemed appropriate as the number of weeks in excess during winter seasons correlated well with levels of influenza circulation [8].

No significant all-age excess mortality was observed for weeks 23–52 of 2009 in England and Wales. This period covers the two peaks of pandemic influenza activity in week 29 and week 43 (Fig. 2).

Significant excess mortality was observed in weeks 52 and 53 of 2009 and week 1 of 2010 (Fig. 2). This excess occurred more than 10 weeks after the second peak of pandemic influenza activity, and coincided

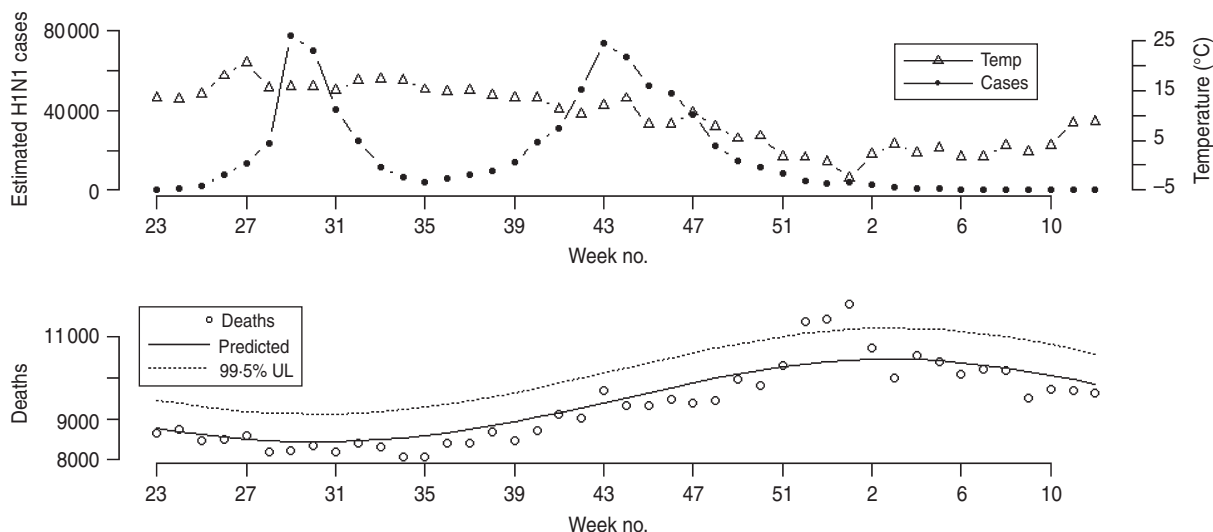
with a decline in weekly mean temperature below 0 °C.

The age-specific analysis found that the excess in all-cause mortality in week 52 to week 1 was restricted to those aged  $\geq 45$  years (Fig. 3). No significant excess mortality was observed in the younger age groups for this period.

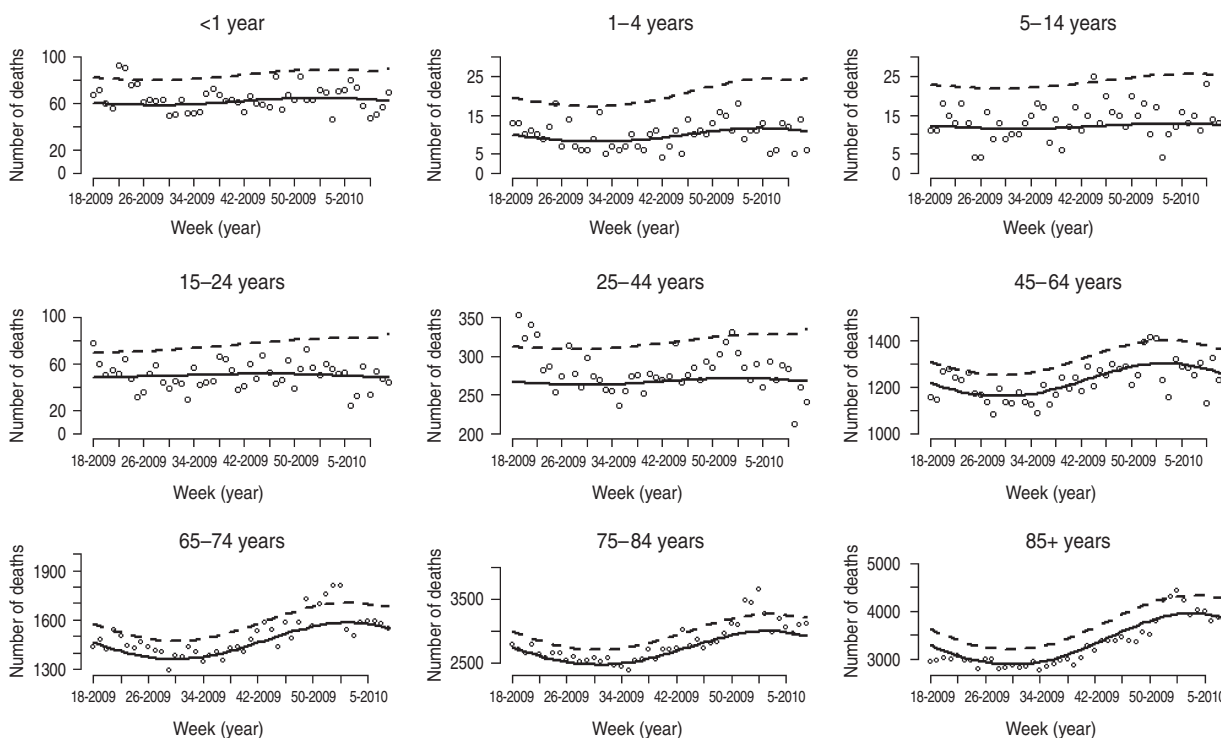
There were also excess deaths during the pre-pandemic period (weeks 18–22 in 2009) in infants aged < 1 year, and in persons aged 15–44 years. The reasons for this excess are not clear; however, this was during a period when the RON system was not utilized by all registry offices, and it is possible that the correction applied to the observed death data to take account of this was not correct for these age groups.

During the pandemic period (week 37, 2009 to week 1, 2010), a small excess was observed in week 43 in individuals aged 75–84 years; however, this was in the age group with the smallest number of H1N1 cases. A significant small excess was observed in those aged 5–14 years, the age group with the highest number of H1N1 cases in week 44, 1 week after the second peak in pandemic influenza activity. Similar excesses in younger age groups have been observed in some previous years, e.g. the 5–14 years age group in 2001/2002 (Fig. 4).

Using the CUSUM approach, only in the 5–14 years age group was a pattern observed which indicated an



**Fig. 2.** Total deaths in England and Wales by week of death, mean Central England Temperature and estimated H1N1 cases (April 2009–January 2010).



**Fig. 3.** Observed and expected weekly deaths by age group, England & Wales, April 2009–March 2010 [dots (○) show observed weekly mortality; solid lines (—) show expected baseline mortality and dashed lines (---) the 99.5% upper limit].

increasing number of deaths during the pandemic period. Figure 5 shows the CUSUMs for the 5–14 years group for weeks 17 (2009) to week 4 (2010), and for the same periods in 2007/2008 and 2009/2010, respectively. The pattern is clearly different in 2009/2010 compared to other years in showing an increase in deaths over the period. Again, this increase in

deaths occurred after the peak in pandemic influenza activity in week 43.

Table 1 shows the total observed and expected number of deaths by age group for the two periods during which 90% of cases of pandemic influenza occurred. There was no excess observed in any age group during the summer wave. When considering the

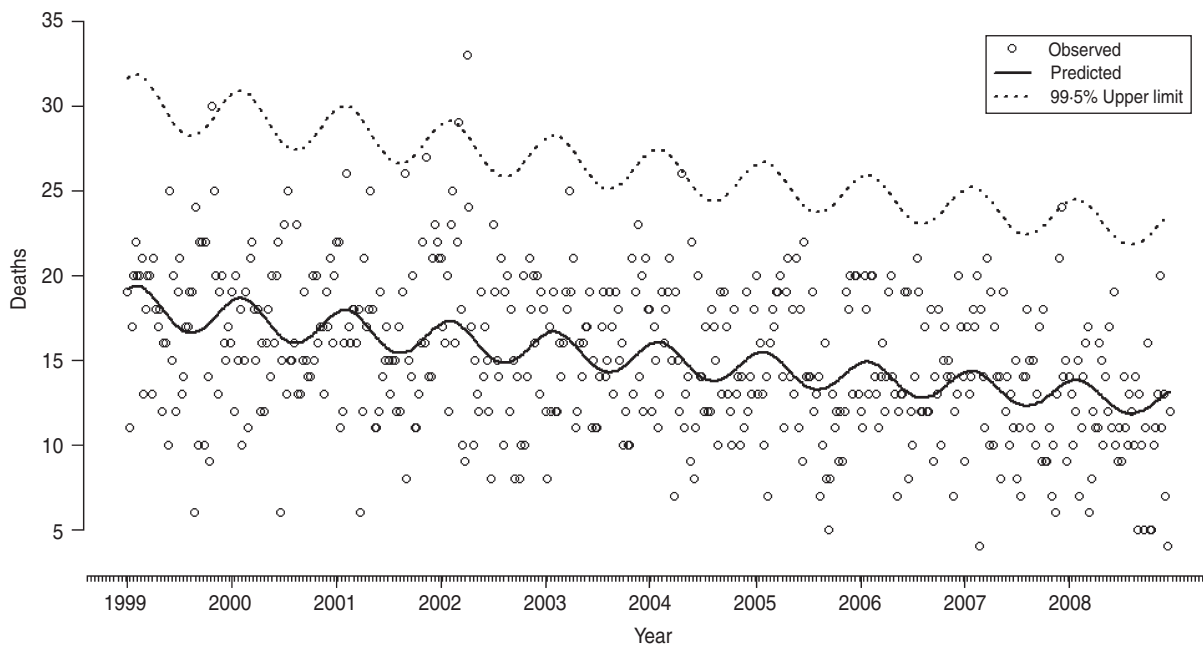


Fig. 4. Observed and expected weekly mortality in the 5–14 years age group, 1999–2008 in England and Wales.

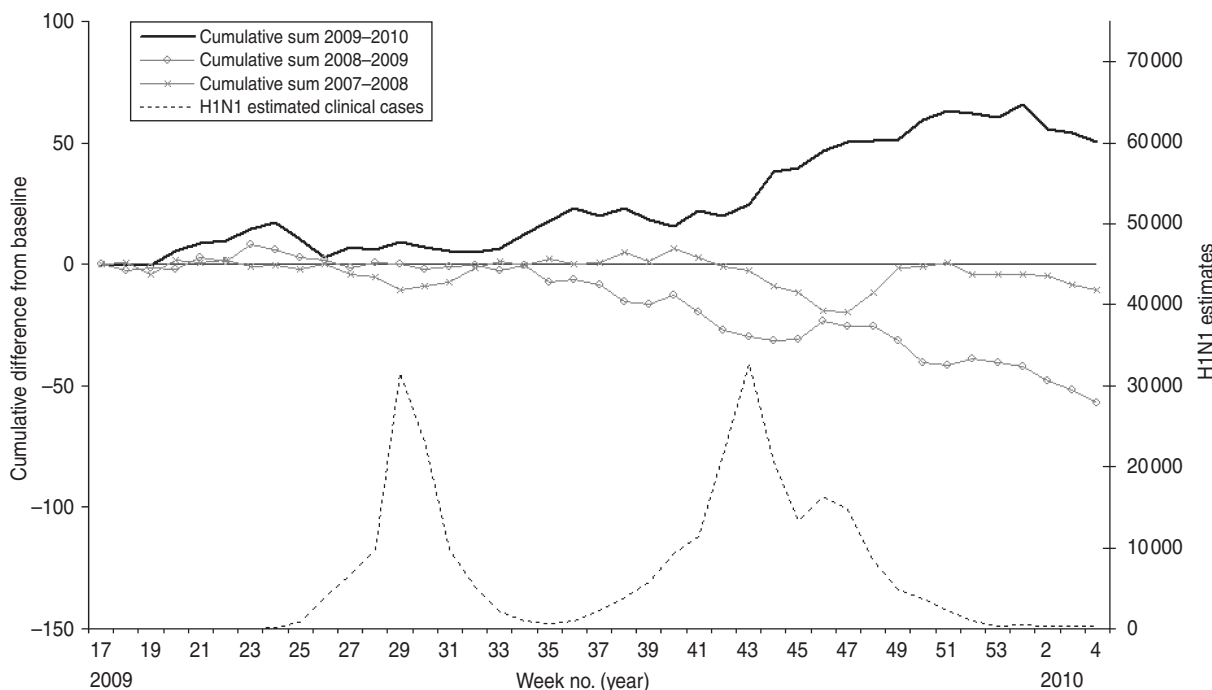


Fig. 5. Cumulative sum of deviations of mortality from baseline in the 5–14 years age group, with estimated clinical cases of pandemic H1N1 in the same age group, April 2009–January 2010. (Note that week 53 for 2007 and 2008 has been interpolated.)

whole autumn wave, the excess observed in the 5–14 years age group was no longer significant.

The only age group for which the total number of deaths during the pandemic influenza peak periods was significantly higher than expected was for those aged 65–84 years, where the observed deaths exceeded

those expected by 3596 deaths. However, for the weeks during which this excess occurred, week 51 (2009) to week 1 (2010) (Fig. 3), the estimated total number of pandemic H1N1 cases was <250 (as shown in Fig. 2). It is therefore highly unlikely that this excess was caused by pandemic influenza. Indeed, if the number

Table 1. Observed and expected (with 95% confidence intervals) number of deaths during the two waves of the H1N1 pandemic in England and Wales July 2009–January 2010

Age group (yr)	Weeks with ~90% cases summer wave + 2 weeks post*		Weeks with ~90% cases autumn wave + 2 weeks post†	
	Observed	Expected	Observed	Expected
<1	393	412 (337–491)	1100	1070 (908–1241)
1–4	56	57 (31–88)	150	147 (92–210)
5–14	64	69 (41–100)	196	157 (103–219)
15–24	411	449 (365–539)	786	769 (638–908)
25–44	2441	2371 (2174–2574)	4238	4031 (3725–4344)
45–64	10 301	10 483 (10 065–10 906)	21 342	21 247 (20 510–21 992)
65–74	12 474	12 286 (11 774–12 806)	26 821	25 624 (24 703–26 556)
75–84	22 711	22 330 (21 243–23 436)	50 063	47 664 (45 686–49 670)
≥85	25 839	26 172 (24 670–27 673)	59 542	60 459 (57 664–63 297)

\* Weeks 26–35 (2009), although the exact period varies by age group.

† Week 37 (2009) to week 1 (2010), although exact period varies by age group.

of weeks over which the excess mortality estimate was made was restricted to a more specific period around the peak week of H1N1 activity [that is, including the peak week of H1N1 activity for the ≥65 years age group, i.e. week 44 (2009), 3 weeks before the peak week and 5 weeks after the peak], no significant excess was observed for either the 65–74 or the 75–84 years age groups. In this period (weeks 41–49, 2009), there were 13 939 observed deaths in the 65–74 years age group, and 25 367 observed deaths in the 75–84 years age group. The expected number of deaths in these age groups in this period was 13 503 (95% CI 12 963–14 051) and 25 055 (95% CI 23 896–26 232), respectively.

In the age group with the highest estimated H1N1 incidence [8], i.e. 5–14 years, no significant excess was observed during the summer wave. During the autumn wave, the observed number of deaths was higher than the point estimate of the expected deaths (196 observed vs. 157 expected deaths); however, this did not exceed the upper limit of the 95% confidence interval of the expected number of deaths.

## DISCUSSION

A new mortality monitoring system established for the H1N1 pandemic has provided the opportunity to obtain timely age-specific estimates of excess mortality in England and Wales for the first time. No excess all-cause all-age mortality was observed during the summer and autumn pandemic influenza peaks. A small excess was observed in children aged 5–14 years, who had the highest number of H1N1 cases, at the

peak of the autumn pandemic wave. Examination of CUSUMs also revealed an increase in the number of deaths, particularly compared to previous years. However, this excess was not observed when the whole autumn wave period was considered.

At the end of 2009, an excess of all-cause mortality in older persons was observed; however, this excess occurred several weeks after the peak of H1N1 activity. Moreover, while the case-fatality ratio was higher in persons aged ≥65 years than in those aged <65 years [7], the estimated total number of cases in those aged ≥65 years was small (<4000 cases) throughout the whole pandemic period [8]. It is therefore highly unlikely that the observed excess in the ≥65 years age group was due to H1N1 activity.

Although methodologies for mortality monitoring differ in other countries, the findings reported here contrast with those from the USA, where the established 122 US city surveillance system [19], uses a more specific case-definition (pneumonia and influenza deaths), for excess in the proportion of deaths due to pneumonia and influenza over several weeks during the pandemic [20]. Similar to our finding of a small excess in mortality in children aged 5–14 years, observations of excess mortality in this age group have been made in a network of European countries which are part of the EuroMOMO project [6] using a CUSUM approach. However, attribution of deaths to a particular cause, like pandemic influenza, was not possible in any of these surveillance systems.

Using the approach presented here, an excess in all-age mortality was observed for 3 weeks at the end of the year, which was accounted for by higher than

expected mortality in older adults. The excess coincided with a drop in temperature across England and Wales at that time, which seems the most likely explanation for the excess observed. Cold weather previously has been linked with excess deaths [21], although other circulating respiratory viruses provide an alternative explanation [22].

The number of excess deaths in the 75–84 years age group was 3596. This can be compared to the winter season of 1999/2000, a period of high influenza A/H3 circulation, when the HPA estimated that over 21 000 deaths occurred [8]. However, it should be noted that the 1999/2000 estimate was obtained using a model using monthly data on all-cause, all-age deaths by date of registration, thus these estimates may not be strictly comparable.

Access to timely disaggregate (by age) mortality data, coupled with a time-series analysis adjusting for reporting delays, is a much more powerful approach than previous methods employed in England and Wales. Using the system presented here, it is possible to produce rapid in-season monitoring, as well as end-of-season estimates of excess mortality. However, some potential weaknesses are associated with this novel monitoring system.

We know from national surveillance between 27 April 2009 and 27 March 2010, that 354 deaths in persons with confirmed H1N1 infection have been identified (the majority in persons with pre-existing health conditions) [7]. The particular method presented here detects all-cause death counts significantly above those expected on a week-to-week basis. One consequence of this approach is that small and gradual increases over several weeks and across several age groups may not be detected. We have attempted to take account of this by considering total deaths over a number of weeks (as presented in Table 1). To take account of this in-season, a prospective CUSUM algorithm with formal control limits run alongside the current system could potentially detect any such gradual increases in mortality.

No formal attribution of the relative contribution of possible explanatory factors has been made, e.g. temperature, influenza, or other respiratory viruses. Differential timing of these factors in the 2009/2010 winter season has allowed their potential impact to be disentangled, whereas in many winters the timing of these factors coincide. Further, by using an all-cause mortality monitoring system without possibility of attribution, it can also be difficult to interpret signals, particularly if no known health event which may

cause excess mortality has been identified. For example, signals were detected in England and Wales at the end of April and early May 2010 for age groups aged 15–44 years; however, the cause of this excess is unknown. Further work needs to be undertaken to permit more accurate attribution of the relevant explanatory factors.

There are long reporting delays in England and Wales for younger persons with no previous contact with health services and for whom the cause of death is more likely to be unknown. We have attempted to correct for this in the current algorithm by a simple age-specific adjustment to the upper detection limit; however, this relies on the assumption that the delay for deaths occurring during important health events such as H1N1 is similar to the observed delay for the last 2 years. If this is different, the adjusted upper limit may not be correct, which may affect the accuracy of the monitoring system.

In conclusion, the novel mortality monitoring system presented here has provided timely signals of excess mortality during the pandemic period. It is an important future resource for monitoring the impact of influenza (both pandemic and seasonal), but also has utility for rapidly estimating excess mortality for other acute public health events such as extreme heat or cold weather.

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All authors are employees of the Health Protection Agency.

## DECLARATION OF INTEREST

None.

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