Critical care surveillance: insights into the impact of the 2010/11 influenza season relative to the 2009/10 pandemic season in England

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In 2010/11, the influenza season in England was marked by a relative increase in impact on the population compared to that seen during the 2009/10 pandemic, with the same influenza subtype, A(H1N1)pdm09, circulating. The peaks in critical care bed occupancy in both seasons coincided with peaks in influenza A(H1N1)pdm09 activity, but onset of influenza in 2010/11 additionally coincided with notably cold weather, a comparatively smaller peak in influenza B activity and increased reports of bacterial co-infection. A bigger impact on critical care services was seen across all regions in England in 2010/11, with, compared to 2009/10, a notable age shift in critical care admissions from children to young adults. The peak of respiratory syncytial virus (RSV) activity did not coincide with critical care admissions, and regression analysis suggested only a small proportion of critical care bed days might be attributed to the virus in either season. Differences in antiviral policy and improved overall vaccine uptake in 2010/11 with an influenza A(H1N1)pdm09 strain containing vaccine between seasons are unlikely to explain the change in impact observed between the two seasons. The reasons behind the relative high level of severe disease in the 2010/11 winter are likely to have resulted from a combination of factors, including an age shift in infection, accumulation of susceptible individuals through waning immunity, new susceptible individuals from new births and cold weather. The importance of further development of severe influenza disease surveillance schemes for future seasons is reinforced.

Introduction

Following the emergence of the novel pandemic influenza A(H1N1)pdm09 virus in April 2009, the United Kingdom (UK) experienced two waves of pandemic virus activity in summer and autumn 2009 resulting in widespread infection in the population, particularly in younger age groups with 65% of 5 to14 year-olds estimated to be infected post-second wave [1,2]. Although overall case-severity was low [3], a substantial number of severe cases (hospitalisations, intensive care admissions and fatalities) were reported, particularly in children under five years-old and individuals with underlying clinical risk factors for severe influenza [4,5]. In 2010/11, despite apparent widespread influenza A(H1N1)pdm09 infection in 2009/10 [2], the first post-pandemic influenza season was marked by reports of an early rapid increase in influenza A(H1N1) pdm09 cases admitted to intensive care, together with an increase in community indicators such as calls to health service help lines over the Christmas period [4,6-8]. The impact and pressure reported on these services at this time over the Christmas period was greater than that seen during the 2009 pandemic in England [6,7,9], with a notable age shift in hospitalised cases apparent from children <15 years of age to young adults aged 15 to 64 years [1,7,9]. The observation of increased influenza A(H1N1)pdm09 impact in the immediate post-pandemic period has been reported in only a few other European countries (Ireland, Denmark and Greece) [4,10,11].

The intensity and severity of any influenza season is influenced by a variety of factors related to the virus, the host and the environment [12-14]. Continual genetic evolution of the influenza virus can modify its ability to invade host tissues and subsequent interaction with the host's immune system. If the virus differs significantly antigenically from previously circulating viruses, there may be an insufficient immune response raised following infection, potentially resulting in a more severe outcome [12]. Various host factors will also dictate the severity of influenza infection – such as age and presence of underlying chronic disease [13]. These can be modified by interventions such as prior vaccination or the use of antivirals. Environmental factors such as cold temperature and low levels of humidity can enhance transmission, both in terms of the stability of the virus and vulnerability of the host to infection [14]. Finally, other viruses or bacteria, often with their own seasonality, may circulate and interact with influenza,

potentially interfering with infection [15] or affecting symptoms through co-infection [16].

In an article in Eurosurveillance, Mytton and colleagues highlighted the increased impact of the 2010/11 influenza season in England compared to the 2009 pandemic and suggested this may be related to differences in intervention strategy between the two periods [6]. One of the data sources examined was critical care bed occupancy with suspected and confirmed influenza cases, with the peak occupancy observed in 2010/11 four times that seen in the pandemic year. This paper analyses this data source in more detail, presenting it alongside data on respiratory virus and bacterial circulation and ambient temperature, together with information on public health interventions over that period to interpret the observed increase in impact.

Methods

The majority of hospitals in England are public and part of the National Health Service (NHS), with many containing critical care beds (including intensive care units and high dependency units). Daily critical care bed occupancy data were available from the Department of Health co-ordinated Winterwatch scheme [17] for both the 2009/10 and 2010/11 influenza seasons for the majority of 163 NHS acute trusts in England (157 in 2009/10 and 163 in 2010/11). Data were collected daily from Monday to Friday from week 51 2010 (week commencing 20 December) to 7 2011 (week commencing 14 February), and from week 29 2009 (week commencing 13 July) to 8 2010 (week commencing 15 February) on the total number of patients who were occupying critical care beds with confirmed or suspected influenza by age group (<5 years, 5–15 years, 16–64 years and ≥65 years) and by Strategic Health Authority (East of England, East Midlands, London, North East, North West, South East, South West, West Midlands and Yorkshire and Humber). For both seasons, data were not collected for four days over the Christmas period. Where results are presented as rates per 100,000 of the population, the population denominator for the 2009/10 season corresponds to the Office for National Statistics (ONS) mid-2009 England estimates and the 2010/11 season to the mid-2010 estimates, both of which are available by age group and region [18,19]. As daily information was only available on the total number of patients in critical care and not on new admissions, the daily prevalence of critical care bed occupancy – critical care bed days – with patients with suspected influenza, was compared. The overall burden of influenza in each season on critical care was then determined by calculating the cumulative number of critical care influenza bed days in 2010/11 and 2009/10.

The data collected from Winterwatch are suspected influenza cases. It cannot be assumed such critical care bed occupancy results solely from influenza infection, as it could also be due to other respiratory infections. Weekly positivity of typical winter circulating respiratory viruses (defined as the proportion of all samples tested weekly that tested positive for a given respiratory virus) by week of sample in England from the English Respiratory Datamart system (RDS) [1,7] were examined for the 2009/10 pandemic period and the 2010/11 influenza season (from week 20 2009 to week 8 2011). Samples received through this system are collected and tested by participating hospitals from secondary care (and to a lesser extent from primary care). This included influenza A(H1N1)pdm09, other influenza A subtypes, influenza B, adenovirus, parainfluenza, respiratory syncytial virus (RSV), rhinovirus and human metapneumovirus (hMPV). Influenza activity was assessed by positivity rates to reduce the effect of possible changes in laboratory testing in the year following the pandemic. Influenza-like illness (ILI) consultation rates were not considered in this study; changes in healthcare seeking behaviour during the pandemic and in the subsequent influenza season mean that the ILI rates seen are unlikely to be a true reflection of ILI in the community. As there were reports of an increased number of bacterial co-infections in 2010/11 [20] and these data were not available through RDS, weekly counts of invasive *Streptococcus pyogenes* and *S. pneumoniae* by week of sample in England were retrieved from Labbase, the national laboratory reporting database [21].
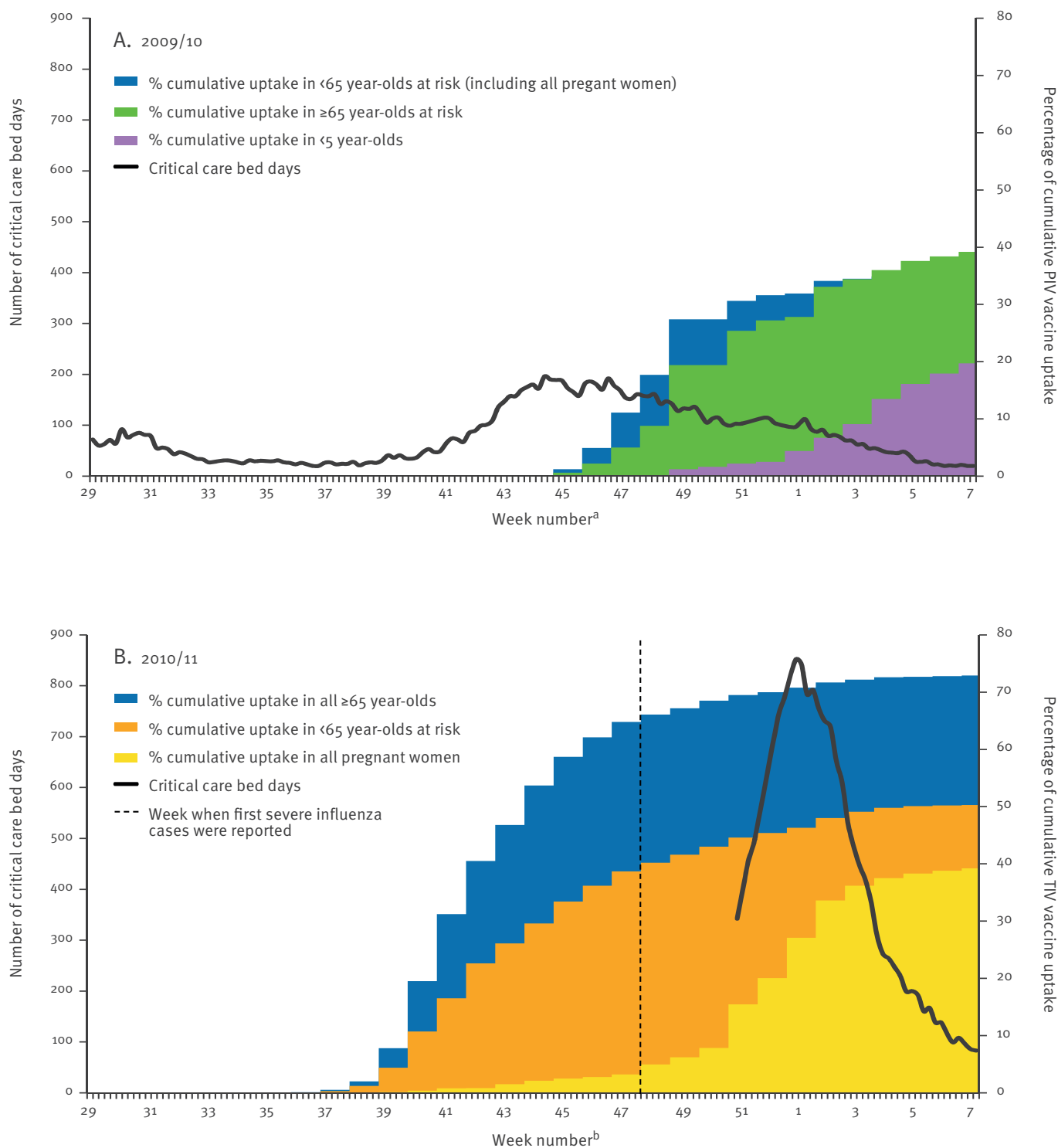
The Joint Committee for Vaccination and Immunisation (JCVI) recommended that the groups offered the monovalent pandemic influenza vaccine (PIV) in October 2009 should include both (i) individuals aged 65 years and older in a clinical risk group for severe influenza and (ii) individuals aged six months to under 65 years in clinical risk groups for severe influenza. All pregnant women were also offered vaccination. Furthermore, all healthy children aged six months up to five years were offered PIV from December 2009 [1]. A trivalent seasonal influenza vaccine (TIV) containing the influenza A(H1N1)pdm09 strain was recommended for use in 2010/11 and offered to all those aged 65 years-old and above and to those aged six months to 65 years-old falling in a clinical risk group. All pregnant women were also offered vaccination with TIV for the first time in 2010/11 [7]. Weekly percentage uptake of vaccinations in the eligible groups across England was reported through Immform, the Department of Health web portal [22].

Daily mean and minimum Central England Temperature (CET), a measurement which is broadly representative of temperatures across England, was obtained over the study period from the Met Office [23]. Weeks of notably cold weather were reported when minimum daily temperatures were below 2°C for more than two consecutive days [24].

Once retrieved, the timing of critical care bed occupancy was compared to respiratory virus activity, influenza vaccine uptake and changes in antiviral usage policy in the two seasons. In an attempt to further validate the contribution of respiratory viruses, a negative

FIGURE 1

Daily number of critical care beds occupied with suspected influenza cases in England and weekly cumulative percentage vaccination uptake by risk groups in England in 2009/10 and 2010/11 influenza seasons

A. 2009/10

- % cumulative uptake in <65 year-olds at risk (including all pregant women)
- % cumulative uptake in ≥65 year-olds at risk
- % cumulative uptake in <5 year-olds
- Critical care bed days

B. 2010/11

- % cumulative uptake in all ≥65 year-olds
- % cumulative uptake in <65 year-olds at risk
- % cumulative uptake in all pregnant women
- Critical care bed days
- Week when first severe influenza cases were reported

PIV: monovalent pandemic influenza vaccine; TIV: trivalent seasonal influenza vaccine.

Uptake of vaccine is only monitored for the groups in which vaccination is recommended. While PIV in 2009/10 was recommended for all <5 year-olds, TIV was not recommended for all <5 year-olds in 2010/11 and so the uptake in this group is not shown in panel B.
In 2009/10, uptake in <65year-olds at risk for severe influenza included all pregnant women regardless of whether they had an underlying risk factor. In 2010/11, uptake in <65year-olds at risk included pregnant women only if they had an underlying risk factor.

a   Begining 13 July 2009.
b   Begining 19 July 2010.

Figure 2

Overview by age groups of cumulative number of critical care bed days occupied with suspected influenza cases per 100,000 population, and cumulative proportions of samples positive for influenza A(H1N1)pdm09 and respiratory syncytial virus, England, influenza seasons 2009/10 and 2010/11

A. Critical care bed days occupied with suspected influenza cases

B. Samples positive for influenza A(H1N1)pdm09[a]

C. Samples positive for respiratory syncytial virus[a]

■ 2009/10   ■ 2010/11   I 95% confidence intervals
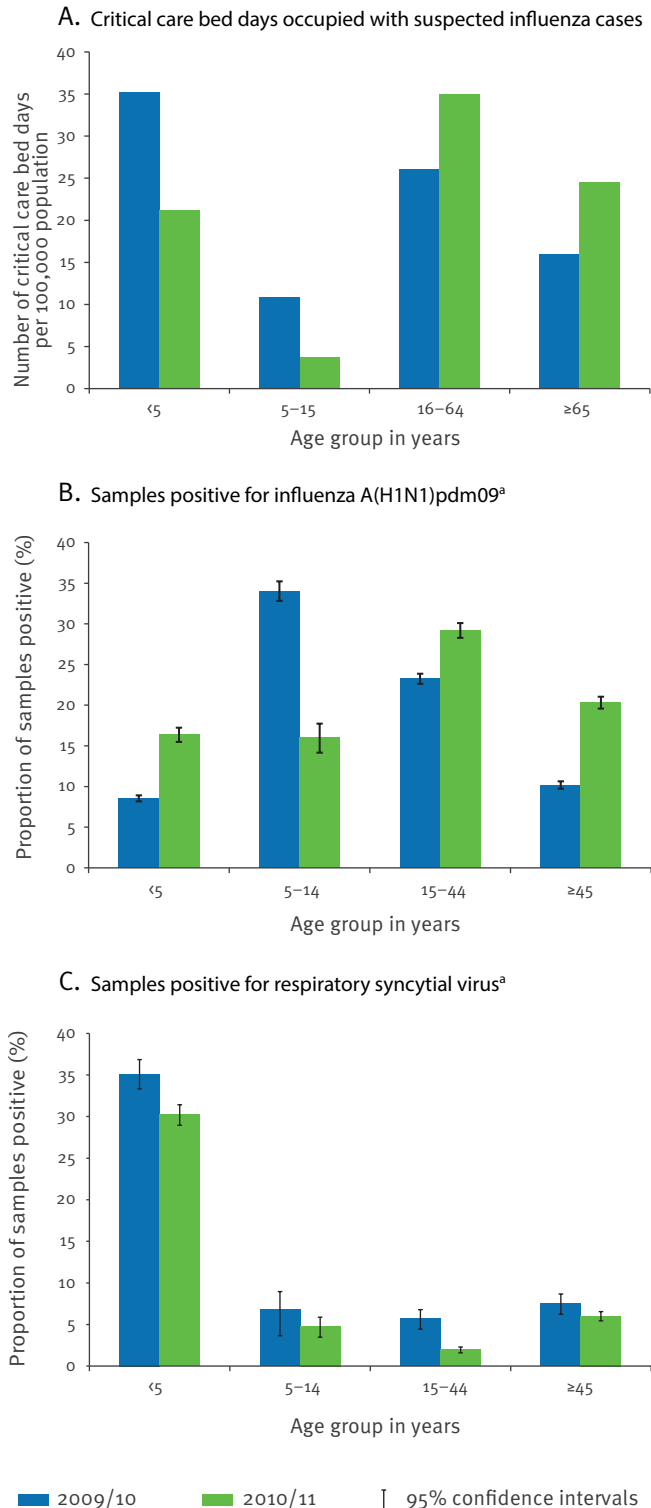
[a] Data obtained through the Respiratory Datamart system.

binomial regression model with an identity link (assuming an additive effect of the respiratory viruses) was used to model the weekly number of critical care bed days, including weekly positivity of respiratory viruses through RDS (as outlined above) as potential explanatory variables. As information on RSV positivity was only collected from week 47 2009 in RDS when it was already circulating, values for positivity for preceding weeks were extrapolated back to zero based on information from other surveillance systems. Linear interpolation of critical care bed days was carried out for the four days when Winterwatch data was not collected each season. To allow for a delay in hospitalisations from infection onset, viral positivity was lagged by up to two weeks and, as seasonal influenza A strains can vary in severity, an interaction term between influenza A positivity and season was included if significant. Stepwise regression was carried out through comparison of Akaike information criterion (AIC) values to remove variables that did not contribute to the model. Remaining variables were kept if their corresponding model coefficients were significant ($p<0.05$) and biologically credible (greater than zero). Information on *S. pyogenes* and *S. pneumoniae* positivity was not available and so their corresponding activity was not included in the regression analysis.

The number of critical care bed days each week attributed to a given respiratory virus was obtained by multiplying the number of bed days by the virus-specific coefficient [25] and summing across each season.

Results

Overall critical care burden by age group and region in 2009/10 and 2010/11

As previously reported [6], a larger burden of suspected influenza cases occupying critical care beds was seen in winter 2010/11 compared to 2009/10, despite a shorter period of time over which influenza activity was detected. In addition, data on critical care bed occupancy was available for only nine weeks in 2010/11 compared to 32 weeks in 2009/10 (Figure 1). The total cumulative number of critical care bed days occupied by patients with suspected influenza in England was almost 30% higher in 2010/11 compared to 2009/10 (15,304 bed days compared to 11,831).

A notable upward shift was observed in the age distribution of critical care bed occupants with suspected influenza in 2010/11 compared to 2009/10 (Figure 2A). On the peak day in both seasons, the majority of critical care bed occupants with suspected influenza were in the 16 to 64 year-old group (82.1% of patients in 2009/10 compared to 78.6 % in 2010/11). However when the population rate was calculated by age group and compared by season, the cumulative number of critical care bed days per 100,000 population was comparatively higher in 2010/11 for adults aged over 15 years (highest rate in 2010/11 of 35.0/100,000 in 16 to 64 year-olds), while children aged 15 years or younger

Daily number of critical care beds occupied per 100,000 population with suspected influenza cases and weekly positivity of influenza A(H1N1)pdm09, influenza B and respiratory syncytial virus recorded in England, influenza seasons 2009/10 and 2010/11
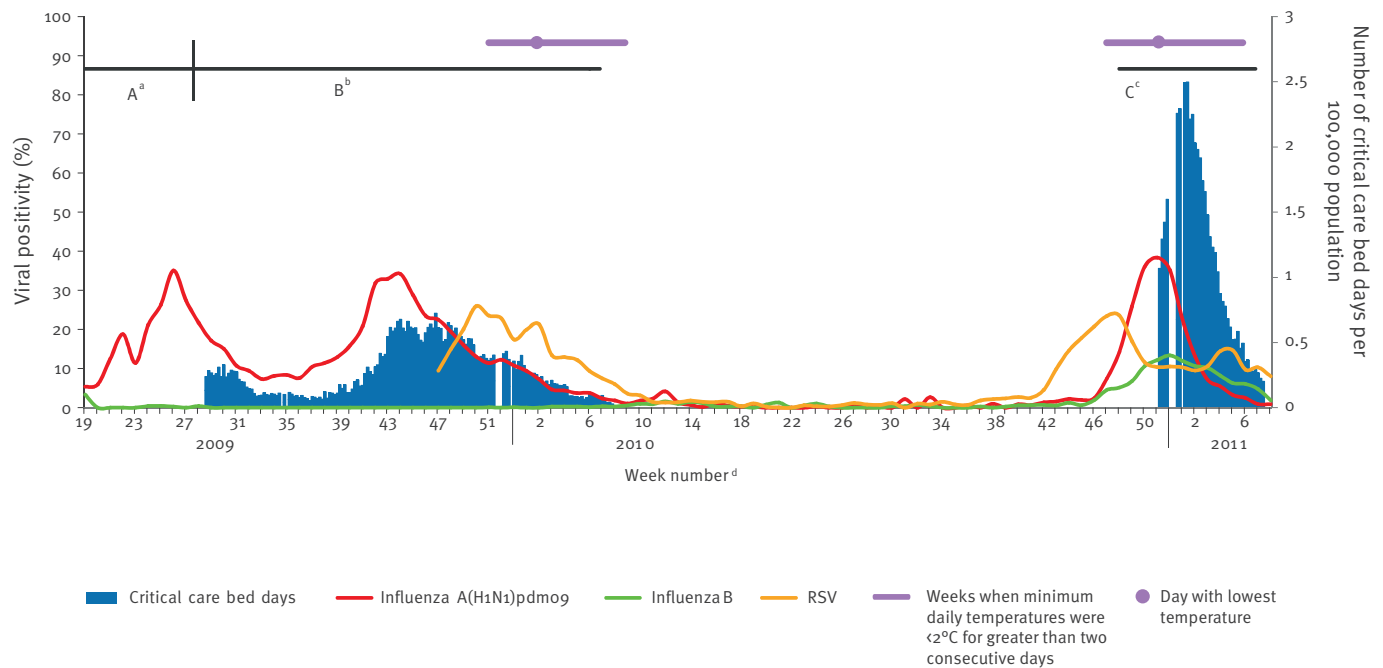
RSV: respiratory syncytial virus.

Positivity is defined as the proportion of all samples tested weekly that tested positive for a given respiratory virus.

[a]   Antivirals distributed as treatment of cases and prophylaxis of close contacts through Flu Response Centres.
[b]   Antivirals distributed as treatment for all via the National Pandemic Flu Service and the National Health Service.
[c]   Antivirals distributed as treatment to those in intensive care with underlying clinical risk factors via the National Health Service.
[d]   Starting 10 May 2009.

were comparatively more affected during 2009/10 (highest rate in 2009/10 of 35.3/100,000 in under five year-olds). The largest number of critical care beds occupied with suspected influenza cases in 2009/10 by region on the peak day was in London (39 cases, 19.9%), whereas on the peak day in 2010/11 the largest was in the North West (169 cases, 19.9%).

Respiratory virus activity in 2009/10 and 2010/11

Influenza A(H1N1)pdm09 was the dominant circulating respiratory virus in both seasons, reaching a peak weekly positivity in 2009/10 of 35.1% in week 26 2009 and 34.2% in week 44 2009, and in 2010/11 of 38.4% in week 51 2010 as detected through RDS (Figure 3). There was additional notable co-circulation of influenza B in 2010/11, reaching a peak of 13.4% positivity in week 52 2010 compared to a peak of 1.6% the previous season (week 12 2010) (Figure 3). A low number of other influenza A viruses (where subtyped, all subtypes were A(H3)) were detected in both 2009/10 and 2010/11 (with a peak positivity of 3.2% in week 52 2009

and 2.5% in week 52 2010). Overall, an age shift was evident in influenza A(H1N1)pdm09 positive samples in RDS between the first two waves of the pandemic (highest positivity in 5–14 year-olds in 2009/10) and the 2010/11 season (highest positivity in 15–44 year-olds) (Figure 2B) which corresponds to the age shift seen in critical care bed days (Figure 2A).

Overall RSV positivity reached a similar peak level in both seasons, 26.0% in week 50 2009 and 23.6% in week 48 2010, although a bimodal distribution either side of peak influenza A(H1N1)pdm09 positivity was observed in 2010/11, with a second peak positivity of 14.7% in week 5 2011 (Figure 3). Overall positivity was highest in under five year-olds in both seasons (Figure 2C), with a comparatively increased positivity in those aged 45 year-olds and older in 2010/11 during December and January relative to the same age group in December and January 2009/10.

Adenovirus, parainfluenza and hMPV activity remained low during the 2009/10 and 2010/11 winter seasons not

exceeding 10% during this period apart from a peak in adenovirus of 17.3% in week 51 2009 (data not shown). Rhinovirus had the highest positivity of 35.8% in week 40 2010 which decreased down to 1.8% by week 52 2010 when reported critical care bed occupancy started to increase.

Allowing for a one to two week lag in influenza detection to hospitalisation, suspected influenza-associated critical care bed days in the 2010/11 season coincides with influenza A(H1N1)pdm09 and influenza B activity reported through RDS, with the shape more closely mirroring that of the pandemic strain (Figure 3). The first peak of RSV positivity in 2010/11 occurred three weeks prior to that of influenza A(H1N1)pdm09 and the second occurred after the number of suspected influenza-associated critical care bed days had already started to decline. In 2009/10, influenza A(H1N1) pdm09 positivity followed a similar pattern to critical care bed occupancy with very low influenza B positivity seen (Figure 3). RSV activity peaked six weeks after influenza A(H1N1)pdm09 and after the peak of critical care bed occupancy in 2009/10.

The final regression model contained significant terms for influenza A(H1N1)pdm09 positivity lagged by two weeks and RSV positivity – no critical care bed days were significantly attributed to influenza B, other influenza A subtypes or other respiratory viruses (Table). Visual inspection of the model showed a good fit to the data, although an overestimation of the number of critical care bed days was seen at the beginning of the critical care bed dataset in 2009/10 and a slight underestimation was seen at the peak of occupancy in 2010/11. The majority of critical care bed days were attributed to influenza A(H1N1)pdm09, 13,142 (95% confidence interval (CI): 11,278–15,005) in 2009/10 and 17,785 (95% CI: 15,217–20,354) in 2010/11. The number attributed to RSV was 1,825 (95% CI: 0–3,689) in 2009/10 and 795 (95% CI: 0–3,364) in 2010/11. This compares to a total number of critical care bed days of 12,629 in 2009/10 and 17,939 in 2010/11 after linear interpolation for days of missing data.

Weekly reports of Labbase *S. pyogenes* specimens remained low during 2009/10 and 2010/11, peaking at 62 in week 14 2010 and 77 in week 52 2010. *S. pneumoniae* invasive specimens increased in number during the winter compared to the summer months in both 2009/10 and 2010/11, reaching a notable peak of 270 in week 53 2009 and 389 in week 52 2010. This compares to weeks of peak critical care bed occupancy in week 44 2009 and week 1 2011.

In 2009/10, the weeks during which minimum temperatures were below 2°C for greater than two consecutive days (weeks 51 2009–8 2010) occurred seven weeks after the peak in critical care bed occupancy in week 44 2009. However in 2010/11, the weeks of low temperatures (weeks 47 2010–5 2011) coincided with the first reports of increases in severe cases of influenza,

TABLE

Estimated critical care bed day attribution in each respective 2009/10 and 2010/11 influenza season by virus, using a negative binomial regression model, England

Virus[a]	Attributed critical care bed days[a,b] (95% confidence interval)	
	2009/10	2010/11
Influenza A(H1N1)pdm09	13,142 (11,278–15,005)	17,785 (15,217–20,354)
Respiratory syncytial virus (RSV)	1,825 (0–3,689)	795 (0–3,364)

[a] Viral activity initially assessed and not included in the final model include: influenza B, other influenza A subtypes, adenovirus, parainfluenza, rhinovirus and human metapneumovirus.

[b] Attributed critical care bed days = (A(H1N1)pdm09 positivity (two week lag))*Season + RSV positivity. Whereby positivity is defined as the proportion of all samples tested weekly that tested positive for a given respiratory virus.

with the peak in influenza activity and critical care bed occupancy occurring four weeks later in week 1 2011 (Figure 3).

Interventions
The PIV vaccination programme began after the autumn 2009 pandemic influenza wave had already peaked (Figure 1). This meant that at the peak of critical care bed occupancy at the end of October (week 44), uptake in both 65 year-olds and older in a clinical risk group, and under 65 year-olds in a clinical risk group (including pregnant women) had only reached 0.1% (Figure 1A). Final cumulative uptake of PIV across England in target groups at the end of the influenza season was 35.4% for those under 65 years in a clinical risk group and 14.9% for pregnant women [26]. The PIV programme in healthy children under five years-old did not start until December 2009, which was over four weeks after the critical care bed peak in the autumn 2009 wave. The programme reached a final cumulative uptake of 23.6%.

In the 2010/11 season, when the first cases of severe influenza were reported in week 48 2010, uptake of TIV in all 65 year-olds and older was already 66.1% and 40.2% in under 65 year-olds in a clinical risk group (Figure 1B). Uptake in pregnant women was only 5.0%. At the peak of critical care bed occupancy in 2010/11, uptake had reached 70.8% in 65 year-olds and older, 46.3% in under 65 year-olds in a clinical risk group and 27.1% in pregnant women.

The changes in antiviral usage policy over 2009 to 2011 are indicated in Figure 3. During the containment phase at the beginning of the pandemic, antivirals

were distributed to the first detected cases as treatment with prophylaxis of their close contacts through Flu Response Centres set up by the Health Protection Agency (HPA) in collaboration with the NHS [27]. Following a sharp increase in the number of cases in June 2009, with evidence of community transmission, the treatment phase began on 2 July 2009 when antivirals were offered as treatment for all suspect cases, and prophylaxis was no longer offered other than in certain specific circumstances. Individuals with underlying clinical risk factors were assessed and received antivirals through the NHS and clinical cases without underlying risk factors were managed through the National Pandemic Flu Service (NPFS), a national telephone and internet-based service set up shortly after the start of the treatment phase. This was continued until February 2010.

During winter 2010/11, antivirals were administered through the NHS following standard National Institute for Health and Care Excellence (NICE) guidance for use during seasonal influenza activity to those with underlying clinical risk factors for severe disease [28].

Discussion

In the winter of 2010/11, the first post-pandemic season, influenza activity due to influenza A(H1N1)pdm09 viruses was high, with a bigger impact on critical care services from suspected influenza cases and a marked age shift in cases from children to adults, relative to 2009/10. There were differences in antiviral policy between the seasons and overall vaccine uptake with an influenza A(H1N1)pdm09 strain-containing vaccine was much higher at the peak level of critical care activity in 2010/11 compared with 2009/10. The peaks in suspect influenza critical care admissions in both seasons coincided with peaks in influenza A(H1N1)pdm09 positivity, but additionally in 2010/11 coincided with influenza B positivity, notably cold weather and increased reports of *S. pneumoniae* infection. Infections due to RSV and other respiratory viruses do not appear to make a large contribution to these critical care admissions in either season.

Following influenza A(H1N1)pdm09 activity in 2009/10, the pandemic virus continued to circulate in the UK with increased activity and impact the following season. The increase in critical care bed occupancy in 2010/11 relative to 2009/10 seems to be driven primarily by influenza A(H1N1)pdm09 and coincided with increases in influenza A(H1N1)pdm09 positivity and other indicators of influenza activity, including general practitioner (GP) consultations, hospitalisations and excess deaths [1,7,9]. In addition, regression analysis suggests that influenza A(H1N1)pdm09 contributed to the increase of critical care admissions of patients with suspected severe influenza rather than other influenza strains. Although influenza B was circulating in 2010/11 and peak positivity coincided with the peak in critical care bed occupancy, terms for this virus were not significant in the regression analysis, suggesting

little contribution to intensive care unit admissions. Through other data sources, cases of influenza B confirmed hospitalised patients and fatalities were reported in 2010/11, though the proportions were low, with the proportion of severe cases due to influenza B increasing with time over the season and the highest rates of hospitalisation seen in children [7,9].

The pandemic influenza virus did appear to circulate predominantly in older age groups in 2010/11 compared to 2009/10. A higher proportion of adults aged over 15 years were admitted to critical care in the winter of 2010/11 relative to that observed during the pandemic in England, with the highest proportion seen in 16 to 64 year-olds. This age shift has been documented following previous pandemics [29] and is in agreement with observations from other surveillance systems in England and elsewhere following the 2009 pandemic, such as in Taiwan and Greece [3,9,11,30,31]. Circulation of the pandemic virus in 2009 mainly occurred in children [1]. The consequences for the following season therefore were lower numbers of susceptible children, but there still remained a pool of susceptible adults within which circulation of the virus could occur once transmission started [2]. The age-dependency in infection-severity of influenza A(H1N1)pdm09 infection is well documented [4], with increasing severity with increasing age at infection. The burden and severity of underlying chronic conditions also increases with increasing age which can be exacerbated by influenza infection. Therefore this observed age shift to older age groups is likely to have been associated with an overall increase in infection severity and thus impact. Other potential contributory factors may include reinfection, resulting from waning immunity and/or vaccine-related-immunity, and introduction of new susceptible infants [31,32].

The circulating influenza A(H1N1)pdm09 viruses were found to be well matched to the influenza A/California/07/2009 strain in the trivalent influenza vaccine used at the time in 2010/11 [7], with reported vaccine effectiveness in 2010/11 of 51% against GP attended virologically confirmed infection, compared to 72% for the adjuvanted monovalent pandemic influenza vaccine used in 2009 [33,34]. Although the PIV was more effective than the 2010/11 TIV, it was supplied generally late in the 2009 pandemic. At the peak of critical care impact in 2010/11, and indeed several weeks prior to when the first severe influenza cases were reported, uptake of the TIV was at very much higher levels than that seen at the peak of critical care impact in 2009/10 with the monovalent pandemic vaccine. Therefore the lower impact of pandemic influenza in 2009/10 cannot be attributed to comparatively higher and more timely vaccine uptake during the pandemic, than in 2010/11.

It has been suggested that a reduced level of antiviral usage in 2010/11 compared to that during the 2009 pandemic could be an explanation of the increased impact

of influenza in the following season [6]. It is unclear, however, how many hospitalisations were averted from distribution of antivirals through the NPFS and the NHS during this pandemic period. Although it is not known during the pandemic what proportion of symptomatic infections in the community received antivirals, only a relatively small proportion of cases that were hospitalised with confirmed influenza infection, 10 to 12%, had reportedly received antivirals prior to admission [5,35], with most cases receiving antivirals after admission. Considering the low level of reported effectiveness of antivirals in preventing hospitalisation of influenza cases [36], using the screening method [37] a crudely estimated 15% of suspect cases received antivirals in the community (assuming 25% effectiveness [36] and 12% of hospitalised cases received antivirals prior to admission). Therefore their use in the community during the pandemic is unlikely to fully explain the difference in impact seen through the Winterwatch scheme between 2009/10 and 2010/11.

Of the other winter circulating respiratory viruses that might explain suspected influenza critical care admissions, RSV positivity was high, though compared to critical care bed occupancy, RSV activity occurred later than the peak in 2009/10 and earlier in 2010/11 than critical care occupancy, suggesting little contribution in both seasons. This observation is supported by the regression analysis which attributed only a small proportion of critical care bed days to RSV in both seasons. No notable circulation of other respiratory viruses was observed at this time. A peak was seen in the number of *S. pneumoniae* invasive infections which, unlike 2009/10 coincided with the peak in critical care bed occupancy in 2010/11 and the circulation of influenza, however no information was available on the number of samples tested, preventing calculation of the positivity and a comparison between seasons. Bacterial co-infections amongst influenza cases were reported in 2010/11 in the UK complicating seasonal influenza, which may have contributed to increases in case severity and thus impact [20].

Compared with 2009/10, lower temperatures were seen in 2010/11 and the timing coincided with the beginning of influenza activity whereas the peak of the second pandemic wave in 2009 occurred prior to winter climate. Transmission of influenza is dependent on temperature, with cold weather thought to favour it [14,31]. From the viral point of view, if the transmission and impact of the virus changed, it could be argued that this resulted from changes in the influenza virus. Despite several genetic changes leading to an increase in genetic diversity observed amongst the 2010/11 circulating pandemic viruses in the UK relative to seen in 2009/10, no significant antigenic drift was detected and there were no immediately obvious genetic differences between viruses recovered from fatal and severe cases compared with those with mild disease [7,38]. However, genome-wide changes observed in pandemic viruses from 2010/11 have been reported and might

have influenced the biological properties of the virus, improving virus fitness and consequently have an impact on virulence and/or transmission [39]. The combination of this, together with the existence of a large pool of susceptible young adults and the possibility of waning antibody protection in children infected the previous season [31,32] may explain the occurrence of further spread of influenza in the population.

There are some limitations with the data used for this analysis. Only prevalence data on critical care bed occupancy of suspected cases were available - no information of length of stay of each patient was collected, with evidence suggesting that, on average, there was a longer length of stay in critical care in the post-pandemic period [40]. There was no coverage through Winterwatch on critical care bed occupancy during the first wave of the pandemic. However, the number of laboratory-confirmed hospitalisations in England in the first wave was less than that seen during the second wave [5] and comparatively lower severity noted [1,3]. It is therefore likely to have resulted in critical care bed occupancy levels similar to, or lower than, seen in the second pandemic wave. It is also important to note this is an ecological study: no individual-level information was available on infection, co-infection or intervention uptake through the Winterwatch data source. Additionally, the outcome of each patient was not known. Observations from separate mortality surveillance schemes operating during these seasons have been reported elsewhere [7] but for future seasons, individual-level severe influenza surveillance will be invaluable to build on these observations and directly assess potential associations.

Some countries observed influenza A(H1N1)pdm09 circulation in 2010/11, others experienced a predominately influenza B season in 2010/11 (e.g. Norway) and yet others predominately an A(H3N2) season (e.g. Canada, United States) [10,41,42]. In the countries where influenza A(H1N1)pdm09 circulated, only a few reported a similar relative increased impact in 2010/11 (e.g. Greece, Taiwan, Denmark and Ireland) [4,10,11]. Such a post-pandemic phenomena has been documented previously, e.g. following the 1918 pandemic [43]. The reasons for this large range of observations between countries are likely to be multifactorial and require further exploration.

The intensity and impact of influenza A(H1N1)pdm09 virus activity in 2010/11 in England was not predicted and occurred at a time of year when extreme cold weather was being experienced and hospital resources were already stretched [8,44]. Data from previous pandemics indicate the occurrence of substantial waves of influenza activity following initial pandemic waves, and might therefore have been an indication that substantial activity would be expected in the winter of 2010/11. On the other hand, serological population based data indicated that a large proportion of the population had experienced influenza A(H1N1)pdm09

infection in 2009/10, many with a sub-clinical illness. The reasons behind the comparative increase in impact of severe influenza in 2010/11 relative to 2009/10 are thus likely to have resulted from a combination of factors, including an age shift in infection, accumulation of susceptible individuals through waning immunity, new susceptible individuals from new births, cold weather and a possible change in the virus. Although the majority of critical care bed days are likely to have resulted from influenza A(H1N1)pdm09 in both seasons, the mechanism resulting in increased impact still remains uncertain. For future seasons, it is important that severe influenza disease surveillance schemes are further developed to collect and analyse data in a timely fashion to inform prevention and control activities.

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