Is the onset of influenza in the community age-related?

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SUMMARY

We studied the spread of influenza in the community between 1993 and 2009 using primary-
care surveillance data to investigate if the onset of influenza was age-related. Virus detections
[A(H3N2), B, A(H1N1)] and clinical incidence of influenza-like illness (ILI) in 12·3 million person-
years in the long-running Royal College of General Practitioners-linked clinical-virological surveillance
programme in England & Wales were examined. The number of days between symptom onset and the
all-age peak ILI incidence were compared by age group for each influenza type/subtype. We found
that virus detection and ILI incidence increase, peak and decrease were in unison. The mean interval
between symptom onset to peak ILI incidence in virus detections (all ages) was: A(H3N2) 20·5 [95%
confidence interval (CI) 19·7–21·6] days; B, 18·8 (95% CI 15·8·0–21·7) days; and A(H1N1) 17·0 (95%
CI 15·6–18·4) days. Differences by age group were examined using the Kruskal–Wallis test. For A
(H3N2) and A(H1N1) viruses the interval was similar in each age group. For influenza B there were
highly significant differences by age group ($P = 0·0001$). Clinical incidence rates of ILI reported in the
8 weeks preceding the period of influenza virus activity were used to estimate a baseline incidence and
threshold value (upper 95% CI of estimate) which was used as a marker of epidemic progress.
Differences between the age groups in the week in which the threshold was reached were small and
not localized to any age group. In conclusion we found no evidence to suggest that influenza
A(H3N2) and A(H1N1) occurs in the community in one age group before another. For influenza B,
virus detection was earlier in children aged 5–14 years than in persons aged ⩾ 25 years.

Key words: Community, influenza, surveillance, transmission.

INTRODUCTION

The incidence of clinically diagnosed influenza-like ill-
ness (ILI) in persons presenting to general practitioners
(GPs) in England and Wales reported in the Royal
College of General Practitioners (RCGP) surveillance
network is now much less than the incidence reported
30 years ago and reductions have been evident in
every decade since the 1960s [1]. This trend has also
been observed in The Netherlands [2]. During this per-
iod several societal factors may have contributed to de-
clining trends in healthcare utilization for ILI,
including changing lifestyles (less smoking, cleaner
air, less overcrowding, better housing, improved hy-
giene). Specific public health interventions have also

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led to significantly increased influenza vaccine coverage, using improved vaccines over this period of time, during which changes in the biological properties of circulating influenza viruses may also have occurred, such as the changes in receptor-binding properties of A(H3N2) viruses since they first emerged in humans in 1968, as a result of adaptive mutations [3].

The continuous decline in incidence of respiratory ILI consultations since 1968 is not attributable to changes in recording protocols involving episode-coding or data-gathering mechanisms in the sentinel practices, which have remained constant, giving continuity and longevity to the datasets and supporting the suggestions that decline in incidence is due to the factors listed above [4].

Studies of influenza incidence in relation to vaccination policies, and undertaken mainly in households or small communities in the 1970s and 1980s, have led to suggestions that children are mainly responsible for the spread of influenza [5–14]. Changes in influenza-attributable mortality associated with the cessation of universal vaccination of schoolchildren in Japan in the mid-1980s provided indirect supporting evidence for the hypothesis [15]. A review of published literature (pre-2006) on influenza vaccination in children indicated that the evidence for indirect benefits to the community from universal vaccination of children was not conclusive [16]. Since then, a study of universal influenza vaccination of children in Ontario was not able to demonstrate that the resulting reduced infection in children was beneficial to other age groups [17]. A study of laboratory-confirmed influenza A(H3N2) infections in hospital admissions during winters 1995/1996 to 2005/2006 and A(H1N1) pdm09 infections in 2009 (also from Canada) showed that in influenza A(H3N2) seasons, infection occurred an average of 3·9 days earlier in the 20–29 years age group than in the 10–19 years age group, throwing doubt on the hypothesis that younger school-age children lead influenza epidemic waves [18]. On the other hand a randomized controlled trial of vaccinating children in small isolated communities in Canada in 2008 (mixed influenza A and B season) provided limited support for the notion that children drive the spread of influenza [14].

The introduction of the UK childhood influenza vaccination programme, which aimed to target all children aged 2–16 years with the intra-nasal administration of a live-attenuated influenza vaccine, commenced with a pilot in autumn 2013 in which responsibility for administration is shared between primary-care and school health services. It will be important to study the impact of the childhood influenza vaccine programme on the spread of influenza in different age groups using existing surveillance mechanisms for influenza and ILI, including the use of detailed observational data for comparative purposes.

The aim of this study was to examine the timing of influenza incidence which prompted GP consultations measured in virologically confirmed cases and in clinical ILI case reports in differing age groups with a view to establishing if one age group precedes others. We postulated that the primary drivers of influenza transmission would be the first age group in which increasing incidence would be seen in the consulting population.

METHODS

Data sources

The Weekly Returns Service (WRS) of the RCGP is a sentinel general practice surveillance programme in England and Wales which has operated continuously since 1967 [1]. Since 1993, the monitored population (registrations in participating practices) has ranged between 600 000 and 900 000 persons each year: (900 000 persons and 600 GPs in 2009 monitoring about 1·8% of the respective populations). Participating GPs record their clinical diagnoses in electronic medical records where they are stored as Read codes [19]. These records are scanned twice weekly and relevant age- and disease-specific data are transmitted using automated routines to a central agency for analysis by diagnosis, region and age group. The monitored population is representative of the national population by age group and deprivation [20]. This study is based on 12·3 million person-years observation. Guidelines are given to aid diagnostic precision (fever/feverishness, cough, acute onset, systemic plus respiratory symptoms).

In collaboration with Public Health England and its predecessor organizations (Public Health Laboratory Service and Health Protection Agency), virological surveillance was introduced in the same population under clinical surveillance in 1993. Weekly trends in the incidence of ILI reported in the WRS are well matched by similar trends in virus detections [21]. Before 1999, laboratory investigation was mainly by virus culture of nose/throat swabs; since 2000 investigation has been based on polymerase chain reaction (PCR) methods [22]. We used these community-based surveillance data over seasons (1993/1994 to summer 2009). In 2009 there were two distinct waves of

A(H1N1)pdm09 infection: this study is restricted to the first of these (weeks 24–34).

Analysis

We first examined virus detection counts in each season to determine the dominant virus strain [A(H3N2), A(H1N1), B] which we defined as a minimum of 60% of all virus detections in the network during the whole winter season. As a preliminary, the weekly age-specific influenza–ILI incidence trend in each virus-dominant season was visually compared with the trend in total influenza virus detections (all strains, all age groups) and found to be similar.

For the analysis of virus detection data, we used the midpoint date of the all-age ILI incidence peak week in each season as a standard reference point for further examination of the data. We had previously shown that winter influenza epidemics lasted about 10 weeks during which, incidence was normally distributed around a central peak [23]. Analyses were made in age groups 0–4, 5–14, 15–24, 25–44, 45–64, ≥65 years. For clinical ILI incidence data (for which the date of onset of symptoms was not recorded), we measured the number of weeks between first presentation to the GP and the all-age ILI incidence peak week. For this analysis of ILI incidence, we combined the 15–24 and 25–44 years age groups.

Virus detections

For the analysis of virus detections we broadly followed the methodology published by Schanzer *et al.* [18]. For each virus detection, the number of days between symptom onset (as recorded on the specimen investigation request form) and the midpoint of the ILI incidence peak week in that season was calculated, the longer this interval, the earlier the individual onset of influenza in the overall epidemic curve. The mean and standard deviation was calculated for each age group. The virus strain-specific distributions were examined by age group and differences investigated using the Kruskal–Wallis (KW) test since the data were skewed. We also examined the interval between symptom onset and the date of swabbing (presentation to the GP).

ILI incidence

Although influenza viruses were detected only rarely in the first 8 of the 15 weeks preceding the ILI incidence peak, cases of ILI were reported every week. For each age group, we calculated the ILI incidence per 100 000 registered population in each week. From the age group ILI incidence data aggregated over all seasons according to the dominant virus and including the first 8 of the 15 weeks before the ILI incidence peak week, we calculated the mean and standard deviation as an ILI incidence baseline. For A(H3N2)-dominant seasons the calculation was based on 80 data points (the product of eight measurements in each of 10 seasons); for influenza B, 24 points (8 × 3) and for A(H1N1), 16 points (8 × 2). A 'threshold' incidence was defined as the upper 95% confidence level of the baseline estimate and the week in which this threshold was reached was used as an indicator of epidemic progress for comparing age groups.

The excess age-specific incidence over baseline was examined by age group according to the dominant seasons and is presented graphically.

RESULTS

Seasonal summaries of cases reported, swabs examined and virus detections (Table 1) disclose ten influenza A(H3N2), three influenza B and two influenza A(H1N1) dominant seasons. There is wide variation in the numbers of swabs examined and influenza detections reflecting improvements in methods of virus detection (in particular the introduction of PCR methods) and increasing use of virology in the community setting from a pilot with four sentinel practices in 1993 to a maximum of 60 practices (66% of the sentinel network) in the first wave of the pandemic in 2009.

The alignment between ILI incidence by age group and all age, all strains influenza virus detections is illustrated for all seasons combined (Fig. 1) from 15 weeks before to 5 weeks after the ILI incidence peak week. The overall congruity of age-specific ILI weekly incidence and all-age virus detection trends was individually evident in most seasons excepting some early seasons in which very few influenza viruses were detected (data not shown). Reported ILI incidence was highest in the 0–4 years age group followed by similar incidence in the 15–44 and 45–64 years age groups and slightly lower in the 5–14 and ≥65 years age groups. Influenza virus detections and clinical ILI incidence start to increase appreciably around week −6.

Virus detections

`In the total study period there were 2167 influenza A(H3N2), 762 influenza B and 801 influenza A(H1N1) detections.

Table 1. *Influenza-like illness (ILI) cases: number reported; number swabbed and percent positive (any strain); distribution of positives by strain type*

Season	ILI cases reported			% distribution of flu positives		
	N	Cases swabbed	% swabbed cases pos.	A(H3N2)	B	A(H1N1)
1993/1994	13 086	292	2	100*		
1994/1995	9702	335	9	13	87*	
1995/1996	10 959	677	39	80*	1	19
1996/1997	12 021	843	42	54	45	1
1997/1998	7371	848	17	64*	1	35
1998/1999	9095	742	11	82*	18	
1999/2000	7761	613	44	96*	4	1
2000/2001	5328	727	37	15	66*	19
2001/2002	3617	386	19	52		48
2002/2003	3080	486	20	68*	27	5
2003/2004	4079	658	35	100*		
2004/2005	3423	475	28	73*	14	13
2005/2006	3722	1049	27	25	65*	9
2006/2007	3988	1538	25	96*	1	3
2007/2008	3703	1219	21	5	27	68*
2008/2009	4577	2329	23	87*	9	4
2009 summer	4856	1498	22	1		99*

* Dominant season.
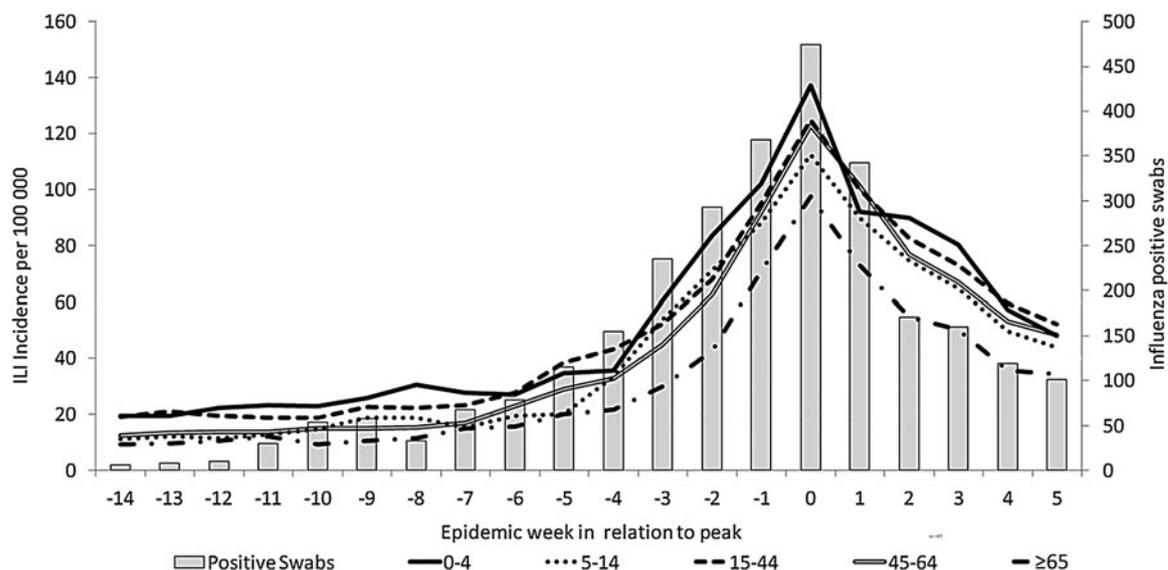
Fig. 1. Average weekly incidence of influenza-like illness (ILI) by age and total influenza virus detections during 15 weeks before and 5 weeks after the ILI incidence peak week.

We calculated the number of days between symptom onset and the midpoint of the ILI incidence peak week for each virus detection and the mean (and 95% confidence interval; CI) for the grouped dominant seasons for each age group (Fig. 2) The mean interval in virus detections (all ages) was: A(H3N2) 20·5 (95% CI 19·5–21·6) days; B, 18·8 (95% CI 15·8–21·7) days; and A(H1N1) 17·0 (95% CI 15·6–18·4) days. Age-group differences were not evident in the grouped data for A(H3N2)-dominant seasons (KW test, P = 0·388) and only marginally in the A(H1N1) seasons (KW test, P = 0·050). In influenza B-dominant seasons the 5–14 years age group had an onset on average 16·51 days before the midpoint
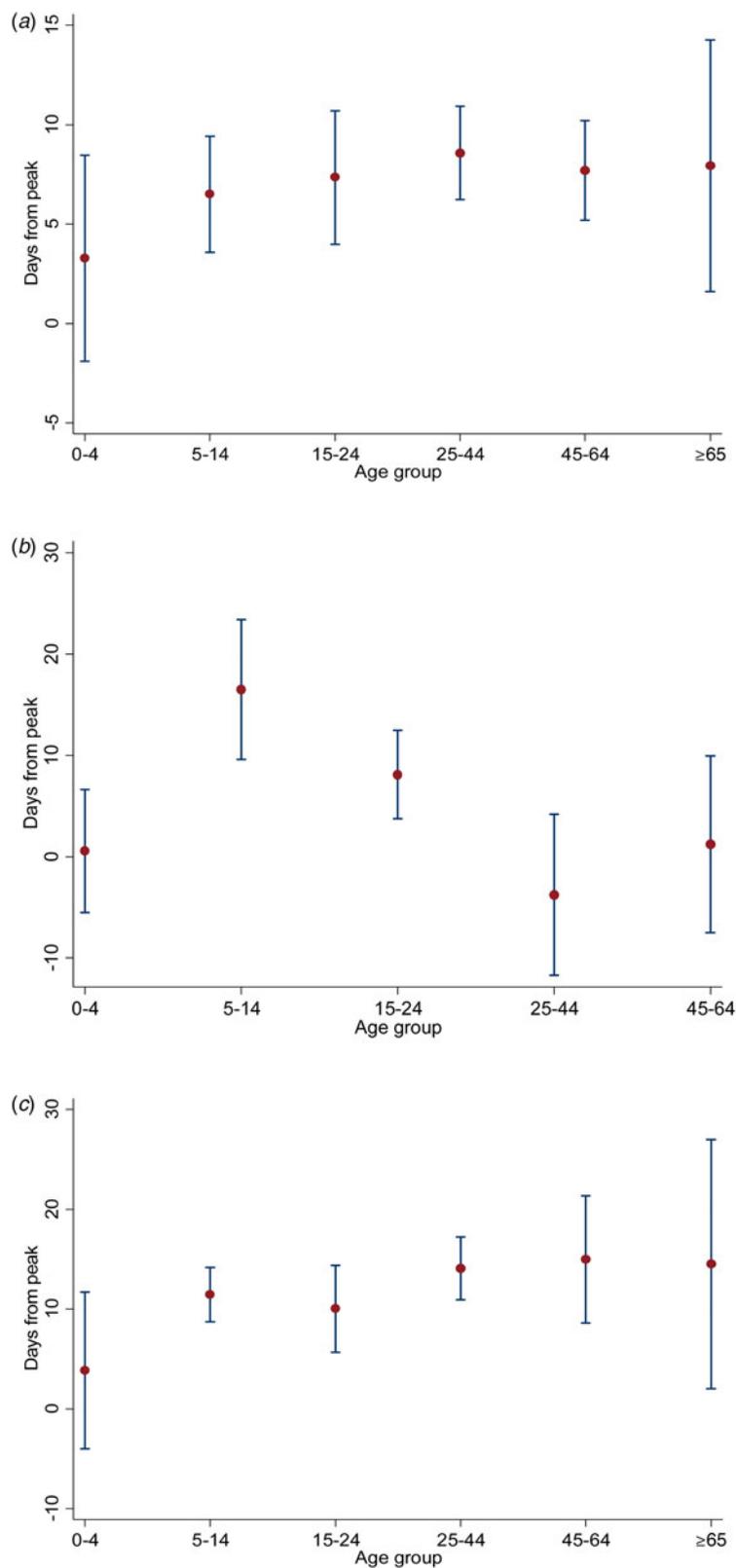
Fig. 2. Interval between reported symptom onset and midpoint of the week of the influenza-like illness clinical incidence peak in virus-confirmed cases in dominant-virus season groups and by age group (mean number of days and 95% confidence interval). (*a*) Influenza A(H3N2), (*b*) influenza B, (*c*) influenza A(H1N1).

of the ILI incidence peak week which differed from the 25–44 years age group which had average onset 3·77 days after the peak (KW test, $P = 0·0001$).

The analysis of the interval symptom onset to date of swabbing (date of presentation to GP) disclosed significant increases in all three strain groups with increasing age-group differences for each virus strain: A(H3N2), KW test, $P = 0·0001$; B, $P = 0·005$; A(H1N1), $P = 0·0001$ (Fig. 3).

ILI incidence

Age- and strain-specific ILI baseline and 'threshold' incidences are given in Table 2, together with the week in which the threshold incidence was reached. The baseline varied substantially according to the strain type, being highest for influenza B and least for A(H1N1). This variation reflects the timing in the year in which they are calculated: influenza B commonly appears in late January and February and the baseline is thus calculated from reported ILI rates in November and December, whereas the A(H3N2) baseline is calculated from weeks earlier in the winter. In contrast the A(H1N1) baseline included spring weeks prior to the summer pandemic wave.

In A(H3N2) and A(H1N1) epidemics there is a general similarity in all age groups with an approximate 3-week interval between the incidence of ILI reaching the threshold level (as measured from the week of presentation) and reaching the week of peak incidence. For influenza B, an age-specific peak distinct from the threshold incidence was seen only in the 5–14 and 15–44 years age groups where the interval between threshold and week of peak incidence was 4–5 weeks.

The weekly excess incidence over baseline is shown by age group and dominant virus in Figure 4. In influenza A(H3N2) and B seasons excesses are first seen around 5 weeks before the clinical incidence peak; and in influenza A(H1N1) seasons, around 3 weeks before. The magnitude of the excesses in each age group and strain type were initially similar for all strain types and remained so for influenza A(H3N2). For influenza B, increasing weekly excesses were most obvious in the 5–14 years age group, clearly apparent in 0–4 and 15–44 years age groups but less apparent in age groups 45–64 and ⩾65 years. For influenza A(H1N1) increasing excesses were also most clearly evident in age groups 0–4, 5–14 and 15–44 years.

DISCUSSION

Virus detections

In the analysis of the number of days between symptom onset to ILI incidence peak in virologically confirmed cases, there was no obvious evidence that influenza A(H3N2) or A(H1N1) viruses were detected consistently in any particular leading age group before others. For influenza B, the 5–14 years age group was the leading age group. The age-stratified analysis of influenza virus detections reported from this community-based surveillance programme over many years, is similar to that described by others using national datasets and similar methods, although we draw attention to some differences [18]. We used the ILI incidence peak as a reference point for the peak of the season, rather than a midpoint chosen from virology data for two reasons: first, because in seasons before year 1998/1999 there were comparatively few reported virus detections, and second, because the spread of the epidemic is determined more by the numbers of persons becoming infected and reporting illness than by the number of virus detections. We used a 60% (Schanzer 80%) virus detection cut-off in determining the dominant virus strain in each season which enabled us to study influenza B seasons.

The results of the KW test must be interpreted recognizing all the biases associated with the swabbing procedure present in observational data. There are often very few viruses detected in the ⩾65 years age group and swabs are often taken early in the season or early in the course of the illness for persons in residential accommodation. The need for specimens to investigate influenza outbreaks is greater early in the course of an epidemic than after the peak.

ILI incidence

The clinical part of this study was based exclusively on the incidence of ILI, although it is well known that the impact of influenza is evident in a wide range of respiratory diagnoses with varying impact according to age and in persons with less severe illness which is not brought to the attention of health professionals [24].

Progress in the incidence of ILI from baseline to threshold levels was similar in all age groups for A(H3N2) and A(H1N1) epidemics. Influenza B in contrast progressed much more slowly and the incidence was more evident in the 5–14 and 15–44 years age groups. The findings in relation to A(H3N2)-dominant
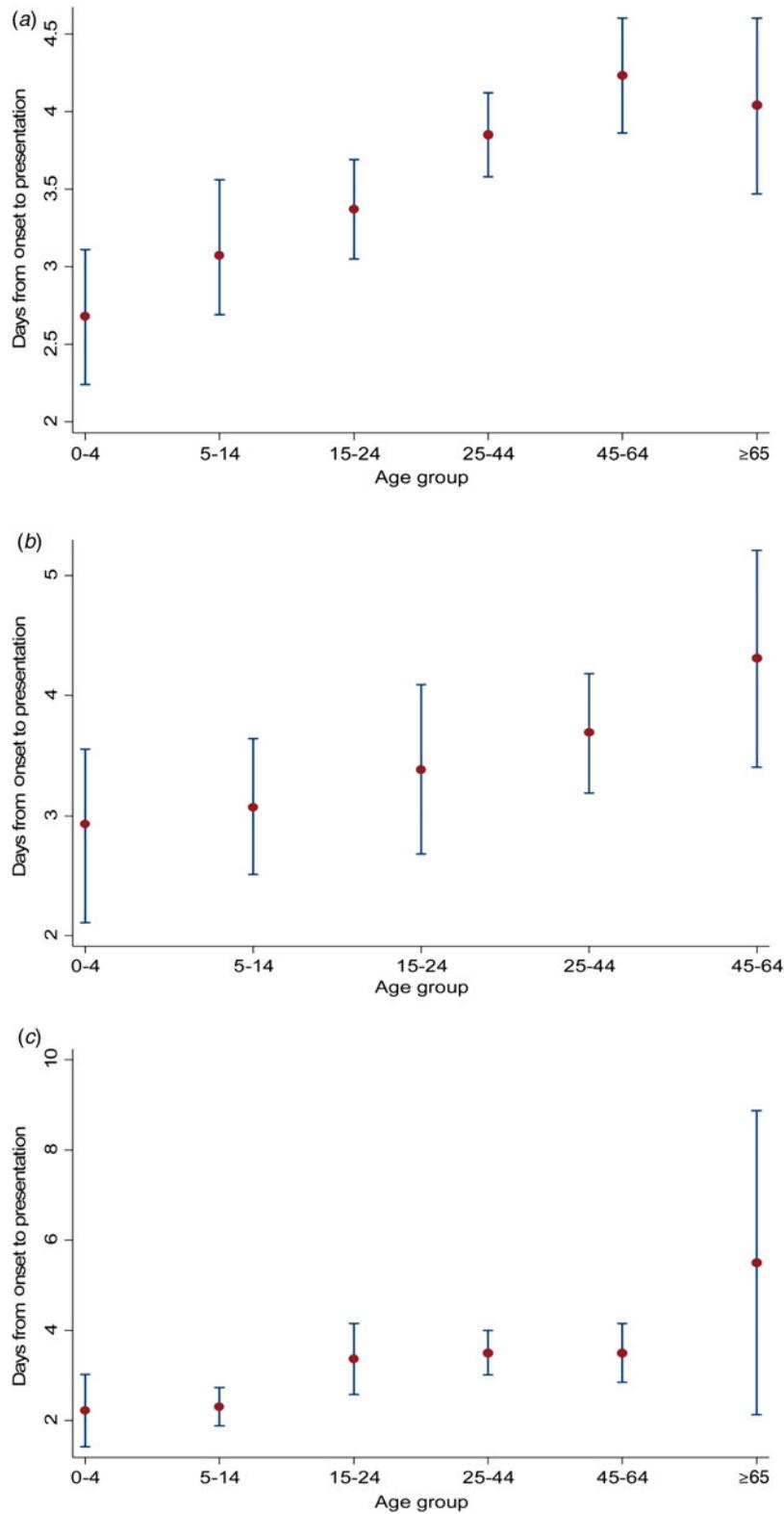
Fig. 3. Interval between reported symptom onset and date swab taken in virus-confirmed cases in dominant-virus season groups and by age group (mean number of days and 95% confidence interval). (*a*) Influenza A(H3N2), (*b*) influenza B, (*c*) influenza A(H1N1).

Table 2. *Baseline and threshold values of influenza-like illness (ILI) incidence per 100 000 by age; week number in which the incidence of ILI reached the threshold*

Age group, years	A(H3N2)-dominant seasons			B-dominant seasons			A(H1N1)-dominant seasons		
	Baseline	Threshold	Threshold week	Baseline	Threshold	Threshold week	Baseline	Threshold	Threshold week
All ages	16	35·6	−3	20·9	41·3	−5	7·6	13·5	−3
0–4	21·3	61·9	−4	30·8	80·6	0	2·4	7·3	−3
5–14	12·4	38·9	−3	19·8	41·8	−4	3·5	9·4	−4
15–44	18·7	40·1	−3	23·3	44·1	−5	8·9	16·9	−3
45–64	13·4	29·5	−2	16·3	30·0	0	6·0	12·1	−3
⩾65	9·6	23·7	−3	13·8	63·6	0	4·2	8·7	−2

seasons are particularly important. We have defined a dominant season but there is no such thing as an exclusive single strain season. The clinical data for ILI were mostly not confirmed virologically and were available only at a weekly level of granularity.

Comparison with other studies

Our findings are based on surveillance data in England and Wales with its specific characteristics of high population density, influenza epidemics A(H3N2) commonly occurring around Christmas and New Year and ~70% levels of influenza vaccine uptake in persons aged ⩾65 years in recent years. The similarity of the findings from our analyses of clinical and virological data is particularly important. These do not support the suggestion that the spread of influenza A in the community was driven primarily by children. Influenza B is currently an illness with a more selective impact in schoolchildren (5–14 years) and young adults. The Seattle Virus Watch study which was one of the earliest studies suggesting the importance of children as the main transmitters of influenza was based on data collected in seasons in which influenza B epidemics were much more common [6].

The findings are broadly similar to those reported from Canada [18] which showed some evidence of a 1-week lead in 10–19 and 20–29 years age groups for A(H3N2) and a 4-day lead in the 10–19 years age group for A(H1N1)pdm but no evidence that younger school-age children were driving the spread. The hypothesis that children drive the spread of influenza is well established but is based mainly on the interpretation of studies based on transmission in households and small communities, whereas our study focused on widespread community transmission.

Limitations of study

The study is particularly strong in the size and detail of the database including > 110 000 episodes of ILI and 17 years of continuous and consistent surveillance with clinical and virological data derived from the same population. It is concerned with information about spread in the community across the age groups and not with close contact transmission such as within households. It is also strong in considering influenza A(H3N2), A(H1N1) and B strain dominant seasons separately, although there were insufficient age-specific virus detections to power the study effectively in individual seasons.

Our findings do not conflict with the importance of increasing herd immunity as a means of reducing the likelihood of influenza transmission. However, they raise questions about population cohorts to be prioritized in order to achieve this aim. Transmission of airborne respiratory viruses is influenced by contact dynamics. It is likely that in the young adult age group, social interaction is increased during the period just before Christmas and the New Year which is particularly relevant to the spread of influenza A(H3N2) viruses. In the determination of vaccination policy, several factors need to be considered including (among others) the effectiveness and price of the vaccine, and the ease and acceptability of administration.

The data are exclusively from persons who consult a GP. Any bias from infected persons who do not consult would pre-suppose that one age group (children) was less likely than others to consult doctors in the early stages of an epidemic. The analysis of onset to swabbing (presentation to GP) in influenza-confirmed cases showed less delay in children compared to adults confirming an earlier observation in surveillance data in persons diagnosed clinically with ILI [25]. This
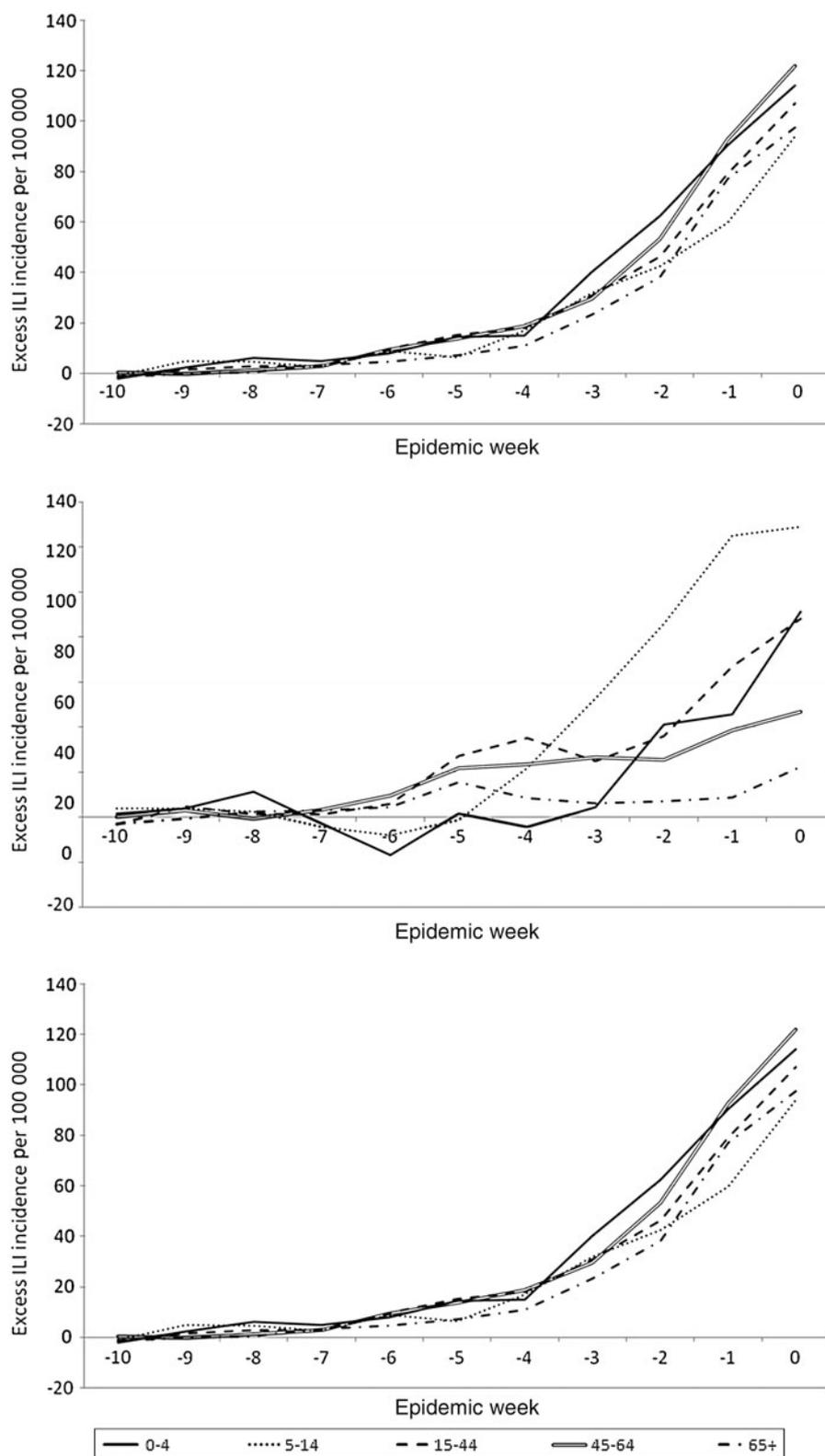
Fig. 4. Excess influenza-like illness (ILI) incidence per 100 000 in 15 weeks before ILI incidence peak by age group.

suggests that our findings from the ILI incidence data which are based on the date of presentation rather than symptom onset tend to underestimate the interval between symptom onset and ILI incidence peak more in children than adults. Influenza is often only a minor illness and consultation is likely to be influenced

by severity and acuteness of symptoms. We suspect that persons with severe symptoms consult earlier and thus infants and young children with high fever might be expected to consult before older children and adults. In swabbed patients we found that children did consult earlier in the natural course of the illness although the onset was not earlier We did not measure severity of illness but the proportion of infected persons who experience a severe illness is relatively low as judged by the proportion who require hospital admission.

CONCLUSIONS

The analysis of virologically confirmed influenza showed that the interval between symptom onset to ILI incidence peak did not differ by age group in influenza A(H3N2)- or A(H1N1)-dominant seasons. For influenza B-dominant seasons, the 5–14 years age group was the leading age group. The clinical data on reported ILI was consistent with these conclusions. Only for influenza B is there any evidence that children might drive the spread of influenza.

The age-related delays between symptom onset and taking the swab (presentation to GP) are consistent with, although less than, those reported in a study of clinical ILI [25]. We suspect that patients presenting early in the acute and febrile phase of the illness are more likely to be investigated virologically and are not representative of all ILI cases.

ACKNOWLEDGEMENTS

DECLARATION OF INTEREST

None.

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