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Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study

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Summary

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Background Young people (aged 0–18 years) have been disproportionately affected by pandemic influenza A H1N1 infection. We aimed to analyse paediatric mortality to inform clinical and public health policies for future influenza seasons and pandemics.

Methods All paediatric deaths related to pandemic influenza A H1N1 infection from June 26, 2009, to March 22, 2010 in England were identified through daily reporting systems and cross-checking of records and were validated by confirmation of influenza infection by laboratory results or death certificates. Clinicians responsible for each individual child provided detailed information about past medical history, presentation, and clinical course of the acute illness. Case estimates of influenza A H1N1 were obtained from the Health Protection Agency. The primary outcome measures were population mortality rates and case-fatality rates.

Findings 70 paediatric deaths related to pandemic influenza A H1N1 were reported. Childhood mortality rate was 6 per million population. The rate was highest for children aged less than 1 year. Mortality rates were higher for Bangladeshi children (47 deaths per million population [95% CI 17–103]) and Pakistani children (36 deaths per million population [18–64]) than for white British children (4 deaths per million [3–6]). 15 (21%) children who died were previously healthy; 45 (64%) had severe pre-existing disorders. The highest age-standardised mortality rate for a pre-existing disorder was for chronic neurological disease (1536 per million population). 19 (27%) deaths occurred before inpatient admission. Children in this subgroup were significantly more likely to have been healthy or had only mild pre-existing disorders than those who died after admission ($p=0.0109$). Overall, 45 (64%) children had received oseltamivir: seven within 48 h of symptom onset.

Interpretation Vaccination priority should be for children at increased risk of severe illness or death from influenza. This group might include those with specified pre-existing disorders and those in some ethnic minority groups. Early pre-hospital supportive and therapeutic care is also important.

Funding Department of Health, UK

Introduction

Seasonal influenza can cause infection and treatment in hospital in children, but mortality is low and the viruses predominantly affect people older than 65 years of age.¹ However, children have been disproportionately affected by pandemic influenza A H1N1 compared with older age-groups,² and this infection has caused severe disease and death in a minority of children.^{3,4}

Despite national and global reports of the complications of pandemic influenza A H1N1, a detailed analysis of paediatric mortality has not been provided. Following the outset of the pandemic in England in April, 2009, we initiated a confidential investigation into all resulting deaths.⁵ This investigation has provided a real-time and comprehensive system of national surveillance, which we have used to examine paediatric deaths in depth. We aimed to provide important evidence to strengthen clinical and public health policies for children during forthcoming influenza seasons and future pandemics.

Methods

Study population

Mandatory daily reporting systems were established for all suspected and confirmed deaths from pandemic influenza A H1N1 in England. Further deaths were identified through cross-checking of records held by the Regional Directors of Public Health and by the Health Protection Agency's influenza reference centres. For all reported cases, a member of the Chief Medical Officer's clinical team contacted the responsible senior physician to obtain further details. A death was confirmed as related to pandemic influenza A H1N1 if there was laboratory evidence of H1N1 infection or if H1N1 infection (or synonym) was recorded on the death certificate. Further details of the method of death ascertainment have been reported previously.⁵

Study design

All validated deaths in children aged less than 18 years were extracted from this dataset. The clinician responsible for each individual child was interviewed by telephone by

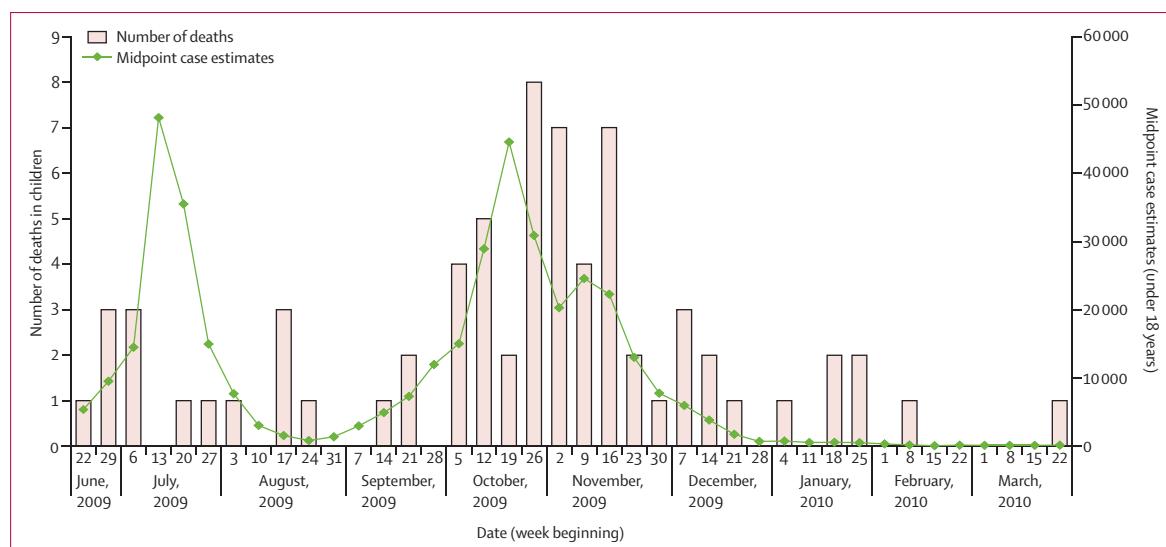


Figure: Estimated incidence of pandemic influenza A H1N1 cases and confirmed deaths in children in England, by week
Data for case estimates provided by the Health Protection Agency.

a paediatrician working for the Chief Medical Officer. The data collection proforma is available in the webappendix. Information gathered included: demographic characteristics, pre-existing disorders and past medical history, and presenting symptoms and clinical course. If results of microbiological, haematological, and radiological investigations were not immediately available from clinicians, they were obtained from hospital or public health laboratories. Information was cross-checked with coroners' reports. In cases for whom past medical information was unavailable, supplementary information was obtained from the general practitioner or local hospital. When the presence or absence of a symptom or pre-existing disorder was not specified, we assumed that none was present.

Collection and processing of data was undertaken under the Health Service (Control Of Patient Information) Regulations 2002 (Statutory Instrument 1438) for the purpose of communicable disease control in England. Therefore, consent from patients was not needed.

The primary outcome measures were population mortality rates (by age-group and for children with pre-existing disorders) and case-fatality rates. Secondary measures included presenting symptoms and signs, pre-existing disorders, and subsequent complications.

The physical status classification scale of the American Society of Anaesthesiologists⁶ was used to establish the general health of the children before acute illness. Children were classified as being healthy (grade one) or having mild (grade two), moderate (grade three), or severe (grade four or five) pre-existing systemic disease. Specific pre-existing disorders (eg, developmental delay) and the severity of presenting symptoms (eg, dyspnoea) were classified as absent, mild, moderate, or severe by the clinicians who cared for the child.

Recurrent hospital admission was defined as an inpatient stay for longer than 6 weeks, or greater than four admissions in the previous year. Bacterial sepsis was confirmed if bacterial growth was identified on laboratory culture after clinical suspicion of bacterial infection. Bacterial sepsis was presumed by clinicians if systemic features of bacterial infection were present (ie, rising inflammatory markers or signs of focal infection) but bacterial cultures were negative.

Age-stratified cases of pandemic influenza A H1N1 were estimated every week by the Health Protection Agency with methods described previously.⁵ Population numbers for England by age-group and ethnic origin are estimated by the Office for National Statistics. The most recent estimates were used to provide denominators for population mortality rates stratified by age⁷ and ethnic origin.⁸

To assess the risk of death associated with pre-existing disorders that would confer an increased risk of seasonal influenza, data from the Department of Health vaccine monitoring system were used to estimate the number of people in England affected by these disorders. This system uses primary care records to estimate the number of patients with specific grouped disorders by age band. These estimates are available only for children aged at least 6 months. Deaths in those aged less than 6 months were therefore excluded from this analysis.

Statistical analyses

Case-fatality rates were calculated for every age-group with Health Protection Agency midpoint case estimates. The upper and lower estimates by age were used to calculate lower and upper estimates for the case-fatality rates, respectively. A 95% confidence interval was calculated around these estimates, to account for the uncertainty around the number of cases. The case-fatality

See Online for webappendix

For more on these Regulations see <http://www.legislation.gov.uk/UKSI/2002/1438/contents/made>

	Number of deaths	Fatality rate per 100 000 cases of pandemic influenza A H1N1 (range)	Mortality rate per million population (95% CI)
< 1 year	9	151 (34–635)	14 (6–26)
1–4 years	15	33 (9–114)	6 (3–10)
5–9 years	22	17 (5–54)	8 (5–12)
10–15 years	15	10 (3–35)	4 (2–7)
16–17 years	9	26 (6–102)	7 (3–13)
0–17 years	70	19 (7–51)	6 (5–8)

Table 1: Case-fatality rates for pandemic influenza A H1N1 infection and population mortality rates by age in England from June 26, 2009, to March 22, 2010

	Number of deaths
Fever	60 (86%)
Cough	47 (67%)
Dyspnoea	46 (66%)
Dehydration	18 (26%)
Altered mental status or encephalopathy	17 (24%)
Diarrhoea	15 (21%)
Nausea or vomiting	14 (20%)
Seizure or convulsion	5 (7%)
Headache	4 (6%)
Sore throat	4 (6%)

Table 2: Frequency of presenting symptoms and signs among children who died from pandemic influenza A H1N1 infection

ranges presented refer to the upper 95% confidence interval of the upper case-fatality rate estimate and the lower 95% confidence interval of the lower estimate. IQRs were calculated for all other ranges other than case-fatality rates. Population mortality rates were calculated by age and ethnic group. Mortality rates for specified pre-existing disorders were calculated and age standardised to the English population.

Fisher’s exact test or the χ^2 test with Yates’ correction were used to test significance of data for categorical data (eg, ethnic origin, those with bacterial sepsis, or those on pre-hospital antivirals). The Mann–Whitney *U* test was used for non-parametric data. Analyses were done with SPSS (version 12.0) and R (version 2.9.2).

Role of the funding source

This work was done as part of the Department of Health’s public health response to the influenza pandemic in England. No additional funding was sought. The funding source had no direct involvement in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. Both authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

A total of 70 paediatric deaths related to pandemic influenza A H1N1 occurred in England during the study

period (figure). All cases were laboratory confirmed. Complete demographic and clinical details were obtained for all deaths. Deaths were evenly distributed between male (31) and female (39) children. Median age at death was 7 years (range 0–25–17 years; IQR 2–12 years). Case-fatality and population mortality rates were highest in children aged less than 1 year (table 1).

Bangladeshi or British Bangladeshi children (47 deaths per million population [95% CI 17–103; n=6]) and Pakistani or British Pakistani children (36 [18–64; n=11]) had the highest population mortality rates, compared with white British children (4 ([3–6; n=37])). Pre-existing health status did not differ between ethnic groups. Calculation of case-fatality rates by ethnic group was not possible because estimates of case numbers were not available by ethnic origin.

Predominantly respiratory symptoms were reported on presentation in 53 of 70 (76%) deaths. Fever, cough, and dyspnoea were the most frequent symptoms on presentation (table 2). The extent of dyspnoea was rated by clinicians as moderate in 28 (40%) and severe in 12 (17%) deaths. Mainly gastrointestinal symptoms were described in two (3%) deaths. Among hospital deaths, most cases (42 of 67; 63%) initially presented to the emergency department with symptoms of influenza and 16 (24%) presented in cardiorespiratory arrest. The rest presented in shock (five; 7%), status epilepticus (three; 4%), or with non-specific symptoms (one; 1%).

Deaths were categorised into those who deteriorated rapidly and died before, or at the point of, hospital admission (early deaths [19 of 70; 27%]), and those who died after hospital admission (late deaths [51; 73%]). The early deaths group had a significantly greater proportion of children with no, or mild, pre-existing disorders (table 3). Of the early deaths, nine of 19 (47%) had consulted a general practitioner during their illness.

Before presentation, fever (47 of 51 vs 13 of 19, p=0.020 [Fisher’s test]) and dyspnoea (40 of 51 vs six of 19, p=0.002) were more common among late deaths than among early deaths. Nausea and vomiting were less common among late deaths (seven of 51 vs seven of 19, p=0.045). Frequency of other symptoms did not differ between the two groups.

Children with severe pre-existing disorders accounted for 64% (45 of 70) of deaths. However, 21% (15 of 70) of children who died were previously healthy. Mild pre-existing disorders were present in 3% (two) of deaths and moderate disorders in 11% (eight) of deaths. For those with data available, 36% (23 of 62) had a history of recurrent hospital admissions. For most deaths in children aged less than 2 years, moderate or severe pre-existing disorders had been reported (87%; 13 of 15). In those older than 2 years, 73% (40 of 55) had moderate or severe pre-existing disorders.

Chronic neurological, gastrointestinal, or respiratory disease were all present in more than half of all deaths (table 4). Of those with chronic neurological disease, 19 had spastic quadriplegic cerebral palsy. Severe

gastro-oesophageal reflux was reported in 11 of the 70 (16%) deaths. Regular gastrostomy or nasogastric feeding took place in 41 of 70 (59%) deaths. A diagnosis of asthma (requiring any treatment) was reported in five of 70 (7%) deaths. Complex congenital cardiac disease was reported in eight of 70 (11%) deaths. Almost a quarter of all children had been born prematurely (17 of 70; median gestation 32 weeks, IQR 27·5–35). 48 (69%) children who died had developmental delay, which had been severe in 31 (44%). Of the 46 children of school age (5–18 years), 23 had attended a school for children with special needs.

Death rates from pandemic influenza A H1N1 for children with pre-existing disorders were higher than for healthy children. Chronic neurological disease and kidney disease conferred the highest risk of any of the disorders studied (table 5). The absence of denominator data prevented the calculation of an age-standardised mortality rate for gastrointestinal disease. Two children with severe underlying disorders received the pandemic influenza A H1N1 vaccine 48 h before developing their terminal illness. No other child was vaccinated against pandemic influenza A H1N1.

Median duration from symptom onset to admission (or death if not formally admitted to hospital) was 2 days (IQR 1–5). Five children with inter-current infection contracted during long-term hospital stays were not included in this calculation. Median time from symptom onset to death was 7·5 days (IQR 3–13). Of the children who died, 40 were admitted to critical care units (38 to intensive care; two to high-dependency units). Of these, 27 were transferred from other hospitals for specialist care. Transfer to critical care occurred a median of 1 day (IQR 0–2) after hospital admission. In the children admitted to critical care, death occurred a median of 6 days later (IQR 2–11). Within the hospital, the critical care facility was most commonly the place of death (40 of 67; 60%), followed by the emergency department (17 of 67; 25%).

Organ failure occurred frequently. 40 (57%) children developed respiratory failure that needed mechanical ventilation: seven needed non-invasive ventilation, ten invasive positive pressure ventilation, 21 high-frequency oscillation, and two extra-corporeal membrane oxygenation. High ventilation pressures were usually needed and pneumothoraces occurred in six of the 40 (15%) children, all of whom had insertion of a chest drain. Intracerebral haemorrhage arose secondary to extra-corporeal membrane oxygenation in one child. Circulatory failure needing inotropic support occurred in 30 of 70 (43%) children. Acute renal failure necessitated renal replacement therapy (haemofiltration or haemodialysis) in five of 70 (7%) children. Acute haematological abnormalities were recorded in 25 (36%) children before death. These abnormalities were thrombocytopenia (16; 23%), lymphopenia (14; 20%), neutrophilia (three; 4%), neutropenia (two; 3%), pancytopenia (two; 3%), and disseminated intravascular coagulation (two; 3%).

	Early death group (n=19)	Late death group (n=51)	p value
Median age (years; IQR)	6 (2–14)	7 (2·5–12)	0·9761*
Ethnic origin			
White British	12 (63%)	25 (49%)	0·7547†
Asian or Asian British (any)	6 (32%)	21 (41%)	
Black or Black British (any)	1 (5%)	3 (6%)	
Healthy or mild pre-existing disorders	9 (47%)	8 (16%)	0·0109‡
Presumed or confirmed bacterial sepsis	9 (47%)	19 (37%)	0·5842‡
Pre-hospital antivirals	2 (10%)	1 (2%)	0·1770‡
Duration from symptom onset to death (days; median, IQR)	2 (1–2·5)	10 (5·5–16·5)	<0·0001*
Duration from symptom onset to first medical consult (days; median, IQR)	1 (0·25–2)	2 (0–3·75)	0·4533*

Data are number of patients (%) unless otherwise stated. *Mann-Whitney U test; † χ^2 with Yates correction; ‡Fisher's test.

Table 3: Characteristics of children presenting with rapid deterioration leading to death before, or at the point of, hospital admission (early death) and of those who died after hospital admission (late death)

	Number of deaths with pre-existing disorders (n=70)	Median age at death (years; IQR)
Any chronic respiratory disease	37 (53%)	7 (2–12)
Chronic lung disease	13 (19%)	4 (1–5)
Home oxygen	12 (17%)	4 (0·54–8)
Scoliosis with restrictive lung disease	10 (14%)	12 (9·5–12)
Pulmonary hypertension	6 (9%)	1·4 (0·65–11)
Tracheostomy	6 (9%)	6 (2·25–10·25)
Asthma needing preventive therapy	4 (6%)	11 (8–14)
Home ventilation	3 (4%)	11 (5·6–11)
Any chronic cardiac disease	17 (24%)	5 (1–14)
Congenital cardiac disease	12 (17%)	1·6 (0·77–10)
Cardiomyopathy	3 (4%)	16 (12–16)
Any chronic gastrointestinal disease or feeding problem	41 (59%)	6 (1·5–10)
Exclusive gastrostomy or nasogastric feeding	33 (47%)	6 (2–9)
Gastro-oesophageal reflux	30 (43%)	7 (8–9·8)
Unsafe swallow	24 (34%)	7 (3·8–9)
Any chronic neurological disease	38 (54%)	7 (2·9–8)
Cerebral palsy	22 (31%)	7 (4–9)
Epilepsy	22 (31%)	8 (6–12)
Other		
Any chronic endocrine disease	7 (10%)	6 (2·7–13)
Any chronic kidney disease	4 (6%)	7·5 (1·42–7)
Any chronic haematological disease	5 (7%)	16 (13–16)
Any chromosomal disorder	5 (7%)	14 (8–16)
Any malignant disease	1 (1%)	16*

*No IQR as only one child in this group.

Table 4: Frequency of pre-existing disorders in paediatric deaths related to pandemic influenza A H1N1 infection

45 of 70 (64%) children received oseltamivir—seven within 48 h of symptom onset (median 5 days [IQR 3–7·75] between symptom onset and treatment with antiviral drugs) and three before admission. Oseltamivir resistance was recorded in two children—one ante-mortem. Viral

	Deaths	Population prevalence estimates (thousands)	Age-standardised mortality rate per million population (95% CI)
Chronic respiratory disease	33	392	167 (89–268)
Chronic cardiac disease	16	72	232 (132–377)
Chronic neurological disease	35	31	1536 (988–2242)
Immunosuppression	7	38	166 (66–343)
Chronic kidney disease	3	6	449 (85–1333)
Diabetes mellitus	0	2	0 (–)
None	13	10 125	1.3 (0.7–2.2)

Table 5: Age-standardised mortality rate for deaths related to pandemic influenza A H1N1 for children aged between 6 months and 18 years with specific pre-existing disorders

pneumonitis was reported in 29 of 70 (41%) children and bacterial pneumonia in 20 of 70 (29%). Bacterial coinfection was clinically presumed in 14 (20%) deaths and confirmed in a further 14. The most common sites of bacterial infection were the lung (20), blood (six), and cerebrospinal fluid (two). Pathogens most frequently isolated were group A *Streptococcus* (three cases), *S pneumoniae* (three cases), *S aureus* (three cases), and *Haemophilus influenzae* (three cases). Excluding long-term inpatients, pre-hospital antibiotics had been given to 23 of the 65 children who died (35% of deaths). All inpatients received antibiotics. Most patients admitted received intravenous antibiotics within 48 h of admission (43 of 45; 96%) or within 48 h of symptom onset for long-term inpatients (three of five; 60%). One case of myocarditis was reported. According to clinical reports or death certification, acute respiratory distress syndrome occurred in 20 children. Intravenous corticosteroids were given in 18 cases.

Death certificates were available for 66 cases. In 46 (70%) cases, pandemic influenza A H1N1 or a synonym was recorded as the direct cause of death. In seven (11%) cases, pandemic influenza A H1N1 or a synonym was recorded as contributing to death. There was no record of pandemic influenza A H1N1 on 13 death certificates; in five of which, positive virological test results were received after the death certificate was issued.

Discussion

Our report of the 70 deaths in children in England related to pandemic influenza A H1N1 has shown that mortality disproportionately affects ethnic minorities and those with pre-existing disorders. Many deaths occurred before hospital admission, especially in healthy children or those with only mild pre-existing disorders.

The overall childhood mortality rate for pandemic influenza A H1N1 reported here (six per million population) is close to that for the Netherlands (five per million population for children under 14 years⁹) but lower than that in Argentina (11 per million population).³ A high disease burden was reported in the southern hemisphere because the pandemic coincided with the influenza season in that region. Delayed presentation and unrecognised illness might have contributed further to

the high mortality rate in Argentina.³ Mortality from seasonal influenza in children is lower than that reported for pandemic influenza A H1N1. Extrapolated data from population mortality estimates in England show a mortality rate from seasonal influenza of two per million population for children aged less than 14 years,¹⁰ which is much the same as for international estimates.¹¹ The occurrence of 70 deaths from pandemic influenza A H1N1 in children in 1 year in England is greater than the number of deaths in children every year from leukaemia, and this high childhood mortality was last seen for a single infectious disease (meningococcal disease) in 2001.¹²

We identified the highest population mortality and case-fatality rates in children aged less than 1 year. A similar pattern has been reported from other countries.³ The high population mortality rates that we identified among Bangladeshi and Pakistani groups are consistent with a US report that ethnic minority groups were disproportionately affected by severe illness.¹³ This finding might be attributable to clustering of pandemic influenza A H1N1 cases in areas of England with high ethnic minority populations (such as London and the West Midlands),² although other areas with lower ethnic minority populations such as the East Midlands and Yorkshire were also greatly affected. An increased occurrence of pre-existing disorders might exist in ethnic minority children, although no reliable data are available to assess this claim. The extent to which ethnic origin itself, through genetic or cultural factors, confers increased susceptibility to severe illness or death remains unclear, and further investigation is needed.

We identified two distinct clinical patterns for deaths in children from pandemic influenza A H1N1. The first group had early deterioration with death before hospital admission—mainly children with no or mild pre-existing disorders. Although these patients had not presented late to medical services, the threshold for hospital admission of these children is likely to have been higher than for those with severe pre-existing disorders. These children might have been cared for at home in the expectation that their illness would be self-limiting. Children dying early did not have more co-existing bacterial infection than those who died later, implying that these children had severe acute viral infection. A fulminant course has previously been described in a cohort of children with pandemic influenza A H1N1 infection who were admitted to critical care after presenting with shock.¹⁴ The mechanism of organ failure in these children is unclear. However, they did have a substantially greater frequency of nausea or vomiting at or before presentation, which could indicate extensive viral replication, leading to early deterioration and death.^{15–17}

The second group of deaths was children with severe underlying disorders who deteriorated during hospital admission. Those with neurological disease, particularly cerebral palsy, were at high risk, as described in the USA.⁴ However, we also noted a high frequency of

gastro-oesophageal reflux, gastrostomy feeding, and unsafe swallowing (when patients do not have a protective gag reflex) that frequently co-exist with severe cerebral palsy. The increased risk associated with chronic neurological disease might be explained partly by secondary aspiration and low respiratory reserves in these children. Because of small case numbers and no denominator data, the relative risk of death for cerebral palsy in the absence and presence of associated respiratory and gastrointestinal complications could not be assessed.

Good-quality data for chronic disease prevalence derived from the National Health Service primary care services enabled the calculation of disease-specific mortality rates. Our analysis showed the highest population mortality rate in children with chronic neurological disease, consistent with the high proportion of children with neurological disease among the deaths. However, although absolute numbers of deaths from chronic kidney disease were low, the population rate of death was fairly high (although with wide confidence intervals) because of a low population prevalence.

We noted that asthma was present in only 7% of paediatric deaths. The prevalence of childhood asthma in England is estimated at up to 14%.¹⁸ Other investigators have suggested that asthma is associated with increased mortality from pandemic influenza A H1N1 in children³ and adults.⁹ Our findings contradict this notion. Although there were deaths in children with asthma, the high population prevalence of asthma will lower the disease-specific mortality rate. An explanation for our observations might be that asthma does not increase the risk of death. Alternatively, there might have been a low threshold for admission and aggressive therapy in these patients because of clinical and parental concern; this explanation is lent support by the high numbers of children with asthma who were admitted to hospital and critical care during the pandemic.^{3,19} If this explanation is true, a wider use of early aggressive treatment measures could reduce mortality.

Our study confirms that most children who died presented with typical respiratory symptoms rather than atypical features that could aid prognosis. Thrombocytopenia and relative lymphopenia, however, might be early predictors of severe illness in children, which lends support to similar findings in adults²⁰ and children treated in hospital.²¹ Confirmed bacterial infection was present in 20% of cases in our study—mainly pneumonia, which is in accord with data for this pandemic in the USA⁴ and for seasonal influenza,²² with similar pathogens described. Early treatment with antibiotics in children with clinical deterioration is important.²³

Only 10% of children in this study received antiviral therapy within 48 h of symptom onset, which is a similar number to reports from Argentina in children treated in hospital.³ Antiviral use for the treatment of influenza in children is controversial.²⁴ However, these drugs are most effective if given within 48 h of symptom onset.²⁵ Our findings suggest that children with pre-existing disorders

are at an increased risk of death. For many of these children, antiviral therapies are one of only a few therapeutic options available if the children are not vaccinated. Although our study was not designed to assess antiviral use, early treatment with antiviral therapy might maximise the effectiveness of this treatment. This approach is especially important in primary care because 27% of children in our study died before admission to hospital. Further investigation into the contribution of pre-hospital antivirals to the outcome of affected children is needed.

Our findings support the vaccination of children against pandemic influenza A H1N1. Children at greatest risk of severe illness or death should be prioritised. Our data indicate that risk groups include children with pre-existing illness (including chronic neurological or gastrointestinal disease) and those in ethnic minority groups (including Bangladeshi and Pakistani children). However, our findings also suggest that protection cannot be confined to risk groups as 21% of deaths in our cohort occurred in healthy children.

Complete death ascertainment is difficult to achieve. However, we believe our reporting system achieved a high level. We have classified deaths according to those occurring before and subsequent to inpatient admission. This classification will not capture deaths occurring within hours of hospital admission; therefore, the true early death group might be larger. By using formal hospital admission, we have been able to examine deaths occurring too rapidly to enable stabilisation.

Case-fatality rates are subject to limitations.⁵ Case estimates in England take into account laboratory-confirmed cases in primary care, in addition to estimates of the proportion of symptomatic individuals who do not seek medical attention. The estimates of case fatality in this study have wide ranges, indicating uncertainty about those not seeking medical help. If this proportion is higher than estimated, our case-fatality rates might be an overestimate. However, this method of case estimation is likely to provide a more meaningful denominator for case fatality than use of laboratory-confirmed cases.

Few countries hold comprehensive prevalence data for chronic diseases in the population. The National Health Service has a strong primary care system and a longstanding vaccination programme that relies on pooled data for the occurrence of risk factors. Although these data are derived from a sample of clinical practices, we believe that they provide reliable estimates of prevalence. Additionally, we have interpreted derived mortality rates comparatively rather than in absolute terms. More extensive comparisons of risk would be possible with a control group.

Although this is a large study of paediatric deaths related to pandemic influenza A H1N1, more detailed analysis would be possible with higher case numbers. An international study that pooled data on childhood deaths from pandemic influenza A H1N1 would be greatly informative.

Contributors

LJD planned this study, oversaw its design, and contributed to writing the paper. NS planned and designed the data collection process, obtained and analysed all data, and drafted the manuscript.

Conflicts of interest

LJD was the Chief Medical Officer for England from 1998 to May, 2010. In this role he advised the government on public health policy, including the management of the pandemic. NS supported him in this task from 2009 to 2010. Both authors declare that they have no additional conflicts of interest.

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