Characteristics and mortality risk of children with life-threatening influenza infection admitted to paediatric intensive care in England 2003-2015

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Abbreviations: AIC – Akaike's Information Criterion; HES – Hospital Episode Statistics; ICD – International Classification of Diseases; IMD – Index of Multiple Deprivation; PICANet – Paediatric Intensive Care Audit Network; PICU – Paediatric Intensive Care Unit

Abstract

Background

Information is lacking about the severity of complications in children with influenza admitted to paediatric intensive care units (PICU) in the UK. In this study, we report risk factors for mortality, invasive ventilation and use of vasoactive drugs for children admitted to PICU with influenza.

Methods

We evaluated all admissions to PICUs in England for resident children with a recorded influenza diagnosis between September 2003 and March 2015. We used the Paediatric Intensive Care Audit Network (PICANet) database linked to hospital admission records to identify influenza cases and high-risk comorbidities among admitted children. We used mixed effects logistic regression models to determine risk factors for mortality, use of invasive ventilation and vasoactive drugs.

Results

We identified 1961 influenza-related PICU admissions in 1778 children. Children with high-risk conditions accounted for 1540 admissions (78.5%). The odds of mortality were significantly higher for girls than boys (adjusted odds ratio 1.91; 95% confidence interval 1.31, 2.79), children from Asian/Asian British (2.70; 1.74, 4.20) or other minority ethnic groups (3.95; 1.65, 9.42) compared to white British children, and significantly increased before and during the A(H1N1)pdm 2009 pandemic compared to the post-pandemic period. Children required invasive ventilation in 1588 admissions (81.0%), and received vasoactive drugs in 586 admissions (29.9%).

Conclusions

Nearly four fifths of influenza-related PICU admissions occurred in children with high-risk conditions, highlighting the burden of severe influenza in this vulnerable population Further research is required to explain sex and ethnic group differences in PICU mortality among children admitted with influenza.

Key words: Influenza, intensive care, paediatrics, mortality, ventilation

Introduction

Approximately 90 million children less than five years are infected with influenza every year globally.[1] Influenza infection can lead to a range of physiological effects from mild upper respiratory symptoms to critical illness including acute respiratory distress syndrome and septic shock requiring intensive care.[2] The impact of influenza on paediatric intensive care unit (PICU) capacity was demonstrated during the influenza A(H1N1)pdm2009 pandemic in 2009 and 2010, when children were more likely to experience severe morbidity and mortality than during seasonal influenza epidemics.[3, 4] Several multicentre observational studies have highlighted the increased risk of influenza-related PICU admission in children with chronic conditions.[5-9]

Since September 2013, it has been recommended that all children in the UK aged two years and older are vaccinated with influenza vaccine every year under a universal programme which is being progressively rolled out. This replaces a policy of vaccinating only children at high risk of influenza complications due to the presence of chronic illness. The targeted strategy towards high risk groups remains for children aged between six months and two years.[10] However, influenza vaccination uptake in children in England is low. In 2016/17, the proportion of children vaccinated in England was 19.5% in children between six months and two years and in a high risk group, 34.4% in preschool children, and 53.6% in six to seven year old schoolchildren.[11, 12] Further, there are no licensed vaccines for children aged less than six months old, due to a lack of evidence of effectiveness and concerns about adverse events.[13]

Studies have shown that parents' views of influenza as a less serious infection may contribute to low uptake of influenza vaccination in children in the UK.[14, 15] An understanding of risk factors for poor outcome among children admitted to PICU is needed to identify which children benefit most from vaccine protection and therefore motivate higher uptake. A mandatory surveillance scheme was set up by Public Health England in 2011 for reporting the number of laboratory confirmed influenza admissions to higher dependency (HDU) or intensive care units in the UK.[16] However, information on risk factors, such as underlying chronic conditions, is only reported for a subset of admissions.[17]

In this study, we describe characteristics of all children admitted to PICU with influenza in England, and examine risk factors for mortality. We also examine risk factors for two other markers of illness severity: invasive ventilation and treatment with vasoactive drugs, and assess whether mortality and illness severity have changed over time. We use data linkage between PICU and a hospital admission database to improve the detection of influenza cases and reduce under-recording of high-risk chronic conditions.

Materials and methods

Data sources

The Paediatric Intensive Care Audit Network (PICANet)[18] is a national clinical audit that receives demographic and clinical data on all admissions to PICUs in the UK and the Republic of Ireland. Data collection started in England and Wales in 2002. Diagnostic and procedure information is coded in PICANet using Clinical Terms 3 (The Read Codes). Hospital Episode Statistics (HES) is a hospital admission database, comprising all hospital admissions paid for by the National Health Service (NHS) in England.[19] Diagnoses in HES are recorded using the International Classification of Diseases version 10 (ICD-10). Each child recorded in PICANet was linked to their longitudinal HES admission record (since April 1997) by the HES data providers (NHS Digital) using a deterministic algorithm based on NHS number, date of birth, sex and postcode.

Study population

We extracted data on all influenza-related admissions to PICUs in England for resident children aged less than 16 years between October 2003 and March 2015. An influenza-related admission was defined as a PICU admission in PICANet where either a) any of the diagnostic fields included an influenza-related Read code (see Supplementary Table S1), or b) a linked hospital admission starting up to 7 days before or three days after a PICANet admission had an ICD-10 code indicating influenza (J09-J11). Readmissions to PICU within 12 hours of discharge from a previous admission in the same unit were excluded, to allow for children being discharged and readmitted in case of surgery. We defined the winter season as 1st October in year *x* to end of March in year *x+1*.

Outcomes

The primary outcome in this study was mortality during PICU admission. The secondary outcomes were type of ventilation and requirement for vasoactive drugs. Data on these outcomes were recorded in PICANet. Where a child died during a readmission within 12 hours of the previous (index) admission, the mortality outcome was applied to the index admission (and the readmission excluded). Type of ventilation was coded into a three-category variable: no ventilation, non-invasive ventilation (including high-flow nasal oxygen and continuous positive airway pressure) and invasive ventilation (endotracheal intubation or tracheostomy). For the statistical models, we collapsed the no ventilation and non-invasive ventilation categories to derive a binary variable: invasive ventilation and no invasive ventilation. Requirement for vasoactive drugs was coded into a binary variable (yes/no).

Risk factors

We hypothesised, based on previous literature, that age, gender and presence of high-risk conditions would be associated with severe influenza symptoms, including invasive ventilation[7, 20, 21], and that severe outcomes would vary over time, particularly between pandemic and non-pandemic seasons. We examined whether a child's ethnic group and socio-economic status were also associated with mortality, or need for invasive ventilation and vasoactive drugs.

Age was derived from PICANet records and coded into a four category variable (<6 months, 6-<24 months, 2-<5 years, 5-<16 years), using standard age groups for influenza surveillance, but splitting the youngest age groups according to current eligibility to receive influenza vaccine in the UK.[22, 23] Sex was derived from PICANet, or if missing, from the child's linked HES record.

Ethnic group was determined from the PICANet record, or if missing, from a child's longitudinal HES record prior to PICANet admission. The ethnic group classification in PICANet and HES maps onto 2011 Census categories.[24] We coded ethnic group into a four category variable to ensure sufficient numbers for analysis: white (including white British, white Irish and other white), mixed or multiple ethnic groups, Asian or Asian British (including Indian, Pakistani, Bangladeshi, Chinese or other Asian), black or black British (including black Caribbean, black African and black other), and other ethnic groups.

Socio-economic status was estimated using the Index of Multiple Deprivation (IMD),[25] a small area-level (between 1000 and 3000 people) based classification of material deprivation. The IMD score was available from the longitudinal HES record, mapped from the child's residential postcode, and coded into quintiles. We assigned a PICANet admission to the IMD quintile recorded during the hospital episode nearest in time to the PICANet admission date.

We defined the presence of a high-risk chronic condition indicating eligibility to receive influenza vaccination under the targeted programme using a previously published Read code list[26] which has been translated into ICD-10 codes.[27, 28] We searched for the relevant Read codes during the PICANet admission or for the corresponding ICD-10 codes during the child's longitudinal HES records at any time before PICANet admission. The conditions were classified into six groups to ensure sufficient numbers for analysis: neurological, respiratory, cardiovascular conditions, immunodeficiency, kidney conditions or diabetes, and liver conditions or obesity. For the statistical models, we used a binary indicator: presence of a high-risk condition: yes/no.

We defined five time periods to examine changes over time in the probability of each outcome: October 2003-March 2009 (pre-pandemic period), April 2009-March 2010 (pandemic waves 1 and 2), April 2010-March 2011 (pandemic wave 3), April 2011-August 2013 (post-pandemic period) and September 2013-March 2015 (roll out of universal paediatric influenza vaccination programme).

Statistical analyses

We estimated the number of admissions and influenza-related PICU admission rates during winter seasons per 100,000 children by sex and age group. Denominators were derived from mid-year population estimates from the Office for National Statistics.[29] We combined admissions for children under two years of age since denominator populations for children aged <6 months were not available.

We determined the proportion of admitted children with a high-risk condition, and the proportion of deaths in PICU where the child had a high-risk condition. To examine risk factors for mortality during PICU admission, we fitted mixed effects logistic regression models with death as the outcome variable, and unit as the random effect. We included unit as a random effect since outcomes within units have been shown to be more similar than across units [30, 31], due to differences in the case-mix of children admitted, as well as differences in care practices. Age group, gender, presence of high-risk conditions and time period were included in the baseline model *a priori*. We added ethnic group and IMD quintile in a forward stepwise fashion. Model fit was compared using the Akaike Information Criterion (AIC). Admissions with missing values for any of the outcomes or risk factors were excluded. We repeated the modelling process for the outcomes ventilation type and requirement for vasoactive drugs.

Ethical approval

Collection of personally identifiable data has been approved by the Patient Information Advisory Group (now the NHS Health Research Authority Confidentiality Advisory Group-CAG) see - http://www.hra.nhs.uk/documents/2017/04/cag-piag-register-march-2017.xls - and ethics approval granted by the Trent Medical Research Ethics Committee, ref. 05/MRE04/17 +5. The CAG and ethics approvals cover linkage between PICANet and other databases, including HES.

Results

We identified 1961 influenza-related PICU admissions in 1778 children to 31 PICUs. 1628 children had one influenza-related PICU admission (91.6%), 123 children (6.9%) had two and 27 children had three or more (1.5%). Of the 183 readmissions, 171 (93.4%) occurred within six months of the first admission.

Of the 1961 admissions, 20.7% (406 admissions) were identified as influenza-related admissions from PICANet only, 52.8% (1035 admissions) from hospital admission records only, and 26.5% (520 admissions) could be identified from both data sources. Of the 926 admissions identified from PICU records, 95.8% (887 admissions) were linked to at least one preceding hospital record. 26% of influenza-related PICU admissions were in infants aged less than six months old (Table 1), and 56% were in children less than two years old.

1540 admissions were in children with at least one high-risk condition (78.5%); and 63.5% of these were among children with high-risk conditions from more than one of the six groups of conditions (978 admissions). Respiratory and neurological conditions were the most common types of high-risk conditions among admitted children. The proportion of children with high-risk conditions increased with age. Among children aged six months to less than two years old, 452 of 589 admissions were in children with high-risk conditions (76.7%), increasing to 473 of 514 admissions (92.2) in children aged 5-15 years.

The crude admission rate was 2.6/100,000 children during winter seasons (95% CI 2.4, 2.7). Boys had significantly higher admission rates than girls: 2.9 (2.7, 3.1) versus 2.3 (2.1, 2.4). Age-specific rates were 10.5 (9.8, 11.3) among <2 year olds, 2.6 (2.3, 2.9) among 2-<5 year olds and 1.0 (0.9, 1.1) among 5-<16 year olds. In the four seasons since the end of the influenza pandemic, 138 children were admitted to PICU with influenza on average each season.

Table 1: Distribution of risk factors among admitted children (*n*=1961)

Risk factor	Number (%)
Sex	
Male	1132 (57.7)
Female	829 (42.3)
Age group	
<6 months	509 (26.0)
6-<24 months	589 (30.0)
2-<5 years	349 (17.8)
5-<16 years	514 (26.2)
Presence of high-risk condition	
No	421 (21.5)
Yes	1540 (78.5)
Type of high-risk condition*	
Neurological conditions	931 (47.5)
Respiratory conditions	969 (49.4)
Heart conditions	746 (38.0)
Immunodeficiency	200 (10.2)
Kidney conditions or diabetes	175 (8.9)
Liver conditions or obesity	182 (9.3)
Time period	
October 2003-March 2009 (Pre-pandemic)	487 (24.8)
April 2009-March 2010 (Pandemic, waves 1 & 2)	375 (19.1)
April 2010-March 2011 (Pandemic Wave 3)	371 (18.9)
April 2011-August 2013 (Post-pandemic)	367 (18.7)
September 2013-March 2015 (Universal paediatric influenza vaccination programme)	361 (18.4)
Ethnic group	
White	1315 (67.1)
Mixed/multiple	53 (2.7)
Asian/Asian British	331 (16.9)
Black/black British	169 (8.6)
Other	51 (2.6)
Missing	42 (2.1)
Index of Multiple Deprivation quintile	
1st Most deprived	677 (34.5)
2nd	416 (21.2)
3rd	338 (17.2)
4th	222 (11.3)
5th Least deprived	267 (13.6)
Missing	41 (2.1)
Total	**1961**

*The number of children with each high-risk condition adds up to more than 1961 since children can have multiple conditions

Risk factors for mortality (primary outcome)

Overall, 143 admissions ended in death (7.3%). Only 3.5% of all deaths (*n*=5) were in children without high-risk conditions; these were not concentrated in any year or in any age group. The odds of mortality was over nine times higher for children with high-risk conditions (Table 2). Girls, and children from Asian/Asian British or other non-majority ethnic groups, apart from black/black British also experienced significantly higher odds of dying during admission. The odds of mortality was significantly increased before and during the pandemic compared to the post-pandemic period.

Table 2 Percentage of children who died during PICU admission, and crude and adjusted* odds ratios from logistic regression models, by risk factor (*n*=1886)

Risk factor	Died during admission *n* (% of children in group)	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sex			
Male	60 (5.3)	1	1
Female	83 (10.0)	1.98 (1.38, 2.85)	1.91 (1.31, 2.79)
Age group			
<6 months	23 (4.5)	0.51 (0.27, 0.96)	0.82 (0.45, 1.49)
6-<24 months	34 (5.8)	1	1
2-<5 years	25 (7.2)	0.78 (0.45, 1.36)	1.29 (0.73, 2.29)
5-<16 years	61 (11.9)	1.66 (1.00, 2.76)	1.77 (1.09, 2.88)
Presence of high-risk condition			
No	5 (1.2)	1	1
Yes	138 (9.0)	11.49 (3.63, 36.42)	9.57 (2.98, 30.73)
Time period			
October 2003-March 2009 (Pre-pandemic)	38 (7.8)	2.11 (1.11, 4.03)	2.36 (1.22, 4.59)
April 2009-March 2010 (Pandemic, waves 1 & 2)	39 (10.4)	3.21 (1.69, 6.08)	2.95 (1.52, 5.73)
April 2010-March 2011 (Pandemic Wave 3)	36 (9.7)	2.87 (1.49, 5.51)	3.33 (1.69, 6.54)
April 2011-August 2013 (Post-pandemic)	18 (4.9)	1	1
October 2013-March 2015 (Universal paediatric influenza vaccination programme)	12 (3.3)	0.84 (0.37, 1.89)	0.79 (0.35, 1.81)
Ethnic group			
White	76 (5.8)	1	1
Mixed/multiple	5 (9.4)	1.51 (0.52, 4.36)	1.75 (0.58, 5.31)
Asian/Asian British	46 (13.9)	2.55 (1.68, 3.88)	2.70 (1.74, 4.20)
Black/black British	4 (2.4)	0.39 (0.14, 1.10)	0.39 (0.14, 1.14)
Other	8 (15.7)	3.29 (1.45, 7.47)	3.95 (1.65, 9.42)
IMD quintile**			
1st, Most deprived	52 (7.7)	1.27 (0.69, 2.34)	
2nd	34 (8.2)	1.46 (0.77, 2.76)	
3rd	21 (6.2)	1.09 (0.54, 2.17)	
4th	13 (5.9)	0.95 (0.43, 2.09)	
5th, Least deprived	16 (6.0)	1	

*Adjusted for all other variables in model

**IMD quintile did not significantly improve the model fit and was therefore excluded from the final model.

Risk factors for invasive ventilation and need for vasoactive drugs (secondary outcomes)

Overall, 156 admissions (8.0 %) involved non-invasive ventilation only, and 1588 admissions (81.0%) required invasive ventilation (Supplementary Table S2). Only 10.8 % (212 admissions) did not require any form of respiratory support. Type of ventilation was unknown for five admissions. Age group, sex, presence of high-risk conditions, ethnic group and time period were included in the final model for invasive ventilation (Table 3). The presence of a high-risk condition was not significantly associated with the odds of invasive ventilation. The probability of invasive ventilation was significantly decreased during the first wave of the pandemic, and during the period since September 2013 compared to the immediate post-pandemic period.

Table 3 Crude and adjusted* odds ratios for invasive ventilation from logistic regression models, by risk factor (*n*=1882)

Risk factor	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sex		
Male	1	1
Female	0.75 (0.58, 0.96)	0.76 (0.59, 0.98)
Age group		
<6 months	1.09 (0.74, 1.61)	1.00 (0.67, 1.49)
6-<24 months	1	1
2-<5 years	1.00 (0.69, 1.44)	0.96 (0.67, 1.40)
5-<16 years	0.82 (0.56, 1.20)	0.84 (0.57, 1.24)
Presence of high-risk conditions		
No	1	1
Yes	0.73 (0.53, 1.01)	0.77 (0.55, 1.07)
Time period		
October 2003-March 2009 (Pre-pandemic)	0.73 (0.49, 1.10)	0.72 (0.48, 1.08)
April 2009-Mach 2010 (Pandemic, waves 1 & 2)	0.53 (0.35, 0.80)	0.54 (0.36, 0.82)
April 2010-March 2011 (Pandemic Wave 3)	0.94 (0.61, 1.45)	0.89 (0.57, 1.38)
April 2011-August 2013 (Post-pandemic)	1	1
Universal paediatric influenza vaccination programme	0.6 (0.40, 0.91)	0.58 (0.38, 0.87)
Ethnic group		
White	1	1
Mixed/multiple	1.21 (0.54, 2.71)	1.27 (0.56, 2.89)
Asian/Asian British	1.09 (0.77, 1.55)	1.17 (0.82, 1.67)
Black/black British	0.58 (0.38, 0.87)	0.59 (0.38, 0.89)
Other	0.77 (0.37, 1.59)	0.75 (0.36, 1.56)
IMD quintile**		
1st, Most deprived	0.90 (0.60, 1.34)	
2nd	1.22 (0.79, 1.88)	
3rd	1.22 (0.78, 1.92)	
4th	1.18 (0.70, 1.96)	
5th, Least deprived	1	

*Adjusted for all other variables in model

**IMD quintile did not significantly improve the model fit and was therefore excluded from the final model.

Children received vasoactive drugs in 586 admissions (29.9%). Information on vasoactive drugs was missing for 40 admissions. Use of vasoactive drugs increased with age, and with presence of high-risk conditions. Children with immunodeficiency were most likely to be treated with vasoactive drugs. (Supplementary Table S3, Table 4). Girls were significantly more likely than boys to be given vasoactive drugs, even after adjustment for age and high-risk conditions. Compared to the post-pandemic period, use of vasoactive drugs was significantly lower during the period after the introduction of universal influenza vaccination.

Table 4. Crude and adjusted* odds ratios for requirement for vasoactive drugs from logistic regression models, by risk factor (*n*=1850)

Risk factor	Crude odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Sex		
Male	1	1
Female	1.44 (1.16, 1.77)	1.40 (1.12, 1.73)
Age group		
<6 months	0.57 (0.41, 0.81)	0.64 (0.45, 0.91)
6-<24 months	1	1
2-<5 years	0.94 (0.69, 1.28)	0.94 (0.68, 1.29)
5-<16 years	1.70 (1.24, 2.31)	1.52 (1.10, 2.08)
Presence of high-risk condition		
No	1	1
Yes	2.58 (1.89, 3.51)	2.18 (1.58, 3.01)
Time period		
October 2003-March 2009 (Pre-pandemic)	0.75 (0.54, 1.04)	0.79 (0.57, 1.11)
April 2009-Mach 2010 (Pandemic, waves 1 & 2)	1.12 (0.81, 1.55)	1.00 (0.71, 1.40)
April 2010-March 2011 (Pandemic Wave 3)	1.22 (0.88, 1.69)	1.28 (0.91, 1.80)
April 2011-August 2013 (Post-pandemic)	1	1
Universal paediatric influenza vaccination programme	0.59 (0.41, 0.84)	0.59 (0.41, 0.84)
Ethnic group**		
White	1	
Mixed/multiple	0.69 (0.34, 1.38)	
Asian/Asian British	1.31 (0.98, 1.75)	
Black/black British	0.93 (0.62, 1.38)	
Other	1.22 (0.62, 2.39)	
Index of Multiple Deprivation (2004) quintile**		
1st Most deprived	0.86 (0.61, 1.21)	
2nd	0.87 (0.61, 1.24)	
3rd	1.02 (0.70, 1.47)	
4th	0.93 (0.62, 1.40)	
5th Least deprived	1	

*Adjusted for all other variables in model

**Ethnic group and Index of Multiple Deprivation quintile did not significantly improve the fit of the final model and was therefore not included.

Discussion

There are around 140 influenza-related PICU admissions every year in England. Over three quarters of children with an influenza diagnosis admitted to PICU had high-risk conditions and a quarter of admissions occurred in children aged less than six months old who are too young to be vaccinated. Children admitted to PICU with influenza were more likely to be boys; and boys were significantly more likely to survive. Older children, and children from an Asian or other ethnic group also had significantly higher odds of mortality even after adjustment for high-risk conditions.

This is the largest UK study to date of severe influenza infections in children resulting in PICU admission. Linkage between PICU and the national hospital admission database improved the ascertainment of high-risk conditions: the proportion of admitted children with high-risk conditions was over 50% higher when using data from linked longitudinal hospital records compared to using intensive care data alone. This underrecording arises since some PICUs tend to report the main reason for admission to PICU only. Linkage between PICU and hospital admission data also allowed more influenza-related PICU admissions to be identified, thus avoiding the low sensitivity of diagnostic coding for specific respiratory infections.[32] National data collection over several years was required to estimate relative odds of mortality according to key risk factors, since influenza-related deaths in children are rare.

Our study also had some weaknesses. First, we did not have access to data on laboratory confirmation of influenza infection. There is no national testing protocol for children presenting to hospital with symptoms of respiratory infections in England. However, we note that the average number of PICU admissions in children aged 0-14 years in this study between weeks 40 and 12 in the 2013/14 and 2014/15 influenza seasons is similar to the number published by Public Health England through the USISS surveillance scheme which only includes laboratory confirmed influenza (although the USISS scheme also covers higher dependency units).[33, 34]

Second, influenza vaccination history is not recorded on PICANet nor HES, and there is currently no national immunisation database anywhere in the UK which captures influenza vaccination in children. We could therefore not estimate the proportion of children admitted to PICU with influenza who had been vaccinated. Similarly, data on antiviral use was not available in PICANet, nor in HES.

Third, we used an extract of linked hospital admission records for children who had had at least one PICU admission. Therefore, we could not estimate the proportion of children admitted to hospital with influenza who were admitted to PICU. Linkage between PICANet and a whole-nation birth cohort created using longitudinal HES data for all children born in England[35] could be used to examine the impact of the introduction of the universal paediatric influenza vaccination policy on children with specific high-risk conditions.

Children with high-risk conditions accounted for over 75% of influenza-related PICU admissions, and 83.5% among admissions in children aged over six months old. These children also accounted for 97% of the deaths. A previous UK study conducted during the 2009 pandemic based on death certification data and clinician reports found that two thirds of deaths were in children with high-risk conditions.[21] In contrast, a study of PICU admissions in Australia and New Zealand 2007-2013 found that 59% of admissions were in previously healthy children.[36]. However this study was based on PICU reports only and high-risk conditions may have been under-recorded, emphasising the value of linking intensive care audit to hospital admission data. Influenza vaccination has been found to reduce the risk of PICU admission in an observational case-negative control study conducted in the United States.[37] Influenza vaccine uptake in England among children with high-

risk conditions has remained below 30% for children aged 6 months to less than two years, and below 50% for children aged 2-15 years since 2009/10. The low uptake has been linked to concerns about vaccine safety and parental views of influenza as a less serious illness, as well as difficulties accessing vaccination services.[14] Increasing the burden of influenza on PICUs should therefore focus on increasing vaccination uptake among children with high-risk chronic conditions, particularly among children aged between six months and two years who have the lowest uptake, and higher PICU admission rates than older children. Children aged less than six months accounted for 26% of PICU admissions. Since there are no influenza vaccines licensed for this age group, alternative strategies including maternal vaccination during pregnancy,[38] and sibling vaccination[28] are likely to reduce the burden of influenza among this age group.

Children from an Asian/Asian British or other non-majority ethnic background were more likely to be admitted to PICU with an influenza-related infection and more likely to die after admission. The increased odds of mortality remained, even after adjusting for the presence of high-risk conditions. Previous studies have also identified an increased risk of death in children from an Asian ethnic group following PICU admission.[39, 40] The type and severity of comorbidities could be different in children from non-majority ethnic groups. A study using a national birth cohort of children with specific high-risk conditions linked to PICANet data is required to determine if this is the case.

Further, we found that girls were significantly more likely than boys to die after admission, despite higher PICU admission rates in boys. Girls were also more likely to require vasoactive drugs, but less likely to require invasive ventilation. A higher mortality rate in girls was also found among children admitted to PICUs in the United States during the pandemic 2009/10 season,[41] and among all PICANet admissions,[31] although the increased odds of mortality for girls among all PICANet admissions was significantly lower than in this study. Other case series of childhood influenza deaths (irrespective of PICU admission) have had a more even sex distrbution.[21, 42] A whole-country birth cohort linked to PICANet and a national hospital admission database would be required to determine whether the increased mortality rate in girls could be explained by a higher proportion of boys dying before PICU admission.

Mortality among admitted children was significantly higher before and during the H1N1 pandemic compared to the four seasons following the pandemic, even after adjustment for age and the presence of high-risk conditions. Higher mortality rates for pandemic, compared to seasonal, influenza in children were also reported in Argentina in 2009/10.[43] In contrast, a multi-centre study in Canada reported no significant difference between mortality rates among children hospitalised during pre-pandemic and pandemic influenza periods.[44] Overall mortality in PICUs in the UK and Ireland have decreased since 2003 when PICANet data collection began.[30] The decreased mortality observed in the seasons since 2009/10 in our study may also be explained by variation over time in case detection and the recording of underlying high-risk conditions. We found a significantly decreased risk of invasive ventilation during the first two waves of the pandemic and in the last two seasons of the study (2013/14 and 2014/15) compared to the two immediate post-pandemic winters (2011/12 and 2012/13). Therefore, admission thresholds may also have varied across the study period. Follow-up studies are required to determine whether the decline in mortality among children with influenza in PICU observed since the end of the pandemic is maintained over subsequent seasons.

Conclusions

Infants and children with high-risk conditions account for three quarters of influenza-associated admissions to PICU Increasing influenza vaccination uptake among children with high-risk conditions is therefore needed to decrease the influenza burden on PICUs. Further research, based on linkage

between PICANet records and a national birth cohort of children created using administrative databases, is required to explain mortality differences among admitted children according to sex and ethnic group.

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Highlights

- 79% of influenza-related PICU admissions were in children with high-risk chronic conditions
- 7.3% of admissions ended in death for the admitted child
- Girls admitted to PICU with influenza had almost twice the odds of dying compared to boys
- Mortality as significantly higher before and during the A(H1N1)pdm 2009 pandemic compared to the post-pandemic period

Supplementary material

Table S1. Read codes used to identify children with influenza in PICANet data

Admissions with codes with an asterisk (*) recorded were only classified as an influenza-related admission either if another non-asterisked code was also recorded, or there was no mention of another viral or bacterial infection listed in Part B of Table S1 below.

Part A: Read codes indicating influenza infection	
Read code	**Description**
65E..	Influenza vaccination
eiX4.	Tamiflu 12mg/mL oral suspension
H27..	Influenza
H270.	Influenzal pneumonia
H2700	Influenza with bronchopneumonia
H2701	Influenza with pneumonia, influenza virus identified
H270z	Influenza with pneumonia NOS
H271.	Influenza with other respiratory manifestation
H2710	Influenza with laryngitis
H271z	Influenza with respiratory manifestations NOS
H27y.	Influenza with other manifestations
H27y0	Influenza with encephalopathy
H27yz	Influenza with other manifestations NOS
Hyu04	[X]Flu+oth respiratory manifestations,'flu virus identified
Hyu05	[X]Influenza+other manifestations,influenza virus identified
Hyu07	[X]Influenza with other manifestations, virus not identified
X001O	Post-influenza encephalitis
X73lf	Influenza virus
X73lh	Influenza virus A
X73li	Influenza virus B
XA1Lu	influenza A virus
Xa9J7	H1N1
XaC1s	Encephalitis due to influenza
XaC2H	Encephalitis due to influenza-virus identified
XaFue	Influenza B antibody level
XaILu	Influenza A antigen level
XaILv	Influenza B antigen level
XaPIN	Influenza H1 virus detected
XaPIP	Influenza H3 virus detected
XaQQp	Influenza due to Influenza A virus subtype H1N1
XE0YK	Influenza NOS
XM0rz	Influenza-like illness
XM0s0	Flu-like illness NOS
H2...	Pneumonia and influenza*
H2y..	Other specified pneumonia or influenza*
H2z..	Pneumonia or influenza NOS*
Part B: Read codes indicating other viral and bacterial infection	
A0762	Enteritis due to rotavirus

A0762	Enteritis due to rotavirus
A3B5.	Haemophilus influenzae infection
A42..	Enteroviral meningitis
A795.	Coronavirus infection
A796.	Parvovirus infection
AyuDB	[X]Enterovirus infection, unspecified
AyuKC	[X]H influenzae as cause/diseases classified/other chapters
F0305	Mumps encephalitis
F0350	Varicella encephalitis
H0608	Acute haemophilus influenzae bronchitis
H060C	Acute parainfluenza virus bronchitis
H060D	Acute respiratory syncytial virus bronchitis
H060E	Acute bronchitis due to rhinovirus
H0615	Acute bronchiolitis due to respiratory syncytial virus
H0616	Acute bronchiolitis due to other specified organisms
H200.	Adenoviral pneumonia
H201.	Pneumonia due to respiratory syncytial virus
H202.	Parainfluenzal pneumonia
H222.	Haemophilus influenzae pneumonia
H243.	Pertussis pneumonia
SLJ6.	Pertussis, including combinations, vaccine poisoning
X000j	Enteroviral encephalitis
X100D	Acute bronchiolitis due to adenovirus
X30BS	Rotavirus gastroenteritis
X30BT	Norwalk virus gastroenteritis
X70Li	Enteroviral infection
X73kR	Rotavirus
X73lE	Coronavirus
X73lK	Parainfluenza virus type 1
X73lM	Parainfluenza virus type 3
X73lN	Parainfluenza virus type 4
X73Rb	Haemophilus influenzae
Xa0BK	Respiratory syncytial virus infection
Xa8VO	Parainfluenza virus
XaIbN	Parainfluenza virus antibody level
XaIdE	Parainfluenza type 3 antibody level
XaJLY	Enterovirus ribonucleic acid detection
XaLTa	RSV nucleic acid detection
XaLTL	Human metapneumovirus nucleic acid detection
XaPOd	Human metapneumovirus detected
XaREr	Enteritis due to norovirus
XE0Qw	Whooping cough
XE0R9	Varicella infection
XE2uH	Adenovirus infection
XE2uI	Rhinovirus infection
XSCDz	Haemophilus infection

Table S2: Number (%) of admissions according to type of ventilation and risk factor (*n*=1956)

Risk factor	Not ventilated	Non-invasive ventilation only	Invasive ventilation
Sex			
Male	114 (10.1)	79 (7.0)	936 (82.9)
Female	98 (11.9)	77 (9.3)	652 (78.8)
Age group			
<6 months	42 (8.3)	41 (8.1)	426 (83.7)
6-<24 months	73 (12.4)	43 (7.3)	471 (80.2)
2-<5 years	42 (12.1)	21 (6.0)	285 (81.9)
5-<16 years	55 (10.7)	51 (10)	406 (79.3)
Presence of chronic condition			
No	37 (8.8)	30 (7.2)	352 (84.0)
Yes	175 (11.4)	126 (8.2)	1236 (80.4)
Ethnic group			
White	130 (9.9)	100 (7.6)	1083 (82.5)
Mixed/multiple	5 (9.4)	3 (5.7)	45 (84.9)
Asian/Asian British	37 (11.3)	26 (7.9)	266 (80.9)
Black/black British	29 (17.2)	20 (11.8)	120 (71.0)
Other or missing*	11 (12.0)	7 (7.6)	74 (80.4)
Time period			
October 2003-March 2009 (Pre-pandemic)	52 (10.8)	30 (6.2)	400 (83.0)
April 2009-Mach 2010 (Pandemic, waves 1 & 2)	66 (17.6)	23 (6.1)	286 (76.3)
April 2010-March 2011 (Pandemic Wave 3)	31 (8.4)	28 (7.6)	312 (84.1)
April 2011-August 2013 (Post-pandemic)	26 (7.1)	31 (8.5)	310 (84.5)
Universal paediatric influenza vaccination programme	37 (10.3)	44 (12.2)	280 (77.6)

Index of Multiple Deprivation (2004) quintile			
1st Most deprived	83 (12.3)	66 (9.8)	527 (78.0)
2nd	46 (11.1)	25 (6.0)	344 (82.9)
3rd	30 (8.9)	27 (8.0)	280 (83.1)
4th	17 (7.7)	18 (8.2)	185 (84.1)
5th Least deprived or missing	36 (11.7)	20 (6.5)	252 (81.8)
Total	212 (10.8)	156 (8.0)	1588 (81.2)
Type of chronic condition			
Neurological conditions	91 (9.8)	86 (9.3)	751 (80.9)
Respiratory conditions	101 (10.4)	95 (9.8)	772 (79.8)
Heart conditions	82 (11.0)	69 (9.3)	595 (79.7)
Immunodeficiency	40 (20.0)	15 (7.5)	145 (72.5)
Kidney conditions or diabetes	32 (18.3)	15 (8.6)	128 (73.1)
Liver conditions or obesity	18 (9.9)	13 (7.1)	151 (83.0)

*Total number adds up to more than 1956 since a child can have multiple chronic conditions

**Missing group is not presented separately due to small number of admissions with missing values

Table S3: Characteristics of children whose PICU admission required vasoactive drugs

Risk factor	Treated with vasoactive drugs *n* (% of all children in group)*
Sex	
Male	308 (27.8)
Female	278 (34.2)
Age group	
<6 months	104 (20.6)
6-<24 months	164 (28.6)
2-<5 years	103 (30.5)
5-<16 years	215 (42.5)
Presence of chronic condition	
No	68 (16.6)
Yes	518 (34.3)
Time period	
October 2003-March 2009 (Pre-pandemic)	124 (27.7)
April 2009-Mach 2010 (Pandemic, waves 1 & 2)	128 (34.1)
April 2010-March 2011 (Pandemic Wave 3)	133 (35.9)
April 2011-August 2013 (Post-pandemic)	121 (33.0)
Universal paediatric influenza vaccination programme	80 (22.2)
Ethnic group	
White	392 (30.4)
Mixed/multiple	13 (24.5)
Asian/Asian British	111 (34.4)
Black/black British	47 (27.8)
Other	14 (28.6)
Missing	9 (23.7)
Index of Multiple Deprivation quintile	
1st Most deprived	189 (28.2)
2nd	119 (29.3)
3rd	105 (31.9)
4th	69 (32.1)
5th Least deprived	83 (32.1)
Missing	21 (51.2)
Total	586 (30.5)
Type of chronic condition*	
Neurological conditions	318 (34.9)
Respiratory conditions	319 (33.4)
Heart conditions	279 (37.8)
Immunodeficiency	81 (40.7)
Kidney conditions or diabetes	72 (41.9)
Liver conditions or obesity	71 (39.0)

*The denominator excludes the 40 admissions where need for vasoactive drugs was missing