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

Pia Hardelid[a,*], Melpo Kapetanstrataki[b], Lee Norman[b], Sarah J. Fleming[b], Paula Lister[c], Ruth Gilbert[a], Roger C. Parslow[b]

[a] UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London, WC1N 1EH, UK
[b] Division of Epidemiology and Biostatistics, Leeds Institute of Cardiovascular and Metabolic Medicine, Worsley Building, Clarendon Way, University of Leeds, Leeds, LS2 9JT, UK
[c] Great Ormond Street Hospital, Great Ormond Street, London, WC1N 3JH, UK

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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.

1. Introduction

Approximately 90 million children aged 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 conditions. 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

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

* Corresponding author.
E-mail address: p.hardelid@ucl.ac.uk (P. Hardelid).

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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.

2. Materials and methods

2.1. 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.

2.2. 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 h 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 $x+1$.

2.3. 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 h 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).

2.4. 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).

2.5. 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