

# Impact of the introduction of a universal childhood influenza vaccination programme on influenza-related admissions to paediatric intensive care units in England

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## ABSTRACT

**Introduction** A universal childhood influenza vaccination programme was introduced in the UK in September 2013. We examine the impact of the gradual introduction of this programme on influenza-related paediatric intensive care unit (PICU) admission rates in England.

**Methods** We extracted data on all influenza-related admissions to PICUs in England in resident children aged 0–15 years old between October 2003 and March 2017 from the Paediatric Intensive Care Audit Network (PICANet) database. We estimated influenza-associated PICU admission rates per 100 000 children by age group, sex and winter season (October to March), and used Poisson regression models to estimate incidence rate ratios (IRRs) in the winter seasons since the introduction of universal childhood vaccination compared with the two winters before the introduction of the programme (2011–2013).

**Results** We identified 929 influenza-related PICU admissions among 873 children. 48.3% of admissions were among children aged less than 2 years old. The influenza-associated PICU admission rate was 1.32 per 100 000 children (95% CI 1.23 to 1.40). We identified a significant increase in influenza PICU admissions in the winters following the introduction of the universal childhood vaccination programme compared with the winters of 2010/2011–2012/2013 among children aged <5 years old: IRR 1.58 (1.05, 2.37) in children <1 year, 2.71 (1.43, 5.17) in 1-year-olds and 1.98 (1.18, 3.31) in children 2–4 years old. No significant difference was found among children aged 5–15 years.

**Conclusion** The universal childhood influenza vaccination has not yet reduced the influenza-associated burden on PICUs in England during its early phase of introduction. Monitoring of influenza PICU admission rates needs to continue in England to assess the long-term impact of universal paediatric influenza vaccination. Linkage between PICANet and national infection surveillance databases would better enable such monitoring.

## INTRODUCTION

Influenza can lead to severe disease in children requiring admission to paediatric intensive care units (PICU), as highlighted during

## Key messages

- ▶ Overall, less than 1% of paediatric intensive care unit (PICU) admissions in England between October and March were influenza related.
- ▶ Influenza-associated PICU admission rates have significantly increased since universal paediatric vaccination was introduced in September 2013 among children less than 5 years old, compared with the two influenza seasons prior to introduction.
- ▶ This is the most comprehensive study to date of the impact of the introduction of the universal childhood influenza vaccination programme on PICUs in the UK.

the H1N1 influenza pandemic in 2009 and 2010.<sup>1–3</sup> Vaccination is the most effective method of preventing influenza infection,<sup>4</sup> and influenza vaccination has been found to reduce the risk of admission to intensive care units (ICU) in children aged 6 months and above in the USA.<sup>5</sup> The UK introduced a new childhood influenza vaccination programme in September 2013, through which all children aged 2–16 years old will be offered live attenuated influenza vaccine annually.<sup>6</sup> The programme is being progressively rolled out, starting in September 2013 with children aged 2 and 3 years old, who were offered vaccination in primary care. In England during the 2016/2017 season, children aged 2–4 years were offered influenza vaccine in primary care, and school-age children up to age 8 were vaccinated through a school-based vaccination programme. The policy was introduced following a modelling study which predicted a reduction in influenza transmission leading to significantly reduced numbers of influenza infections and deaths in the population, even if only 30% of children aged 5–16 years are vaccinated annually.<sup>7</sup> Prior to September

2013, only children aged 6 months to 2 years with chronic conditions at high risk for influenza complications were eligible to receive influenza vaccine. This targeted policy to high-risk groups remains for children aged 6 months to less than 2 years old, who are offered inactivated influenza vaccine.<sup>8</sup> Although children aged less than 6 months old are at highest risk of hospital admission due to influenza, there are no licensed vaccines for this age group. Instead, maternal vaccination during pregnancy was introduced in the UK in 2010 to protect pregnant women and newborn infants.<sup>9</sup>

Influenza vaccination uptake among children in England is much lower than for other childhood vaccinations. Between 2009 and 2016, uptake in children aged 6 months to 2 years in high-risk groups remained below 26%, and among children aged 2–15 years in high-risk groups uptake has remained below 50%.<sup>10</sup> Uptake of influenza vaccination among older children through the universal programme is also relatively low: 38.1% of children of preschool age and 54.9% of 6 to 8-year-old children took up the offer of influenza vaccination in the winter of 2016/2017.<sup>10 11</sup>

Since prevention of severe influenza outcomes was one of the goals of introducing the universal childhood influenza vaccination programme, there is great interest in examining whether this programme is likely to relieve pressures on PICUs, particular during winter periods when demand on PICUs is higher.<sup>12</sup> A previous evaluation of the paediatric influenza vaccination programme in England conducted during the 2014/2015 season found no evidence of a statistically significant reduction in intensive care admissions due to influenza as a result of the introduction of a school-based influenza vaccination programme.<sup>13</sup> However, this study compared ICU admission rates across selected areas of England in one influenza season only. In this study, we used a national PICU database across 14 influenza seasons to assess differences in PICU admission rates before and after the introduction of the universal childhood influenza vaccine programme. Our aim was to examine whether the roll-out of universal childhood influenza vaccination to date has had an impact on influenza-associated admission rates to PICU.

## METHODS

We used data from the Paediatric Intensive Care Audit Network (PICANet), a national clinical audit database containing data on all children admitted to a PICU in the UK and the Republic of Ireland.<sup>14</sup> We extracted data on all English resident children aged less than 16 years old admitted to PICUs in England with influenza, between October 2003 and March 2017. Diagnostic information in PICANet is entered by staff in each reporting PICU using Clinical Terms 3 (the Read codes, a clinical coding system originally developed for use in UK primary care<sup>15</sup>), based on information recorded in the children's medical notes. Influenza-related admissions were identified as an admission where an influenza-associated Read

code had been recorded as either the primary, secondary or comorbidity diagnosis.<sup>16</sup> Note that the Read codes are selected by PICU staff responsible for data entry, and it is not possible to determine whether a child has laboratory-confirmed influenza infection based on the Read code. Therefore, admissions were defined as influenza related based on diagnostic coding alone.

If multiple admissions occurred for the same child within 12 hours, we included only the first of these admissions. This is to allow for children being discharged and readmitted if they require surgery. Admissions for the same child with a 12-hour gap or longer between discharge and subsequent admission were assumed to be independent admissions. Denominator data were based on midyear population estimates for England obtained from the Office for National Statistics.<sup>17</sup>

We classified admissions according to sex and age group, coded as <1 year, 1 year, 2–4 and 5–15 years, following the age groups delineating eligibility for the paediatric influenza vaccination programme. Children with missing information on sex or age group were excluded from the analyses. We did not subdivide the <1 year age group since the population denominators were only available for single years of age, and this group therefore included children aged between 0 and 11 months inclusive. We examined influenza-related PICU admission rates during winter periods, where a winter period was defined as first of October in year  $x$  to end of March in year  $x+1$ .

We defined five time periods to examine differences in PICU admission rates: October 2003 to March 2009 (prepandemic period), October 2009 to March 2010 (influenza A(H1N1)pdm2009 pandemic wave 2), October 2010 to March 2011 (pandemic wave 3), October 2011 to March 2013 (postpandemic period) and October 2013 to March 2017 (roll-out of universal childhood influenza vaccination programme). Years were grouped to reduce the effect of annual variations in influenza-related PICU admission rates.

We defined the presence of a high-risk chronic condition (and therefore eligibility for influenza vaccination under the targeted programme), using a previously published Read code list.<sup>18</sup> We searched for the relevant Read codes during the PICANet admission. The conditions were classified into six groups: neurological, respiratory, cardiovascular conditions, immunodeficiency, kidney conditions or diabetes, and liver conditions or obesity. As for influenza diagnoses, chronic conditions are entered by PICU staff based on information on children's clinical notes, and a previous study has shown that chronic conditions are under-reported in PICANet.<sup>16</sup>

We calculated the proportion of total PICU admissions related to influenza during winter periods, and the proportion of admitted children who had high-risk conditions. We estimated influenza PICU admission rates per 100 000 children by age group, sex and winter period with 95% CIs. The child population at risk in each winter period was estimated as

$$population_{winter} = \frac{3}{12} (MYE_{year\ x} + MYE_{year\ x+1})$$

where MYE is the midyear population estimates in a particular age group. We fitted Poisson regression models with counts of PICU admissions as the outcome variable and population size as the offset to examine risk factors for influenza-related PICU admission during winter seasons, and assess whether the introduction of universal influenza vaccination for children reduced admission rates. The regression model allowed us to estimate incidence rate ratios (IRR) by time period, using the two postpandemic seasons (2011/2012 and 2012/2013) as the baseline period. We included age group, sex and time period as the exposure variables in the model a priori. We then added effect modifier terms between age group and time period to examine whether differences in admission rates by period (ie, the IRRs) differed by age group. Likelihood ratio (LR) tests were used to examine whether inclusion of the time period:age group effect modifier terms significantly improved the fit of the statistical model. An LR test p value <0.05 comparing a model with and without the effect modifier terms was seen to indicate a statistically significant improvement in model fit. We used Stata V.14<sup>19</sup> for statistical analyses.

### 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>. The CAG and ethics approvals cover linkage between PICANet and other databases, including Hospital Episode Statistics.

### RESULTS

We included 929 influenza-related admissions in 873 children admitted to 28 PICUs in the winter seasons between October 2003 and March 2017. Of the 873 children, 829 (95.0%) had one influenza-related admission, 35 (4.0%) had two, and 9 children (1.0%) had three or more influenza-related PICU admissions. The influenza-related admissions accounted for 0.9% of the total PICU admissions during these periods. The proportion of total PICU admissions accounted for by influenza-associated admissions varied between 0.3% in the winters between 2004/2005 and 2006/2007 and 2.7% in the winter of 2010/2011.

Table 1 shows the child characteristics for the 929 admissions. Children aged 6 months or older who had high-risk conditions that would make them eligible to receive influenza vaccination under the targeted vaccination programme accounted for 414 influenza-related admissions (44.6%). Neurological conditions were the most common type of high-risk condition, present in children for 302 admissions (32.5%). A total of 449

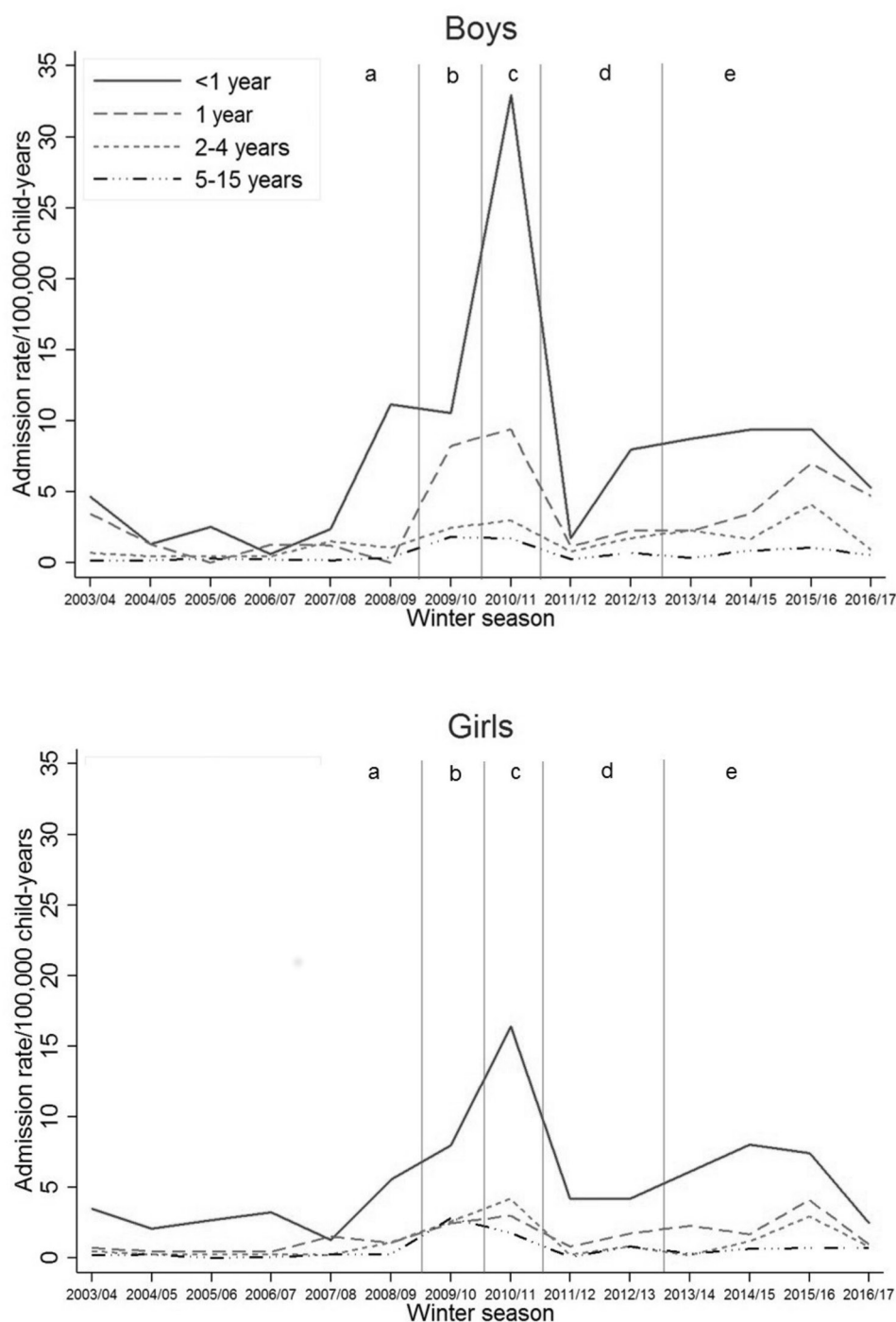
**Table 1** Number and percentage of influenza-related admissions in the study according to child characteristics and time period

Variable	Number of admissions (%)
<b>Sex</b>	
Male	521 (56.1)
Female	406 (43.7)
Missing	2 (0.2)
<b>Age group (years)</b>	
<1	306 (32.9)
1	143 (15.4)
2–4	183 (19.7)
5–15	297 (32.0)
<b>High-risk conditions present</b>	
No	451 (48.5)
Yes	478 (51.5)
<b>Time period</b>	
October 2003 to March 2009 (prepandemic period)	161 (17.3)
October 2009 to March 2010 (influenza A(H1N1)pdm2009 pandemic wave 2)	152 (16.4)
October 2010 to March 2011 (pandemic wave 3)	208 (22.4)
October 2011 to March 2013 (postpandemic period)	90 (9.7)
October 2013 to March 2017 (roll-out of universal childhood influenza vaccination programme)	318 (34.2)

admissions (48.3%) were in children aged <2 years who would not be eligible to receive influenza vaccination through the new universal paediatric influenza vaccination programme (table 1), and 213 of the 929 admissions (22.9%) were in children less than 6 months old.

The influenza-associated PICU admission rate during the 14 winters of the study period was 1.32/100 000 children (95% CI 1.23 to 1.40). There was substantial variability between winter seasons in influenza-related PICU admission rates (figure 1). Rates peaked in the 2010/2011 winter in children aged less than 5 years, and in the 2009/2010 seasons in children aged 5–15 years. Boys had higher admission rates than girls: 1.45/100 000 children (1.32, 1.57) compared with 1.18/100 000 children (1.07, 1.30), respectively. Admission rates were highest among children aged <1 year old (6.70; 5.97, 7.49) and decreased with increasing age: 3.15/100 000 children (2.66, 3.72) in children aged 1 year; 1.36 (1.17, 1.58) in children aged 2–4 years; and 0.62 (0.55, 0.69) in children aged 5–15 years.

We identified significant (LR test P=0.001) effect modification between age group and time period on



\* a) Pre-pandemic period (October 2003-March 2009); b) Pandemic Wave 2 (October 2009-March 2010); c) Pandemic Wave 3 (October 2010-March 2011); d) Post-pandemic (October 2011-March 2013); e) Universal paediatric influenza vaccination programme (October 2013 - March 2017)

**Figure 1** Influenza-related PICU admission rates (per 100 000 children) by age group, sex and winter season\*.

admission rates, thus the age:time period effect modifier terms were included in the regression model. Children aged 5–15 years, unlike children aged less than 5 years old, had significantly lower influenza-related PICU admission rates in the prepandemic period than in the postpandemic period (table 2). In addition, admission

rates peaked during the second pandemic wave among children aged 5–15 years, but during the third pandemic wave for younger children.

We did not identify a significant decrease in admission rates in the period since the introduction of the universal paediatric influenza vaccination programme



compared with the two postpandemic winters in any age group (table 2). Instead, admission rates were significantly higher in the four seasons since the introduction of universal paediatric influenza vaccination in 2013 compared with the two immediate postpandemic seasons for children aged less than 5 years old. The IRR was not significantly increased in the period since October 2013 compared with the two postpandemic winters in children aged 5–15 years old.

## DISCUSSION

We did not find evidence that the rate of influenza-related PICU admissions has declined during the first four seasons of the roll-out of the universal childhood influenza vaccination programme in England. Among children aged less than 5 years old, we found that influenza-related admission rates to PICU were significantly increased in the seasons since the introduction of the programme compared with the winters of 2010/2011 and 2012/2013. Throughout the study period, influenza-related PICU admission rates were highest among children aged less than 2 years old, who are not eligible to receive influenza vaccination through the universal childhood vaccination programme.

This study included all children admitted to a PICU in England with a diagnosis of influenza recorded during a 14-year period. The use of a database covering all PICU admissions in England allowed population-based rates to be calculated. Since influenza-related PICU admissions are rare, national data collection is required for timely monitoring of the impact of universal vaccination on PICU admissions.

We did not have access to data on laboratory confirmation of influenza infection in this study, and instead relied on diagnostic coding of influenza to identify cases. Diagnostic coding for influenza in hospital databases has been found to have low sensitivity.<sup>20</sup> Therefore, we are likely to underestimate the number of influenza-related admissions to PICU. However, our results are valid as long as the underascertainment is relatively constant over time (see below). 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 2013/2014 to the 2016/2017 influenza seasons is generally lower than the number reported through the UK Severe Influenza Surveillance Scheme (USISS) to Public Health England.<sup>21–24</sup> This scheme requires hospitals in England to report all laboratory-confirmed influenza cases admitted to higher dependency or ICUs.<sup>25</sup> Unlike the USISS, our study does not include children admitted to high dependency units, which may explain the difference in reported admissions.

In addition, there is no standardised testing protocol for children with symptoms of respiratory infections who present to secondary care in the English NHS. Therefore, not all children admitted to PICU with influenza infection would have a laboratory-confirmed diagnosis.

**Table 2** Incidence rate ratios (IRR) with 95% CIs by gender, age group and time period\*

Risk factor	IRR (95% CI)
<b>Sex</b>	
Male	1 (baseline)
Female	0.82 (0.72 to 0.93)
<b>Age group and period†</b>	
<b>&lt;1 year</b>	
Prepandemic (October 2003 to March 2009)	0.77 (0.50 to 1.18)
Pandemic wave 2 (October 2009 to March 2010)	2.06 (1.25 to 3.39)
Pandemic wave 3 (October 2010 to March 2011)	5.51 (3.65 to 8.32)
Postpandemic (October 2011 to March 2013)	1 (baseline)
Universal paediatric influenza vaccination programme (October 2013 to March 2017)	1.58 (1.05 to 2.37)
<b>1 year</b>	
Prepandemic	0.82 (0.40 to 1.67)
Pandemic wave 2	3.56 (1.69 to 7.48)
Pandemic wave 3	5.61 (2.81 to 11.2)
Postpandemic	1 (baseline)
Universal paediatric influenza vaccination programme	2.71 (1.43 to 5.17)
<b>2–4 years</b>	
Prepandemic	0.68 (0.38 to 1.21)
Pandemic wave 2	2.80 (1.52 to 5.16)
Pandemic wave 3	3.98 (2.26 to 7.03)
Postpandemic	1 (baseline)
Universal paediatric influenza vaccination programme	1.98 (1.18 to 3.31)
<b>5–15 years</b>	
Prepandemic	0.44 (0.27 to 0.70)
Pandemic wave 2	5.18 (3.40 to 7.89)
Pandemic wave 3	3.90 (2.51 to 6.05)
Postpandemic	1 (baseline)
Universal paediatric influenza vaccination programme	1.45 (0.96 to 2.19)

\*The models exclude two children with missing sex information.

†The IRRs by period are presented for each age group separately since the age group:time period effect modification term significantly improved the fit of the model and was therefore included.

Further, both laboratory testing practices and recognition and coding of suspected or laboratory-confirmed influenza in children in PICANet are likely to vary over time. In particular, PICUs were specifically asked to report confirmed influenza H1N1 cases to PICANet during the H1N1 pandemic between June 2009 and March 2011. It is likely that similar testing practices have

remained in place since March 2011 in English hospitals. In our study, we used the two postpandemic seasons as the baseline for our statistical model to assess changes in admission rates. We deem that the changes in laboratory techniques and sampling practices are likely to be much smaller between seasons during the years following the pandemic compared with between the prepandemic and postpandemic periods. Linkage to laboratory surveillance data from England on children tested for influenza would allow for validation of diagnostic coding of influenza in PICANet. Linkage between hospital databases and national laboratory surveillance data for influenza and other respiratory viruses is already available for children in Scotland.<sup>26</sup> Further linkage to hospital admission records for all children in England would be required to examine whether changes in PICU admission thresholds explain some of the annual variation in influenza-related PICU admission rates since the H1N1 pandemic.

We did not have information about whether children had been vaccinated against influenza. These data are not collected in PICANet, and there is currently no national immunisation database in England that records influenza vaccination receipt in children across the childhood age range. We could therefore not assess what proportion of admitted children were vaccinated, and if this proportion had changed over time. Instead, we relied on comparing influenza-related PICU admission rates before and after the introduction of the universal childhood influenza vaccination programme. Regular reporting of the number of vaccinated children admitted in England to PICU with influenza through the Public Health England USISS system would provide data on the number of vaccine failures and PICU admissions potentially preventable through vaccination.

A previous study of the impact of universal vaccination of schoolchildren in England did not find a statistically significant effect of vaccinating primary school-age children on influenza admissions.<sup>13</sup> That study was based on comparing rates of laboratory-confirmed influenza ICU admissions by age between selected areas of England which had piloted different school-based influenza vaccination programmes (no school-based programme, primary school or secondary school-based programmes). The study was based on data for the 2014/2015 season only, and underlying differences in PICU admission rates between areas (not related to the influenza vaccination programme) were not accounted for. In contrast, our study included all influenza-related PICU admissions across England since 2003. Influenza-related PICU admission rates were low in the postpandemic period, and in particular the 2011/2012 season. Therefore, the significant increase in admission rates since the introduction of universal influenza vaccination for children may be explained by a low baseline rate.

We identified a significant increase in influenza-related PICU admission rates in England since the introduction of the universal paediatric influenza vaccination programme in children aged less than 5 years old, and

no significant change in children aged 5 years and over. Monitoring of influenza-associated PICU admission rates should continue as part of the evaluation of the universal childhood influenza vaccination programme as it is being rolled out. Linkage between PICANet, national infection surveillance and hospital admission databases would allow improved characterisation of the influenza burden on PICUs nationally.

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**Patient consent** Not required.

**Ethics approval** Trent Medical Research Ethics Committee, Ref 05/MRE04/17 +5.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** The original data for this study were collected under section 251 approval; therefore they cannot be shared.

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