Risk factors for admission to hospital with laboratory confirmed influenza in young children: birth cohort study

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Take home message: Older siblings pose risk of serious influenza for babies and toddlers

Abstract

We determined risk factors for influenza hospital admission in children aged <2 years to guide the design of paediatric vaccination programmes.

We linked all singleton live births in Scotland from 2007 to 2015 to hospital administrative data and influenza laboratory reports. Cox proportional hazard models were used to identify birth and family risk factors for influenza admissions.

There were 1115 influenza admissions among 424,048 children. 85.1% of admitted children were born at term and were not in a high risk group. Presence of an older sibling was strongly associated with increased risk of influenza admission, particularly for children aged <6 months: hazard ratio for second vs first born child was 2.02 (95% confidence interval 1.52, 2.69). Maternal age <30 years and birth during autumn (age <6 months) or spring (age 6-23 months) were also associated with admission risk.

Targeting vaccination programmes to high risk children will not prevent the vast majority of influenza admissions. Parents of children aged less than two years should be advised that vaccination of older siblings will protect younger children against influenza infection.
.. As evidence of the impact of the universal influenza vaccine programme emerges, there may be a need to reconsider universal influenza vaccination in children aged 6 months to 2 years in the UK

Introduction

Between 3% and 11% of children aged less than 2 years old in developed countries acquire influenza associated illness every year,[1] creating a major burden on both primary and secondary care services.[2] This has led many countries to implement influenza immunisation programmes. Inactivated influenza vaccines (IIV) are licensed for use in children aged six months and older, and live attenuated vaccines (LAIV) for children two years and older. Children less than six months old are at highest risk of influenza hospital admission,[3] however no influenza vaccines are licensed for this age group due to reports of limited effectiveness.[4]. Instead, the preferred strategy for preventing influenza in this age group is through vaccination of pregnant women. Although both clinical trials and observational studies have reported a protective effect of maternal influenza vaccination on infections in babies less than six months old,[5-7] this appears to be limited to the first eight weeks of life.[8]

Paediatric influenza vaccination policies vary between countries (Table 1). The United States and Canada use a universal approach, while the majority of European countries employ a targeted strategy aimed at reducing the burden of influenza morbidity among children at high risk of complications due to underlying chronic conditions.

Table 1. Influenza vaccination policy in children in selected developed countries

Country	Influenza vaccination recommendation for children	Description
US,[9] Canada[10]	Universal	Age 6 months and over: vaccination recommended for all children but priority for vaccine supply given to children aged 6-59 months and children in high risk groups and (in Canada) Aboriginal children.
Australia[11, 12]	Universal	Age 6 months and over: vaccination recommended for all children but offered free to Aboriginal/Torres Strait Islander children aged 6-59 months and children in high risk groups -Children in Western Australia aged 6-59 months are offered free vaccination
United Kingdom	Mixed	Age 6-23 months: Targeted vaccination offer for children in high risk groups. Age 24 months -16 years: Universal offer of vaccination (since September 2013)
Finland[13]	Mixed	Age 6-35 months: Universal offer of vaccination to children 36 months and over: Targeted vaccination offer for children in high risk groups.
Slovakia[13]	Mixed	Age 6 months -12 years: Universal offer of vaccination to children Age 12 years and over: Targeted vaccination offer for children in high risk groups.
Germany, France , Italy, Spain, Sweden, Denmark,[13] New Zealand[14]	Targeted	Six months and above: Targeted vaccination for children in high risk groups.

The evidence regarding whether universal influenza vaccination programmes lead to higher uptake in high risk groups is conflicting,[15, 16] however both universal and targeted programmes have lower rates of uptake than other routine childhood vaccination programmes. [17-19] In the UK, 18.6% of children aged between 6 months and two years in a high risk group were vaccinated,[20] whereas 32.9%-57.1% of preschool children were vaccinated under the universal programme in 2015/16, depending on UK country.[21] Likewise, vaccination uptake in pregnant women in the UK and many other countries remains below 50%.[20, 22, 23] Improved evidence is needed to guide policy about which children should be offered influenza vaccination and to improvements in uptake in children most likely to benefit.

A recent systematic review of observational studies found that children aged less than two years, born prematurely, or with neurological conditions, immunosuppression or diabetes were at significantly increased risk of influenza hospital admission.[24] There are few studies regarding risk

factors not associated with underlying chronic conditions, however young maternal age (<26 years), poverty/ education level, minority ethnic group, smoking in the home and number of children in the household have been identified as risk factors for influenza hospital admission in three case-control studies.[25-27] There are no studies in children aged less than six months old.

We carried out a cohort study to determine risk factors for influenza hospital admissions in children aged less than two years throughout Scotland. We focussed on examining birth and family risk factors that are readily identifiable and could be included in programmes that aim to target the offer of vaccination and/or to improve the uptake of vaccination among children and pregnant women.

Methods

Data sources, study period and population

We analysed a national cohort of all singleton births in Scotland between October 2007 and April 2015 by linking electronic birth and death registration data held by National Records for Scotland (NRS), to hospital admission records (Scottish Morbidity Records -SMR-01), Scottish Birth Records, Scottish Maternity Records (SMR-02) and the national laboratory surveillance database, Electronic Communication of Surveillance in Scotland (ECOSS). ECOSS contains details of all positive detections reported to Health Protection Scotland (HPS), the national public health agency, from microbiology laboratories serving primary and secondary care in the National Health Service (NHS). Deterministic linkage between databases was carried out by the electronic Data Research and Innovation Service (eDRIS) using the Community Health Index (CHI) number, a unique individual identifier assigned at birth and recorded on all interactions with the Scottish National Health Service, including on ECOSS. This study was approved by the Public Benefit and Privacy Panel for Health and Social Care, reference number 1516-0405.

Children were followed from birth or the start of the follow-up period (whichever occurred last) until two years of age, date of death or out-migration, or the end of the follow-up period, whichever occurred first. We excluded births before 24 weeks of gestation to minimise misclassification of stillbirths, and births to non-resident Scottish mothers. We measured influenza-confirmed admissions during the follow-up period from 1st September 2009 to 31st May 2015. Laboratory surveillance for influenza through ECOSS became routine during the summer of 2009 and 2014/2015 was the last full influenza season in the dataset.

We present results separately for infants aged less than six months and children aged 6-23 months. For both age groups, we assumed that children had not been vaccinated. While true for infants aged less than six months, we estimate that 0.6% of children aged 6-23 months were misclassified as unvaccinated under this assumption. Vaccine coverage data from primary care indicate that 3% of two year olds would be in a clinical risk group and 18.5% of them would be vaccinated.[20]

Outcome: influenza-confirmed hospital admission

We defined a laboratory-confirmed influenza admission as an emergency hospital admission in SMR-01 with a linked influenza positive ECOSS episode, where the specimen date was up to 7 days before or after the admission date, and the primary diagnosis was not an injury (International Classification of Diseases version 10 (ICD-10) codes S00-T79). We allowed any sample that was positive for influenza (irrespective of place of collection, type of sample or testing method) between 25th August 2009 and 7th June 2015 that met these criteria to be linked to an emergency admission to allow for tests carried out up to a week before or after an admission, and to include both seasonal and pandemic strains of influenza. A person may test positive for the same pathogen multiple times

during their illness. Therefore, HPS derives infection episodes to identify positive laboratory tests relating to the same illness period. If more than one emergency hospital admission linked to an ECOSS episode within the 14-day period, the admission with the admission date closest to the ECOSS specimen date was selected as the influenza-confirmed admission.

Risk factors

We examined risk factors that are routinely recorded in infant delivery and hospitalisation records and are known to be associated with morbidity from respiratory tract infections. Gestational age was coded into a three category variable to ensure sufficient numbers for analysis: preterm (<37 weeks), term (37-40 weeks) and post-term (41 weeks and above). Season of birth was coded into quarters of the year (January-March, April-June, July-September and October-December). We examined presence of older siblings (coded using parity information into none, one, or two or more), maternal age (grouped as <20, 20-29, 30-39 and 40+ years), and qunitiles of the Scottish Index of Multiple Deprivation (SIMD), which is based on area-level indicators of deprivation for areas of 500 to 1000 people.[28]

We adjusted all models for presence of high risk conditions. High risk conditions were identified using ICD-10 diagnostic codes recorded in either the Scottish Birth Record (neonatal diagnoses) or in SMR-01 until six months of age. The code list for identifying high risk conditions builds on a previously published list,[29] which we extended by cross-checking against a list of conditions used to define high risk groups in primary care, [30] and including chromosomal abnormalities (Supplementary Table S1). Since not all high-risk conditions are recorded in hospital databases, we further adjusted for prolonged postnatal stay in hospital (defined as >14 days) as an indicator of birth trauma or neonatal intensive care with potential neurological and/or respiratory sequelae.

Statistical analyses

We included only the first influenza-confirmed admission for each child within each of the two age groups. We used Stata (version 13; StataCorp, College Station, TX, USA) for statistical analyses. We calculated influenza-confirmed admission rates per 1000 child years by age group (<6 months and 6-23 months), each exposure variable, and also by influenza season (defined as 1st September in year *x* to 31st May in year *x+1*). The dominant strains in each season were also derived from ECOSS.[31]

We used Cox proportional hazards regression models to examine the association between the exposure variables and the risk of influenza-confirmed hospital admission. An admitted child was censored at their admission date. The proportional hazards assumption was checked using cumulative hazard plots. All exposure variables were included in the models a priori, and associations with a Wald test p <0.05 were considered to be statistically significant. Due to a non-negligible proportion of children with missing data on risk factors, we used multiple imputation with 15 imputations.[32] The main results are based on the imputed datasets. We carried out a sensitivity analysis where we also classified children who had a clinically coded influenza admission without a linked ECOSS positive episode as having had an influenza-confirmed admission. Clinically coded influenza admissions were identified using ICD-10 codes J09-J11 in any of the diagnostic fields.

We estimated population attributable fractions (PAFs) for all risk factors which were significantly associated with the outcome and considered amenable via vaccination policy or health/social policy: maternal age, number of older siblings and season of birth, and for 6-23 month olds also presence of high risk conditions, smoking during pregnancy and gestational age. PAFs were estimated using the *punafcc* function with robust standard errors,[33] using the complete case models.

Role of the funding source

This study was funded by the National Institute of Health Research. The study sponsor had no role in the study design, data analysis, interpretation, writing the report, or in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

This study included a birth cohort of 424,048 children born in Scotland and 636,428 child-years of follow-up. There were 1115 influenza-confirmed admissions during the follow up period in children aged less than two years old. 1109 children had one influenza-confirmed admission during the study period; three children had two. The linkage between hospital admission and laboratory data is summarised in Figure 1. Of the 849 influenza positive ECOSS samples that did not link to an admission within the birth cohort, 174 (20.5%) were collected in GP surgeries and 649 (76.4%) were collected in hospital (Emergency or Outpatients' Department) or elsewhere (Supplementary Figure S1). These unlinked samples were therefore unlikely to relate to a hospital admission. Supplementary Table S2 shows the characteristics of the cohort children, including the proportion with missing data. Less than 3% of children in the birth cohort aged 6-23 months old were in a clinical risk group and would therefore qualify for influenza vaccination (Table S2).

Of the 1115 confirmed influenza admissions, 414 (37.1%) had a hospital diagnosis indicating influenza (Supplementary Figure S2), and 344 (33.6%) had a primary diagnosis which was not from the respiratory conditions chapter of the ICD-10 (Supplementary figure S3).

Admission rates for confirmed influenza during influenza seasons (per 1000 child years) were 2.68 (95% confidence interval 2.40, 2.99) in children <6 months and 2.09 (1.95, 2.49) in children aged 6-23 months. Influenza-confirmed admission rates peaked in the 2012/13 influenza season in both age groups (Figure 2). Admission rates using diagnosis codes to define influenza admissions were significantly lower at 1.89 (1.65, 2.14) and 1.09 (0.99, 1.20) for children aged <6 months and 6-23 months respectively. Rates of influenza-confirmed admissions peaked in January (Supplementary Figure S4).

Table 2. Number of influenza-confirmed admissions and rates (per 1000 child years with 95% confidence intervals) by birth and family characteristics in each of the two study cohorts, September 2009-May 2015.

*<5 children had missing information on SIMD quintile

	<6 months		6-23 months	
Variable	**Number of events (%) Total *n*=333**	**Rate/1000 cy (95% CI)**	**Number of events N=780 (%)**	**Rate/1000 cy (95% CI)**
Gestational age				
Preterm (<37 weeks)	26 (7.8)	3.15 (2.14, 4.62)	79 (10.1)	3.16 (2.53, 3.94)
term 37-40	223 (67.0)	2.08 (1.82, 2.37)	508 (65.1)	1.60 (1.46, 1.74)
late term 41+	58 (17.4)	1.57 (1.21, 2.03)	159 (20.4)	1.39 (1.19, 1.63)
Missing	26 (7.8)	3.90 (2.65, 5.72)	34 (4.4)	1.70 (1.21, 2.37)
Sex				
Boys	192 (57.7)	2.26 (1.96, 2.60)	448 (57.4)	1.8 (1.65, 1.98)
Girls	141 (42.3)	1.90 (1.61, 2.24)	332 (42.6)	1.45 (1.3, 1.61)
High risk condition recorded before 6 months				
No	307 (92.2)	1.98 (1.77, 2.22)	708 (90.8)	1.52 (1.41, 1.64)
Yes	26 (7.8)	6.00 (4.09, 8.82)	72 (9.2)	5.84 (4.63, 7.35)
Postnatal stay in hospital				
≤14 days	308 (92.5)	2.02 (1.80, 2.26)	717 (91.9)	1.57 (1.46, 1.69)
>14 days	12 (3.6)	6.87 (3.90, 12.1)	34 (4.4)	6.31 (4.51, 8.83)
Missing	13 (3.9)	2.71 (1.57, 4.66)	29 (3.7)	1.93 (1.34, 2.78)
Season of birth				
January-March	34 (10.2)	0.92 (0.65, 1.28)	202 (25.9)	1.75 (1.52, 2.00)
April-June	26 (7.8)	0.68 (0.47, 1.01)	253 (32.4)	2.10 (1.86, 2.38)
July-September	138 (41.4)	3.22 (2.72, 3.80)	168 (21.5)	1.36 (1.17, 1.58)
October-December	135 (40.5)	3.27 (2.76, 3.87)	157 (20.1)	1.34 (1.14, 1.56)
Number of older siblings (parity)				
None	86 (25.8)	1.25 (1.01, 1.55)	307 (39.4)	1.47 (1.32, 1.65)
One	122 (36.6)	2.30 (1.93, 2.75)	253 (32.4)	1.61 (1.42, 1.82)
Two or more	106 (31.8)	3.39 (2.80, 4.10)	184 (23.6)	1.99 (1.73, 2.3)
Missing	19 (5.7)	3.03 (1.93, 4.75)	36 (4.6)	1.91 (1.38, 2.65)
Maternal smoking during pregnancy				
No	239 (71.8)	2.02 (1.78, 2.29)	535 (68.6)	1.54 (1.42, 1.68)
Yes	61 (18.3)	2.22 (1.72, 2.85)	179 (22.9)	2.13 (1.84, 2.47)
Missing	33 (9.9)	2.45 (1.74, 3.44)	66 (8.5)	1.41 (1.11, 1.80)

Maternal age group				
<20y	19 (5.7)	2.20 (1.40, 3.45)	61 (7.8)	2.16 (1.68, 2.78)
20-29y	161 (48.3)	2.29 (1.96, 2.67)	368 (47.2)	1.74 (1.57, 1.92)
30-39y	123 (36.9)	1.78 (1.49, 2.12)	299 (38.3)	1.47 (1.31, 1.64)
40+	11 (3.3)	1.94 (1.08, 3.51)	22 (2.8)	1.30 (0.86, 1.98)
Missing	19 (5.7)	3.46 (2.21, 5.43)	30 (3.8)	1.80 (1.26, 2.58)
SIMD quintile				
Most deprived quintile	105 (31.5)	2.54 (2.10, 3.08)	193 (24.7)	1.55 (1.35, 1.79)
2	74 (22.2)	2.19 (1.75, 2.75)	178 (22.8)	1.77 (1.52, 2.04)
3	54 (16.2)	1.77 (1.35, 2.30)	155 (19.9)	1.69 (1.45, 1.98)
4	55 (16.5)	1.93 (1.48, 2.52)	149 (19.1)	1.75 (1.49, 2.05)
Least deprived quintile/Missing	45 (13.5)	1.79 (1.33, 2.39)	105 (13.5)	1.39 (1.15, 1.69)

Crude admission rates were significantly higher among children in high risk groups (Table 2), however they represented a small minority of admitted children: 895 of the 1052 children (85.1%) who were admitted with at least one influenza-confirmed admission and had their gestational age recorded were born at or after term without recorded high risk conditions. In fully adjusted models for children aged <6 months, being born between July and September, having at least one older sibling, and maternal age less than 30 years were most strongly associated with an increased risk of influenza-confirmed admission (Table 3).

Table 3 Crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI) from Cox proportional hazards model (based on multiply imputed data) for influenza-confirmed admissions in children less than six months old (Age group 1, 333 events, 343,068 children)

Risk factor	Crude HR (95% CI)	Adjusted HR (95% CI)
Gestational age		
Preterm (<37 weeks)	1.68 (1.14, 2.47)	1.29 (0.82, 2.04)
Term (37-40 weeks)	1	1
Late term (41+ weeks)	0.75 (0.56, 1.01)	0.84 (0.63, 1.12)
Sex		
Boys	1	1
Girls	0.84 (0.68, 1.04)	0.86 (0.69, 1.06)
High risk condition recorded before six months		
No	1	1
Yes	3.04 (2.04, 4.53)	2.46 (1.59, 3.80)
Postnatal stay in hospital		
≤14 days	1	1
>14 days	3.37 (1.89, 5.99)	1.79 (0.88, 3.67)
Season of birth		
January-March	1	1
April-June	0.74 (0.44, 1.23)	0.74 (0.44, 1.23)
July-September	3.45 (2.37, 5.03)	3.49 (2.40, 5.08)
October-December	3.53 (2.43, 5.15)	3.56 (2.44, 5.19)
Number of older siblings (parity)		
None	1	1
One	1.82 (1.38, 2.40)	2.02 (1.52, 2.69)
Two or more	2.72 (2.06, 3.61)	3.13 (2.32, 4.22)
Maternal smoking during pregnancy		
No	1	1
Yes	1.12 (0.85, 1.49)	0.86 (0.64, 1.15)
Maternal age group		
<20 years	1.24 (0.77, 2.00)	1.98 (1.20, 3.29)
20-29 years	1.28 (1.01, 1.61)	1.47 (1.15, 1.87)
30-39 years	1	1
40+ years	1.08 (0.59, 2.00)	0.94 (0.51, 1.74)
SIMD quintile		

Most deprived quintile	1.48 (1.04, 2.11)	1.28 (0.89, 1.84)
2nd	1.28 (0.88, 1.86)	1.15 (0.79, 1.69)
3rd	1.03 (0.69, 1.53)	0.97 (0.65, 1.45)
4th	1.12 (0.75, 1.67)	1.10 (0.74, 1.64)
Least deprived quintile	1	1

Among children aged 6-23 months, premature birth, season of birth (January to June), high risk conditions, maternal smoking during pregnancy, presence of one or more older siblings, maternal age <30 years and having a prolonged postnatal hospital stay were associated with a significantly increased risk of influenza-confirmed admission (Table 4). The HRs for presence of siblings, season of birth, and maternal age group were weaker for 6-23 year olds than for children aged <6 months.

These results remained very similar in the complete case analyses (Supplementary Table S3). For children less than 6 months old, the HR for prematurity (born at <37 weeks) became statistically significant when we also classified admissions with a clinical code indicating influenza as an influenza-confirmed admission (Supplementary Table S4).

Table 4 Crude and adjusted hazard ratios (HR) with 95% CI from Cox proportional hazards model (based on multiply imputed data) for influenza-confirmed admissions in children aged six to 23 months (Age group 2, 780 events, 399,454 children)

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)
Gestational age		
Preterm (<37 weeks)	1.95 (1.55, 2.46)	1.36 (1.03, 1.80)
Term (37-40 weeks)	1	1
Late term (41+ weeks)	0.87 (0.73, 1.04)	0.90 (0.75, 1.07)
Sex		
Boys	1	1
Girls	0.81 (0.70, 0.93)	0.82 (0.71, 0.95)
High risk condition recorded before six months		
No	1	1
Yes	3.83 (3.00, 4.88)	3.04 (2.33, 3.96)
Postnatal stay in hospital		
≤14 days	1	1
>14 days	4.04 (2.87, 5.68)	1.82 (1.18, 2.80)
Season of birth		
January-March	1	1
April-June	1.20 (1.00, 1.45)	1.21 (1.00, 1.45)
July-September	0.78 (0.63, 0.96)	0.78 (0.64, 0.96)
October-December	0.77 (0.62, 0.95)	0.77 (0.63, 0.95)
Number of older siblings (parity)		
None	1	1
One	1.09 (0.93, 1.29)	1.18 (0.99, 1.40)
Two or more	1.37 (1.14, 1.64)	1.49 (1.23, 1.80)
Maternal smoking during pregnancy		
No	1	1
Yes	1.39 (1.17, 1.66)	1.25 (1.03, 1.50)
Maternal age group		
<20 years	1.48 (1.13, 1.95)	1.65 (1.23, 2.23)
20-29 years	1.18 (1.01, 1.38)	1.24 (1.05, 1.46)
30-39 years	1	1
40+ years	0.89 (0.58, 1.37)	0.81 (0.53, 1.25)

SIMD quintile		
Most deprived quintile	1.10 (0.87, 1.40)	0.89 (0.69, 1.14)
2nd	1.25 (0.99, 1.60)	1.08 (0.84, 1.38)
3rd	1.20 (0.94, 1.54)	1.09 (0.85, 1.41)
4th	1.24 (0.97, 1.59)	1.18 (0.92, 1.52)
Least deprived quintile	1	1

The highest proportion of cases could be prevented by reducing variation in risk according to season of birth, number of siblings and maternal age in both age groups (Table 5). Targeted strategies towards high risk groups would only prevent between 4% and 6% of cases.

Table 5. Population attributable fractions (expressed as %) of the proportion of admissions prevented by setting the named risk factors to the value of the specified categories

Risk factor and scenario*	**Population attributable fraction (95% CI)**
Age group 1: <6months	
Number of siblings=none	45.5 (33.5, 55.3)
Maternal age=30-39 years	18.5 (5.5, 29.7)
High risk=No	4.5 (1.3, 7.7)
Season of birth=April to June	65.8 (49.9, 76.6)
Age group 2: 6-23 months	
Number of siblings=none	13.7 (5.2, 21.4)
Maternal age=30-39 years	11.4 (2.5, 19.4)
High risk=No	5.6 (3.5, 7.7)
Season of birth=October to December	19.2 (6.4, 30.3)
Gestational age =41+ weeks	9.9 (-3.8, 21.7)
Maternal smoking during pregnancy=No	4.9 (0.6, 9.1)
Postnatal stay<14 days	1.5 (0, 3)

* Note all other variables are held constant on their observed values in the data in the adjusted complete case models

Discussion

Presence of an older sibling, season of birth, maternal age <30 years and presence of a high risk condition were all risk factors for laboratory confirmed influenza hospital admission in children aged less than two years old. Preterm birth was a significant risk factor for influenza admission among children aged 6-23 months. However, the low prevalence of high risk conditions and preterm births resulted in low estimated population attributable risk fractions for these characteristics. Targeting vaccination at children with these risk factors would be expected to achieve a very small reduction in the number of influenza admissions among all children in the age group. Among children aged less than six months old, presence of an older sibling and birth during autumn accounted for the highest

population attributable risk. For children aged 6-23 months old, the population attributable risk was relatively low (<20%) for each risk factor.

We used a national birth cohort of over 400,000 children constructed using linked administrative health databases, and exploited linkage between hospital and laboratory surveillance databases to define influenza-confirmed hospital admissions. This avoided reliance on diagnostic coding, which has been shown to have low sensitivity in previous studies[34, 35] and would have underestimated admission rates in our study by up to 50%. The large sample size and national coverage allowed us to examine key risk factors that could be readily targeted and monitored in a vaccination programme.

There is no national testing protocol in the UK for children presenting to hospital with symptoms of respiratory infections. Our ECOSS database extract included only influenza positive test results, hence we could not examine how testing probabilities vary by child characteristics. The likelihood of sample collection is likely to increase with severity of illness, and we may have misclassified children who were admitted with influenza but did not have a diagnostic sample taken. In addition, testing may be more likely among children with high-risk conditions or who were born prematurely. If this is the case, it would mean that the true population attributable risk for high risk conditions may be even lower than our estimate. Since our method is likely to underestimate the true number of children admitted to hospital with influenza, we carried out sensitivity analysis also including children with a clinical code mentioning influenza (but no recorded positive test result), which yielded similar results. In the absence of universal sampling of all children presenting to hospital with respiratory symptoms or fever, the methods used here is likely to yield the most comprehensive and unbiased picture of risk factors for influenza hospitalisations in young children that is achievable using routinely collected administrative health data.

A second limitation is that we could not take into account vaccination status. During the study period there was no individual national data collection on paediatric influenza immunisation in any UK country, although recording is improving over time in Scotland. However, only a small minority of eligible 6-23 month old children are vaccinated. Such misclassification would be expected to bias hazard ratios for clinical risk factors towards the null effect. Further, although we had information on parity, we could not examine the effect of sibling ages. Childcare attendance is strongly associated with an increased risk of respiratory tract infections in early childhood,[36] however there is no national register of preschool childcare in Scotland. Finally, we could only identify children in high risk groups based on hospital records. This may miss children whose chronic condition is managed in primary care, such as children with severe wheeze. However, we also adjusted for prolonged postnatal stay for allow potential underascertainment of children in risk groups.

The rates of hospital admission during influenza seasons reported in our study are similar to previous studies based on laboratory confirmed influenza in the US and England.[35, 37] Our laboratory confirmed influenza admission rates are higher than rates reported by studies relying only on clinical coding.[38, 39] We examined risk factors across six influenza seasons combined to ensure sufficient numbers of influenza-associated hospital admissions. Since our results were based on data from A/H1N1, A/H3N2 and B-dominant seasons, they should therefore be broadly representative across multiple influenza seasons with a similar strain circulation pattern.

This is the first study to specifically examine multiple risk factors for influenza in children aged less than six months old. We found that the presence of older siblings and season of birth were the strongest risk factors for influenza-confirmed admission in this age group, with PAFs of 46% and 66% respectively. Higher parity has previously been identified as a risk factor for respiratory infection-related hospital admissions.[40] Since there is no influenza vaccine licensed for this young age group,

reducing the risk of influenza complications will rely on improving vaccination uptake among siblings and pregnant women. Pregnant women and parents of children less than two years old should be encouraged to vaccinate older siblings if they are eligible under the universal programme. Pregnant women should also be given information about the influenza risk reduction in newborns conferred by maternal influenza vaccination. One clinical trial has indicated that the effects may only last for up to two months.[8] In our study, 26% of admissions in children less than six months old occurred in the first two months of life. Thus, maternal influenza vaccine would not prevent the majority of admissions in this age group. Further research into the duration of maternal influenza vaccine protection in infants, and efforts to develop influenza vaccines for children less than six months old are required.

Parity and season of birth were also significantly associated with admission risk in children aged 6-23 months. However the associations with influenza hospital admission risk were weaker, most likely because of greater mixing through childcare. None of the risk factors were associated with a PAF of more than 20% in this age group, indicating that targeting specific risk groups (such as children with older siblings or children born prematurely) is unlikely to prevent the majority of cases. Instead, extending the universal influenza vaccination programme to children aged 6-23 would prevent more hospital admissions in this age group. Vaccination of all children aged 6-23 months is not recommended in the UK, despite evidence of cost-effectiveness,[41] due to the perceived lack of evidence of effectiveness of IIV in this age group.

Since universal vaccination of school-aged children is predicted to reduce influenza transmission overall,[41] the risk of influenza admission by season of birth and parity in children less than two years may attenuate over the coming years. These risks should be monitored as part of the evaluation of the universal paediatric influenza vaccine programme in the UK. As evidence of the population impact of universal influenza vaccine and effectiveness of inactivated influenza vaccines in young children emerges,[18] there may be a need to reconsider the extension of influenza vaccination to children less than two years old. However, this study only includes influenza-confirmed hospital admissions, and we do not examine risk factors influenza infections that do not require healthcare intervention, or those presenting only in primary care. Further, although our results indicate that a targeted vaccination programme may not reduce the majority of influenza associated hospital admissions in children with high risk conditions, children in clinical high-risk groups are over-represented among influenza-related intensive care admissions and deaths.[42, 43] Any reconsideration of the influenza vaccination programme for 6-23 month olds will need to take into account the full range of severity of influenza-related illness in children as well as social impacts including time off work for parents.

In agreement with a previous systematic review,[24] we found that children born preterm were more likely to be admitted to hospital with influenza than children born at or after term. However, the increased risk was only significant among children aged 6-23 months. Children born prematurely without other high-risk conditions are currently not recommended to receive influenza vaccine in the UK. This study adds to the growing evidence[24] to support an extension of the targeted vaccination programmes to children born prematurely and aged between six to 23 months. Larger studies are required to examine the risk of admission according to more specific groups of gestational age.

Vaccination of children who are eligible for influenza vaccination under a universal programme (children aged two years and older in the UK) who have a sibling aged less than two years during the influenza season should be strongly encouraged to be vaccinated in order to prevent influenza-associated hospital admissions among young children. Further research is required into the duration

of maternal antibody protection and influenza vaccine development for children less than six months old.

Conflicts of interest

PH reports receiving a travel award from the European Society for Paediatric Infectious Diseases, supported by GSK, to attend a conference in 2016. All other authors report no conflicts of interest.

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Figure legends

Figure 1. Flowchart of linkage outcomes between birth cohort, emergency hospital admissions and laboratory confirmed influenza positive episodes. Red dashed lines indicate linkages between datasets.

Figure 2. Influenza-confirmed admission rates (per 1000 child years) by influenza season and age group

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Figure 1

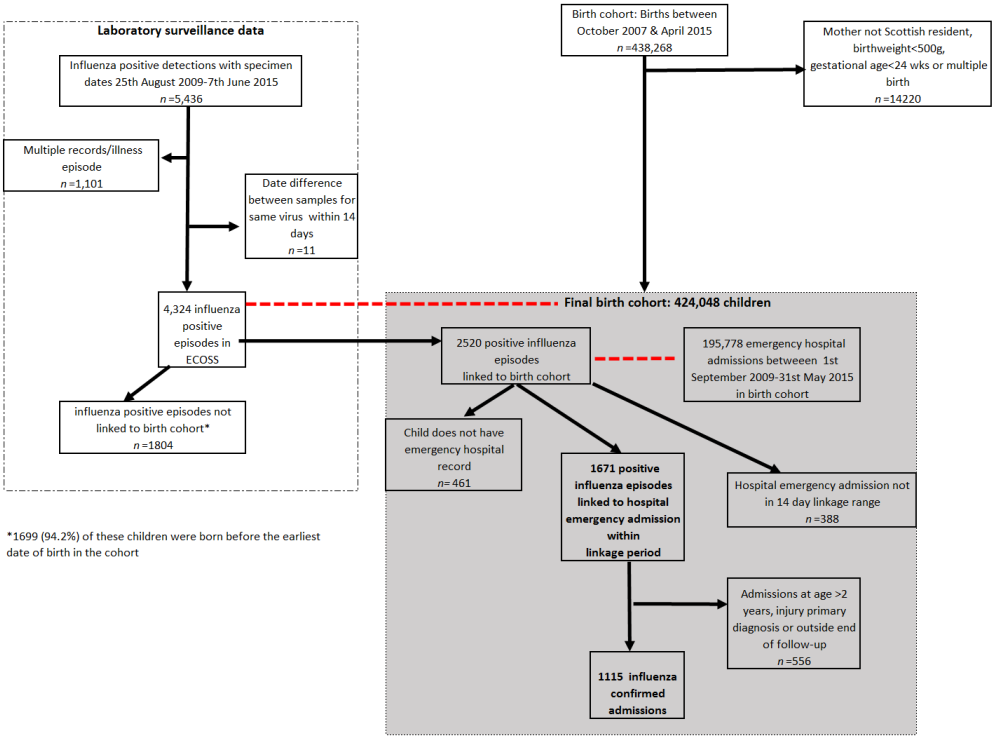
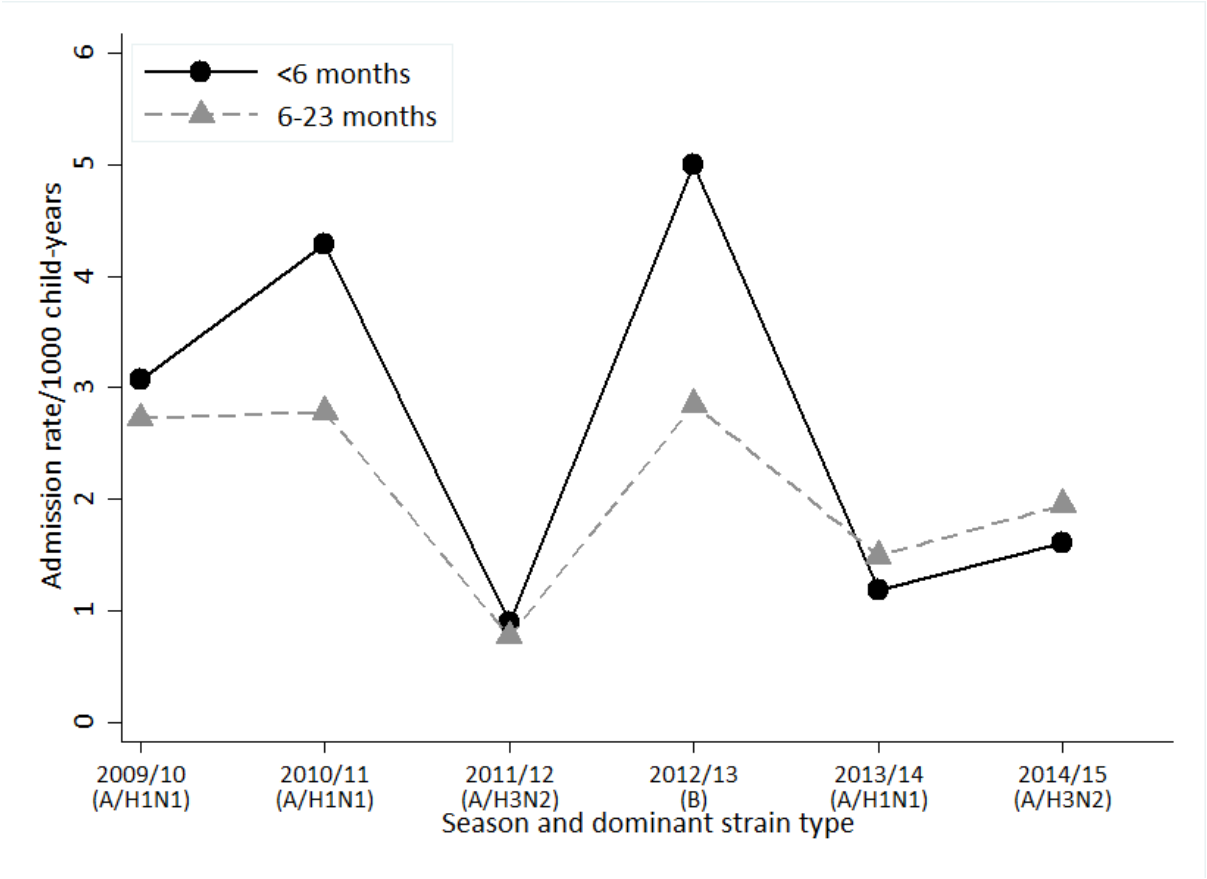

Laboratory surveillance data
Influenza positive detections with specimen dates 25th August 2009-7th June 2015
n =5,436
Multiple records/illness episode
n =1,101
Date difference between samples for same virus within 14 days
n =11
4,324 influenza positive episodes in ECOSS
influenza positive episodes not linked to birth cohort*
n =1804
*1699 (94.2%) of these children were born before the earliest date of birth in the cohort
Birth cohort: Births between October 2007 & April 2015
n =438,268
Mother not Scottish resident, birthweight<500g, gestational age<24 wks or multiple birth
n =14220
Final birth cohort: 424,048 children
2520 positive inflluenza episodes linked to birth cohort
195,778 emergency hospital admissions betweeen 1st September 2009-31st May 2015 in birth cohort
Child does not have emergency hospital record
n= 461
1671 positive influenza episodes linked to hospital emergency admission within linkage period
Hospital emergency admission not in 14 day linkage range
n =388
Admissions at age >2 years, injury primary diagnosis or outside end of follow-up
n =556
1115 influenza confirmed admissions

Figure 2


<6 months
6-23 months
Admission rate/1000 child-years
0
1
2
3
4
5
6
2009/10 (A/H1N1)
2010/11 (A/H1N1)
2011/12 (A/H3N2)
2012/13 (B)
2013/14 (A/H1N1)
2014/15 (A/H3N2)
Season and dominant strain type

Supplementary Tables and Figures

Supplementary Table S1: ICD-10 code lists to identify children in high-risk groups in longitudinal hospital record

Condition	ICD-10 codes
Chronic heart disease	I05 I06 I07 I08 I09 I11 I12 I13 I20 I21 I22 I23 I24 I25 I26 I27 I28 I30 I31 I32 I33 I34 I35 I36 I37 I38 I39 I40 I41 I42 I43 I44 I45 I47 I48 I49 I50 I51 I52 Q20 Q21 Q22 Q23 Q24 Q25 Q26 Q27 Q28 Q89.3 T82 T86.2 T86.3 Y60.5 Y84.0 Z45.0 Z94.1 Z94.3 Z95 Z99.4
Chronic kidney disease	M31.0 N00 N01 N02 N03 N04 N05 N06 N07 N08 N11 N12 N14 N15 N16 N18 N19 N25 Q60 Q61 Q62 Q63 T86.1 Y60.2 Y61.2 Y62.2 Y84.1 Z49.0 Z49.1 Z90.5 Z94.0 Z99.2
Chronic liver disease	B18 K70 K71 K72 K73 K74 K75 K76 K77 P78.8 Q44 T86.4 Z94.4
Chronic neurological disease	G10 G14 G20 G22 G26 G35 G64 G92 G98 I64 Q02 E75 E83.0 F00 F01 F02 F03 F71 F72 F73 G11 G12 G13 G21 G23 G24 G25 G30 G31 G32 G36 G37 G40 G41 G43 G44 G45 G46 G47 G50 G51 G52 G53 G54 G55 G56 G57 G58 G60 G61 G62 G63 G70 G71 G72 G73 G80 G81 G82 G83 G90 G91 G93 G94 G95 G96 G97 G99.1 I60 I61 I62 I63 I65 I66 I67 I68 I69 P11.0 P11.1 P11.2 P21 P91 Q00 Q01 Q03 Q04 Q05 Q90 Q99.2 Q91 Q92 Q93 95.2 Q95.3 Q97 S06.2 S06.3 S06.4 S06.5 S06.6 S06.7 S06.8 S06.9 T85.0 Z96.2
Chronic respiratory disease	D86.0 D86.2 E84 J40 J41 J42 J43 J44 J45 J46 J47 J60 J61 J62 J63 J64 J65 J66 J67 J68 J69 J70 J81 J82 J84 J90 J91 J92 J96.1 J98 P27 P75 Q30 Q31 Q32 Q33 Q34 Q35 Q36 Q37 Q79.0 Z90.2 Z94.2
Diabetes	E10 E11 E12 E13 E14 G59.0 G63.2 G99.0 I79.2 M14.2 N08.2 N08.3 O24 P70.2
Immunosuppression & splenic dysfunction	B20 B21 B22 B23 B24 C00-C97 D37 D38 D39 D40 D41 D42 D43 D44 D45 D46 D47 D48 D56 D57 D61 D70 D71 D72 D73 D76 D80 D81 D82 D83 D84 D89 K90.0 Q89.0 S36.0 T86.0 T86.8 T86.9 Y83.0 Z21 Z22.6 Z85 Z94.5 Z94.6 Z94.7 Z94.8 Z94.9
Obesity	E66

Supplementary Table S2: Distribution of the number of children in each cohort (%) according to the birth and family risk factors

	Age group 1: <6 months	Age group 2: 6-23 months
Risk factor		
Gestational age		
Preterm (<37 weeks)	17998 (5.3)	20865 (5.2)
Term 37-40	230950 (67.3)	266298 (66.7)
Late term 41+	79494 (23.2)	94426 (23.6)
Missing	14626 (4.3)	17865 (4.5)
Sex		
Boys	183154 (53.4)	210510 (52.7)
Girls	159914 (46.6)	188944 (47.3)
High risk condition recorded before 6 months		
No	333627 (97.3)	388977 (97.4)
Yes	9441 (2.8)	10477 (2.6)
Postnatal stay in hospital		
≤14 days	328694 (95.8)	381504 (95.5)
>14 days	3787 (1.1)	4580 (1.2)
Missing	10587 (3.1)	13370 (3.4)
Season of birth		
January-March	84230 (24.6)	94041 (23.5)
April-June	87896 (25.6)	97167 (24.3)
July-September	87801 (25.6)	102199 (25.6)
October-December	83141 (24.2)	106047 (26.6)
Number of older siblings (parity)		
None	148555 (43.3)	174204 (43.6)
One	113891 (33.2)	131706 (33)
Two or more	66989 (19.5)	76983 (19.3)
Missing	13633 (4)	16561 (4.2)
Maternal smoking during pregnancy		
No	254591 (74.2)	288158 (72.1)
Yes	59320 (17.3)	69476 (17.4)
Missing	29157 (8.5)	41820 (10.5)
Maternal age group		
<20y	18640 (5.4)	23311 (5.8)
20-29y	151311 (44.1)	176582 (44.2)
30-39y	148885 (43.4)	170662 (42.7)
40+	12204 (3.6)	14009 (3.5)
Missing	12028 (3.5)	14890 (3.7)

SIMD quintile		
Most deprived quintile	88738 (25.9)	103486 (25.9)
2nd	72590 (21.2)	84354 (21.1)
3rd	65957 (19.2)	76423 (19.1)
4th	61303 (17.9)	71705 (18)
Least deprived quintile or missing	54480 (15.9)	63486 (15.9)
Total	**343,068**	**399,454**

Supplementary Table S3: Results from Cox proportional hazards models - complete case analysis: adjusted hazard ratios (HRs) with 95% CI

	Age group 1: <6 months*	Age group 2: 6-23 months**
Risk factor	**Adjusted HR (95% CI)**	
Gestational age		
Preterm	1.24 (0.77, 2.00)	1.43 (1.07, 1.91)
Term (37-40 weeks)	1	1
Late term (41+ weeks)	0.81 (0.60, 1.10)	0.91 (0.76, 1.09)
Sex		
Boys	1	1
Girls	0.84 (0.66, 1.05)	0.79 (0.68, 0.92)
High risk condition recorded before six months		
No	1	1
Yes	2.66 (1.66, 4.27)	2.96 (2.22, 3.95)
Postnatal stay in hospital		
≤14 days	1	1
>14 days	1.20 (0.48, 3.00)	1.71 (1.06, 2.74)
Season of birth		
January-March	1	1
April-June	0.79 (0.46, 1.36)	1.16 (0.96, 1.41)
July-September	3.49 (2.32, 5.24)	0.77 (0.62, 0.95)
October-December	3.68 (2.45, 5.52)	0.74 (0.60, 0.92)
Number of older siblings (parity)		
None	1	1
One	2.21 (1.64, 2.98)	1.19 (1.00, 1.42)
Two or more	3.28 (2.39, 4.52)	1.49 (1.22, 1.82)
Maternal smoking during pregnancy		
No	1	1
Yes	0.85 (0.63, 1.14)	1.25 (1.04, 1.49)
Maternal age group		
<20 years	2.22 (1.32, 3.73)	1.63 (1.19, 2.22)
20-29 years	1.43 (1.11, 1.84)	1.23 (1.04, 1.45)
30-39 years	1	1
40+ years	1.01 (0.54, 1.88)	0.78 (0.50, 1.23)
SIMD quintile		
Most deprived quintile	1.27 (0.86, 1.86)	0.86 (0.66, 1.12)
2nd	1.06 (0.70, 1.59)	1.08 (0.83, 1.40)

3rd	0.99 (0.65, 1.51)	1.09 (0.84, 1.41)
4th	1.06 (0.69, 1.61)	1.18 (0.91, 1.53)
Least deprived quintile	1	1

*Cohort 1: 291 events, 309,734 children
**Cohort 2: 704 events, 352,958 children

Supplementary Table S4. Results from Cox proportional hazards models also classifying admissions with an ICD-10 diagnostic code indicating influenza as influenza-confirmed admissions: adjusted hazard ratios (HRs) with 95% CI

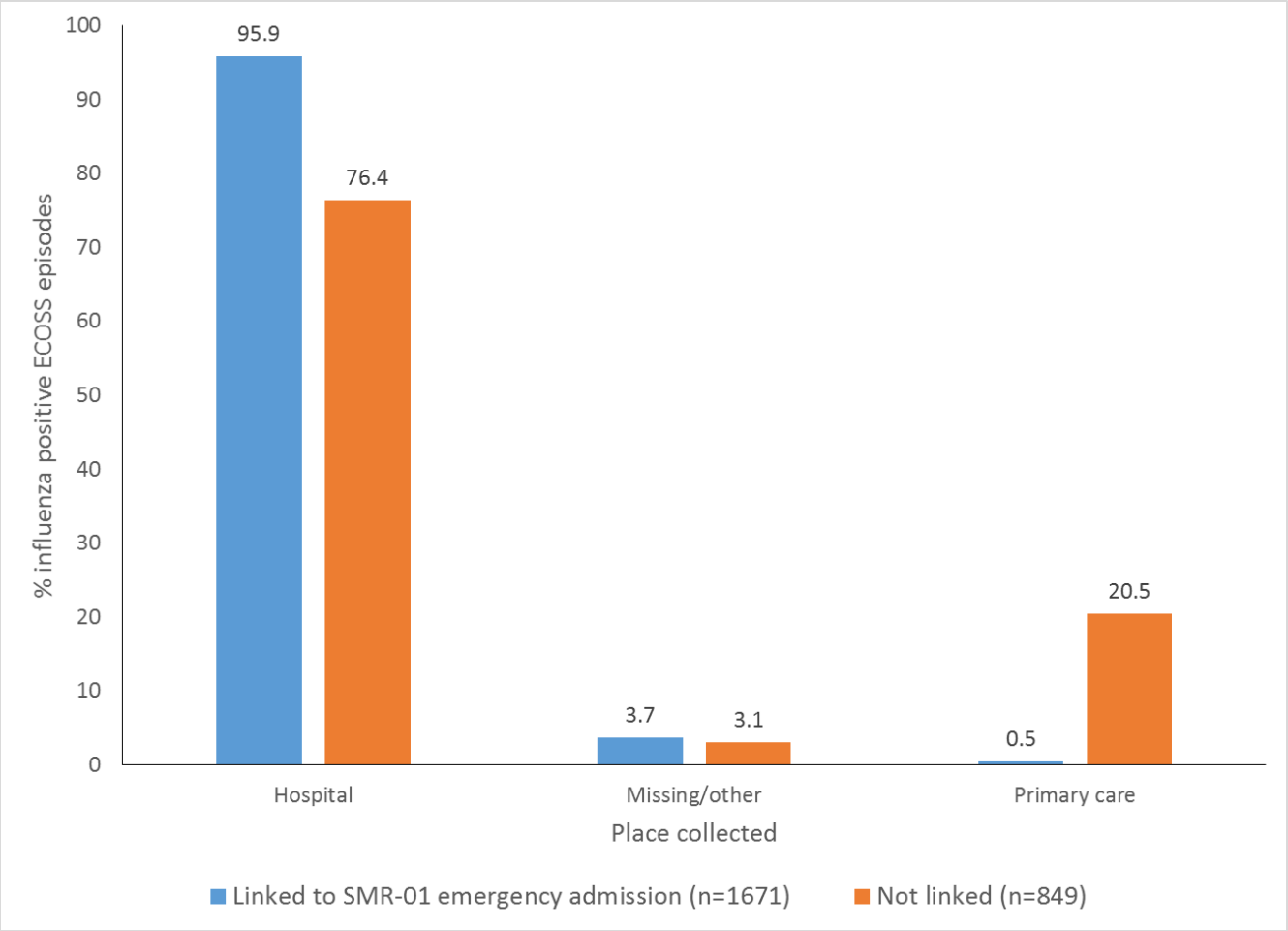
Risk factor	**Age group 1: <6 months***	**Age group 2: 6-23 months****
Gestational age		
Preterm (<37 weeks)	1.88 (1.33, 2.65)	1.44 (1.12, 1.85)
Term (37-40 weeks)	1	1
Late term (41+ weeks)	0.86 (0.66, 1.12)	0.88 (0.74, 1.04)
Sex		
Boys	1	1
Girls	0.89 (0.73, 1.08)	0.80 (0.7, 0.91)
High risk condition recorded before six months		
No	1	1
Yes	3.25 (2.31, 4.57)	3.68 (2.93, 4.62)
Postnatal stay in hospital		
≤14 days	1	1
>14 days	1.54 (0.89, 2.66)	1.75 (1.20, 2.56)
Season of birth		
January-March	1	1
April-June	0.72 (0.48, 1.06)	1.20 (1.01, 1.42)
July-September	2.26 (1.68, 3.04)	0.83 (0.69, 1.00)
October-December	2.50 (1.86, 3.36)	0.80 (0.66, 0.97)
Number of older siblings (parity)		
None	1	1

One	2.02 (1.56, 2.62)	1.23 (1.05, 1.44)
Two or more	3.50 (2.69, 4.55)	1.65 (1.38, 1.96)
Maternal smoking during pregnancy		
No	1	1
Yes	0.95 (0.74, 1.23)	1.22 (1.03, 1.45)
Maternal age group		
<20 years	1.79 (1.12, 2.85)	1.62 (1.22, 2.14)
20-29 years	1.46 (1.18, 1.81)	1.22 (1.05, 1.42)
30-39 years	1	1
40+ years	0.74 (0.41, 1.33)	0.79 (0.54, 1.17)
SIMD quintile		
Most deprived quintile	1.09 (0.79, 1.50)	0.81 (0.65, 1.02)
2nd	1.05 (0.75, 1.47)	0.98 (0.79, 1.22)
3rd	0.96 (0.68, 1.35)	0.96 (0.77, 1.21)
4th	1.06 (0.75, 1.50)	1.06 (0.85, 1.33)
Least deprived quintile	1	1

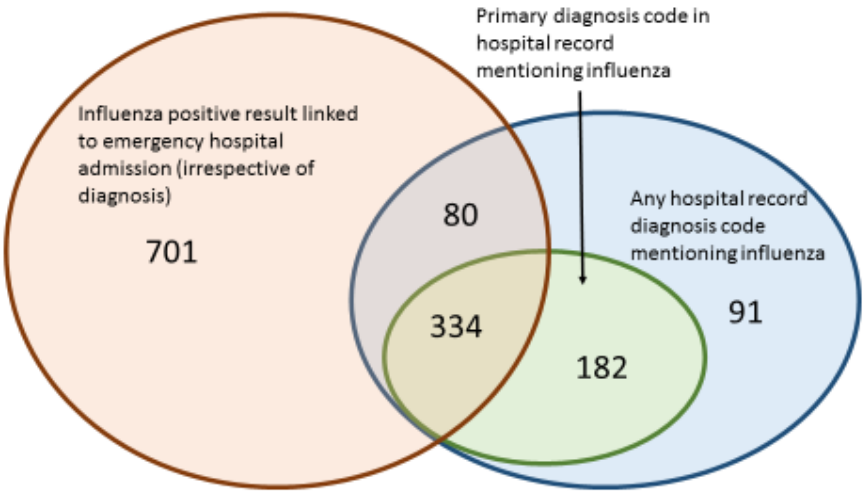
*Cohort 1: 426 events, 343,068 children

**Cohort 2: 925 events, 399,454 children

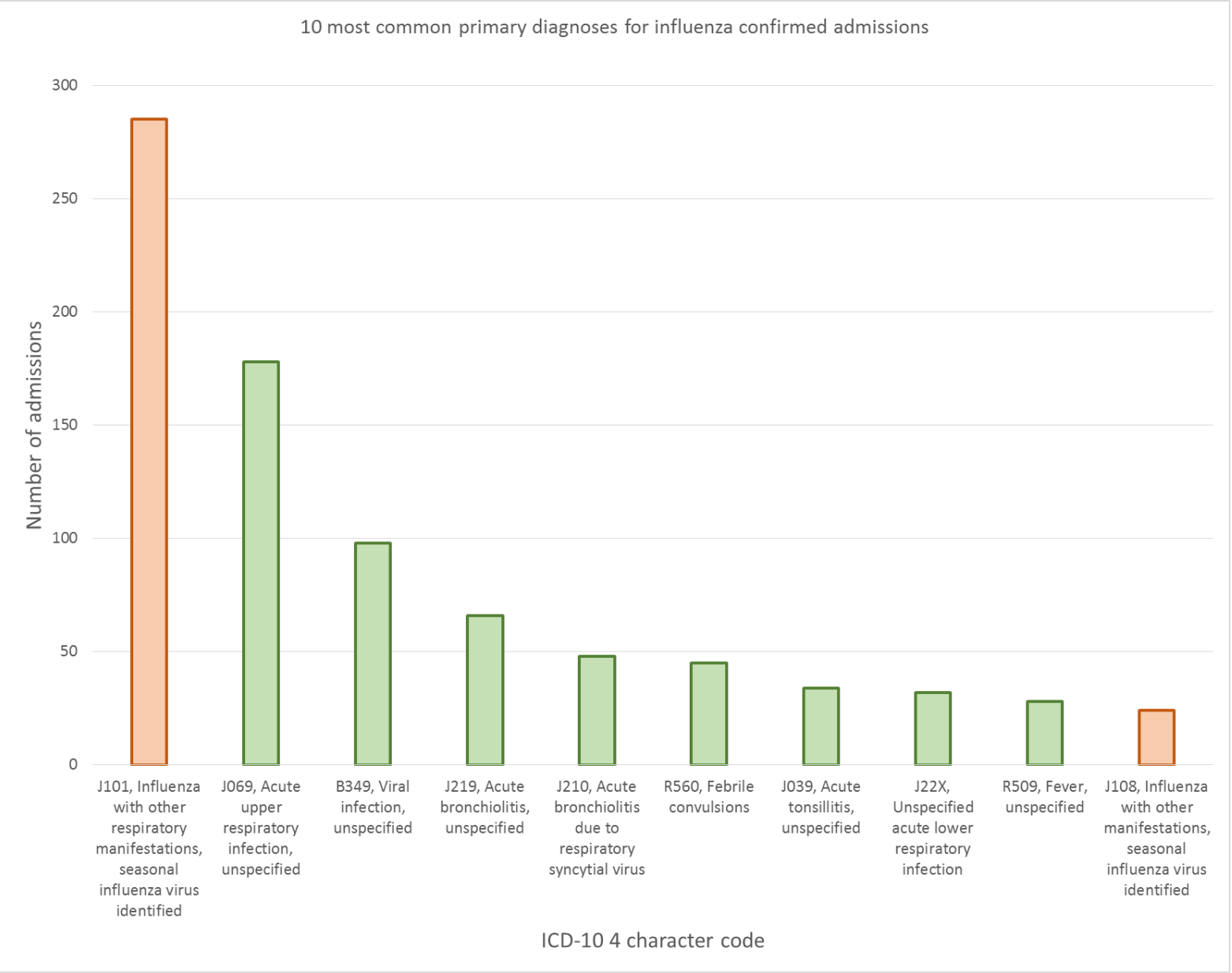
Supplementary Figure S1. Proportion of influenza positive ECOSS episodes by linkage status and place of specimen collection



Supplementary Figure S2. Overlap between influenza admissions identified through diagnostic coding in hospital records and via linkage to ECOSS laboratory surveillance data



Supplementary Figure S3. 10 most common primary diagnoses (coded in four character ICD-10) among children admitted with confirmed influenza*



*The orange bar indicates admissions with an ICD-10 code mentioning influenza as the primary diagnosis

Supplementary Figure S4. Rates of influenza confirmed admissions by age group and month of the year (per 1000 children)