**Epidemiology and Infection**

**Article title: Risk factors for influenza-related complications in children during the 2009/10 pandemic: A UK primary care cohort study using linked routinely collected data**

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**Supplementary material**

**S1: Definitions of potential risk factors and outcomes**

**S1.1: Potential risk factors**

Potential risk factors were defined as binary variables based on the absence or presence of pre-specified Read codes for the following conditions:

1. Neurological conditions (cerebral palsy, epilepsy, muscular dystrophy)
2. Premature birth (i.e. born before 37 weeks gestation)
3. Haematological conditions (leukaemia, lymphoma, sickle cell anaemia)
4. Immunosuppression (asplenia or splenic dysfunction, HIV infection)
5. Metabolic conditions (diabetes mellitus, other metabolic conditions [i.e. congenital hypothyroidism, phenylketonuria, maple syrup urine disease, galactosaemia, medium chain acyl-coA dehydrogenase deficiency, glutaric aciduria type 1, homocystinuria])
6. Cardiac conditions (congenital heart disease, congenital cardiac failure)
7. Non-haematological malignancies (bone and connective tissue tumours [i.e. osteosarcoma, sarcoma, rhabdomyosarcoma], central nervous system tumours [i.e. astrocytoma, ependymoma], other malignancies [i.e. germ cell tumours, embryonal tumours, neuroblastoma, retinoblastoma, Wilms’ tumour, hepatoblastoma])
8. Respiratory conditions (e.g. asthma, cystic fibrosis, bronchiectasis, interstitial lung disease, other respiratory conditions [i.e. bronchopulmonary dysplasia, primary ciliary dyskinesia]).
9. Renal conditions (polycystic kidneys, renal agenesis or dysplasia, nephritic syndrome, other renal conditions [i.e. Alport’s syndrome, ectopic kidney, congenital renal])
10. Liver conditions (hepatitis, sclerosing cholangitis, biliary atresia, hepatic fibrosis, hepatic failure, other liver conditions [i.e. Alagille syndrome, alpha1-antitrypsin deficiency, non-alcoholic fatty liver, Wilson’s disease])

Read codes relating to cerebral palsy, muscular dystrophy, sickle cell disease, asplenia or splenic dysfunction, HIV infection, cystic fibrosis, or premature birth were defined as potential risk factors if they had been recorded at any time before the index consultation with influenza/ILI. Read codes relating to other conditions were only used to identify potential risk factors if they were recorded during the two-year period before the index consultation.

**S1.2: Outcomes**

We defined influenza-related complications as complications relating to the respiratory tract (sinusitis, bronchitis, bronchiolitis, respiratory tract infections, respiratory failure, pneumonia, tonsillitis, acute exacerbation of asthma, croup, lung abscess, or pneumothorax), heart (myocarditis or pericarditis), central nervous system (meningitis, psychosis, seizures, or neuropathies), kidneys (acute renal failure, glomerulonephritis, or nephrotic syndrome), or other complications (parotitis, aplastic anaemia, myositis, otitis media). These were identified by CPRD medcodes supplemented by ICD10 codes from HES data where available.

Pneumonia outcomes were identified using CPRD medcodes supplemented by ICD10 codes from HES data where available. Data on deaths were obtained from Office for National Statistics (ONS) mortality data. Data on outcomes relating to hospitalisations were obtained from inpatient Hospital Episode Statistics (HES) data. Hospitalisations were defined as hospital admission episodes lasting 24 hours or longer.

**S2: Subgroup analyses by age category**

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| **Children aged 0-4 years (N = 5,503)****Influenza-related complications** |
| **Underlying condition** | **n (%)** | **Influenza-related complications (695 events)** | **Influenza-related complications requiring intervention (325 events)** | **Pneumonia (81 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 231 (4.2) | 28 (12.1) | 0.95 (0.63-1.43; 0.8122) | 1.38 (0.895-2.136; 0.1442) | 17 (7.4) | 1.28 (0.77-2.13; 0.3396) | 1.603 (0.93-2.771; 0.091) | 7 (3) | 2.20 (1.00-4.82; 0.0501) | 2.715 (1.16-6.38; 0.0219) |
| **Premature birth** | 108 (2) | 15 (13.9) | 1.12 (0.64-1.94; 0.6908) | 1.23 (0.70-2.18; 0.4692) | 10 (9.3) | 1.646 (0.85-3.19; 0.1394) | 1.717 (0.87-3.40; 0.1204) | <5 | 1.27 (0.31-5.23; 0.7411) | 1.368 (0.30-6.15; 0.6829) |
| **Neurological** | 17 (0.3) | <5 | 1.49 (0.43-5.18; 0.5354) | 1.818 (0.50-6.68; 0.3678) | <5 | 3.437 (0.98-12.02; 0.0533) | 3.474 (0.94-12.90; 0.0628) | <5 | 4.223 (0.55-32.23; 0.1647) | 3.969 (0.45-34.90; 0.2139) |
| **Metabolic** | 16 (0.3) | <5 | 0.46 (0.061-3.49; 0.453) | 0.68 (0.08-5.27; 0.7082) | <5 | 1.062 (0.14-8.07; 0.9534) | 1.611 (0.21-12.55; 0.649) | 0 (0) | NC | NC |
| **Hospitalisation (N = 3,435)** |
| **Underlying condition** | **n (%)** | **All cause hospitalisation (55 events)** | **Hospitalisation due to influenza-related complication (32 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 134 (3.9) | <5 | 1.431 (0.44-4.64; 0.5507) | 2.307 (0.67-7.92; 0.1842) | <5 | 2.584 (0.78-8.59; 0.1215) | 4.23 (1.177-15.204; 0.0271) |
| **Premature birth** | 76 (2.2) | <5 | 1.686 (0.40-7.05; 0.4742) | 2.051 (0.48-8.72; 0.3306) | 0 (0) | NC | NC |
| **Neurological** | 13 (0.4) | 0 (0) | NC | NC | 0 (0) | NC | NC |
| **Metabolic** | 14 (0.4) | <5 | 4.796 (0.62-37.39; 0.1342) | 4.426 (0.59-37.13; 0.1704) | <5 | 8.412 (1.07-66.295; 0.0432) | 10.409 (1.158-93.576; 0.0366) |

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| **Children aged five to 11 years (N = 6,127)****Influenza-related complications** |
| **Underlying condition** | **n (%)** | **Influenza-related complications (399 events)** | **Influenza-related complications requiring intervention (212 events)** | **Pneumonia (80 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 898 (14.7) | 71 (7.9) | 1.28 (0.98-1.68; 0.0674) | 1.495 (1.11-2.01; 0.0074) | 36 (4) | 1.2 (0.83-1.73; 0.3307) | 1.371 (0.92-2.05; 0.1245) | 12 (1.3) | 1.03 (0.55-1.91; 0.9303) | 1.356 (0.7-2.63; 0.3669) |
| **Premature birth** | 110 (1.8) | 9 (8.2) | 1.29 (0.65-2.56; 0.475) | 1.219 (0.6-2.46; 0.5804) | <5 | 0.51 (0.13-2.09; 0.3506) | 0.474 (0.12-1.95; 0.3002) | <5 | 0.69 (0.1-5; 0.7131) | 0.695 (0.1-5.11; 0.721) |
| **Neurological** | 69 (1.1) | 7 (10.1) | 1.63 (0.74-3.59; 0.2233) | 1.696 (0.76-3.79; 0.1979) | <5 | 1.73 (0.63-4.8; 0.2914) | 1.796 (0.64-5.05; 0.2668) | <5 | 2.29 (0.55-9.51; 0.2545) | 2.329 (0.55-9.94; 0.2534) |
| **Metabolic** | 43 (0.7) | <5 | 1.08 (0.33-3.5; 0.9014) | 1.353 (0.41-4.5; 0.6223) | <5 | 2.11 (0.65-6.87; 0.2159) | 2.454 (0.73-8.28; 0.1481) | <5 | 1.81 (0.25-13.31; 0.5601) | 2.251 (0.29-17.36; 0.4362) |
| **Hospitalisation (N = 3,544)** |
| **Underlying condition** | **n (%)** | **All cause hospital admissions (39 events)** | **Hospitalisation due to influenza-related complication (15 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 478 (13.5) | 8 (1.7) | 1.666 (0.761-3.647; 0.2013) | 1.578 (0.664-3.753; 0.3019) | <5 | 2.344 (0.743-7.39; 0.1461) | 2.355 (0.671-8.264; 0.1813) |
| **Premature birth** | 63 (1.8) | <5 | 1.461 (0.197-10.813; 0.7102) | 1.214 (0.157-9.385; 0.8524) | 0 (0) | NC | NC |
| **Neurological** | 43 (1.2) | <5 | 10.157 (3.444-29.955; <0.0001) | 10.084 (3.215-31.626; 0.0001) | 0 (0) | NC | NC |
| **Metabolic** | 26 (0.7) | <5 | 3.663 (0.484-27.73; 0.2087) | 3.816 (0.456-31.91; 0.2165) | 0 (0) | NC | NC |

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| **Children aged 12 to 17 years (N =5,149)****Influenza-related complications** |
| **Underlying condition** | **n (%)** | **Influenza-related complications (245 events)** | **Influenza-related complications requiring intervention (131 events)** | **Pneumonia (46 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 939 (18.2) | 53 (5.6) | 1.25 (0.92-1.71; 0.1592) | 1.521 (1.08-2.14; 0.0161) | 29 (3.1) | 1.28 (0.84-1.95; 0.2427) | 1.429 (0.9-2.27; 0.1308) | 10 (1.1) | 1.25 (0.62-2.52; 0.5374) | 1.553 (0.74-3.27; 0.2473) |
| **Premature birth** | 73 (1.4) | <5 | 1.16 (0.42-3.21; 0.7708) | 1.219 (0.44-3.41; 0.7056) | <5 | 0.53 (0.07-3.83; 0.528) | 0.536 (0.07-3.93; 0.5397) | 0 (0) | NC | NC |
| **Neurological** | 86 (1.7) | <5 | 0.98 (0.36-2.69; 0.9625) | 1.028 (0.37-2.87; 0.9583) | <5 | 1.39 (0.44-4.47; 0.5767) | 1.356 (0.42-4.42; 0.6131) | 0 (0) | NC | NC |
| **Metabolic** | 66 (1.3) | <5 | 1.3 (0.47-3.59; 0.6179) | 1.595 (0.55-4.6; 0.3881) | <5 | 1.2 (0.29-4.96; 0.801) | 1.145 (0.26-5; 0.8568) | <5 | 1.72 (0.23-12.69; 0.5935) | 2.529 (0.32-20.15; 0.3808) |
| **Hospitalisation (N = 2,738)** |
| **Underlying condition** | **n (%)** | **All cause hospital admissions (22 events)** | **Hospitalisation due to influenza-related complication (10 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 467 (17.1) | <5 | 0.766 (0.226-2.6; 0.6694) | 0.941 (0.236-3.752; 0.9309) | <5 | 0.54 (0.07-4.27; 0.5585) | 0.775 (0.1-6.31; 0.8114) |
| **Premature birth** | 42 (1.5) | 0 (0) | NC | NC | 0 (0) | NC | NC |
| **Neurological** | 43 (1.6) | 0 (0) | NC | NC | 0 (0) | NC | NC |
| **Metabolic** | 31 (1.1) | 0 (0) | NC | NC | 0 (0) | NC | NC |

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| CI = confidence interval, n = number of children, N = number of children with outcome event, NC = not calculable\*Adjusted for age, sex, socioeconomic deprivation, vaccination status (2008/9 seasonal influenza vaccine, pandemic influenza vaccine, pneumococcal conjugate vaccine and *Haemophilus influenzae b*), prescription of medications at index consultation (antivirals, antibiotics, antivirals\*antibiotics, inhaled bronchodilators, inhaled corticosteroids), presence of other underlying conditions and acute hospitalisation in the previous year.  |

**S3: Sensitivity analyses**

**S3.1: Asthma treated with preventer therapy**

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| **Asthma treated with preventer therapy** |
|  **All children presenting with influenza-like illness (n = 16,779)** | **Linkage to HES data (N = 9,717)** |
| **Definition, and number of children with asthma (%)** | **Influenza-related complications (1,339)** | **Influenza-related complications requiring intervention (668 events)** | **Pneumonia****(207 events)** | **All cause hospitalisation** **(116 events)** | **Hospitalisation due to influenza-related complication (57 events)** |
| **N (%) with event** | **Odds ratio** **(95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio** **(95% CI; p)** | **N (%) with factor** | **N (%) with event** | **Odds ratio** **(95% CI; p)** | **N (%) with event** | **Odds ratio** **(95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma (all)** | 2068 (12.3) | 152 (7.4) | 0.90 (0.76-1.08; 0.259) | 1.48 (1.21-1.8; 0.0001) | 82 (4.0) | 1.00 (0.79-1.26; 0.9683) | 1.44 (1.11-1.88; 0.0069) | 29 (1.4) | 1.16 (0.78-1.72; 0.4585) | 1.64 (1.07-2.51; 0.0236) | 2068 (12.3) | 152 (7.4) | 0.90 (0.76-1.08; 0.259) | 1.48 (1.21-1.8; 0.0001) | 82 (4.0) | 1.00 (0.79-1.26; 0.9683) | 1.44 (1.11-1.88; 0.0069) |
| **Asthma treated with preventer therapy** | 1,013 (6.0) | 86 (8.5) | 1.08 (0.86-1.35; 0.5371) | 1.74 (1.35-2.25; 0) | 44 (4.3) | 1.1 (0.81-1.51; 0.543) | 1.54 (1.09-2.19; 0.0145) | 16 (1.6) | 1.31 (0.78-2.19; 0.3051) | 1.97 (1.13-3.45; 0.0176) | 523 (6.0) | 8 (1.5) | 1.31 (0.63-2.7; 0.4685) | 1.9 (0.85-4.27; 0.1205) | 5 (1) | 1.7 (0.68-4.27; 0.2609) | 3.41 (1.26-9.23; 0.0157) |
| HES = Hospital Episode Statistics, CI = confidence interval, n = number of children, N = number of children with outcome event, NC = not calculable\*Adjusted for age, sex, socioeconomic deprivation, vaccination status (2008/9 seasonal influenza vaccine, pandemic influenza vaccine, pneumococcal conjugate vaccine and *Haemophilus influenzae b*), prescription of medications at index consultation (antivirals, antibiotics, antivirals\*antibiotics, inhaled bronchodilators, inhaled corticosteroids), presence of other underlying conditions and acute hospitalisation in the previous year.  |

**S3.2: Linkage to Index of Multiple Deprivation score and Hospital Episode Statistics**

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| **Linkage to Index of Multiple Deprivation score and Hospital Episode Statistics data (N = 9,705)****Influenza-related complications** |
| **Underlying condition n(%)** | **All complications (792 events)** | **Influenza-related complications with intervention (385 events)** | **Pneumonia (126 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 1079 (11.1) | 81 (7.5) | 0.90 (0.71-1.15; 0.4055) | 1.46 (1.12-1.91; 0.0056) | 41 (3.8) | 0.95 (0.68-1.32; 0.7654) | 1.325 (0.92-1.92; 0.1345) | 16 (1.5) | 1.17 (0.69-1.98; 0.5704) | 1.435 (0.8-2.56; 0.2218) |
| **Premature birth** | 181 (1.9) | 18 (9.9) | 1.25 (0.76-2.04; 0.3771) | 1.22 (0.73-2.01; 0.4473) | 10 (5.5) | 1.43 (0.75-2.72; 0.2809) | 1.401 (0.73-2.7; 0.313) | <5 | 0.85 (0.21-3.45; 0.8168) | 0.816 (0.2-3.37; 0.7787) |
| **Neurological** | 99 (1) | 8 (8.1) | 0.99 (0.48-2.05; 0.9767) | 1.36 (0.65-2.85; 0.4195) | 5 (5.1) | 1.29 (0.52-3.19; 0.5798) | 1.58 (0.63-3.97; 0.3302) | <5 | 2.41 (0.75-7.71; 0.1383) | 2.484 (0.76-8.15; 0.1335) |
| **Metabolic** | 71 (0.7) | <5 | 0.67 (0.24-1.84; 0.4381) | 0.99 (0.35-2.77; 0.9786) | <5 | 1.07 (0.34-3.41; 0.9109) | 1.46 (0.45-4.77; 0.5303) | 0 (0) | NC | NC |
| **Hospitalisation** |
| **Underlying condition n (%)** | **All cause hospitalisation (115 events)** | **Hospitalisation due to influenza-related complication (56 events)** |
| **N (%) with event** | **Odds ratio (95% CI; p)** | **N (%) with event** | **Odds ratio (95% CI; p)** |
| **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| **Asthma** | 1079 (11.1) | 14 (1.3) | 1.11 (0.63-1.95; 0.7172) | 1.52 (0.81-2.86; 0.1885) | 8 (0.7) | 1.34 (0.63-2.83; 0.451) | 2.45 (1.08-5.54; 0.032) |
| **Premature birth** | 181 (1.9) | <5 | 1.42 (0.45-4.5; 0.5552) | 1.22 (0.38-3.95; 0.7394) | 0 (0) | NC | NC |
| **Neurological** | 99 (1) | <5 | 3.6 (1.3-9.97; 0.0136) | 4.24 (1.49-12.05; 0.0067) | 0 (0) | NC | NC |
| **Metabolic** | 71 (0.7) | <5 | 2.44 (0.59-10.08; 0.2171) | 2.86 (0.67-12.31; 0.1574) | <5 | 2.49 (0.34-18.23; 0.3697) | 3.87 (0.5-29.88; 0.1946) |
| CI = confidence interval, n = number of children, N = number of children with outcome event, NC = not calculable\*Adjusted for age, sex, socioeconomic deprivation, vaccination status (2008/9 seasonal influenza vaccine, pandemic influenza vaccine, pneumococcal conjugate vaccine and *Haemophilus influenzae b*), prescription of medications at index consultation (antivirals, antibiotics, antivirals\*antibiotics, inhaled bronchodilators, inhaled corticosteroids), presence of other underlying conditions and acute hospitalisation in the previous year.  |