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

3

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15

16 **Keywords:** Influenza, risk factors, children, primary care

17

18 **Summary:** Primary care clinicians have a central role in managing influenza/influenza-like
19 illness (ILI) during influenza pandemics. This study identifies risk factors for influenza-
20 related complications in children presenting with influenza/ILI in primary care. We
21 conducted a cohort study using routinely collected linked data from the Clinical Practice
22 Research Datalink on children aged 17 years and younger who presented with influenza/ILI
23 during the 2009/10 pandemic. We calculated odds ratios for potential risk factors in
24 relation to influenza-related complications, complications requiring intervention,
25 pneumonia, all-cause hospitalisation, and hospitalisation due to influenza-related
26 complications within 30 days of presentation. Analyses were adjusted for potential
27 confounders including age, vaccination, and socioeconomic deprivation. Asthma was a risk
28 factor for influenza-related complications (adjusted odds ratio [OR] 1.48, 95% confidence
29 interval (CI) 1.21-1.80, $P < 0.001$), complications requiring intervention (adjusted OR 1.44,
30 95% CI 1.11-1.88; $P = 0.007$), pneumonia (adjusted OR 1.64, 95% CI 1.07-2.51, $P = 0.024$), and
31 hospitalisation due to influenza-related complications (adjusted OR 2.46, 95% CI 1.09-5.56,
32 $P = 0.031$). Neurological conditions were risk factors for all-cause hospitalisation (adjusted
33 OR 4.25, 95% CI 1.50-12.07, $P = 0.007$) but not influenza-related complications (adjusted OR
34 1.46, 95% CI 0.83-2.56, $P = 0.189$). Community-based early interventions to prevent
35 influenza-related clinical deterioration should therefore be primarily targeted at children
36 with asthma and neurological conditions.

37

38

39

40

41 **Manuscript**

42 **Introduction**

43 Primary care clinicians play a principal role in providing front line care to patients presenting
44 with influenza-like illness (ILI) during influenza pandemics.[1] This includes prioritising
45 influenza vaccination in high risk groups[2, 3] and accurately targeting antibiotics and
46 antiviral medications to maximise clinical benefit without driving antimicrobial resistance.[4,
47 5]

48

49 The highest rates of primary care consultations for influenza A-attributable respiratory
50 disease in the UK are observed in children under 5 years of age, while the highest seasonal
51 incidence rates for influenza B occur in children aged 5 to 17 years.[6] Universal childhood
52 vaccination strategies for seasonal influenza are already being implemented in the US[3]
53 and UK.[7]

54

55 Preliminary data from England suggest that vaccination of children aged 4 to 11 years may
56 have a direct impact on reducing illness absenteeism in primary schools.[8] However, no
57 significant indirect impact on illness absenteeism in secondary schools has been
58 demonstrated.[8] There is also still insufficient evidence on whether universal childhood
59 vaccination is effective at reducing influenza-related complications and hospitalisations, and
60 which types of communities are likely to benefit most from this type of approach.[9]

61

62 Targeted strategies which prioritise groups at highest risk of clinical deterioration are
63 therefore still important in primary care, particularly during influenza pandemics, when

64 there is increased demand on health care resources and suitable vaccines may not initially
65 be available.[10]
66 [A systematic review of studies involving children with seasonal or pandemic influenza/ILI](#)
67 [identified n](#)Neurological conditions, premature birth, sickle cell disease,
68 immunosuppression, diabetes mellitus and age under two years ~~have been identified~~ as risk
69 factors for hospitalisation ~~in children with influenza/ILI~~.[11] However, these findings are
70 mainly based on data from studies ~~of seasonal influenza~~ conducted in hospital ~~ambulatory~~
71 ~~care~~ settings, and represent risk factors for all-cause hospitalisation rather than influenza-
72 related complications. Additionally, current definitions of high risk groups do not provide
73 evidence-based guidance on which risk factors are particularly relevant to paediatric
74 primary care populations.[2, 3]

75

76 The present study therefore aims to identify risk factors for influenza-related complications
77 in children presenting in primary care using routinely collected linked data from the Clinical
78 Practice Research Datalink (CPRD).

79

80 **Methods**

81 ***Source data and population***

82 The Clinical Practice Research Datalink (CPRD) (www.cprd.com) provides anonymised
83 routinely collected data from patients presenting in UK primary care.[12] Linkage to
84 Hospital Episode Statistics (HES), Office for National Statistics mortality data, and Index of
85 Multiple Deprivation (IMD) scores are available for a subset of CPRD practices in England,
86 representing about 58% of patients registered at practices contributing to CPRD. The HES

87 database contains details of admissions to NHS hospitals and NHS-funded admissions to
88 private or charitable hospitals in England.[13]

89
90 We extracted data from the CPRD records of children aged 17 years or younger who
91 consulted with influenza/ILI during the 2009/10 influenza pandemic (i.e. between 27 April
92 2009 and 23 May 2010). We excluded records that did not meet CPRD quality standards[12]
93 and where data were not available for at least 12 months before the index consultation in
94 children aged 1 year or older, or at least 30 days before the index consultation in children
95 younger than 12 months of age.

96

97 ***Potential risk factors***

98 Potential risk factors were defined as binary variables based on records of pre-specified
99 Read codes for neurological, haematological, metabolic, cardiac, renal, liver and respiratory
100 conditions, as well as premature birth and non-haematological malignancies. Supplement
101 S1.1 describes these definitions in further detail.

102

103 ***Outcomes***

104 Our primary outcome was influenza-related complications recorded within 30 days of
105 presentation with influenza/ILI. These included respiratory, cardiac, neurological and renal
106 complications.[14] Secondary outcomes (all within 30 days of presentation with
107 influenza/ILI) were pneumonia, influenza-related complications requiring further
108 intervention (prescription of medication, further investigations or hospitalisation),
109 hospitalisation or death due to influenza-related complications and all-cause hospitalisation
110 or death. At the request of journal reviewers, 'pneumonia or hospitalisation' was included

111 as an additional secondary outcome. Supplement S1.2 provides full details of how we
112 defined and obtained data for these outcomes.

113

114 ***Potential confounders***

115 Potential confounders considered in this study were: age, sex, socioeconomic deprivation,
116 vaccination status (2008/9 seasonal influenza, pandemic influenza, pneumococcal conjugate
117 vaccine and *Haemophilus influenzae* b), prescription of other medications at the index
118 presentation with influenza/ILI (e.g. corticosteroids, antibiotics, antivirals), presence of
119 other potential risk factors, and acute hospitalisations during the 12-month period before
120 the index presentation. Socioeconomic deprivation was measured based on Index of
121 Multiple Deprivation (IMD) score quintiles at Office for National Statistics small area level
122 (100 houses) using the patient's postcode. For children aged less than 12 months at the
123 index presentation, baseline data on acute hospitalisations between the date of birth and
124 the date of the index presentation were extracted.

125

126 ***Data analysis***

127 Baseline data on potential risk factors and confounders were summarised using numbers
128 and percentages for categorical variables and means and standard deviations for continuous
129 variables. To minimise the possibility of unintentional disclosure, categorical variables with
130 fewer than five patient records were either not reported or combined with related
131 variables. Data on duration between the index consultation and influenza-related
132 complications were summarised as medians and interquartile ranges.

133

134 Statistical analyses were conducted using Stata version 14. To examine the association
135 between potential risk factors and each of our outcomes, we performed logistic regression
136 to calculate odds ratios with 95% confidence intervals for each potential risk factor, both
137 unadjusted and adjusted for potential confounders. Age was modelled as a continuous
138 fractional polynomial (Stata command mfp). We created a 'missing' category for our
139 variable on socioeconomic deprivation to use in our main analysis where IMD score data
140 were not available. The outcomes all-cause hospitalisation and hospitalisation due to
141 influenza-related complications were analysed using only CPRD records which were linkable
142 to Hospital Episode Statistics (HES) data.

143

144 Subgroup analyses were conducted according to three age categories (0-4 years, 5-11 years,
145 12-17 years). Pre-specified sensitivity analyses were undertaken in children whose CPRD
146 records were linked to both IMD score and inpatient HES data, and to examine asthma
147 requiring treatment with inhaled corticosteroids or other preventer therapies as a potential
148 risk factor.[15]

149

150 The project was approved by the CPRD Independent Scientific Advisory Committee (protocol
151 number 15_252R). The protocol was made available to the journal reviewers.

152

153 **Results**

154 ***Study population***

155 Our study population included 16,779 children who presented with influenza-like illness (ILI)
156 at CPRD general practices during the 2009/10 influenza pandemic. Table 1 summarises the
157 baseline characteristics of these children. Pandemic influenza vaccination was only

158 recorded in 100 children (0.6%) and the 2008/9 seasonal influenza vaccination in 715
159 children (4.3%). Antivirals were prescribed at the index consultation in 4037 children
160 (24.1%) and antibiotics in 985 children (5.9%).

161
162 At least one underlying condition was present in 2575 children (15.4%). Asthma was the
163 most prevalent condition (n=2068, 12.3%). Neurological conditions were coded in 172
164 children (1.0%) of whom 146 had epilepsy. Metabolic conditions were found in 125 children
165 (0.7%) of whom 95 had diabetes mellitus. Haematological or immunological conditions
166 were only recorded in 15 children, renal conditions in seven children and non-
167 haematological malignancies in fewer than five children. No children were recorded as
168 having cardiac or liver conditions.

169
170 Influenza-related complications were recorded in 1339 of 16,779 children (8.0%). Median
171 time to development of an influenza-related complication following the index consultation
172 was one day (interquartile range 0-8 days). Forty-six percent of complications (617/1339)
173 were observed on the same day as the index consultation. Complications requiring
174 intervention were observed in 668 children (4.0%) and pneumonia in 207 children (1.2%).
175 Influenza-related complications were recorded in 695 of 5503 children aged 0 to 4 years
176 inclusive (13%), accounting for just over half the total number of children who developed
177 influenza-related complications (695/1339, 52%).

178
179 All-cause hospitalisations occurred in 116 of 9717 children whose CPRD records were linked
180 to HES data (1.2%). Around half of all-cause hospitalisations (55/116, 47.4%) and

181 hospitalisations due to influenza-related complications (32/57, 56.1%) were observed in
182 children aged 0 to 4 years inclusive.

183

184 ***Risk factors for influenza-related complications***

185 Table 2 summarises crude and adjusted odds ratios with 95% confidence intervals in relation
186 to influenza-related complications, complications requiring further intervention, or
187 pneumonia. Univariable analyses did not identify any statistically significant risk factors for
188 these outcomes. However, after adjustment for baseline covariates and other risk factors,
189 asthma was found to be a statistically significant risk factor for influenza-related
190 complications (adjusted odds ratio (OR) 1.48, 95% confidence interval (CI) 1.21-1.80,
191 $P<0.001$), complications requiring intervention (adjusted OR 1.44, 95% CI 1.11-1.88,
192 $P=0.007$), and pneumonia (adjusted OR 1.64, 95% CI 1.07-2.51, $P=0.024$). The association
193 between neurological conditions and influenza-related complications requiring intervention
194 was of borderline statistical significance (adjusted OR 1.94, 95% CI 1.01 to 3.75, $P=0.047$).

195

196 In the multivariable model, prescription of antibiotics or antiviral medications at the index
197 consultation was associated with significantly reduced likelihood of influenza-related
198 complications (antibiotics: adjusted OR 0.38, 95% CI 0.26-0.55, $P<0.001$; antivirals: adjusted
199 OR 0.33, 95% CI 0.28-0.4, $P<0.001$). In contrast, concurrent prescription of both antibiotics
200 and antivirals together was associated with significantly greater likelihood of influenza-
201 related complications (adjusted OR 4.06, 95% CI 2.02-8.13, $p<0.001$). Since this interaction
202 was statistically significant, an interaction term for prescription of antibiotics and antivirals
203 was also included in the multivariable model.

204

205 ***Risk factors for hospitalisation***

206 CPRD records of 9,717 of the 16,779 included children (58%) were eligible for linkage to
207 Hospital Episode Statistics (HES) data. All-cause hospitalisations were recorded in 116
208 children (1.2%). Following the index consultation, median time to hospital admission was
209 two days (interquartile range 0 to 16 days). Thirty-five children were admitted to hospital
210 on the same day as the index consultation (30.2%). Nearly half of hospitalisations were
211 coded as being for influenza-related complications (n=57, 49.1%). Median time to
212 hospitalisation for influenza-related complications was one day (interquartile range 0 to 12
213 days). Sixteen children were admitted to hospital on the same day as the index consultation
214 (28.1%). Pneumonia or hospitalisation was recorded in 224 children (2.3%). No deaths
215 were recorded in our study population.

216

217 Table 3 summarises crude and adjusted odds ratios with 95% confidence intervals in relation
218 to all-cause hospitalisations and hospitalisations due to influenza-related complications.

219 The presence of neurological conditions was found to be a statistically significant risk factor
220 for all-cause hospitalisation in both crude and adjusted analyses (crude OR 3.57, 95% CI

221 1.29-9.89, P=0.014, adjusted OR 4.25, 95% CI 1.49-12.06, P=0.007). Neurological conditions

222 were also associated with significantly greater risk of pneumonia or hospitalisation (crude

223 OR 3.30, 95% CI 1.51-7.19, P=0.003, adjusted OR 3.62, 95% CI 1.62-8.08, P=0.002).

224

225

226 Asthma was a statistically significant risk factor for hospitalisation due to influenza-related
227 complications after adjustment (adjusted OR 2.45, 95% CI 1.08-5.55, P=0.031), but was not a
228 risk factor for all-cause hospitalisation (crude OR 1.10, 95% CI 0.63-1.93, P=0.740; adjusted

229 OR 1.53, 95% CI 0.81-2.86, P=0.188) or for pneumonia or hospitalisation (crude OR 1.01,
230 95% CI 0.66-1.53, P=0.979, adjusted OR 1.28, 95% CI 0.8-2.05, P=0.300).

231

232 In the multivariable model, prescription of antiviral medications was associated with a
233 significantly reduced likelihood of ~~both~~ influenza-related hospitalisations (adjusted OR 0.43,
234 95% CI 0.19-0.94; P=0.036) ~~and~~ all-cause hospitalisations (adjusted OR 0.60, 95% CI 0.36-
235 0.99; P=0.044) and pneumonia or hospitalisation (adjusted OR 0.3, 95% CI 0.19-0.47,
236 P<0.001).

237

238 ***Subgroup and sensitivity analyses***

239 After adjustment for baseline covariates and other risk factors, asthma was a significant risk
240 factor for pneumonia and hospitalisations due to influenza-related complications in children
241 aged 4 years and younger (Supplement S2). Asthma was also a significant risk factor for
242 influenza-related complications in children aged 5-11 years and 12-17 years after
243 adjustment. The presence of a neurological condition was a risk factor for all-cause
244 hospitalisation in children aged 5-11 years.

245

246 Supplement S3 summarises the results of our pre-specified sensitivity analyses on asthma
247 requiring preventer therapy (S3.1) and CPRD records linked to both IMD score and inpatient
248 HES data (S3.2). The findings of these analyses were consistent with those of our main
249 analyses. We also conducted post hoc sensitivity analysis excluding children in whom
250 influenza-related complications were recorded on the same day as the index consultation.
251 The findings of this analysis were broadly consistent with the main analysis. However,
252 asthma was no longer a significant risk factor for pneumonia (adjusted OR 0.99, 95% CI 0.3-

253 3.29, P=0.98). The association between antibiotic prescriptions and influenza-related
254 complications was also no longer statistically significant (adjusted OR 0.74, 95% CI 0.51-1.08,
255 P=0.115). There were insufficient data to estimate an odds ratio for neurological conditions
256 in relation to complications requiring intervention.

257

258 **Discussion**

259 ***Principal findings***

260 Our study provides a comprehensive assessment of risk factors for influenza-related
261 complications and all-cause hospitalisations in children using routinely collected data from a
262 large UK primary care cohort. Asthma is a strong risk factor for influenza-related
263 complications, including pneumonia, in children presenting with influenza/ILI in primary
264 care. Children with neurological conditions, mainly epilepsy (which is not mentioned in
265 current risk group definitions), are ~~associated with~~ at increased ~~greater~~ risk of all-cause
266 hospitalisation, but not influenza-related complications. At least half of influenza-related
267 complications and hospitalisations occur within one day of initial presentation in primary
268 care.

269

270 **Comparison with existing literature**

271 The rapid onset of influenza-related complications which we observed in our cohort is
272 consistent with previous reports that around 80% of intensive care admissions among
273 children with laboratory-confirmed influenza occur within 24 hours of hospitalisation.[16]

274

275 Previous systematic reviews have identified asthma as a risk factor for pneumonia[17] and
276 found that neurological conditions are associated with greater risk of all-cause

277 hospitalisation.[11, 17] However, these analyses were based on data from adults and
278 children[17] and did not adjust for important potential confounders, including
279 socioeconomic deprivation and vaccination status.[11, 17]

280

281 Neuromuscular and neurocognitive disorders have previously been identified as risk factors
282 for pneumonia in patients with seasonal influenza.[17] However, we did not observe a
283 significant association between neurological conditions and influenza-related complications
284 or hospitalisations. This may have been due to health care professionals using different
285 codes to record complications, or having a lower threshold for admitting these children to
286 hospital for observation, since clinical prognosis is reported to be worse if complications do
287 develop.[18]

288

289 We did not find premature birth or diabetes to be significant risk factors in our cohort,
290 although these have previously been reported as risk factors in children presenting in
291 hospital ambulatory care settings.[11] This may reflect differences between these settings
292 in the complexity and severity of these conditions among children presenting with
293 influenza/ILI. Coding of premature birth may also be less reliable in primary care records.
294 Additionally, we did not have sufficient data to examine whether immunosuppression was a
295 risk factor in primary care as well as hospital ambulatory care settings[11] due to the limited
296 number of children with haematological or immunological conditions in our cohort. This
297 may reflect recommendations for these children to be referred early or seen directly in
298 hospital when acutely unwell to facilitate prompt management of suspected neutropenic
299 sepsis.[19]

300

301 Our observation that children who were prescribed antibiotics or antivirals were less likely
302 to develop influenza-related complications should be interpreted with caution, since it was
303 not possible to adjust for severity of the acute illness episode or other unmeasured
304 confounders. The statistically significant interaction we observed between antibiotic and
305 antiviral prescriptions may suggest some confounding by illness severity. Lower re-
306 attendances with cough within one month have also been observed in patients with acute
307 lower respiratory tract infections given immediate or delayed prescriptions for
308 antibiotics.[20]

309

310 ***Strengths and limitations***

311 Our study identifies risk factors for influenza-related complications of direct relevance to
312 children presenting in primary care, where most influenza/ILI episodes are initially assessed.
313 Linkage to inpatient Hospital Episodes Statistics data and Index of Multiple Deprivation
314 score data enabled more detailed analyses than have previously been possible on unlinked
315 routinely collected primary care data from the General Practice Research Database.[14]

316

317 Our methods of identifying relevant consultations using consultation codes for influenza-like
318 illness are likely to be robust, given that these codes were used more frequently during the
319 2009/10 pandemic, with the highest peak in consultations observed in children under 15
320 years of age.[21] Studying consultations during the 2009/10 pandemic also helped enrich
321 our sample for patients with influenza and minimise potential confounding due to antiviral
322 treatment at the index consultation, since during the pandemic, antivirals were
323 recommended in all patients with influenza/ILI, not just those considered to be at greater
324 risk of complications.

325

326 The available data allowed us to identify risk factors for influenza-related complications
327 managed in the community, and to examine risk factors for hospitalisations due to
328 influenza-related complications separately from all-cause hospitalisations. We also adjusted
329 our analyses for a range of potential confounders, including socioeconomic status,
330 vaccination status, and prescription of medications at the index consultation.

331

332 To increase our focus on risk factors for hospital admissions for clinical deterioration, we
333 defined hospitalisation outcomes as hospital admissions lasting 24 hours or longer.
334 Previous studies did not specify the minimum duration of hospital admissions which they
335 considered as hospitalisation outcome events[11, 17] and may therefore have included a
336 considerable proportion of admissions for short periods of observation rather than
337 treatment of complications. In our cohort, nearly half of hospitalisations coded in HES were
338 for less than 24 hours (110/226, 48.7%).

339

340 Our main limitation was the lack of an established linkage between data from the National
341 Pandemic Flu Service (NPFS) and CPRD. This linkage would have been highly informative, as
342 during the 2009/10 influenza pandemic, almost six times as many patients contacted the
343 NPFS instead of their general practice for advice on influenza/ILI.[22] Additionally, CPRD
344 records may not have contained complete data on antiviral medications dispensed during
345 the 2009/10 pandemic, since general practices did not consistently record allocation of 'flu
346 vouchers', which were required to authorise supply of antivirals from the national stockpile.

347

348

349 We did not have sufficient data to assess haematological or immunological conditions, renal
350 conditions, non-haematological malignancies, cardiac conditions or liver conditions, which
351 may also be important risk factors for influenza-related complications in children. Our
352 definition of influenza-related complications was based on the definition used in a
353 previously published analysis of data from the General Practice Research Database.[14] This
354 definition was intentionally broad to facilitate inclusion of the wide range of complications
355 managed in the community, as well as allow for variations in coding practices among
356 primary care clinicians. However, we recognise that certain consultation codes may be used
357 in association with presentations other than influenza/ILI and complications related to this.
358 Ascertainment of clinical deterioration specifically related to the index influenza/ILI
359 consultation would require analysis of free text entries. However, this was not feasible with
360 the resources available for this study.

361

362 It was not possible to address confounding due to severity of the index influenza/ILI
363 episode, as data on clinical features relating to illness severity, including vital sign
364 measurements, indicators of respiratory distress, and duration of illness, are not
365 consistently coded in CPRD. We were also unable to adjust our analyses for additional social
366 determinants such as access to health care and ethnicity due to lack of available data.
367 Although we had intended to adjust our analyses relating to asthma according to British
368 Thoracic Society treatment step, we did not conduct this analysis because of difficulties with
369 defining this variable reliably using the available data. Nevertheless, we were still able to
370 conduct our pre-specified subgroup analysis examining asthma requiring treatment with
371 inhaled corticosteroids or other preventer therapies as a risk factor.

372

373 ***Implications for clinical practice and further research***

374 Primary care services should target children with asthma and neurological conditions when
375 delivering interventions to prevent influenza and influenza-related clinical deterioration.

376 Although asthma requiring regular preventer therapy is already highlighted as a risk
377 factor,[2] clinicians should also assess risk in other children with asthma, particularly high
378 users of short-acting bronchodilators who may have poor disease control and hence also be
379 at greater risk.[23] Children with epilepsy should also be highlighted as a risk group. In our
380 study, 85% of children with neurological conditions had epilepsy. However, epilepsy is not
381 mentioned in current risk group definitions,[2, 3] and is less commonly recognised by
382 clinicians as a risk factor.[24]

383

384 Nevertheless, most influenza-related complications still occur in children who do not have
385 known risk factors.[25] Influenza vaccination is therefore still important in these children.

386 Based on recommendations from the Joint Committee on Vaccination and Immunisation,[7]

387 the UK introduced a universal childhood seasonal influenza vaccination programme in

388 2013/14, starting with children aged 2 and 3 years, and extending up to children aged eight

389 to nine years (i.e. year 4 of school) since winter 2017/18.[26] However,

390 Clinicians who consider intervening with antibiotics or antivirals should be aware that most

391 complications and clinical deteriorations occur soon after presentation. Early treatment with

392 antibiotics and antivirals should particularly be considered in children with asthma and

393 neurological conditions, even if they have been vaccinated. eEffectiveness of the 2015/16

394 seasonal influenza vaccination was only around 58% in children aged 2 to 17 years in the

395 UK.[27] Furthermore, seasonal influenza vaccination rates in children with 'at risk'

396 conditions have not improved from around 40% since 2013/14-[28] and may be even lower

397 during an influenza pandemic due to the time needed to develop and implement a suitable
398 vaccine. Primary care clinicians may therefore need to consider more readily available
399 treatments such as antibiotics and antiviral medications, especially given our observation
400 that at least half of complications and hospitalisation occur within one day of initial
401 presentation.

402 ~~Greater emphasis should particularly be placed on improving vaccination rates in school~~
403 ~~aged children[28] given our findings that asthma and neurological conditions are risk~~
404 ~~factors in this age group.~~

405

406 Strategies to inform efficient use of antibiotics and antivirals may include [validated clinical](#)
407 [decision rules](#) ~~and involving use of~~ point-of-care testing for inflammatory markers [such as](#)
408 [C-reactive protein \(CRP\)](#)[29] and potential respiratory pathogens including influenza.[30]

409 Further research is needed to inform efficient and cost-effective implementation of such
410 strategies.

411

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417

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425

426 **Conflicts of interest**

427 None.

428

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508 **Table 1: Baseline characteristics of study population (N = 16,779)**

| Characteristic | Number (%) or Mean (SD) |
|--|-------------------------|
| Age (years) | 8.40 (5.09) |
| Male | 8492 (50.6) |
| Underlying conditions*: | |
| Asthma | 2068 (12.3) |
| Premature birth | 291 (1.7) |
| Neurological | 172 (1.0) |
| Metabolic | 125 (0.7) |
| Haematological conditions/immunosuppression | 15 (0.1) |
| Renal | 7 (0.04) |
| Socioeconomic deprivation (IMD quintile)**: | |
| 1. (Least deprived) | 2125 (12.7) |
| 2. | 1844 (11.0) |
| 3. | 1729 (10.3) |
| 4. | 2012 (12.0) |
| 5. (Most deprived) | 2002 (11.9) |
| Not linked to IMD | 7067 (42.1) |
| Vaccination status: | |
| 2008/9 seasonal influenza vaccine | 715 (4.3) |
| Pandemic influenza vaccine | 100 (0.6) |
| Pneumococcal conjugate vaccine | 5432 (32.4) |
| <i>Haemophilus influenzae</i> b vaccine | 15,470 (92.2) |
| Prescriptions at index consultation: | |
| Antibiotic | 985 (5.87) |

| | |
|--|-------------|
| Antiviral | 4037 (24.1) |
| Inhaled bronchodilator | 112 (0.7) |
| Inhaled corticosteroid | 184 (1.1) |
| One or more acute hospitalisations in previous year | 214 (1.28) |
| SD = Standard Deviation; IMD = Index of Multiple Deprivation | |
| *One or more underlying conditions recorded in 2575 children. | |
| ** IMD quintiles based on IMD scores according to patient's postcode at Office for National Statistics small area level (100 houses). Linked IMD score data available for 9712 children. | |

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| Table 2: Crude and adjusted odds ratios with 95% confidence intervals in relation to influenza-related complications (N = 16,779) | | | | | | | | | | |
|--|-------------|--|-------------------------|-------------------------|---|-------------------------|-------------------------|------------------------|-------------------------|-------------------------|
| Underlying condition | n (%) | Influenza-related complications (1,339 events) | | | Influenza-related complications requiring intervention (668 events) | | | Pneumonia (207 events) | | |
| | | N (%) | Odds ratio (95% CI; p) | | N (%) | Odds ratio (95% CI; p) | | N (%) | Odds ratio (95% CI; p) | |
| | | | Crude | Adjusted* | | Crude | Adjusted* | | Crude | Adjusted* |
| Asthma | 2068 (12.3) | 152 (7.4) | 0.90 (0.76-1.08; 0.259) | 1.48 (1.21-1.8; <0.001) | 82 (4.0) | 1.00 (0.79-1.26; 0.968) | 1.44 (1.11-1.88; 0.007) | 29 (1.4) | 1.16 (0.78-1.72; 0.459) | 1.64 (1.07-2.51; 0.024) |
| Premature birth | 291 (1.7) | 28 (9.6) | 1.23 (0.83-1.83; 0.298) | 1.23 (0.82-1.84; 0.312) | 13 (4.5) | 1.13 (0.65-1.98; 0.669) | 1.09 (0.62-1.93; 0.76) | <5 | 0.83 (0.26-2.62; 0.752) | 0.86 (0.27-2.73; 0.799) |
| Neurological | 172 (1.0) | 14 (8.1) | 1.02 (0.59-1.77; 0.938) | 1.46 (0.83-2.56; 0.189) | 10 (5.8) | 1.5 (0.79-2.85; 0.220) | 1.94 (1.01-3.75; 0.047) | <5 | 1.43 (0.45-4.51; 0.544) | 1.67 (0.52-5.36; 0.390) |
| Metabolic | 125 (0.7) | 8 (6.4) | 0.79 (0.38-1.62; 0.514) | 1.24 (0.59-2.58; 0.571) | 6 (4.8) | 1.22 (0.53-2.78; 0.639) | 1.74 (0.75-4.04; 0.196) | <5 | 1.31 (0.32-5.31; 0.710) | 2.03 (0.49-8.46; 0.332) |
| CI = confidence interval, n = number of children, N = number of children with outcome event. *Adjusted for age, sex, socioeconomic deprivation, vaccination status (2008/9 seasonal influenza vaccine, pandemic influenza vaccine, pneumococcal conjugate vaccine and <i>Haemophilus influenzae b</i>), | | | | | | | | | | |

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.

| Table 3: Crude and adjusted odds ratios with 95% confidence intervals in relation to hospitalisation (n = 9,717) | | | | | | | |
|--|----------------|--|--------------------------------------|--------------------------|---|--------------------------|-------------------------|
| Underlying condition | n (%) | All-cause hospitalisation (116 events) | | | Hospitalisation due to influenza-related complication (57 events) | | |
| | | N (%) | Odds ratio (95% CI; p) | | N (%) | Odds ratio (95% CI; p) | |
| | | | Crude | Adjusted | | Crude | Adjusted |
| Asthma | 1079 (11.1) | 14 (1.3) | 1.10 (0.63-1.93; <u>p=0.740</u>) | 1.53 (0.81-2.86; 0.187) | 8 (0.7) | 1.31 (0.62-2.77; 0.481) | 2.46 (1.09-5.56; 0.031) |
| Premature birth | 181 (1.9) | <5 | 1.41 (0.44-4.47; <u>p=0.564</u>) | 1.22 (0.38-3.95; 0.739) | 0 (0) | NC | NC |
| Neurological | 99 (1) | <5 | 3.57 (1.29-9.89; 0.014) | 4.25 (1.5-12.07; 0.007) | 0 (0) | NC | NC |
| Metabolic | 71 (0.7) | <5 | 2.42 (0.59-10.01; 0.221) | 2.88 (0.67-12.36; 0.155) | <5 | 2.45 (0.33-17.92; 0.379) | 3.88 (0.5-29.93; 0.194) |

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.