# Identification of children at risk of influenza-related complications in primary and ambulatory care: a systematic review and meta-analysis

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## Summary

**Background** **Interventions to prevent influenza-related complications are recommended for individuals at the greatest risk of serious clinical deterioration. However, guidelines are based on consensus opinion rather than evidence, and do not specify risk factors in children. We aimed to provide an evidence-based definition of children who are most at risk of such complications.**

**Methods** **In this systematic review, we searched the Medline and Medline In Process, Embase, Science Citation Index, and CINAHL databases for studies published between inception and April 3, 2013. We included studies that reported data for underlying disorders and complications in children presenting in primary or ambulatory care with influenza or influenza-like illness. We requested unpublished data from investigators of studies that had obtained, but not published, relevant data. We analysed data with univariable meta-analysis and individual patient data multivariable meta-analysis methods. The primary outcome was admission to hospital as a proxy for complications of influenza or influenza-like illness.**

**Findings** **We included 28 articles that reported data from 27 studies (14 086 children). Strong risk factors for hospital admission were neurological disorders (univariable odds ratio [OR] 4·62, 95% CI 2·82–7·55), prematurity (4·33, 2·47–7·58), sickle cell disease (3·46, 1·63–7·37), immunosuppression (2·39, 1·24–4·61), diabetes (2·34, 1·20–4·58), and age younger than 2 years (2·51, 1·71–3·69). However, reactive airways disease including asthma (1·36, 0·82–2·26) and obesity (0·99, 0·61–1·62) were not found to be risk factors. On the basis of individual patient data multivariable analysis (1612 children, four studies), the risk of hospital admission was higher in children with more than one risk factor than in children with just one risk factor, when age younger than 2 years was included as a risk factor (92 [74%] of 124 *vs* 428 [52%] of 817; difference 22%, 95% CI 13–30%, p<0·0001).**

**Interpretation** **We identified prematurity as a new strong risk factor for influenza-related complications in children. Our findings also support the inclusion of neurological disorders, sickle cell disease, immunosuppression, diabetes, and age younger than 2 years as risk factors in existing guidelines. Interventions to prevent influenza-related complications should be prioritised in these groups, but should also be considered for other children, especially those with more than one risk factor or severe underlying comorbidities.**

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## Introduction

Influenza in children is a major burden on health-care resources, especially during epidemics and pandemics.[1,2] Around a quarter of otherwise healthy children who develop influenza or influenza-like illness have further complications[3] including pneumonia, otitis media, neurological complications, and death.[1]

At-risk children (ie, children with underlying medical disorders) are at increased risk of influenza-related complications.[4] Around 20% of children who present with influenza or influenza-like illness have at least one medical disorder,[5] and the presence of comorbidities increases the rates of influenza-related hospital admissions almost six times in children aged 5 to 14 years (from 0·1 per 1000 children to 0·56 per 1000).[6] After being admitted to hospital, such at-risk patients are also at higher risk of further complications.[7]

The UK Department of Health[8] and the WHO Strategic Advisory Group of Experts on Immunization[9] recommend influenza vaccination in specific groups who are considered to be at high risk of serious complications. The US Advisory Committee on Immunization Practices recommends that all individuals aged 6 months and older should receive annual influenza vaccinations,[10] but still recommends that antiviral medications should be targeted at specific high-risk groups.[11] However, these definitions of high-risk groups have several limitations: the level of detail used to define risk groups is inconsistent, the quality of evidence cited is variable, and risk factors are not specifically defined for children. Previous studies aiming to identify risk factors for influenza-related complications have also not defined these risks specifically in children.[12,13]

An understanding of risk factors in children is important, in view of the different comorbidity profiles encountered in paediatric versus adult populations and the high burden of disease associated with influenza in children.[9] Additionally, early intervention to prevent complications is important, because 35% of influenza-

related deaths in children occur before their admission to hospital, according to data from the USA.[14] We aimed to provide an evidence-based definition of which children presenting with influenza or influenza-like illness in primary or ambulatory care are at increased risk of developing influenza-related complications through a systematic review of published and unpublished data.

## Methods

### Search strategy and selection criteria

We systematically searched Medline and Medline In Process (OvidSP)[1946–], Embase(OvidSP) [1974–], Science Citation Index (Web of Science, Thomson Reuters)[1945–], and CINAHL(EbscoHOST)[1980–] from inception to April 3, 2013. Our search strategy (appendix), combined subject headings with free text search terms encompassing both established risk categories defined by the UK Department of Health,[8] the US Advisory Committee on Immunization Practices (ACIP),[11] and WHO,[9] and more recently identified candidate risk factors (eg, obesity and coeliac disease).[15,16] We used a validated child filter[17] and did not apply any language restrictions to our search. The electronic search was supplemented by review of reference lists of included articles, relevant reviews and guidelines, snowballing, and by use of PubMed's related articles function.

See Online for appendix

We requested unpublished data from the investigators of studies that we understood had obtained, but not published, data relevant for this review. We contacted investigators by email, and sent up to two email reminders after 1 month and 3 months to those who did not respond. We asked content experts to review our list of included articles for any obvious omissions. Ethics approval was not required for this study. We reported the systematic review in accordance with the PRISMA statement.

We included cohort and case-control studies based in primary or ambulatory care settings that included children aged up to 18 years with influenza (confirmed by laboratory or near-patient testing) or influenza-like illness (based on clinical features), and reported data about risk factors for admission to hospital or other complications. Primary care settings included general practices and primary care centres. Ambulatory care settings included hospital outpatient clinics and emergency departments. We included studies for which sufficient published or unpublished data were available to construct 2×2 tables for the presence or absence of risk factors with respect to the complication under assessment. We excluded studies for which all patients were admitted to hospital.

One researcher (PJG or KW) screened the titles of articles identified by our search to exclude any obviously irrelevant studies. Two authors (PJG and KW or HFA) independently screened abstracts and reviewed the full texts of potentially relevant articles. Any disagreements were resolved by discussion or adjudication with a third author (CH or SM).

### Risk of bias assessment and data extraction

We developed a standardised form to assess risk of bias from an early version of the Prediction Study Risk of Bias Assessment Tool (PROBAST),[18] Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2,[19] and Quality In Prognosis Studies (QUIPS).[20] Our form included domains from previous work on the reliability of prognostic models,[21] and was piloted by two researchers (PJG and HFA) who then completed assessments independently. Any disagreements were resolved by discussion or adjudication with a third author (KW, CH, or SM). The appendix describes the coding criteria used for each domain.

We developed a standardised data extraction form that was piloted by two reviewers (PJG and HFA) who independently extracted data. Disagreements were resolved by discussion or adjudication with a third author (KW, CH, or SM). The form included study characteristics, design, recruitment, inclusion and exclusion criteria, participant characteristics, type of influenza strain, method of influenza diagnosis, definition of influenza-like illness, complications (ie, hospital admissions and other complications—eg, otitis media), and duration of follow-up. For studies which reported prognostic models, we extracted detailed information about unadjusted and adjusted regression coefficients, and information relating to the candidate variables considered, handling of missing data, and model building, presentation, and validation.

Because of differences in the terminology and level of detail used to describe comorbidities in different studies, one author (PJG) grouped these terms into the following types of disorders after consultation with two practising primary care clinicians (HFA and KW): respiratory, neurological, metabolic, cardiac, prematurity, immunosuppression, haematological, cancer, renal, obesity, and congenital or structural disorders (eg, Down's syndrome). We extracted data for admissions to hospital for these disorders and for three age categories. When possible, we also extracted data for asthma, cystic fibrosis, bronchopulmonary dysplasia, diabetes, and sickle cell disease.

### Statistical analysis

We calculated odds ratios (ORs) with 95% CIs for individual risk factors in relation to hospital admission as a proxy for influenza-related complications. We classified all disorders and risk factors apart from age as present or absent. Age was categorised as the following three risk groups: age younger than 2 years, 2–5 years, and >5–18 years. Where only published data were available, we included studies in age group analyses where age categories were very similar, and reported any minor differences. Individual patient data analysis included fixed effects of immunological, neurological, respiratory, cardiac, renal, and metabolic disorders, prematurity, and all three age categories. Immunological

disorders included immunosuppression, haematological disorders, sickle cell disease, and cancer.

We planned to analyse the following subgroups: clinical versus laboratory-confirmed influenza; seasonal versus pandemic influenza, and length of follow-up (<9 days, 9–30 days, >30 days). Post hoc, we undertook sensitivity analyses in studies with a low risk of bias for patient selection and influenza diagnosis.

We used meta-analyses of binary outcome data for hospital admissions from individual patient data and univariable study estimates with a mixed multilevel, subject-specific (conditional) analysis, fitted by adaptive Gaussian quadrature using ten integration points or two if required for model convergence (xtmelogit in STATA 11.2). We used stratified one-stage models, ensuring correct clustering of patients within studies by use of separate intercepts for each study.[22,23] The binary one-step approach using the exact binomial distribution is preferred over other meta-analysis methods (eg, DerSimonian and Laird, Mantel Haenszel, and Peto's OR), because for these data, the event rate is low with many instances of zero cells (which would require continuity correction when other methods are used) and, because patients with a specific medical disorder are only a small proportion of patients in each study, comparison groups are very unequal.[22–26] The univariable meta-analysis of hospital admissions was completed when there were more than three studies for each disorder or subgroup. For individual patient data, multivariable models were fitted to data for which more than one disorder was included per patient, including age and one or more comorbid medical disorders, enabling analysis of potential confounding, if present, between the included disorders and age. Data for deaths and admissions to intensive-care units were pooled as one study for each disorder, because these events are rare.

### Role of the funding source

The funder of the study had no role in study design, data collection, analysis, or interpretation, report writing, or submission for publication. PJG, SM, HFA, and KW had full access to all the data in the study. KW, SM, and AH had final responsibility for the decision to submit for publication.

## Results

We identified 10 360 records, from which 148 full-text articles were assessed (figure 1). Of these, we included 28 articles, which reported data from 27 studies (table 1). The review included 14 086 children, of whom 3086 (22%) had an underlying disorder (ie, comorbidity not including age younger than 2 years). Rates of hospital admission varied tenfold between studies (6–65%) and the prevalence of comorbidities ranged from 3% to 82%. Most studies included patients with pandemic influenza (20 of 27 studies). Only one study included patients with influenza C.[45] 17 studies were retrospective cohort studies and two were case-control studies.[40,48]

The appendix summarises our risk of bias assessment of included studies. We identified 20 studies with satisfactory methods of diagnosis of influenza. Methods of patient selection were satisfactory in only 13 studies and definitions of outcome were satisfactory in only ten studies. Definitions of underlying disorders were consistent within studies, but varied between studies. In 12 studies that included immunosuppression as a potential risk factor, seven defined cancer,[39] haematological disorders,[27,31,37,44] or

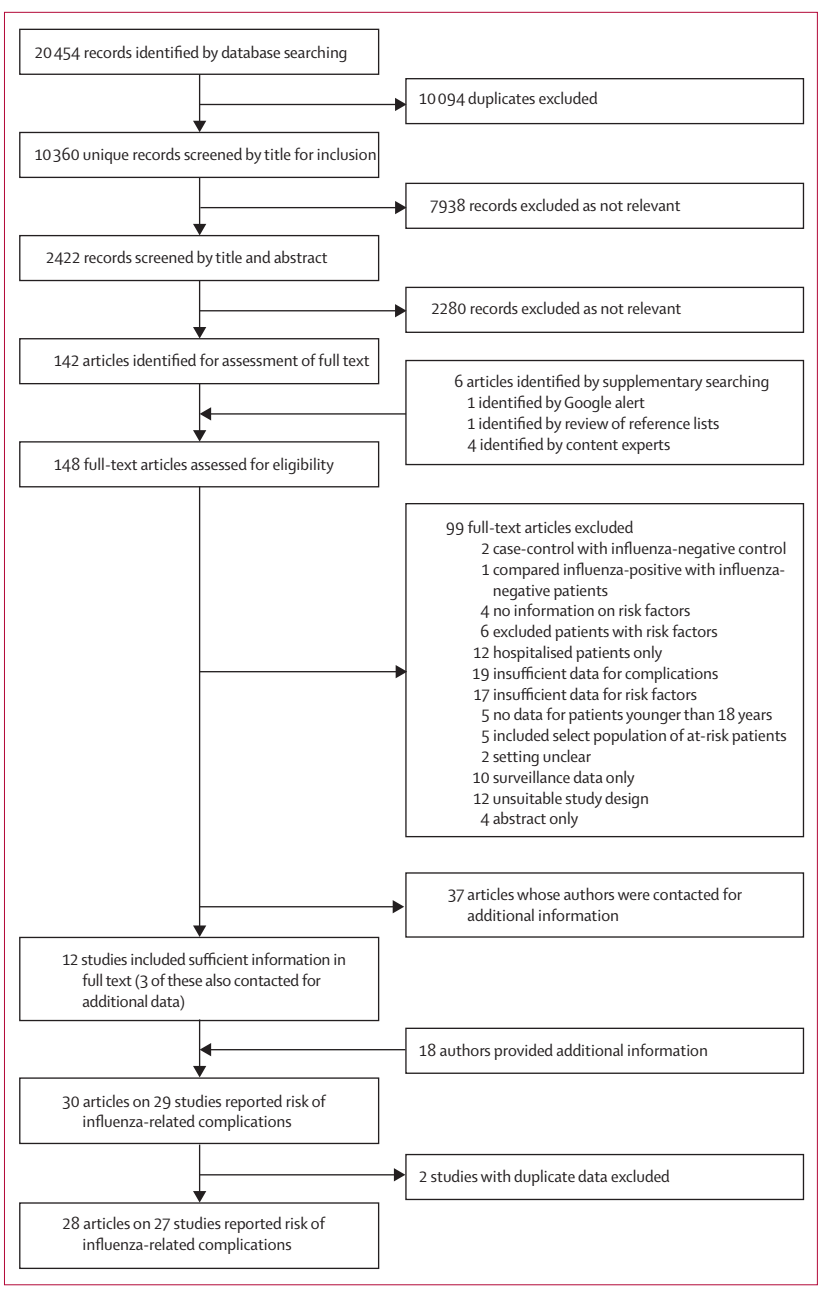


*Figure 1*: **Study selection**

sickle cell disease[33,35] as additional, separate disorders. Four studies did not classify these disorders separately from immunosuppression.[34,38,40,50] For one study, we defined children as having immunosuppression if they had congenital or acquired immunodeficiency, idiopathic thrombocytopenic purpura, or a previous splenectomy.[51] One study combined cancer with aplastic anaemia.[36]

Figure 2 presents our meta-analysis of univariable results for the primary outcome, admission to hospital, across studies according to underlying disorders and our three age categories. Strong risk factors for admission to hospital were neurological disorders, prematurity, sickle cell disease, immunosuppression, diabetes, and age younger than 2 years.

Respiratory disorders (including reactive airways disease), reactive airways disease including asthma, obesity, and older age groups (ie, age 2–5 years and age >5–18 years) were not risk factors. In this analysis, cancer and cardiac conditions had ORs with fairly narrow 95% CIs and were not associated with hospitalisation; however, inclusion of data from future studies could result in a statistically significant association.

| | Country | Ambulatory setting* | Study type | Type of influenza (pandemic, seasonal, or influenza C) | Dates of recruitment | Age range of children (years) | Total number of children | Number of children with risk factors | Number of children admitted to hospital |
|---|---|---|---|---|---|---|---|---|---|
| Aguirre et al[27] | Canada | ED of paediatric hospital | RDR | Both† | 2006–09 | 0–17 | 127 | 62 (49%) | 43 (34%) |
| Bailhache et al[28] | France | Paediatric hospital, regional hospitals | RDR | Pandemic | 2009–10 | 0–0·5 | 74 | 16 (22%) | 48 (65%) |
| Bender et al[29] | USA | ED of paediatric hospital | RDR | Seasonal | 2001–04 | 0–18 | 1230 | 241 (20%) | 541 (44%) |
| Bogie et al[30] | USA | Paediatric hospital | RDR | Both | 2009 | 0–18 | 287 | 185 (64%) | 128 (45%) |
| Carcione et al[31,32] | Australia | Not specified | RDR; Q | Both | 2009 | 0–18 | 436‡ | 119 (27%) | 39 (9%) |
| Crisinel et al[33] | Switzerland | Paediatric hospital | POS | Pandemic | 2009–10 | 0–18 | 75 | 32 (43%) | 12 (16%) |
| De Marco et al[34] | Italy | Paediatric hospital | POS | Seasonal | 2001–03 | 0–16 | 351 | 47 (13%) | 92 (26%) |
| Desmoulins et al[35] | France | ED, and university and paediatric hospitals | POS | Pandemic | 2009 | 0–17 | 466 | 208 (45%) | 192 (41%) |
| Dubnov-Raz et al[36] | Israel | Paediatric hospital | RDR | Pandemic | 2009 | 1–17 | 73 | 39 (53%) | 37 (51%) |
| Gastanaduy et al[37] | USA | Paediatric hospital | RDR | Pandemic | 2009–10 | 0–16 | 1463 | 411 (28%) | 155 (11%) |
| Goodacre et al[38] | UK | ED | POS | Pandemic | 2009–10 | 0–16 | 347 | 44 (13%) | 39 (11%) |
| Hite et al[39] | USA | Paediatric hospital | RDR | Seasonal | 2002–03 | 0–18 | 205 | 99 (48%) | 79 (39%) |
| Launes et al[40] | Spain | Public NHS centres | CCS | Pandemic | 2009–10 | 0·5–18 | 379 | 147 (39%) | 195 (51%) |
| Lee CY et al[41] | Taiwan | Not specified | RDR | Pandemic | 2009 | 0–15 | 819 | 76 (9%) | 47 (6%) |
| Lee MC et al[42] | South Korea | Not specified | RDR | Pandemic | 2009–10 | 0–18 | 3777 | 219 (6%) | 221 (6%) |
| Lenzi et al[43] | Brazil | Not specified | RDR | Pandemic | 2009 | 0–12 | 1307 | 239 (18%) | 475 (36%)§ |
| Lera et al[44] | Spain | ED of paediatric hospital | POS | Pandemic | 2009 | 0–19¶ | 412 | 336 (82%) | 85 (21%) |
| Matsuzaki et al[45] | Japan | Paediatric clinics, hospital | RDR | Influenza C | 1990–2004 | 0–15 | 170 | 5 (3%) | 29 (17%) |
| Na et al[46] | South Korea | Medical centre converted to primary-care centre | POS | Pandemic | 2009 | 0–14 | 240 | 19 (8%) | \|\| |
| Peltola et al[47] | Finland | Paediatric hospital (inpatients and outpatients) | RDR | Seasonal | 1980–99 | 0–19¶ | 683 | 167 (24%) | 389 (57%) |
| Perez-Padilla et al**[48] | Mexico | Many settings | CCS | Pandemic | 2009 | 0–18 | .. | 35 (..) | .. |
| Plessa et al[49] | Greece | Paediatric department of hospital | POS; RDR | Pandemic | 2009–10 | 0–13 | 51 | 16 (31%) | 15 (29%) |
| Quach et al[50] | Canada | ED of paediatric hospital | RDR | Seasonal | 1999–2002 | 0–19¶ | 294 | 84 (29%) | 180 (61%) |
| Rabasco et al[51] | Spain | Not specified | RDR | Pandemic | 2009–10 | 0–18 | 202 | 119 (59%) | 109 (54%) |
| Rodriguez-Valero et al[52] | Mexico | ED | RDR | Pandemic | 2009 | 0–18 | 118 | 31 (26%) | 35 (30%) |
| Sessa et al[53] | Italy | General practice | POS | Seasonal | 1998–99 | 10–14 | 368 | 42 (11%) | ** |
| Smit et al[54] | Netherlands | ED, outpatient influenza clinic | POS | Pandemic | 2009 | 0–16 | 132 | 48 (36%) | 22 (17%) |
| Overall | .. | .. | .. | .. | 1980–2010 | 0–19 | 14 086 | 3086 (22%) | Mean 32% |

Data are number (%). ED=emergency department. RDR=retrospective database review. Q=questionnaire. POS=prospective observational study. NHS=national health service. CCS=case-control study. *If the hospital setting was specified (eg, outpatient clinic or emergency department), the study only included patients in ambulatory care. If the exact hospital setting was not specified (eg, paediatric hospital) or if the overall setting was not specified, the description provided in the study was consistent with ambulatory care, and the authors were satisfied that the setting met the inclusion criteria for the systematic review. †Study included seasonal and pandemic influenza but only pandemic data were available. ‡Data were unavailable to establish if patients had more than one comorbidity, but the total provided assumes that patients did not. §No data for individual comorbidities for patients admitted to hospital. ¶For studies where individual patient data were available (Peltola et al, and Quach et al), participants aged older than 18 years were excluded. ||Study investigators did not obtain outcome data about whether patients were admitted to hospital. **Case-control study that only included patients with Down's syndrome. Data only reported for total population including adults.

***Table 1*: Characteristics of 27 included studies**

The appendix contains Forest plots and details of results from individual studies for each disorder and age category, showing the heterogeneity between studies. Evidence was insufficient to assess the risk of hospital admission for haematological and metabolic disorders (excluding diabetes). Evidence was also insufficient to assess the risk of hospital admission associated with congenital disorders (including Down's syndrome), bronchopulmonary dysplasia, epilepsy, cystic fibrosis, or renal disorders.

We did an individual patient data meta-analysis for four studies where these data were provided by the investigators (1612 children, 677 admissions to hospital).[31,39,47,50] Neurological and immunological disorders, prematurity, and age younger than 2 years were shown to be independent risk factors for hospital admission, but cardiac and respiratory disorders were not (appendix). Obesity could not be included in this model because only five children in this dataset were obese. Additionally, multivariable analysis of individual patient data from two separate studies showed an increased risk of hospital admission associated with immunological conditions,[39,47] neurological conditions,[39,47] prematurity,[39] and age younger than 2 years.[47]

Fewer children (48% [186 of 391]) with only one type of medical disorder were hospitalised than were children with more than one type of disorder (74% [29 of 39]; difference 27%; 95% CI 12–41%, p=0·001). 20 (51%) of 39 children with more than one type of disorder were born prematurely (not including age younger than 2 years as a risk factor). When age younger than 2 years was also included as a risk factor, the percentage of children hospitalised increased from 52% (428 of 817) in children with one condition to 74% (92 of 124) in children with more than one condition, a difference of 22% (95% CI 13–30, p<0·0001).

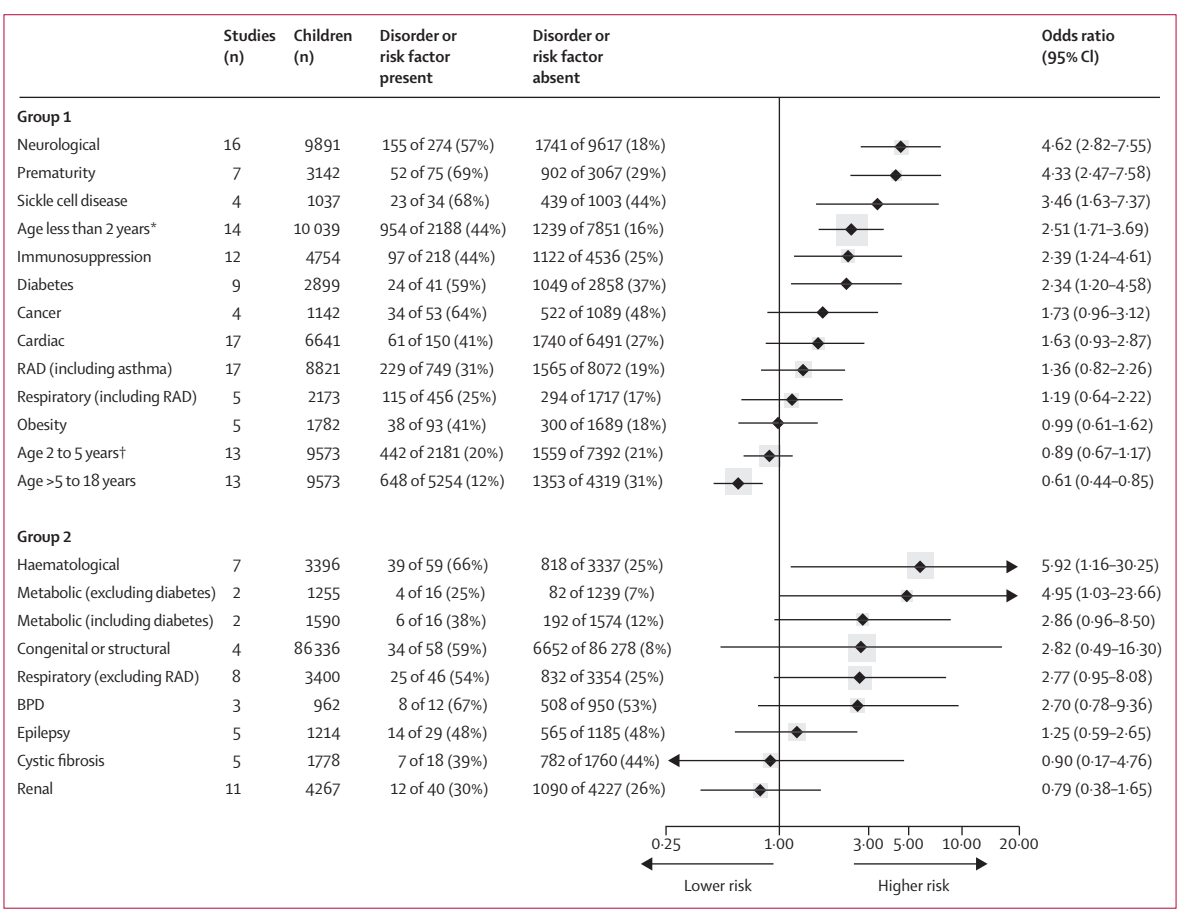


***Figure 2*: Univariable results for patients admitted to hospital**

Group 1: disorders or risk factors for which data were sufficient to assess the associated risk of hospital admission. Group 2: disorders or risk factors for which there was a high degree of heterogeneity between different studies (haematological disorders, respiratory disorders excluding reactive airways disease, or congenital or structural disorders) or a low number of occurrences of hospital admission among children with the following conditions: bronchopulmonary dysplasia, metabolic conditions including diabetes, metabolic conditions excluding diabetes, cystic fibrosis, epilepsy, and renal conditions. Disorder or risk factor present=number of children with the disorder or risk factor admitted to hospital/total number of children with disorder or risk factor. Disorder or risk factor absent=number of children without a disorder or risk factor admitted to hospital/number of children without disorder or risk factor. RAD=reactive airways disease. BPD=bronchopulmonary dysplasia. *One study[27] in this age category included children aged 2 years. †In this age category, one study[27] did not include children aged 2 years and four studies[29,31,37,42] did not include children aged 5 years.

We undertook subgroup analyses of studies with pandemic influenza, seasonal influenza, and laboratory-confirmed influenza (data not shown). The results were generally consistent with our main meta-analysis of univariable results (figure 2) with respect to the disorders that were associated with hospital admission. We noted two exceptions in the seasonal influenza subgroup, which were inconsistent with both the univariable analysis of all studies (figure 2) and the individual patient data analysis that adjusted for concurrent medical disorders (appendix). First, the presence of a cardiac disorder (subgroup of four of 17 studies) was significantly associated with admission to hospital, but individual patient data analysis of these four studies did not show a significant association (appendix). Second, age younger than 2 years (subgroup of five of 14 studies) was not significantly associated with hospital admission, by contrast with the individual patient data analysis that included three of these five studies. This inconsistent subgroup result was due to the study by Bender and colleagues[29] (appendix), which was not available for the individual patient data analysis. Analysis by length of follow-up was not possible because only two studies specified follow-up periods[27,35] and in one of these studies,[27] whether the follow-up period specified related to children admitted to hospital only, was unclear.

We undertook sensitivity analyses for studies with a low risk of bias for patient selection and for diagnosis of influenza (data not shown). Results were also generally consistent with our main meta-analysis of univariable results apart from the following two exceptions: for cardiac disorders, we noted a significant association in the subgroup with low risk of bias for patient selection (nine of 17 studies). This association was not noted in the main meta-analysis, but results from future studies might result in a statistically significant association. Age younger than 2 years was not associated with hospital admission in the subgroup with low bias for influenza diagnosis (seven of 14 studies), but again, this inconsistent result was due to the study by Bender and colleagues[29] (appendix).

Nine studies had data for deaths according to absence or presence of comorbidities. 26 deaths occurred, of which 15 were children with comorbidities.[35,37–39,41,43,47,50,54] Of 13 studies that reported data for admissions to ICUs (110 admissions), eight reported whether these occurred in the presence of comorbidities (51 ICU admissions including 31 [4%] of 717 children with comorbidities).[27,28,35,36,38,42,50,54] Because of the few deaths and admissions to ICU for each comorbidity, the results are summarised as absolute numbers and percentages (appendix).

## Discussion

Prematurity, neurological disorders, sickle cell disease, immunosuppression, diabetes, and age younger than 2 years were all risk factors for hospital admission in children who presented with influenza or influenza-like illness in primary or ambulatory care. Unlike the other factors identified in this systematic review, prematurity is not defined as an at-risk disorder in any existing guidelines. The presence of more than one coexisting condition significantly increases the risk of hospital admission, from 52% (one condition only) to 74% (more than one condition) when aged younger than 2 years is included as a risk condition.

Table 2 compares the risk factors identified in this review with those outlined by the UK Department of Health,[8] the US Advisory Committee on Immunization Practices (ACIP),[11] and WHO.[9] Although we found that prematurity was a risk factor for admission to hospital, data were not reported in sufficient detail to assess the association between extent of prematurity and risk of hospital admission. We found that age younger than 2 years and sickle cell disease are risk factors for hospital admission, but these are only included in the ACIP and WHO definitions.[9,11]

Our findings support the inclusion of neurological disorders, immunosuppression, and diabetes in all three guidelines. For influenza-related deaths in children reported in the USA between October, 2004, and September, 2012, neurological disorders were present in 33% of children whose medical histories were known.[14] A prospective cohort study also reported that the presence of neurological or neuromuscular disorders was associated with a fourfold increased risk of severe complications (including respiratory failure, pneumonia, and death) in children who presented in a hospital emergency department with moderate to severe influenza-like illness.[55] Children with neurological conditions that do not obviously impair their ability to handle respiratory secretions have been proposed as an at risk-group because of the high burden of influenza in these children.[56] However, this recommendation was based only on data obtained from children who had already been admitted to hospital. Data for this review were not reported in sufficient detail to separately assess the risk of hospital admission associated with neurological disorders that did or did not compromise handling of respiratory secretions.

A systematic review of published studies by Mertz and colleagues[13] investigated risk factors for all-cause admissions to hospital in children and adults with influenza or influenza-like illness. However, although that review included 234 studies, few of them assessed each medical disorder. For example, four studies assessed asthma compared with 22 in our review and three studies assessed age younger than 2 years compared with 14 in our review. Furthermore, Mertz and colleagues' review did not include any risk factors in children other than age. Our review included a more up-to-date search (until April, 2013, *vs* March, 2011) and sought additional unpublished data, which we obtained from two-thirds of

our included studies. Publication bias is known to be widespread in prognostic studies.[57]

Mertz and colleagues[13] identified obesity as a risk factor for influenza-related complications; however, we did not find it to be a risk factor in children. Although obesity has been reported as a risk factor for influenza-related hospitalisation and death,[2,15,58] this result is only based on data from adults, for whom obesity is associated with more advanced comorbidity than in children. Mertz and colleagues also identified cardiac, respiratory, and renal disorders as risk factors based on data from patients from a wide age range, including adults. Conversely, our univariable analysis and our individual patient data meta-analysis did not show cardiac or respiratory disorders to significantly increase risk of admission to hospital for children. However, inclusion of data from future studies could result in a significant association. We were unable to establish whether the presence of renal disorders was a risk factor because few children with these disorders were admitted to hospital.

The increased risk of hospital admission associated with multimorbidity that we noted is consistent with the findings of a case-control study undertaken in the US of children with laboratory-confirmed influenza.[59] But by contrast with our findings, the same study showed that respiratory disorders were associated with an increased risk. This difference could have resulted from the inclusion of a narrower and more severe range of illness in children with these disorders. Data for the severity of underlying disorders were not reported in studies included in our review.

Strengths of our study include our specific focus on children, and the extensive search and use of univariable and individual patient data multivariable analyses including unpublished data from two-thirds of included studies. We also excluded study types at highest risk of bias for prognostic factor research, including cross-sectional and population-specific studies.[57]

The individual patient data analysis methods allowed assessment of the independent strength of medical disorders with admissions to hospital, without confounding with age and other coexisting disorders. The agreement between the three analysis approaches (univariable and individual patient-data meta-analyses, and within-study multivariable analysis of individual patient data), and subgroup and sensitivity meta-analyses, lend support to the risk factors identified. We did not have access to data to allow adjustment for other potential confounders, such as vaccination and severity of underlying medical disorders.

To establish whether any studies that might have affected our findings had been published since we completed our search, we updated our search on Oct 9, 2014. This search retrieved an additional 1680 articles (3445 articles minus 1765 duplicates), which were independently reviewed by two authors (PJG and KW). Only two of these studies might have been suitable for inclusion in our meta-analysis if unpublished data were available.[55,60] However, even if these data had been available, they probably would not have affected our findings. One study[60] included 146 children and adults with laboratory-confirmed influenza, of whom only 22 had chronic lung disease and 18 were immunocompromised. 56 hospital admissions occurred. Inclusion of data from children only would have reduced the numbers with underlying disorders and admissions to hospital. The other study[55] reported data only for severe complications (including pneumonia, seizures, and death) in children aged 0–19 years who presented in a hospital emergency department with influenza or influenza-like illness. However, whether all patients were admitted to hospital was unclear, in which case this study would not have been eligible for inclusion.

Most included studies in our review were undertaken in hospital ambulatory care or emergency department settings, which served as the closest approximation to primary care, although this could restrict the generalisability of our findings. Definitions and details of risk factor classifications were also often inadequate; in particular, no studies stratified reporting of influenza-related complications in children born prematurely according to gestational age, or reported complications separately in children with different types of neurological disorders. Only two studies defined prematurity in terms of gestational age; less than 36 weeks in one study (since last menstrual period)[28] and less than 37 weeks in the other (method of establishing gestational age was not specified).[47] In our

| | UK Department of Health[8] | US Advisory Committee on Immunization Practices[11] | WHO[9] | Findings of present study |
|---|---|---|---|---|
| Neurological | Included | Included | Included | Included |
| Diabetes | Included | Included | Included | Included |
| Immunosuppression | Included | Included | Included | Included |
| Sickle cell disease | Excluded | Included | Included | Included |
| Age less than 2 years | Excluded | Included | Included | Included |
| Haematological | Excluded | Included | Included | Included (insufficient data) |
| Prematurity | Excluded | Excluded | Excluded | Included |
| RAD (including asthma) | Included | Included | Included | Excluded* |
| Cardiac | Included | Included | Included | Equivocal† |
| Obesity | Excluded | Included‡ | Included‡ | Excluded |
| Respiratory (excluding RAD) | Included | Included | Included | Excluded (insufficient data) |
| Renal | Included | Included | Included | Excluded (insufficient data) |
| Metabolic (including diabetes) | Included | Included | Included | Excluded (insufficient data) |
| Liver | Included | Included | Included | No result§ |

RAD=reactive airway disease. *Data include range of asthma severity; insufficient data on severe asthma. †High odds ratio but not significant. ‡Morbid obesity (body mass index ≥40). §No data available for risk of children with these disorders being admitted to hospital.

*Table 2*: **Conditions included or excluded in definitions of at risk**

individual patient data analysis, only 11 of the 48 children identified as having been born prematurely were aged 2 years or older. We were therefore unable to assess whether prematurity was still a risk factor for children older than 2 years of age.

Although influenza is usually diagnosed on the basis of clinical features in primary care settings, only four studies diagnosed influenza clinically.[34,38,48,53] Retrospective cohort studies which recruited children with laboratory-confirmed influenza could have preferentially performed laboratory tests for children with underlying disorders, or with more severe influenza or influenza-like illness. Nevertheless, the results of our subgroup analysis in children with laboratory-confirmed influenza, and our sensitivity analysis of data from studies with low risk of bias for influenza diagnosis, were consistent with those of our main analysis of univariable results. Only nine studies collected prospective longitudinal data and only one study, which was done in an emergency department, presented a model for predicting admission to hospital that incorporated both clinical features and underlying disorders.[29] This finding underlines the need for more research in this area, especially in primary care settings. More research is also needed to help clinicians to identify risk factors for influenza-related clinical deterioration and complications in the community, which can also be a source of substantial burden on health-care resources.

Although we noted more than tenfold variation in overall rates of admissions to hospital between different study populations (6–65%), our results did not show any obvious relation between ORs for admission to hospital with respect to individual disorders and overall rates of admission to hospital (appendix). Because thresholds for hospital admissions are likely to vary between different health-care settings, intensive care unit admissions and death are more robust indicators of clinical deterioration than admission to hospital. However, these are rare outcomes and we had insufficient data for meta-analysis.

To our knowledge, this systematic review provides the first evidence-based definition of at-risk groups of children at whom interventions to reduce the risk of influenza-related complications should be targeted. Prematurity, identified as a new strong risk factor in children, has important implications for present definitions of at-risk groups, which do not include children born prematurely. Rates of preterm delivery before 37 weeks' gestation are reported to be 6·2% in Europe, 10·6% in North America, and 11·9% in Africa.[61] Other risk factors in children, which are already defined in existing guidelines, are neurological disorders, sickle cell disease, immunosuppression, diabetes, and being aged younger than 2 years.

The effect of prematurity on the risk of influenza-related complications needs to be established in children of different ages, and those born after different gestational periods. However, a national cohort study using data from Sweden has shown that preterm birth before 37 weeks is associated with increased mortality during early childhood (age 1–5 years) and young adulthood (18–36 years), even in individuals born late preterm (34–36 weeks).[62] This study also showed a strong inverse association between gestational age at birth and mortality from congenital anomalies and respiratory, endocrine, and cardiovascular disorders during young adulthood. In view of these findings and the inclusive nature of childhood influenza vaccination policies, preterm birth before 37 weeks should be considered as a risk factor for influenza-related complications in children of any age until further data to inform more precise targeting become available.

Identification of groups at risk is a key cornerstone of strategies to plan for and respond to seasonal influenza epidemics and influenza pandemics,[63,64] and guidelines from the UK Department of Health[8] and WHO[9] recommend that annual seasonal influenza vaccinations should be targeted specifically towards such groups. However, in the UK, vaccination uptake in children in at-risk groups was low during the 2012–13 influenza season, with the highest uptake rate in children with diabetes (44·3% in children aged 6 months to <2 years; and 61·6% in children aged 2 to <16 years) and the lowest uptake rate in children with chronic neurological disease (18·6% in children aged 6 months to <2 years) and chronic cardiac disease (27·2% in children aged 2 to <16 years).[65] Several countries recommend universal vaccination of all children, but uptake rates are still low. In the USA, influenza vaccine uptake during the 2011–12 season ranged from 24·9% in children aged 13 to 18 years[66] to 44·3% in children aged 6–23 months.[67] During a pilot childhood influenza vaccination scheme in England during winter 2013–14, vaccine uptake was 52·5% overall, and a significant decrease in uptake was reported with increasing age (56·1% in children aged 4–5 years, 49·7% in children aged 10–11 years).[68] Therefore, to implement national vaccination programmes with maximum efficiency, strategies to increase seasonal vaccine uptake should specifically target the at-risk groups that our study has identified.

During influenza pandemics, antiviral drugs might be used more widely, because the development and establishment of a suitable vaccine might take some time. Prepandemic vaccination of all children and adults in at-risk groups is thought to be prudent policy. However, this would have substantial logistical implications, because about 40% of the UK population would need to be vaccinated.[69] Furthermore, supplies of antiviral drugs could be rapidly depleted because of the widespread nature and unpredictable severity of the influenza virus. In these situations, delivery of vaccinations and other interventions aimed at preventing influenza-related complications, including antivirals and antibiotics, should be prioritised for at-risk groups.

Although consideration of at-risk disorders is already recommended in the clinical management of children presenting with influenza or influenza-like illness,[70] estimation of the level of risk associated with different disorders still relies upon the subjective judgment of individual clinicians. Our findings help to inform more accurate and consistent clinical assessments of the importance of different at-risk disorders through quantification of the degree of risk associated with these conditions and the significant increase in risk in individuals with more than one risk factor. This will in turn help with more efficient clinical triage systems and more prudent use of health-care resources for children presenting in primary and ambulatory care settings with influenza or influenza-like illness.

Although guidelines list people with obesity and asthma as at-risk groups, we did not find these disorders to be risk factors in children. However, our review might not have shown a significant association between some disorders and admission to hospital, because averaging might have occurred across a wide range of disease severity, or a lack of statistical power when disorders are rare.

Interventions to reduce the risk of influenza-related complications should therefore still be considered for children with other disorders, particularly in the presence of more than one risk factor or severe comorbidities. To guide appropriate targeting of interventions to prevent influenza-related complications in children, our findings should be used to update definitions of patients regarded as at risk of such complications and to specifically define at-risk groups in children.

#### Contributors

PJG, HFA, KW, CH, AH, and SM developed the systematic review protocol. KW and NWR developed the search strategy. NWR performed the electronic database searches. PJG, HFA, and KW screened articles for inclusion. PJG and HFA completed data extraction and risk of bias assessments. PJG contacted authors for unpublished data. SM designed the analysis, did data cleaning, analysed data, graphs, and statistical interpretation. HFA, PJG, and SM all contributed to figures. PJG, SM, KW, HFA, and AH all contributed to manuscript drafting. All authors contributed comments and edits to the manuscript. PJG, SM, HFA, and KW had full access to all the data in the review.

#### Declaration of interests

We declare no competing interests.

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#### References

1 Nair H, Brooks WA, Katz M, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. *Lancet* 2011; **378:** 1917–30.

2 Van Kerkhove MD, Vandemaele KA, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med* 2011; **8:** e1001053.

3 Belongia EA, Irving SA, Waring SC, et al. Clinical characteristics and 30-day outcomes for influenza A 2009 (H1N1), 2008-2009 (H1N1), and 2007–2008 (H3N2) infections. *JAMA* 2010; **304:** 1091–98.

4 Loughlin J, Poulios N, Napalkov P, Wegmuller Y, Monto AS. A study of influenza and influenza-related complications among children in a large US health insurance plan database. *Pharmacoeconomics* 2003; **21:** 273–83.

5 Irwin DE, Weatherby LB, Huang WY, Rosenberg DM, Cook SF, Walker AM. Impact of patient characteristics on the risk of influenza/ILI-related complications. *BMC Health Services Research* 2001; **1:** 8.

6 Cromer D, van Hoek AJ, Jitb M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. *J Infect* 2014; **68:** 363–71.

7 Myles PR, Semple MG, Lim WS, et al. Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009-2010 in the UK. *Thorax* 2012; **67:** 709–17.

8 Department of Health. Influenza. In: Salisbury D, Ramsay M, Noakes K, eds. Immunisation against infectious disease: the green book. London: The Stationery Office; 2013.

9 WHO Strategic Advisory Group of Experts on Immunization. Background paper on influenza vaccines and immunization SAGE Working Group. World Health Organisation, 2012. http://www.who.int/immunization/sage/meetings/2012/april/1_Background_Paper_Mar26_v13_cleaned.pdf (accessed Nov 14, 2014).

10 Grohskopf LA, Olsen SJ, Sokolow LZ, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP)—United States, 2014–15 influenza season. *MMWR Recomm Rep* 2014; **63:** 691–97.

11 Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM. Antiviral agents for the treatment and chemoprophylaxis of influenza - recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011; **60:** 1–24.

12 Hak E, Verheij TJ, van Essen GA, Lafeber AB, Grobbee DE, Hoes AW. Prognostic factors for influenza-associated hospitalization and death during an epidemic. *Epidemiol Infect* 2001; **126:** 261–68.

13 Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013; **347:** f5061.

14 Wong KK, Jain S, Blanton L, et al. Influenza-associated pediatric deaths in the United States, 2004–2012. *Pediatrics* 2013; **132:** 796–804.

15 Morgan OW, Bramley A, Fowlkes A, et al. Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS One* 2010; **5:** e9694.

16 Marild K, Fredlund H, Ludvigsson JF. Increased risk of hospital admission for influenza in patients with celiac disease: a nationwide cohort study in Sweden. *Am J Gastroenterol* 2010; **105:** 2465–73.

17 Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Arch Pediatr Adolesc Med* 2008; **162:** 111–16.

18 Wolff R, Whiting PF, Mallett S, et al. Prediction study risk of bias assessment tool (PROBAST). 21st Cochrane Colloquium; Quebec City, QC Canada; Sept 19–23, 2013. O1.06.

19 Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155:** 529–36.

20 Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; **158:** 280–86.

21 Mallett S, Royston P, Dutton S, Waters R, Altman DG. Reporting methods in studies developing prognostic models in cancer: a review. *BMC Med* 2010; **8:** 20.

22 Abo-Zaid G, Guo B, Deeks JJ, et al. Individual participant data meta-analyses should not ignore clustering. *J Clin Epidemiol* 2013; **66:** 865–73.

23 Debray TP, Moons KG, Abo-Zaid GM, Koffijberg H, Riley RD. Individual participant data meta-analysis for a binary outcome: one-stage or two-stage? *PLoS One* 2013; **8:** e60650.

24 Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007; **26:** 53–77.

25 Greenland S, Salvan A. Bias in the one-step method for pooling study results. *Stat Med* 1990; **9:** 247–52.

26 Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med* 2004; **23:** 1351–75.

27 Aguirre E, Papenburg J, Ouakki M, et al. Comparison of pandemic and seasonal influenza in the pediatric emergency department. *Pediatr Infect Dis J* 2011; **30:** 633–39.

28 Bailhache M, Sarlangue J, Castella C, Richer O, Fleury H, Koeck JL. [Influenza A(H1N1)v virus infection in infants less than 6 months of age in southwestern France]. *Arch Pediatr* 2011; **18:** 383–89.

29 Bender JM, Ampofo K, Gesteland P, et al. Development and validation of a risk score for predicting hospitalization in children with influenza virus infection. *Pediatr Emerg Care* 2009; **25:** 369–75.

30 Bogie AL, Grant K, Hallford G, Anderson M. The epidemiology of pediatric patients seen at the Children's Hospital of Oklahoma with laboratory confirmed influenza in 2009. *JOkla State Med Assoc* 2011; **104:** 345–51.

31 Carcione D, Giele C, Dowse GK, et al. Comparison of pandemic (H1N1) 2009 and seasonal influenza, Western Australia, 2009. *Emerg Infect Dis* 2010; **16:** 1388–95.

32 Goggin LS, Carcione D, Mak DB, et al. Chronic disease and hospitalisation for pandemic (H1N1) 2009 influenza in Indigenous and non-Indigenous Western Australians. *Commun Dis Intell Q Rep* 2011; **35:** 172–76.

33 Crisinel P-A, Barazzone C, Kaiser L, et al. Comparison of clinical presentation of respiratory tract infections in H1N1/09-positive and H1N1/09-negative patients. *Eur J Pediatr* 2012; **171:** 159–66.

34 De Marco G, Mangani S, Correra A, et al. Reduction of inappropriate hospital admissions of children with influenza-like illness through the implementation of specific guidelines: a case-controlled study. *Pediatrics* 2005; **116:** e506–11.

35 Desmoulins C, Michard-Lenoir AP, Naud J, Claudet I, Nouyrigat V, Cheron G. Clinical features and outcome of 2009 H1N1 influenza in the pediatric setting. Multicenter prospective study in the ED. *Arch Pediatr* 2011; **18:** 505–11.

36 Dubnov-Raz G, Somech R, Warschawski Y, Eisenberg G, Bujanover Y. Clinical characteristics of children with 2009 pandemic H1N1 influenza virus infections. *Pediatr Int* 2011; **53:** 426–30.

37 Gastanaduy AS, Begue RE. Experience with pandemic 2009 H1N1 influenza in a large pediatric hospital. *South Med J* 2012; **105:** 192–98.

38 Goodacre S, Challen K, Wilson R, Campbell M. Evaluation of triage methods used to select patients with suspected pandemic influenza for hospital admission: cohort study. *Health Technol Assess* 2010; **14:** 173–236.

39 Hite LK, Glezen WP, Demmler GJ, Munoz FM. Medically attended pediatric influenza during the resurgence of the Victoria lineage of influenza B virus. *Int J Infect Dis* 2007; **11:** 40–47.

40 Launes C, Garcia-Garcia JJ, Martinez-Planas A, et al. 2009 H1N1: risk factors for hospitalization in a matched case-control study. *Eur J Pediatr* 2012; **171:** 1127–31.

41 Lee CY, Chuang YF, Huang WY, Cheng SH, Pei JS. Epidemiology, clinical features, treatment, and outcomes of cases of influenza A infection during the 2009 influenza pandemic in northern Taiwan. *Pediatr Neonatol* 2012; **53:** 257–63.

42 Lee MC, Kim HY, Kong SG, et al. Clinical characteristics of pandemic influenza A (H1N1) 2009 pediatric infection in Busan and Gyeongsangnam-do: one institution. *Tuberc Respir Dis (Seoul)* 2012; **72:** 493–500.

43 Lenzi L, Mello ÂMd, Silva LRd, Grochocki MHC, Pontarolo R. Manifestações clínicas, desfechos e fatores prognósticos da influenza pandêmica A (H1N1) de 2009 em crianças. *Revista Paulista de Pediatria* 2012; **30:** 346–52.

44 Lera E, Worner NT, Sancosmed M, et al. Clinical and epidemiological characteristics of patients with influenza A (H1N1) 2009 attended to at the emergency room of a children's hospital. *Eur J Pediatr* 2011; **170:** 371–78.

45 Matsuzaki Y, Katsushima N, Nagai Y, et al. Clinical features of influenza C virus infection in children. *J Infect Dis* 2006; **193:** 1229–35.

46 Na S, Kim M-N, Kim WY, et al. Prevalence and clinical features of pneumonia in patients with laboratory-confirmed pandemic influenza A H1N1 2009 infection in South Korea. *Scand J Infect Dis* 2011; **43:** 19–26.

47 Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. *Clin Infect Dis* 2003; **36:** 299–305.

48 Perez-Padilla R, Fernandez R, Garcia-Sancho C, et al. Pandemic (H1N1) 2009 virus and Down syndrome patients. *Emerg Infect Dis* 2010; **16:** 1312–14.

49 Plessa E, Diakakis P, Gardelis J, Thirios A, Koletsi P, Falagas ME. Clinical features, risk factors, and complications among pediatric patients with pandemic influenza A (H1N1). *Clin Pediatr* 2010; **49:** 777–81.

50 Quach C, Piche-Walker L, Platt R, Moore D. Risk factors associated with severe influenza infections in childhood: implication for vaccine strategy. *Pediatrics* 2003; **112:** e197–201.

51 Rabasco MAC, Capistros MT, Castan AR, Castellvi PS, Solas VP, Martinez-Roig A. Clinical and epidemiological characteristics of children with 2009 influenza A (H1N1) infection. [Catalan]. *Pediatria Catalana* 2011; **71:** 91–95.

52 Rodriguez-Valero M, Prado Calleros HM, Bravo Escobar GA, et al. Difference between early clinical features of swine origin A H1N1 influenza confirmed and not confirmed infection in Mexico. *J Infect Dev Ctries* 2012; **6:** 302–10.

53 Sessa A, Costa B, Bamfi F, Bettoncelli G, D'Ambrosio G. The incidence, natural history and associated outcomes of influenza-like illness and clinical influenza in Italy. *Fam Pract* 2001; **18:** 629–34.

54 Smit PM, Bongers KM, Kuiper RJL, von Rosenstiel IA, Smits PHM, Brandjes DPM. Characterization of 2009 H1N1 pandemic influenza in a population of Dutch children with influenza-like signs and symptoms. *Acta Paediatr* 2012; **101:** 67–72.

55 Mistry RD, Fischer JB, Prasad PA, Coffin SE, Alpern ER. Severe complications in influenza-like illnesses. *Pediatrics* 2014; **134:** e684–90.

56 Burton C, Vaudry W, Moore D, et al. Burden of seasonal influenza in children with neurodevelopmental conditions. *Pediatr Infect Dis J* 2014; **33:** 710–14.

57 Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med* 2013; **10:** e1001380.

58 Louie JK, Acosta M, Samuel MC, et al. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). *Clin Infect Dis* 2011; **52:** 301–12.

59 Dharan NJ, Sokolow LZ, Cheng PY, et al. Child, household, and caregiver characteristics associated with hospitalization for influenza among children 6–59 months of gge: an Emerging Infections Program study. *Pediatr Infect Dis J* 2014; **33:** e141–50.

60 Chen K-F, Hsieh Y-H, Gaydos CA, Valsamakis A, Rothman RE. Derivation of a clinical prediction rule to predict hospitalization for influenza in EDs. *Am J Emerg Med* 2013; **31:** 529–34.

61 Beck S, Wojdyla D, Say L, et al. The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ* 2010; **88:** 31–38.

62 Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA* 2011; **306:** 1233–40.

63 WHO. Department of Communicable Disease Surveillance and Response, Global Influenza Programme. WHO global influenza preparedness plan–the role of WHO and recommendations for national measures before and during pandemics. 2005. http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf (accessed Oct 13, 2014).

64 UK Department of Health. UK Influenza Pandemic Preparedness Strategy 2011. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213717/dh_131040.pdf (accessed Oct 13, 2014).

65 Public Health England. Influenza vaccine uptake amongst GP patient groups in England, winter season 2012/13. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/207134/Influenza_vaccine_uptake_amongst_GP_patient_groups_in_England_for_winter_season_2012_2013.pdf (accessed Oct 13, 2014).

66 Rodgers L, Grohskpf L, Pabst LJ, Harris L, Chaves SS. Uptake of live attenuated influenza vaccine among children in selected populations of the United States, 2008–2012. https://cste.confex.com/cste/2013/webprogram/Paper2149.html (accessed Sept 17, 2014).

67 Lu PJ, Santibanez TA, Williams WW, et al. Surveillance of influenza vaccination coverage–United States, 2007–08 through 2011–12 influenza seasons. *MMWR Surveill Summ* 2013; **62:** 1–28.

68 Pebody RG, Green HK, Andrews N, et al. Uptake and impact of a new live attenuated influenza vaccine programme in England: early results of a pilot in primary school-age children, 2013/14 influenza season. *Euro Surveill* 2014; **19:** 20823.

69 Civil Contingencies Secretariat, UK Cabinet Office. Overarching government strategy to respond to an influenza pandemic–analysis of the scientific evidence base. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/61968/flu_pandemic_science_paper1.pdf (accessed Oct 13, 2014).

70 Lim WS. Pandemic flu: clinical management of patients with an influenza-like illness during an influenza pandemic. *Thorax* 2007; **62:** 1–46.