

Children at risk of influenza-related complications in primary and ambulatory care: a systematic review of published and unpublished data

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Abstract

Background

Interventions to prevent influenza-related complications are recommended in individuals considered to be at greatest risk of serious clinical deterioration. However, current guidelines are based on consensus opinion rather than evidence, and do not specify risk factors in children. This systematic review provides an evidence-based definition of 'at risk' in children.

Methods

We searched MEDLINE and MEDLINE In Process, EMBASE, Science Citation Index, and CINAHL until 3rd April 2013. We included studies which reported data on underlying conditions and complications in children presenting in primary/ambulatory care with influenza/influenza-like illness. We requested unpublished data from authors of studies which had collected, but not published, relevant data. We analysed data by univariable meta-analysis and individual patient data (IPD) multivariable meta-analysis.

Findings

We included 28 articles which reported data from 27 studies (n=14,086 children). Strong risk factors for hospitalisation were neurological conditions (univariable Odds Ratio [OR] 4.62, 95% confidence interval 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 mellitus (2.34, 1.20-4.58), and age under 2 years (2.34, 1.62-3.37). However, asthma (1.36, 0.82-2.26) and obesity (0.99, 0.61-1.62) were not found to be risk factors. Based on IPD multivariable analysis (n=1612 children, 4 studies), risk of hospitalisation was significantly higher in children with multiple versus single risk factors when age under 2 years was included as a risk factor (92/124, 74% versus 428/817, 52%; difference 22%, 13%-30%, p<0.0001).

Interpretation

This systematic review identifies prematurity as a new strong risk factor for influenza-related complications in children, and supports the inclusion of neurological conditions, sickle cell disease, immunosuppression, diabetes mellitus, and age under 2 years in existing guidelines. Interventions to prevent influenza-related complications should be prioritised in these groups, but should also be considered in other children, especially those with multiple or severe co-morbidities.

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Introduction

Influenza in children is a major source of burden on health care resources, particularly during epidemics and pandemics.^{1, 2} Around one-quarter of otherwise healthy children who develop influenza or influenza-like illness (ILI) experience further complications³ including pneumonia, otitis media, neurological complications and death.¹

‘At risk’ children with underlying medical conditions are considered to be at even greater risk of influenza-related complications.⁴ Around 20% of children who consult with influenza/ILI have one or more medical conditions⁵ and the presence of co-morbidities is reported to increase influenza-related hospital admission rates almost sixfold in children aged 5 to 14 years (0.1 to 0.56 per 1000).⁶ Once hospitalised, ‘at risk’ patients are also at greater risk of further complications.⁷

The UK Department of Health⁸ and the WHO Strategic Advisory Group of Experts on Immunization⁹ recommend influenza vaccination in certain groups considered to be at high risk of serious complications. The US Advisory Committee on Immunization Practices recommends that all individuals aged 6 months and over 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 specifically in children.^{12, 13}

An understanding of risk factors in children is important, given the different co-morbidity 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 vital, since 35% of influenza-related deaths in children are reported to occur before hospitalisation based on data from the United States.¹⁴ We provide an evidence-based definition of which children presenting with influenza/ILI in primary or ambulatory care are ‘at risk’ of influenza-related complications by performing a systematic review of published and unpublished data.

Methods

Search strategy

We 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 3rd April 2013. Appendix 1 presents our search strategy, which combined subject headings with free text search terms encompassing both established risk categories defined by the UK Department of Health,⁸ US Advisory Committee on Immunization Practices (ACIP),¹¹ and WHO,⁹ and more recently identified candidate risk factors (*e.g.* obesity and coeliac disease).^{15, 16} We used a validated child filter¹⁷ and did not apply any language restrictions to our search. The electronic search was supplemented by reviewing reference lists of included articles, relevant reviews and guidelines, snowballing, and using the PubMed ‘Related articles’ function.

We requested unpublished data from the authors of studies which we understood to have collected, but not published, data relevant for this review. We contacted authors by e-mail,

and sent up to two e-mail reminders after one and three months to authors who did not respond. We asked content experts to review our list of included articles for any obvious omissions.

Study selection

We included cohort and case-control studies based in primary or ambulatory care settings which included children up to 18 years of age with influenza (confirmed by laboratory or near patient testing) or influenza-like illness (based on clinical features), and reported data on risk factors for hospitalisation and/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 from which sufficient published and/or unpublished data were available to construct 2x2 tables on the presence or absence of risk factors in relation to the complication of interest. We excluded studies where all patients were hospitalised.

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

Risk of bias and quality assessment

We developed a standardised risk of bias form informed by 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 models²¹ and was piloted by two researchers (PG and HA) who then completed assessments independently. Any disagreements were resolved by discussion and/or adjudication with a third author (KW, CH, or SM). Appendix 2 describes the coding criteria used for each domain.

Data Extraction

We developed a standardised data extraction form that was piloted by two reviewers (PG and HA) 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/exclusion criteria, participant characteristics, type of influenza strain, method of influenza diagnosis, definition of influenza-like illness, complications, and duration of follow-up. Detailed information was extracted on unadjusted and adjusted regression coefficients, and information related to the prognostic model.

Due to differences in the terminology and level of detail used to describe co-morbidities in different studies, one author (PG) grouped these terms into the following types of conditions in consultation with two practising primary care clinicians (HA and KW): respiratory, neurological, metabolic, cardiac, prematurity, immunosuppression, haematological, cancer, renal, obesity, and congenital/structural disorders (*e.g.* Down's syndrome). We extracted data on hospitalisations for these conditions as well as for three age categories: under 2 years, 2 to 5 years, and >5 to 18 years. Where possible, we also extracted data on asthma, cystic fibrosis, bronchopulmonary dysplasia, diabetes mellitus, and sickle cell disease.

Data analysis

Medical conditions extracted consisted of those shown in figure 2. All conditions apart from age were categorised as present or absent. Age was categorised as three risk groups: 0 to <2

years (one of 16 studies included children aged 2 years²²), 2 to 5 years (except one study not including children aged 2 years²² and four studies not including children aged 5 years²³⁻²⁶), and >5 to 18 years. Individual patient data (IPD) analysis included fixed effects of medical conditions for immunological conditions, neurological conditions, prematurity, respiratory, cardiac, renal, and metabolic conditions, and all three age categories. Immunological conditions included immunosuppression, haematological conditions, sickle cell disease, and cancer.

The following subgroups by study were specified *a priori*: a) clinical versus laboratory-confirmed influenza; b) seasonal versus pandemic influenza, and c) length of follow-up (<9 days, 9-30 days, >30 days) with post hoc subgroups for low risk of bias due to d) patient selection and e) influenza diagnosis.

We used meta-analysis of binary outcome hospitalisation data from IPD and univariable study estimates using mixed multilevel subject-specific (conditional) analysis, fitted by adaptive Gaussian quadrature using 10 integration points or 2 if required for model convergence (xtmelogit, STATA 11.2, StataCorp LP, Texas, USA). We used stratified one-stage models, ensuring correct clustering of patients within studies by using separate intercepts for each study.^{27, 28} The binary one-step approach using the exact binomial distribution is preferred over other meta-analysis methods (DerSimonian and Laird, Mantel Haenszel, Peto's Odd ratio), as in these data, the event rate is low with many instances of zero cells (which would require continuity correction when other methods are used) and, since patients with a specific medical condition are only a small proportion of patients in each study, comparison arms are highly unequal.²⁷⁻³¹ Univariable meta-analysis of hospitalisation outcomes was completed where there were more than three studies for each condition or subgroup. In IPD data, multivariable models were fitted to data where more than one condition was included per patient, including age and one or more co-morbid medical conditions enabling analysis of potential confounding between conditions and/or age. Data on deaths and intensive care unit admissions were pooled as a single study for each condition, as these are rare events.

Role of the funding source

The funding sources had no role in study design, data collection, analysis or interpretation, report writing, or submission for publication. PG, SM, HA, 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. Ethics approval was not required for this study.

Results

Search results

We identified 10,360 records of 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 which 3086 (22%) had an underlying condition (*i.e.* co-morbidity not including age under 2 years). There was a ten-fold variation in hospitalisation rate (6% to 65%) and the prevalence of co-morbidities ranged from 3% to 82%. Most studies included patients with pandemic influenza (20 of 27 studies). Only one study included patients with Influenza C.³² The majority were retrospective cohort studies (n=17) and two were case-control studies.^{33, 34}

Appendix 3 summarises our risk of bias assessment of included studies. Satisfactory methods of diagnosing influenza were reported in 20 studies. Methods of patient selection and

definition of outcome were satisfactory in only 13 and 10 studies respectively. Definitions of underlying conditions were consistent within studies, but varied between studies. Among 12 studies which considered immunosuppression as a potential risk factor, seven defined cancer,³⁵ haematological conditions,^{22, 24, 25, 36} or sickle cell disease^{37, 38} as additional separate conditions. Four studies did not consider these conditions separately from immunosuppression.^{33, 39-41} In one study, we defined children as having immunosuppression if they were reported as having congenital or acquired immunodeficiency, idiopathic thrombocytopenic purpura or a previous splenectomy.⁴² One study combined cancer with aplastic anaemia.⁴³

Hospitalisation

Figure 2 presents meta-analysis of univariable results for hospitalisation across studies according to underlying conditions and age categories. Group 1 shows results for conditions where stronger evidence was available, *i.e.* larger number of hospitalisation events in children with specific conditions and lower variability between studies.

Strong risk factors for hospitalisation were neurological conditions (Odds Ratio [OR] 4.62, 95% confidence interval [CI] 2.82 to 7.55), prematurity (OR 4.33, 95% CI 2.47 to 7.58), sickle cell disease (OR 3.46, 95% CI 1.63 to 7.37), immunosuppression (OR 2.39, 95% CI 1.24 to 4.61), diabetes mellitus (OR 2.34, 95% CI 1.20 to 4.58), and age under 2 years (OR 2.34, 95% CI 1.62 to 3.37).

Reactive airways disease including asthma (RAD), respiratory conditions (including RAD), obesity, and older age groups (*i.e.* age 2 to 5 years and age >5 to 18 years) were not found to be risk factors. In this analysis cancer and cardiac conditions had ORs with fairly narrow 95% CIs and were not shown to be significantly associated with hospitalisation; however, inclusion of future studies may alter this result.

Appendix 4 presents Forest plots and details of individual study results for each condition allowing visualisation of heterogeneity between studies. Insufficient evidence was available to assess the risk of hospitalisation for haematological and metabolic conditions (excluding diabetes mellitus) due to the small numbers of hospitalisations among children with these conditions and heterogeneity between studies (Figure 2, Appendix 4). There was also insufficient evidence to assess the risk of hospitalisation associated with congenital disorders (including Down's syndrome), bronchopulmonary dysplasia, epilepsy, cystic fibrosis, and renal conditions.

Individual patient data (IPD) analyses

IPD meta-analysis was conducted for four studies whose authors provided individual patient data (1612 children, 677 hospitalisations).^{24, 35, 41, 44} Neurological conditions, immunological conditions, prematurity and age under 2 years were found to be independent risk factors for hospitalisation, whereas cardiac and respiratory conditions were not (Appendix 5). Obesity could not be included in this model as there were only five children with this condition in this IPD dataset. Additionally, multivariable analysis of IPD from two individual studies showed increased risk of hospitalisation associated with immunological conditions,^{35, 44} neurological conditions,^{35, 44} prematurity,³⁵ and age under 2 years.⁴⁴

Forty-eight percent (186/391) of children with one type of medical condition were hospitalised compared to 74% (29/39) of children with more than one type of condition (significant difference 27%; 95% CI 12% to 41%, $p=0.001$). Around half of children with

more than one type of condition (20/39, 51%) were reported as having been born prematurely (not including age under 2 years as a 'risk condition'). When age under 2 years was also included as a risk condition, the percentage of children hospitalised increased from 52% (428/817) in children with one condition to 74% (92/124) in children with more than one condition, a significant difference (22%; 95% CI 13% to 30%, $p<0.0001$).

Subgroup analysis

We undertook subgroup analyses of studies with pandemic influenza, seasonal influenza, and laboratory-confirmed influenza. Results were generally consistent with our main meta-analysis of univariable results (Figure 2) in terms of which conditions were significantly associated with hospitalisation. There were two exceptions in the seasonal influenza subgroup, which were inconsistent with both the univariable analysis of all studies (Figure 2) and the IPD analysis which adjusted for concurrent medical conditions (Appendix 5). Firstly, the presence of a cardiac condition (subgroup of 4 out of 17 studies) was significantly associated with hospitalisation, but IPD analysis of these same four studies did not show a significant association (Appendix 5). Secondly, age under 2 years (subgroup of 5 out of 14 studies) was not significantly associated with hospitalisation, in contrast to the IPD analysis which included three of these five studies. This inconsistent subgroup result was due to the study by Bender et al²⁶ (Appendix 4), which was not available for IPD analysis. Analysis by length of follow-up was not possible because only two studies specified follow-up periods^{22, 38} and in one of these studies²² it was unclear whether the follow-up period specified related to hospitalised children only.

Sensitivity analysis

We undertook sensitivity analyses in studies with low risk of bias for patient selection and for influenza diagnosis. Results were also generally consistent with our main meta-analysis of univariable results apart from two exceptions. In cardiac conditions, there was a statistically significant association in the subgroup with low risk of bias for patient selection (9 of 17 studies). This was not seen in the main meta-analysis, but as mentioned previously, addition of future studies might change this result. Age under 2 years was not significantly associated with hospitalisation in the subgroup with low bias for influenza diagnosis (7 of 14 studies), but again, this inconsistent result was due to the study by Bender et al²⁶ (Appendix 4).

Deaths and Intensive Care Unit (ICU) admissions

Nine studies provided data on deaths according to absence or presence of co-morbidities. There were 26 deaths of which 15 were in children with co-morbidities.^{25, 35, 38, 40, 41, 44-47} Of the 13 studies which reported data on ICU admissions (110 admissions), eight studies reported these in relation to presence of co-morbidities (51 ICU admissions including 31 in 717 children with co-morbidities).^{22, 23, 38, 40, 41, 43, 47, 48} Due to the small numbers of deaths and ICU admissions for each co-morbidity, results are summarised as numbers and percentages (Appendix 6).

Discussion

Summary of main findings

We found that prematurity was a strong risk factor for hospitalisation in children presenting with influenza/ILI in primary or ambulatory care. However, prematurity is not currently defined as an 'at risk' condition in any existing guidelines. Our findings also demonstrate that neurological conditions, sickle cell disease, immunosuppression, diabetes mellitus, and age under 2 years are strong risk factors and support their inclusion in existing guidelines. The presence of multiple co-existing conditions significantly increases the risk of hospitalisation

from 52% (one condition only) to 74% (multiple conditions) when age under 2 years is included as a 'risk condition'.

Comparison with existing guidelines and literature

Table 2 compares the risk factors identified in this review with those outlined by the UK Department of Health,⁸ US Advisory Committee on Immunization Practices (ACIP),¹¹ and World Health Organization (WHO).⁹ We show that prematurity is a strong independent risk factor for hospitalisation in children presenting in primary or ambulatory care with influenza/ILI. However, prematurity is not specified as a risk factor in any of these guidelines. Data were not reported in sufficient detail to assess the association between extent of prematurity and risk of hospitalisation. We also found that age under 2 years and sickle cell disease were risk factors for hospitalisation, but these are currently only included in the ACIP and WHO definitions.^{9, 11}

Our findings support the inclusion of neurological conditions, immunosuppression, and diabetes mellitus in all three guidelines. Among paediatric influenza-related deaths reported in the US between October 2004 and September 2012, 33% of children whose medical histories were known had neurological conditions.¹⁴ A recent prospective cohort study also found that the presence of neurological or neuromuscular conditions 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 ILI.⁴⁹ Children with neurological conditions which do not obviously compromise handling of respiratory secretions have been proposed as an 'at risk' group due to the high burden of influenza observed in these children.⁵⁰ However, this recommendation was based only on data collected from children who had already been hospitalised. Data available for this review were not reported in sufficient detail to separately assess risk of hospitalisation associated with neurological conditions which did or did not compromise handling of respiratory secretions.

A recent systematic review of published studies by Mertz et al.¹³ investigated risk factors for all-cause hospitalisation in children and adults with influenza/ILI. However, although this review included 234 studies, the number of studies assessed for each medical condition was small: for example, four studies for asthma compared to 22 in our review and three studies for age under 2 years compared to 15 in our review. Furthermore, the review by Mertz et al. did not consider any risk factors in children other than age. Our review included a more up to date search (until April 2013 versus 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.⁵¹

Mertz et al. identified obesity as a risk factor for influenza-related complications.¹³ However, we did not find obesity to be a risk factor in children. Although obesity has been reported as a risk factor for influenza-related hospitalisation and death,^{2, 15, 52} this finding is only based on data from adults, in whom obesity is associated with more advanced co-morbidity than in children. Mertz et al. also identified cardiac, respiratory and renal conditions as risk factors based on data including adult populations. Neither our univariable analysis nor our IPD meta-analysis showed cardiac or respiratory conditions to significantly increase risk of hospitalisation in children. However, for cardiac conditions inclusion of future studies may alter this result. We were unable to determine whether the presence of renal conditions was a risk factor for influenza-related hospitalisation in children due to the low number of hospitalisation events among children with these conditions.

The increased risk of hospitalisation associated with multiple versus single medical conditions, which we demonstrated in our study, is consistent with the findings of a case-control study conducted in the United States involving children with laboratory-confirmed influenza.⁵³ In contrast to our findings, the same study also found that haematological and respiratory conditions were associated with increased risk of hospitalisation. This may have been due to inclusion of a narrower and more severe spectrum of illness in children with these conditions. Data relating to the severity of underlying conditions were not reported in studies included in our review.

Strengths and limitations

Strengths of our study include our specific focus on children, extensive search and use of univariable and IPD 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.⁵¹

We used three approaches to analyse the data: univariable meta-analysis of data from all studies, IPD multivariable meta-analysis, and within-study multivariable analysis of IPD data. The IPD methods allowed us to assess the independent strength of medical conditions with hospitalisation without confounding with age and other co-existing conditions. The agreement between the three analysis approaches, as well as subgroup and sensitivity meta-analyses, support the risk conditions identified. We did not have access to data to allow adjustment for other potential confounders, such as vaccination and severity of underlying medical conditions.

The time taken to complete this systematic review reflects the time required to contact authors, obtain unpublished data, resolve data queries, clean, analyse, and interpret the data. To determine whether any studies which might have influenced our findings had been published since we completed our search, we performed an updated search on 9th October 2014. This search retrieved an additional 1680 articles (3445 articles minus 1765 duplicates), which were independently reviewed by two authors (PG and KW). Only two of these studies might have been suitable for inclusion in our meta-analysis if unpublished data were available.^{54, 55} However, even if these data had been available, it is unlikely they would have affected our findings. One study⁵⁴ included 146 children and adults with laboratory-confirmed influenza, of whom only 22 had chronic lung disease and 18 were immunocompromised. There were 56 hospitalisation events in total. Inclusion of data from children only would have reduced the numbers with underlying conditions and hospitalisation events. The other study⁵⁵ reported data only on severe complications (including pneumonia, seizures and death) among children aged 0 to 19 years who presented in a hospital emergency department with influenza/ILI. However, it was unclear whether all patients were hospitalised, in which case this study would not have been eligible for inclusion. The majority of included studies were conducted in hospital ambulatory care or emergency department settings, which served as the closest approximation to primary care, although this may limit generalisability of our findings to primary care. Definitions and details of risk factor categories 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 conditions. Only two studies defined prematurity in terms of gestational age: less than 36 weeks in one study (since last menstrual period)⁴⁸ and less than 37 weeks in the other (method of establishing gestational age not specified).⁴⁴ In our IPD analysis, only 11 out 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 among children in this age group.

Although influenza is usually diagnosed based on clinical features in primary care settings, only four studies diagnosed influenza clinically.^{34, 39, 40, 56} Retrospective cohort studies which recruited children with laboratory-confirmed influenza may have preferentially performed laboratory testing in children with underlying conditions and/or with more severe symptoms of influenza/ILI. 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 conducted in an emergency department, presented a model for predicting hospitalisation which incorporated both clinical features and underlying conditions.²⁶ This highlights the need for more research to be conducted in this area, particularly in primary care settings. More research is also needed to help clinicians identify risk factors for influenza-related clinical deterioration and complications in the community, which can also be a source of considerable burden on healthcare resources.

Although there was a greater than tenfold variation in overall hospitalisation rates among different study populations (6 to 65%), our results did not show any obvious relationship between ORs for hospitalisation in relation to individual conditions and overall hospitalisation rates (Appendix 4). Since thresholds for hospital admission are likely to vary between different health care settings, ICU admissions and death are more robust indicators of clinical deterioration than hospitalisation. However, these are rare outcomes and there were insufficient data for meta-analysis.

Implications for influenza preparedness planning

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 was identified as a new strong risk factor in children. This has important implications for current definitions of ‘at risk’ groups, which do not include children born prematurely. Rates of preterm delivery before 37 weeks gestation are reported to range from 6.2% in Europe to 10.6% in North America and 11.9% in Africa.⁵⁷ Other risk factors in children, which are already defined in existing guidelines, were neurological conditions, sickle cell disease, immunosuppression, diabetes mellitus, and age under 2 years.

The impact of prematurity on risk of influenza-related complications still needs to be established in children of different ages and born after varying gestational periods. However, a national cohort study conducted in Sweden has already demonstrated that preterm birth before 37 weeks is associated with increased mortality during early childhood (age 1 to 5 years) and young adulthood (18 to 36 years), even among individuals born late preterm (34 to 36 weeks).⁵⁸ 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 given the inclusive nature of current childhood influenza vaccination policies, inclusion of preterm birth before 37 weeks as a risk factor in children of any age should be considered until further data to inform more precise targeting become available.

Identification of 'at risk' groups is a key cornerstone of strategies to plan for and respond to seasonal influenza epidemics and influenza pandemics.^{59, 60} The UK Department of Health⁸ and WHO⁹ guidelines recommend that annual seasonal influenza vaccination should be targeted specifically towards 'at risk' groups. However, in the UK, vaccination uptake among 'at risk' children was limited during the 2012/13 influenza season, with the highest uptake rate among children with diabetes mellitus (44.3% in children aged 6 months to under 2 years; 61.6% in children aged 2 years to under 16 years) and the lowest uptake rate among children with chronic neurological disease (18.6% in children aged 6 months to under 2 years) and chronic cardiac disease (27.2% in children aged 2 years to under 16 years).⁶¹ Several countries recommend universal vaccination of all children but uptake rates are still low. In the United States, influenza vaccine uptake during the 2011/12 season ranged from 24.9% among children aged 13 to 18 years⁶² to 44.3% in children aged 6 to 23 months.⁶³ During a pilot childhood influenza vaccination scheme in England during winter 2013/14, vaccine uptake was 52.5% overall, and a significant decline in uptake was observed with increasing age (56.1% in children aged 4 to 5 years, 49.7% in children aged 10 to 11 years).⁶⁴ Therefore, in order to implement national vaccination programmes with maximum efficiency, strategies to increase seasonal vaccine uptake should specifically target the 'at risk' groups which our study has identified.

During influenza pandemics, more widespread use of antiviral medications may occur, since it may take some time to develop and establish supplies of a suitable vaccine. Pre-pandemic vaccination of all children in addition to 'at risk' adults is considered to be prudent policy. However, this has considerable logistical implications, as it would involve vaccinating around 40% of the UK population.⁶⁵ Furthermore, antiviral medication supplies may be rapidly depleted due to 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 in 'at risk' groups.

Although consideration of 'at risk' conditions is already recommended in the clinical management of children presenting with influenza/ILI,⁶⁶ estimation of the level of risk associated with different conditions still relies upon the subjective judgement of individual clinicians. Our findings help inform more accurate and consistent clinical assessment of the relative importance of different 'at risk' conditions by quantifying the degree of risk associated with these conditions and demonstrating the significant increase in risk among individuals with multiple risk factors. This will in turn facilitate more efficient clinical triage systems and more prudent use of health care resources among children presenting in primary and ambulatory care settings with influenza/ILI.

Although current guidelines list obesity and asthma as 'at risk' groups, we did not find these to be risk factors in children. However, our review may not have shown certain conditions to be significantly associated with hospitalisation due to averaging across a wide spectrum of disease severity or lack of statistical power when conditions are rare.

Interventions to reduce the risk of influenza-related complications should therefore still be considered in children with other conditions, particularly in the presence of multiple or severe co-morbidities. To guide appropriate targeting of interventions to prevent influenza-related complications in children, our findings should be used to update current definitions of patients considered to be 'at risk' of such complications and to specifically define 'at risk' groups in children.

Figure 1: PRISMA flowchart of included studies

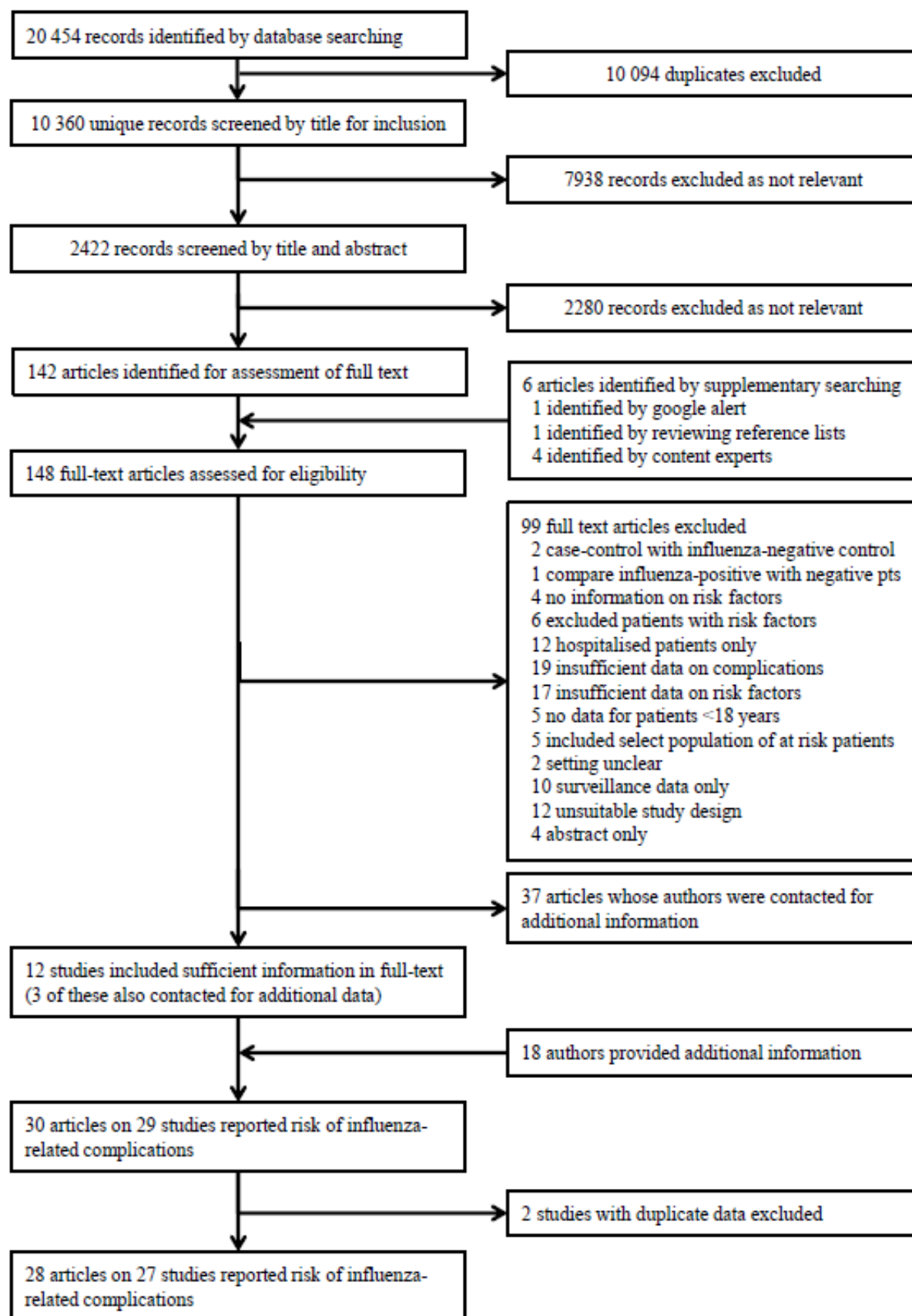


Table 1: Characteristics of 27 included studies

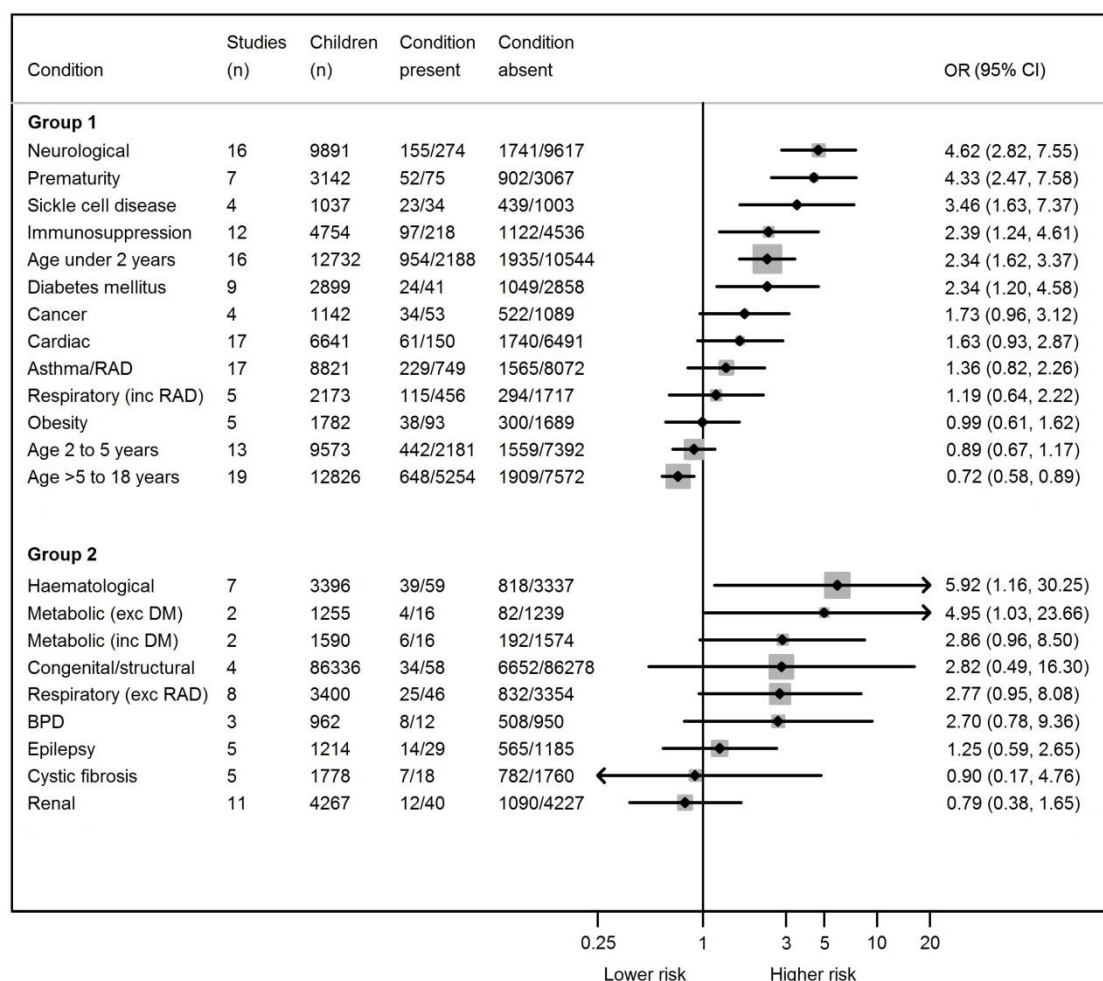
Study	Country	Ambulatory setting *	Study type	Type of influenza	Dates of recruitment	Age range of children, years	Total number of children	Total number of children with risk factors	Total number of children admitted to hospital
Aguirre et al ²²	Canada	ED of paediatric hospital	RDR	Both**	2006-2009	0-17	127	62 (49%)	43 (34%)
Bailhache et al ⁴⁸	France	paediatric hospital, regional hospitals	RDR	Pandemic	2009-2010	0-0.5	74	16 (22%)	48 (65%)
Bender et al ²⁶	US	ED of paediatric hospital	RDR	Seasonal	2001-2004	0-18	1230	241 (20%)	541 (44%)
Bogie et al ⁶⁷	US	paediatric hospital	RDR	Both	2009	0-18	287	185 (65%)	128 (45%)
Carcione et al ^{24, 68}	Australia	NS	RDR; Q	Both	2009	0-18	436 †	119 (27%)	39 (9%)
Crisinel et al ³⁷	Switzerland	paediatric hospital	POS	Pandemic	2009-2010	0-18	75	32 (43%)	12 (16%)
De Marco et al ³⁹	Italy	paediatric hospital	POS	Seasonal	2001-2003	0-16	351	47 (13%)	92 (26%)
Desmoulins et al ³⁸	France	ED, university and paediatric hospitals	POS	Pandemic	2009	0-17	466	208 (45%)	192 (41%)
Dubnov-Raz et al ⁴³	Israel	paediatric hospital	RDR	Pandemic	2009	1-17	73	39 (53%)	37 (51%)
Gastanaduy et al ²⁵	US	paediatric hospital	RDR	Pandemic	2009-2010	0-16	1463	411 (28%)	155 (11%)
Goodacre et al ⁴⁰	England	ED	POS	Pandemic	2009-2010	0-16	347	44 (13%)	39 (11%)
Hite et al ³⁵	US	paediatric hospital	RDR	Seasonal	2002-2003	0-18	205	99 (48%)	79 (39%)
Launes et al ³³	Spain	public NHS centres	CCS	Pandemic	2009-2010	0.5-18	379	147 (39%)	195 (52%)

Lee CY et al ⁴⁵	Taiwan	NS	RDR	Pandemic	2009	0-15	819	76 (9%)	47 (6%)
Lee MC et al ²³	Korea	NS	RDR	Pandemic	2009-2010	0-18	3777	219 (6%)	221 (6%)
Lenzi et al ⁴⁶	Brazil	NS	RDR	Pandemic	2009	0-12	1307	239 (18%)	475 (36%) ‡
Lera et al ³⁶	Spain	ED of paediatric hospital	POS	Pandemic	2009	0-19	412	336 (82%)	85 (21%)
Matsuzaki et al ³²	Japan	paediatric clinics, hospital	RDR	Influenza C	1990-2004	0-15	170	5 (3%)	29 (17%)
Na et al ⁶⁹	Korea	medical centre converted to primary care centre	POS	Pandemic	2009	0-14	240	19 (8%)	¶
Peltola et al ⁴⁴	Finland	paediatric hospital (inpatients and outpatients)	RDR	Seasonal	1980-1999	0-19	683	167 (25%)	389 (57%)
Perez-Padilla et al ⁸³⁴	Mexico	multiple settings	CCS	Pandemic	2009	0-18	-	35 (-)	-
Plessa et al ⁷⁰	Greece	paediatric department of hospital	POS; RDR	Pandemic	2009-2010	0-13	51	16 (31%)	15 (30%)
Quach et al ⁴¹	Canada	ED of paediatric hospital	RDR	Seasonal	1999-2002	0-19	294	84 (29%)	180 (61%)
Rabasco et al ⁴²	Spain	NS	RDR	Pandemic	2009-2010	0-18	202	119 (59%)	109 (54%)
Rodriguez-Valero et al ⁷¹	Mexico	ED	RDR	Pandemic	2009	0-18	118	31 (26%)	35 (30%)
Sessa et al ⁵⁶	Italy	general practice	POS	Seasonal	1998-1999	10-14	368	42 (11%)	¶
Smit et al ⁴⁷	Netherlands	ED, outpatient influenza clinic	POS	Pandemic	2009	0-16	132	48 (36%)	22 (17%)
Totals					1980-2010	0-19	14 086	3086 (22%)	Mean, 32%

Data are number (%). RDR, retrospective database review; POS, prospective observational study; CCS, case-control study; Q, questionnaire; ED, emergency department; NHS, national health service; NS, not specified.

* Where hospital setting specified (e.g. outpatient clinic, emergency department), study only included ambulatory care patients. Where exact hospital setting not specified (e.g. paediatric hospital) and where overall setting not specified (NS), the description provided in the study was consistent with ambulatory care, and the authors were satisfied that the setting met inclusion criteria for the systematic review.** Study included seasonal and pandemic influenza but only pandemic data available. † Data were unavailable to determine if patients had multiple co-morbidities; total provided assumes patients do not. ‡ No data on individual co-morbidities for hospitalised patients. ¶ Study did not collect data on hospitalisation. § Case-control study which only included patients with Down's syndrome. - Data only reported for total population including adults.

Figure 2: Meta-analysis of univariable results for hospitalisation



RAD = Reactive airways disease; DM = Diabetes mellitus; BPD = Bronchopulmonary dysplasia; inc = including; exc = excluding.

Condition present: number of children with condition hospitalised/total number of children with condition;
Condition absent: number of children without condition hospitalised/total number of children without condition.
Odds ratio greater than 1 indicates increased risk of hospitalisation.

Group 1: Conditions for which data were sufficient to assess associated risk of hospitalisation.

Group 2: Conditions for which there was a high degree of heterogeneity between different studies (haematological conditions, respiratory conditions excluding reactive airways disease, congenital/structural disorders) or a low number of hospitalisations among children with the condition (bronchopulmonary dysplasia, metabolic conditions including diabetes mellitus, metabolic conditions excluding diabetes mellitus, cystic fibrosis, epilepsy, renal conditions).

Notes on age categories:

Age under 2 years: One study included in this category included children aged 2 years (Aguirre 2011).

Age 2 to 5 years: One study did not include children aged 2 years (Aguirre 2011) and four studies did not include children aged 5 years (Lee MC 2012, Carcione 2010, Gastanaduy 2012, Bender 2009).^{23-26 23-26}

Table 2: Summary of study findings versus current definitions of ‘at risk’

Condition	Green Book, UK ⁸	Advisory Committee on Immunization Practices, US ¹¹	World Health Organisation ⁹	Findings of present study
Neurological	✓	✓	✓	✓
Diabetes mellitus	✓	✓	✓	✓
Immunosuppression	✓	✓	✓	✓
Sickle cell disease	✗	✓	✓	✓
Age <2 years	✗	✓	✓	✓
Haematological	✗	✓	✓	(✓)
Prematurity	✗	✗	✗	✓
Asthma/RAD	✓	✓	✓	✗ [§]
Cardiac	✓	✓	✓	(?)
Obesity	✗	✓ [†]	✓ [†]	✗
Respiratory (excluding RAD)	✓	✓	✓	(✗)
Renal	✓	✓	✓	(✗)
Metabolic (including DM)	✓	✓	✓	(✗)
Liver	✓	✓	✓	*

DM, diabetes mellitus; RAD, reactive airway disease

✓ Condition included in ‘at risk’ definition.

✗ Condition not included in ‘at risk’ definition. ? Data from future studies may alter this result.

() Conditions for which data were insufficient to draw firm conclusions.

[§] Data include range of asthma severity. Insufficient data on severe asthma.

[†] Morbid obesity (Body Mass Index 40 or higher).

* No data available on risk of hospitalisation in children.

Contributors

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

Conflicts of interest

We declare that we have no conflicts of interest.

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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**(9807): 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**(7): 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**(10): 1091-8.
4. Loughlin J, Poullos 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**(4): 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, Jit 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**(4): 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**(8): 709-17.

8. Department of Health. Influenza: Chapter 19. 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.
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**: 691-7.
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): 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**(2): 261-8.
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**(3): 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**(11): 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**(2): 111-6.
18. Wolff R, Whiting PF, Mallett S, et al. Prediction study risk of bias assessment tool (PROBAST). 21st Cochrane Colloquium. Quebec City Canada; 2013 (conference proceeding).
19. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine* 2011; **155**(8): 529-36.
20. Hayden JA, van der Windt DA, Cartwright JL, Cote P, Bombardier C. Assessing bias in studies of prognostic factors. *Annals of internal medicine* 2013; **158**(4): 280-6.
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. Aguirre E, Papenburg J, Ouakki M, et al. Comparison of pandemic and seasonal influenza in the pediatric emergency department. *Pediatric Infectious Disease Journal* 2011; **30** (8): 633-9.
23. 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**(6): 493-500.
24. Carcione D, Giele C, Dowse GK, et al. Comparison of pandemic (H1N1) 2009 and seasonal influenza, Western Australia, 2009. *Emerging Infectious Diseases* 2010; **16**(9): 1388-95.
25. Gastanaduy AS, Begue RE. Experience with pandemic 2009 H1N1 influenza in a large pediatric hospital. *South Med J* 2012; **105**(4): 192-8.

26. Bender JM, Ampofo K, Gesteland P, et al. Development and validation of a risk score for predicting hospitalization in children with influenza virus infection. *Pediatric Emergency Care* 2009; **25**(6): 369-75.
27. Abo-Zaid G, Guo B, Deeks JJ, et al. Individual participant data meta-analyses should not ignore clustering. *J Clin Epidemiol* 2013; **66**(8): 865-73 e4.
28. 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**(4): e60650.
29. 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**(1): 53-77.
30. Greenland S, Salvan A. Bias in the one-step method for pooling study results. *Stat Med* 1990; **9**(3): 247-52.
31. 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**(9): 1351-75.
32. Matsuzaki Y, Katsushima N, Nagai Y, et al. Clinical features of influenza C virus infection in children. *J Infect Dis* 2006; **193**(9): 1229-35.
33. 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**(7): 1127-31.
34. Perez-Padilla R, Fernandez R, Garcia-Sancho C, et al. Pandemic (H1N1) 2009 virus and Down syndrome patients. *Emerg Infect Dis* 2010; **16**(8): 1312-4.
35. 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**(1): 40-7.
36. 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**(3): 371-8.
37. 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**(1): 159-66.
38. 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**(5): 505-11.
39. De Marco G, Mangani S, Correria 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**(4).
40. 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**(46): 173-236.
41. 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**(3 Pt 1): e197-201.
42. 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]. *Pediatría Catalana* 2011; **71**(3): 91-5.
43. 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**(4): 426-30.
44. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. *Clin Infect Dis* 2003; **36**(3): 299-305.

45. 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**(4): 257-63.
46. 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.
47. 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**(1): 67-72.
48. 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**(4): 383-9.
49. Mistry RD, Fischer JB, Prasad PA, Coffin SE, Alpern ER. Severe Complications in Influenza-like Illnesses. *Pediatrics* 2014; **134**: 1-7.
50. 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.
51. Riley RD, Hayden JA, Steyerberg EW, et al. Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med* 2013; **10**(2): e1001380.
52. 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**(3): 301-12.
53. Dharan NJ, Sokolow LZ, Cheng PY, et al. Child, Household, and Caregiver Characteristics Associated with Hospitalization for Influenza among Children 6-59 Months of Age: An Emerging Infections Program Study. *Pediatr Infect Dis J* 2014.
54. 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. *American Journal of Emergency Medicine* 2013; **31**(3): 529-34.
55. Mistry RD, Fischer JB, Prasad PA, Coffin SE, Alpern ER. Severe Complications in Influenza-like Illnesses. *Pediatrics* 2014; **134**(3): e684-90.
56. 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**(6): 629-34.
57. 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**: 31-8.
58. Crump C, Sundquist K, Sundquist J, Winkleby MA. Gestational age at birth and mortality in young adulthood. *JAMA* 2011; **306**: 1233-40.
59. World Health Organization 2005. 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. Available from: http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5.pdf (Accessed 13th October 2014).
60. Department of Health. UK Influenza Pandemic Preparedness Strategy 2011. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/213717/dh_131040.pdf (Accessed 13th October 2014).
61. Public Health England. Influenza Vaccine Uptake amongst GP Patient Groups in England, Winter Season 2012/13. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/207134/Influe

[nza vaccine uptake amongst GP patient groups in England for winter season 2012 2013.pdf](#) (Accessed 13th October 2014).

62. Rodgers L, Grohskopf L, Pabst LJ, Harris L, Chaves SS. Uptake of live attenuated influenza vaccine among children in selected populations of the United States, 2008–2012. Abstract available from: <https://cste.confex.com/cste/2013/webprogram/Paper2149.html> (Accessed 17th September 2014). Annual Conference of Council of State and Territorial Epidemiologists, United States. Pasadena, CA, United States; 2013.
63. 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**(4): 1-28.
64. 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**(22): pii: 20823.
65. Civil Contingencies Secretariat, UK Cabinet Office. Overarching Government Strategy to respond to an Influenza Pandemic – Analysis of the scientific evidence base. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/61968/flu_pandemic_science_paper1.pdf (Accessed 13th October 2014).
66. Lim WS. Pandemic flu: clinical management of patients with an influenza-like illness during an influenza pandemic. *Thorax* 2007; **62**: 1-46.
67. 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. *Journal - Oklahoma State Medical Association* 2011; **104**(9): 345-51.
68. 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**(2): 172-6.
69. 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**(1): 19-26.
70. 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**(8): 777-81.
71. 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**(4): 302-10.