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RESEARCH

Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis

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Abstract

Objective To evaluate risk factors for severe outcomes in patients with seasonal and pandemic influenza.

Design Systematic review.

Study selection Observational studies reporting on risk factor-outcome combinations of interest in participants with influenza. Outcomes included death, ventilator support, admission to hospital, admission to an intensive care unit, pneumonia, and composite outcomes.

Data sources Medline, Embase, CINAHL, Global Health, and the Cochrane Central Register of Controlled Trials to March 2011.

Risk of bias assessment Newcastle-Ottawa scale to assess the risk of bias. GRADE framework to evaluate the quality of evidence.

Results 63 537 articles were identified of which 234 with a total of 610 782 participants met the inclusion criteria. The evidence supporting risk factors for severe outcomes of influenza ranged from being limited to absent. This was particularly relevant for the relative lack of data for non-2009 H1N1 pandemics and for seasonal influenza studies. Limitations in the published literature included lack of power and lack of adjustment for confounders was widespread: adjusted risk estimates were provided for only 5% of risk factor-outcome comparisons in 39 of 260 (15%) studies. The level of evidence was low for "any risk factor" (odds ratio for mortality 2.77, 95% confidence interval 1.90 to 4.05 for pandemic influenza and 2.04, 1.74 to 2.39 for seasonal influenza), obesity (2.74, 1.56 to 4.80 and 30.1, 1.74 to 2.39), cardiovascular diseases (2.92, 1.76 to 4.86 and 1.97, 1.06 to 3.67), and neuromuscular disease (2.68, 1.91 to 3.75 and 3.21, 1.84 to 5.58). The level of evidence was very low for all other risk factors. Some well accepted risk factors such as pregnancy and belonging to an ethnic minority group could not be identified as risk factors. In contrast, women who were less than four weeks post partum had a significantly increased risk of death from pandemic influenza (4.43, 1.24 to 15.81).

Conclusion The level of evidence to support risk factors for influenza related complications is low and some well accepted risk factors, including pregnancy and ethnicity, could not be confirmed as risks. Rigorous and adequately powered studies are needed.

Introduction

Influenza is a major global cause of illness and death, resulting in an estimated three to five million cases of severe influenza illness and 250 000 to 500 000 deaths annually.[1-3] The risk of complications from influenza, including lower respiratory tract infection, admission to hospital, and death vary depending on factors such as age and the type of comorbidity that may be present.[1 2] Currently, the World Health Organization and most countries prioritise specific high risk groups for vaccination.[2-6] Although some recommendations are consistent, such as vaccination of healthcare workers, pregnant women, and those

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Appendices

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Video abstract

with certain high risk conditions, there are also discrepancies, such as the age groups that need to be prioritised (table 1⇓). Despite the widely accepted public health policy of recommending vaccination to groups believed to be at high risk for complications of influenza, a comprehensive and systematic review of the evidence defining these groups is lacking. Assessment of the quality of evidence supporting these risk groups and identifying the most important risk groups is essential when making decisions about the allocation of influenza vaccination and antiviral therapy, and planning about health system utilisation. We summarised this evidence for seasonal and pandemic influenza.

Methods

All decisions regarding eligibility criteria, search strategy, study selection, assessment of risk for bias, explanations for heterogeneity, data collection, and analysis were established a priori.

Eligibility criteria

We included studies reporting on at least one risk factor-outcome combination in participants with evidence of influenza infection. The latter included laboratory confirmed influenza or the presence of influenza-like illness during a period of known influenza circulation. Studies on H5N1 avian influenza were considered but are not reported here. Eligible study designs included randomised controlled trials, cohort, case-control, and cross sectional. We included case series if participants with and without a specific outcome for a particular risk factor were reported, and we considered studies in English, French, German, Spanish, and Korean, based on the language skills of the study team. We excluded case reports.

Outcomes

Outcomes of interest included community acquired pneumonia, mortality, admission to hospital, admission to an intensive care unit, need for ventilator support, and any composites consisting of all or some of these outcomes. We chose these outcomes because they are patient important, most commonly reported in studies reporting on severe outcomes of influenza, and used for the clinical assessment in interventional studies on influenza.[7 8]

We defined community acquired pneumonia as involvement of the lower respiratory tract within 72 hours of hospital admission or according to the criteria in the original study. Ventilator support was defined as the need for respiratory support beyond applying oxygen alone.

Risk factors

We used the age categories that were most commonly reported in the original articles: >65 years for elderly, <18 years for children, 2 to <5 years, <2 years, and <6 months. If other categories were reported, we chose the closest to these cut-offs. We compared other ethnic groups with white participants. Definitions of comorbidities by the original studies were used. Obesity was defined as a body mass index of >30 kg/m^2 or as defined by the original studies.

Search strategy and data extraction

We searched Medline, Embase, CINAHL, Global Health, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 25 March 2011. The search strategy was created in collaboration with a librarian (NB) and included a combination of keywords and subject headings for all major concepts (see supplementary appendix A). We also searched reference lists of identified articles and review articles.

We screened titles or abstracts and full text articles, extracted data using a standardised and piloted electronic database, and assessed risk of bias. Pairs of reviewers independently conducted all the steps. A third reviewer (DM) resolved any disagreement between reviewers by consensus or arbitration.

Quality assessment

We used the Newcastle-Ottawa scale to assess the risk of bias in observational studies.[9] This scale allocates up to 9 points for the least risk of bias in four domains: selection of study groups (4 points), comparability of groups (2 points), and ascertainment of exposure and outcomes (3 points). Vaccination status for influenza and antiviral treatment were defined as the most important covariates that would define comparability.

We evaluated the quality of evidence for each risk factor using criteria selected from the grading of recommendations assessment, development, and evaluation (GRADE) framework.[10] GRADE is a standardised approach to assess the quality of evidence, and ranges from very low to high. Two researchers (DM and JJ) independently assessed the GRADE of evidence by combining pandemic and seasonal influenza and considering all outcomes but giving additional weight to death.

Meta-analyses

Assuming that heterogeneity exists in findings across studies, we adopted a random effects model in Review Manager 5.0 (Cochrane Collaboration)[11] to obtain a summary estimate of the average effect with its 95% confidence interval.[12] We used Stata/IC 11.2 (StataCorp LP, Texas, USA) to calculate the 95% prediction intervals. The width of prediction intervals is affected by the uncertainty in the summary estimate and by the estimate (and its uncertainty) of the between-study standard deviation of the true effect, and prediction intervals are therefore affected by the heterogeneity across the studies.[12]

If risk estimates alone and no data were reported, we pooled the individual studies using the inverse variance method and converted to odds ratios and 95% confidence intervals in a secondary analysis.[13] We pooled case-control studies separately, whereas we included cross-sectional studies in the meta-analyses of cohort studies. Meta-analyses were performed overall and separately for pandemic and seasonal influenza. The I^2 statistic was used to evaluate heterogeneity.[14] We explored heterogeneity between subgroups that were defined a priori (according to place of enrolment, risk of bias, laboratory confirmation of influenza, influenza vaccination status) whenever I^2 was greater than 60%.[15] The term used to define the place of enrolment included "community" (participants presenting in an outpatient setting at enrolment), "hospital" (participants admitted to hospital in a non-intensive care unit setting), and "intensive care unit" (participants admitted to hospital in the intensive care unit). Publication bias was assessed by visual interpretation of funnel plots and the Egger's test[16] and, as a sensitivity analysis, with the test by Harbord.[17]

Results

We identified 63 537 citations in the search of electronic databases and an additional 16 citations by searching bibliographies of relevant articles (figure⇓). A total of 239 studies described in 234 articles met our eligibility criteria, comprising data on 610 782 participants (table 2⇓, see supplementary appendix B). The majority were cohort studies

(n=231, 97%) that used laboratory confirmation to ascertain influenza infection (n=220, 92%) and most were conducted during pandemic influenza seasons (n=183, 77%). Since only six studies (3% of all studies) with 1278 participants (0.2% of the study population) were case-control studies, tables 3⇓ and 4⇓ present the results of only cohort studies. No studies included in the final synthesis needed to be excluded because of a failure to report either odds ratios and the 95% confidence intervals or raw data from which the odds ratios could be calculated. The summary estimates reported here were based on unadjusted risk estimates.

Risk of bias and quality of evidence assessment

The Newcastle-Ottawa scale scores for risk of bias ranged from 1 to 8 out of a maximum of 9, with a median of 6 across studies (table 2). Notably, adjusted risk estimates were provided for only 152 of 2788 (5.4%) risk factor-outcome comparisons in 39 of 260 (15%) studies. Because of the limited availability of adjusted risk estimates and the diversity of covariates adjusted for, meta-analyses of adjusted risk estimates were not conducted. However, when they were available, adjusted and crude odds ratio estimates were similar.

Based on an adaptation of the GRADE approach to assess the quality of evidence, our confidence in risk estimates was low for the presence of "any risk factor," obesity, any cardiovascular disease, and any neuromuscular disease, and very low for all other risk factors (table 5⇓). All major risk factors with multiple studies were downgraded because of study quality, as their median Newcastle-Ottawa scale score was always below 7. Inconsistency and imprecision were also common for most major risk factors (tables 3-5). For a given risk factor we would have expected consistency of associations with all outcomes. Thus, we considered heterogeneity in findings across outcomes within risk groups to be inconsistent using GRADE methodology as was heterogeneity across studies for each risk factor-outcome combination.

While the presence of heterogeneity and the small number of studies for each risk factor-outcome comparison limited the ability to assess the risk of publication bias, there was no convincing evidence of publication bias for the risk factor-mortality combinations that were deemed to be at low level of evidence. The presence of publication bias would not have further decreased the level of evidence for risk factors already deemed to be very low.

Seasonal influenza

Age as a risk factor

We found a significant increase in the risk of death among elderly people compared with non-elderly people (odds ratio 2.95, 95% confidence interval 1.53 to 5.70, I^2=11%, n=4) (table 3). Elderly participants also had a higher risk of admission to hospital. Children aged less than 5 years were at lower risk of death (0.40, 0.20 to 0.80, I^2=0%, n=8), had lower hospital admission rates, and were less likely to need ventilator support than older children but were at higher risk of developing pneumonia. When very young children (<2 years of age) were compared with the other age groups, they were at significantly lower risk for admission to hospital, admission to an intensive care unit, and the need for ventilator support.

Ethnicity and pregnancy

Data on ethnicity was rare for seasonal influenza, and no ethnicity studied was associated with a significant higher risk for severe outcomes. In contrast with pandemic influenza, pregnancy as a risk factor was not well studied for seasonal influenza, with only one study having data on this with no significant association with death.

Comorbidity

Based largely on comorbidity, the presence of "any risk factor" was significantly associated with death (2.04, 1.74 to 2.39, I^2=0%, n=4), pneumonia, hospital admission, and admission to an intensive care unit. Only one seasonal influenza study with a small event rate provided data on obesity as a risk factor, which showed an increased risk of death (30.1, 1.17 to 773.12).

The presence of chronic lung disease was associated with a higher risk for admission to hospital and to an intensive care unit, and the need for ventilator support. Asthma was only associated with a higher risk of developing pneumonia, whereas chronic obstructive pulmonary disease was associated with a higher likelihood of needing ventilator support. Cardiovascular disease increased the risk of death (1.97, 1.06 to 3.67, I^2=46%, n=8) as well as of pneumonia, hospital admission, and need for ventilator support. Immunocompromised participants were at higher risk for death (3.81, 1.28 to 11.35, I^2=71%, n=4) but at lower risk of developing pneumonia. The presence of any neuromuscular disease was associated with a higher risk for death (3.21, 1.84 to 5.58, I^2=0%, n=4), whereas diabetes mellitus but not any of the other risk factors of interest was associated with a higher risk for hospital admission.

Pandemic influenza

Age as a risk factor

Elderly people were at higher risk for death compared with younger adults during pandemic influenza (2.69, 1.53 to 4.71, I^2=86%, n=29 studies) (table 4). The summary estimate was even greater when only community based studies were pooled (6.35, 1.26 to 31.94, I^2=93%, n=5). However, there was a large overlap in the 95% confidence interval across subgroups, specifically: 1.26 to 31.94 (I^2=93%, n=4) in the community and 2.24 to 5.48 (I^2=68%, n=16) in participants admitted to hospital. Similarly there was overlap between 95% prediction intervals in these settings: 0.01 to 2900 in the community and 0.87 to 14.07 in participants admitted to hospital. Elderly participants were also at higher risk for hospital admission but at lower risk of being admitted to the intensive care unit.

In contrast, the risk of death in children (compared with non-elderly adults) was reduced (0.28, 0.19 to 0.41, 95% prediction interval 0.09 to 0.82, I^2=39%, n=21). Again, the effect was accentuated in community based studies (0.19, 0.10 to 0.36, I^2=39%, n=4), but with overlapping 95% prediction intervals (0.02 to 1.49 in the community, 0.08 to 0.84 in the hospital, and 0.28 to 0.72 in the intensive care unit setting). Children aged less than 5 years were at a higher risk of developing pneumonia and requiring hospital admission but tended to be at lower risk of death (0.59, 0.29 to 1.22, I^2=49%, n=15) and were at a lower risk for admission to an intensive care unit. Compared with non-elderly adults, children were less likely to be admitted to hospital with pandemic influenza.

Ethnicity

Despite the availability of a larger number of studies for pandemic influenza than for seasonal influenza addressing

ethnicity as a potential risk factor, we found no significant differences in all cause mortality among Asian, black, or native populations compared with white participants. The only significant difference was a higher risk for hospital admission for black and Hispanic participants but a lower risk for admission to an intensive care unit for black participants. For Australian natives, the likelihood of hospital admission was lower compared with white participants.

Pregnancy

Pregnancy did not increase the risk of death. However, pregnant women were at higher risk for hospital admission but were not at increased risk of pneumonia and, in fact, were at significantly reduced risk of admission to an intensive care unit. In contrast, women who were less than four weeks post partum had a significantly increased risk of death (4.43, 95% confidence interval 1.24 to 15.81, I^2=0%, n=3). When compared with those in the first or second trimester, women in the third trimester had an increase in all cause mortality (1.22, 1.01-1.48, I^2=0%, n=5).

Comorbidity

The presence of "any risk factor" was associated with higher all cause mortality (2.77, 1.90 to 4.05, I^2=88%, n=53) and also with higher admission rates to hospital and an intensive care unit. Reports on obesity as a risk factor from 59 studies showed that obesity not only increased the risk of death (2.74, 1.56 to 4.80, I^2=92%, n=33) but was significantly associated with the need for admission to hospital and an intensive care unit, as well as for ventilator support.

The presence of any chronic lung disease (1.71, 1.17 to 2.51, I^2=79%, n=27), chronic obstructive pulmonary disease (1.49, 1.15 to 1.92, I^2=0%, n=13), or obstructive sleep apnoea (2.63, 1.25 to 5.52, I^2=0%, n=2) also increased the risk for death. We also found associations between the presence of any chronic lung disease and admission to hospital as well as admission to an intensive care unit, and between chronic obstructive pulmonary disease and admission to an intensive care unit. Cardiovascular disease increased the risk of death significantly (2.92, 1.76 to 4.86, I^2=89%, n=28). We also found an association with admission to hospital and an intensive care unit. In contrast with seasonal influenza, hypertension was associated with a higher risk for death (1.49, 1.10 to 2.10, I^2=0%, n=7). Immunosuppression increased the risk of death from pandemic influenza (3.67, 1.78 to 7.58, I^2=94%, n=23), and immunocompromised participants were more likely to be admitted to hospital. Participants with malignancy (3.10, 2.35 to 4.10, I^2=0%, n=12 for mortality) and neuromuscular disease had an increased risk of death (2.68, 1.91 to 3.75, I^2=25%, n=16). Neurocognitive diseases were not significantly associated with death but were with admission to hospital and an intensive care unit and with ventilator support. Further risk factors found to be associated with a higher risk of death included anaemia or haemoglobinopathy, diabetes mellitus, and liver, metabolic, and renal disease (table 4).

Heterogeneity

In most instances heterogeneity was due to differences in magnitude rather than a different direction of the effect. Risk estimates were typically highest in the community based populations, lower in participants admitted to hospital, and lowest in participants admitted to an intensive care unit, both across studies in the meta-analysis and within studies. One example was the presence of "any risk factor" for total mortality: the study by Buda et al[18] showed an odds ratio of 72.48 (95% confidence interval 50.35 to 104.33) in the overall community sample but only 19.18 (13.26 to 27.73) in the subgroup of participants who needed hospital admission. In our meta-analysis, we found an odds ratio of 10.06 (2.32 to 43.61, I^2=86%, n=9) in the community, 3.01 (2.01 to 4.51, I^2=85%, n=30) in participants admitted to hospital, and 1.56 (1.28 to 1.90, I^2=9%, n=22) in participants admitted to an intensive care unit. However, when considering the 95% prediction intervals, there was a large overlap across the subgroups (0.08 to 1287.99, 0.50 to 17.97, and 1.09 to 2.21, respectively). Other than stratification by population, our hypotheses to explain heterogeneity were of limited value: data on vaccination was often lacking, rendering subgrouping impossible, only a few studies did not use laboratory confirmation of influenza, and subgrouping by risk of bias was not helpful because most studies (n=196, 75%) were in the middle range of risk of bias (4-6 Newcastle-Ottawa scale points).

Only a few risk factors were associated, significantly or at least in a trend, with all outcomes of interest for both types of influenza (table 5). With the exception of pneumonia in studies during pandemic influenza, these included the presence of "any risk factor," obesity, and neuromuscular diseases. Chronic lung diseases were associated with all outcomes other than pneumonia and ventilator support during pandemic influenza. Cardiovascular diseases were associated with all outcomes other than pneumonia during pandemic influenza and admission to an intensive care unit during seasonal influenza. Neurocognitive disease was not associated with all cause mortality during seasonal influenza, but was with all other outcomes with data available.

Discussion

The evidence supporting risk factors for severe outcomes of influenza ranges from being limited to absent. This was particularly relevant in the relative lack of data for studies on non-2009 H1N1 pandemics and for seasonal influenza. The level of evidence was low for "any risk factor," obesity, cardiovascular diseases, and neuromuscular disease, and was very low for all other risk factors.

Why the evidence was limited

There were widely accepted risk factors, such as pregnancy, as well as more recently described risks, such as belonging to an ethnic minority group, for which we could not find a trend for higher rates of severe outcomes other than more frequent hospital admission. Given the lack of a demonstrable effect for these comparisons despite large sample sizes, lack of power is an unlikely explanation. On the other hand, we found positive effects that did not reach statistical significance in some risk factor-outcome comparisons for which there were only small sample sizes. For example, the association between chronic lung diseases and mortality during seasonal influenza (odds ratio 1.8, 95% confidence interval 0.81 to 4.01) was not statistically significant. Calculating the optimal information size[19] with consideration of the heterogeneity found for this comparison,[20] approximately 5000 participants would have been required in each arm to detect a difference of 25% in mortality. Given that only 1200 participants were available, the lack of statistical significance was most likely due to a lack of power. Because influenza vaccination was not adjusted for, the calculated risk estimates may have underestimated the true effect size—for example, because chronic lung disease is a well known risk factor, participants with chronic lung diseases may have been more likely to be vaccinated than the comparison group thus

mitigating the risk for severe outcomes in participants with underlying chronic lung disease. We also found that such a lack of adjustment for confounders was widespread: adjusted risk estimates were provided for only 5.4% of risk factor-outcome comparisons in 39 of 260 (15%) studies. Although such a lack of adjusted risk estimates could potentially be misleading, we did find similar effect sizes in those studies that reported both adjusted and unadjusted risk estimates.

The relative lack of eligible studies on non-H1N1 pandemic influenza and on seasonal influenza before 1991 was surprising. Therefore the findings from the meta-analyses on pandemic influenza cannot necessarily be extrapolated to non-H1N1 pandemic strains, and the findings on seasonal influenza cannot necessarily be extrapolated to non-H3N2 and non-influenza B strains.

Variability in definitions of risk factors and the potential for differential ascertainment of risk factors possibly contributed to the heterogeneity in the affected comparisons. Differing lengths of follow-up may have also resulted in heterogeneity, and studies that were deemed to have an inadequate length of follow-up (16%) may have missed events and therefore biased the results towards smaller effect sizes. Owing to the differing length of follow-up used in the included studies, meta-analysis of hazard ratios instead of odds ratios might have reduced heterogeneity. In contrast with odds ratios, hazard ratios are more likely to be constant over time.[21] Unfortunately, hazard ratios were rarely reported and thus meta-analysis of hazard ratios was not feasible. Another limitation of the data was inconsistency in outcomes—that is, for a given risk factor we would have expected to see an increase in all types of severe outcomes. Thus when evaluating risk factors with inconsistent findings across outcomes, we downgraded the level of evidence.

The presence of poor quality of evidence in studies on prognostic factors in general is well known[22]; we found a similar picture for risk factors for severe outcomes with influenza in our study, despite the important public health implications of these studies.

Interpretation of meta-analysis results

Our meta-analysis showed that elderly people had the highest risk of death during both seasonal and pandemic influenza seasons. In contrast, children and young people aged less than 18 years had a significantly reduced risk of death compared with non-elderly adults during pandemics. Children aged less than 5 years, in particular those aged 2 to less than 5 years, were at increased risk of pneumonia from both pandemic and seasonal influenza when compared with older children.[23 24] Age less than 2 years was not a risk factor for any outcome other than hospital admission during pandemic influenza.

Pregnancy increased the risk of admission to hospital but not for any of the other outcomes. In contrast, women in the postpartum period were at higher risk for severe outcomes.[25 26] In studies comparing the third trimester of pregnancy with the first and second trimesters, the third trimester placed women at higher risk of severe outcomes.[27 28] These data suggest that risk increases in the late stages of pregnancy.[29 30] Notably, the results of ongoing systematic reviews on adverse effects, outcomes, and effectiveness of influenza vaccination in pregnancy will be of interest.[31 32] Our findings are in keeping with recommendations to prioritise vaccination of pregnant women because of the increased risk for mortality post partum, and elderly people. In contrast, we did not found convincing evidence to prioritise vaccination of young children compared with adults.

Our findings also suggest that obesity (body mass index >30) is an important cause of death with both pandemic and seasonal influenza.[28 33] It remains unclear whether obesity in itself is a risk factor or whether it reflects the presence of other comorbidities such as cardiovascular diseases and diabetes mellitus.[34] However, morbid obesity was identified as a potential independent risk factor after adjustment for these comorbidities.[33]

It has been suggested that certain ethnic groups may have been at higher risk for severe outcomes due to influenza during the 2009 pandemic[30]; however, we found no significant differences in all cause mortality among Asian, black, or native populations compared with white participants for either seasonal or pandemic influenza.[28-36] Hispanic and black participants as well as pregnant women were more likely to have been admitted to hospital during the 2009 H1N1 pandemic but were at lower risk for more severe outcomes.[28 37] It may be that because of a perception among healthcare providers of an increased risk of complications that these groups were selectively admitted to hospital during the 2009 H1N1 pandemic. This is in contrast with seasonal influenza where people of Hispanic ancestry were almost half as likely to be admitted to hospital.

As expected, chronic illness, including immunosuppression, cardiovascular disease, chronic lung disease, neuromuscular disease, neurological disease, chronic renal disease, and metabolic diseases increased the risk of mortality from influenza. Mortality did not differ among the sexes.

We found slightly greater effect sizes in community based studies compared with hospital based and intensive care unit based studies. We speculate that this is because heterogeneity among participants in community based studies is greater than among participants admitted to hospital—that is, participants admitted to hospital may share a level of comorbidity that, apart from the risk factor in question, leads to more similar outcomes.[38] An overlap did occur in the prediction intervals in these instances, either due to heterogeneity or due to the small number of studies available. It thus remains uncertain whether these differences were due to chance alone.

Strengths and limitations of this review

Strengths of this review were the comprehensive search strategy, the extensive amount of data reviewed, the assessment for study quality, the high percentage of studies using laboratory confirmation to diagnose influenza, and the breadth of outcomes and risk factors examined. In addition to the limitations of the included studies, it should be noted that the GRADE methodology used was developed to assess quality of evidence for interventions and not for prognostic factors. Therefore it remains unclear whether similar standards need to apply to the types of studies in this review because randomised controlled trials on risk factors are not feasible and therefore a high level of evidence according to GRADE methodology is unlikely ever to be achieved.[10]

Implications of the findings

Policy makers and public health organisations such as WHO should acknowledge the poor quality of evidence supporting vaccine recommendations for those deemed to be at high risk from influenza and to outline the level of evidence in their vaccination recommendations. This is of particular relevance when vaccine supply is insufficient. Obesity and the postpartum period were identified as potentially important risk factors that should be included in future vaccination recommendations. Given the limited level of evidence, however, any well designed

and adequately powered and conducted study is likely to affect the conclusions of this systematic review. This being said, our findings highlight the importance of conducting rigorous studies and of adequately reporting the results when assessing complications due to influenza.

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Contributors: All authors were involved in the conception and design of the study and the interpretation of data. DM and ML were responsible for the analysis and drafting of the article. All authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, had full access to all data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. DM and ML are guarantors.

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Data sharing: No additional data available.

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What is already known on this topic

Certain patient populations are thought to be at higher risk for developing complicated or severe influenza illness

These groups are prioritised for vaccination as well as for antiviral treatment

What this study adds

The quantity and quality of evidence on risk factors for developing complicated or severe influenza illness is limited

While some risk factors could be corroborated, evidence to support other, well established risk factors for severe outcomes could not be found

Tables

Table 1| Current World Health Organization and Center for Disease Control and Prevention (CDC) recommendations for influenza vaccination

	WHO		CDC
Groups	**Pandemic 2009[6]**	**Seasonal 2012[5]**	**Seasonal 2011[2]**
Healthcare workers	1	Recommended	Recommended
Pregnant women	2	1	Recommended
Aged >6 months with “chronic medical conditions”	3	Recommended	—
Aged >6 months with specific chronic medical conditions*	—	—	Recommended
Aged 6 months to 18 years and receiving long term aspirin treatment	—	—	Recommended
Healthy people:			
Young children (6-59 months)	—	Recommended	Recommended
Healthy children	5	—	—
Young adults (>15 and <49 years)	4	—	—
Adults (>40 and <65 years)	6	—	—
Adults (≥50 years)	—	—	Recommended
Adults (>65 years)	7	Recommended	—
Residents of nursing homes and other chronic care facilities	—	—	Recommended
American Indians/Alaska Natives	—	—	Recommended
Morbidly obese (body mass index ≥40)	—	—	Recommended
Household contacts and caregivers of children aged <5 years and adults aged ≥50 years or of people with high risk conditions	—	—	Recommended

Numbers indicate priority level (where applicable), recommended indicates vaccination recommendation.

CDC recommends routine vaccination of all individuals aged 6 months and older. The table summarises groups prioritised by CDC in the setting of limited vaccine supply.

*Chronic pulmonary including asthma, cardiovascular except hypertension, renal, hepatic, neurological, haematological, metabolic including diabetes mellitus, immunosuppressed.

Table 2| Study characteristics of 239 studies in 234 included articles. Values are numbers (percentages) unless stated otherwise

Characteristics	Overall	Pandemic influenza	Seasonal influenza
Range of publication year	1918-2011	1918-2011	1970-2011
No of studies	239	183	56
Pandemic influenza:			
1918/1919 H1N1	NA	3 (2)	NA
1957/1958 H2N2	NA	3 (2)	NA
1968/1969 H3N2	NA	1 (0.5)	NA
1977/1978 H1N1	NA	1 (0.5)	NA
2009/2010 H1N1	NA	175 (96)	NA
Seasonal influenza:			
1961-70	NA	NA	1 (2)
1971-80	NA	NA	3 (5)
1981-90	NA	NA	4 (7)
1991-2000	NA	NA	15 (27)
2001-10	NA	NA	33 (59)
No of participants	610 782	534 911	75 871
English articles	223 (93)	171 (93)	52 (93)
Geographical region:			
North America	82 (34)	50 (27)	32 (57)
Europe	58 (24)	49 (27)	9 (16)
Central/South America	25 (10)	24 (13)	1 (2)
Asia	49 (21)	39 (21)	10 (18)
Others	25 (10)	21 (12)	4 (7)
Cohort studies	231 (97)	175 (96)	56 (100)
Laboratory confirmation of influenza	220 (92)	173 (95)	47 (84)
Median (range) Newcastle-Ottawa scale points:			
Overall	6 (1-8)	6 (1-8)	6 (3-8)
Selection of study groups	3 (1-4)	3 (1-4)	3 (2-4)
Comparability of groups	0 (0-1)	0 (0-1)	0 (0-1)
Ascertainment of diseases	3 (0-3)	3 (0-3)	3 (0-3)

NA=not applicable.

If reporting across more than one 10 year band, the band with the most participants was chosen.

Table 3| Summary estimates for seasonal influenza. Values are odds ratios (95% confidence intervals), I^2 (%), and number of studies

Variables	Pneumonia	All cause hospital admission	Intensive care unit admission	Ventilator support	All cause mortality
Sex and age:					
Male sex	1.22 (0.82 to 1.81), 23, n=6	1.26* (1.07 to 1.47), 17, n=5	1.50 (0.17 to 13.23), NA, n=1	1.18 (0.37 to 3.73), NA, n=1	0.96 (0.69 to 1.34), 23, n=13
Elderly *v* non-elderly adults	1.48 (0.21 to 10.57), 0, n=2	4.65* (1.74 to 12.41), 71, n=2	NA	NA	2.95* (1.53 to 5.70), 11, n=4
Paediatric† *v* non-elderly adults	0.41 (0.01 to 11.46), NA, n=1	NA	NA	NA	1.48 (0.37 to 5.93), 21, n=3
2-<5 years *v* 5-<18 years	1.74* (1.39 to 2.17), 0, n=2	0.51* (0.34 to 0.76), NA, n=1	NA	NA	0.53 (0.21 to 1.34), 0, n=3
<5 years *v* 5-<18 years	1.53* (1.06 to 2.20), 65, n=5	0.58* (0.43 to 0.78), 82, n=4	0.57 (0.27 to 1.18), 58, n=2	0.47* (0.26 to 0.86), 0, n=2	0.40* (0.20 to 0.80), 0, n=8
<2 years *v* 2-<18 years	0.66 (0.41 to 1.07), 75, n=5	0.59* (0.47 to 0.75), 0, n=2	0.62* (0.43 to 0.89), 0, n=3	0.55* (0.28 to 0.88), 0, n=2	0.76 (0.26 to 2.24), 67, n=8
<6 months *v* <6 months to 2 years	0.39* (0.29 to 0.52), 14, n=4	1.18 (0.97 to 1.44), 0, n=2	0.56* (0.35 to 0.89), 0, n=4	0.61 (0.31 to 1.21), 0, n=3	1.30 (0.41 to 4.05), 1, n=3
Ethnicity:					
Asian/Pacific *v* white	1.22 (0.79 to 1.87), NA, n=1	1.55 (0.94 to 2.55), NA, n=1	NA	NA	NA
Black *v* white	1.16 (0.95 to 1.40), 0, n=2	2.06 (0.75 to 5.63), NA, n=1	NA	NA	7.22 (0.28 to 189.19), 11, n=1
Hispanic *v* white	1.20 (0.98 to 1.47), 0, n=2	0.56* (0.43 to 0.73), NA, n=1	NA	NA	NA
Native American *v* white	NA	0.70 (0.23 to 2.17), NA, n=1	NA	NA	NA
Native Australian *v* white	NA	NA	NA	NA	NA
Pregnancy and postpartum period:					
Pregnancy	NA	NA	NA	NA	1.07 (0.79 to 1.45), 0, n=2
<4 weeks post partum	NA	NA	NA	NA	NA
3rd trimester *v* 1st or 2nd trimester	NA	NA	NA	NA	NA
Any risk factor or comorbidity	1.53* (1.04 to 2.24), 11, n=7	3.39* (2.60 to 4.42), 92, n=3	1.74* (1.32 to 2.29), 0, n=3	1.71 (0.99 to 2.96), 30, n=4	2.04* (1.74 to 2.39), 0, n=14
Weight (body mass index):					
Obese (>30)	NA	NA	NA	NA	30.10* (1.17 to 773.12), NA, n=1
Underweight (<18.5)	NA	NA	NA	NA	NA
Lung disease:					
Any chronic lung disease	1.94 (0.45 to 8.42), 52, n=3	2.38* (1.58 to 3.57), NA, n=1	4.46* (1.34 to 14.79), NA, n=1	4.02* (1.69 to 9.58), NA, n=1	1.80 (0.81 to 4.01), 52, n=6
Asthma	1.35* (1.12 to 1.62), NA, n=1	NA	1.39 (0.28 to 6.81), NA, n=1	NA	0.89 (0.10 to 7.71), 0, n=2
Chronic obstructive pulmonary disease	NA	NA	NA	3.64* (1.81 to 7.32), 0, n=2	0.79 (0.34 to 1.81), 0, n=2
Obstructive sleep apnoea	NA	NA	NA	NA	NA
Cardiovascular disease:					
Any cardiovascular disease	1.56* (1.06 to 2.28), 0, n=3	16.45* (9.89 to 27.37), NA, n=1	1.09 (0.30 to 4.01), NA, n=1	3.31* (1.03 to 10.61), NA, n=1	1.97* (1.06 to 3.67), 46, n=8
Hypertension	NA	NA	NA	NA	3.53 (0.32 to 38.87), 0, n=2
Cerebrovascular insult	NA	NA	NA	NA	1.27 (0.16 to 10.07), NA, n=1
Immunosuppression:					
Immunocompromised host	0.61* (0.42 to 0.89), 60, n=3	NA	0.25 (0.06 to 1.12), NA, n=1	NA	3.81* (1.28 to 11.35), 71, n=4
HIV	NA	NA	NA	NA	3.87 (0.52 to 28.96), NA, n=1

Table 3 (continued)

Variables	Pneumonia	All cause hospital admission	Intensive care unit admission	Ventilator support	All cause mortality
Chronic steroid therapy	NA	17.49* (6.97 to 43.92), NA, n=1	NA	NA	1.79 (0.66 to 4.87), NA, n=1
Malignancy	1.19 (0.51 to 2.77), NA, n=1	19.35* (10.55 to 35.48), NA, n=1	NA	NA	2.67 (0.22 to 32.23), NA, n=1
Neurological disease:					
Any neuromuscular disease	1.57 (1.05 to 2.36), NA, n=1	NA	NA	NA	3.21* (1.84 to 5.58), 0, n=4
Neurocognitive disease	1.45* (1.05 to 1.99), NA, n=1	NA	2.07 (0.75 to 5.72), NA, n=1	NA	1.33 (0.33 to 5.33), 0, n=2
Seizure	0.99 (0.70 to 1.40), NA, n=1	NA	NA	NA	6.53 (0.24 to 177.39), NA, n=1
Other risk factors:					
Alcohol with or without illicit drug use	0.47 (0.07 to 2.96), NA, n=1	NA	NA	NA	0.13 (0.01 to 2.34), NA, n=1
Anaemia or haemoglobinopathy	0.54 (0.34 to 0.84), NA, n=1	NA	0.12 (0.01 to 1.99), NA, n=1	NA	NA
Autoimmune disease	NA	NA	NA	NA	NA
Diabetes mellitus	0.91 (0.26 to 3.24), 0, n=2	9.91* (5.46 to 17.99), NA, n=1	NA	NA	0.59 (0.23 to 1.50), 0, n=2
Endocrinological disease	NA	NA	NA	NA	13.92* (3.71 to 52.13), NA, n=1
Gastrointestinal disease	NA	NA	NA	NA	NA
Liver disease	NA	NA	NA	NA	0.38 (0.04 to 3.98), NA, n=1
Metabolic disease	0.89 (0.53 to 1.50), NA, n=1	NA	NA	NA	0.52 (0.12 to 2.21), NA, n=1
Prematurity or preterm birth	NA	NA	NA	NA	NA
Renal disease	1.25 (0.70 to 2.23), 0, n=3	NA	NA	0.68 (0.08 to 5.66), NA, n=1	2.16 (0.58 to 8.08), 0, n=2

NA=not applicable (only one study reporting on this risk factor-outcome comparison).

*Statistically significant.

†Children up to 18 years of age or as defined by original study.

Table 4| Summary estimates for pandemic influenza with odds ratios (95% confidence intervals), I^2 (%), and number of studies

Variables	Pneumonia	All cause hospital admission	Intensive care unit admission	Ventilator support	All cause mortality
Sex and age:					
Male sex	1.23 (0.99 to 1.52), 0, n=10	0.99 (0.93 to 1.05), 24, n=12	0.93 (0.86 to 1.01), 0, n=19	1.31 (0.80 to 2.12), 0, n=15	1.04 (0.94 to 1.16), 5, n=64
Elderly *v* non-elderly adults	1.67 (0.36 to 7.77), 74, n=3	2.84* (1.76 to 4.59), 84, n=7	0.62* (0.39 to 1.00), 36, n=6	0.71 (0.28 to 1.77), 0, n=7	2.69* (1.53 to 4.71), 86, n=29
Paediatric† *v* non-elderly adults	0.34 (0.10 to 1.15), 45, n=3	0.79* (0.64 to 0.98), 72, n=7	0.65 (0.33 to 1.26), 73, n=7	0.68 (0.35 to 1.31), 0, n=7	0.28* (0.19 to 0.41), 39, n=21
2-<5 years *v* 5-<18 years	2.05* (1.26 to 3.33), 0, n=2	0.96 (0.52 to 1.75), 0, n=2	0.79* (0.64 to 0.97), 0, n=7	1.29 (0.59 to 2.85), 0, n=2	0.46 (0.20 to 1.07), 38, n=7
<5 years *v* 5-<18 years	1.56* (1.07 to 2.26), 0, n=3	2.97* (2.55 to 3.45), 24, n=6	0.66* (0.53 to 0.84), 23, n=12	0.97 (0.52 to 1.82), 0, n=6	0.59 (0.29 to 1.22), 49, n=15
<2 years *v* 2-<18 years	1.05 (0.71 to 1.55), 0, n=3	5.38 (0.45 to 64.52), NA, n=1	0.53* (0.37 to 0.75), 0, n=5	0.74 (0.26 to 2.08), 25, n=4	0.53 (0.17 to 1.64), 0, n=6
<6 months *v* 6 months to <2 years	1.03 (0.20 to 5.37), 0, n=2	NA, NA	1.83 (0.47 to 7.11), 0, n=2	3.33 (0.03 to 343.77), 69, n=2	1.00 (0.17 to 5.98), NA, n=1
Ethnicity:					
Asian/Pacific *v* white	NA	1.60 (0.91 to 2.70), 0, n=2	1.12 (0.61 to 2.08), 0, n=4	NA	0.64 (0.40 to 1.03), 0, n=5
Black *v* white	NA	2.19* (1.52 to 3.16), 0, n=3	0.53* (0.36 to 0.78), 0, n=5	NA	0.70 (0.42 to 1.18), 11, n=6
Hispanic *v* white	NA	1.93* (1.38 to 2.70), 0, n=3	0.80 (0.57 to 1.14), 0, n=4	NA	0.76 (0.48 to 1.19), 36, n=4
Native American *v* white	1.49 (0.56 to 3.92), NA, n=1	3.07 (0.62 to 15.20), NA, n=1	0.95 (0.79 to 1.13), 0, n=5	NA	0.93 (0.67 to 1.30), 0, n=4
Native Australian *v* white	NA	0.40* (0.21 to 0.75), NA, n=1	0.91 (0.73 to 1.14), 0, n=3	NA	0.57 (0.12 to 2.69), 47, n=3
Pregnancy and postpartum period:					
Pregnancy	1.13 (0.76 to 1.67), 69, n=7	3.50* (1.65 to 7.40), 90, n=7	0.62* (0.52 to 0.75), 67, n=19	1.12 (0.42 to 2.99), 58, n=8	0.99 (0.67 to 1.46), 62, n=26
<4 weeks post partum	3.62 (0.42 to 30.9), NA, n=1	NA	2.34 (0.56 to 9.82), NA, n=1	1.43 (0.33 to 6.32), NA, n=1	4.43* (1.24 to 15.81), 0, n=3
3rd trimester *v* 1st or 2nd trimester	0.97 (0.78 to 1.20), NA, n=1	3.98* (1.65 to 9.57), 88, n=2	1.48* (1.05 to 2.09), 0, n=3	NA	1.22* (1.01 to 1.48), 0, n=5
Any risk factor or comorbidity	1.19 (0.64 to 2.22), 61, n=10	2.73* (1.89 to 3.95), 95, n=14	1.93* (1.59 to 2.35), 63, n=27	1.60 (0.96 to 2.69), 12, n=14	2.77* (1.90 to 4.05), 88, n=53
Weight (body mass index):					
Obese (>30)	1.44 (0.99 to 2.10), NA, n=1	3.44* (2.14 to 5.54), 71, n=8	1.81* (1.48 to 2.22), 48, n=16	1.79* (1.38 to 2.32), 0, n=9	2.74* (1.56 to 4.80), 92, n=33
Underweight (<18.5)	1.06 (0.41 to 2.76), NA, n=1	NA	1.26 (0.52 to 3.04), n NA, n=1	0.56 (0.16 to 1.98), NA, n=1	1.35 (0.43 to 4.22), NA, n=1
Lung disease:					
Any chronic lung disease	1.19 (0.12 to 11.44), 0, n=2	2.37* (1.56 to 3.61), 89, n=9	1.48* (1.19 to 1.83), 47, n=2	1.06 (0.35 to 3.15), 0, n=5	1.71* (1.17 to 2.51), 79, n=27
Asthma	1.88 (0.87 to 4.08), 0, n=4	1.40 (0.96 to 2.03), 42, n=4	0.83 (0.59 to 1.17), 25, n=18	0.91 (0.36 to 2.31), 0, n=9	0.92 (0.49 to 1.28), 31, n=21
Chronic obstructive pulmonary disease	1.11 (0.03 to 46.71), 79, n=2	8.00 (0.58 to 110.27), NA, n=1	1.84* (1.40 to 2.41), 50, n=5	2.46 (0.62 to 9.74), 37	1.49* (1.15 to 1.92), 0, n=13
Obstructive sleep apnoea	NA	NA	1.70 (0.06 to 47.95), NA, n=1	NA	2.63* (1.25 to 5.52), 0, n=2
Cardiovascular disease:					
Any cardiovascular disease	0.92 (0.44 to 1.93), 0, n=3	3.54* (2.29 to 5.47), 71, n=9	1.70* (1.39 to 2.08), 55, n=17	1.66 (0.78 to 3.56), 0, n=7	2.92* (1.76 to 4.86), 89, n=28
Hypertension	NA	0.80 (0.24 to 2.65), NA, n=1	0.87 (0.49 to 1.58), 0, n=4	0.82 (0.19 to 3.50), 0, n=3	1.49* (1.10 to 2.01), 0, n=7
Cerebrovascular insult	NA	5.83* (1.52 to 22.27), NA, n=1	NA	NA	2.27 (0.77 to 6.71), 0, n=2
Immunosuppression:					

Table 4 (continued)

Variables	Pneumonia	All cause hospital admission	Intensive care unit admission	Ventilator support	All cause mortality
Immunocompromised host	0.56 (0.12 to 2.56), NA, n=1	4.61* (2.41 to 8.82), 85, n=11	1.02 (0.78 to 1.33), 28, n=16	1.40 (0.43 to 4.53), 0, n=5	3.67* (1.78 to 7.58), 94, n=23
HIV	1.78 (0.90 to 3.53), 0, n=2	NA	0.94 (0.28 to 3.22), NA, n=1	0.80 (0.25 to 2.58), 0, n=4	0.97 (0.47 to 1.99), 7, n=9
Chronic steroid therapy	NA	2.19 (0.20 to 24.38), NA, n=1	0.83 (0.28 to 2.48), NA, n=2	NA	1.54 (0.69 to 3.44), NA, n=1
Malignancy	0.75 (0.28 to 2.00), NA, n=1	4.77* (2.10 to 10.83), 0, n=3	1.37 (0.99 to 1.90), 50, n=9	1.46 (0.47 to 4.51), 0, n=5	3.10* (2.35 to 4.10), 0, n=12
Neurological disease:					
Any neuromuscular disease	1.00 (0.53 to 1.90), 0, n=3	2.64* (1.57 to 4.43), 15, n=6	2.63* (1.83 to 3.79), 0, n=8	1.93 (0.67 to 5.54), 26, n=4	2.68* (1.91 to 3.75), 25, n=16
Neurocognitive disease	NA	14.69* (8.96 to 24.08), 0, n=2	2.26* (1.49 to 3.45), 0, n=4	5.90* (1.21 to 28.77), 30, n=2	5.01 (0.48 to 52.34), 97, n=8
Seizure	0.78 (0.03 to 23.53), NA, n=1	4.76* (1.61 to 14.02), NA, n=1	1.51 (0.59 to 3.83), 54, n=3	1.31 (0.10 to 16.55), 14, n=2	1.46 (0.93 to 2.31), 0, n=7
Other risk factors:					
Alcohol with or without illicit drug use	0.57 (0.15 to 2.12), NA, n=1	3.57 (0.32 to 39.92), NA, n=1	1.70 (0.59 to 4.89), NA, n=1	NA	6.48 (0.95 to 44.16), 0, n=2
Anaemia or haemoglobinopathy	0.78 (0.03 to 23.53), NA, n=1	6.55* (2.32 to 18.52), 0, n=3	1.28 (0.54 to 3.08), 0, n=3	0.28 (0.03 to 2.82), 0, n=2	2.28* (1.35 to 3.84), 0, n=8
Autoimmune disease	NA	3.73 (0.82 to 17.06), 0, n=2	29.05* (1.49 to 567.79), NA, n=1	0.81 (0.03 to 22.24), NA, n=1	4.96 (0.41 to 60.6), 58, n=3
Diabetes mellitus	0.97 (0.30 to 3.12), 0, n=2	4.26* (3.14 to 5.77), 31, n=9	1.60* (1.32 to 1.94), 37, n=18	1.54 (0.60 to 3.91), 0, n=8	2.21* (1.37 to 3.57), 86, n=32
Endocrinological disease	NA	4.00* (2.23 to 7.18), NA, n=1	1.49 (0.18 to 12.45), NA, n=1	NA	NA
Gastrointestinal disease	NA	1.47 (0.15 to 14.36), NA, n=1	0.47 (0.06 to 3.93), NA, n=1	NA	0.97 (0.60 to 1.59), 23, n=2
Liver disease	NA	1.93 (0.29 to 12.72), 0, n=2	2.65* (1.44 to 4.88), 0, n=6	8.11 (0.17 to 377.11), 66, n=2	2.00* (1.32 to 3.04), 22, n=8
Metabolic disease	0.66 (0.17 to 2.53), NA, n=1	0.62 (0.17 to 2.24), 0, n=2	2.77 (0.36 to 21.33), 65, n=2	14.22* (3.35 to 60.34), NA, n=1	1.83* (1.19 to 2.79), 54, n=4
Prematurity or preterm birth	2.33 (0.28 to 19.22), 0, n=2	31.59* (1.80 to 552.94), NA, n=1	1.25 (0.47 to 3.31), 87, n=2	10.41* (1.02 to 106.13), 0, n=2	1.94 (0.76 to 4.98), 0, n=4
Renal disease	0.20 (0.01 to 5.57), NA, n=1	5.11* (2.50 to 10.42), 46, n=5	1.27 (0.88 to 1.84), NA, n=11	1.65 (0.07 to 36.96), 70, n=3	3.11* (1.54 to 6.28), 90, n=16

NA=not applicable (only one study reporting on this risk factor-outcome comparison).

*Statistically significant.

†Children up to 18 years of age or as defined by original study.

Table 5| **Risk estimates of identified risk factors during pandemic (p) and seasonal (s) influenza, and assessment of quality of evidence using an adaptation of the GRADE approach**

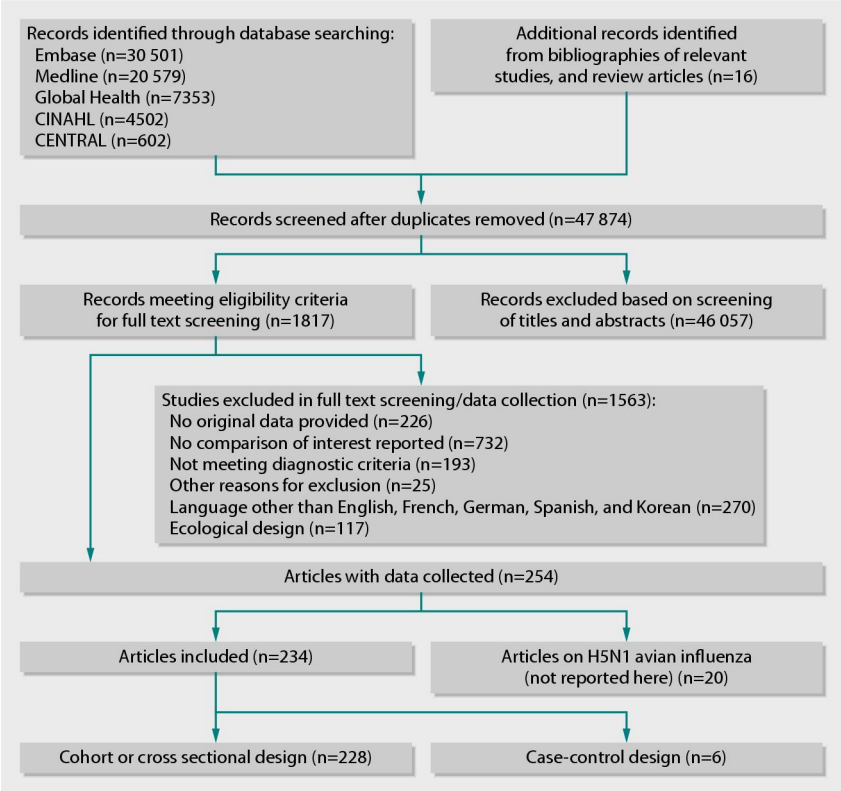
	Pneumonia		All cause hospital admission		Intensive care unit admission		Ventilator support		All cause mortality						
Risk factors	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**Study design**	**Inconsistency**	**Imprecision**	**Strong evidence of association**	**GRADE**
Sex and age:															
Elderly *v* non-elderly adults	*	Ntrl	+	+	(+)	NA	Ntrl	NA	+	+	Down	Down		Up	Very low
Paediatric *v* non-elderly adults	(*)	(*)	(+)	NA	(*)	NA	Ntrl	NA	(*)	Ntrl	Down	Down			Very low
Pregnancy and postpartum period:															
<4 weeks post partum	*	NA	NA	NA	*	NA	Ntrl	NA	+	NA	Down		Down	Up	Very low
3rd trimester *v* 1st/2nd trimester	Ntrl	NA	+	NA	+	NA	NA	NA	+	NA	Down				Very low
Prematurity or preterm birth	*	NA	+	NA	Ntrl	NA	+	NA	*	NA	Down		Down	Up	Very low
Any risk factor or comorbidity	Ntrl	+	+	+	+	+	*	*	+	+	Down			Up	Low
Obesity (BMI >30)	Ntrl	NA	+	NA	+	NA	+	NA	+	+	Down			Up	Low
Lung disease:															
Any chronic lung disease	Ntrl	*	+	+	+	+	Ntrl	+	+	*	Down				Very low
Asthma	*	+	Ntrl	NA	Ntrl	Ntrl	Ntrl	NA	Ntrl	Ntrl	Down				Very low
Chronic obstructive pulmonary disease	Ntrl	NA	*	NA	+	NA	*	+	+	Ntrl	Down		Down		Very low
Obstructive sleep apnoea	NA	NA	NA	NA	*	NA	NA	NA	+	NA	Down		Down		Very low
Cardiovascular disease:															
Any cardiovascular disease	Ntrl	+	+	+	+	Ntrl	*	+	+	+	Down			Up	Low
Hypertension	NA	NA	Ntrl	NA	Ntrl	NA	Ntrl	NA	+	*	Down		Down		Very low
Cerebrovascular insult	NA	NA	+	NA	NA	NA	NA	NA	*	Ntrl	Down		Down		Very low
Immunosuppression:															
Immunocompromised participant	(*)	(+)	+	NA	Ntrl	(*)	Ntrl	NA	+	+	Down	Down	Down	Up	Very low
HIV	*	NA	NA	NA	Ntrl	NA	Ntrl	NA	Ntrl	*	Down				Very low
Chronic steroid therapy	NA	NA	*	+	Ntrl	NA	(+)	NA	*	*	Down		Down		Very low
Malignancy	Ntrl	Ntrl	+	+	Ntrl	NA	Ntrl	NA	+	*	Down		Down	Up	Very low
Neurological disease:															
Any neuromuscular disease	Ntrl	*	+	NA	+	NA	*	NA	+	+	Down			Up	low
Neurocognitive disease	NA	+	+	NA	+	*	+	NA	+	Ntrl	Down		Down	Up	Very low
Seizure	Ntrl	Ntrl	+	NA	*	NA	Ntrl	NA	Ntrl	*	Down		Down		Very low
Other risk factors:															
Anaemia or haemoglobinopathy	Ntrl	(*)	+	NA	Ntrl	(*)	(*)	NA	+	NA	Down				Very low
Autoimmune disease	NA	NA	*	NA	+	NA	Ntrl	NA	*	NA	Down		Down		Very low
Diabetes mellitus	Ntrl	Ntrl	+	+	+	NA	*	NA	+	(*)	Down	Down			Very low
Endocrinological disease	NA	NA	+	NA	Ntrl	NA	NA	NA	NA	+	Down		Down		Very low
Liver disease	NA	NA	*	NA	+	NA	*	NA	+	(*)	Down		Down		Very low
Metabolic disease	(*)	Ntrl	(*)	NA	*	NA	+	NA	+	(*)	Down	Down			Very low

Table 5 (continued)

	Pneumonia		All cause hospital admission		Intensive care unit admission		Ventilator support		All cause mortality						
Risk factors	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**P**	**S**	**Study design**	**Inconsistency**	**Imprecision**	**Strong evidence of association**	**GRADE**
Renal diseases	(*)	Ntrl	+	NA	Ntrl	NA	*	Ntrl	+	*	Down	Down		Up	Very low

GRADE=grading of recommendations assessment, development, and evaluation; COPD=chronic obstructive pulmonary disease; +=significant risk factor; *potential risk factor: odds ratio >1.5, trend; Ntrl=neutral; (*)=potentially protective: odds ratio <0.67, trend, (+)=significant protective factor; NA=not available.

Figure



Flow of studies included and excluded