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Corticosteroids as adjunctive therapy in the treatment of influenza (Review)

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[Intervention Review]

Corticosteroids as adjunctive therapy in the treatment of influenza

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ABSTRACT

Background

Specific treatments for influenza are limited to neuraminidase inhibitors and adamantanes. Corticosteroids show evidence of benefit in sepsis and related conditions, most likely due to their anti-inflammatory and immunomodulatory properties. Although commonly prescribed for severe influenza, there is uncertainty over their potential benefit or harm.

Objectives

To systematically assess the effectiveness and potential adverse effects of corticosteroids as adjunctive therapy in the treatment of influenza, taking into account differences in timing and doses of corticosteroids.

Search methods

We searched CENTRAL (2015, Issue 5), MEDLINE (1946 to June week 1, 2015), EMBASE (1974 to June 2015), CINAHL (1981 to June 2015), LILACS (1982 to June 2015), Web of Science (1985 to June 2015), abstracts from the last three years of major infectious disease and microbiology conferences, and references of included articles.

Selection criteria

We included randomised controlled trials (RCTs), quasi-RCTs and observational studies that compared corticosteroid treatment with no corticosteroid treatment for influenza or influenza-like illness. We did not restrict studies by language of publication, influenza subtypes, clinical setting or age of participants. We selected eligible studies in two stages: sequential examination of title and abstract, followed by full text.

Data collection and analysis

Two pairs of review authors independently extracted data and assessed risk of bias. We pooled estimates of effect using random-effects meta-analysis models, where appropriate. We assessed heterogeneity using the I^2 statistic and assessed the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Main results

We identified 19 eligible studies (3459 individuals), all observational; 13 studies (1917 individuals) were suitable for inclusion in the meta-analysis of mortality. Of these, 12 studied patients infected with 2009 influenza A H1N1 virus (H1N1pdm09). Risk of bias was greatest in the 'comparability domain' of the Newcastle-Ottawa scale, consistent with potential confounding by indication. Data specific to mortality were of very low quality. Reported doses of corticosteroids used were high and indications for their use were not well reported. On meta-analysis, corticosteroid therapy was associated with increased mortality (odds ratio (OR) 3.06, 95% confidence interval (CI) 1.58 to 5.92). Pooled subgroup analysis of adjusted estimates of mortality from four studies found a similar association (OR 2.82, 95% CI 1.61 to 4.92). Three studies reported greater odds of hospital-acquired infection related to corticosteroid therapy; all were unadjusted estimates and we graded the data as very low quality.

Authors' conclusions

We did not identify any completed RCTs of adjunctive corticosteroid therapy for treating influenza. The available evidence from observational studies is of very low quality with confounding by indication a major potential concern. Although we found that adjunctive corticosteroid therapy was associated with increased mortality, this result should be interpreted with caution. In the context of clinical trials of adjunctive corticosteroid therapy in sepsis and pneumonia that report improved outcomes, including decreased mortality, more high-quality research is needed (both RCTs and observational studies). Currently, we do not have sufficient evidence in this review to determine the effectiveness of corticosteroids for patients with influenza.

PLAIN LANGUAGE SUMMARY

Steroids for the treatment of influenza

Review question

We reviewed the evidence regarding the effect of additional ('adjunctive') steroid treatment in individuals with influenza infection.

Background

The majority of individuals with influenza have a fever, headache and a cough and get better without any specific treatment. However, a small proportion of people develop a more severe form of influenza, requiring admission to an intensive care unit in hospital. These patients are often prescribed steroids as part of their treatment, although the evidence that steroids are beneficial in these circumstances is controversial.

Study characteristics

We searched for studies comparing additional steroid treatment with no additional steroid treatment in individuals with influenza. This evidence is current to June 2015. We identified a total of 19 studies with 3459 individuals; none of them were clinical trials. The majority of studies investigated adults admitted to hospital with pandemic influenza in 2009 and 2010.

Key results

We did not find any relevant clinical trials on this topic. The evidence available from existing observational studies was of very low quality. We found that patients with influenza who received additional steroid treatment might have had a greater risk of death compared to patients who did not receive steroid treatment. Hospital-acquired infection was the main 'side effect' related to steroid treatment that was reported in the included studies; all studies reported a greater risk of hospital-acquired infection in the group treated with steroids. However, it was not possible to be certain if patients with more severe influenza were selected to receive steroid treatment in the first place. Therefore, it is not possible to be certain whether additional steroid treatment in patients with influenza is truly harmful, or not. Clinical trials of additional steroids in the treatment of individuals with influenza are therefore warranted to clarify the situation. In the meantime, the use of steroids in influenza remains a clinical judgement call.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Effect of corticosteroid therapy on influenza-related outcomes

Patient or population: individuals with influenza
Settings: in-hospital
Intervention: corticosteroid therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Control	Corticosteroid therapy			
Mortality	**141 per 1000**	**334 per 1000** (206 to 493)	**OR 3.06** (1.58 to 5.92)	1915 (13 studies)	⊕○○○ **very low**[a]
Hospital-acquired infection	See comment	See comment	Not estimable	619 (3 studies)	⊕○○○ **very low**[b]
Critical illness (composite outcome including death and intensive care unit admission)	See comment	See comment	Not estimable	322 (2 studies)	⊕○○○ **very low**[c]
Mechanical ventilation	See comment	See comment	Not estimable	377 (2 studies)	⊕○○○ **very low**[d]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Pooled analysis. We downgraded the quality of evidence from low (observational data) to very low due to high risk of indication bias (sicker adults with influenza were more likely to receive corticosteroids) and clinical/statistical heterogeneity (unadjusted estimates of odds ratio for mortality were presented in some studies and the definition of mortality varied across the studies). We upgraded the quality of evidence once as plausible confounding was likely to change the effect estimate.

[b]Results were not pooled. We downgraded the quality of evidence from low (observational data) to very low due to high risk of indication bias (sicker adults with influenza were more likely to receive corticosteroids) and clinical and statistical heterogeneity (unadjusted estimates of odds ratio for hospital-acquired infection were presented in all studies, and the definitions for hospital-acquired infection varied across the studies). We upgraded the quality of evidence once as plausible confounding was likely to change the effect estimate.

[c]Results were not pooled. We downgraded the quality of evidence from low (observational data) to very low due to high risk of indication bias (sicker adults with influenza were more likely to receive corticosteroids) and clinical and statistical heterogeneity (unadjusted estimates of odds ratio and risk ratio for critical illness were presented in all studies, and the definitions for critical illness varied across the studies). We upgraded the quality of evidence once as plausible confounding was likely to change the effect estimate.

[d]Results were not pooled. We downgraded the quality of evidence from low (observational data) to very low due to high risk of indication bias (sicker adults with influenza were more likely to receive corticosteroids) and clinical and statistical heterogeneity (unadjusted estimates of odds ratio for mechanical ventilation were presented in all studies). We upgraded the quality of evidence once as plausible confounding was likely to change the effect estimate.

BACKGROUND

Description of the condition

Influenza is a significant cause of morbidity and mortality worldwide and has a high financial burden. Seasonal influenza occurs annually during the winter months in temperate zones of both the Northern and Southern hemispheres and all year round in the tropics (Viboud 2006). Global estimates of seasonal influenza from the World Health Organization (WHO) report one billion cases, including three to five million cases of severe illness annually (WHO 2008). About 210,000 influenza-related respiratory deaths occur globally per influenza season; 81% of these in persons aged 65 years and above (Simonsen 2013). The reported per capita total cost of a case of influenza illness in national studies ranges from USD 27 to USD 52 in European countries and USD 45 to USD 63 in the United States (Peasah 2013). Estimates of the influenza-related hospitalisation rate in the United States range from 63 to 107 per 100,000 persons annually at a cost of USD 11,096 to USD 83,216 per admission; amongst adults, hospitalisation rates are highest in persons aged 65 years age and above (309/100,000) (Peasah 2013; Zhou 2012). The population-based incidence estimate for influenza-associated critical illness in the USA is 12 per 100,000 person-years; this represents 1.3% of all critical illness hospitalisations or 3.4% of critical illness hospitalisations during the influenza season (Ortiz 2014a). Estimates from the United Kingdom indicate an influenza-attributable annual GP consultation rate of 2156 per 100,000 population and a corresponding annual hospitalisation rate of 34 per 100,000 population (Cromer 2014).

Pandemic influenza occurs unpredictably and infrequently due to reassortment of the influenza virus or adaptive mutation of a virus that has crossed the species barrier (Taubenberger 2008). Although the case fatality ratio associated with the recent influenza A (H1N1) pandemic in 2009 and 2010 was lower in comparison to previous pandemics (0.03% versus 2.5% in 1918 and 1919) (Donaldson 2010), a modelling study of global mortality due to the recent pandemic estimated 201,200 respiratory deaths and 83,300 cardiovascular deaths, with 80% of the deaths in individuals younger than 65 years (Dawood 2012). This shift in mortality towards younger age groups was estimated to have led to between 334,000 and 1,973,000 'years of life lost' in the United States alone (Viboud 2010). Worldwide clinical data from the influenza A (H1N1) pandemic in 2009 revealed that more than one-fifth of hospitalised individuals experienced severe disease requiring admission to an intensive care unit (Jain 2009; Muthuri 2013; Richard 2012). The onset of critical illness following hospital admission occurred rapidly (median one day) and was commonly due to acute respiratory distress syndrome with refractory hypoxaemia, septic shock and/or multisystem organ failure, often requiring prolonged ventilation (Jain 2009; Kumar 2009). Critical care delivery systems were overwhelmed, especially in low and middle-income countries, affecting entire hospital services downstream (Ortiz 2013). The mortality associated with critical care admission due to severe influenza was high (14% to 22%) (Jain 2009; Richard 2012).

Current antiviral treatment options for influenza are limited to the neuraminidase inhibitors (NI) and adamantanes, although widespread adamantane use has been hampered by the global emergence of drug resistance (Deyde 2007). A Cochrane systematic review of randomised placebo-controlled trials (RCTs) reported a reduced time to first alleviation of symptoms by 0.6 to 0.7 days in NI treated adults, but no differences were seen between the two groups with regard to hospitalisation rates or occurrence of influenza-related adverse events (Jefferson 2014). In contrast, an individual patient level meta-analysis of over 29,000 patients with 2009 influenza A H1N1 virus (H1N1pdm09) infection from 78 observational studies across the world found that NI treatment at any time, in comparison to no treatment, was associated with a 19% reduction in mortality risk; early treatment (within two days of symptom onset) was associated with a 52% reduction in mortality risk in comparison to late treatment (Muthuri 2013).

Description of the intervention

Endogenous corticosteroids are produced principally in the adrenal glands from cholesterol and are regulated by the hypothalamic-pituitary-adrenal (HPA) axis (Molenaar 2012); they possess several anti-inflammatory, immunomodulatory and vascular properties including inhibition of pro-inflammatory cytokines, reduction of leucocyte trafficking, stimulation of apoptosis of T-lymphocytes, maintaining endothelial integrity and vascular permeability and regulation of vascular tone by inhibition of vasodilators (nitrous oxide) and increasing sensitivity to vasopressors (Coutinho 2011; Kaufmann 2007; Rhen 2005). These properties form the rationale for testing corticosteroids in sepsis and related conditions.

A systematic review of RCTs investigating sepsis and septic shock reported that low-dose corticosteroid use increased 28-day shock reversal and reduced intensive care unit length of stay and 28-day mortality (Annane 2009). For the treatment of bacterial meningitis, corticosteroids appear to reduce hearing loss and neurological complications (Brouwer 2010), while in tuberculous meningitis, an improvement in survival was reported (Prasad 2008).

With regard to respiratory infections, a Cochrane systematic review of systemic corticosteroid use in all-cause pneumonia found no overall mortality benefit, but a reduction in time to resolution of symptoms was seen; in a subgroup of individuals with severe pneumonia, a reduction in the need for mechanical ventilation and improved oxygenation was found (Chen 2011). A further meta-analysis that included additional RCTs reported a survival benefit from corticosteroid therapy in the subgroup of severe pneumonia (Nie 2012). A RCT in 2015 found a lower risk of treatment failure with adjunctive corticosteroid therapy in hospitalised pa-

tients with severe community-acquired pneumonia with a high inflammatory response (Torres 2015), while a RCT in hospitalised patients with community-acquired pneumonia found adjunctive corticosteroids were associated with a reduction in the time to clinical stability (Blum 2015). The most recent meta-analysis, including the latest studies, suggests an overall beneficial effect from adjunctive corticosteroids in the treatment of patients with community-acquired pneumonia (Siemieniuk 2015). There is limited evidence that systemic corticosteroids as adjunctive therapy to antibiotics in people with acute sinusitis may offer modest benefits for short-term symptom relief (Venekamp 2014). In children with croup, a review found that corticosteroid treatment was associated with a lower symptom score at six hours, re-admission rate and length of stay (Russell 2011). In infants and young children with acute viral bronchiolitis, no benefits were seen in hospital admission rates, or length of stay in hospital following systemic or inhaled corticosteroid use (Fernandes 2013).

The role of corticosteroids for the treatment of influenza is highly controversial. While some case series have reported improved outcomes with corticosteroid treatment of severe influenza (Quispe-Laime 2010), other cohort studies have suggested the opposite (Diaz 2012; Liem 2009). Despite the ongoing controversy, 9% of hospitalised individuals and up to 69% of critically ill individuals during the 2009 influenza A (H1N1) pandemic were prescribed corticosteroid therapy (Brun-Buisson 2011; Diaz 2012; Kumar 2009; Muthuri 2013). The WHO consultation on human influenza A (H5N1) infection reported that 47% to 70% of patients received corticosteroids during the 2004 to 2005 outbreak in South East Asia (WHO 2005).

How the intervention might work

Viral replication and production of cytokines through activation of the host innate immune system are central to the pathogenesis of influenza infection (de Jong 2006). Elevated or excessive production of cytokines (hypercytokinaemia) correlates with symptoms and fever in acute influenza (Kaiser 2001). Comparisons between patients with mild and severe pandemic influenza have revealed significantly higher levels of cytokines (especially interleukin-6) in the plasma of patients with severe disease (Yu 2011) and similar findings have been replicated in studies of severe seasonal influenza (Heltzer 2009). A combination of excessive pro-inflammatory cytokine induced inhibition of the HPA axis, substrate (cholesterol) deficiency, structural damage to the adrenal gland due to infarction of haemorrhage and peripheral corticosteroid resistance could lead to absolute or relative corticosteroid insufficiency during critical illness (Jaattela 1991; Liu 2002; Marik 2009). The overall incidence of adrenal insufficiency in patients with critical illness is estimated to be around 20% and up to 60% in those with sepsis and septic shock (Marik 2009). Administration of corticosteroids during critical illness, including severe influenza, may attenuate this state of adrenal insufficiency and help maintain homeostasis.

Why it is important to do this review

Treatment options for influenza are limited. Corticosteroids may offer an additional therapeutic option and although they are frequently prescribed for severely ill individuals with influenza, there is controversy regarding the benefits and harms. A systematic review of the current evidence would a) highlight the quality of the available evidence and b) valuably inform current clinical practice and future research needs.

OBJECTIVES

To systematically assess the effectiveness and potential adverse effects of corticosteroids as adjunctive therapy in the treatment of influenza, taking into account differences in timing and doses of corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), quasi-experimental designs and observational cohort studies of individuals with influenza investigating corticosteroid treatment versus no corticosteroid therapy were considered for inclusion. We excluded studies with case-control designs due to the inability to determine temporal effects of corticosteroids on the development of non-mortality outcomes. We excluded studies with fewer than 10 participants.

Types of participants

Individuals with:

1. clinically diagnosed influenza or influenza-like illness (defined as fever, cough, symptoms of upper respiratory tract infection (coryza, sore throat) and constitutional symptoms (headache, myalgia) of acute onset); and/or
2. microbiologically confirmed influenza through sampling of the respiratory tract (nasal swabs, throat swabs or bronchoalveolar lavage).

There were no restrictions on age, influenza subtypes or study setting.

Types of interventions

We considered studies investigating corticosteroid treatment versus no corticosteroid treatment for inclusion. There were no restrictions on the doses of corticosteroid nor the types of corticosteroid used. We considered corticosteroid administration by oral and intravenous routes.

Types of outcome measures

Primary outcomes

1. For studies of hospitalised patients:
   i) number of deaths at 30 days following admission (30-day mortality);
   ii) rate of admission to intensive care units.
2. For studies in the community setting:
   i) rate of hospitalisation;
   ii) time to resolution of symptoms;
   iii) 30-day mortality.

When studies reported mortality as an outcome following adjustment for potential confounders such as disease severity and patient demographics among other variables, this is referred to as 'adjusted mortality'.

Secondary outcomes

1. For studies of hospitalised patients:
   i) hospital re-admission rate at 30 days post-discharge;
   ii) number and nature of adverse events secondary to corticosteroid use, such as incidence of gastrointestinal bleeding, hospital-acquired infections and metabolic complications (e.g. hyperglycaemia, hypernatraemia);
   iii) proportion of patients requiring mechanical ventilation;
   iv) length of stay in hospital.
2. For studies in the community setting:
   i) number and nature of adverse events secondary to corticosteroid use, such as incidence of gastrointestinal bleeding, hospital-acquired infections and metabolic complications (e.g. hyperglycaemia, hypernatraemia).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 5), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to June week 1, 2015), EMBASE (1980 to June 2015), CINAHL (1981 to June 2015), LILACS (1982 to June 2015) and Web of Science (1985 to June 2015).

The search strategy implemented in CENTRAL and MEDLINE is listed below. We used the Cochrane Highly Sensitive Search Strategy for identifying randomised trials for the initial search in the MEDLINE database (Lefebvre 2011). We then repeated the MEDLINE search, replacing the randomised trial filter with the Scottish Intercollegiate Guidelines Network (SIGN) filter to identify observational studies (SIGN 2011). We combined these two searches to give the search results for MEDLINE. We repeated this process to search EMBASE (Appendix 1), CINAHL (Appendix 2), LILACS (Appendix 3) and Web of Science (Appendix 4), adapting the filter as needed.

MEDLINE (Ovid)

1 Influenza, Human/
2 exp Influenzavirus A/
3 exp Influenzavirus B/
4 (influenza* or flu).tw.
5 (h1n1 or h5n1 or h3n2).tw.
6 or/1-5
7 exp Adrenal Cortex Hormones/
8 corticosteroid*.tw,nm.
9 adrenal cortex hormon*.tw.
10 (adren* cortic* adj1 (hormone* or steroid*)).tw.
11 adrenocorticosteroid*.tw,nm.
12 adrenocorticoid*.tw,nm.
13 corticoid*.tw,nm.
14 glucocorticoid*.tw,nm.
15 hydroxycorticosteroid*.tw,nm.
16 exp Steroids/
17 steroid*.tw,nm.
18 (hydrocortisone* or prednisolone* or prednisone* or dexamethasone* or methylprednisolone*).tw,nm.
19 or/7-18
20 6 and 19

There will be no date, publication or language restrictions.

Searching other resources

We searched the Controlled Trials Registry for ongoing clinical trials (www.controlled-trials.com). We scrutinised the bibliographies of included studies and the last three years of three major infectious diseases conferences (Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asia Pacific Society of Infection Control (APSIC)) to identify potentially eligible studies. Following execution of the search strategy, we individually contacted four domain experts to ensure relevant studies had been identified (see Acknowledgements).

Data collection and analysis

Selection of studies

Two review authors (CR, WSL) independently reviewed all the citations retrieved using the search strategy described above. We selected studies in two stages: analysis of study titles and abstracts in the first stage, followed by analysis of the full text of the articles.

A third review author (JVT) resolved disagreements at any of these stages through discussion.

Data extraction and management

Two review authors independently extracted data (CR extracted data from all eligible studies independently; JLB, JVT and WSL shared the data extraction of all included studies) using a standardised proforma that was previously piloted and specifically adapted for this review. We obtained the following data from studies:

1. characteristics of study (design, setting, country, enrolment period, methodological details including 'risk of bias' criteria for RCTs and the Newcastle-Ottawa Scale for non-randomised trials and comparative observational studies);
2. characteristics of participants (inclusion and exclusion criteria, demographics, co-morbid illnesses, disease severity, numbers in each group);
3. characteristics of intervention (type of steroid, route of administration, dose, timing of corticosteroid use (early versus late) and duration of treatment, co-interventions administered);
4. outcome measures.

Assessment of risk of bias in included studies

Two authors (CR, JLB) independently assessed the methodological quality of experimental studies using the Cochrane 'Risk of bias' tool in the following domains (Higgins 2011):

1. adequacy of the method for generating the randomisation sequence;
2. adequacy of the method for allocation concealment;
3. blinding of participants, clinicians and outcome assessors with regards to the intervention given;
4. incomplete outcome data (participants lost to follow-up in each treatment group and reasons for losses reported);
5. analysis of participants in the groups to which they were originally randomised (intention to treat (ITT) principle);
6. selective outcome reporting (all primary outcomes listed in the study protocol that are relevant to this review reported);
7. other potential sources of bias.

We used the validated 'star system' of the Newcastle-Ottawa Scale to assess the risk of bias at the outcome level in observational studies in the following three domains (Newcastle-Ottawa Scale 2014):

1. selection of study groups;
2. comparability of groups;
3. ascertainment of outcome.

Measures of treatment effect

We extracted dichotomous outcome data from individual studies as tabulated data from which risk ratios (RR) or odds ratios (OR) and 95% confidence intervals (CI) were estimated. We extracted adjusted outcome measures as ORs or hazard ratios (HRs) with 95% confidence intervals (CIs) and presented these separately in pooled analyses. For normally distributed continuous data, we calculated mean difference or standardised mean difference with corresponding 95% CIs. We used medians and inter-quartile ranges for continuous data that were not normally distributed.

Unit of analysis issues

We considered the individual participant to be the unit of analysis for RCTs. We analysed cluster-RCTs allowing for that level of randomisation.

Dealing with missing data

We analysed data on an ITT basis. For dichotomous outcomes, we assessed the effect assuming participants with missing data had a poor outcome. We did not use any form of imputation for participants with missing continuous outcome data. We consulted the CONSORT-type flow chart of participants through the study if available (Schulz 2010). If a flow chart was not available, we looked for information in the text of the results to determine whether all participants included in the study had been analysed. In case of ambiguity, we contacted the trial authors to seek further information.

In the case of missing data relating to results, for example, measures of dispersion, we contacted the trial authors of the study to request further information.

Assessment of heterogeneity

We used the I^2 statistic to assess heterogeneity across experimental and observational studies. We considered a value greater than 50% to reflect substantial heterogeneity between the findings of RCTs (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). However, for observational studies, due to the inherent biases within their design, we considered a value greater than 75% to reflect substantial heterogeneity.

Assessment of reporting biases

We assessed funnel plots for publication bias (small study bias).

Data synthesis

One review author (CR) entered data into Review Manager (RevMan 2014), and two review authors (CR, JLB) independently summarised the data. In the case of experimental studies, where the interventions and populations were similar, we used a random-effects meta-analysis to pool data due to the potential for inherent biases in the studies. We elected only to use the random-effects model to pool data due to the likely differences in the effectiveness of corticosteroids by patient characteristics. We did not use a fixed-effect model to analyse the data because a) there was a clear

rationale for choosing the random-effects model, and b) there was no concern about the influence of small study effects.
For observational studies, we extracted tabulated data, crude estimates and adjusted estimates of effect from the studies. We extracted adjusted outcome measures as ORs or HRs with 95% CIs and presented separately in pooled analyses. We used a similar meta-analysis method to pool data from observational studies as described for the RCTs. Where data were available, we presented subgroup analyses of adjusted or unadjusted estimates separately (if both types of data were available, we used adjusted estimates of effect in preference to minimise potential confounding between the treatment groups).

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table for the outcomes of mortality, adverse events, rates of mechanical ventilation and critical disease (composite outcome including death and intensive care unit admission). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and we used GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade or upgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses in the following areas if possible:

1. daily corticosteroid dose (low versus high; in adults low-dose is defined as hydrocortisone ≤ 300 mg, dexamethasone ≤ 12 mg, prednisolone ≤ 75 mg, methylprednisolone ≤ 60 mg) (Annane 2004);
2. timing of corticosteroid use (early versus late; early defined as < four days of onset of symptoms and late ≥ four days) (Annane 2002; Jain 2009; Nguyen-Van-Tam 2010);
3. duration of corticosteroid course (short versus long course, short course defined as < five days and long course ≥ five days) (Annane 2004);
4. adult versus child population (adult defined as ≥ 16 years);
5. route of administration (intravenous, oral);
6. seasonal influenza versus pandemic/outbreak influenza.

Sensitivity analysis

We performed sensitivity analyses to assess the effect of study design on the primary and secondary outcomes using stratification if a sufficient number of studies were present.

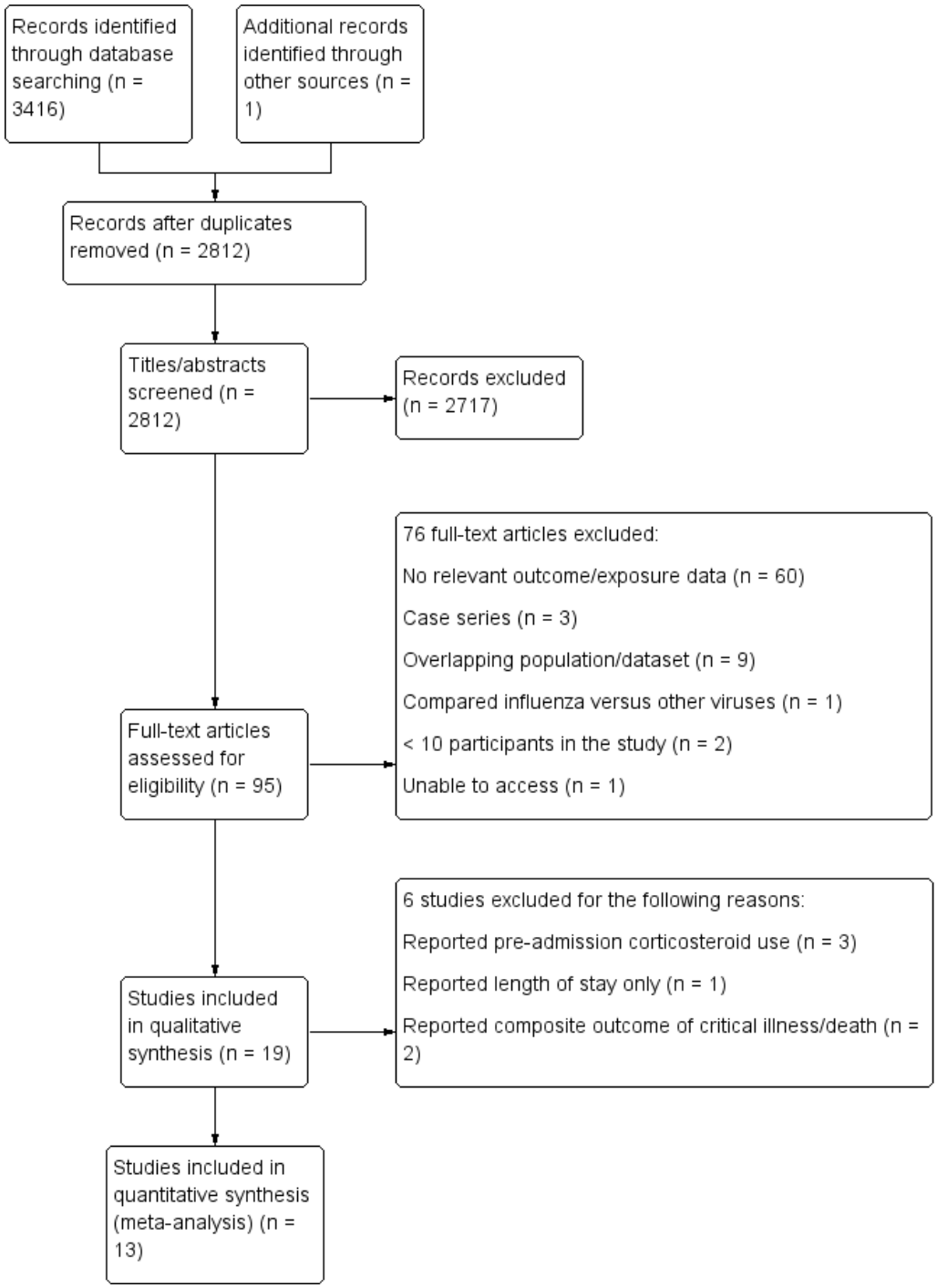
RESULTS

Description of studies

Results of the search

The search strategy identified 3416 articles, of which we assessed 2812 articles in first stage of the selection process after removal of duplicate articles (Figure 1). We scrutinised the full text of 95 potentially eligible articles, yielding 19 articles for inclusion in the systematic review. The main reason for exclusion of 76 articles was the lack of data comparing corticosteroid use versus no corticosteroid use; 10 of these studies that came closest to being included in the review and their respective reasons for exclusion have been summarised in the Characteristics of excluded studies table. Of articles included in the systematic review, 13 were included in the meta-analysis of mortality (Balaganesakumar 2013; Brun-Buisson 2011; Chawla 2013; Diaz 2012; Kim 2011; Li 2012; Liem 2009; Linko 2011; Mady 2012; Patel 2013; Sertogullarindan 2011; Viasus 2011; Xi 2010). We included the remaining six articles in the narrative synthesis only, as three studies investigated corticosteroid therapy prior to the diagnosis of influenza (Boudreault 2011; Delgado-Rodriguez 2012; Wu 2012). Three reported outcomes other than mortality according to corticosteroid use (Han 2011; Jain 2009; Kudo 2012).

Figure 1. Study flow diagram.



Included studies

The study design, participant, intervention and outcome characteristics of the included studies are summarised in Table 1. All were observational designs. Outcome data according to corticosteroid use were reported for a total of 3459 individuals. All studies were conducted, at least in part, within a hospital setting: seven studies consisted only of individuals admitted to the intensive care unit (ICU) (n = 1140); 10 studies investigated admissions to both ICUs and hospital wards (n = 1970); one study included individuals from non-ICU wards only (n = 143); and one study investigated both out-patients and in-patients (n = 206). The viral aetiology of individuals included in the studies was as follows: 13 studies of 2009 influenza A H1N1 virus (H1N1pdm09) (n = 3072); two studies of seasonal influenza (n = 349); and one study of influenza A (H5N1) (n = 38).

The median age of the cohort or corticosteroid treatment groups was reported in 13 studies (varying from 8 to 51 years). Of seven studies reporting disease severity according to corticosteroid treatment, adults receiving corticosteroid therapy had higher disease severity scores in comparison to their respective comparator groups in three studies (n = 543) (Kim 2011; Linko 2011; Viasus 2011), while the remaining four studies reported no difference in disease severity scores between the two groups (n = 749) (Table 1) (Brun-Buisson 2011; Diaz 2012; Han 2011; Mady 2012).

In all studies, comparisons were made between patients treated with or without corticosteroids in addition to supportive treatment, including antiviral agents. Eight studies reported the doses or regimens of corticosteroid administered; in four studies, the mean/median dose of corticosteroid therapy varied between 67.5 mg to 117.5 mg of prednisolone equivalent per day (Brun-Buisson 2011; Kim 2011; Linko 2011; Xi 2010), and four studies reported daily regimens of methylprednisolone 1 mg to 6 mg per kg (equivalent to 1.25 mg to 7.5 mg prednisolone per kg) (Table 1) (Kudo 2012; Liem 2009; Mady 2012; Patel 2013). The median duration of corticosteroid therapy was reported in four studies and varied from 5.1 to 11.0 days.

Risk of bias in included studies

As all identified studies were observational, we used the Newcastle-Ottawa Scale to assess risk of bias throughout this review. The risk of bias for 27 reported outcomes from 19 studies included in this review is summarised in Table 2. We awarded a maximum score of four stars for the 'selection' domain to the following studies and their respective outcomes: Jain 2009 (ICU admission/death versus survival/no ICU admission); Kim 2011 (mortality, mechanical ventilation, length of stay and hospital-acquired infection); Kudo 2012 (length of stay); Liem 2009 (in-hospital mortality); Linko 2011 (in-hospital mortality, length of stay, mechanical ventilation); Viasus 2011 (in-hospital mortality, hospital-acquired infection) and Wu 2012 (influenza requiring hospitalisation). We gave the lowest score of two stars for the 'selection' domain to the following studies: Balaganesakumar 2013 (mortality); Boudreault 2011 (time to death); Li 2012 (mortality) and Patel 2013 (mortality).

The 'comparability' domain performed the poorest across all the studies in the risk of bias assessment. We awarded a maximum of two stars to the following studies and their respective outcomes: Brun-Buisson 2011 (in-hospital mortality); Delgado-Rodriguez 2012 (composite outcome of ICU admission and mortality); Diaz 2012 (ICU mortality); Han 2011 (critical illness); Kim 2011 (mortality) and Linko 2011 (in-hospital mortality). The majority of the remainder of the studies failed to score any stars for this domain.

The 'outcome' domain performed the best across all studies, with 15 of the 19 studies achieving a maximum score of three stars across all assessed outcomes; the remainder of the four studies achieved two stars: Balaganesakumar 2013 (mortality); Boudreault 2011 (time to death); Diaz 2012 (ICU mortality); and Kudo 2012 (length of stay).

Effects of interventions

See: **Summary of findings for the main comparison** Effect of corticosteroid therapy on influenza-related outcomes

The 15 studies of 2009 influenza A H1N1 virus (H1N1pdm09) reported no difference in or greater adverse outcomes associated with corticosteroid use. The single study of influenza A/H5N1 found that corticosteroid therapy was associated with increased mortality following adjustment for neutropenia as a marker of disease severity (Liem 2009). Two studies of individuals with seasonal influenza failed to find any benefits associated with corticosteroid therapy (Boudreault 2011; Wu 2012). The inclusion criteria in these studies included any influenza-related hospital admission or intensive care unit (ICU) admission, severe respiratory failure (adult respiratory distress syndrome (ARDS) or requiring mechanical ventilation), septic shock, multi-organ failure or 'critical illness'. However, it was not clear why some patients within these cohorts received systemic corticosteroid therapy while others did not. In particular, whether corticosteroid therapy was initiated primarily for treatment of unstable co-morbid illnesses (including asthma and chronic obstructive pulmonary disease (COPD)) was not apparent.

Primary outcomes

Studies of hospitalised patients

1. Number of deaths at 30 days following admission (30-day mortality)

Due to heterogeneity in studies reporting timing of mortality from hospital admission, stratification by 30-day mortality was not possible as stated in the protocol (Table 3). We graded the quality of the evidence specific to mortality as very low (Summary of findings for the main comparison) (GRADE 2011). Meta-analysis of 13 studies (n = 1917 patients) revealed a significant increase in the odds of mortality with corticosteroid use, with substantial statistical heterogeneity (odds ratio (OR) 3.06, 95% confidence interval (CI) 1.58 to 5.92; I^2 statistic = 80%) (Analysis 1.1; Figure 2). Subgroup analysis of unadjusted and adjusted estimates of mortality showed a similar association with corticosteroid therapy (OR 2.99, 95% CI 1.18 to 7.57; I^2 statistic = 86% (Analysis 1.1.1.) and OR 2.82, 95% CI 1.61 to 4.92 (Analysis 1.1.2); I^2 statistic = 0%, respectively). The test for subgroup differences between adjusted and unadjusted mortality was not statistically significant (P value = 0.92). There was no clear indication of publication bias on funnel plot analysis (Figure 3).

Figure 2. Meta-analysis of studies reporting mortality

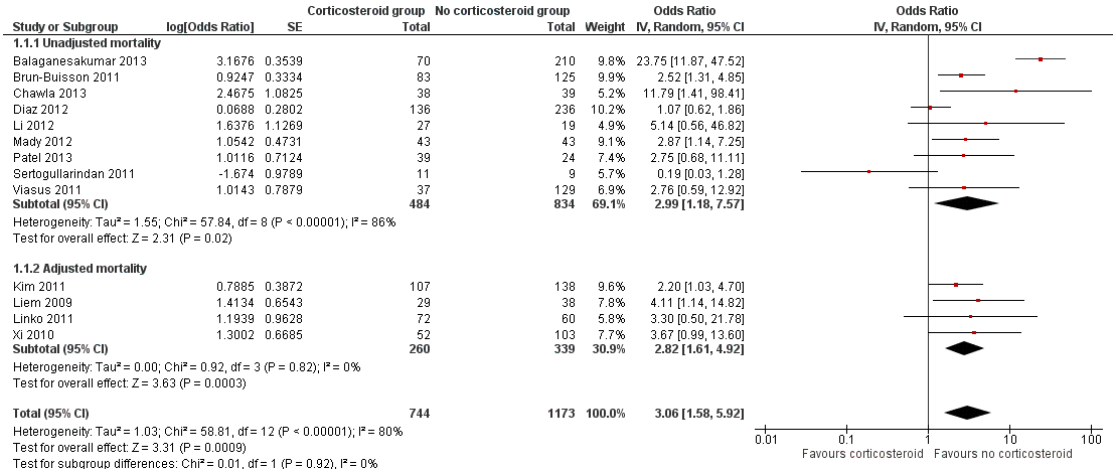
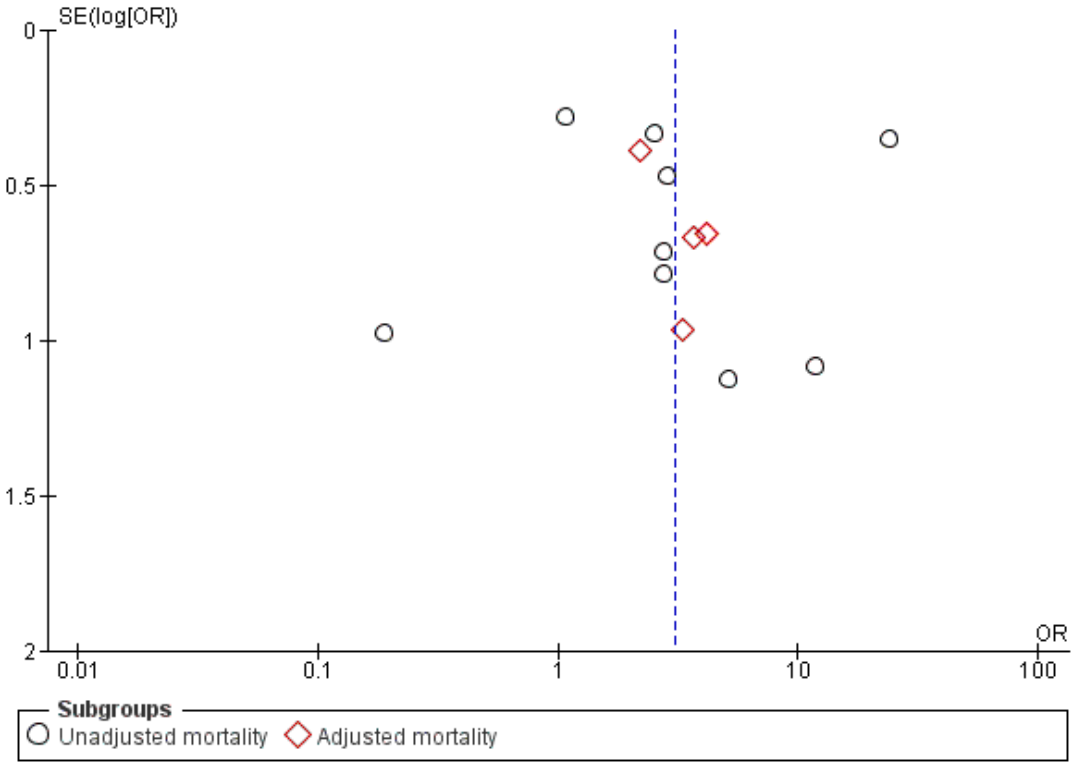


Figure 3. Funnel plot of studies reporting mortality



Two studies reported adjusted hazard ratios (HRs) for mortality associated with corticosteroid therapy; the first reported harm (HR 2.59, 95% CI 1.42 to 4.73) (Brun-Buisson 2011), while the second study found no association (HR 1.06, 95% CI 0.63 to 1.80) (Diaz 2012).

2. Rate of admission to intensive care units

Studies reporting outcomes other than mortality are summarised in Table 4. Of the studies that were not conducted entirely in an ICU setting (n = 12), two studies reported composite outcomes including ICU admission ('critical disease'), which were stratified according to corticosteroid therapy (Han 2011; Jain 2009). We graded the quality of the evidence specific to 'critical disease' as very low (Summary of findings for the main comparison). A retrospective cohort study in the USA of individuals hospitalised with 2009 influenza A H1N1 virus (H1N1pdm09) infection reported a greater risk of critical care admission/death (unadjusted OR 2.37, 95% CI 1.29 to 4.37) associated with corticosteroid therapy (Jain 2009). In the other retrospective cohort study from China, the risk of critical disease (defined as death, respiratory failure, septic shock, failure or insufficiency of ≥ two non-pulmonary organs, mechanical ventilation or ICU admission) adjusted for co-morbid illness, obesity and pregnancy, was greater in the group treated with corticosteroid therapy (adjusted risk ratio (RR) 2.4, 95% CI 1.3 to 4.4) (Han 2011).

Studies in the community setting

We did not identify any studies conducted entirely in a community setting.

1. Rate of hospitalisation

None of the included studies reported this outcome stratified according to corticosteroid use.

2. Time to resolution of symptoms

None of the included studies reported this outcome stratified according to corticosteroid use.

3. 30-day mortality

None of the included studies reported this outcome stratified according to corticosteroid use.

Secondary outcomes

For studies of hospitalised patients

1. Hospital re-admission rate at 30 days post-discharge

None of the included studies reported this outcome stratified according to corticosteroid use.

2. Number and nature of adverse events secondary to corticosteroid use, such as incidence of gastrointestinal bleeding, hospital-acquired infections and metabolic complications (e.g. hyperglycaemia, hypernatraemia)

A summary of studies reporting nosocomial infections according to corticosteroid use is provided in Table 5. The unadjusted odds of nosocomial infection were generally greater in the groups treated with corticosteroid therapy compared to no corticosteroid. We graded the quality of the evidence related to hospital-acquired infection as very low (Summary of findings for the main comparison)

3. Proportion of patients requiring mechanical ventilation

Two studies reported greater unadjusted odds for mechanical ventilation in the group treated with corticosteroid therapy (Kim 2011; Linko 2011) (Table 4).

4. Length of stay in hospital

Four studies reported length of stay according to corticosteroid use; all were unadjusted for disease severity (Table 4). Two studies found a longer length of stay associated with corticosteroid use (Kim 2011; Linko 2011), while the others reported no statistically significant difference (Brun-Buisson 2011; Kudo 2012).

For studies in the community setting

1. Number and nature of adverse events secondary to corticosteroid use

None of the included studies reported this outcome stratified according to corticosteroid use.

Sensitivity analysis

Pooled analysis of 12 studies investigating individuals with 2009 influenza A H1N1 virus (H1N1pdm09) infection only, excluding one study of influenza A/H5N1 (Liem 2009), found corticosteroid use to be associated with greater odds of mortality (OR 2.98, 95% CI 1.47 to 6.04) with high statistical heterogeneity (I^2 statistic = 81%).

Subgroup analysis

A summary of outcomes according to the different corticosteroid regimens is in Table 6; the number of studies was insufficient to perform subgroup analyses according to the various reported regimens. Only one study compared low versus high doses of corticosteroid treatment (Xi 2010). Two studies compared early verus later/no corticosteroid treatment; one defined early treatment as within three days of mechanical ventilation (Brun-Buisson 2011), and the other as within three days from onset of symptoms (Han 2011). Outcomes stratified according to age groups (children versus adults) and route of corticosteroid administration (intravenous versus oral) were not reported in the studies included in this review.

Impact of systemic corticosteroid use prior to the diagnosis of influenza

A study of corticosteroid use for the treatment of graft versus host disease in haematopoietic stem cell transplant (HSCT) recipients, in the two weeks prior to the diagnosis of seasonal influenza, found no observed differences in time to death between individuals receiving low-dose corticosteroid therapy (< 1 mg/kg/day of methylprednisolone) (adjusted HR 1.1, 95% CI 0.4 to 3.6) or high-dose corticosteroid therapy (≥ 1 mg/kg/day of methylprednisolone) (adjusted HR 1.1, 95% CI 0.3 to 3.5), in comparison to no prior corticosteroid therapy (Boudreault 2011). A mixed cohort of outpatients and in-patients with seasonal influenza reported increased odds of 'complicated influenza' (defined as the need for hospitalisation due to pneumonia, neurological complications, invasive bacterial infection, myocarditis or pericarditis) associated with corticosteroid therapy (adjusted OR 12.19, 95% CI 3.26 to 45.53) (Wu 2012). Corticosteroid therapy in the 90 days prior to hospital admission was independently associated with poor outcome (defined as a composite outcome of ICU admission and death) (adjusted OR 3.37, 95% CI 1.39 to 8.20) in a study of individuals hospitalised with 2009 influenza A H1N1 virus (H1N1pdm09) infection (Delgado-Rodriguez 2012).

DISCUSSION

Summary of main results

The main findings of this systematic review are that: 1) there are no completed randomised controlled trials (RCTs) reporting the impact of adjunctive corticosteroid therapy on clinical outcomes in patients with influenza infection; the available data from observational studies are of very low quality, and 2) the available data suggest corticosteroid therapy might be associated with up to a three-fold greater odds of mortality. These results should be interpreted with caution.

Overall completeness and applicability of evidence

The findings from this review must be viewed in the light of two important considerations. Firstly, the indications for corticosteroid therapy were not fully specified in many studies. In some instances, the stated rationale was adult respiratory distress syndrome (ARDS) and septic shock (Brun-Buisson 2011; Diaz 2012; Kim 2011; Xi 2010). However, at one extreme, corticosteroid therapy may have been used as 'a last attempt' in individuals with refractory illness. Conversely, they may have been used to treat less severe underlying comorbid illnesses such as exacerbations of asthma. The majority of studies included in this review relate to the 2009 pandemic when revised guidance from the World Health Organization (WHO) in February 2010 would have applied (WHO 2010). However, adherence to that guidance, which recommended that "patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons or as part of an approved research protocol" is not known. Over the same period, the 'Surviving Sepsis Campaign' recommended the use of corticosteroid therapy only in the setting of vasopressor-dependent septic shock (Dellinger 2013). The use of corticosteroids in the context of influenza infection, but for different clinical indications (notably asthma), has been previously shown to be associated with different outcomes (Myles 2013); this may reflect both the different mechanisms of action of corticosteroids depending on the underlying pathophysiology and the impact of bias by indication in reports from observational studies. This is compounded by the lack of consistent adjustment for disease severity across available studies.

The second consideration relates to the doses of corticosteroids used. These were poorly specified in many instances and, where reported, a higher daily dose was used (prednisolone equivalent > 50 mg daily) than is typically recommended for the treatment of septic shock or exacerbations of airways disease such as asthma (BTS 2008; Dellinger 2013; NICE 2010). Variability in corticosteroid dose and administration schedule are both factors associated with treatment outcomes in the setting of severe sepsis; in particular, high doses given in short bursts have not been associated with benefit compared to low doses given for longer durations (≥ five days) (Annane 2009). The use of higher doses of corticosteroids may explain the greater risk from secondary bacterial pneumonias due to *S. aureus*,*K. pneumoniae*,*A. baumannii and P. aeruginosa* observed with corticosteroid therapy in some studies (Kim 2011). In a study elsewhere, corticosteroid use was also found to be an independent risk factor for the development of invasive fungal infections in adults admitted to the intensive care unit (ICU) with influenza (Wauters 2012).

The mechanisms behind potential harm from corticosteroids, aside from the risks from nosocomial infections, are not well defined. In patients with influenza A (H3N2) infection, systemic corticosteroid use for exacerbations of asthma or chronic obstructive pulmonary disease (COPD) was found to be associated with delayed viral clearance (Lee 2009). A study of individuals hospitalised with 2009 influenza A H1N1 virus (H1N1pdm09) infection found that corticosteroid therapy was associated with persistent viral shedding (defined as the detection of virus on real-time polymerase chain reaction (RT-PCR) at day seven after diagnosis on nasopharyngeal swabs) (Giannella 2011). A similar observation was made in haematopoietic stem cell transplant recipients with 2009 influenza A H1N1 virus (H1N1pdm09) infection (Choi 2011). In turn, slower clearance of viral load was associated with mortality from ARDS in patients with 2009 influenza A H1N1 virus (H1N1pdm09) infection (To 2010). Though causation cannot be inferred from these studies, exposure to systemic corticosteroids without concurrent antiviral treatment, as was likely for some patients in the studies reviewed, may proffer the highest risk of harm (Jain 2009; Wu 2012).

There was no evidence of publication bias in the effect of corticosteroids on the odds of mortality, where we found that the treatment effects in smaller studies were similar to those estimated in the larger studies. Although the test was likely to have sufficient power from including 13 studies in the funnel plot, we acknowledge their limitation of being subjective.

Quality of the evidence

The pooled analysis of mortality showed high statistical heterogeneity, most likely due to the inclusion of unadjusted estimates of mortality. Clinical heterogeneity was apparent across included studies. Specifically, disease severity was measured using a wide variety of clinical risk scores and mortality was reported at different time points; the rationale for corticosteroid use was inconsistent across studies; there was variation in the treatment groups with regard to the timing, dosage, duration and type of corticosteroid used; and the co-interventions for the comparator groups across studies were not uniform as varying proportions of adults were treated with antivirals and/or antibiotics. We graded the overall quality of the evidence for mortality, adverse events, rate of mechanical ventilation and critical disease as 'very low' due to the high likelihood of indication bias, and clinical and statistical heterogeneity in the included observational studies (Summary of findings for the main comparison).

Potential biases in the review process

The available evidence identified consists solely of observational data. We noted a high degree of correlation between corticosteroid therapy and potential confounders for measured outcomes (such as disease severity and the presence of co-morbid illness) in some studies (Kim 2011; Linko 2011; Viasus 2011); hence unadjusted effect estimates are likely to be confounded by indication.

Agreements and disagreements with other studies or reviews

A large, multicentre, prospective cohort study of 220 individuals admitted to ICUs across Europe with 2009 influenza A H1N1 virus (H1N1pdm09) infection was not included in this review due to overlapping study populations; it found no association between corticosteroid use and ICU admission and ICU mortality, following adjustment for age, co-morbid illnesses and disease severity (adjusted HR 1.3, 95% CI 0.7 to 2.4, P value = 0.4) (Martin-Loeches 2011).

The association of increased odds of mortality with adjunctive corticosteroid therapy, as found in this review, is also in contrast to the evidence base from clinical trials of corticosteroids in the setting of sepsis and pneumonia. Specifically, in a meta-analysis of 17 RCTs (n = 2138) of corticosteroids in severe sepsis, subgroup analysis found that prolonged low-dose corticosteroid therapy was associated with lower 28-day mortality (Annane 2009). Similarly, a meta-analysis of 12 RCTs (n = 1974) of adults with community-acquired pneumonia concluded that adjunctive corticosteroid therapy may reduce mortality, need for mechanical ventilation and hospital length of stay (Siemieniuk 2015). Larger trials of corticosteroid therapy in severe sepsis and severe pneumonia are in progress and should provide more robust data within the next few years (Bos 2012; Bridges 2011; Venkatesh 2013).

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence from observational studies is of low quality with confounding by indication a major potential concern. We do not have sufficient evidence in this review to determine the effectiveness of corticosteroids for patients with influenza. There is a need for more robust evidence on the role of corticosteroids in the management of influenza before a firm recommendation for clinical practice can be made.

Implications for research

The most important need is for high-quality, blinded randomised controlled trials (RCTs), which will minimise the biases inherent in observational designs and thereby provide the necessary evidence base to inform future clinical practice. Future observational studies investigating corticosteroids for the treatment of influenza should state the precise rationale for the administration of corticosteroid therapy in study participants (such as treatment of complications of influenza, co-morbid illness or use solely as adjunctive therapy). The regimens of corticosteroid therapy should be explicitly stated with regards to the dose, timing of initiation and duration of therapy, and differences in regimens need to be considered when interpreting the results of studies. Differences in the administration of co-interventions between the corticosteroid treated and untreated groups, including antiviral drugs and antibiotics, also need to be accounted for. Outcome measures need to be adjusted for potential confounders including imbalances in baseline characteristics and disease severity at the very least. A meta-analysis of individual patient level data from observational studies may be able to overcome some of the inconsistencies across study-level data.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Balaganesakumar 2013

Methods	Multicentre, prospective cohort study
Participants	**Country:** India (Tamil Nadu) **Setting:** in-hospital **Number of individuals:** 1302 (280 included in case-control analysis) **Inclusion criteria:** individuals with laboratory-confirmed influenza **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age of cohort (years):** 26 (IQR 1 to 82) **Female sex:** 666 (51%)
Interventions	**Groups:** corticosteroids (n = 70) and no corticosteroids (n = 210)
Outcomes	**Mortality**
Risk of bias (Newcastle-Ottawa Scale)	**Mortality** Selection domain score (max 4): 2 Comparability domain score (max 2): 1 (no adjustment for disease severity) Outcome domain score (max 3): 2
Notes	-

Boudreault 2011

Methods	Single-centre, retrospective cohort
Participants	**Country:** USA (Washington) **Setting:** in-hospital **Number of individuals:** 143 **Inclusion criteria:** individuals undergoing haematopoietic stem cell transplantation presenting with respiratory tract infections **Definition of influenza:** laboratory-confirmed **Influenza type:** seasonal **Median age (years):** cohort 42.0 (IQR 31.0 to 53.0); no CS group 42.0 (IQR 32.0 to 51.0); low-dose CS group 42.0 (IQR 28.0 to 53.0); high-dose CS group 40.0 (IQR 32.0 to 54.0) **Male sex:** cohort 83 (58.0); no CS group 36 (57.0); low-dose CS group 29 (67.0); high-dose CS group 18 (49.0)
Interventions	**Groups: highest CS dose in 2/52 preceding influenza diagnosis.** No CS (n = 63); low-dose CS (n = 43); high-dose CS (n = 37) **Definitions for dose:** low-dose (prednisolone/methylprednisolone < 1 mg/kg/day); high-dose (prednisolone/methylprednisolone >= 1 mg/kg/day) **Co-interventions:** antiviral therapy

Boudreault 2011 (*Continued*)

Outcomes	**Time to death/time to influenza-associated death:** hazard ratios presented following multivariate analysis. Variables in the multivariate models included CS treatment, antiviral therapy and lymphocyte count **Hypoxaemia** **Lower respiratory tract disease** **Mechanical ventilation** **Adverse events:** prolonged viral shedding
Risk of bias (Newcastle-Ottawa Scale)	**Time to death** Selection domain score (max 4): 2 Comparability domain score (max 2): 1 (no adjustment for age/disease severity) Outcome domain score (max 3): 2
Notes	-

Brun-Buisson 2011

Methods	Multicentre, retrospective analysis of prospectively collected data
Participants	**Country:** France (French REVA-SRLF registry) **Setting:** ICU **Number of sites:** 78 **Number of individuals:** 208 **Inclusion criteria:** severe respiratory failure (defined as adult respiratory distress syndrome or need for mechanical ventilation) **Exclusion criteria:** chronic steroid use or steroid use in ICU other than for respiratory failure; patients receiving CS as rescue therapy (initiated 2 weeks after commencing mechanical ventilation); admitted for other decompensated underlying illness **Definition of influenza:** laboratory-confirmed or clinically suspected **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** cohort 47.0 (IQR 35.0 to 55.0); no CS group 45.0 (IQR 35.0 to 55.0); CS group 49.0 (IQR 34.0 to 56.0) **Female sex:** cohort 103 (49.5); no CS group 56.0 (44.8); CS group 47 (56.6) **C-morbid illnesses:** immunodepression; no CS 23 (18.4); CS 23 (18.4) **Disease severity:** Median Simplified Acute Physiology Score (version 3) (SAPS 3): cohort 52.0 (IQR 44.0 to 64.0); no CS group 53.0 (IQR 46.0 to 66.0); CS group 51.0 (IQR 44.0 to 61.0) (P value = 0.25 for 2 groups)
Interventions	**Groups:** no CS (n = 125) versus CS (n = 83) **Median daily dose:** 270 (IQR 200 to 400) mg of hydrocortisone equivalent **Timing of therapy:** initiated within median 1 day (IQR 0 to 6) of mechanical ventilation **Duration of treatment:** median 11 days (IQR 6 to 20)
Outcomes	**Hospital mortality:** hazard ratios presented following a) adjustment for immunosuppression, SAPS3 and vasopressor use in a Cox regression model; and b) propensity score matching **Length of ICU stay** **Adverse events** (ICU-acquired infections)

Brun-Buisson 2011 (*Continued*)

Risk of bias (Newcastle-Ottawa Scale)	**In-hospital mortality** Selection domain score (max 4): 3 Comparability domain score (max 2): 2 Outcome domain score (max 3): 3 **Length of ICU stay** Selection domain score (max 4): 3 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3 **ICU-acquired infection** Selection domain score (max 4): 3 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Chawla 2013

Methods	Single-centre, retrospective cohort study
Participants	**Country:** India (New Delhi) **Setting:** ICU **Number of individuals:** 77 **Inclusion criteria:** individuals with laboratory-confirmed influenza **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** cohort 41 (10 to 72) **Male sex:** cohort 44 (57.1)
Interventions	**Groups:** CS (n = 38) versus no CS (n = 39)
Outcomes	**Mortality**
Risk of bias (Newcastle-Ottawa Scale)	**Mortality** Selection domain score (max 4): 3 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Delgado-Rodriguez 2012

Methods	Multicentre, prospective cohort
Participants	**Country:** Spain (Andalusia, Catalonia, Castile and Leon, Madrid, Navarre, the Basque Country and Valencia) **Setting:** in-hospital **Number of sites:** 36 **Number of individuals:** 813

Delgado-Rodriguez 2012 (*Continued*)

	Inclusion criteria: influenza-like illness, acute respiratory tract infection, septic shock, multi-organ failure **Exclusion criteria:** nosocomial influenza infection **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** cohort 41.0 (IQR 19.0 to 55.0); not reported for individual treatment groups **Female sex:** cohort 410 (50.4); not reported for individual treatment groups **Co-morbid illness:** no data for individual CS groups **Disease severity:** not reported
Interventions	Groups: CS use 90 days prior to admission (n = 31) versus no prior CS use (n = 782)
Outcomes	Reported independent association between CS use with poor outcome (composite outcome of ICU admission and in-hospital death) and length of stay
Risk of bias (Newcastle-Ottawa Scale)	**ICU admission and mortality** Selection domain score (max 4): 3 Comparability domain score (max 2): 2 Outcome domain score (max 3): 3
Notes	Study reporting outcomes according to pre-admission antibiotic use

Diaz 2012

Methods	Multicentre, retrospective analysis of prospectively collected data
Participants	**Country:** Spain (voluntary ICU registry) **Setting:** ICU **Number of sites:** 148 **Number of individuals:** 372 **Inclusion criteria:** influenza-like illness; respiratory failure requiring ICU admission; microbiological confirmation of influenza **Exclusion criteria:** **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Mean age (years):** cohort 43.4 (± 13.3); no CS group 43.6 (± 13.6); CS group 43.1 (12.9) **Male sex:** cohort 205 (55.1); no CS group 69 (57.6); CS group 69 (50.7) **Co-morbid illnesses:** asthma - no CS 7.6 (18), CS 15.4 (21); COPD - no CS 11.4 (27), CS 13.2 (18) **Disease severity** (Mean Acute Physiology and Chronic Health Evaluation Score II score (APACHE II)): cohort 12.8 (± 6.5); no CS group 12.5 (± 6.7); CS group 13.2 (± 6.3) (P value = 0.318 for 2 groups)
Interventions	**Groups:** CS (n = 136) versus no CS (n = 236) treatment Data regarding dose, duration and timing not available **Co-interventions:** antiviral therapy administered to all

Diaz 2012 (*Continued*)

Outcomes	**ICU mortality:** presented as adjusted hazard ratios adjusted for severity and co-morbid illness (asthma, chronic kidney disease, morbid obesity, haematological disease) using Cox regression analysis **Length of stay** (hospital and ICU presented separately) **Mechanical ventilation**
Risk of bias (Newcastle-Ottawa Scale)	**ICU mortality** Selection domain score (max 4): 3 Comparability domain score (max 2): 2 Outcome domain score (max 3): 3
Notes	-

Han 2011

Methods	Multicentre, retrospective cohort
Participants	**Country:** China (Shenyang City) **Setting:** in-hospital **Number of sites:** 4 **Number of individuals:** 83 **Inclusion criteria:** age > 3 years **Exclusion criteria:** **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** no CS group 38 (IQR 5 to 75); CS group 43 (IQR 3 to 70) **Male sex:** no CS group 18 (49.0); CS group 29 (63.0) **Co-morbid illnesses:** not reported individually **Disease severity:** Median Pandemic Medical Early Warning Score (PMEWS): no CS group 2 (IQR 0 to 5); CS group 2 (0 to 5)
Interventions	**Groups:** no CS group (n = 37) versus CS group (n = 46) CS group further subdivided into early treatment (<= 72 hours n = 17) and late treatment (> 72 hours n = 29) **Type:** methylprednisolone and dexamethasone **Co-interventions:** antivirals
Outcomes	**Critical illness:** defined as >= 1 of the following: death, respiratory failure, septic shock, failure or insufficiency of >= 2 non-pulmonary organs, mechanical ventilation or ICU admission A proportional hazards model was used to estimate the probability of developing critical disease after controlling for the presence of underlying co-morbid illnesses and presence of risk factors (age >= 65 years, pregnancy, obesity)
Risk of bias (Newcastle-Ottawa Scale)	**Critical illness** Selection domain score (max 4): 3 Comparability domain score (max 2): 2 Outcome domain score (max 3): 3

Han 2011 (*Continued*)

Notes	Study also compared outcomes with regard to timing of CS initiation (< 72 hours versus > 72 hours)

Jain 2009

Methods	Multicentre, retrospective cohort
Participants	**Country:** USA **Setting:** in-hospital **Number of sites:** national surveillance data **Number of individuals:** 272 (CS data available for 239) **Inclusion criteria:** individuals hospitalised with influenza-like illness **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** cohort 21 years (IQR, 21 days to 86 years) **Male sex:** not reported for CS groups **Co-morbid illnesses:** not reported for CS groups **Disease severity:** not reported for CS groups
Interventions	**Groups:** no CS (n = 153); CS (n = 86) **Type:** not reported **Co-interventions:** antivirals 200/268 (74.6); antibiotics 206/260 (79.2)
Outcomes	**Death/ICU admission versus survival/no ICU admission**
Risk of bias (Newcastle-Ottawa Scale)	**Death/ICU admission versus survival/no ICU admission** Selection domain score (max 4): Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Kim 2011

Methods	Multicentre, retrospective cohort/case-control
Participants	**Country:** Korea **Setting:** ICU **Number of sites:** 28 **Number of individuals:** 245 **Inclusion criteria:** age >= 15 years; presence of critical illness defined as i) admitted to ICU or required mechanical ventilation (invasive or non-invasive), or ii) had ratio of partial pressure of oxygen in arterial blood (PaO2) to inspired fraction of oxygen (FiO2) less than 300 mmHg, or iii) required intravenous infusion of an inotropic or vasoconstrictive medication) **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Mean age (years):** no CS group 54.1 (± 19.3); CS group 56.9 (± 17.2)

Kim 2011 (*Continued*)

	Male sex: no CS group 73 (53.0); CS group 61 (57.0) **Co-morbid illnesses:** Asthma: CS 10 (9); no CS 9 (7) COPD: CS 14 (13); no CS 6 (4) Solid tumour: CS 30 (28); no CS 19 (14) **Disease severity** (Mean Acute Physiology and Chronic Health Evaluation Score II (APACHE II)): no CS group 17.5 (± 8.5); CS group 21.2 (± 7.7); P value = 0.001
Interventions	**Groups:** CS treatment (n = 107) versus no CS treatment (n = 138) **Dose:** median prednisolone equivalent 75 (IQR 50 to 81) mg/day **Duration of treatment:** median 6 (IQR 6 to 13) days **Antibiotics:** CS group 107 (100.0); no CS group 136 (99.0) **Antivirals:** CS group 44 (41.0); no CS group 68 (49.0)
Outcomes	**Mortality:**14-day, 30-day and 90-day mortality reported. Adjusted estimates presented for 90-day mortality (following adjustment for age, SOFA score, mechanical ventilation, lymphocyte count and propensity score) Unadjusted estimates given for mechanical ventilation and length of stay **Adverse events:** secondary bacterial infections
Risk of bias (Newcastle-Ottawa Scale)	**Mortality** Selection domain score (max 4): 4 Comparability domain score (max 2): 2 Outcome domain score (max 3): 3 **Mechanical ventilation** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3 **Length of stay** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3 **Hospital-acquired infection** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	Adjusted estimates for 90-day mortality presented following logistical regression in a cohort study. Separate estimates given in a propensity matched case-control study

Kudo 2012

Methods	Single-centre, retrospective cohort
Participants	**Country:** Japan **Setting:** in-hospital **Number of individuals:** 89 **Inclusion criteria:** hospitalised patients with respiratory disorders (upper respiratory tract

Kudo 2012 (*Continued*)

	infection, wheezing illness, pneumonia with wheezing and pneumonia without wheezing) **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** 8 (IQR 0 to 71) for cohort **Male sex:** 45 (50.6) in cohort **Co-morbid illnesses:** asthma: cohort 26 (29.2) **Disease severity:** not reported
Interventions	**Groups:** CS treatment (n = 46) versus no CS treatment (n = 12) *based on 58 individuals in cohort **Dose:** methylprednisolone 1 to 1.5 mg/kg, 2 to 4 times/day **Duration of treatment:** median 5.1 days **Timing of treatment:** median 2.1 days following symptom onset **Antibiotics:** n = 63 (70.8) given antibiotics in cohort **Antivirals:** all individuals received antiviral therapy
Outcomes	**Length of stay**
Risk of bias (Newcastle-Ottawa Scale)	**Length of stay** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Li 2012

Methods	Multicentre, retrospective cohort
Participants	**Country:** China (Anhui province) **Setting:** in-hospital **Number of sites:** not known **Number of individuals:** 46 **Inclusion criteria:** pregnant, severe disease (defined as high fever for > 3 days, haemoptysis with purulent sputum, chest pain, dyspnoea, cyanosis, altered mental state, severe vomiting, diarrhoea and dehydration, radiologically confirmed pneumonia, elevated cardiac enzymes, respiratory failure, sepsis, multi-organ dysfunction or admission to intensive care units **Exclusion criteria:** discharge within 24 hours, individuals managed in the out-patient setting **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** adults who died 21 (IQR 18 to 31) and survivors 21 (IQR 18 to 27) **Female sex:** 46 (100.0) **Disease severity:** not reported
Interventions	**Groups:** CS treatment (n = 27) versus no CS treatment (n = 19) **Dose:** not reported **Duration of treatment:** not reported **Antibiotics:** not reported **Antivirals:** all given antivirals

Outcomes	**Mortality**
Risk of bias (Newcastle-Ottawa Scale)	**Mortality** Selection domain score (max 4): 2 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Liem 2009

Methods	Multicentre, retrospective cohort
Participants	**Country:** Vietnam **Setting:** in-hospital **Number of individuals:** 67 **Inclusion criteria:** all hospitalised patients with influenza A (H5N1) infection **Definition of influenza:** laboratory-confirmed **Influenza type:** A/H5N1 **Age, median years:** cohort 25 (IQR 16 to 42) **Male sex:** cohort 37 (55.0) **Co-morbid illnesses:** not reported
Interventions	**Groups:** CS treatment (n = 29) versus no CS treatment (n = 38) **Dose:** methylprednisolone 1 to 3 mg/kg/day **Duration of treatment:** up to 7 days **Antibiotics:** given to 63 (94.0) of cohort **Antivirals:** given to 55 (82.0) of cohort
Outcomes	**In-hospital mortality** Adjusted for the presence or absence of neutropenia as a marker of disease severity to investigate the effect of steroid treatment on outcome
Risk of bias (Newcastle-Ottawa Scale)	**In-hospital mortality** Selection domain score (max 4): 4 Comparability domain score (max 2): 1 Outcome domain score (max 3): 3
Notes	-

Linko 2011

Methods	Multicentre, prospective cohort
Participants	**Country:** Finland **Setting:** ICU **Number of individuals:** 132 **Inclusion criteria:** ICU admissions with influenza **Definition of influenza:** high clinical suspicion or laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** no CS group 44 (IQR 25 to 57); CS group 51 (40 to 56) **Male sex:** no CS group 39 (65.0); CS group 46 (64.0) **Co-morbid illnesses:** COPD: no CS 3 (5); CS 6 (8) Other obstructive pulmonary disease: no CS 14 (23); CS 15 (21) **Disease severity (median IQR):** Simplified Acute Physiology score II (SAPS II) no CS group 22 (15 to 30), CS group 31 (24 to 36). Sequential Organ Failure Assessment score (SOFA) no CS group 3 (2 to 6); CS group 6 (2 to 8); P value < 0.01
Interventions	**Groups:** CS treatment (n = 72) versus no CS treatment (n = 60) **Type of steroid:** methylprednisolone and/or hydrocortisone **Dose:** mean (SD) of the highest methylprednisolone dose was 94 (± 43) mg and hydrocortisone 214 (± 66) mg **Timing of steroid therapy:** median (IQR) days after symptom onset 5.0 (2.8 to 8.3) **Co-interventions:** antibiotics (84% of cohort); antivirals (96% of cohort)
Outcomes	**Hospital mortality:** odds ratios given following adjustment for disease severity (SAPS II) Unadjusted estimates given for mechanical ventilation and length of stay
Risk of bias (Newcastle-Ottawa Scale)	**Hospital mortality** Selection domain score (max 4): 4 Comparability domain score (max 2): 2 Outcome domain score (max 3): 3 **Mechanical ventilation** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3 **Length of stay** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Mady 2012

Methods	Single-centre, retrospective cohort
Participants	**Country:** Saudi Arabia **Setting:** ICU **Number of individuals:** 86 **Inclusion criteria:** influenza with respiratory failure **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Mean age (years):** cohort 40.8. Not reported for treatment groups **Male sex:** cohort 64 (74.4). Not reported for treatment groups **Co-morbid illnesses:** cohort 33 (38.3) **Disease severity** (mean APACHE IV score): cohort 105.6 (41 to 190); CS group versus no CS group 110.5 versus 100.6 (P value > 0.05) *NB not specified for which treatment group in article
Interventions	**Groups:** CS treatment (n = 43) versus no CS treatment (n = 43) **Type of steroid:** methylprednisolone **Dose:** 1 mg/kg per day for 7 days **Timing of steroid therapy:** not reported
Outcomes	**In-hospital mortality:** unadjusted estimates
Risk of bias (Newcastle-Ottawa Scale)	**Selection domain score (max 4):** 3 **Comparability domain score (max 2):** 0 **Outcome domain score (max 3):** 3
Notes	-

Patel 2013

Methods	Single-centre, retrospective cohort study
Participants	**Country:** India (Gujarat) **Setting:** in-hospital **Number of individuals:** 63 **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** 34 (IQR 3 to 69) **Male sex:** 41 (65%)
Interventions	**Groups:** CS treatment (n = 39); no CS treatment (n = 24) **Type of steroid:** methylprednisolone **Dose:** 40 mg 3 times daily for 1 week, twice daily for 1 week and once daily for 1 week **Route of administration:** intravenous **Timing of steroid therapy:** not reported
Outcomes	**Mortality**

Patel 2013 (*Continued*)

Risk of bias (Newcastle-Ottawa Scale)	**Selection domain score (max 4):** 2 **Comparability domain score (max 2):** 0 **Outcome domain score (max 3):** 3
Notes	-

Sertogullarindan 2011

Methods	Single-centre, prospective cohort
Participants	**Country:** Turkey **Setting:** ICU **Number of individuals:** 20 **Inclusion criteria:** ICU admissions with severe community-acquired pneumonia and influenza **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** cohort 36 (IQR 15 to 72); not reported by CS treatment groups **Male sex:** cohort 10 (50.0); not reported by CS treatment groups **Co-morbid illnesses:** COPD: cohort 2 (10) Malignancy: cohort 2 (10) **Disease severity:** not reported
Interventions	**Groups:** CS treatment versus (n = 11) no CS treatment (n = 9) **Co-interventions:** antibiotics (90% of cohort); antivirals (100% of cohort)
Outcomes	**Mortality** (unadjusted estimates)
Risk of bias (Newcastle-Ottawa Scale)	**Selection domain score (max 4):** 3 **Comparability domain score (max 2):** 0 **Outcome domain score (max 3):** 3
Notes	-

Viasus 2011

Methods	Multicentre, prospective cohort study
Participants	**Country:** Spain **Setting:** in-hospital **Number of sites:** 13 **Number of individuals:** 197 **Inclusion criteria:** non-immunosuppressed individuals admitted for at least 24 hours with influenza A **Exclusion criteria:** chemotherapy/solid organ transplant/HIV/neutropenia/ICU admission on admission to hospital

Viasus 2011 (*Continued*)

	Definition of influenza: laboratory-confirmed (PCR or culture) **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Median age (years):** no CS group 35 (IQR 28 to 47); CS group 44 (IQR 36 to 53) **Male sex:** no CS group 73 (53.0); CS group 61 (57.0) **Co-morbid illnesses:** chronic pulmonary disease: no CS 22 (17.1); CS 17 (45.9) **Disease severity:** number of individuals in high risk Pneumonia Severity Index (PSI) risk classes: CS group 8 (21.6) and no CS group 8 (6.4); P value < 0.05
Interventions	**Groups:** compared adults receiving immunomodulatory therapy (n = 68) (CS (n = 37), statins (n = 12) or macrolides (n = 31)) versus adults not receiving immunomodulatory therapy (n = 129) **Duration:** median days 9 (5 to 13.5)
Outcomes	**In-hospital mortality** **Hospital-acquired infection**
Risk of bias (Newcastle-Ottawa Scale)	**In-hospital mortality** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3 **Hospital-acquired infection** Selection domain score (max 4): 4 Comparability domain score (max 2): 0 Outcome domain score (max 3): 3
Notes	-

Wu 2012

Methods	Single-centre, prospective cohort
Participants	**Country:** Taiwan **Setting:** mixed cohort of out-patients and in-patients **Number of individuals:** 206 **Inclusion criteria:** > 16 years with influenza-like illness. Compared complicated (requiring hospital admission) versus uncomplicated influenza (n = 176) **Exclusion criteria:** not reported **Definition of influenza:** laboratory-confirmed **Influenza type:** seasonal influenza **Age >= 65 years**: cohort 26 (12.6) **Male sex:** cohort 110 (53.4) **Co-morbid illness:** Chronic lung disease: cohort 20 (9.7) Malignancy: cohort 18 (8.7) **Disease severity:** complicated influenza (n = 30) and uncomplicated influenza n = 176
Interventions	**Groups:** CS therapy use n = 17; no CS use n = 189 Unclear if CS was used prior to or following diagnosis **Dose/timing/duration:** not reported

Wu 2012 (*Continued*)

	Antiviral therapy: cohort 68 (33.0)
Outcomes	Complicated influenza (adjusted for age, co-morbid illnesses, clinical features, laboratory findings and CS use)
Risk of bias (Newcastle-Ottawa Scale)	**Complicated influenza** Selection domain score (max 4): 4 Comparability domain score (max 2): 1 Outcome domain score (max 3): 3
Notes	-

Xi 2010

Methods	Multicentre, retrospective cohort study
Participants	**Country:** China (Beijing) **Setting:** in-hospital **Number of sites:** 23 **Number of individuals:** 155 **Inclusion criteria:** adults aged >= 18 years admitted to hospital **Definition of influenza:** laboratory-confirmed **Influenza type:** 2009 influenza A H1N1 virus (H1N1pdm09) **Mean (SD) age (years):** cohort 43 (± 18.6) **Male sex:** cohort 90 (58.1) **Co-morbid illness:** chronic obstructive pulmonary disease: cohort 10 (6.5%) **Disease severity:** acute respiratory failure (24/103 (23.3%) in the no CS group versus 38/52 (73.1%) in the CS group); septic shock (5/103 (4.9%) in the no CS group versus 13/103 (25.0%) in the CS group); invasive ventilation (16/103 (15.5%) in the no CS group versus 27/52 (51.9%) in the CS group)
Interventions	**Groups:** primary comparison was survivors versus non-survivors. Secondary comparison made of CS treatment (n = 52) versus no CS treatment (n = 103) **Dose:** daily median dose equivalent to 80 mg (IQR 80 mg to 160 mg) of methylprednisolone **Co-interventions:** antivirals given to n = 132 (85.2) of cohort; antibiotics 139 (89.7) of cohort
Outcomes	**Hospital mortality:** raw numbers for mortality were derived from data given in article. Adjusted odds ratio for mortality were given for CS use in multivariate analysis Adjustment was made for ethnicity, co-morbid illness (hypertension, diabetes), symptoms at disease onset (dyspnoea, sore throat), clinical presentation (dyspnoea), laboratory testing (lactate dehydrogenase) and CS treatment, in the multivariate analysis No difference in mortality for low-dose (< 80 mg of methylprednisolone) versus high-dose CS in a subgroup analysis (9/30 versus 8/22, P value = 0.854)
Risk of bias (Newcastle-Ottawa Scale)	**Selection domain score (max 4):** 3 **Comparability domain score (max 2):** 1 **Outcome domain score (max 3):** 3

Xi 2010 (*Continued*)

Notes	-

APACHE: Acute Physiology and Chronic Health Evaluation
COPD: chronic obstructive pulmonary disease
CS: corticosteroid
ICU: intensive care unit
IQR: inter-quartile range
PCR: polymerase chain reaction
SAPS: Simplified Acute Physiology Score
SD: standard deviation
SOFA: Sequential Organ Failure Assessment

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chan 2014	No outcome data comparing corticosteroid treatment versus no corticosteroid treatment
Fujikura 2014	No outcome data comparing corticosteroid treatment versus no corticosteroid treatment
Gao 2013	No outcome data comparing corticosteroid treatment versus no corticosteroid treatment
Garnacho-Montero 2013	Overlapping populations*
Hu 2013	No outcome data comparing corticosteroid treatment versus no corticosteroid treatment
Martin-Loeches 2013	Overlapping populations*
Mckenna 2013	Overlapping populations*
Ning 2014	Fewer than 10 participants in study
Okur 2013	Overlapping populations*
Smud 2010	No outcome data comparing corticosteroid treatment versus no corticosteroid treatment

*Overlapping populations refers to studies where data from cohorts included in the review were duplicated, either due to multiple reporting of the same cohort, or inclusion of the cohort within the study population of a larger study.

DATA AND ANALYSES

Comparison 1. Corticosteroid therapy versus no corticosteroid therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	13	1917	Odds Ratio (Random, 95% CI)	3.06 [1.58, 5.92]
1.1 Unadjusted mortality	9	1318	Odds Ratio (Random, 95% CI)	2.99 [1.18, 7.57]
1.2 Adjusted mortality	4	599	Odds Ratio (Random, 95% CI)	2.82 [1.61, 4.92]

Analysis 1.1. Comparison 1 Corticosteroid therapy versus no corticosteroid therapy, Outcome 1 Mortality.

Review: Corticosteroids as adjunctive therapy in the treatment of influenza

Comparison: 1 Corticosteroid therapy versus no corticosteroid therapy

Outcome: 1 Mortality

Study or subgroup	Corticosteroid group N	No corticosteroid group N	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Unadjusted mortality						
Balaganesakumar 2013	70	210	3.1676 (0.3539)		9.8 %	23.75 [11.87, 47.52]
Brun-Buisson 2011	83	125	0.9247 (0.3334)		9.9 %	2.52 [1.31, 4.85]
Chawla 2013	38	39	2.4675 (1.0825)		5.2 %	11.79 [1.41, 98.41]
Diaz 2012	136	236	0.0688 (0.2802)		10.2 %	1.07 [0.62, 1.86]
Li 2012	27	19	1.6376 (1.1269)		4.9 %	5.14 [0.56, 46.82]
Mady 2012	43	43	1.0542 (0.4731)		9.1 %	2.87 [1.14, 7.25]
Patel 2013	39	24	1.0116 (0.7124)		7.4 %	2.75 [0.68, 11.11]
Sertogullarindan 2011	11	9	-1.674 (0.9789)		5.7 %	0.19 [0.03, 1.28]
Viasus 2011	37	129	1.0143 (0.7879)		6.9 %	2.76 [0.59, 12.92]
Subtotal (95% CI)	**484**	**834**			**69.1 %**	**2.99 [1.18, 7.57]**
Heterogeneity: Tau^2 = 1.55; Chi^2 = 57.84, df = 8 (P<0.00001); I^2 =86%						
Test for overall effect: Z = 2.31 (P = 0.021)						
2 Adjusted mortality						
Kim 2011	107	138	0.7885 (0.3872)		9.6 %	2.20 [1.03, 4.70]
Liem 2009	29	38	1.4134 (0.6543)		7.8 %	4.11 [1.14, 14.82]

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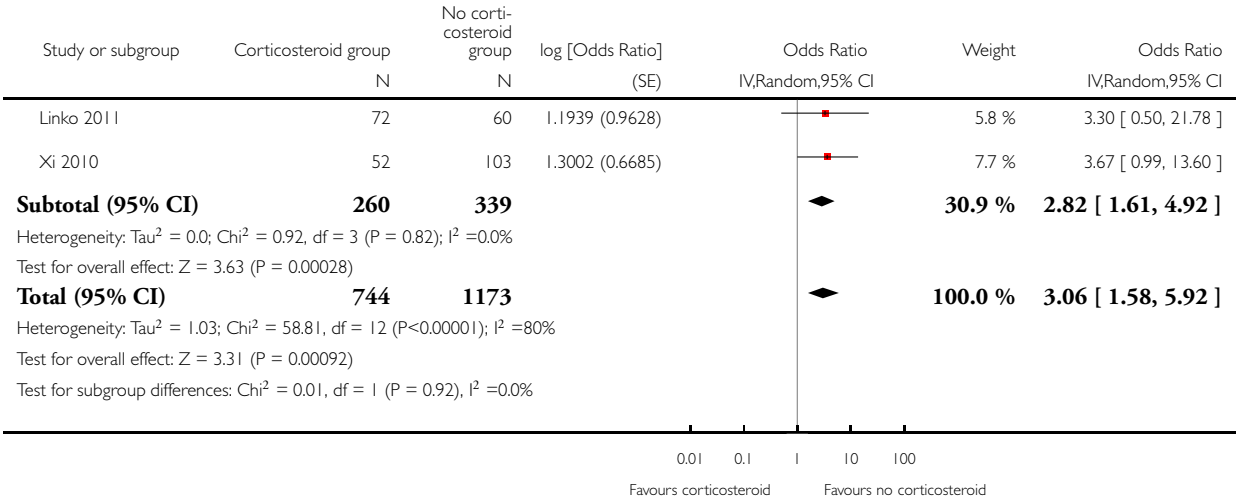

ADDITIONAL TABLES

Table 1. Summary of included studies - studies included in meta-analysis

Study/year (country)	Design	Setting/inclusion criteria	CS given (n)	CS not given (n)	Demographics	Disease severity scores	Corticosteroid therapy dose/ timing/ duration	Outcomes reported
Influenza 2009 influenza A H1N1 virus (H1N1pdm09)								
Balaganesakumar 2013 (India - Tamil Nadu)	Multicentre, prospective cohort study	In-hospital/ admissions with influenza	70	210	Median age (years): 26 (1 to 82)	Not reported	Not reported	Mortality
Brun-Buisson 2011 (France)	Multicentre, retrospective analysis of prospectively collected data	ICU/severe respiratory failure (ARDS or MV)	83 (early CS 50 and late CS 33)	125	Median age (years): no CS 45 (35 to 55); CS 49 (34 to 56) Immunosuppression: no CS 18. 4%; CS 21.	Median SAPSIII cohort 52. 0 (44.0 to 64.0); no CS 53.0 (46.0 to 66.0); CS group 51.0 (44.0 to 61.	Median daily dose: 270 (200 to 400) mg of hydrocortisone equivalent Timing: within me-	Hospital mortality, length of ICU stay, adverse events

Table 1. Summary of included studies - studies included in meta-analysis (*Continued*)

					7%	0); P value = 0.25	dian 1 day (0 to 6) of MV Duration: median 11 days (6 to 20)	
Chawla 2013 (India - New Delhi)	Single-centre, retrospective cohort study	ICU/admissions with influenza	38	39	Mean age (years): 40.9 (± 13.4)	Not reported	Duration of therapy: mean (days) 10.6 (± 7.8)	Mortality
Diaz 2012 (Spain)	Multicentre, retrospective analysis of prospectively collected data	ICU/ ILI; respiratory failure requiring ICU admission	136	236	Mean age (years): no CS 43.6 (± 13.6); CS 43.1 (12.9) Asthma: no CS 18%; CS 21% COPD: no CS 27%; CS 18%	Mean (SD) APACHEII: no CS group 12.5 (± 6.7) ; CS group 13.2 (± 6.3) (P value = 0.318)	Not reported	ICU mortality, MV, LOS
Kim 2011 (South Korea)	Multicentre, retrospective cohort/ case-control	ICU/age ≥ 15 years; presence of critical illness	107	138	Mean age (years): no CS 54.1 (± 19.3); CS 56.9 (± 17.2) Asthma: CS 9%; no CS 7% COPD: CS 13%; no CS 4%	Mean (SD) APACHE II: no CS group 17.5 (± 8.5) ; CS group 21.2 (± 7.7); P value = 0.001	Dose: median pred equivalent 75 (50 to 81) mg/ day Duration: median days 6 (3 to 14)	Mortality (14-day, 30-day and 90-day), LOS, acquired infections
Li 2012 (China - Anhui province)	Multicentre, retrospective cohort study	In-hospital/ pregnant, severe disease	27	19	Median age (years) : adults who died 21 (18 to 31) and survivors 21 (18 to 27)	Not reported	Not reported	Mortality
Linko 2011 (Finland)	Multicentre, prospective cohort study	ICU/admissions with influenza	72	60	Median age (years): no CS 44 (25 to 57); CS 51	Median SAPSII: no CS 22 (15 to 30); CS 31	Methylpred and/or hydrocortisone Dose: mean	In-hospital mortality, MV, LOS

Table 1. Summary of included studies - studies included in meta-analysis (*Continued*)

					(40 to 56) COPD: no CS 5%; CS 8% Other obstructive pulmonary disease: no CS 23%; CS 21%	(24 to 36); P value = 0. 001	(SD) of highest methylpred dose 94 (± 43) mg and hydrocortisone 214 (± 66) mg Timing: median (IQR) days after symptom onset 5.0 (2. 8 to 8.3)	
Mady 2012 (Saudi Arabia)	Single-centre, retrospective cohort study	ICU/ influenza with respiratory failure	43	43	Cohort mean age (years): 40.8 Asthma or COPD: 38. 3%	Mean APACHEIV: 110.5 versus 100.6 (P value > 0. 05), not specified for which treatment group	Methylpred Dose: 1 mg/ kg per day for 7 days	Mortality
Patel 2013 (India - Gujarat)	Single-centre, retrospective cohort study	In-hospital/ admissions with influenza	39	24	Cohort median age (years): 34 (3 to 69)	Not reported	Dose: methylprednisolone 40 mg 3 times a day, twice a day and once a day, for week 1, 2 and 3 respectively	Mortality
Sertogullarindan 2011 (Turkey)	Single-centre, prospective cohort study	ICU/severe community-acquired pneumonia and influenza	11	9	Cohort median age (years): 36 (15 to 72) COPD: 10%	Not reported	Not reported	Mortality
Viasus 2011 (Spain)	Multicentre, prospective cohort	In-hospital/ non-immunosup-	37	129	Median age (years): no CS 35 (28 to	Number in high-risk PSI classes:	Duration: median days 9 (5 to 13.5)	Severe disease (composite

Table 1. Summary of included studies - studies included in meta-analysis (*Continued*)

	study	pressed, admitted > 24 hours			47); CS 44 (36 to 53) Chronic pulmonary disease: no CS 17.1%; CS 45.9%	CS 8 (21.6); no CS 8 (6.4); P value < 0.05		outcome of ICU admission/death), acquired infection
Xi 2010 (China - Beijing)	Multicentre, retrospective cohort study	In-hospital/age ≥ 18 years	52	103	Cohort mean age (years): 43 (± 18.6) COPD: 6.5%	Not reported	Dose: daily median dose equivalent to methylpred 80 mg (IQR 80 to 160 mg)	In-hospital mortality Subgroup analysis of mortality by CS dose
Avian influenza A (H5N1)								
Liem 2009 (Vietnam)	Multicentre, retrospective cohort	In-hospital/hospitalised patients with influenza	29	38	Cohort median age (years): 25 (16 to 42)	Not reported	Dose: methylpred 1 to 3 mg/kg/day for 7 days	In-hospital mortality
Studies not included in meta-analysis **Influenza** 2009 influenza A H1N1 virus (H1N1pdm09)								
Delgado-Rodriguez 2012 (Spain)	Multicentre, prospective cohort	In-hospital/ILI, RTI, septic shock, multi-organ failure	31	782	Cohort median age (years): 41 (19 to 55)	Not reported	Corticosteroid use 90 days prior to admission	Poor outcome (ICU admission and in-hospital death), LOS
Han 2011 (China - Shenyang City)	Multicentre, retrospective cohort	In-hospital/age > 3 years	46 (early CS 17 and late CS 29)	37	Median age (years) : no CS 38 (5 to 75); CS 43 (3 to 70)	Median PMEWS: no CS group 2 (0 to 5); CS group 2 (0 to 5)	Methylpred and dexamethasone	Critical illness
Jain 2009 (USA)	Multicentre, retrospective cohort	In-hospital/ILI with hospital admission ≥ 24 hours	86	153	Cohort median age: 21 years (21 days to 86 years)	Not reported	Not reported	Death/ICU admission versus survival/no ICU ad-

Table 1. Summary of included studies - studies included in meta-analysis (*Continued*)

					Asthma: 28%; COPD: 8% Immunosuppression: 15%			mission
Kudo 2012 (Japan)	Single-centre, retrospective cohort	In-hospital/ hospitalised patients with respiratory disorders	46	12	Cohort median age (years): 8 (0 to 71) Asthma: 29.2%	Not reported	Dose: methylpred 1 to 1.5 mg/kg, 2 to 4 times/day Duration: median 5.1 days Timing: median 2.1 days following symptom onset	LOS
Interpandemic (seasonal) influenza								
Boudreault 2011 (USA)	Single-centre, retrospective cohort	Non-ICU/ HSCT recipients with RTI	80 (low-dose 43 and high-dose 37)	63	Median age (years): no CS 42 (32 to 51); low-dose CS 42 (28 to 53) ; high-dose CS 40 (32 to 54)	Not reported	Highest dose in 2/52 preceding influenza Low-dose (pred/ methylpred < 1 mg/kg/ day); high-dose (pred/ methylpred >= 1 mg/kg/ day)	MV, time to death, PVS
Wu 2012 (Taiwan)	Single-centre, prospective cohort	Mixed cohort of outpatients and in-patients	17	189	Age >= 65 years in cohort: 12.6% Chronic lung disease: 9.7% Malignancy: 8.7%	Not reported	Dose/duration: not reported Unclear if CS commenced prior to or following diagnosis	Complicated influenza (requiring hospitalisation)

APACHE: Acute Physiology and Chronic Health Evaluation
ARDS: adult respiratory distress syndrome
COPD: chronic obstructive pulmonary disease
CS: corticosteroid therapy
HSCT: haematopoietic stem cell transplant
ICU: intensive care unit
ILI: influenza-like illness
IQR: inter-quartile range
LDH: lactate dehydrogenase
LOS: length of stay
methylpred: methylprednisolone
MV: mechanical ventilation
PMEWS: Pandemic Modified Early Warning Score
pred: prednisolone
PSI: Pneumonia Severity Index
PVS: persistent viral shedding
RTI: respiratory tract infection
SAPS: Simplified Acute Physiology Score
SD: standard deviation
SOFA: Sequential Organ Failure Assessment

Table 2. Risk of bias in observational studies using the Newcastle-Ottawa Scale

Study	Outcome	Selection domain (maximum 4 stars)	Comparability domain (maximum 2 stars)	Outcome domain (maximum 3 stars)
Balaganesakumar 2013	Mortality	2	1	2
Boudreault 2011 †	Time to death	2	1	2
Brun-Buisson 2011	In-hospital mortality	3	2	3
Brun-Buisson 2011	Length of ICU stay	3	0	3
Brun-Buisson 2011	ICU-acquired infection	3	0	3
Chawla 2013	Mortality	3	0	3
Delgado-Rodriguez 2012 †	Composite outcome of ICU admission and mortality	3	2	3
Diaz 2012	ICU mortality	3	2	2
Han 2011 †	Critical illness	3	2	3
Jain 2009 †	ICU admission death versus survival/no ICU admission	4	0	3

Table 2. Risk of bias in observational studies using the Newcastle-Ottawa Scale (*Continued*)

Kim 2011	Mortality	4	2	3
Kim 2011	MV	4	0	3
Kim 2011	LOS	4	0	3
Kim 2011	Hospital-acquired infection	4	0	3
Kudo 2012 †	LOS	4	0	2
Li 2012	Mortality	2	0	3
Liem 2009	In-hospital mortality	4	1	3
Linko 2011	In-hospital mortality	4	2	3
Linko 2011	MV	4	0	3
Linko 2011	LOS	4	0	3
Mady 2012	Mortality	3	0	3
Patel 2013	Mortality	2	0	3
Sertogullarindan 2011	Mortality	3	0	3
Viasus 2011	In-hospital mortality	4	0	3
Viasus 2011	Hospital-acquired infection	4	0	3
Wu 2012 †	Influenza requiring hospitalisation	4	1	3
Xi 2010	In-hospital mortality	3	1	3

ICU: intensive care unit
LOS: length of stay
MV: mechanical ventilation
† studies not included in meta-analysis (three studies investigating CS therapy before influenza diagnosis (Boudreault 2011; Delgado-Rodriguez 2012; Wu 2012); three studies with no mortality data according to CS use (Han 2011; Jain 2009; Kudo 2012).

Table 3. Summary of studies reporting mortality

Study	Outcome reported	Mortality in CS treatment group	Mortality in group not treated with CS	Reported unadjusted risk of mortality	Reported adjusted risk of mortality	Variables included in model for adjusted estimates
Balaganesakumar 2013	Mortality	50/70 (71.4)	20/210 (9.5)	OR 23.8 (95% CI 11.3 to 50.8)	Not reported	-
Brun-Buisson 2011	In-hospital mortality	28/83 (33.8)	21/125 (16.8)	HR 2.39 (95% CI 1.32 to 4.31)	aHR 2.59 (95% CI 1.42 to 4.73)	Immunosuppression, disease severity (SAPS3), vasopressor use
Chawla 2013	Mortality	9/38 (23.7)	1/39 (2.6)	OR 11.8 (95% CI 1.4 to 98.4)	Not reported	-
Diaz 2012	ICU mortality	25/136 (18.4)	41/236 (17.4)	HR 0.91 (95% CI 0.55 to 1.48)	aHR 1.06 (95% CI 0.63 to 1.80)	Disease severity (APACHEII), co-morbid illnesses
Kim 2011	90-day mortality (also unadjusted estimates provided for 14-day and 30-day)	62/107 (57.9)	37/138 (26.8)	OR 3.76 (95% CI 2.19 to 6.44)	aOR 2.20 (95% CI 1.03 to 4.71)	Age, disease severity (SOFA), MV, lymphocyte count, propensity score)
Li 2012	Mortality	6/27 (22.2)	1/19 (5.2)	OR 5.14 (95% CI 0.56 to 46. 82)	Not reported	N/A
Liem 2009	In-hospital mortality	17/29 (58.6)	9/36 (25.0)	OR 4.25 (95% CI 1.48 to 12. 22)	aOR 4.11 (95% CI 1.14 to 14. 83)	Neutropenia as surrogate for severity
Linko 2011	In-hospital mortality	8/72 (11.1)	2/60 (3.3)	OR 3.63 (95% CI 0.74 to 17. 77)	aOR 3.3 (95% CI 0.5 to 23.4)	Disease severity (SAPS2)
Mady 2012	In-hospital mortality	20/43(46.5)	10/43 (23.2)	OR of 2.87 (95% CI 1.14 to 7.25)	Not reported	N/A
Patel 2013	Mortality	11/39 (28.2)	3/24 (12.5)	OR 2.75 (95% CI 0.68 to 11.1)	Not reported	-
Sertogullarindan 2011	Mortality	3/11 (27.3)	6/9 (66.7)	OR 0.19 (95% CI 0.03 to 1.28)	Not reported	N/A

Table 3. Summary of studies reporting mortality (*Continued*)

Viasus 2011	Mortality (primary outcome was 'severe disease' = ICU admission/death)	3/37 (8.1)	4/129 (3.1)	OR 2.76 (95% CI 0.59 to 12.92)	Not reported	N/A
Xi 2010	In-hospital mortality	17/52 (32.7)	10/103 (9.7)	OR 4.52 (95% CI 1.89 to 10.81)	aOR 3.67 (95% CI 0.99 to 13.64)	Ethnicity, comorbid illness, symptoms at onset, laboratory tests

aHR: adjusted HR
aOR: adjusted OR
APACHE: Acute Physiology and Chronic Health Evaluation ventilation
CI: confidence interval
CS: corticosteroid
HR: hazard ratio
ICU: intensive care unit
MV: mechanical
OR: odds ratio
RR: risk ratio
SAPS: Simplified Acute Physiology Score

Table 4. Summary of studies reporting relevant outcomes other than mortality

Outcome	Study	Group treated with corticosteroids	Group not treated with corticosteroids	Unadjusted estimate of effect
Critical disease	Han 2011	Early CS 12/17 (70.6)	Late or no CS 26/66 (39.4)	RR 1.8, 95% CI 1.2 to 2.8†
Composite outcome of ICU admission/death	Jain 2009	29/86 (33.7)	27/153 (17.6)	OR 2.37, 95% CI 1.29 to 4.37
Rate of MV	Kim 2011	91/107 (85.0)	71/138 (51.4)	OR 5.37, 95% CI 2.87 to 10.05
Rate of MV	Linko 2011	53/72 (73.6)	14/60 (23.3)	OR 9.17, 95% CI 4.14 to 20.30
Length of ICU stay: median days (IQR)	Brun-Buisson 2011	22 (13 to 39)	17 (11 to 30)	P value = 0.11
LOS: mean days (SD)	Kim 2011	30.8 (36.9)	18.9 (20.0)	P value < 0.001

Table 4. Summary of studies reporting relevant outcomes other than mortality (*Continued*)

LOS median days (IQR)	Kudo 2012	8.2 (5 to 14)	7.7 (3 to 14)	P value = 0.607
LOS: median days (IQR)	Linko 2011	20 (12 to 34)	8 (5 to 13)	P value < 0.001

aRR: adjusted risk ratio
CI: confidence interval
CS: corticosteroid
ICU: intensive care unit
LOS: length of stay
MV: mechanical ventilation
OR: odds ratio
RR: risk ratio
† adjusted risk ratio 1.8, 95% CI 1.2 to 2.8 (following adjustment for co-morbid illnesses, age, pregnancy and obesity).

Table 5. Summary of studies reporting corticosteroid-related adverse events or nosocomial infection

Adverse effect	Study	Group treated with corticosteroids	Group not treated with corticosteroids	Unadjusted estimate of effect
ICU-acquired infection	Brun-Buisson 2011	38/83 (45.8)	44/125 (35.2)	OR 1.55, 95% CI 0.88 to 2.74
Hospital-acquired infection	Kim 2011	54/107 (50.5)	24/138 (17.4)	OR 4.84, 95% CI 2.71 to 8.65
Hospital-acquired infection	Viasus 2011	6/37 (16.2)	4/129 (3.1)	OR 6.05, 95% CI 1.61 to 22.75

ICU: intensive care unit
OR: odds ratio

Table 6. Summary of studies reporting outcomes stratified according to different corticosteroid regimens

Subgroup analysis	Study	Outcome	Comments
Early and late CS therapy compared with no CS therapy	Brun-Buisson 2011	Hospital mortality Early CS: HR 3.42, 95% CI 1.73 to 6.75; P value = 0.001 Late CS: HR 1.93, 95% CI, 0.84 to 4.43; P value = 0.12	Early treatment defined as 'within 3 days of mechanical ventilation' Propensity score adjusted analysis
Early CS therapy versus late/no CS therapy groups combined	Han 2011	Critical illness RR 1.8, 95% CI 1.2 to 2.8	Early treatment defined as < 72 hours from influenza-like illness Multivariate analysis following ad-

Table 6. Summary of studies reporting outcomes stratified according to different corticosteroid regimens (*Continued*)

			justment for underlying co-morbid illnesses, age, pregnancy and obesity
Low-dose versus high-dose CS therapy	Xi 2010	In-hospital mortality 9/30 versus 8/22, P value = 0.854	Low-dose CS therapy defined as ≤ 80 mg methylprednisolone or equivalent daily dose Unadjusted outcome

CI: confidence interval
CS: corticosteroid
HR: hazard ratio
RR: risk ratio

APPENDICES

Appendix 1. EMBASE (Elsevier) search strategy

#42 #18 AND #41
#41 #26 OR #40
#40 #27 OR #28 OR #29 #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
#39 ('cross sectional' NEXT/1 (study OR studies)):ab,ti
#38 (epidemiologic* NEXT/1 (study OR studies)):ab,ti
#37 (observational NEXT/1 (study OR studies)):ab,ti
#36 ('follow up' NEXT/1 (study OR studies)):ab,ti
#35 ('case control' NEXT/1 (study OR studies)):ab,ti
#34 (cohort NEXT/1 (study OR studies)):ab,ti
#33 'cohort analysis'/de
#32 'prospective study'/de
#31 'retrospective study'/de
#30 'longitudinal study'/de
#29 'family study'/de
#28 'case control study'/de
#27 'clinical study'/de
#26 #21 NOT #25
#25 #22 NOT #24
#24 #22 AND #23
#23 'human'/de
#22 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#21 #19 OR #20
#20 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
#19 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#18 #5 AND #17
#17 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#16 hydrocortisone*:ab,ti OR prednisolone*:ab,ti OR prednisone*:ab,ti OR dexamethasone*:ab,ti OR methylprednisolone*:ab,ti

#15 steroid*:ab,ti
#14 'steroid'/exp
#13 hydroxycorticosteroid*:ab,ti
#12 glucocorticoid*:ab,ti
#11 corticoid*:ab,ti
#10 adrenocorticoid*:ab,ti
#9 adrenocorticosteroid*:ab,ti
#8 (adren* NEAR/2 (hormon* OR steroid*)):ab,ti
#7 corticosteroid*:ab,ti
#6 'corticosteroid'/exp
#5 #1 OR #2 OR #3 OR #4
#4 h1n1:ab,ti OR h5n1:ab,ti OR h3n2:ab,ti
#3 influenza*:ab,ti OR flu:ab,ti
#2 'influenza virus a'/exp OR 'influenza virus b'/de
#1 'influenza'/exp

Appendix 2. CINAHL (Ebsco) search strategy

S17 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S16 TI (hydrocortisone* or prednisolone* or prednisone* or dexamethasone* or methylprednisolone*) OR AB (hydrocortisone* or prednisolone* or prednisone* or dexamethasone* or methylprednisolone*)
S15 TI steroid* OR AB steroid*
S14 (MH "Steroids+")
S13 TI hydroxycorticosteroid* OR AB hydroxycorticosteroid*
S12 TI glucocorticoid* OR AB glucocorticoid*
S11 TI corticoid* OR AB corticoid*
S10 TI adrenocortic* OR AB adrenocortic*
S9 TI (adren* N2 (hormone* or steroid*)) OR AB (adren* N2 (hormone* or steroid*))
S8 TI corticosteroid* OR AB corticosteroid*
S7 (MH "Adrenal Cortex Hormones+")
S6 S1 OR S2 OR S3 OR S4 OR S5
S5 TI (h1n1 or h5n1 or h3n2) OR AB (h1n1 or h5n1 or h3n2)
S4 TI (influenza* or flu) OR AB (influenza* or flu)
S3 (MH "Influenza B Virus")
S2 (MH "Influenzavirus A+")
S1 (MH "Influenza+")

Appendix 3. LILACS (BIREME) search strategy

(mh:"Influenza, Human" OR influenza$ OR flu OR grippe OR or gripe OR mh:"Influenzavirus A" OR mh:b04.820.545.405$ OR mh:b04.909.777.545.405$ OR mh:"Influenzavirus B" OR mh:b04.820.545.407$ OR mh:b04.909.777.545.407$ OR h1n1 OR h5n1 OR h3n2) AND (mh:"Adrenal Cortex Hormones" OR mh:d06.472.040$ OR corticoesteroides OR corticosteróides OR corticoid$ OR corticosteroid$ OR "adrenal cortex hormone" OR "adrenal cortex hormones" OR adrenocorticosteroid$ OR glucocorticoid$ OR hydroxycorticosteroid$ OR mh:glucocorticoids OR glucocorticóides OR mh:steroids OR esteróides OR mh:d04.808$ OR hydrocortison$ OR hidrocortisona OR mh:prednisolone OR prednisolone OR prednisolona OR mh:prednisone OR prednisone OR prednisona OR mh:dexamethasone OR dexamethasone OR dexametasona OR mh:methylprednisolone OR methylprednisolone OR metilprednisolona) AND db:("LILACS") AND type˙of˙study:("clinical˙trials" OR "case˙control" OR "cohort" OR "overview" OR "systematic˙reviews")

Appendix 4. Web of Science (Thomson Reuters) search strategy

# 5	361	#4 AND #1 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespa*n = *All Years*
# 4	2,897,717	#3 OR #2 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespa*n = *All Years*
# 3	1,700,524	Topic=((case NEAR/1 control) or cohort or "follow up" or observational or longitudinal or retrospective or prospective or cross-section* or "cross sectional") *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespa*n = *All Years*
# 2	1,425,723	Topic=(random* or placebo* or crossover* or "cross over" or allocat* or ((doubl* or singl*) NEAR/1 (blind* or mask*))) OR Title=(trial) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespa*n = *All Years*
# 1	1,082	Topic=(influenza* or flu or h1n1 or h5n1 or h3n2) AND Topic=("adrenal cortex hormone*" or corticosteroid* or adrenocorticosteroid* or adrenocorticoid* or corticoid* or glucocorticoid* or hydroxycorticosteroid* or steroid* or hydrocortisone* or prednisolone* or prednisone* or dexamethasone* or methylprednisolone*) *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespa*n = *All Years*

CONTRIBUTIONS OF AUTHORS

All the co-authors designed and conceived the systematic review. CR and WSL performed study selection independently. Paired data extraction was performed by all the co-authors. CR and JLB performed data synthesis and quantitative analyses. CR drafted the article and all the co-authors critically reviewed the article prior to submission.

DECLARATIONS OF INTEREST

Chamira Rodrigo received salaries part funded by an unrestricted grant from Pfizer and the NIHR.

Jo Leonardi-Bee is a co-applicant of an Educational Grant from Roche to carry out further research in the area of pandemic influenza. Dr. Leonardi-Bee will be using this to carry out a systematic review and individual patient meta-analysis of the evidence (published and unpublished) of the impact of antiviral use on public health outcomes for 2009 pandemic influenza A/H1N1. This systematic review has been registered with PROSPERO (international prospective register of systematic reviews).

Wei Shen Lim's department has received an unrestricted investigator-initiated research grant from Pfizer in support of a study in pneumococcal pneumonia, which is unrelated to the submitted work, and research funding from the National Institute for Health Research for a clinical trial in pandemic influenza.

Jonathan Nguyen-Van-Tam: The University of Nottingham Health Protection Research Group is currently in receipt of research funds from GlaxoSmithKline. The group has an unrestricted educational grant for influenza research from F. Hoffmann-La Roche. Research

on influenza funded by an unrestricted educational grant from Astra Zeneca has also been completed. The aforementioned funding received from GSK, F. Hoffmann-La Roche and Astra Zeneca did not support any aspect of this work. JSN-V-T has received funding to attend influenza-related meetings, lecture and consultancy fees, and research funding from several influenza antiviral drug and vaccine manufacturers. All forms of personal remuneration ceased in September 2010, but departmental funding for influenza-related research from GlaxoSmithKline and F. Hoffmann-La Roche remains current. He is a former employee of SmithKline Beecham plc. (now GlaxoSmithKline), Roche Products Ltd and Aventis-Pasteur MSD (now Sanofi-Pasteur MSD), all prior to 2005, with no outstanding pecuniary interests by way of shareholdings, share options or accrued pension rights.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the Objectives of this review to add "taking into account differences in timing and doses of corticosteroids".

We amended the Types of studies to state "We excluded studies with case-control designs due to the inability to determine temporal effects of corticosteroids on the development of non-mortality outcomes. We excluded studies with fewer than 10 participants."

We used the Newcastle-Ottawa Scale to assess the risk of bias in studies instead of the Cochrane 'Risk of bias' tool as all identified studies were observational. Stratification by 30-day mortality was not possible as stated in the protocol due to the heterogeneity across studies when reporting mortality. All the studies were conducted at least in part in a hospital setting, and stratification of outcomes according to in-/out-patient setting was not possible. Subgroup analyses according to corticosteroid regimens and age of study participants could not be performed due to an insufficient number of studies reporting outcomes stratified according to these variables.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects; *therapeutic use]; Chemotherapy, Adjuvant [adverse effects]; Cross Infection [etiology]; Influenza A Virus, H1N1 Subtype; Influenza, Human [*drug therapy; mortality]; Intensive Care Units [statistics & numerical data]; Observational Studies as Topic

MeSH check words

Humans