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[Intervention Review]

Corticosteroids for dengue infection

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ABSTRACT

Background

Dengue is a common and important mosquito-borne viral infection. In many low- and middle-income countries it is endemic and is an important public health problem. Severe dengue is an important cause of death in children. There is no specific treatment for dengue, but observational studies suggest corticosteroids may have a benefit in dengue-related shock, and some people believe corticosteroids may prevent the progression to severe illness if given early in the course of the illness.

Objectives

To compare treatment of dengue with and without use of corticosteroids or placebo in relation to preventing shock-related death and disease progression in children and adults.

Search methods

We searched the Cochrane Infectious Disease Group Centralized Register; CENTRAL; MEDLINE; EMBASE; and LILACS, up to 6 January 2014. We screened reference lists and contacted the relevant study authors for additional information where required.

Selection criteria

Randomized controlled trials or quasi-randomized controlled trials comparing corticosteroids with placebo or no corticosteroids in patients diagnosed with dengue-related shock, or patients in an early symptomatic state of dengue with positive serology.

Data collection and analysis

Two researchers independently screened eligibility of records, extracted data and assessed quality of the studies. We presented findings in meta-analysis and summary of findings tables and evaluated the quality of evidence using GRADE.

Main results

We included eight studies enrolling 948 participants in this review.

Paitents with dengue-related shock

Four studies enrolled children younger than 15 years with dengue-related shock at hospitals in Southeast Asia and evaluated intravenous corticosteroids. The trials did not detect an effect on death (four trials, 284 participants, *very low quality evidence)*, the need for blood transfusion (two trials, 89 participants, *very low quality evidence*), pulmonary haemorrhage (one trial, 63 participants, *very low quality evidence*), convulsions (one trial, 63 participants, *very low quality evidence*), or duration of hospitalization (one trial, 63 participants, *very*

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low quality evidence). The body of evidence is too small to confidently prove or exclude clinically important effects. Furthermore, the trials are more than 20 years old with several methodological limitations.

Patients with dengue at an early stage

Four studies enrolled 664 children and adults with dengue at an early stage of infection (without shock) in Columbia, India, Sri Lanka and Vietnam. In these participants there were no evidence of effects of oral or intravenous corticosteroids on mortality (four trials, 664 participants, *low quality evidence),* or on the development of complications of severe dengue such as shock (two trials, 286 participants, *very low quality evidence*), severe bleeding (two trials, 425 participants, *very low quality evidence*), severe thrombocytopaenia (one trial, 225 participants, *very low quality evidence*), ascites (one trial, 178 participants, *very low quality evidence*) and intensive care unit (ICU) admissions (two trials, 286 participants, *very low quality evidence*).

Authors' conclusions

The evidence from trials using corticosteroids in dengue is inconclusive and the quality of evidence is low to very low. This applies to both the use of corticosteroids in dengue-related shock and for dengue at an early stage. There is insufficient evidence to evaluate the effects of corticosteroids in the treatment of early stage dengue fever and dengue-related shock outside of the context of a randomized controlled trial.

15 April 2019

No update planned

Other

This is not a current research question

PLAIN LANGUAGE SUMMARY

Corticosteroids for treating dengue infection in children and adults

Dengue is a disease caused by a virus transmitted by mosquitoes, occurring in many resource-limited countries, and children are often most severely affected. Most infected patients will recover with mild symptoms, but a few progress to severe dengue and may die. There is no specific treatment for dengue, but some clinicians provide corticosteroids at an early stage to prevent progression to severe dengue disease; and some treat patients with dengue-related shock with corticosteroids to improve survival. It is important to summarise the effects of corticosteroids in dengue.

We conducted a search up to 6 January 2014 and included eight studies which enrolled 948 participants in total. Four studies of corticosteroids in the treatment of dengue-related shock assessed if corticosteroids could improve survival, but these studies were small and older than 20 years. The evidence we found is of very low quality and do not provide any reliable evidence for corticosteroids for treating dengue-related shock. Four trials evaluated whether corticosteroids provided at an early stage of dengue could prevent development of complications of severe dengue. These trials were more recent, but data were insufficient to be sure whether corticosteroids have an effect on the course of the disease.

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SUMMARY OF FINDINGS

Summary of findings for the main comparison. Corticosteroid for dengue-related shock

Corticosteroid for dengue-related shock

Patient or population: Patients with dengue-related shock
Settings: Endemic settings
Intervention: Corticosteroid

Outcome: Complications of severe dengue

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Corticosteroid				
Death	**21 per 100**	**15 per 100** (9 to 24)	**RR 0.68** (0.42 to 1.11)	284 (4 studies)	⊕⊖⊖⊖ **very low** [1,2,3,4]	
Need for blood transfusion	**24 per 100**	**26 per 100** (12 to 54)	**RR 1.08** (0.52 to 2.24)	89 (2 studies)	⊕⊖⊖⊖ **very low** [5,6,7,8]	
Pulmonary haemorrhage	**3 per 100**	**3 per 100** (0 to 48)	**RR 0.97** (0.06 to 14.82)	63 (1 study)	⊕⊖⊖⊖ **very low** [9,10,11]	
Convulsions	**0 per 100**	**0 per 100** (0 to 0)	**RR 6.79** (0.36 to 126.24)	63 (1 study)	⊕⊖⊖⊖ **very low** [9,10,11]	
Days in hospital	The mean duration of hospital stay in the control group was **6 days**	The mean duration of hospital stay in the intervention group was **1.1 days higher** (1.83 lower to 4.03 higher)		63 (1 study)	⊕⊖⊖⊖ **very low** [9,10,11]	

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk 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.

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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.

[1] Downgraded by 1 for serious risk of bias: Three out of four studies were at unclear risk of selection bias, as sequence generation and allocation concealment were not reported in sufficient detail. Blinding was adequate in two out of four studies. The only study that was at low risk of bias did not find an effect.
[2] No serious inconsistency: Statistical heterogeneity was low. Three out of four studies found no evidence of a benefit with corticosteroids. Only the oldest study which was at unclear risk of bias suggested a benefit.
[3] No serious indirectness: All trials were performed in children aged below 15 years in hospitals in Southeast Asia, and the data may not be easily generalizable to other populations or settings. All diagnoses were confirmed by a laboratory test, and an intravenous corticosteroid was used in all studies. Not downgraded.
[4] Downgraded by 2 for very serious imprecision: The 95% CI is wide and includes a clinically important effect and no effect. The trials are too small to detect an effect. To confidently detect a 25% relative reduction in mortality would require a sample size of more than 1700 participants.
[5] Downgraded by 1 for serious risk of bias: Sequence generation, allocation concealment and blinding was only reported adequately in one of the two studies. This study at low risk of bias did not find an effect.
[6] No serious inconsistency. No statistical heterogeneity.
[7] No serious indirectness: Both trials were conducted in children in referral hospitals in Thailand. They used viral and serologic diagnostic tests and a similar total dose of intravenous corticosteroids. The data may not be easily generalizable to other populations or settings. Not downgraded.
[8] Downgraded by 2 for very serious imprecision: The 95% CI of RR was wide and the trials too small to detect an effect. To confidently detect a 25% relative reduction in need for transfusion would require a sample size of more than 1400 participants.
[9] No serious risk of bias: The one trial in this comparison reported adequate sequence generation, blinding and allocation concealment.
[10] Downgraded by 1 for serious indirectness: Only a single small study evaluated this outcome. Further studies in different patient groups are needed to have confidence in the results.
[11] Downgraded by 2 for very serious imprecision: The 95% CI of the RR was wide and the trials too small to detect an effect. To confidently detect a 25% relative reduction would require a sample size of more than 10,000 participants.

Summary of findings 2. Corticosteroid for dengue at an early stage

Corticosteroid for dengue at an early stage

Patient or population: Patients with dengue infection at an early stage
Settings: Endemic settings
Intervention: Corticosteroids

Outcome: Complications of dengue

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Corticosteroid				
Death	-	-	-	664 (4 studies)	⊕⊕⊝⊝ **low** [1,2,3]	No deaths occurred

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Severe dengue: shock	**7 per 100**	**9 per 100** (3 to 23)	**RR 1.30** (0.48 to 3.51)	286 (2 studies)	⊕⊖⊖⊖ **very low** [4,5,6]	
Severe dengue: severe bleeding	**1 per 100**	**1 per 100** (0 to 5)	**RR 1.51** (0.24 to 9.43)	425 (2 studies)	⊕⊖⊖⊖[7,8,9,10] **very low**	Kularatne 2009 reported that no bleeding complications occurred
Severe thrombocytopaenia [11]	**3 per 100**	**4 per 100** (1 to 19)	**RR 1.51 (CI** (0.31 to 7.28)	225 (1 study)	⊕⊖⊖⊖ **very low** [12,13,14]	
Ascitis	**4 per 100**	**1 per 100** (0 to 9)	**RR 0.12** (0.01 to 2.13)	178 (1 study)	⊕⊖⊖⊖ **very low** [12,15,16]	
ICU admission	**8 per 100**	**8 per 100** (8 to 106)	**RR 0.88** (0.38 to 1.99)	286 (2 studies)	⊕⊖⊖⊖ **very low** [4,5,6]	

*The basis for the **assumed risk** (eg the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk 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.

[1] No serious risk of bias: Three out of four trials reported adequate random sequence generation, adequate allocation concealment and blinding of clinicians and participants. Two out of four trials reported adequate blinding of outcome assessors. One of the trials was available as conference abstract only and we got relevant information by email with the author.

[2] No serious indirectness: The studies were conducted in different settings in South Asia (India, Sri Lanka), Southeast Asia (Vietnam) and Latin America (Colombia) in both adults and children.

[3] Downgraded by 2 for very serious imprecision: No deaths were reported in either the intervention or placebo/no intervention group.

[4] Downgraded by 1 for serious risk of bias: One study reported adequately on sequence generation, allocation concealment and blinding of participants, clinicians and outcome assessors. Another study was an open-label trial, and did not describe allocation concealment.

[5] Downgraded by 1 for serious indirectness: These studies were conducted in different settings in India and Vietnam, which may not be easily generalizable to a variety of settings.

[6] Downgraded by 2 for very serious imprecision: One trial reported that results for this outcome did not show a statistically significant difference and might be underpowered to detect an effect. Another trial reported no case of shock in either the treatment or control groups. The 95% CI of the RR was wide and the trials too small to detect an effect. To confidently detect a 25% relative reduction would require a sample size of more than 8000 participants.

[7] No serious risk of bias: The two trials that reported on this outcome both described adequate allocation concealment and blinding of clinicians and participants. The method of sequence generation was not clear in one study.

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[8] No serious inconsistency. No statistical heterogeneity.

[9] Downgrade by 1 for serious indirectness: The two trials that reported on this outcome were conducted in Sri Lanka and Vietnam. The studies used different diagnostic criteria for dengue and for the diagnosis of haemorrhage and gave different doses of Prednisolone.

[10]Downgraded by 2 for very serious imprecision: Only four events were reported in the corticosteroid group, with only event in the placebo group. One of the two studies, conducted in Sri Lanka, did not report any events. The 95% CI of the RR was wide and the trials too small to detect an effect. To confidently detect a 25% relative reduction would require a sample size of more than 70,000 participants.

[11] Severe thrombocytopaenia: platelet nadir < 10,000/µl.

[12] No serious risk of bias: The one trial in this comparison reported adequate sequence generation, blinding and allocation concealment.

[13]Downgraded by 1 for serious indirectness: The one study reporting on this outcome was conducted in Vietnam, which may not be easily generalizable to a variety of settings.

[14]Downgraded by 2 for very serious imprecision: The single trial reporting on this outcome reported few events. The 95% CI of the RR was wide and the trials too small to detect an effect. To confidently detect a 25% relative reduction would require a sample size of more than 2000 participants.

[15] Downgraded by 1 for serious indirectness: This single study from Colombia may not easily be generalizable to a variety of settings.

[16]Downgraded by 2 for very serious imprecision: The single trial that reported on this outcome reported few events. The 95% CI of the RR was wide and the trials too small to detect an effect. To confidently detect a 25% relative reduction would require a sample size of more than 9000 participants.

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BACKGROUND

Description of the condition

Dengue is a viral infection that causes fever, malaise (general feeling of discomfort and illness) and is occasionally fatal. There are in total four different strains of the dengue virus. The bite of the female infected *Aedes* mosquito, most commonly *Aedes aegypti*, transmits the virus to humans (WHO 2009; Simmons 2012).

Onset of the illness is sudden after an incubation period of three to 14 days (average four to seven days). In the early phases of the illness people have non-specific flu-like symptoms, nausea and vomiting, and half of them have a rash. The course of dengue is usually mild and people recover. However, sometimes complications occur in the critical phase when fever resolves on the third to seventh day of illness, usually on the fifth day (WHO 2009; Simmons 2012).

Before 2009, the WHO classified dengue fever (DF) and four stages of dengue haemorrhagic fever (DHF) according to clinical manifestations as shock or bleeding. Grade I and II were termed non-shock DHF while grade III and IV were defined as dengue shock syndrome (DSS) (WHO 1997). This classification did not reliably identify severely sick patients, therefore the WHO introduced a new classification in 2009. This new classification differentiates between dengue, an uncomplicated disease with full recovery; and severe dengue. In severe dengue, an effect of the infection on the capillaries causes complications: the permeability of the capillaries increases and fluid leaks from the vessels into the tissue, causing a fall in blood pressure and shock. The WHO defines severe disease as:

- plasma leakage leading to shock or breathing difficulties, or both;
- severe bleeding;
- severe organ impairment (WHO 2009).

Signs of dengue-related shock are a narrow pulse pressure of 20 mmHg or less, and poor skin perfusion (Simmons 2012). Blood tests show increasing concentration of the blood and low levels of platelets and protein. The mechanisms leading to plasma leakage and the role of the immune system in the development of shock are unclear. Researchers suggest that the immune response can result in increased permeability of the capillaries. No animal models exist (WHO 2009; Simmons 2012).

Epidemiology

Dengue is the most common vector born viral infection in humans and the most rapidly spreading viral disease globally, and an important public health problem in low- and middle-income countries in the tropics where most of the dengue infection happens The dispersal of the efficient mosquito vectors across much of the tropical and subtropical latitudes is crucial for the cause of public health problems. The primary vector has been widely distributed across these tropics (Simmons 2012). And the dengue epidemics are closely related to the seasonal climatic change and there are epidemics waves following each rainy season (Rajapakse 2012).

Over 40% of the world's population (about 2.5 billion) live in dengue-endemic areas, and about 50 to 100 million people are infected with the dengue virus every year. Cases across the Americas, Southeast Asia and the Western Pacific exceeded 2.3 million in 2010. Its incidence has "multiplied many times over the last five decades at an alarming rate"(Rajapakse 2012). An estimated 500,000 people with severe dengue, of which a large proportion are children, require hospitalization every year. About 2.5% of these patients die of the disease (WHO 2009, WHO 2012a).

The Southeast Asia and the Western Pacific regions carry more than 75% (about 1.8 billion population) of the disease burden. These two regions plus the Americas are the three most seriously affected regions. Many tropical diseases are more common in rural areas, but dengue infections are acquired mostly in urban and semi-urban areas, which puts tourists at higher risk and is an important reason for its increasing endemicity (WHO 2009).

All age groups are affected, but infants and young children are at greater risk of dengue-related shock which is proved by epidemiological studies. The potential mechanism may explain this. Further risk factors include female sex, high body-mass index (BMI), infection with certain virus strains, or individual genetic susceptibility (Greenfacts 2012; Simmons 2012; WHO 2012b).

Diagnosis

Clinicians diagnose severe dengue (including dengue-related shock) on clinical grounds. Laboratory tests confirm the clinical diagnosis. Blood tests support diagnosis and guide management (WHO 2009). Current diagnostic methods include the detection of virus (or virus isolation), viral nucleic acid and viral antigen, and the detection of dengue-specific antibodies in the blood.

Management

Currently there is no evidence-base for a specific drug for dengue. Medical interventions remain supportive instead of curative. Patients receive fluid transfusions when hospitalized. Platelets are given when platelet counts drop too low. Severe anaemia in dengue is treated with blood transfusions. For dengue-related shock , the WHO provides detailed recommendations for intravenous fluid resuscitation (WHO 2009; Simmons 2012). Non-steroidal anti-inflammatory drugs such as ibuprofen should be avoided as they can worsen bleeding tendency.

Description of the intervention

Corticosteroids are potent anti-inflammatory agents with multiple effects on the immune system and a wide range of applications. In the twentieth century, some researchers conducted studies on the effect of intravenous corticosteroids on dengue-related shock. More recently, researchers began to investigate whether intravenous or oral corticosteroids were effective in preventing disease progression from dengue at an early stage of infection to severe dengue (Kularatne 2009; Shashidhara 2013; Tam 2012; Villar 2009). Currently, the WHO does not recommend the use of corticosteroids either in severe dengue or in dengue at an early stage of infection (WHO 2009).

How the intervention might work

The mechanism in dengue resulting in plasma leakage is still unclear. Complications such as dengue-related shock are occasionally reported during primary infection (the first time a person is infected by a dengue virus), but are strongly associated with secondary infection (the second time a person is infected, possibly by a different serotype of the dengue virus). This indicates

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an involvement of the immune system, and the mechanism is mediated and enhanced by antibodies against the dengue virus (WHO 2009). Clinicians give corticosteroids when they think the host immune response contributes to the disease process. In some areas, corticosteroids have been used for the treatment of dengue-related shock or at an early stage of dengue infection. Observational studies have suggested corticosteroids may benefit people with dengue-related shock (WHO 2009; Kularatne 2009; Tam 2012).

Clinicians have employed the anti-inflammatory effect of corticosteroids for the treatment of shock caused by sepsis. Patients with sepsis have elevated blood levels of pro-inflammatory cytokines for weeks after clinical resolution of infection, during which shock may become manifest. Studies that have used lower doses of hydrocortisone (≤ 300 mg per day or equivalent) for longer durations have reported earlier reversal of shock and improved survival (Sprung 2008). A recent systematic review demonstrated that corticosteroids had no clear benefit on mortality in severe sepsis and septic shock (Annane 2009).

However, recent trials have investigated corticosteroids for treating dengue at an early stage because researchers assumed that corticosteroids might be effective in preventing complications when given early in the course of infection (Tam 2012).

Why it is important to do this review

Dengue poses a relevant global public health problem in resource-poor settings. It is important to evaluate effective treatment options to establish the best possible therapy, and to identify ineffective treatment options which consume limited resources and might do harm.

With the revision of the WHO classification in 2009, the case definition of severe dengue has become broader(WHO 2009). Therefore, all cases classified as Dengue shock syndrome according to the previous, stricter WHO definition (WHO 1997) will also meet the criteria for severe dengue of the WHO definition of 2009.

OBJECTIVES

To compare treatment of dengue with and without use of corticosteroids or placebo with regards to prevention of shock-related death and disease progression in children and adults.

1. To assess the effects of corticosteroids for treating patients with dengue-related shock
2. To assess the effects of corticosteroids in preventing severe dengue in patients with dengue at an early stage

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials.

Types of participants

Children and adults patients diagnosed with dengue (at an early stage and in patients with dengue-related shock).

Types of interventions

Intervention

Intravenous or oral corticosteroids (methylprednisolone, hydrocortisone, dexamethasone or any other kind of corticosteroid mentioned in the trial).

Control

Placebo or no corticosteroids.

Types of outcome measures

Primary outcomes

- Death

Secondary outcomes

- For patients with dengue-related shock, measures of severity including:
  - Blood transfusion
  - Complications, such as pulmonary haemorrhage and convulsion
  - Duration of shock (hours)
  - Days in hospital or duration of hospitalization (days)
  - Adverse events
- For patients with dengue at an early stage, measures of the onset of severe dengue including:
  - Dengue-related shock
  - Severe bleeding
  - Severe thrombocytopaenia
  - Ascites
  - Intensive care uni (ICU)) admission
  - Any bleeding
  - Hospital admission (frequency of hospitalization)
  - Platelet count
  - Haematocrit
  - White blood cell count

Adverse events

- Patients with serious adverse events
- Patients with any adverse events
- Patients with drug-related adverse events
- Patients with other reported events
- Patients with adverse events (for different comparisons: low-dose corticosteroids versus placebo; high-dose corticosteroids versus placebo; low-dose versus high-dose corticosteroid)

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press and in progress).

Electronic searches

We searched the following databases up until 6 January 2014 using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published in *The*

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Cochrane Library; MEDLINE(via Pubmed); EMBASE; LILACS. We also searched the *meta*Register of Controlled Trials (*m*RCT) using "dengue" AND ("steroid* OR corticosteroid*") as search terms.

Searching other resources

We screened the reference lists of existing reviews and of all trials identified by the above mentioned searches.

Data collection and analysis

Selection of studies

Two authors (Fan Zhang,FZ; Veronika Christine Kramer, VK) independently screened the titles and abstracts identified by the above search strategy and retrieved full-text articles of potentially relevant trials. For the identified full-text articles, we also independently used an eligibility form to decide on the final list of included studies. We listed excluded studies with the reason for exclusion. We contacted trial authors for clarification if eligibility was unclear. We resolved disagreements by discussion with Paul Garner (PG) and David Sinclair (DS).

Data extraction and management

Two authors independently extracted data using a pre-specified, pre-piloted data extraction form. For each outcome we extracted, where available, the number of participants randomized, the number of participants analyzed in each treatment group, the main methods, as well as detail about the interventions and outcomes. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number assessed in each intervention group. For continuous outcomes, we extracted arithmetic means and standard deviations for each intervention group, together with the numbers assessed in each group. Two authors independently extracted and cross-checked data to minimize errors. We contacted the trial authors for clarification or missing data where necessary.

Assessment of risk of bias in included studies

For this review update, we applied the latest Cochrane Collaboration methods for assessing risk of bias in included studies (Higgins 2011). FZ and VK independently assessed the risk of bias for each trial. We followed the guidance to assess whether adequate steps had been taken to reduce the risk of bias across six domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data; selective reporting; and other sources of bias. We categorized the risk of bias as 'high', 'low', or 'unclear' as per the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where our judgment was unclear, we attempted to contact the trial authors for clarification. We resolved any disagreements by discussion with PG or DS. We presented this information in a risk of bias summary table and used it for our interpretation of results. We used the GRADE approach to assist our assessment of the quality of evidence and to prepare of 'Summary of findings' tables.

Measures of treatment effect

We calculated results using the risk ratio (RR) for dichotomous data, and the mean difference (MD) for continuous data. These effect estimates were presented with 95% confidence intervals (CI).

Unit of analysis issues

The unit of analysis in all included trials was individual participants. One of our included studies, Tam 2012 had multiple intervention arms with 150 patients in each arm including 75 in high-dose group and 75 in low-dose group and 75 in the placebo group. When we did data analysis, we treat the study as two comparisons: one comparing high-dose (75) with placebo (37) while another one comparing low-dose (75) with placebo (38). We proportionately divided the placebo into two parts.

Dealing with missing data

Where no data was missing or unclear, we analyzed data according to the intention-to-treat principle (ie all randomized participants were analyzed in the groups to which they were originally assigned). Where there was a discrepancy between the number randomized and the number analyzed, we calculated and presented the percentage loss to follow-up for each intervention group. We contacted trial authors for missing or unclear data. Where we got no response from them, we carried out the complete-case analysis (ie only the available data was analyzed and the missing data ignored).

Assessment of heterogeneity

We looked for statistical heterogeneity by inspecting the forest plots for overlapping confidence intervals, applying the Chi^2 test (P value < 0.10 considered to be statistically significant), and the I^2 statistic (I^2 value of 50% used to denote moderate levels of heterogeneity).

Assessment of reporting biases

The number of trials per meta-analysis was insufficient to construct a funnel plot to assess publication bias.

Data synthesis

We analyzed participants with dengue-related shock and participants with dengue at an early stage separately.

One author (FZ) analyzed the data using Review Manager 5.2, and where appropriate we combined studies using a fixed-effect model. If we detected heterogeneity, but still considered it was clinically meaningful to combine studies, we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

The number of the trials was insufficient to carry out a meaningful subgroup analysis. According to our protocol, we would consider potential sources of heterogeneity and do possible subgroup analysis, such as study design, study setting and location, patient characteristics,, and the intervention given (different drug regimens).

Sensitivity analysis

The number of the trials was insufficient to carry out a meaningful sensitivity analysis. We have planned to do the sensitivity analysis with regarding to the risk of bias.

RESULTS

Description of studies

All eight of the included studies (948 participants in total) were randomized controlled trials.

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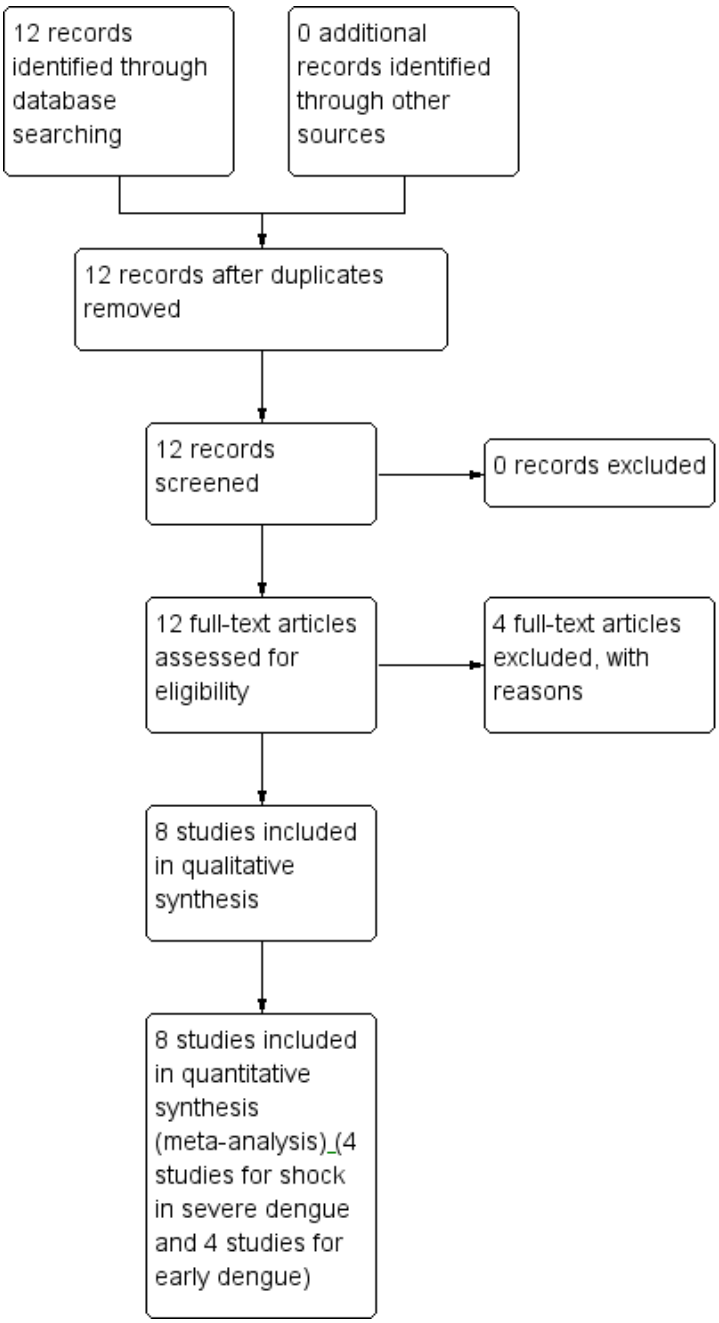
For further detail refer to the tables Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The previous review authors conducted the original search in January 2006 and included four unique trials which assessed the effects of corticosteroids on dengue shock syndrome. An update search in August 2009 did not yield any new trials.

We conducted an update search with a broader scope in June 2013, and repeated this search in January 2014. We identified four new studies which explored the effects of corticosteroids in an early stage of dengue infection rather than in dengue-related shock. Figure 1 shows the study flow diagram. We contacted authors of five studies which provided email addresses of the contact author or we found from other methods, and the contact author of three studies(Tam 2012, Villar 2009, Tassniyom 1993) replied and provided additional information (*see* 'Characteristics of included studies').

Figure 1. Study flow diagram.



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Included studies

Dengue-related shock

Four randomized controlled trials (Min 1975; Pongpanich 1973; Sumarmo 1982; Tassniyom 1993) including 284 participants met the inclusion criteria (*see* 'Characteristics of included studies') The participants enrolled were all children less than 15 years old.

All four included trials originated from Southeast Asia: two were conducted in Thailand (Pongpanich 1973; Tassniyom 1993), one in Myanmar (Min 1975), and one in Indonesia (Sumarmo 1982). All studies were hospital-based. Tassniyom 1993 enrolled patients across two hospitals while the other three trials had patients enrolled in one hospital each.

Three trials compared intravenous hydrocortisone hemisuccinate with no intervention (Pongpanich 1973; Min 1975) or with placebo (Sumarmo 1982), and one compared intravenous methylprednisolone with placebo (Tassniyom 1993).

All four trials reported on death, two reported the number needing a blood transfusion (Pongpanich 1973; Tassniyom 1993), and one reported complications (pulmonary haemorrhage and convulsion) and duration of hospitalisation (Tassniyom 1993). None of these studies reported adverse events as an outcome (Table 1).

One trial was funded by the WHO (Sumarmo 1982), one by the Rockefeller Foundation (Tassniyom 1993), and funding was not specified for the other two trials (Min 1975; Pongpanich 1973).

Dengue at an early stage

Four randomized controlled trials (Kularatne 2009; Shashidhara 2013; Tam 2012; Villar 2009) including 664 participants (children and adults) met the inclusion criteria (*see* 'Characteristics of included studies') for the review.

Among these four studies, two were conducted in South Asia(Sri Lanka (Kularatne 2009) and India (Shashidhara 2013); one in Southeast Asia (Vietnam, Tam 2012), and the fourth in Colombia, Latin America (Villar 2009).

Two trials used intravenous corticosteroids, and two evaluated oral corticosteroids. Shashidhara 2013 compared intravenous dexamethasone with a control group which received no treatment. Kularatne 2009 compared intravenous dexamethasone with placebo. Tam 2012 compared oral prednisolone with placebo. Villar 2009 compared oral methylprednisolone with placebo.

Shashidhara 2013 enrolled adults (aged above 18 years) only. Tam 2012 enrolled children aged between ten and 15 years. The other two trials (Kularatne 2009; Villar 2009) recruited both adults and children.

Villar 2009 reported on the clinical outcomes death, ascites and frequency of hospitalization. Tam 2012 reported on shock, shock-related complications and thrombocytopaenia. Shashidhara 2013 reported on death, shock and shock-related complications and platelet counts. Kularatne 2009 reported on laboratory parameters (platelet count, haematocrit and white blood cell count).

Three trials (Kularatne 2009; Tam 2012; Villar 2009) reported either spontaneous haemorrhage, severe bleeding or any bleeding.

Two trials reported on adverse events (Tam 2012, Villar 2009). Tam 2012 used prospective, active surveillance to monitor adverse events in a double-blind study (Table 1). Villar 2009 monitored adverse events prospectively, according to the trial protocol, but did not describe the method of data collection. Clinicians and participants were blinded. The author stated in the trial protocol that events were reported to an independent committee as fatal serious adverse effects, life-threatening or clinically significant adverse events (Table 1).

One trial was funded by the Wellcome Trust (Tam 2012). Funding was not specified for the other three trials (Kularatne 2009; Shashidhara 2013; Villar 2009).

Excluded studies

Four trials (Futrakul 1981; Futrakul 1987; Sumarmo 1975; Sumarmo 1987) detected by the search specifications were excluded from the review (*see* 'Characteristics of excluded studies').

Risk of bias in included studies

See Figure 2 for a summary of the risk of bias assessment. Further details are presented in the Characteristics of included studies tables.

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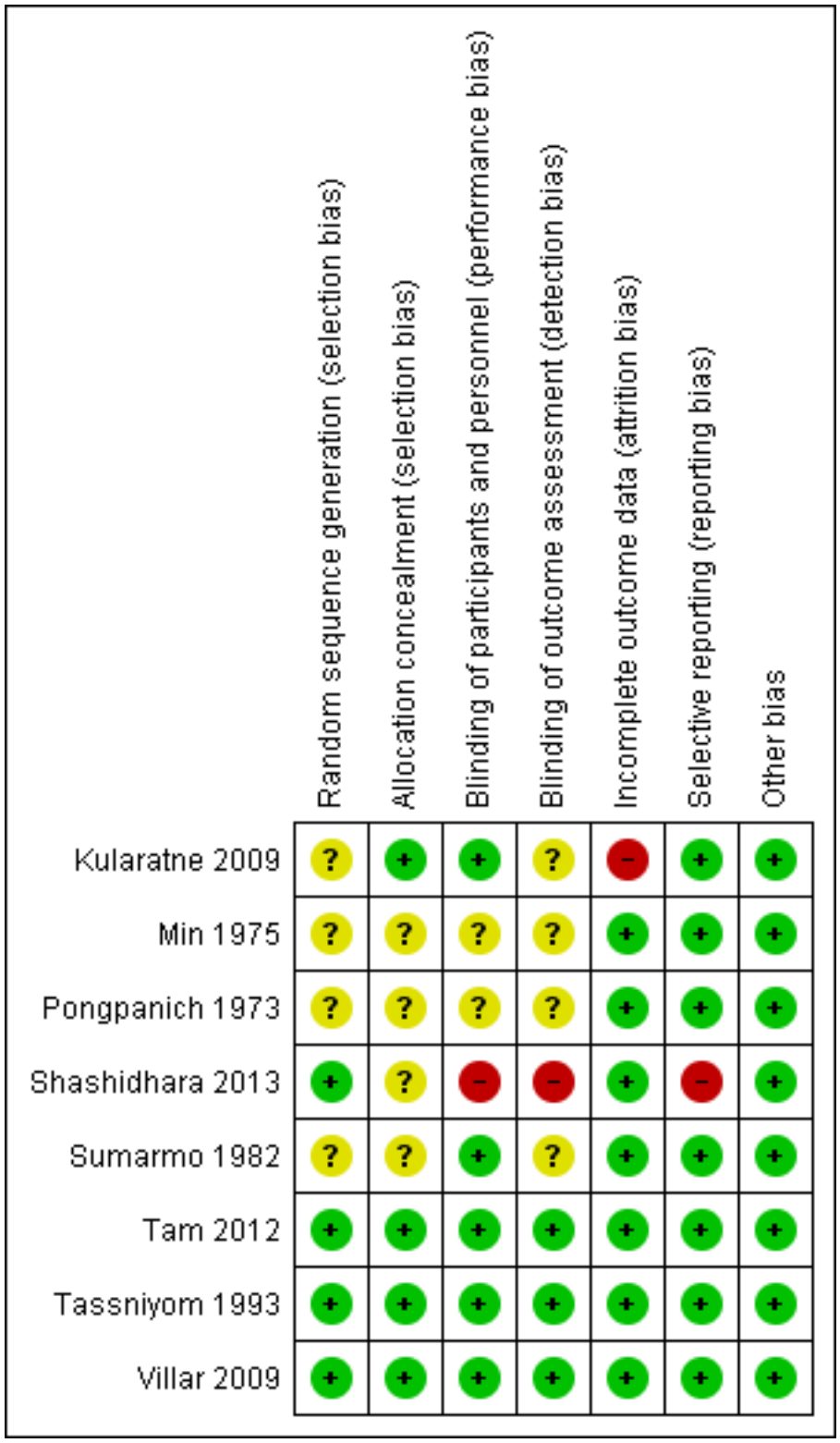
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



1) Dengue-related shock

For dengue-related shock, sequence generation and allocation concealment were adequate in one trial (Tassniyom1993) while the other three trials did not describe sequence generation in sufficient detail to allow a judgment.

Blinding was adequate in two trials (Tassniyom 1993; Sumarmo 1982), and unclear in the two other trials. No loss to follow-up

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occurred in these four hospital-based trials. We found no evidence of selective outcome reporting and identified no other sources of bias.

2) Dengue at an early stage

Sequence generation was adequate in three trials (Shashidhara 2013; Tam 2012; Villar 2009) while a fourth trial did not describe sequence generation in sufficient detail to allow a judgment Kularatne 2009).

Allocation concealment and blinding of participants and personnel were adequate in three trials (Kularatne 2009; Tam 2012; Villar 2009) and inadequate in the fourth trial (Shashidhara 2013). Blinding of outcome assessment was adequate in two trials (Tam 2012; Villar 2009) and unclear in one trial (Kularatne 2009). The fourth trial was described as an open-label study (Shashidhara 2013)

Villar 2009 clearly stated that they used the intention-to-treat principle and gave the number of participants originally randomized into two groups. Shashidhara 2013 reported no loss to follow-up. Tam 2012 reported a small loss of follow-up. Kularatne 2009 was the only study with a high loss of follow-up which was due to poor patient compliance in comparatively healthy children. Both studies (Kularatne 2009; Tam 2012) reported the number of participants originally randomized.

Only one trial (Shashidhara 2013) did not report all the pre-specified outcomes. No evidence of selective outcome reporting was detected in the other three trials (Kularatne 2009; Tam 2012; Villar 2009).

No other sources of bias were identified.

Effects of interventions

See: **Summary of findings for the main comparison** Corticosteroid for dengue-related shock; **Summary of findings 2** Corticosteroid for dengue at an early stage

1) Corticosteroids for treating dengue-related shock

Death

Corticosteroid treatment in dengue-related shock does not reduce mortality significantly when compared to placebo (four trials, 284 participants, I^2=0%, Analysis 1.1). In Pongpanich 1973, no one died either in the corticosteroid or in the placebo group. In Min 1975, treatment with corticosteroids significantly reduced the risk of death. In Sumarmo 1982 and Tassniyom 1993, corticosteroids showed no statistically significant benefit.

Blood transfusion

There was no statistically significant difference between the groups in the number of participants needing blood transfusion (two trials, 89 participants, Analysis 1.2) (Pongpanich 1973; Tassniyom 1993).

Complications

Tassniyom 1993 reported no statistically significant difference between the corticosteroids and placebo groups for pulmonary haemorrhage and convulsions (63 participants, Analysis 1.3).

Days in hospital

Tassniyom 1993 reported an average stay of 7.3 days in hospital in the corticosteroid group and 6.2 days in the placebo group, without statistically significant difference between two groups (63 participants, Analysis 1.4).

Adverse events

None of the studies reported on adverse event monitoring.

Other outcomes: duration of shock

Data for outcomes we could not present as meta-analysis were summarized in Table 2.

One out of two studies (Min 1975) reported a significantly shorter duration of shock in the corticosteroid group than in the placebo group, while the second study (Pongpanich 1973) found no difference. These studies were small (124 participants across two trials). Another study (Sumarmo 1982) reported the number of participants who recovered from shock within a certain time period after corticosteroid or placebo treatment, and differences between the two groups appeared small (97 participants, one study). Statistical significance was not reported.

2) Corticosteroids for treating dengue at an early stage

Death

No deaths in either the treatment or control (placebo or no treatment) group were reported in any of the trials (664 participants, four trials, Analysis 2.1).

Severe dengue: dengue-related shock

Two trials (Shashidhara 2013; Tam 2012) reported no difference in patient numbers developing dengue-related shock after preventive treatment with corticosteroids when compared to placebo or no corticosteroid (286 participants, Analysis 2.1).

One trial (Tam 2012) with three study arms detected no significant difference in the risk of dengue-related shock after low-dose corticosteroids, high-dose corticosteroids or placebo. Eleven per cent of participants in the high-dose corticosteroid group and 7% in each of the low-dose and placebo groups developed shock. Another study reported no case of shock occurred in either the corticosteroid or in the control group (Shashidhara 2013).

Severe dengue: severe bleeding

Two trials reported that corticosteroids did not significantly reduce the risk of bleeding complications when compared to placebo (425 participants, Analysis 2.1).

Significant bleeding or bleeding complications were rare. Kularatne 2009 observed no bleeding complications in either the corticosteroid or placebo group. Tam 2012 detected four cases (2.67%) of significant or clinical bleeding in the group receiving corticosteroids (one in high-dose and three in low-dose group). Two patients had dengue-related shock, one developed gross haematuria, and one suffered isolated upper gastrointestinal bleeding. One case (1.33%) was detected in the placebo group.

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Severe thrombocytopaenia

Corticosteroids did not significantly reduce the incidence of severe thrombocytopaenia when compared to placebo in the one trial that reported this outcome (225 participants, Analysis 2.1). Severe thrombocytopaenia occurred in 4% of participants in the corticosteroid group and in 1% in the placebo group.

Ascitis

One trial (Villar 2009) reported that corticosteroids did not reduce the risk to develop ascites (178 participants, Analysis 2.1). While no one developed ascites in the corticosteroid group, four participants (4.40%) presented with ascites in the control group. However, the difference was not statistically significant (178 participants, Analysis 2.1) and the study was not powered to detect an effect.

Intensive care unit (ICU) admission

Two trials (Shashidhara 2013; Tam 2012) reported on ICU admissions (286 participants, Analysis 2.1). Shashidhara 2013 recorded no ICU admissions either in the corticosteroid or control group. Tam 2012 did not find a significant difference in ICU admissions between study arms (8% in the low-dose group, 10% in both the high-dose and the placebo groups).

Any bleeding

Corticosteroids reduced the risk of any bleeding by 15% when compared to the placebo (RR 0.85, 95% CI 0.72 to 0.99, 403 participants, two studies, Analysis 2.1). Definitions of "any bleeding" differed between the two studies: Tam 2012 found that approximately 70% of patients across all intervention groups experienced some form of bleeding as minor skin bleedings (petechiae), skin bruising or mild to moderate mucosal bleeding. Villar 2009 defined bleeding as "spontaneous haemorrhage", and reported proportions of 36% (in the corticosteroid group) to 50% (in the placebo group) suffered bleeding. The study protocol (Villar 2009) specified gastrointestinal bleeding or oral bleeding, nosebleed, blood in the urine (haematuria), minor skin bleedings (petechiae), bruising or purple skin as spontaneous bleeding manifestations.

Hospital admission

Villar 2009 found that corticosteroids had no significant effect on the number of hospitalizations required (178 participants, Analysis 2.1). Ten percent of patients in the corticosteroid and 16% in the placebo group were hospitalized. The study was not powered to detect an effect.

Platelet count on days one to four

The combined results of two studies (Shashidhara 2013, Kularatne 2009) showed no statistically significant difference in platelet counts between corticosteroid and control group on the first, second, third or fourth day (261 participants, Analysis 2.2). The results was heterogenous on the second day.

Haematocrit on days one to four

The study(Kularatne 2009) showed no significant difference between the groups on days one, two, three or four (200 participants, one study, Analysis 2.3).

White blood cell count on days one to four

Kularatne 2009 found a significantly lower white blood cell count in the corticosteroid group on day 1 (mean difference, 4.8 cells/mcL for corticosteroid and 5.7 cells/mcL for placebo group) (200 participants, Analysis 2.4), but no significant difference between the groups was detected on days 2, 3 or 4.

Patients with adverse events

Villar 2009 recorded adverse events prospectively and reported in the conference abstract that "no adverse or severe events" occurred.

Tam 2012 used prospective, active surveillance to monitor serious and any adverse events (Table 1).

Serious adverse events: There was no difference in the number of people who had serious adverse events after high-dose corticosteroids, low-dose corticosteroids or placebo (403 participants, Tam 2012, Analysis 2.5, Analysis 2.8, Analysis 2.9, Analysis 2.10).

Any adverse event: There was no significant difference in participants who experienced any adverse events across treatment groups. The proportion of participants with any adverse events was high with 30% in both the high-dose corticosteroid and placebo groups and 20% in the low-dose corticosteroid group (403 participants, Tam 2012, Analysis 2.5, Analysis 2.8, Analysis 2.9, Analysis 2.10).

Drug-related adverse events: Tam 2012 found no significant difference in the number of patients with hyperglycaemia, hypertension, pneumonia and upper respiratory tract infection after corticosteroid treatment when compared to placebo. The study authors thought these diagnoses to be possibly drug-related (225 participants, Analysis 2.6). The study also reported three other adverse events, which they deemed not related to the study drug. Again, the study detected no significant difference between study arms (225 participants, Analysis 2.7).

DISCUSSION

Summary of main results

Dengue-related shock

The four trials evaluating corticosteroids in children with dengue-related shock were conducted before 1988 and had small participant numbers a high risk of bias. The meta-analysis was underpowered with very low quality evidence, and did not demonstrate an effect on mortality (four studies, 284 participants), the need for blood transfusion (two studies, 89 participants), pulmonary haemorrhage (one study, 63 participants), or convulsions (one study, 63 participants).

Dengue at an early stage

Intravenous or oral corticosteroids in children and adults with dengue infection have not been shown to reduce the risk of death (four trials, 664 participants, low quality of evidence) or the risk to develop complications of severe dengue, such as shock (two trials, 286 participants, very low quality of evidence), severe bleeding (two trials, 403 participants, very low quality of evidence), severe thrombocytopaenia (one trial, 225 participants, very low quality of evidence), ascites (one trial, 178 participants, very low quality

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evidence) and ICU admissions (two trials, 286 participants, very low quality of evidence).

Only four trials were included in this part of the review, and many of the outcomes were reported by one trial only.

Overall completeness and applicability of evidence

Dengue-related shock

For the trials evaluating corticosteroids in shock the data was limited, and confined to studies in children only. All trials were conducted in Southeast Asia. These small trials were similar in terms of location, setting, and types of participants.

Dengue at an early stage

The body of evidence for corticosteroids in dengue at an early stage is limited. We identified four small trials from Colombia, India, Sri Lanka and Vietnam, which included both children and adults. They used different oral corticosteroids (prednisolone and methylprednisolone) (Tam 2012; Villar 2009) or intravenous dexamethasone in different doses (Kularatne 2009, Shashidhara 2013) and were conducted in different settings. Ten of our review's outcomes were reported by only one trial (Analysis 2.1-Analysis 2.10). It is therefore difficult to generalize the findings.

Quality of the evidence

Dengue-related shock

We found the quality of evidence to be very low for all outcomes of this comparison. The four trials were conducted more than 25 years ago from 1960s to 1980s. They preceded newer guidance for transparent reporting on sequence generation and allocation concealment, and have methodological limitations. For our risk of bias assessment, please see Figure 2. These trials were conducted in hospital settings with low loss to follow-up, and no evidence of selective outcome reporting. The trials were also underpowered and thus too small to reliably detect an effect in the outcomes that they measured. For an estimation for the sample sizes that would be required per study and per meta-analysis please see Table 3.

Dengue at an early stage

The quality of evidence for this comparison of the review was low for the outcome death, and very low for dengue-related shock, ICU admission, severe bleeding, severe thrombocytopaenia and ascites. The four trials have lower risk of bias and were conducted more recently between 2004 and 2011. One out of four trials reported high loss to follow-up. Nevertheless, they are seriously underpowered (Table 3) and cannot be easily generalized to various settings. This was our reason for downgrading the quality of evidence.

Agreements and disagreements with other studies or reviews

The findings of a former systematic review (Panpanich 2010) and two other literature reviews (Rajapakse 2009, Rajapakse 2012) that evaluated the effects of corticosteroids in dengue-related shock are consistent with our findings. However, these reviews did not address the effects of corticosteroids in dengue at an early stage infection.

A study nested in the trial by Tam 2012 explored the effects of low-dose corticosteroids, high-dose corticosteroids and placebo on the immune response of patients with dengue at an early stage (Nguyen 2013). The study reported a limited effect of corticosteroids on patients' cytokine levels and immune modulation. This is consistent with results of the clinical trial (Tam 2012) which detected no significant clinical benefits after corticosteroids. The authors concluded that "early prednisolone therapy has little impact on the host immune response", even if the dose might be "too little or too late".

The current WHO strategy focusses on early diagnosis of dengue cases and on staff training for improved case management, but also emphasises the importance of a greater evidence-base for interventions (WHO 2012c).

AUTHORS' CONCLUSIONS

Implications for practice

At present, there is insufficient evidence to know if routinely using corticosteroids in treating dengue-related shock in children and adults has an effect.

There is also insufficient evidence to know if using corticosteroids in treating dengue at an early stage influences the course of the disease.

Implications for research

At present, recommended treatment for severe dengue is restricted to supportive therapy. More research is needed to evaluate if drug therapies such as corticosteroids are effective and safe and should be recommended or not.

For corticosteroid use in people with dengue-related shock, it would require a trial of probably more than 1672 people to identify an effect on death (sufficient sample size, Table 3). Whether this is a priority for care depends on balancing other potentially important interventions are worth testing for managing severe dengue infection.

For people with symptomatic dengue early in the illness, large, rigorously conducted randomized controlled trials that measure death or other severe dengue-related complications as an outcome would be needed to justify the use of corticosteroids, but these would need to be even larger, with an estimate sample size of over 8000 people (Table 3).

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CHARACTERISTICS OF STUDIES

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

Kularatne 2009

Methods	Study design: randomized controlled trial Study dates: June 2004 to February 2006 Diagnostics: clinical, serological (haemagglutinin inhibiting antibody essay (HIA), IgM and IgG ELISA)
Participants	Number of participants randomized: 200 enrolled (100 in corticosteroid group; 100 in placebo group) Age: 12 to 65 years Inclusion criteria: with acute, serologically confirmed dengue, without any concomitant illnesses Exclusions: patients with evidence of bleeding and shock
Interventions	1. Dexamethasone: intravenous 4 mg as the initial dose and 2 mg every 8 hours thereafter for 24 hours 2. Placebo: intravenous isotonic saline
Outcomes	1. Platelet count 2. Haematocrit 3. White blood cell count (WBC) 4. Bleeding complications
Notes	Location: Central Hospital, Peradeniya , Sri Lanka Transmission: not specified Funding: not specified

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Kularatne 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned patients", no more detail about sequence generation
Allocation concealment (selection bias)	Low risk	Quote: "using sealed envelop method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "placebo group received intravenous isotonic saline identical in appearance to the active drug according to the same regimen"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	High losses to follow-up on days 3 and 4 were reported Treatment group: day 1: 0, day 2: 7%, day 3: 24%, day 4: 54% Control group: day 1: 0, day 2: 8%, day 3: 21%, day 4: 64%
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Min 1975

Methods	Study design: randomized controlled trial Study dates: February 1973 to February 1974 Diagnostics: clinical, "serologically proven"
Participants	Number of participants randomized: 98 enrolled (48 in corticosteroid group; 50 in control group). Age: not reported Inclusion criteria: children diagnosed with dengue shock syndrome using serological confirmation Exclusions: not specified
Interventions	1. Hydrocortisone hemisuccinate: single dose of 25 mg/kg intravenous on day 1, 15 mg/kg on day 2, 10 mg/kg on day 3 2. No medication (fluid replacement only)
Outcomes	1. Death 2. Duration of shock
Notes	Location: Children's hospital, Rangoon, Burma (Myanmar) Transmission: not specified

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Min 1975 *(Continued)*

	Funding: not specified Fluid replacement included normal saline, Ringer lactate solution, plasma, and blood products

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly selected in 2 groups after carefully matching them by age groups and sex", no detail about method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blind" No placebo given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Double blind" No placebo given
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Pongpanich 1973

Methods	Study design: randomized controlled trial Study dates: 1969 to 1971 Diagnostics: clinical diagnosis and serological or virological. Haemagglutination inhibition (HI) test performed on paired sera; positive result was a fourfold rise in titre or a fixed level at 1:640 or more.
Participants	Number of participants: randomized: 26 enrolled (7 in corticosteroid group; 19 in control group) Age: 6.6 to 9.5 years Inclusion criteria: children diagnosed with dengue shock syndrome using serological confirmation Exclusions: not specified
Interventions	1. Hydrocortisone hemisuccinate: intravenous 25 mg/kg/day; 5 mg/kg at start, rest given in divided doses every four to six hours in addition to fluid replacement 2. No medication (fluid replacement only)
Outcomes	1. Death 2. Duration of shock 3. Number requiring fluid replacement

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Pongpanich 1973 *(Continued)*

	4. Number needing blood transfusion
Notes	Location: Ramathibodi Hospital, Bangkok, Thailand Transmission: not specified Funding: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A card was drawn at onset of shock to decide which treatment program would be given", no more detail about sequence generation
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Shashidhara 2013

Methods	Study design: randomized controlled trial Study dates: June 2010 to June 2011 Diagnostics: serological (IgM ELISA)
Participants	Number of participants randomized: 61 enrolled (30 in corticosteroid group; 31 in control group) Age: above 18 years Inclusion criteria: aged above 18 years; serologically confirmed IgM ELISA, when platelet counts dropped below 50,000/cumm during the acute stage of illness Exclusions: patients with evidence of bleeding and shock; patients with HIV, autoimmune disease, connective tissue disorders and vasculitis, ITP, malignancy during direct examination and clinical investigations if necessary; patients with diabetes mellitus, hypertension, history of peptic ulcer, hypersensitivity to corticosteroids, total leucocyte counts of more than 11,000/cumm
Interventions	1. Dexamethasone: intravenous 8 mg as the initial dose and 4 mg every 8 hours thereafter for 4 days (iv fluids were given whenever necessary)

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Shashidhara 2013 *(Continued)*

	2. Control: only intravenous fluids and antipyretics whenever necessary
Outcomes	1. Platelet count 2. Death 3. Number developing dengue-related shock 4. Number requiring transfusion
Notes	Location: JSS Hospital Mysore, Karnataka, India (tertiary medical care centre) Transmission: not specified Funding: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were allotted randomly by blocked randomisation by using a fixed blocking method"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote:"open label"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote:"open label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported
Selective reporting (reporting bias)	High risk	Among all data recorded, only platelet counts was reported
Other bias	Low risk	No other bias identified

Sumarmo 1982

Methods	Study design: randomized controlled trial Study dates: February 1978 to May 1979 Diagnostics: clinical and serological or virological: Haemagluttinin Inhibition (HI) test on acute and convalescent paired sera, technique of Clarke and Casals. Virus isolation by mosquito inoculation, technique of Rose and Gubler for patients with a fourfold increase of the HI antibody titre or patients who died.
Participants	Number of participants: randomized: 97 enrolled (47 in corticosteroid group; 50 in placebo group) Age: 0.9 to 10 years

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Sumarmo 1982 *(Continued)*

	Inclusion criteria: children with serologically confirmed dengue shock syndrome Exclusions: not specified
Interventions	1. Hydrocortisone hemisuccinate: 50 mg/kg, single intravenous dose in addition to fluid replacement 2. Placebo: sodium chloride 0.9% with same colour and turbidity
Outcomes	1. Death 2. Duration of shock 3. Requirement of fluid replacement (mL)
Notes	Location: Dr Cipto Mangunkusumo Hospital, Jakarta, Indonesia Transmission: not specified Funding: WHO Project ICPRPD 001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "divided group using a simple random assignment method", no more detail about the method of sequence generation
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind" and "Placebo packaged in indistinguishable coded vials"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Tam 2012

Methods	Study design: randomized controlled trial Study dates: August 2009 to January 2011 Diagnostics: virological diagnosis (rapid test for dengue non-structural protein NS1 silver strip)
Participants	Number of participants: randomized: 225 enrolled (150 in corticosteroid group including 75 in high-dose group and 75 in low-dose group; 75 in placebo group)

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Tam 2012 *(Continued)*

	Inclusion criteria: children and young adults Age: 5 to 20 years (enrolled participants were 10 to 15 years of age) with clinically suspected dengue, supported by a positive antigen test for dengue, fever for ≤72 hours and negative pregnancy test Exclusions: those weighing < 20 kg, those with evidence for any dengue-related complications, symptoms suggesting another infectious disease, or a past history of serious illness or chronic disease including psychiatric/behavioural problems, and those taking regular medications
Interventions	1. prednisolone: low-dose (0.5 mg/kg) orally once daily for three days 2. prednisolone: high-dose (2 mg/kg) orally once daily for three days 3. placebo: placebo group was additionally 1:1 randomized to low- or high-dose placebo
Outcomes	1. Number of complications: dengue shock syndrome; ICU admission; severe thrombocytopaenia; significant bleeding; severe abdominal pain; increased liver enzymes 2. Number of adverse events: hyperglycaemia, hypertension, pneumonia, upper respiratory infection Platelet nadir days 3 to 8, 10^9/L Laboratory endpoints: maximum haematocrit at days 3 to 8; %haemoconcentration Virological endpoints (not of interest for this review) Area under the curve (AUC) log viraemia at days 3 to 6, log 10 copies/mL; time to undetectable viraemia, number and % with undetectable viraemia; days from enrolment, median (interquartile range, IQR) to undetectable viraemia; time to negative NS1: number with negative NS1 %; days from enrolment, median (IQR) to negative NS1
Notes	Location: Hospital for Tropical Diseases, Ho Chi Min City, Vietnam Transmission: not specified Funding: Wellcome Trust Tam 2012 defined platelet nadir < 10,000/µl L = SAE as severe thrombocytopaenia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "block randomisation"
Allocation concealment (selection bias)	Low risk	Quote: "All participants and study staff were blind to the treatment allocation" and "did not blind the dose allocation, but the placebo group was additionally 1:1 randomized to low- or high-dose placebo to maintain blinding of the drug"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "identical prednisolone and placebo were available", and "placebo group was additionally 1:1 randomized to low- or high-dose placebo to maintain blinding of the drug". They were blind to intervention or placebo, but not to high or low dose.
Blinding of outcome assessment (detection bias)	Low risk	Email correspondence with author: "The study staff were the outcome assessors and they were blind"

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Tam 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses to follow-up were reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Tassniyom 1993

Methods	Study design: randomized controlled trial Study dates: 1987 to 1988 Diagnostics: viral isolation, serological diagnosis: haemagglutinin inhibition (HI) test, ELISA for dengue antibodies
Participants	Number of participants: randomized: 63 enrolled (32 in corticosteroid group; 31 in placebo group) Age: 3 to 14 years Inclusion criteria: children diagnosed with dengue shock syndrome using World Health Organization clinical criteria and serological confirmation Exclusions: not specified
Interventions	1. Methylprednisolone (Solumedrol, Upjohn): single intravenous dose of 30 mg/kg in addition to fluid replacement 2. Placebo: 5% dextrose in normal saline solution
Outcomes	1. Death 2. Number needing blood transfusion 3. Duration of hospitalization 4. Number getting complications (separate data for each complication)
Notes	Location: Khon Kaen University Hospital, and Khon Kaen Provincial Hospital in Khon Kaen, Thailand Transmission: not specified Funding: Rockefeller Foundation (grant RF 87006#95)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Block randomisation" and "Generation of allocation sequence: generated by statistician and running number put on drug package"
Allocation concealment (selection bias)	Low risk	Email correspondence with author: "By using sealed envelopes"

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Tassniyom 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind", "All specimens were identified only by code number" and "identical placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Email reply from author: outcome assessors was blinded to the intervention, they "knew patients by code number" only
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up were reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

Villar 2009

Methods	Study design: randomized controlled trial Study dates: July 2006 to January 2009 Diagnostics: clinical diagnosis or immuno chromatography test
Participants	Number of participants randomized: 189 enrolled (87 in corticosteroid group; 91 in placebo group) Age: not stated Inclusion criteria: fever over 48 hours but less than 120 hours, with clinical diagnosis of dengue or immuno chromatography test, and free of clinical signs of plasma leakage Exclusion criteria: leukocytosis; evidence of plasma leakage, hypotension, or major bleeding and bruising, hematemesis, melena, rectal bleeding and purple; oral intolerance; women of reproductive age with amenorrhoea than 4 weeks; cancer, HIV/AIDS or haematological disorders; breast-feeding patients and those with a history of diseases; patients who have visited a malaria endemic area in the last 30 days
Interventions	1. Metylprednisolone: single oral dose 1.5 mg/kg 2. Placebo
Outcomes	1. Complications such as number developing spontaneous haemorrhages and ascites 2. Frequency of hospitalization 3. Adverse or severe events or mortality
Notes	Location: Bucaramanga, Colombia Transmission: not specified Funding: not specified

Risk of bias

Bias	Authors' judgement	Support for judgement

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Villar 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Email correspondence with author: "generated in the computer 4 lists of 25 randomly selected blocks with replacement"
Allocation concealment (selection bias)	Low risk	Email correspondence with author: "lists of numbers will be generated by project engineer, who will be the only person to know that each code contains measures of treatment during the period of collection of information"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "blinded for participants, care givers"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "blinded for outcome adjudicators"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low losses of follow-up were reported
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	No other bias identified

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

Study	Reason for exclusion
Futrakul 1981	Not a randomized or quasi-randomized controlled trial
Futrakul 1987	Not a randomized or quasi-randomized controlled trial
Nguyen 2013	The clinical outcomes of this trial are reported in Tam 2012
Sumarmo 1975	Not a randomized or quasi-randomized controlled trial
Sumarmo 1987	Duplicate data with an included trial

DATA AND ANALYSES

Comparison 1. Steroids versus placebo/no steroids in patients with dengue-related shock

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4	284	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.42, 1.11]
2 Blood transfusion	2	89	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.52, 2.24]

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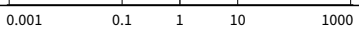
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Complications	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Pulmonary haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Convulsions	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Days in hospital	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Steroids versus placebo/no steroids in patients with dengue-related shock, Outcome 1 Death.

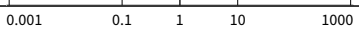
Study or subgroup	Corticosteroid n/N	Placebo or no steroid n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Min 1975	9/48	19/50		59.28%	0.49[0.25,0.98]
Pongpanich 1973	0/7	0/19			Not estimable
Sumarmo 1982	8/47	9/50		27.78%	0.95[0.4,2.25]
Tassniyom 1993	4/32	4/31		12.94%	0.97[0.27,3.54]
Total (95% CI)	**134**	**150**		**100%**	**0.68[0.42,1.11]**
Total events: 21 (Corticosteroid), 32 (Placebo or no steroid)					
Heterogeneity: Tau^2=0; Chi^2=1.68, df=2(P=0.43); I^2=0%					
Test for overall effect: Z=1.54(P=0.12)					



Favours steroid — Favours no steroid

Analysis 1.2. Comparison 1 Steroids versus placebo/no steroids in patients with dengue-related shock, Outcome 2 Blood transfusion.

Study or subgroup	Corticosteroid n/N	Placebo or no steroid n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Pongpanich 1973	0/7	4/19		24.04%	0.28[0.02,4.59]
Tassniyom 1993	11/32	8/31		75.96%	1.33[0.62,2.86]
Total (95% CI)	**39**	**50**		**100%**	**1.08[0.52,2.24]**
Total events: 11 (Corticosteroid), 12 (Placebo or no steroid)					
Heterogeneity: Tau^2=0; Chi^2=1.19, df=1(P=0.28); I^2=16.05%					
Test for overall effect: Z=0.2(P=0.84)					



Favours steroid — Favours no steroid

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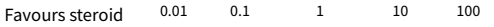
Analysis 1.3. Comparison 1 Steroids versus placebo/no steroids in patients with dengue-related shock, Outcome 3 Complications.

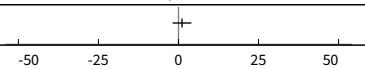
Study or subgroup	Corticosteroid n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Pulmonary haemorrhage				
Tassniyom 1993	1/32	1/31		0.97[0.06,14.82]
1.3.2 Convulsions				
Tassniyom 1993	3/32	0/31		6.79[0.36,126.24]



Favours steroid — Favours placebo

Analysis 1.4. Comparison 1 Steroids versus placebo/no steroids in patients with dengue-related shock, Outcome 4 Days in hospital.

Study or subgroup	Favours steroid N	Favours steroid Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Tassniyom 1993	32	7.3 (7.5)	31	6.2 (3.9)		0%	1.1[-1.83,4.03]



Favours steroid — Favours placebo

Comparison 2. Steroids versus placebo/no steroids in patients with dengue at an early stage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications in dengue at an early stage	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Death	4	664	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Severe dengue: dengue-related shock	2	286	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.48, 3.51]
1.3 Severe dengue: severe bleeding	2	425	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.24, 9.30]
1.4 Severe thrombocytopaenia	1	225	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.31, 7.28]
1.5 Ascites	1	178	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 2.13]
1.6 ICU admission	2	286	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.38, 1.99]
1.7 Any bleeding	2	403	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.72, 0.98]
1.8 Hospital admission	1	179	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.29, 1.37]
2 Platelet count on days one to four	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Day 1	2	261	Mean Difference (IV, Fixed, 95% CI)	-0.88 [-3.55, 1.80]

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Day 2	2	246	Mean Difference (IV, Fixed, 95% CI)	0.35 [-5.02, 5.71]
2.3 Day 3	2	216	Mean Difference (IV, Fixed, 95% CI)	2.58 [-5.81, 10.96]
2.4 Day 4	2	143	Mean Difference (IV, Fixed, 95% CI)	-6.97 [-20.69, 6.75]
3 Haematocrit on days one to four	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Day 1	1	200	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.54, 1.54]
3.2 Day 2	1	185	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.70, 2.50]
3.3 Day 3	1	155	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-2.29, 1.09]
3.4 Day 4	1	82	Mean Difference (IV, Fixed, 95% CI)	2.0 [-0.16, 4.16]
4 White blood cell count on days one to four	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Day 1	1	200	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.64, -0.16]
4.2 Day 2	1	185	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.86, 0.86]
4.3 Day 3	1	155	Mean Difference (IV, Fixed, 95% CI)	-0.5 [-1.49, 0.49]
4.4 Day 4	1	81	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-1.68, 1.10]
5 Adverse events in dengue at an early stage	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Patients with serious adverse events	2	403	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.50, 2.03]
5.2 Patients with any adverse events	2	403	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.57, 1.38]
6 Patients with drug-related adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Hyperglycaemia	1	225	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.69, 7.90]
6.2 Hypertension	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.10]
6.3 Pneumonia	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.03, 7.88]

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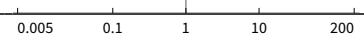
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.4 Upper respiratory infection	1	225	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [0.24, 9.41]
7 Patients with other reported events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Urticaria	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.10]
7.2 Febrile convulsion	1	225	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.06, 35.96]
7.3 Diarrhoea	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Patients with adverse events low-dose steroids versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Patients with serious adverse events	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.23, 1.57]
8.2 Patients with any adverse events	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.42, 1.27]
9 Patients with adverse events high-dose steroids versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Patients with serious adverse events	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.66, 2.95]
9.2 Patients with any adverse events	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.64, 1.70]
10 Patients with adverse events low-dose versus high-dose steroids	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Patients with any serious adverse events	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.17, 1.06]
10.2 Patients with any adverse events	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.40, 1.21]

Analysis 2.1. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 1 Complications in dengue at an early stage.

Study or subgroup	Corticosteroids n/N	Placebo or no steroids n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Death					
Kularatne 2009	0/100	0/100			Not estimable
Shashidhara 2013	0/30	0/31			Not estimable
Tam 2012	0/75	0/37			Not estimable
Tam 2012	0/75	0/38			Not estimable
Villar 2009	0/87	0/91			Not estimable
Subtotal (95% CI)	**367**	**297**			**Not estimable**
Total events: 0 (Corticosteroids), 0 (Placebo or no steroids)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



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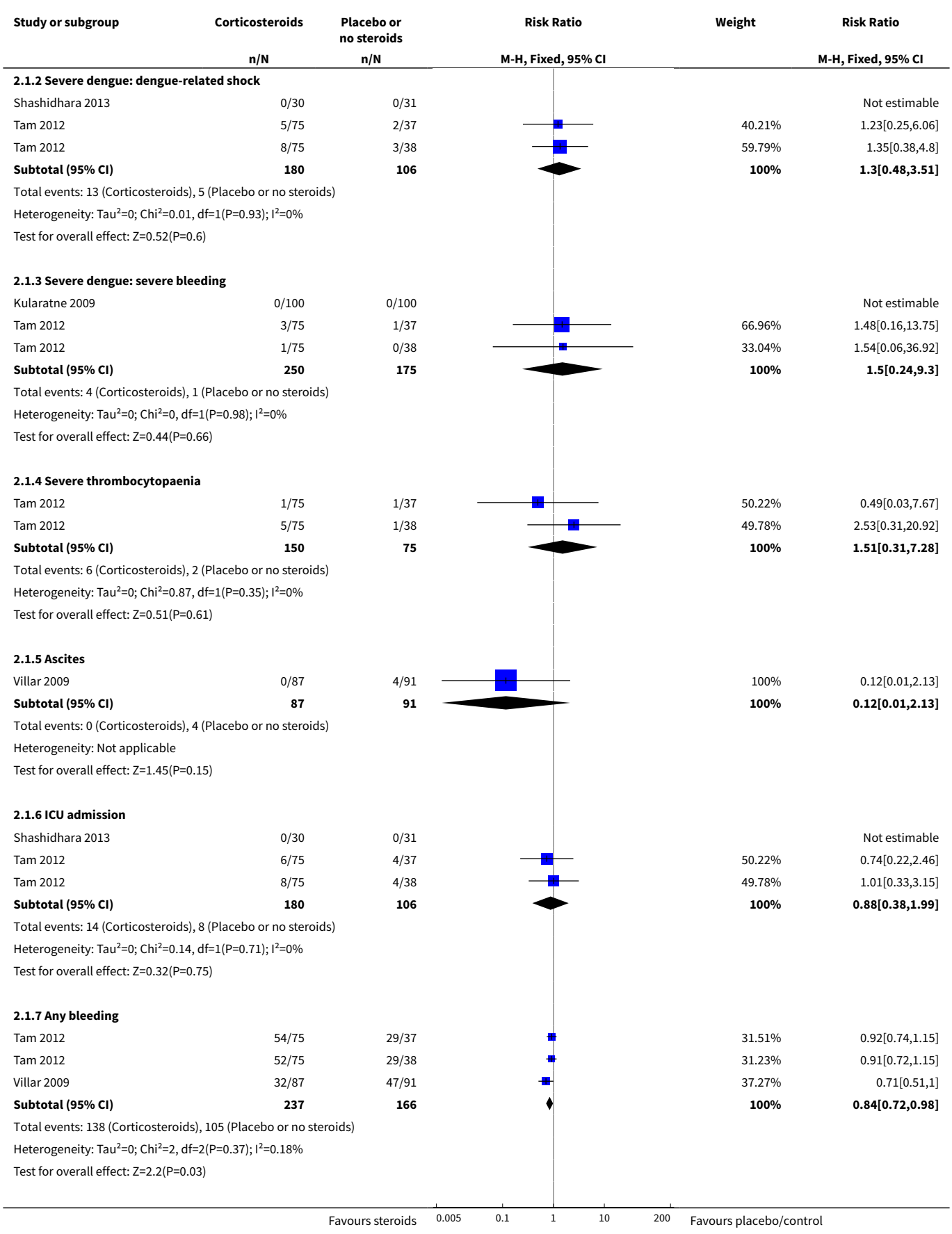

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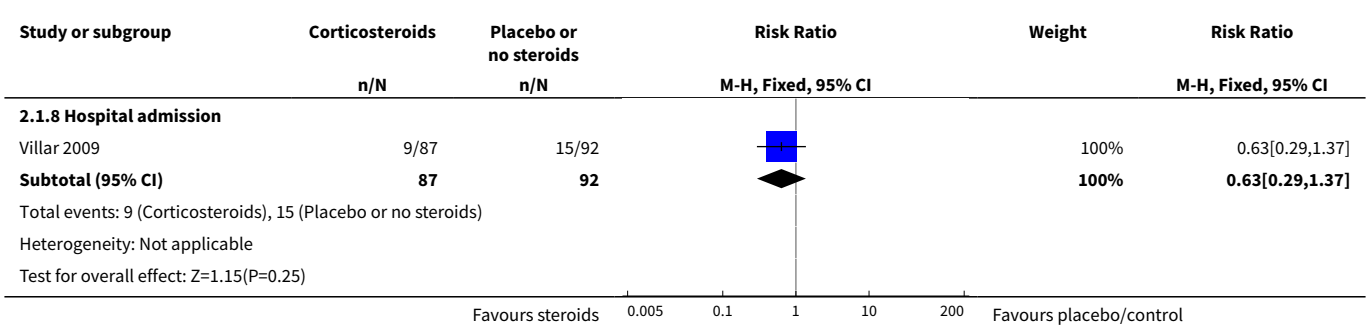
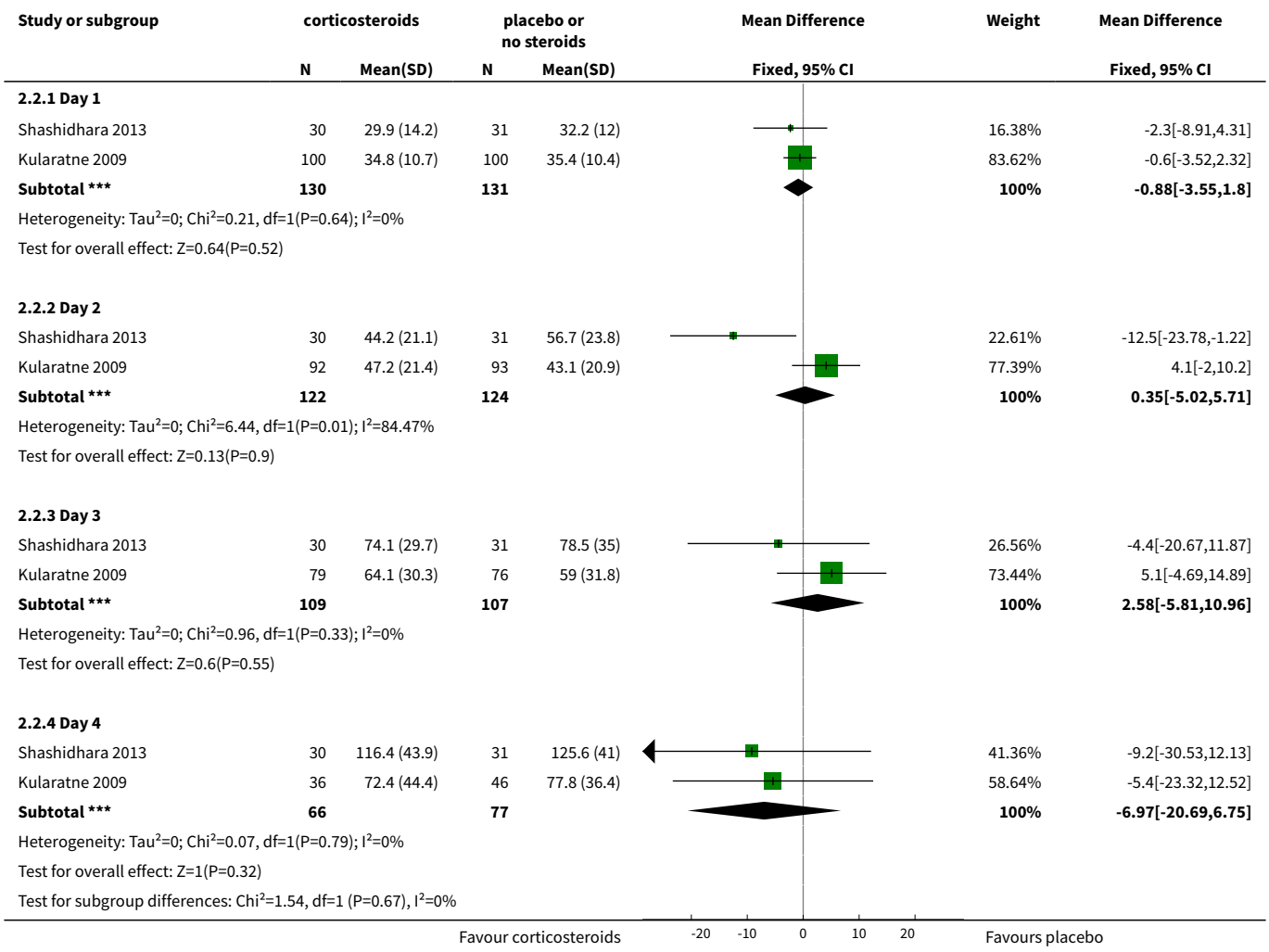


Analysis 2.2. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 2 Platelet count on days one to four.



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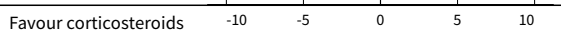
Analysis 2.3. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 3 Haematocrit on days one to four.

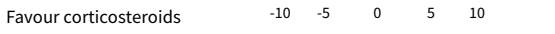
Study or subgroup	corticosteroids N	corticosteroids Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.3.1 Day 1							
Kularatne 2009	100	40.6 (5.5)	100	40.6 (5.6)		100%	0[-1.54,1.54]
Subtotal ***	**100**		**100**			**100%**	**0[-1.54,1.54]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.3.2 Day 2							
Kularatne 2009	92	40.4 (5.2)	93	39.5 (5.9)		100%	0.9[-0.7,2.5]
Subtotal ***	**92**		**93**			**100%**	**0.9[-0.7,2.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							
2.3.3 Day 3							
Kularatne 2009	79	38.3 (4.9)	76	38.9 (5.8)		100%	-0.6[-2.29,1.09]
Subtotal ***	**79**		**76**			**100%**	**-0.6[-2.29,1.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.69(P=0.49)							
2.3.4 Day 4							
Kularatne 2009	36	39.2 (4.5)	46	37.2 (5.5)		100%	2[-0.16,4.16]
Subtotal ***	**36**		**46**			**100%**	**2[-0.16,4.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.81(P=0.07)							
Test for subgroup differences: Chi^2=4.07, df=1 (P=0.25), I^2=26.3%							



Favour corticosteroids — Favours placebo

Analysis 2.4. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 4 White blood cell count on days one to four.

Study or subgroup	corticosteroids N	corticosteroids Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.4.1 Day 1							
Kularatne 2009	100	4.8 (2.4)	100	5.7 (2.9)		100%	-0.9[-1.64,-0.16]
Subtotal ***	**100**		**100**			**100%**	**-0.9[-1.64,-0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.39(P=0.02)							
2.4.2 Day 2							
Kularatne 2009	92	5.9 (2.6)	93	5.9 (3.3)		100%	0[-0.86,0.86]
Subtotal ***	**92**		**93**			**100%**	**0[-0.86,0.86]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.4.3 Day 3							
Kularatne 2009	79	6.6 (3)	76	7.1 (3.3)		100%	-0.5[-1.49,0.49]
Subtotal ***	**79**		**76**			**100%**	**-0.5[-1.49,0.49]**
Heterogeneity: Not applicable							



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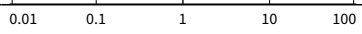
Study or subgroup	corticosteroids N	Mean(SD)	placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=0.99(P=0.32)							
2.4.4 Day 4							
Kularatne 2009	36	7 (2.8)	45	7.3 (3.6)		100%	-0.29[-1.68,1.1]
Subtotal ***	**36**		**45**			**100%**	**-0.29[-1.68,1.1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.41(P=0.68)							
Test for subgroup differences: Chi^2=2.53, df=1 (P=0.47), I^2=0%							

Favour corticosteroids — Favours placebo

Analysis 2.5. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 5 Adverse events in dengue at an early stage.

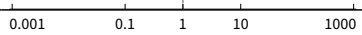
Study or subgroup	steroids n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Patients with serious adverse events					
Tam 2012	14/75	5/38		49.78%	1.42[0.55,3.64]
Tam 2012	6/75	5/37		50.22%	0.59[0.19,1.81]
Villar 2009	0/87	0/91			Not estimable
Subtotal (95% CI)	**237**	**166**		**100%**	**1[0.5,2.03]**
Total events: 20 (steroids), 10 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.37, df=1(P=0.24); I^2=27.04%					
Test for overall effect: Z=0.01(P=0.99)					
2.5.2 Patients with any adverse events					
Tam 2012	23/75	11/38		49.78%	1.06[0.58,1.94]
Tam 2012	16/75	11/37		50.22%	0.72[0.37,1.39]
Villar 2009	0/87	0/91			Not estimable
Subtotal (95% CI)	**237**	**166**		**100%**	**0.89[0.57,1.38]**
Total events: 39 (steroids), 22 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.73, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=0.53(P=0.6)					
Test for subgroup differences: Chi^2=0.08, df=1 (P=0.77), I^2=0%					



Favours steroids — Favours placebo

Analysis 2.6. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 6 Patients with drug-related adverse events.

Study or subgroup	corticosteroids n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.6.1 Hyperglycaemia					
Tam 2012	5/75	2/38		66.47%	1.27[0.26,6.23]
Tam 2012	9/75	1/37		33.53%	4.44[0.58,33.74]
Subtotal (95% CI)	**150**	**75**		**100%**	**2.33[0.69,7.9]**
Total events: 14 (corticosteroids), 3 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.95, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=1.36(P=0.17)					



Favour placebo — Favours corticosteroids

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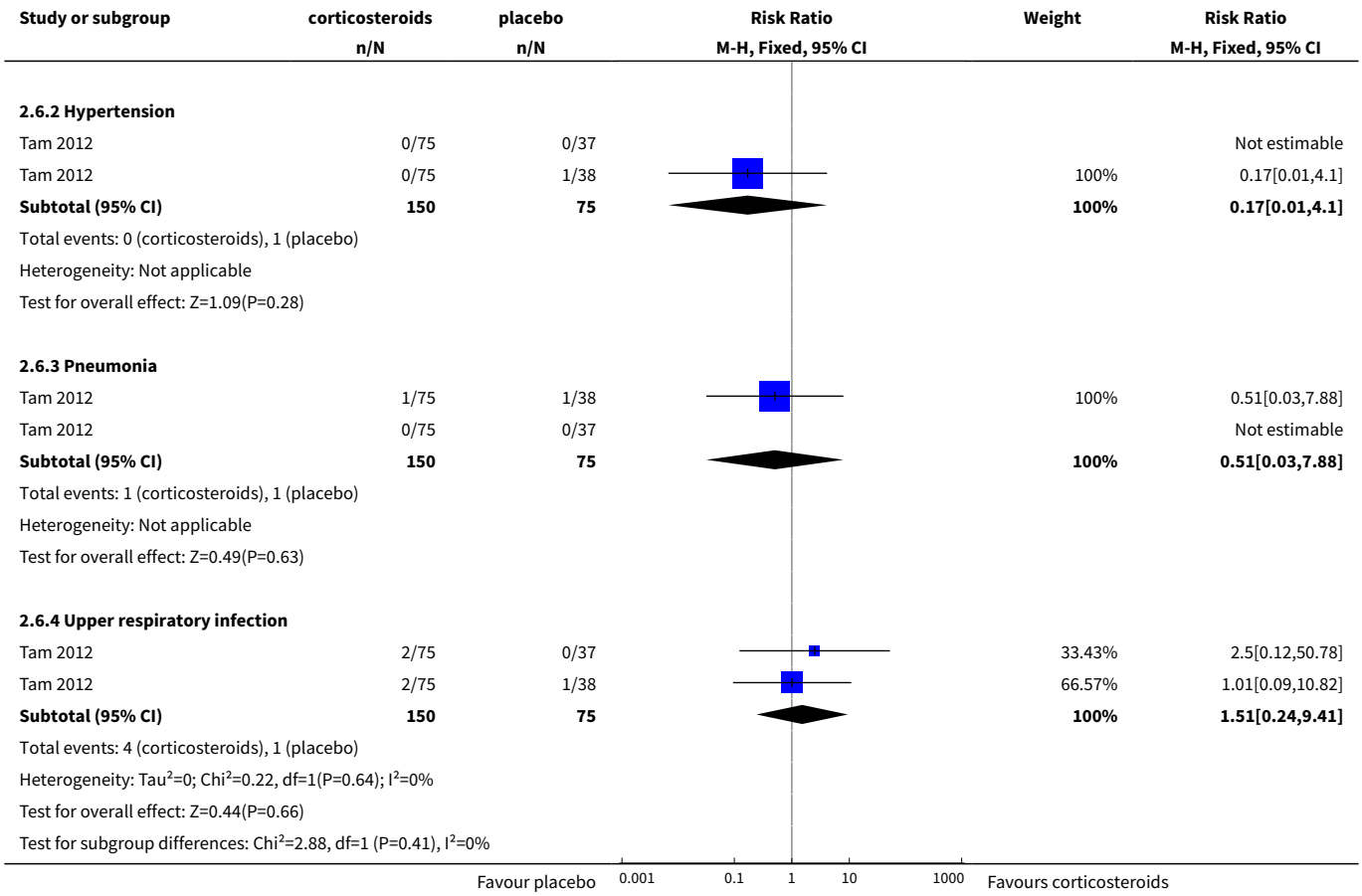
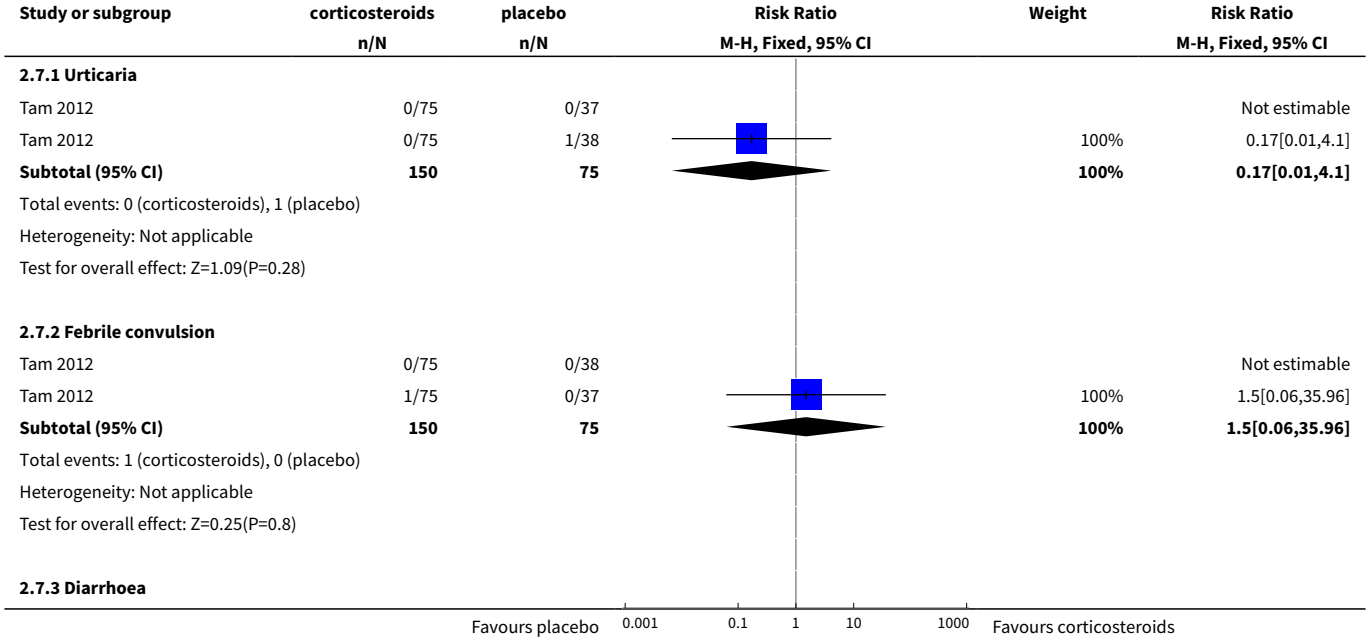


Analysis 2.7. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 7 Patients with other reported events.



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Study or subgroup	corticosteroids n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Tam 2012	0/75	0/37			Not estimable
Tam 2012	0/75	0/38			Not estimable
Subtotal (95% CI)	**150**	**75**			**Not estimable**
Total events: 0 (corticosteroids), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi^2=0.9, df=1 (P=0.34), I^2=0%					

Favours placebo 0.001 0.1 1 10 1000 Favours corticosteroids

Analysis 2.8. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 8 Patients with adverse events low-dose steroids versus placebo.

Study or subgroup	low-dose corticosteroids n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 Patients with serious adverse events					
Tam 2012	6/75	10/75		100%	0.6[0.23,1.57]
Subtotal (95% CI)	**75**	**75**		**100%**	**0.6[0.23,1.57]**
Total events: 6 (low-dose corticosteroids), 10 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
2.8.2 Patients with any adverse events					
Tam 2012	16/75	22/75		100%	0.73[0.42,1.27]
Subtotal (95% CI)	**75**	**75**		**100%**	**0.73[0.42,1.27]**
Total events: 16 (low-dose corticosteroids), 22 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.12(P=0.26)					
Test for subgroup differences: Chi^2=0.12, df=1 (P=0.73), I^2=0%					

favours placebo 0.005 0.1 1 10 200 favours low-dose steroids

Analysis 2.9. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 9 Patients with adverse events high-dose steroids versus placebo.

Study or subgroup	high-dose corticosteroids n/N	placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.9.1 Patients with serious adverse events					
Tam 2012	14/75	10/75		100%	1.4[0.66,2.95]
Subtotal (95% CI)	**75**	**75**		**100%**	**1.4[0.66,2.95]**
Total events: 14 (high-dose corticosteroids), 10 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.88(P=0.38)					
2.9.2 Patients with any adverse events					
Tam 2012	23/75	22/75		100%	1.05[0.64,1.7]
Subtotal (95% CI)	**75**	**75**		**100%**	**1.05[0.64,1.7]**

favours placebo 0.002 0.1 1 10 500 favours high-dose steroid

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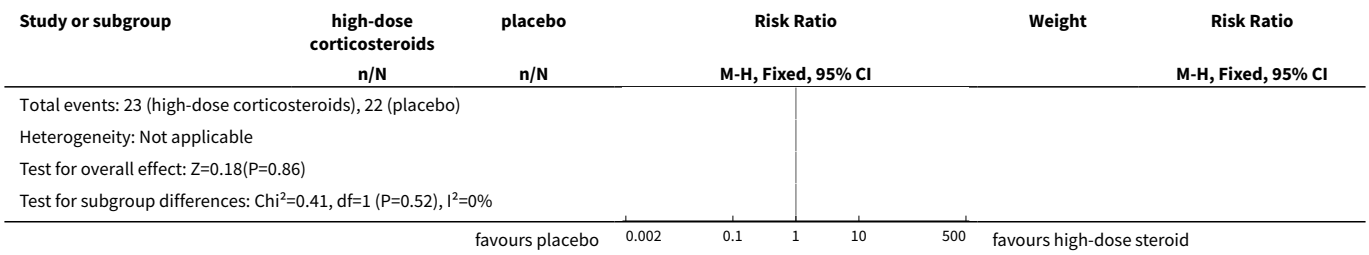
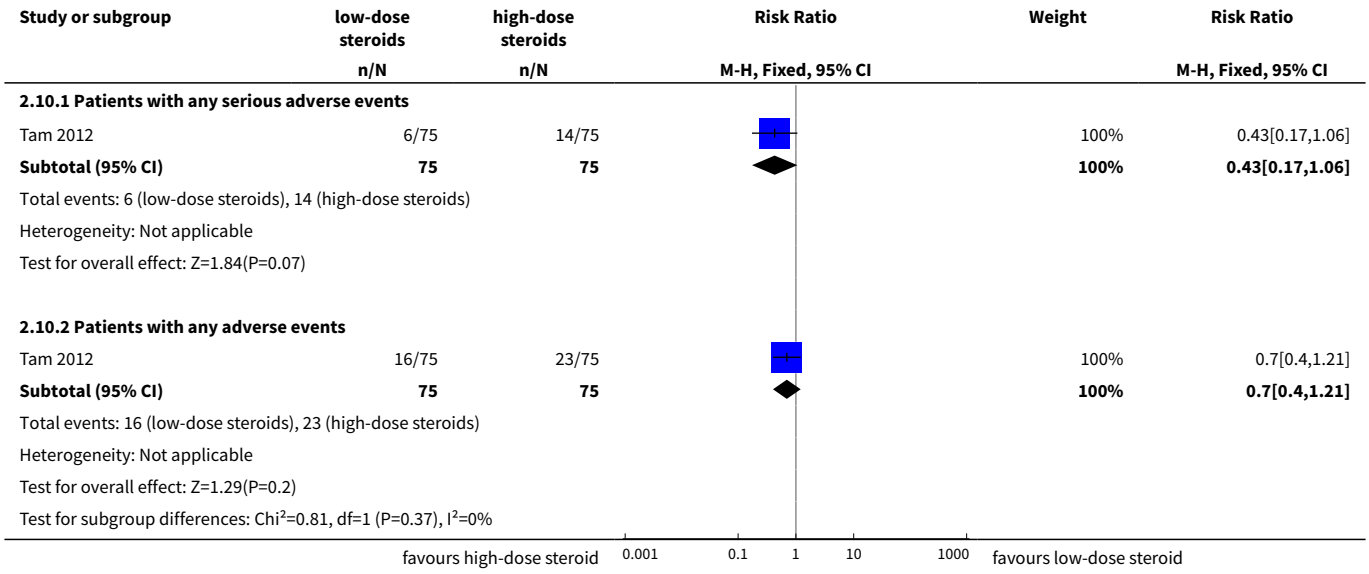


Analysis 2.10. Comparison 2 Steroids versus placebo/no steroids in patients with dengue at an early stage, Outcome 10 Patients with adverse events low-dose versus high-dose steroids.



ADDITIONAL TABLES

Table 1. Adverse events reported in the included studies

Study ID	Number of participants	Methods to monitor adverse events	Blinding		Comment on AE
			Participants	Clinicians	
Min 1975	48	No comment	unclear	unclear	No comment
Pongpanich 1973	7	No comment	unclear	unclear	No comment
Sumarmo 1982	47	No comment	blinded	unclear	No comment
Tassniyom 1993	32	Physical examination, blood test No specific recording of adverse events	blinded	blinded	No significant difference between treatment and control groups in occurrence of fever af-

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Table 1. Adverse events reported in the included studies *(Continued)*

					ter shock, pneumonia, convulsion, cardiac arrest, pulmonary haemorrhage, and positive hemo-culture No specific comments on adverse events
Kularatne 2009	100	Clinical signs recorded at baseline: mean axillary temperature, headache, nausea, flush, pulse rate, blood pressure Laboratory tests: hematocrit and white blood cell count (day 0 to 4) No specific recording of adverse events	blinded	unclear	No comment
Shashidhara 2013	61	No comment	not blinded	not blinded	No comment
Tam 2012	150	Prospective adverse events reporting active surveillance of patient-reported symptoms and laboratory results Laboratory tests: full blood count and random glucose level daily, with a fasting glucose test performed if the random glucose test showed a high level Biochemistry and coagulation profiles, heparan sulfate (HS) at day 0 (enrolment) day, days 5 to 6, and at follow-up 2 to 3 weeks after discharge Recording: by trained study physicians using standardized structured case report form (severity, relatedness of study drugs). daily recording throughout the disease course Reporting: regularly to the Data and Safety Monitoring Board (DSMB).	blinded	blinded	Transient hyperglycaemia in a small number of cases, but no significant clinical or virological adverse events detected
Villar 2009	87	Recording: systematic evaluation of adverse events during and after drug administration and monitoring Reporting: to an independent committee to evaluate the safety and efficacy by interim analysis. These reports are available immediately, and the final report after 30 days (from protocol).	blinded	blinded	No adverse events reported. Adverse events reported to the committee were defined as fatal serious adverse effects, life-threatening or clinically significant

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Table 2. Duration of dengue-related shock as reported in the relevant included studies

Study ID	Measure	Duration of shock		P value (statistical significance)	Comments
		Corticosteroid group	Control group		
Min 1975	Average hours Sample size	4.8 N = 48	13.5 N = 50	P < 0.01 (significant)	Hydrocortisone hemisuccinate: single dose of 25 mg/kg intravenous on day 1, 15 mg/kg on day 2, 10 mg/kg on day 3 2. No medication Quote: "There was a significant excess in the duration of shock in the non-steroid group"
Pongpanich 1973	Average hours (range) Sample size	13.5 (3 to30) N = 7	10.3 (1 to23) N =19	P > 0.5 (not significant)	1. Hydrocortisone hemisuccinate: intravenous 25 mg/kg/day; 5 mg/kg at start, rest given in divided doses every four to six hours 2. No medication Quote: "Duration of shock showed no statistically significant difference between the two programs of treatment"

Study ID	Time period	Participants per time period of shock (N)		P value	Comments
		Corticosteroid group (N = 47)	Control group (N = 50)		
Sumarmo 1982	0.5 to 2.4h 2.5 to 4.4h 4.5 to 6.4h 6.5+h	31 12 4 3	28 13 3 3	Not reported	1. Hydrocortisone hemisuccinate: 50 mg/kg, single intravenous dose 2. Placebo: sodium chloride 0.9% Quote: "there was no significant differences between the treatment groups"

Table 3. Sample size calculations for corticosteroids in dengue-related shock and in dengue at an early stage versus placebo or no intervention

Outcome	Assumed risk	Source	Clinically important relative reduction	Sample size required[1,2]	Sample size in meta-analysis
Dengue-related shock					
Death	21.3%	Analysis 1.1	25%	1.672	284
Need for blood transfusion	24.0%	Analysis 1.2	25%	1.440	89
Pulmonary haemorrhage	3.2%	Analysis 1.3	25%	13.348	63
Convulsions	1% (assumed, instead of 0%)	Analysis 1.3	25%	43.576	63

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Table 3. Sample size calculations for corticosteroids in dengue-related shock and in dengue at an early stage versus placebo or no intervention *(Continued)*

Dengue at an early stage					
Dengue-related shock	4.7%	Analysis 2.1	25%	8.568	286
Severe bleeding	0.6%	Analysis 2.1	25%	72.886	425
Severe thrombocytopaenia	2.6%	Analysis 2.1	25%	16.518	225
ICU admission	7.5%	Analysis 2.1	25%	5.318	286
Ascitis	4.4%	Analysis 2.1	25%	9.600	178
Death	1% (assumed, instead of 0%)	Analysis 2.1	25%	43.576	664

[1] The sample size was calculated for binary outcomes for superiority trials. We estimated that a 25% reduction of risk to develop a complication in the intervention group when compared to the control group would be clinically important. The "assumed risk" is the risk in the control group. All calculations are based on: 2-sided tests, with a ratio of 1:1, power of 0.8, and confidence level of 0.95.
[2] All calculations were performed using the software available at http://www.sealedenvelope.com/power/binary-superiority/.

APPENDICES

Appendix 1. Search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	EMBASE[b]	LILACS[b]
1	adrenal cortex hormone	adrenal cortex hormone	exp DENGUE	exp DENGUE	dengue
2	corticosteroids	corticosteroids	dengue	dengue	corticosteroids
3	hydrocortisone	hydrocortisone	HEMORRAGIC FEVER	HEMORRAGIC FEVER	dexamethasone
4	dexamethasone	dexamethasone	hemorrhagic fever	hemorrhagic fever	prednisolone
5	methylprednisolone	methylprednisolone	('break-bone fever').ti,ab	('break-bone fever').ti,ab	2 or 3 or 4
6	prednisolone	prednisolone	1 or 2 or 3 or 4 or 5	1 or 2 or 3 or 4 or 5	1 and 5
7	hemorrhagic fever	hemorrhagic fever	ADRENAL CORTEX HORMONES	adrenal cortex hormones	—
8	dengue fever	dengue fever	corticosteroids	corticosteroids	—
9	1 or 2 or 3 or 4 or 5 or 6	1 or 2 or 3 or 4 or 5 or 6	steroid*	steroid$	—

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(Continued)

10	7 or 8	7 or 8	cortisol*	cortisol$	—
11	9 and 10	9 and 10	HYDROCORTISONE	HYDROCORTISONE	—
12	—	—	hydrocortisone	hydrocortisone	—
13	—	—	DEXAMETHASONE	DEXAMETHASONE	—
14	—	—	dexamethasone	dexamethasone	—
15	—	—	METHYLPREDNISOLONE	METHYLPREDNISOLONE	—
16	—	—	methylprednisolone	methylprednisolone	—
17	—	—	PREDNISOLONE	PREDNISOLONE	—
18	—	—	prednisolone	prednisolone	—
19	—	—	7 - 18/OR	7- 18/OR	—
20	—	—	6 and 19	6 and 19	—
21	—	—	Limit 20 to human	Limit 20 to human	—

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Higgins 2011; upper case: MeSH or EMTREE heading; lower case: free text term.)

WHAT'S NEW

Date	Event	Description
15 November 2016	Amended	corrected link in methods section

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 3, 2006

Date	Event	Description
10 June 2014	New search has been performed	Objectives: we included studies evaluating steroids given early in dengue to prevent the disease, and adjusted the inclusion criteria and search strategy.We improved the assessment of risk of bias and calculated the optimal sample size to help interpret our results.
10 June 2014	New citation required but conclusions have not changed	Authors: changed from Panpanich R, Sornchai P and Kanjanaratanakorn K to Zhang F and Kramer CV.

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CONTRIBUTIONS OF AUTHORS

Both review authors contributed to the development of the review, extraction of the data, data analysis, and presentation and interpretation of the results.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department of International Development, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this review update, we focus not only on the dengue shock, but also the early dengue. The changing of the scope is the only difference.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Blood Transfusion [statistics & numerical data]; Randomized Controlled Trials as Topic; Severe Dengue [*drug therapy] [mortality]; Shock, Hemorrhagic [*drug therapy] [mortality]

MeSH check words

Adult; Child; Humans

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