5.5.1. Artesunate

Clinical Question/ PICO

Population: Children with severe malaria (malaria-endemic areas)
Intervention: Artesunate
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.76 (CI 95% 0.65 — 0.9) Based on data from 5,765 patients in 4 studies. (Randomized controlled)	109 per 1000 Difference:	83 per 1000 **26 fewer per 1000** (CI 95% 38 fewer — 11 fewer)	High [1]	
Neurological sequelae on day 28	Relative risk 1.23 (CI 95% 0.74 — 2.03) Based on data from 4,857 patients in 1 studies. (Randomized controlled)	11 per 1000 Difference:	14 per 1000 **3 more per 1000** (CI 95% 3 fewer — 11 more)	Moderate Due to serious risk of bias [2]	
Neurological sequelae at discharge	Relative risk 1.36 (CI 95% 1.01 — 1.83) Based on data from 5,163 patients in 3 studies. (Randomized controlled)	28 per 1000 Difference:	38 per 1000 **10 more per 1000** (CI 95% 0 fewer — 23 more)	Moderate Due to serious imprecision [3]	
Hypoglycaemia episodes	Relative risk 0.62 (CI 95% 0.45 — 0.87) Based on data from 5,765 patients in 4 studies. (Randomized controlled)	30 per 1000 Difference:	19 per 1000 **11 fewer per 1000** (CI 95% 16 fewer — 4 fewer)	High [4]	
Time to hospital discharge (days)	Based on data from: 113 patients in 3 studies. (Randomized controlled)	See comment.		Moderate Due to serious imprecision [5]	

1. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria,

Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: no serious.** Both limits of the 95% CI of the pooled effect imply an appreciable clinical benefit with artesunate. The number of people who must be treated to prevent one childhood death is 38.
2. **Risk of Bias: serious.** 41/170 (24%) patients with neurological sequelae at discharge were not available for assessment at day 28. **Indirectness: no serious.** This trial was conducted in 11 centres in Africa, with standard dosing of artesunate and quinine. The nature of the neurological sequelae is not described. **Imprecision: no serious.** The 95% CI around the absolute effect is narrow. The worst-case scenario is a 1.2% increase in neurological sequelae at day 28.
3. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: serious.** The effect estimate indicates clinically important harm; however, the 95% CI includes the possibility of no clinically important difference between the two interventions.
4. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** There was no statistical heterogeneity between the trials (I^2 = 0%). **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: no serious.** The result is statistically significantly in favour of artesunate. The sample size is adequate to detect a 40% risk reduction with 80% power and 95% confidence.
5. **Risk of Bias: no serious.** All the trials adequately concealed allocation and can be considered at low risk of bias. The trials were unblinded, but this is unlikely to have biased this objective outcome. **Inconsistency: no serious.** None of the trials found evidence of a large difference between the two treatment groups. **Indirectness: no serious.** Most of the data are from the single multicentre trial with centres in the Democratic Republic of Congo, the Gambia, Ghana, Kenya, Mozambique, Nigeria, Rwanda, Uganda and the United Republic of Tanzania, where the established, standard doses of artesunate and quinine (with loading dose) were used. The median age of children in this trial was 2.9 years in the quinine group and 2.8 in the artesunate group. **Imprecision: serious.** We were unable to pool the data as they were reported only as medians and range or intraquartile range. There is no evidence of a clinically important benefit with artesunate on this outcome.

Clinical Question/ PICO

Population: Adults with severe malaria (malaria-endemic areas)
Intervention: Artesunate
Comparator: Quinine

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Death	Relative risk 0.61 (CI 95% 0.5 — 0.75) Based on data from 1,664 patients in 5 studies. (Randomized controlled)	**241** per 1000 Difference:	**147** per 1000 **94 fewer per 1000** (CI 95% 120 fewer — 60 fewer)	**High** [1]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Quinine	**Intervention** Artesunate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Neurological sequelae at day 28	Relative risk		CI 95%		
Neurological sequelae at discharge	Relative risk 2.97 (CI 95% 0.6 — 14.64) Based on data from 1,259 patients in 1 studies. (Randomized controlled)	3 per 1000 Difference:	9 per 1000 **6 more per 1000** (CI 95% 1 fewer — 41 more)	Moderate Due to serious imprecision [2]	
Hypoglycaemia episodes	Relative risk 0.62 (CI 95% 0.45 — 0.87) Based on data from 5,765 patients in 4 studies. (Randomized controlled)	30 per 1000 Difference:	19 per 1000 **11 fewer per 1000** (CI 95% 16 fewer — 4 fewer)	High [3]	
Time to hospital discharge (days)	Based on data from: 113 patients in 2 studies. (Randomized controlled)	See comment.		Moderate Due to serious imprecision [4]	

1. **Risk of Bias: no serious.** Two of the smaller studies did not conceal allocation, and none of the studies was blinded; however, most data are from studies in which allocation was concealed, and the lack of blinding is unlikely to introduce bias for an objective outcome such as death. **Inconsistency: no serious.** The point estimates of all five trials favoured artesunate. No significant statistical heterogeneity was detected (I^2 = 0%). **Indirectness: no serious.** All five trials were conducted in Asia but in a variety of settings (Bangladesh, India, Indonesia, Myanmar, Thailand and Viet Nam), and included age groups > 15–16 years. Of the four small trials, two did not give the loading dose of quinine, but there was no statistical heterogeneity between these two trials and the large multicentre trial, in which the loading dose was given. **Imprecision: no serious.** Both limits of the 95% CI imply a clinically important benefit with artesunate.
2. **Risk of Bias: no serious.** This trial was unblinded, but the nature of the sequelae makes observer or reporting bias unlikely. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: no serious.** This trial was conducted in sites in four countries in Asia with the standard doses of artesunate and quinine (with loading dose). Of the 10 sequelae that occurred in this trial (the additional two were in children), five were psychiatric sequelae, four were a persistent problem with balance, and two were hemiparesis. **Imprecision: serious.** Neurological sequelae appear to be rare after severe malaria in adults; however, the 95% CI includes the possibility of clinically important harm with artesunate.
3. **Risk of Bias: no serious.** The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not. Neither trial was blinded. **Inconsistency: no serious.** There was no statistical heterogeneity (I^2 = 0%). **Indirectness: no serious.** This evidence is from multiple sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses. **Imprecision: no serious.** This result is statistically significantly in favour of artesunate. The sample size was adequate to detect a 75% risk reduction with 80% power and 95% confidence..
4. **Risk of Bias: no serious.** The large multicentre study adequately concealed allocation and can be considered at low risk of bias. The smaller trial did not. Neither trial was blinded. **Inconsistency: no serious.** Neither trial found a statistically significant difference in time to hospital discharge. **Indirectness: no serious.** This evidence is from multiple

sites in Asia (Bangladesh, India, Indonesia and Myanmar), and both trials used standard drug doses. **Imprecision: serious.** We were unable to pool data because of the way in which they were presented, but there is no evidence of a benefit on this outcome with artesunate.