

SUPPLEMENTARY TABLE 1 – RISK OF BIAS ASSESSMENTS OF INCLUDED STUDIES

Abbreviations: D1: Domain 1 – Randomisation process; D2: Domain 2 - Deviations from the intended interventions; D3: Domain 3 - Missing outcome data; D4: Domain 4 - Measurement of the outcome; D5: Domain 5 - Selection of the reported result



Low risk of bias



Some concerns/moderate risk of bias



High/serious/critical risk of bias





















| Study | Experimental vs comparator | Outcome | D1 | D2 | D3 | D4 | D5 | Overall | Reviewer's notes |
|--------------------------------------------|-------------------------------------|-----------------------------------------------------------------------------|----|----|----|----|----|---------|------------------|
| Trials of antivirals (Table 2) | | | | | | | | | |
| Tricou 2010 | Chloroquine vs. placebo | Time to resolution of DENV viraemia and DENV NS1 antigenaemia | | | | | | | |
| Nguyen 2013 | Balapiravir vs. placebo | Safety and tolerability: Adverse events, laboratory parameters, vital signs | | | | | | | |
| Low 2014 | Celgosivir vs. placebo | Virological Log Reduction, Fever Reduction | | | | | | | |
| Suputtamongkol 2021, phase 2 | Ivermectin vs. placebo | Log-transformed or viraemia AUC, time to viraemia and NS1 clearances | | | | | | | |
| Suputtamongkol 2021, phase 3 | Ivermectin vs. placebo | fever clearance, proportion of patients developing DHF | | | | | | | |
| Trials of corticosteroids (Table 3) | | | | | | | | | |
| Pongpanich 1973 | Hydrocortisone vs. standard of care | Duration of shock | | | | | | | |

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| Min 1975 | Hydrocortisone vs. "identical fluids" | Mortality | ! | ! | + | + | ! | ! | Randomisation method not specified, except 'randomly selected...double blind trial'. Participants were 'carefully matched by age group and sex'. |
| Sumarmo 1982 | Hydrocortisone vs. placebo | Mortality | ! | + | + | + | ! | ! | Only age and sex reported as baseline information, no prognostic factors reported. |
| Tassniyom 1993 | Methylprednisolone vs. placebo | Mortality | ! | + | + | + | + | ! | 'A prescribed randomized schedule'. |
| Waly 1998 | Methylprednisolone vs. placebo | Duration of thrombocytopenia | - | - | ! | + | - | - | Unclear allocation method: 'double blind test grouping' but only 8/29 patients were reported to use steroids. Inappropriate analysis method for duration (chi-square). |
| Kularatne 2009 | Dexamethasone vs. placebo | Platelet count | + | ! | - | + | ! | - | Uncertain concealment as 'the envelope was re-sealed and kept attached to the patient's records for future identification of the allocation at the final analysis of the results.' Very high loss to follow-up - only 82/200 patients had platelet count at day 4. |
| Tam 2012 | Prednisolone vs. placebo | Development of Dengue shock | + | + | + | + | ! | ! | - |
| Shashidhara 2013 | Dexamethasone vs. standard of care | Platelet rise | ! | ! | + | + | ! | ! | Mean day of illness was around 6 in both groups, when PLT is often lowest. |
| Aslam 2021 | Dexamethasone vs. several comparators | Platelet count | ! | - | - | - | ! | - | Intervention and comparator groups unclear due to four distinct treatment combinations of antimalarials, antibiotics, and dexamethasone, administered via different routes (oral or intravenous). Treatment in Group D, which involved intravenous dexamethasone, was particularly difficult to blind, making the study's design challenging to mask without further details on the blinding procedure. |

Trials of other host-directed therapies for treatment of dengue (Table 4)

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| Tassniyom 1997 | AC-17 vs. placebo | Shock | ! | + | + | + | ! | ! | - |
| Dimaano 2007 | Intravenous immunoglobulin vs. Standard of care | Increase in PLT count | ! | ! | - | + | ! | - | |
| Castro 2011 | Doxycycline, Tetracycline vs. control | Cytokines/cytokine receptor/antagonist | - | - | ! | + | ! | - | |
| Salgado 2012 | Pentoxifylline vs. standard of care | TNF α levels, ICU admissions, length of stay | ! | ! | + | + | ! | ! | |
| Qazi 2012 | Colchicine vs. placebo | Platelet count | - | - | - | + | ! | - | - Quasi-randomisation based on even or odd registration numbers. - Discrepancy in participant numbers: The total number of participants is stated as 152 (76 per group). The authors then claim to have recruited 150 males and 62 females, for a total of 212 participants (150+62=212). |
| Borges 2013 | Chloroquine vs. placebo | Duration of disease | ! | + | + | + | + | - | |
| Suliman 2014 | Interleukin-11 vs. placebo | Platelet count | - | - | + | + | - | - | Lack of baseline information (day of illness) Inclusion criteria not clearly reported. Selective reporting results: The authors stated "The platelets response in patients with severe thrombocytopenia was greater in the treatment group" but there wasn't any reported result which was stratified by severe thrombocytopenia. |
| Fredeking 2015 | Doxycycline + vs. standard of care | Mortality | ! | - | + | + | ! | - | Severity of illness in 2 groups at the time of enrolment not assessed. Only patients who actually received doxycycline were considered in the doxycycline group for analysis. |

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| Whitehorn 2016 | Lovastatin vs. placebo | Safety | + | + | + | + | + | + | |
| Pannu 2017 | Anti-D immune globulin vs. standard of care | Rise in PLT > 50 G/L | ! | ! | + | + | ! | ! | |
| Ahmad 2018 | Montelukast vs. standard of care | Development of Dengue shock syndrome | ! | ! | + | + | - | - | <ul style="list-style-type: none"> - Retrospective registration. - Missing baseline data (day of illness, severity). - Unclear allocation method using "Lottery". - Data reporting discrepancy: The paper refers to a "Table 3" that contains key logistic regression results, but table is absent from the publication. |
| Malavige 2018 | Rupatadine vs. placebo | Incidence of ascites | + | + | + | + | ! | + | Single blinded trial. |
| Chakraborty 2020 | Eltrombopag vs. standard of care | % patients with PLT > 150G/L | ! | ! | + | + | + | ! | |
| Tunjungputri 2022 | Oseltamivir vs. placebo | Plasma leakage (HCT, Albumin, Syndecan-1, fluid accumulation on US) | ! | + | + | + | ! | ! | |
| | Oseltamivir vs. placebo | Time to PLT ≥100G/L or discharge | ! | + | ! | + | ! | ! | |
| Malavige 2022 | Rupatadine vs. placebo | Reduction in incidence of DHF | + | + | + | + | + | + | |
| Kumar 2024 | Doxycycline vs. standard of care | Effect on inflammatory markers (Ferritin, CRP, IL-6, TNF-a) | ! | ! | + | + | + | ! | |
| Nitinaï 2024 | Montelukast vs. placebo | Incidence rate of onset of any warning sign | + | + | + | + | + | + | |

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| Khan 2024 | Interleukin-11 vs. control | Not specified. Authors focused on platelet count. | | | | | |  (ROBINS-I) Critical risk of bias | Redundant data presentation: PLT count spread in 3 tables and 3 figures. Implausible platelet trajectory: Table 4 and Figure 2 – in both arms PLT still <50 G/L after 5 days since the lowest point. Table 2 – Statistically incorrect. |
| Nguyen 2025 | Metformin vs standard of care | Safety and tolerability | | | | | |  (ROBINS-I) | Non-randomised trial |
| Trials of <i>Carica papaya</i> leaf extract/juice (CPLE) (Table 5) | | | | | | | | | |
| Sathyapalan 2020 | CPLE vs. placebo | Platelet count and haematocrit |  |  |  |  |  |  | |
| Perumal 2019 | CPLE vs. placebo | Platelet count |  |  |  |  |  |  | |
| Srikanth 2019 | CPLE vs. standard of care | Platelet count |  |  |  |  |  |  | Retrospective registration. Missing baseline information (day of illness and platelet). Incomplete statistical reporting: no confidence interval reported for platelet count in control group (and similarly WBC/RBC). |
| Cordeiro 2019 | CPLE (DENPAP) | Platelet count | | | | | | (ROBINS-1) Critical risk of bias  | Single arm. |
| Srikrishna HA 2018 | CPLE plus other herbal vs. CPLE alone | Platelet count |  |  |  |  |  |  | |
| Subenthiran 2013 | CPLE vs. standard of care | Platelet count |  |  |  |  |  |  | Outcome missing for 34/145 participants in the intervention group and 28/145 in the control group ‘38 lost to follow-up, 24 with incomplete data due to sample rejection.’ |

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| Yunita 2012 | CPLE vs. standard of care | Platelet count | ! | - | ! | + | - | - | Platelet count of control group on day 3 was compared with platelet count of intervention group on day 5 (Table 3). Day of illness at enrolment not provided. Inclusion criteria is fever for 2-7 days, no dengue confirmation test. |
| Trials of micronutrients and miscellaneous compounds (Table 6) | | | | | | | | | |
| Cabrera-Cortina 2008 | Calcium carbonate vs. standard of care | Platelet count | | | | | | (ROBINS-1) Critical risk of bias - | Non-randomised trial |
| Vaish 2012 | Vitamin E vs. standard of care | Platelet Count | ! | ! | + | + | ! | ! | |
| Chathurangana 2017 | Vitamin E vs. placebo | Duration of plasma leak | ! | ! | ! | - | ! | - | Inconsistencies in reporting interventions in control group between the paper and trial registration, i.e. "a commercially prepared placebo" vs. "standard care only" PLT<100 or PCV rise >20% only is not diagnostic of vascular leak. No continuous monitoring to ensure exact time of leaking. |
| Rammohan 2018 | Vitamin C vs. NA | Platelet count | ! | - | - | + | - | - | No information on day of illness at baseline. Range of creatinine and platelet count is not interpretable (Table 6). Number of patients assessed for main results not reported. Spelling errors in abstract of main results. Repetitive presentation of results: Table 7 and Table 8, Table 5 and Figure 3, Fig 2 and Table 4 reporting the same thing. |
| Mittal 2024 | Vitamin E, Vitamin B vs. placebo | Platelet Count | ! | + | ! | ! | ! | ! | - |
| Rerksuppaphol 2018 | Bis-glycinate zinc vs. placebo | Time to defervescence | + | + | + | + | + | + | - |

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| Jacob 2007 | Homeopathy vs. Placebo | Fever clearance time | ! | + | + | ! | ! | - | Only 3 subjects were confirmed to have dengue. Temperature is patient-assessed by oral strips at home. |
| Mir 2012 | Euphorbia hirta linn | Full blood count parameters | | | | | | - | Non-randomised trial. |
| Soroy 2014 | Propoelix™ vs. placebo | Clinical course in patients with DHF | ! | ! | ! | + | ! | ! | Platelet recovery, TNF-α levels, length of hospitalisation |
| Nayak 2019 | Homeopathy vs. Standard of care | Platelet count | | | | | | - | Non-randomised trial. |
| Muhamad 2020 | Kelulut honey vs corn syrup | | - | ! | ! | - | - | - | Retrospective registration. Lack of blinding , although stated as “a double-blind randomized control trial”, as honey was “pre-packaged into 4 ml sachets of pure Kelulut (Trigona) Honey” while corn syrup was “obtained from conventional supermarket.” |
| Kumar 2022 | Nivalembu Kunideer, paracetamol and honey water vs. Paracetamol and honey | NA | ! | - | - | - | - | - | <ul style="list-style-type: none"> - Lack of blinding and high drop-out rate: “5 participants in the NKN group discontinued as they did not like the taste of NKN”. - Selective reporting: Discrepancy between the number of participants who completed treatment (5 in the honey group) and the number included in the results section (3). - Data inconsistencies and errors: inconsistency between the reported mean temperature and the individual patient data, e.g. D5 in honey group is 99.2±0.16 but in another table which specified temperature at D5 of each patient in the same group, no measurement exceed 98.6 |
| Pawar 2024 | Guduchi Kwath vs. Kiratatikta Kwath vs. ‘natural group’ | Not specified | | | | | | (ROBINS-1) Critical risk of bias - | Non-randomised trial |

