THE LANCET
Infectious Diseases

## Supplementary appendix

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Supplement to: Sangkaew S, Ming D, Boonyasiri A, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. *Lancet Infect Dis* 2021; published online Feb 25. https://doi.org/10.1016/S1473-3099(20)30601-0.

**Supplement table 1: Search terms used in the literature review. We searched for all combinations of the terms in column 1 and 2 (e.g. "dengue shock syndrome AND risk factor(s)", "dengue shock syndrome AND risk parameter(s)", "dengue shock syndrome AND risk variable(s)", "dengue shock AND risk factor(s)" etc).**

| Complicated dengue | Predictors |
|---|---|
| - dengue shock syndrome- dengue shock<br>- dengue haemorrhagic fever/dengue<br>- hemorrhagic fever<br>- dengue with warning sign(s)<br>- severe dengue<br>- complicated dengue<br>- dengue severity | - risk factor(s)<br>- risk parameter(s)<br>- risk variable(s)<br>- predictive/predicting factor(s)<br>- predictive/predicting parameter(s)<br>- prognostic factor(s)<br>- prognostic parameter(s)<br>- Associated factor(s)<br>- Associated parameter(s)<br>- Associated characteristic(s)<br>- Risk(s)<br>- Prognosis<br>- Biomarker(s)<br>- Marker(s) |

**Supplement table 2: Search syntaxes applied in the Ovid platform for searching MEDLINE database. We searched for all combinations of the terms in column 1 and 2. The explode command (exp) was used to retrieve records that contained the specific term and its subheadings (e.g. Severe dengue, risk factors, and prognosis). Terms in the columns were search using multiple-purpose command (.mp), searching keywords in a set of fields usually including Title, Original Title, Abstract, and Subject Heading.**

| 1. Terms for dengue with progression to severe disease | 2. Terms for predictors |
|---|---|
| 1. [exp Severe Dengue/]<br>2. severe dengue.mp.<br>3. dengue shock syndrome*.mp.<br>4. dengue h?emorrhagic fever.mp<br>5. dengue with warning sign*.mp.<br>6. dengue severity.mp.<br>7. dengue death.mp.<br>8. dengue death.mp.<br>9. dengue shock.mp.<br>10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 | 11. [exp Risk Factors/]<br>12. risk factor*.mp.<br>13. [exp RISK/]<br>14. risk*.mp.<br>15. [exp PROGNOSIS/]<br>16. prognosis.mp.<br>17. [exp BIOMARKERS/]<br>18. biomarker*.mp.<br>19. marker*.mp.<br>20. ((risk* or predictive or prognostic or associated) adj (factor* or parameter* or characteristic* or variable*)).mp. [mp=title, abstract, full text, caption text]<br>21. predictor*.mp.<br>22. prediction.mp.<br>23. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 |
| 10 AND 23 | |

13 **Supplement table 2: Template used to assess the eligibility criteria.**

| | |
|---|---|
| Reviewer name: | Date: |
| Author name/Study ID: | Year: |
| Title | Journal: |
| Study designs | **Include**<br><br>☐ Original papers<br>☐ Research in human<br><br>**Exclude**<br><br>☐ Descriptive studies (case reports, case studies), Sero-epidemiological studies, ecological or mathematical modelling studies |
| Population | **Include**<br><br>☐ Symptomatic infected individuals in the febrile phase **AND**<br>☐ Laboratory confirmed dengue diagnosis according to WHO Dengue Guideline in 1997 and 2009*<br><br>**Exclude**<br><br>☐ Individuals who had developed clinical manifestation of severe dengue (severe plasma leakage, hemodynamic instability and organ impairment) |
| Exposure(s) | **Include**<br><br>☐ Demographic features, clinical manifestations (signs and symptoms), laboratory parameters, or imaging techniques AND<br>☐ Parameters collected during the febrile phase<br><br>**Exclude**<br><br>☐ Genetic factors or gene expression |
| Outcome(s) | **Include**<br><br>☐ Association between predictors and risk of development severe clinical manifestations of dengue infection according to WHO guideline (dengue haemorrhagic fever grade I-IV, dengue shock syndrome, and severe dengue) compared with dengue fever |

| | |
|---|---|
| **Overall:** | ☐ **Include**<br>☐ **Exclude** |

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**Supplement Table 3: Template used for extracting information from the studies included in the systematic review.**

| |
|---|
| **Paper ID** |
| **Title** |
| **Reviews** |
| **First author's surname** |
| **Year of publication** |
| **Study design** |
| **Data collection** |
| **Year of patient recruitment** (Month/Year - Month/year) |
| **Country** where patients were recruited |
| **Hospital/centre** names where patient were recruited |
| **Population** inclusion and exclusion criteria |
| **Dengue classification**<br>1: WHO 1997 (DS, DHF, and DSS)<br>2: WHO 2009 (DWS-, DWS+,and SD) |
| When were samples or information collected |
| **Reference group** (e.g. a DF group) |
| **Comparative group** (i.e. DHF, DSS, DHF/DSS, DWS+/SD, or SD) |
| **Continuous factors**_1 name (unit) |
| Description (if applicability) |
| How were samples or information measured (if applicable) |
| Sample size of a reference groups |
| Sample size of a comparative group |
| Ref: Mean, Median, Mean difference |
| Ref: SD, Upper 95% CI, Lower 95% CI, IQR, Upper IQR, Lower IQR |
| Ref: Odds ratio, Relative risk, Adjusted odds ration, Adjusted relative risk |
| Ref: 95% CI of OR |
| Comp: Mean, Median, Mean difference |
| Comp: SD, Upper 95% CI, Lower 95% CI, IQR, Upper IQR, Lower IQR |
| P-value |
| Statistic test |
| Comp: Odds ratio, Relative risk, Adjusted odds ratio, Adjusted relative risk |
| Comp: 95% CI of OR |
| P-value |
| Statistic test |
| Adjusted variables |
| **Categorical factors**_1 name (unit): |
| Description (if necessary) |
| How were samples or information measured (if necessary) |
| Sample size of a reference groups |
| Sample size of a comparative group |

| |
|---|
| Level 1: The number of non-events (in reference group) |
| Level 1: The number of events (in comparison group) |
| Level 2: The number of non-events (in reference group) |
| Level 2: The number of events (in comparison group) |
| Level 3: The number of non-events (in reference group) |
| Level 3: The number of events (in comparison group) |
| P-value |
| Statistic test |
| Comp: Odds ratio, Relative risk, Adjusted odds ratio, Adjusted relative risk |
| Comp: Upper 95% CI |
| Comp: Lower 95% CI |
| Comp: Odds ratio, Relative risk, Adjusted odds ratio, Adjusted relative risk |
| Comp: Upper 95% CI |
| Comp: Lower 95% CI |
| P-value |
| Statistic test |

**Supplement Table 5. Definitions of progression to severe disease taken from the included studies in this systematic review and meta-analysis**

| Terminology | Definitions |
|---|---|
| Definition A (based on DHF in the 1997 WHO Classification) | Thrombocytopenia<br><br>- A platelet count less than 100,000 cells/micro litre |
| | and<br><br>Plasma leakage<br><br>- Haematocrit rising 20% from baseline haematocrit, haematocrit levels measured during the first 96 hours of illness, average haematocrit levels based on population data<br><br>OR<br><br>- Fluid accumulation by chest X-ray, ultrasonography, or physical examinations (depending on health facility and completeness of medical records) |
| | and |

| | |
|---|---|
| | Haemorrhagic tendencies<br><br>- Presence of spontaneous bleeding<br><br>OR<br><br>- Mucosal bleeding including positive tourniquet test |
| Definition B (based on DSS in the 1997 WHO Classification) | Shock<br><br>- Narrow pulse pressure less than 20 mmHg<br><br>OR<br><br>- Systolic blood pressure less than 90 mmHg (or hypotension in accordance with the sex and age specific reference of population data)<br><br>OR<br><br>- Poor tissue perfusion such as clammy skin, urine output less than 0.5 ml/kg/hr |
| Definition C (based on SD in the 2009 WHO Classification) | Severe plasma leakage<br><br>- Plasma leakage resulting in shock, defined as<br><br>- Narrow pulse pressure less than 20 mmHg<br><br>OR<br><br>- Systolic blood pressure less than 90 mmHg (or hypotension in accordance with the sex and age specific reference of population data)<br><br>OR<br><br>- Poor tissue perfusion such as clammy skin, urine output less than 0.5 ml/kg/hr<br><br>- Plasma leakage resulting in respiratory distress<br><br>- Evidence of pleural effusion or ascites<br><br>AND |

| | |
|---|---|
| | - Clinical indicators of respiratory distress such as tachypnoea or low oxygen saturations. |
| | OR<br><br>Severe clinical bleeding<br><br>- Bleeding in vital organs<br>- Spontaneous bleeding from a mucosal area with indication for blood transfusion |
| | OR<br><br>Severe organ involvement<br><br>- Aspartate aminotransferase (AST) level >1,000 units/litre,<br>- Alanine aminotransferase (ALT) level >1,000 units/litre,<br><br>- Serum creatinine level equal or more than 3 times above baseline<br><br>- Myocarditis<br><br>- Encephalitis |

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22 **Supplement Table 6: Publications included in the systematic review and meta-analysis**

| Number | First author's name (Publication year) | Countries | Study design | Population age groups | Classification | Included in meta-analysis |
|---|---|---|---|---|---|---|
| **1** | Butthep et al.(2012)[1] | Thailand | prospective cohort | N/A | 1997 WHO Classification | No |
| **2** | Hernandez et al.(2014)[2] | Mexico | case-control | Adults | 1997 WHO Classification | Yes |
| **3** | Butthep et al.(2006)[3] | Thailand | prospective cohort | Children | 1997 WHO Classification | No |
| **4** | Conroy et al.(2015)[4] | Columbia | nested case control or case-cohort | Mixed population | 1997 WHO Classification | Yes |
| **5** | Wang et al.(2003)[5] | Taiwan | nested case control or case-cohort | DENV-3 infection | 1997 WHO Classification | Yes |
| **6** | Voraphani et al.(2010)[6] | Thailand | prospective cohort | Children | 1997 WHO Classification | Yes |
| **7** | Alexander et al.(2011)[7] | Thailand, Philippines, Vietnam, Malaysia, Nicaragua, Venezuela, and Brazil | prospective cohort | Mixed population | Intervention criteria | Yes |
| **8** | Yung et al.(2015)[8] | Singapore | prospective cohort | Adults | Both 1997 and 2009 WHO Classifications | Yes |
| **9** | Bongsebandhu et al.(2008)[9] | Thailand | prospective cohort | Children | 1997 WHO Classification | Yes |
| **10** | Yong et al.(2017)[10] | Malaysia | nested case control or case-cohort | Adults | 2009 WHO Classification | Yes |
| **11** | Vicente et al.(2017)[11] | Brazil | nested case control or case-cohort | Mixed population | The classification of Brazilian Ministry of Health | Yes |
| **12** | Vejchapipat et al.(2006)[12] | Thailand | prospective cohort | N/A | 1997 WHO Classification | Yes |
| **13** | Vasanwala et al.(2014)[13] | Singapore | prospective cohort | Adults | 1997 WHO Classification | Yes |
| **14** | Teixeira et al.(2015)[14] | Bazil | case-control | Mixed population | 1997 WHO Classification | Yes |
| **15** | Tricou et al.(2011) [15] | Vietnam | retrospective cohort | Adults | 1997 WHO Classification | Yes |
| **16** | Trairatvorakul et al.(2005)[16] | Thailand | case-control | Children | 1997 WHO Classification | Yes |
| **17** | Rocha et al.(2017)[17] | Brazil | prospective cohort | Mixed population | 2009 WHO Classification | Yes |
| **18** | Tang et al.(2017)[18] | Singapore | nested case control or case-cohort | Adults | 1997 WHO Classification | Yes |
| **19** | Sreenivasan et al.(2018)[19] | India | prospective cohort | Children | 2009 WHO Classification | Yes |

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|---|---|---|---|---|---|---|
| **20** | Sosothikul et al.(2007)[20] | Thailand | prospective cohort | Children | 1997 WHO Classification | Yes |
| **21** | Sirikutt et al.(2014)[21] | Thailand | retrospective cohort | Children | 1997 WHO Classification | Yes |
| **22** | Restrepo et al.(2008)[22] | Columbia | case-control | Infants | N/A | Yes |
| **23** | Zain et al.(2016)[23] | Indonesia | case-control | Adults | 2009 WHO Classification | No |
| **24** | Oliveira et al.(2017)[24] | Brazil | nested case control or case-cohort | N/A | 1997 WHO Classification | Yes |
| **25** | Pang et al.(2015)[25] | Singapore | case-control | Matching with age, gender, laboratory, year of diagnosis, type of care at provisional site | Both 1997 and 2009 WHO Classifications | Yes |
| **26** | Sani et al.(2017)[26] | Malaysia | retrospective cohort | Adults | 2009 WHO Classification | Yes |
| **27** | Pandey et al.(2015)[27] | India | case-control | Mixed population | 2009 WHO Classification | Yes |
| **28** | Tuan et al.(2017)[28] | Vietnam | prospective cohort | Children | 2009 WHO Classification | Yes |
| **29** | Maron et al.(2010)[29] | El Savador | case-control | Children | 1997 WHO Classification | Yes |
| **30** | Mohammed et al.(2010)[30] | Puerto Rico | case-control | Mixed population | 1997 WHO Classification | Yes |
| **31** | Mallhi et al.(2015)[31] | Malaysia | retrospective cohort | Adults | 1997 WHO Classification | Yes |
| **32** | Lee et al.(2015)[32] | Taiwan | retrospective cohort | Adults | 2009 WHO Classification | Yes |
| **33** | Lam et al.(2017)[33] | Vietnam | prospective cohort | Children | 1997 WHO Classification | Yes |
| **34** | Mohamed et al.(2013)[34] | Yemen | retrospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **35** | Oishi et al.(2006)[35] | Philipines | prospective cohort | Children | 1997 WHO Classification | Yes |
| **36** | Zhang et al.(2017)[36] | China | retrospective cohort | Adults | 2009 WHO Classification | No |
| **37** | Wong et al.(2014)[37] | Singapore | prospective cohort | Adults | 1997 WHO Classification | Yes |
| **38** | Wichmann et al.(2004)[38] | Thailand | retrospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **39** | Sharmin et al.(2013)[39] | Bangladesh | nested case control or case-cohort | Mixed population | 1997 WHO Classification | No |
| **40** | Kurane et al.(1991) [40] | Thailand | case-control | Children | 1997 WHO Classification | Yes |
| **41** | Kurane et al.(1993) [41] | Thailand | case-control | Children | 1997 WHO Classification | Yes |
| **42** | Kuo et al.(2017) [42] | Taiwan | retrospective cohort | Adults | 2009 WHO Classification | Yes |
| **43** | Kumar et al.(2012)[43] | Singapore | nested case control or case-cohort | Adults | 1997 WHO Classification | Yes |

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|---|---|---|---|---|---|---|
| **44** | Kulasinghe et al.(2016)[44] | Sri Lanka | prospective cohort | Children | 1997 WHO Classification | Yes |
| **45** | Koraka et al.(2004) [45] | Indonesia | nested case control or case-cohort | Children | 1997 WHO Classification | Yes |
| **46** | Malavige et al.(2013)[46] | Sri Lanka | prospective cohort | Adults | 2009 WHO Classification | Yes |
| **47** | Romero et al.(2013)[47] | Brazil | cross-sectional study | Female aged 15 to 49 years | 1997 WHO Classification | Yes |
| **48** | Libraty et al.(2002)[48] | Thailand | nested case control or case-cohort | DENV-2 infection | 1997 WHO Classification | Yes |
| **49** | Liao et al.(2015)[49] | China | nested case control or case-cohort | Adults | 2009 WHO Classification | Yes |
| **50** | Lee et al.(2008)[50] | Singapore | retrospective cohort | Adults | 1997 WHO Classification | Yes |
| **51** | Lee et al.(2006)[51] | Taiwan | retrospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **52** | Kalayanarooj et al.(1997)[52] | Thailand | prospective cohort | Children | 1997 WHO Classification | No |
| **53** | Kalayanarooj et al.(2005)[53] | Thailand | cross-sectional study | Children | 1997 WHO Classification | No |
| **54** | Hoang et al.(2010)[54] | Vietnam | nested case control or case-cohort | Mixed population | 1997 WHO Classification | No |
| **55** | Harris et al.(2000)[55] | Nicaragua | cross-sectional study | Mixed population | 1997 WHO Classification | Yes |
| **56** | Hammond et al.(2005)[56] | Nicaragua | prospective cohort | Mixed population | 1997 WHO Classification | No |
| **57** | Libraty et al.(2002)[57] | Thailand | nested case control or case-cohort | DENV-3 infection | 1997 WHO Classification | Yes |
| **58** | Ha et al.(2011)[58] | Vietnam | case-control | Children | 1997 WHO Classification | No |
| **59** | Green et al.(1999)[59] | Thailand | case-control | Children | 1997 WHO Classification | No |
| **60** | Fried et al.(2010)[60] | Thailand | prospective cohort | Children | 1997 WHO Classification | Yes |
| **61** | Fragnound et al.(2015)[61] | Cambodia and Columbia | nested case control or case-cohort | Mixed population | 1997 WHO Classification | Yes |
| **62** | Flamand et al.(2017)[62] | French Guiana | cross-sectional study | Mixed population | 2009 WHO Classification | Yes |
| **63** | Chen et al.(2015)[63] | Taiwan | retrospective cohort | Mixed population | 2009 WHO Classification | Yes |
| **64** | Colbert et al.(2007)[64] | Nicaragua | prospective cohort | Children | 1997 WHO Classification | Yes |
| **65** | Cui et al.(2016)[65] | Singapore | nested case control or case-cohort | Adults | 1997 WHO Classification | Yes |
| **66** | Bur et al.(2016)[66] | Indonesia | prospective cohort | Adults | Both 1997 and 2009 WHO Classifications | Yes |
| **67** | Chaiyaratana et al.(2008)[67] | Thailand | prospective cohort | Children | 1997 WHO Classification | No |

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|---|---|---|---|---|---|---|
| **68** | Andries et al.(2016)[68] | Cambodia | nested case control or case-cohort | Children | 2009 WHO Classification | Yes |
| **69** | Murgue et al.(2001)[69] | French Polynesia | nested case control or case-cohort | Children | 1997 WHO Classification | Yes |
| **70** | Biswas et al.(2015)[70] | Nicaragua | prospective cohort | Children | Both 1997 and 2009 WHO Classifications | Yes |
| **71** | Carier et al.(2006)[71] | Venezuela | prospective cohort | N/A | 1997 WHO Classification | No |
| **72** | Lee et al.(2012)[72] | Singapore | retrospective cohort | Mixed population | Both 1997 and 2009 WHO Classifications | No |
| **73** | Alagarasu et al.(2012)[73] | India | nested case control or case-cohort | Mixed population | Both 1997 and 2009 WHO Classifications | Yes |
| **74** | Rathakrishnan et al.(2014)[74] | Malasia | prospective cohort | Adults | 2009 WHO Classification | Yes |
| **75** | Aung et al.(2013)[75] | Thailand | retrospective cohort | Adults | 2009 WHO Classification | Yes |
| **76** | Bandyopadhyay et al.(2016)[76] | India | retrospective cohort | Adults | 1997 WHO Classification | No |
| **77** | Bozza et al.(2008)[77] | Brazil | prospective cohort | Adults | Both 1997 and 2009 WHO Classifications | Yes |
| **78** | Brasier et al.(2012)[78] | Venezuela | prospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **79** | Carrasco et al.(2014)[79] | Singapore | retrospective cohort | Mixed population | 2009 WHO Classification | No |
| **80** | Endy et al.(2004)[80] | Thailand | prospective cohort | Children | 1997 WHO Classification | Yes |
| **81** | Fadilah et al.(1999)[81] | Malaysia | prospective cohort | Adults | 1997 WHO Classification | Yes |
| **82** | Flores-Mendoza et al.(2017)[82] | Mexico | prospective cohort | Adults | 1997 WHO Classification | Yes |
| **83** | Fox et al.(2011)[83] | Vietnam | prospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **84** | Furuta et al.(2012)[84] | Vietnam | case-control | Children | 1997 WHO Classification | Yes |
| **85** | Gopal et al.(2017)[85] | India | case-control | Adults | 2009 WHO Classification | Yes |
| **86** | Green et al.(1999)[86] | Thailand | nested case control or case-cohort | Children | 1997 WHO Classification | Yes |
| **87** | Guerrero et al.(2013)[87] | Colombia | case-control | Adults | 2009 WHO Classification | Yes |
| **88** | Hoffmeister et al.(2014)[88] | Germany | retrospective cohort | Adults | 2009 WHO Classification | Yes |
| **89** | Juffrie et al.(2001)[89] | Indonesia | case-control | Children | 1997 WHO Classification | No |
| **90** | Khan et al.(2010)[90] | Pakistan | cross-sectional study | Mixed population | 1997 WHO Classification | No |
| **91** | Khan et al.(2007)[91] | Pakistan | cross-sectional study | Mixed population | 1997 WHO Classification | Yes |

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|---|---|---|---|---|---|---|
| **92** | Khan et al.(2013)[92] | Pakistan | prospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **93** | Kuo et al.(2008)[93] | Taiwan | retrospective cohort | Adults | 1997 WHO Classification | Yes |
| **94** | Koraka et al.(2001)[94] | Indonesia | nested case control or case-cohort | Children | 1997 WHO Classification | Yes |
| **95** | Lee et al.(2009)[95] | Singapore | retrospective cohort | Adults | 1997 WHO Classification | Yes |
| **96** | Lye et al.(2009)[96] | Singapore | retrospective cohort | Adults | 1997 WHO Classification | Yes |
| **97** | Mairuhu et al.(2005)[97] | Indonesia | prospective cohort | Children | 1997 WHO Classification | Yes |
| **98** | Giraldo et al.(2011)[98] | Brazil | retrospective cohort | Children | Both 1997 and 2009 WHO Classifications | Yes |
| **99** | Singla et al.(2016)[99] | India | prospective cohort | Children | 2009 WHO Classification | Yes |
| **100** | Vuong et al.(2016)[100] | Vietnam | prospective cohort | Mixed population | 2009 WHO Classification | Yes |
| **101** | Pereira et al.(2018)[101] | India | cross-sectional study | Adults | 2009 WHO Classification | Yes |
| **102** | Phakhounthong et al.(2018)[102] | Cambodia | retrospective cohort | Children | 2009 WHO Classification | Yes |
| **103** | Mondragon et al.(2017)[103] | Mexico | nested case control or case-cohort | Adults | 1997 WHO Classification | Yes |
| **104** | Pothapregada et al.(2015)[104] | India | cross-sectional study | Children | 1997 WHO Classification | Yes |
| **105** | Potts et al.(2010)[105] | Thailand | retrospective cohort | Children | 1997 WHO Classification | Yes |
| **106** | Raza et al.(2014)[106] | Pakistan | cross-sectional study | Mixed population | 1997 WHO Classification | Yes |
| **107** | Sirivichayakul et al.(2012)[107] | Thailand | prospective cohort | Children | 1997 WHO Classification | Yes |
| **108** | Sharmar et al.(2015)[108] | India | prospective cohort | Adults | 1997 WHO Classification | Yes |
| **109** | Thein et al.(2015)[109] | Singapore | prospective cohort | Adults | 1997 WHO Classification | Yes |
| **110** | Tissara et al.(2017)[110] | Sir Lanka | nested case control or case-cohort | Children | 1997 WHO Classification | Yes |
| **111** | Thanachartwet et al.(2016)[111] | Thailand | prospective cohort | Adults | 2009 WHO Classification | Yes |
| **112** | Thanacharwet et al.(2015)[112] | Thailand | prospective cohort | Adults | 2009 WHO Classification | Yes |
| **113** | Thanachartwet et al.(2016)[113] | Thailand | prospective cohort | Adults | 2009 WHO Classification | Yes |
| **114** | Thanachratwet et al.(2016)[114] | Thailand | prospective cohort | Adults | 2009 WHO Classification | Yes |
| **115** | Vasanwala et al.(2011)[115] | Singapore | prospective cohort | Mixed population | 1997 WHO Classification | Yes |
| **116** | Villar-Centrno et al.(2008)[116] | Colombia | prospective cohort | Mixed population | 1997 WHO Classification | Yes |

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|---|---|---|---|---|---|---|
| **117** | Garcia-Rivera et al.(2003)[117] | Puerto Rico | cross-sectional study | Mixed population | 1997 WHO Classification | Yes |
| **118** | Prasad, D.; Bhriguvanshi, A. et al. (2020)[118] | India | cohort | children | 2009 WHO Classification | Yes |
| **119** | Chandrashekhar et al. (2019) [119] | India | cohort | children | 2009 WHO Classification | No |
| **120** | Elenga et al. (2019) [120] | French Guiana | cohort | children | 2009 WHO Classification | No |
| **121** | Goncalves, B. S. et al. (2019) [121] | Brazil | cohort | mixed population | 2009 WHO Classification | Yes |
| **122** | Goncalves, B. S. et al. (2) et al. (2019) [122] | Brazil | cohort | mixed population | 2009 WHO Classification | Yes |
| **123** | Phuong, N. T. N. et al. (2019) [123] | Vietnam | cohort | children | 2009 WHO Classification | Yes |
| **124** | Ta, T. V. at al. et al. (2019) [124] | Vietnam | cohort | children | 1997 WHO Classification | Yes |
| **125** | May, W. L. et al. et al. (2019) [125] | Myanma | cross-sectional study | children | 2009 WHO Classification | Yes |
| **126** | Nguyen Phung [126], N. T. et al. (2019) | Vietnam | cross-sectional study | children | 2009 WHO Classification | No |
| **127** | Patra, Goutam et al. (2019) [127] | India | cohort | mixed population | 2009 WHO Classification | Yes |
| **128** | Wang, W. H. et al. (2019) [128] | Taiwan | cohort | mixed population | 1997 WHO Classification | Yes |
| **129** | Opasawatchai, A et al. (2019) [129] | Thailand | cohort | others | 1997 WHO Classification | No |
| **130** | Kularatnam, G. A. M. et al (2019) [130] | Sri Lanka | cohort | children | 1997 WHO Classification | Yes |
| **131** | Agrawal, V. K. et al. et al. (2018) [131] | India | cohort | mixed population | 2009 WHO Classification | Yes |
| **132** | Athira, P. P. et al. (2018) [132] | India | cross-sectional study | children | 2009 WHO Classification | No |
| **133** | Boillat-Blanco, N. et al. (2018) [133] | Tanzania | cohort | others | 2009 WHO Classification | Yes |
| **134** | Lee, I. K. et al. (2018) [134] | Taiwan | cross-sectional study | others | 2009 WHO Classification | Yes |
| **135** | Low, G. K. K. et al. (2018) [135] | Malaysia | cohort | others | 2009 WHO Classification | Yes |
| **136** | Saniathi, N. K. E et al. (2018) [136] | Indonesia | case-control | children | 1997 WHO Classification | Yes |
| **137** | Srivastava, G.; Chhavi, N.; Goel, A. (2018) [137] | India | cohort | children | 2009 WHO Classification | Yes |
| **138** | Temprasertrudee, S. et al. (2018) [138] | Thailand | cohort | others | 2009 WHO Classification | Yes |
| **139** | Villamor, E. et al. (2018) [139] | Colombia | case-control | mixed population | 1997 WHO Classification | Yes |
| **140** | Wakimoto, M. D. et al. (2018) [140] | Brazil | case-control | children | 2009 WHO Classification | Yes |
| **141** | Masood, Kiran Iqbal et al. (2018) [141] | Pakistan | case-control | mixed population | 2009 WHO Classification | Yes |
| **142** | Wijeratne, D. T. et al. (2018) [142] | Colombia | cohort | others | 1997 WHO Classification | Yes |

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|---|---|---|---|---|---|---|
| **143** | Zhang, H. et al. (2018) [143] | China | cohort | others | 2009 WHO Classification | Yes |
| **144** | Ralapanawa, U. et al. (2018) [144] | Sri Lanka | cross-sectional study | others | 1997 WHO Classification | Yes |
| **145** | Mapalagamage, M. et al. (2018) [145] | Sri Lanka | cohort | others | 1997 WHO Classification | Yes |
| **146** | Hegazi, M. A. et al. (2020) [146] | Saudiarabia | cohort | mixed population | 2009 WHO Classification | Yes |
| **147** | Mapalagamage, M. et al. (2019) [147] | Sri Lanka | case-control | mixed population | 2009 WHO Classification | No |
| **148** | Patra, G.; Saha, B.; Mukhopadhyay, S. (2019) [148] | India | cohort | mixed population | 2009 WHO Classification | Yes |
| **149** | Sani, H. et al et al. (2019) [149] | Malaysia | cross-sectional study | others | 2009 WHO Classification | Yes |
| **150** | Mahmud, Muhammad Rizwan et al. (2018) [150] | Pakistan | cohort | mixed population | 1997 WHO Classification | Yes |

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352 **Supplement Table 7.** Definitions of associated factors taken from the included studies in this systematic review
353 and meta-analysis

| Associated factors | Definition |
|---|---|
| Age | Age of participants in year or month units according to medical records or history taking |
| Sex | Physical sex according to medical records or history taking |
| Nutritional status | For children (≤ 18 years old), weight for age based on local standardized guidelines or BMI-for-age >2 Z score according to WHO sex-specific growth reference for children.<br><br>For adults (>18 years old) the BMI criterion was used, malnourished BMI < 18 and obese BMI > 30 $kg/m^2$ |
| Weight | Weight of patients measured at presenting at hospitals or medical records |
| Mixed comorbidity | Unspecific pre-existing comorbidities including cancer, asthma, chronic obstructive pulmonary disease, etc. according to medical records or history taking |
| Hypertension | Pre-existing hypertension disease according to medical records or history taking |
| Diabetes mellitus | Pre-existing diabetes mellitus according to medical records or history taking |

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|---|---|
| Renal disease | Pre-existing renal diseases excepting acute kidney injury on dengue episode according to medical records or history taking |
| Cardiovascular disease | Pre-existing cardiovascular disease including chronic heart failure, myocardial infarction according to medical records or history taking |
| Rash | Presence of unspecific rash during the first four days of the illness according to history taking or physical examinations |
| Vomiting | Presence of vomiting with any episodes during the first four days of the illness according to history taking or physical examinations |
| Abdominal pain and tenderness | Presence of abdominal pain and tenderness with any episodes during the first four days of the illness according to history taking or physical examinations |
| Headache | Presence of headache during the first four days of illness according to history taking |
| Minor bleeding | Presence of either mucosal or spontaneous bleeding that do not require blood transfusion and present during the first four days of illness. This includes skin bleeding (petechiae, ecchymosis, or purpura), mucosal bleeding (epistaxis, gum bleeding, or other sites), haematemesis or melena. |
| Positive tourniquet test | Tourniquet test with the presence of ≥20 petechiae per square inch. |

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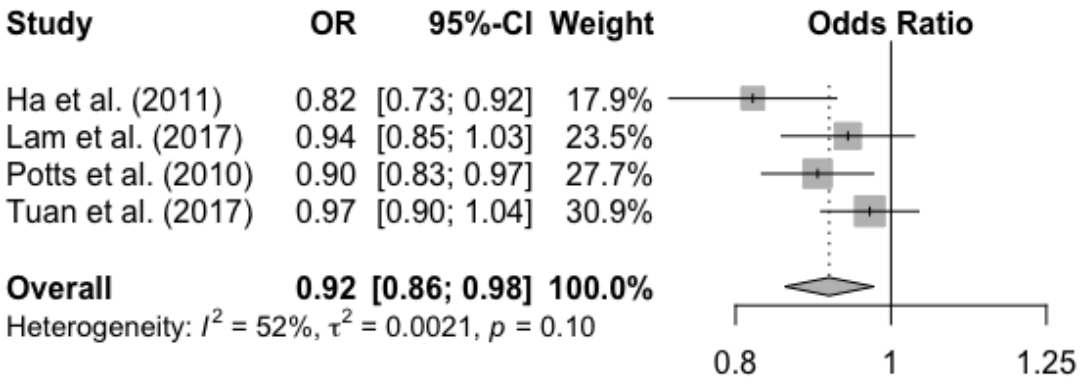
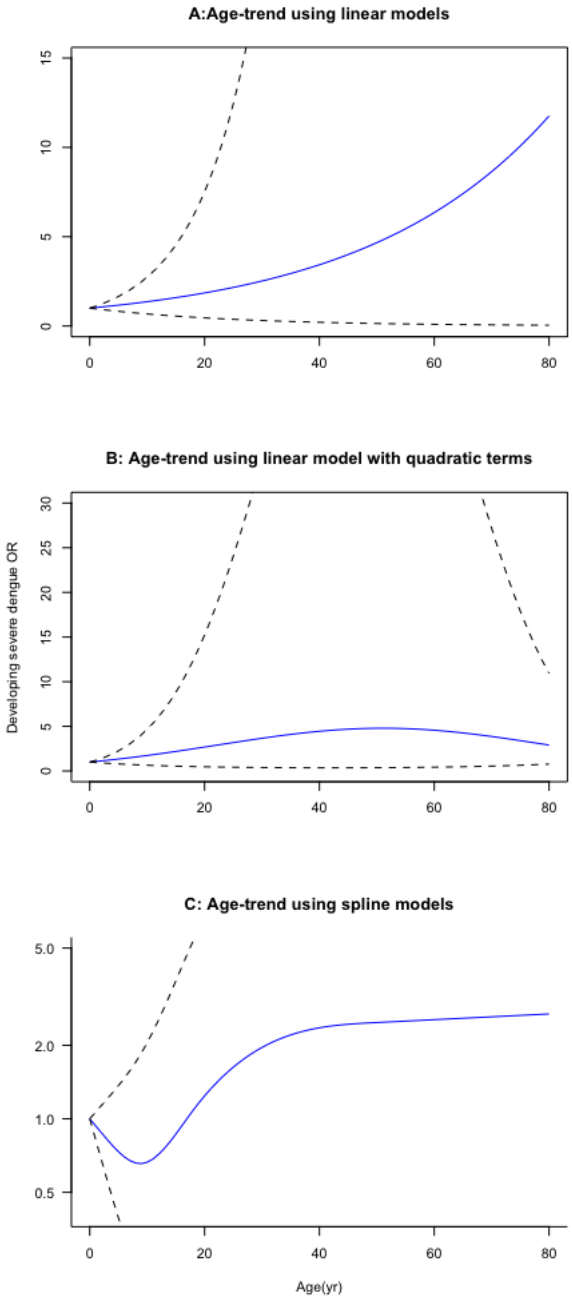
|---|---|
| Immune status | Secondary infection determined with the use of serological tests (i.e. either IgM or IgG ELISA during the first four days of illness or the convalescence phase.) |
| Clinical fluid accumulation | Presence of fluid accumulation (i.e. either pleural effusion or ascites) during the first four days of illness according to chest X-ray, ultrasonography, or physical examination |
| Serotypes | Infecting dengue serotypes determined using patients' serum collected during the first four days of illness with conventional or real-time RT-PCR assays, or viral isolation by mosquito inoculation. |
| Viraemia levels | Viral RNA levels were quantified using real-time PRC or quantitative RT-PCR assays in the patients' plasma specimens collected during the first four days of illness |
| Platelet count | The number of platelets during the first four days of illness. If there are reports of platelet count for more than one day, platelet count on day 3 of illness was chosen. |
| Leukocyte cell count | The number of leukocytes during the first four days of illness. If there are reports of leukocyte count for more than one day, leukocyte count on day 3 of illness was chosen. |
| Haematocrit | Haematocrit detected during the first four days of illness. If there are reports of haematocrit for more than one day, haematocrit on day 3 of illness was chosen. |

| | |
|---|---|
| Aspartate transaminase (AST) | AST levels detected during the first four days of illness. If there are reports of AST on more than one day, AST on day 3 of illness was chosen. |
| Alanine transaminase (ALT) | ALT levels detected during the first four days of illness. If there are reports of ALT on more than one day, ALT on day 3 of illness was chosen. |
| Serum albumin | Serum albumin levels detected during the first four days of illness. If there are reports of serum albumin on more than one day, albumin levels on day 3 of illness was chosen. |



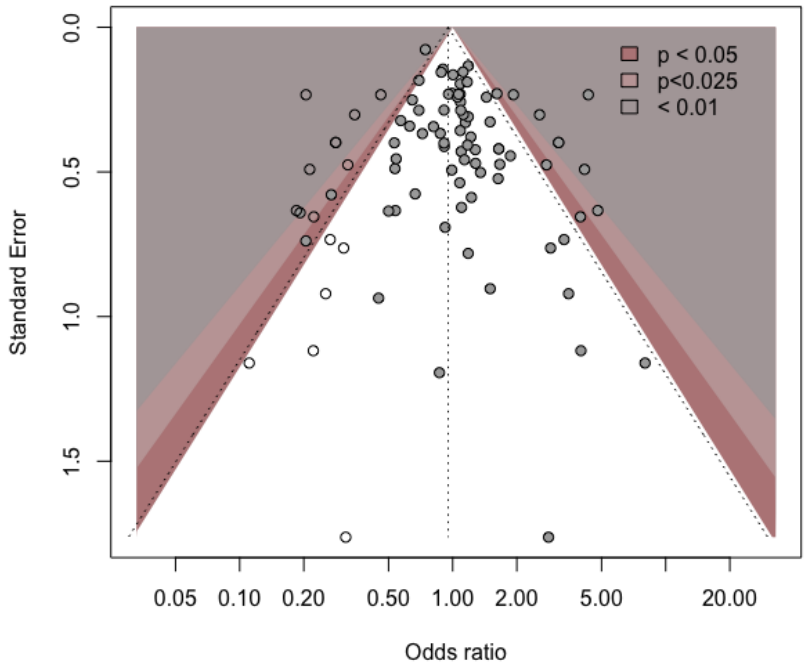

**Supplement Figure 1:** Forest plot of associations from multivariable models between age and severe progression. Four studies conducted among children (≤ 18 years old) were included in the meta-analysis. The pooled OR was 0.92 (95% CI (0.86, 0.98)) and $I^2$ was 52%.




**Supplement Figure 2:** Association between odd ratios of severe progression (y-axis) and age (x-axis) from dose-response meta-analysis based on linear models (A), linear models with quadratic terms (B), and spline models with knots at age 2, 9, 18, and 50 (C). The blue solid line indicates the central estimate and the dotted line indicates the 95% CI.

**Supplement Table 4: Model fitting parameters of linear and non-linear models estimating trends in the risk of developing severe manifestations with age in dose-response meta-analysis**

| Model | AIC | BIC |
|---|---|---|
| Linear model | 65.8 | 67.6 |
| Linear model with quadratic terms | 83.1 | 87.3 |
| Spline model with 4 knots at age 2, 9, 18, and 50 | 71.5 | 78.4 |

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372 **Supplement Figure 3:** Funnel plot for association between sex and severe progression. The grey dots indicate
373 association of each study and the clear dots indicate the imputed associations.

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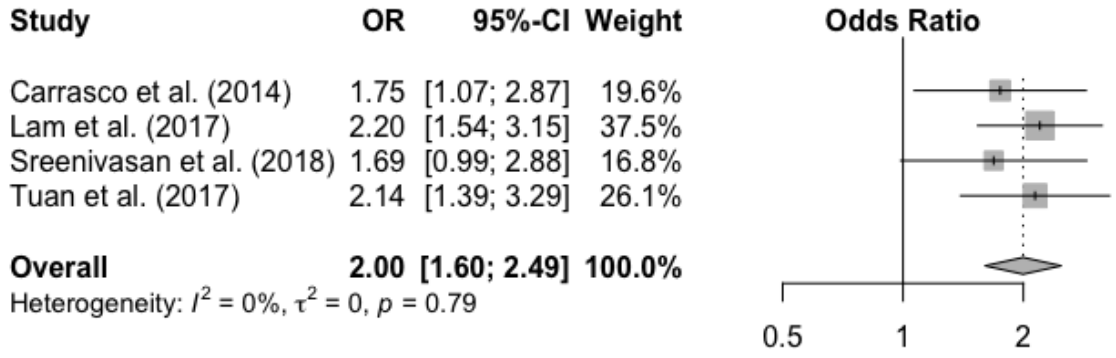


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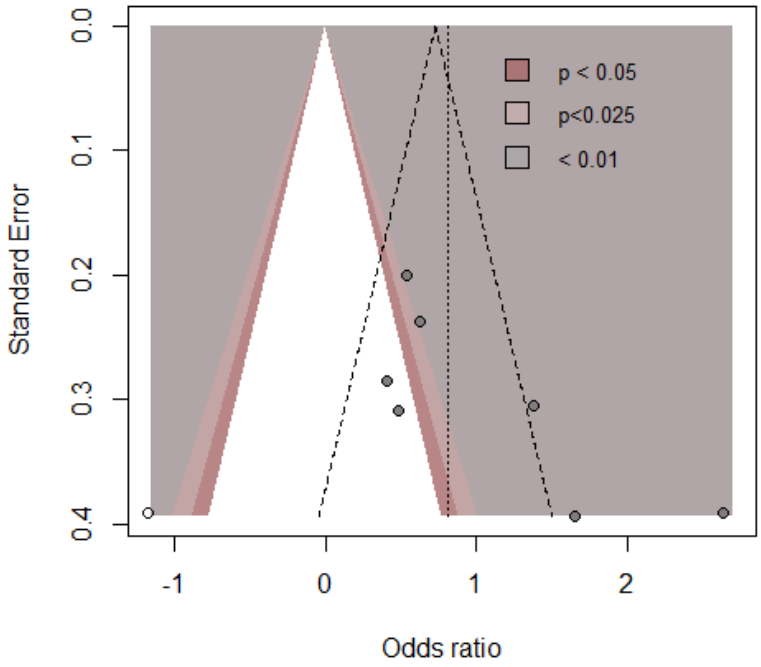
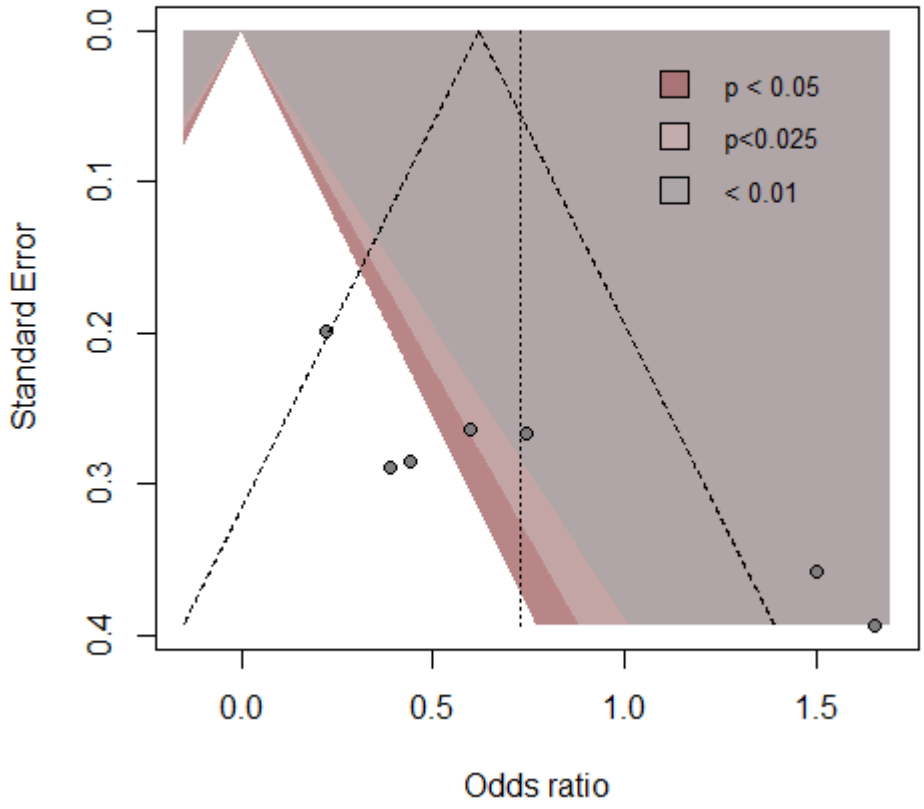
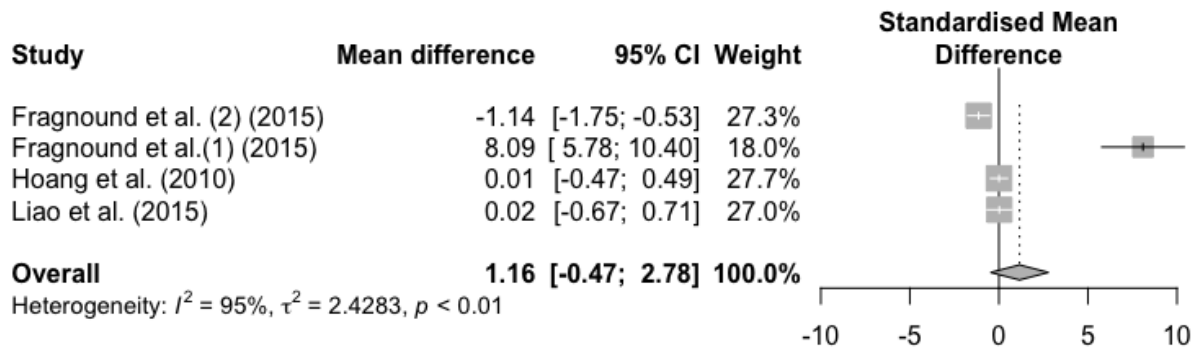
**Supplement Figure 4:** Forest plot of associations from multivariable models between vomiting and progression to severe disease. Four studies were included in the meta-analysis. The pooled OR was 2.00 (95% CI (1.60, 0.2.49)) and $I^2$ was 0%.




**Supplement Figure 5:** Funnel plot for association between AST and progression to severe disease. The grey dots indicate association of each study and the clear dots indicate the imputed associations. Dots on the coloured background indicate statistically significant ORs (red: p-value < 0.05, pink < 0.025 and brown p-value <0.01); dots on the white background indicate non-significant ORs (p-value ≥ 0.05).




**Supplement Figure 6:** Funnel plot for association between ALT and progression to severe disease. The grey dots indicate association of each study. While dots on the colour background indicate statistically significant ORs (red: p-value < 0.05, pink < 0.025 and brown p-value <0.01), on white indicates non-significant.




**Supplement Figure 7:** Forest plot of associations between viraemia and progression to severe disease. Four studies were included in the meta-analysis. The pooled OR was 1.16 (95% CI (-0.47 to 2.78)) and $I^2$ was 95%.

**Supplement Table 7. Associated factors with progression to severe dengue illness reported in studies with children and adults**

| Associated factors reported in studies with children during the febrile phase of disease | Associated factors reported in studies with adults during the febrile phase of disease |
|---|---|
| 1. Age | 1. Age |
| 2. Sex | 2. Sex |
| 3. Nutritional status | 3. Mixed comorbidity |
| 4. Weight | 4. Diabetes mellitus |
| 5. Presence of vomiting | 5. Chronic kidney disease |
| 6. Presence of abdominal pain and tenderness | 6. Cardiovascular disease |
| 7. Presence of bleeding | 7. Platelet count |
| 8. Platelet count | 8. Haematocrit |

| | |
|---|---|
| 9. Haematocrit<br><br>10. Aminotransferase levels<br><br>11. Immune status<br><br>12. Serotypes | 9. Immune status<br><br>10. Serotype |

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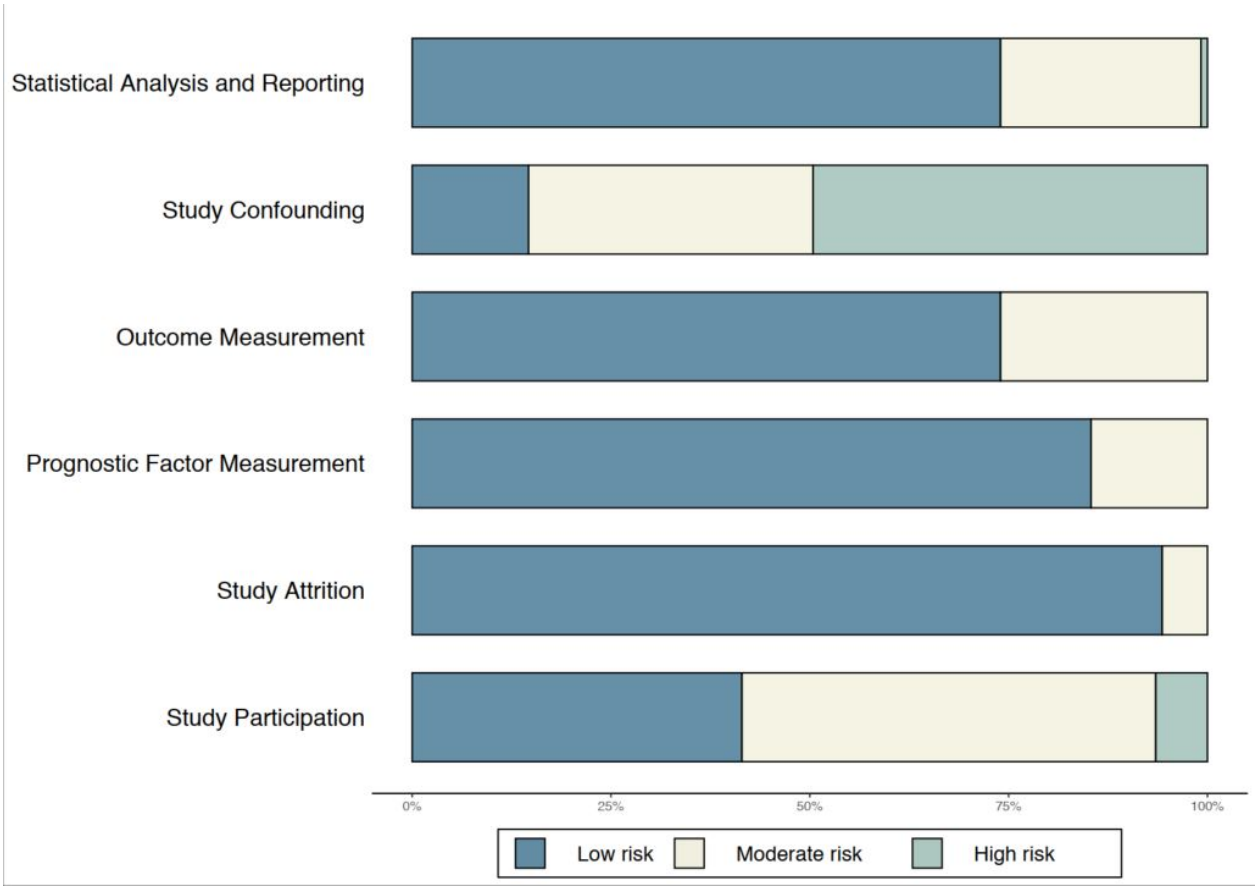
401 **Supplement Figure 8: Risk of bias in the included studies assessed by the Quality in Prognostic Studies**
402 **tool**

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