Review Article

Duration of Fever in Patients with Dengue: A Systematic Review and Meta-Analysis

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Abstract. Dengue is an acute febrile illness endemic to tropical countries and associated with high mortality rates. Despite being a viral infection, there is rampant misuse of antibiotics in patients with dengue because of perceived delay in defervescence and fear of secondary bacterial infections. Therefore, there is a need to establish the average fever duration with a confidence interval among patients with dengue. Studies up to October 21, 2022 from two databases (PubMed and Embase) were included using the search terms related to dengue and duration of fever. All retrieved articles were screened for eligibility by two independent reviewers. Studies where the average duration of fever was available were included for systematic review. Articles with at least more than 20 patients where a mean and standard deviation for the total duration of fever was available were included for meta-analysis. A total of 643 articles were included from the two databases after duplicate deletion. After two rounds of screening, 31 articles (*n* = 7,905) were finally included. The mean duration of fever in the 20 articles included for meta-analysis was 5.1 (95% CI: 4.7–5.5) days. Longer duration of fever was seen in those with a higher grade of fever, those with higher disease severity, and those with concurrent bacterial infections. In the absence of risk factors for concurrent bacteremia, antimicrobials may be unnecessary in those with dengue fever duration of less than 5.5 days.

INTRODUCTION

Dengue is a flavivirus transmitted by the bite of *Aedes* mosquitoes.[1] It can either be an asymptomatic or symptomatic febrile disease. The presentation of symptomatic dengue varies from mild to severe disease. The severe disease is associated with increased capillary permeability and/or hemorrhagic manifestations (dengue hemorrhagic fever), often leading to shock (dengue shock syndrome).[1] Severe dengue cases are associated with high morbidity and mortality. In a recent WHO report, more than five million dengue cases and 5,000 dengue-related deaths were reported globally in 2023.[2] Dengue is usually diagnosed by NS1 antigen test or polymerase chain reaction (PCR) in the early part of the illness and by IgM antibody–based serological assays after 5 days of illness.[3] Dengue virus has four serotypes, DENV-1 to 4, each may be associated with a different disease severity.[4] The treatment of dengue is primarily supportive.[1] Because of the acute nature of the disease and the possibility of rapid deterioration, there is rampant misuse of antibiotics in patients with dengue.[5] In a recent study from Indonesia, 17.5% of the hospitalized dengue patients received antimicrobials.[5] One of the primary reasons for adding an antibiotic to a patient with dengue is a perceived delay in defervescence and a fear of secondary bacterial infections.[5] Therefore, there is a need to establish the average fever duration with a confidence interval among patients with dengue to help clinicians decide on antimicrobial prescriptions.

MATERIALS AND METHODS

This Systematic Review and Meta-Analysis (SRMA) was started after it was registered with PROSPERO (Registration number-CRD42022355256) and is reported according to the PRISMA guidelines.[6] This SRMA included studies from two databases (PubMed and Embase). We also used snowballing (searching the citations of retrieved papers for possible inclusion). The following search string was used: (dengue OR chikungunya) AND ("fever duration" OR "duration of fever" OR defervescence). Chikungunya was included as a comparator for dengue, both being mosquito-borne acute febrile diseases with short fever duration. Articles in all languages available in the two databases between 1852 and October 21, 2022 were retrieved and transferred into the Rayyan software. They were then reviewed for duplicates, and after removing the duplicates, the title and abstract were independently screened for eligibility by two authors (N. Gupta and C. Boodman). The conflicts were resolved by a third author (S. Van Den Broucke). After the initial screening, full-length articles were retrieved for full-text screening. The articles that met the eligibility criteria were included in the systematic review.

Studies where the average duration of fever for clinically or microbiologically diagnosed dengue (or chikungunya) in individuals of any age or sex was available were included. We excluded studies in which the duration of fever at the time of admission or presentation was available but the total duration of fever was not. Studies where the duration of illness or symptoms was mentioned but the duration of fever was not explicitly mentioned, studies on coinfections, and studies on nonhuman subjects were also excluded. Case reports, conference abstracts, reviews, systematic reviews, and letters to the editor were excluded from the systematic review.

Those articles with more than 20 patients where a mean and standard deviation for the total duration of fever was directly or indirectly available were put into a meta-analysis. The meta-analysis was performed with a random effects model (Der Simonian and Laird) using the open-source meta-analysis software developed by Wallace et al.[7] This software uses the R environment as the statistical engine and Python for the graphical user interface.[7] The mean pooled duration of the fever, along with a 95% CI, was calculated using the mean and standard deviation of the

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duration of the fever in individual studies. When mean and standard deviation were unavailable, they were indirectly inferred from the median, interquartile range, range, or 95% CI using previously described procedures.[8,9] In the meta-analysis, the duration of fever for all included patients was considered. Subgroups were defined based on age, severity, history of prior dengue, serotype, immunosuppression, and concurrent infections. Wherever the duration of fever was mentioned exclusively for subgroups, the duration for those individual subgroups was entered into meta-analysis as separate entries, provided each had more than 20 cases. The critical appraisal of articles included in the meta-analysis used the Joanna Briggs Institute checklist for observational studies.[10]

RESULTS

A total of 784 articles (PubMed = 539, Embase = 245) were retrieved. After duplicate deletion (n = 151), 633 articles were included. After two rounds of screening, 31 articles were finally included (Figure 1). Ten articles were added after citation searching. The final 41 articles included 31 articles for dengue and 10 articles for chikungunya to serve as a comparator for dengue.[11–49] Two articles included for dengue had data on patients with chikungunya as well.[19,41] The PRISMA flow chart was generated using the package developed by Haddaway et al.[50]

All included studies were observational. Most studies were reported from the Indian subcontinent (n = 18) between 2000 and 2015 (Table 1). Most of the studies included hospitalized patients with dengue (Table 1). Antigen/antibody-based tests and PCR were the commonest diagnostic modalities (Table 1). The total number of included cases was 7,905, with a mean of 255 cases per study (range: 20–2,843) (Table 1). Except for five studies that included only pediatric patients, all others included adult patients[17,22,33,38,39] (Table 1). The average age of adult patients ranged from 24 to 45 years (Table 1). The detailed

definition of fever and assessment techniques used in different studies are compiled in Supplemental Table 1.

Twenty studies were included in the final meta-analysis.[11,13,14,16,17,20,22,24–26,28,30–33,35–39] In the Joanna Briggs Institute appraisal tool, of the eight criteria for evaluation, the description of exposure criteria did not apply to any of the studies. Of the seven applicable criteria, all studies met at least five criteria. Only two studies addressed confounding.[32,33] The mean duration of fever in all included patients was 5.1 (95% CI: 4.7–5.5) days, ranging from 3 to 7.4 days (Figure 2). The mean duration in adult and pediatric patients was 5.2 (95% CI: 4.6–5.8) and 5.2 (95% CI: 4.5–5.9) days, respectively (Supplemental Figures 1 and 2). Longer duration of fever was seen in those with a higher grade of fever, those with higher disease severity and those with a concurrent bacterial infection.[14,22,24] It must be noted here that there was significant heterogeneity in the results ($I^2 = 97.4\%$).

Of the 12 studies on chikungunya (n = 1468) included in the systematic review, the mean duration of fever in patients with chikungunya was 4.2 (95% CI: 3.6–4.7) days (Supplemental Figure 3). The details of the included studies for chikungunya have been compiled in Supplemental Table 2.

DISCUSSION

The mean duration of fever in patients with dengue was 5.1 days (95% CI: 4.7–5.5 days). This was significantly higher than the mean duration of fever in chikungunya (4.2 [95% CI: 3.6–4.7] days). The duration of fever in adult and pediatric patients was similar. Most of the patients in this review were diagnosed by reliable diagnostic methods, such as PCR and/or antigen/antibody-based methods. Even though IgM serology can be cross-reactive with other flaviviruses and can persist in individuals after asymptomatic infection, they are less likely to be falsely positive in patients with relevant clinical features presenting during an outbreak.[51] Considering the retrospective nature of studies and the
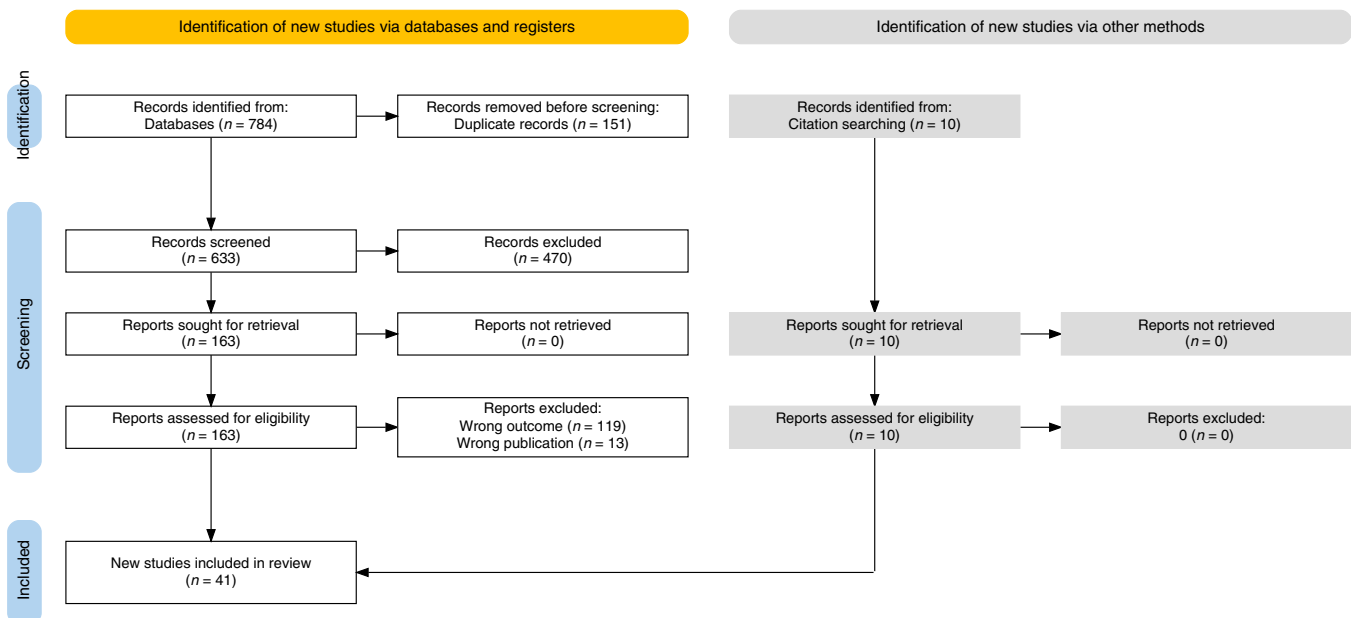

FIGURE 1.   PRISMA flow diagram showing the screening and inclusion of studies.

TABLE 1
Characteristics of dengue studies included in the systematic review

Sn	Author	Year of Study	No. of Cases	Average Age (years)	Age Group	Country	Inpatient/Outpatient	Diagnostic Modality
1	Kularatne 2005[11]	2001–2002	239	28–30	Adult	Sri Lanka	Inpatient	Ag/Ab
2	Limkittikul 2005[12]	2002	53	10.2	Both	Thailand	Inpatient	PCR, Ag/Ab
3	Singh 2005[13]	2002	185	26	Adult	India	Inpatient	NR
4	Lee 2005[14]	2005	100	52–70*	Adult	China	Inpatient	Ag/Ab
5	Sharma 2006[15]	2003	27	29.8	Adult	India	Inpatient	Ag/Ab
6	Armien 2008[16]	2005	130		Both	Panama	Outpatient	PCR, Ag/Ab
7	Chuansumrit 2008[17]	2002–2005	165	NR	Ped	Thailand	Both	Ag/Ab
8	Lo 2009[18]	2006	37	45.4	Adult	Taiwan	Inpatient	PCR, Ag/Ab
9	Kularatne 2009[19]	2006–2007	20	30	Adult	Sri Lanka	Inpatient	Ag/Ab
10	Humayoun 2010[20]	2008	110		Adult	Pakistan	Inpatient	PCR, Ag/Ab
11	Almas 2010[21]	NR	699	31.9	Adult	Pakistan	Inpatient	Ag/Ab
12	Mittal 2012[22]	2010	135	8.3	Ped	India	Inpatient	Ag/Ab
13	Bhattacharya 2013[23]	2010	91	NR	NR	India	Both	Ag/Ab
14	Nasim 2013[24]	2009–2010	102	28	Adult	Pakistan	Inpatient	Ag/Ab
15	Ho 2013[25]	2007	376	NR	Both	Taiwan	Both	PCR, Ag/Ab
16	Ahmed 2014[26]	2010	353	37.1	Both	Pakistan	Both	Clinical Scoring System‡
17	Verma 2014[27]	2010–2013	58	31.4	Adult	India	Both	Ag/Ab
18	Kittitrakul 2015[28]	2000–2002	127	26.4	Adult	Thailand	Both	Ag/Ab
19	Soundravally 2021[29]	2012–2013	48	25.06	Both	India	Both	PCR, Ag/Ab
20	Trojánek 2015[30]†	2004–2013	132	33	Adult	Czech Republic	Both	Ag/Ab
21	Ng 2016[31]	2004–2008	2843	34	Adult	Singapore	Inpatient	PCR
22	Thanachartwet 2016[32]	2013–2015	162	24.5	Adult	Thailand	Inpatient	PCR, Ag/Ab
23	Diaz-Quijano 2018[33]	2014–2015	219	9.8	Ped	Brazil	Outpatient	PCR, Ag/Ab
24	Pradeepa 2018[34]	NR	15	41.2	Adult	India	Inpatient	Ag/Ab
25	Temprasertrudee 2018[35]	2013–2015	357	27.9	Adult	Thailand	Inpatient	Ag/Ab
26	John 2019[36]	2014–2018	159	31.3	NR	India	Inpatient	Ag/Ab
27	Saba 2019[37]	2015	361	NR	Both	Pakistan	Inpatient	Ag/Ab
28	Kumar 2020[38]	2019	55	7.8	Ped	India	Inpatient	Ag/Ab
29	Sharma 2022[39]	NR	50	NR	Ped	India	Inpatient	Ag/Ab
30	Sarin 2022[40]	2014 and 2019	184	40.7	Adult	India	Inpatient	Ag/Ab
31	Trojánek 2023[41]†	2004–2019	313	34	Adult	Czech Republic	Both	Ag/Ab

Ag/Ab = antigen or antibody-based assay; Adult = adult patients as defined by the study; both = both adults and pediatric patients; NR = not recorded; NA = not applicable; Ped = pediatric patients as defined by the study; PCR = polymerase chain reaction assay; Sn = serial number.
* Average age was 70 years in the dual-infection group and 52 years in the no coinfection group.
† There could be possible overlap in the two studies.
‡ The scoring system has a sensitivity and specificity of 91% and 87%, respectively. This did not include any laboratory tests.

duration of fever rarely being the primary outcome, it might be assumed that the estimate of actual fever duration might vary from the reported time. However, the greater representation of admitted patients in the studies adds some credibility to the reported estimates because temperature is routinely and reliably measured during hospitalization.

Some studies reported the duration of fever in different subgroups. In a study by Mittal et al.,[22] fever duration was longer in severe forms of dengue (mean duration in dengue hemorrhagic fever 6.2 ± 3.1 days, mean duration in dengue shock syndrome 6.5 ± 4.7) compared with those with milder forms (mean duration 5.7 ± 2.1 days). In the study by Temprasertrudee et al.,[35] the duration of fever was longer in severe disease (median duration 4 days, interquartile range [IQR]: 3–5) compared with nonsevere disease (median duration 3 days; IQR: 2–4). However, the difference was not significant. Similarly, Ng et al.[31] found that the severity of dengue was associated with a longer duration of fever in dengue patients. Given that the latter study predominantly included patients with severe dengue, the overall average duration of fever was slightly longer (6.3 days).[31] This is similar to the study on chikungunya patients by Hayd et al.,[52] where patients with chikungunya arthritis (4.9 days) had a longer duration of fever compared with those without arthritis (3.2 days). In the study by Kularatne et al.,[11] the duration of fever between patients with primary and secondary dengue was not significantly different. Although secondary

dengue is expected to be more severe, in this study, the frequency of bleeding in the two groups was similar, explaining the comparability between the two arms. In a study by Limkittikul et al.,[12] the average duration of fever varied with the serotypes, but the difference was not significant.

Although one of the studies included kidney transplant recipients, no identified studies compared the duration of fever in dengue patients with or without immunosuppression.[24] While the effect of various forms of immunosuppression on fever duration in dengue is unclear, diabetes mellitus (DM) was associated with longer fever duration among patients with chikungunya. The study by Jean-Baptiste et al.[53] showed that the duration of fever was longer in chikungunya patients with DM (5.1 days) than in patients without DM (3.7 days).

Longer duration of fever has been cited as a common cause for concurrent antibiotic administration in patients with dengue.[5] Rampant antibiotic administration in endemic settings can have a far-reaching impact on antimicrobial resistance, thus it is important to understand the prevalence of bacterial coinfections in dengue and the relation between the duration of fever and bacterial coinfection.[5] We found four studies focusing on bacterial coinfections in dengue, two of which were not included because they did not mention the duration of fever.[54,55] In the study by Ng et al.,[31] prolonged fever (fever for more than 7 days) was seen in 20% of the patients. Compared with 0.5% of nosocomial infections

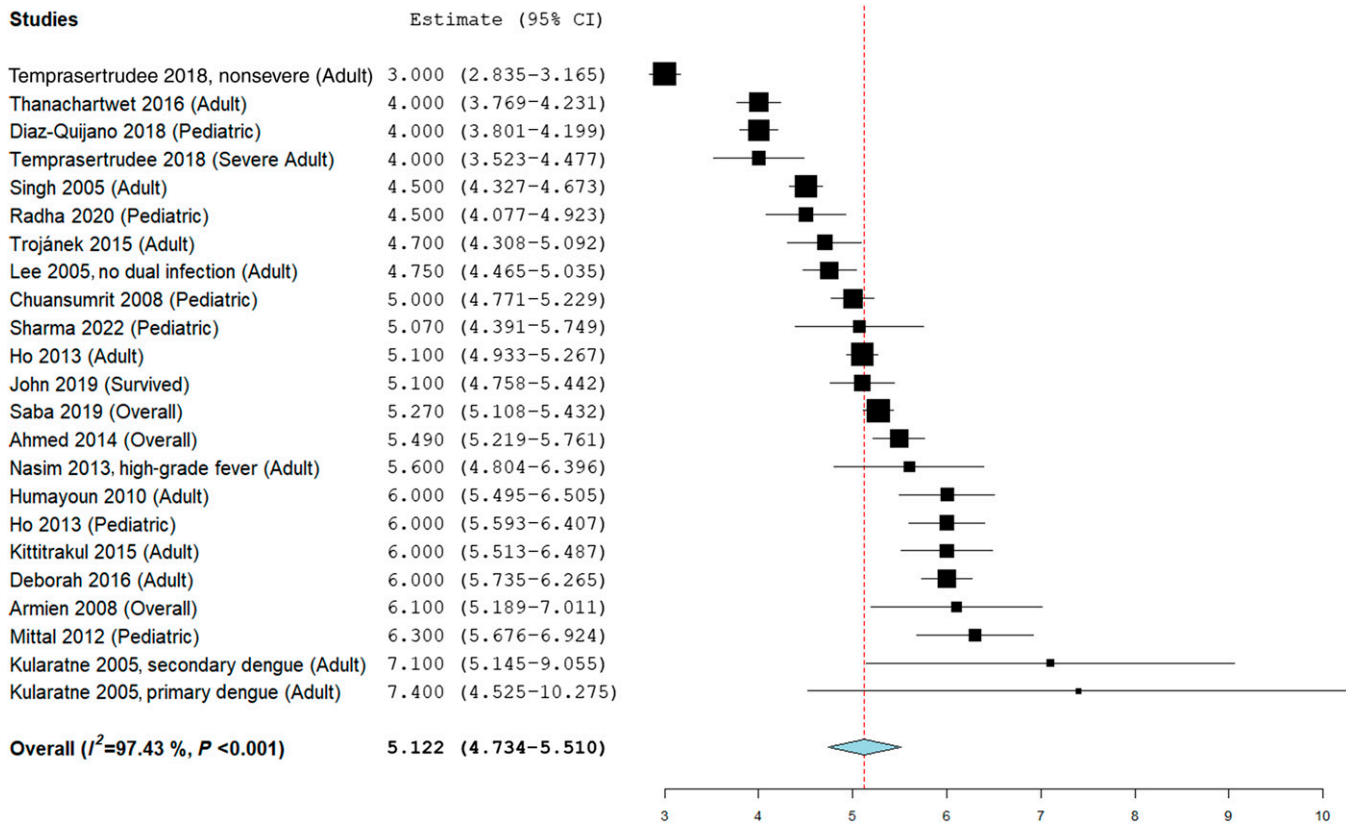| Studies	Estimate (95% CI)	
Temprasertrudee 2018, nonsevere (Adult)	3.000 (2.835–3.165)	
Thanachartwet 2016 (Adult)	4.000 (3.769–4.231)	
Diaz-Quijano 2018 (Pediatric)	4.000 (3.801–4.199)	
Temprasertrudee 2018 (Severe Adult)	4.000 (3.523–4.477)	
Singh 2005 (Adult)	4.500 (4.327–4.673)	
Radha 2020 (Pediatric)	4.500 (4.077–4.923)	
Trojánek 2015 (Adult)	4.700 (4.308–5.092)	
Lee 2005, no dual infection (Adult)	4.750 (4.465–5.035)	
Chuansumrit 2008 (Pediatric)	5.000 (4.771–5.229)	
Sharma 2022 (Pediatric)	5.070 (4.391–5.749)	
Ho 2013 (Adult)	5.100 (4.933–5.267)	
John 2019 (Survived)	5.100 (4.758–5.442)	
Saba 2019 (Overall)	5.270 (5.108–5.432)	
Ahmed 2014 (Overall)	5.490 (5.219–5.761)	
Nasim 2013, high-grade fever (Adult)	5.600 (4.804–6.396)	
Humayoun 2010 (Adult)	6.000 (5.495–6.505)	
Ho 2013 (Pediatric)	6.000 (5.593–6.407)	
Kittitrakul 2015 (Adult)	6.000 (5.513–6.487)	
Deborah 2016 (Adult)	6.000 (5.735–6.265)	
Armien 2008 (Overall)	6.100 (5.189–7.011)	
Mittal 2012 (Pediatric)	6.300 (5.676–6.924)	
Kularatne 2005, secondary dengue (Adult)	7.100 (5.145–9.055)	
Kularatne 2005, primary dengue (Adult)	7.400 (4.525–10.275)	
Overall (I^2=97.43 %, P <0.001)	5.122 (4.734–5.510)	

FIGURE 2. Pooled estimates of mean duration of fever in patients with dengue. Wherever available, the duration of fever in all study patients has been included. In those studies where duration was reported according to the subgroups, the subgroup names have been added after the first author's name. Those subgroups with <20 cases were not included in the meta-analysis. The study name in the first column includes the name of the first author, followed by the year of publication, special characteristics of the population (if any), and age group (overall, adult, pediatric).

in patients without prolonged fever, 3.6% of the patients with prolonged fever had nosocomial infections.[31] In the study by Lee et al.,[14] concurrent bacteremia in dengue was evaluated, but the authors explicitly differentiated concurrent bacteremia from nosocomial bacteremia by including only those patients whose blood cultures were positive within the first 3 days of illness. Patients with concurrent bacteremia were found to have a longer duration of fever (8 days versus 4 days).[14] In the absence of other factors predicting bacterial coinfections in patients with dengue, duration of fever can be considered for the decision to send blood cultures. Our meta-analysis found that the upper limit of 95% CI was 5.5 days, and we suggest that this can be taken as the cutoff for sending blood cultures.

Although the objective of this SRMA was to look at the average duration of fever, we did collect information on the pattern of fever whenever it was reported. In a study by Nasim et al.,[24] fever duration was longer in those with fever >38°C (5.6 days) than those with a fever of <38°C (3.4 days). Dengue fever has also been traditionally described as a biphasic fever with a saddleback pattern. In the study by Ng et al.,[31] saddleback fever was seen in 6% of the patients. In this study, the saddleback pattern was defined as two fever peaks separated by ≥24 hours of defervescence, and the second peak lasted for ≥24 hours.[31] In the study by Pradeepa et al.,[34] three peaks in a single day were characteristically described in patients with dengue.

This review had several limitations. All the included studies were observational, mostly dealing with retrospective data. Duration of fever was never the primary outcome in the included studies. Few studies described the temperature cutoffs, site of temperature assessment, definition of defervescence, and exclusion of the use of antipyretics. The lack of a standardized definition of characterizing fever led to increased baseline heterogeneity. This heterogeneity in the definition of the primary outcome of our review made it challenging to rely on the pooled estimates. Citation searching was done for only included articles and reviews were excluded; thus, some articles could have been missed.

CONCLUSION

In conclusion, the average duration of fever in patients with dengue is approximately 5 days. Patients with severe dengue and those with concurrent infections can have a longer duration of fever. In the absence of risk factors for concurrent bacteremia, it might be prudent to avoid unnecessary antimicrobials in those with dengue fever of less than 5.5 days.

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