Review

Dengue virus infection in Ethiopia: A Systematic review and Meta-analysis

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Review

Dengue Virus Infection in Ethiopia: A Systematic Review and Meta-Analysis

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Abstract: Dengue virus infection is caused by a positive stranded RNA virus called Dengue virus, which is spread by arthropods. It is a fast growing acute febrile disease with potentially lethal consequences that is a global public health problem, mostly in tropical and subtropical countries. In Ethiopia dengue fever is understudied despite the fact that the virus is still being transmitted and viral infection rates are rising. This systematic review and meta-analysis was aimed to estimate the pooled prevalence of DENV infection in Ethiopia. A literature search was done on PubMed, Hinari and Google Scholar databases to identify studies published before July, 2023. Random effects and fixed effects models were used to estimate pooled prevalence of all the three markers. The Inconsistency Index was used to assess the level of heterogeneity. A total of 11 articles were included in this review. Majority of the studies had moderate risk of bias and no study had a high risk of bias. A meta-analysis estimated pooled IgG prevalence of 21% (95% CI: 19-23), a pooled prevalence of IgM 9% (95%CI: 4-13) and a pooled DENV-RNA prevalence of 48% (95% CI: 33-62). There is evidence of possible publication bias in IgG but not found in the rest of markers. The prevalence of DENV infection is high in Ethiopia. Healthcare providers, researchers and policymakers should give more attention to dengue fever.

Keywords: dengue; dengue virus; systematic review; meta-analysis; ethiopia

Introduction

Dengue virus (DENV) is a positive stranded RNA virus of the family Flaviviridae and genus Flavivirus that is spread by arthropods. The four different dengue virus serotypes (DENV 1-4) are all spread by Aedes mosquitoes, primarily *Aedes aegypti* and to a lesser extent *Aedes albopictus* (1, 2). All serotypes are known to produce the whole spectrum of dengue fever (DF) illnesses and share similar geographic patterns and host/vector interactions (3, 4).

Dengue fever (DF) is a fast growing acute febrile disease with potentially lethal consequences that is a global public health problem, mostly in tropical and subtropical countries (5, 6). This infection can result in a variety of clinical illnesses, from asymptomatic or moderate febrile disease to classic DF to the most serious types of illness, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) (7,8). The main clinical signs of each category would be a persistent high fever lasting 2–7 days, bleeding indicated by petechiae, epistaxis, a positive tourniquet test, or thrombocytopenia, and shocks from plasma leakage indicated by hemoconcentration (hematocrit above 20%), pleural effusion, and ascites (9).

The dengue fever is endemic in many countries across the WHO regions of Africa, the Americas, the Eastern Mediterranean, Asia, Australia, and the Western Pacific (4,5), though the Americas, South-East Asia, and the Western Pacific are the most severely affected, Asia accounting for 70% of the global DF disease burden (10). Dengue virus infects 390 million individuals worldwide, with 96 million developing clinical symptoms that result in 500,000 hospitalizations and 25,000 fatalities each year (5, 10).

The epidemiology of DF in Africa is poorly understood, despite the fact that all DENV serotypes circulate in many of the continent's nations, and the vector mosquitoes are abundant in the

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neighboring Middle East and Sub-Saharan Africa [9]. With an estimated burden of 25% (21-29%) by IgG, 10% (9-11%) by IgM, and 14% (12-16%) by viral RNA assays, DENV infection appears to be a considerable burden for public health in the region of Sub-Saharan Africa (11). Additionally, numerous countries in the region have suffered DF outbreaks that have been reported to the Africa CDC (12), including Burkina Faso in 2016 and 2017, Côte d'Ivoire in 2017, Cape Verde in 2009, and Egypt in 2015.

Ethiopia has a low level of research on DF despite the fact that the virus is still being transmitted and viral infection rates are rising (13). In the first DF outbreak reported in 2013, which was in the Dire Dawa city administration in the east of the country, 12,000 suspected cases of DF were registered. Of these, 88 cases were confirmed by ELISA and RT-PCR, and 50 of these cases were found to be positive for DENV infection (14). In Dire Dawa city, Godey Town, and the Adar area of the Afar region the next year, numerous further outbreaks were noted year-round fashion (15, 16). In a few serological studies, DENV infections from various regions of the country were reported, including 7.5% current and 13.0% past DENV infections from northwest Ethiopia (7), 22.9% anti-IgG and 7.9% anti-IgM DENV infections from the Borena zone in southern Ethiopia (17), and 25.1% anti-IgG and 8.1% anti-IgM DENV infections from the Arba Minch district (8). Overall the prevalence of DENV infection is vary in Ethiopia (18-23).

Due to its global distribution, DENV infections should be closely monitored and any outbreaks should be quickly identified in order to reduce the resulting mortality and morbidity. However, it is well known that low-income countries like Ethiopia lack the infrastructure and resources required for effective surveillance of this disease. This systematic review and meta-analysis was aimed to estimate the pooled prevalence of DENV infection markers; DENV-specific Immunoglobulin G (IgG), Immunoglobulin M (IgM), and DENV RNA in Ethiopia.

Methods

This systematic review and Meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (24). The review protocol was registered on Prospero (CRD42023445570).

Eligibility Criteria

This review was considered studies that have reported the prevalence of Dengue virus infection in Ethiopia. The study participants were both sex and any age range. We considered observational studies (cross-sectional and Case control) in both outbreak and out of outbreak periods. Studies that had report to a prevalence of at least one of the three biological markers of DENV-RNA, IgM, or IgG were included. We considered all studies written in English language and published before July, 2023. Review studies, studies with only abstracts, studies report infection rates in non-human animals, entomologic and vector related studies were excluded.

Dengue infection was defined as febrile illness presenting with fever and at least two of the following clinical manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and leukopenia confirmed by laboratory criteria through the detection of DENV RNA using reverse transcription polymerase chain reaction (RT-PCR) or NS1 antigens using enzyme-linked immunosorbent assay (ELISA) and/or rapid tests (25).

Search Strategy

To find pertinent literature published on DENV infection in Ethiopia, a comprehensive search of PubMed, Hinari, and Google Scholar was carried out. The databases were queried search by using keywords “Dengue”, “Dengue virus”, “Dengue infection”, “Dengue fever” and “DENV” in combination with Ethiopia context. A manual search that consists of scanning reference lists of eligible studies and relevant reviews was performed. The search strategy used in PubMed and Hinari is demonstrated in Supplementary Text S1.

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Study Selection

The titles and abstracts of all retrieved citations were imported into EndNote reference manager. Duplicates were removed using this software. Two investigators independently screened titles and abstracts for eligibility based on predetermined selection criteria. The full-texts of articles thought to be potentially eligible were retrieved for further assessment. Further, the investigators independently assessed the full-text of each study for eligibility, and consensually retained studies to be included. Any discrepancies that arise between the reviewers at each level of the selection process were solved through conversation.

Data Extraction

The data have been extracted using a predefined, piloted and standardized data extraction form. Two investigators independently extracted data including: name of first authors, year of publication, study design, sample size, study setting (clinical or community), target population (suspected, Acute febrile patients), time frame (During outbreak or Out of outbreak periods), types of diagnostic techniques (RT-PCR, ELISA and IFA), and types of detected biological markers (RNA, IgM and IgG).

Quality Assessment

Two reviewers assessed the quality and risk of bias of all articles included in this review using a modified version of the Critical Appraisal Tool for prevalence studies designed by the Joanna Briggs Institute (JBI) (26). The risk of selection bias, confounding bias, and bias relating to measurement and data analysis were all assessed using JBI tool. Each question was answered either with “yes”, “no”, “unclear” or “not/applicable”. The number of questions for each study that had a "yes" response was used to determine a score. According to this score, studies were categorized into three groups based on their risk of bias; high risk (a score of 0-3), intermediate risk (a score of 4-6), and low risk (a score of 7-9).

Statistical Analysis

To determine the pooled prevalence of DENV markers, the retrieved data were analyzed using Stata software (version 17, StataCorp LLC, Texas, USA). Multiple markers were provided by some researches, and the estimates were input independently in the meta-analysis. In order to quantify the effect, we used the prevalence estimates from each study. The stated prevalence estimates and the sample size of each study were used to compute the standard error (SE). Fixed-effects model (for DENV-IgG) and random-effects model (for DENV-IgM and RNA) were used to generate summary pooled prevalence data with 95% confidence intervals (CI) and the result present in forest plots. Heterogeneity was assessed using the Inconsistency Index (I^2). In order to check for potential publication bias, funnel plots were created and visually examined. Egger tests was used to confirm heterogeneity.

Results

Study Selection and Characteristics

A total of 1,071 records were retrieved from database searches**.** After removal of duplicates and screening, 11 studies were finally included in the review (Figure 1). The methodological quality of studies ranged from intermediate to low risk of bias. Four (36.4%) studies had low, 7(63.6%) had moderate and no study had a high risk of bias. Majority of the included studies were cross-sectional and two were case-control studies. Six studies were conducted in dengue fever suspected participants whereas five were among acute febrile participants (Supplementary Table S1).

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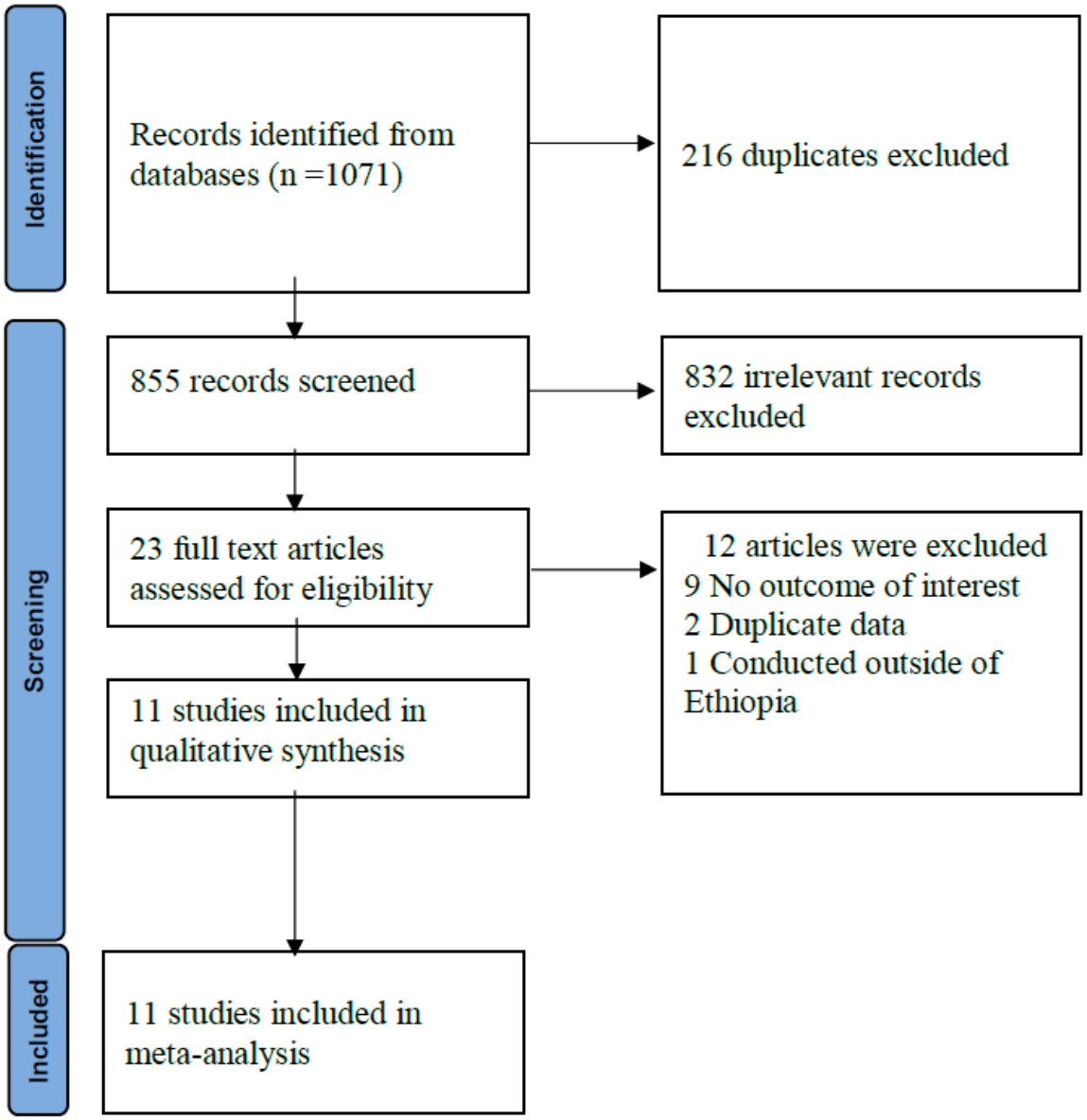

Figure 1. PRISMA flow diagram illustrating studies selection process.

Prevalence of Dengue Virus infection

Data from all included studies were analyzed in the quantitative meta-analysis to estimate pooled prevalence. Meta-analysis was performed separately for each of the DENV infection markers (IgG, IgM and RNA). Fixed effects analysis estimated a pooled prevalence of IgG 21% (95% CI: 19-23) (Figure 2). Random effects analysis estimated a pooled prevalence of IgM 9% (95%CI: 4-13) and a pooled DENV-RNA prevalence of 48% (95% CI: 33-62) (Figures 3 and 4). Significant levels of heterogeneity between studies were found in all three meta-analysis, 83.61%, 94.74%, and 83.16% for IgG, IgM and RNA respectively (Figures 2–4). Visual inspection of the generated funnel plots revealed evidence of potential publication bias in all three meta-analyses (Supplementary Figure S5 and S7). But, egger regression test showed that there is publication bias in DENV IgG studies (p = 0.002), but no publication bias was detected among DENV-RNA (p = 0.7) and IgM (p = 0.052) markers.

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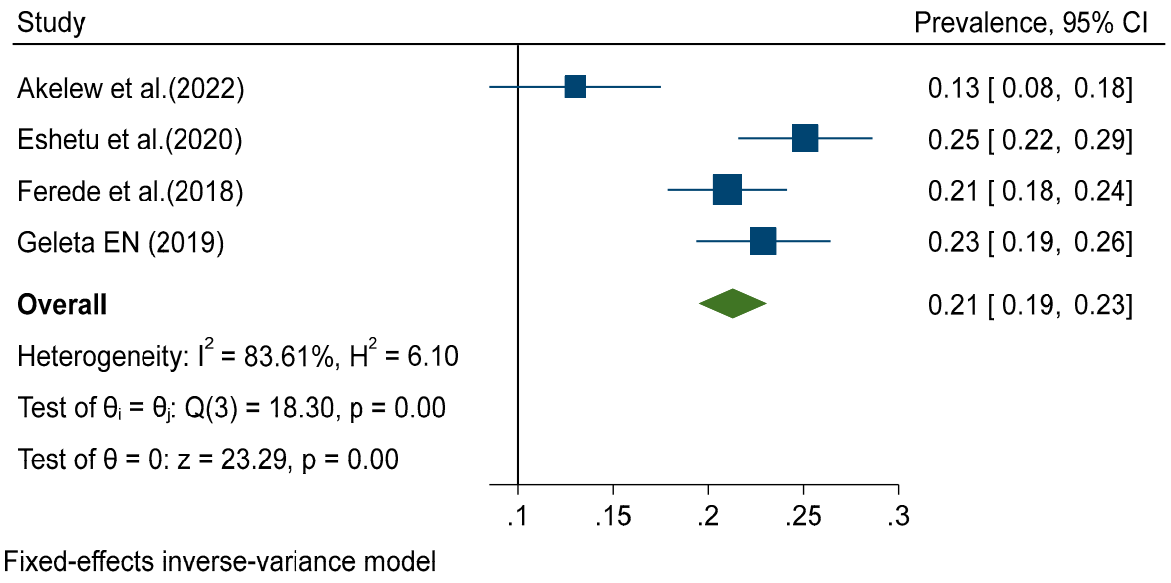

Figure 2. Meta-analysis of Dengue virus Immunoglobulin G prevalence in Ethiopia.

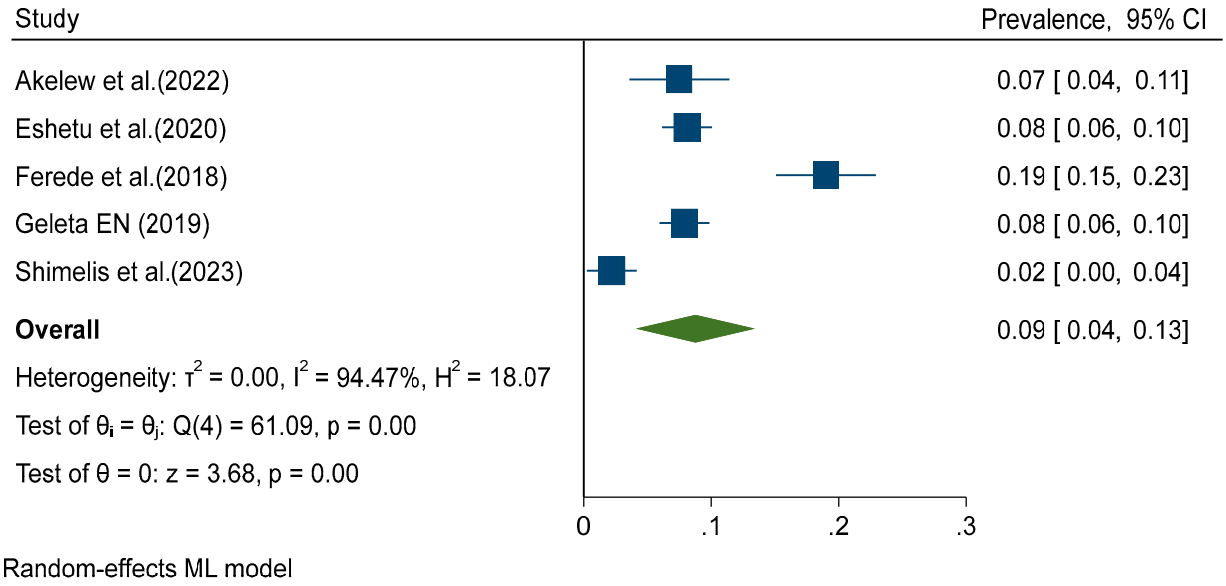

Figure 3. Meta-analysis of Dengue virus Immunoglobulin M prevalence in Ethiopia.

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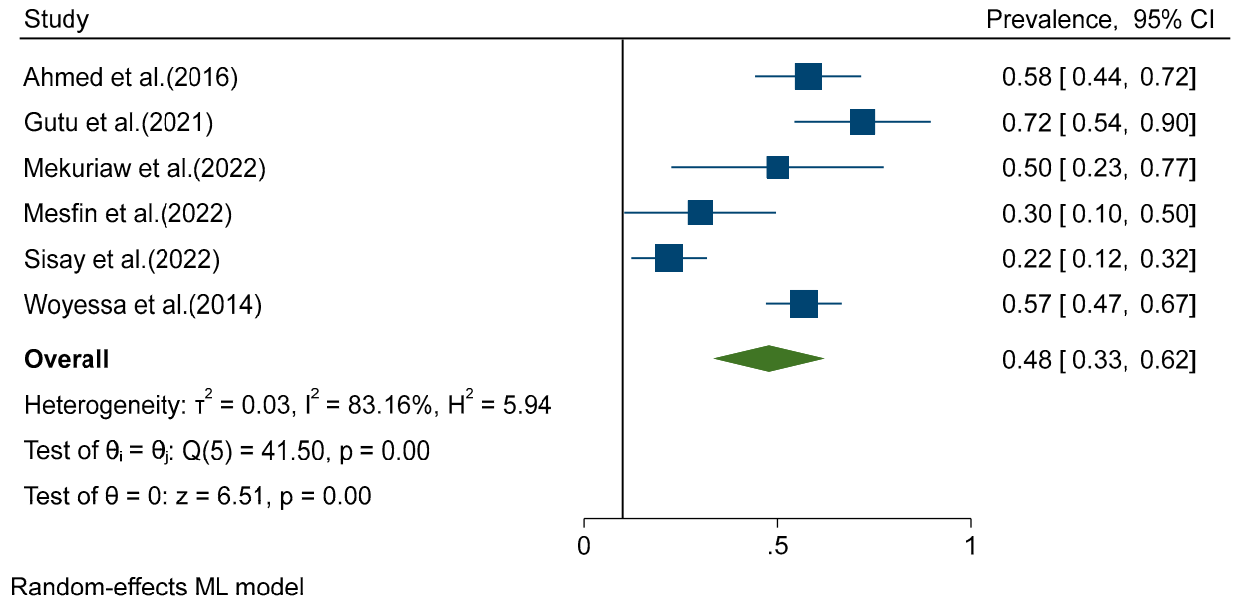

Figure 4. Meta-analysis of Dengue virus RNA prevalence in Ethiopia.

Discussions

The epidemiological patterns of dengue virus infections are recognized to generally mimic those of other re-emerging infections, including other arboviral diseases. This trend causes apparent fluctuations in the clinical and serological prevalence estimates of these diseases because of the spikes in prevalence that are frequently observed during outbreaks and the sharp decline that immediately follows. As a result, it is better to explain the epidemiology of emerging and re-emerging infectious diseases over an extended period of time, as a point estimate rarely captures the real burden of these conditions in a given area. This systematic review and meta-analysis of the prevalence of DENV infection in Ethiopia showed high prevalence estimates with a meaningfully high level of heterogeneity that differs according to the infection marker of interest.

Meta-analysis results have showed that the prevalence of dengue virus in Ethiopia is 9%, 21%, and 48% for DENV- IgM, IgG, and DENV-RNA respectively. According to the finding of this review 9% of Ethiopian population has developed acute DENV infection and 21% have had a history of exposure to DENV at some time in their life. The seroprevalence of DENV-RNA was significantly higher than DENV-IgM and IgG, this might be most studies those determine DENV-RNA were at outbreak periods. The estimated IgM prevalence is lower compared to IgG and RNA, RNA is detectable in patients only from infection up to six days after the onset of the fever. IgM are detectable five days after the onset of fever up to three months while IgG appear on the tenth day after the onset of fever and can continue for many years (27).

The prevalence of DENV-IgG was in agreement with results reported from Sub-Saharan Africa (11), and Africa (28). In Contrast, the finding of this review is lower than result reported from Sudan (29). An estimated IgM prevalence is similar with reviews reported from Africa (28) and Sub-Saharan Africa (11) and lower than report from Sudan (29). In addition DENV-RNA finding of this review is higher than reviews reported from elsewhere (11, 28). This discrepancy might be due to the selection and time frame of included studies. For instance, studies conducted during ongoing epidemics or following outbreaks are likely to contribute to a higher number of dengue positive cases (30). Overall the significant difference in prevalence estimate might be due to sample size, geographical variation, time frame of sample collection, type of assay methods, and way of life hood of community (31).

We found that the pooled prevalence estimate of all DENV markers are high in Ethiopia. The DENV-specific RNA can record a four to five fold increase during outbreak. This evidence indicate that there is circulation of the virus in this country, as a result the residents are at high risk of infections such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).

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The high prevalence outcome of this review may be an indication of the ineffectiveness of current public health efforts to control DENV vector transmission. Weak health systems in low-income settings can be attributed to the failure to sustain effective and ongoing interventions to manage vector-borne disease (32-34). The growing speed of urbanization with poor infrastructure increase mosquitoes breeding sites. The ecological environment and climatic patterns of tropical and subtropical regions where countries like Ethiopia located favor vector long-life and eggs conservation and development (35-39). Additionally, appearance of insecticides resistance of DENV vectors and human mobility in the country as well as in the region increase challenge of controlling spread of those vectors (38). The majority of studies included in this review were reported from eastern part of the country as well as South and Northwest of Ethiopia. This may suggest that there is dengue virus circulating in Ethiopian neighboring countries including Sudan, Kenya and Djibouti, which is raising possibility of cross-border transmission, particularly with the open borders and free mobility between these countries.

The finding of this review contain important information for researchers, health policy makers as well as clinical practices. Such studies will generate base line information for development of effective public health policies for dengue fever prevention and control. And also, a key information that a surveillance program is required to investigate actual prevalence and burden of DENV, vector distribution, the virus serotypes and genotypes. Currently, there is no effective antiviral and vaccination for dengue fever (39). Proper implementation of routine diagnosis and management of early diagnosed illnesses reduces morbidity and fatality rates. It would be interesting to explore differential diagnosis with other infectious diseases with close clinical presentations, such as malaria. There is also issue of cross-reactivity of serological diagnostic techniques among arboviruses including DENV (40, 41). As a result, confirmatory tests such as real-time (quantitative) polymerase chain reaction (qPCR) and plaque reduction neutralization test (PRNT) are required to validate the findings of these serologic assays. Cost-effective control measures are required. Because treatment and immunization are ineffective, vector management is the primary strategy for reducing the burden of DENV infection. The WHO integrated vector control strategy is useful in combating vector-borne diseases. This mechanism is environmentally safe when using insecticides for the elimination of mosquito's larva from their artificial and natural habitats (42).

This is the first systematic review and meta-analysis of DENV seroprevalence estimates in Ethiopia. We attempted to summarize the pooled prevalence of studies conducted in Ethiopia those were reported prevalence of DENV. However, this review has certain limitations. There is substantial heterogeneity between studies, it may be due to diagnostic techniques, time frame of sample collection or population. We were not conduct sub-group analysis because the studies were investigated different types of DENV markers of interest using different diagnostic techniques, time frames and populations. This review does not cover all part of the country. This may have an impact on the generalizability of our findings.

Conclusion

The prevalence of DENV infection is high and the virus is spreading in Ethiopia. This suggests that healthcare providers, researchers and policymakers in the country should give more attention to dengue fever. Routine and differential laboratory dengue virus diagnosis is required to detect cases early, to manage cases appropriately and plan for outbreak. Since, there is no effective treatment or vaccine, prevention and vector control should be the primary DENV control mechanism. Mosquito surveillance is essential for identifying mosquito breeding areas, and health education and environmental control can help to limit the spread of dengue virus. To track DENV epidemiology in Ethiopia, a national arbovirus surveillance program should be implemented.

Abbreviations

DENV	Dengue virus
DF	Dengue fever
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
ELISA	Enzyme-linked immunosorbent assay
IFA	Immunofluorescence assay
IgG	Immunoglobulin G
IgM	Immunoglobulin M
RNA	Ribonucleic acid
RT-PCR	Real-time Polymerase Chain Reaction
WHO	World Health Organization

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