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The social determinants of health of dengue seroprevalence: A systematic review & meta-analysis

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2020

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An abstract of
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Abstract

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By Mia Colton

Background: Social determinants are integral in health outcomes associated with dengue. A systematic review of the literature and meta-analysis was conducted to determine what social determinants are associated with dengue virus (DENV) seroprevalence.

Methods: A systematic review was conducted following PRISMA guidelines in Embase, PubMed, and Web of Science. We used the following search strategy, “(Dengue) AND ("risk factors" or "Social Determinants of Health" or "health disparities")” to gather relevant research. Studies with an observational design on risk factors of dengue seroprevalence, confirmed by IgG serology, were included. Covidence was used in the screening and data collection process. A random-effects meta-analysis was conducted to estimate the pooled odds ratio (OR) for each variable with sufficient data.

Results: The initial search of studies resulted in a total of 4,373 published manuscripts, 203 of which were included after screening by title abstract and duplicates removed. A total of 41 manuscripts with complete raw data from 24 countries were included. The following social determinants had sufficient data to be included in the meta-analysis: gender (n=36), education (n=6), employment (n=4), income (n=5), urban-rural status (n=13), presence of stagnant water (n=5), use of bed net (n=9), spraying insecticides (n=4), and marital status (n=5). Most studies yielded no statistical associations between DENV seropositivity and several of these social determinants. Urban-rural status was statistically associated with DENV seropositivity, with a rural residence as protective (OR 1.54; 95% CI=1.14-2.07). Similarly, insecticide spraying significantly correlated with DENV seropositivity (OR 1.31; 95% CI=1.05-1.64). Gender was not statistically associated with DENV seropositivity.

Discussion: Dengue virus is the most common arbovirus globally, posing a significant health and economic burden. This systematic review and meta-analysis revealed a relative paucity of data on social determinants of DENV seroprevalence. Further research to explore the role of social risk factors of DENV must include more rigorous assessments correlated with serosurvey data to better inform the nature of comprehensive risk-based prevention and control interventions.

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1. INTRODUCTION

Dengue virus (DENV) is the most prevalent cause of arboviral illness worldwide and a disease of concern due to its growing annual incidence (Kularatne & Dalugama, 2022). The anthropophilic mosquito vector *Aedes aegypti* transmits DENV, which poses a risk to over 2.5 billion people living in the tropics. DENV is a leading cause of illness, hospitalization and death among children in these regions, with 400 million infections and more than 10,000 deaths yearly (Solar & Irwin, 2010).

DENV infections are typically asymptomatic or very mild. The most common symptoms associated with the condition known as dengue fever include headaches, rash, fatigue, fever, arthralgia or bone pain, myalgia, and retro-orbital pain. A small proportion of these cases can develop into a severe illness, such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), with bleeding, organ failure, plasma leakage, and even death (Brathwaite Dick et al., 2012; Kalayanarooj, 2011).

Dengue imposes a significant global social and economic burden exceeding other viral illnesses, including rotavirus and human papillomavirus (HPV) (Shepard et al., 2011). The economic costs associated with dengue include both direct and indirect costs. The direct costs include hospitalization, emergency care, outpatient care, and drug costs, with 86.09% of the costs attributable to hospitalization (Luh et al., 2018). Indirect costs refer to the loss of productivity due to symptomatic illness, the need for treatment, and premature death (Hung et al., 2020). Luh et al. (2018) found these costs to increase 12.3 times during epidemic years compared to non-epidemic years.

The estimated economic costs of dengue burden in just the Americas were determined in 2010 as USD 2.1 billion per year (Shepard et al., 2011). Globally, the economic burden of dengue was estimated to be USD 8.9 billion per year (Hung et al., 2020). According to two studies, productivity loss accounts for 40-70% of the estimate (Hung et al., 2020; Luh et al., 2018). The high economic and social costs associated with dengue emphasize the importance of implementing effective prevention and control strategies.

Despite having two primary strategies for controlling dengue fever, neither vector control measures nor vaccination has effectively reduced the global health burden of the disease (Horstick et al., 2018). Furthermore, there are currently no antiviral drugs for dengue (Kularatne & Dalugama, 2022). Unreliable surveillance systems for DENV in many endemic regions and suboptimal diagnostic tools limit comprehensive data collection (Brathwaite Dick et al., 2012; Horstick et al., 2018; Kularatne & Dalugama, 2022). Thus, dengue represents a major global health problem that urgently needs accurate assessments of disease burden and better solutions.

DENV is endemic, mainly in tropical and urban regions (Kularatne & Dalugama, 2022). Although DENV is common in regions where there is poverty and health disparity, there is limited knowledge of the relationship between social determinants of health and risk of DENV infection. Moreover, it is unknown whether certain socioeconomic factors may increase the rate of infection c or may increase the burden or severity of dengue infection. The focus on improving health outcomes of arboviruses has predominantly been studied from a biomedical and epidemiological perspective with minimal integration of social sciences. In recent social research, poverty has become a common denominator for arboviral illnesses (Carabali et al., 2020). Nevertheless, various methods and indicators are used to measure poverty, producing inconsistencies in the association between poverty and the risk of contracting dengue (Mulligan et al., 2015). Understanding the role of social determinants of health (SDH) in dengue transmission and disease can provide invaluable information for prevention and mitigation efforts.

Problem statement

The social determinants of health of contracting the dengue virus are under-researched and need to be better understood globally.

Purpose statement

This systematic review aims to summarize the evidence on the relationship of different categories of social determinants health associated with previous dengue infection using the World Health Organization (WHO)'s social determinants of health (SDH) conceptual framework and identify key knowledge gap to guide further research.

Research question

1. What social determinants of health are related to prior infection with the dengue virus?
2. What social determinants of prior infection with dengue are understudied?

Significance statement

The significance of this research is threefold: first, to present the scope of available SDH data on people seropositive for DENV for future research. Second, to identify gaps in understanding the social implications of dengue illness and determine where further research is necessary.

Third, to provide potential solutions and potential steps towards reducing the growing rate of dengue infections and global burden.

2. LITERATURE REVIEW

Introduction

Knowledge of the social determinants of dengue illness is critical in recognizing and addressing potential factors contributing to the global burden of dengue. Social determinants are interconnected and integrated into social systems and significantly impact health outcomes. Several published frameworks for mapping the social determinants of health can provide a valuable foundation for evaluating factors influencing individuals' health and overall well-being (Committee on Educating Health Professionals to Address the Social Determinants of et al., 2016). To evaluate dengue's potential social risk factors, the World Health Organization (WHO)'s Commission of Social Determinants of Health (CSDH) created a conceptual framework that has been selected as the reference for the SDH of dengue burden and severity. In this literature review, we will examine existing reviews assessing and analyzing the potential association between social determinants of health and seropositivity for DENV, with the CSDH framework as a reference point.

As seen in **Figure 1**, the WHO conceptual framework of SDH consists of two main types of determinants, structural and intermediary. As the basis of the following systematic review, the findings of previous reviews will be evaluated based on the categories and definitions of this framework. A single systematic review created a conceptual framework of determinants impacting dengue transmission. However, the focus is on Puerto Rico, only on extrinsic factors, and excludes intrinsic factors such as demographics and biological factors.

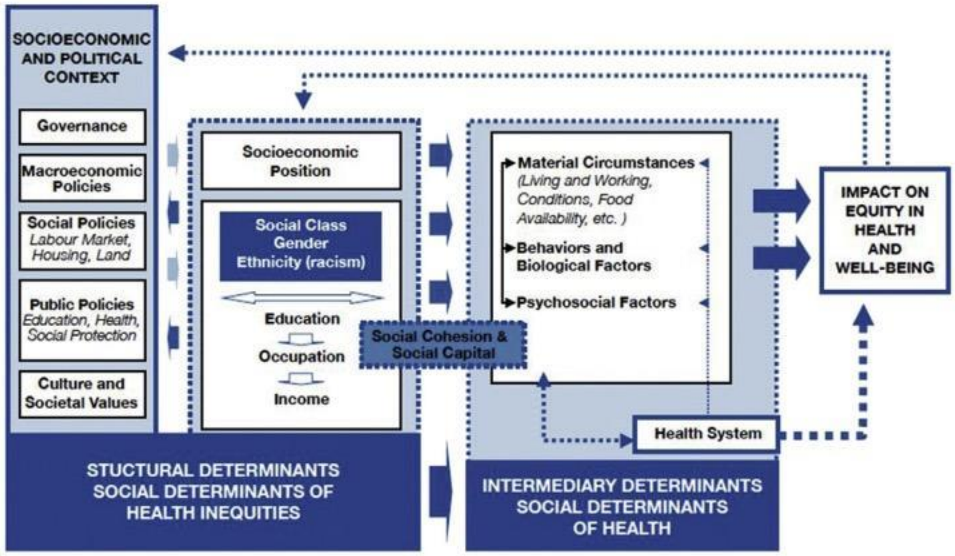

Figure 1. Final WHO CSDH conceptual framework (Solar & Irwin, 2010, p. 6).

Structural Determinants

Based on the CSDH conceptual framework, structural determinants are mechanisms "that generate stratification and social class divisions in the society and define the individual socioeconomic position within hierarchies of power, prestige, and access to resources" (Solar & Irwin, 2010, p. 5). These structural mechanisms are divided into the socioeconomic and political context and socioeconomic position. The socioeconomic and political context is the basis of the structural tools that determine an individual's socioeconomic status within a society and, in turn, impacts their access to social factors that either benefit or reduce their health outcomes. This division encompasses governance, macroeconomic policies, social and public policies, and culture and societal values. This systematic review will combine social and public policies due to countries' varying definitions. Socioeconomic position is an indicator on an individual level that determines one's place in society, which includes social class, gender, ethnicity (race), education, occupation, and income.

Socioeconomic and Political Context

The broader structural determinants in the socioeconomic and political context tend to be studied less regarding their relationship with dengue infection. One review observed social determinants of dengue transmission in the “Culture and societal values” domain. Matysiak and Roess (2017) identified the following cultural factors with the emergence and transmission of dengue in Puerto Rico: “social organization,” “gender roles,” “community knowledge, attitudes, and practices (KAP),” and “perceptions of economic, emotional, and health impact.”

According to the WHO SDH conceptual framework, the researchers combined cultural values with behavioral factors, which fall under the umbrella of intermediary determinants. While the WHO defines ‘culture and societal values’ as a separate domain of social determinants from ‘behaviors and biological factors,’ as seen in this article, there can be overlapping determinant themes. Specifically, the findings around community KAP involved reviewing cultural values and individual behaviors.

Social norms surfaced in the knowledge and attitudes assessment, such as different perceptions of the importance of dengue based on gender. On the other hand, the KAP assessments in studies also identified behaviors that protected against dengue infection, including education and implementation of vector control practices (Matysiak & Roess, 2017). The review found behavior change valuable in long-term vector control, yet it is advantageous to understand the cultural values of communities for these behavioral changes to occur.

Carabali et al. (2015) found that increasing government health expenditure (GHE) allowed for expanding population health coverage associated with lower dengue mortality rates. When the private sector was more involved in health coverage, there were "limitations in disease management and consequent worse outcomes" (Carabali et al., 2015, p. 6). Moreover, another study indicated that cities' economic hubs could increase dengue transmission. The researchers defined these findings as the social factor of 'health systems,' which falls into the WHO social determinant category of intermediary determinants. The above findings are also overarching macroeconomics impacting health systems and outcomes.

De Sousa et al. (2021), a previously conducted systematic review, identified a social or public policy associated with the occurrence of a dengue epidemic. Brazil reformed its healthcare system in the 1980s to offer universal healthcare, establishing various healthcare models. The Ministry of Health of Brazil established the Community Health Agent Program (Programa de Agentes Comunitários de Saúde) in 1994, which was later converted to the Family Health Program (Programa de Saúde da Família) to provide primarily vulnerable local communities access to healthcare at home and all community health facilities (Bastos et al., 2017). De Sousa et al. (2021) came across two studies that evaluated the impact of the Family Health Program and the frequency of dengue epidemics. One study found a positive correlation between the number of field supervisors and dengue epidemics. In contrast, another determined a negative correlation between dengue epidemics and the percentage of coverage by field teams (De Sousa et al., 2021). Some reviews assessed studies that included vector control intervention programs as a social factor for dengue. It is unclear whether most of the programs were implemented by the national or local government, and therefore, unable to classify the programs as social or public policies,

One review briefly touched on the potential impact an unstable political environment has on DENV transmission (Khan et al., 2018). Carabali et al. (2015) identified a study that reported dengue as a political issue. However, there needs to be an in-depth review of the relationship between this aspect of governance and dengue infection. Measuring a clear association between government and dengue burden is complex and has yet to be studied. This review revealed the need for unifying definitions or measurements in assessing social determinants in the socioeconomic and political context associated with dengue transmission due to their vastness or complexity.

Socioeconomic Position

Social class

Social class is a determinant defined as an indicator based on the number of productive resources one owns. As a determinant, social class was not identified in any of the studies of the existing reviews as a potential social determinant of dengue. Several systematic reviews acquired many studies evaluating similar indicators of social class as determinants of dengue, but only one found evidence of socioeconomic status as a factor. Mulligan et al. (2015) reported inconclusive findings on the impact of socioeconomic position on dengue or the proclamation that dengue is associated with poverty. Across 12 studies, they found a mixture of positive, null, and negative associations between measures of poverty and dengue, with socioeconomic status as one of the gauges of poverty in some studies.

Gender

Across systematic reviews, there were various findings on the association between sex or gender and multiple measurements of dengue. Carabali et al. (2015) found that a third of studies ruled sex as not playing a role in dengue mortality, which Yuan et al. (2022) also found regarding progression to severe dengue infection after meta-analysis. The other two-thirds of the studies reviewed are divided on the association of gender with dengue mortality, with half observing a higher risk in men and the other half in women. Chagas et al. (2022) similarly found split findings regarding gender and dengue mortality. After conducting a meta-analysis, two systematic reviews (Guo et al., 2017; Khan et al., 2018) found an association between dengue infection and the male gender globally and across Pakistan. Three systematic reviews found a strong association between the female sex and severe dengue or dengue seropositivity after meta-analysis and pooling of data (Emeribe et al., 2021; Huy et al., 2013; Sangkaew et al., 2021). Sangkaew et al. (2021) specifically saw a strong association between the progression to severe dengue and females in older adults. Matysiak and Roess (2017, p. 10) found that gender plays a role in the knowledge and attitudes around dengue such as: "Women considered dengue important because of the burden and impact on society, while men thought it was a serious disease because of an individual's lack of perceived health risk."

Ethnicity

Ethnic group or race as a determinant of dengue incidence or mortality can vary from study to study based on the region or country of interest. In researching ethnicity or race as a social determinant of dengue mortality, Carabali et al. (2015) found that it was either reported as an ethnic group, self-assessment of ethnicity, or country of origin. While some papers reviewed by Carabali et al. (2015) said that all ethnic groups had a similar risk of contracting dengue, others found that Africans or individuals of African ancestry appeared to have a protective effect. Conversely, some studies suggested that severe forms of dengue were more common among Whites. In contrast, others identified Black individuals or those of African ancestry as being particularly vulnerable to dengue mortality. De Sousa et al. (2021) identified one study that found an association between the variable of skin color or race, explicitly being black or brown, and the occurrence of dengue. As the determinant can be based on cultural aspects of a country or region, understanding the relationship between ethnic group or skin color and the incidence of a disease, such as dengue, is complex and not easily quantified.

Education

Education can range in how it is measured or quantified across research investigations to identify a correlation with the disease of interest. The determinant is described across the research as either by individual or household level of education and literacy rate. Two systematic reviews found evidence in a few studies of a correlation between low or lack of education and the risk of dengue infection and mortality (Carabali et al., 2015; Mwanyika et al., 2021). Similarly, Emeribe et al. (2021) found an association between educational level and pooled DENV seropositivity, with the secondary level of education being protective. On the other hand, Mulligan et al. (2015) found null and negative associations between education level as an indicator of poverty and dengue infection.

Interestingly, some studies found that low schooling in low or intermediate socioeconomic areas is linked to lower infection rates. Conversely, high-income areas had higher attack rates and individuals with higher education levels were more likely to be hospitalized due to dengue (Mulligan et al., 2015). Literacy rate as an indicator of education was found to be positively and negatively associated with the incidence of dengue, according to a review by De Sousa et al. (2021). There needs to be a clear consensus on the effects of education level on contracting dengue. However, many of the reviews attribute education and knowledge of dengue can be beneficial in preventing dengue transmission.

Occupation

Occupation as a social determinant of dengue can be complex due to the variety of occupation types and many factors that can play into one's potential contact with mosquitoes that transmit the virus. Two systematic reviews identified occupation status and type as significant risk factors for dengue infection (Emeribe et al., 2021; Mwanyika et al., 2021). Emeribe et al. (2021) found that being employed is significantly associated with DENV seropositivity. The types of occupations related to dengue infection were not provided in Mwanyika et al. (2021)'s review of dengue virus infection and risk factors. Carabali et al. (2015) found three studies identifying no correlation between occupation and a fatal outcome due to dengue. Based on the review's findings, some assumptions can be made about the correlation between occupation type or status and dengue infection based on the review's findings. However, there is still minimal research on the impact of this social factor and dengue transmission.

Income

Mulligan et al. (2015) found income to be one of the more commonly used indicators for a socioeconomic position as it is quantifiable and can be categorized on a country level. However, analyzing the determinant across countries can lead to some uncertainty in distinguishing income levels. Three reviews found studies identifying a positive correlation between income and DENV infection (De Sousa et al., 2021; Mulligan et al., 2015; Mwanyika et al., 2021). Moreover, De Sousa et al. (2021) identified income as a risk predictor of dengue incidence and outbreaks. On the other hand, two reviews found some studies identifying a negative relationship between DENV infection and income level on a household and national scale. Both found those with higher income at higher risk for contracting the disease (Li et al., 2020; Mulligan et al., 2015). Li et al. (2020) found this association correlated with temperature. Mulligan et al. (2015) found an equal distribution of studies finding positive and null associations between income and dengue. Although income is a standard indicator for socioeconomic position, Carabali et al. (2015) did not find any reports researching the association between dengue mortality rates and income. However, socioeconomic status was used as a potential risk factor. With conflicting results, it can be challenging to determine the impact of income as a determinant of dengue infection and transmission.

Intermediary Determinants

Several systematic and scoping reviews have been conducted with a research question focused on the connection between dengue and intermediary determinants. The intermediary determinants focus on behavioral and biological factors, psychosocial factors, material circumstances, and health systems as the primary categorization.

Biological Factors & Behaviors

Age is a biological factor that is one of the most common variables evaluated in research studies. Across six of the systematic reviews on risk factors of dengue, age as a determinant was considered correlated to dengue incidence and mortality (Carabali et al., 2015; Chagas et al., 2022; Huy et al., 2013; Mwanyika et al., 2021; Sangkaew et al., 2021; Yuan et al., 2022). Five of these reviews found a positive correlation between age and either dengue incidence or fatal outcomes, primarily in adults or with older age. Chagas et al. (2022) did not find a significant association (Carabali et al., 2015; Mwanyika et al., 2021; Sangkaew et al., 2021; Yuan et al., 2022). Two of these reviews found younger age to be a risk factor for dengue fever progression and mortality (Carabali et al., 2015; Sangkaew et al., 2021). Another two reviews found that higher hospitalization rates and DENV seroprevalence were identified in adults greater than 30 years of age with no significant association (Khan et al., 2019). Moreover, Guo et al. (2017) determined that the pool mean age of outbreak dengue patients is 30.1 years. In ten studies, Yuan et al. (2022) found no correlation between children and severe progression. On the other hand, one review found a pooled negative correlation between age and dengue shock syndrome (DSS), especially in children. However, it was considered highly variable in adults (Huy et al., 2013). Two of the reviews did note that the age profile and average age of individuals infected with dengue varied from outbreak to outbreak (Guo et al., 2017; Khan et al., 2019). Guo et al. (2017) noted that the mean age in outbreaks after 2010 was more significant than before 2010. Lastly, Carabali et al. (2015) determined that the dengue mortality rate, primarily in the Americas, was reported in adults concerning immunological status, comorbidities, and type of infection. For the most part, it appears that older age can impact the risk of dengue infection, especially the progression of severe dengue. However, it is important to note how valuable contextual demographics are to understanding the role age plays as a determinant of dengue.

Comorbidities are another biological factor that is known to impact the progression of diseases. Most studies primarily focus on diabetes mellitus, followed by cardiovascular diseases, renal disease, and hypertension, as potential risk factors for acquiring a severe case of dengue. Some studies address co-infection as a comorbidity impacting the risk of contracting dengue; however, most research solely examines co-infection separate from social determinants of health. Five out of six systematic reviews found a positive association between diabetes mellitus and the progression of dengue illness or dengue mortality (Chagas et al., 2022; Guo et al., 2017; Mwanyika et al., 2021; Sangkaew et al., 2021; Yuan et al., 2022). Guo et al. (2017) further determined that those with diabetes mellitus, hypotension, or renal insufficiency had higher odds of developing DHF.

Furthermore, patients with pre-existing conditions such as diabetes mellitus and hypertension were at greater mortality risk. Similarly, Sangkaew et al. (2021) found a positive association between diabetes, hypertension, renal disease, and cardiovascular disease with the progression of dengue infection, with the strongest association observed for diabetes and renal disease. However, mixed comorbidities are not associated with severe progression. The sixth systematic review determined inconclusive results for comorbidities as a determinant of dengue mortality (Carabali et al., 2015). The review found the presence of comorbidities was reported in two ways: either as pre-existing conditions like diabetes, hypertension, cardiac disorders, renal transplants, use of anti-platelet drugs, and pregnancy-related conditions, or as illnesses that were confirmed during the dengue infection, such as malaria, bacterial infections, or other diseases. However, the descriptions of these comorbidities were not explicitly identified as determinants for dengue mortality. The presence of multiple diseases or comorbidities can make it challenging to distinguish between them, and they may be regarded as distinct factors contributing to the severity of dengue infection and even mortality.

Another biological factor considered a risk factor for dengue is the individual's nutritional status. Studies range from examining malnourishment to obesity, primarily through measuring body weight or BMI and the potential relationship between dengue incidence and severity. One systematic review’s results suggest a possible association between malnourishment and reduced risk of severe dengue and an association between obesity and increased risk of severe disease. However, these associations were not statistically significant (Sangkaew et al., 2021). Pooling nine studies in another review revealed a positive correlation between malnutrition and DSS

(Huy et al., 2013). Malnutrition and obesity can harm immune function, potentially influencing the severity of dengue infection and transmission dynamics (Weger-Lucarelli et al., 2018). Therefore, assessing their role as risk factors for dengue is essential.

One last biological factor strongly considered as a determinant of dengue burden and severity is the immunological status regarding the type of infection. Primary versus secondary or previous infection can determine the risk of severe or even fatal outcomes of dengue. Carabali et al. (2015) decided that secondary infection is a determinant of dengue mortality. Patients with secondary infections were more likely to experience fatal cases than those with primary infections, with no fatal cases reported. Another systematic review similarly found that secondary infections had higher odds of having dengue hemorrhagic fever (DHF) (Guo et al., 2017). These reviews evaluate the risk of developing severe dengue increases with subsequent infections, specifically secondary infections. Nevertheless, no consideration has assessed the type of infection with the risk of contracting dengue.

Behaviors can significantly impact and determine the risk for health outcomes. As a determinant of dengue, most behaviors evaluated are related to knowledge, attitudes, and practices (KAP) or vector control practices. In a systematic review of the interconnectedness among ecological, cultural, social, and climatic factors in Puerto Rico as determinants of dengue, two studies reported increased KAP of dengue in child-focused intervention and control methods. In comparison, two studies found a correlation between misconceptions about dengue and its incidence in the community. Pre-travel dengue prevention education was also identified as a restorative measure (Matysiak & Roess, 2017).

Additionally, Mwanyika and colleagues (2021) discovered six studies that suggested inadequate mosquito control practices as a possible contributor to dengue transmission.

However, a systematic review found no significant results indicating that a lack of knowledge about dengue connects poverty and dengue. Understanding the connection between behaviors and dengue, particularly relative to knowledge and attitudes, can be challenging to measure and further study.

Another behavior that significantly impacts dengue transmission is travel. Many studies have reviewed the impact of travel on contracting dengue if traveling from a non-endemic area to an endemic region. Our review focuses on social determinants for individuals in endemic areas so that travel history will be evaluated. Only one systematic review found the recent travel history between epidemic and endemic areas as a potential risk factor for dengue infection in Africa. The researchers note that infected people traveling throughout Africa have introduced new strains of DENV into parts of Africa that previously did not see these strains (Mwanyika et al., 2021).

Psychosocial Factors

Social-environmental or psychosocial factors include psychosocial stressors, stressful living conditions, social support (or lack thereof), and coping styles. These factors are experienced to varying degrees by different social groups and can cause feelings of fear and difficulty in managing daily life. Marital status is one social determinant that can be easily quantified and measured, indicating social support or potential stress. Across the three relevant studies, Emeribe et al. (2021) found that married individuals had a considerably higher risk of DENV immunoglobulin G (IgG) pooled antibody seroprevalence compared to single persons. In exploring the relationship between marital status and dengue, marriage has been a factor in behaviors and practices around dengue (Wong et al., 2015). More social-environmental aspects concerning dengue incidence or seroprevalence and severity deserve further exploration.

Material Circumstances

For dengue illness burden and severity, material circumstances include living and working conditions, environmental factors, and ecological factors that impact interaction with the mosquito vector. In the realm of living and working conditions, most reviews identified variables on living conditions over working conditions. One of the most common determinants analyzed was residing in either urban or rural areas. The main finding across reviews was that living in a rural area was more protective compared to a higher risk for dengue incidence and severity of living in urban areas (De Sousa et al., 2021; Emeribe et al., 2021; Mwanyika et al., 2021). Moreover, Khan et al. (2019) found increased urbanization to be a risk factor for residents contracting dengue with unplanned urbanization, increasing the disease's emergence. Some articles reviewed found a positive correlation between the existence of highways and marginal roads to dengue epidemics (De Sousa et al., 2021). In addition to urbanization, higher population density, overcrowding, and a high number of residents in households were noted in two reviews to be positively associated with dengue epidemics and incidence (De Sousa et al., 2021; Khan et al., 2019; Matysiak & Roess, 2017; Mulligan et al., 2015). One article reported a negative association between rural residence and dengue epidemics, contrasting most findings (De Sousa et al., 2021).

Structural conditions were also reviewed in varying methods across reviews and research but were found to be the most poorly defined and measured determinate in one review. Structural factors were relatively equal to positive and null results when considering the absence of air conditioning, poor housing qualities, and standard of living (Mulligan et al., 2015). Furthermore, Khan et al. (2019) found reports that living in a single-story home with many residents increased the risk of dengue.

Another important factor impacting dengue transmission is access to water and sanitation. Across reviews, water containers without proper coverage were positively correlated with dengue and addressed as a significant risk factor (Emeribe et al., 2021; Guo et al., 2017; Mulligan et al., 2015). Regarding access to regular water supply and sewage infrastructure, there were mixed results between positive and null findings regarding the risk of dengue from study to study (Khan et al., 2019; Mulligan et al., 2015). Other living conditions considered in research around dengue but should be further studied include the proximity to parks and waste dumpsites, land use, deforestation, and an influx of refugees (De Sousa et al., 2021; Emeribe et al., 2021; Khan et al., 2019). Many risk factors related to one's physical environment have been considered. Still, a significant barrier is a need for unified definitions and measurements to comprehensively analyze the relationship between dengue and these determinants.

The two most common categories used across research to address the environmental determinants are climate and ecology. Throughout the systematic reviews, temperature and precipitation were two factors that were positively associated with and greatly influenced the risk of dengue (De Sousa et al., 2021; Fan et al., 2014; Hii et al., 2016; Khan et al., 2019; Li et al., 2020; Matysiak & Roess, 2017). Fan et al. (2014) found that the climate temperature range with the highest risk for dengue is 22°C to 29°C. Dengue risk decreases when the temperature is outside of this range. Although the consensus across reviews is that rainfall and even humidity impact the risk of contracting dengue, some research was inconsistent with these findings (Hii et al., 2016).

Moreover, the relationship between temperature or precipitation and dengue incidence was found to vary spatially based on the climate of each region in Puerto Rico and Pakistan (Khan et al., 2019; Matysiak & Roess, 2017). Subtropical regions face a higher dengue risk than tropical regions (Li et al., 2020). Seasonality was also a risk factor for dengue transmission, with Khan et al. (2019) finding the highest number of cases occurring between July and September. Matysiak and Roess (2017) found that for every one °C increase in sea surface temperature, dengue transmission was determined to increase by a factor of 3.4. However, the incidence of dengue, despite global warming, has been constant. On the other hand, Mwanyika et al. (2021) determined that climate change is a significant risk factor for dengue risk across 21 studies.

Only two systematic reviews explored the ecological factors of the vector as a determinant of dengue. De Sousa et al. (2021) found a positive association between the incidence of dengue and the number of eggs in ovitraps and the entomological indices determined by the researchers. Mulligan et al. (2015, p. 16) determined null findings between the “spatial distribution of recent infections and mosquito density by income areas.” A third systematic review did identify many factors that contribute to a high population of Ae. aegypti in local water sources but did not analyze those factors with dengue incidence and transmission.

Health Systems

Health systems play a significant role as a social determinant in health outcomes. They can reduce disparities by improving fair access to care and promoting intersectoral efforts to improve health (Solar & Irwin, 2010). In the case of dengue, surveillance contributes to a health system and the effectiveness of the system in identifying and treating those with the disease. Matysiak and Roess (2017) found that the significance of Puerto Rico's surveillance system was emphasized in multiple articles as a factor for the detection of dengue emergence and transmission on the island. The surveillance system used in Puerto Rico consists of passive and active surveillance. The passive component is a laboratory-based system called the passive dengue surveillance system (PDSS). In contrast, the active part involves diagnostic testing and the collection of serum samples from individuals suspected of having dengue fever. One article "concluded that the island's enhanced surveillance system allowed for a more accurate, population-based estimate of dengue incidence and severity" (Matysiak & Roess, 2017, p. 8).

Moreover, it was emphasized in a. couple of articles the need for virologic and entomologic surveillance in accurately detecting and diagnosing dengue. In another systematic review of risk factors for dengue epidemics in Brazil, surveillance was also crucial in predicting dengue epidemics and incidence in the country at the time of diagnosis and the disease registry of importance (De Sousa et al., 2021). This review focused more on risk factors associated with the Family Health Program mentioned earlier. Some articles identified that the ability of those with dengue to receive the health assistance needed by field agents or lack thereof significantly increased the likelihood of a dengue epidemic (De Sousa et al., 2021). Access to healthcare and accurate diagnostic tools prevent transmission and provide adequate care. Surveillance and public health programs can make or break a health system in successfully identifying, preventing, and responding to dengue infections. To reduce health inequalities, the health system needs to play a more active role in establishing public health initiatives and collaborating with other policy entities to improve the well-being of underprivileged communities (Benzeval, 1995).

Conclusion

In the past two decades, understanding the social factors linked to dengue infection has yet to be rigorously and systematically studied. Reviewing the existing data is necessary to probe what is known about the relationship between social determinants and dengue infection. By examining the current data collected from global research studies, the social determinants of dengue infection that have been characterized thus far can be realized across continents and borders. Previous analyses of social determinants of dengue conducted only focused on specific regions and countries or with a narrow scope (Fan et al., 2014; Matysiak & Roess, 2017). A foundational study of the social determinants of health of dengue burden and severity, in its entirety, has yet to be conducted. Utilizing the conceptual framework of SDH by the WHO would provide a practical guide in designing research studies to better understand the fundamental social factors influencing the global burden of dengue.

3. METHODS

Selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for the following review. The inclusion criteria for the review included observational studies of children, adults, and pregnant women that address the relationship of SDH with seroprevalence (IgG) of DENV only. Articles from all countries and regions were included as well as any in English and Spanish. The exclusion criteria included excluding articles where the data on seroprevalence was only in percentages. Many studies included were cross-sectional, with only four identified as cohort studies.

Search Strategy

The databases Pubmed, Web of Science, and Embase was utilized to search for all studies. The following search strategy and keywords were used in the search strategy of studies: (Dengue) AND ("risk factors" or "Social Determinants of Health" or "health disparities"). The search returned over 3,000 research articles; all databases were last consulted in January 2023. Covidence, a screening and data collection tool, was utilized to determine whether a study met the inclusion criteria during the title, abstract screening, and full-text review. Two reviewers independently screened and reviewed each study, and the consensus of conflicting conclusions was resolved with input from a third reviewer.

Data collection and analysis

Covidence was further used for the data collection process. Two reviewers independently collected data from the remaining articles. One of the reviewers evaluated and resolved any data discrepancies in the data collection process. During this process, articles were excluded if there was no data on the variables or indicators of interest to be used in the data analysis.

The primary outcome for which data were sought was DENV seroprevalence counts. Total seroprevalence, the seroprevalence, and the total count of each variable of interest were collected. Initially, numeric data on the following variables was pulled: age, gender, education level, income level, social class, employment status, urban-rural status, and marital status. Variables related to the subcategories of interest in the WHO SDH conceptual framework and their levels, if applicable, were reported in data collection. After exporting the data, these variables were reviewed to determine overlapping variables from the research. The following variables were reviewed, and the data was added for analysis: bed net use, insecticide spraying, and stagnant water. All studies utilized questionnaires or surveying of the environment by field teams to collect data for each social determinant. Thus, only quantitative data on the counts based on questionnaire responses and positive or negative DENV IgG results were analyzed.

The data was cleaned removing studies with missing data before data analysis and tabulated to include seropositive and seronegative totals for each dichotomous variable. Variables with two or fewer studies were excluded from the analysis, which included social class and age. Due to varying ranges used by studies and preliminary studies reporting the mean or median age of seropositive prevalence, age was excluded from the analysis. Studies with missing data on a variable were excluded from the analysis. Due to the small number of cohort studies, analysis was conducted without grouping by study type. The variables education and income were combined to provide two levels for the meta-analysis. The primary, secondary, and tertiary education levels were consolidated and labeled as 'any education' to compare no education to any education in the analysis. Income had three levels that were not easily divisible. To compare the differences between low and high income on DENV seroprevalence, low income was compared to middle- and high-income combined while high-income was compared to low- and middle-income.

The statistical analysis was conducted utilizing RStudio software, version 2022.12.0+353, with the ‘metafor' package. A meta-analysis of random effects was conducted to estimate the pooled odds ratio (OR) with a 95% confidence interval (CI) of the outcome, prior dengue infection, and social determinants (Viechtbauer, 2010). Forest plots for each variable with three or more studies worth of data were produced to visualize the outcome. To conduct a sensitivity analysis, studies with high bias, a 1–4-star rating from Observational Study Quality Evaluation

(OSQE), were removed from the initial meta-analysis model. Publication bias was further evaluated for each social determinant analyzed with funnel plots.

The default restricted maximum-likelihood (REML) estimator was used to determine heterogeneity and consistency of studies by variable providing I^2 and Q test statistics. The I^2 statistic was provided as a percentage with substantial heterogeneity falling between 50-75% and considerable heterogeneity greater than 75%. Meta-analyses and tests for heterogeneity were only conducted when a variable had three or more studies with viable data.

Study quality and risk of bias

The studies included in the current analysis were all observational; thus, a tool assessing the quality of observational studies was utilized. The OSQE tool template was selected as the ideal method to evaluate the studies (Drukker et al., 2021). Each study was scored by a summary of stars with cross-sectional studies evaluated with 7 criteria and cohort studies with 14 criteria. Criteria on effect modifiers and sample size are optional and were excluded in the assessment of the studies as the meta-analysis accounted for effect size. Thus, the highest rating a cohort and cross-sectional study could receive was 13 and 8, respectively. One reviewer assessed the quality of the studies independently, with a second aiding in determining bias levels. We determined that high-bias studies had 1-4-star ratings, some bias as 5-7-star ratings, and low bias with eight or more-star ratings. These levels determined what studies to exclude from the sensitivity analysis.

4. RESULTS

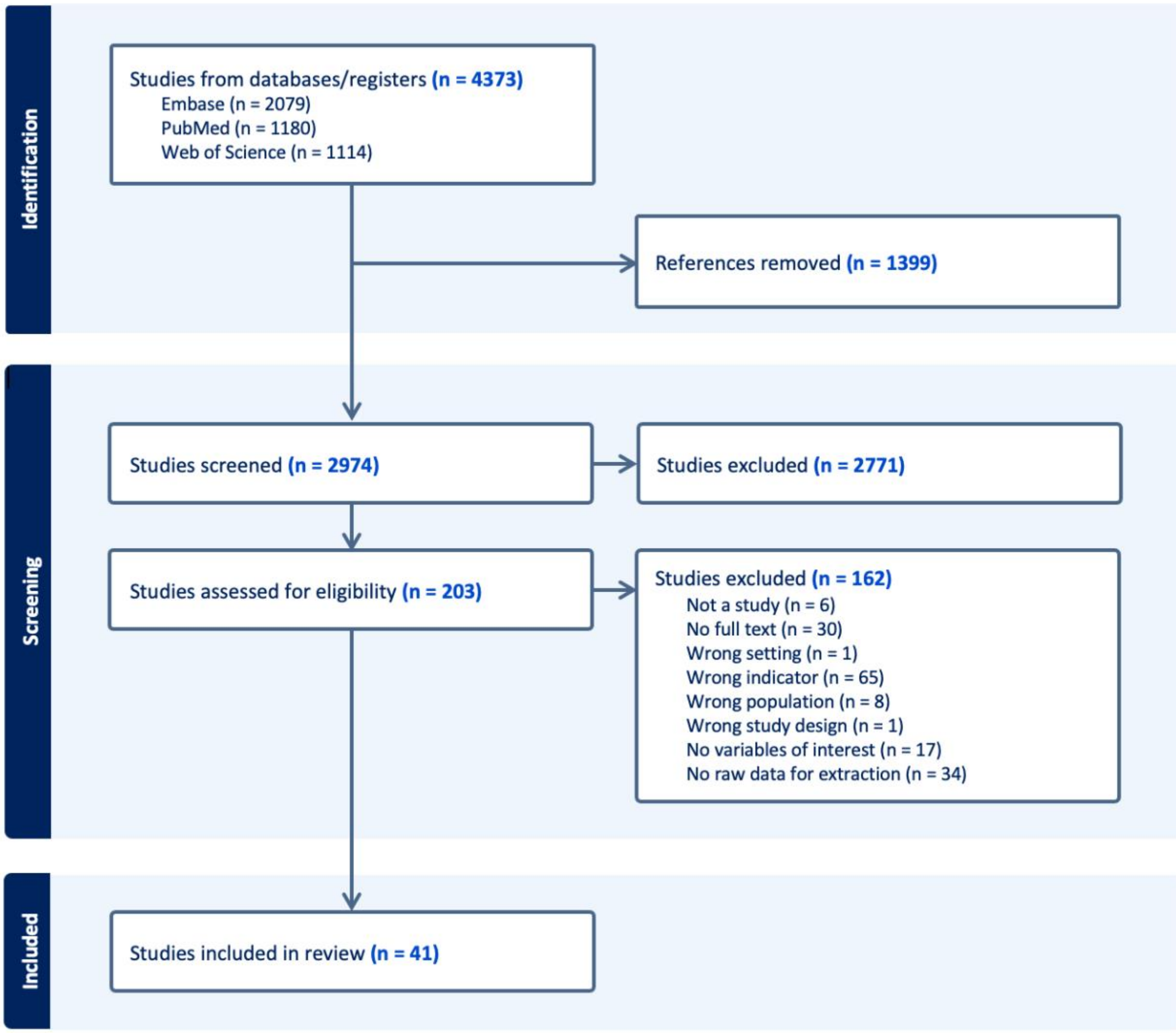

Figure 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the selection of studies.

The initial search of studies resulted in 4,373 published manuscripts. After duplicates were removed and the screening of titles and abstracts, 203 studies were assessed by full text for eligibility. The final count of 41 manuscripts was included in data collection and quality assessment (**Figure 2**).

Table 1. Characteristics of the included studies

Author (Year)	WHO Region	Country	Study Design	Study Year	Sample Size	Total Seroprevalence	Male Total Count	Female Total Count
Braga et al., 2010	Americas	Brazil	Cross sectional	2005-2006	2819	2381 (84%)	1220	1601
Mwanyika et al., 2021	Africa	Tanzania	Cross sectional	2018	1818	292 (16%)	829	989
Obaidat & Roess, 2018	Eastern Mediterranean	Jordan	Cross sectional	2015-2016	892	219 (25%)	345	546
Eldigail et al., 2018	Africa	Sudan	Cross sectional	2016-2017	701	334 (48%)	419	282
Mai et al., 2018	Western Pacific	Vietnam	Cross sectional	2011	1,485	308 (21%)		
Eshetu et al., 2020	Africa	Ethiopia	Cross sectional	2016	529	133 (25%)	226	303
Sacramento et al., 2018	Americas	Brazil	Cross sectional	2015	280	62 (22%)	116	164
Dhar-Chowdhury et al., 2017	Southeast Asia	Bangladesh	Cohort	2012	1125	900 (80%)	487	638
Chien et al., 2019	N/A	Taiwan	Cross sectional	2015	1391	242 (17%)	586	805
Dhanoa et al., 2018	Southeast Asia	Malaysia	Cross sectional	2015	277	240 (87%)	116	161
Telle et al., 2021	Southeast Asia	India	Cohort	2013	2098	711 (34%)		
Siqueira et al., 2004	Americas	Brazil	Cross sectional	2001	1589	506 (32%)	519	1066
Omatola et al., 2021	Africa	Nigeria	Cross sectional	2019	200	43 (22%)	78	122
Geleta, 2019	Africa	Ethiopia	Cross sectional	2016	519	119 (23%)	266	253
Jing et al., 2019	Western Pacific	China	Cross sectional	2015	850	56 (7%)	393	457
Chiaravalloti-Neto et al., 2019	Americas	Brazil	Cross sectional	2015-2016	1347	986 (73%)	521	801
Al-Raddadi et al., 2019	Eastern Mediterranean	Saudi Arabia	Cross sectional	2016-2017	6596	1710 (26%)	3846	2551
Al-Azraqi et al., 2013	Eastern Mediterranean	Saudi Arabia	Cross sectional		965	306 (32%)	672	293
Doum et al., 2020	Southeast Asia, Western Pacific	Thailand and Laos	Cross sectional	2018-2019	975	897 (92%)	323	652
Garg et al., 2017	Southeast Asia	India	Cross sectional	2011-2012	2591	1525 (59%)		
Piedrahita et al., 2018	Americas	Colombia	Cohort	2010-2012	1788	962 (54%)	867	921
Ferede et al., 2018	Africa	Ethiopia	Cross sectional	2016-2017	600	126 (21%)	394	206
Yew et al., 2009	Western Pacific	Singapore	Cross sectional	2004	4152	2449 (59%)	2058	2094
Reiskind et al., 2001	Americas	Peru	Cross sectional	1996	1225	361 (29%)	551	674
Pavía-Ruz et al., 2018	Americas	Mexico	Cross sectional	2014	1667	1227 (74%)	632	1035
Salje et al., 2019	Southeast Asia	Bangladesh	Cross sectional	2014-2015	5866	1403 (24%)	2821	3044
Low et al., 2015	Western Pacific	Singapore	Cross sectional	2009-2010	3627	1885 (52%)	1753	1874
Amaya-Larios et al., 2014	Americas	Mexico	Cohort	2011	929	713 (77%)	381	547
Ochieng et al., 2015	Africa	Kenya	Cross sectional	2007	1091	143 (13%)	430	661
Khor et al., 2020	Western Pacific	Malaysia	Cross sectional		872	43 (5%)	374	498

Author (Year)	WHO Region	Country	Study Design	Study Year	Sample Size	Total Seroprevalence	Male Total Count	Female Total Count
Wang et al., 2021	Western Pacific	China	Cohort	2016	2076	46 (2%)		2076
Shauri et al., 2021	Africa	Tanzania	Cross sectional	2020	180	68 (38%)	171	9
Hoque et al., 2022	Southeast Asia	Bangladesh	Cross sectional	2018	695	349 (50%)		
Hussen et al., 2020	Eastern Mediterranean	Egypt	Cross sectional	2019	91	11 (12%)	57	34
Sawadogo et al., 2020	Africa	Burkina Faso	Cross sectional	2016	1007	721 (72%)	638	369
Muhammad et al., 2016	Eastern Mediterranean	Pakistan	Cross sectional	2012	302	171 (57%)	242	60
Jamjoom et al., 2016	Eastern Mediterranean	Saudi Arabia	Cross sectional		1939	927 (48%)	656	1280
Brown et al., 2009	Americas	Jamaica	Cross sectional		277	277 (100%)	105	172
Vairo et al., 2014	Africa	Tanzania	Cross sectional	2011	500	253 (51%)	486	14
Rodríguez-Barraquer et al., 2015	Southeast Asia	India	Cross sectional	2011	800	744 (93%)		
Lee et al., 2021	N/A	Taiwan	Cross sectional	2010	1308	284 (22%)	517	791

The studies were conducted from 2001 to 2021, with most published between 2018 and 2021 (n=28; **Table 1**). One study conducted point-prevalence surveys over three consecutive years, which were analyzed as three separate observations. All studies included research on the seroprevalence of DENV IgG antibodies utilizing either enzyme-linked immunosorbent assay (ELISA, n=35), indirect immune fluorescent test (IIFT, n=2), or rapid diagnostics test (RDT, n=3). Most of the studies were cross-sectional, with only 5 having a cohort study design.

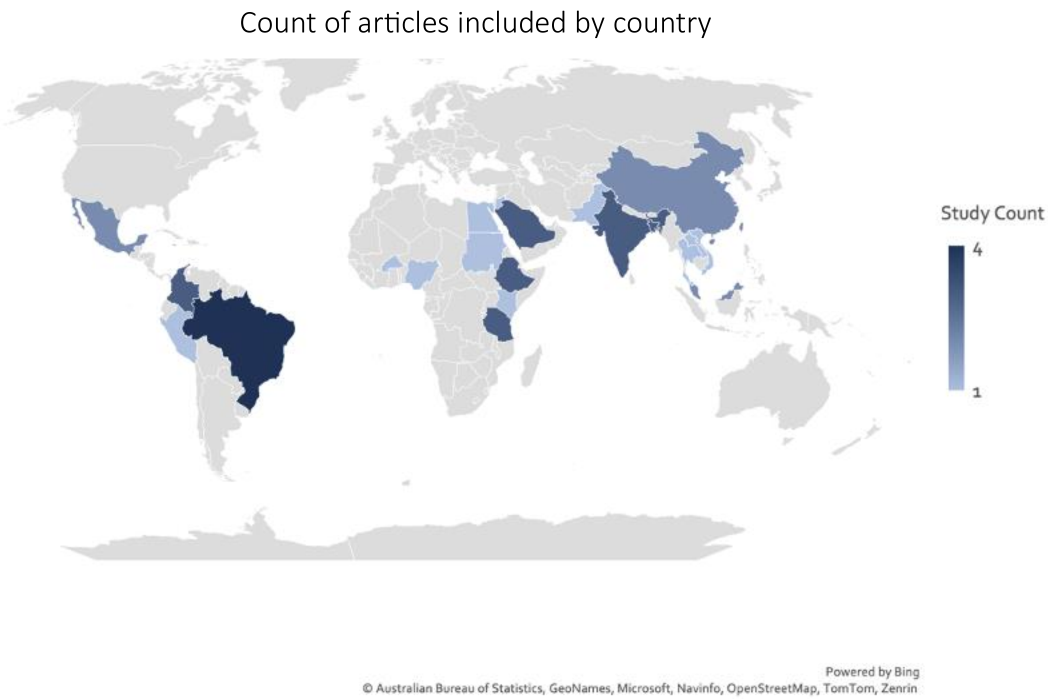

Figure 3. Map showcasing the number of articles per country included in the review.

The research included extended globally coming from the following WHO Regions: Africa (n=10), the Americas (n=11), Eastern Mediterranean (n=6), Southeast Asia (n=8), and Western Pacific (n=7). Two studies were from the non-member state of Taiwan. Included studies were conducted in 24 countries: Bangladesh (n=3), Brazil (n=4), Burkina Faso (n=1), China (n=2), Colombia (n=3), Egypt (n=1), Ethiopia (n=3), India (n=3), Jamaica (n=1), Jordan (n=1), Kenya (n=1), Malaysia (n=2), Mexico (n=2), Nigeria (n=1), Pakistan (n=1), Peru (n=1), Saudi Arabia (n=3), Singapore (n=2), Sudan (n=1), Taiwan (n=2), Tanzania (n=3), Thailand (n=1), Laos (n=1), and Vietnam (n=1) (**Figure 3**).

Table 2. Number of studies with SDH indicators of interest

SDH Indicators	No. of Studies	Variables
<u>Structural Determinants</u>		
Socioeconomic and Political Context		
Governance	0	
Macroeconomic Policies	0	
Social and Public Policies	1	Insecticide spraying (fogging) in street; Insecticide spraying inside house by municipality workers
Cultural and Societal Values	8	Dengue education in past 2 years; Awareness campaigns; Flyers distribution; Heard of dengue; Frequency of mosquito control awareness or education; Awareness of dengue
Socioeconomic Position		
Social Class	4	SES typology; Socioeconomic status; Wealth quintiles
Gender	36	Sex; Gender
Ethnicity (racism)	7	Ethnicity; Self-reported ethnic group; Ethnic group; Race; Nationality
Education	15	Education; Highest education; Education level; Highest level of education completed; Schooling; Household head education; Maternal education; Literacy
Occupation	17	Occupation; Job; Main work status over last 12 months; Maternal occupation; Work (yes/no); Main activity
Income	9	Family income; Household income; Head-of-household income; Income (minimum salaries - MS); Yearly income per capita; Monthly income (BDT)
<u>Intermediary Determinants</u>		
Material Circumstances (Living and Working Conditions, Food Availability, etc.)		
Living conditions		Type of household; Persons per room; Sampling setting; Has garden; Densely inhabited area within 50 m of the household; Residing in masonry house; Insect protection at home; Number of indoor potted plants; Place; Type of housing; Number per bed; Livestock ownership; Used tires around home; Stream near home; Grasses around home; Hours at home (per day); Number of residents; Number of rooms; Number of occupants by household; Pest control works; Duration of living in residence; Window screen; Country; Province; Type of residential premises; Floor level; City; Electricity in home; Air-conditioner use; Contact with camels; Presence of uncovered flower vases; Presence of stagnant water in fountains or swimming pools; Presence of open water tanks in nearby construction sites; Water accumulation from air conditioners; Stagnant water in animal pits; Locality; Trees around compound
	29	
Sanitation		Connected to public water supply; Regular water supply; Water containers at residence; Sewage disposal; Garbage collection; Stagnant water; Piped water; Municipal water; Presence of clean water container; Presence of stagnant water in the village; Water supply; Habit to store water; Waste destination; Number of uncovered water tank outdoor; Colony level tap water access; Uncovered containers around home; Water interruption; Sanitation; Indoor piped public water supply; Connected to public sewer; Indoor or outdoor water storage; Water source; Access to water in home; Overflow of sewage water; Water storage in tanks and containers in house; Coverage of water containers; Any stagnant water in house; Use of rainwater collection cisterns; Any use of filtered water
Vector ecology		Mosquito larvae observed in water pooled in old tires, Mode of transmission; Presence of mosquitos in the home; Reproduction foci at home; Breeding sites; Presence of mosquitoes inside house; Presence of mosquitoes outside house
Urban-rural status	13	Study site; Residence; Urban vs. Rural
Climate	1	Season; Ecological zone; Lives in a dry climate; Lives in a rainy climate

SDH Indicators	No. of Studies	Variables
Behaviors and Biological Factors		
Age	39	
Comorbidities	4	Chronic disease (hypertension, diabetes, etc.); Presence of breakbone fever; Comorbidity; No. of medical illness; Hypertension; Diabetes; High cholesterol; Asthma; High blood pressure; Hematologic disease; Heart disease; Liver disease; Kidney disease; History of previous dengue; Previous confirmation of dengue
Behaviors	21	Commutes outside study area for school or work; Mosquito net use; Visiting mines; Never travelled abroad; Ever travelled abroad; Practices agriculture; Sleeping outdoor; Mosquito control; Types of shirts worn in the evening; Types of shirts worn during sleep; Habit of staying outside at the night; Recent mosquito bite; Attendance in public gatherings; Types of mosquito control measure; Any family member suffered from febrile illness within last 6 months; Use of insecticide; Repellent use; Know the transmission vector of DENV; Pest control works by occupant; Any kind of larval mosquito control; Any kind of adult mosquito control; Frequent mosquito biting; Indoor insecticidal spraying; Keeping animal at home; Animal slaughter; Seasonal migrant laborer; History of travel to abroad; Reported having had dengue; Last time left community; Previous exposure with DENV;Us of mosquito coils; Exercise; Vitamin consumption; Vegetable consumption; Sleeping practice; Always lived in same neighborhood
Psychosocial Factors	5	
Health System	0	

Structural Determinants

Socioeconomic and Political Context

No studies addressed variables for the structural determinants of governance and macroeconomic policies (**Table 2**). One study included a variable where the municipalities implemented insecticide spraying by municipality workers in the streets and the houses. It also considered access to municipality-provided water and sewage. This was the only study that considered the impact of social and public policies on water and sanitation and the implementation of insecticide use on dengue seroprevalence (Jamjoom et al., 2016).

Cultural and societal values were explored in eight studies with variables related to dengue or mosquito control education and awareness campaigns (n=3), heard of dengue (n=2), awareness of dengue disease (n=2), and knowledge of the vector of DENV (n=1). Due to varying definitions and denotations of response, no analysis was conducted to compare the outcomes of these variables.

Socioeconomic Position

Social class, for this review, was considered any variable termed as 'social class,' 'social status', 'social stratum', or 'socioeconomic status' based on the WHO CSDH framework (Solar & Irwin, 2010). Four studies referred to social class; only two were defined as 'socioeconomic status' for data collection. The other two studies created indexes with at least five categories to interpret the level of wealth or social class. Doum et al. (2020) found low socioeconomic status protective compared to high socioeconomic status, which was statistically significant (OR 0.53; 95% CI=0.29-0.99; $p = 0.046$). On the other hand, Piedrahita et al. (2018), after analyzing the 2010 survey, high and middle socioeconomic status are protective compared to low socioeconomic status with high as the most protective (OR 0.53; 95% CI=0.36-0.77). For the survey conducted in 2011, middle and high socioeconomic status were protective but not statistically significant. The survey conducted in 2012 only had data comparing low and middle socioeconomic status with a higher odds risk for middle socioeconomic status compared to low with statistical significance (OR 1.37; 95% CI=1.0-1.85).

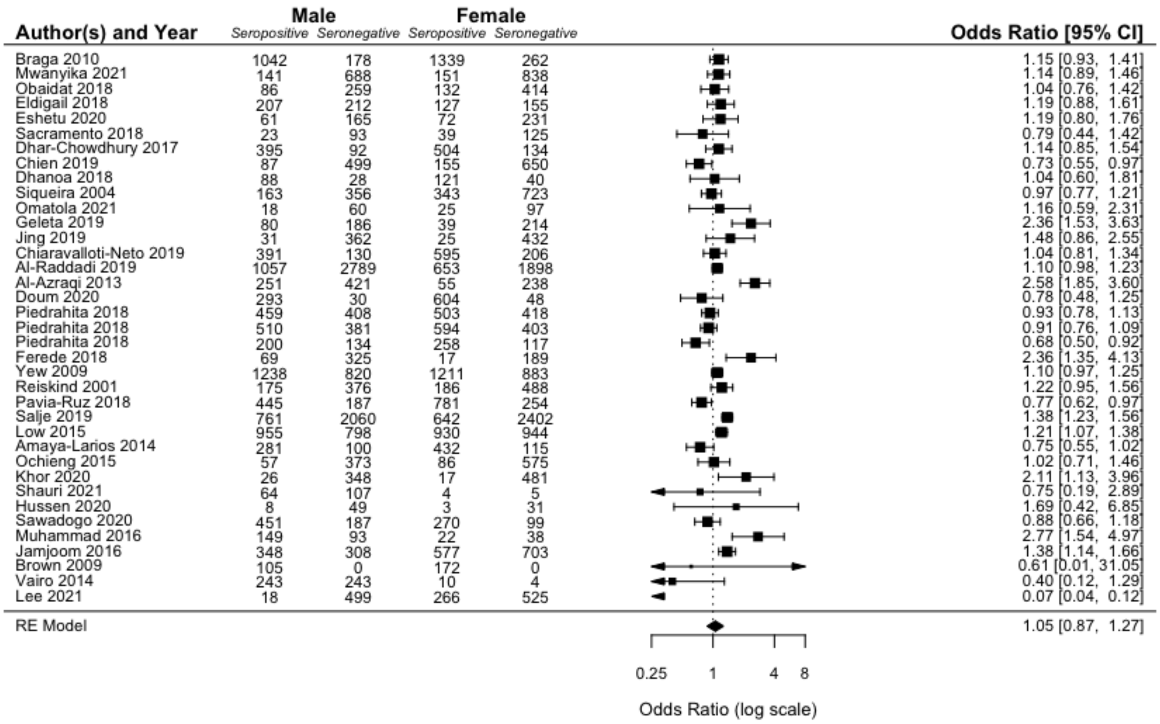

Figure 4. Meta-analysis of the association of sex and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

The social determinant, sex or gender, was evaluated by 35 studies, with one study accounting for three observations. One study considered only pregnant women and was not included in the meta-analysis. Four studies found the odds of risk of dengue as protective for males statistically significant, while eight found the odds of risk of dengue as harmful for males statistically significant (**Figure 4**). Males were found to have slightly higher odds for risk of seropositivity; however, it was not significantly associated with dengue seropositivity in either males or females (OR 1.05; 95% CI=0.87-1.27). Even after a sensitivity analysis, the risk of seropositivity in males compared to females hardly changed (OR 1.06; 95% CI=0.88-1.27; see Appendix A). The heterogeneity of the studies varied between 94.39% to 94.55% before and after sensitivity analysis, respectively (see Appendix B).

Regarding studies including a variable on ethnicity or accounting for racism, seven studies accounted for the indicator by referring to ethnic groups (n=3) or nationality (n=3). These studies were in the following countries: Saudi Arabia, Brazil, Malaysia, Thailand, Laos, Taiwan, Colombia, and Singapore. Ethnic groups were appropriate for the region of interest in the study. At the same time, variables on nationality were primarily considered those who identify with the nationality or as a citizen versus immigrants. Due to differences in ethnic groups and nationalities considered by country, these studies could not be compared in the meta-analysis. One study, Chiaravalloti-Neto et al. (2019), considered race in a neighborhood of São Paolo, Brazil, and compared whites to non-whites finding a significant association between risk of dengue seropositivity and race (OR 1.42; 95% CI=1.08-1.89).

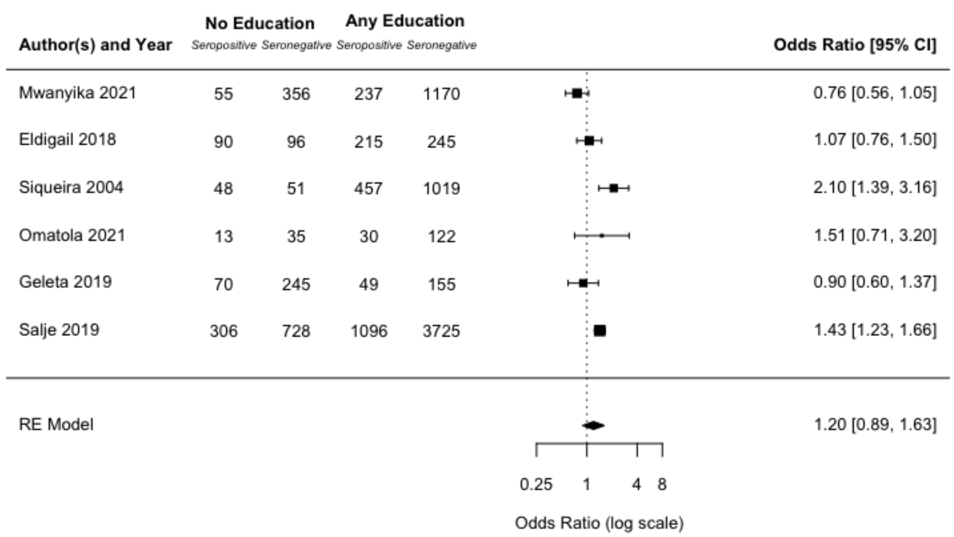

Figure 5. Meta-analysis of the association of education and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

Education was evaluated in six studies. For the analysis, no education was compared to any education to determine if there is a significant difference between the two. Two studies found the odds of dengue seropositivity higher in those with no education compared to any education with statistical significance (**Figure 5**). Overall, there is no significance between no education or any education across studies although having any education appears to be protective (OR 1.20; 95% CI=0.89-1.63). The heterogeneity was high across the studies with an I^2 statistic of 79.04% (see Appendix B). All six studies included had moderate bias; therefore, a sensitivity analysis was unnecessary.

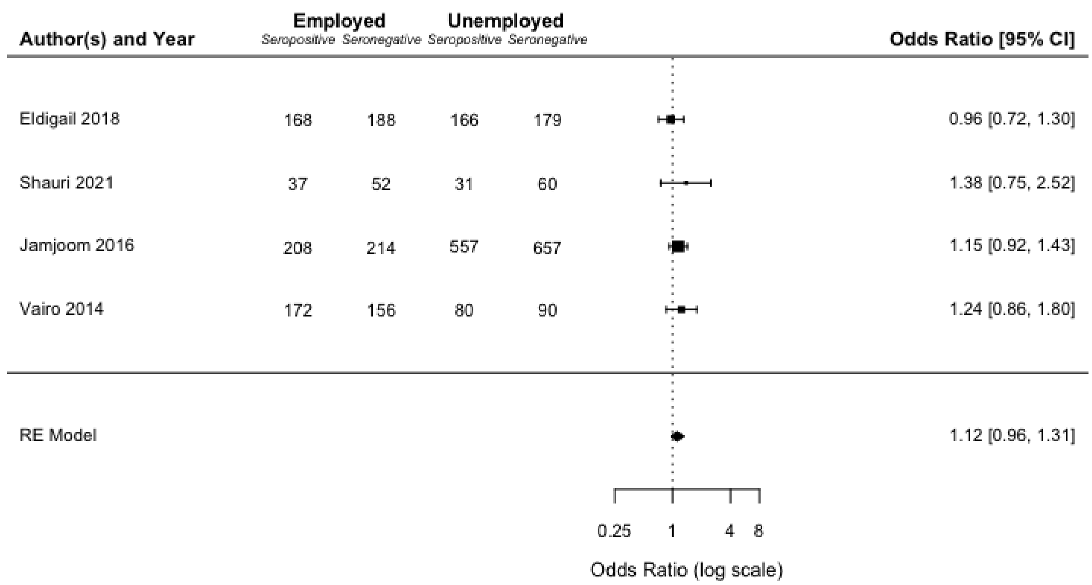

Figure 6. Meta-analysis of the association of employment status and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

The occupation variable was considered in 14 studies; however, consistent definitions were only used in 4. Most studies considered multiple types of occupations in the data collection process, such as farmer, student, civil servant, homemaker, and industry worker, to name a few. Occupation types by study varied based on the region or country of interest. The studies pulled for analysis considered occupation as employed or working vs. unemployed or not working. None of the studies found employment to be associated with dengue seropositivity, and overall, there was no statistical significance in the risk of dengue based on employment (OR 1.12; 95%

CI=0.96-1.31; **Figure 6**). The I^2 test statistic is 0% indicating no evidence of significant heterogeneity among the studies, and any differences are due to chance (see Appendix B).

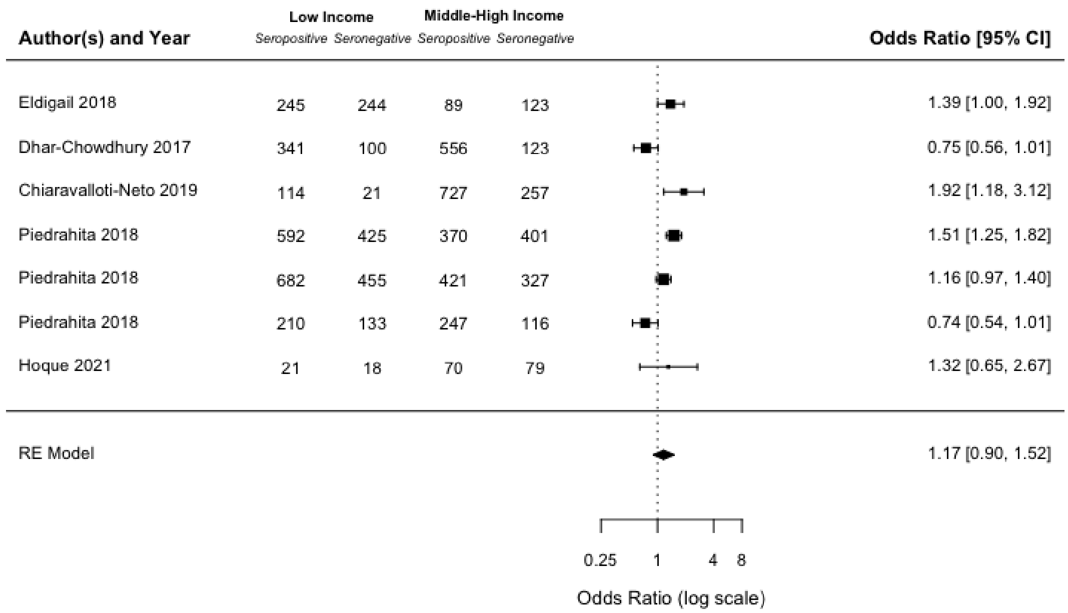

Figure 7. Meta-analysis of the association of low income and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

Levels of income were evaluated in nine studies. Five studies had consistent low, middle, and high-income levels, with one covering three observations and being included in the analysis. The first round of analysis compared low-income to middle-high income, where the overall association of low income and dengue seropositivity is insignificant (OR 1.17; 95% CI=0.90-1.52). Three of the observations assessed determined statistical significance in the odds of dengue seropositivity higher than those with middle-high income (**Figure 7**). After a sensitivity analysis, the odds ratio increased by 0.1, but the association was still insignificant (OR 1.26; 95% CI=0.95-1.68; see Appendix A). Heterogeneity was high in both analyses, with the I^2 test statistic as 81.59% in the preliminary analysis and 82.43% in the sensitivity analysis (see Appendix B).

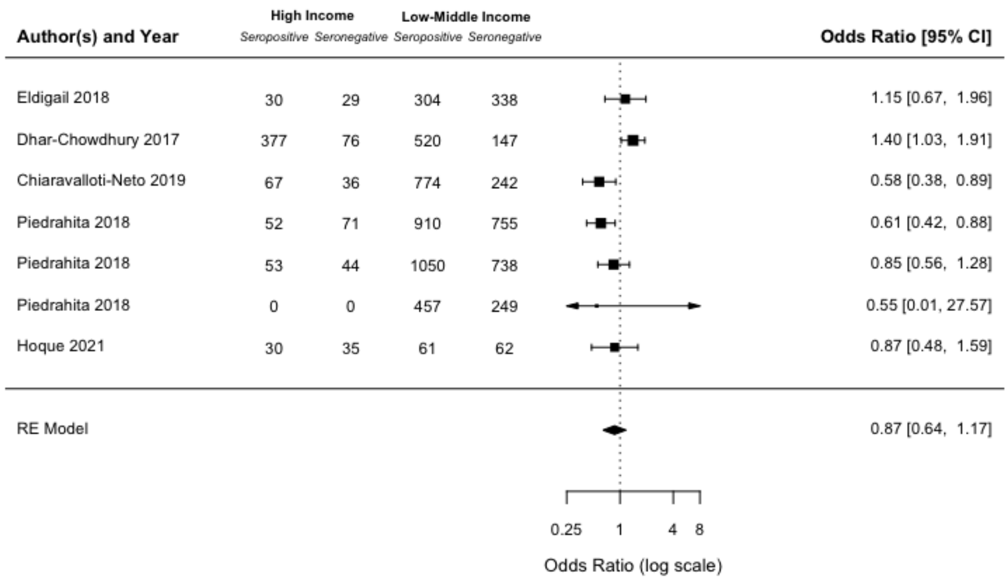

Figure 8. Meta-analysis of the association of high income and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

When comparing high-income to low-middle income, overall high income was protective; however, not statistically significant (OR 0.87; 95% CI=0.64-1.17). One study found dengue seropositivity to be higher in those with high income compared to low-middle income statistically significant (**Figure 8**). After the sensitivity analysis, the odds ratio did not change (OR 0.87; 95% CI=0.61-1.23; see Appendix A). Both analyses had substantial heterogeneity with the I^2 test statistic increasing from 63.07% to 74.17% after sensitivity analysis (see Appendix B).

Intermediary Determinants

Material Circumstances

Variables related to the living and working conditions and one's environment ranged from housing type and the number of occupants to water and sanitation (**Table 2**). Only two variables related to one's material circumstances had consistent definitions: urban-rural status (n=13) and stagnant water (n=5).

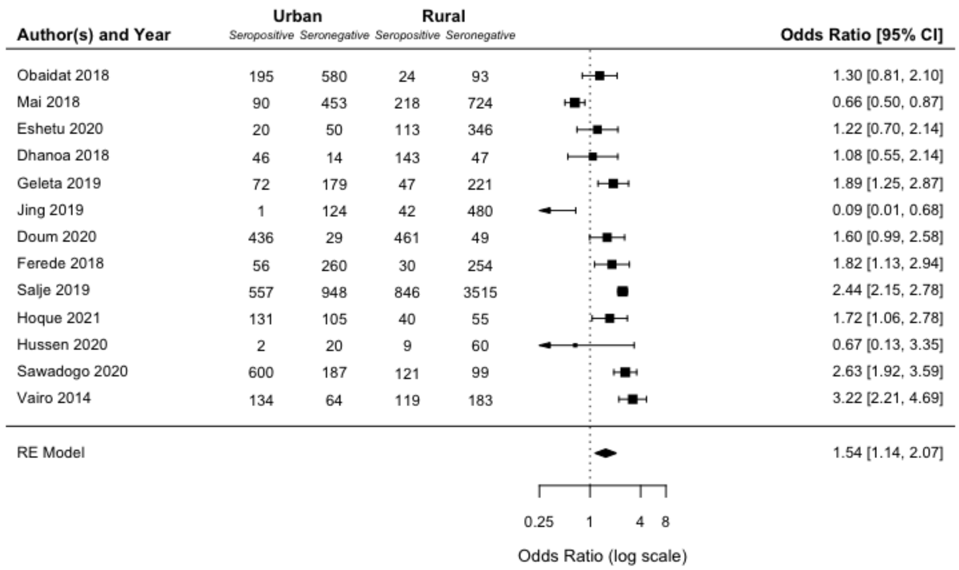

Figure 9. Meta-analysis of the association of urban-rural status and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

Urban-rural status was compared across 13 studies and is significantly associated with dengue seropositivity (**Figure 9**). Overall, the odds of dengue seropositivity are 1.54 times higher if one resides in an urban area compared to a rural area (95% CI=1.14-2.07). Even after sensitivity analysis, the odds were still significant (OR 1.51; 95% CI=1.09-2.09; see Appendix A). The heterogeneity of the studies was considerable, with 85.72% in the preliminary analysis and 87.51% in the sensitivity analysis (see Appendix B).

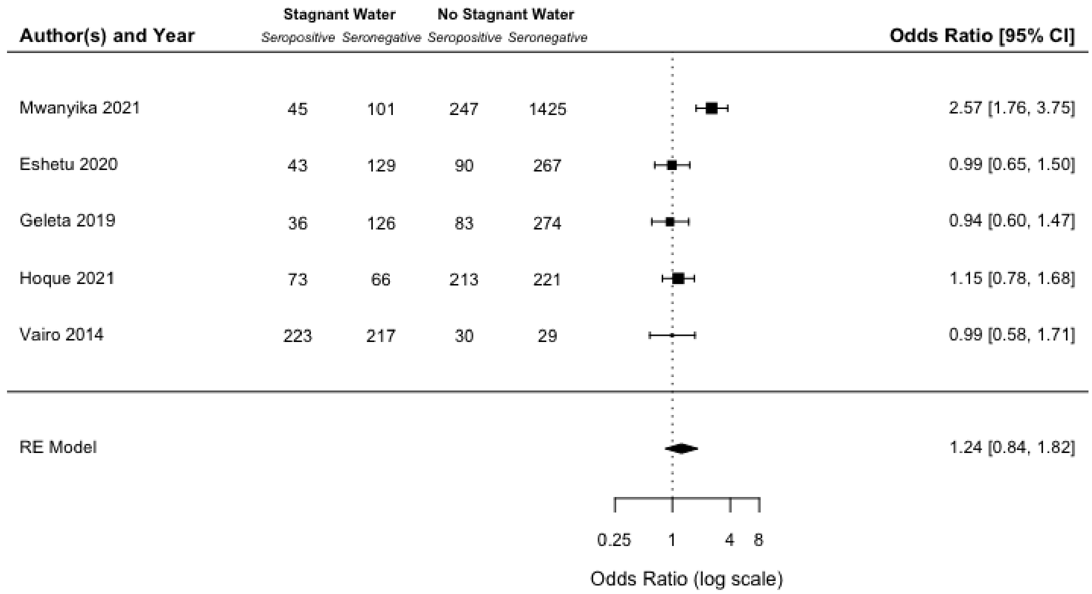

Figure 10. Meta-analysis of the association of the presence of stagnant water and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

Stagnant water was defined as the presence in and around the house or within the village. Overall, the presence of stagnant water was not significantly associated with dengue seropositivity (OR 1.24; 95% CI=0.84-1.82). Only one study identified a significant association between the presence of stagnant water and dengue seropositivity (**Figure 10**). A sensitivity analysis was conducted with no substantial difference in results (OR 1.26; 95% CI=0.77-2.07; see Appendix A). The heterogeneity of the studies was considerable with a 75.45% variability in the initial analysis and 80.24% in the sensitivity analysis (see Appendix B).

Behaviors and Biological Factors

Most studies included all ages (n=31), with eight studies only including adults and two only investigating dengue seroprevalence in children. Out of the 31 studies evaluating age, 17 found the prevalence of seropositive DENV IgG increased with age and the association to be statistically significant. Six other studies found a similar prevalence increasing with age however was either not statistically significant between groups or only for one age group. Two studies did not analyze the association between age and DENV IgG seroprevalence.

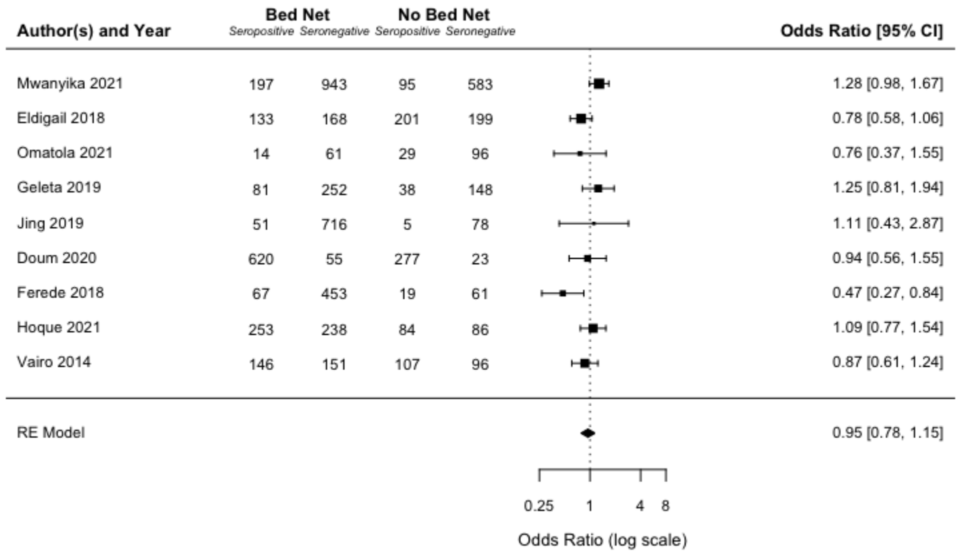

Figure 11. Meta-analysis of the association of bed net use and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

The use of bed nets was evaluated in nine studies, with only one study determining a statistically significant protective association between bed net use and seroprevalence of dengue (**Figure 11**). Overall, bed net use was slightly protective without statistical significance (OR 0.95; 95% CI =0.78-1.15). A sensitivity analysis was conducted and revealed no significant difference in the reported results (OR 0.92; 95% 0.73-1.15; see Appendix A). Some heterogeneity was identified between the studies ranging from an I^2 of 45.96%-51.26% between initial and sensitivity analysis; however, it was not statistically significant (see Appendix B).

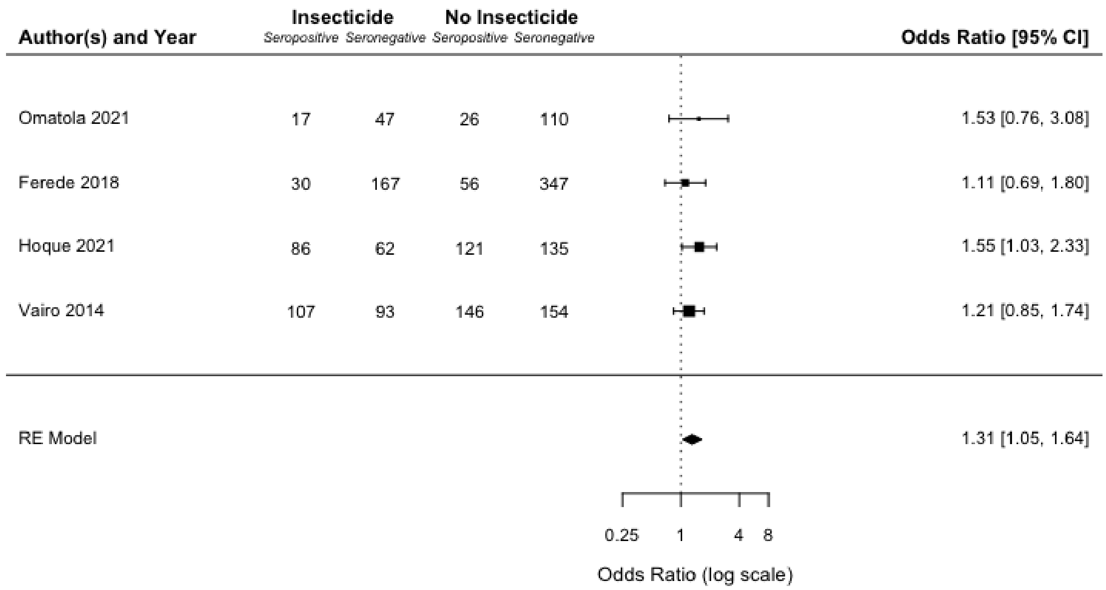

Figure 12. Meta-analysis of the association of the use of insecticide spray and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

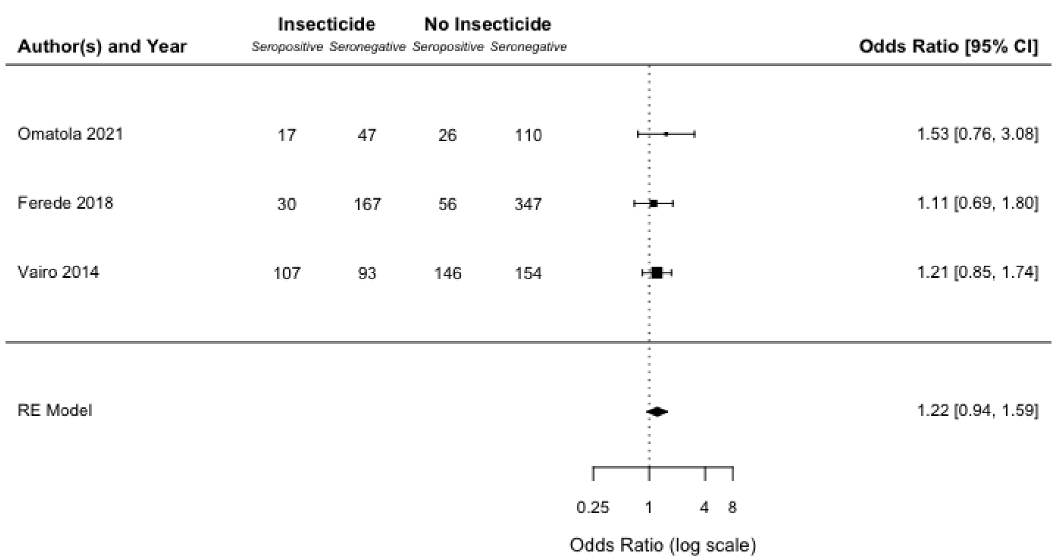

Figure 13. Meta-analysis with a sensitivity analysis of the association between the use of insecticide spray and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

Insecticide spraying, also referred to as mosquito spraying in the research, was evaluated by four studies in and around the house or within the city or village. Overall, insecticide spraying is significantly associated with seropositivity for dengue (OR 1.31; 95% CI=1.05-1.64; **Figure 12**). After a sensitivity analysis, the association was no longer significant (OR 1.22; 95% 0.94-1.59; **Figure 13**). For both analyses, $I^2 = 0\%$, indicating no evidence of significant heterogeneity between the studies, and any heterogeneity is due to chance (see Appendix B).

Psychosocial Factors

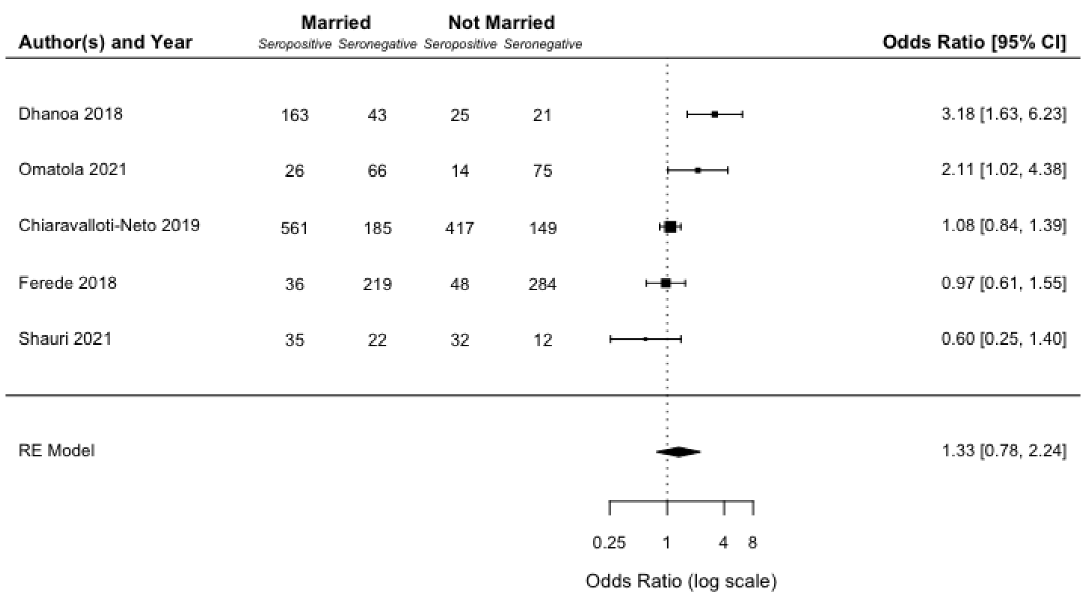

Figure 14. Meta-analysis of the association of marital status and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

Marital status was evaluated in five studies. Due to differences in levels of marital status categories, only married versus single was included in the meta-analysis. Two studies found a significant association between the odds of dengue seropositivity and being married (**Figure 14**). The association between being married and seroprevalence of DENV IgG was insignificant (OR 1.33; 95% CI=0.78-2.24). The heterogeneity was considerable across studies (I^2=79.39%; p<0.01; see Appendix B). A sensitivity analysis was not conducted.

Health System

No studies evaluated variables related to health systems in the country or region of interest.

6. DISCUSSION & CONCLUSION

In this systematic review and meta-analysis, the asymmetry in the data available was striking. Not all DENV seroprevalence studies ascertained data for the social determinants of interest. Across 41 studies included in the final analysis, the majority included data on gender and age, while many other determinants were considered in less than half of the studies.

Determinants relating to the socioeconomic and political context had the least number of studies evaluating the association between relatable variables and dengue seroprevalence. Measurable variables for governance, macroeconomic policies, and social and public policies are rarely considered or do not exist in studies assessing the social risk factors of dengue. A qualitative study on the influence of government on the prevention and control of dengue reveals the barriers and opportunities for governments to initiate change (Manaf et al., 2021). However, it is difficult to measure the incidence or seroprevalence of dengue in association with government action. The economics of the dengue burden is thoroughly investigated, yet translating the impact of macroeconomic policies on reducing this burden is rarely investigated. Carabali et al. (2015) analyzed the negative association between global health expenditure (GHE) and dengue mortality rates displaying one way the impact of macroeconomics can be quantified. Although the relationship between governance and policies with dengue can be assumed, creating, and utilizing standardized variables to measure their relationship is necessary to determine the effectiveness of government-implemented solutions.

Indicators relating to the determinant of cultural and societal values primarily focused on the knowledge, attitudes, and practices (KAP) around dengue. Awareness of dengue and access to education individuals received on dengue was the primary focus of the studies. These indicators are valuable in understanding the existing knowledge and habits of a community and were exhibited to be quantifiable. Nevertheless, only eight studies evaluated this criterion with varying definitions and levels of measuring. Unfortunately, some studies excluded in the screening process looked only at behavioral interventions or lacked seroprevalence data. KAP of dengue is extensively analyzed on a qualitative level however future research on risk factors of dengue should consider including dengue seroprevalence data.

The structural determinant of socioeconomic position provided some insight into potential social risk factors of dengue. The highest number of studies assessed the influence of gender on dengue virus seropositivity. Generally, gender is associated with dengue infection; however, no statistical significance was found between the two, indicating that future prevention interventions should not target one gender over the other. Education and occupation were evaluated in less than half of the studies. Even fewer of those were included in the meta-analysis, primarily due to differences in levels or categorization of the measurement. Countries and regions have varying education levels and occupation types that can hinder the homogeneity of variable definitions. These status indicators are essential in understanding which populations should be targeted in intervention programs.

Income as a determinant provides exciting insight into the association between high and low income with dengue seroprevalence. High income was overall protective, while low income was harmful, but these findings were not statistically significant. Studies finding high income to be a risk compared to low income could be due a lot of things including access to testing and adequate healthcare or wealthy individuals owning swimming pools or ponds in endemic areas with minimal amounts of chlorine for aesthetic purposes, consequently harboring mosquito larvae. This is an instance where looking at the data and local context holistically can guide prevention and control interventions. Social class is an indicator that can be used interchangeably with income, yet can be more complicated due to lack of consistency across variable categorization, thus social class was not included in the meta-analysis.

Ethnicity and race are essential determinants of health, mainly when evaluated with other indicators of socioeconomic position. Seven studies included a variable on ethnicity or race, but due to differences in the regions and countries of the studies, they could not be assessed in the meta-analysis.

A tremendous number of studies predominantly considered the determinant of material circumstances in their research. Most studies extensively explored variables specific to dengue, including the type of housing, access to water, use of water storage, use of bed nets, use of mosquito repellent, and length of clothing. The variety and consideration of behavioral factors, including prevention and control practices, that may associate with dengue seroprevalence were invaluable; however, it needed to be done consistently across studies, and the definition varied slightly. Only two variables from each category of intermediary determinants had sufficient studies for inclusion in the meta-analysis.

Urban versus rural status resulted in an interesting conclusion, with those seropositive for dengue at higher odds of residing in an urban area than rural. This observation is consistent with findings that urbanization favors the proliferation of mosquitoes such as *Aedes aegypti* in low-income under-developed urban areas (Wilke et al., 2020). As noted in Geleta (2019) and Salje et al. (2019), higher seropositivity rates in centralized urban centers are reported when considering the development of the study site, sustained endemic transmission in the area, and the vector species most prevalent. Urban areas or centers should be considered in future interventions.

Insecticide or mosquito spraying as a tool for preventing and controlling dengue is another variable that produced significant results. Those with dengue seropositive were at higher odds of using or their village using insecticide spray than those without. There are two potential reasons for this finding. First, insecticide spraying is being used in endemic areas with already high rates of dengue, meaning those who are seropositive may be using the spray more than those who are seronegative (Hoque et al., 2022). Second, there is evidence of potential insecticide resistance by the targeted mosquito species (Gan et al., 2021). Insecticides are a valuable tool in reducing the rate of dengue infection and may not be the best measurement for dengue seroprevalence.

This systematic review has many limitations, primarily due to the complexity of social determinants of health. Most of the findings were inconclusive due to the differing definition of variables or lack thereof in many of the studies. A significant limitation of the meta-analysis was the minimal data related to the determinants outlined in the WHO CSDH framework. The research may have considered many other published frameworks before conducting the study. However, frameworks should be included *a priori* and referenced in the data collection process to aid in a thorough review of the social indicators of dengue infection. The nature of the studies is also a limitation in fully measuring the associations. The studies included were predominantly cross-sectional which cannot fully address or determine the association. Another limitation may include selection bias in the studies, as only two reviewers from differing backgrounds assessed the research. Articles only in English and Spanish were included in the screening process and therefore, those conducted in Asia and published in another language were not included leading to further selection bias. Lastly, most of the studies included in the meta-analysis contained inconsistencies in statistical heterogeneity, possibly due to a lack of randomization, publication bias, or sufficient sample sizes.

Thus far, seroprevalence surveys have been inconsistent in indicating DENV infection in systematic reviews examining the impact of social determinants. Utilizing this marker of DENV infection gauge captures all individuals with past illnesses, including those asymptomatic and symptomatic. There can be a limit to understanding the relationship between dengue infection, as measured by DENV IgG antibodies, and social determinants as it is based on past infection, not current infection. Establishing an association between specific time-sensitive determinants and disease can be challenging. Despite this challenge, some potential relationships can still be identified.

By and large, there is scant literature about the social risk factors of interest. A comprehensive understanding of the influences of social determinants of health is vital in improving and implementing prevention and control methods around dengue. There is a substantial amount of research on different areas of social determinants, however, there needs to be prioritization in studying dengue from an exhaustive and broad perspective. Dengue may be evaluated regionally rather than globally as different communities may require different approaches to prevention and control. Based on the findings in this systematic review, the primary objective for research studying the association of social determinants and dengue seroprevalence is to have standardized indicators, potentially on a regional basis, to improve the analysis and reporting of associations between dengue and social risk factors. Furthermore, there needs to be more data relating to government, policies, and healthcare systems, which are upstream players and can significantly improve dengue health outcomes and burden. Urbanization and densely populated areas should also be of significant focus for future research.

Researchers across disciplines studying dengue must thoroughly evaluate how social determinants of health may impact their work and the future of the global dengue burden.

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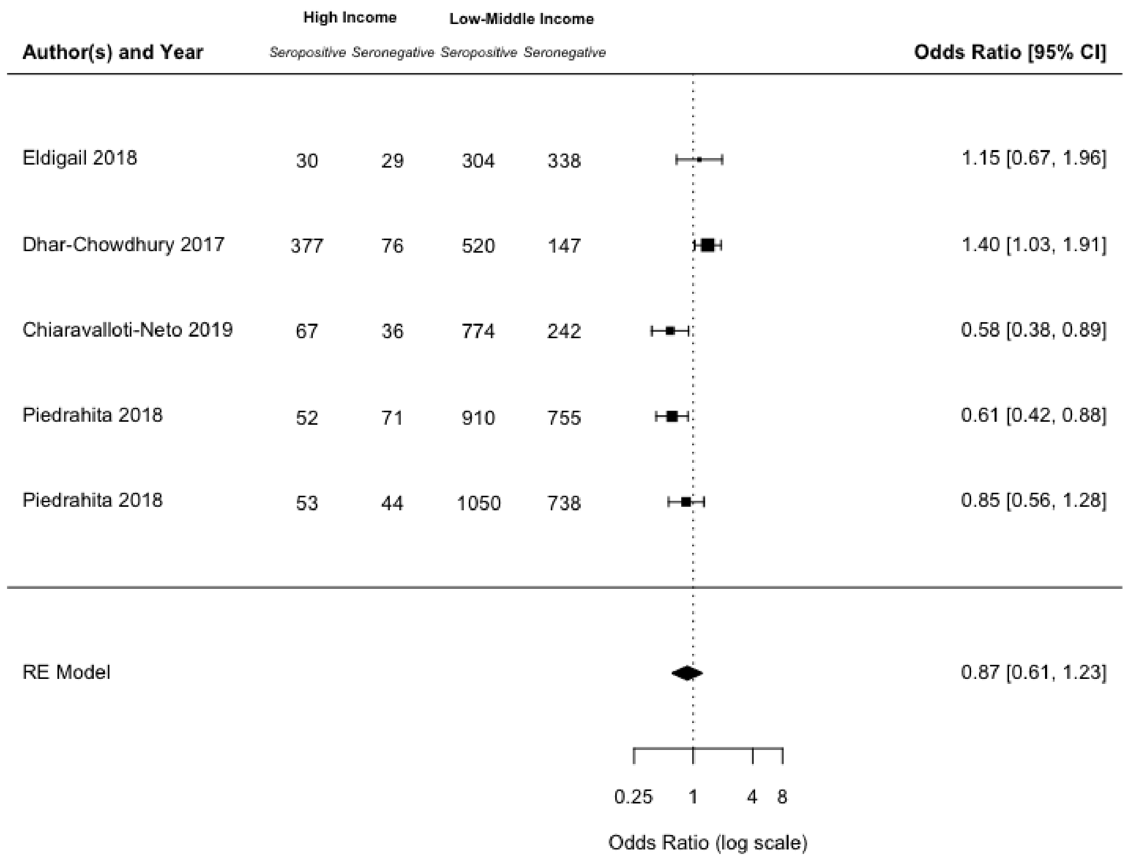
8. APPENDIX A

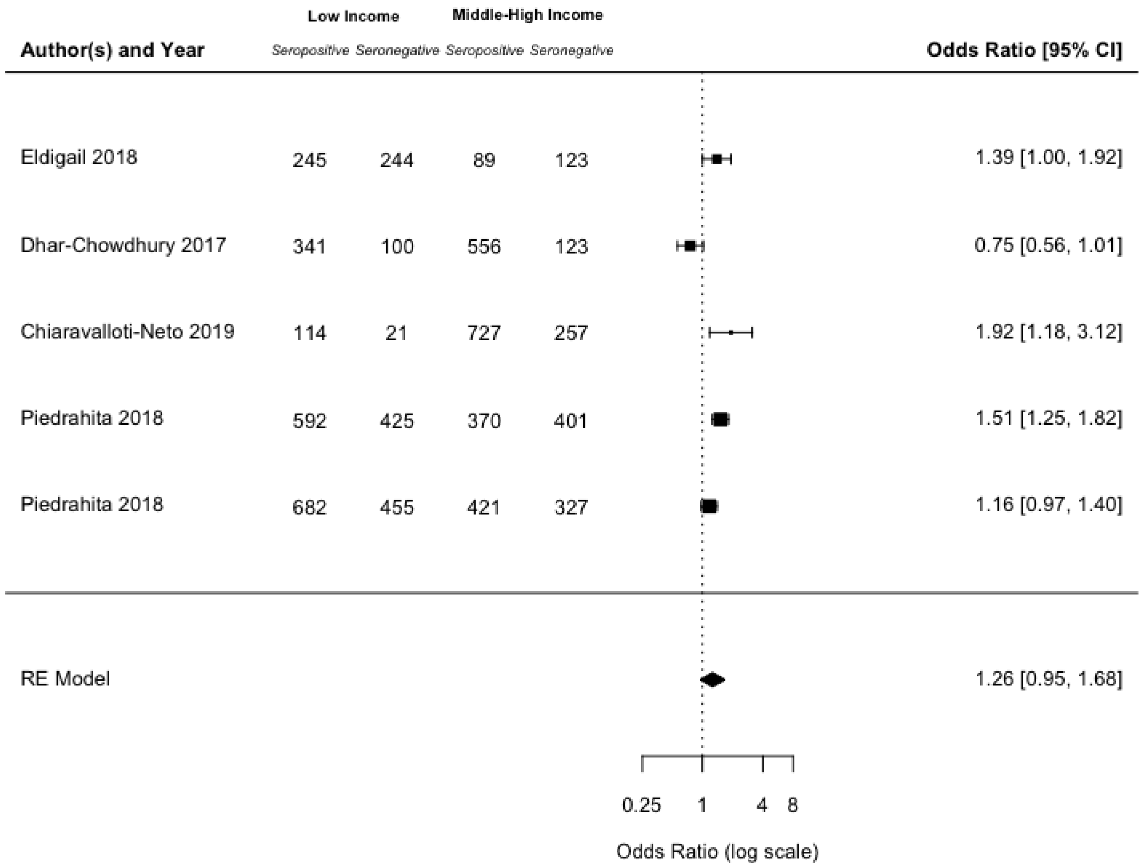
Forest plots of the sensitivity analysis of variables of interest

Author(s) and Year	Male Seropositive	Male Seronegative	Female Seropositive	Female Seronegative	Odds Ratio [95% CI]
Braga 2010	1042	178	1339	262	1.15 [0.93, 1.41]
Mwanyika 2021	141	688	151	838	1.14 [0.89, 1.46]
Obaidat 2018	86	259	132	414	1.04 [0.76, 1.42]
Eldigail 2018	207	212	127	155	1.19 [0.88, 1.61]
Eshetu 2020	61	165	72	231	1.19 [0.80, 1.76]
Sacramento 2018	23	93	39	125	0.79 [0.44, 1.42]
Dhar-Chowdhury 2017	395	92	504	134	1.14 [0.85, 1.54]
Chien 2019	87	499	155	650	0.73 [0.55, 0.97]
Dhanoa 2018	88	28	121	40	1.04 [0.60, 1.81]
Siqueira 2004	163	356	343	723	0.97 [0.77, 1.21]
Omatola 2021	18	60	25	97	1.16 [0.59, 2.31]
Geleta 2019	80	186	39	214	2.36 [1.53, 3.63]
Jing 2019	31	362	25	432	1.48 [0.86, 2.55]
Chiaravalloti-Neto 2019	391	130	595	206	1.04 [0.81, 1.34]
Al-Raddadi 2019	1057	2789	653	1898	1.10 [0.98, 1.23]
Al-Azraqi 2013	251	421	55	238	2.58 [1.85, 3.60]
Doum 2020	293	30	604	48	0.78 [0.48, 1.25]
Piedrahita 2018	459	408	503	418	0.93 [0.78, 1.13]
Piedrahita 2018	510	381	594	403	0.91 [0.76, 1.09]
Piedrahita 2018	200	134	258	117	0.68 [0.50, 0.92]
Ferede 2018	69	325	17	189	2.36 [1.35, 4.13]
Yew 2009	1238	820	1211	883	1.10 [0.97, 1.25]
Reiskind 2001	175	376	186	488	1.22 [0.95, 1.56]
Pavia-Ruz 2018	445	187	781	254	0.77 [0.62, 0.97]
Salje 2019	761	2060	642	2402	1.38 [1.23, 1.56]
Low 2015	955	798	930	944	1.21 [1.07, 1.38]
Amaya-Larios 2014	281	100	432	115	0.75 [0.55, 1.02]
Ochieng 2015	57	373	86	575	1.02 [0.71, 1.46]
Khor 2020	26	348	17	481	2.11 [1.13, 3.96]
Shauri 2021	64	107	4	5	0.75 [0.19, 2.89]
Hussen 2020	8	49	3	31	1.69 [0.42, 6.85]
Sawadogo 2020	451	187	270	99	0.88 [0.66, 1.18]
Muhammad 2016	149	93	22	38	2.77 [1.54, 4.97]
Jamjoom 2016	348	308	577	703	1.38 [1.14, 1.66]
Vairo 2014	243	243	10	4	0.40 [0.12, 1.29]
Lee 2021	18	499	266	525	0.07 [0.04, 0.12]
RE Model					1.06 [0.88, 1.27]

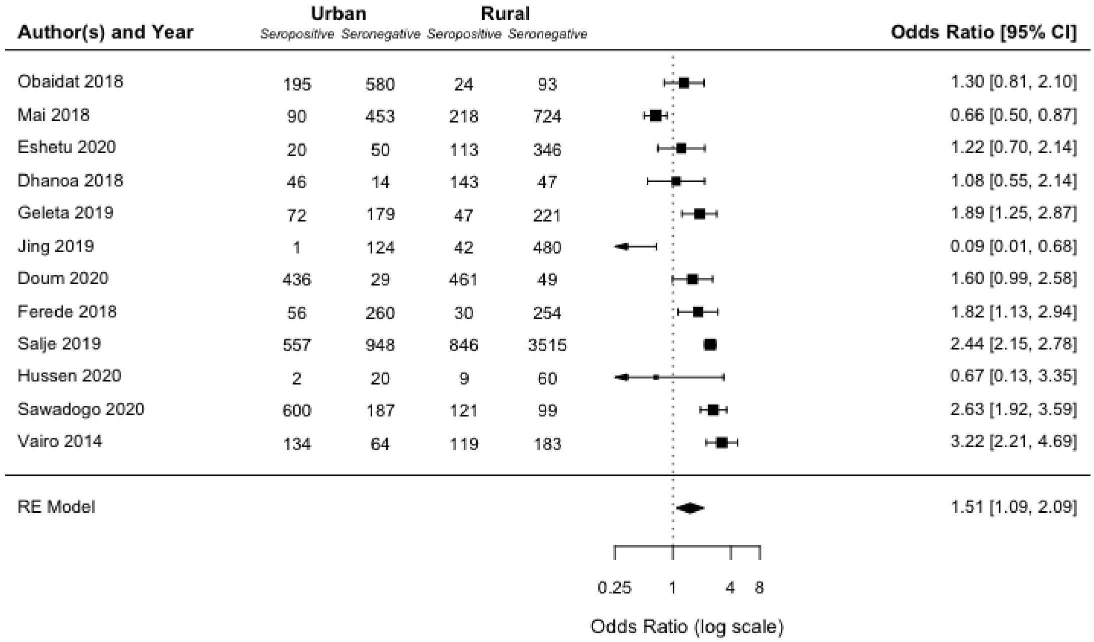
The above figure is a forest plot of the sensitivity analysis of the association of sex and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.



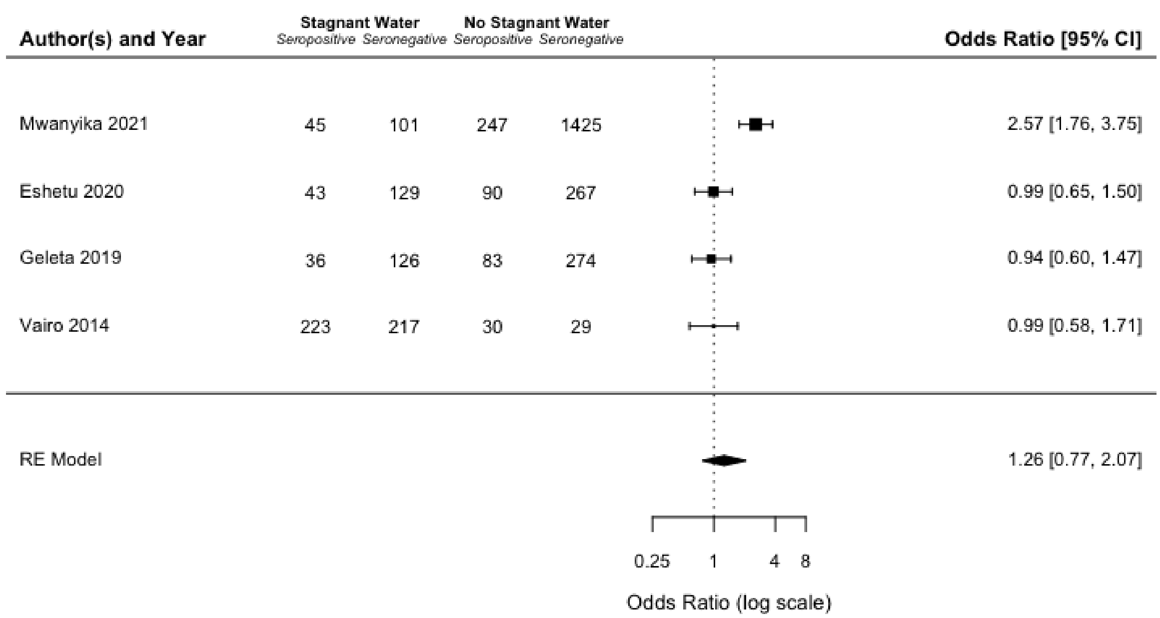
The above figure is a forest plot of the sensitivity analysis of the association of high income versus low-middle income and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.



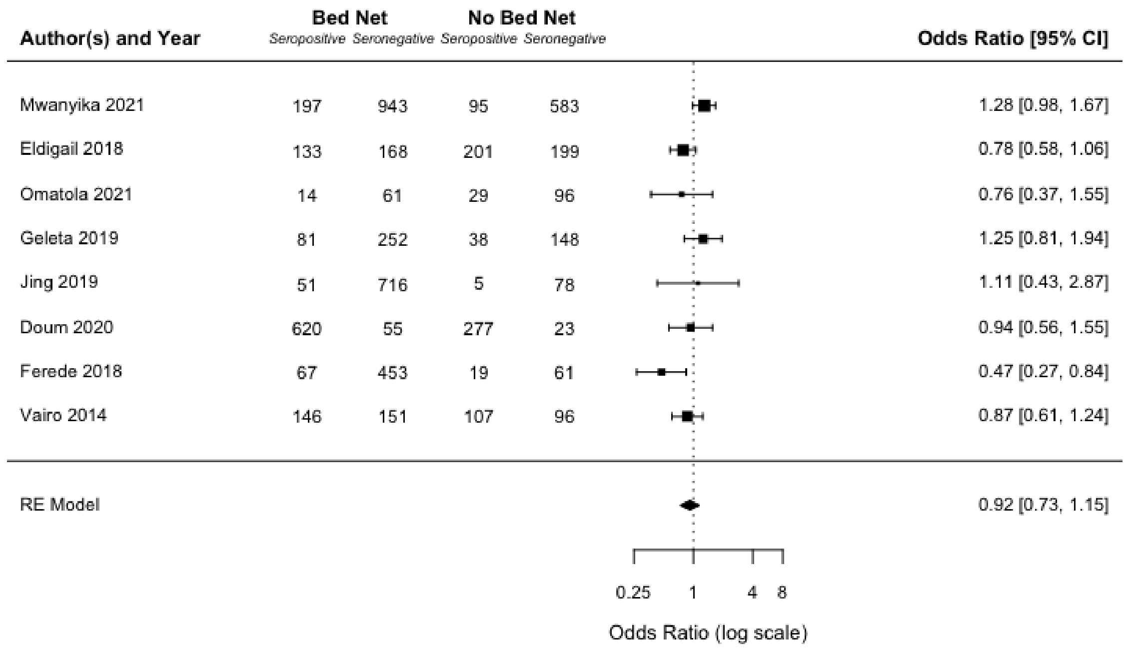
The above figure is a forest plot of the sensitivity analysis of the association of low-income versus middle-high income and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.



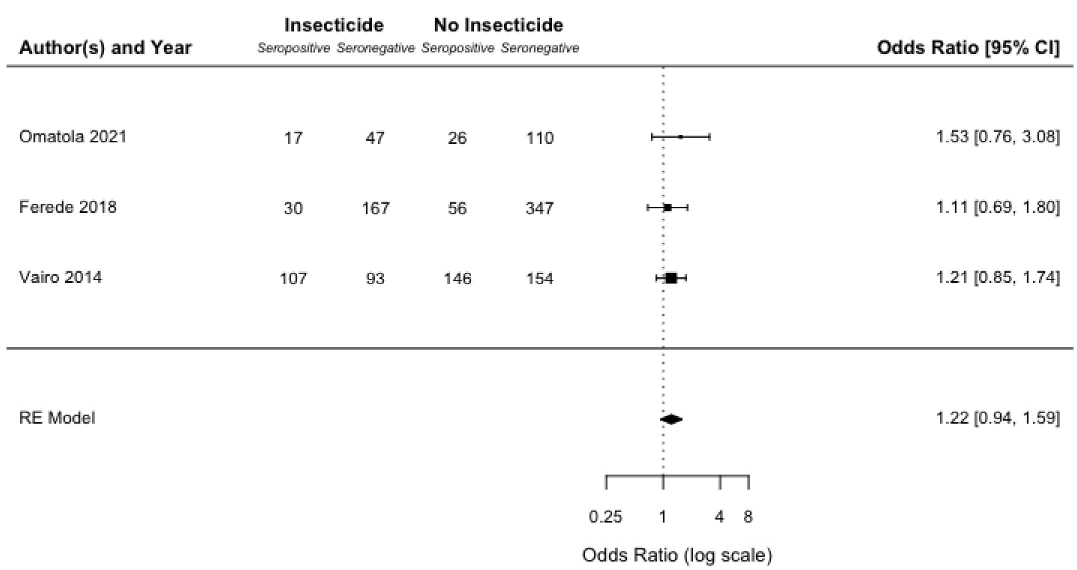
The above figure is a forest plot of the sensitivity analysis of the association of urban-rural status and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.



The above figure is a forest plot of the sensitivity analysis of the association of the presence of stagnant water and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.



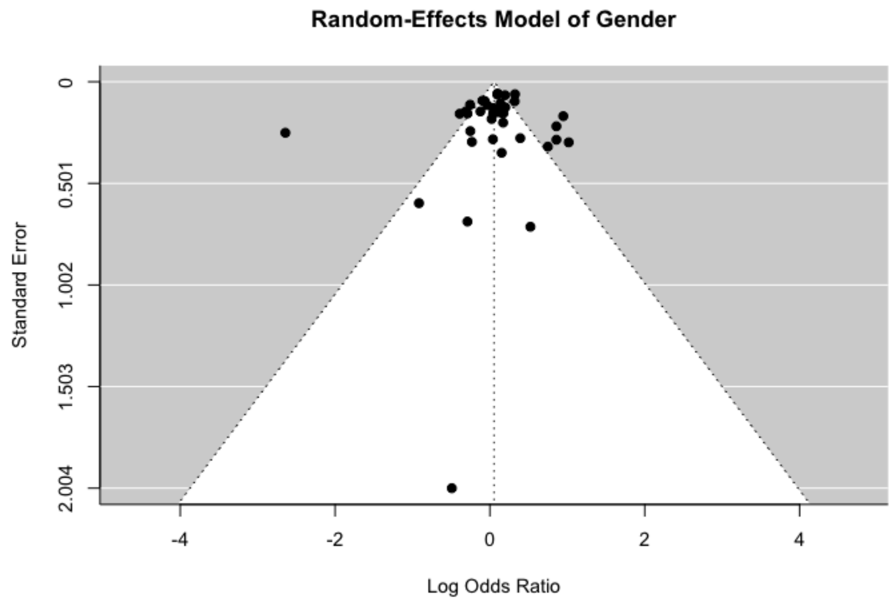
The above figure is a forest plot of the sensitivity analysis of the association of use of bed nets and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.



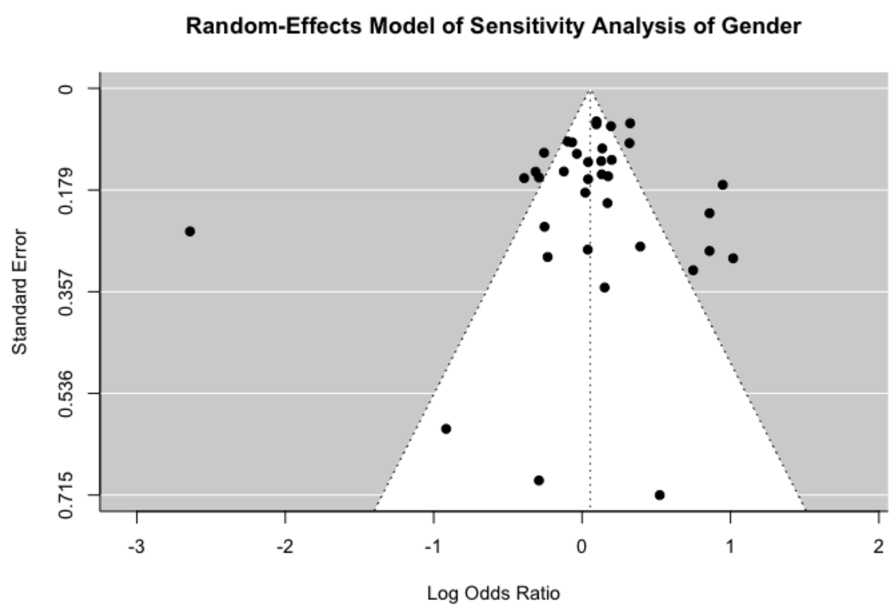
The above figure is a forest plot of the sensitivity analysis of the association of use of insecticide spray and dengue seroprevalence. Pooled estimates of the odds ratio using the random-effects analyses reported.

9. APPENDIX B

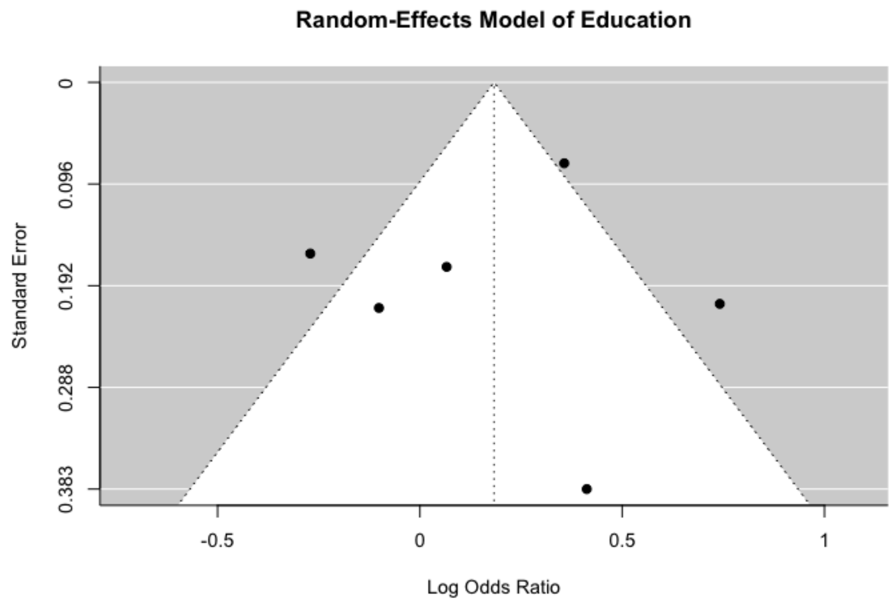
Funnel plots of the random-effects meta-analysis of all variables of interest



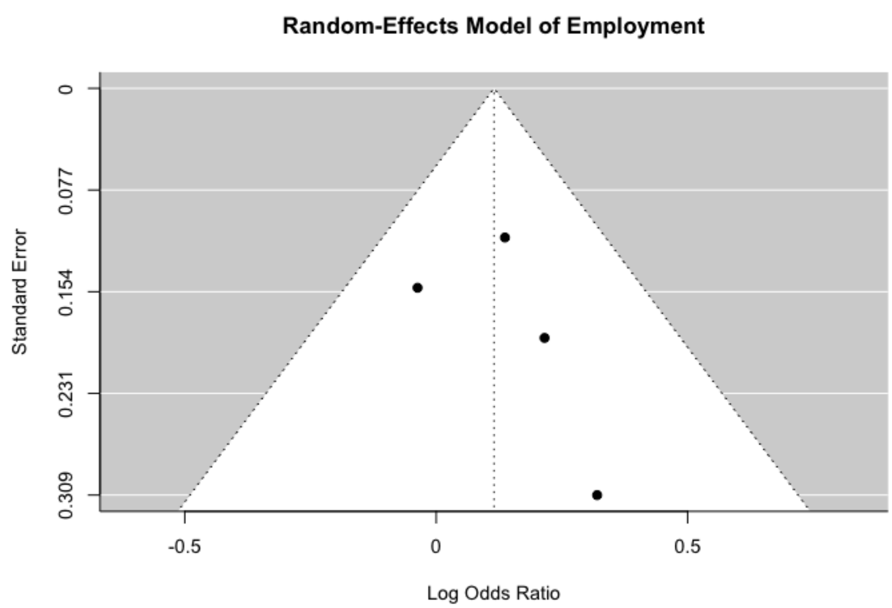
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of gender and dengue seroprevalence.



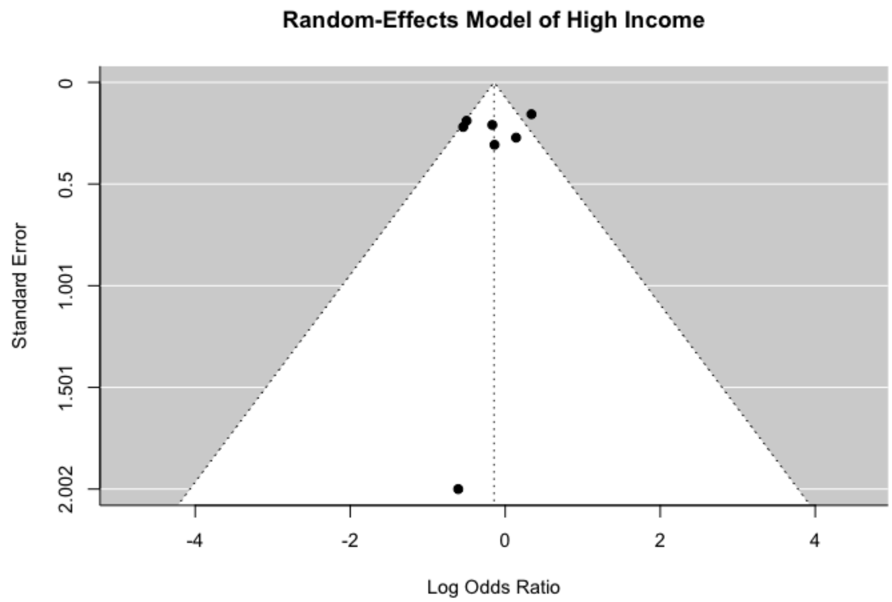
The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of gender and dengue seroprevalence.



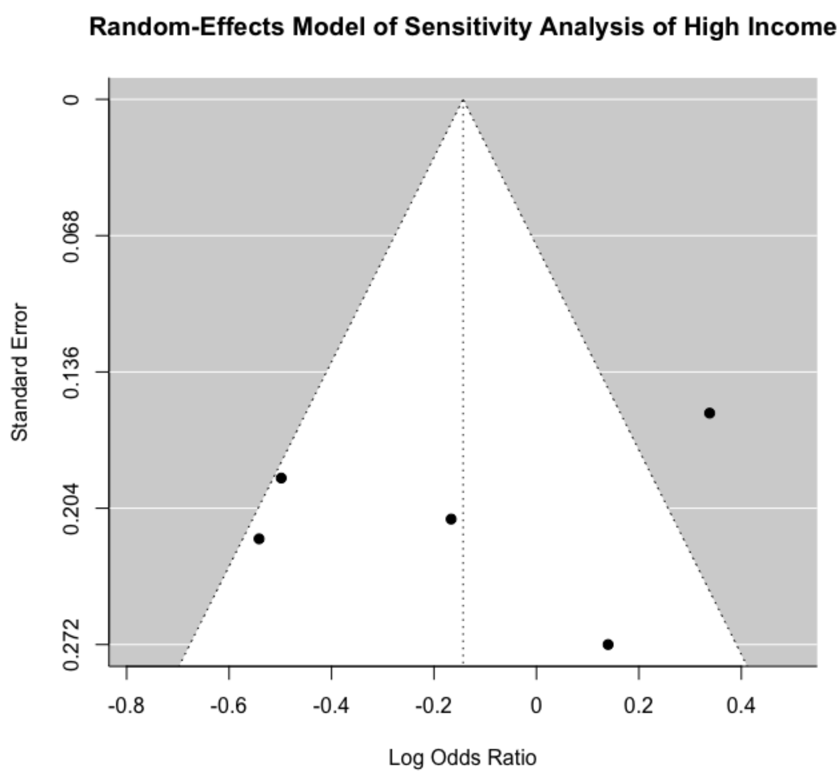
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of education and dengue seroprevalence.



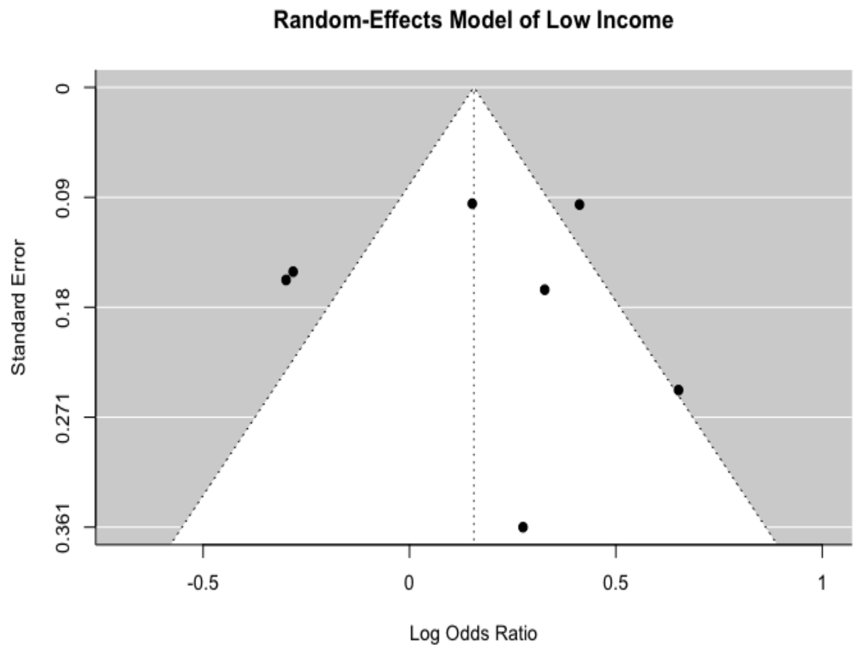
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of employment and dengue seroprevalence.



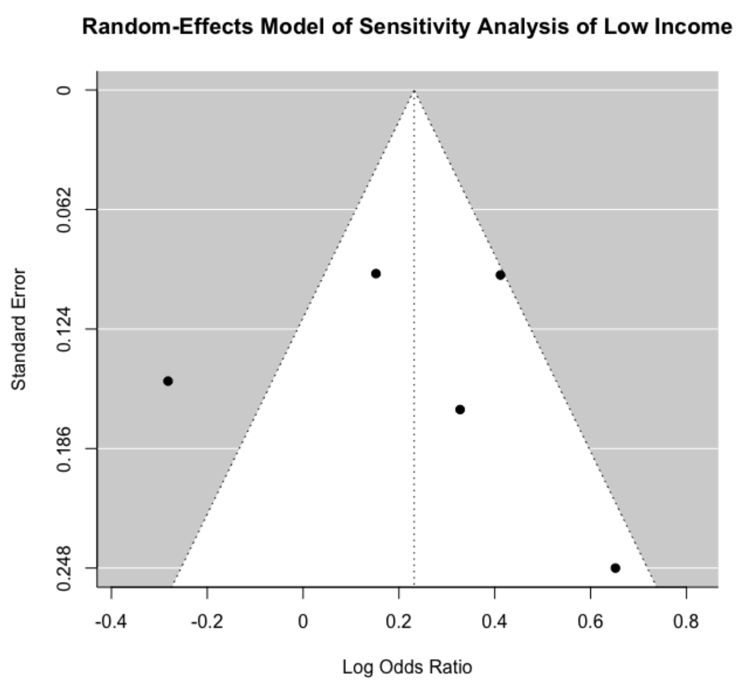
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of high income versus low-middle income and dengue seroprevalence.



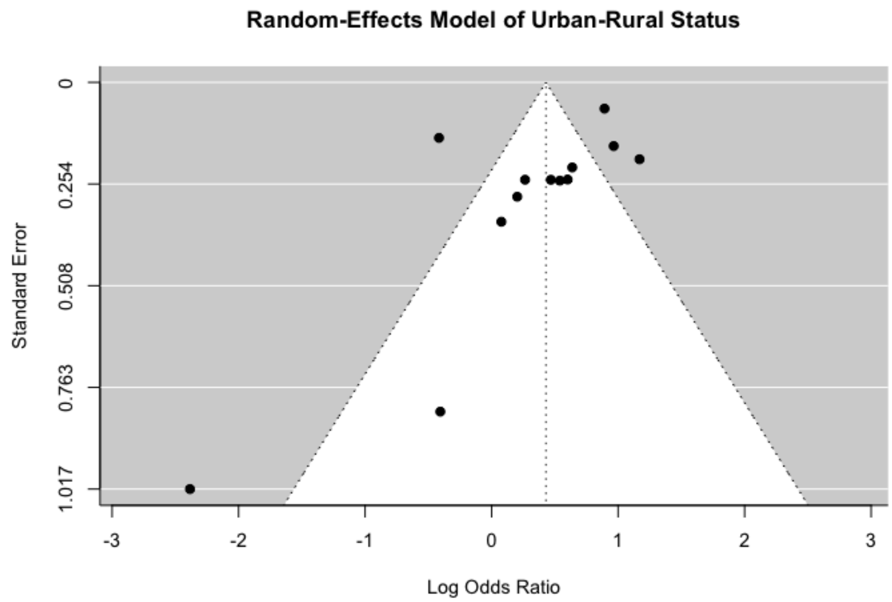
The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of high income versus low-middle income and dengue seroprevalence.



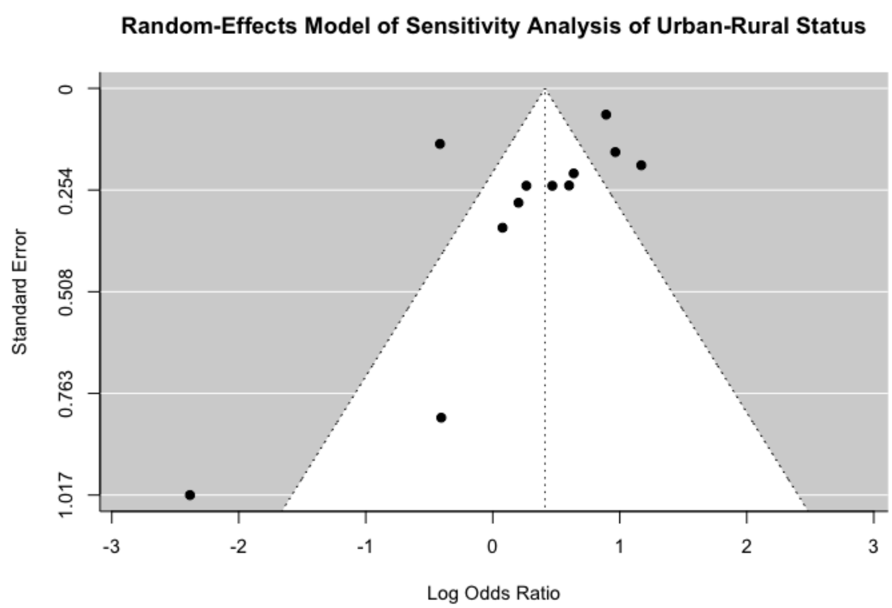
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of low income versus middle-high income and dengue seroprevalence.



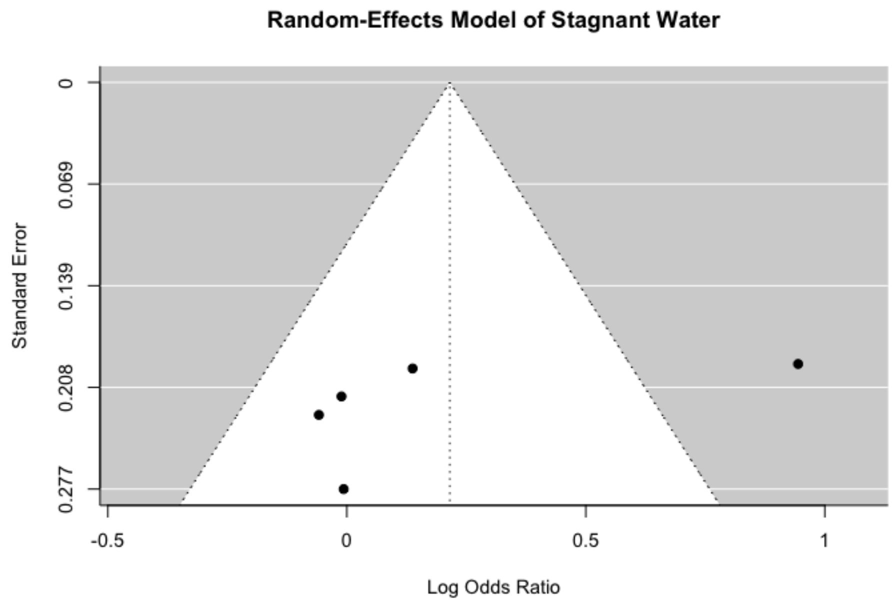
The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of low income versus middle-high income and dengue seroprevalence.



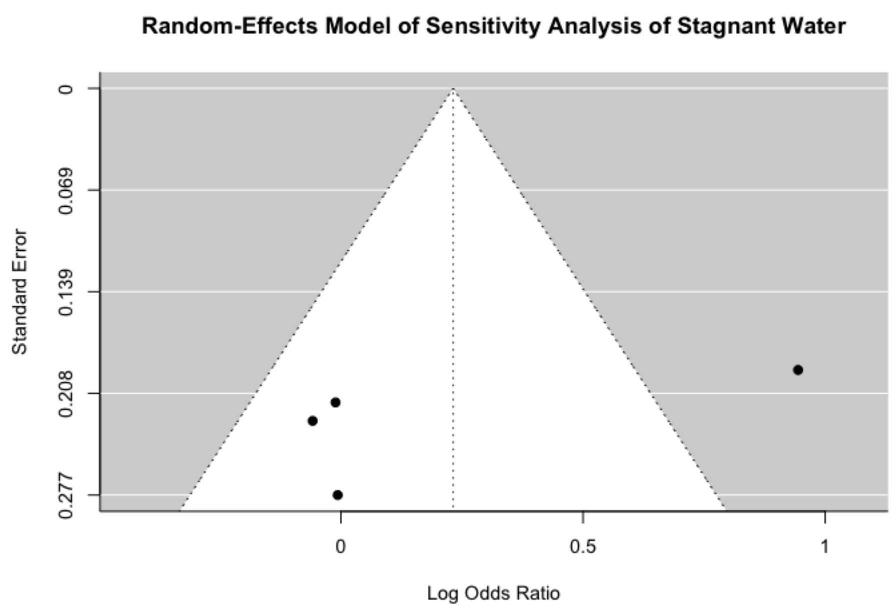
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of urban-rural status and dengue seroprevalence.



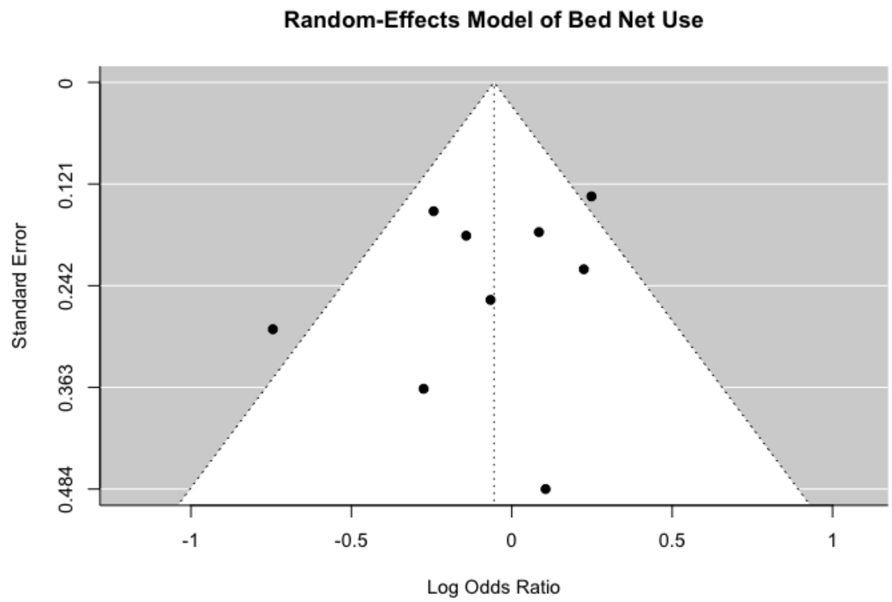
The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of urban-rural status and dengue seroprevalence.



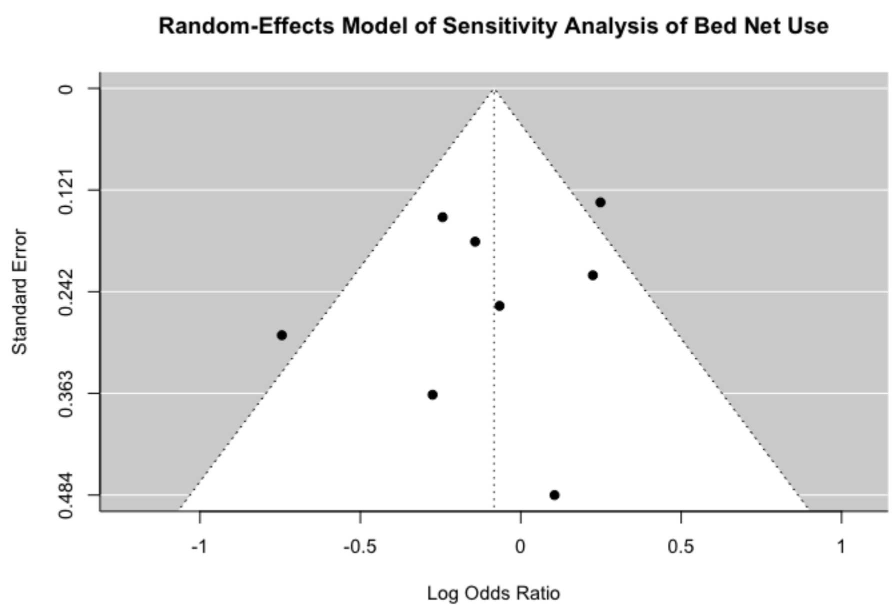
The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of presence of stagnant water and dengue seroprevalence.



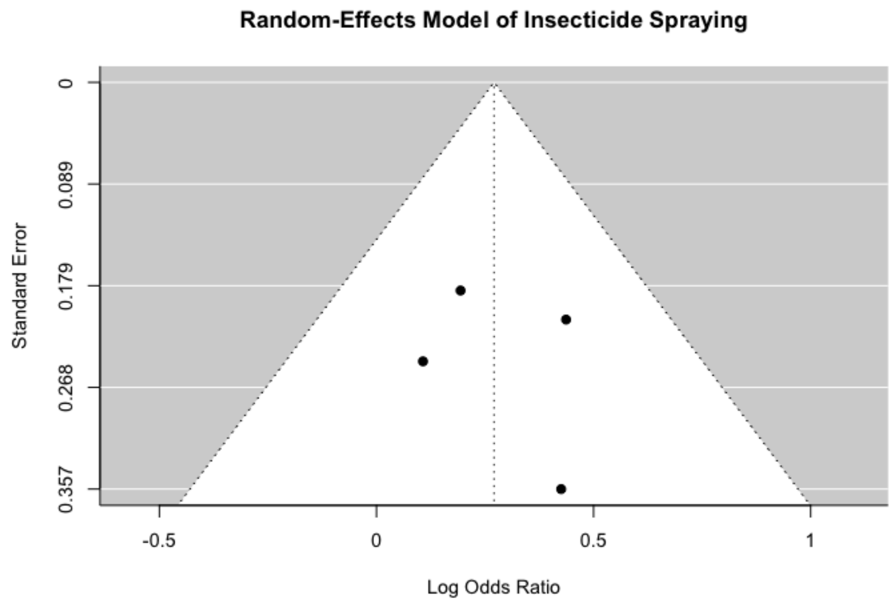
The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of presence of stagnant water and dengue seroprevalence.



The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of use of bed nets and dengue seroprevalence.

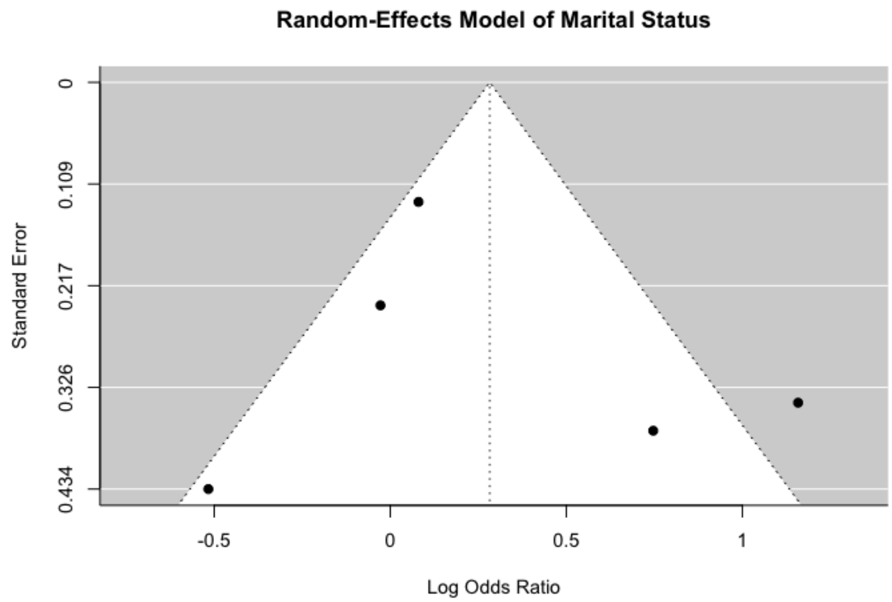


The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of use of bed nets and dengue seroprevalence.



The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of use of insecticide spray on mosquitoes and dengue seroprevalence.

The above figure is a funnel plot of the random-effects meta-analysis with sensitivity analysis conducted on the association of use of insecticide spray on mosquitoes and dengue seroprevalence.



The above figure is a funnel plot of the random-effects meta-analysis conducted on the association of marital status and dengue seroprevalence.