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REVIEW

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Clinical manifestations of dengue, Zika and chikungunya in the Pacific Islands: A systematic review and meta-analysis

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Abstract

Dengue, Zika and chikungunya outbreaks pose a significant public health risk to Pacific Island communities. Differential diagnosis is challenging due to overlapping clinical features and limited availability of laboratory diagnostic facilities. There is also insufficient information regarding the complications of these arboviruses, particularly for Zika and chikungunya. We conducted a systematic review and meta-analysis to calculate pooled prevalence estimates with 95% confidence intervals (CI) for the clinical manifestations of dengue, Zika and chikungunya in the Pacific Islands. Based on pooled prevalence estimates, clinical features that may help to differentiate between the arboviruses include headache, haemorrhage and hepatomegaly in dengue; rash, conjunctivitis and peripheral oedema in Zika; and the combination of fever and arthralgia in chikungunya infections. We estimated that the hospitalisation and mortality rates in dengue were 9.90% (95% CI 7.67–12.37) and 0.23% (95% CI 0.16–0.31), respectively. Severe forms of dengue occurred in 1.92% (95% CI 0.72–3.63) of reported cases and 23.23% (95% CI 13.58–34.53) of hospitalised patients. Complications associated with Zika virus included Guillain-Barré syndrome (GBS), estimated to occur in 14.08 (95% CI 11.71–16.66) per 10,000 reported cases, and congenital brain malformations such as microcephaly, particularly with first trimester maternal infection. For chikungunya, the hospitalisation rate was 2.57% (95% CI 1.30–4.25) and the risk of GBS was estimated at 1.70 (95% CI 1.06–2.48) per 10,000 reported cases. Whilst ongoing research is required, this systematic review enhances existing knowledge on the clinical manifestations of dengue, Zika and chikungunya infections and will assist Pacific Island clinicians during future arbovirus outbreaks.

KEYWORDS

chikungunya, dengue, meta-analysis, Pacific Islands, systematic review, Zika

Abbreviations: CI, confidence intervals; DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome; ELISA, enzyme-linked immunosorbent assay; GBS, Guillain-Barré syndrome; OSF, Open Science Framework; PCR, polymerase chain reaction; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RT, reverse transcriptase.

1 | INTRODUCTION

Arthropod-borne viruses (arboviruses) pose a significant global public health risk due to the unprecedented increase in disease epidemics over recent decades.[1] The emergence (or re-emergence) of arboviruses has been attributed to changing patterns of virus-vector-host interactions due to urbanisation, globalisation and international mobility.[1,2] Globally, the three most prevalent arboviruses per year are dengue (400 million cases),[3] chikungunya (693,000 cases) and Zika virus (500,000 cases).[4] Dengue, Zika and chikungunya are transmitted via the same principal vector, *Aedes aegypti*, and share similar epidemiology and clinical expressions.[5]

The arboviruses have now spread to the Pacific Islands, which have distinct socioeconomic, climatic and human-activity related factors that predispose the population to recurrent arbovirus epidemics.[6] Outbreaks of dengue have been reported in the Pacific as early as the mid 19th century, whereas Zika and chikungunya have only recently emerged in the region.[7] In 2007, the first outbreak of Zika in the Pacific Islands was reported in Federated States of Micronesia and in 2011, the first chikungunya outbreak occurred in New Caledonia.[8] Since then, the arboviruses have disseminated throughout the region. Between 2014 and 2020, 104 unique arbovirus outbreaks were recorded in the Pacific Islands, including 72 dengue outbreaks, 18 Zika outbreaks and 14 chikungunya outbreaks.[9]

Clinical differential diagnosis of dengue, Zika and chikungunya is challenging as there are several overlapping non-specific symptoms, such as fever, headache, myalgia, arthralgia, rash, retro-orbital pain and lymphadenopathy.[10,11] There is limited evidence for the few available algorithms that aim to distinguish the clinical features of these arboviruses.[10,11] As a result, emphasis is placed on laboratory tests such as reverse transcriptase-polymerase chain reaction or enzyme-linked immunosorbent assay for diagnosis.[11] However, these diagnostic tests are not readily available in under-resourced areas such as the Pacific Islands[5,9] and is further complicated by cross-reactivity of antibodies.[10,12]

For each arbovirus, treatment is supportive and is usually sufficient given the self-limiting clinical course of infection in most cases.[13] However, early detection remains essential due to the risk of severe acute manifestations of disease and the potential for long-term sequelae. For dengue, patients are at risk of progressing to severe dengue, which is characterised by capillary leakage with or without haemorrhage (i.e., dengue haemorrhagic fever (DHF)) and possible shock (i.e., dengue shock syndrome (DSS)).[14] Zika is generally considered a mild disease, but outbreaks in the Pacific have been associated with clusters of Guillain-Barré syndrome (GBS) and neurodevelopmental birth defects.[1] Chikungunya can cause debilitating joint pain resulting in either acute, subacute or chronic disease, and there have been recent reports of various cardiac and neurological complications.[13,15] For Zika and chikungunya, the natural history of disease continues to be a research priority.[16]

Thus, there remains a gap in the literature regarding the clinical manifestations of dengue, Zika and chikungunya, and in particular, the differential diagnosis and prevalence of disease complications. Whilst there are some reviews that explore the clinical features of each arbovirus,[17–19] there is yet to be a meta-analysis in the global literature that compares the clinical manifestations of these three arboviruses. Furthermore, despite the Pacific Islands experiencing recurrent outbreaks of all three arboviruses, they are largely underrepresented in existing reviews.

Hence, we conducted a systematic review and meta-analysis on the clinical manifestations of dengue, Zika and chikungunya in the Pacific Islands. The primary objectives of our review were to estimate the prevalence of the clinical features and complications of dengue, Zika and chikungunya in Pacific Island populations and compare the clinical manifestations of each arbovirus. The secondary objective was to compare our findings to studies conducted in other geographical locations.

2 | METHODS

Our systematic review was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[20] The study protocol was registered on Open Science Framework registries (https://osf.io/c3jzf).

2.1 | Search strategy and selection process

PubMed, Scopus and Ovid Embase electronic databases were searched in November 2023 using search terms in the title, keyword and abstract fields as well as subject headings in PubMed and Embase (i.e., MeSH and Emtree, respectively) with no language or date restrictions (see supplementary material 1 for search strategy).

For study selection, all identified articles were imported into Covidence. Two reviewers manually removed duplicates and independently screened articles by title and abstract and then for full-text eligibility according to the following criteria: (a) epidemiological study, including cohort, case-control, cross-sectional studies, and case series; (b) presents quantitative data regarding the clinical features or complications of dengue, Zika or chikungunya infections in humans; (c) study location in a Pacific Island; and (d) full text published in a peer-reviewed journal. Grey literature, case reports, reviews, conference proceedings, editorials and book chapters were excluded. Despite initially being specified in the protocol, confirmatory laboratory diagnosis was not part of the inclusion criteria due to the limited number of laboratory-confirmed cases in the Pacific Islands.

Furthermore, the reference and citation lists of included studies were obtained using Google Scholar and screened for additional relevant articles.

Any discrepancies that arose during the study selection process were resolved through discussion and consensus decision between the two reviewers.

2.2 | Data extraction and quality assessment

For each included article, two reviewers manually and independently extracted the following data for each arbovirus: (a) citation details; (b) study period; (c) study location; (d) study design; (e) sample size; (f) sample characteristics (age, gender/sex and cohort characteristics e.g., inpatient vs. outpatient and clinically suspected vs. laboratory-confirmed cases); (g) method of laboratory diagnosis; (h) virus subtype (for dengue); (i) clinical features; and (j) complications (including hospitalisations and deaths).

For risk of bias assessment, each article was evaluated using the Newcastle-Ottawa Scale. The Newcastle-Ottawa Scale is used to assess the methodological quality of non-randomised studies in healthcare, with an overall score out of nine.[21] In this review, cross-sectional studies and case series were evaluated using the criteria for cohort studies.

2.3 | Data synthesis and analysis

For each arbovirus, meta-analysis of prevalence (proportions) was performed in Stata version 18.0 (StataCorp LLC) to calculate pooled prevalence estimates with 95% confidence intervals (CI) for clinical features and complications that were reported in at least two studies. We used the DerSimonian-Laird random-effects model[22] rather than a fixed-effect model because it was anticipated that the variability between effect sizes would be due to a range of unique differences in true population effect sizes.[23] In addition, the inverse Freeman-Tukey double arcsine transformation was adopted because it stabilises variances in studies with proportions close to or at 0% or 100%.[24]

Several articles reported the prevalence of clinical manifestations in distinct patient cohorts and for meta-analysis, these patient cohorts were treated as separate studies. For articles that presented identical results from a shared cohort (i.e., same study period, location, sample size and reported frequency of symptoms and/or complications), only one study was included for meta-analysis. For complications, pooled prevalence estimates were computed separately for general population cohorts and hospitalised patients. Moreover, as the definition for severe forms of dengue has changed over time (i.e., DHF and DSS to severe dengue),[25,26] severe cases were grouped together to estimate the combined prevalence of severe forms of dengue, and then if permitted by sample size, prevalence estimates were calculated for each definition of severity.

Statistical heterogeneity across studies was evaluated using the I^2 statistic, with low heterogeneity defined as less than 25%, moderate 25%–50% and high heterogeneity greater than 75%.[27] To explore sources of heterogeneity, subgroup analyses were conducted based on study characteristics (e.g., study period, location and sample size) and participant characteristics (e.g., age, hospitalisation status and clinical vs. laboratory-confirmed cases) as well as the predominant virus subtype for dengue studies. Effect sizes with 95% CIs and I^2 values were computed for subgroups containing at least two studies. Test of group differences were performed using a chi-squared test (Cochran's Q),[28] with the difference between subgroups considered statistically significant if p-value less than 0.05 (i.e., $p < 0.05$).

Publication bias was evaluated through visual inspection of the funnel plot and Egger's test.[29] Egger's test was only performed for clinical manifestations with at least 10 studies included in meta-analysis as the power of the test is too low to distinguish chance from real asymmetry if fewer studies are included.[30] The cut-off value was set at $p < 0.05$ and if significant publication bias was detected, the trim-and-fill method was used to impute potentially missing studies to adjust for publication bias.[31] Furthermore, a sensitivity analysis was conducted using leave-one-out meta-analysis to evaluate the influence of each study on the overall effect size.[32]

Lastly, to compare the clinical manifestations of dengue, Zika and chikungunya, a chi-squared test was performed to test for differences between the pooled prevalence estimates of clinical features and complications, where meta-analysis was performed in at least two out of the three arboviruses. The difference in prevalence was considered statistically significant if $p < 0.05$.

3 | RESULTS

3.1 | Study selection process

Out of the 74 included articles (see supplementary material 1 for references), 62 articles were included in meta-analysis, with 51 for dengue, 8 for Zika and 5 for chikungunya (including one study which reported findings for all three arboviruses)[33] (see Figure 1). Several articles were excluded from meta-analysis due to the nature of patient cohorts analysed,[34–37] unclear sample sizes[38–40] or undefined clinical manifestations.[41] Furthermore, two studies reported identical findings for the same patient cohort[42,43] and hence one of the studies was not included in meta-analysis.[42] The remaining three articles reported prevalence data for a clinical manifestation that was not investigated in any other articles.[44–46]

3.2 | Study characteristics

For dengue studies, data collection periods ranged from 1943 to 2020 and the predominant study designs were retrospective cohort studies ($n = 28$) and case series ($n = 19$). Studies represented a total of 19 different Pacific Islands, most commonly French Polynesia ($n = 22$) followed by New Caledonia ($n = 11$) and Fiji ($n = 11$). The predominant dengue virus subtypes identified were as follows: DENV-1 ($n = 22$), DENV-3 ($n = 19$), DENV-2 ($n = 16$) and DENV-4 ($n = 7$) (see supplementary material 1 for further details).

In studies of Zika infections, study periods ranged from 2009 to 2016 and the main study designs were retrospective cohort ($n = 5$)

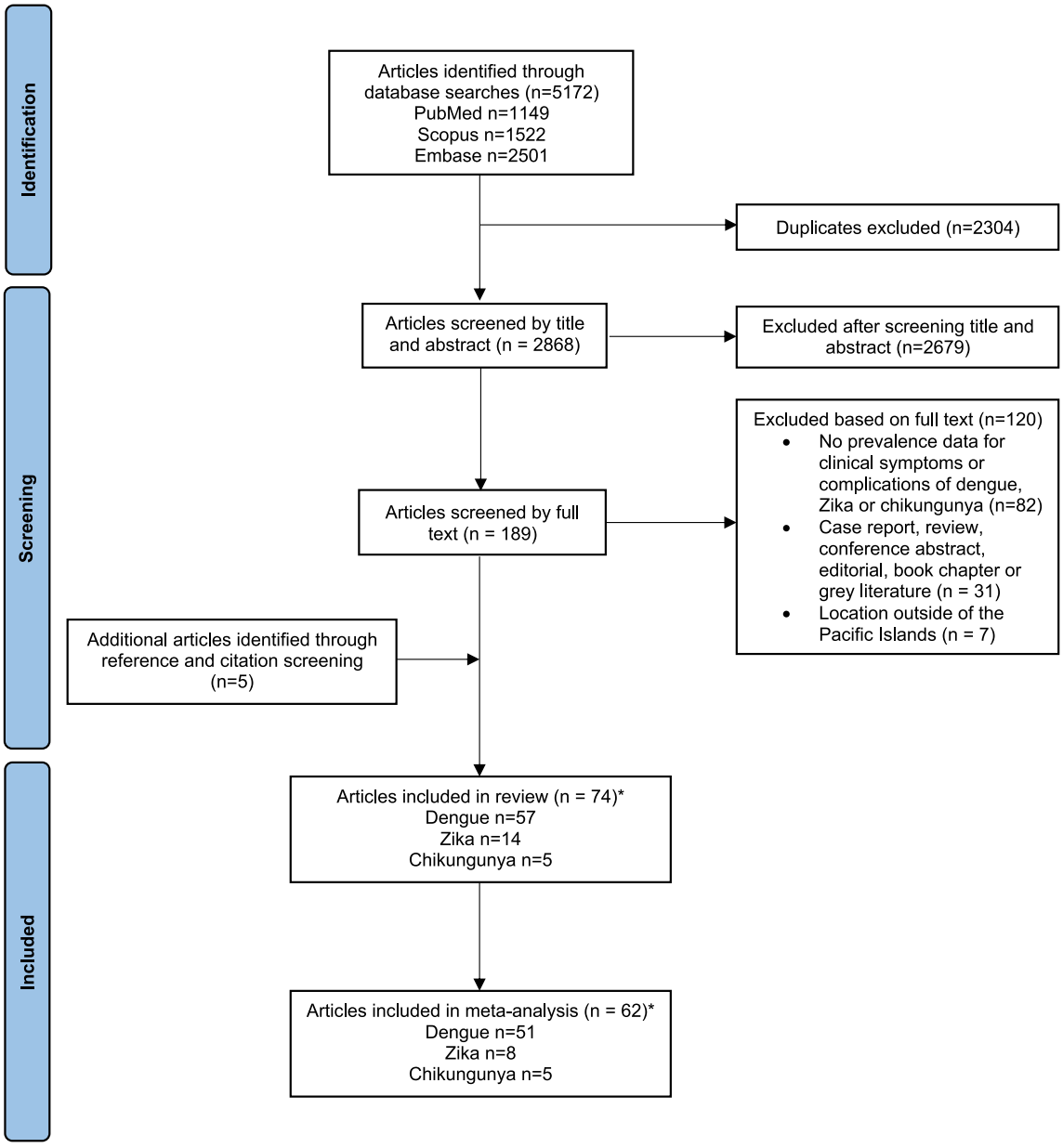

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection process.[20]

and case control studies ($n = 3$). The majority of patient cohorts were sampled in French Polynesia ($n = 9$), with others based in Federated States of Micronesia ($n = 2$), New Caledonia ($n = 2$), Hawaii ($n = 1$) (see supplementary material 1 for further details).

Of the five chikungunya studies, patient cohorts were reported from 2012 to 2015, representing patients from French Polynesia ($n = 2$), Papua New Guinea ($n = 1$), Federated States of Micronesia ($n = 1$) and American Samoa ($n = 1$). Study designs included prospective cohort ($n = 2$), retrospective cohort ($n = 2$), cross-sectional ($n = 1$) and case series designs ($n = 1$) (see supplementary material 1 for further details).

3.3 | Quality of included studies

Using the Newcastle-Ottawa Scale, seven studies were of high quality (overall score ≥8), 45 studies were of moderate quality (overall score 5–7) and 22 studies were of low quality (overall score ≤5). The study quality did not differ significantly between dengue (mean overall score 5.14), Zika (mean overall score 5.93) and chikungunya studies (mean overall score 5.80). The primary domains associated with a high risk of bias were the selection of non-exposed cohorts and the comparability of cohorts. These criteria were largely irrelevant to the aim of many studies, which reported a single cohort

of patients without a comparison group (see supplementary material 1 for further details).

3.4 | Clinical manifestations of dengue

The most frequent symptoms reported for dengue cases were fever (97.45%), headache (81.62%), myalgia (74.20%), chills (65.29%) and arthralgia (57.47%) (see Figure 2). Haemorrhagic manifestations were reported in 17.31% of cases. The most frequent form of haemorrhage was petechiae, purpura or ecchymosis, occurring in 14.88% (95% CI 7.32–24.33) of cases, followed by epistaxis (7.28%, 95% CI 5.00–9.92), haematuria (3.25%, 95% CI 0.72–7.20), gum bleeding (2.94%, 95% CI 0.86–6.02) and gastrointestinal bleeding (2.75%, 95% CI 0.88–5.41). Heavy menstrual bleeding was also reported in a minority of female patients.[43,47] Despite the significant heterogeneity ($I^2 > 75\%$) identified for several clinical features, subgroup analysis based on study period, sample size, age, clinically suspected versus laboratory-confirmed cases and virus subtype generally were not significant ($p > 0.05$). However, there were significant differences in prevalence estimates based on study location for fever, asthenia, nausea/vomiting, diarrhoea, rash and lymphadenopathy (all $p < 0.05$). Studies that examined hospitalised patients also had lower prevalence of respiratory symptoms and rash, and higher prevalence of

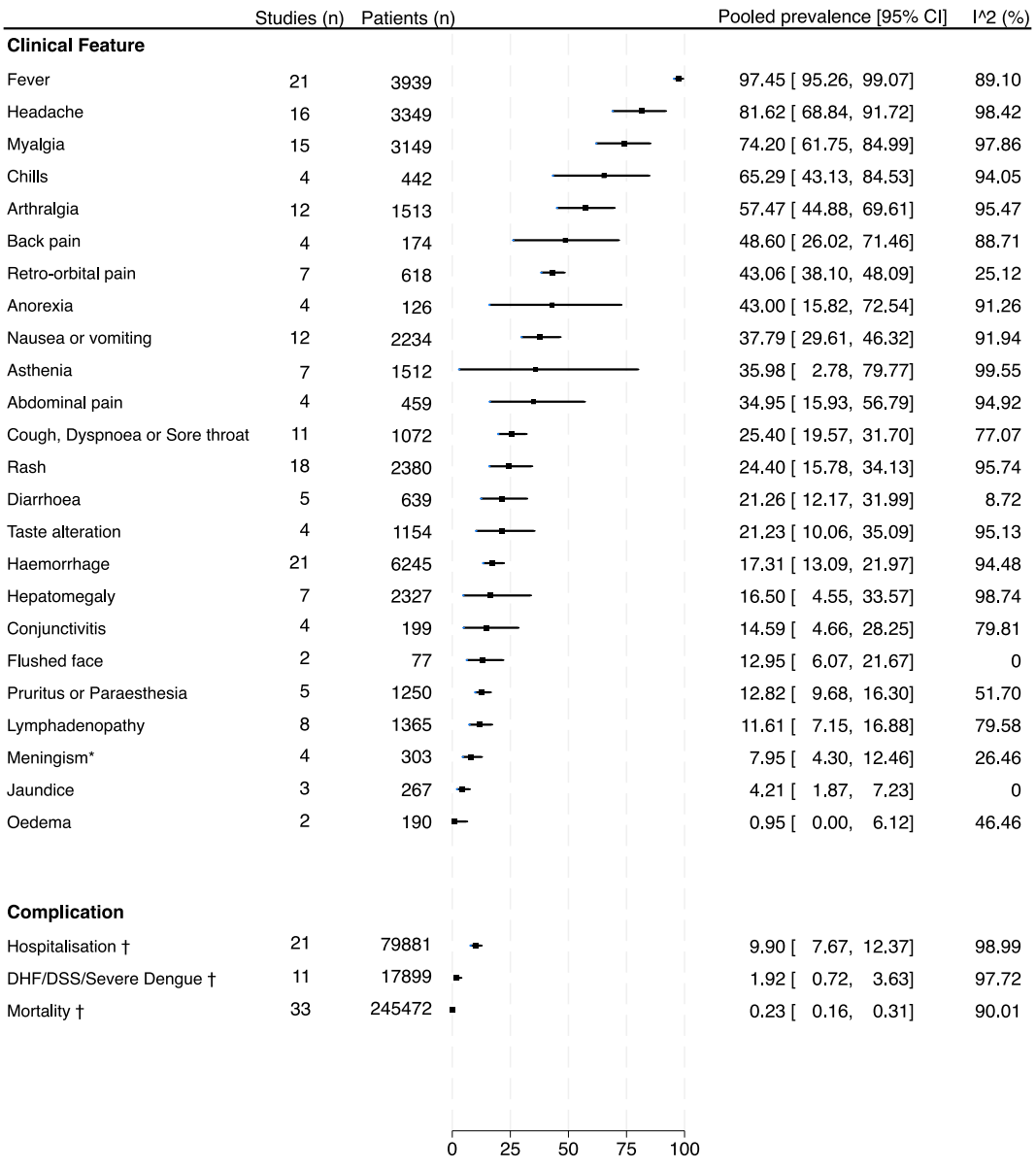

FIGURE 2 Forest plot of pooled prevalence estimates for the clinical manifestations of dengue in the Pacific Islands. DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome.

fever, hepatomegaly and haemorrhage compared to studies examining the general population (all $p < 0.05$). Notably, pooled prevalence of haemorrhage and hepatomegaly in hospitalised patients were 30.66% (95% CI 19.34–43.24) and 40.43% (95% CI 21.86–60.46), respectively, compared to 14.01% (95% CI 10.47–17.95) and 5.42% (95% CI 1.05–12.79) in the general population. Furthermore, no publication bias was detected through funnel plots and Egger's test apart from lymphadenopathy, hepatomegaly and haemorrhage. Funnel plots for these clinical features demonstrated asymmetry and was supported by Egger's test for haemorrhage ($p < 0.05$). However, no additional studies were imputed using the trim-and-fill method. Moreover, sensitivity analysis through the leave-one-out meta-analysis method identified that for chills, back pain, asthenia, anorexia, taste alteration, abdominal pain, conjunctivitis and hepatomegaly, there were one or two studies that presented a significantly different prevalence to others and consequently resulted in a substantial change to the overall estimate once excluded (see supplementary materials 2 and 3 for further details).

The estimated hospitalisation rate for dengue across the Pacific Islands was 9.90%. Whilst subgroup analysis, publication bias testing and sensitivity analysis were unremarkable, three studies reported a substantially higher hospitalisation rate of approximately 30%,[48–50] which likely contributed to the observed heterogeneity (I^2 = 98.99%). The mortality rate in the general population was estimated at 0.23% and higher mortality was observed in patient cohorts prior to the year 2000 (0.40%, 95% CI 0.20–0.65) compared to patient cohorts after 2000 (0.16%, 95% CI 0.10–0.23) ($p < 0.05$). DENV-2 also had higher estimated mortality (0.47%, 95% CI 0.08–1.13) compared to DENV-1 (0.29%, 95% CI 0.13–0.49), DENV-3 (0.25%, 95% CI 0.00–0.88) and DENV-4 (0.24%, 95% CI 0.01–0.65) but the difference was not significant ($p > 0.05$). Furthermore, there was evidence of publication bias, which was supported by the higher mortality rates observed in studies with sample sizes less than 1000 patients compared to larger samples ($p < 0.05$). However, no studies were imputed using the trim-and-fill method. In hospitalised patients, pooled prevalence for mortality increased to 2.84% (95% CI 1.34–4.81) with a reduction in heterogeneity to I^2 = 71.37%. There were higher case fatality rates in hospitalised children (3.06%, 95% CI 1.83–4.57) than other patient cohorts, although the difference was not significant due to the limited sample size ($p > 0.05$). Lastly, the pooled prevalence estimate for severe forms of dengue (DHF, DSS or severe dengue) was 1.92% in the general population, with DHF estimated at 2.34% (95% CI 0.61–5.04) and severe dengue estimated at 1.10% (95% CI 0.39–2.14). The prevalence of these severe forms increased to 23.23% (95% CI 13.58–34.53) in hospitalised cohorts, with DHF prevalence estimated at 21.06% (95% CI 7.48–39.07), DSS estimated at 4.11% (95% CI 0.02–13.39) and one study reporting severe dengue in 24.64% of patients.[51] In both patient cohorts, no publication bias was detected and excluding one study at a time during sensitivity analysis did not alter effect size significantly apart from one study in the general population cohort[52] and another study in the cohort of hospitalised patients,[53] both of which reported significantly higher rates of DHF (see supplementary materials 2 and 3 for further details).

3.5 | Clinical manifestations of Zika virus

Rash (85.13%) was the most common symptom in Zika infections, followed by arthralgia (66.63%), myalgia (59.34%) and fever (54.50%) (see Figure 3). Peripheral oedema also occurred in 23.31% of patients. Low to moderate heterogeneity was detected for all symptoms except for asthenia (I^2 = 94.55%). Similarly, subgroup analysis and sensitivity testing revealed no significant differences in overall pooled prevalence estimates apart from studies reporting asthenia. There was also no evidence of publication bias through funnel plot inspection. Furthermore, there were three studies that investigated a cohort of GBS patients with preceding Zika illness.[54–56] Patients who

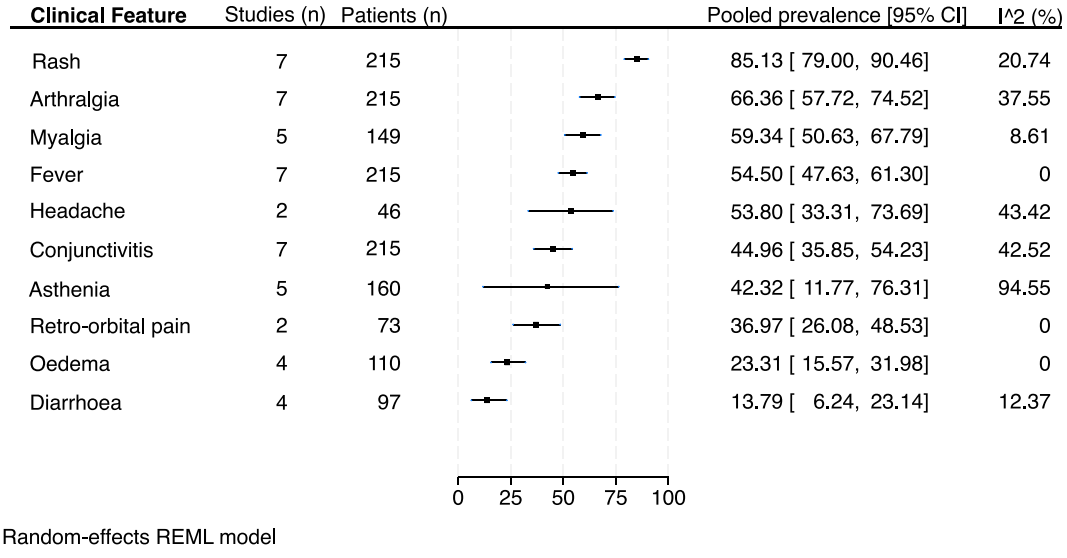

FIGURE 3 Forest plot of pooled prevalence estimates for the clinical features of Zika infections in the Pacific Islands.

developed GBS were estimated to have a higher frequency of diarrhoea (20.51%, 95% CI 8.01–35.95) and oedema (28.08%, 95% CI 17.50–39.95) during their Zika illness compared to other patients (10.10%, 95% CI 3.01%–19.94% and 17.16%, 95% CI 7.06–29.99, respectively), although the differences were not significant (both $p > 0.05$) (see supplementary materials 2 and 3 for further details).

Pooled prevalence estimates were calculated for GBS based on studies from the 2013–2014 Zika outbreak in French Polynesia. Studies either described the prevalence of the 42 GBS cases in relation to the number of reported Zika cases, which differed in quantity between each study,[56–58] or based on an estimate of the total number of Zika infections during the outbreak.[54,57] The pooled prevalence of GBS was estimated at 14.08 (95% CI 11.71–16.66) per 10,000 reported Zika cases and 2.30 (95% CI 1.75–2.85) per 10,000 estimated Zika infections. For both estimates, there was no heterogeneity observed, sensitivity analysis revealed no major differences to the overall estimate and no publication bias was detected (see supplementary materials 2 and 3 for further details). Congenital brain malformations such as microcephaly were reported in several studies. However, only one study provided prevalence data for microcephaly, with an estimated risk of 95 (95% CI 34–191) per 10,000 women infected with Zika in the first trimester.[44] The remaining studies reported increased odds of congenital brain abnormalities with maternal Zika infection, ranging from a seven-fold increase in the odds of congenital brain defects[34] to a 14-fold increase in the risk of microcephaly.[37] When stratified by the timing of maternal Zika infection, the highest risk of congenital brain malformations was observed when infection occurred during the first trimester.[36] Furthermore, hospitalisation and mortality were outcomes of only one study, which reported no hospitalisation or deaths out of 59 probable cases in Federated States of Micronesia.[59] One study additionally reported a statistically significant association between acute flaccid paralysis, which most often occurs in the form of GBS, and Zika infections in the Solomon Islands ($p \leq 0.001$) but not elsewhere.[45]

3.6 | Clinical manifestations of chikungunya

In cases of chikungunya, fever and arthralgia were the only symptoms reported in at least two studies, and both were present in almost all subjects (100.00%, 95% CI 100.00%–100.00% and 100.00%, 95% CI 99.97–100.00, respectively) (see supplementary materials 2 and 3 for further details). Other symptoms reported in hospitalised chikungunya patients in Papua New Guinea were headache (81 out of 91), nausea (25 out of 98) and cough (30 out of 98).[60] Rash was additionally reported in the preceding chikungunya illness of three out of eight GBS patients in French Polynesia.[61]

The hospitalisation rate of chikungunya infections was estimated at 2.57% (95% CI 1.30–4.25) from two studies.[58,62] A cluster of GBS cases also occurred following the 2014–2015 outbreak in French Polynesia, and the estimated pooled prevalence of GBS was 1.70 (95% CI 1.06–2.48) per 10,000 reported chikungunya cases (see supplementary materials 2 and 3 for further details). Furthermore, in a sample of 64 intensive care unit patients, additional complications of chikungunya included shock ($n = 40$), encephalitis ($n = 5$), renal failure ($n = 30$), respiratory failure ($n = 33$) and myocarditis ($n = 2$; both of which were fatal) and 18 patients died during their admission.[63]

3.7 | Comparison of the clinical manifestations of dengue, Zika and chikungunya

The prevalence estimates for overlapping symptoms of dengue, Zika and chikungunya are shown in Figure 4. Test of group differences using chi-squared tests between dengue and Zika studies demonstrated that patients with dengue were significantly more likely to report fever and headaches, whereas rash, conjunctivitis and oedema were more frequent in Zika infections (all $p < 0.05$). Furthermore, fever and arthralgia were significantly more common in chikungunya compared to dengue and Zika cases (both $p < 0.05$) (see supplementary material 2 for further details).

Hospitalisation rates were significantly higher in dengue (9.90%) compared to chikungunya (2.57%) ($p < 0.05$), whilst for Zika, no hospitalisations were reported apart from GBS patients. Mortality rates could not be compared as there was insufficient mortality data for Zika and chikungunya. Furthermore, GBS was more likely to occur in Zika (14.08 per 10,000 suspected cases) compared to chikungunya (1.70 per 10,000 suspected cases) ($p < 0.05$) and no GBS cases were reported in any dengue studies (see supplementary material 2 for further details).

4 | DISCUSSION

In this systematic review and meta-analysis, pooled prevalence estimates were calculated for the clinical features and complications of dengue, Zika and chikungunya in the Pacific Islands.

For dengue, the frequency of common symptoms such as fever, headache, myalgia, chills, arthralgia, back pain and retro-orbital pain in Pacific Island populations were similar to global estimates.[64] Notably, rash occurred in less than a quarter of patients and as noted in other studies,[64,65] the typical rash associated with dengue may not be as frequent as described in current guidelines.[26] Haemorrhage and hepatomegaly were more common in hospitalised patients compared to the general population, which is unsurprising as both clinical features are recognised as warning signs for progression to severe dengue.[10] Haemorrhage most often occurred in the form of petechiae/purpura/ecchymosis, followed by epistaxis, particularly in children, which is consistent with the existing literature.[66,67] Meningism was another important clinical feature identified in 7.95% of hospitalised dengue patients and is seldom reported in existing guidelines despite several reports of both meningitis and encephalitis associated with dengue.[68]

The hospitalisation rate for dengue was estimated at 9.90%. However, there was significant heterogeneity across studies, most

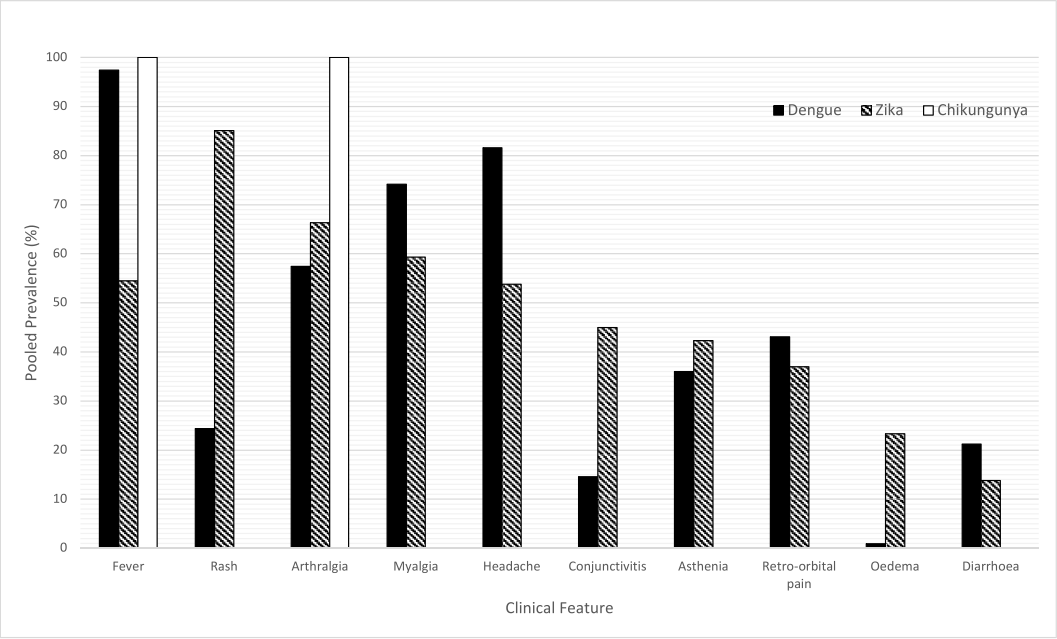

FIGURE 4 Clustered bar chart of pooled prevalence estimates for overlapping symptoms of dengue, Zika and chikungunya in the Pacific Islands.

likely attributed to the substantially higher proportion of hospitalised cases during outbreaks in American Samoa,[48] Guam[49] and Federated States of Micronesia.[50] The overall hospitalisation rate of dengue in the Pacific Islands was significantly lower than hospitalisation rates identified in Mexico (23.4%),[69] Singapore (26%),[70] Puerto Rico (32.6%)[49] and Thailand (63.3%).[71] The comparatively lower rate of hospitalisation in the Pacific Islands may be attributed to the limited capabilities of healthcare facilities which consequently results in a higher severity threshold for hospital admission. Mortality associated with dengue in the general population was 0.23%, with a decrease in mortality over time, most likely associated with improvements in the quality of healthcare. These estimates are lower than estimated dengue mortality rates in Malaysia (0.29%),[72] India (0.39%),[73] Latin America (2.44%)[74] and globally (1.3%).[64] The difference could be due to underreporting of deaths in the Pacific Islands; however, it is difficult to make further conclusions as estimated mortality is ultimately influenced by the inclusion of mild or asymptomatic cases that may or may not have been reported. Furthermore, higher mortality rates were identified in children, which adds to existing evidence that children are more likely to experience complications resulting from dengue infections.[75] Mortality was also highest in DENV-2-infected patients, which is concerning given the large number of DENV-2 outbreaks in the Pacific Islands.[9] In terms of the prevalence of severe forms of dengue (DHF, DSS or severe dengue) in hospitalised patients (23.23%), estimates were similar to findings from Europe (21%)[19] and slightly lower than in India (28.9%).[73]

In Zika infections, rash, arthralgia, myalgia, fever, headache and conjunctivitis were the most common symptoms and occurred at a similar frequency to estimates from global studies.[76] Oedema also occurred in approximately a quarter of patients, most commonly affecting the distal limbs or extremities. Interestingly, almost half of patients with Zika were afebrile, which is an important consideration for clinicians given that Zika is traditionally recognised as a febrile illness.[77] Furthermore, GBS patients were more likely to present with diarrhoea and oedema compared to other patients. This difference in symptomatology may be useful to predict patients at risk of developing GBS, although significantly more research is required.

Patients with Zika generally had mild, self-limiting illnesses with no hospitalisations reported apart from patients with GBS. The pooled prevalence estimate of GBS was 14.08 per 10,000 reported Zika cases or 2.30 per 10,000 estimated total Zika infections, which is slightly lower than the risk of GBS associated with *Campylobacter jejuni* infection (2.5 to 6.5 GBS cases per 10,000 C. *jejuni* infections).[78] Several studies also reported a significant increase in the risk of congenital brain malformations associated with maternal Zika infection, particularly when infection occurred during the first trimester.[36,44] This conclusion is supported by large body of evidence in the literature[79] and has significant implications for the care of pregnant women during Zika outbreaks.

For chikungunya, fever and arthralgia were present in almost all patients as the symptoms were generally required to meet the case definition for chikungunya. The limited number of studies meant that pooled prevalence estimates were not calculated for other common symptoms, notably headache and rash.[80] The rate of hospitalisation for chikungunya in the Pacific Islands was 2.57%, which is consistent with existing estimates which suggest that hospitalisation for chikungunya is relatively uncommon and ranges between 0.5% and 8.7%.[81] Furthermore, a cluster of GBS cases were reported following the 2014–2015 chikungunya outbreak in French Polynesia, shortly after the 2013–2014 Zika outbreak. The prevalence of GBS was estimated

at 1.70 per 10,000 reported chikungunya cases, which was significantly lower than the risk of GBS associated with the preceding Zika outbreak. There have also been reports of GBS associated with chikungunya in Réunion Island (2 cases),[82] French West Indies (1 case)[83] and India (2 cases).[84] Moreover, several cases of encephalitis and myocarditis were reported in intensive care patients with chikungunya.[63] Myocarditis and encephalitis are both increasingly recognised as serious potential complications of chikungunya infections.[85,86]

Although there are several overlapping clinical features of dengue, Zika and chikungunya, our findings suggest that symptoms that may differentiate between the arboviruses include the presence of headaches in dengue, in addition to haemorrhage and hepatomegaly in severe forms of the disease; rash, conjunctivitis and peripheral oedema in Zika; and the combination of fever and arthralgia in chikungunya infections. These distinguishing features provide further depth to existing algorithms for clinical differential diagnosis of these arboviruses.[10]

There were several limitations in our systematic review that should be considered. First, the limited number of studies on Zika and chikungunya infections compared to dengue made it challenging to compare the clinical manifestations of each arbovirus. The difference in the number of studies is most likely due to the recent emergence of Zika and chikungunya in the Pacific and future research can build on our findings. Secondly, there was significant heterogeneity detected for the clinical manifestations of dengue. Given the differences in findings based on study location, differing reporting standards in each country were potentially a significant contributor to the observed heterogeneity. Hence, we advocate for continued efforts to improve the transparency and consistency of disease reporting in low socioeconomic areas like the Pacific Islands. Lastly, asymptomatic and mild cases are often underreported and thus pooled prevalences were likely overestimates of the true frequency of clinical manifestations for each arbovirus.

5 | CONCLUSION

In this systematic review and meta-analysis, we calculated pooled prevalence estimates for the clinical features and complications of dengue, Zika and chikungunya infections in the Pacific Islands. Despite often being reported to be clinically indistinguishable, our results indicate that potential differentiating features between the three arboviruses include headache, haemorrhage and hepatomegaly in dengue; rash, conjunctivitis and peripheral oedema in Zika; and the combination of fever and arthralgia in chikungunya. We also advocate for greater clinician awareness into the possible occurrence of GBS following Zika and chikungunya infections, and the increased likelihood of congenital brain malformations such as microcephaly with maternal Zika infection. Our findings add to the growing knowledge base on the clinical manifestations of arboviruses and will assist clinicians in the Pacific Islands when faced with future arbovirus outbreaks.

AUTHOR CONTRIBUTIONS

SK conceptualised the study and conducted database searches. Both authors (SK and NH) conducted the study selection process, data extraction and statistical analysis. SK draughted the article and both authors edited and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

ETHICS APPROVAL STATEMENT

Ethics approval was not required for this review.

PATIENT CONSENT STATEMENT

Patient consent was not required for this review.

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No AI-generated content was used for this review.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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