Clinical symptoms and complications of Dengue, Zika and Chikungunya infections in Pacific Island countries: a systematic review and meta-analysis

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Summary

Background

Dengue fever (DENV), Zika virus (ZIKV) and chikungunya (CHIKV) pose a significant public health risk to Pacific Island countries. However, there is limited existing research that compares the clinical manifestations of these arboviruses.

Methods

We searched PubMed, Embase and Scopus for epidemiological studies that presented quantitative data for symptoms or complications of DENV, ZIKV or CHIKV in a Pacific Island country. Risk of bias assessment was conducted using the Newcastle-Ottawa Scale (NOS). For each arbovirus, we used descriptive statistics and performed random-effects meta-analysis to calculate pooled prevalence estimates with 95% confidence intervals. Heterogeneity was assessed using the I^2 statistic and was further investigated through subgroup analysis. Publication bias was assessed via Egger's test.

Findings

We found that fever, headache, arthralgia, myalgia, rash and gastrointestinal symptoms were common in all three arboviruses. Complications for ZIKV included Guillain-Barré syndrome (GBS) (0.5%) and microcephaly (56%), and for CHIKV, were shock or organ failure (3%), liver disease (1%), myocarditis (0.1%) and neurological complications (1%). Through meta-analysis, we estimated the rates of hospitalisation (12.45% [7.88-17.87]), mortality (0.25% [0.05-0.54]) and severe dengue (4.47% [0.97-10.17]) in DENV. Subgroup analysis revealed clinical heterogeneity based on age, geographical location, study design and whether studies only examined hospitalised patients. Publication bias was also detected for studies assessing complications of DENV.

Interpretation

We identified overlapping symptoms as well as clinical features that were specific to each arbovirus: For DENV, haemorrhagic symptoms, flushed face and taste alteration; and for ZIKV, limb oedema, Guillain-Barré syndrome and microcephaly. Despite CHIKV being recognised as a classically mild disease, we also identified the potential for severe complications such as myocarditis, encephalitis and shock or organ failure. We proposed updated clinical criteria for DENV, ZIKV and CHIKV to guide clinicians in Pacific Island countries. Our review was limited by lack of data availability and consequently we advocate for efforts to improve the transparency and consistency of disease reporting systems in the

region. Overall, our research will assist healthcare providers in Pacific Island countries to better understand these clinically challenging arboviruses.

Funding
There was no funding for this study.

Panel: Research in context

Evidence before this study

We searched PubMed, Embase and Scopus with the search terms "dengue" AND "zika" AND "chikungunya" in title, abstract and keyword fields to identify all articles in any language published from inception to May 2022 that assessed the clinical features of dengue fever (DENV), Zika virus (ZIKV) and chikungunya (CHIKV). There is yet to be a study which compares the clinical features of these three arboviruses using quantitative methods. Previous articles have identified that the clinical features may be difficult to distinguish and frameworks for comparison have been proposed. However, statistical analysis has not been conducted. Furthermore, we identified that Pacific Island countries were under-represented in the literature despite having significant burden of all three arboviruses. Hence, the aim of our research is to estimate the prevalence of the symptoms and complications of DENV, ZIKV and CHIKV in Pacific Island countries.

Added value of this study

Using a combination of descriptive statistics and meta-analysis, we identified symptoms that were common amongst all three arboviruses, as well as identifying potentially distinguishing features. For example, haemorrhagic symptoms, flushed face and taste alteration were symptoms only seen in DENV, whereas limb oedema was a finding specific to ZIKV. Based on our findings, we propose an updated version of the World Health Organization (WHO)/ Pan American Health Organization (PAHO) clinical criteria to provide a comprehensive set of symptoms for each arbovirus. Furthermore, for DENV, we estimated the rates of hospitalisation (12.45% [7.88-17.87]), mortality (0.25% [0.05-0.54]) and severe dengue (4.47% [0.97-10.17]) in Pacific Island countries. We also identified Guillain-Barré syndrome (0.5%) and microcephaly (56%) as significant complications of ZIKV, as well as observing numerous (albeit infrequent) complications of CHIKV such as shock or organ failure (3%), liver disease (1%), myocarditis (0.1%) and encephalitis (1%).

Implications of all the available evidence

Our research provides a comprehensive picture of possible symptoms and complications of DENV, ZIKV and CHIKV in Pacific Island countries. Our findings will provide physicians in the region with greater confidence when they encounter these diseases. A challenge that we faced was the lack of data availability and limited number of studies, particularly for ZIKV and CHIKV. Hence, we propose that greater efforts are required to improve local disease reporting systems. Similar studies should also be conducted in different regions or at a global level to prepare physicians worldwide for impending outbreaks given the global re-emergence of these arboviruses.

Introduction

Arthropod-borne viruses (arboviruses) account for more than 17% of all infectious disease cases worldwide.[1] Globally, the three most prevalent arboviruses per year are dengue fever (DENV; 96 million cases), chikungunya virus (CHIKV; 693,000 cases) and Zika virus

(ZIKV; 500,000 cases).[2] DENV, ZIKV and CHIKV are transmitted via the same vector, *Aedes aegypti*, and share similar epidemiology and clinical expressions.[3] Together, these three arboviruses pose a significant global public health risk given their rising incidence and expanding geographic distribution.

The (re)emergence of arboviruses in recent decades has been driven by increased population density from urbanisation, increased international mobility with globalisation and increased agricultural capacity, which has facilitated greater contact between contemporary arthropods and humans.[4] Furthermore, climate change has increased the abundance and global distribution of *A. aegypti*, an ectotherm species dependent on warm and humid conditions for reproduction and disease transmission.[5] The vector has now spread to previously non-endemic areas, with the greatest burden of disease experienced in tropical areas, closest to the equatorial belt.

Pacific Island countries are a group of low-lying, small island developing states which are vulnerable to arboviruses and infectious diseases more broadly. Their vulnerability is a product of their tropical climate; poor sanitation, hygiene and vector control; exposure to climate change and variability; and insufficient capacity of healthcare systems.[6] Outbreaks of DENV have been reported in the Pacific as early as the mid 19th century, however, ZIKV and CHIKV have only recently emerged in the region.[7] In 2007, the first outbreak of ZIKV in the Pacific was reported in Federated States of Micronesia, and in 2011, the first CHIKV outbreak in the region was reported in New Caledonia.[8] Since then, the arboviruses have disseminated throughout the region. Between 2014 and 2020, 104 unique arboviral outbreaks were recorded in Pacific Island countries, including 72 DENV outbreaks, 18 ZIKV outbreaks and 14 CHIKV outbreaks.[1]

Definitive diagnosis of each arbovirus is achieved through enzyme-linked immunosorbent assay (ELISA) or reverse transcriptase-polymerase chain reaction (RT-PCR).[9] However, these diagnostic tests are not readily available in Pacific Island countries due to under-resourced healthcare facilities with limited capacity for laboratory testing.[1, 3] Therefore, it is critical for clinicians in the region to effectively diagnose these diseases based on clinical presentation alone.

This is often challenging as the clinical features of DENV, ZIKV and CHIKV may be indistinguishable, especially in the early stages, where many patients present with a non-specific febrile illness.[9] For each arbovirus, treatment is supportive and is usually sufficient given the self-limiting clinical course in most cases.[10] However, there is the potential for severe complications which may range from severe dengue (formally referred to as dengue haemorrhagic fever) in DENV[11] to Guillain-Barré syndrome (GBS) and microcephaly in ZIKV[9] to cardiac and neurological complications in CHIKV. [10, 12]

Current literature has failed to clearly distinguish the clinical characteristics of these arboviruses.[9] There is limited existing research that compares the clinical features of DENV, ZIKV and CHIKV on a global level, let alone in the Pacific. Frameworks for their comparison exist, however, this has not been performed through statistical methods.[9] Given the increasing burden of disease, more research is required to determine the prevalence of symptoms and complications of DENV, ZIKV and CHIKV in Pacific Island countries.

The primary objective of our systematic review and meta-analysis is to estimate the prevalence of clinical features for each arbovirus. The secondary objective is to identify distinguishing features between their clinical presentations. We acknowledge that there is limited data available in these developing nations and that this poses a challenge for statistical analysis. However, this obstacle has resulted in Pacific Island countries being under-represented and neglected in the global literature. Hence, we have confined the location of studies to Pacific Island countries to present findings specific to the region, which will make our findings beneficial to local clinicians.

Methods

Search strategy and selection criteria

Our systematic review and meta-analysis follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[13]

We conducted a literature search using the following electronic databases: PubMed (1848-2022), Embase (Ovid interface; Jan 1, 1974, to June 9, 2022) and Scopus (1960-2022). We searched title, keyword and abstract fields as well as subject headings in PubMed and Embase (e.g., Emtree and MeSH, respectively). Searches were conducted on June 12, 2022, with no date restrictions. Language was restricted to English to ensure that the abstracts of all identified citations were published in English. This provided appropriate context to extract relevant data from the full text, even if it was written in another language, using Google Translate.

The search included two clusters of terms: one for arboviruses ("dengue", "zika" and "chikungunya") and one for Pacific Island countries, where "melanesia", "micronesia" and "polynesia" were searched along with the countries which they contain. The Boolean operator "AND" was used between each search term cluster to retrieve articles that contained at least one term from each cluster. The complete set of search terms is provided in the appendix.

Following the literature search, all identified citations were collated and imported into the screening and data extraction tool, Covidence, which automatically removed duplicates. Two reviewers (Author S.K. and N.H.) independently screened articles by title and abstract and then for full-text eligibility according to the following inclusion criteria: (a) Epidemiological study, including cohort, case-control, cross-sectional studies, and case reports; (b) Presents individual patient-level quantitative data regarding the symptoms or complications of DENV, ZIKV or CHIKV; (c) Study location in a Pacific Island country (d) Laboratory confirmation of diagnosis; (e) Published in a peer-reviewed journal; and (f) Abstract available in English language.

Case reports investigating travellers to or from a Pacific Island country were excluded, along with reviews, conference proceedings, editorials and book chapters. Grey literature was also excluded as they are not from peer-reviewed sources and would impact the validity of statistical analysis conducted in our review.

In addition, the reference and citation list of included studies were manually inspected to identify other potentially relevant articles for inclusion. The citation lists were obtained from Scopus and Google Scholar.

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

Data extraction and quality assessment

For each study that satisfied the selection criteria, both reviewers (Authors S.K. and N.H.) independently extracted data into an Excel spreadsheet. Studies were categorised according to the arbovirus investigated, and the following data were extracted: (a) Citation details; (b) Study period; (c) Study location; (d) Sample size; (e) Mean age and gender distribution; (f) Method of laboratory confirmation; (g) Dengue virus subtype (for dengue studies); (h) Symptoms; (i) Complications; (j) Hospitalisations; and (k) Deaths.

For each symptom and complication (including hospitalisations and deaths), the number of patients and the percentage of the sample size were recorded.

For quality assessment, each article was evaluated against the Newcastle-Ottawa Scale.[14] The Newcastle-Ottawa Scale is used to assess the methodological quality of non-randomised studies in healthcare. The scale has an overall score out of nine and evaluates three domains: (1) the selection of study groups; (2) the comparability of the groups; and (3) the ascertainment of the exposure or outcome.[14] In addition, the Australian National Health and Medical Research Council (NHMRC) levels of evidence were ascribed to each study to reflect the intrinsic risk of bias of its study design.[15] The NHMRC evidence hierarchy consists of levels of evidence from I to IV, where level IV donates the study design least robust at answering research questions.

Data analysis

For data analysis, the symptoms and complications of each arbovirus were synthesised using descriptive statistics, whereby the number of patients and the proportion of cases, represented as percentages, were calculated. All studies, including case reports, were included for descriptive statistics. However, some articles had overlapping clinical data, meaning that only one data set was included in these scenarios.

For clinical features with at least two studies (excluding case reports), meta-analysis was then conducted to obtain pooled prevalence estimates and 95% confidence intervals. Due to the limited number of studies available, meta-analysis was only conducted for symptoms and complications of DENV and symptoms of ZIKV. For the same reason, direct statistical comparison between the clinical features of these arboviruses was not undertaken given the differing sample sizes and reporting standards.

We used *metaprop* in Stata (version 17.0) to conduct meta-analysis with inverse-variance weights obtained from the DerSimonian-Laird random-effects model.[16] We used the Freeman-Turkey double arcsine transformation to stabilise the variances in studies with proportions close to or at 0% or 100%. Meta-analyses were conducted individually for each clinical feature with the data represented collectively using a forest plot.

To explore the heterogeneity between studies, we used the I^2 statistic, which describes the proportion of total variation of study estimates due to heterogeneity.[17] I^2 values of 25%, 50% and 75% represented low, moderate and high heterogeneity, respectively.

As substantial heterogeneity ($I^2 > 75\%$) was consistently present across studies, we further investigated potential sources of heterogeneity through subgroup analyses based on patient age (by comparing studies with mean age less or greater than 25 years old), study period (by comparing study periods before and after the year 2000), study location (by comparing French Polynesia-based studies with those based elsewhere), study design and whether studies examined only hospitalised patients. Differences between subgroups were considered statistically significant if $p < 0.05$, where more than one study was included in each subgroup. Gender was not included as all studies contained mixed-sex samples and almost all had roughly even gender distribution. DENV serotype was not included in subgroup analysis as there were too few studies within each subgroup. Similarly, subgroup analysis was not conducted for ZIKV given the limited total number of studies.

Egger's test was used to assess for publication bias where there were at least 10 studies included in a meta-analysis.[18] If fewer than 10 studies were included, the power of Egger's test would be too low to distinguish chance from real asymmetry.[19] Due to the limited number of studies, Egger's test was only performed for some clinical features of DENV.

The study protocol was registered prior to the study selection process on Open Science Framework (OSF) registries (https://osf.io/c3jzf).

Role of the funding source
There was no funding source for this review.

Results

A total of 2315 studies were screened after duplicates were removed. 88 studies remained after title and abstract screening and 49 studies were included after full-text review. There were 27 studies included for DENV, 16 for ZIKV, five for CHIKV and one for DENV and ZIKV co-infection (***Figure 1***).

Figure 1**:** PRISMA flow diagram of the study selection process[13]

The study characteristics of articles are shown in ***Table 1***. In terms of study location, a total of 11 Pacific Island countries were included (American Samoa, Federated States of Micronesia, Fiji, French Polynesia, Hawaii, Marshall Islands, New Caledonia, Palau, Papua New Guinea, Solomon Islands and Tuvalu). More than half of the studies were from French Polynesia (n = 23). Studies were of fair overall quality (Mean NOS score = 6/9) and were generally either of NHMRC level III or IV, with retrospective cohort studies being the most common study type (n =20).

Study	Virus (subtype)	Study location	Study period	Study design	Sample size	Method of diagnosis	Symptoms or complications or both	NOS overall score (/9)	NHMRC level of evidence
[20]	DENV (DENV-4)	Palau	1995	Cross-sectional study	817 (78 for symptoms)	IgM ELISA	Both	6	IV
[21]	DENV (DENV-1)	PNG	2013	Prospective cohort study	23	Dengue NS1-RDT	Both	6	II

[22]	DENV (DENV-1, 2)	French Polynesia	2019	Retrospective cohort study	331	Dengue IgM, NS1-RDT, RT-PCR	Complications	6	III
[23]	DENV (DENV-1)	New Caledonia	2003	Retrospective cohort study	170	IgM ELISA, RT-PCR	Complications	9	III
[24]	DENV (DENV-3)	New Caledonia	1995-96	Retrospective cohort study	68	RT-PCR	Both	3 (full text in French)	III
[25]	DENV (DENV-1)	French Polynesia	1988-89	Retrospective cohort study	691	IgM ELISA	Both	7	III
[26]	DENV (DENV-2)	French Polynesia	1996-97	Prospective cohort study	298 (196 for symptoms)	IgM ELISA	Both	9	II
[27]	DENV (DENV-2)	French Polynesia	1996-97	Prospective cohort study	62	IgM ELISA	Complications	7	II
[28]	DENV (subtype NR)	French Polynesia	NR	Case report	1	IgM or IgG, NS1-RDT	Both	5	IV
[29]	DENV (DENV-4)	FSM	2012-13	Retrospective cohort study	729	NS1-RDT, IgM antibody	Complications	5	III
[30]	DENV (DENV-3)	French Polynesia	1989-90	Retrospective cohort study	213	NR	Complications	3 (abstract)	III
[31]	DENV (DENV-2)	American Samoa	2016-18	Retrospective cohort study	1081	RT PCR	Both	7	III
[32]	DENV (DENV-1)	FSM	2004	Retrospective cohort study	658	RT-PCR	Complications	6	III
[33]	DENV (DENV-1)	Hawaii	2001-2002	Prospective cohort study	122	IgM, IgG dengue	Both	9	II
[34]	DENV (DENV-1)	Fiji	1989-90	Prospective cohort study	3686	IgM ELISA	Complications	7	II
[35]	DENV (DENV-3)	Fiji	2014	Retrospective cohort study	5221	IgM ELISA	Complications	7	III
[36]	DENV (DENV-1)	French Polynesia	2001	Retrospective cohort study	1379	RT PCR, IgM or IgG ELISA	Complications	7	III

[37]	DENV (DENV-1)	Hawaii	2015-16	Prospective cohort study	264	RT-PCR, IgM ELISA	Both	7	II
[38]	DENV (subtype NR)	Hawaii	2015	Prospective cohort study	107	IgM ELISA	Complications	6	II
[39]	DENV (DENV-2, 3)	French Polynesia	1989-97	Retrospective cohort study	403	IgM ELISA, RT-PCR	Complications	7	III
[40]	DENV-2	French Polynesia	1996-97	Retrospective cohort study	123	IgM ELISA, RT-PCR	Complications	8	III
[41]	DENV (DENV-3)	Solomon Islands	2013	Prospective cohort study	5254	NS1-RDT, RT-PCR, IgM ELISA	Complications	6	II
[42]	DENV (subtype NR)	PNG	2016	Cross - sectional study	165	NS1-RDT, IgM, IgG	Both	8	IV
[43]	DENV (subtype NR)	PNG	2007-08	Prospective cohort study	46	NS1-RDT, IgG, IgM serology	Symptoms	5	II
[44]	DENV (DENV-4)	Marshall Islands	2011-12	Retrospective cohort study	867	RT-PCR, IgM ELISA, NS1-RDT	Complications	7	III
[45]	DENV (DENV-1)	New Caledonia	2012-13	Case reports	3	RT-PCR	Both	4 (abstract)	IV
[46]	DENV (subtype NR)	Tuvalu	NR	Prospective cohort study	132	RT-PCR, NS1-RDT	Complications	5 (abstract)	II
[47]	ZIKV	French Polynesia	2013-14	Case reports	4	RT PCR	Both	6	IV
[48]	ZIKV	French Polynesia	2014-15	Retrospective cohort study	4	RT PCR	Complications	6	III
[49]	ZIKV	French Polynesia	2013-14	Case-control study	42*	RT PCR	Both	7	III
[50]	ZIKV	French Polynesia	2013	Case reports	3	RT PCR	Symptoms	4	IV
[51]	ZIKV	French Polynesia	2013-15	Retrospective cohort study	8	IgG ELISA	Complications	7	III
[52]	ZIKV	FSM	2007	Prospective cohort study	49 (31 for symptoms)	RT PCR	Both	8	II
[53]	ZIKV	French Polynesia	2013	Case reports	4	RT PCR	Both	5	IV

[54]	ZIKV	New Caledonia	2015-16	Prospective cohort study	48	RT PCR	Symptoms	5	II
[55]	ZIKV	French Polynesia	2013-14	Case Reports	4	RT PCR	Complications	3	IV
[56]	ZIKV	French Polynesia	2013-14	Retrospective cohort study with modelling	42*	RT PCR	Complications	6	III
[57]	ZIKV	Hawaii	2009-12	Case control study	3	IgM, IgG ELISA	Complications	7	III
[58]	ZIKV	French Polynesia	2013	Case report	1	IgM ELISA	Both	6	IV
[59]	ZIKV	French Polynesia	2013-14	Cross-sectional study	42*	RT PCR	Complications	6	IV
[60]	ZIKV	New Caledonia	2014-15	Case-control study	5	RT PCR, IgM ELISA	Complications	7	III
[61]	ZIKV	French Polynesia	2013-16	Case-control study	21	IgM ELISA	Complications	4	III
[62]	ZIKV	French Polynesia	2013	Retrospective cohort study	42*	RT PCR	Complications	6	III
[63]	CHIKV	PNG	2012	Prospective cohort study	98	RT PCR	Symptoms	6	II
[64]	CHIKV	French Polynesia	2014-15	Retrospective cohort study	64†	RT PCR, IgM	Both	9	III
[65]	CHIKV	French Polynesia	2014-15	Prospective cohort study	9†	RT PCR, IgM, IgG	Both	5	II
[66]	CHIKV	FSM	2013	Prospective cohort study	1761	RT PCR, IgM ELISA	Complications	6	II
[59]	CHIKV	American Samoa	2012-2014	Cross-sectional	823	NR	Complications	6	IV
[67]	Co-infection ZIKV and DENV (DENV-1, 3)	New Caledonia	2014	Case Reports	2	RT PCR, IgM ELISA	Both	6	IV

* Overlapping data for ZIKV; † Overlapping data for CHIKV

Note: ELISA, enzyme-linked immunosorbent assay; RT PCR, reverse transcriptase polymerase chain reaction; NS1-RDT, NS1-rapid diagnostic test; PNG, Papua New Guinea; FSM, Federated States of Micronesia

***Table 1*:** Summary of studies included in the review

The number of studies and patients for each clinical feature are represented according to the arbovirus in ***Table 2***.

For DENV, fever (95%), headache (68%), myalgia (65%), gastrointestinal symptoms (31%), arthralgia (18%) and rash (17%) were identified as the most common symptoms. Hospitalisation and mortality rates were estimated at 13% and 0.5%, respectively. Shock or organ failure, which included dengue haemorrhagic fever, dengue shock syndrome and severe dengue, were observed in 10% of cases.

For ZIKV, the most common symptoms were arthralgia (61%), rash (58%), fever (57%), myalgia (41%), headache (37%), conjunctivitis (28%) and retro-orbital pain (19%). Limb oedema (17%) was another notable symptom that was only reported in one patient with DENV and no patients with CHIKV. GBS (0.5%) was reported more frequently than in DENV (0.03%) and CHIKV (0.01%). Microcephaly was another complication that was only observed in ZIKV patients and occurred in 56% of patients where complications of congenital ZIKV was an outcome.

For CHIKV, results were limited as few studies were included (n=3), after exclusion of overlapping data. However, fever (100%), arthralgia (99%) and headache (47%) were identified as the most common symptoms. Respiratory (18%) and gastrointestinal symptoms (15%) were also noted in a significant proportion of patients. Rates of hospitalisation (2%), death (1%) and shock or organ failure (3%) were significantly lower than the corresponding rates for DENV. However, other complications such as liver disease (1%), neurological complications (1%) and myocarditis (0.1%) occurred at higher rates.

One study also investigated a ZIKV and DENV co-infection in two patients, where fever, headache, arthralgia, myalgia and malaise were shared symptoms and a mild clinical course with no complications resulted.[67]

	DENV		**ZIKV**		**CHIKV**	
	Number of studies (n= 12)	**Number of patients (%)**	**Number of studies** (n= 8)	**Number of patients (%)**	**Number of studies** (n= 3)	**Number of patients (%)**
Symptoms						
Fever	12	2604/2378 (95%)	6	77/133 (58%)	3	171/171 (100%)
Headache	11	1875/2378 (68%)	3	51/133 (38%)	1	81/171 (47%)
Arthralgia	9	497/2378 (18%)	4	84/133 (63%)	3	170/171 (99%)
Myalgia	11	1787/2378 (65%)	4	55/133 (41%)	1	8/171 (5%)
Rash	10	479/2378 (17%)	7	80/133 (60%)	1	3/171 (2%)
Gastrointestinal	11	862/2378 (31%)	2	17/133 (13%)	1	25/171 (15%)
Eye pain	5	237/2378 (9%)	2	26/133 (20%)	0	0

Conjunctivitis	2	35/2378 (1%)	5	39/133 (29%)	0	0
Respiratory	3	140/2378 (5%)	0	0	1	30/171 (18%)
Malaise	2	222/2378 (8%)	2	7/133 (5%)	0	0
Pruritus	2	103/2378 (4%)	1	2/133 (2%)	0	0
Limb oedema	1	1/2378 (0.04%)	4	24/133 (18%)	0	0
Chills	5	281/2378 (10%)	0	0	0	0
Haemorrhage	7	202/2378 (7%)	0	0	0	0
Adenopathy	5	198/2378 (7%)	0	0	0	0
Taste alteration	2	115/2378 (4%)	0	0	0	0
Neurological*	2	72/2378 (3%)	0	0	0	0
Oral ulcers	0	0	1	1/133 (1%)	0	0
Flushed face	2	22/2378 (1%)	0	0	0	0
Jaundice	1	5/2378 (0.2%)	0	0	0	0
Complications						
Hospitalisation	12	1791/13978 (13%)†	0	NR	2	60/2584 (2%) [a]
Death	22	109/22445 (0.5%)	0	NR	2	18/1825 (1%)
Shock or organ failure	17	1046/10040 (10%)	0	NR	1	55/1932 (3%)
Liver disease	2	15/10902 (0.1%)	0	NR	1	16/1932 (1%)
Guillain-Barre syndrome	1	3/10902 (0.03%)	2	48/8759 (0.5%)	1	9/66000 (0.01%)
Microcephaly	0	0	7	24/43 (56%)‡	0	0
Myocarditis	0	0	0	NR	1	2/1932 (0.1%)
Other neuro complication	1	1/10902 (0.01%)	0	NR	1	25/1932 (1%)

* Excluding patients with an identified neurological complication.
† Excluding studies that only assessed hospitalised patients.
‡ Out of samples where congenital abnormalities of ZIKV was an outcome of the study.

***Table 2*:** Clinical symptoms and complications of DENV, ZIKV and CHIKV patients in Pacific Island countries represented as the number of patients affected and proportion of cases

For DENV, pooled prevalence estimates using meta-analysis revealed similar findings for the frequency of symptoms and complications (***Figure 2***). The notable exceptions were the significantly increased prevalence of malaise (67.01% [61.82-72.00]), chills (63.62% [43.10-81.93]), conjunctivitis (34.35% [25.21-44.09]), retro-orbital pain (32.79% [10.02-60.91]), respiratory symptoms (31.20% [19.30-44.48] and flushed face (29.51% [19.08-41.06]. These symptoms were identified in fewer studies and consequently were under-represented in descriptive statistics.

Figure 2: Forest plot of pooled prevalence estimates for symptoms and complications of DENV

For ZIKV, pooled prevalence estimates were consistent with the descriptive statistics described above and showed a similar pattern of frequency for symptoms (**Figure 3**).

Figure 3: Forest plot of pooled prevalence estimates for symptoms of ZIKV

Across most studies, there was significant heterogeneity as represented by $I^2 > 75\%$. Subgroup analysis was conducted to investigate sources of heterogeneity in DENV studies (appendix). Studies with younger patients had lower prevalence of chills, retro-orbital pain, rash and gastrointestinal symptoms (all $p < 0.05$). Geographically, studies from French Polynesia had higher prevalence of headache and adenopathy, as well as lower prevalence of haemorrhage and hospitalisation compared to studies based elsewhere (all $p < 0.05$). Studies that only assessed hospitalised patients had significantly higher rates of fever, haemorrhage and shock or organ failure, but had lower rates of myalgia (all $p < 0.05$). In terms of study design, cross-sectional, retrospective cohort and prospective cohort studies differed significantly in terms of the prevalence of fever, headache, arthralgia, retro-orbital pain, myalgia, adenopathy, haemorrhage and hospitalisation rates (all $p < 0.05$). Subgroup analysis based on study period was not significant.

Egger's test in DENV studies found no evidence of publication bias for gastrointestinal symptoms but found significant publication bias in studies assessing shock or organ failure ($p = 0.024$) and hospitalisation ($p = 0.006$).

Discussion

Using a combination of descriptive statistics and meta-analysis, we found that the common symptoms amongst all three arboviruses were fever, arthralgia, myalgia, headache, rash and gastrointestinal symptoms. We also found that patients with ZIKV were more likely to be asymptomatic than DENV and CHIKV patients. For example, fever was present in only half of ZIKV cases (51.75% [32.45-65.18]) compared to 98% of DENV cases (98.00% [94.70-99.86]) and all CHIKV cases (100%). These findings are consistent with the existing World Health Organization (WHO)/ Pan American Health Organization (PAHO) clinical criteria for DENV (https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue), ZIKV (https://www.who.int/news-room/fact-sheets/detail/zika-virus) and CHIKV (https://www.who.int/news-room/fact-sheets/detail/chikungunya).

However, our results suggest that the arboviruses may be differentiated through the presence or absence of the following symptoms: retro-orbital pain and conjunctivitis, limb oedema, flushed face, haemorrhagic symptoms, neurological symptoms and taste alteration. Whilst malaise, chills and adenopathy were identified only in DENV, they are non-specific symptoms which may occur in all viral infections and hence were likely not part of the reporting criteria for ZIKV and CHIKV studies. Similarly, pruritus is often implicitly associated with rash, which is a potential explanation for its absence in ZIKV and CHIKV studies.

Retro-orbital pain and conjunctivitis were present in both DENV (32.79% [10.02-60.91] and 34.35% [25.21-44.09], respectively) and ZIKV (26.77% [18.29-36.16] and 24.81% [8.41-45.95], respectively), but were not identified for CHIKV. There are reports of ophthalmic manifestations in CHIKV, but they seem to occur at a lower frequency when compared to other arboviruses.[68]

Limb oedema was identified as a prevalent symptom in ZIKV (16.05% [5.43-30.44]), whereas it was virtually absent in DENV and CHIKV cases. Limb oedema in ZIKV has also been widely reported in the literature, yet it is not mentioned in the WHO/ PAHO criteria.[69] Furthermore, we identified rash as a more frequent symptom in ZIKV (50.87% [26.63-74.89]) compared to DENV (24.90% [12.68-39.51]). This finding is supported by similar results in a comparative study on DENV and ZIKV in Mexico.[70]

For DENV, flushed face (29.51% [19.08-41.06]) and taste alterations (15.01% [12.49-7.72]) were observed and have also been established as symptoms of DENV in other studies.[71, 72] Both symptoms were not identified in ZIKV or CHIKV cases. Respiratory symptoms were also prevalent in DENV (31.20% [19.30-44.48]) and in CHIKV (18%), but not in ZIKV. Respiratory symptoms have been reported for DENV and CHIKV elsewhere in the literature and should be incorporated into the WHO/ PAHO criteria.[73, 74]

Haemorrhagic symptoms such as epistaxis, petechiae and purpura were only recorded in DENV patients (18.23% [8.48-30.57]). Haemorrhagic symptoms are warning signs for severe dengue and may distinguish DENV from ZIKV and CHIKV at initial presentation, as well as indicating the risk of progression to severe dengue.[10]

Our findings also identified neurological symptoms in DENV cases, but not in ZIKV and CHIKV cases. However, existing literature suggests that neurological symptoms are rare in all three arboviruses.[75, 76] The discrepancy with our analysis is likely due to the limited number of studies examining neurological symptoms.

The complication rates of DENV, namely hospitalisation (12.45% [7.88-17.87]), death (0.25% [0.05-0.54]) and severe dengue (4.47% [0.97-10.17]), were consistent with prevalence estimates from systematic reviews conducted outside of the Pacific.[77, 78]

GBS (0.5%) and microcephaly (56%) were significant complications identified for ZIKV. Microcephaly was reported in seven studies for ZIKV and was present in over half of the patients with congenital ZIKV infection. However, this was most likely subject to reporting bias as many samples only included infants with foetal complications.

For CHIKV, complications of shock and organ failure (3%), liver disease (1%), GBS (0.01%), myocarditis (0.1%) and encephalitis (1%) were recorded, albeit infrequently.

Despite being known as a classically mild disease, our results indicate that the potential for serious complications should not be neglected.

Furthermore, our subgroup analyses revealed differences based on age, study location, study design and whether studies only investigated hospitalised patients. Age was a significant confounder; thus, future prevalence studies should aim to treat paediatric and adult populations as distinct groups. In terms of study location, there was geographic heterogeneity between studies based in French Polynesia compared to those based elsewhere. These differences may be due to unique risk factor profiles and comorbidities as well as differing reporting standards between countries. Hence, future studies should aim to focus on individual Pacific Island nations as there is wide diversity in topography, socioeconomic status, demography and health status.[79] Furthermore, studies which only examined hospitalised patients had higher prevalence of complications when compared to studies which included both hospitalised and non-hospitalised patients. Further research should also aim to identify differences between DENV serotypes, which we were unable to investigate due to limited data availability.

In terms of limitations, there were a limited number of studies, particularly for ZIKV and CHIKV, which made it difficult to carry out meta-analysis. This is most likely due to the poor reporting systems in Pacific Island countries. Given that we also detected publication bias, we believe that it should be of high priority to strengthen disease reporting and surveillance systems in the region. Improving the transparency and consistency of disease reporting will guide more accurate research and ultimately facilitate more effective outbreak management. The inclusion of grey literature may also provide a comprehensive picture of arboviral cases, but at the same time, may compromise the validity of findings. Furthermore, our review only examined Pacific Island countries, and hence it is important that our findings are used appropriately when applied to other countries. With the global re-emergence of these arboviruses, it may be appropriate for similar studies to be conducted in other regions or at a global level to prepare physicians worldwide for future outbreaks.

Despite its limitations, our review offers crucial, unique findings to educate clinicians in Pacific Island countries about the clinical symptoms and complications of DENV, ZIKV and CHIKV. ***Table 3*** presents our updated version of the WHO/ PAHO clinical criteria, which can be used to guide clinical diagnosis of these arboviruses. However, clinicians must not solely rely on these criteria as atypical presentations may occur.

DENV	ZIKV	CHIKV
DENV should be suspected when high fever (40°C/104°F) or **chills** is accompanied by 2 of the following symptoms: • Severe headache • **Arthralgia or myalgia** • Rash • Retro-orbital pain or **conjunctivitis** • Nausea, vomiting or **diarrhoea** • Lymphadenopathy • **Cough, sore throat or rhinorrhoea** • **Flushed face**	ZIKV may be asymptomatic or should be suspected with the following symptoms: • Fever • Rash • **Retro-orbital pain** or conjunctivitis • Arthralgia or myalgia • Headache • Malaise • **Swelling of extremities** • **Nausea, vomiting or diarrhoea**	CHIKV may present with abrupt onset of fever, frequently with joint pain which is often very debilitating and may be accompanied by the following symptoms: • Myalgia • Joint swelling • Headache • Nausea • Fatigue • Rash • **Cough**

• **Changes to taste** • **Haemorrhagic symptoms** • **Malaise**		

Note: Text in **bold** indicates changes from existing WHO/PAHO criteria.

Table 3: Clinical criteria for DENV, ZIKV or CHIKV infection, adapted from the WHO/PAHO guidelines

Our paper represents the first systematic review and meta-analysis to estimate the prevalence of symptoms and complications of DENV, ZIKV and CHIKV in Pacific Island countries. We identified similarities and differences between the clinical features of these similar yet distinct arboviruses. Whilst further research is needed in this area, particularly to assess the clinical features of ZIKV and CHIKV, our findings will assist Pacific Island clinicians to effectively diagnose these clinically challenging arboviral diseases.

Contributors
SK developed the review protocol and conducted the literature search, with input from NH. Both authors (SK and NH) conducted the study screening process, data extraction and statistical analysis. Both authors contributed to the interpretation of the data and drafting of the article. Both authors approved the final version of the article for publication.

Declaration of Interests
We declare no competing interests.

Data sharing
There will be no further sharing of data other than the information provided in the appendix and the registered protocol on OSF registries.

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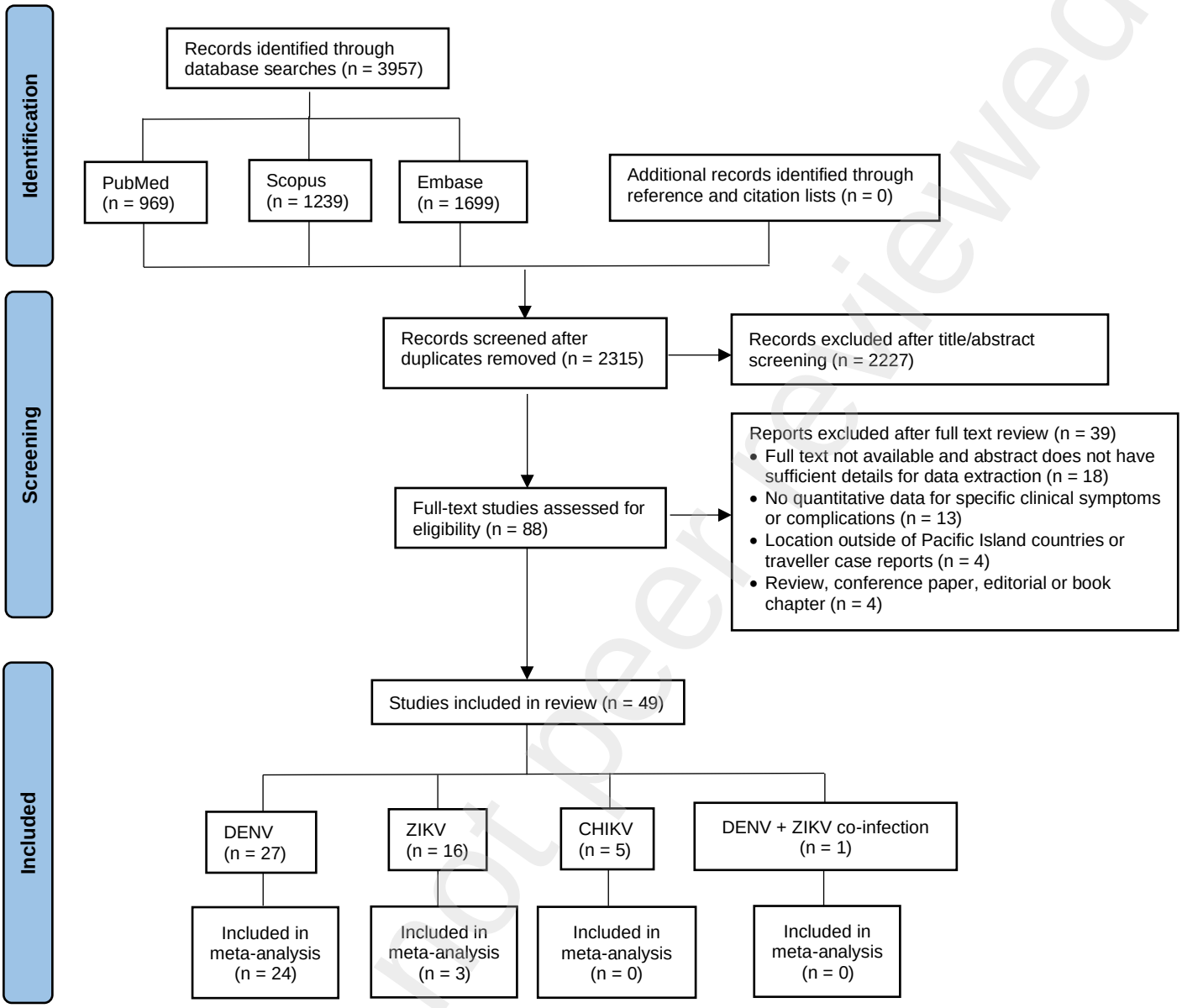

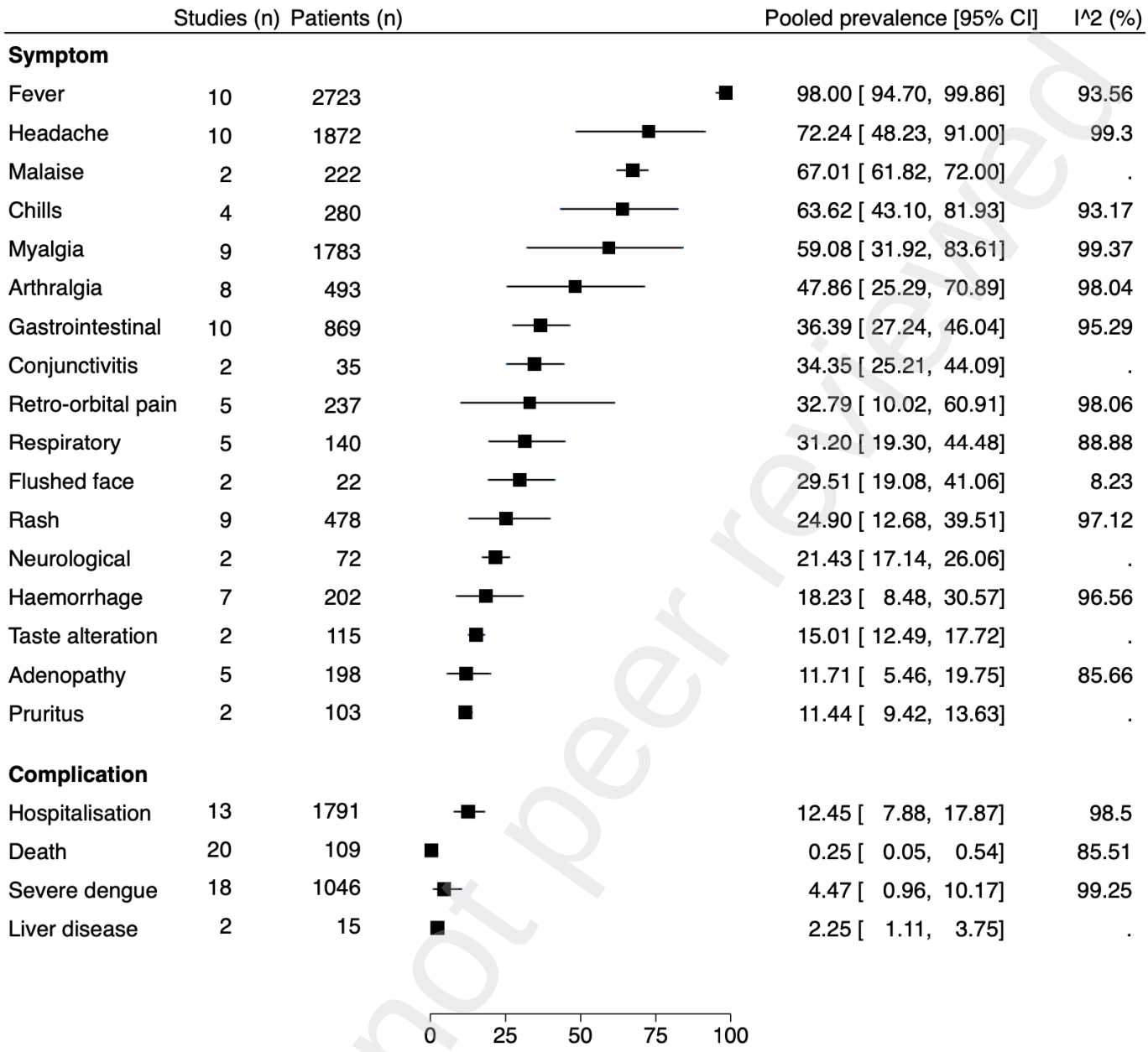

	Studies (n)	Patients (n)	Pooled prevalence [95% CI]	I^2 (%)
Symptom				
Arthralgia	3	81	58.83 [35.41, 80.38]	87.24
Myalgia	2	53	55.31 [45.22, 65.18]	.
Fever	3	72	51.75 [32.45, 70.80]	81.51
Rash	3	70	50.87 [26.63, 74.89]	88.69
Headache	2	48	49.45 [39.42, 59.49]	.
Retro-orbital pain	2	26	26.77 [18.29, 36.16]	.
Conjunctivitis	3	36	24.81 [8.41, 45.95]	85.61
Limb Oedema	3	23	16.04 [5.43, 30.44]	75.49
Gastrointestinal	2	17	15.92 [9.13, 24.05]	.