Chikungunya seroprevalence, force of infection, and prevalence of chronic disability after infection in endemic and epidemic settings: a systematic review, meta-analysis, and modelling study

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Summary

Background Chikungunya is an arboviral disease transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes with a growing global burden linked to climate change and globalisation. We aimed to estimate chikungunya seroprevalence, force of infection (FOI), and prevalence of related chronic disability and hospital admissions in endemic and epidemic settings.

Methods In this systematic review, meta-analysis, and modelling study, we searched PubMed, Ovid, and Web of Science for articles published from database inception until Sept 26, 2022, for prospective and retrospective cross-sectional studies that addressed serological chikungunya virus infection in any geographical region, age group, and population subgroup and for longitudinal prospective and retrospective cohort studies with data on chronic chikungunya or hospital admissions in people with chikungunya. We did a systematic review of studies on chikungunya seroprevalence and fitted catalytic models to each survey to estimate location-specific FOI (ie, the rate at which susceptible individuals acquire chikungunya infection). We performed a meta-analysis to estimate the proportion of symptomatic patients with laboratory-confirmed chikungunya who had chronic chikungunya or were admitted to hospital following infection. We used a random-effects model to assess the relationship between chronic sequelae and follow-up length using linear regression. The systematic review protocol is registered online on PROSPERO, CRD42022363102.

Findings We identified 60 studies with data on seroprevalence and chronic chikungunya symptoms done across 76 locations in 38 countries, and classified 17 (22%) of 76 locations as endemic settings and 59 (78%) as epidemic settings. The global long-term median annual FOI was 0·007 (95% uncertainty interval [UI] 0·003–0·010) and varied from 0·0001 (0·00004–0·0002) to 0·113 (0·07–0·20). The highest estimated median seroprevalence at age 10 years was in south Asia (8·0% [95% UI 6·5–9·6]), followed by Latin America and the Caribbean (7·8% [4·9–14·6]), whereas median seroprevalence was lowest in the Middle East (1·0% [0·5–1·9]). We estimated that 51% (95% CI 45–58) of people with laboratory-confirmed symptomatic chikungunya had chronic disability after infection and 4% (3–5) were admitted to hospital following infection.

Interpretation We inferred subnational heterogeneity in long-term average annual FOI and transmission dynamics and identified both endemic and epidemic settings across different countries. Brazil, Ethiopia, Malaysia, and India included both endemic and epidemic settings. Long-term average annual FOI was higher in epidemic settings than endemic settings. However, long-term cumulative incidence of chikungunya can be similar between large outbreaks in epidemic settings with a high FOI and endemic settings with a relatively low FOI.

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Introduction

Chikungunya virus is an alphavirus in the Togaviridae family that causes chikungunya disease. The virus is primarily transmitted to humans through the bites of infected *Aedes aegypti* or *Aedes albopictus* mosquitoes, which serve as vectors for the virus.[1] Clinical manifestations of acute chikungunya include high fever (>39°C), arthralgia, headache, or nausea, which lasts for less than 2 weeks.[2] Although the reported mortality directly attributable to chikungunya disease is considered low, the infection exacerbates pre-existing comorbidities, resulting in deaths for which chikungunya is not reported as the primary cause.[3] Chikungunya disease can also develop into chronic disability in individuals who have at least one symptom, such as pain, rigidity, or oedema, with symptoms lasting 3 months to several years.[1]

The potential for the emergence and re-emergence of chikungunya is increasing due to climate change,

Research in context

Evidence before this study

To date, more than 110 countries have reported chikungunya outbreaks. The potential for the emergence and re-emergence of chikungunya is escalating due to climate change, globalisation, and urbanisation. Since 2017, the Coalition for Epidemic Preparedness Innovations has been supporting chikungunya vaccine development, and WHO has also shortlisted chikungunya as a priority pathogen. We searched the Web of Science (Core Collection), Embase (Ovid), and PubMed (MEDLINE) from database inception to Sept 26, 2022, for peer-reviewed articles published in English, using the terms "Chikungunya," "Seroprevalence," "Seroepidemiological studies," "incidence," "outbreak," "sequelae," "morbidity," "complication," "mortality," and "Disability Adjusted Life Years". We also did a risk of bias assessment. We identified a gap in the literature regarding the estimation of global chikungunya transmission intensities from serological surveys and meta-analysis of chikungunya sequalae. Our search identified modelling studies that estimated force of infection (FOI) of chikungunya at the country level (Vietnam, India, the Philippines, Burkina Faso, and Gabon), but no studies that compiled serological studies globally and estimated comparable long-term average annual FOI. One systematic review provided disability-adjusted life-years estimates at the WHO regional level between 2010 and 2019, while another systematic review provided overall seroprevalence estimates without age stratifications. A 2023 meta-analysis provided overall seroprevalence but did not examine the pooled prevalence of chikungunya sequalae.

Added value of this study

We did a systematic literature review, incorporating mathematical modelling and meta-analyses, to gain a comprehensive understanding of global chikungunya transmission intensities, and the prevalence of long-term sequelae of chikungunya and related hospital admissions. To our knowledge, this is the first study to compile global, age-stratified data on chikungunya seroprevalence, by survey site, survey-specific FOI estimates, and pooled estimates of the proportion of chikungunya infections resulting in chronic sequelae and hospital admission. We developed a novel method for estimating long-term mean annual FOI that was comparable across each location.

Implications of all the available evidence

In our systematic literature review, we identified serological surveys in 30 countries and across 76 sub-country level settings and analyses of chronic chikungunya sequalae from 11 countries. In total, data were available for 38 countries. We observed that a larger proportion of settings (78%) were classified as epidemic than endemic to chikungunya, and the average annual FOI was higher in epidemic settings than endemic settings. More than half of the patients with confirmed symptomatic chikungunya had chronic sequalae lasting between 5 months and 5 years. We found that 4% of people with acutely confirmed chikungunya were admitted to hospital following infection. Four studies reported chikungunya-related mortality, ranging from 0·19% to 9·5% across different subpopulations of varying disease severity, such as individuals in intensive care units, patients who were clinically diagnosed, and patients with serologically confirmed infection. The results from our synthesis underscore the need for chikungunya control strategies, such as vaccines, to mitigate its long-term burden and manage outbreaks, especially in epidemic-prone settings with a high FOI. Our research provides a basis for future studies aiming to estimate the burden of chikungunya and evaluate the impact of vaccine introduction.

globalisation, and urbanisation. Temperature changes are associated with chikungunya infection altering *Ae albopictus* mosquito gene expression in immune and stress-related pathways, bacterial microbiota, and chikungunya evolutionary dynamics.[4] Since 1952, chikungunya outbreaks have been reported in more than 110 countries.[5] Chikungunya disease is usually associated with tropical and sub-tropical regions. However, the increased climatic suitability for *Aedes* mosquitoes can boost their reproduction and vectorial capacity, and expand their habitats, potentially reaching parts of the world where chikungunya is yet to be introduced.[6] Since the start of the 21st century, chikungunya has increasingly become a problem for travellers, as shown by the importation of the chikungunya virus to non-endemic areas such as Europe and North America.[7]

Global efforts have facilitated preventive strategies for chikungunya, such as the development of vaccines. Since 2017, the Coalition for Epidemic Preparedness Innovations has supported chikungunya vaccine development,[8] and WHO has shortlisted chikungunya for priority research since 2018.[9] Gavi, the Vaccine Alliance has also included chikungunya on the longlist of vaccines assessed through its Vaccine Investment Strategy 2024.[10] In November, 2023, the US Food and Drug Administration approved Ixchiq, the first chikungunya vaccine developed by Valneva.[11]

There is a need for robust evidence on the global burden of chikungunya to guide effective vaccination strategies on optimal timing and target populations.[12,13] Since 2010, constrained resources and competing disease priorities have underscored the need for evidence-based decisions in vaccine introduction and implementation.[14] Burden of disease estimations and economic evaluations are crucial for decision makers and advisory committees, such as National Immunisation Technical Advisory Groups.[14] The introduction of the haemophilus influenzae type b, pneumococcal conjugate, and rotavirus

vaccines was supported by comprehensive scientific evidence including disease burden, cost-effectiveness, and impact estimation, facilitating informed investments and support at national and regional levels.[15] Robust estimates of the transmission intensity of chikungunya and its disease burden are needed to effectively guide the decision making processes for vaccine introduction.

The estimation of the global burden of chikungunya disease is complex due to the absence of systematic analyses regarding transmission intensities and long-term severity. In existing research the disability-adjusted life-years lost at the WHO regional and global levels has been estimated, but data were only available between 2010 and 2019 and varying levels of disease severity were not considered.[16–18] Filling this gap in knowledge is crucial to better understand the current burden of chikungunya in different countries and to assess the burden of chronic stages of the disease.

In this study, we aimed to use age-stratified IgG seroprevalence data to estimate the proportion of the population previously infected with chikungunya, generating comparable estimates of the force of infection (FOI; the rate at which susceptible individuals acquire an infectious disease in the unit time) in different locations. Additionally, we aimed to use data on sequalae after chikungunya infection to ascertain the proportion of people who were chronically disabled or admitted to hospital among patients with symptomatic laboratory confirmed chikungunya.

Methods

Search strategy and selection criteria

Our approach combined a systematic literature review and mathematical modelling to identify studies with data on age-stratified seroprevalence of chikungunya infection. Concurrently, we did a meta-analysis on long-term chikungunya sequelae and associated hospital admissions. We searched PubMed, Ovid, and Web of Science from database inception to Sept 26, 2022, for studies published in English without geographical restrictions, using the search terms "Chikungunya", "Chikungunya virus", "Chikungunya fever", "Seroepidemic studies", "Seroepidemiology", "Seroprevalence", "Disease outbreaks", "Outbreaks", "Disability", "DALY", "Sequelae", "Morbidity" (appendix pp 21–23).

Our systematic review protocol followed the PRISMA guidelines and is registered in the PROSPERO database, CRD42022363102.[19]

Our main outcomes of interest were divided into three components: (1) chikungunya seroprevalence by age, (2) proportion of cases with long-term sequelae, and (3) proportion of cases admitted to hospital. We did not include fatal cases in our main outcomes due to paucity of studies and different population groups between studies, which limited the pooling of results. The inclusion criteria were developed using the patient, intervention, comparison, outcome strategy.

For the chikungunya seroprevalence studies, we included population-based studies involving healthy individuals who tested positive for IgG antibodies using validated serological tests. We included prospective and retrospective cross-sectional studies that addressed serological chikungunya virus infection in any geographical region, age group, and population subgroup. The population subgroups included: blood donors, pregnant women, children aged younger than 15 years, serum samples from residual sera, and specific occupations such as military workers and nomadic pastoralists. Serum samples that tested positive solely for IgM antibodies were excluded, since the presence of IgM antibodies indicate recent infection rather than all past infections. Studies that did not report the total number of tested samples, or did not specify validated serological methods, and those that reported only case counts or incidence, were excluded.

For the studies of chronic chikungunya sequelae, we included both longitudinal prospective and retrospective cohort study designs. We estimated the proportion of patients who developed chronic chikungunya or were admitted to hospital among all reported cases with symptomatic chikungunya infection. We included individuals with serologically confirmed chikungunya, identified through the detection of anti- chikungunya IgM or IgG antibodies or RT-quantitative PCR tests, who initially presented with symptoms such as fever (>39°C) or arthralgia. We defined chronic symptoms as persistent chikungunya, as indicated by long-term survey scores, persistent arthralgia, myalgia, and chronic arthritic disability (appendix pp 12–13).

Ethical approval for this study was obtained from the London School of Hygiene and Tropical Medicine in January 2023 (reference number 28292).

Data analysis

Two researchers (HK, MA) independently screened abstracts and titles, screened full-texts, did risk of bias assessments. Abstract and title screening was done independently by HK and MA using Rayann software. For the risk of bias assessment, we used JBI critical appraisal tools for prevalence studies and cohort studies. We scored each survey based on the proportion of positive responses (yes) from the checklist questions. Studies with over 60% of positive responses were classified as low risk of bias, those with 50–60% as moderate risk of bias, and those below 50% as high risk of bias (appendix pp 32–38).

To estimate survey-specific annual FOI rates, we used catalytic models to analyse age-stratified seroprevalence data. Based on Muench's method,[20] we employed two types of models: a constant FOI model and time-varying FOI model. We assumed that a survey best fitting a constant FOI model indicates an endemic setting, while a survey best fitting a time-varying FOI model indicates an epidemic setting. We fitted both models to each survey and categorised chikungunya-affected settings into

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See **Online** for appendix

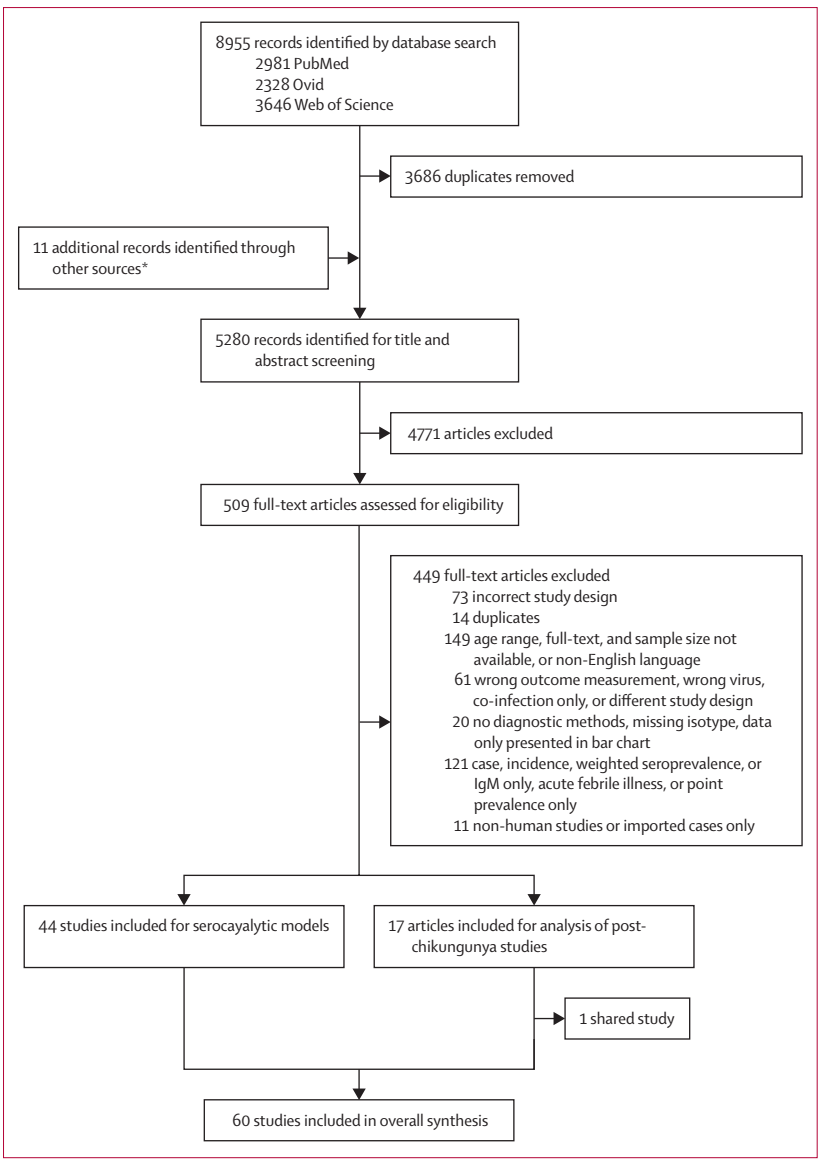


Figure 1: **Study selection**
*Other sources included published literature identified from a 2023 systematic literature review by Skalinski and colleagues.[84]

endemic or epidemic based on the model selection results (appendix pp 25–29). We used Deviation Information Criterion to test the model fit. Within a Bayesian inference framework, we employed Markov Chain Monte Carlo simulations to generate the posterior distribution of FOI, assuming a non-informative, uniform prior distribution (range 0–1). The 95% Bayesian uncertainty intervals (UIs) were derived from the posterior distribution of FOI. We used R (version 4.2.2) and the RJAGS package, running the model for 100 000 iterations for each chain with a burn-in period of 10 000. We examined the convergence of the model parameters through visual inspections of the posterior distributions using density and trace plots, and Gelman-Rubin diagnostics.[21]

For the constant FOI model, we assumed no seroreversion, non-differential mortality rates between infected and uninfected individuals, and age-time homogeneous transmission.[20] We defined seropositivity as:

$$p(a) = 1 - e^{(-\lambda * a)}$$

where p (a) denotes the seropositivity over age (a), λ signifies FOI, and e represents the exponential function.

For time-varying FOI models, we estimated epidemic timing by applying a piece-wise threshold function that converts age to years of exposure based on the survey year. We introduced $\delta_1 \ldots \delta_N$ parameters for epidemic years (1 to N, with N being the maximum number of age group in the survey) and time-varying FOIs (λ_i) for each epidemic. The year of epidemic occurrence was estimated within a range determined by a uniform distribution. We assume no transmission between consecutive outbreaks, resulting in a step-wise increase in the seropositivity and the number of FOIs equals the number of epidemics. We defined the probability that an individual acquires an antibody by time (t) at age (a), accounting for the cumulative effect of time-varying force of infection over multiple time interval as:

$$p(a,t) = 1 - e\left(-\sum_{i=1}^{n} \lambda_i\right) \quad (t - a_{i2} < \delta_i < t - a_{i1})$$

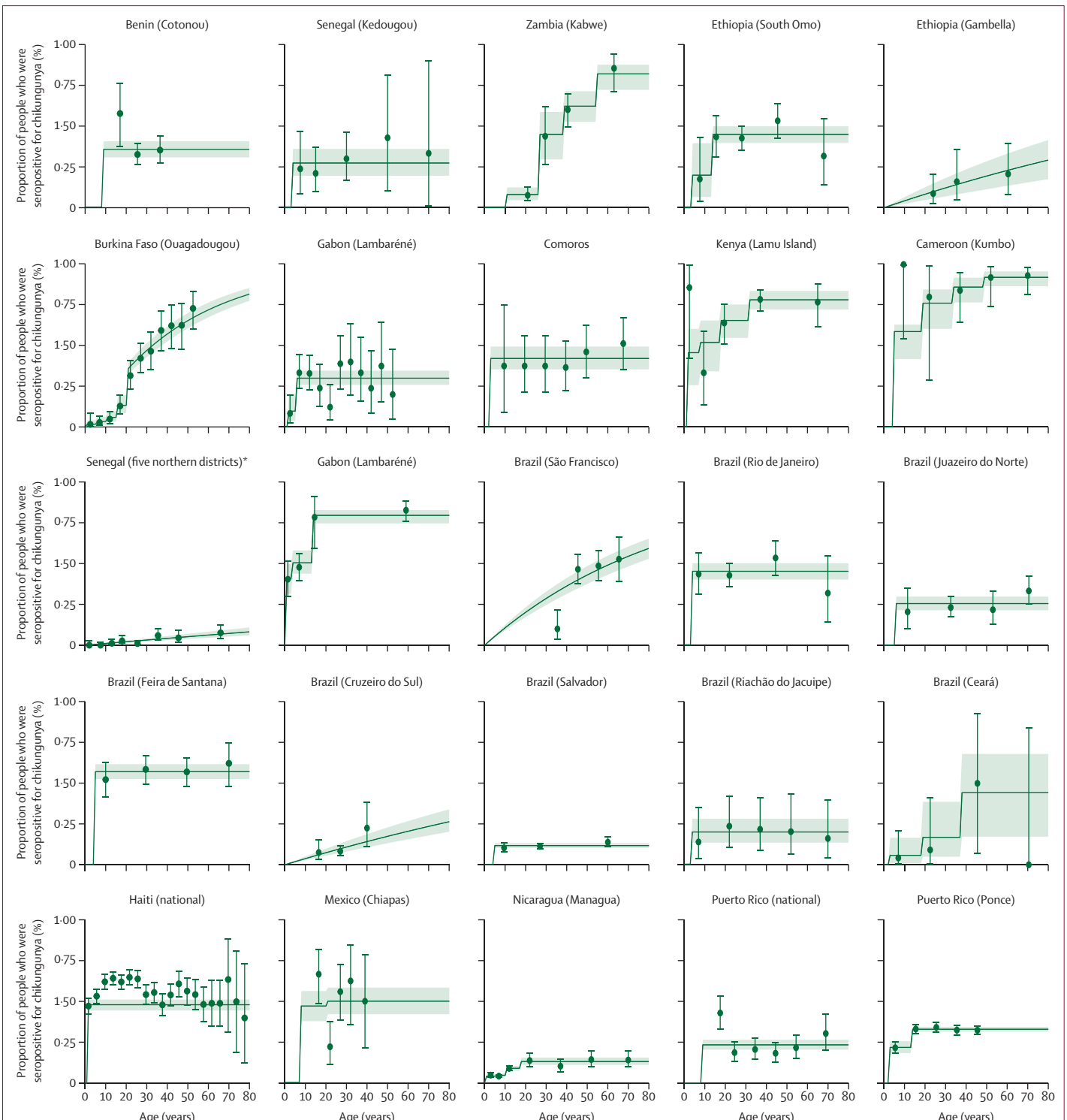
Where n denotes the total number of age cohorts available in survey, t denotes the year of the survey, δ_i denotes the epidemic year for ith age cohort, a_{i1} denotes the lower age limit of the ith age cohort, a_{i2} denotes the upper age limit of the ith age cohort.

Since FOI values inferred from time-varying models and various age group samples could potentially misrepresent long-term average conditions when a survey was conducted immediately after an outbreak, we developed a more representative approach to estimate comparable long-term average annual FOIs. This was achieved by simulating outbreak frequencies over a theoretical 100-year period. We performed 1000 stochastic simulations over a hypothetical 100-year period, where the annual outbreak probability was given by the inverse of the average interepidemic period inferred in the time-varying FOI models (appendix p 24).

We did a meta-analysis using the meta package in R (version 4.2.2) to summarise proportions among patients with chikungunya who were symptomatic. We used a random-effects model, assuming the true effect could between studies due to heterogeneity among them.[22] We used I^2 to estimate between-study heterogeneity. I^2 scores were categorised as low (0–30%), moderate (>30 to 60%), substantial (>60 to 90%), and considerable (>90%).[23] The outcomes considered were (1) the proportion of patients with chronic sequalae among all patients with confirmed chikungunya with 95% CIs, and (2) the proportion of

hospitalised chikungunya patients who were admitted to hospital among all patients with confirmed chikungunya with 95% CIs.

The proportion of patients with chronic sequalae was calculated by dividing the number of patients with symptoms lasting more than 3 months by the number of



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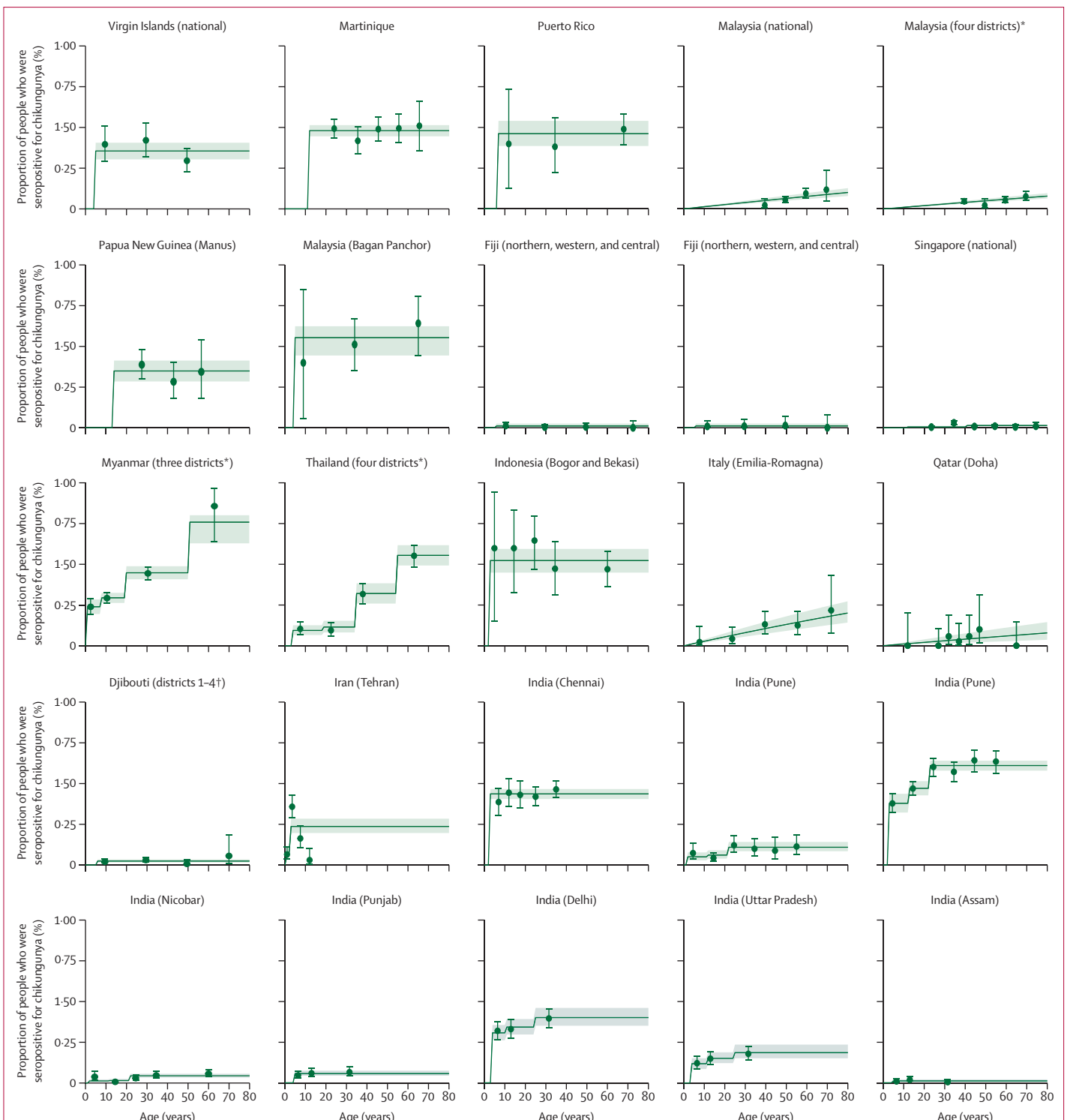
symptomatic patients with confirmed chikungunya. Similarly, the proportion of patients with chikungunya who were admitted to hospital was calculated by dividing the number of patients with chikungunya who were admitted to hospital by the number of symptomatic patients with confirmed chikungunya. To assess the linear



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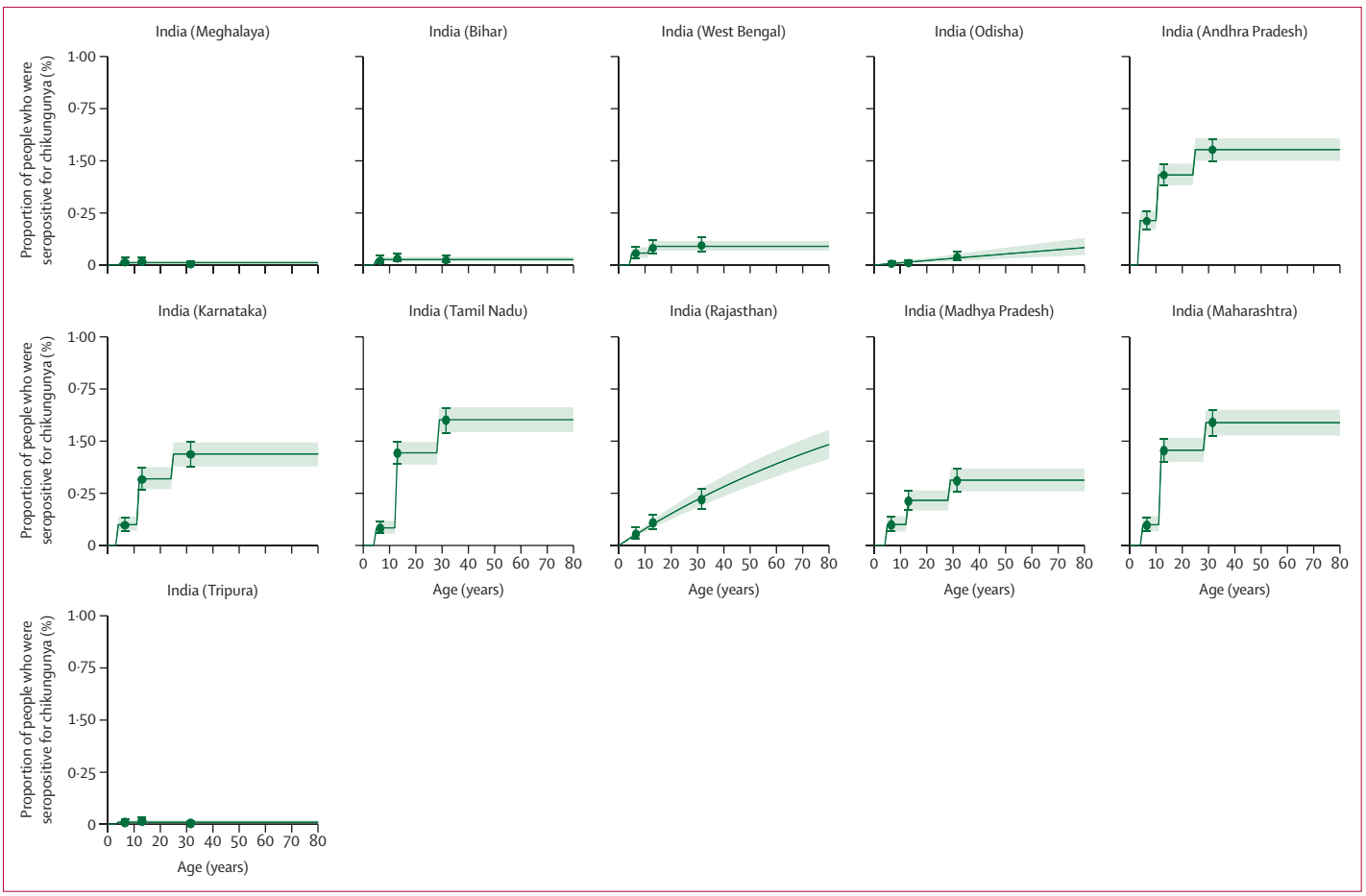

Figure 2: **Chikungunya seroprevalence**

Seroprevalence data in each survey was fitted to catalytic models. Subcountry locations are in parentheses. Senegal, Ethiopia, Brazil, Puerto Rico, Malaysia, Fiji, Myanmar, Thailand, Indonesia, and India had more than two subcountry locations reported. *In Senegal, five districts were identified in Dagana, Podor, Pété, Ranérou, and Kanel; in Malaysia, four districts were identified in Negeri Sembilan, Pahang, Kuala Lumpur, and Selangor; in Myanmar, three districts were identified in Mandalay, Yangon, and Myeik; and in Thailand, four districts were identified in Ayutthaya, Lop Buri, Narathiwat, and Trang. †The four administrative districts of Djibouti were classified as district 1 (city centre and Einguela area), district 2 (Arhiba area), district 3 (Gabode and Ambouli areas); and district 4 (Balbala and Damerjob areas).

relationship between prevalence of chronic sequelae and follow-up length, we incorporated a quadratic term into a linear regression model. In this model, the outcome variable was the continuous measure of chronic prevalence, and the predictor was the follow-up length in years. If the ANOVA p value was less than 0·05, we assumed that the quadratic term provided a better fit to the model and rejected the assumption of linearity between follow-up length and prevalence of chronic sequalae.[24]

Role of the funding source

The study funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

We identified 8955 studies in our systematic review, which were screened based on our inclusion and exclusion criteria. We included a total of 60 studies (Azami NAM, Universiti Kebangsaan Malaysia, Malaysia; personal communication),[25–83] of which 11 were from a systematic review by Skalinski and colleagues.[84] Among the 60 studies, there were 44 studies contributing data on age-stratified seroprevalence, 17 studies with data on chronic chikungunya sequalae, and one study with data on seroprevalence and chronic chikungunya sequalae (figure 1).

We fitted seroprevalence data from 44 publications to catalytic models to generate age-specific seroprevalence curves (figure 2). In regions such as Gambella (Ethiopia) and Rajasthan (India), a steady increase in seroprevalence was observed with age, indicating an endemic setting. In contrast, in regions such as Lamu Island (Kenya) and Puerto Rico, show stepwise increases in seroprevalence were observed due to sporadic outbreaks, indicating an epidemic setting.

We observed marked geographical variation in the long-term average annual FOI between endemic and epidemic settings, and across continents. Globally,

	Region	Age range (years)	Country (location)	Diagnostics used	Antibody	Population	Year of survey	Median seroprevalence from study, % (95% CI)	Median seroprevalence at age 10 years, % (95% UI)*
Bacci et al[25]	Sub-Saharan Africa	14–42	Benin (Cotonou)	ELISA	IgG	Non-febrile pregnant women	2006–07	41·7% (29·9–53·4)	12·5% (7·7–17·2)
Lim et al[26]	Sub-Saharan Africa	1–55	Burkina Faso (Ouagadougou)	arbo-MIA	IgG	Non-febrile individuals	2015	36·3% (27·5–45·8)	3·4% (1·8–4·5)
Demanou et al[27]	Sub-Saharan Africa	5–59	Cameroon (Kumbo)	ELISA	IgG	Non-febrile individuals	2007	89·8% (60·3 – 98·5)	25·7% (18·5–35)
Sergon et al[28]	Sub-Saharan Africa	1–80	Comoros	ELISA	IgG	Non-febrile individuals	2005	41·1% (23·0–61·9)	4·9% (2·3–8·7)
Asebe et al[29]	Sub-Saharan Africa	5–80	Ethiopia (Gambella)	ELISA	IgG	Non-febrile individuals	2018–19	15·1% (5·0–32·2)	3·9% (2·4–6·6)
Endale et al[30]	Sub-Saharan Africa	18–80	Ethiopia (South Omo)	ELISA	IgG	Non-febrile individuals	2018	37·9% (25·3–54·0)	26·5% (17·7–50·2)
Lim et al[26]	Sub-Saharan Africa	1–55	Gabon (Lambaréné, 2015)	arbo-MIA	IgG	Non-febrile individuals	2015	27·7% (13·7–46·3)	16·4% (10·8–34·1)
Ushijima et al[31]	Sub-Saharan Africa	1–100	Gabon (Lambaréné, 2014–17)	ELISA	IgG	Non-febrile individuals	2014–17	62·4% (50·9–72·3)	67·6% (50·1–86)
Sergon et al[32]	Sub-Saharan Africa	1–80	Kenya (Lamu Island)	ELISA	IgG	Non-febrile individuals	2004	67·6% (47·7–81·5)	47·9% (34·6–69·9)
Seck et al[33]	Sub-Saharan Africa	5–80	Senegal (five northern districts†)	MFI-bg	IgG	Nomadic pastoralists	2014	2·9% (1·2–6·4)	1·0% (0·8–1·4)
Sow et al[34]	Sub-Saharan Africa	0–81	Senegal (Kedougou)	ELISA	IgG	Non-febrile individuals	2012	30·2% (9·0–60·6)	3·0% (1·2–4·7)
Chisenga et al[35]	Sub-Saharan Africa	18–80	Zambia (Kabwe)	ELISA	IgG	Non-febrile individuals	2016	49·2% (37·6–60·0)	22·9% (8·5–62·8)
Rodriguez-Barraquer et al[36]	South Asia	5–40	India (Chennai)	ELISA	IgG	Non-febrile individuals	2011	42·9% (35·5–50·5)	13·7% (8·7–19·3)
Kumar et al[37]	South Asia	5–45	India (Punjab)	ELISA	IgG	Non-febrile individuals	2011	5·7% (3·3–9·1)	5·7% (4·0–9·3)
Kumar et al[37]	South Asia	5–45	India (Karnataka)	ELISA	IgG	Non-febrile individuals	2017	28·3% (23·4–33·7)	23·9% (11·5–38)
Kumar et al[37]	South Asia	5–45	India (Tamil Nadu)	ELISA	IgG	Non-febrile individuals	2017	37·5% (32·6–42·6)	33·8% (17–54·5)
Kumar et al[37]	South Asia	5–45	India (Rajasthan)	ELISA	IgG	Non-febrile individuals	2017	12·8% (9·1–17·3)	8·0% (6·5–9·6)
Kumar et al[37]	South Asia	5–45	India (Madhya Pradesh)	ELISA	IgG	Non-febrile individuals	2017	20·7% (16·2–25·9)	15·9% (10·2–28·6)
Kumar et al[37]	South Asia	5–45	India (Maharashtra)	ELISA	IgG	Non-febrile individuals	2017	38·1% (32·8–43·6)	31·7% (18·8–50·5)
Kumar et al[37]	South Asia	5–45	India (Tripura)	ELISA	IgG	Non-febrile individuals	2017	0·9% (0·2–2·8)	1·2% (0·8–2·7)
Kumar et al[37]	South Asia	5–45	India (Delhi)	ELISA	IgG	Non-febrile individuals	2017	34·9% (29·1–41·1)	8·7% (5·3–19·3)
Kumar et al[37]	South Asia	5–45	India (Uttar Pradesh)	ELISA	IgG	Non-febrile individuals	2017	15·0% (11·0–19·8)	8·4% (4·8–16·4)
Kumar et al[37]	South Asia	5–45	India (Assam)	ELISA	IgG	Non-febrile individuals	2017	1·0% (0·2–3·1)	1·5% (0·8–2·6)
Kumar et al[37]	South Asia	5–45	India (Meghalaya)	ELISA	IgG	Non-febrile individuals	2017	1·1% (0·2–3·2)	0·3% (0·2–0·4)
Kumar et al[37]	South Asia	5–45	India (Bihar)	ELISA	IgG	Non-febrile individuals	2017	2·5% (1·0–5·2)	0·6% (0·4–1·0)
Kumar et al[37]	South Asia	5–45	India (West Bengal)	ELISA	IgG	Non-febrile individuals	2017	7·7% (4·8–11·7)	1·1% (0·6–1·7)
Kumar et al[37]	South Asia	5–45	India (Odisha)	ELISA	IgG	Non-febrile individuals	2017	1·8% (0·7–3·9)	1·1% (0·7–1·7)

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	Region	Age range (years)	Country (location)	Diagnostics used	Antibody	Population	Year of survey	Median seroprevalence from study, % (95% CI)	Median seroprevalence at age 10 years, % (95% UI)*
(Continued from previous page)									
Kumar et al[37]	South Asia	5–45	India (Andhra Pradesh)	ELISA	IgG	Non-febrile individuals	2017	39·9% (34·8–45·1)	29·9% (20·6–53·3)
Tomar et al[38]	South Asia	0–60	India (Pune, 2009)	ELISA	IgG	Non-febrile individuals	2009	8·9% (4·6–15·4)	3·7% (2·7–5·2)
Tomar et al[38]	South Asia	0–60	India (Pune, 2019)	ELISA	IgG	Non-febrile individuals	2019	55·0% (48·7–61·1)	26·0% (19·7–38·5)
Padbidri et al[39]	South Asia	0–80	India (Nicobar)	Haemag-glutination inhibition	HI antibody	Non-febrile individuals	1989	3·6% (1·9–6·1)	0·3% (0·2–0·5)
Luvai et al[40]	East Asia and Pacific Islands	35–74	Myanmar (three districts‡)	ELISA	IgG and IgM	Non-febrile and febrile individuals	2013/15/18	45·8% (37·2–52·0)	39·3% (25·2–55·8)
Laras et al[41]	East Asia and Pacific Islands	35–74	Indonesia (Bogor and Bekasi)	ELISA and PCR	IgG and IgM	Non-febrile individuals	2001–03	55·8% (32·1–76·2)	6·5% (2·1–10·4)
Ang et al[42]	East Asia and Pacific Islands	0–69	Singapore (national)	ELISA	IgG	Non-febrile individuals	2010	1·2% (0·5–2·6)	0·4% (0·2–0·8)
Graham et al[43]	East Asia and Pacific Islands	0–80	Papua New Guinea (Manus)	ELISA	IgG	Non-febrile individuals	2019	33·9% (21·9–47·9)	7·2% (4·5–11·2)
Azami et al[44]	East Asia and Pacific Islands	20–62	Malaysia (four districts§)	ELISA	IgG	Non-febrile individuals	2009	5·0% (3·0–8·0)	1·0% (0·8–1·3)
Vongpunsawad et al[45]	East Asia and Pacific Islands	2–85	Thailand (four districts¶)	ELISA	IgG	Non-febrile individuals	2014	26·7% (21·6–32·6)	13·5% (4·8–21·8)
Ayu et al[46]	East Asia and Pacific Islands	4–80	Malaysia (Bagan Panchor)	Neutralisation for serum samples in 96-well microplates	Serum containing neutralisation activity	Non-febrile individuals	2007	51·9% (28·0–78·1)	7·6% (2·7–11·6)
Kama et al[47]	East Asia and Pacific Islands	18–79	Fiji (2013)	Antigen-based microsphere immunoassay	IgG	Non-febrile individuals	2013	0·6% (0·1–3·4)	0·1% (0·0–0·2)
Kama et al[47]	East Asia and Pacific Islands	0–80	Fiji (2015)	Antigen-based microsphere immunoassay	IgG	Non-febrile individuals	2015	0·8% (0·0–6·5)	0·1% (0·0–0·2)
Azami et al (personal communication)‖	East Asia and Pacific Islands	0–80	Malaysia (national)	ELISA	IgG	Non-febrile individuals	2008	7·2% (3·8–12·8)	1·3% (1·0–1·7)
Andayi et al[48]	Middle East	1–80	Djibouti	ELISA	IgG	Non-febrile individuals	2010–11	2·8% (0·8–7·8)	0·2% (0·1–0·4)
Solgi et al[49]	Middle East	10–14	Iran (Tehran)	ELISA	IgG	Non-febrile children	2018	15·4% (10·7–22·4)	44·4% (35·8–66·5)
Humphrey et al[50]	Middle East	0–44	Qatar (Doha)	ELISA	IgG	Blood donors	2013–16	3·4% (0·4–18·5)	1·0% (0·5–1·9)
Moro et al[51]	Europe and Central Asia	0–100	Italy (Emilia Romagna)	Immuno-fluorescence assay	IgG	Non-febrile individuals	2007	10·8% (4·4–22·1)	2·2% (1·5–3·1)
Braga et al[52]	Latin America and Caribbean	31–70	Brazil (Ceará)	ELISA	IgG and IgM	Non-febrile individuals	2018–19	15·8% (1·8–60·0)	12·8% (5·3–21)
Rogier et al[53]	Latin America and Caribbean	0–80	Haiti (national)	ELISA	IgG	Non-febrile individuals	2014	55·1% (44·2–65·9)	5·9% (3·2–10·9)
Barreto et al[54]	Latin America and Caribbean	4–80	Brazil (Juazeiro do Norte)	ELISA	IgG and IgM	Non-febrile individuals	2018	24·7% (16·1–35·4)	2·7% (1·3–4·8)
Kuan et al[55]	Latin America and Caribbean	1–80	Nicaragua (Managua)	ELISA	OD level at 450 nm	Non-febrile individuals	2014–15	10·1% (7·1–13·8)	7·8% (4·9–14·6)
Simmons et al[56]	Latin America and Caribbean	14–45	Puerto Rico (national)	ELISA	IgG	Non-febrile individuals	2014–15	25·5% (18·0–34·1)	3·1% (1·2–4·9)
Dias et al[57]	Latin America and Caribbean	5–80	Brazil (Feira de Santana)	ELISA	IgG and IgM	Non-febrile individuals	2015	57·5% (46·6–67·9)	8·1% (3·0–13·1)

(Table continues on next page)

	Region	Age range (years)	Country (location)	Diagnostics used	Antibody	Population	Year of survey	Median seroprevalence from study, % (95% CI)	Median seroprevalence at age 10 years, % (95% UI)*
(Continued from previous page)									
Kanunfre et al[58]	Latin America and Caribbean	14–43	Brazil (Cruzeiro do Sul)	ELISA	IgG	Non-febrile pregnant women	2015–16	12·8% (6·4–22·0)	3·8% (2·8–5·0)
Eligio-García et al[59]	Latin America and Caribbean	14–43	Mexico (Chiapas)	ELISA	IgG	Non febrile pregnant women	2019	51·4% (30·6–71·2)	23·6% (14·6–53·8)
Adams et al[60]	Latin America and Caribbean	0–99	Puerto Rico (Ponce)	ELISA	IgG	Non-febrile individuals	2019	30·6% (27·4–33·9)	17·6% (12·6–27·0)
Hennessey et al[61]	Latin America and Caribbean	14–43	Virgin Islands (national)	ELISA	IgG	Non-febrile individuals	2015	37·2% (27·8–47·3)	6·8% (4·4–10·3)
Nicacio et al[62]	Latin America and Caribbean	10–80	Brazil (São Francisco)	ELISA	IgG	Indigenous and non-Indigenous individuals	2016	39·5% (29·7–50·7)	10·7% (9·1–12·4)
Anjos et al[63]	Latin America and Caribbean	20–78	Brazil (Salvador)	ELISA	IgG	Non-febrile individuals	2016–17	11·8% (9·2–14·9)	1·3% (0·6–2·1)
Cunha et al[64]	Latin America and Caribbean	11–50	Brazil (Riachão do Jacuipe)	ELISA	IgG and IgM	Non-febrile individuals	2016	18·8% (6·1–40·3)	2·1% (1·1–3·8)
Gallian et al[65]	Latin America and Caribbean	0–59	Martinique	ELISA	IgG	Blood donors	2013–15	48·3% (38·9–57·7)	9·4% (6·2–15·7)
Sharp et al[66]	Latin America and Caribbean	18–70	Puerto Rico (Guayama, Salinas)	ELISA	IgG or IgM	Non-febrile individuals	2015	42·4% (24·5–63·0)	8·7% (4·7–13·1)
Perisse et al[67]	Latin America and Caribbean	5–86	Brazil (Rio de Janeiro)	RDT	IgG and IgM	Non-febrile individuals	2018	42·9% (30·6–56·6)	6·7% (3·1–10·2)

arbo-MIA=arthropod-borne microsphere-based multiplex immunoassay. MFI-bg=median fluorescence intensity background. RDT=rapid diagnostic test. *Estimated from our model, based on the long-term average annual force of infection. †In Senegal, five districts were identified in Dagana, Podor, Pété, Ranérou, and Kanel. ‡In Myanmar, three districts were identified in Mandalay, Yangon, and Myeik. §In Malaysia, four districts were identified in Negeri Sembilan, Pahang, Kuala Lumpur, and Selangor. ¶In Thailand, four districts were identified in Ayutthaya, Lop Buri, Narathiwat, and Trang. ||Personal communication from Nor Azila Muhammad Azami, UKM Medical Molecular Biology Institute, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

Table: **Chikungunya seroprevalence surveys**

the long-term average annual FOI ranged from 0·0001 to 0·113 (median 0·007 [95% UI 0·003–0·01]). This indicates that the median long-term annual rate at which a susceptible individual acquires chikungunya infection is 0·7%, ranging from 0·3% to 1·0%. The median long-term average annual FOI was 0·001 (95% UI 0·0008–0·0014) in endemic settings and 0·009 (0·005–0·014) in epidemic settings. The highest median long-term average annual FOI was in south Asia (0·0083 [0·005–0·010]), followed by Latin America and the Caribbean (0·0080 [0·004–0·013]), and was lowest in Middle Eastern countries (0·001 [0·0005–0·002]). The estimated long-term average annual FOI values can be translated into age-specific seroprevalence. South Asia had the highest median seroprevalence at age 10 years (8·0% [95% UI 6·5–9·6]; range 0·3–33·8), followed by Latin America and Caribbean (7·8% [4·9–14·6]; range 1·3–23·6). The median seroprevalence at age 10 years was 6·5% (2·1–10·4; range 0·1–39·3) in East Asia and the Pacific Islands. The median seroprevalence in sub-Saharan Africa at age 10 years was 3·9% (95% UI 2·4–6·6; range 1·0–67·6) and 2·2% (1·5–3·1; a single observation) in Europe and Central Asia. The lowest median seroprevalence at age 10 years was in the Middle East (1·0% [0·5–1·9]), ranging from 0·2% to 44% (table; figure 3).

High observed seroprevalence does not always correspond to a high long-term average annual FOI since it is based on the annual average outbreak probability and accounts for a 100-year period. For example, the highest seroprevalence was observed in Cameroon (89·8% [95% CI 60·3–98·5]), while the highest long-term average FOI was observed in South Asia. Direct comparison of observed seroprevalence is inappropriate, but seroprevalence derived from long-term average FOI is comparable. The model-based seroprevalence at age 10 years in Cameroon is estimated at 26% (95% UI 18·5–35·0), with a long-term average annual FOI of 0·03 (0·02–0·04). Although the highest seroprevalence was observed in Cameroon, the long-term average annual FOI was lower than some south Asian regions, such as Tamil Nadu in India, which had a long-term average annual FOI of 0·04 (0·02–0·08) and seroprevalence of 34% (95% UI 17–55) at age 10 years (figure 3; appendix pp 30–31).

Among all symptomatic patients with chikungunya, the pooled proportion of patients who had chronic sequelae was 51% (95% CI 45–58; I^2=89%), which suggests substantial heterogeneity between studies. The

total length of the follow-up period varied from 4·7 months to 5 years. Four studies reported hospitalisation among patients with serologically confirmed chikungunya, with a pooled proportion of 4% (95% CI 3–5). The corresponding I^2 score was 46%, suggesting moderate heterogeneity between studies. The prevalence of patients with chronic sequelae varied from 31% to 67% and more than 60% of the observed data were from Latin America and Caribbean countries (figure 4).

(Figure 3 continues on next page)

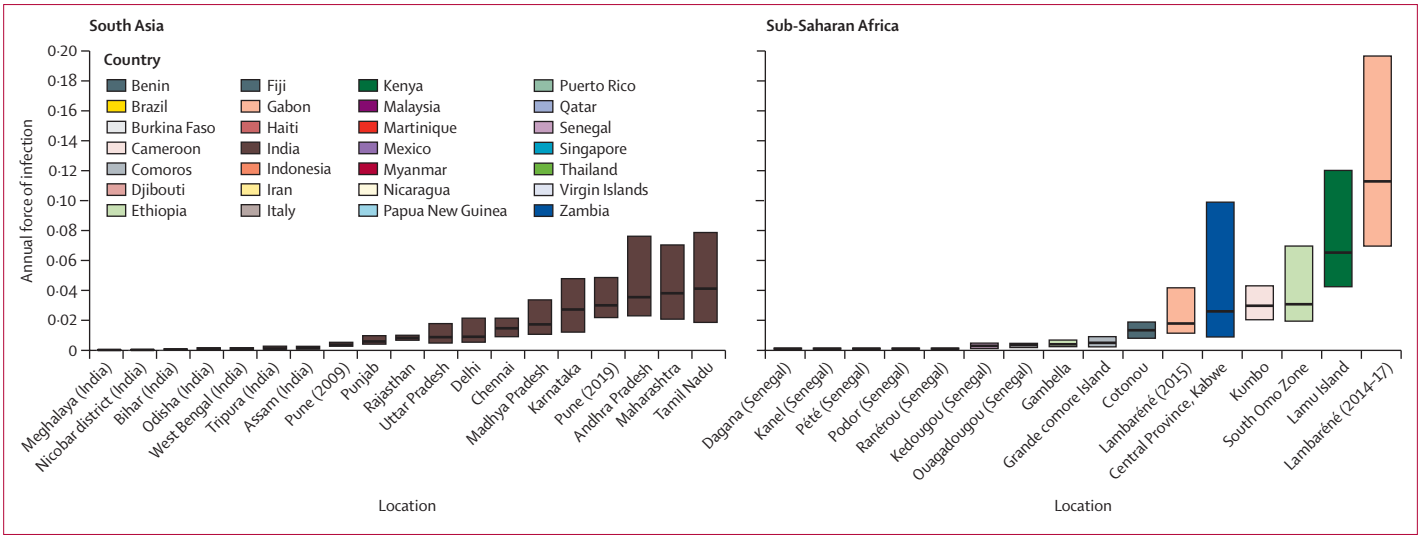
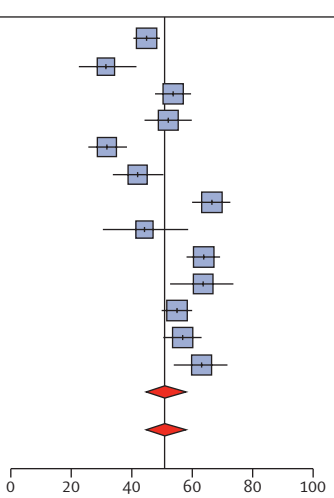


Figure 3: **FOI estimates for chikungunya by survey site**
Map showing a median estimate of long-term average annual force of infection (A); the FOI values are categorised into five levels, with darker colours indicating higher FOI; and 95% UIs for the long-term mean annual FOI, by survey location (B). FOI=force of infection. *The study was conducted in four administrative districts of Djibouti (district 1 [city centre and Einguela area]; district 2 [Arhiba area]; district 3 [Gabode and Ambouli areas]; and district 4 [Balbala and Damerjob areas]).

A

	Country	Duration of follow up	n/N	Proportion, % (95% CI)
Chronic arthritic disability (Kularatne et al[78])	Sri Lanka	4·7 months	230/512	45% (41–49)
pCHIK rheumatic or musculoskeletal pain (Bonifay et al[79])	France	6·0 months	31/99	31% (22–41)
pCHIK–CIR (Rodriguez-Morales et al[69])	Colombia	6·1 months	152/283	54% (48–60)
Chronic chikungunya arthritis (Bertolotti et al[68])	French Polynesia	12·0 months	87/167	52% (44–60)
Persistent arthralgia (Murillo-Zamora et al[73])	Mexico	12·0 months	69/217	32% (26–38)
pCHIK–CIR (Hossain et al[80])	Bangladesh	12·0 months	60/143	42% (34–50)
Arthralgia, myalgia, or asthenia (presence of at least one; Moro et al[76])	Italy	13·0 months	151/227	67% (60–73)
Persistent arthralgia (Peters et al[72])	Saint Martin	15·0 months	23/52	44% (30–59)
Chronic chikungunya from the CLTCS survey (Elsinga et al[75])	Curacao	15·0 months	194/304	64% (58–69)
Persistent arthralgia (Borgherini et al[74])	Reunion Island	18·7 months	56/88	64% (53–74)
Unrecovered CHIKV symptoms (Rodriguez-Morales et al[69])	Colombia	23·0 months	215/391	55% (50–60)
pCHIK (based on long–term CHIK scores; Doran et al[71])	Curaçao	29·0 months	141/248	57% (50–63)
Persistent arthralgia (Ninla-Aesong et al[77])	Thailand	60 months	77/122	63% (54–72)
Random effects model				**51% (45–58)**
Heterogeneity: I^2=89%, p<0·01				
Random effects model				**51% (45–58)**
Heterogeneity: I^2=89%, p<0·01				
Test for subgroup differences: χ^2=0·00, df=0 (p=NA)				



B

	Country	n/N	Proportion, % (95% CI)
Hospitalisation (Sissoko et al[81])	Mayotte	12/318	4% (2–6)
Hospitalisation (neurological symptoms; Braga et al[52])	Brazil	10/289	3% (2–6)
Hospitalisation (Pastula et al[82])	Federated States of Micronesia	45/1345	3% (2–4)
Hospitalisation (Alam et al[83])	Pakistan	5/52	10% (3–21)
Random effects model			**4% (3–5)**
Heterogeneity: I^2=46%, p=0·13			
Random effects model			**4% (3–5)**
Heterogeneity: I^2=46%, p=0·13			
Test for subgroup differences: χ^2=0·00, df=0 (p=NA)			

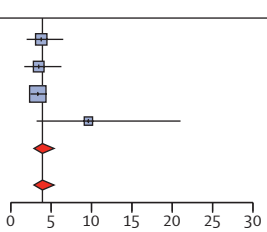


Figure 4: **Forest plots of pooled estimates of the proportion of people with chronic chikungunya sequelae (A) and proportion of people admitted to hospital after chikungunya infection (B)**
Meta-analyses of data were done using a random-effects model. The red diamonds represent the pooled estimate from the meta-analysis. n=number of events. N=number of participants. pCHIK=persistent chikungunya. CIR=chronic inflammatory rheumatism. CLTCS=Curaçao long-term chikungunya sequelae. NA=not applicable.

The ANOVA test, conducted on the added quadratic term in the linear regression, yielded a p value larger than 0·05. Based on this result, we did not find evidence to refute the linearity between follow-up length and prevalence of chronic sequelae (appendix pp 39–40).

Discussion

The principal finding from of our analysis was that the long-term average annual FOI was significantly higher in epidemic settings (0·009 [95% UI 0·005–0·014]) than endemic settings (0·001 [0·0008–0·0014]). 59 (78%) of 76 locations were categorised as epidemic settings and 17 (22%) locations as endemic to chikungunya across 38 countries. Large outbreaks in epidemic settings with high FOI can result in similar levels of infections in the long-term as endemic settings with relatively lower FOI. Notably, there was marked heterogeneity in the long-term average annual FOI across countries and continents and we found substantial subnational heterogeneity in FOI and transmission dynamics that are not well represented by national-level averages.

Although a previously published review provided an overview of seroprevalence per survey location,[16,17] it did not quantify comparable survey-specific transmission intensities through model-based estimation. Conversely, we estimated long-term average annual forces of infection for individual surveys and incorporated uncertainties in interepidemic period in non-endemic settings, resulting in forces of infection that are comparable across study sites. Our inferred values of long-term average annual FOI for chikungunya are lower than those for dengue.[85] This is because dengue has four distinct serotypes that co-circulate and can all contribute to seroprevalence, and thus to FOI. However, this does not mean that chikungunya is not capable of high attack rates, as demonstrated in some settings. For example, Gabon has a higher FOI for chikungunya (0·11) than the global average FOI for dengue (0·06). Our results also show that chikungunya can occur at low FOI, such as in Fiji, where the FOI for chikungunya is estimated at 0·0001, while in Taiwan, the FOI for dengue is estimated at 0·001. However, this can be reflected by large, but rare, epidemics of public health concern.

Our findings align with previous research. Previous research that addressed the geographical distribution and environmental suitability of chikungunya[86] identified a strong presence of chikungunya in central and western Africa, with less presence in northern Africa. This pattern was echoed in our results, particularly with the high FOI recorded in Gabon and Cameroon and no observation in North Africa. Moreover, our study extends on this previous work, estimating FOI in locations such as Ethiopia and Zambia. Furthermore, an environmental suitability map published by Nsoesie et al[86] suggested that coastal states in Brazil are particularly conducive to chikungunya. This observation aligns with our findings of relatively higher FOI levels in areas such as São Francisco, Rio de Janeiro, and Ceará, all of which are situated near coastal areas. In Asia, there is consensus regarding chikungunya suitability and presence in most regions of India, a finding that aligns with our study findings, since we identified 18 different states across India from our review. There is also consensus on chikungunya suitability in Myanmar, Indonesia, and Papua New Guinea, which aligns with our study results. The proportion of patients with chronic chikungunya and proportion who were admitted to hospital in our study also align with previous findings. From previous literature, the proportion of people with chronic chikungunya ranged between 40% and 80% and the hospitalisation rate ranged between 0·6% and 13%.[1]

Our study had limitations. Reporting of seroprevalence data in broad age groupings restricted our ability to reliably estimate the number and frequency of epidemics and to distinguish between epidemic and endemic settings in some surveys. Some surveys demonstrated minimal differences in the fit between epidemic and endemic models, due to the resolution of the data or the reflection of settings transitioning between epidemic and endemic states over time. If case incidence data were available for the survey locations, this could be used to generate informative priors about the heterogeneity of FOI over time. The varying sensitivity and specificity of test diagnostics could have influenced the accuracy and comparability of estimated seroprevalence results. However, sensitivity and specificity rates of different testing methods were not available during our review. Some of our seroprevalence estimates for Brazil might have been overestimated due to the cross-reactivity with Mayaro virus. A molecular screening study that identified co-infection between chikungunya virus and Mayaro virus in Brazil confirms the existence of co-circulation and differential diagnosis is required. However, there is little evidence available on co-infections in other regions between the two viruses.[87] Additionally, the proliferation of the East Central South African strain of chikungunya virus between 2020 and 2021 might have also influenced our estimates, specifically in Brazil.[88] However, we were not able to detect any major changes in long-term FOI in areas with outbreaks of the East Central South African strain during 2020 and 2021. In our study of people with chronic sequelae, we observed a small number of reported fatal cases (appendix pp 14–15). The four studies that reported mortality among people with chikungunya included different populations, such as patients admitted to the intensive care unit, patients clinically diagnosed with chikungunya, and patients with serologically confirmed chikungunya, which inhibits the generation of the pooled estimates for chikungunya case fatality rate. For people with chronic chikungunya sequelae, reliance on self-reported

symptoms in some surveys might have introduced potential reporting bias. High rates of loss-to-follow-up in some studies might have led to the underestimation of the proportion of people with chronic chikungunya infection.

Our study provides a foundational basis for future research. We offer a methodological framework to estimate the future burden of chikungunya by disease stage. Additionally, the impact of the chikungunya vaccine can be estimated based on the annual force of infection and proportion of people who would be susceptible to chikungunya infection derived from seroprevalence profiles in each survey location. Future studies should aim to spatially extrapolate the FOI to regions without age-stratified seroprevalence surveys, to produce globally comprehensive estimates of chikungunya virus infection and disease burden.

Contributors

HK, SS, OB, and KA conceptualised the study. HK and MA conducted the systematic review. HK and MA accessed and verified all of the underlying data. HK conducted the meta-analysis, mathematical modelling of chikungunya seroprevalence surveys, and wrote the original draft. All authors contributed to the methods, interpretation of results and discussion, critical review and editing of the manuscript, and have approved the final version. The authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy, or views of their affiliated organisations.

Declaration of interests

We declare no competing interests.

Data sharing

The statistical code and data for our main model is available online on GitHub (https://github.com/hyolimkang/CHIK). Data extracted from published articles and used in our analysis will be made available upon request to the corresponding author. Data provided to us directly by authors of the included studies will be shared after the investigators requesting data obtain permission from the original study authors.

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