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ORIGINAL ARTICLE

Prevalence of Post-Chikungunya Infection Chronic Inflammatory Arthritis: A Systematic Review and Meta-Analysis

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Objective. **To determine the percentage of patients who would develop chronic inflammatory rheumatism (CIR) following chikungunya (CHIK) virus disease.**

Methods. **We conducted a systematic review of the literature in 3 databases (PubMed, Science Citation Index, and Scopus) to identify studies assessing the proportion of patients who progress to CHIK-CIR. We performed a random-effects model meta-analysis to calculate the pooled prevalence and 95% confidence intervals (95% CIs). A 2-tailed alpha level of 5% was used for hypothesis testing. Measures of heterogeneity, including Cochran's Q statistic, the I^2 index, and the tau-squared test, were calculated and reported. Subgroup analyses were conducted by type of study and country, by studies evaluating chronic arthritis, and by studies with ≥200 patients and followup ≥18 months. Publication bias was assessed using a funnel-plot.**

Results. **Up to June 15, 2015, our literature search yielded 578 citations. The pooled prevalence of CHIK-CIR in 18 selected studies among 5,702 patients was 40.22% (95% CI 31.11–49.34; $\tau^2 = 0.0838$). From studies derived from India, prevalence was 27.27% (95% CI 15.66–38.88; $\tau^2 = 0.0411$), while from France, prevalence was 50.25% (95% CI 25.38–75.12; $\tau^2 = 0.1797$). The prevalence of CHIK chronic arthritis was 13.66% (95% CI 9.31–18.00; $\tau^2 = 0.0060$). Considering just those studies with ≥200 patients assessed, prevalence was 34.14% (95% CI 23.99–44.29; $\tau^2 = 0.0525$). In studies with a followup ≥18 months, prevalence was 32.13% (95% CI 22.21–42.04; $\tau^2 = 0.0453$).**

Conclusion. **According to our results in the most conservative scenario, approximately 25% of CHIK cases would develop CHIK-CIR (34% if we just consider the most representative studies), and 14% would develop chronic arthritis.**

INTRODUCTION

Chikungunya (CHIK) virus disease has emerged in the Americas as a significant tropical infectious disease (1). Along with the disease burden attributable to the acute phase of CHIK, there is a concerning previous estimate of 47.57% (95% confidence interval [95% CI] 45.08–50.13) of affected people in the new endemic areas in Latin America in 2014 who would develop post-CHIK chronic inflammatory rheumatism (CHIK-CIR) in a median time of 20.12 months (2). The articular sequelae that follow, which are a major cause of morbidity, have been reported not only in tropical and subtropical areas but also worldwide (e.g., European countries) (3).

There is evidence that links CHIK virus disease with the development of unspecific postviral arthritis, rheumatoid arthritis, seronegative spondylitis, and other noninflammatory musculoskeletal symptoms like persistent arthralgia (4,5). Such developments affect the quality of life and lead to increased direct and indirect economic loss (6,7), imposing a significant burden of disease, with considerable impacts on restrained health systems (8). However, previous preliminary estimates of the proportion of patients evolving to CHIK-CIR (2) were the result of pooled data on inflammatory and noninflammatory chronic manifestations of the disease in different countries. Those estimates used both prospective and retrospective studies and were not obtained through a systematic review of the literature, with the consequent risk of biases.

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Significance & Innovations

- Chronic inflammatory rheumatism (CIR) associated with chikungunya virus disease has multiple clinical and epidemiologic implications.
- At least a quarter of patients who have chikungunya virus would develop CIR, the disease being more frequent in patients from La Réunion, France, than India.

Furthermore, the continued and still out-of-control spread of CHIK virus disease in the new endemic areas in Latin America raises concern about the possibility of a coming CHIK-CIR epidemic, with consequent higher disability and economic costs for the region (6). Thus, we conducted a systematic review and meta-analysis to establish an accurate proportion estimate of patients who progress to CHIK-CIR.

MATERIALS AND METHODS

Literature search. In June 2015, MEDLINE (PubMed), Scopus, and Science Citation Index (Web of Knowledge) were searched to identify potentially relevant articles using the search strategy "chikungunya" and "arthritis." The review was conducted according to the recommendations of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group (9). No limit was set for the publication year. The search strategy was limited to articles in English or Spanish. All the authors initially screened the retrieved articles by title and abstract to identify possible eligible studies. Full-text of the possible eligible articles was reviewed and information abstracted by 3 authors (AJR-M, JAC-O, and SFU-G) and when 2 authors disagreed on the inclusion of a study, a third made the final decision. Cohort studies and cross-sectional studies were originally considered. Case–control studies and case series were not included, since they are not suitable (10), nor were cross-sectional studies, given the fact that these have not been used for estimations of CHIK-CIR.

Study eligibility and selection. We included original studies that assessed the proportion of patients with serologic diagnosis of acute CHIK fever, persisting with arthritis or arthralgia after a minimum followup of 2 months. If an article presented data from multiple study groups, of which some were eligible for inclusion, the eligible study groups were included if the pertinent data could be extracted (followup period, serologic confirmation, and arthritis or arthralgia assessment).

Studies that included only patients with established CHIK-CIR, populations with previous rheumatologic disease, or previous musculoskeletal symptoms were excluded, along with therapeutic clinical trials. Articles were also excluded if they were duplicates from already included articles (in a bibliographic database search) or if the followed population was fewer than 10 patients. In addition, articles were excluded if no or insufficient data were presented to analyze the total followup period and the diagnosis criteria for CHIK virus disease or CHIK-CIR were not clear.

Definition of CHIK virus disease and CHIK-CIR. A definition of CHIK virus disease included the following criteria: a history of acute febrile arthralgia (acute attack) with duration ≥48 hours, with positive anti-CHIK virus-specific immunoglobulin M; or RNA virus by reverse-transcriptase polymerase chain reaction; or postexposure anti-CHIK virus-specific immunoglobulin G–positive serologic test detected by enzyme-linked immunosorbent assay (11).

We defined CHIK-CIR as including: arthritis (history or finding of articular rigidity, erythema, edema, and pain), musculoskeletal pain or nonspecific arthralgia (self-reported or with medical diagnosis) lasting >2 months from acute attack, both relapsing or lingering, fulfilling the above CHIK virus disease criteria, and without a history of previous rheumatologic disease or musculoskeletal symptoms. Rheumatoid arthritis, unspecific or postviral arthritis, and seronegative spondylitis were included in the arthritis group. Postviral polyarthralgia, fibromyalgia, chronic articular pain, and frozen shoulder or plantar fasciitis were included in the musculoskeletal symptoms (12). Other conditions were excluded from the subgroup analysis.

Data abstraction and quality assessment. All identified possible articles were entered in EndNote X7 and were first screened on title and abstract and reviewed independently by 2 research team members. Those articles marked for inclusion by either team member went on to full-text screening. The researchers completed full data abstraction, and a third member verified all extracted data. Extracted data were author, title, year of the study, followup months, total population with CHIK, total number of patients who developed CHIK-CIR, total number of patients who developed either arthritis or musculoskeletal symptoms as explained above, type of study (prospective or retrospective), institution, city, and country. For studies that evaluated the same population at different times during the followup period, the considered number of patients was the one reported when the study finished. All data were checked in a third round of verification. The MOOSE guidelines were used for reporting (9). The quality assessment of the included studies was conducted using the Newcastle-Ottawa method for assessing the quality of nonrandomized studies in meta-analyses (13). Adequacy of followup of cohorts was considered good if loss of patients was lower than 10%, and followup time was considered enough for CHIK-CIR to occur if it was 3 months or higher.

Statistical approach. Unit discordance for variables was resolved by converting all units to a standard measurement for that variable. Percentages and mean ± SDs were calculated to describe the distributions of categorical and continuous variables, respectively. Since individual patient information was not available for all patients, we

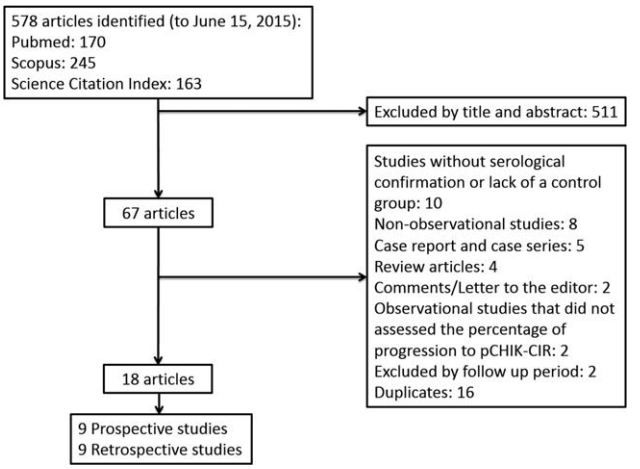

Figure 1. Search strategy for identification of studies. pCHIK-CIR = post-chikungunya virus disease chronic inflammatory rheumatism.

report weighted means and SDs. The baseline data were analyzed using the Statistical Package for Social Scientists, version 21.0.

The meta-analyses were performed using Stata, version 11.0, and the Microsoft Excel spreadsheet developed by Neyeloff et al (14), particularly for the forest plots. Pooled prevalences and their 95% CIs were used to summarize the weighted effect size for each study grouping variable, using the random-effects model (the weighting took into consideration the sample sizes of the individual studies). A random-effects meta-analysis model involves an assumption that the effects being estimated in the different studies are not identical but follow some distribution. For random-effects analyses, the pooled estimate and 95% CIs refer to the center of the distribution of pooled prevalences, but do not describe the width of the distribution. Often the pooled estimate and its 95% CI are quoted in isolation as an alternative estimate of the quantity evaluated in a fixed-effect meta-analysis, which is inappropriate. The 95% CI from a random-effects meta-analysis describes uncertainty in the location of the mean of systematically different prevalences in the different studies.

Measures of heterogeneity, including Cochran's Q statistic, the I^2 index, and the tau-squared test, were estimated and reported. We performed subgroup analyses by study design (retrospective or prospective) and by country (those with enough studies to include, India and France). We also performed a meta-analysis for those studies assessing specifically chronic arthritis, including only those studies with ≥200 patients or with a followup time ≥18 months. Publication bias was assessed using a funnel-plot. A random-effects model was used to calculate the pooled prevalence and 95% CI, given variable degrees of data heterogeneity and given the inherent heterogeneity in any systematic review of studies from the published literature.

RESULTS

Our literature search yielded 578 citations. The last day of the literature search was June 15, 2015. After scrutinizing the titles and abstracts of retrieved articles, we accessed 67 articles in full text. Among these 67 articles, 49 studies were excluded because they did not include information regarding serologic information, were nonobservational studies, corresponded to case report and case series, were

Table 1. Characteristics of included studies*

Author, year (ref.)	Country	Place	Study period	Cohort type	No.	CHIK-CIR, no.	Followup, months	Quality score
Javelle et al, 2015 (22)	France	Saint Denis, La Réunion	2006–2012	Retrospective	159	94	72	6
Miner et al, 2015 (42)	US	St. Louis	2014	Retrospective	10	8	2.5	5
Chaaithanya et al, 2014 (34)	India	Dakshina Kannada	2008	Prospective	203	9	36	4
Yaseen et al, 2014 (5)	France	La Réunion	2006–2008	Retrospective	403	181	30	7
Gerardin et al, 2013 (19)	France	La Réunion	2007–2008	Retrospective	346	261	18	8
Thiberville et al, 2013 (21)	France	La Réunion	2006	Prospective	26	6	10	6
Schilte et al, 2013 (43)	France	Saint-Pierre	2006–2009	Prospective	102	62	36	6
Chopra et al, 2012 (44)	India	Bavi	2006–2008	Prospective	509	24	24	8
Couturier et al, 2012 (7)	France	France (mainland)	2005–2007	Retrospective	338	12	30	6
Kularatne et al, 2012 (45)	Sri Lanka	Galagedara-Madige	2007	Prospective	512	230	36	7
Mathew et al, 2011 (4)	India	Kerala	2007–2008	Retrospective	1,396	437	15	5
Gerardin et al, 2011 (41)	France	La Réunion	2007–2008	Retrospective	413	177	16	8
Chopra and Vanugopalan, 2011 (46)	India	Village Modnimb	2006–2007	Retrospective	212	172	12	8
Ganu and Ganu, 2011 (35)	India	Maharashtra	2006–2008	Prospective	625	37	18	5
Chow et al, 2011 (47)	Singapore	Singapore	2008	Prospective	30	4	3	5
Manimunda et al, 2010 (48)	India	Dakshina Kannada	2008–2009	Prospective	203	94	10	6
Soumahoro et al, 2009 (49)	France	La Réunion	2006	Retrospective	199	185	17	7
Taubitz et al, 2007 (50)	Germany	Hamburg, Heidelberg, Munich	2006	Prospective	16	9	9	7

* CHIK-CIR = chikungunya virus disease chronic inflammatory rheumatism; ref. = reference.

Table 2. Characteristics of study subjects*

Author, year	No.	CHIK-CIR, no.	Chronic arthritis, no.	Women	Mean age, years	Other symptoms	Anti IgM	Anti IgG	Comorbidity	Recovered	Sites of arthralgia at disease onset					RF/ ACPA	Origin†
											Hand	Ankle	Knee	MCP	DIP		
Javelle et al, 2015	159	94	94	74.8	51	–	–	–	89.9	–	16.3	–	–	–	–	–	–
Miner, et al, 2015	10	8	8	80.0	39	20.0	80.0		–	–	60.0	–	–	–	–	–	Haiti
Chaaithanya et al, 2014	203	9	9	4.4	58	1.0	2.5	3.4	–	1.5	–	–	–	–	–	6.4	–
Yaseen et al, 2014	403	181	57	0.7	40	19.4	–	–	–	–	–	–	–	–	–	–	–
Gerardin et al, 2013	346	261	–	62.1	50	–	–	–	15.3	24.6	75.7	–	–	–	–	–	–
Thiberville et al, 2013	26	6	–	37.0	40	100.0	–	-	19.2	44.0	–	–	–	74	–	–	–
Schilte et al, 2013	102	62	–	50.3	35	62.7	–	16.8	–	17.2	–	-	–	–	–	–	–
Chopra et al, 2012	509	24	1	60.1	45	34.0	48.9	61.9	—	65.0	–	11.39	–	–	–	–	–
Couturier et al, 2012	338	12	–	53.5	50	–	–	–	67.2	45.0	–	–	–	–	–	–	ICUN
Kularatne et al, 2012	512	230	14	53.8	44	25.0	–	–	6.6	20.0	33.7	33.7	–	–	–	–	–
Mathew et al, 2011	1396	437	113	71.6	48	8.7	–	–	22.9	–	–	–	83.3	–	–	0.1	–
Gerardin et al, 2011	413	177	–	59.0	36	100.0	–	–	–	–	–	–	–	–	–	–	–
Chopra and Vanugopalan, 2011	212	172	26	57.8	45	–	–	43.9	–	–	–	–	78.9	–	–	–	–
Ganu and Ganu, 2011	625	37	37	56.3	50	–	0.8	–	–	–	–	–	–	–	12.5	–	–
Chow, 2011	30	4	–	13.3	45	46.7	-	–	–	83.3	–	–	–	–	–	–	–
Manimunda et al, 2010	203	94	94	52.7	35	73.4	100.0	–	100.0	51.0	–	–	27.5	–	–	0.0	–
Soumahoro et al, 2009	199	185	–	50.8	42	100.0	35.7	–	87.9	56.0	19.0	–	–	–	–	–	–
Taubitz et al, 2007	16	9	–	70.0	45	93.8	–	100.0	–	–	90.0	–	–	–	–	–	Mauritius, India, La Réunion, Malaysia, Seychelles, Madagascar, Indonesia
Total-	5702	2002	453	51.5	44	33.3	9.5	7.9	20.3	17.4	9.9	4.1	2.7	0.7	0.0	0.3	

* Values are the percentage, unless indicated otherwise. CHIK-CIR = chikungunya virus disease chronic inflammatory rheumatism; IgM = immunoglobulin M; IgG = immunoglobulin G; MCP = metacarpophalangeal; DIP = distal interphalangeal; RF/ACPA = rheumatoid factor and anti–citrullinated protein antibody; ICUN = imported cases from unspecified origin.
† If travel history was taken, the origin of patients is specified.

Table 3. Meta-analysis outcomes (random-effects model)*

CHIK-CIR	Studies	No. (%)	Combined effect % (95% CI)	Q†	I^2‡	τ^2§	*P*
All studies	18	5,702 (100)	40.22 (31.11–49.34)	36.6	99.6	0.0838	< 0.001
Prospective	9	2,226 (39.0)	25.33 (16.46–34.21)	21.6	98.6	0.0247	< 0.001
India	6	3,148 (55.2)	27.27 (15.66–38.88)	21.2	99.6	0.0411	< 0.001
France	8	1,986 (34.8)	50.25 (25.38–75.12)	4.4	99.7	0.1797	< 0.001
Chronic arthritis	10	4,232 (74.2)	13.66 (9.31–18.00)	62.0	98.6	0.0060	< 0.001
≥200 patients	11	5,160 (90.5)	34.14 (23.99–44.29)	26.13	99.6	0.0525	< 0.001
≥18-month followup	9	3,197 (56.1)	32.13 (22.21–42.04)	29.13	99.5	0.0453	< 0.001

* 95% CI = 95% confidence interval; CHIK-CIR = chikungunya virus disease chronic inflammatory rheumatism.
† Cochran's Q statistic for heterogeneity.
‡ I^2 index for degree of heterogeneity (percentage).
§ Tau-squared measure of heterogeneity.

review articles or other types of articles, did not contain extractable data on prevalence of CHIK-CIR, or were duplicates. Of the total 18 remaining eligible studies, 9 were retrospective cohort studies and 9 were prospective cohort studies. Data were extracted from both types in an effort to extract the maximum available data. We included 18 studies in the final analysis coded from 18 articles. The details of the selection process of eligible articles are shown in Figure 1.

The studies included in our analysis were published from 2007 to 2015 (Table 1) and reported data on 5,702 patients (Tables 2 and 3). We stratified the analyses according to the type of cohort (analyzing only prospective studies), by country of the study (India and France), and by occurrence of chronic arthritis, and we also selected those studies with ≥200 patients and followup time ≥18 months (Table 3). Among these studies, 2,226 patients (39%) were assessed in prospective cohorts (9 studies); 3,148 patients (55.2%) were from India (6 studies) and 1,986 (34.8%) from France (8 studies); 4,232 patients (74.2%) were in studies where arthritis occurrence was assessed (10 studies, 5 prospective and 5 retrospective). There were 11 studies (5 prospective and 6 retrospective) including ≥200 patients each, combining 5,160 patients (90.5%). Regarding followup time, there were 9 studies including 3,197 patients (56.1%). Data from individual studies are shown in Table 1, and all studies were considered of adequate quality on the basis of the Newcastle-Ottawa scale.

Geographical location varied among the included articles. Among the 18 studies, 8 were conducted in France (La Réunion), 6 in India, 1 in the US, 1 in Sri Lanka, 1 in Singapore, and 1 in Germany. Median time of followup was 17.5 months (range 2.5–72 months). In 15 studies, the followup was longer than 9 months, and 9 studies had more than 18 months (Table 1). Other demographic and clinical characteristics of the individual studies are included in Table 2.

The pooled prevalence of CIR among 5,702 patients who had CHIK virus disease was 40.22% (95% CI 31.11–49.34; $\tau^2 = 0.0838$) (Figure 2A). Publication bias was assessed with a funnel-plot for the SE by logit event, with no evidence of bias (Figure 3). The funnel-plot showed symmetric distribution of all studies at both extremes as well as around the midline. As the 18 pooled meta-analyses of retrospective cohorts seems to overestimate the prevalence of CHIK-CIR (Figure 2A), we also stratified our data based on the types of studies. Excluding retrospective cohorts and keeping prospective ones, the prevalence of CHIK-CIR was 25.33% (95% CI 16.46–34.21; $\tau^2 = 0.0247$) (Figure 2B). The prevalence of CHIK-CIR derived from studies in India was 27.27% (95% CI 15.66–38.88; $\tau^2 = 0.0411$) (Figure 2C), while for studies from France prevalence was 50.25% (95% CI 25.38–75.12; $\tau^2 = 0.1797$) (Figure 2D). The prevalence of CHIK chronic arthritis was 13.66% (95% CI 9.31–18.00; $\tau^2 = 0.0060$). Considering just those studies with ≥200 patients assessed, the prevalence of CHIK-CIR was 34.14% (95% CI 23.99–44.29; $\tau^2 = 0.0525$) (Table 3). In studies with a followup ≥18 months, the prevalence of CHIK-CIR was 32.13% (95% CI 22.21–42.04; $\tau^2 = 0.0453$). The 95% CI of those studies with ≥18 months did not differ significantly from the global 95% CI of the whole group of studies, nor from those with <18 months.

Although we had no detailed data to subanalyze a pooled prevalence comparing by sex, the proportion of women (as described in Table 2) was used as an independent variable in a nonlinear regression model to see its influence in the proportion of CHIK-CIR in the studies. The model showed a significant positive association ($r^2 = 0.7483$, $P < 0.0001$), those studies including a higher proportion of women also had a higher proportion of CHIK-CIR. Finally, we proceeded in a similar way analyzing by age, but we found no significant differences when we included the mean age reported by each study ($P > 0.05$).

DISCUSSION

Chronic sequelae derived from CHIK virus disease seem to be a worrisome coming epidemic in the endemic areas in Latin America (1). According to our results in the most conservative scenario, approximately 25% of CHIK virus disease cases would develop CHIK-CIR (34% if we just consider the most representative studies), and 14% would develop chronic arthritis.

Given the time passed since CHIK virus disease was discovered, more than a half century ago (15), research has

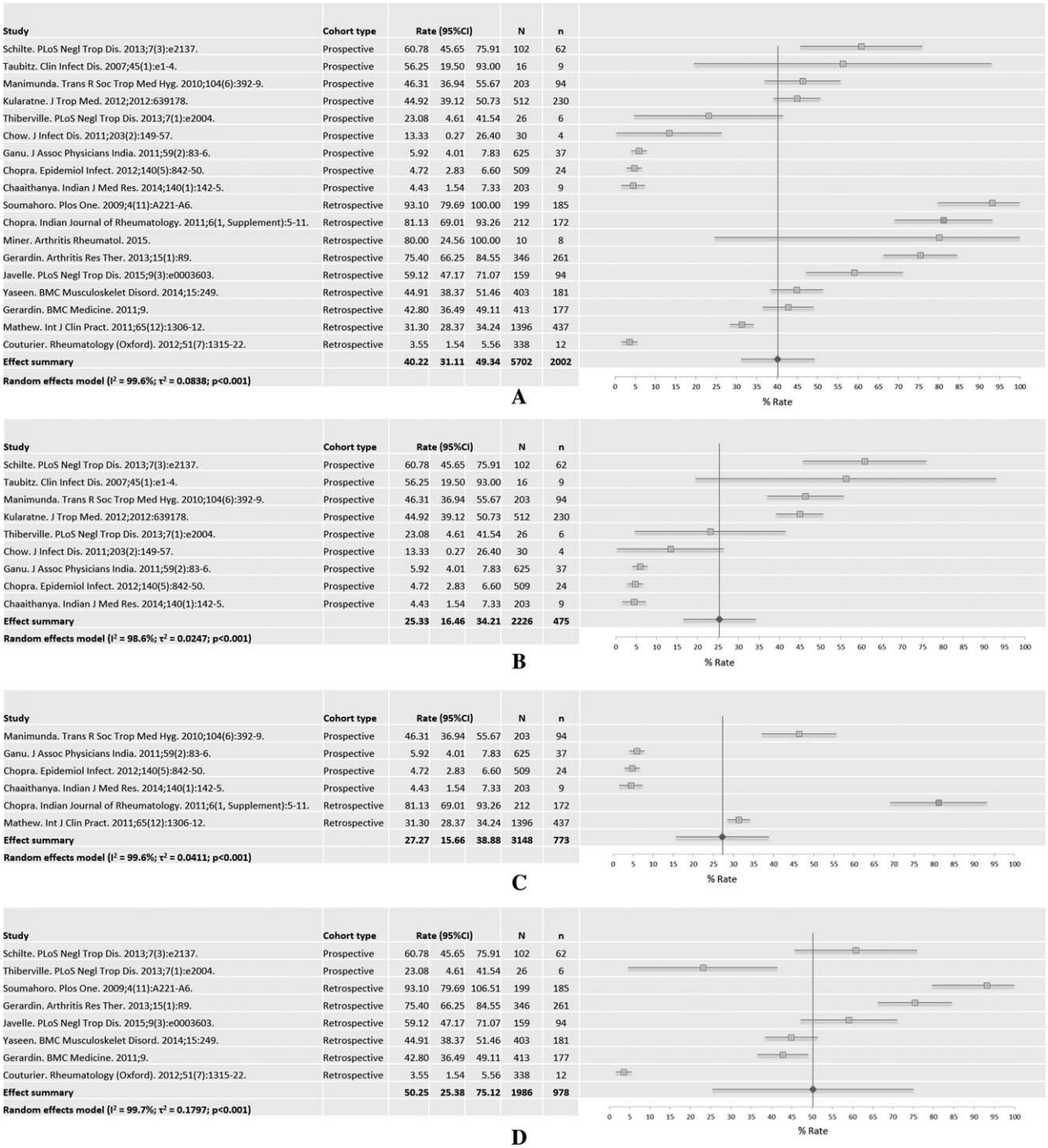

Figure 2. Prevalence of chikungunya virus disease chronic inflammatory rheumatism estimates (boxes) with 95% confidence limits (bars) for each study selected; pooled prevalence estimates are represented as a diamond. **A,** All selected cohort studies (prospective and retrospective). **B,** Prospective cohort studies. **C,** Studies from India. **D,** Studies from France.

only been triggered since the 2005–2006 epidemics in La Réunion, overseas France. This research has involved observational studies assessing the prevalence of CHIK-CIR. In fact, it seems remarkable that after a decade, and with enough research, a systematic review and meta-analysis was not previously conducted as done here.

Otherwise, considering the pooled prevalence of CIR, our results coincide with previous estimations (2). There is no significant difference between our 95% CIs and those found previously, although this similarity could also be explained due to limitations in statistical power, given the fact that some studies are small (4 of the prospective and 2 of the retrospective). The subanalysis by country showed differences (although not significant) between the prevalence of CHIK-CIR in populations from France (La Réunion) and India. Although this finding could be the

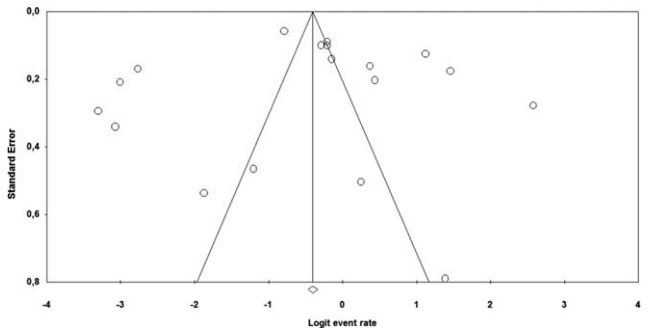

Figure 3. Funnel-plot for the SE by logit event rate to assess for publication bias.

result of the different number of followed patients and study design, since studies from France were mainly retrospective (4 of them with <200 patients, which can lead to prevalence overestimation), and since all the studies from India had >200 patients, including the largest cohort (1,396 patients), the difference among countries could be attributable to other variables like ethnic variability between and within studied cohorts, virus lineage, comorbidities, or sex of the included population, as well as other nonassessed immune host response and environmental conditions (16).

Nevertheless, this question highlights the importance of proper assessments in regions where CHIK virus disease is endemic, since along with the virus lineage, differences in the risk of progression to chronic forms of the disease depend on immune and environmental variables (17). Additionally, while the majority of studies evaluated endemic cases, comprehensive assessment of imported cases is desirable in view of the fact that the importance of the ethnic background and place of infection is not completely understood. Our systematic review included only 3 studies of imported cases from various countries to different origins and did not allow conducting such a subanalysis. Nonetheless, studies have found some factors associated with CHIK-CIR development. The condition seems to be less likely in children, and the risk apparently increases in older people, women, and patients with multiple comorbidities (7,18–20). As we analyzed the results, a significantly higher frequency of CHIK-CIR was found in those studies including a higher proportion of women. But we were not able to find a significant association with age (given the fact that we have no detailed age information of each case from each study). Likewise, acute immune response apparently impacts the risk of evolution to chronic forms, as the duration of initial rheumatologic symptoms and immunoglobulin levels are related with evolution to CHIK-CIR (7,18,19). Nevertheless, there are no large specific studies designed to address risk factors for the development of CHIK-CIR, but arthralgia of hands and wrists, myalgia, and lymphopenia appear to predict its occurrence (21).

Regarding followup, there was a large heterogeneity of followup time in the included studies; however, there were no significant differences between the frequency of CHIK-CIR according to time. As we reported previously (2), high prevalences of CHIK-CIR are found in studies of short and long followup times. The longest study following patients found a frequency of 59% after 6 years (22), but the concern is whether CHIK-CIR may last for more years. According to our meta-analysis and previous studies (2,22), we would not expect that the CHIK-CIR proportion in 10 years would be zero. Thus, CHIK-CIR could be considered a long-standing condition such as other rheumatologic diseases, also implying longer followup for such patients.

In the acute phase of the disease, skin fibroblasts support viral replication following the mosquito bite, being the initial target of CHIK virus (23). CHIK virus enters the circulatory system and triggers an early type I interferon (IFN) response (17). In mouse models, altered IFN response has been associated with more severe disease and even death (24). From the blood, the virus spreads to various organs and tissues, and it can persist in immune-privileged niches (23). It has been found to replicate to high titers in the joints and skeletal muscles of mice and nonhuman primates and is associated with extensive inflammatory cell recruitment (17,25,26). Mononuclear cells, including macrophages, infiltrate those tissues, and CHIK virus infection can persist in these cells in lymphoid, muscle, and joint tissues (27,28). Macrophages probably are another primary cellular target that may assist in virus dissemination and have an important role in the pathogenesis of CHIK-CIR, as macrophages may mediate CHIK virus inflammatory disease and regulate viral clearance and resolution of inflammation (23,29,30). Viral persistence has been associated with expression of IFNα, interleukin-10, monocyte chemotactic protein 1 (MCP-1 or CCL2), and proinflammatory cytokines (17).

Likewise, elevated expression of MCP-1, MCP-2, and MCP-3, which modulate the chemotaxis of osteoblasts and osteoclasts, has been associated with bone resorption and bone loss. CHIK virus seems to favor a pro-osteoclastic microenvironment, disrupting the RANKL/osteoprotegerin ratio (26,31). The fact that inflammation was reduced in CHIK virus–infected mice receiving the MCP inhibitor, Bindarit, highlights the importance of MCP and monocytic cells in the pathogenesis of CHIK virus (31).

Furthermore, viral characteristics have been related not only with disease clinical course but also with disease spread and enhancement of mosquito infectivity. Genetic changes, such as the E1-A226V mutation, have been related to the adaptation of the virus to vectors such as *Aedes albopictus*, favoring its spread (32). Likewise, virus strains have shown genetic changes through time that have been associated with higher and faster viral replication in the human host, (33) which would increase the number of viruses available to reinfect mosquitoes and then transmit CHIK virus to other human hosts.

However, more studies are necessary to characterize host-pathogen relations to lead to the development of CHIK-CIR preventive interventions and adequate treatment for patients that already have it. The expected prevalence of CHIK chronic arthritis raises concern about the need for adequate diagnosis, evaluation, and treatment of patients, given that erosive forms of the disease have been reported, and probably those patients would need disease-

modifying antirheumatic drugs (34,35). Even more, retrospective and prospective studies are necessary in those new endemic areas such as the countries in Latin America where these chronic consequences are highly expected (1,2,8), although there is still a lack of publications. Recently our group reported a similar CHIK-CIR frequency in a cohort in Colombia (44.3% [95% CI 35.39–53.16], not a significant difference from our pooled estimated prevalence) (36), which is consistent with the current meta-analysis findings.

However, our estimations are still limited regarding the high heterogeneity of the included studies, in part because studies published in languages other than English or Spanish were not considered. This restriction leaves out potentially important works written in French. Besides this limitation, the funnel-plot suggested no publication bias in this report. The quality assessment showed good quality of most of the studies, and our results are consistent with previous estimates (2). In order to manage the heterogeneity of the studies, we conducted subgroup analysis by the type of cohort followup, removing retrospective studies, which overestimated CHIK-CIR, and still the prevalence remained high enough to raise concern of what we could expect in 2016, given the time frame of evolution. Followup time was another aspect to consider. In studies with ≥18 months, CHIK-CIR was over 32%. In 5 of those studies, prevalence was higher. The study with the highest followup time (72 months) reported 59% of CHIK-CIR (22).

These findings have clear concerning implications regarding the future disability and direct and indirect economic costs of the disease. Taking into account only rheumatologic chronic sequelae of the disease, previous disability-adjusted life years loss estimates in Latin America have shown higher disease burden than those reported in Indian epidemics (8,37). Those previous results were based on estimations that did not result from a systematic review; even so, they coincide with ours. CHIK-CIR could overload not only countries that have already shown problems controlling vector-borne diseases (38), but also health systems in crisis due to other socioeconomic factors, affecting health care in communicable and noncommunicable diseases. As has been described, according to the model of epidemiologic transition (39,40), where developing countries would advance in reducing infectious diseases but face increasing morbidity and mortality of noncommunicable chronic diseases, this double burden of disease is theoretically applicable to chikungunya, which affects the population during its acute phase but also carries with it chronic conditions such as CHIK-CIR.

In this setting, there is a call to health care managers to establish prompt disease spread control and to educate physicians to prepare them for the future challenge of disease, specifically for CHIK-CIR proper diagnosis and management (6,36,41). There is a lack of high-quality evidence to guide assessment and diagnosis, and also a lack of local followup studies in Latin America to address the real proportion of CHIK-CIR evolving patients. CHIK virus disease is a problem at the present, and could be a major problem in the future, including significant economic implications, given the high cost associated with the chronic condition of disease (6).

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