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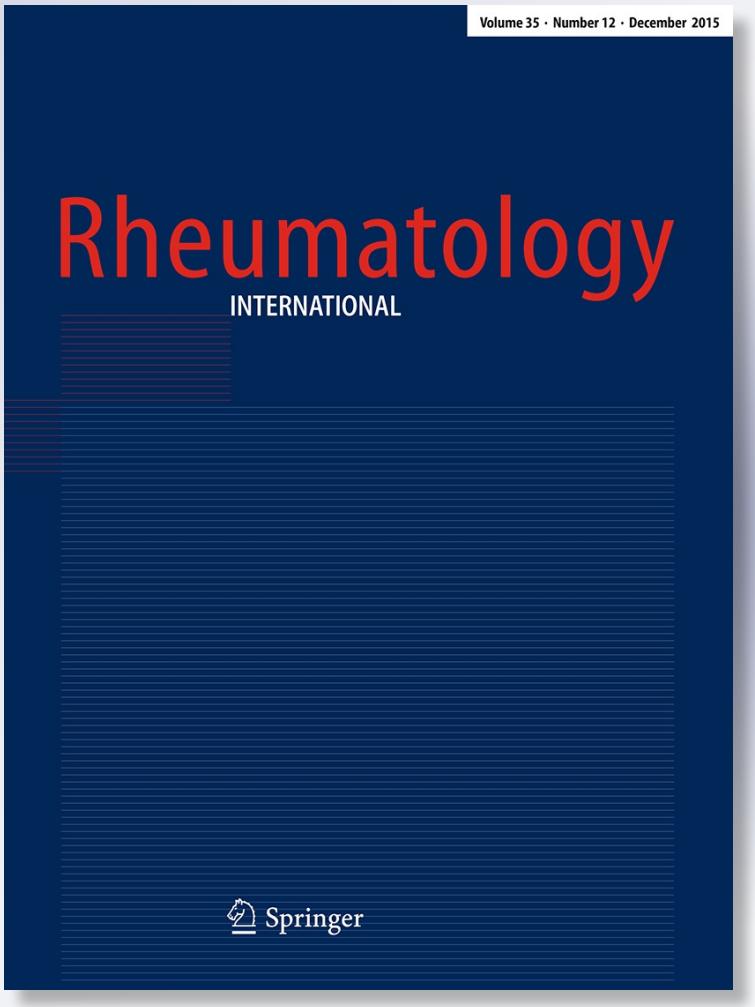

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SHORT COMMUNICATION - OBSERVATIONAL RESEARCH

How many patients with post-chikungunya chronic inflammatory rheumatism can we expect in the new endemic areas of Latin America?

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Abstract Post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) is one of the consequences that are impacting new endemic countries, such as those in the Americas. The relative frequency of pCHIK-CIR is highly variable, ranging from 14.4 % to 87.2 % (including variable number of patients and follow-up times). Based on those non-weighted values, it is difficult to estimate which would be the expected number of patients with CHIK who will develop CIR. For these reasons, we modeled weighted estimations based on pooled data extracted from those eight representative studies in order to provide cumulative proportion of pCHIK-CIR over time and median time of it, but also estimations of the number of patients with CHIK reported in Latin American countries (within a 95 % CI). This model estimated a prevalence of 47.57 % for pCHIK-CIR (95 % CI 45.08–50.13), with a median time to 50 % of pCHIK-CIR in 20.12 months. Given the reported number of patients with acute CHIK during 2014 in the Americas, our estimates suggest that from those patients, 385,835–429,058 patients will develop pCHIK-CIR. Despite the limitations of these estimates, the provided figures of pCHIK-CIR presented here are preliminary approximations of what the future burden of related rheumatic disease in the region as a consequence of CHIK infection for 2015–2016 could be, given the timeframe of median time of occurrence.

Keywords Chikungunya · Chronic inflammatory rheumatism · Estimations · Epidemiology · Americas

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Introduction

Chikungunya (CHIK) has emerged as a major public health threat in Latin America affecting extensive tropical and temperate areas, where the disease, originally imported to the Caribbean, has now rapidly expanded into new regions to become endemic [1–3]. Although classically presenting as an acute febrile syndrome, CHIK is well known to produce severe acute and chronic musculoskeletal manifestations ranging from eruptive polyarthritis to persistent rheumatologic and disabling symptoms [4]. Post-CHIK (pCHIK) chronic inflammatory rheumatism (CIR) was first reported in 1979 [4, 5]; however, it was not until the last decade that due to its re-emergence in Africa, Asia, Pacific Islands, Europe, and now the Latin America, clinical studies have started to resurge and assess its occurrence [4–12]. Among these studies, the relative frequency of pCHIK-CIR is highly variable, ranging from 14.4 % to 87.2 % (including variable number of patients and follow-up times). Based on those non-weighted values, it is difficult to estimate which would be the expected number of patients with CHIK who will go on to develop CIR.

Materials and methods

Following an initial search through MEDLINE®, trying to identify studies evaluating pCHIK-CIR, we found and

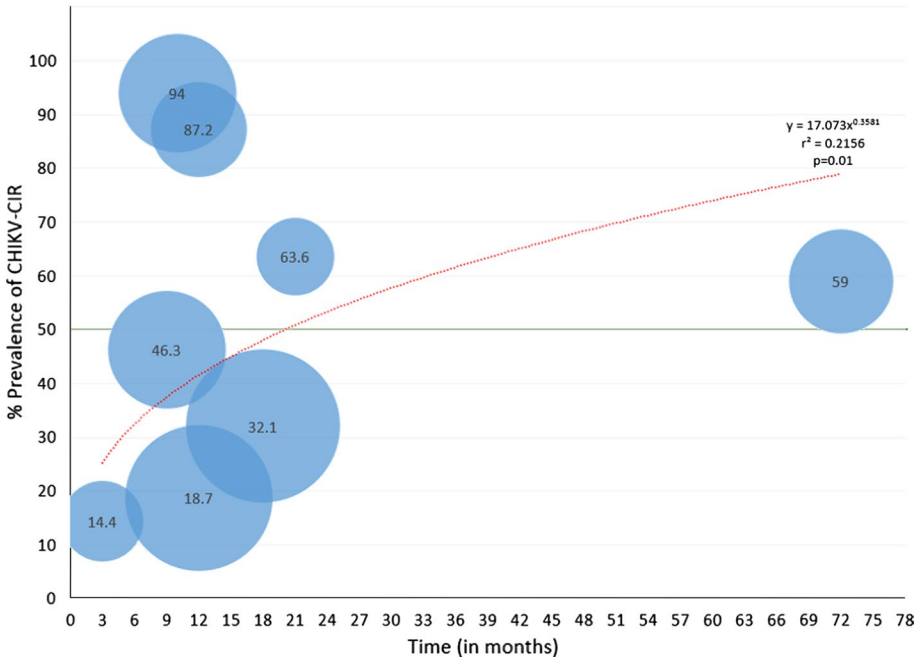

Fig. 1 Nonlinear regression model for estimations of the cumulative proportion of patients with pCHIK-CIR over the time (bubble size is relative to each study sample size)

selected eight representative observational studies [5–12] assessing the relative frequency (%) of pCHIK-CIR. We pooled data ($n = 1544$) and subsequently weight the final follow-up time prevalence according to the population sizes among these studies. Additionally, we ran nonlinear regression models to estimate the cumulative proportion of pCHIK-CIR over time and median time of it (time estimation for 50 % of patients could present pCHIK-CIR). Finally, we estimated 95 % confidence intervals (95 % CI) from pCHIK-CIR proportion estimations to the number of patients with CHIK reported in Latin American countries in order to predict the expected number of patients with pCHIK-CIR and its median time for presentation.

Results

Of the total population assessed in selected studies, during a follow-up median time of 18.8 months (range 3–72 months), 911 developed pCHIK-CIR (crude prevalence of 59.0 %). Then, after weighting the prevalence according to the sample size, a prevalence of 47.57 % was estimated (95 % CI 45.08–50.13). With the nonlinear regression model (Fig. 1), prevalence of pCHIK-CIR in relation to time was estimated (obtained with the following equation, which was the best fit, $y = 17.073 \times x^{0.3581}$) revealing 25.30 % at 3 months, 32.43 % at 6 months, 37.5 % at 9 months and 41.57 % at 12 months. Median time to 50 % of pCHIK-CIR was estimated in 20.12 months (Fig. 1).

Based on data reported to the Pan American Health Organization (PAHO) up to epidemiological week 1° (January 9, 2015) [13], we proceeded to estimate the 95 % CI of the number of patients with pCHIK-CIR per country (Table 1). Estimates suggest that from those patients who suffered CHIK during 2014 in the region (855,890), 385,835–429,058 patients will go on to develop pCHIK-CIR (Table 1).

Discussion

Despite the limitations of these estimates, the provided figures of pCHIK-CIR presented here are preliminary approximations of what the future burden of related rheumatic disease in the region as a consequence of CHIK infection for 2015–2016 could be, given the timeframe of median time of occurrence. Modeled data came from other countries outside the Americas, and then, this is one potential limitation of this analysis related to the extrapolation of these data in the region. Then, prospective studies about pCHIK-CIR should be made in countries in the Americas now becoming endemic for CHIK. This would be useful in order to see whether these findings would be similar or change, compared to the findings of this report and those from previous studies.

Non-adjusted estimates have grossly indicated that the cumulative number of CHIK-infected individuals suffering from long-lasting pain and disabilities could affect not <1–2 million people around the world [5]. Such numbers as well as current adjusted estimates for Latin America signal that CHIK virus is on the verge of causing a chronic rheumatism epidemic in the hemisphere [5]. Because of the

Table 1 Estimations of the number of patients which will develop pCHIK-CIR in Latin American countries

Country	Autochthonous cases					Projected number of pCHIK-CIR (95 % CI)	
	Suspected	Confirmed	Imported	Total cases	Incidence rate[a]	Lower limit	Upper limit
Dominican Republic	537,628	84	0	537,712	3051.71	242,401	269,555
El Salvador	135,226	157	0	135,383	1201.70	61,031	67,867
Colombia	83,228	578	26	83,832	202.27	37,791	42,025
Venezuela	34,642	2,303	70	37,015	1086.44	16,686	18,556
Puerto Rico	24,349	4,239	31	28,619	740.66	12,901	14,347
Guatemala	21,859	198	0	22,057	72.54	9,943	11,057
Honduras	4,072	9	5	4,086	83.87	1,842	2,048
Nicaragua	1,598	1,918	40	3,556	3.01	1,603	1,783
Brazil	792	2,165	93	3,050	1.52	1,375	1,529
Costa Rica	185	13	40	238	0.78	107	119
Mexico	0	155	13	168	0.35	76	84
Panama	0	22	32	54	0.34	24	27
Cuba	0	20	20	40	0.38	18	20
Argentina	0	0	28	28	0.41	13	14
Chile	0	0	19	19	0.18	9	10
Peru	0	0	11	11	0.17	5	6
Ecuador	0	3	7	10	0.06	5	5
Paraguay	0	1	7	8	0.10	4	4
Bolivia	0	0	4	4	0.07	2	2
Uruguay	0	0	0	0	0.00	0	0
Total Latin America	843,579	11,865	446	855,890	144.25	385,835	429,058

[a] Cases/100,000 pop; 95 % CI = 95 % confidence interval; pCHIK-CIR = post-chikungunya chronic inflammatory rheumatism

highly debilitating nature of CHIK disease and its possible deleterious economic consequences [5], long-term follow-ups (>5 years) should be performed in order to improve disease characterization and distinguish the different disease landscapes and endemic variability for each country as recently suggested by other authors [2, 3].

Until May 2015, no specific antiviral treatment or vaccines are available for CHIK. For acute phase of CHIK, nonsteroidal anti-inflammatory drugs (NSAIDS) and physiotherapy have been suggested for symptomatic treatment [4–7, 9]. Cautious use of steroids, because of the risk of reactivation of the rheumatic manifestations after tapering, have been also recommended [14]. The use of aspirin must be avoided due to the risk of Reye syndrome. It has been suggested that chloroquine, being capable of reducing viral replication, could be effective in the prophylaxis and treatment of early-stage disease, although no efficacy has been demonstrated in the chronic phase [14–16]. Moreover, methotrexate has been used successfully in a group of patients with chronic destructive polyarthritis (ACPA+) after CHIK infection [14, 17, 18]. The maintenance of inflammatory activity with elevated proinflammatory cytokines is a fact in the chronic phase. This opens the door to further studies of efficacy with disease-modifying drugs and even biological therapy [14].

Detailed clinical trials regarding early use of methotrexate and other drugs to prevent joint damage and long-term corticotherapy should be conducted in the future [5], aiming to positively modify the disease outcome [19]. Even more, recent ex vivo studies have found that doxycycline exhibited significant anti-CHIK activity. Used plus ribavirin reduced viral infectivity and replication in infected cells. Further experimental and clinical studies should be carried out to investigate their potential utilization for the attenuation of the clinical symptoms pathognomonic to CHIK disease [20].

Conflict of interest None.

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