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Neurological Compromise in Chikungunya: A Meta-Analysis of its Prevalence

Compromiso Neurológico en Chikungunya: Un Meta-Análisis de su Prevalencia

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ABSTRACT

Objective
To determine the percentage of patients that would develop neurological manifestations and/or complications of chikungunya infection (NeuroCHIK).

Methods
We conducted a systemic review of the literature in three databases (PubMed, SCI, Scopus and SciELO) in order to identify studies assessing the proportion of patients that present NeuroCHIK. We performed a random-effects model meta-analysis to calculate the pooled prevalence and 95% CI. Measures of heterogeneity, including Cochran's Q statistic, the I^2 index, and the tau-squared test, were estimated and reported. Subgroup analyses were conducted by type of study, country, studies with ≥200 patients, studies evaluating attention difficulties, encephalitis and seizures. Publication bias was assessed using a funnel-plot.

Results
Up to June 15, 2015, our literature search yielded 143 citations. The pooled prevalence of NeuroCHIK at nine selected studies among 2,161 patients was 34.53% [95%CI, (20.78–48.27%), $\tau^2 = 0.0734$]. Prospective cohorts shown a prevalence of NeuroCHIK of 36.87% [95%CI, (5.17%-68.57%), $\tau^2 = 0.0818$]. Occurrence of attention difficulties prevalence was 16.46% [95%CI, (5.65%-27.27%), $\tau^2 = 0.0149$]. In the case of encephalitis its prevalence was 9.90% [95%CI, (8.25%-11.54%), $\tau^2 < 0.0001$]. Finally, analyzing the prevalence of seizures this was 3.43% [95%CI, (0.55%-6.31%), $\tau^2 = 0.0006$].

Conclusions
According with our results, in the most conservative scenario, about 33% of CHIK cases would develop NeuroCHIK (36% if we just consider prospective studies), 10% encephalitis, and 3% seizures.

Key words
Neuroinfection, chikungunya, seizures, emerging, Latin America, meta-analysis, clinical epidemiology.

RESUMEN

Objetivo
Determinar la proporción de pacientes que desarrollan manifestaciones y/o complicaciones neurológicas de la infección por chikungunya (NeuroCHIK).

Métodos
Se llevó a cabo una revisión sistemática de la literatura en tres bases de datos (PubMed, SCI y Scopus) con el fin de identificar estudios que evaluaran la proporción de pacientes que presentan NeuroCHIK. Se realizó un modelo de meta-análisis de efectos aleatorios para calcular la prevalencia combinada y su IC95%. Se estimaron y reportaron medidas de heterogeneidad, incluyendo el estadístico Q de Cochrane, el índice I^2 y la prueba de tau cuadrado. Se hicieron análisis de subgrupos por tipos de estudios, países, estudios

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con ≥200 pacientes, estudios evaluando dificultades de atención, encefalitis y convulsiones. El sesgo de publicación se evaluó usando un funnel-plot.

Resultados

Up to june 15, 2015, our literature search yielded 143 citations. The pooled prevalence of NeuroCHIK at nine selected studies among 2,161 patients was 34.53% [95%ci, (20.78–48.27%), τ^2 = 0.0734]. Prospective cohorts shown a prevalence of NeuroCHIK of 36.87% [95%ci, (5.17%-68.57%), τ^2 = 0.0818]. Occurrence of attention difficulties prevalence was 16.46% [95%ci, (5.65%-27.27%), τ^2 = 0.0149]. In the case of encephalitis its prevalence was 9.90% [95%ci, (8.25%-11.54%), τ^2 <0.0001]. Finally, analyzing the prevalence of seizures this was 3.43% [95%ci, (0.55%-6.31%), τ^2 = 0.0006].

Conclusión

De acuerdo a los resultados, en el escenario más conservador, cerca de 33% de casos CHIK desarrollarían NeuroCHIK (36% si consideramos solo los estudios prospectivos), 10% encefalitis y 3% convulsiones.

Palabras Clave virus chikungunya, encefalitis, convulsiones, América Latina, metanálisis, epidemiología.

INTRODUCTION

Chikungunya has emerged in the World and recently in the Americas as a significant cause of morbidity.[1] This vector-borne disease caused by chikungunya virus (CHIK) has arrived to the Americas ending 2013 to stay, affecting significantly countries in the tropical Latin America area.[2,3] The epidemiological scenario was set with the wide distribution and ecoepidemiological suitable conditions for their vectors *Aedes aegypti* and *A. albopictus*, both transmitting dengue since decades.[4-7] Preparedness for CHIK was a significant aspect that would affect its morbidity and mortality evolution in affected countries,[8,9] which has begun also to be reported in countries in the region of the Americas, such as Colombia and Venezuela.[10,11] Even more, before CHIK, control of vector-borne diseases such as dengue and malaria has been a hard task for many government and their health authorities.[3,6,12,13] Although would be considered amazing, research in CHIK at Latin Americas still is scarce and limited as has been recently stated,[14] and after 16 months of epidemics in the region, there are many gaps in knowledge of its epidemiological and clinical aspects.[15,16] Even more, this has been an epidemic of rapid progress, with initial imported cases and then a significant spreading of autochthonous cases in most countries in the tropics,[1] which counts for more than a million cases in 2014 and close to 400 thousand cases during half of 2015.[17] This imply serious implications not just for its acute phase but also its chronic one.

In countries such as Colombia, there are municipalities, particularly in the north Caribbean Coastal region, with incidence rates over 2,500 cases/100,000 population, in departments such as Bolivar, Atlántico, Córdoba or Sucre.[18] But given the ecoepidemiological conditions, CHIK has begun to significantly increase its morbidity in other regions of the country.[19]

After an infective bite, *Aedes* mosquitoes can transmit the virus which can disseminate to multiple organs after infect monocytes and macrophages, pass through lymph nodes and microvasculature and reach liver, spleen, muscle, joints and even the Central Nervous System (CNS).[20,21] This would lead to its clinical consequences in different organs and systems.

Symptoms of CHIK include sudden onset of fever, rash, and arthralgia, which predominantly affect the wrist, knee, ankle, and small joints of the hands and feet.[1,15,22,23] Other manifestations include headache, myalgia, joint swelling, and nausea, which have been reported to occur at varying frequencies. Symptoms are generally resolved within 7–10 days, but some patients are plagued with chronic arthralgia that could persist for months or years.[1,15,22,23]

A spectrum of neurological manifestations including meningoencephalitis, myelopathy and neuropathy have been reported following chikungunya infection.[24-27] A retrospective study (the largest until today) on atypical manifestations of CHIKV infection during the epidemic on Reunion Island,[28] describes 147 (24.1%) patients with neurological manifestations out of 610 patients with CHIKV infection. The range of presentations included encephalitis (69, 11%), meningoencephalitis (15, 2%), epileptic seizures (12, 2%), Guillain-Barre syndrome (GBS) (4,1%), cerebellar syndrome (3, < 1%) stroke (2, < 1%) and myelomeningoencephalitis (1, < 1%). However, there are many other studies assessing

neurological manifestations or complications but most studies are limited in population size. Until today most of the global research on CHIK has been focused on acute and chronic rheumatological consequences of infection, such as the arthralgia, arthritis and the chronic inflammatory rheumatism,[1,15,17,29,30] given its relatively high frequency, which has been recently estimated in around 47.57% (95%CI 45.08-50.13).[17] Consequently, only one systematic review and meta-analysis have been published,[31] which focused on the association between levels of CHIKV load with arthralgia as an indicator of acute CHIKV infection. No other meta-analyses have been published. Furthermore, the continued and still out of control spread of CHIK in the new endemic areas in Latin America, including Colombia and Venezuela, rise concern about the possibility of its consequences at CNS, the so-called NeuroCHIK. Hence, we conducted a systematic review and meta-analysis in order to establish an accurate proportion estimate of patients that develop neurological manifestations and/or complications of CHIK (NeuroCHIK).

MATERIALS AND METHODS

LITERATURE SEARCH

In June 2015, MEDLINE (PubMed), SCOPUS, Science Citation Index (Web of Knowledge) and SciELO were searched to identify potentially relevant articles using the search strategy ("Chikungunya" AND "Neurological"). The review was conducted according to the recommendations of the Meta-Analysis of Observational Studies in Epidemiology group.[32] No limit was set for the publication year. The search strategy was limited to articles in English, Spanish or Portuguese. The retrieved articles were initially screened by title and abstract in order to identify possible eligible studies by all the authors. Full-text of the possible eligible articles were reviewed and information abstracted by three authors, when two authors disagree in the inclusion of a study a third makes the final decision. Cohort studies and cross-sectional studies were originally considered, whereas case-control studies and case series where not included since they are not suitable,[33] nor cross-sectional studies, giving the fact these have not been used for estimations of neurological complications associated to CHIK.

STUDY ELIGIBILITY AND SELECTION

Original studies that assessed the proportion of patients with serological diagnosis of acute CHIK fever that evaluated neurological complications were included. If an article presented data from multiple study groups, of which some were eligible for inclusion, eligible study groups were included if the pertinent data could be extracted (follow up period, serological confirmation and neurological assessment).

Studies that included only patients with previous neurological disease or previous neurological symptoms where excluded, along with therapeutic clinical trials. Articles were also excluded if they were duplicates from already included articles (in a bibliographical database search) or if the followed population was lower than ten patients. Articles were also excluded if no or insufficient data were presented to analyze the diagnosis criteria for CHIK or NeuroCHIK were not clear.

DEFINITION OF CHIK AND NEUROCHIK

CHIK: History of acute febrile arthralgia (acute attack) with duration of at least 48 hours with positive anti-CHIK virus-specific immunoglobulin M; or RNA virus by reverse-transcriptase polymerase chain reaction; or post-exposure anti-CHIK virus-specific immunoglobulin G positive serological test detected by enzyme-linked immunosorbent assay (ELISA).[34]

NeuroCHIK: Any neurological symptoms, particularly encephalitis and Guillain-Barre syndrome, but also headache, seizures, meningitis, associated with CHIK infection, fulfilling the above CHIK criteria and without history of previous neurological complaints before. Other non-neurological conditions were excluded of the group analysis.

DATA ABSTRACTION AND QUALITY ASSESSMENT

All identified possible eligible articles were entered in EndNote X7 ® and were first screened on title and abstract and reviewed independently by two research team members. Those articles marked for inclusion by either team member went on to full-text screening, they completed full data abstraction and a third member verified all extracted data. Extracted data were: Author, Title, Year of the study, Follow-Up months, Total

population with CHIK (N), total of patients that develop NeuroCHIK (n), total of patients that develop either arthritis or musculoskeletal symptoms as explained before, Type of study (prospective or retrospective), Institution, City and Country. For studies that evaluated in different times, a same population during the follow-up period the considered (n) was the reported when the study finished. All data were checked in a third round of verification. The MOOSE guidelines were used for reporting.[32] The quality assessment of the included studies was conducted using the New Castle Ottawa for assessing the quality of non-randomized studies in meta-analyses.[35]

STATISTICAL APPROACH

Unit discordance for variables was resolved by converting all units to a standard measurement for that variable. Percentages and means ± SDs were calculated to describe the distributions of categorical and continuous variables, respectively. Since individual patient information was not available for all patients, we report weighted means and SDs. A Student's t-test for independent samples was used for continuous variables and the chi-square test with Yates' correction was used for proportions. A 2-tailed alpha level of 5% was used for hypothesis testing. The baseline data were analyzed using the Statistical Package for Social Scientists, version 21.0 (IBM). The meta-analyses were performed using Stata, version 11.0 and the Microsoft Excel spreadsheet developed by Neyeloff et al,36 particularly for the forest plots. Pooled prevalences and their 95% confidence intervals (95% CIs) were used to summarize the effect size for each study-grouping variable using the random-effects model. 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 considering only prospective cohorts as well retrospective, also by countries, India and France; a meta-analysis for those studies assessing specifically attention difficulties and encephalitis occurrence and finally including only those studies with ≥200 patients. 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 143 articles and the last day of the literature search was June 15, 2015. After scrutinizing the titles and abstracts of retrieved articles, 52 articles were accessed in full text (Figure 1). Among these 52 articles, 43 studies were excluded because they did not included information regard serological information, were non-observational studies, corresponded to case report and case series, review ar-

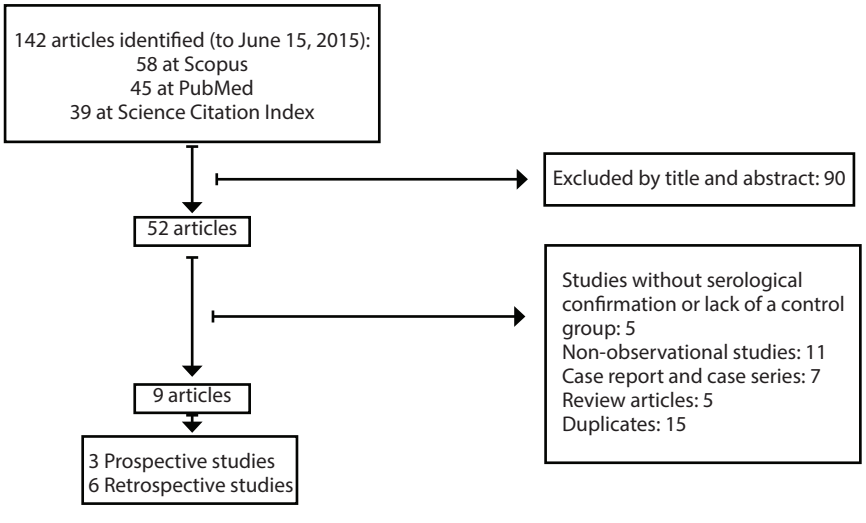

Figure 1. Search strategy for identification of studies.

ticles or other type of articles, not contain extractable data on prevalence of NeuroCHIK or were duplicates (Figure 1). Of the total nine remaining eligible studies, six corresponded to retrospective cohort studies and three to prospective cohort studies. Data were extracted from both types in an effort to extract the maximum available data. We included nine studies in the final analysis coded from nine articles. The details of the selection process of eligible articles are presented in the Flow chart (Figure 1).

The studies included in our analysis were published from 2007–2012 (Table 1) and reported data on 2,161 patients (Tables 2 and 3). We stratified the analyses according to the type of cohort (analyzing together and separate, prospective and retrospective studies) as well by country of the study (India and France), by occurrence of attention difficulties and encephalitis and selecting also those studies with ≥200 patients (Table 3).

Among them 332 (15.4%) of the patients were assessed in prospective cohorts (three studies) and 1829 (84.6%) in retrospective cohorts; 825 (38.2%) were from India (six studies) and 1,336 (61.8%) from France (three studies). At five studies (three prospective and two retrospective) with 931 (43.1%) patients attention difficulties occurrence were assessed; 1424 (65.9%) corresponded to studies (5, 3 prospective and 2 retrospective) where encephalitis occurrence was assessed. There were five studies (1 prospective and 4 retrospective) including at least 200 patients each, combining 1,936 patients (89.6%). Data from individual studies are presented in Table 1 and all studies were considered of a minimum adequate quality on the basis of Newcastle-Ottawa scale (Table 1).

Demographical and clinical characteristics of the individual studies are included in Table 2.

The pooled prevalence of NeuroCHIK among 2,161 patients was 34.53% [95%CI, (20.78–48.27%), $\tau^2 = 0.0734$] (Figure 3A). Publication bias was assessed with a funnel-plot for the standard error by logit event, with no evidence of bias (Figure 2). The funnel-plot showed symmetric distribution of all studies at both extremes as well as around the midline. A sub-analysis of prospective cohorts shown a prevalence of NeuroCHIK of 36.87% [95%CI, (5.17%-68.57%), $\tau^2 = 0.0818$] (Figure 3B). At retrospective cohorts, the prevalence of NeuroCHIK was 33.39% [95%CI, (16.83%-49.94%), $\tau^2 = 0.0790$] (Figure 3C). Analyzing only studies assessing >200 patients the prevalence was 38.54% [95%CI, (19.48%-57.60%), $\tau^2 = 0.0811$] (Figure 3D). A sub-analysis per country, shown a NeuroCHIK prevalence at studies from India of 22.79% [95%CI, (14.49%-31.10%), $\tau^2 = 0.0734$] (Figure 3E) whilst in studies from France was 54.20% [95%CI, (17.47%-90.93%), $\tau^2 = 0.0985$] (Figure 3F). Occurrence of attention difficulties prevalence was 16.46% [95%CI, (5.65%-27.27%), $\tau^2 = 0.0149$] (Figure 3G). In the case of encephalitis its prevalence was 9.90% [95%CI, (8.25%-11.54%), $\tau^2 < 0.0001$] (Figure 3H). Finally, analyzing the prevalence of seizures this was 3.43% [95%CI, (0.55%-6.31%), $\tau^2 = 0.0006$] (Figure 3I) (Table 3).

Table 1. Characteristics of included studies.

Author	Year	Country	Place	Study period	Cohort type	N	n (NeuroCHIK)	Quality score	Reference
Staikowsky	2009	France	La Réunion	2006	Prospective	214	136	7	43
Rampal	2007	India	Rajasthan	2006	Prospective	60	20	4	41
Lewthwaite	2009	India	Bellary	2006	Prospective	58	8	6	44
Singh	2012	India	Uttar Pradesh	2006-2008	Retrospective	20	3	5	42
Gerardin	2011	France	La Réunion	2006	Retrospective	512	386	7	45
Kashyap	2010	India	Nagpur	2006	Retrospective	300	46	5	46
Chandak	2009	India	Nagpur	2006	Retrospective	300	49	4	47
Suryawanshi	2009	India	Maharashtra	2006	Retrospective	87	48	6	23
Economopoulou	2009	France	La Réunion	2005	Retrospective	610	147	8	28

NeuroCHIK = Neurological manifestations and/or complications of CHIK.

Table 2. Characteristics of study subjects.

Studies	Author	Staikowsky	Ramped	Lewthwaite	Singh	Gerardin	Kashyap	Chandak	Suryawanshi	Economopoulou
Characteristics	Year	2009	2007	2009	2012	2011	2010	2009	2009	2009
	N	214	60	58	20	512	300	300	87	610
Women	%	47.1	10.00	44.0	35.0	57.4	15.2	14.3	29.9	44.4
Age	(y)	44% >65	Range 12-84	100% <16	85% >30	82% >20	98% >20	98% >20	26, mean	85% >25
NeuroCHIK	n	136	20	8	3	386	46	49	48	147
General symptoms	%	19% fever, 97% arthralgia	100% fever, 67% arthralgia	-	100% fever, 75% arthralgia	54% fatigue, 43% musculoskeletal pain	-	-	100% fever, 100% arthralgia	90% fever, 45% malaise
Attention difficulties	n	13	20	7	-	143	-	-	6	-
Encephalitis	n	24	-	-	-	-	24	27	-	69
Seizures	n	-	15	6	-	-	-	3	-	12
Headache	n	146	-	-	3	100	-	-	48	-
Meningeal irritation	n	-	-	3	-	-	-	2	-	8
Myelopathy	n	-	-	-	-	-	7	7	-	1
Myeloneuropathy	n	-	-	-	-	-	7	7	-	-
Peripheral neuropathy	n	-	-	-	-	-	7	7	-	-
Myopathy	n	-	-	-	-	-	1	1	-	-
Meningoencephalitis	n	-	-	-	-	-	-	-	-	15
Hyperesthesia	n	-	-	-	-	-	-	-	-	8
Guillain-Barré syndrome	n	-	-	-	-	-	-	-	-	4
Light Cerebral disorders	n	-	-	-	-	386	-	-	-	-
Sleep disorders	n	-	-	-	-	120	-	-	-	-
Memory troubles	n	-	-	-	-	163	-	-	-	-
Mood disturbances	n	-	-	-	-	148	-	-	-	-
Sensorineural disorders	n	-	-	-	-	188	-	-	-	-
Mean time to zcomplications	days	1.8-6.2	2-3	-	-	-	20	35	-	-

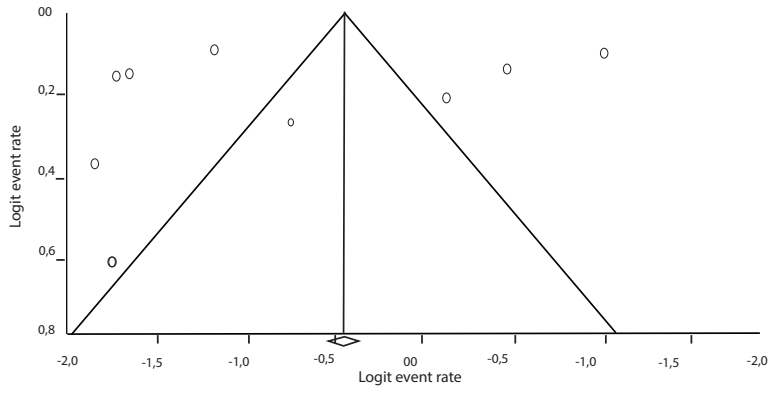

Figure 2. Funnel-plot for the Standard Error by Logit Event rate to assess for publication bias.

Figure 3. Prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each study selected; pooled prevalence estimates are represented as a diamonds in this plot. A, All selected cohort studies (prospective and retrospective). B, Prospective cohort studies. C, Retrospective cohort studies. D, Studies including at least 200 patients. E, Studies from India. F, Studies from France. G. Prevalence of attention difficulties. H, Prevalence of encephalitis. I, Prevalence of seizures.

Study A	Cohort type	Prevalence (95%CI)			N	n
Staikowsky. PloS one. 2009:4(10):e7603	Prospective	63.55	52.87	74.23	214	136
Rampal. The Journal of the Association of Physicians of India. 2007:55:765-9.	Prospective	33.33	18.72	47.94	60	20
Lewthwaite. Emerging infectious diseases. 2009;15(2):329-31.	Prospective	13.79	4.23	23.35	58	8
Singh. Journal of virological methods. 2012:185(2):213-20.	Retrospective	15.00	0.00	31.97	20	3
Gerardin. BMC medicine. 2011:9:5.	Retrospective	75.39	67.87	82.91	512	386
Kashyap. Cerebrospinal fluid research. 2010:7:12.	Retrospective	15.33	10.90	19.76	300	46
Chandak. Neurology India. 2009;57(2):177-80.	Retrospective	16.33	11.76	20.91	300	49
Suryawanshi. The Indian journal of medical research. 2009;129(4):438-41.	Retrospective	55.17	39.56	70.78	87	48
Economopoulou. Epidemiology and infection. 2009;137(4):534-41.	Retrospective	24.10	20.20	27.99	610	147
Effect summary		**34.53**	**20.78**	**48.27**	**2161**	**843**
Random effects model (I^2 = 99.0%; τ^2 = 0.0734; p<0.001)						

Figure 3A. Forest plot of all selected cohort studies (Prospective and Retrospective), showing unadjusted prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study B	Cohort type	Prevalence (95%CI)			N	n
Staikowsky. PloS one. 2009;4(10):e7603.	Prospective	63.55	52.87	74.23	214	136
Rampal. The Journal of the Association of Physicians of India. 2007:55:765-9.	Prospective	33.33	18.72	47.94	60	20
Lewthwaite. Emerging infectious diseases. 2009:15(2):329-31.	Prospective	13.79	4.23	23.35	58	8
Effect summary		**36.87**	**5.17**	**68.57**	**332**	**164**
Random effects model (I^2 = 97.6%; τ^2 = 0.0818; p<0.001)						

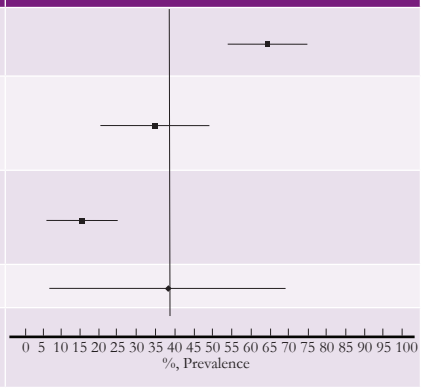

Figure 3B. Forest plot of Prospective cohort studies, showing unadjusted prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study C	Cohort type	Prevalence (95%CI)			N	n
Singh. Journal of virological methods. 2012:185(2):213-20.	Retrospective	15.00	0.00	31.97	20	3
Gerardin. BMC medicine. 2011;9:5.	Retrospective	75.39	67.87	82.91	512	386
Kashyap. Cerebrospinal fluid research. 2010:7:12.	Retrospective	15.33	10.90	19.76	300	46
Chandak. Neurology India. 2009;57(2): 177-80.	Retrospective	16.33	11.76	20.91	300	49
Suryawanshi. The Indian journal of medical research. 2009;129(4):438-41.	Retrospective	55.17	39.56	70.78	87	48
Economopoulou. Epidemiology and infection. 2009;137(4):534-41.	Retrospective	24.10	20.20	27.99	610	147
Effect summary		**33.39**	**16.83**	**49.94**	**1829**	**679**
Random effects model (I^2 = 99.3%; τ^2 = 0.0790; p<0.001)						

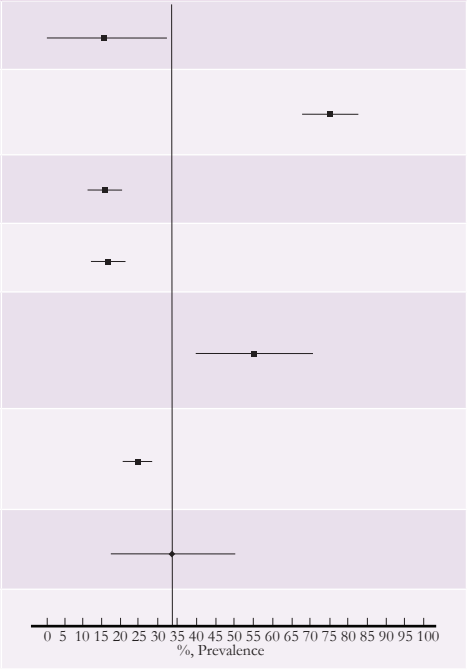

Figure 3C. Forest plot of Prospective cohort studies, showing unadjusted prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study D	Cohort type	Prevalence (95%CI)			N	n	
Staikowsky. PloS one. 2009;4(10):e7603.	Prospective	63.55	52.87	74.23	214	136	
Gerardin. BMC medicine. 2011;9:5.	Retrospective	75.39	67.87	82.91	512	386	
Kashyap. Cerebrospinal fluid research. 2010;7:12.	Retrospective	15.33	10.90	19.76	300	46	
Chandak. Neurology India. 2009;57(2): 177-80.	Retrospective	16.33	11.76	20.91	300	49	
Economopoulou. Epidemiology and infection. 2009;137(4): 534-41.	Retrospective	24.10	20.20	27.99	610	147	
Effect summary		**38.54**	**19.48**	**57.60**	**1936**	**764**	
Random effects model (I^2 = 99.5%; τ^2 = 0.0811; p<0.001)							

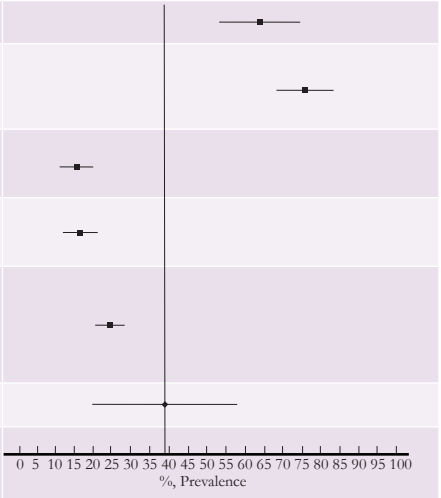

Figure 3D. Forest plot of Prospective cohort studies, showing unadjusted prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study E	Cohort type	Prevalence (95%CI)			N	n	
Rampal. The Journal of the Association of Physicians of India. 2007:55:765-9	Prospective	33.33	18.72	47.94	60	20	
Lewthwaite. Emerging infectious diseases. 2009;15(2): 329-31.	Prospective	13.79	4.23	23.35	58	8	
Singh. Journal of virological methods. 2012;185(2):213-20.	Retrospective	15.00	0.00	31.97	20	3	
Kashyap. Cerebrospinal fluid research. 2010:7:12.	Retrospective	15.33	10.90	19.76	300	46	
Chandak. Neurology India. 2009;57(2): 177-80.	Retrospective	16.33	11.76	20.91	300	49	
Suryawanshi. The Indian journal of medical research. 2009:129(4):438-41.	Retrospective	55.17	39.56	70.78	87	48	
Effect summary		**22.79**	**14.49**	**31.10**	**825**	**174**	
Random effects model (I^2 = 99.0%; τ^2 = 0.0734; p<0.001)							

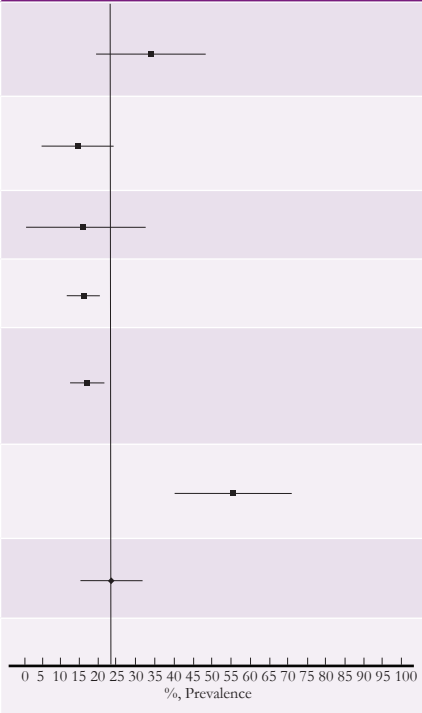

Figure 3E. Forest plot of studies from India, showing unadjusted prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study F	Cohort type	Prevalence (95%CI)			N	n	
Staikowsky. PloS one. 2009;4(10):e7603.	Prospective	63.55	52.87	74.23	214	136	
Gerardin. BMC medicine. 2011;9:5.	Retrospective	75.39	67.87	82.91	512	386	
Economopoulou. Epidemiology and infection. 2009;137(4):534-41.	Retrospective	24.10	20.20	27.99	610	147	
Effect summary		**54.20**	**17.47**	**90.93**	**1336**	**669**	
Random effects model (I^2 = 99.5%; τ^2 = 0.0985; p<0.001)							0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 %, Prevalence

Figure 3F. Forest plot of studies from France, showing unadjusted prevalence of NeuroCHIK estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study G	Cohort type	Prevalence (95%CI)			N	n	
Staikowsky. PloS one. 2009;4(10):e7603.	Prospective	6.07	2.77	9.38	214	13	
Rampal. The Journal of the Association of Physicians of India. 2007:55:765-9.	Prospective	33.33	18.72	47.94	60	20	
Lewthwaite. Emerging infectious diseases. 2009;15(2):329-31.	Prospective	12.07	3.13	21.01	58	7	
Gerardin. BMC medicine. 2011;9:5.	Retrospective	27.93	23.35	32.51	512	143	
Suryawanshi. The Indian journal of medical research. 2009;129(4):438-41.	Retrospective	6.90	1.38	12.41	87	6	
Effect summary		**16.46**	**5.65**	**27.27**	**931**	**189**	
Random effects model (I^2 = 95.6%; τ^2 = 0.0149; p<0.001)							0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 %, Prevalence

Figure 3G. Forest plot of studies assessing the occurrence of attention difficulties, showing its unadjusted prevalence estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study H	Cohort type	Prevalence (95%CI)			N	n	
Staikowsky. PloS one. 2009;4(10):e7603.	Prospective	11.21	6.73	15.70	214	24	
Kashyap. Cerebrospinal fluid research. 2010:7:12.	Retrospective	8.00	4.80	11.20	300	24	
Chandak. Neurology India. 2009;57(2):177-80.	Retrospective	9.00	5.61	12.39	300	27	
Economopoulou. Epidemiology and infection. 2009;137(4):534-41.	Retrospective	11.31	8.64	13.98	610	69	
Effect summary		**9.90**	**8.25**	**11.54**	**1424**	**144**	
Random effects model (I^2 = 10.5%; τ^2 <0.0001; p<0.001)							0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 %, Prevalence

Figure 3H. Forest plot of studies assessing the occurrence of encephalitis, showing its unadjusted prevalence estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

Study I	Cohort type	Prevalence (95%CI)			N	n	
Rampal. The Journal of the Association of Physicians of India. 2007;55:765-9	Prospective	25.00	12.35	37.65	60	15	
Lewthwaite. Emerging infectious diseases. 2009;15(2):329-31.	Prospective	10.34	2.07	18.62	58	6	
Chandak. Neurology India. 2009:57(2):177-80.	Retrospective	1.00	0.00	2.13	300	3	
Economopoulou. Epidemiology and infection. 2009;137(4):534-41.	Retrospective	1.97	0.85	3.08	610	12	
Effect summary		**3.43**	**0.55**	**6.31**	**1028**	**36**	
Random effects model (I^2 = 87.4.0%; τ^2 = 0.0006;p<0.001)							0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 %, Prevalence

Figure 3I. Forest plot of studies assessing the occurrence of seizures, showing its unadjusted prevalence estimates (boxes) with 95% confidence limits (bars) for each Study selected; pooled prevalence estimates is represented as a diamonds in this plot.

DISCUSSION:

Neuroinfection caused by arbovirus is a serious concern given their consequences.[37-47] This is well known in the case of West Nile Virus (WNV) or dengue,[37-40] but still unknown for many aspects in CHIK, then be a concerning aspect of the ongoing epidemic in the endemic areas in Latin America. According with our results in the most conservative scenario about 33% of CHIK cases would present with neurological manifestations and/or complications, NeuroCHIK

(36% if we just consider the prospective studies), with 3% developing seizures, 10% encephalitis and 16% attention difficulties.

As has been stated, although more than 6 decades have passed since CHIK discovery, only the 2005-2006 epidemics in La Réunion, overseas France, have stimulated increased research on this tropical disease.[14] After a decade and different cohort studies there and in India, there was not previous published systematic review and meta-analysis as done herein.

Data for this meta-analysis come from studies done in those two countries, showing differences (although not significant) in the prevalence of NeuroCHIK between them, with 54% in studies from La Réunion, Francia and 23% in India. A trend that coincide with the fact that in a concurrent meta-analysis from our group focusing on chronic inflammatory rheumatism associated to CHIK infection (pCHIK-CIR), this was also higher in studies from France (50%) compared to those from India (27%).[48]

This consistent finding, would be result of the different number of followed patients and because studies from France were mainly retrospective, although all of them with >200 patients, including the largest cohort (610 patients). Most studies from India were with <200 patients, which can lead to prevalence over estimation. Nevertheless, this highlights the importance of proper assessments in regions where CHIK is endemic since, along with the virus lineage or genotype, differences in the risk of developing acute compromise of CNS, as well progression to chronic forms of the disease, can depend on immune host response and environmental conditions.[20,26,27,41,42] In the future, if other CHIK genotypes begun to circulate in the same areas, comparison would allow to assess if they impose different clinical impacts on neurological manifestations, as currently assessing this with past epidemics where other genotypes and lineages were present, as the Indian Ocean one, would also imply potential differences in population immunogenetics and responses probably based in HLA and other ethnic factors. This has been recently showed regard the differences of pCHIK-CIR prevalences between studies in La Reunión island, France and India, being higher in the first, as evidenced in a meta-analysis which is coming out in the next weeks from our group.[48,49]

If we extrapolate the findings of current meta-analyses to the ongoing epidemics in the Americas, including there Colombia and Venezuela, where 1,100,034, 106,592 and 39,810 cases, respectively, were reported, we can anticipate that 363,011, 35,175 and 13,137 cases, respectively, of CHIK presented neurological manifestations and/or complications, but of them 176,005, 17, 055 and 6,370 attention difficulties, as well 110,003, 10,659 and 3981 encephalitis and 33,001, 3,198 and 1,194 seizures. These figures are highly concerning given the fact that during half of 2015 the Americas have reported 366,469 new cases of CHIK, with 266,993 in Colombia and 12,780 in Venezuela. Then we can expect at least 241,870, 176,215 and 8,435 cases of NeuroCHIK for the ending of 2015 with 117,270, 85,438 and 4,090 cases of attention difficulties, 73,294, 53,399 and 2,556 cases of encephalitis and 21,988, 16,020 and 767 cases of seizures, if the trend is kept with no significant increases in the number of CHIK cases in the region and in these countries.

However, our estimations would be still limited regarding the high heterogeneity of the included studies and because studies published in other languages different than English, Spanish or Portuguese were not considered. This leave potentially important works written in French. Besides this, the funnel-plot suggested no publication bias in this report. The quality assessment showed good quality of most of the studies. In order to manage the heterogeneity of the studies we conducted sub-group analysis by assessing differences including only retrospective and only prospective studies, with a not significant difference. Still the prevalence remained high (one third of patients with NeuroCHIK) enough to raise concern of what we could expect in the coming months and years.

In this setting, there is a call to healthcare managers to establish prompt disease spread control and to educate physicians in order to prepare them for the future challenge of disease[22] as well specifically for proper diagnosis and management of CHIK with manifestations and complications of CNS. There is still a lack of high quality evidence to guide its assessment and diagnosis, and also of local studies in Latin America to address the real clinical impact of CHIK. CHIK is a problem in the present, and could be a major problem in the future including its neurological compromise. Even more, from 2015, cocirculation of Zika (ZIKV) is another emerging neuroinfection that would be of interest, that should be included in the differential diagnostic and require more attention to complications and even associated deaths, even more given its rapid spread in Latin America.[50-52]

CONFLICT OF INTERESTS

We declare we have no conflict of interests.

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