Perspective Piece

Chikungunya Case Classification after the Experience with Dengue Classification: How Much Time Will We Lose?

Luciano Pamplona de Góes Cavalcanti,^{1,2*} Luís Arthur Brasil Gadelha Farias,¹ Francisca Kalline de Almeida Barreto,¹ André Machado Siqueira,³ Guilherme Sousa Ribeiro,^{4,5} André Ricardo Ribas Freitas,⁶ Scott C. Weaver,⁷ Uriel Kitron,⁸ and Carlos Alexandre Antunes Brito⁹

¹Department of Community Health, School of Medicine, Federal University of Ceará, Fortaleza, Brazil; ²Faculty of Medicine, Unichristus University Center, Fortaleza, Brazil; ³Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil; ⁴Gonçalo Moniz Institute, Oswaldo Cruz Foundation, Salvador, Brazil; ⁵School of Medicine, Federal University of Bahia, Salvador, Brazil; ⁶São Leopoldo Mandic Faculty, Campinas, Brazil; ⁷University of Texas Medical Branch, Galveston, Texas; ⁸Emory University, Atlanta, Georgia; ⁹Aggeu Magalhães Institute, Oswaldo Cruz Foundation – FIOCRUZ, Recife, Brazil

Abstract. In 2013, cases of chikungunya virus (CHIKV) infection were first detected in the Caribbean. Chikungunya virus rapidly spread through Central and South America, causing explosive outbreaks in naive populations. Since its emergence in 2004, the number of case and series reports describing severe, atypical manifestations seen in chikungunya patients has increased substantially, calling into question whether clinicians and health services are failing to diagnose these atypical cases because of not only insufficient knowledge but also limitations in the case classification. Although this classification based on the duration of the musculoskeletal (acute, subacute, and chronic forms) complaints helped guide therapeutic approaches directed to these manifestations, patients presenting severe or complicated forms, which are less frequent but produce most of the fatal outcomes, were not properly addressed. In Brazil and the Caribbean, a clear temporal and spatial association between excess overall mortality and the occurrence of chikungunya epidemics has been shown, supporting the hypothesis that many of these excess deaths were a consequence of CHIKV infections. Thus, accumulated experience has highlighted that the current chikungunya case classification does not encompass the actual needs presented by certain cases with atypical features nor does it contribute to early detection and management of potentially severe cases. With continued CHIKV circulation in three continents and recent reemergence in Asia and Europe, we need a classification that is prospective and informed both by initial clinical presentation and by progression of signs and symptoms.

Since the 1980s, a broad consensus has begun to develop among dengue specialists that the classification of dengue cases (developed in 1975 and updated in 1986 and 1997 by the WHO) into dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was essentially retrospective, limiting its usefulness for patient management and global surveillance.^{1–3} Furthermore, it did not cover severe and life-threatening atypical dengue presentations with involvement of specific organs, such as the central nervous system, liver, lungs, and heart.^{4,5} To accommodate these deficiencies, these atypical clinical forms were recorded as acute dengue with severe multisystem manifestation, which did not fit into the categories of the past dengue case classification.

Based on this context and following a multicentric dengue study (DENCO), a new classification of dengue cases was proposed in 2009.^{4,5} The new classification showed higher sensitivity and specificity in discriminating the most severe cases.⁶ The new dengue classification also contributed to reorganization of health service protocols for clinical management of cases, allowing prompt intervention targeting patients with warning signs or already with severe disease.⁷ Despite its advantages, some countries waited years to adopt the new classification (e.g., Brazil: implemented the new classification only 5 years later, in 2014).

Chikungunya emerged in 2004 in coastal East Africa and Indian Ocean; in 2013, cases of chikungunya virus (CHIKV) infection, which like dengue virus are transmitted by *Aedes*

aegypti and *Aedes albopictus*, were first detected in the Caribbean. Chikungunya virus rapidly spread through Central and South America, causing explosive outbreaks in naive populations.^{8,9} After these outbreaks in the Indian Ocean and Western Hemisphere, it became clear that the classification of chikungunya cases as acute, subacute, and chronic forms, based on the duration of clinical signs and symptoms, especially arthralgia, did not encompass the actual classification needs presented by some cases, nor did it contribute to early detection and management of potentially severe cases.^{10,11} Although this classification based on the duration of the musculoskeletal complaints helped guide therapeutic approaches directed to these manifestations, patients presenting severe or complicated forms, which are less frequent but produce most of the fatal outcomes, were not properly addressed.¹²

Like dengue cases, the clinical spectrum of CHIKV infection varies widely and includes life-threatening manifestations related to the involvement of specific organs. Variation in the severity and duration of arthralgia appears to be due, in part, to virulence differences among CHIKV strains,^{13–15} but determinants of more severe, life-threatening outcomes have not been defined, other than underlying medical conditions and age. Although severe and fatal dengue virus infections tend to present early during the disease course, typically 3–5 days after symptoms onset, complicated chikungunya can occur during both the acute illness phase and weeks later, possibly because of decompensation of comorbidities.^{10,11,16}

Acute, severe presentations of chikungunya may include central and peripheral nervous system involvement (encephalitis, Guillain-Barré syndrome, and myelitis), pneumonitis, myocarditis,

* Address correspondence to Luciano Pamplona de Góes Cavalcanti, Federal University of Ceará, Rua João Adolfo Gurgel, 133, Fortaleza 60000-000, Brazil. E-mail: pamplona.luciano@gmail.com

myositis/rhabdomyolysis/renal failure, gastrointestinal bleeding, and even shock, and may be due to direct virus effects on the infected organ or to immune response.^{11,16,17} In addition, CHIKV infection may evolve with late complications, mainly associated with comorbidities decompensation in patients with a history of diabetes, or cardiovascular (hypertension or heart failure), renal, or pulmonary diseases (chronic obstructive pulmonary disease, asthma, and pulmonary thromboembolism).^{16,18}

Since the emergence in 2004, the number of case and series reports describing severe, atypical manifestations seen in chikungunya patients has increased substantially, calling into question whether clinicians and health services are failing to diagnose these atypical cases because of insufficient knowledge and limitations in the case classification. This is especially worrisome because, as stated earlier, the current official clinical guidelines target the typical acute musculoskeletal manifestations and arthralgia duration but not the atypical and potentially more severe disease forms.^{19–21}

Studies in Reunion Island, India, and Mauritius have warned about the possibility of a large number of CHIKV-related deaths during epidemics, the two latter epidemics being not captured by epidemiologic surveillance nor recorded in death certificates.^{22–24} In addition, studies in Brazil and the Caribbean have identified an increase in overall population mortality rates during the months of chikungunya epidemics, when compared with previous months without outbreaks. In these studies, there was a clear temporal and spatial association between excess overall mortality and the occurrence of chikungunya epidemics, supporting the hypothesis that these excess deaths were a consequence of CHIKV infections, although an increase in chikungunya-specific mortality has not been detected.^{25–29} Failures by health professionals and surveillance systems to recognize and report fatal outcomes as complications of CHIKV infection may explain why the increased number of deaths during chikungunya epidemics was not clearly attributed to infection.²¹

To address this issue, a panel of experts met at Nicaragua in 2015 and proposed a new chikungunya case classification, which distinguishes four categories: 1) acute (based on the presence of fever and arthralgia, either suspected or confirmed), 2) atypical (an acute laboratory-confirmed clinical case with specific organ involvement evidenced by neurological, cardiovascular, dermatological, ophthalmological, hepatic, renal, respiratory, or hematological manifestations), 3) severe acute (an atypical, life-threatening form that requires hospitalization), and 4) chronic (based on the presence of articular manifestations lasting more than 12 weeks, either suspected or confirmed).³⁰ Although the classification proposed in 2015 represents an important advance over the presently used classification (in acute, subacute, and chronic forms), an evaluation performed in elderly people with chikungunya in Martinique showed that 42.7% of cases were not properly classified by this system,³¹ suggesting that it is still unsatisfactory and that further revision is needed.

Will it take another two or three decades until clinicians and health policy officers realize the need of revising, evaluating, and adopting a new chikungunya case classification, as occurred with dengue? We hope not. An updated chikungunya case classification that is useful for risk stratification and case management is urgently needed. With continued circulation in three continents and recent reemergence in Asia and Europe,³² we need a classification that is prospective and informed by

initial clinical presentation and progression of signs and symptoms. Unlike the current classification, it should be applied at the first medical evaluation to screen patients with foreseeable risk for disease complications.

Factors that may be incorporated in a revised classification aimed at better risk stratification may include older age, history of comorbidities, presence of warning signs and symptoms, and type and severity of the initial clinical presentation. Further prospective cohort studies enrolling chikungunya patients at the acute disease stage are critical to better refine which patient characteristics are accurate predictors of severe and complicated diseases. Such classification will aid in standardization of clinical management according to the case complexity and severity. They will also guide decisions regarding which patients should receive close outpatient follow-up versus hospitalization and initiation of supportive therapy and which patients should receive complementary laboratory tests. In addition, it will allow surveillance efforts to produce consistent reports regarding the initial clinical presentation and outcome patterns of chikungunya cases. This will enable frequency comparisons of the severe disease forms, as well as comparisons of case fatality ratios and population mortality among locations, and help guide disease management during future epidemics.

Classification models involving different clinical characteristics at disease presentation have been applied to different epidemic diseases that require a rapid presumptive diagnosis, possibly intensive care, and initiation of effective therapeutic interventions, ultimately targeting reduction of fatal outcomes.

The documented chikungunya outbreaks experienced by Reunion Island, the Caribbean, and Brazil revealed the limitations of the current classification in guiding clinicians in patient management and in surveillance for severe and complicated cases worldwide. Consequently, we should avoid further delays in revising the current case classification to better ascertain the real number of severe cases, provide effective clinical management, and ultimately decrease the number of deaths caused by CHIKV infection.

Received August 16, 2019. Accepted for publication October 15, 2019.

Published online November 25, 2019.

Financial support: This work was partially supported by the Network of Clinical and Applied Research into Chikungunya (REPLICK) through funds from the Department of Science and Technology (DECIT), Brazilian Ministry of Health, the National Council for Scientific and Technological Development, and FUNCAP. G. S. R. and L. P. G. C. are recipients of the fellowship for research productivity granted by the Brazilian National Council for Scientific and Technological Development (CNPq/Brazil).

Disclosures: S. C. W. reports grants from National Institutes of Health, Emergent Biotechnologies, Valneva, and Themis Biosciences during the conduct of the study. In addition, S. C. W. has two patents for alphavirus vaccine development issued.

Authors' addresses: Luciano Pamplona de Góes Cavalcanti, Luís Arthur Brasil Gadelha Farias, and Francisca Kalline de Almeida Barreto, Department of Community Health, School of Medicine, Federal University of Ceará, Fortaleza, Brazil, E-mails: pamplona.luciano@gmail.com, luisarthurbrasilk@gmail.com, and kallineabarreto@gmail.com. André Machado Siqueira, Evandro Chagas National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, E-mail: amsiqueira@gmail.com. Guilherme Sousa Ribeiro, Centro de Pesquisas Gonçalo Moniz, Ministério da Saúde, Salvador, Brazil, and Instituto de Saúde Coletiva, Universidade Federal da Bahia, Salvador,

Brazil, E-mail: gsribeiro@gmail.com. André Ricardo Ribas Freitas, Faculdade São Leopoldo Mandic Curso de Medicina, Epidemiologia, Campinas, Brazil, E-mail: arrfreitas2010@gmail.com. Scott C. Weaver, University of Texas Medical Branch, Galveston, TX, E-mail: sweaver@utmb.edu. Uriel Kitron, Emory University, Atlanta, GA, E-mail: ukitron@emory.edu. Carlos Alexandre Antunes Brito, Medicina Clínica, Universidade Federal de Pernambuco, Recife, Brazil, E-mail: cbritoc@gmail.com.

REFERENCES

1. Bandyopadhyay S, Lum LCS, Kroeger A, 2006. Classifying dengue: a review of the difficulties in using the WHO case classification for dengue haemorrhagic fever. *Trop Med Int Health* 11: 1238–1255.
2. Basuki PS, Budiyanto, Puspitasari D, Husada D, Darmowandowo W, Ismoedijanto, Soegijanto S, Yamanaka A, 2010. Application of revised dengue classification criteria as a severity marker of dengue viral infection in Indonesia. *Southeast Asian J Trop Med Public Health* 41: 1088–1094.
3. Akbar NA et al., 2012. Regarding “dengue—how best to classify it”. *Clin Infect Dis* 54: 1820–1821.
4. World Health Organization, 2009. *Dengue Guidelines for Diagnosis Treatment Prevention and Control: New Edition 2019*. Geneva, Switzerland: WHO, Available at: <https://apps.who.int/iris/handle/10665/44188>. Accessed September 22, 2019.
5. Alexander N et al.; European Union, World Health Organization (WHO-TDR) supported Denco Study Group, 2011. Multi-centre prospective study on dengue classification in four south-east Asian and three Latin American countries. *Trop Med Int Health* 16: 936–948.
6. Tsai C-Y, Lee I-K, Lee C-H, Yang KD, Liu J-W, 2013. Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes. *J Microbiol Immunol Infect* 46: 271–281.
7. Horstick O, Farrar J, Lum L, Martinez E, San Martin JL, Ehrenberg J, Velayudhan R, Kroeger A, 2012. Reviewing the development, evidence base, and application of the revised dengue case classification. *Pathog Glob Health* 106: 94–101.
8. Chretien J-P et al., 2007. Drought-associated chikungunya emergence along coastal east Africa. *Am J Trop Med Hyg* 76: 405–407.
9. Sergon K et al., 2008. Seroprevalence of chikungunya virus (CHIKV) infection on lamu island, Kenya, October 2004. *Am J Trop Med Hyg* 78: 333–337.
10. Lemant J et al., 2008. Serious acute chikungunya virus infection requiring intensive care during the reunion island outbreak in 2005–2006*. *Crit Care Med* 36: 2536–2541.
11. Rajapakse S, Rodrigo C, Rajapakse A, 2010. Atypical manifestations of chikungunya infection. *Trans R Soc Trop Med Hyg* 104: 89–96.
12. Schilte C, Staikowsky F, Staikovskiy F, Couderc T, Madec Y, Carpentier F, Kassab S, Albert ML, Lecuit M, Michault A, 2013. Chikungunya virus-associated long-term arthralgia: a 36-month prospective longitudinal study. *PLoS Negl Trop Dis* 7: e2137.
13. Paixão ES, Rodrigues LC, Costa MdaCN, Itaparica M, Barreto F, Gérardin P, Teixeira MG, 2018. Chikungunya chronic disease: a systematic review and meta-analysis. *Trans R Soc Trop Med Hyg* 112: 301–316.
14. Langsjoen RM, Haller SL, Roy CJ, Vinet-Oliphant H, Bergren NA, Erasmus JH, Livengood JA, Powell TD, Weaver SC, Rossi SL, 2018. Chikungunya virus strains show lineage-specific variations in virulence and cross-protective ability in murine and nonhuman primate models. *MBio* 9: e02449-17.
15. Yoon I-K et al., 2015. High rate of subclinical chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. *PLoS Negl Trop Dis* 9: e0003764.
16. Economopoulou A, Dominguez M, Helynck B, Sissoko D, Wichmann O, Quenel P, Germonneau P, Quatresous I, 2009. Atypical chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Réunion. *Epidemiol Infect* 137: 534–541.
17. Gérardin P et al.; Encephalchik Study Group, 2016. Chikungunya virus-associated encephalitis. *Neurology* 86: 94–102.
18. De Almeida Barreto FK, Montenegro RM, Fernandes VO, Oliveira R, De Araújo Batista LA, Hussain A, De Góes Cavalcanti LP, 2018. Chikungunya and diabetes, what do we know? *Diabetol Metab Syndr* 10: 1–6.
19. Pan American Health Organization, 2011. *Preparedness and Response for Chikungunya Virus Introduction in the Americas*. 1st edition. Washington, DC: Pan American Health Organization.
20. Beserra FLCN et al., 2019. Clinical and laboratory profiles of children with severe chikungunya infection. *Rev Soc Bras Med Trop* 52: e20180232.
21. De Brito CAA, 2017. Alert: severe cases and deaths associated with Chikungunya in Brazil. *Rev Soc Bras Med Trop* 50: 585–589.
22. Mavalankar D, Shastri P, Bandyopadhyay T, Parmar J, Ramani KV, 2008. Increased mortality rate associated with chikungunya epidemic, ahmedabad, India. *Emerg Infect Dis* 14: 412–415.
23. Beesoon S, Funkhouser E, Kotea N, Spielman A, Robich RM, 2008. Chikungunya fever, Mauritius, 2006. *Emerg Infect Dis* 14: 337–338.
24. Josserean L, Paquet C, Zehgnoun A, Caillere N, Tertre AL, Solet J-L, Ledrans M, 2006. Chikungunya disease outbreak, reunion island. *Emerg Infect Dis* 12: 1994–1995.
25. Freitas ARR, Alarcón-Elbal PM, Donalisio MR, 2018. Excess mortality in Guadeloupe and Martinique, Islands of the French west Indies, during the chikungunya epidemic of 2014. *Epidemiol Infect* 146: 2059–2065.
26. Freitas ARR, Alarcón-Elbal PM, Paulino-Ramírez R, Donalisio MR, 2018. Excess mortality profile during the Asian genotype chikungunya epidemic in the Dominican Republic, 2014. *Trans R Soc Trop Med Hyg* 112: 443–449.
27. Freitas ARR, Gérardin P, Kassab L, Donalisio MR, 2019. Excess deaths associated with the 2014 chikungunya epidemic in Jamaica. *Pathog Glob Health* 113: 27–31.
28. Freitas ARR, Cavalcanti L, Zuben APVon, Donalisio MR, 2017. Excess mortality related to chikungunya epidemics in the context of co-circulation of other arboviruses in Brazil. *PLoS Curr* 112: 650–651.
29. Brito CAA, Teixeira MG, 2017. Increased number of deaths during a chikungunya epidemic in Pernambuco, Brazil. *Mem Inst Oswaldo Cruz* 112: 650–651.
30. Ramon-Pardo P, Cibrelus L, Yactayo S, 2015. Chikungunya: case definitions for acute, atypical and chronic cases. *Wkly Epidemiol Rec* 90: 410–414.
31. Godaert L, Najioullah F, Bartholet S, Colas S, Yactayo S, Cabié A, Fanon JL, Césaire R, Dramé M, 2017. Atypical clinical presentations of acute phase chikungunya virus infection in older adults. *J Am Geriatr Soc* 65: 2510–2515.
32. Rezza G, Weaver SC, 2019. Chikungunya as a paradigm for emerging viral diseases: Evaluating disease impact and hurdles to vaccine development. *PLoS Negl Trop Dis* 13: e0006919.