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LETTER TO THE EDITOR

Surveillance of deaths caused by arboviruses in Brazil: From Dengue to Chikungunya

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Abstract

Did death occur DUE TO dengue, or in a patient WITH dengue virus infection? It seems a matter of semantics, but in fact, it underscores how challenging it is to distinguish whether the disease contributed to death, or was itself the underlying cause of death. Can a death be attributed to chikungunya virus, when some deaths occur after the acute phase? Did the virus decompensate the underlying diseases, leading to death? Did prolonged hospitalisation lead to infection, resulting in the patient's progression to death? Were there iatrogenic complications during patient care? The dengue question, for which there has not yet been a definitive response, resurfaces prominently under the chikungunya surveillance scenario. We are facing an epidemic of a disease that seems to be more lethal than previously thought. The major challenge ahead is to investigate deaths suspected of occurring due to arbovirus infections and to understand the role of each infection in the unfavourable outcome.

Keywords: surveillance, death, arboviruses, dengue, chikungunya.

The circulation of dengue virus (DENV) in Brazil was only definitively proven in 1982, when the DENV-1 and DENV-4 viruses were isolated in Boa Vista, the capital of the former federal territory of Roraima (Osanai et al. 1983). However, there have been reports of dengue outbreaks in the nineteenth and twentieth centuries (Rego. 1872; Reis. 1896; Mariano. 1916; Pedro. 1923). The disease was viewed as one with high epidemic potential, with an expected lethality in severe forms of less than 1% (Osanai. 1984). The first major epidemic of dengue occurred in 1986/87 (Teixeira et al. 1999); the first severe cases were reported since 1990 with the introduction of the second serotype DENV-2 (Schatzmayr. 2000; Silva Jr et al. 2002; Cavalcanti et al. 2010). Since then, the challenge faced in association with training of professionals in the management of patients and organization of care for the treatment of severe cases has become a serious concern.

Despite all of the government's efforts, the lethality rate due to dengue virus in Brazil has remained higher than the optimal rate recommended by the World Health Organization (Teixeira et al. 2013). It is important to emphasise that all dengue epidemics are predictable, months before they are established, and that the deaths resulting from these epidemics are almost entirely preventable. A network of health services is required for this, and should be carefully organized by advanced preparations in order to reduce mortalities (Cunha et al. 2015).

Even after the significant advances over more than 30 years of dengue surveillance in Brazil, it has only recently been recognized that there are many deaths that are as yet not being detected by the health services. In Brazilian cities between 2011 and 2012, with organised, structured autopsy services and the use of surveillance and laboratory teams, the lethality rate due to dengue has tripled, suggesting that in many places the number of dengue-related deaths is underestimated (Braga. 2014; Cavalcanti et al. 2016).

Although considerable advances have been made in the field, and knowledge regarding dengue has been revealed, epidemiological surveillance and death investigation committees have faced challenges in determining whether a death occurred DUE TO dengue virus or in a patient WITH dengue virus infection. This question reflects the difficulty in establishing whether the disease contributed to death, or was in fact the underlying cause of death. Importantly, this is an acute infectious disease in which most

of the documented deaths usually occur prior to day 10 of illness (Cavalcanti et al. 2016; Campos et al. 2015).

Why is this question relevant now? Because we are in the process of commencing the organisation and systematisation of information and scientific evidence regarding the history of chikungunya fever in Brazil (Vasconcelos. 2014; Honório et al. 2015; Donalisio et al. 2015).

Following the isolation of chikungunya virus (CHIKV) in 1952 in Tanzania, the virus has been identified in Southeast Asia and India, establishing an urban transmission cycle that continues today. The second emergence of CHIKV occurred in Kenya in 2004, with the virus spreading over many islands of the Indian Ocean in the following years and reaching India and Southeast Asia. Between 2005 and 2006, an epidemic hit the islands of Reunion. At the end of 2013, the Pan American Health Organization issued an epidemiological alert due to the detection of the first local cases of chikungunya in the Americas. In August 2015, autochthonous transmission had been detected in 33 countries and territories of the Americas, and Latin America reported almost one million cases (Yakob et al. 2013; PAHO. 2011).

In Brazil, autochthonous transmission of CHIKV was simultaneously detected in September 2014 in Feira de Santana (Bahia) and Oiapoque (Amapá). During 2014, there were 2,772 confirmed cases of CHIKV in six Federative Units. In 2015, 38,332 probable cases were reported in the country, distributed over 696 municipalities (Brasil. 2014; Teixeira et al. 2015; Brasil. 2016).

Before the outbreak on Reunion Island, this disease was not associated with high fatality rates (Economopoulou et al. 2009). In recent years, however, many studies have challenged the conventional view of the non-lethal nature of CHIKV (Economopoulou et al. 2009; De la Hosz et al. 2015). The severe form of CHIKV infection can be associated with multiple organ failure, hepatitis, meningitis, nephritis, encephalitis, bullous dermatitis, myocarditis, and cardiac arrhythmias. While severe or atypical manifestations of CHIKV infection are uncommon, the overall fatality rate of these complications appears to be high (Couderc et al. 2015).

It was during the outbreak of chikungunya that affected Reunion Island in 2005–2006 that the severity of neonatal forms of infection, acquired by transmission from mother to

child during childbirth, was observed. When the mother is viremic at the time of delivery, the rate of mother-to-child transmission is about 50%. All neonates contaminated during labour and delivery present with symptomatic disease and the rate of severe forms is approximately 50%, primarily due to damage to the central nervous system, which often results in permanent, severe outcomes such as seizures and cerebral palsy (Gerardin et al. 2008). While CHIKV infection is not recognized among neonatal sepsis cases, the burden of neonatal complications due to this alphavirus may also be underestimated.

From January to August 2016, about 220,000 cases of chikungunya have been reported in Brazil, indicating a troubling scenario with respect to morbidity and mortality. The current epidemic has the potential to be explosive, reaching great magnitudes because of the large population of susceptible individuals and the wide-reaching spread of its main vector. This is likely to result in many suspicious deaths, mainly in the northeast of the country where more than 90 deaths were confirmed from January to August 2016 (Brasil. 2014; Brasil. 2016). Brazil has been slow to confirm cases, with difficulties associated with the identification of deaths through information systems, despite mandatory reporting of CHIKV infection within 24 hours. Therefore, these data on CHIKV deaths in Brazil are likely to be still underestimated, as was the case on Reunion Island (2005/2006), where less than one-third of deaths were reported (Josseran et al. 2006).

The Ministry of Health of Brazil has appropriately adapted the dengue death investigation protocols by changing them to arbovirus death investigation protocols, owing to the triple occurrence of dengue, chikungunya, and zika (Coelho et al. 2016; Carvalho et al. 2016).

As a diagnosis of dengue can be confirmed serologically after 7–10 days, many deaths during the first week are "probable cases"; this is a limitation in the investigation of deaths. Distinguishing underlying disease or causes of death is impossible during surveillance for most diseases, and useless from the perspective of a transmissible disease. However, it is necessary to know the fatality rates in order to direct actions of surveillance and control.

The current challenge is to investigate and classify deaths caused by chikungunya, considering that patients can die not only in the acute phase (up to 21 days), but also in

the subsequent non-acute phase (22 days to three months post-infection) or even in the chronic phase (> 3 months), due to complications triggered by the virus itself. The cause of death cannot be confirmed by direct methods (RT-PCR or virus isolation), especially in the sub-acute or chronic phases (Brasil. 2016).

The question remains how one can assign a particular cause of death to chikungunya. Did chikungunya infection decompensate underlying diseases, which led to death? Did the disease progress unsatisfactorily owing to the presence of another underlying disease? Did the disease engender the need for a prolonged hospitalisation, leading to nosocomial infection, and subsequent progression to death? Was the therapeutic management inadequate? Was there an iatrogenic complication during patient care? What is the role of neurological complications in the causation of death due to CHIKV? Whether chikungunya is the basic or underlying cause of deaths, the associated co-morbidities, secondary infections and inappropriate use of non-steroidal anti-inflammatory drugs appear to contribute to the fatal outcome.

Thus, the question, for which there has not yet been a definitive response in relation to dengue virus infections, resurfaces prominently with regard to the chikungunya surveillance scenario in Brazil. In the case of a patient that has died, did chikungunya have a secondary role, or was CHIKV infection the underlying cause of death? Irrespective of whether a patient's death was solely due to CHIKV infection, due to unrelated causes, or due to an interaction between CHIKV infection and other causes, we should be concerned about the epidemic of a disease that we are facing that may be more lethal than previously thought. We have a major challenge ahead to appropriately capture and investigate deaths suspected of being caused by arbovirus infections and to understand the role of each virus in the unfavourable outcome. A comparable database is important to help us understand this disease and its pathophysiology, as well as the impact of the association between arboviruses and underlying diseases.

Moreover, specific protocols need to be developed regarding the medical attention given to patients with a suspected and / or clinical diagnosis of chikungunya associated with co-morbidities, with the aim of enhancing clinical management in order to reduce deaths.

References:

1. Braga DNM. Aspectos laboratoriais e anatomopatológicos no diagnóstico da dengue no Ceará em 2011 e 2012: papel do serviço de verificação de óbitos de Fortaleza [Dissertação]. Fortaleza (CE): UFC; 2014. Disponível em: http://www.repositorio.ufc.br/handle/riufc/9544
2. Campos KB, Amâncio FF, Araújo VE, Carneiro M. Factors associated with death from dengue in the state of Minas Gerais, Brazil: historical cohort study. Trop Med Int Health. 2015; 20(2): 211-8.
3. Carvalho FHC, Cavalcanti LPG. The triple epidemic of arboviroses in Brazil. Whats does this mean? Are we ready? Rev Med UFC. 2016; 56(1): 6-7.
4. Cavalcanti LPG, Braga DN, da Silva LM, Aguiar MG, Castiglioni M, Silva-Junior JU et al. Postmortem Diagnosis of Dengue as an Epidemiological Surveillance Tool. Am J Trop Med Hyg. 2016; 94(1): 187-192.
5. Cavalcanti LPG, Coelho ICB, Vilar DCLF, Holanda SGS, Escóssia KNF, Souza-Santos R. Clinical and epidemiological characterization of dengue hemorrhagic fever cases in northeastern Brazil. Rev Soc Bras Med Trop. 2010; 43(4): 355-58.
6. Coelho GE, Martins J, Percio J (Org). Protocolo de investigação de óbitos por arbovírus urbanos no Brasil: dengue, chikungunya e zika [Internet]. Brasília: Ministério da Saúde; 2016 [acesso: 2016 9 9] Disponível em: http://portalsaude.saude.gov.br/images/pdf/2016/agosto/30/Protocolo-de-investiga----o-de---bitos-de-dengue-chikv--Zika.13.06.2016.pdf
7. Couderc T, Lecuit M. Chikungunya virus pathogenesis: from bedside to bench. Antivir Res. 2015; 121 (9):120–31.
8. Cunha RV; Martinez E. Manejo clínico do paciente com dengue. In: Valle D, Pimenta DN, Cunha RV (Orgs). Dengue: teorias e práticas. Rio de Janeiro: Fiocruz; 2015. p. 221-45.
9. De la Hoz JM, Bayona B, Viloria S, Accini JL, Juan-Vergara HS, Viasus D. Fatal cases of Chikungunya virus infection in Colombia: diagnostic and treatment challenges. J Clin Virol. 2015; 69(8):27–9.
10. Donalísio MR, Freitas ARR. Chikungunya no Brasil: um desafio emergente. Rev Bras Epidemiol. 2015; 18(1): 283-5.
11. Economopoulou A, Domínguez M, Helynck B, Sissoko D, Wichimann O, Quenel P et al. Atypical chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005-2006 outbreak on Réunion. Epidemiol Infect. 2009; 137(4): 534-41.

12. Gerardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G et al. Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the Island of La Reunion. PLoS Med. 2008; 5(3): e60.

13. Honório NA, Camara DCP, Calvet GA, Brasil P. Chikungunya: uma arbovirose em estabelecimento e expansão no Brasil. Cad Saúde Pública. 2015; 31(5): 906-8.

14. Josseran L, Paquet C, Zehgnoun A, Caillere N, Tertre AL Solet JL et al. Chikungunya Disease Outbreak , Reunion Island. Emerg Infect Dis. 2006; 12(12): 1994–5.

15. Mariano F. A dengue. Considerações a respeito de sua incursão no Rio Grande do Sul, em 1916. Arch Med Res. 1917; 7: 272-277.

16. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Preparação e resposta à introdução do vírus Chikungunya no Brasil. Brasília: Ministério da Saúde; 2014.

17. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a semana epidemiológica 32, 2016. Boletim Epidemiológico [Internet]. 2016 [acesso 2016 9 9]; 47(33): 1-10. Disponível em: http://portalsaude.saude.gov.br/images/pdf/2016/setembro/16/2016-028---Dengue-SE32.pdf

18. Osanai CH, Rosa APT, Tang A, Amaral R, Passos ADC, Tauil PL. Surto de dengue em Boa Vista, Roraima. Rev Inst Med Trop São Paulo. 1983; 25(1): 53-4.

19. Osanai CH. A epidemia de dengue em Boa Vista, território Federal de Roraima, 1981- 1982. [Dissertação]. Rio de Janeiro (RJ): Escola Nacional de Saúde Pública, 1984.

20. Pan American Health Organization. Preparedness and Response for Chikungunya Virus: Introduction in the Americas. Washington, DC: PAHO; 2011. 161p.

21. Pedro A. O dengue em Nictheroy. Brazil Médico. 1923; 1(13): 174-7.

22. Rego JP. Esboço histórico das epidemias que tem grassado na cidade do Rio de Janeiro desde 1830 a 1870. Rio de Janeiro: Typhographia Nacional. 1872; 2(1): 44-50.

23. Reis TJ. A febre dengue em Curityba. Gaz Med Bahia. 1896; 97: 163-266.

24. Schatzmayr HG. Dengue situation by year 2000. Mem Inst Oswaldo Cruz. 2000; 95(s1): 179-81.

25. Silva JB Jr, Siqueira JB Jr, Coelho GE, Vilarinhos PT, Pimenta FG Jr. Dengue in Brazil: current situation and control activities. Epidemiol Bull. 2002; 23(1): 3-6.
26. Teixeira MG, Barreto ML, Guerra Z. Epidemiologia e medidas de prevenção do dengue. Inf Epidemiol Sus. 1999; 8(4): 5-33.
27. Teixeira MG, Siqueira JB Jr, Ferreira GLC, Bricks L, Joint G. Epidemiological trends of dengue disease in Brazil (2000-2010): a systematic literature search and analysis. PLoS Negl Trop Dis. 2013; 7(12):e2520.
28. Teixeira MJ, Andrade A, Costa MN, Castro J, Oliveira F, Goes C, et al. East/Central/South African Genotype Chikungunya Virus, Brazil, 2014. Emerg Infect Dis. 2015; 21(5): 906-907.
29. Vasconcelos PFC. Emergência do vírus Chikungunya: risco de introdução no Brasil. Rev Pan-Amaz Saude. 2014; 5(3): 9-10.
30. Yakob L, Clements ACA. A mathematical model of chikungunya dynamics and control: the major epidemic on Réunion Island. PLoS One. 2013; 8(3): e-57448.