Review Article

Alert: Severe cases and deaths associated with Chikungunya in Brazil

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Abstract

Since the detection of the Chikungunya virus in America in 2013, two million cases of the disease have been notified worldwide. Severe cases and deaths related to Chikungunya have been reported in India and Reunion Island, estimated at 1 death per 1,000 inhabitants. Joint involvement in the acute and chronic phase is the main clinical manifestation associated with Chikungunya. The severity of the infection may be directly attributable to viral action or indirectly, owing to decompensation of preexisting comorbidities. In Brazil, the virus was identified in 2014, and recently, there has been a significant increase in the number of deaths caused by the Chikungunya virus infection, especially in Pernambuco. However, the numbers of fatalities are probably underreported, since for many cases, the diagnosis of Chikungunya infection may not be considered, for deaths by indirect causes. An increase in the mortality rate within months of epidemic occurrence, compared to previous years has also been reported and may be associated with Chikungunya virus infection. An in-depth investigation of reported mortality in Brazil is necessary, to measure the actual impact of the deaths, thereby, allowing the identification of possible causes. This will alert professionals about the risks, and hence, enable creation of protocols that target reducing mortality.

Keywords: Chikungunya. Lethality. Severe cases. Epidemiology. Review.

INTRODUCTION

The Chikungunya virus (CHIKV) is a single-stranded ribonucleic acid (RNA) organism, of the family Togaviridae and genus Alphavírus, with three subtypes (two African and one Asian). *Aedes aegypti* and *Aedes albopictus* are the main carriers involved in the transmission of CHIKV. Although the first report of surges associated with Chikungunya was in 1952 in Tanzania, it was not until after 2005 that a large number of cases in the Indian Ocean islands emerged. The most extensive surge occurred on Reunion Island in 2005, hitting one third of the population, with 266,076 reports and 237 deaths attributed directly to CHIKV infection. In 2013, it struck the Western hemisphere, initially on the Caribbean Islands of Saint Martin and spread quickly until June 2014, hitting 20 other countries in the Caribbean, and South and Central America, with over 400,000 reports[1,2].

In Brazil, the first cases were reported in the second half of 2014 in the Cities of Oiapoque and Amapá, in the North, and in Feira de Santana, Bahia, in the Northeastern region. The epidemic only hit other Northeast states in the second half of 2015. In 2015, 20,598 cases were reported, and in 2016, until the 32nd epidemiological week, there were 216,102 notifications in the entire country. Of those, 189,814 (87.8%) happened in the Northeast of the country[3]. In the Northeast, Pernambuco was one of the states with highest numbers of reports, with 53,601 suspected cases until the 36th epidemiological week.

The disease presents high attack rates and 75-95% of individuals infected by CHIKV are symptomatic, which is in contrast to infections with other arboviruses. The attack rates struck 35-75% of a population in only one epidemic[2,4]. During the outbreak on Reunion Island, surveillance figures from a serosurvey confirmed 16,050 cases, and estimated 244,000 reports, which corresponded to a 35% attack rate[5].

Chikungunya presents with articular pain as the main clinic manifestation at different stages of the disease, and it is an important cause of physical incapacity, significantly impacting on the quality of life of those affected[6-8]. After the acute phase, which lasts about 10 days, studies show that 40-80% of patients can chronically evolve with the articular clinical manifestation for months or even years. A prospective study by Schilte et al, on Reunion Island, reported that 69% of patients persisted with arthralgia after 36 months[8].

In a recent meta-analysis, the global prevalence of chronification found after computing the results was 40% (27.7-50.5%) and for studies with more than 18 months of follow up, the prevalence was 32%[9].

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DEATHS RELATED TO CHIKUNGUNYA

Besides the incapacitating articular pain, severe cases and deaths related to Chikungunya have been reported. In the 2005-2006 epidemic on Reunion Island, of a population of approximately 800,000 inhabitants, 244,000 cases of Chikungunya were estimated and 203 deaths were confirmed, in a proportion of 1 death for each 1000 notified cases and a global mortality of 25/100,000 inhabitants[5]. The most commonly affected are the elderly with an average age of 79 years. Of the 244,000 cases, 121 (60%) deaths were caused either directly because of the infection, or indirectly, mainly due to decompensation of previous comorbidities. The remaining 123,000 severe cases reported the following as main reasons for hospitalization: respiratory failure (19 cases); cardiovascular decompensation (18), meningoencephalitis (16), severe hepatitis (11), major cutaneous lesions (10), renal insufficiency (7), among others[5].

Atypical cases that needed hospitalization, and exhibited risks of complications, were reported in another study by Economopoulo A et al. Among 610 adults with complications, cardiovascular changes occurred in 37% of cases (heart failure, arrhythmia, myocarditis, acute coronary disease), 24% had neurological disorders (encephalitis, meningoencephalitis, seizure, Guillain Barré syndrome), 20% pre-renal insufficiency, 17% developed pneumonitis, and 8% developed respiratory failure[10]. Although 89% had a history of medical conditions, for some complications were not related to previous comorbidities, thereby, reinforcing the severity of this disease regardless of associated medical conditions. Of 120 hospitalized patients of renal failure, 66% did not report previous renal illness. Of 44 arrhythmia cases, 63% did not have any cardiovascular background and of 131 cases with changes on the glycemic level, 20% were diagnosed diabetes mellitus for the first time[10].

Seventy-five patients died from the following complications: heart failure (15 cases), multiple organ failure (11 cases), acute hepatitis (7 cases), encephalitis or meningoencephalitis (6 cases), epidermolysis bullosa (6), myocarditis or pericarditis (5), respiratory insufficiency (3), renal failure (3), pneumonia (2), acute myocardial infarction (2), cerebrovascular event (1), hypothyroidism (1), and sepsis (1)[10].

POTENTIAL DEATHS ASSOCIATED WITH CHIKUNGUNYA

In addition to the suspected and confirmed deaths due to infection by Chikungunya, there is a high possibility of greater numbers than those officially confirmed (**Table 1**). Josseran L, was first to use methods estimate surplus deaths in the Chikungunya outbreak in Reunion Island. The authors compared the numbers of fatalities for all causes, which occurred on Reunion Island in the peak months of Chikungunya waves, with the deaths in previous years. From January until April of 2006, a surplus of 260 fatalities and a lethality rate of 1/1,000 were identified[11].

A similar study performed in Ahmedabad city, compared the average deaths for any cause during 2002-2005 with the year of 2006, which was struck with a Chikungunya outbreak. Considering population increase, 3,506 excess deaths occurred above the expected rate for that year. Of these, 2,994 occurred between the months of August and November alone, especially in September, within which 41% of excess deaths (1,448) occurred, corresponding to the peak of Chikungunya epidemic. The expected mortality rate increased by 57% within those months[12]. The city had a population around 6 million inhabitants and officially, the government registered only 66,777 cases of Chikungunya and 10 confirmed deaths. The initial data showed an attack rate of 1.1% for Chikungunya cases and a proportion of one death for each 6,677 symptomatic infection cases, reflecting a flaw in the reporting system and investigations of deaths[12].

Two other studies, one on Mauritius Island (with a population of 1.2 million), and another in Port Blair City, India (with 136,000 inhabitants) also observed respectively, 742 and 72 surplus deaths, after a Chikungunya epidemic during the peak months of the outbreak[13,14]. In Port Blair, the study evaluated the two years following the CHIKV epidemic (2007-2008); it showed that the numbers of fatalities had reduced and no Chikungunya epidemic was identified during these years[13].

An editorial published by Mavalankar D, in 2007, cautioned about the severity of the epidemic in India, suggesting an increase in death rates, noticed by the assistants but registered by the government, and this was attributed to a limited surveillance and investigation system in the country. The author suggests that among the 1,391,165 cases officially notified, 1,194 deaths occurred; however, but consider that the number is probably five times higher, something around 6,5 million cases and 6.389 deaths for an intermediate estimation and of 19,168 deaths (3/1,000) for a higher estimate, considering those numbers the mortality could have been three times worse than the ones reported on Reunion Island (1/1,000)[15].

A possibility for a potentially larger number of death cases related to Chikungunya not reported by the official systems,

TABLE 1
Estimation of lethality rates based on excess deaths potentially related to CHIKV infection.

City/Country	Population	Cases	Official deaths	Lethality rate*	Mortality rate**	Estimated excess deaths	Lethality rate*	Mortality rate**
Ahmedabad (ref)	6,000,000	66,777	10	0,1	0,02	2,994	44,8	5,0
Port Blair (ref)	136,000	4,469	NI	NI	-	72	16,1	5,3
Mauritius (ref)	1,250,000	12,260	NI	NI	-	743	60,6	5,9

CHIKV: Chikungunya virus; **NI:** not informed. *Deaths per 1,000 cases. **Deaths per 100,000 habitants.

can be linked not only to the flaws of the surveillance system for case notifications or investigation of deaths, but also to situations of unregistered cases of Chikungunya infection in the death certificate filled by the health professionals.

Many causes of deaths related to the infection are due to decompensation of comorbidities, which include patients with previous cardiac disorders, renal or pulmonary diseases that may be registered in the official death certificate without reference to CHIKV, especially in first outbreak situations in regions without previous experience with the disease. Besides that, the diagnosis of CHIKV infection may not be considered for cases of deaths caused by neurological cases and pneumonitis in young patients or those without comorbidity.

A difficulty in the identification of deaths associated with the arbovirus was recently reported in a publication by Cavalcanti L et al. The authors evaluated deaths in a reference service of deaths verification and detected 90 deaths from dengue, which were not suspected during disease progression. The cases of deaths were referred to this service alongside other diagnosis, in which the pathologists suspected dengue as the cause of death. These excesses of unidentified and suspected deaths for a disease that had already existed in the country for 30 years, such as dengue, reinforces caution and the need to investigate these surplus deaths, in relation to Chikungunya, which has a pattern associated with a severe form of the disease[16].

CHIKUNGUNYA X DENGUE: COMPARING THE SEVERITY

Brazil has recorded over 80% of cases of dengue in Latin America[17]. In the last three decades, with outbreaks happening since 1982, around 10,906,332 cases were notified in Brazil by the Ministry of Health in the last 25 years (1990 to 2015) and 5,224 deaths, a lethality rate of 0.5/1,000 cases. In 2015, the year with the largest number of notifications in history, there were 1,649,008, with 863 deaths, suggesting the same lethality rate and with a mortality rate of 0.04/100,000 inhabitants[3] (**Table 2**).

In Pernambuco, the second most populated State of Northeast Brazil, nearly 9 million inhabitants, between 1990 and 2015, there were 556,220 officially notified cases and 260 deaths (lethality rate 0.5/1,000). The year 2013 recorded the highest number of deaths in the stated, totaling 37 (**Table 2**).

Until the 36th epidemiological week, 53,601 suspected cases of Chikungunya were notified in Pernambuco. Among the 313 registered cases of death due to arboviruses, 88 were

confirmed, with the remaining under investigation. Seventy cases were positive for Chikungunya (79.5%), with fifty-three (60.2%) isolated CHIKV infection only and the other 17 (19.3%) confirmed as being accompanied by co-infection through laboratory results. Dengue was isolated for 18 (20.5%) cases[18]. These numbers already exceed the number of previously reported deaths due to arboviruses in the state, which shows a pattern of higher severity of the outbreak. Considering that in the epidemic week there were 53,601 suspected cases notified of Chikungunya, we would have a lethality rate of 1.3/1,000.

The first confirmation of death by arboviruses in 2016 was due to Chikungunya, recorded in a bulletin in epidemiological week 10, with other 95 death cases notified by investigation[19]. During the epidemic, the number of cases of fatalities increased and surveillance investigation was amplified, identifying in epidemiological week 26, a total of 26 (86.6%) deaths owing to Chikungunya and 7, owing to dengue, with another 240 cases under investigation[20]. Based on this tendency, it is possible to estimate that by the end of the investigation of all 313 cases in the year 2016, more than 70% will be associated with Chikungunya, which would represent 219 deaths, a number that is close to the total of fatalities in the state due to dengue in the last 25 years. Considering that in this epidemiological week there were 53,601 suspected notified cases of Chikungunya, we would have an increase in lethality of 4.1/1,000.

ESTIMATIONS FOR BRAZIL

The isolated analysis of high attack rates for the disease and its lethality, like the ones described on Reunion Island, when projected for tropical countries with large number of inhabitants, has a potential to generate an elevated absolute number of fatalities. Even without considering the sub notifications or excess deaths unnoticed by assistance potentially related to CHIKV. In Brazil, a country with continental dimensions, these numbers can assume alarming proportions.

When compared with dengue, is pertinent to question if the greater number of deaths by Chikungunya is due to a more expressive virulence of the virus or a reflex of the high attack rates. In virtue of the inaccuracy of available numbers in Brazil, the analysis can be made for different scenarios.

Considering most conservative and available data in literature, the lethality of Chikungunya (1/1000) is higher than that of dengue (0.5/1,000), which in a way reflects higher severity. Besides that, what really causes an impact is the large

TABLE 2

Official lethality rate for dengue epidemic in Brazil and in Pernambuco.

City/country	Cases	Deaths due to dengue	Lethality rate deaths/1,000 cases
Brazil 2015*	1,649,008	863	0,5
Brazil (1990-2015)	10,906,332	5,224	0,5
Pernambuco (1990-2015)	556,220	260	0,5

TABLE 3

Number of deaths estimations in epidemic of dengue and Chikungunya based on historical lethality rates and percentage of symptomatic for type of infection.

Country or State	Population	Virus	Attack rate (%)	Number of infected	Symptomatic (%)	Number of symptomatic	Number of death
Ilha Reunion	800,000	CHIKV	30.0	240,000	**90.0**	216,000	216
Pernambuco	9,000,000	Dengue	5.0	450,000	20.0	90,000	45
		CHIKV	30.0	2,700,000	90.0	2,430,000	2,430
Brazil	200,000,000	Dengue	5.0	10,000,000	20.0	2,000,000	1,000
		CHIKV	30.0	60,000,000	90.0	54,000,000	54,000

CHIKV: Chikungunya virus.

absolute number of deaths expected in an epidemic, especially seen in larger populations, as a reflex of the high attack rates and numbers of symptomatics in epidemics of CHIKV, which generates a higher number of cases of the disease and, consequently, of deaths in absolute numbers.

Dengue exhibits estimation of attack rates of 3-25%, in which only 5-25% of infected patients are symptomatic[21-23]. When analyze the Chikungunya epidemics, the attack rates can reach 35-75% of the population, with 75-95% of the individual infected by Chikungunya, presenting with the symptomatic form[2,4,5]. Therefore, by estimating deaths based on these variants, there are large absolute numbers of expected deaths for Chikungunya if compared to dengue (**Table 3**).

In Brazil, with 200 million inhabitants, the epidemic reached the various states of the federation in different years, as in the case of dengue; therefore, we have during the years, 60 million cases (attack rate: 30%) and an estimation of 60,000 deaths (**Table 3**).

In this way, even if the relationship existing between cases and deaths is only described by the Reunion Island incidence, this fact by itself is preoccuping, especially for developing countries, with large populations and some fragilities of an already overloaded health system.

This scenario may be even more preoccuping with higher number of deaths, if we consider the possibility of parts of these cases not being notified and therefore, not registered by the official system, due to issues with sub-notification. An estimation based on the studies in which surplus deaths were potentially related to Chikungunya, would drastically alter these variables and its lethality rate.

CONCLUSION

Severe cases and deaths attributable to Chikungunya have been reported in different countries, presenting high lethality rates and initially being described in the proportion of 1 death per each 1,000 cases of Chikungunya; however, these numbers may have been underestimated, owing to the fact that some deaths are not being identified as chikungunya-related and therefore, not included as part of the official records.

Moreover, considering future adjustments in the lethality rates, as a result of more accurate analysis, those numbers are already alarming. Given the high attack rates and large amount of symptomatics in chikungunya outbreaks, countries like Brazil, with continental dimensions and large populations, may have substantial absolute numbers of deaths that can even exceed those related to other important arboviruses, like dengue.

An in-depth investigation about the deaths now noted in Brazil, is necessary and urgent, to measure the actual impact of those deaths, by allowing the identification of possible causes of these deaths, as well as to alert the professionals about the risks and to create protocols that targeting reducing mortality.

Conflict of interest

The author declares that there is no conflict of interest.

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