Major Article

Estimated mortality rate and leading causes of death among individuals with chikungunya in 2016 and 2017 in Brazil

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Abstract

Introduction: In 2014, the first cases of autochthonous chikungunya (CHIK) were recorded in Brazil. Lethality associated with this disease is underestimated. Thus, this study aimed to analyze the causes of death among individuals with CHIK in Brazil. Methods: A descriptive observational study was conducted on individuals with CHIK who died within 6 months from symptom onset. Data pairing between the Information System for Notifiable Diseases and the Mortality Information System was performed. Deaths were classified according to case confirmation criterion, mention of CHIK in the death certificates (DCs), and disease phase. The lethality rate per 1,000 cases was corrected for underreporting and was estimated according to region, sex, age, years of education, race/color, and cause groups. Results: We identified 3,135 deaths (mention of CHIK in the DCs, 764 [24.4%]). In 17.6% of these cases, CHIK was the underlying cause. Most deaths occurred in the acute (38.1%) and post-acute (29.6%) phases. The corrected LR (5.7; x1,000) was 6.8 times higher than that obtained from the Information System for Notifiable Diseases (0.8). The highest corrected LRs were estimated for among individuals living in the Northeast region (6.2), men (7.4), those with low years of education and those aged <1 year (8.6), 65-79 years (20.7), and ≥80 years (75.4). Conclusions: The LR of CHIK estimates based on information system linkage help to reveal the relevance of this disease as the direct cause or as a cause associated with serious or fatal events, provide timely interventions, and increase the knowledge about this disease.

Keywords: Chikungunya fever. Mortality. Matched-pair analysis. Death certificate.

INTRODUCTION

Chikungunya (CHIK) is a viral disease caused by the chikungunya virus (CHIKV)1. It belongs to the genus Alphavirus, which is transmitted mainly by the vectors of the Aedes genus. This virus was first identified in 1953 in Africa2 and later in Asia and Oceania. Meanwhile, the first autochthonous cases in America were only identified in 2013. In Brazil, the first autochthonous cases of CHIK were recorded in 2014 in Oiapoque in the state of Amapá3 and in Feira de Santana in the state of Bahia4.

A small proportion of individuals with CHIK are asymptomatic. Meanwhile, in symptomatic cases, the most common manifestations are fever, arthralgia, and exanthema5. Approximately 0.3-1% of symptomatic patients can develop atypical manifestations, with neurological, cardiovascular, pulmonary, hepatic, renal, cutaneous, and ocular involvement, and the atypical manifestations in one-third of the patients are severe and characterized by the need for support for at least one vital function6,7.

The clinical course of CHIK include the following: the acute phase lasting for up to 21 days, post-acute phase lasting between 22 and 90 days, alternating between periods of temporary improvement and relapse7,8 and chronic phase, which involves pain in the joints that lasts over 90 days and even years after diagnosis. Studies conducted in some places in Brazil have found chronic cases,
with rates varying between 45.7% and 75%.

Deaths can occur in any of these phases, by direct or indirect action of the virus. The age groups who are at higher risk of severe diseases include neonates who acquire the disease in the perinatal period, elderly individuals, and those with pre-existing diseases.

According to the Brazilian Health Ministry data, a total of 552,023 cases were identified between 2014 and 2017 (incidence coefficient of 266 cases per 100,000 inhabitants), 403 deaths were caused by the disease, with a lethality rate (LR) of approximately 0.7 deaths per 1,000 cases. However, the health care systems are still not alert and sensitive in detecting and recording severe CHIK cases and deaths, thereby resulting in classification errors in death certificates (DCs) and underestimation of the mortality and lethality rate of CHIK. Studies have reported an excess of deaths during the CHIK epidemics in Brazil and in other countries, which may be associated with the disease. However, these cases were not appropriately recorded in the information systems.

Thus, this study aimed to estimate the magnitude and to describe the distribution and declared causes of death among individuals notified to CHIK in Brazil between 2016 and 2017.

**METHODS**

This descriptive observational study was based on routine data obtained from the Brazilian Health Surveillance System.

The study population comprised individuals with CHIK who died within 6 months from symptom onset, regardless of the underlying cause stated in the DC.

The study population was selected using the following criteria:

- **Criterion 1**: Individuals notified to CHIK, as reported in the Information System for Notifiable Diseases [Sinan], who died (according to the Mortality Information System [SIM]) within 6 months after symptom onset, regardless of the underlying cause of death.

- **Criterion 2**: Individuals whose DCs mentioned CHIK in SIM in the study period even if there was no prior notification of the case in Sinan.

Data for the years 2016 and 2017 in the Sinan and SIM databases were used, and the following procedures were utilized to link these two databases.

**Stage 1**: All CHIK cases recorded in Sinan during the study period were identified, regardless of case progression in this system. The database was linked with the complete SIM database for the same period, regardless of the cause of death recorded in this system.

**Stage 2**: The scores obtained from pairing varied between 0 and 10,000. The scores equal to 10,000 were considered as pairs since most cases were from perfect pairs. Meanwhile, scores less than 9,000 were not used. We calculated the time between symptom onset and death, which was obtained using the difference between the date of death (SIM) and date of symptom onset (Sinan).

This information was used to exclude pairs for which time to death was greater than 6 months, except when CHIK was mentioned in the DC.

**Stage 3**: Pairs with scores between 9,000 and <10,000 were considered doubtful pairs and were selected for manual inspection after excluding duplicates. As described previously, the same variables used for linkage were used for final checking and identification of true pairs.

**Stage 4**: In cases of death recorded in SIM but were not paired with any CHIK record in Sinan, the DCs mentioning chikungunya (ICD A92.0) as an underlying cause or cause associated with death in the study period were added to the final database for analysis, thereby meeting criterion 2 for the study population.

**Stage 5**: The last stage involved the exclusion of deaths due to external causes (underlying cause in SIM) and those with final classification as discarded CHIK cases in Sinan, regardless of the information shown in the DC.

Based on the pairing stage, the cases were classified according to the case confirmation criterion (Sinan) and mention of CHIK in the DC (SIM).

Two categories were considered for the case confirmation criterion: confirmed case (i.e., laboratory-confirmed cases [presence of a specific laboratory test with positive results - real-time polymerase chain reaction [RT-PCR], virus isolation, and IgM or IgG serology) and probable case (i.e., those cases confirmed using the clinical epidemiological criteria or having unknown or blank as their final classification and/or confirmation criterion).

Regarding the mention of CHIK in the DC, the following categories were analyzed: (1) mention of CHIK as an underlying cause, (2) mention of CHIK but not as an underlying cause, and (3) no mention of CHIK.

Moreover, the following variables were analyzed: region of residence, sex (male or female), age, years of education, race/color, other underlying and associated causes of death, and phase of the disease in which death occurred. Age was categorized as <1, 1-14, 15-44, 45-64, 65-79, and ≥80 years. Meanwhile, education was categorized according to the years of study, which was as follows: none; 1-3, 4-7, 8-11, and ≥12 years; and unknown. ICD-10 was used to define the underlying causes of death.

The phase of the disease in which death occurred was based on the time (days) between symptom onset and death, and it was categorized as follows: acute phase, death that occurred within 21 days of symptom onset, post-acute phase, between 22 and 90 days, and chronic phase, more than 90 days from disease onset. The IBM Statistical Package for the Social Sciences software version 22 and Microsoft Excel were used for all analyses. The study was approved by the ethics committee of the University of Brasília Faculty of Medicine Research (report number: 2.523.210).
**RESULTS**

We identified 552,023 suspected cases of CHIK in Sinan in 2016 and 2017 (Figure 1). Of these cases, 10,938 were linked to death notifications (DCs in SIM) in the same period (pairing score of ≥9,000). Based on the eligibility criteria, 3,994 deaths (time to death >6 months) were not included, and 1,094 cases were further excluded owing to duplications generated by pairing, thus, 5,850 cases were finally included.

Of the 5,850 pairs that were included, 1,827 had a score of 10,000 (considered to be perfect pairs), and 1,875 were manually selected from those with a score between 9,000 and <10,000. Furthermore, 330 deaths were added, which had been notified exclusively in SIM with mention of CHIK. Thus, a total of 4,032 deaths were recorded. Finally, 155 deaths due to external causes were excluded owing to duplications generated by pairing, thus, a total of 3,135 deaths were recorded. Finally, 155 deaths due to external causes were excluded. Thus, a total of 3,135 deaths were recorded. Approximately 90% (n=2,807) of deaths had been recorded as deaths in SIM and as cases in Sinan. Meanwhile, 10% (n=328) had been recorded as deaths in SIM but had not been as cases in Sinan (Figures 1 and 2).

Of the 2,807 paired SIM/Sinan notifications, 874 (31%) eventually died based on the data in Sinan (death from CHIK or other causes). Among them, 379 (43.4%) had DCs with mention of CHIK in SIM (Figure 2). In the remaining paired SIM/Sinan notifications (n=1,933, 68.8%), the disease progression field had been filled in with cure or unknown/blank. Among them, 57 (3%) had mention CHIK in SIM. CHIK was identified as the underlying cause of death in 551 (17.6%) of 3,135 patients, and CHIK was mentioned in the DC but was not identified as the underlying cause in 213 (6.8%) patients. Moreover, CHIK was not mentioned in the DCs of 2,371 (75.6%) patients.

Approximately 21.4% of cases had been laboratory-confirmed, and the remainder (78.6%) were classified as probable cases (Table 1).

CHIK identified as the underlying cause (n=551; 17.6%) was considered a part of the arthropod-borne viral fever and viral hemorrhagic fever groups, which accounted for 20.1% (n=631) of all deaths (Table 1). Among the 551 deaths with CHIK as the underlying cause, 253 were laboratory-confirmed. For both the confirmed and probable cases, arthropod-borne viral and viral hemorrhagic fevers were the most common underlying cause. However, this underlying cause was 2.8 times more common in confirmed cases (40.4%) than in probable cases (14.6%).

Among the other underlying causes of death, malignant neoplasm (7.9%), influenza and pneumonia (6.9%), ischemic heart disease (6.1%), diabetes mellitus (5.7%), and cerebrovascular disease (6.1%) were the most common causes of death.

**FIGURE 1:** Flow selection of chikungunya patients who died within 6 months in Brazil in 2016 and 2017 using the SINAN and SIM information system linkage process. *Except for individuals with mention of chikungunya in the DC (n=14). **Duplicates generated using the database linkage process when one DC was paired with two cases in SINAN. ***Patients who died with DCs mentioning chikungunya as an underlying or associated cause but was not paired with any cases in SINAN. ****In two of these cases, chikungunya was not an underlying cause. *****In sixteen of these cases chikungunya was not an underlying cause.
diseases (5.5%) are significant (Table 1). No variation was observed in the six leading underlying causes of death for confirmed or probable cases, except for diabetes mellitus, which is more relevant as an underlying cause of death among probable CHIK cases (6.3%). Moreover, conditions occurring in the perinatal period, viral infection of the central nervous system (CNS) and systemic atrophy primarily affecting the CNS, were more commonly observed in confirmed cases (Table 1).

The proportion of deaths (23.9%) that occurred in the chronic phase was higher when CHIK was not mentioned in the DCs. In contrast, the highest proportion of deaths in the acute phase was found when CHIK was mentioned in the DCs (Table 2).

This study included 3,135 deaths of individuals notified to CHIK. In Sinan, 464 CHIK deaths were recorded in the same period. The corrected lethality rate (CLR; 5.7 per 1,000 cases) was 6.8 times higher than the LR in Sinan alone (0.8 per 1,000 cases). The ratio of these LRs (LR in Sinan) varied according to the groups analyzed. That is, correction had a more significant effect in individuals living in the Northern region (CLR: 13.1 times higher than the uncorrected rate), those aged 15-44 years (7.9 times) and 45-64 years (8.6 times), those who did not attend school (11.8 times), and those with black race/skin color (10.8 times).

Based on the CLR (per 1,000 cases), the following individuals have a higher risk of death: residents in the Northeast region (6.2); men (7.4); those aged under 1 year (8.6), 65-79 years (20.7), and ≥80 years (75.4); those with low years of education (none: 16.8; 1-3 years: 33.7), and those with white (14.6) or black race/skin color (11.1) (Table 3).

**DISCUSSION**

This study first analyzed the causes of death among patients who had CHIK in Brazil based on deaths that occurred within 6 months after diagnosis. This analysis facilitated the identification of a relevant volume of unreported CHIK deaths (85%).

The proportion of underreporting was relevant in individuals living in the North and Midwest regions, women, those aged 45-64 years, those who were not able to attend school, and those of black race/skin color. The corrected LR might be attributed to CHIK, which indicates a higher risk of death among individuals in the Northeast region, men, those aged <1 year and ≥65 years, those with low years of education, and those of white race/skin color. The causes of death identified alert as to the association of this disease with atypical forms and worsening of pre-existing conditions.

The pairing of the 2016 and 2017 Sinan and SIM databases suggests that the corrected CHIK LR in Brazil (5.7%) in those years might be 6.8 times higher than the LR (0.8%) obtained from Sinan alone.

Moreover, the data in SIM may have been underreported. Only 24% (764/3,135) of DCs mentioned CHIK as the underlying or associated cause, thereby indicating some limitations in
### TABLE 1: Distribution of underlying causes recorded in SIM for death certificates mentioning chikungunya after SIM/Sinan pairing according to the case confirmation criterion* recorded in Sinan, 2016 and 2017 in Brazil.

| Underlying cause group | Confirmed case | Probable case | Total |
|------------------------|----------------|---------------|-------|
|                        | n   | %  | n   | %  | n   | %  |
| Arthropod-borne and viral hemorrhagic fevers (A90-A99) | 271 | 40.4 | 360 | 14.6 | 631 | 20.1 |
| Chikungunya (A920) | 253 | 27.4 | 298 | 10.8 | 551 | 17.6 |
| Malignant neoplasms (C00-C97) | 27 | 4.0 | 220 | 8.9 | 247 | 7.9 |
| Influenza and pneumonia (J09-J18) | 38 | 5.7 | 177 | 7.2 | 215 | 6.9 |
| Ischemic heart diseases (I20-I25) | 27 | 4.0 | 164 | 6.7 | 191 | 6.1 |
| Diabetes mellitus (E10-E140) | 26 | 3.9 | 154 | 6.3 | 180 | 5.7 |
| Cerebrovascular diseases (I60-I69) | 30 | 4.5 | 143 | 5.8 | 173 | 5.5 |
| Other types of heart disease (I30-I52) | 17 | 2.5 | 120 | 4.9 | 137 | 4.4 |
| Ill-defined conditions (R00-R99) | 18 | 2.7 | 115 | 4.7 | 133 | 4.2 |
| Other bacterial diseases (A30-A49) | 13 | 1.9 | 81 | 3.3 | 94 | 3.0 |
| Other respiratory system diseases (J60-J99) | 15 | 2.2 | 79 | 3.2 | 94 | 3.0 |
| Diseases of the blood and certain immune disorders (D50-D89) | 21 | 3.1 | 70 | 2.8 | 91 | 2.9 |
| Chronic diseases of the lower respiratory tract (J40-J47) | 9 | 1.3 | 47 | 1.9 | 56 | 1.8 |
| Diseases of the liver (K70-K77) | 7 | 1.0 | 48 | 1.9 | 55 | 1.8 |
| Kidney failure (N17-N19) | 8 | 1.2 | 47 | 1.9 | 55 | 1.8 |
| Other urinary system diseases (N30-N39) | 9 | 1.3 | 45 | 1.8 | 54 | 1.7 |
| Hypertensive diseases (I10-I15) | 8 | 1.2 | 42 | 1.7 | 50 | 1.6 |
| Systemic atrophy affecting the CNS (G10-G59 and G70-G99) | 13 | 1.9 | 34 | 1.4 | 47 | 1.5 |
| HIV disease (B20-B24) | 4 | 0.6 | 41 | 1.7 | 45 | 1.4 |
| Viral infection of the central nervous system (A80-A89) | 12 | 1.8 | 22 | 0.9 | 34 | 1.1 |
| Certain conditions that occurred in the perinatal period (P00-P96) | 5 | 0.7 | 5 | 0.2 | 10 | 0.3 |
| Other causes | 93 | 13.9 | 450 | 18.3 | 543 | 17.3 |
| Total | 671 | 21.4 | 2,464 | 78.6 | 3,135 | 100 |

Source: Sinan/SIM. *Confirmed case: laboratory-confirmed cases (presence of a specific laboratory test with positive results – real-time polymerase chain reaction, virus isolation, and IgM and IgG serology). Probable case: cases confirmed clinical epidemiological criterion or with the final classification and/or confirmation criterion unknown and blank or deaths identified exclusively in SIM (n=328).

### TABLE 2: Phase* of the disease during which death occurred, with mention of chikungunya in the death certificate (DC), and final case classification (confirmed or probable) in 2016 and 2017 in Brazil.

| Chikungunya mentioned in the DC | Phase | Confirmed case | Probable case | Total |
|---------------------------------|-------|----------------|---------------|-------|
|                                  |       | n   | %  | n   | %  | n   | %  |
| Chikungunya as an underlying cause | Acute | 140 | 57 | 72 | 75 | 212 | 62 |
|                                  | Post-acute | 88 | 36 | 19 | 20 | 107 | 31 |
|                                  | Chronic | 17 | 7 | 5 | 5 | 22 | 6 |
|                                  | Total | 245 | 100 | 96 | 100 | 341 | 100 |
| Chikungunya as the associated cause | Acute | 17 | 43 | 18 | 49 | 35 | 45 |
|                                  | Post-acute | 18 | 45 | 10 | 27 | 28 | 36 |
|                                  | Chronic | 5 | 13 | 9 | 24 | 14 | 18 |
|                                  | Total | 40 | 100 | 37 | 100 | 77 | 100 |
| No mention of chikungunya | Acute | 151 | 41 | 795 | 42 | 946 | 41 |
|                                  | Post-acute | 141 | 38 | 653 | 34 | 794 | 35 |
|                                  | Chronic | 79 | 21 | 466 | 24 | 545 | 24 |
|                                  | Total | 371 | 100 | 1,914 | 100 | 2,285 | 100 |

*Cases with inconsistent or missing symptom onset date were excluded from the analysis (n=432).
# TABLE 3: Corrected indicators according to the region of residence and characteristics of patients who died with death certificates mentioning chikungunya in Sinan and/or SIM in 2016 and 2017 in Brazil.

| Characteristics | No. of cases* | Incidence coefficient | No. of deaths in Sinan | No. of corrected deaths | Lethality rate in Sinan | Corrected lethality rate | Lethality ratio** | Relative risk*** |
|----------------|--------------|-----------------------|------------------------|-------------------------|------------------------|--------------------------|-------------------|-----------------|
| **Region**     |              |                       |                        |                         |                        |                          |                   |                 |
| N              | 39,466       | 220.0                 | 9                      | 118                     | 0.2                    | 3.0                      | 13.1              | 1.6             |
| NE             | 437,327      | 763.8                 | 414                    | 2,703                   | 0.9                    | 6.2                      | 6.5               | 3.3             |
| SE             | 60,774       | 69.9                  | 37                     | 273                     | 0.6                    | 4.5                      | 7.4               | 2.4             |
| S              | 5,876        | 19.8                  | 0                      | 11                      | 0.0                    | 1.9                      | ...               | 1.0             |
| MW             | 8,872        | 55.9                  | 4                      | 30                      | 0.5                    | 3.4                      | 7.5               | 1.8             |
| Unknown/blank  | 36           |                       |                        |                         |                        |                          |                   |                 |
| **Sex**        |              |                       |                        |                         |                        |                          |                   |                 |
| Male           | 208,249      | 203.2                 | 237                    | 1,541                   | 1.1                    | 7.4                      | 6.5               | 1.6             |
| Female         | 343,671      | 326.7                 | 227                    | 1,594                   | 0.7                    | 4.6                      | 7.0               | 1.0             |
| Unknown/blank  | 431          |                       |                        |                         |                        |                          |                   |                 |
| **Age range (years)** |          |                       |                        |                         |                        |                          |                   |                 |
| <1             | 7,484        | 274.2                 | 19                     | 64                      | 2.5                    | 8.6                      | 3.4               | 5.6             |
| 1-14           | 64,475       | 149.2                 | 22                     | 106                     | 0.3                    | 1.6                      | 4.8               | 1.1             |
| 15-44          | 281,567      | 299.6                 | 54                     | 428                     | 0.2                    | 1.5                      | 7.9               | 1.0             |
| 45-64          | 139,571      | 379.7                 | 78                     | 673                     | 0.6                    | 4.8                      | 8.6               | 3.2             |
| 65-79          | 47,490       | 425.2                 | 137                    | 982                     | 2.9                    | 20.7                     | 7.2               | 13.6            |
| ≥80            | 11,695       | 400.9                 | 154                    | 882                     | 13.3                   | 75.4                     | 5.7               | 49.6            |
| Unknown/blank  | 69           |                       |                        |                         |                        |                          |                   |                 |
| **Years of education** |          |                       |                        |                         |                        |                          |                   |                 |
| None           | 36,782       | 175.3                 | 52                     | 618                     | 1.4                    | 16.8                     | 11.8              | 3.4             |
| 1-3            | 23,836       | 71.6                  | 107                    | 803                     | 4.5                    | 33.7                     | 7.5               | 6.9             |
| 4-7            | 39,220       | 117.9                 | 73                     | 486                     | 1.9                    | 12.4                     | 6.7               | 2.5             |
| 8-11           | 83,725       | 110.8                 | 90                     | 408                     | 1.1                    | 4.9                      | 4.5               | 1.0             |
| ≥12            | 19,471       | 58.8                  | 41                     | 155                     | 2.1                    | 8.0                      | 3.8               | 1.6             |
| Unknown        | 349,308      | 60                    | 495                    |                          |                        |                          |                   |                 |
| **Race/skin color** |          |                       |                        |                         |                        |                          |                   |                 |
| White          | 65,131       | 71.5                  | 192                    | 949                     | 3.0                    | 14.6                     | 4.9               | 16.0            |
| Black          | 16,475       | 113.5                 | 17                     | 183                     | 1.0                    | 11.1                     | 10.8              | 12.2            |
| Yellow         | 4,402        | 211.2                 | 0                      | 4                       | 0.0                    | 0.9                      | ...               | 1.0             |
| Brown          | 301,053      | 365.9                 | 242                    | 1871                    | 0.8                    | 6.2                      | 7.7               | 6.8             |
| Indigenous     | 1,923        | 235.1                 | 1                      | 7                       | 0.5                    | 3.6                      | 7.0               | 4.0             |
| Unknown        | 163,367      | 12                    | 121                    |                          |                        |                          |                   |                 |
| **Total**      | 552,351      | 266                   | 464                    | 3,135                   | 0.8                    | 5.7                      | 6.8               |                 |

Source: Sinan/SIM and Brazilian Institute of Geography and Statistics–IBGE. *Sinan cases plus 328 cases recovered from SIM. **Corrected Sinan/SIM lethality ratio. ***Corrected lethality rate.
surveillance, healthcare, notification, and DC issuing\textsuperscript{23}. Excess deaths (all causes) in SIM were documented during the CHIK epidemic in three Brazilian states, and the estimated number of deaths was 50 times higher than the expected number\textsuperscript{21}.

Factors that can contribute to the underreporting of deaths include access to health services and to conclusive diagnosis and effective case investigation\textsuperscript{24}. The unavailability of medical supplies and the recommendation for using the clinical epidemiological confirmation criterion after autochthonous transmission have been assessed\textsuperscript{25,26} and are considered barriers in laboratory case confirmation and causal relationship with death. Moreover, CHIK is associated with the decompensation of pre-existing diseases, which are more likely to be considered as the underlying cause of death\textsuperscript{24}.

The percentage of chronic CHIK cases may be higher than 45\%, and some deaths may occur in this phase\textsuperscript{27}. Nonetheless, the Brazilian CHIK surveillance system follows the model established for acute diseases that determines timely case closure within 60 days\textsuperscript{26,28}. In cases that extend beyond the acute phase, this can have a negative impact on death notification in Sinan.

Based on previous studies, the number of deaths from CHIK was lower than that of deaths from dengue\textsuperscript{29}. This phenomenon may have contributed to the low sensitivity in recognizing deaths both in Sinan and SIM. Thus, CHIK was not mentioned in the DCs. However, the re-emergence of CHIK in America has shown that its lethality is high, as observed in Colombia\textsuperscript{30,31}, Guadeloupe, and Martinique\textsuperscript{32}.

Another factor associated with the underreporting of death is the severe atypical forms of the disease\textsuperscript{5,33,34} and chronification due to the longer interval between symptom onset and death. Moreover, when a lower number of events is recorded in Sinan and SIM, a causal relationship is more challenging to assess.

The number of deaths in Brazil in 2016 and 2017 might have been higher than that obtained in the current study owing to the lack of diagnosis and underreporting of suspected cases in Sinan, considering that this system was used as the starting point for pairing. A study conducted in Feira de Santana estimated that only 20\% of suspected CHIK cases were recorded in 2015\textsuperscript{4}. Notably, the Zika virus was introduced\textsuperscript{36} soon after the detection of the first autochthonous CHIK cases in Brazil in 2014\textsuperscript{43}. Thus, some CHIK cases may have been confused with Zika at that time, apart from dengue. Thus, they were not recorded by the surveillance service or were not appropriately classified.

The estimates obtained from the attack rate, the percentage of symptomatic cases, and an estimate of 1 death per 1,000 cases (1/1,000)\textsuperscript{7} in relation to the population of Pernambuco state indicates that there might have been approximately 2,400 CHIK deaths in 2016 in that state alone\textsuperscript{23}.

Some authors have found excess deaths among individuals under different age groups in the states of Pernambuco, Bahia, and Rio Grande do Norte in 2015 and 2016. That increase had a strong spatial and temporal relationship with the occurrence of CHIK in those places\textsuperscript{21}, indicating that the magnitude found in this study was similar to that of other studies.

The percentage of patients who died in the acute phase was similar between those who had CHIK as an associated cause and those for whom there was no mention of CHIK in the DCs. Moreover, a considerable percentage of deaths occurred in the chronic phase, as reported in other studies\textsuperscript{27}. This result reinforces that even deaths that occurred after the acute phase in this study might have been attributed to CHIK, despite the difficulty of association between the disease and death in the chronic phase\textsuperscript{38}.

A higher risk of death was observed in individuals in the Northeast region (6.2\%), where transmission was concentrated in 2016 and 2017\textsuperscript{17}.

In this study, the most common characteristics among individuals who died include male sex (7.4\%), age under 1 year (8.6\%), 65-79 years (20.7\%), and 80 years (75.4\%), low years of education (none: 16.8\%; 1-3 years: 33.7\%), and white (14.6\%) or black race/skin color (11.1\%).

During the epidemic in Puerto Rico, individuals aged under 1 year and >70 years were 9.2 and 2.4 times, respectively, more at risk of hospital admission than those aged 1-69 years, which is considered the reference age group\textsuperscript{20}. Moreover, hospitalization was a factor correlated to disease severity and death. Neonates born to mothers who presented with viremia near childbirth can have severe CHIK with neurological involvement and hemorrhagic manifestations\textsuperscript{31}. In Brazil, a study conducted based on surveillance data identified that the median age of death was 75 years\textsuperscript{39}.

In the CHIK seroprevalence studies of adults in Guadeloupe and Martinique in 2014, statistically significant differences were observed between the participants in terms of age and male sex\textsuperscript{35}. In contrast, a study conducted in Senegal in 2009 and 2010 has found no difference in terms of sex and age between the confirmed cases of chikungunya\textsuperscript{41}. Male sex was significantly associated with the risk of death among individuals in the state of Ceará (OR: 2.05). The same study has found a high proportion of individuals with low education level, and no association was observed between mortality and race/skin color\textsuperscript{41}.

Studies have shown that the presence of comorbidities, such as diabetes, hypertension, and kidney disease, were significantly associated with death from CHIK\textsuperscript{10,39,45}, and the number of comorbidities increased with age, which may explain the high number of deaths among individuals aged over 65 years in this study.

Regarding the underlying cause of death identified in the DCs, CHIK was the most common (17.6\%), regardless of case classification (confirmed or probable). The other causes include cardiac, liver, and central nervous system diseases\textsuperscript{41}.

Even deaths with underlying causes, such as diabetes, kidney failure, chronic diseases of the upper airways, and hypertensive diseases, may have resulted from the exacerbation of pre-existing diseases, or CHIK may have directly caused these deaths, considering that the decompensation of pre-existing diseases might have increased the risk of death from CHIK\textsuperscript{41}.

During the CHIK epidemic in Reunion Island, 610 patients presented with atypical manifestations. Among them, 546 had pre-existing conditions, the most frequent of which are hypertension,
diabetes mellitus, cardiovascular diseases, neurological disorders, chronic pulmonary diseases, alcohol abuse, kidney disease, and cancer. Heart disease and hypertension are independently associated with severe disease, and a high number of severe cases and deaths were found to be associated with CHIK.

This study had some limitations that are worthy of attention. The definition of the period between symptom onset and death (6 months) might have indicated that some deaths included in the analysis did not have a direct relationship with CHIK. However, the study considered both death from and death with CHIK. By contrast, defining the 6-month period and the overall study period of 2 years might have indicated that CHIK deaths that occurred outside of this time window were not included. This result raises the hypothesis that the rate of underreporting may be higher.

The corrected CHIK LR might have been overestimated owing to the possibility of underreported suspected cases, considering that there is a higher risk of reporting severe cases or cases that led to death, rather than benign cases. Moreover, another limitation is that not all cases of CHIK were laboratory-confirmed. Nevertheless, this problem was mitigated by stratifying the analyses as confirmed deaths and probable deaths.

The other limitations are those inherent to the use of secondary data and probabilistic database linkage. However, these procedures are found in the literature, and all possible procedures were adopted with the aim of minimizing possible pairing and under-recording of errors.

CHIK can cause epidemics with a high number of deaths. In relation this, health professionals must be aware about the importance of early case detection and prevention of death. In particular, they must be alert about atypical forms with high potential for hospitalization and fatalities.

Surveillance services should aim in detecting CHIK deaths to identify the actual magnitude of the disease, particularly among groups who are at higher risk, and to prevent future deaths.

The use of Sinan or SIM in calculating the LR of CHIK in Brazil does not identify the magnitude of the problem. The LR of from/with CHIK based on database linkage helped identify the relevance of this disease as a direct cause or as a cause associated with serious or fatal events in the country and provide guidance for timely actions and advancement of knowledge about this disease.

Future studies that use the results of specific tests and clinical data about hospitalizations and deaths can help elucidate and distinguish deaths that are directly or indirectly associated with CHIK.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

AUTHORS’ CONTRIBUTION

Frutuoso LCV, Freitas ARR, Cavalcanti LPG, and Duarte EC contributed to the conception and design of the study and writing and critical review of the manuscript for intellectual content. All authors have approved the final version and are responsible for all aspects of the study. Thus, they ensure the accuracy and integrity of the data.

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