

## Short Communication

# Is the recent increment in attributable deaths to type-2 diabetes (T2D) associated with the latest chikungunya outbreak in a major epidemic area in Brazil?

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### Abstract

**Introduction:** Chikungunya virus (CHIKV) can negatively influence outcomes in patients with pre-existing conditions. We investigated the association between the recent CHIKV outbreak and increased type 2 diabetes (T2D)-attributable deaths. **Methods:** Monthly averages of T2D-attributable deaths between 2001 and 2016 were determined and compared to the equivalent data for 2017 and the recent CHIKV outbreak. **Results:** CHIKV outbreak peaked in April 2017 with 4,394.4 cases/100,000 inhabitants, while T2D-attributable deaths in the same period increased by 35.2%. **Conclusions:** T2D-attributable deaths significantly increased compared to the previous data, which overlapped with CHIKV incidence. The pathophysiology of this association warrants further investigations.

**Keywords:** Chikungunya. Diabetes. Arbovirus. Deaths.

Similar to most developing countries, the prevalence of type 2 diabetes (T2D) in Brazil has been continuously increasing, with the prevalence of 10.3% in 2012<sup>1</sup>. Patients with diabetes are at a greater risk to develop clinical complications following infections (e.g., tuberculosis and melioidosis), thus significantly adding to the existing burden in healthcare systems in low- and middle-income nations<sup>2</sup>. Several infections interact with T2D by compromising glucose metabolism, thus aggravating patient conditions and leading to increased mortality<sup>3</sup>. More than three-quarters of patients with T2D live in developing countries<sup>3</sup>, where many infections are endemic. A recent review on T2D interaction with neglected infections, while presenting evidence of detrimental effect of dengue infection, failed to identify any literature on the consequences of Chikungunya (CHIKV)<sup>3</sup>.

CHIKV was first described in 1952 in South Tanzania<sup>4</sup>. In Brazil, during the epidemic seasons in 2016 and 2017, more than 300,000 cases were reported, which in fact represent

a significant understatement since diagnostic tests are not universally available, particularly in remote regions. In the same period, 300 attributable deaths were confirmed, and while the risk of death has been estimated to be approximately 1:1,000 cases<sup>5</sup>, the number of actual fatalities arising from CHIKV is more likely higher since under-diagnosis of CHIKV infections<sup>6</sup> has directly impacted on the assessment of deaths by indirect causes<sup>7-9</sup>. In the Federal State of Ceará, in the Northeast great region of Brazil, the first cases occurred in 2015 culminating with a large outbreak in 2017 where the incidence was more than 1,460.6 cases per 100,000 inhabitants with 150 confirmed attributable deaths. The median death age of these subjects was 77 years, a population segment that inherently displays a higher prevalence of metabolic diseases like T2D.

Given that CHIKV can negatively influence metabolism in T2D patients and further derange glucose homeostasis, we sought to investigate, through an ecological approach, the association between a CHIKV outbreak and a recent upsurge in the number of deaths attributable to T2D in the same area.

We determined the historical mean number of monthly deaths attributed to T2D (ICD10:E10-E15) between 2001 and 2016 in the State of Ceara. Next, we compared these numbers

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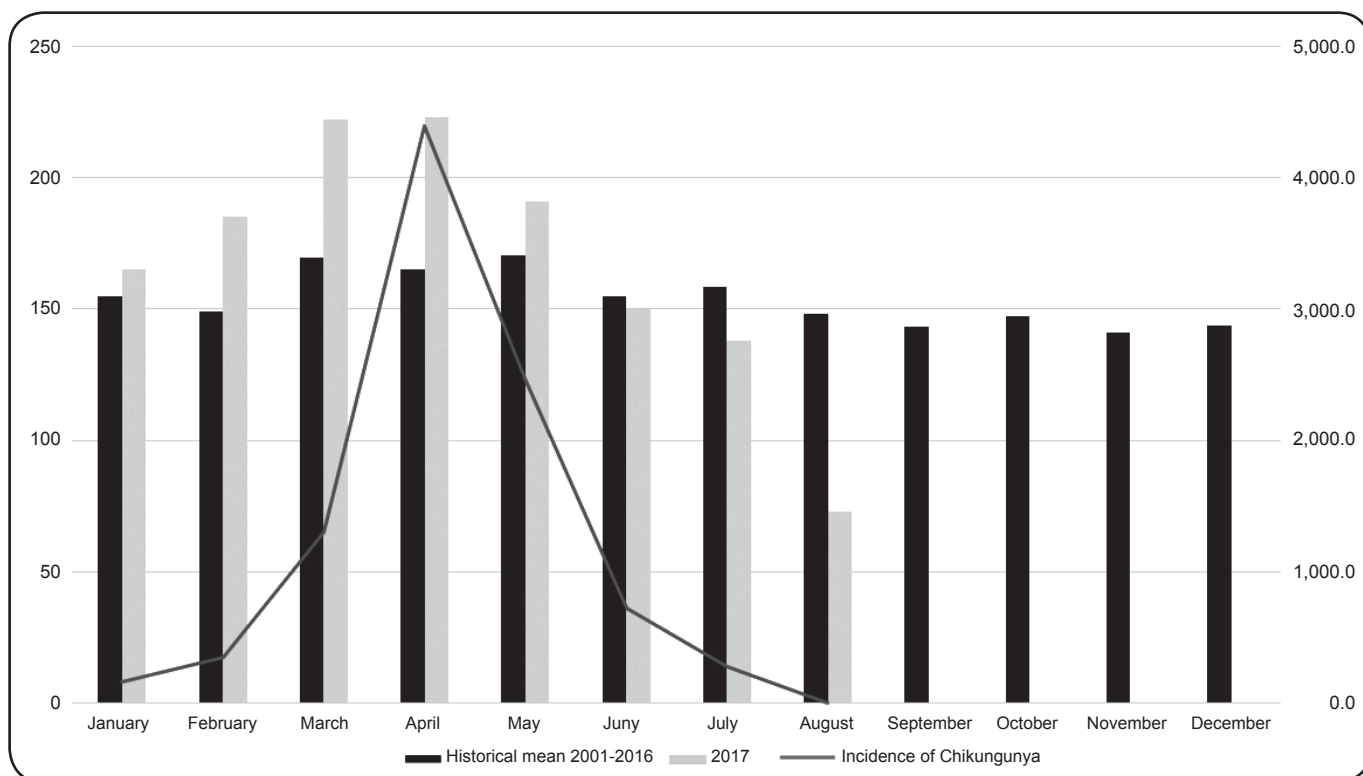
with: a) The respective monthly figures for 2017. b) The monthly incidence figures of CHIKV in the state in 2017.

Between 2001 and 2016, the historical monthly mean of deT2D-attributable deaths was 154 and remained generally stable over the years with small seasonal variability. Conversely, during the CHIKV outbreak season in 2017, the number of T2D-attributable deaths increased by 35.2% in April 2017 when compared with the historical data. This increase coincided with the peak of CHIKV incidence, with a recorded 4,394.4 cases per 100,000 inhabitants in the same month. Considering only the first 6 months of the current year, CHIKV incidence significantly increased by 17.95% (173 deaths) as compared to the historical data (**Figure 1**).

These figures are likely to be an underestimate since the 2017 statistics are still being computed. Such a sudden spike in the number of deaths attributed to a non-communicable chronic disease led us to conjecture the manifestation of an acute triggering factor with the CHIKV outbreak as an important element. Reports documenting the progression of T2D patients toward diabetic ketoacidosis, a life-threatening condition, have been found following CHIKV infection<sup>10</sup> in individuals who have had the need to scale-up anti-diabetic medication<sup>11</sup> and others who had severe CHIKV requiring hospitalization<sup>12,13</sup>. Our study highlights the need for thorough investigations of secondary causes, because of the fact that CHIKV incidence is increasing worldwide and its consequences are still not fully clarified.

With the presence of biological plausibility, the pathophysiology of this association remains elusive, by either worsening the glucose metabolism or the diabetes could modify the course of infection. A probable hypothesis is that CHIKV deregulates the balance of key cytokines, debilitating an already vulnerable immune system. For instance, the malfunctioning of type I interferon response in T2D patients could hamper response to CHIKV, thus leading to increased viral load and severity of the disease<sup>14</sup>. However, T2D-attributable deaths are difficult to associate with the CHIKV incidence due to substantial inter-individual differences in CHIKV disease progression and the inherent complexity of investigating an unpredictable disease that largely affects the elderly<sup>15</sup>. Another complication is related to CHIKV infection leading to chronic musculoskeletal symptoms in approximately 50% of cases, which are frequently treated with either nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids, whose continuous use has been associated with aggravation of T2D.

Comprehensive investigations on the interactions between CHIKV infection and T2D progression are pivotal to establish a strategic agenda and promote actions to 1) elucidate the mechanistic basis of this association; 2) enhance management protocols for at-risk subjects; 3) evaluate visual and kidney complications arising from T2D aggravation; 4) stewardship on the rational use of corticosteroids and NSAIDs; and 5) assess the impact and economic costs of T2D in CHIKV endemic zones.



**FIGURE 1:** Historical mean of attributable deaths to T2D per calendar month (2001-2016) versus corresponding data for 2017 until August\* and incidence of CHIKV virus infection in the same period in the State of Ceara. **T2D:** type-2 diabetes; **CHIKV:** Chikungunya virus \*Data collection for T2D attributable deaths performed until mid-August 2017.

**Conflict of interest**

The authors declare that there is no conflict of interest.

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