Excess mortality profile during the Asian genotype chikungunya epidemic in the Dominican Republic, 2014

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**Background:** In 2014 there was a large chikungunya epidemic in the Dominican Republic, with 539,099 reported cases and 6 deaths. Although chikungunya is considered a low-mortality disease, studies have suggested this is an underestimation. This study assessed deaths associated with the epidemic.

**Methods:** Mortality data were obtained from the National Statistics Office, the surveillance system for acute febrile illnesses, and the National Epidemiological Surveillance System. Expected all-cause mortality by age group was estimated using the years 2010–2012 as the baseline. The excess deaths were calculated as the difference between observed and expected deaths during the epidemic.

**Results:** The mortality rate increased during the chikungunya epidemic in 2014. There was a strong correlation between monthly excess of deaths and chikungunya cases (Pearson’s $r=0.89$). There was an excess of deaths ($>99\%$ confidence interval) among individuals $<5$ y and $>40$ y of age. The mortality rates were higher among the elderly. The death excess was 2853. Correcting for the estimated underreporting, there were 4952 deaths during the chikungunya epidemic (49.8 deaths/100,000 population).

**Conclusion:** This study suggests that chikungunya is an important cause of death (underlying or contributing). It is urgent to review clinical protocols and investigate the causes associated with deaths during chikungunya epidemics.

**Keywords:** aging, chikungunya virus, dominican republic, excess deaths, mortality

**Introduction**

Chikungunya is an arbovirus (arthropod-borne virus) of the genus \textit{Alphavirus} transmitted by the \textit{Aedes} mosquitoes. Chikungunya is a disease characterized by fever, intense joint pain and other symptoms such as myalgia and headache. Until the early twenty-first century it was considered a benign disease with very rare cases of death.\textsuperscript{1,2}

Since the epidemic in the Reunion Islands in 2005–2006, a large number of serious cases have been reported in the medical literature.\textsuperscript{3} Over the past 15 years, chikungunya has caused major epidemics in regions of the Indian Ocean and Pacific and continental Asia, in addition to small outbreaks in Europe.\textsuperscript{4} In December 2013, the first autochthonous chikungunya infections in the Americas were reported on the French side of Saint Martin, in the northeast Caribbean Sea. Soon after the Saint Martin cases, cases were reported throughout most of the Caribbean islands and South, Central and North America, affecting 45 countries and territories. By December 2016, $>2.4$ millions cases and 440 deaths had been reported.\textsuperscript{5}

There are three genotypes of chikungunya: Asian, Eastern/Central/Southern Africa (ECSA) and Western Africa. ECSA was disseminated throughout northeastern and southeastern Brazil and the Asian genotype spread throughout other areas of the Americas.\textsuperscript{6,7} During epidemiological week 8 (February 2014), an increase in cases of febrile illnesses accompanied with cutaneous rash and painful arthralgia were reported in the Dominican Republic. Later in April the outbreak of chikungunya was confirmed.\textsuperscript{8} By the end of 2014, 539,099 cases of chikungunya had been reported. Surveys carried out with public transport users in the metropolitan area of the capital city of Santo Domingo showed that $>60\%$ of the population had at some point displayed clinical symptoms of the disease.\textsuperscript{5,8}
Despite the large number of cases, the Dominican Republic reported only six deaths to the Pan American Health Organization (PAHO). These data draw our attention, given that recent studies show that the actual proportion of chikungunya-associated deaths is underestimated in some contexts. For example, in the Republic of Mauritius there were 743 excess deaths (59.4/100,000 population) that coincided with the epidemic curve of the chikungunya outbreaks in 2006. Mavalankar et al. estimated 2944 excess deaths in Ahmedabad (~3 800,000 inhabitants) during a chikungunya epidemic in 2006. Similar studies were recently conducted in Brazil, where we found 7231 excess deaths in the northeast region during the chikungunya epidemic in 2016, while the official surveillance system confirmed only 120 deaths. The aforementioned studies were performed during chikungunya epidemics of the ECSA genotype. The objective of this study was to evaluate excess deaths associated with the Asian chikungunya genotype epidemic in the Dominican Republic in 2014.

Materials and methods
This is a time series study in which we analysed monthly rates of all-cause mortality by age group in the Dominican Republic between 2010 and 2014. We used the years 2010–2012 to estimate the expected mortality for 2013 and 2014. Excess deaths were estimated by the difference between observed and expected monthly deaths.

Locality
The Dominican Republic is located in the centre of the Caribbean basin. The country has 9,883,486 inhabitants and an equatorial climate (Af by the Köppen climate classification).

Data collection
Population and mortality data were obtained from the official website of the National Statistics Office. Estimates of underreporting of deaths were obtained from the Dominican Republic’s Ministry of Public Health.

The number of patients with chikungunya was provided by the Directorate General of Epidemiology (DIGEPI) of the Ministry of Health. Two official databases were constructed by the DIGEPI, one based on cases reported through specific forms for chikungunya (passive surveillance) and another based on syndromic surveillance of acute febrile illnesses (AFIs) of patients who received services at health care facilities (active surveillance). The epidemic period was defined by the DIGEPI as April–November 2014 using their criteria based on a cyclic predictor model of autoregressive integrated moving average (ARIMA) for the weekly cases of patients with AFI. As not all symptomatic patients sought health services, a household survey of symptomatic patients was conducted by the DIGEPI in the cities of San Gregorio de Nigua and Santo Domingo and in the capitals of the provinces of Azua, Ocoa, La Romana and La Altagracia. These data were used to calculate the case fatality rate (CFR).

Data from suspected cases of dengue were also analysed in order to control possible interference of dengue virus occurrence due to the frequent co-circulation of these arboviruses in the country and due to the difficulty of differential diagnosis.

Statistical analysis
Age-specific death rates (ASDRs) were calculated by month by dividing the number of deaths recorded by the estimated age group population. The monthly expected deaths were calculated using the mean of the monthly ASDRs observed during 2010–2012 and projecting it to the estimated population for 2013 and 2014. The expected deaths for the epidemic period by age group were calculated using the ASDR average observed during the same period during 2010–2012. Excess deaths were the difference between observed and expected deaths. We also calculated the upper limit of the confidence interval (CI) at 99%. The age-adjusted death rate (AADR) was calculated by the direct method using equation 1 and the World Health Organization World Standard Population.

\[ \text{Age-adjusted rate} = \frac{\sum (P_k m_k)}{\sum P_k} \]

where \( P_k \) = standard population in age group k, \( m_k \) = rate in age group and k = age/sex group 0–4, 5–9, …, ≥80 y.

The Pearson correlation coefficient (r) was calculated for the monthly excess deaths during 2014 and the number of cases of acute febrile syndrome, reported chikungunya and dengue cases, with and without a 1-month lag. The CFR for chikungunya was calculated using the incidence by age group estimate from a survey conducted in the southwestern province of San Cristóbal in the municipality of San Gregorio de Nigua. This work was done with public databases and without identifying any patient, so there was no need for approval by an ethics committee.

Results
There were 2853 excess deaths. Correcting for estimated underreporting, excess deaths totalled 4952 during the chikungunya epidemic in the Dominican Republic in 2014. The excess deaths were higher among the elderly, but there were also excess deaths among children <5 y of age and adults >40 y of age above the 99% CI. Table 1 shows the population by age group estimated for 2014, as well as the number of deaths observed and the number of deaths expected for the epidemic period.

The all-age death rate associated with the chikungunya epidemic was 28.9 deaths/100,000 population; correcting for underreporting, the rate was 49.8 deaths/100,000 population. The AADR was 60.6 deaths/100,000 population and the ASDR attributable to chikungunya corrected for underreporting among individuals >80 y of age was almost 2% of the population of this age group (Table 2).

Considering the incidence by age group found in San Gregorio de Nigua, the estimated global CFR would be 0.7 deaths/1000 cases of chikungunya. Considering the correction of mortality by
underreporting CFR among those >80 y of age would be 44.7 deaths/1000 cases. In other words, 5% of those >80 y of age who presented symptoms of chikungunya during the period of the epidemic would have died (Table 2).

The Pearson’s correlation between chikungunya incidence and excess mortality was positive and significant with and without a lag of 1 month (r=0.893, p<0.0001 and r=0.712, p<0.005, respectively). There was also a strong correlation between the cases of acute febrile syndrome and the excess of monthly deaths in 2014 with and without a 1-month lag (r=0.839, p<0.001 and r=0.885, p<0.0001, respectively). A non-significant correlation was found between excess deaths and dengue cases (Table 3).

Figure 1 shows the temporal distribution of cases of AFI, chikungunya and dengue at the top. At the bottom are the monthly death excesses (above the upper limit of the 99% CI) and the absolute number of monthly deaths. Note that there is a clear temporal coincidence between the peak of acute febrile

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**Table 1.** Population and observed, expected and excess deaths by age group (Dominican Republic, 2014)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>974 068</td>
<td>758</td>
<td>535</td>
<td>501 to 569</td>
<td>223</td>
<td>385</td>
</tr>
<tr>
<td>5–9</td>
<td>973 480</td>
<td>105</td>
<td>115</td>
<td>99 to 131</td>
<td>9 to 10</td>
<td>−17</td>
</tr>
<tr>
<td>10–19</td>
<td>1 930 340</td>
<td>556</td>
<td>559</td>
<td>525 to 593</td>
<td>−3</td>
<td>−4</td>
</tr>
<tr>
<td>20–29</td>
<td>1 722 165</td>
<td>1 368</td>
<td>1 419</td>
<td>1 363 to 1 475</td>
<td>−51</td>
<td>−88</td>
</tr>
<tr>
<td>30–39</td>
<td>1 397 484</td>
<td>1 499</td>
<td>1 583</td>
<td>1 524 to 1 642</td>
<td>−84</td>
<td>−146</td>
</tr>
<tr>
<td>40–49</td>
<td>1 123 523</td>
<td>2 191</td>
<td>1 972</td>
<td>1 906 to 2 038</td>
<td>219</td>
<td>377</td>
</tr>
<tr>
<td>50–59</td>
<td>841 091</td>
<td>3 210</td>
<td>3 031</td>
<td>2 950 to 3 112</td>
<td>179</td>
<td>309</td>
</tr>
<tr>
<td>60–69</td>
<td>516 164</td>
<td>4 338</td>
<td>4 008</td>
<td>3 915 to 4 101</td>
<td>330</td>
<td>569</td>
</tr>
<tr>
<td>70–79</td>
<td>281 892</td>
<td>5 711</td>
<td>4 906</td>
<td>4 802 to 5 010</td>
<td>805</td>
<td>1 388</td>
</tr>
<tr>
<td>≥80</td>
<td>123 792</td>
<td>8 104</td>
<td>6 856</td>
<td>6 733 to 6 979</td>
<td>1 248</td>
<td>2 151</td>
</tr>
<tr>
<td>Total</td>
<td>9 883 486</td>
<td>27 840</td>
<td>24 984</td>
<td>24 318 to 25 650</td>
<td>2 856</td>
<td>4 925</td>
</tr>
</tbody>
</table>

Observed deaths above the 99% CI are in bold.

**Table 2.** Excess mortality rate associated with chikungunya epidemic, incidence rate and case fatality rate by age group, crude rate and age-adjusted rate (Dominican Republic, 2014)

<table>
<thead>
<tr>
<th>Age group (y)</th>
<th>Excess death rate (reported)</th>
<th>Excess death rate corrected to underreport</th>
<th>Attack rate (estimate based in household survey), %</th>
<th>Case fatality rate (deaths/1000 cases)</th>
<th>Case fatality rate corrected to underreport (deaths/1000 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>22.9</td>
<td>39.5</td>
<td>37</td>
<td>0.6</td>
<td>1.1</td>
</tr>
<tr>
<td>5–9</td>
<td>−1.0</td>
<td>−1.7</td>
<td>37</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>10–19</td>
<td>−0.1</td>
<td>−0.2</td>
<td>44</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>20–29</td>
<td>−3.0</td>
<td>−5.1</td>
<td>40</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>30–39</td>
<td>−6.0</td>
<td>−10.4</td>
<td>40</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>40–49</td>
<td>19.5</td>
<td>33.6</td>
<td>40</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>50–59</td>
<td>21.3</td>
<td>36.8</td>
<td>45</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>60–69</td>
<td>64.0</td>
<td>110.3</td>
<td>42</td>
<td>1.5</td>
<td>2.6</td>
</tr>
<tr>
<td>70–79</td>
<td>285.5</td>
<td>492.2</td>
<td>39</td>
<td>7.3</td>
<td>12.6</td>
</tr>
<tr>
<td>≥80</td>
<td>1012.1</td>
<td>1744.9</td>
<td>39</td>
<td>26.0</td>
<td>44.7</td>
</tr>
</tbody>
</table>

Observed mortality rate above the 99% CI in bold.
syndrome, chikungunya reported cases (confirmed and suspected) and death excess in the Dominican Republic in 2014. Figure 2 shows that the age distribution of excess mortality increases after 40 y of age during the year 2014, when the chikungunya epidemic was recorded in the country.

**Discussion**

There was a substantial increase in the overall mortality in the Dominican Republic during the year 2014. This increase was temporarily coincident with the chikungunya epidemic. There was a strong correlation between the monthly excess of deaths and monthly cases of chikungunya and acute febrile syndrome, but there was no correlation between excess deaths and the number of monthly dengue cases. The year 2014 was a year of low influenza circulation in the Dominican Republic and the rest of the Caribbean.21 The Dominican health system has not reported any other epidemiological or environmental events that could be responsible for this increase in overall mortality, so we suggest that the increase in mortality is a consequence of infections caused by chikungunya.18 Studies carried out in India, Mauritius and Brazil have already described an increase in the mortality rate during ECSA genotype chikungunya epidemics that were not adequately identified by passive surveillance systems.12–15 The present study is the first that describes excess deaths associated with the chikungunya Asian genotype. These findings weaken the theory that the increase in mortality observed in the middle of the first decade of this century was a consequence of mutations in the chikungunya ECSA lineage that could confer greater virulence.12,22

Several problems in mortality case reporting in the Dominican Republic have been observed: the cause of death is poorly reported or not well characterized, a lack of molecular infrastructure for post-mortem analysis of viral-associated illnesses, insufficient human resources to perform autopsies or case definitions of deaths that were neither hospitalized nor followed up by family care providers and underreported deaths. These aspects may help explain why even with nearly 10 million inhabitants only 6 deaths due to chikungunya were officially reported in the Dominican Republic (cause-specific death rate 0.06/100 000 population), while in Guadeloupe, with 466 000 inhabitants, reported 67 deaths by chikungunya (14.38/100 000 population) and Martinique, with 404 000 inhabitants, reported 83 deaths (20.54/100 000 population) during the same 2014 chikungunya epidemic.23 During the 2005–2006 chikungunya epidemic in the Reunion Island, with a population of 785 000, 254 deaths were of low-resource settings.

We found 4952 excess deaths associated with the chikungunya epidemic (49.8/100 000 population correcting for underreporting of deaths). Similar studies conducted in developing countries have found excess deaths during chikungunya epidemics much greater than the number of deaths reported for official epidemiological surveillance. In Brazil, we estimated 7231 excess deaths associated with chikungunya infections in 2015, while the official epidemiological surveillance system reported only 120 deaths due to chikungunya. Broadly, these findings suggest that the absence of chikungunya as a cause on death certificates could be due to the difficulty of diagnosis in low-resource settings.25

Excess mortality and CFR were higher in the elderly, as has also been described for other epidemics.3 As such, this issue cannot be neglected. A study conducted in the French Antilles showed that only 8.2% of elderly chikungunya patients had a classic clinical presentation (fever>38.5°C associated with arthralgia during the acute phase of the disease) and 32% did not have arthralgia, a hallmark of this disease.26 These aspects may hinder clinical diagnosis and, as a consequence, may lead to

<table>
<thead>
<tr>
<th>Month</th>
<th>Acute febrile illness</th>
<th>Chikungunya reported cases</th>
<th>Dengue reported cases</th>
<th>Monthly death excess (observed–expected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>10 266</td>
<td>5</td>
<td>884</td>
<td>82</td>
</tr>
<tr>
<td>February</td>
<td>11 218</td>
<td>8</td>
<td>540</td>
<td>–25</td>
</tr>
<tr>
<td>March</td>
<td>15 019</td>
<td>40</td>
<td>510</td>
<td>–56</td>
</tr>
<tr>
<td>April</td>
<td>26 218</td>
<td>282</td>
<td>429</td>
<td>–26</td>
</tr>
<tr>
<td>May</td>
<td>73 424</td>
<td>1614</td>
<td>640</td>
<td>251</td>
</tr>
<tr>
<td>June</td>
<td>185 737</td>
<td>2473</td>
<td>627</td>
<td>687</td>
</tr>
<tr>
<td>July</td>
<td>129 420</td>
<td>1418</td>
<td>479</td>
<td>683</td>
</tr>
<tr>
<td>August</td>
<td>64 274</td>
<td>329</td>
<td>308</td>
<td>501</td>
</tr>
<tr>
<td>September</td>
<td>48 621</td>
<td>111</td>
<td>356</td>
<td>285</td>
</tr>
<tr>
<td>October</td>
<td>41 562</td>
<td>98</td>
<td>604</td>
<td>291</td>
</tr>
<tr>
<td>November</td>
<td>19 010</td>
<td>51</td>
<td>448</td>
<td>184</td>
</tr>
<tr>
<td>December</td>
<td>23 814</td>
<td>37</td>
<td>373</td>
<td>208</td>
</tr>
</tbody>
</table>

Correlation with monthly death excess: \( R = 0.885 \), \( p < 0.0001 \);

Correlation with 1-month lag death excess: \( R = 0.839 \), \( p < 0.001 \).
underreporting of chikungunya deaths, as well as delaying supportive measures that could prevent deaths.\textsuperscript{12,13,26,27}

At present, chikungunya continues to be a serious problem in many parts of the world. Since August 2017, France and Italy have reported indigenous transmission of chikungunya.\textsuperscript{4} It is of vital importance to generate tools that improve our understanding of the transmission, prevention, treatment and outcomes of this disease. Vector control must be the spearhead in terms of

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Temporal distribution of cases of acute febrile illness (AFI), chikungunya fever (CHIK), dengue (DENV), monthly death excess (above the upper limit of 99% CI) and the absolute number of monthly deaths. At the top, the weekly cases of chikungunya (CHIK, black line), dengue (DENV, red line), below that acute febrile illness (AFI, black line) and upper limit of weekly cases. At the bottom is the monthly death excess (black bar, above the upper limit of the 99% CI), the absolute number of monthly deaths (black bar) and the upper limit of the 99% CI (red line).}
\end{figure}
As such, there is a need to recognize chikungunya as a potentially lethal virus and re-evaluate investment priorities in prevention.

control of the disease, especially when considering the absence of a commercial vaccine. However, the success of intervention strategies relies on social factors, such as knowledge, attitudes and perceptions of the disease, that may be deeply impacted by socio-economic factors such as education and poverty. As such, those at highest risk may have a low-risk perception or few resources to modify their risk environment.

This study has some limitations. It is an analysis based on secondary data from a low-resource setting that may have some inaccuracies. Some of the calculated excess deaths may be the result of other diseases that have seasonal patterns of occurrence similar to that of chikungunya. Other types of case-control studies could overcome these weaknesses. However, we have tried to reduce these limitations by using various sources of information and by checking for the occurrence of other diseases that could interfere with mortality in the region, including other viruses. In addition, the strong temporal correlation, the fact that no other event occurred in the region that could explain the excess deaths and similar findings during chikungunya epidemics in other countries convinced us that the excess deaths can be attributed to chikungunya.

The concept of excess deaths has been used for many years to describe mortality associated with influenza and natural disasters (hurricanes, earthquakes, hot and cold waves). We believe that this concept should be used to assess the impact of chikungunya on population health. The present study suggests that excess deaths were induced by chikungunya infection. Therefore chikungunya should no longer be considered a benign and non-fatal disease. As such, there is a need to review protocols and manuals for chikungunya fever cases and to investigate the causes associated with deaths during epidemics in order to identify clinical complications of the infection, the influence of the immune system and inflammatory markers in severe cases and the mechanisms by which previous chronic diseases worsen in the presence of chikungunya infection. Health professionals and public health authorities need to recognize chikungunya as a potentially lethal virus and re-evaluate investment priorities in prevention.

Supplementary data

Supplementary data are available at Transactions online (http://trstmh.oxfordjournals.org/).

Authors' contributions: ARRF conceived the work; ARRF, PMAE, RPR, and MRD analysed the data outputs and wrote. All authors read and approved the final manuscript.

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Competing interest: None declared.

Ethical approval: Not required.

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