Clinical profile of dengue in the elderly using surveillance data from two epidemics

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ABSTRACT

Background: Population aging and mobility have increased the exposure of elderly individuals to dengue. This study evaluated the clinical features of dengue in the elderly during the epidemic (2008 and 2012) and interepidemic (2009 and 2010) periods.

Methods: This cross-sectional study was based on dengue surveillance data from Rio de Janeiro, Brazil: 2008 (n=31,210), 2009–2010 (n=2,884), and 2012 (n=30,773). The analysis was stratified by age group (<60 and ≥60 years).

Results: Case-fatality rates were higher in the elderly. In 2008, elderly individuals were found to be more prone to hematuria and thrombocytopenia.

Conclusions: These results can improve the understanding of dengue in elderly individuals who live in or travel to tropical regions.

Keywords: Dengue. Elderly. Disease attributes. Public health surveillance.

Dengue in the Americas primarily affects adults1,2. Population aging has led to an increase in the proportion of elderly residents in tropical areas, increasing their vulnerability to dengue infection. The elderly are frailer and more prone to developing complications from diseases, which can be associated with physiological factors, immune alterations, comorbidities, or external factors, such as environmental conditions in the place of residence. Compared to younger individuals, elderly persons tend to remain hospitalized longer, and their comorbidities can aggravate the clinical condition of dengue3. Atypical presentations of dengue in the elderly can hinder the diagnosis of this arboviral infection3. The typically low frequency of mucosal bleeding in the elderly, in addition to physiological factors and frequent comorbidities in this age group, can be associated with the use of multiple medications4,5.

Early identification and timely treatment of dengue cases with the potential to evolve with severity are necessary to reduce morbidity and mortality from this disease6. However, although elderly individuals represent the fastest growing population group worldwide and are potentially more susceptible to dengue infection, there are few specific studies on the clinical profile of dengue in this population. Most studies have assessed small hospital samples in Asia and the Americas without identifying the viral serotype7. Few existing studies have employed widely varying methods, which affects the comparability of their results.

In Brazil, dengue is a mandatorily reported disease, the cases of which are periodically recorded in the Information System on Diseases of Notification (SINAN8), which allows a dynamic
diagnosis of the occurrence of events in the population, helping
to draft appropriate public health strategies.

Two major dengue epidemics occurred in the city of Rio
de Janeiro in 2008 and 2012, and the predominant circulating
serotypes were DENV-2 and DENV-4, respectively. Dengue
classification in these two epidemics was based on national
manuals in force at the time. In 2008, dengue was classified by
the WHO as dengue fever (DF) and dengue hemorrhagic fever (DHF);
Brazil included a new category, dengue with complications (DC),
for cases that evolved with severity or caused mortality but failed
to meet the clinical and laboratory criteria for DHF. In the 2012
epidemic, although the new WHO classification, namely DF with
or without warning signs and severe dengue, was already in force
(2009), Brazil still used the classification from the national manual.

However, none of the manuals presented specificities related to
clinical management in the elderly, probably because of the small
number of studies in this population subgroup, particularly in the
Americas. The current study aimed to assess the clinical features
of dengue in the elderly in two epidemics in the city of Rio de
Janeiro in 2008 and 2012, when the main circulating serotypes
were DENV-2 and DENV-4, respectively. Moreover, we compared
the potential clinical differences or similarities observed among
elderly patients during the 2008 epidemic with those during the
interepidemic period (2009-2010).

A cross-sectional descriptive study was conducted according
to the guideline REporting studies Conducted using Observational
 Routinely collected health Data – RECORD16, based on the available
information in the Information System on Diseases of Notification
(SINAN). Rio de Janeiro is the second largest Brazilian city in
both demographic and economic terms, with a population of
6,320,446 in 2010, located on the seacoast in the southeast of the
country with great tourist potential, having hosted several major
international events.

This study included dengue cases reported to SINAN in the
resident population of the city of Rio de Janeiro. Confirmatory
criteria for dengue were those of the Brazilian Ministry of
Health9, namely viral RNA detection by reverse transcriptase
polymerase chain reaction (RT-PCR) and capture enzyme-linked
immunosorbent assay (ELISA) for IgM antibodies or IgM or IgG
seroconversion (ELISA) in paired samples. In the absence of
laboratory confirmation, a clinical-epidemiological criterion was
applied, defined as a clinical picture consistent with dengue, an
epidemiological link to a laboratory-confirmed dengue case, and
the absence of other differential diagnoses consistent with the
patient’s age group5. To avoid selection bias, we opted to include
cases confirmed by the clinical-epidemiological criterion because,
during epidemics, most cases with laboratory confirmation were
those evolving to severe forms, such as DHF. The exclusion criteria
were patients without information on age, place of residence, or
clinical variables.

In 2008 and 2012, 124,037 and 178,805 dengue cases were
reported in the city of Rio de Janeiro, respectively. Of the 302,842
reports in this sample, 51,172 were ruled out as dengue, 809 had
no information on residence, 154 resided outside the city of
Rio de Janeiro, and 65 individuals were 100 years or older, totaling
250,642 (120,381 in 2008 and 130,261 in 2012). Of these, 61,983
reports had complete information on clinical characteristics (31,210
in 2008 and 30,773 in 2012).

The following clinical and sociodemographic variables
were analyzed: age (less than 60 vs. 60 years or older), sex,
clinical classification (dengue fever, dengue with complications,
and dengue hemorrhagic fever) according to the prevailing
classification at time7, and evolution (cure/death). For cases
classified as DC or DHF, we evaluated the presence of hemorrhagic
manifestations, signs of plasma leakage, and platelet count nadir
(per mm3).

The analyses were stratified according to the age group.
Due to the descriptive cross-sectional design and sample size,
the association between qualitative variables and the clinical
form (dengue fever, dengue with complications, and dengue
hemorrhagic fever) was based on the comparison of absolute and
relative frequencies, considering the level of statistical significance
(p <0.01), or differences of 10 percentage points for comparisons
in strata with a small number of cases. Platelet count is described
in values of median and interquartile range. Single and multiple
regression analyses were not performed because clinical predictors,
such as bleeding and plasma leakage, are part of the outcome
definition criterion (clinical form), which would cause a common
source bias. Statistical analyses were performed using the SPSS
version 16.

The study used the municipal database of SINAN, obtained
from the Rio de Janeiro Municipal Health Department, following
approval by the Institutional Review Boards of the National School
of Public Health Sergio Arouca of the Oswaldo Cruz Foundation
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Department (CAAE 58814516.2.3001.5279).

The current study included 64,867 cases with complete
information on clinical characteristics, 31,210 reports from 2008,
2,884 from 2009 to 2010, and 30,773 from 2012, of which 2,328
(7.5%), 213 (7.4%), and 2,788 (9.1%) were elderly individuals,
respectively. In the epidemic years, there were more elderly
women. In both the epidemic and interepidemic periods, elderly
patients had less schooling on average than younger patients
(p < 0.001). The criteria used for dengue diagnosis were mostly
clinical-epidemiological in the epidemic in 2008 and laboratory
in 2012, and the elderly had a higher proportion of laboratory
confirmation (p <0.001) (Table 1).

The epidemic in 2008 was more severe, as evidenced by the
higher proportion of cases of DC, DHF, and deaths (Table 1). In
2008, of the 902 cases classified as DHF, 741 had information on
the level of severity, 90 of which presented with dengue shock
syndrome (< 60 years: n=79, 11.5%; ≥ 60 years: n=11, 21.2%). In
2012, only 94 cases evolved to DHF, 16 of 81 with information
on level of severity evolved to dengue shock syndrome (< 60:
≥ 60: n=4, 50%); in the interepidemic period, they represented
7 of 85 DHF cases (< 60: n=5, 6.3%; ≥ 60: n=2, 33.3%) (data not shown).

Although the proportion of cases with greater severity was
similar across age groups, case fatality in the elderly was higher
during both epidemics, approximately seven-fold in 2008
and five fold in 2012 when compared to younger individuals (Table 1).

In 2008, elderly patients classified as having dengue with
complications showed a higher proportion of petechiae (p=0.012)
and hematuria (p<0.001), whereas mucosal bleeding was less
evident. In both age groups, plasma leakage was more frequent
than bleeding, with hemocoagulation as the main sign, followed
by cavitary effusions, which was less frequent in individuals 60 years or older. The median platelet nadir did not differ between age groups (Table 2 and Table 3).

Our study showed that case fatality from dengue was higher in the elderly, especially in 2008, the year with the most severe epidemic, probably due to the circulation of the DENV-2 serotype 11. In cases that developed complications in 2008, the elderly had a higher proportion of petechiae and hematuria, while plasma leakage was less frequent.

Higher fatality from dengue in the elderly has also been a frequent finding in other studies 6,12-14 and appears to be related to the senescent immune system and common comorbidities in this population group. In the presence of dengue infection, in vitro experimental studies have demonstrated that both newborns and the elderly exhibit physiological immunosuppression, resulting in a lower inflammatory response and control of the infection 15.

Comorbidities such as hypertension, diabetes, and cardiovascular, renal, and chronic obstructive pulmonary diseases 5,6,14 are commonly associated with polypharmacy, which can influence the correct diagnosis and clinical management of the disease, thus leading to more severe evolution and death 7,11.

The epidemic in 2008 had a higher proportion of severe cases, possibly due to the predominant circulation of the DENV-2 serotype. A meta-analysis of 20 studies showed that infection with this serotype increased the odds of developing dengue shock syndrome by 66% 11.

Our results suggest that the distribution of complications and DHF in the elderly was similar to that in younger patients, contrary to other studies showing a higher frequency of DHF in the elderly 6,12. Although the frequency of bleeding was similar between the age groups, our findings showed that the elderly who developed complications in 2008 had higher proportions of petechiae and hematuria.

In both epidemics, hemoconcentration was the principal manifestation of plasma leakage, with no difference between the age groups. Cavitary effusions were less frequent in elderly patients who developed complications in 2008 had higher proportions of DHF:

**TABLE 1:** Sample's description (N=64,867).

| Variables          | 2008 (n=31,210) | 2009-2010 (n=2,884) | 2012 (n=30,773) |
|--------------------|-----------------|---------------------|-----------------|
|                    | < 60 years | ≥ 60 years | ** | < 60 years | ≥ 60 years | ** | < 60 years | ≥ 60 years | ** |
| Sex                |          |          |   |          |          |   |          |          |   |
| Female             | 15556   | (53.9)  | 1.400 | (60.1)  | 1247   | (46.7)  | 116 | (54.5)  | 14973  | (53.5)  | 1668 | (59.8)  |
| Male               | 13326   | (46.1)  | 928  | (39.9)  | 1423   | (53.3)  | 97  | (45.5)  | 13012  | (46.5)  | 1120 | (40.2)  |
| Color              |          |          |   |          |          |   |          |          |   |
| White              | 4324    | (48.6)  | 412  | (68.3)  | 472    | (55.1)  | 45  | (73.8)  | 5016   | (44.8)  | 538  | (53.8)  |
| Other              | 4566    | (51.4)  | 191  | (31.7)  | 385    | (44.9)  | 16  | (26.2)  | 6178   | (55.2)  | 462  | (46.2)  |
| Education          |          |          |   |          |          |   |          |          |   |
| Primary            | 4289    | (49.9)  | 303  | (88.1)  | 307    | (38.2)  | 17  | (58.6)  | 2713   | (40.8)  | 221  | (61.6)  |
| Secondary or +     | 671     | (7.8)   | 32   | (9.3)   | 198    | (24.7)  | 11  | (37.9)  | 2289   | (34.4)  | 138  | (38.4)  |
| Not applicablea    | 3641    | (42.3)  | 9    | (2.6)   | 298    | (37.1)  | 1   | (3.4)   | 1653   | (24.8)  | -    | -       |
| Diagnostic         |          |          |   |          |          |   |          |          |   |
| Laboratory         | 9858    | (34.1)  | 1035 | (44.5)  | 981    | (37.1)  | 109 | (52.4)  | 19638  | (70.2)  | 2.084 | (74.7)  |
| Clinical           | 19024   | (65.9)  | 1293 | (55.5)  | 1661   | (62.9)  | 100 | (47.8)  | 8347   | (29.8)  | 704  | (25.3)  |
| Epidemiological    |          |          |   |          |          |   |          |          |   |
| Evolution          |          |          |   |          |          |   |          |          |   |
| Cure               | 21272   | (99.5)  | 1.622| (96.7)  | 1777   | (99.5)  | 127 | (96.2)  | 25127  | (99.9)  | 2.476 | (99.4)  |
| Death dengue       | 101     | (0.5)   | 55   | (3.3)   | 8      | (0.4)   | 3   | (2.3)   | 22     | (0.1)   | 12   | (0.5)   |
| Death others       | 1       | (0.0)   | 1    | (0.0)   | 1      | (0.1)   | 2   | (1.5)   | 2      | (0.0)   | 4    | (0.2)   |
| Classification     |          |          |   |          |          |   |          |          |   |
| Dengue fever       | 20423   | (70.8)  | 1.607| (69.1)  | 2161   | (80.9)  | 167 | (78.4)  | 27478  | (98.4)  | 2.726 | (98.0)  |
| Dengue with        | 7594    | (26.3)  | 660  | (28.4)  | 422    | (15.8)  | 39  | (18.3)  | 371    | (1.3)   | 46   | (1.7)   |
| complication       | 844     | (2.9)   | 58   | (2.5)   | 88     | (3.3)   | 7   | (3.3)   | 85     | (0.3)   | 9    | (0.3)   |

P-value of χ² Pearson: *p< 0.001, **p<0.01, ***p<0.05; P-value of Fisher’s test: *p<0.001, **p<0.01; aChildren; bDHF: Dengue hemorrhagic fever.
TABLE 2: Signs of Dengue with Complications (DC) and Dengue Hemorrhagic Fever (DHF).

| Variables         | 2008 (n=9,156) |       | 2009-2010 (n=556) |       |
|-------------------|----------------|-------|-------------------|-------|
|                   | DC             | DHF   | DC                | DHF   |
|                   | < 60           | ≥ 60  | < 60              | ≥ 60  |
|                   | n (%)          | P     | n (%)             | P     |
| Hemorrhages       | 8224           | 2452  | (36.3)            | 169   |
|                   | 169 (30.0)     | **    | 56 (96.6)         |       |
| Epistaxis         | 3531           | 683   | (27.0)            | 29    |
|                   | 29 (16.9)      |       | 9 (17.0)          |       |
| Gums              | 3516           | 625   | (24.8)            | 26    |
|                   | 26 (15.2)      | **    | 19 (10.2)         |       |
| Metrorrhagia      | 3485           | 255   | (10.2)            | 5     |
|                   | 5 (3.0)        |       | 1 (1.9)           |       |
| Petechiae         | 3545           | 877   | (34.5)            | 76    |
|                   | 76 (43.9)      | ***   | 31 (58.5)         |       |
| Hematuria         | 3473           | 93    | (3.7)             | 32    |
|                   | 32 (12.8)      |       | 18 (11.4)         |       |
| Gastrointestinal  | 3493           | 433   | (17.3)            | 32    |
|                   | 32 (18.9)      |       | 19 (11.4)         |       |
| Tourniquet test + | 3041           | 186   | (7.2)             | 14    |
|                   | 14 (7.9)       |       | 9 (5.6)           |       |
| Plasma leakage    | 7957           | 3715  | (56.7)            | 223   |
|                   | 223 (42.3)     | *     | 138 (40.9)        | 10    |
| Evidenced by      |                |       |                   |       |
| Hemoconcentration | 3599           | 2875  | (77.4)            | 202   |
|                   | 202 (90.6)     |       | 104 (75.4)        | 10    |
| Cavitary effusions| 1068           | 773   | (20.8)            | 16    |
|                   | 16 (7.2)       |       | 120 (80.4)        | 1    |
| Hypoproteinemia   | 119            | 67    | (1.8)             | 5     |
|                   | 5 (2.2)        |       | 3 (5.6)           |       |
| Nadir Platelet (*1000/mm$^3$) | 8462 | 34 (21.52) | 29 (19.45) | 25 (16.39) | 10 (13.37) | 93 | 43.5 (24.89) | 43.5 (23.78) | 28.5 (15.492) | 33 (30.44) |

*Total valid cases; **P-value of Pearson’s χ2 test: *p<0.001, **p<0.01, ***p<0.05; *P-value of Fisher’s test: *p<0.001, **p<0.01; *median (interquartile interval).

TABLE 3: Characteristics of Dengue with Complications (DC) and Dengue Hemorrhagic Fever (DHF), 2012 (n=511).

| Variables               | n$^a$ | DC                  |       | DHF                  |       |
|-------------------------|-------|---------------------|-------|---------------------|-------|
| Hemorrhages (yes)       | 451   | 152 (34.6)          | 18     | (40.9)              | 80     |
|                         |       | (94.1)              |       | 10 (100)            |       |
| Epistaxis               | 245   | 31 (20.8)           | 1 (5.9)| 20 (7.8)            | 1 (14.3)|
| Bleeding gums           | 245   | 34 (22.8)           | 2 (11.8)| 17 (23.6)          | -       |
| Metrorrhagia            | 244   | 15 (10.1)           | -      | 9 (12.5)            | -       |
| Petechiae               | 248   | 61 (41.5)           | 4 (23.5)| 29 (38.2)          | 3 (37.5)|
| Hematuria               | 243   | 18 (12.2)           | 2 (11.8)| 5 (7.0)            | 1 (14.3)|
| Gastrointestinal        | 244   | 27 (18.2)           | 4 (23.5)| 11 (15.3)          | 1 (14.3)|
| Tourniquet test +       | 232   | 24 (17.5)           | 10 (58.2)| 20 (28.2)       | 3 (42.9)|
| Plasma leakage (yes)    | 423   | 139 (47.3)          | 22 (53.7)| 65 (81.2)        | 7 (87.5)|

*Total valid cases; Non-significant statistical differences Pearson’s chi-square or Fisher’s exact test (p>0.05); Fisher’s exact test p<0.01 in DC strata.

The elderly have used hospital samples and may present a selection bias. In addition, elderly individuals tend to present with dehydration and lower fluid intake during an illness, which can combine with immune senescence to clinically mask plasma leakage 15. To our knowledge, this is the first study to assess the clinical profile of dengue in the elderly in a large population-based sample of dengue cases across the Americas.
clinical variables and the criteria used for dengue definition. Our study sample was older than that of the entire database. While the clinical-epidemiological criterion could lead to a classification bias, the exclusion of cases without laboratory confirmation could produce a selection bias, particularly in epidemic periods when resources are depleted. In addition, the high positive predictive value for dengue diagnosis associated with a higher incidence tends to minimize classification errors from the case definition criteria.

We conclude that in both epidemic and interepidemic years, older dengue patients were at larger risk of mortality, but presented with less evidence of plasma leakage. Therefore, physicians should be alert when performing fluid replacement in these cases, because capillary permeability may be altered, even if clinical evidence is lacking. Another finding in this study was the higher frequency of petechiae and hematuria in the elderly in 2008, which was probably related to the DENV-2 serotype\(^\text{11}\). New prospective studies with population-based samples would improve our understanding of the clinical evolution of dengue in the elderly, with special attention paid to elucidating possible differences in the mechanisms and clinical manifestations related to plasma leakage.

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