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Factors associated with death from dengue in the state of Minas Gerais, Brazil: historical cohort study

Kauara Brito Campos[1,2], Frederico Figueiredo Amâncio[1,3], Valdelaine Etelvina Miranda de Araújo[3,4] and Mariângela Carneiro[1,3]

1 *Programa de Pós-Graduação em Ciências da Saúde, Infectologia e Medicina Tropical, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil*
2 *Coordenação Geral do Programa Nacional de Controle da Dengue, Departamento de Vigilância das Doenças Transmissíveis, Secretaria de Vigilância em Saúde, Ministério da Saúde, Brasília, Brazil*
3 *Laboratório de Epidemiologia de Doenças Infecciosas e Parasitárias, Departamento de Parasitologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil*
4 *Secretaria Municipal de Saúde, Prefeitura de Belo Horizonte, Belo Horizonte, Minas Gerais, Brazil*

Abstract

OBJECTIVES To analyse the clinical and epidemiological profiles of dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS) and complicated dengue cases and deaths from 2008 to 2010 that occurred in the state of Minas Gerais, south-eastern Brazil, and to identify factors associated with death from dengue.

METHODS Historical cohort study using data from the Brazilian Information System for Notifiable Diseases. A descriptive analysis of the DHF, DSS and complicated dengue cases and deaths was performed; the incidence, mortality and case-fatality rates were estimated. Logistic regression analysis was used to identify factors associated with death from dengue. Comorbidities were not included in the analysis because the information system does not contain such data.

RESULTS During the study period, 2214 DHF, DSS and complicated dengue cases were reported, including 156 deaths. The annual case-fatality rates for DHF/DSS and complicated dengue cases in the period of 2008–2010 were 7.3%, 4.8% and 7.9%, respectively. The factors associated with death from dengue included residence in a municipality with a population of fewer than 100 000 inhabitants [odds ratio (OR) 2.46; 95% confidence interval (CI) 1.71–3.55], age over 65 years (OR 3.05; 95% CI 1.99–4.68) and plasma leakage (OR 1.69; 95% CI 1.16–2.46).

CONCLUSIONS The results support the importance of plasma leakage as a warning sign associated with death from dengue as well as the signs and symptoms that allow the diagnosis of DHF. Moreover, our findings suggest that increased attention is necessary for individuals over 65 years of age and in municipalities with populations under 100 000 inhabitants to ensure a better quality of care during the management of severe patients of dengue in these locations. Differences in the interpretation of the DHF definition have hindered the comparison of data from different countries; it can improve from the WHO 2009 dengue classification.

keywords dengue fever, dengue haemorrhagic fever, dengue shock syndrome, plasma leakage, factors associated with death, case-fatality rate, Brazil

Introduction

Dengue fever, an acute febrile disease transmitted by *Aedes* mosquitoes, is the most important vector-borne viral disease in the world. There are four closely related dengue virus serotypes. The four different serotypes cause a spectrum of clinical manifestations ranging from mild disease to severe cases, manifesting as bleeding, plasma leakage and shock (World Health Organization, WHO 1997; Gubler 1998).

In the past century, Asian countries were most affected by the disease; however, in recent years, there has been a dramatic increase in the rate of dengue transmission in the American continent, resulting in significant numbers of cases and deaths (WHO 1997). Brazil currently accounts for approximately 70% of the cases reported in the Americas (PAHO 2008). The cocirculation of different serotypes in most Brazilian states has increased the number of dengue haemorrhagic fever (DHF), dengue shock syndrome (DSS) and complicated dengue cases and

the rate of hospitalisation (Siqueira *et al.* 2005). Despite the efforts of the Brazilian government to control the vector and reduce morbimortality in the country, the case-fatality rate reached over 5% in recent years (PAHO 2007).

The state of Minas Gerais in the south-eastern region of Brazil had its first dengue outbreak in 1998, with a total of 147 418 reported cases. Beginning in 2006, with the cocirculation of serotypes DENV-1, 2 and 3, significant increases in viral transmission occurred. Approximately 79 000 cases were reported in 2008, 83 000 cases were reported in 2009, and 260 000 cases were reported in 2010 (SES-MG 2009). In 2010, Minas Gerais had the highest number of reported dengue cases of all of the Brazilian states (Brazil 2011).

Although several articles from Asian countries describe the factors associated with death from dengue (Lee *et al.* 2012; Huy *et al.* 2013; Thein *et al.* 2013; Runge-Ranzinger *et al.* 2014), there is a lack of information about severe cases in Brazil and in the state of Minas Gerais, where primarily adults are affected, but all age groups are still very susceptible to the disease (Pessanha *et al.* 2010).

The aims of this study were to analyse the clinical and epidemiological profiles of DHF, DSS and complicated cases and deaths from dengue that occurred between 2008 and 2010 in the state of Minas Gerais, Brazil, and to identify risk factors associated with death from dengue.

Methods

Minas Gerais is located in south-eastern Brazil. It is Brazil's fourth largest state (586 528 km^2) and has the second largest population (19 597 330 inhabitants). The 853 municipalities of Minas Gerais are divided into 28 politic-administrative regions (Brazilian Institute of Geography and Statistics – Instituto Brasileiro de Geografia e Estatística – IBGE 2010).

In this historical cohort, the study population consisted of all DHF, DSS and complicated dengue cases of the residents of Minas Gerais who were registered in the Brazilian Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação-SINAN) from 1 January 2008 to 31 December 2010. All cases confirmed by laboratory or clinical and epidemiological criteria were included.

Patients were classified as having DHF or DSS according to the WHO (1997) criteria. Complicated dengue cases comprised all cases that did not fulfil the DHF/DSS criteria but had at least one of the following clinical manifestations: cardiac dysfunction, liver failure, neurological manifestation, gastrointestinal bleeding, plasma leakage manifested as pleural effusion, pericardial effusion and/or ascites, thrombocytopaenia <50 000/mm^3 and leucopaenia <1000/mm^3 (Brazil 2009b).

The secondary data were obtained from notification forms, epidemiological investigations and the medical records of severe cases available from the following sources: the Brazilian Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação-SINAN), the Brazilian Mortality Information System (Sistema de Informações sobre Mortalidade-SIM) and the State Health Department of Minas Gerais. The population data of the 853 municipalities of Minas Gerais state were obtained from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro de Geografia e Estatística – IBGE 2010).

According to the Brazilian Ministry of Health recommendations (Brazil 2009a), all suspected dengue deaths are investigated by the local epidemiology service (Municipal Health Department), which is supported by the regional epidemiology service (State Health Department); standardised forms were used to record this information.

Data analysis

The databases were prepared using the Microsoft Office Starter 2010 EXCEL® software, and the data analysis was performed using STATA version 11.0 (Stata Corp., College Station, TX, USA). The descriptive analysis included the frequencies of categorical variables and the rates of incidence, mortality and case-fatality. Furthermore, we calculated the intervals between symptom onset, hospitalisation and death. Thematic maps were designed using TABWIN software version 3.6b (http://www2.datasus.gov.br/DATASUS/index.php?area=060805&item=1).

After evaluating the data consistency, the following variables were retained in the study: age, gender, municipality of residence, hospitalisation, patient outcomes, final classification (DHF, DSS or complicated dengue case), bleeding manifestations, signs of plasma leakage and confirmation criteria (laboratory or clinical and epidemiological).

Univariate and multivariate logistic regression analyses were used to evaluate the associations among the demographic and clinical variables with the occurrence of death from dengue. Variables with more than two categories were transformed into dummy variables. With the aim of avoiding selection bias and to allow for better adjustment of the models, the 'unknown' category was used to represent missing data on each of the variables studied. However, variables with high percentages of missing data were excluded from the final models.

The variables associated with death from dengue at a significance level of 0.25 in the univariate logistic regression analyses were included in the multivariate analysis using the backward selection procedure. Among the variables presenting collinearity, the final model included those that better explained the occurrence of death from dengue. Only the variables showing significant associations ($P < 0.05$) with death from dengue remained in the final model. The strength of association was determined by an odds ratio (OR) and a 95% confidence interval (CI). A likelihood ratio test was used to define the final model.

This study was approved by the Minas Gerais Federal University Ethical Review Board). Informed consent was not obtained from the patients, as this was a retrospective study based on secondary data and did not use patient-identifying data (e.g. name, address, name of parents or guardians).

Results

From 2008 to 2010, there were 281 159 dengue cases in Minas Gerais. Among those cases, 2214 were classified as DHF, DSS or complicated dengue, including 156 deaths and 2058 survivors. Both the highest number of dengue cases and the highest number of DHF, DSS and complicated dengue cases were reported in 2010 (Table 1). Among the 2058 dengue cases that survived, 1733 (84.2%) were classified as complicated dengue and 325 (15.8%) were classified as DHF/DSS. Among the 156 deaths, 97 (62.2%) were classified as complicated dengue and 59 (37.8%) were classified as DHF/DSS. Males comprised 77 (49.4%) of the patients who died (Table 2). Among the 97 deaths classified as complicated dengue, 40.2% were not classified as DHF/DSS because of the absence of just one of the following criteria: thrombocytopaenia (≤100 000/mm^3), haemorrhagic manifestations, plasma leakage or a specific laboratory confirmation.

The median time interval from illness onset to hospital admission was 5 days. In those patients who died, the median duration from illness onset to death was 8 days. Of the patients who died, 135 (86.5%) were laboratory-confirmed cases: 123 by IgM antibodies, seven by autopsy (identification of DENV antigen by immunohistochemical microscopy) and five by PCR (DENV-2 was identified in three patients, DENV-1 and DENV-3 in one patient each). Comorbid conditions were reported for 59 (37.8%) of the deaths; the most frequent were hypertension (11 cases), cardiovascular diseases (9 cases), diabetes mellitus (6 cases), Alzheimer's disease (5 cases) and chronic renal disease (3 cases).

Table 1 Dengue cases in Minas Gerais, Brazil, from 2008 to 2010

	Year		
Variable	2008	2009	2010
Number of dengue cases	42 347	48 546	190 266
Incidence rate of dengue cases (per 100 000)	211.4	242.3	949.7
Number of DHF, DSS and complicated dengue cases	261	564	1389
Percentage of DHF, DSS and complicated cases*	0.6	1.2	0.7
Number of dengue deaths	19	27	110
Case fatality rate (%)†	7.3	4.8	7.9

Sources: Brazilian Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação-SINAN) and the Minas Gerais State Health Department.
DHF, dengue haemorrhagic fever; DSS, dengue shock syndrome.
*Number of DHF, DSS and complicated cases/number of dengue cases.
†Number of deaths from dengue/number of DHF, DSS and complicated dengue cases.

The northern and southern regions reported the lowest incidence rates of DHF, DSS and complicated dengue cases (Figure 1a) and the lowest mortality rates (Figure 1b). We observed heterogeneous distributions of incidence and mortality rates around the state, with an overlap of the areas with higher incidence and higher mortality. Of the 156 dengue deaths, 79 (50.6%) occurred in municipalities with populations of <100 000 inhabitants.

The age groups with the highest incidence rates of DHF/DSS and complicated dengue cases were over 65 years (20.2 cases per 100 000 inhabitants), 50–65 years (14.9 cases per 100 000 inhabitants) and 6–14 years (12.9 per 100 000 inhabitants). The case-fatality rate for dengue was higher in the extreme age groups: those under 5 years of age (8.5%) and those over 65 years of age (16.0%). The lowest case-fatality rate (4.6%) was observed in the 6- to 14-year-old age group (Figure 2).

Univariate and multivariate analyses

The factors associated with death ($P < 0.05$) in the univariate logistic regression analyses included residing in a municipality with a population of fewer than 100 000 inhabitants, age over 65 years, plasma leakage, cases reported as DHF/DSS, laboratory-confirmed cases, the presence of epistaxis and the presence of gastrointestinal bleeding (Table 2).

Table 2 Demographic and clinical variables according to death from dengue, Minas Gerais, Brazil, 2008–2010 (univariate analysis, $n = 2214$*)

	Death from dengue						
	Yes		No				
Variable	*n*	(%)	*n*	(%)	Odds ratio	95% CI	*P*
Population of the municipality							
≥100 000 ($n = 1500$)†	77	49.4	1423	69.1	1.00		
<100 000 ($n = 714$)	79	50.6	635	30.9	2.30	1.66–3.19	0.000
Sex							
Male ($n = 1070$)	77	49.4	993	48.3	1.00		
Female ($n = 1144$)	79	50.6	1065	51.7	0.96	0.69–1.32	0.789
Age group (years)							
0–5 ($n = 141$)	12	7.7	129	6.3	1.00		
6–14 ($n = 366$)	17	10.9	349	17.0	0.52	0.24–1.13	0.098
15–49 ($n = 979$)	52	33.3	927	45.0	0.60	0.31–1.16	0.130
50–65 ($n = 428$)	27	17.3	401	19.5	0.72	0.36–1.47	0.430
>65 ($n = 300$)	48	30.8	252	12.2	2.00	1.05–3.99	0.043
Plasma leakage	64	41.0	523	25.4	1.98	1.40–2.81	0.000
Cavitary effusion ($n = 290$)	25	16.0	265	12.9	1.00		
Haemoconcentration ($n = 241$)	28	17.9	213	10.3	1.39	0.79–2.46	0.253
Hypoproteinaemia ($n = 38$)	7	4.5	31	1.5	2.39	0.96–5.99	0.062
Two or more evidence of plasma leakage ($n = 12$)	2	1.2	10	0.4	2.12	0.44–10.22	0.349
Haemorrhagic manifestations	89	57.1	1162	56.5	1.07	0.14–8.24	0.946
Epistaxis ($n = 1202$)	31	19.9	282	13.7	1.63	1.03–2.59	0.036
Gingival bleeding ($n = 1184$)	21	13.5	242	11.8	0.88	0.51–1.53	0.652
Haematuria ($n = 1170$)	9	5.8	115	5.6	1.01	0.49–2.08	0.971
Spontaneous petechiae ($n = 1206$)	40	25.6	575	27.9	0.89	0.61–1.29	0.537
Positive tourniquet test ($n = 1027$)	31	19.9	421	20.5	0.96	0.59–1.56	0.865
Gastrointestinal bleeding ($n = 1195$)	27	89.2	224	10.8	1.74	1.08–2.81	0.022
Hospitalisation ($n = 2034$)	136	82.3	1693	87.2	1.98	0.95–4.10	0.066
Case confirmation criteria							
Clinical epidemiological ($n = 613$)	21	13.5	592	28.8	1.00		
Laboratory ($n = 1601$)	135	86.5	1466	71.2	2.60	1.62–4.15	0.000
Case classification							
Dengue with complications ($n = 1830$)	97	62.2	1733	84.2	1.00		
DHF/DSS ($n = 384$)‡	59	37.8	325	15.8	3.24	2.29–4.58	0.000

Sources: Brazilian Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação-SINAN) and Minas Gerais State Health Department.
*2214 DHF, DSS and complicated dengue cases, including 156 deaths and 2058 survivors.
†Number of individuals for which the variable was recorded (yes or no).
‡DHF/DSS: dengue haemorrhagic fever or dengue shock syndrome.

In the final model resulting from the multivariate logistic regression analysis (Table 3), the factors associated with death from dengue ($P < 0.05$) included residing in a municipality with a population of <100 000 inhabitants (OR 2.46; 95% CI 1.71–3.55), age over 65 years (OR 3.05; 95% CI 1.99–4.68), plasma leakage (OR 1.69; 95% CI 1.16–2.46), laboratory confirmation (OR 2.34; 95% CI 1.34–4.07) and cases classification as DHF/DSS (OR 3.00; 95% CI 2.02–4.47).

Discussion

The case-fatality rate for DHF/DSS and complicated dengue cases in the state of Minas Gerais was high during the study period. While the WHO has suggested that the case-fatality rate for DHF/DSS may be lower than 1% (WHO 2010), the results showed that the case-fatality rate for DHF/DSS and complicated cases ranged from 4.8% (in 2009) to 7.9% (in 2010).

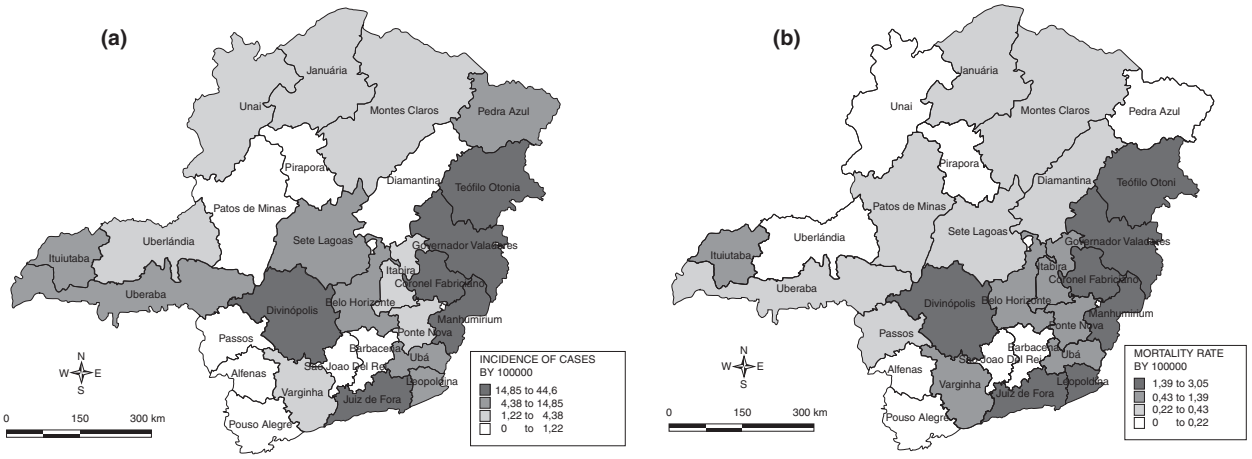

Figure 1 Distribution of dengue haemorrhagic fever, dengue shock syndrome and complicated dengue cases in 28 politic-administrative regions of Minas Gerais, Brazil, 2008–2010. (a) Incidence rate per 100 000 inhabitants and (b) mortality rate per 100 000 inhabitants.

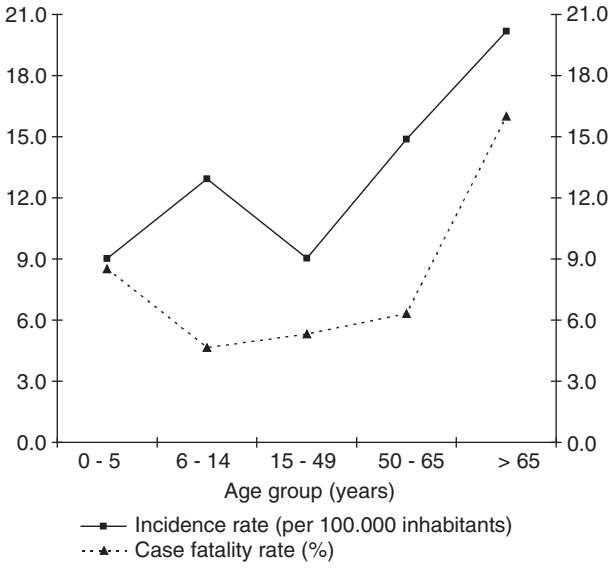

Figure 2 Incidence and case-fatality rates of dengue haemorrhagic fever, dengue shock syndrome and complicated dengue cases according to age group, Minas Gerais, Brazil, 2008–2010.

DHF/DSS and complicated dengue cases were recorded statewide; however, their case-fatality rate was significantly higher in municipalities with fewer than 100 000 inhabitants, where patients were 2.5 times more likely to die than patients in larger municipalities, independent of other factors. The quality of the healthcare system in smaller municipalities, fewer health professionals and a lack of hospital beds may be the cause of this association (Machado 1997).

A higher case-fatality rate was observed among patients whose dengue diagnoses were confirmed by laboratory criteria, even when controlling for other significant variables. We believe that this result is likely associated with more frequently asking for dengue laboratory confirmation for cases exhibiting severe forms of the disease. Furthermore, the Brazilian Ministry of Health and the State Health Department of Minas Gerais strongly recommend that samples be sent *post-mortem* from all suspected dengue deaths (Brazil 2009a). This effort could increase the trend of a higher frequency of laboratory confirmation in cases resulting in death.

Patients over 65 years were more likely to die than other age groups. This association has also been reported in other studies (Lee *et al.* 2008, 2012; Rowe *et al.* 2014) and may be related, in part, to the higher frequency of comorbid conditions in older age groups (Lee *et al.* 2012). Comorbidities complicate the clinical management of patients with dengue, especially in case of cardiovascular, chronic renal and pulmonary disease (WHO 2010). This study did not include the comorbidity conditions in the models because we did not know the frequency of comorbidities in the group that survived. This information is not part of the Brazilian Information System for Notifiable Diseases and is only obtained through the investigation of fatal dengue cases.

Patients with DHF/DSS were three times more likely to die than cases reported as complicated dengue. Despite the controversies surrounding DHF classification and

Table 3 Factors associated with death from dengue, Minas Gerais, Brazil, 2008–2010 (final logistic regression model, $n = 1859$ cases)

Variable	Odds ratio (95% CI)	Odds ratio adjusted (95% CI)	*P*
Specific laboratory tests	2.60 (1.62–4.15)	2.34 (1.34–4.07)	0.003
Cases classificated as DHF/DSS*	3.24 (2.29–4.58)	3.00 (2.02–4.47)	0.000
Plasma leakage	1.98 (1.40–2.81)	1.69 (1.16–2.46)	0.006
Age group > 65 years	2.00 (1.02–3.90)	3.05 (1.99–4.68)	0.000
Municipality < 100 000 inhabitants	2.30 (1.66–3.19)	2.46 (1.71–3.55)	0.000

*DHF/DSS: dengue haemorrhagic fever or dengue shock syndrome.

taking into account the current WHO (2009) dengue classifications (dengue, dengue with warning signs and severe dengue), our data suggest that patients presenting signs and symptoms corresponding to DHF/DSS syndrome should be monitored closely. However, it is important to note that among dengue deaths, only 37.8% fulfilled the DHF criteria (WHO 1997). These data suggest that the DHF classification is unable to identify severe patients, mainly those with a high probability of death. Based on our findings, from an epidemiological viewpoint, countries that use only the DHF criteria in their *strict sense* may tend to underreport dengue deaths.

Plasma leakage denotes an increased probability for shock, and it is one of the mandatory criteria necessary to confirm a case as DHF. In our study, the presence of any sign of plasma leakage was associated with an increased risk of death. Unlike the WHO dengue classification (WHO 1997, 2009), which recognises plasma leakage as a warning sign only when it is concurrent with a rapid decrease in platelet count, our findings reinforce the idea that the presence of plasma leakage alone is enough to consider a patient as having an increased chance of death from dengue. This finding is supported by other studies (Tee *et al.* 2009; Gupta *et al.* 2011; Lee *et al.* 2012).

Therefore, considering clinical management, DHF classification highlights plasma leakage, which is its major hallmark and leads to more severe manifestation of shock. Delayed diagnosis of shock without proper intervention leads to prolonged shock, massive bleeding and organ(s) failure. Despite the current changes in dengue definitions (WHO 2009), DHF classification remains helping in clinical management of patients with dengue. Early detection of plasma leakage, before shock, is important in DHF case management (WHO 2011).

Some limitations of this study should be highlighted, especially those related to retrospective study such as misclassification and missing data. Misclassification bias may have occurred because dengue cases were identified based on either the laboratory or the clinical and epidemiological criteria. However, the inclusion of dengue cases identified by clinical and epidemiological criteria guarantees that cases occurring during epidemic periods or in small cities, where it is more probable that patients do not undergo confirmatory exams, could be studied. Another limitation is that some variables of the Brazilian Information System for Notifiable Diseases exhibited high frequencies of unknown data, restricting the understanding of other factors that may be associated with death from dengue (Kalayanarooj *et al.* 1997; Guzman *et al.* 1999; Cavalcanti *et al.* 2010; Tomashek *et al.* 2012). The inclusion of the 'unknown' category in the multivariate logistic regression analysis had no effect on the results generated by the model because the ORs and the 95% CIs remained unchanged in either the presence or absence of this category. However, the presence of this category improved the fit of the models to the data. Data on comorbidities for all severe cases are not available in the information system. Also, a prospective study with data collected by health professionals with reasonable experience may be a more appropriate design to analyse the clinical and epidemiological profiles of dengue cases and prognostic factors associated with deaths. However, our study allowed the identification of risk factors taking into account the large diversity of dengue care in the state of Minas Gerais and health professionals of different levels of expertise in the management of patients with dengue in different settings (outpatient clinics, intensive care units and medical wards) using information found in a database such as Brazilian Information System for Notifiable Diseases (Sistema de Informação de Agravos de Notificação-SINAN).

Our study found a higher case-fatality rate than studies conducted in other countries (Bin Ghouth *et al.* 2012; Arima *et al.* 2013; Mia *et al.* 2013). However, it is difficult to compare dengue case-fatality rates between countries because of differences in the interpretation of the DHF definition. We believe that with the current WHO dengue classification (WHO 2009), the results and data from different countries would be more comparable.

Conclusions

This study confirms the importance of plasma leakage as a warning sign associated with death from dengue as well

as the signs and symptoms that allow the diagnosis of dengue haemorrhagic fever. Moreover, our findings suggest increased attention should be paid to individuals over 65 years and to those living in municipalities with fewer than 100 000 inhabitants, to ensure better quality of care during the management of patients with severe dengue.

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Corresponding Author **Mariângela Carneiro**, Laboratório de Epidemiologia das Doenças Infecciosas e Parasitárias, Parasitologia, Instituto de Ciências Biológicas, Campus Pampulha, Universidade Federal de Minas Gerais, Avenida Antônio Carlos, 6627, CEP 31270-901, Belo Horizonte, Minas Gerais, Brazil. E-mail: mcarneir@icb.ufmg.br