Comparison of severity signs between patients with primary and secondary dengue infection during the 2016 Burkina Faso (West Africa) outbreak

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Research Article

Keywords: Dengue fever, Severe dengue, Primary dengue, Secondary dengue, Severe bleeding, Africa

Posted Date: October 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-85397/v1

Abstract

Background

The factors that expose the severity of dengue are still controversial, particularly the relationship between severe dengue and secondary dengue. More importantly, the severity of dengue infection remains poorly studied in Africa. The objective of this study was to compare severity signs between patients with primary and secondary dengue infection during the 2016 dengue outbreak in Burkina Faso.

Methods

This was a cross-sectional study through a retrospective examination of patient medical records managed in Ouagadougou for dengue fever from 1 January 2015 to 31 December 2017. All health facilities with the capacity to perform dengue diagnosis in Ouagadougou were considered in the survey. Primary dengue was defined as the presence of AgNS1 and/or IgM and secondary dengue as the presence of IgG associated with one of these two markers. Patients with only IgG were excluded. Univariate and multivariable analyzes were performed using a logistic regression with dengue infection (primary or secondary dengue) as the binary dependent variable. The statistical significant level was set at 0.05.

Results

Of the 811 patients managed for dengue fever during the study period, 418 (51.5%) were male. Thirty-five patients (4.3%) had primary dengue infection (AgNS1 + and / or IgM + with negative IgG) and seven hundred seventy-six (776) patients (95.7%) had secondary dengue infection. 245 patients (30.2%) experienced severe signs. Renal failure (13.1%) was the main sign of severity, followed by severe bleeding (10.6%). In univariate analysis, severe bleeding were associated with primary dengue infection (OR = 2.65, 95%IC: 1.16 -6.03, p = 0.01). Twenty-four deaths (9.8%) were reported during the period.

Conclusion

Signs of gravity can occur during primary dengue fever. This study highlight the need to conduct more studies on the severity factors of dengue fever.

1. Introduction

Dengue is the most common arboviruses in the tropics. It is a potentially serious disease with about 500,000 cases of severe dengue each year worldwide and 2.5% of deaths (1). While this endemic disease is known in Africa, several sources of data indicate a lack of knowledge on its epidemiology background and severity in this region (2,3). Several West African countries have experienced dengue outbreaks during the past decade. Meanwhile the medical and clinical environment is characterized by the deficiency of the diagnostic capacity and the low knowledge on the infection and clinical signs by local health workers. In addition, until now the disease has been very infrequent and poorly taught and the

surveillance system in place is inadequate (2,4). Moreover, the context of malaria prevalence contributes to a significant underestimation of the disease and its fatality rate in the region (5).

Severe dengue is clinically defined by the presence of severity signs and symptoms such as plasma leakage, severe bleeding and organ failure. However, severe dengue fever remains poorly described in Africa (6,7). The most frequently reported sign of severity is hemorrhage, however shock syndrome or organ failure have been also reported in very few studies in Africa (8,9). In addition, the pathogenesis of severe dengue fever is not fully understood (10). The theory of Antibody-dependent enhancement (ADE) is supported by several publications to explain plasma leakage with shock syndrome. According to the ADE- theory, the risk of dengue hemorrhagic fever (DHF) is increased during re-infection with heterologous serotypes (sequential theory). The presence of a number of biological and inflammatory phenomena may lead to an increase of vascular permeability and leakage plasma. However, this hypothesis is subject to many controversies and could not explain all the biological disturbances and organ failures (encephalitis, hepatitis, myocarditis ...) observed during severe forms (11).

Although complications are most often reported during dengue re-infection, it should be noted that some publications report cases of severe dengue fever during primary dengue infection (12–14). For instance, in India about 10 to 30% of patients hospitalized for dengue hemorrhagic fever had primary dengue infection (15). Some viral serotypes could expose to a higher frequency of DHF.

The pathogenicity of severe dengue fever is often described by a combination of factors involving the patient's pre-existence of clinical conditions and medical history, the serotype virulence, viral load, vectorial skills which reinforces the controversy over the theory of ADE (16–18).

The first cases of dengue fevers were reported in 1925 in Burkina Faso (19). Other outbreaks subsequently appeared in 1980 and 2013. Since 2013, cases of severe dengue fever have been regularly reported in Burkina Faso. On 18 November 2016, WHO recognized dengue fever outbreak in Burkina Faso, with a total of 1061 suspected cases notified between August and November 2016 mainly in the capital city, Ouagadougou (20). This disease represents one of the most important causes of infectious diseases in Burkina Faso and has a significant economic impact for the country (21). Meanwhile, the prevalence of severity signs as well as case fatality rate remains poorly studied. Indeed, so far, only one study conducted on 98 patients reports a prevalence of 18.4% and 11.2%, for DHF and dengue shock syndrome (DSS) respectively (22).

Entomological surveillance data indicate the circulation of *Aedes aegypti* and data from the National Reference Laboratory for Viral Haemorrhagic Fevers confirmed the presence of the 3 serotypes in the country (DENV-1, DENV-2 and DENV-3) (23). Routine surveillance of dengue fever has recently been initiated in Burkina Faso but is still restricted to seven sentinel sites in four cities (Ouagadougou, Bobo-Dioulasso, Pouytenga and Dori).

Our objective in this study was to compare severity signs between patients with primary dengue infection and secondary dengue infection during the 2016 outbreak in Burkina Faso.

2. Methods

2.1 Study design and study population

This was a cross-sectional study through the retrospective examination of patient medical records managed in Ouagadougou (capital city of Burkina Faso) for dengue fever from 1 January 2015 to 31 December 2017. The city of Ouagadougou is situated on the central plateau (12.4°N 1.5°W), in the Kadiogo province. The total population is estimated at about 2.700.000 with 48% of men and 52% of women. We considered all the health facilities that had the capacity to perform dengue testing in the city of Ouagadougou. We identified in total 15 health structures divided as follows: 4 tertiary health facilities, 3 secondary health facilities, 8 private clinics.

We included in this study all patients managed for dengue diagnosed on the basis of antigenic and/or serological tests (NS1 antigen positive and/or IgM positive). Patients who were tested positive for NS1 antigen and/or IgM were classified as primary dengue. When these two markers were isolated or simultaneously associated with IgG positivity, the patient was classified as secondary dengue. Patients who had only anti-dengue IgG and patients with dengue suspicion (not documented by an antigenic and serological test) were not included in the study.

The biological test used was the SD Bioline dengue duo which allows the detection of AgNS1, IgM and IgG.

2.2 Operational definitions

- For the dengue classification into primary or secondary, the following parameters were used: Primary dengue was defined as the presence of AgNS1 and/or IgM, whereas secondary dengue was defined as the presence of IgG associated with AgNS1 or IgM.
- In this study, the following dengue clinical definitions were used according to the WHO 2009:

2.3 Severe dengue fever: probable dengue fever with at least one of the following severity signs:

- Plasma leakage with hemoconcentration defined by a hematocrit> 45%;
- Severe bleeding: defined as diffuse and / or abundant bleeding with deglobulization requiring blood transfusion.
- Organ failure: acute hepatitis defined by acute cytolysis (Aspartame aminotransferase or ASAT> 1000 IU / liter, Alanine aminotransferase or ALAT> 1000 IU / liter); encephalopathy defined by Glasgow score <13; renal failure defined by creatinine elevation> 120 micromoles / liter.
- Hypovolemic shock: plasma leakage with shock syndrome or respiratory distress.
- Severe thrombocytopenia: defined by a platelet count of less than 20×10^3 per µ

2.4 Collection of data and statistical analysis

Data were extracted from patient medical file and laboratory records. When clinical data were not available, patients were contacted by telephone to obtain more information about their signs and care pathways.

The questionnaire included socio-demographic characteristics (age, sex, educational level, and occupational activities), history and co-morbidities (asthma, diabetes, hypertension), clinical characteristics, biological results (thick blood smear or malaria RDT, blood cells count, biochemistry), the WHO dengue classification 2009, the status of patient evolution (complications, deaths).

For the investigation of severity signs, we compared, respectively, patients with primary dengue fever and patients with secondary dengue fever. The data analysis was performed using Epi-Info version 7 software. The statistical tests used for the statistical comparisons are the Chi 2 test or the Fisher's exact test (if Chi2 conditions were not met). Univariate and multivariable analyzes were performed using a logistic regression with dengue infection as the dependent variable. This dependent variable was a binary variable considering the value 1 if it is a primary infection and 0 if it is a secondary infection. The significant level was set at 0.05.

3. Results

3.1 Socio-demographic characteristics of the study participants

Of the 811 patients managed for dengue fever during the study period, 418 (51.5%) were male. The median age was 30.5 years (Min = 1; max= 83 years). The peak prevalence (38.5% of patients) of registered cases was observed in November 2016. The number of hospitalized patients was 793 (97.8%). The majority of patients (477; 58.8%) were treated in private clinics. The distribution of patients according to their level of education and socio-professional level shows that respectively 464 patients (60.0%) had a secondary and higher education and 263 patients (35.4%) were public or private sector employees (Table 1).

Table 1: Sociodemographic and Clinical Characteristics of Patients

	Dengue fever (N = 811)	
Characteristics	**Primary infection n (%)**	**Secondary infection n (%)**
Age (in years)		
	0	85 (10.9)
	26 (74.3)	522 (67.2)
	6 (17.1)	108 (14.0)
	3 (8.6)	61 (7.9)
Sex		
	21 (60.0)	372 (47.7)
	14 (40.0)	404 (52.3)
Arterial hypertension		
	4 (11.4)	67 (8.6)
	31 (88.6)	709 (91.4)
Diabetes		
	0 (0.0)	30 (3.9)
	35 (100.0)	746 (96.1)
Asthma		
	2 (5.7)	18 (2.3)
	33 (94.3)	758 (97.7)
Malaria		
	3 (8.6)	180 (23.2)
	32 (91.4)	596 (76.8)
WHO Classification 2009		
	6 (17.1)	266 (34.3)
	12 (34.3)	282 (36.3)
	17 (48.6)	228 (29.4)

3.2 *Clinical characteristics of patients and prevalence of severity signs*

Hypertension, diabetes and asthma were comorbidities found in respectively 71 (8.8%), 30 (3.7%) and 20 (2.5%) of patients. Malaria co-infections were diagnosed in 183 patients (22.6%).

A total of 669 (75.0%) patients were NS1 antigen positive and 100 patients (12.3%) had anti-dengue IgM. Thirty-five patients (4.3%) had primary dengue infection (AgNS1 + and / or IgM + with negative IgG) and 776 patients (95.7%) had secondary dengue infection.

The classification of patients by severity showed the following figure: dengue without warning signs in 272 patients (33.5%), dengue fever with warning signs in 294 patients (36.3%) and severe dengue in 245 patients (30.2%).

Severity signs were distributed as follows: 106 (13.1%) renal failure, 86 (10.6%) severe bleeding, 56 (6.9%) plasma leakage, 52 (6.4%) encephalopathy, 43 (5.3%) severe hepatic cytolysis. Hypovolemic shock occurred in 11 patients (1.4%).

Severe thrombocytopenia was observed and confirmed in 37 patients (4.6%). (Figure 1).

3.3 Relationship between the severity signs of dengue fever and primary or secondary dengue infection

In univariate analysis, severe bleeding was associated with primary dengue infection (OR = 2.65, 95%IC: 1.16 -6.03), p = 0.01). However, in multivariable analysis, none of the signs of severity are statistically associated with primary or secondary dengue fever (Table 2).

Table 2: Comparison of severity signs, thrombocytopenia and death between patients with primary and secondary dengue infections. Univariate and multivariate analyzes.

Severity signs	Total N = 811	Type of infection		Univariate analysis		Multivariable analysis	
		Primary dengue N = 35 (%)	Secondary dengue N = 776 (%)	OR, IC95%	*p*	OR, IC95%	*p*
ALAT > 1000							
	797	34 (97.1)	763 (98.3)	Ref.		Ref.	
	14	1 (2.9)	13 (1.7)	1.72 (0.21 -13.58)	0.46	1.04 (0.03- 35.47)	0.97
ASAT > 1000							
	782	34 (97.14	748 (96.39	Ref.		Ref.	
	29	1 (2.9)	28 (3.6)	0.78 (0.10- 5.94	0.99	0.28 (0.01 -7.07)	0.44
Encephalopathy							
	759	32 (91.4)	727 (93.7)	Ref.		Ref.	
	52	3 (8.6)	49 (6.3)	1.39 (0.41 -4.70)	0.48	0.54 (0.11- 2.50)	0.43
Severe bleeding							
	725	27 (77.1)	698 (89.9)	Ref.			
	86	8 (22.9)	78 (10.1)	2.65 (1.16 -6.03)	***0.01***	2.21 (0.87- 5.57)	**0.09**
Shock syndrom							
	800	33 (94.3)	767 (98.8)	Ref			
	11	2 (5.7)	9 (1.2)	5.16 (0.73- 22.65)	**0.07**	NA*	NA*
Hematocrit > 45%							
	755	30 (85.7)	725 (93.4)	Ref.		Ref.	
	56	5 (14.3)	51 (6.6)	2.36 (0.88 -6.36)	**0.08**	2.37 (0.85- 6.59)	**0.09**
Renal failure							
	705	27 (77.1)	678 (87.4)	Réf.		Réf.	
	106	8 (22.9)	98 (12.6)		**0.07**		0.27

				2.04 (0.90 - 4.63)		1.65 (0.66 -4.13)	
Platelets < 20 000/mm^3							
	774	34 (97.1)	740 (95.4)	Réf.		Réf.	
	37	1 (2.9)	36 (4.6)	0.60 (0.08 - 4.54)	0.99	0.53 (0.06- 4.24)	0.55

**Not applicable*

Although the results were not statistically different, a greater frequency of plasma leakage, hypovolemic shock, and renal failure was observed during primary dengue fever.

4. Discussion

In our study, about 1/3 of patients experienced severe dengue episode. The most common severity signs observed were renal failure followed by severe bleeding, and plasma leakage. Severe bleeding was statistically more common in primary dengue fever.

According to the WHO, nearly 500,000 cases of severe dengue (DHF and DSS) occur each year with nearly 20,000 deaths in the world. In the Americas, the incidence of severe dengue has been estimated at more than 200 cases per 100 000 persons in 2010 (24). Prothapregada et al. reported 37.4% of severe dengue in hospitalized children in India which is quite similar to the 33,5% of prevalence reported in our study (25).

Severe dengue fever is underestimated, particularly in Africa, where many cases probably remain undiagnosed due to the high frequency of other febrile non-malarial diseases and limited diagnostic capabilities (8,26).

The high prevalence of severe dengue in this study may be related both to the WHO classification used for organ failure and to the definition of severity signs that vary from one study to another (27). Indeed, these severity signs are not precisely defined by WHO, and most studies published so far have used the 1997 definition. The new WHO definition has improved sensitivity for earlier identification of severe cases and better screening of patients (28).

Renal failure appears in this study as the most common severity sign (13.1%). In the literature, the frequency of renal failure during severe dengue fever varies widely (0.2 to 36%) (29–31). In addition, the thresholds defining renal failure during dengue fever are also variable according to these studies. The high frequency of renal failure in our study could be explained by the choice of creatinine threshold at 120 µmol/l. There are few published studies on renal failure during dengue fever in Africa. However, renal failure is common in this region, particularly because of malaria or other tropical infections. During dengue infection, several mechanisms may cause renal failure: renal hypoperfusion in the setting of

sepsis, immunological damage and other unsolved mechanisms. Renal failure may also be a result of severe bleeding and plasma leakage. Sepsis, advanced age, use of nephrotoxic drugs, a history of high blood pressure or diabetes are also risk factors for renal failure during dengue fever (17,32).

The frequency of severe bleeding varies from one study to another. This can be explained by a lack of homogeneity in the definitions of severe bleeding between studies. In our study, we considered severe bleeding patients with extensive bleeding and significant deglobulization that required blood transfusion. This strict definition may explain the lower frequency of severe bleeding in our study compared to those reported in several studies (33). However, in West Africa, although the majority of the published work is case studies or small series, bleeding is the most common clinical severity sign that usually leads to the biological diagnosis of dengue fever and patients hospitalization (8,33). This could be explained by the fact that, in the context of limited resources, hemorrhage is a sign of severity that is easier to identify than other signs for which laboratory diagnosis remains essential. It is also one of the symptoms that is increasingly leading to the use of rapid diagnostic tests.

Plasma leakage was observed in 6.9% of study's patients and only 1.4% of the patients experienced hypovolemic shock.

In India, the frequency of DSS was 39% in children and was higher than the frequency of DHF (34). A frequency of 11.1% of DSS was reported by Abdallah et al. in East Sudan (35). Plasma leakage is suspected being underestimated complication in West-Africa due to lack of knowledge about the disease, the lack of systematic measurement of vital parameters and the unavailability of hematocrit test (4,36).

Regular monitoring of these clinical and biological parameters during the disease evolution is rarely done in the West- African context and more especially in Burkina Faso. As previously described, plasma leakage occurs during the critical phase of the disease, which varies according to the individual from 3 to 7 days, thus after the onset of symptoms and corresponds to the moment of thermal decline. A standardized surveillance study would better assess the frequency and importance of plasma leakage, its risk factors in the West- African context and therefore take appropriate measures to prevent patient deaths.

In our study, the rate of hemorrhage was significantly higher in primary dengue. This is in contrast with the majority of studies reporting that severe bleeding complications occur during secondary dengue infection which is consistent with ADE theory. Similar to our findings other authors have reported, a higher prevalence of DHF in primary dengue infection (12,37). Furthermore, Soo et al. in a meta-analysis showed that the severity of dengue fever during primary infection was related to the virulence of the viral serotype (38). Tee et al. showed that severe bleeding occurred more frequently in elderly patients with primary dengue fever (39). An important pathogenic role of pro-inflammatory cytokines, including a significant elevation of IFN-γ, IL-12, TNF-α and IL-6 during primary dengue with serotype 2 could explain the severity of the disease during primary infection (40). Data from the national reference laboratory during the same outbreak in 2016 showed a predominant circulation of DENV-2 in Burkina Faso (41).

The difference between primary dengue and secondary dengue fever is often difficult and requires more advanced diagnostic techniques, including the measurement of antibody titration and for this, WHO also recommended haemagglutination inhibition technique which is limited in Burkina Faso (42). Therefore, the results of our study need to be interpreted with caution, since only 4% of our patients were confirmed and tested by PCR primary dengue infection. Thanachartwet et al. reported similar results with 3.5% of patients with primary dengue fever (43). Previous data from studies of patients who developed fever in community showed a seroprevalence of 66% IgG and confirm the endemic circulation of the dengue virus in the country (21). The proportion of severe dengue in these two groups may influence a difference in favor of the lower strength group.

The limits of our study are mainly related to the nature of the diagnostic test being performed. In addition, the type of cross-sectional study did not enable to standardize the biological checkup performed and standardize the periods of achievement of dengue rapid diagnostic test to facilitate results interpretation. Meanwhile the absence of IgG is a good negative predictive value of a primary dengue, however, its presence, does not exclude primary dengue since IgG can appear from the 7th day of the disease occurrence. The isolated presence of IgG excluded patients from the study since the antibody titration test was not feasible.

5. Conclusion

This study showed that severe dengue fever is a reality in West Africa and that its prevalence is high. The most common severity signs observed, were renal failure, severe bleeding and plasma leakage. As demonstrated, primary dengue is a source of hemorrhagic complications. This study confirms the need to conduct further studies to investigate on the severity factors of dengue fever. In addition, environmental sanitation and better knowledge of dengue fever by health workers are urgently needed to reduce the social and demographic consequences of dengue fever. However, this requires the commitment of all socio-political and health stakeholders in order to reach successful actions.

6. Declarations

Ethics approval and consent to participate

An authorization from the Ministry of Health was obtained to carry out the data collection and the study in all health structures (2016/16-474/MS/SG). The data were reported to the Information and Freedoms Commission of Burkina Faso. The para clinical investigation was done as part of the routine management of the disease and therefore no additional cost was generated by the study for the patient. The data were anonymous collected on a paper questionnaire to ensure confidentiality according to the ICHGCP standards.

Hospitalization of the patient was dependent on the severity level and/or tolerance of the disease by the patient. Burkina Faso government health subsidy scheme, which was launched in October 2016, allows

free treatment for cases of severe dengue in tertiary level structures.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding sources.

Authors' contributions

DEA, SKA, DI and KBA designed the study, wrote the research protocol, collected and analyzed the data, and wrote the manuscript. LD collected data. BR, LD, ZJ, SA and PA provided the bibliography. RT, YYD, GO, TH, PA and HT directed the study, gave a critical reading and final correction of the article. All authors read and approved the final manuscript.

Acknowledgements

We especially thank the Ministry of Health of Burkina Faso for their support in the realization of this study, the heads of the public and private structures of the city, who have authorized access to their data, including CHU Yalgado Ouedraogo, CHU of Tengandogo, the pediatric CHU Charles de Gaulle, and 8 private health facilities.

References

1. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue [Internet]. 2020 [cité 20 sept 2020]. Disponible sur: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue
2. Amarasinghe A. Dengue Virus Infection in Africa. Emerg Infect Dis [Internet]. août 2011 [cité 4 août 2020]; Disponible sur: http://wwwnc.cdc.gov/eid/article/17/8/10-1515_article.htm
3. Guo C, Zhou Z, Wen Z, Liu Y, Zeng C, Xiao D, et al. Global Epidemiology of Dengue Outbreaks in 1990–2015: A Systematic Review and Meta-Analysis. Front Cell Infect Microbiol [Internet]. 12 juill 2020 [cité 19 août 2020];7. Disponible sur: http://journal.frontiersin.org/article/10.3389/fcimb.2017.00317/full

4. Jaenisch T, Junghanss T, Wills B, Brady OJ, Eckerle I, Farlow A, et al. Dengue expansion in Africa-not recognized or not happening? Emerg Infect Dis [Internet]. oct 2014 [cité 19 août 2020];20(10). Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4193177/
5. Mordecai EA, Ryan SJ, Caldwell JM, Shah MM, LaBeaud AD. Climate change could shift disease burden from malaria to arboviruses in Africa. Lancet Planet Health. sept 2020;4(9):e416-23.
6. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. The global distribution and burden of dengue. Nature. 7 avr 2013;496(7446):504-7.
7. Were F. The dengue situation in Africa. Paediatr Int Child Health. mai 2012;32 Suppl 1:18-21.
8. Fagbami AH, Onoja AB. Dengue haemorrhagic fever: An emerging disease in Nigeria, West Africa. J Infect Public Health [Internet]. 26 avr 2018 [cité 25 sept 2020]; Disponible sur: https://linkinghub.elsevier.com/retrieve/pii/S1876-0341(18)30064-9
9. Faye O, Ba Y, Faye O, Talla C, Diallo D, Chen R, et al. Urban epidemic of dengue virus serotype 3 infection, Senegal, 2009. Emerg Infect Dis. mars 2014;20(3):456-9.
10. Guzman MG, Harris E. Dengue. The Lancet. janv 2015;385(9966):453-65.
11. Halstead SB. Controversies in dengue pathogenesis. Paediatr Int Child Health. mai 2012;32(sup1):5-9.
12. Anantapreecha S, Chanama S, A-nuegoonpipat A, Naemkhunthot S, Sa-Ngasang A, Sawanpanyalert P, et al. Serological and virological features of dengue fever and dengue haemorrhagic fever in Thailand from 1999 to 2002. Epidemiol Infect. juin 2005;133(3):503-7.
13. Cárdenas-Perea ME, Flores-Mendoza LK, Pérez-Contreras I, Díaz-Orea MA, Gómez-Conde E, Cortés-Hernández P, et al. Primary Dengue Infection in Patients Requiring Hospitalization During an Outbreak in a Low Incidence Mexican Region. Vector Borne Zoonotic Dis Larchmt N. 2020;20(5):380-6.
14. Martínez-Cuellar C, Lovera D, Galeano F, Gatti L, Arbo A. Non-structural protein 1 (NS1) of dengue virus detection correlates with severity in primary but not in secondary dengue infection. J Clin Virol Off Publ Pan Am Soc Clin Virol. mars 2020;124:104259.
15. Anuradha S, Singh NP, Rizvi SN, Agarwal SK, Gur R, Mathur MD. The 1996 outbreak of dengue hemorrhagic fever in Delhi, India. Southeast Asian J Trop Med Public Health. sept 1998;29(3):503-6.
16. Mallhi TH, Khan AH, Sarriff A, Adnan AS, Khan YH. Determinants of mortality and prolonged hospital stay among dengue patients attending tertiary care hospital: a cross-sectional retrospective analysis. BMJ Open. juill 2017;7(7):e016805.
17. Pang J, Hsu JP, Yeo TW, Leo YS, Lye DC. Diabetes, cardiac disorders and asthma as risk factors for severe organ involvement among adult dengue patients: A matched case-control study. Sci Rep. 3 janv 2017;7:39872.
18. Thein S, Aung MM, Shwe TN, Aye M, Zaw A, Aye K, et al. Risk factors in dengue shock syndrome. Am J Trop Med Hyg. mai 1997;56(5):566-72.

19. Gonzalez JP, Du Saussay C, Gautun JC, McCormick JB, Mouchet J. [Dengue in Burkina Faso (ex-Upper Volta): seasonal epidemics in the urban area of Ouagadougou]. Bull Soc Pathol Exot Filiales. 1985;78(1):7-14.
20. World Health Organization. Dengue Fever – Burkina Faso. Disease Outbreak News [Internet]. 2016. Disponible sur: http://www.who.int/csr/don/18-november-2016-dengue-burkina-faso/en/
21. Ridde V, Agier I, Bonnet E, Carabali M, Dabiré KR, Fournet F, et al. Presence of three dengue serotypes in Ouagadougou (Burkina Faso): research and public health implications. Infect Dis Poverty [Internet]. déc 2016 [cité 4 août 2020];5(1). Disponible sur: http://www.idpjournal.com/content/5/1/23
22. Diallo I, Sondo KA, Tieno H, Tamelokpo EY, Zoungrana J, Sagna Y, et al. [About 98 cases of dengue hospitalized in a private clinic of Ouagadougou: epidemiology, diagnostic and evolution]. Bull Soc Pathol Exot 1990. déc 2017;110(5):291-6.
23. Lim JK, Seydou Y, Carabali M, Barro A, Dahourou DL, Lee KS, et al. Clinical and epidemiologic characteristics associated with dengue during and outside the 2016 outbreak identified in health facility-based surveillance in Ouagadougou, Burkina Faso. PLoS Negl Trop Dis. déc 2019;13(12):e0007882.
24. San Martín JL, Brathwaite Dick O, del Diego J, Montoya RH, Dayan GH, Zambrano B. The History of Dengue Outbreaks in the Americas. Am J Trop Med Hyg. 3 oct 2012;87(4):584-93.
25. Pothapregada S, Kamalakannan B, Thulasingam M. Clinical Profile of Atypical Manifestations of Dengue Fever. Indian J Pediatr. juin 2016;83(6):493-9.
26. Baba M, Villinger J, Masiga DK. Repetitive dengue outbreaks in East Africa: A proposed phased mitigation approach may reduce its impact. Rev Med Virol. mai 2016;26(3):183-96.
27. Srikiatkhachorn A, Rothman AL, Gibbons RV, Sittisombut N, Malasit P, Ennis FA, et al. Dengue--how best to classify it. Clin Infect Dis Off Publ Infect Dis Soc Am. sept 2011;53(6):563-7.
28. Tsai C-Y, Lee I-K, Lee C-H, Yang KD, Liu J-W. Comparisons of dengue illness classified based on the 1997 and 2009 World Health Organization dengue classification schemes. J Microbiol Immunol Infect Wei Mian Yu Gan Ran Za Zhi. août 2013;46(4):271-81.
29. Basu G, Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JAJ, et al. Acute kidney injury in tropical acute febrile illness in a tertiary care centre--RIFLE criteria validation. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. févr 2011;26(2):524-31.
30. Vachvanichsanong P, Thisyakorn U, Thisyakorn C. Dengue hemorrhagic fever and the kidney. Arch Virol. avr 2016;161(4):771-8.
31. Mallhi TH, Khan AH, Sarriff A, Adnan AS, Khan YH, Jummaat F. Defining acute kidney injury in dengue viral infection by conventional and novel classification systems (AKIN and RIFLE): a comparative analysis. Postgrad Med J. févr 2016;92(1084):78-86.
32. Basu B, Roy B. Acute Renal Failure Adversely Affects Survival in Pediatric Dengue Infection. Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med. janv 2018;22(1):30-3.

33. Franco L, Palacios G, Martinez JA, Vázquez A, Savji N, De Ory F, et al. First report of sylvatic DENV-2-associated dengue hemorrhagic fever in West Africa. PLoS Negl Trop Dis. août 2011;5(8):e1251.
34. Pothapregada S, Kamalakannan B, Thulasingham M, Sampath S. Clinically Profiling Pediatric Patients with Dengue. J Glob Infect Dis. sept 2016;8(3):115-20.
35. Abdallah TM, Ali AAA, Karsany MS, Adam I. Epidemiology of dengue infections in Kassala, Eastern Sudan. J Med Virol. mars 2012;84(3):500-3.
36. Carabali M, Hernandez LM, Arauz MJ, Villar LA, Ridde V. Why are people with dengue dying? A scoping review of determinants for dengue mortality. BMC Infect Dis [Internet]. déc 2015 [cité 15 févr 2020];15(1). Disponible sur: http://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-015-1058-x
37. Khurram M, Qayyum W, Hassan SJU, Mumtaz S, Bushra HT, Umar M. Dengue hemorrhagic fever: comparison of patients with primary and secondary infections. J Infect Public Health. déc 2014;7(6):489-95.
38. Soo K-M, Khalid B, Ching S-M, Chee H-Y. Meta-Analysis of Dengue Severity during Infection by Different Dengue Virus Serotypes in Primary and Secondary Infections. Huy NT, éditeur. PLOS ONE. 23 mai 2016;11(5):e0154760.
39. Tee HP, How SH, Jamalludin AR, Safhan MNF, Sapian MM, Kuan YC, et al. Risk factors associated with development of dengue haemorrhagic fever or dengue shock syndrome in adults in Hospital Tengku Ampuan Afzan Kuantan. Med J Malaysia. déc 2009;64(4):316-20.
40. Cruz Hernández SI de la, Puerta-Guardo HN, Flores Aguilar H, González Mateos S, López Martinez I, Ortiz-Navarrete V, et al. Primary dengue virus infections induce differential cytokine production in Mexican patients. Mem Inst Oswaldo Cruz. mars 2016;111(3):161-7.
41. Tarnagda Z, Cissé A, Bicaba BW, Diagbouga S, Sagna T, Ilboudo AK, et al. Dengue Fever in Burkina Faso, 2016. Emerg Infect Dis. janv 2018;24(1):170-2.
42. World Health Organization, éditeur. Dengue haemorrhagic fever: diagnosis, treatment, prevention, and control. 2nd ed. Geneva: World Health Organization; 1997. 84 p.
43. Thanachartwet V, Oer-areemitr N, Chamnanchanunt S, Sahassananda D, Jittmittraphap A, Suwannakudt P, et al. Identification of clinical factors associated with severe dengue among Thai adults: a prospective study. BMC Infect Dis [Internet]. déc 2015 [cité 3 oct 2019];15(1). Disponible sur: http://www.biomedcentral.com/1471-2334/15/420

Figures

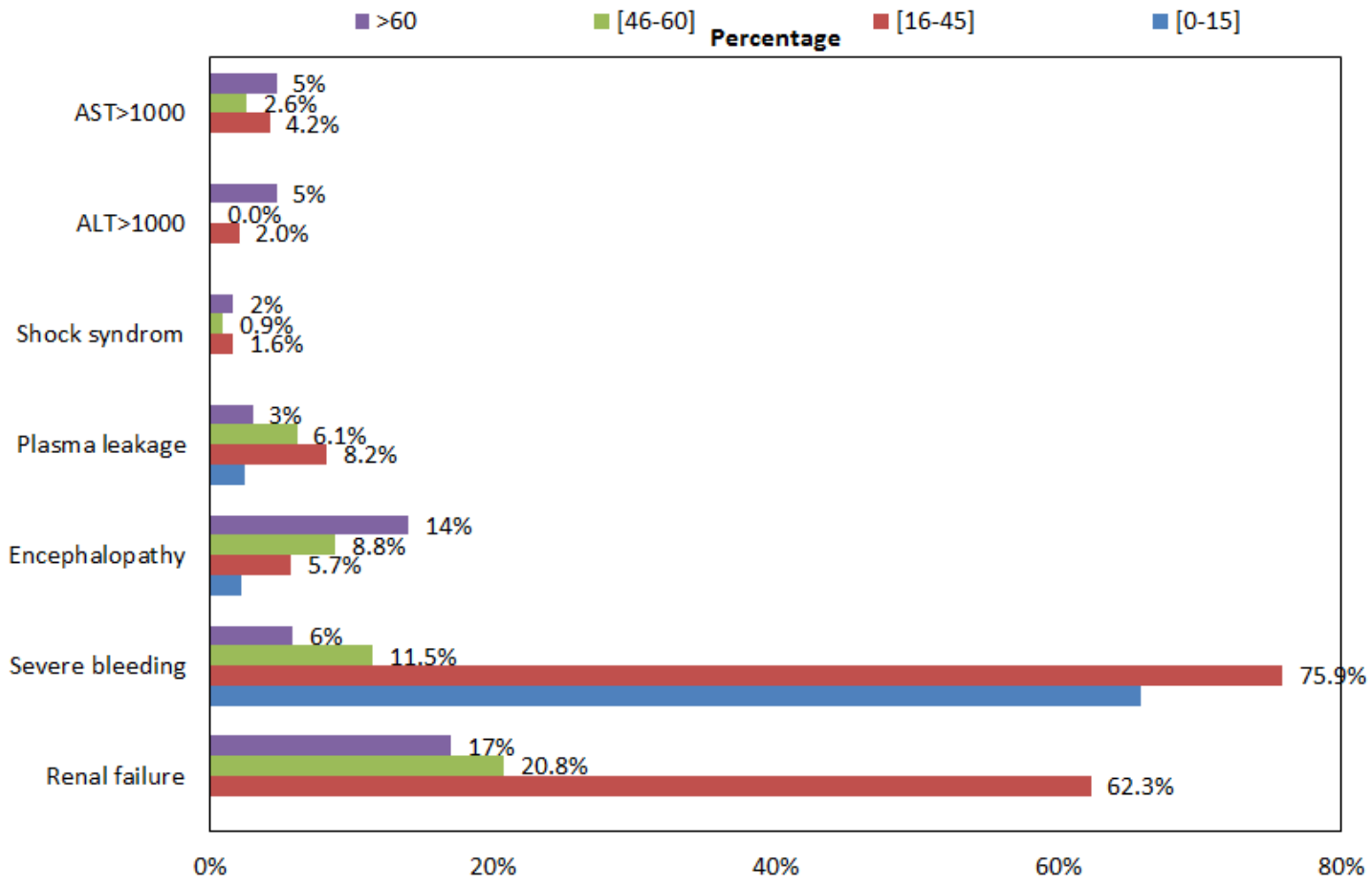

Figure 1

Prevalence of dengue severity signs according age. N = 811