Dengue in children: from notification to death

Dengue em crianças: da notificação ao óbito

Dengue en niños: de la notificación al óbito

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ABSTRACT

Objectives: To report the historical aspects, epidemiological and clinical features of dengue fever in children, stressing the importance of disease reporting for prevention of deaths and morbidity in children.

Data source: A review of the major studies published on dengue and dengue in children was performed. The following databases Lilacs, SciELO, Medline and Scopus were studied along with official documents of the Ministry of Health of Brazil. The search covered the period from January 1980 to March 2011 and a combination of the following terms was applied: dengue, dengue in children, pediatric dengue, and disease notification.

Data synthesis: All studied found were evaluated and a timeline and key information connected to the theme were established; factors related to the virus and the vector were also included, and information on the clinical characteristics and importance of reporting the disease have been identified, as well as relevant research and elucidation of all deaths reported. There are a number of studies on the subject, but a greater emphasis was given to those relevant to children.

Conclusions: The knowledge of this disease, which constitutes the main emerging and reemerging disease at the present, is essential for early diagnosis, timely treatment and prevention of deaths. Adequate report of cases is still lacking as well as an improvement of description of deaths in children with dengue.

Key-words: dengue; child; disease notification.

RESUMO

Objetivo: Descrever aspectos históricos, epidemiológicos e clínicos da dengue em crianças, demonstrando a importância das notificações e conhecimento destas para prevenir a evolução de gravidade e os óbitos nessa população.

Fontes de dados: Revisão narrativa dos principais trabalhos publicados sobre dengue e dengue em crianças. Buscaram-se estudos nas seguintes bases de dados: Lilacs, SciELO, Medline e Scopus, além de documentos oficiais do Ministério da Saúde. A busca incluiu trabalhos publicados no período de janeiro de 1980 a março de 2011. Os descritores utilizados foram: dengue, dengue em criança, dengue em pediatria e notificação de doenças.

Síntese dos dados: Todos os artigos encontrados foram avaliados e procurou-se estabelecer uma linha de tempo e principais informações alusivas ao tema, fatores referentes ao vírus e ao vetor também foram incluídos; informações sobre as características clínicas e importância das notificações foram apontadas, além da relevante investigação e elucidação de todos os óbitos notificados. Existe um grande número de estudos sobre o assunto, porém foi dada maior ênfase àqueles pertinentes às crianças.

Conclusões: O conhecimento desta doença, que se configura como principal doença emergente e reemergente na atualidade, é fundamental para diagnóstico precoce, tratamento oportuno e prevenção de óbitos. Há uma lacuna na notificação adequada em Pediatria, assim como no detalhamento dos óbitos em crianças vítimas de dengue.

Palavras-chave: dengue; criança; notificação de doenças.

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RESUMEN

Objetivo: Describir aspectos históricos, epidemiológicos y clínicos del dengue en niños, demostrando la importancia de las notificaciones y conocimiento de estas para la prevención de evolución de gravedad y óbitos en esta población.

Fuentes de datos: Revisión narrativa de los principales trabajos publicados sobre dengue y dengue en niños. Se buscaron estudios en las siguientes bases de datos: Lilacs, SciELO, Medline y Scopus, además de documentos oficiales del Ministerio de Salud. La búsqueda incluyó trabajos publicados en el periodo de enero de 1980 a marzo de 2011. Los descriptores utilizados fueron: dengue, dengue en niño, dengue en pediatría y notificación de enfermedades.

Síntesis de los datos: Todos los artículos encontrados fueron evaluados y se buscó establecer una línea de tiempo y principales informaciones alusivas al tema, factores referentes al virus y al vector también fueron incluidos; informaciones sobre las características clínicas y la importancia de las notificaciones fueron señaladas, además de la relevante investigación y elucidación de todos los óbitos notificados. Existe un gran número de estudios sobre el tema, pero se dio más énfasis a aquellos relativos a los niños.

Conclusiones: El conocimiento de esta enfermedad, que se configura como principal enfermedad emergente y reemergente en la actualidad, es fundamental para diagnóstico temprano, tratamiento oportuno y prevención de óbitos. Hay una laguna en la notificación adecuada en Pediatría, así como en el detallar los óbitos en niños víctimas de dengue.

Palabras clave: dengue; niño; notificación de enfermedades.

Introduction

Dengue is considered the fastest growing human arboviral disease in the world. It is currently the most important emerging and re-emerging infectious disease in terms of morbidity and mortality[1]. With no prospect of change in the near future, 55% of the world population is at risk of contracting dengue. It has been calculated that dengue hemorrhagic fever is responsible for 500 thousand hospital admissions annually, primarily among children. Around 2.5% of patients die, although in Brazil lethality can reach 10%[2]. The dengue virus' propensity for transmission is similar to that of diseases that are propagated by direct contagion[3].

Many different factors have been identified as responsible for the emergence and re-emergence of this epidemic: changes in climate, demographics and society, urbanization and the transportation of goods, complacency with relation to infectious diseases and vectors, failures of surveillance, lack of resources devoted to public health and research and ineffective control and prevention programs[4]. International transit of people and goods also plays a role in the increased prevalence and worldwide dispersal of the virus and its vector, to the extent that even countries free from autochthonous cases are concerned[5].

The social costs of dengue are difficult to measure, but they include elevated demand for medical services, absenteeism from work and school and a negative impact on the quality of life of patients and their relatives[6]. A recent study found that economic cost of dengue is greater than that caused by any other viral disease in the Americas and found that Brazil alone spends 40.9% of the entire expenditure on dengue for the American continent[7]. The literature suggests that climate change will increase the impact of dengue on the population as a result of sustained vector transmission, leading to complications cause by the disease and increased numbers of deaths[8].

Although significant advances have been achieved in the struggle to develop an effective vaccine, there is still no specific immunization nor antiviral drugs available for routine use[9]. Management of the disease is limited to controlling the vector and providing palliative treatment for patients[10].

This paper provides a brief review of the history of dengue, with emphasis on pediatric aspects including clinical manifestations and diagnosis. Additionally, the article discusses the importance of prompt notification. This is a simple method of passive surveillance, but its utility in the fight to reduce deaths should not be underestimated. Notification provides a more complete picture of the true status of the disease in the population and provides information for early diagnosis and appropriate management.

The objective of this narrative review is therefore to describe the historical, epidemiological, clinical and treatment-related aspects of dengue in children, with emphasis on the importance of notifications as a tool for delineating strategies for the control and treatment of dengue in the pediatric population. A review was conducted of the most important published studies on dengue and dengue in children. The following descriptors were used to search for publications from January 1980 to March 2011 in the Lilacs, SciELO, Scopus and Medline databases: "dengue", "dengue in children", "dengue in pediatrics" and "disease notification". Official Brazilian Ministry of Health publications were also consulted.

Dengue in children

Over recent years, studies in Brazil have detected a trend for severe cases of the disease to migrate to younger age groups, which had already been happening in some countries in Asia, and which leads to increased hospitalizations and deaths in this population[11]. In 2008, the disease caused panic and insecurity and both political and institutional arguments in Brazil, with repercussions on a national and international scale, in particular because of the severity with which the child population was affected[12].

Diagnosing dengue in children is a constant challenge and is particularly difficult during the initial phase, because in this population its clinical manifestations are superimposed on countless other conditions that are common in this age group[13]. This age group is subject to a risk of greater severity if comorbidities such as asthma, diabetes mellitus and sickle-cell anemia are present and white-skinned children are also at greater risk[14].

Pediatricians must constantly remain alert to dengue as a diagnostic possibility among children since, during the last 10 years, at least 25% of notified and hospitalized cases were in patients under the age of 15[15]. The current situation with relation to dengue in pediatrics can be improved by initiating treatment when patients are still in the initial phase of the disease, according to clinical staging, so that adequate hydration can be maintained, and by raising awareness about the disease's warning signs.

History

Up until the Second World War, dengue was restricted to a smaller geographic area, but its area then expanded, which was a turning point in its reemergence and spread in the West and the intensification of its occurrence in Asia[16].

The first outbreak of dengue hemorrhagic fever in the Americas, caused by serotype 2, occurred in Cuba in 1981. During that epidemic, 344,203 dengue cases were notified and there were 116,151 hospitalizations, 24 thousand cases of hemorrhagic dengue and dengue shock syndrome, 10,312 patients had circulatory failure and profound shock and 158 deaths were recorded, 101 of which were in the pediatric age group[17].

The epidemiological data on dengue in the Americas paints a worrying picture, with a progressive increase in the number of cases, greater incidence among adolescents and young adults and growing incidence of hemorrhagic fever in children. In some locations, dengue is already a pediatric public health problem[18]. The vector population has increased, there are four serotypes in circulation and increases have been observed in hemorrhagic viremia expression and the number of epidemics[14], demanding a redoubling of prevention efforts and strategies[19].

Dengue in Brazil

The introduction of serotypes 2 and 4, observed in Boa Vista, Roraima, in 1981 and 1982, marked the official arrival of the dengue virus to Brazil, when 11,000 cases were reported, all restricted to a single area[20].

After 1986, a number of cases of dengue caused by DEN 1 were observed in several different states. The hemorrhagic form, caused by serotype 2, was documented in 1990 in Rio de Janeiro, when eight deaths were recorded[21]. With the introduction of serotype 3, from 2000 onwards, severe and rare symptoms began to be observed, spreading rapidly to 24 Brazilian states, with different levels of contagion risk (Figure 1)[21,22].

The epidemiological data show that four million dengue cases were notified in Brazil from 2000 to 2010, with peaks in 2002 and 2008. In 2010 there was a significant increase in the number of cases, probably because DEN 1 came back into circulation[22].

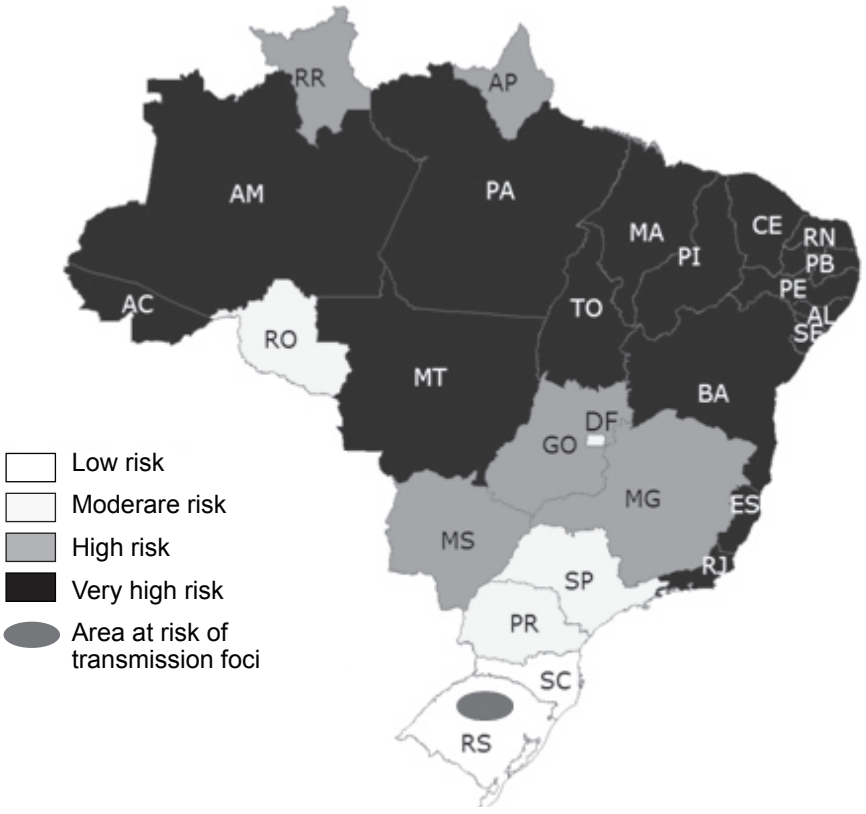
The fact that all four serotypes are circulating in Brazil means that there is a possibility of further, significant dengue epidemics including the severe forms. Furthermore, population growth has meant that the number of individuals susceptible to viruses that are in circulation or have previously been in circulation has increased, thereby also increasing the likelihood of progression to severe manifestations and the proportion of children who are affected[23].

Historically, the Brazilian Ministry of Health (MoH) evaluated the mechanisms for combating *Aedes aegypti* in 1996, developing a national Plan for the Eradication of *Aedes Aegypti* (PEA). However, as the incidence of dengue continued to increase, and with it the gravity of the situation, additional programs were also implemented[24]. The most important of these are the National Dengue Control Program and the National Guidelines for the Prevention and Control of Dengue Epidemics and Dengue Risk. These tools prioritize reduction of dengue mortality, the fight to control the transmission vector, permanent surveillance, adequate communication and education of the public.

The dengue virus and its vector

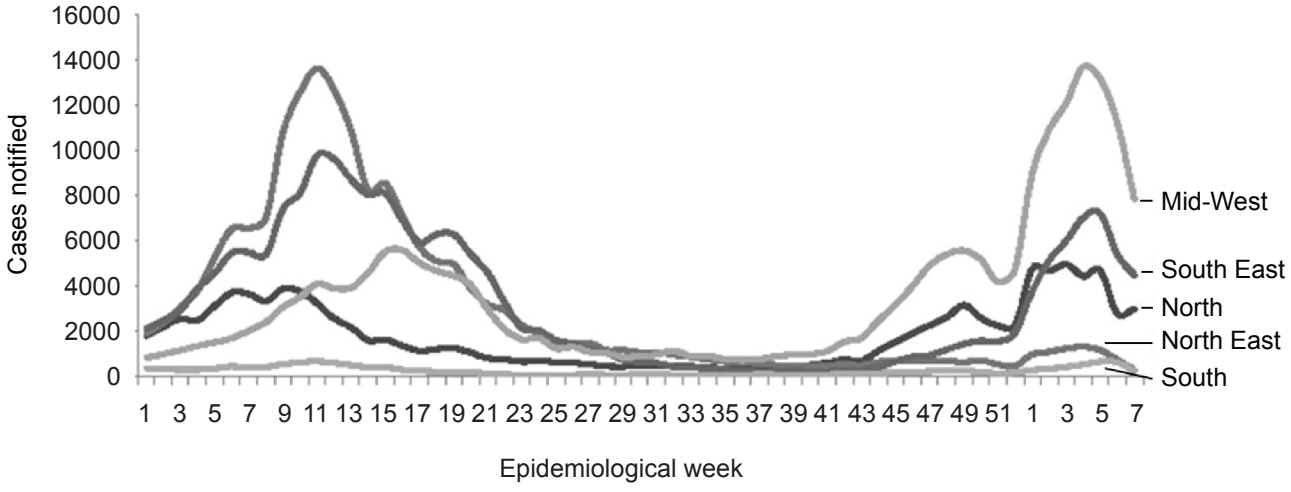
The dengue virus belongs to the genus *Flavivirus,* and the *Flaviviridae* family, and is one of a group of more than 68 viral agents linked by a phylogenetic relationship. These are genome viruses composed of single chain ribonucleic acid (RNA) that multiply in the cells of vertebrates and vector insects. It is believed that the disease originated in monkeys and migrated to humans around 800 years, probably due to increasing populations[25].

A. Current map of dengue risk in Brazil



OBS 1: The map does not show dispersion of DEN-4 to the states.
OBS 2: Santa Catarina state (SC) has never had an autochthonous case of dengue

B. Cases of dengue notified, by epidemiological week and region of Brazil , 2009–2010



Source: Ministry of Health[15]

Figure 1 - Dengue distribution in Brazil

Susceptibility to the virus is universal and infection by one serotype leads to lifelong immunity to that specific serotype and partial and temporary protection against the others[26].

Aedes aegypti probably originated in Africa, in the vicinity of Ethiopia, and was introduced to the Americas during colonization. In addition to being the most important dengue vector, *A. aegypti* is also responsible for transmitting yellow fever. This arthropod is rarely observed beyond the area between the 45th parallel North and the 35th parallel South. As world temperatures increase, its distribution will probably increase globally[27]. The only method currently available for controlling and preventing a transmission of the dengue virus is to attack its vectors, since they are the only link in the chain of transmission that can be eliminated[2].

Transmission

The primary form of transmission is by being bitten by a blood-feeding female of the *Aedes* genus that needs to mature its eggs and is infected with the dengue virus. In rare cases, dengue transmission has occurred after organ transplantation or blood transfusion from infected donors[28]. There are also a small number of reports of transmission in laboratories by accidental inoculation of workers with the virus[29]. Transmission cannot occur as a result of contact between healthy people and infected people or their secretions, nor via water or food[30]. Vertical transplacental transmission is a risk factor for development of the hemorrhagic form in small children and is caused by the presence of maternal antibodies to a primary infection[31].

Pathogenesis

The pathogenesis of the immunoresponse to acute dengue infection can be primary or secondary. Primary reactions occur in people who have not previously been exposed and in these cases antibody titers increase gradually. In contrast, antibody levels rise rapidly in response to secondary reactions, indicating prior infection by any of the viral serotypes. There are at least three established theories that attempt to explain the occurrence of dengue hemorrhagic fever (DHF), but none of them is by itself able to fully explain the severe form of the disease or its development in each person[10]. The first theory is related to the virulence of the strain contracted, suggesting that the more severe forms of the disease are caused by extremely virulent strains[32]. The second theory, proposed by Halstead, postulates that the severe form of the disease is related to sequential infections by different serotypes, at intervals of 3 months to 5 years. According to this theory, immunoresponse is exacerbated in the second infection, causing the increased severity. Dengue hemorrhagic fever can occur in 95% of second infections and in 5% of children suffering a first infection and with low levels of maternal dengue antibodies[33]. The last of the established theories, and the most widely accepted one, is the Integral Multicausality Theory, which was proposed by Cuban researchers. This theory combines a series of risk factors with the sequential infections theory and the theory based on the virulence of different strains, suggesting that it is interaction between these factors that provide the conditions for DHF[34].

Clinical and laboratory findings

The MoH has ruled that dengue is notifiable disease and made it obligatory to notify all suspected cases. A suspected case is defined as an acute fever lasting less than 7 days accompanied by two or more signs or symptoms such as headaches, retro-orbital pain, myalgia, arthralgia, prostration and exanthema, associated or not with hemorrhage, plus a positive epidemiological history. Classification is based on clinical and laboratory findings (Figure 2)[15].

The clinical manifestations of dengue can vary from undifferentiated fever to severe, life-threatening cases and infection from any of the four serotypes can result in death or recovery[35]. Systemic vascular leakage, thrombocytopenia and hypovolemic shock are observed in fatal cases. Cases presenting as undifferentiated fever are not always diagnosed, which primarily occurs with first infections[36]. Oligosymptomatic cases can also lead to severe complications, such as Guillain Barré syndrome[37].

In children less than 2 years old, and especially among infants less than 6 months old, the general symptoms that are part of the diagnostic criteria for dengue, such as headaches, retro-orbital pain, arthralgia and myalgias are manifest as persistent crying, asthenia and irritability, which can easily be confused with one of the countless other infectious causes of fever that this age group is subject to. As a result, the first clinical manifestations detected may be those of the severe form, particularly because progression from the mild to the severe presentation is sudden, unlike with adults[15].

A prospective study of children in India found that the most common symptoms of dengue were vomiting, abdominal pains and myalgia. The most common hemorrhagic manifestations were a positive tourniquet test and spontaneous bleeding in the form of epistaxis; all of the children studied had fever [38]. In the majority of cases vascular leakage manifests as perivesicular edema, ascites and pleural hemorrhage[39]. Dengue should be the primary diagnostic suspicion when faced with a child with exanthema and fever in an endemic area[40]. Complications include liver failure and renal failure[41], encephalopathies[42], rupture of the spleen[43], sepsis and bacterial infections, hemorrhages of the retina and middle ear, cerebral

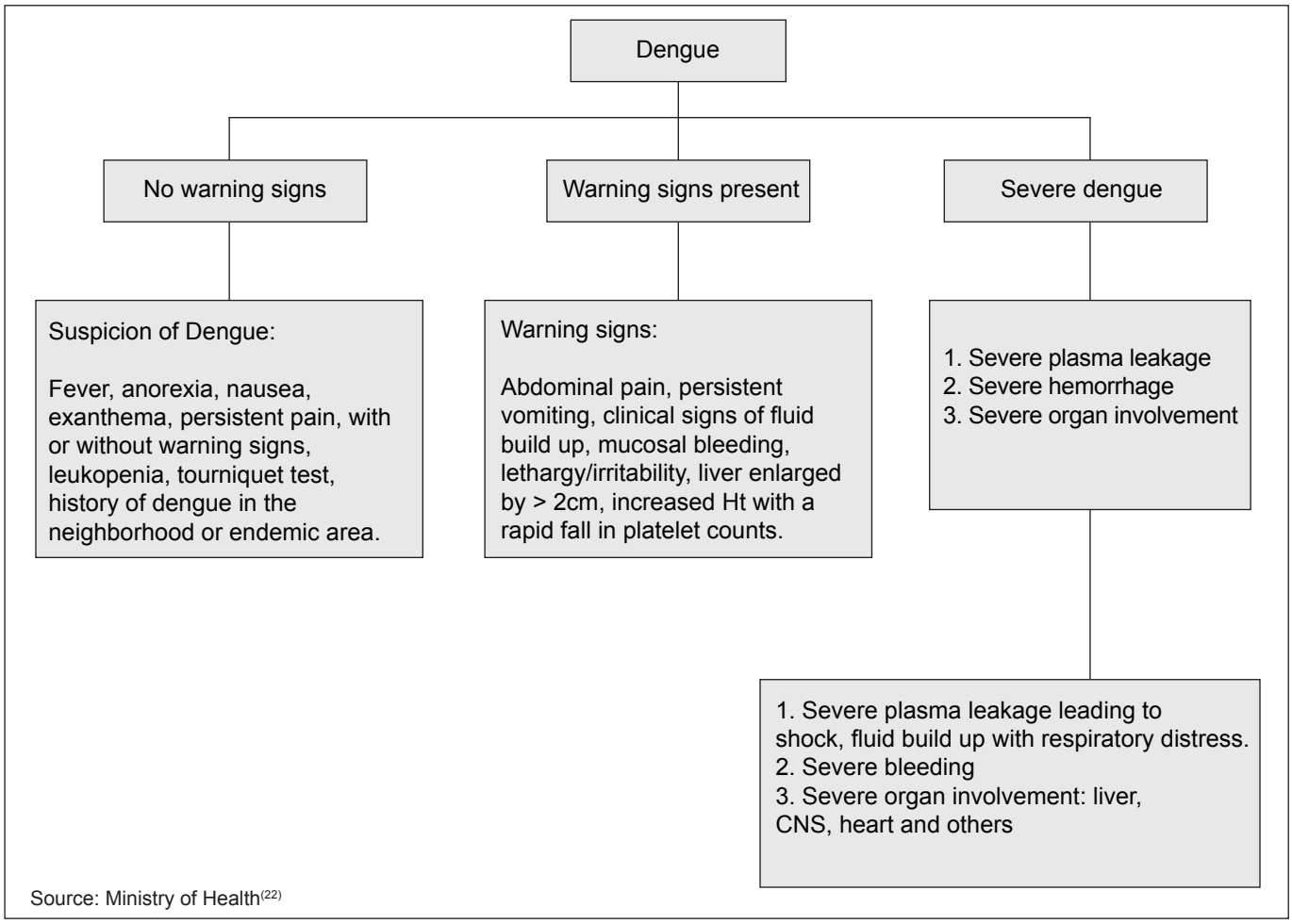


Figure 2 - New clinical classification of dengue

hemorrhages, shock, respiratory distress syndrome, Reye syndrome, massive hemorrhages, noncardiogenic pulmonary edema and disseminated intravascular coagulation[35].

All of the clinical, epidemiological and laboratory data are taken into considerations before reaching a final diagnosis of dengue. The final clinical classification of each case is a variable that is of fundamental importance to monitoring potential exacerbation of the epidemiological profile of dengue and for early detection of cases[44].

Initial laboratory work up for clinical management of suspected cases is a complete blood count. This test is obligatory for children under 5 because of the barriers to adequate clinical assessment in this age group and it is recommended for patients with comorbidities and expectant mothers younger than 15. Dengue has a variable white blood cell count distribution profile since, although leukopenia and lymphocytosis are expected, leukocytosis does not rule the disease out. As the infection progresses, hemoconcentration and thrombocytopenia may occur, primarily as fever reduces[15].

It is important to investigate and attempt to identify possible determinant factors of mortality, in order to better prevent them in the future. In 2009, the MoH took a step in this direction, implementing a dengue mortality investigation protocol that analyzes quality of care as a determinant factor of death from dengue. The protocol stresses that care is understood to mean: organization of services, accessibility of services and patient management[45]. To achieve an effective quality of care, it is necessary to acquire knowledge about the disease in question.

Differential diagnosis

The wide clinical and progressive spectrum of dengue means that it should be included in differential diagnosis for: flu, enteroviruses, parvovirus, mononucleosis, liver abscess, acute abdomen, urinary tract infection, scarlet fever, pneumonia, sepsis, salmonella infection, rickets, autoimmune purpura, Henoch Schonlein purpura, Kawasaki disease, rubella, measles, erythema infectiosum, drug-induced skin disorders, skin allergies, hantavirus, leptospirosis, yellow fever, malaria, hepatites,

influenza and meningococcemia, in addition to other diseases that are to be expected in the affected region or the region from which the patient originates[9].

Treatment

Currently, treatment is based on early institution of palliative care, the main pillar of which is assisted hydration. The type of hydration needed varies in intensity, route of administration and duration, depending on clinical stage. The details of this are beyond the scope of this review, but have been specified in an MoH reference for pediatric professionals, published in 2011[15]. The current recommendations emphasize the importance for adequate treatment of recognizing warning signs, signs of plasma leakage and signs of shock, rather than relying on falling platelet counts or hemorrhagic phenomena[15].

Aspirin and other non-steroidal anti-inflammatories should be avoided because they increase the risk of Reye syndrome and hemorrhagic phenomena[46]. Palliative use of aspirin is not recommended for children with high fever or pain and only paracetamol and dipyrone have been approved for pediatric use by the MoH[15]. There is a very limited number of antiviral drug options for the dengue virus (RNA), but they have such low efficacy and high toxicity[47] that there are still no antivirals recommended for routine pediatric use with dengue[15].

Information

Information must be as up-to-date, complete and trustworthy as possible and is dependent on correct completion of instruments (notification forms, investigation protocols, declarations, care reports and others) and on collection and organization of data that allows them to be analyzed. It is of fundamental importance that all health professionals both provide timely, high-quality data and are provided with the resulting information, thereby contributing to raising awareness in the community and informing the population[48].

Notification is reporting the occurrence of certain diseases or health problems, irrespective of whether the sanitary authorities are informed by health professionals or some other citizen, with the objective of adopting appropriate interventions. The mere suspicion of a notifiable disease must be reported, with no delays to await diagnostic confirmation, since this could lead to loss of the opportunity to adopt the most recommended preventative and control measures. Notification must be confidential and should only be discussed outside of the public-health/healthcare environment if there is a risk to the community and even in such cases individuals' rights to anonymity must be respected[48].

The diseases on Brazil's list of compulsory notifications are included on the basis of an assessment of the magnitude of the problem, measured as its frequency and its potential to spread; its lethality and socioeconomically relevant severity; its potential for elimination and control; and on the list of conditions in the International Health Regulations[48].

Dengue is on the national list of notifiable diseases and there has been a dengue surveillance system in Brazil since the early 1980s, when the outbreak in Roraima was detected. Suspected cases must be notified and investigated, particularly when cases are the first to be diagnosed in a given area or when DHF is suspected. Deaths from dengue must be investigated immediately.

Out of all cases in the Americas, 78% of those notified occur in Brazil and 61% of all cases notified to the WHO occur in Brazil[23].

Notifiable Diseases Information Database

Brazil's Notifiable Diseases Information System (Sinan) was created in 1990 by the National Epidemiology Center with technical support from Datasus, the Brazilian National Health Service's IT department, and from the Municipal Data Processing Service, Prodabel[49]. Sinan was designed to be implanted at the local level within the services that receive cases with a clinical suspicion of dengue. Its objective is to facilitate the formulation and assessment of health policies, plans and programs, providing a foundation for the decision-making process, with the intention of contributing to improving the population's health status[48].

Sinan is responsible for collecting, transmitting and publishing data that are routinely generated by the epidemiological surveillance system, providing information that can be used to analyze the morbidity profile of populations at all three tiers of Brazilian government. Sinan's database is populated with data originating from notifications and investigations of cases of diseases that are on the current list of compulsorily notifiable diseases in Brazil (in force since it was updated by a ministerial directive), facilitating states' and municipalities' task of inputting data on significant diseases at the local level. It is now the official source of case data and it should be stressed that it is this exact information that the health and surveillance systems analyze[44].

The likelihood of under-reporting to Sinan has reduced over the years, which could indicate improvements on the organization and efficiency of the health services, but incomplete and incorrectly filled out reports are still observed, primarily when less severe cases are notified[50].

Information systems are essential to efforts to modernize health services, even acknowledging the quantity of under-notified cases. The surveillance system works on the assumption that notification data provide information on dengue in parallel with the true situation experienced by the population[44].

Effective utilization of Sinan makes it possible to dynamically diagnosis the occurrence of an event in the population and can provide a basis for explanations of the causes of the conditions it tracks, including dengue, in addition to indicating the risks to which people are exposed[48].

The surveillance systems themselves also undergo evaluations that trace their details, detect problematic areas and provide avenues for the formulation of intervention proposals to continuously improve surveillance. Surveillance in Brazil is now standardized and decentralized in all of the country's municipalities[51].

The primary functions of an integrated surveillance system are detection, notification, investigation, confirmation, analysis, interpretation and response. Politically, disease control is more important than prevention and, for this to occur, surveillance must be adequate[52].

Taking patients' histories and recording their clinical progression and laboratory test results contributes to increasing survival rates among dengue patients and to qualifying the information that makes it possible to conduct analyses that are relevant to better management of this condition in human populations[51]. Information on the details of child deaths from dengue is still sparse and there is a lack of relevant studies and publications.

Vaccines

It is known that an infection from one of the dengue virus serotypes (DENV) only confers long-term immunity against that serotype. Therefore, for a dengue vaccine to protect against all four DENV serotypes, it must be tetravalent. Some vaccine candidates are already in pre-clinical or clinical stages of evaluation (Table 1).

The Pediatric Dengue Vaccine Initiative (PDVI) has been working for the last 6 years to unite scientists, clinical investigators, epidemiologists, economists, social scientists and industry specialists to accelerate the development of dengue vaccines. During the last 6 years, PDVI has brought together a research group based in Asia and the Americas to determine the incidence of dengue, to work on diagnostic methods and to conduct economic studies and clinical trials. A tetravalent live attenuated virus vaccine is currently at an advanced stage of testing (phase III)[53].

Table 1 - Dengue vaccines under development

Technique	Laboratory
Recombinant vaccines	IPK/CIGB
	VaxInnate
	ICGEB
	NHRI
DNA vaccines	Inovio Pharmaceuticals
	Kobe University
	CDC
	NMRC
Virus-like particle vaccines	Cytos Biotechnology
	ICGEB
	Kobe University
Viral vector vaccines	ICGEB
	GenPhar/NMRC
	UNC
	UTMB
	Themis Bioscience/ Pasteur
Inactivated virus vaccines	NMRC
	GSK/WRAIR/Fiocruz
Attenuated virus vaccines	Fiocruz

CDC: Centers for Disease Control and Prevention; CIGB: Center for Genetic Engineering and Biotechnology; Fiocruz: Fundação Oswaldo Cruz; GSK: GlaxoSmithKline Biologicals; ICGEB: International Center for Genetic Engineering and Biotechnology; IPK: Pedro Kourí Tropical Medicine Institute; NHRI: National Health Research Institutes; NMRC: Naval Medical Research Center; UNC: University of North Carolina at Chapel Hill; UTMB: University of Texas Medical Branch; WRAIR: Walter Reed Army Institute of Research
Source: Schmitz *et al*[53]

Final comments

Children's vulnerability to the impact of dengue imposes a need for studies and knowledge about the subject, particularly in pediatrics. Clinical suspicion should be followed by detailed notification in order to explore the best forms of surveillance and the best strategies to combat the disease. The number one priority is early diagnosis in order to avoid exacerbation and the deaths that result. It is necessary that care be focused in pediatrics, particularly when presented with febrile infants and especially so in endemic areas and areas of sustained transmission, when other diagnostic possibilities have been ruled out. The struggle for efficacy in the fight against this epidemic, for improved quality patient care and for correct patient management has overrun the frontiers of consultation rooms and primary care centers and must now be the responsibility of all. There is a lack of information and publications on progression to severe forms and death in children.

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