

DENGUE FEVER IN SOUTH AFRICA: AN IMPORTED DISEASE

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Introduction

Dengue fever occurs in Asia, the Pacific, the Caribbean, the Americas and Africa.¹ It is the fastest-spreading mosquito-borne disease in the world and causes major epidemics in urban areas. The World Health Organization estimates 50 to 100 million cases resulting in 25 000 deaths annually.¹ Urbanisation and increased travel have contributed to a 30-fold increase in dengue cases between 1960 and 2010.²

Humans acquire dengue virus infections through the bites of *Aedes aegypti* mosquitoes (and, to a lesser extent, other *Aedes* species), primarily in urban areas. In forested areas, however, the dengue virus transmission cycle is maintained by non-human primate hosts and *Aedes* mosquitoes. *Aedes aegypti* is widely distributed in Africa and has adapted to breeding in artificial containers such as used tyres etc. in close proximity to human populations. This, coupled with increasing international travel, growing urbanization and expanding human populations, suggests that the risk of local transmission is considerable, as is the potential to produce extensive autochthonous disease spread.² There are four closely related dengue viruses and infection with one type gives little immune protection against the other types.

Following virus infection and an incubation of 8-10 days, a mild and usually self-limiting influenza-like illness develops.¹ However, severe forms including dengue haemorrhagic fever and dengue fever with shock syndrome can develop, inducing mortality rates of 26%.³ There are currently no licensed vaccines or specific therapeutics for dengue, and substantial vector control interventions have not halted its rapid emergence and global spread.⁴

The overall burden of dengue fever in Africa is poorly described despite sporadic reports of local outbreaks from 22 African countries.⁵ An additional twelve African countries have reported cases in returning travellers only.⁵ Diagnostic capacity is limited and active surveillance is not available in most of these countries.

In South Africa, a confirmed dengue outbreak with local transmission occurred in Durban, KwaZulu-Natal Province, in the summer of 1926/27.^{6,7} During the past twenty-five years sporadic cases of dengue have been reported in returning travellers to South Africa. Current surveillance for dengue in South Africa is passive and is based on the submission of specimens collected from suspected arboviral disease cases. The aim of this study was to collate the results and describe the epidemiology of laboratory-tested dengue cases in South Africa from 2008 to date.

Materials and Methods

The Special Viral Pathogens Laboratory of the Centre for Emerging and Zoonotic Diseases (CEZD), National Institute for Communicable Diseases (NICD), is the national reference laboratory for the investigation of human arbovirus infections, including dengue, in South Africa. The testing protocol includes screening for total humoral antibody response against various arbovirus antigens using a haemagglutination inhibition assay (HAI).⁸ Reactive specimens are then tested using a virus specific antigen-based Immunoglobulin M capture Enzyme-Linked Immunosorbent Assay (IgM C-ELISA) which includes dengue virus antigen.⁹ Reverse transcription PCR and virus isolation in suckling mice or in Vero cell culture are also attempted for acute cases. Cases are considered laboratory-confirmed if PCR and/or virus isolation results are positive, or if IgM C-ELISA

is positive on paired sera and/or if a 4-fold increase in IgG titre is detected in paired sera. An IgM positive on a single submission is highly suggestive of recent infection with dengue virus.⁸

Laboratory-confirmed dengue cases from South Africa for the period January 2008 to June 2013 are described in this review. Non-human specimens and requests from other countries were excluded. Analysis was based on data patient files using a Microsoft Excel database, Stata 11 (StataCorp, 2011) and EpiInfo software version 3.5 (Centres for Disease Control and Prevention, 2008). Travel histories to countries where dengue is endemic were collected in order to describe the origins of imported disease. Gender ratio and age distribution among lab requests and dengue-confirmed cases were described using median age and inter-quartile range (middle 50% of the cases around the median). Clinical

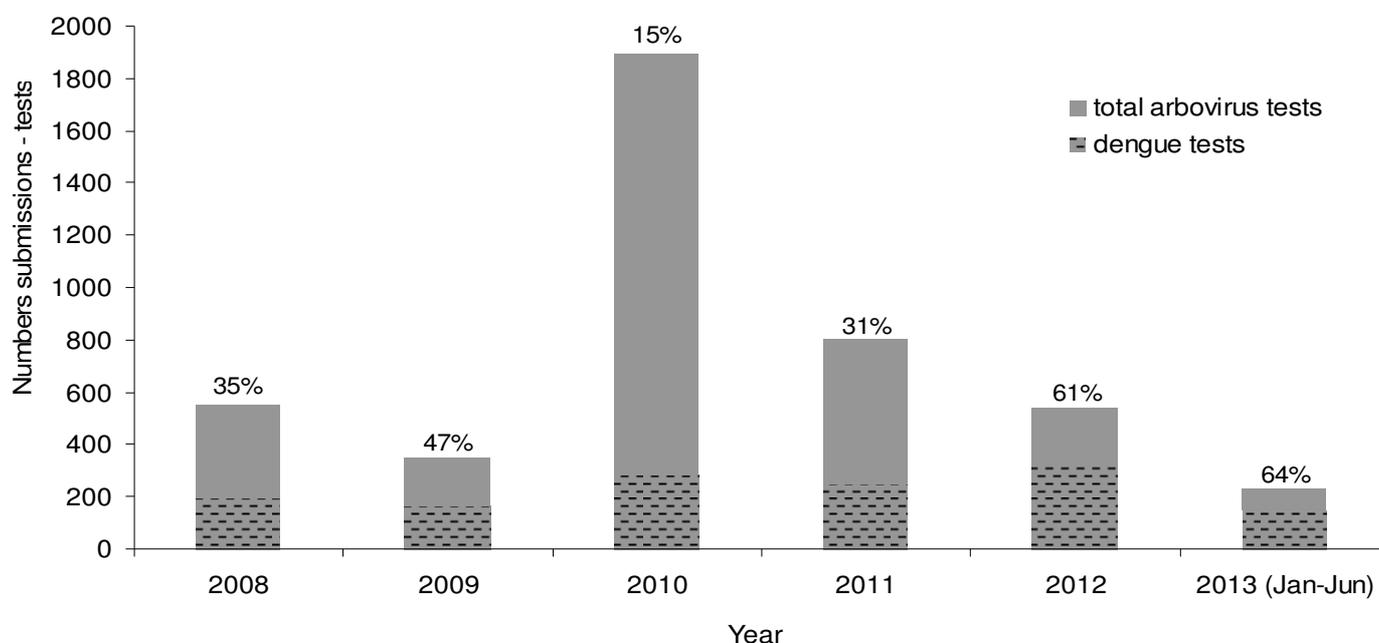
findings for laboratory-confirmed cases were documented.

Results

Laboratory investigation of suspected dengue cases

For the period 2008 to 2012 a total of 4 133 specimens from patients in South Africa was submitted for arbovirus laboratory confirmation of which 1 218 specimens were specifically requested to be tested for dengue. The proportion of arbovirus tests including those for dengue fever increased significantly during the reporting period: 195/551 in 2008, 165/348 in 2009, 283/1893 in 2010, 249/804 in 2011, 326/537 in 2012 ($P < 0.0001$) (Figure 1). During the period January to end June 2013, the NICD received a total of 146 specimens requesting dengue testing from a total of 228 suspected arbovirus patients in South Africa.

Figure 1: Total arbovirus and dengue tests* (percentages of total) for cases in South Africa, 2008-2012, and 2013 (January - June).



*Repeated tests of a case were included in interpretation of results but not counted. Numbers are estimates of patients treated locally in South Africa. The increased number of submissions for arbovirus investigation in 2010 and 2011 coincided with the outbreak of Rift Valley fever (RVF) in South Africa during this time.

From January 2008 to June 2013, 83 acute dengue infections were identified through laboratory based surveillance. Evidence suggesting recent infection was found in 69 patients by the IgM C-ELISA. Of 28 suspected acute cases, 16 were confirmed by PCR. Among the 16 acute patients, 14 had either not developed a detectable antibody response at the time of diagnosis or were not tested by IgM ELISA.

On further investigation, 3 patients in 2008, 10 patients in 2009, 21 patients in 2010, 9 patients in 2011 and 19 patients in 2012 tested positive for dengue infection. Until June 2013, 21 locally treated dengue cases have been laboratory confirmed.

The average detection rate for dengue in submitted specimens is 6.1% (83 confirmed cases per 1364 dengue tests) over the past 5 years and including the first half of 2013. There is an increasing trend in the number of tests for dengue and the number of cases diagnosed: 4% (9/249) in 2011, 6% (19/326) in 2012 and 14% (21/146) in 2013 (January-June) ($P < 0.0001$).

Demographics of confirmed dengue cases

Of the 4 361 specimens submitted from 2008 through June 2013, almost twice as many were received from

men than women (male/female ratio: 1.9, range of 1.5 to 2.2 annually). The male/female ratio amongst anti-dengue IgM antibody and/or RT-PCR-positive cases was more equal (male/female ratio: 1.3, range of 0.5 to 2.3 between years). The age distribution of cases tested between 2008 and June 2013 ranged from 26 to 49 years, with a median of 37 years. The median age among dengue positive cases was 43 years, with an inter-quartile range of 29 to 50 years. A high proportion of samples from male farmers were received during the 2008-2011 Rift Valley fever outbreaks in South Africa.

Travel histories of dengue cases

Travel histories were only available for 16 cases that tested positive for dengue between 2008 and 2011. Positive dengue cases diagnosed in 2012 and 2013 were followed up more proactively and travel reports for 12/19 and 17/21 cases, respectively, were obtained. The majority of cases had travelled to South East Asia, with fewer numbers having visited Central Africa and South America (figure 2). Dengue cases in South Africa were detected throughout the year. Approximately 50% to 60% of the cases originated from provinces where international airports are based (Gauteng, Western Cape and KwaZulu Natal provinces).

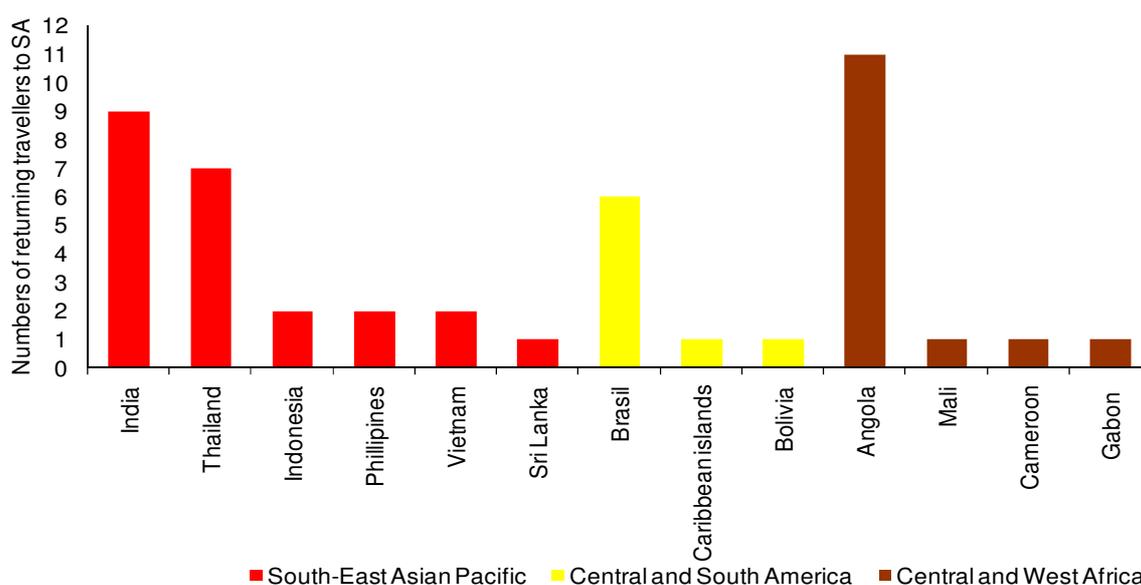


Figure 2: Travel destinations (n=45) of South African cases treated for dengue and confirmed by laboratory testing for the period January 2008 to June 2013.

Clinical findings

Based on a review of the patient files and active follow up case investigations for 2012 and 2013, the most frequently observed symptom associated with dengue infection was fever (80%, 24/30) (table 1). Other symptoms included headache (10/30), myalgia (11/30), nausea/vomiting/gastric pain (9/30), conjunctivitis (4/30), lymphadenopathy (4/30) and sore throat (2/30). Development of rash, which is typical for dengue, was recorded in 30% (11/30) of patients and manifested in maculopapular, haemorrhagic or petechial forms in the abdominal area, on the legs, or on other parts of the body. Thrombocytopenia was recorded in 8/30 patients and sub-conjunctival haemorrhage was recorded for one patient. Although very few incidents of haemorrhagic

fever have been recorded to date in South Africa, more complicated forms of dengue occurred amongst the patients suffering from prolonged fever, headache, body pains and lymphadenopathy lasting for five to ten days. These symptoms, combined with skin rash, liver and blood pathology, required admission to a hospital. No deaths were reported due to acute disease amongst these cases.

The NICD performs diagnosis on patients referred by other physicians and does not extend activities to long term follow up of individual dengue cases. Recurrence of disease through probable secondary infection with other dengue types was however noted in two related cases in 2010 and 2011.

Table 1: Clinical and pathological symptoms of confirmed dengue cases (n=30) in South Africa from 2012 and 2013.

Symptom	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	TOTAL
Fever & chills	+	+	+	+	-	+	+	+		+	+		+	+	+	+	+	+			+		+	+	+	+	+	+	+	+	24
Headache		+	+			+	+			+			+									+	+				+	+			10
Sore throat														+												+					2
Body/muscle pain/myalgia	+	+				+	+				+				+	+		+				+	+		+						11
Painful joints																							+		+						2
Rigor				+												+															2
Fatigue																							+	+							2
Nausea				+							+	+											+								4
Vomiting/gastric pain										+		+					+						+								5
Cough																							+								1
Sore eyes/conjunctivitis			+			+	+					+																			4
Rash		-	+	+	+	-	-	+		+		+				-		+			+		+		+		-		+		11
Painful swollen lymph nodes						+	+																+				+				4
Low platelets	+									+				+		+									+			+	+		8
Low white blood cells	+																								+			+			3
Pleural effusions																	+														1
Low heart rate																	+														1
Liver tenderness																				+											1
Fluid in abdomen																				+											1
Subconjunctival haemorrhage										+																					1
Meningism ¹		+																													1
Segmental myoclonus ²									+																						1

¹ Triad of neck stiffness, photophobia, headache

² Involuntary twitching of muscle

Conclusion

The occurrence of dengue fever is increasing with cases reported from more than 100 countries worldwide. With increasing ease of travel, South African travellers are more likely to be exposed to dengue fever than ever before. Despite the explosive prevalence of dengue worldwide it remains an underreported, undiagnosed or misdiagnosed infection in returning travellers to South Africa. These data, however, do show an increasing trend in requests and confirmations of dengue fever cases. Male and female travellers appear to be at equal

risk. Travellers returning from South-East Asia and Central-West Africa are most affected. Dengue fever should be considered in travellers returning from known endemic areas and presenting with febrile illness (often with rash and severe myalgia).

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