

# Mosquitoes as vectors of human disease in South Africa

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## Abstract

While malaria is the most important mosquito-borne disease in South Africa, there are also several mosquito-borne viruses that also cause human disease. The most significant are chikungunya, West Nile, Sindbis and Rift Valley fever viruses. In this review these are compared with malaria, mainly in regard to their ecology and epidemiology.

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### Introduction

Only the female mosquito sucks blood to obtain protein to develop her eggs. Spielman and D'Antonio have described the detection of the human host and subsequent blood feeding in detail.<sup>1</sup> Briefly, this is as follows. Consider a human "victim" sitting outside- a mosquito will respond to his scent plume, a mixture of exhaled carbon dioxide and lactic acid, because sensors on her antennae are tuned to these chemicals and other chemicals in the person's body odour.

The scent plume, heavier than air, sinks to the ground and the mosquito flies in low to intersect the plume at its widest part. As the mosquito gets close, the host's movement and body heat will guide her to any uncovered flesh. She probes with her proboscis until her fascicle nicks a venule or arteriole. With each insertion, a fine salivary tube in her fascicle will deliver an anticoagulant to inhibit any bleeding. What is left behind in the saliva that was pumped into the host's skin often irritates the host and sometimes may lead to illness or even death.

It is well known that malaria is the most important mosquito-borne disease in South Africa. However, what is less well known is that there are also several mosquito-borne viruses that also cause human disease. The arthropod-borne viruses in South

Africa, the so-called arboviruses, have been reviewed in some detail by McIntosh.<sup>2</sup> The aim of the present paper is to give an updated brief review which includes comparison of the mosquito-borne viruses with mosquito-borne malaria. Only one vertebrate host-humans- are needed in the transmission cycle of human malaria, and certain species of *Anopheles* mosquito, whereas mosquito-borne arboviruses are true zoonoses.

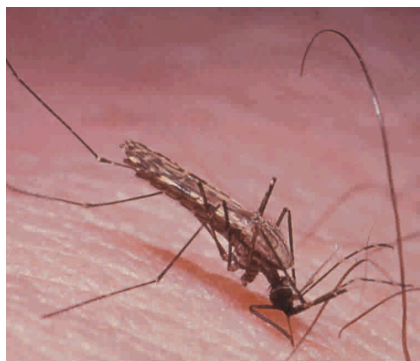
Zoonoses are infections that are intertransmissible between animals and human beings. Hence there is mosquito transmission between wild vertebrates or domestic livestock as well as mosquito transmission to humans, sometimes including human to human transmission. The viruses multiply in both vertebrates and vectors. The viruses produce a viraemia in vertebrates to infect the vector mosquitoes and must infect the salivary gland of these vectors so that vectors can secrete virus in their saliva to infect further vertebrates. Twenty-two mosquito-borne viruses have been isolated in southern Africa of which 10 are known to cause human illness. Out of the 10 viruses, 4 are of significant medical importance. Chikungunya and Sindbis viruses are both classified in the genus *Alphavirus* (family *Togaviridae*) while West Nile virus belongs to the genus *Flavivirus*

(family *Flaviviridae*) and Rift Valley fever virus to the genus *Phlebovirus* (family *Bunyaviridae*). Additionally, imported dengue, another *Flavivirus*, has infected man in KwaZulu Natal. A human being is always regarded as an incidental host as humans are not usually involved in the maintenance of the viruses in nature. Nevertheless, in certain cases humans become highly viraemic and readily infect mosquitoes.

### Malaria

The high risk area for malaria in South Africa is a narrow strip on our eastern border stretching from Musina (previously Messina) in the north to Swaziland in the south, where it consists mainly of the Kruger National Park and adjacent private game reserves. It also includes eastern Swaziland and northern KwaZulu Natal. Rarely, limited focal transmission may occur in the North-West and Northern Cape provinces along the Molopo and Orange rivers.<sup>3</sup>

The 2 vectors in South Africa are *Anopheles arabiensis* and *Anopheles funestus*, belonging to 2 different complexes of mosquito species. Within each complex, final identification can only be achieved by examining their chromosomes (karyotyping) or portions of their DNA (sequence analysis). Both species lay separate floating eggs in ground

**Figure 1: *Anopheles arabiensis***

water. *An. arabiensis* prefers temporary to semi-permanent ground pools with a moderate amount of vegetation that develop after rain so that they become widespread during the rainy season. *An. funestus* larvae are found mainly in the shady margins of warm perennial streams where the vegetation is rank and the current slow.

As they are confined to perennial streams, heavy rains do not favour this mosquito because they flush the eggs and larvae down stream.<sup>3</sup> Up until 1996 houses, particularly traditional huts, were sprayed annually with residual DDT when the treatment changed to the pyrethroid deltamethrin. This resulted in an upsurge in malaria between 1995 and 1999, for example a 6- fold increase in incidence at Ndumu in northern KwaZulu Natal.<sup>4</sup> During the DDT period the only significant vector was *An. arabiensis* as the more endophilic *An. funestus* had been well controlled. However, in 1999 *An. funestus* had reappeared in northern KwaZulu Natal showing resistance to pyrethroid insecticides.<sup>4</sup> In 2003, resistance tests on *An. arabiensis* from northern KwaZulu Natal also showed that a degree of resistance to DDT had developed which has serious implications for vector control operations in South Africa.<sup>5</sup> Since the new political dispensation in South Africa in April, 1994, human traffic from neighbouring African states has greatly increased. This has probably been the cause of chloroquine resistant strains of the parasite entering the country while concurrently mosquito control and malaria prophylaxis have deteriorated in both Mozambique and Zimbabwe. Hence our South African

Health Departments have had to deal with an increase in vector populations (especially after good rains), vector resistance to insecticides and our whole malaria area becoming chloroquine resistant.

Studies on the biting behaviour of *An. arabiensis* in the Limpopo province have shown that the great majority of bites occur during the night time at ground level, decreasing markedly 72cm or higher above the ground.<sup>6</sup> Furthermore, in another study in the same area, 81% of mosquitoes of this species were shown to bite the ankles and feet rather than other parts of the body and the application of DEET (diethyltoluamide) repellent to ankles and feet provided 69.2% protection against *An. arabiensis* bites.<sup>7</sup> These results indicate therefore that wearing socks and closed shoes, emphasizing the lower legs when applying repellents and raising feet above ground level at night could considerably reduce the risk of contracting malaria. These studies need to be repeated with *An. funestus*, although it is well known that *Anopheles* species in general are most active at ground level.

### Chikungunya

Outbreaks of this virus have occurred infrequently in the rural tropical wooded savannah of the eastern Limpopo Province, northern KwaZulu Natal and the Zimbabwe lowlands. Hence its distribution is similar to that of malaria.

The primary vectors are *Aedes furcifer* and possibly also *Aedes cordellieri*. Because females of these 2 species are indistinguishable it has not always been possible to know whether one or both have acted as vectors.<sup>8</sup> However, *Ae. furcifer* s. s. accounted for most mosquitoes in this group during the chikungunya outbreak at Mica in 1975/76 when 16 isolations of the virus were made from the *Ae. furcifer* group and in vector competence experiments it was shown to be a moderately efficient vector of the virus.<sup>9,10</sup> How *Ae. cordellieri*, which is more prevalent at some localities than *Ae. furcifer* s. s., would compare with *Ae. furcifer* in such experiments remains to be evaluated.

There is a feral transmission cycle between these 2 mosquito species and both baboons and vervet monkeys. Viral transmission occurs at night while the wild primates are sleeping in the canopies of trees or in high rocky outcrops or cliffs. The vectors show a higher feeding rate in the canopy of trees than on the ground but nevertheless will bite humans on the ground in the vicinity of the wild primate sleeping places. Thus human infection has been entirely rural.<sup>9</sup> Both *Ae. furcifer* and *Ae. cordellieri* are tree hole breeding mosquitoes. Their eggs are deposited on the moist wood within such holes, sometimes deep within the tree. Some of the eggs hatch each time rain fills or partially fills the tree hole and when the hole dries out again any unhatched eggs remaining can survive provided a high relative humidity persists deep within the hole.

In this way the vectors can survive several years without rain.

**Figure 2: *Aedes furcifer* – vector of chikungunya**

Human outbreaks of chikungunya occurred in the eastern Northern Province in 1956,<sup>11</sup> 1975/76<sup>9</sup> and 1977<sup>12,13</sup> and in southern Zimbabwe in 1961/62<sup>14</sup> and 1971.<sup>15</sup> More recently in 2001 one case of chikungunya was diagnosed in a person who had stayed in the eastern Northern Province.<sup>16</sup> An epizootic in monkeys without human cases is known to have occurred in northern KwaZulu Natal in 1964. As has been discussed previously, in the absence of extensive evergreen rain forest in southern Africa with an enzootic vector like *Aedes africanus*, it is unlikely that a mosquito-monkey forest cycle occurs for viral maintenance. Vertical transmission by the *Ae. furcifer* group, following virus survival in the egg stage, does

not appear to occur and this is the only other mechanism that would ensure virus persistence.<sup>17</sup> It seems therefore that chikungunya virus enters southern Africa from countries to the north through a series of *Ae. furcifer/Ae. cordellieri*-transmission cycles covering a large geographic area. Widespread heavy rainfall would be required to provide sufficiently high mosquito population densities. The absence of significant anthropophilic populations of *Aedes aegypti* inland in South Africa may explain why previous chikungunya outbreaks have not spread over large areas but have remained focal and rural. *Ae. aegypti* has been the urban vector in several tropical countries outside South Africa.

### West Nile and Sindbis

West Nile and Sindbis viruses have the same ecology in South Africa with human infection commonest in the moister parts of the Highveld. Both viruses are endemic to the Highveld and Karoo regions (inland plateau) with human cases occurring sporadically each year in the Highveld.

*Culex univittatus* is the primary mosquito vector on the temperate inland plateau, while *Culex neavei*, another ornithophilic species, plays that role in the KwaZulu Natal lowlands.<sup>18,19</sup> These *Culex* mosquitoes deposit their eggs in ground water, their eggs being unable to withstand any drying. *Cx. univittatus* prefers temporary to semi-permanent rain-flooded grassland and the margins of temporary or permanent vleis as breeding places. Emergent vegetation and clearer, cleaner water are important to this species.<sup>20</sup> In contrast to the *Aedes* species described above, *Culex* species pass through the dry winters by means of quiescent larvae and pupae in permanent water collections or as dormant adult females.

There is a maintenance transmission cycle in the summer in which these mosquito vectors feed on several species of wild birds, the primary vertebrate hosts of the viruses. Human infection depends entirely on the vectors acquiring infection from birds and it is therefore closely associated with avian infection.<sup>18,19,21,22</sup> As humans

are poorly viraemic after infection with either virus, they cannot significantly infect mosquitoes so would usually represent a dead end in the transmission cycle. On the Highveld, *Culex univittatus* has a low feeding rate on humans which tends to limit human infection. However, when climatic conditions-heavy rain and higher than usual temperatures-have favoured mosquito breeding and virus multiplication within the vectors, there have been significant outbreaks of the viruses.<sup>23-26</sup> Sindbis clinical infections have been more readily recognized than West Nile infections, probably because West Nile fever is a more benign illness. The single occasion when clinical West Nile infections predominated was in the Karoo during the 1974 floods when 1000's of cases were seen.<sup>26</sup> At that time there was a massive epizootic of both viruses in birds and high densities of *Cx. univittatus*.

### Rift Valley fever

Rift Valley fever is important mainly because of the disease it causes in sheep, cattle and goats where there is high viraemia, hepatitis, gastroenteritis, haemorrhages, abortion and death.<sup>27</sup> However, it also causes human disease, usually a mild febrile illness but there may be complications and even death as described below under 'Clinical Symptoms'. Outbreaks of this virus occurred principally in the Karoo and Highveld in the 1950's and 1970's during years of much above average rainfall.<sup>28</sup> At these times the Panveld of the western Free State Province and the eastern part of the Northern Cape Province becomes so saturated that large pans and areas of pasture are flooded. Under these conditions large populations of floodwater *Aedes* are the first mosquitoes produced, originating from dormant eggs lying up to 6cms below the soil surface in the pans.<sup>29,30</sup> This is followed by the appearance of equally large populations of *Culex* mosquitoes. Virus outbreaks have also occurred in the KwaZulu Natal lowlands where the last outbreak was in 1981.<sup>31</sup> Isolations of the virus from field mosquitoes and vector competence tests have indicated that species belonging to the genus

*Ochlerotatus* and the *Aedes* subgenus *Neomelanicolonia* are vectors. In the latter, *Aedes mcintoshi* appears to be the most important species on the inland plateau while *Aedes circumluteolus* has the vectorial role in the KwaZulu Natal coastal lowlands.

*Culex theileri* and *Culex zombaensis* are also vectors on the plateau and in the KwaZulu Natal lowlands respectively. In Kenya, isolations of the virus have been made from *Ae. mcintoshi* reared from field collected larvae which suggests that the dormant eggs of this species act as the virus reservoir carrying virus through the dry season to the next generation of mosquitoes.<sup>32</sup> Evidence is still awaited to show whether this also occurs in South Africa. A wild primary vertebrate host of this virus has not yet been firmly identified but the African buffalo (*Syncerus caffer*) might be such a host. Recently Rift Valley fever emerged as a small outbreak in buffaloes at Skukuza in the Kruger National Park, Mpumalanga,<sup>33</sup> and the retrospective testing of buffalo sera from the park has indicated the presence of the virus in this area at times when no epidemics were occurring in livestock in South Africa.<sup>34</sup>

Human infection has occurred mainly in the farming community, veterinarians and abattoir personnel and has always been associated with concurrent infections in domestic ruminants, particularly sheep. Infection by the contagious route by handling infected animal carcasses accounts for most human cases. However, infection by mosquito bite also occurs as most of the vector species transmitting the virus to livestock also bite man readily when the opportunity arises. It seems that significant human infection occurs after there has been sufficient amplification of virus in livestock and mosquitoes. The severest human outbreaks were in 1975 when human mortality was first recognized.<sup>35,36</sup> Because such high viraemias are reached in livestock and humans with this virus, mechanical transmission can also take place by a range of mosquito species and several other biting insects. This is in addition to the biological transmission by the vectors described above.<sup>37,38</sup>

## Dengue

The potential for future outbreaks of chikungunya, dengue and yellow fever in South Africa by importation of virus in viraemic persons entering the country was evaluated in 1996.<sup>39</sup> There were dengue outbreaks in KwaZulu Natal in 1897, 1901 and again in 1926/1927 when a large outbreak of dengue 1 occurred in Durban after unusually high rainfall i.e. 5669 mm and 8839mm in those 2 years compared to the normal 1008mm. In 1984 Mozambique experienced an outbreak of dengue 3. In 1985 several people who returned to Durban after visits to India suffered dengue 1 infections and between 1997 and 2003 there were 11 more imported cases of which 2 have been typed as dengue 1 and 3 as dengue 2 strains.<sup>40-42</sup> Ecological studies showed that several localities along the KwaZulu Natal coast had substantial anthropophilic populations of *Ae. aegypti*.<sup>43</sup>

Vector competence tests have shown that these KwaZulu Natal coastal populations of *Ae. aegypti* are competent vectors of dengue 1 and dengue 2 viruses, with the Durban population being the most efficient vector.<sup>44</sup> All this suggests that another outbreak could occur in South Africa through viraemic travellers entering the country from Asia. An individual could become infected with dengue in Asia and reach South Africa before becoming clinically ill and viraemic. If such a person was then bitten by *Ae. aegypti* mosquitoes, a secondary transmission cycle could be set up which could lead to a dengue epidemic.

## Clinical Symptoms

### Malaria

Several of the symptoms of malaria are common to the illnesses caused by the 4 arboviruses that have been discussed in this paper. These are fever, headache and myalgia. However, whereas malaria has a severe periodic fever, fever is mild and non-periodic with the 4 viruses. Furthermore, the incubation period for malaria from the time the patient is bitten by an infected mosquito is 10-16 days compared to about 2-7 days

for the viruses. An enlarged spleen and anaemia, symptoms developing after about one week in malaria, are not characteristic of the viruses. All these viruses except Rift Valley fever usually cause a rash that is another difference from malaria. However, a person who develops a significant fever after having been in a malaria area should always have his blood examined or tested for malarial parasites.

**Figure 3:** *Aedes aegypti*, urban vector of the dengue virus



### Chikungunya

This fever has a sudden onset with chills, flushed face, nausea, vomiting, backache, headache, photophobia, lymphadenopathy, arthralgia and rash. The acute stage of chikungunya lasts for 3-5 days and recovery 5-7 days. The arthralgia is the most significant symptom, present in 70% of cases and affects one joint or several. Swelling and reddening of the joint usually occurs. In a few cases this arthritis may last for months or years and mimic rheumatoid arthritis. Patients with persistent joint pain and stiffness have shown higher antibody titres in the haemagglutination inhibition test.<sup>12,45,46</sup> The rash most common on the trunk, is macular or maculopapular and may occur in short-lived episodes.<sup>11,46</sup>

### Sindbis

Symptoms are a mild fever, headache, and rash together with pain in the joints and tendons. The acute illness lasts 3-10 days but arthralgia occasionally lasts for several weeks. The rash, mainly on the trunk, limbs, palms and soles, is maculopapular and may be widespread. The discrete papules are 3mm in diameter and often ringed by

a pale halo. The lesions may disappear to reappear later leaving brown stains.<sup>47,23-25</sup>

### West Nile

West Nile fever can vary from asymptomatic infections, mild infections, to severe meningo-encephalitis. Children experience a mild disease while meningo-encephalitis is a rare complication in the aged.<sup>23,24,48,49</sup> The usual illness includes fever, headache, lymphadenopathy, sore throat, myalgia, arthralgia as well as a rash. West Nile fever is indistinguishable from Sindbis fever, although joint pain and rash are less frequent and less prominent.<sup>23,24,48,49</sup>

### Rift Valley fever

Patients usually have a mild febrile illness during which high viraemia, headache, malaise, low back myalgia, flushed face, conjunctival suffusion, photophobia, nausea and vomiting are among the symptoms recorded. The illness lasts 4-7 days and there is usually complete recovery within 2 weeks but rarely there may be one or more of the following 3 serious complications. These are a generalized haemorrhagic state, meningo-encephalitis and retinopathy.<sup>35,36,50-53</sup> As to the latter, it appears within 5-15 days of onset of the disease, presenting as a partial loss of vision, which may be bilateral. There is an exudate on the retina, accompanied by oedema and haemorrhage in the region of the macula. Retinal detachment may occur. Approximately half the patients with severe lesions develop permanent loss of central vision.<sup>54</sup>

## Laboratory Diagnosis

Diagnosis of malaria is normally done in South Africa by a morphological examination of a blood film. In some cases, however, other tests are useful, particularly if the patient has taken anti-malarial drugs or other drugs such as sulphonamides that greatly reduce the accuracy of blood films. Hence another test frequently used in South Africa is the dipstick antigen-capture assay based on qualitative detection of *Plasmodium falciparum* histidine-

rich protein 2 (Pf HRP-2).<sup>55</sup>

Since the clinical presentation of the mosquito-borne viruses in South Africa varies considerably, diagnosis should be confirmed in the laboratory. This can be done by isolation of virus or the demonstration of seroconversion during convalescence. Virus isolation is carried out using serum obtained as early as possible in the acute phase that is inoculated into infant mice or tissue culture, usually Vero cells. The acute serum and a further "convalescent" serum collected 14-21 days later is required to demonstrate seroconversion, i.e. a significant antibody titre rise using the haemagglutination inhibition, immunofluorescence, IgG ELISA or neutralisation test. Thirdly the demonstration of specific IgM antibody in serum indicates a recent infection. More recently, probes have become available in certain laboratories such as the Special Pathogens Unit of the National Institute for Communicable Diseases, Johannesburg, for detecting the specific viral RNA of each of the important mosquito-borne viruses by reverse transcription-polymerase chain reaction (RT-PCR). The occurrence of arboviral infections is seasonal, usually only from mid-summer to autumn.

### Mosquito Control

The control of anopheline malaria vectors by house spraying with residual insecticides and some of the personal protection methods that can be taken to prevent bites by these vectors have been mentioned above. In the case of these vectors, such measures are always important. However, with the mosquito-borne viruses, because of their intermittency, mosquito control and personal protection against their culicine vectors is recommended only during outbreaks of these viruses. Methods to protect livestock against mosquito-borne Rift Valley fever have been described.<sup>29</sup> Personal protection methods are the same against all mosquitoes and include mosquito nets, screening of houses, and use of repellents. However, the behaviour of each vector should be taken into account. The behaviour of anophelines

has been discussed in relation to avoiding bites and in the case of the culicine vectors it should be borne in mind that the floodwater *Aedes* bite in the day and night, *Ae. aegypti* bites in the day and at dusk, while the *Culex* vectors and *Ae. furcifer*, like *Anopheles*, bite only after dark. ☛

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