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Odyssean malaria in South Africa, 2014 - 2023

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Summary

Odyssean malaria is caused by malaria parasite-infected mosquitoes that have inadvertently travelled to non-malarious areas via various transport mechanisms (sea, air, rail, road). A person/s bitten by such a mosquito may result in a case/s of malaria in the absence of travel to an endemic area. In South Africa (SA), active malaria transmission predominantly occurs in the north-eastern regions bordering on Mozambique and Zimbabwe. Local acquisition of malaria outside of these areas is unexpected, often leading to delayed diagnosis, complications and death. Malaria is a notifiable medical condition in SA, and notified cases from non-endemic areas in individuals with no recent travel history warrant further investigation of their clinical, epidemiological and entomological aspects. Here we describe odyssean malaria investigations from 2014 to 2023 in SA with which the National Institute for Communicable Diseases (NICD) assisted.

Introduction

Malaria transmission in South Africa (SA) is restricted to low-altitude border regions of Limpopo, Mpumalanga, and KwaZulu-Natal provinces.[1] The elevated temperatures, humidity, and increased rainfall in these areas are recognised as key factors that create a conducive environment for *Anopheles* mosquitoes, the vectors of human malaria. However, although rare, there is also additional risk beyond these endemic areas. Cases of malaria in non-endemic areas without an apparent recent travel history warrant investigation of the cryptic nature of the infection and implementation of public health interventions if required. Reasons for cryptic cases include initial inadequate travel history, late detection of infection acquired in an endemic area, person-to-person transmission through direct contact with infected blood or tissue (e.g. by transfusion of infected blood, transplantation of infected human tissues or by mother-to-child transmission during pregnancy), nosocomial transmission via cross-contamination of materials or fluids used invasively, and importation of an infective *Anopheles* mosquito to a non-endemic area. The last occurs due to the ability of mosquitoes to travel via various means of transportation such as air, road, rail, or sea. This phenomenon, known as odyssean malaria, is also referred to as airport, suitcase, minibus, or taxi-rank malaria.[2]

Odyssean malaria is an unusual but recurrent entity in SA, especially in Gauteng Province (GP). Between 2007 and 2013, the province reported 14 laboratory-proven (microscopy and/or rapid diagnostic test result positive for malaria) and 7 probable cases (i.e. acute febrile flu-like illness with no other cause and compatible non-specific laboratory findings, especially thrombocytopenia, and epidemiologically linked to confirmed malaria cases) of this form of malaria. All but one, a case of *Plasmodium ovale,* were confirmed or presumed to be *P. falciparum* infections. Case fatality rate over this seven-year period was 9.5% (2 deaths), which was ten times greater than the national case fatality rate and nearly 20 times that of the national target of 0.5%.[3]

Delayed diagnosis and treatment of odyssean malaria can lead to severe and sometimes fatal complications. It is therefore crucial to investigate and review cases of this type of malaria to raise awareness among clinicians and the general public. This report provides a summarised update of odyssean malaria outbreak investigations in SA from 2014 to 2023.

Methods

This is a descriptive analysis of investigations conducted between 2014 and 2023. This comprised reviewing the clinical and laboratory records, site visits and assessments, patient interviews and entomological investigations for adult mosquitoes and for larvae in potential aquatic breeding sites at index houses and other places of interest.

Case definition

A case of odyssean malaria was defined as any case that occurred in a non-endemic area where there was no recent travel history to a malaria-endemic area, and the possibility of mechanical transmission (such as by blood transfusion, injection or needlestick injury) was excluded. These are malaria cases where epidemiologic investigations failed to identify an apparent mode of acquisition other than mosquitoes that had inadvertently travelled to non-endemic areas via various transport mechanisms (sea, air, rail, road). Malaria is a category one notifiable medical condition in SA that has to be notified within 24 hours of diagnosis. Thus, most of the cases were reported by local health authorities that requested support from the National Institute for Communicable Diseases (NICD) for clinical, epidemiological and entomological investigations. This report only includes cases that NICD personnel investigated.

Case and site investigations at index houses

The clinical details of the cases were obtained from clinicians caring for the patients, where possible. Laboratory diagnosis of malaria was reviewed with the private or public-health sector pathologist or obtained from the National Health Laboratory Services (NHLS) laboratory information system. Outbreaks were investigated in conjunction with local health officials, including environmental health officers. Site visits were undertaken and, where possible, surviving patients and their families were interviewed from whom detailed clinical and travel histories were obtained. Surveillance for adult *Anopheles* mosquitoes included indoor searches of houses and other buildings on or adjacent to the patients' dwellings. Local *Anopheles* mosquito breeding assessments included spot-checking water bodies (rain puddles, ponds, streams, rivulets, birdbaths, outdoor baths, runoff puddles and canals) in the immediate vicinity of the index houses for the presence of anopheline larvae. Standard entomological techniques were used to identify any collected mosquitoes to species.[4]

Results

Over this ten-year period 97 laboratory-proven and two probable cases of odyssean malaria were investigated (Table 1). The majority (98%) of the confirmed cases were due to *P. falciparum*. Two unrelated cases in GP in 2022 were due to *Plasmodium malariae*, the first such cases of non-falciparum odyssean malaria described in SA. There were 27 clusters (>1 case related in time and place) of cases, most within the same household. Four clusters occurred at three different game lodges/reserves. Cases were reported among males (49%, 43/87) and females (51%, 44/87) at almost equal proportion for cases with recorded gender. Three of the cases were reported among pregnant females. Where age data were available, ages ranged between four months to 70 years; however, most cases (69%, 58/84) were among adults aged 18 years and older. There was no evidence of local ongoing malaria transmission at any of the index houses.

Table 1. Summary of odyssean malaria cases reported in South Africa, 2014 to 2023 (N=99).

Year	Cases	Province/s (Deaths)	Case fatality rate/year	*Plasmodium* species	Putative source/s of infective *Anopheles* mosquitoes
2014	7 (including 2 clusters)	6 GP (2) 1 WC	29%	*P. falciparum*	Proximity to major highways. Labourers from Malawi working on property.
2015	21 (including 4 clusters, 1 comprising staff members at a game lodge)	16 GP (1) 5 NW	5%	*P. falciparum*	Proximity to busy local roads or bus depots. Staff or neighbours from or with recent travel to Zimbabwe, Mozambique or Kruger National Park.
2016	8 (including 2 clusters, 1 comprising residents on a subsistence farm)	4 GP (1) 4 MP*	13%	*P. falciparum*	Mine employees, one residing in mine hostel with foreign mine workers.
2017	21 (including 8 clusters, 1 comprising siblings staying at a game reserve)	16 GP (4) 2 NW (1) 1 EC 2 LP*	24%	*P. falciparum* (2 presumed, based on malaria severity)	Proximity to long-distance taxi route/major highways. Neighbours from/visited Mozambique. Proximity to migrant settlements. Labourers returning from Mozambique working on property. Close proximity to streams. Multinational team (Zimbabwe, Mozambique) on site at reserve.
2018	15 (including 6 clusters, 4 within one informal settlement)	15 GP (5)	33%	*P. falciparum* (2 presumed, based on fatal outcome)	Proximity to major highway/busy road. Friend had recent travel to LP. Residents in informal settlement with many foreign nationals in community (Mozambique, Zimbabwe).
2019	7	7 GP (1)	14%	*P. falciparum*	Proximity to major highway. Neighbours and domestic workers include foreign nationals (Nigeria, Zimbabwe, Mozambique).
2020	2	1 GP 1 NW (1)	50%	*P. falciparum*	Proximity to busy road. Community comprises foreign nationals (Zimbabwe). Travel overnight in a car that came from LP.
2021	10 (including 4 clusters, 2 at same game reserve 4 months apart)	10 GP	-	*P. falciparum*	Proximity to major road. Dinner at game reserve with other guests after being in lockdown during COVID-19 pandemic.
2022	7 (including 1 cluster)	6 GP (1) 1 WC	14%	*P. falciparum* *P. malariae*	Proximity to taxi rank. Neighbours/family members' recent travel to Mozambique, Malawi or Giyani in LP.
2023	1	1 GP	-	*P. falciparum*	Proximity to taxi hub and train station. Community comprises foreign nationals and migrant workers.

Provinces: LP=Limpopo; MP=Mpumalanga; KZN=KwaZulu-Natal; GP=Gauteng; EC=Eastern Cape; FS=Free State; NC=Northern Cape; NW=North West; WC=Western Cape. * In a malaria non-endemic area in the province.

Most of the odyssean malaria cases were reported in the months of December, January, March and May (Figure 1). June and July had the least number of cases reported throughout the ten-year period. Of the 99 cases reported, a total of 17 deaths was recorded. This represented a case fatality rate of 17%, which is approximately 17 times higher than the national fatality rate for malaria in SA.

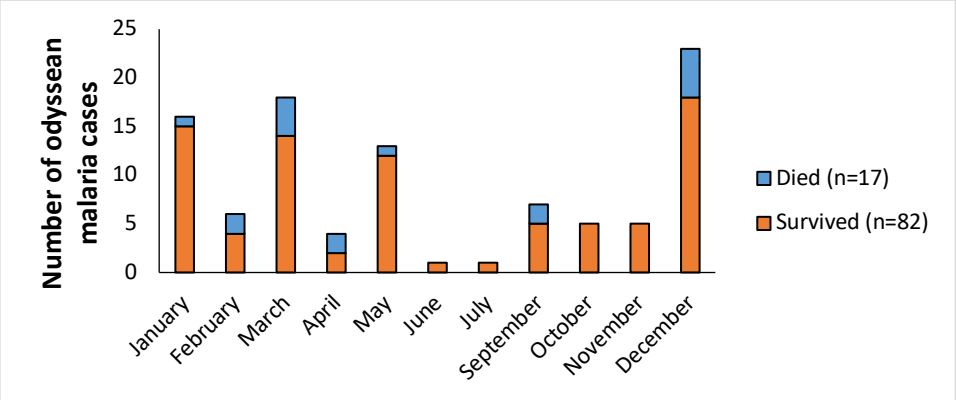

Figure 1. Number of recorded odyssean malaria cases in South Africa by month, 2014 to 2023.

Geographical distribution

The vast majority of the cases were reported in GP (84%, 83/99) followed by NW (7%, 7/99), both known to be non-endemic to malaria. In GP, the cities of Johannesburg and Tshwane (two metropolitan municipalities in GP and major economic and travel hubs) accounted for most of the reported cases. Furthermore, most of the cases resided in close proximity to major national roads that are travel routes from high-risk malaria areas in SA and neighbouring countries (Figure 2). Although some cases occurred in secluded lodges and game reserves, most occurred in urban areas.

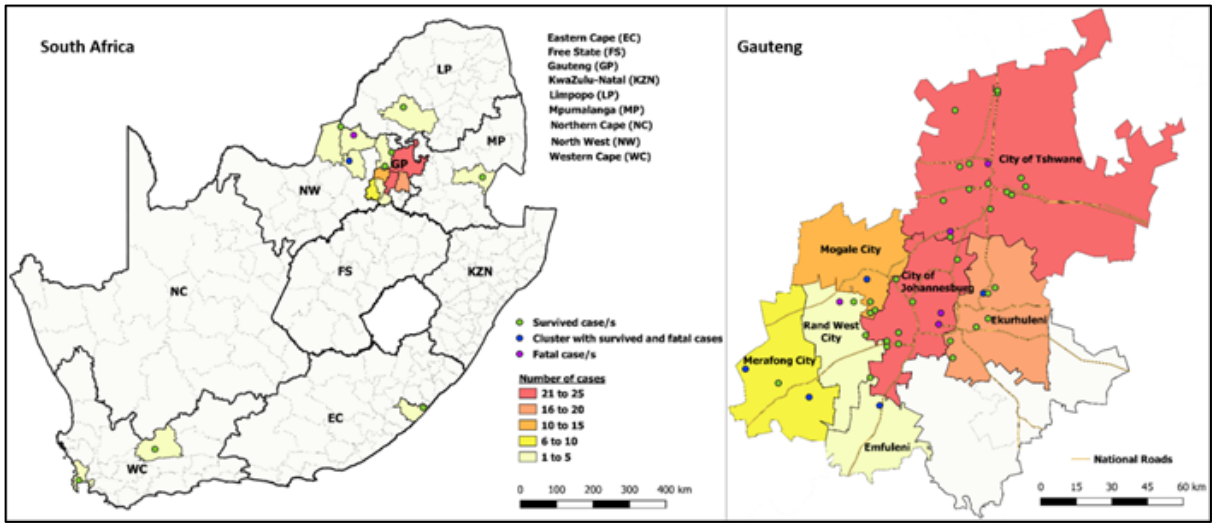

Figure 2. Geographical distribution of odyssean malaria cases in South Africa, 2014 to 2023.
Maps were created using QGIS Geographic Information System (Open Source Geospatial Foundation Project, http://qgis.org)

Entomological investigations

No adult *Anopheles* mosquitoes were found at any of the index houses or in their vicinity, and there were no *Anopheles* larvae in any of the potential aquatic breeding sites investigated. *Culex* and *Aedes* mosquitoes (adults and larvae) were however observed at some localities as expected, given that several species within these genera are widespread in SA.

Discussion

Clinical aspects

Missed or delayed diagnosis of malaria is associated with a high complication rate and mortality.[5] Initial malaria symptoms can be non-specific and patients can present with fever and flu-like or, more recently, COVID-like symptoms. Alerting health-care workers in non-endemic provinces about the existence of this form of malaria is key to improving patient outcomes.

Any patient with a febrile illness in whom a diagnosis is not apparent, especially if there is an accompanying thrombocytopenia, should alert the healthcare worker to the possibility of malaria. Point-of-care (rapid diagnostic) malaria tests should be more widely utilised when routine laboratory microscopy diagnosis is delayed or not available, such as in primary health clinics (provided users are appropriately trained). Inexperience in recognising and managing clinically severe malaria contributes to mortality,[6] and patients should be managed at the highest level of care available.

Malaria parasites with partial artemisinin resistance have emerged in parts of Asia and Africa.[7] So too have those with genetic mutations rendering them undetectable by certain rapid diagnostic tests.[7] Therefore, a potential risk exists for travelling infected mosquitoes to transmit malaria infections that may be difficult to detect or treat with first-line drugs.

Epidemiological and entomological aspects

Critical first steps in these outbreak investigations are to establish that the infected person(s) have not recently travelled to a malaria-endemic area and that mechanical transmission has been excluded. From an outbreak investigation perspective, the following pertinent information needs to be gathered: (i) proximity to travel hubs, including national highways, airports, train stations, bus depots, taxi ranks and other public transport nodes (ii) recent travel history of household members and neighbours (i.e. have they travelled to a malaria-affected region during the past 2-3 weeks), (iii) presence of mosquitoes or mosquito bites in the preceding 2-3 weeks and (iv) use of insecticides (for domestic use) in the home.

There are several *Anopheles* malaria vector species in the endemic areas of the southern African region. These include (but are not entirely limited to) the major vectors *Anopheles funestus* and *An. arabiensis*, and the secondary vectors *An. merus*, *An. vaneedeni*, *An. parensis* and *An. rivulorum*.[8] Inadvertent long-distance dispersal of malaria-infective adult female mosquitoes of any of these species, certainly by land transport, can lead to odyssean malaria in South Africa's non-endemic provinces (note that odyssean malaria can also occur in endemic areas but is not clinically distinguishable from local malaria).

The most likely origins of infective mosquitoes that cause odyssean malaria in SA's non-endemic provinces are Mozambique, Zimbabwe and the endemic districts of LP, MP and KZN.[9]

The entomological investigations did not yield any mosquitoes of significance in terms of malaria transmission. The absence of *Anopheles* mosquitoes is not surprising as they are comparatively rare in the Highveld region of SA primarily owing to climatic unsuitability. *Culex* and *Aedes* mosquitoes on the other hand are common across SA but currently have no public health importance, although they are a biting nuisance.

The chances of finding culprit infective mosquitoes during odyssean malaria investigations are extremely low. An adult mosquito's lifespan is 4-6 weeks at most. These vectors must have been more than two weeks old at the time of delivering the infective bite and will almost certainly have died by the time of an investigation at the index house (generally at least three weeks after the infective bite). The primary reason for conducting an entomological investigation at each index house is therefore to assess any localised *Anopheles* breeding that could theoretically lead to further local transmission.

The period under review includes the COVID-19 pandemic from March 2020 to May 2023. International and inter-provincial travel restrictions were imposed in SA between March and August 2020 and no investigations were conducted during lockdown.

Peaks in odyssean malaria cases typically followed major holiday periods in December, January, March and May when travellers (and potentially infected mosquitoes) returned from malaria-endemic areas, both within and outside SA borders.

Conclusions

Although six of SA's provinces are non-endemic for malaria, odyssean malaria cases are inevitable due to the volume of road, rail and air traffic from malaria-risk areas, including the three malaria-endemic provinces. The increase in odyssean malaria cases during the period under review, compared with the previous series, especially in the light of SA's sustained success in malaria control,[10] is probably related to increased travel within the region and improved awareness and recognition of cases. The impact of COVID-19 pandemic-related travel restrictions is not clear, but it is noteworthy that outbreak investigations continued throughout the rest of the pandemic. Odyssean malaria will remain a risk in SA's non-endemic provinces until malaria is eliminated in the region. The emergence on the African continent of malaria parasites with artemisinin resistance and the ability to evade rapid diagnostic tests makes detection of imported and odyssean malaria cases in SA all the more important. Although these outbreaks are rare, findings emphasise the need for clinicians to think about malaria as a differential diagnosis in febrile patients with unexplained fever and thrombocytopenia, even in the absence of a travel history. A multidisciplinary team is essential for the comprehensive investigation of clinical and public health aspects of odyssean malaria outbreaks.

Recommendations

Clinicians should maintain a high index of suspicion for malaria in febrile patients with unexplained illness, even in the absence of a travel history to a malaria endemic area. Although no specific vector control interventions were indicated in any of the cases investigated, homeowners of index houses and those in their immediate vicinity can reduce mosquito breeding by draining unutilised standing bodies of water and covering water containers.
Mosquito bites can be reduced or prevented by personal protection measures including use of DEET-based mosquito repellents and pyrethroid-based insecticidal products (plug-in mats and room sprays), wearing long-sleeved clothing and socks in the evenings, and sleeping under a bed net.

Acknowledgements

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Ethical Considerations

Ethical clearance was obtained from the University of the Witwatersrand, Human Research Ethics (Medical) Committee – M210752. Project title: Essential communicable disease surveillance and outbreak investigation activities of the National Institute for Communicable Diseases (NICD).

Conflict of Interest Statement

Authors reported no conflicts of interest.

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