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Review Article

Perils, pearls, pitfalls, pathogens, pitbulls and public health – an infectious diseases journey

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INTRODUCTION

This mini-review focuses on emerging and well-established infectious diseases that may pose risks to travellers in the region, as well as residents in South Africa. The content does not represent a comprehensive review of the diseases, but rather a journey by the authors, drawing on many years of practice and the best guidance for prevention and management.

MALARIA

South Africa (SA) recorded just under 10,000 malaria cases, with 113 deaths, in 2023.(1,2) The country's malaria-endemic districts are in Limpopo, Mpumalanga, and KwaZulu-Natal provinces, all of which share borders with malaria-endemic neighbouring countries. The majority of the malaria cases notified from KwaZulu-Natal and Mpumalanga provinces are imported,(3,4) notably from Mozambique. In response to sustained reductions in locally acquired malaria, South Africa initiated a malaria elimination strategy in 2012, aiming to halt the local transmission of malaria. A longstanding national and provincial malaria control programme has focused on early case detection, prompt notification, and effective management. In endemic areas, vector control involves indoor residual spraying of houses using long-acting insecticides and larviciding of water sources. Active case detection and treatment of symptomatic and asymptomatic parasitaemic individuals around households of confirmed locally acquired malaria cases, the introduction of primaquine as a gametocytocidal therapy for malaria cases, and enhanced surveillance in border areas are key components of the elimination programme. (5) The emergence of antimalarial drug and insecticide resistance in Africa, together with the potential invasion of urban-breeding vectors such as *Anopheles stephensi*, poses significant challenges to control and elimination efforts, and they must be closely monitored.(6) Funding cuts to malaria programmes are a massive threat to control and elimination efforts. Malaria transmission is rapidly re-established when control efforts are reduced.

While malaria transmission is absent in Gauteng Province, the province reports a high number of cases. Most of these cases, classified as imported, involve visitors or travellers returning from endemic areas within or outside South Africa. Rare cases of Odyssean malaria (also called 'taxi' or 'suitcase' malaria) are caused by infected mosquitoes being transported from endemic malaria areas to non-endemic areas. These are rare incidents, but morbidity and mortality are high, due to late diagnosis consequent on the absence of a history of travel to a malaria transmission area. (7) Malaria should always be considered in any patient with unexplained fever, especially if thrombocytopenia, progressive jaundice, or a depressed mental state are noted. Most cases of malaria in sub-Saharan Africa, including those in South Africa, are caused by infection with *Plasmodium falciparum*, the parasite species most commonly associated with the most severe disease and antimalarial drug resistance. Early recognition, prompt and accurate diagnosis, and timely treatment with effective medications are key elements in successful management.(8)

The early clinical presentation of malaria is characterized by an acute, undifferentiated febrile illness, resembling that of many other infections, particularly COVID-19 and influenza. Fever, rigors, headache, and myalgia are common. Depending on the exposure history, the differential diagnosis includes viral hepatitis, bacterial pneumonia, septicaemia, meningitis, tick bite fever, typhoid, viral hemorrhagic

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fever, arbovirus infection, and East African trypanosomiasis, among others. Malaria in young children and pregnant women may be rapidly progressive, is frequently misdiagnosed, and consequently is often complicated when finally confirmed. In children, common symptoms include fever, poor feeding, lethargy, and vomiting. Malaria in pregnancy is often misdiagnosed as a urinary tract infection or pregnancy-related infection, posing significant risks to both the unborn foetus and the pregnant woman.(9) Thrombocytopenia is almost invariable in malaria, and its unexplained presence should trigger suspicion of malaria.

The microscopic examination of Giemsa-stained blood smears remains the gold standard for diagnosing clinical malaria.(10) Rapid diagnostic tests (RDTs) are generally used at the community clinic or emergency department level, enabling prompt diagnosis. A single negative test does not exclude malaria. If it is suspected, tests should be repeated until either malaria or another diagnosis is confirmed. The widespread uptake of malaria RDTs as the point-of-care malaria diagnostic in Africa has played a significant role in improving treatment outcomes. Correct storage, attention to expiry dates, proper amounts of lysis buffer and blood sample used, and reading the test at the time recommended by the manufacturer are key to obtaining an accurate diagnosis. Test lines for low parasite loads take longer to develop, so these infections may be missed if the test is read too early. Although deletions in the falciparum histidine-rich protein 2 (*hrp2*) gene have resulted in the failure of HRP2-based falciparum-specific RDTs elsewhere in Africa,(11) these genetic changes have not yet been detected in South Africa.(12)

Malaria is a treatable and curable disease, particularly if diagnosed early and promptly treated with an effective antimalarial. In line with the WHO recommendation, South Africa uses artemisinin-based combination therapy (ACT), specifically artemether-lumefantrine (Coartem), as the first-line treatment for uncomplicated malaria.(9) Artemether-lumefantrine is administered as a 6-dose regimen over three days, with the dosage based on patient weight. Each dose should be taken with a fat-containing food to optimise absorption of the lumefantrine component. Nonsteroidal anti-inflammatory drugs should not be used to reduce fever; paracetamol is recommended as an alternative. Patients weighing over 85 kg treated with artemether-lumefantrine should be monitored closely to ensure complete cure and parasite clearance. For these large patients, current SA treatment guidelines advise extending the treatment course to five days, administering four tablets per dose for a total of 10 doses (an off-label recommendation).(9)

Severe malaria is a medical emergency requiring prompt parenteral treatment, intensive nursing care, careful monitoring, and management of complications.(9) Severe malaria may affect any body organ; cerebral malaria, early onset renal failure, ARDS, as well as hypoglycaemia, are important complications. An increase in respiratory rate, typically a sign of metabolic acidosis, is a good predictor of impending deterioration in individuals with malaria, even in the absence of other signs of severe illness. The presence of jaundice, regardless of its severity, is a significant indicator of severe malaria. Intravenous artesunate is the treatment of choice for severe malaria due to its favourable safety profile, rapid action, and ease of administration. Meticulous attention to fluid administration, measurement of urine output, and monitoring of renal function are crucial in the treatment of severe malaria.

Plasmodium falciparum parasites with specific mutations in the propeller domain of the *kelch13* gene, which have been confirmed to cause delayed parasite clearance, namely the artemisinin-partial resistance phenotype, have been identified in several East and Central African countries.(13) Although artemisinin-partially resistant parasites may still be cleared by the partner drug, the increased pressure on the partner drug increases the risk of partner drug resistance, ultimately resulting in ACT treatment failure. Parasites with *kelch13* mutations associated with artemisinin-partial resistance are rare in South Africa.(12) High levels of these mutations have, however, been identified in Zambia and Namibia,(14,15) emphasizing the need to ensure patient compliance and adherence supported by drug efficacy surveillance.

Prevention of malaria in travellers focuses on raising awareness of fever and the need for prompt diagnosis and treatment if symptoms appear after travel.(16) Measures to prevent mosquito bites by *Anopheles* species mosquitoes using effective personal protective measures applied from sunset are key, together with chemoprophylactics such as doxycycline or atovaquone-proguanil, depending on the risk assessment. Doxycycline has been down-regulated to Schedule 2 for malaria chemoprevention and is available in the public sector at no cost.

RABIES

Rabies is a zoonosis that can affect the nervous system of all mammals, including humans, causing an acute and invariably fatal encephalomyelitis. The disease in Africa and Asia is caused by a lyssavirus, most often associated with domestic dog rabies, which in turn leads to human rabies cases.(17) Most other lyssaviruses are associated with bat hosts, with the Duvenhage lyssavirus linked to a few human cases in Southern and East Africa.(18) Rabies may also be found in various wildlife species, such as mongoose and jackal, as well as domestic livestock. Rabies is endemic in South Africa, and despite dog vaccination being a regulated requirement for owners to action, and the availability of biologicals for pre- and post-exposure prophylaxis (PEP), human cases continue to be reported. Between five and 25 laboratory-confirmed cases are usually notified annually, the majority in children less than 10 years of age after

exposure to rabid dogs.(19) This is likely an underestimate of the true burden, given the relatively low awareness and recognition of clinical rabies in humans, poor sensitivity of antemortem tests, and difficulties obtaining brain tissue post-mortem. Most human cases are reported from Limpopo, Eastern Cape, and KwaZulu-Natal provinces. They are a result of a lack of community awareness to seek medical care after animal bites, or failure to administer appropriate PEP at the health facility.

Zero by 30, which aims to eliminate dog-mediated rabies in humans by 2030, is a strategy proposed by the World Health Organization (WHO) and other agencies, utilizing a One Health approach.(20) Control of rabies in domestic dogs by vaccination is the most critical measure for reducing human rabies.(21) Rabies can be prevented in almost 100% of human bite victims by the administration of PEP applied timeously and according to evidence-based guidelines. These guidelines were updated in 2018 by the WHO to simplify the recommended regimens, reduce costs, and be dose-sparing.(22) National guidelines in South Africa for the prevention of rabies have followed these recommendations.(23) Pre-exposure prophylaxis, using a two-dose vaccine schedule administered intradermally or intramuscularly to those at risk through occupational or recreational exposure, is recommended. The intradermal route is highly effective and is dose- and cost-saving. Post-exposure prophylaxis includes thorough wound cleansing, a course of WHO-pre-approved cell-based vaccines, and administration of rabies immunoglobulin infiltrated only into the wound, in accordance with international expert guidance.(23) With the onset of symptoms, rabies is invariably fatal.

In May 2024, rabies was diagnosed in Cape fur seals along the coast of the Western Cape Province.(24) Several human victims of seal bites were identified both pre- and post-2024, and fortunately, no human rabies infections have been reported to date. Pre-exposure prophylaxis has been administered timeously since May 2024, and retrospectively to some identified as pre-2024 bite victims, albeit with long delays. Wound cleaning with seawater and the wearing of wetsuits by some may have protected against infection. Molecular techniques have linked the origin of the outbreak in seals to the introduction of rabies from rabid jackals and bat-eared foxes, which harvest seal pups in land-breeding colonies along the Atlantic coast of southern Africa. Seal-to-seal rabies transmission is now well established and very difficult to control. Vaccination trials are underway on habituated seals in harbours to test the efficacy of vaccines, but wide-scale vaccination is unlikely to be an implementable control strategy. Prevention of rabies in the victim species is vital: ensuring dogs that frequent beaches with their owners are vaccinated and leashed to avoid any contact with seals, and pre-vaccination of those employed in at-risk industries. A One Health approach, which brings together human, veterinary, marine, and wildlife practitioners, researchers, ecologists, and other stakeholders, has been crucial to the response to this unprecedented outbreak.

MPOX

Mpox is an emerging zoonotic viral infection caused by infection with the monkeypox virus (MPXV), an orthopoxvirus closely related to variola virus, the causative agent of smallpox. The first human case was identified in the Democratic Republic of the Congo (DRC) in 1972. The natural reservoir is unknown. Direct contact with infected rodents and small mammals is the likely source of most human cases of infection. For many years, the human disease was confined to tropical forests in the DRC and the Central African Republic, with children being disproportionately affected by the MPXV Clade 1a.(25) Worldwide vaccination during the smallpox eradication campaign led to protection from MPXV. Vaccination ceased more than 40 years ago after smallpox was declared eradicated, and immunity has waned or is absent in unvaccinated persons. In recent years, the number of mpox cases reported in endemic African countries, and notably in the DRC, has been rising.(25)

In 2017, Nigeria experienced its first major outbreak of human mpox.(26) In May 2022, mpox appeared suddenly and spread rapidly across Europe, the Americas, and then all six WHO regions. This global outbreak has affected primarily men who have sex with men and spread person-to-person through intimate contact and social networks. By August 2024, over 120,000 confirmed Clade 11b mpox cases were reported from 120 countries, including several cases in South Africa. A Public Health Emergency of International Concern (PHEIC) was declared by the WHO in 2022 in response. It was subsequently rescinded as the number of new cases decreased following public awareness campaigns and the introduction of vaccine programs using vaccines developed for smallpox.

More recently, Clade 1b has emerged in cities in the DRC among sex workers and mobile populations. Spread to several countries in Africa and globally through travellers resulted in the declaration of a second PHEIC by the WHO in 2024 (rescinded in August 2025) and a Public Health Emergency of Continental Concern by the Africa CDC. The focus has been on intensive surveillance programs to detect and isolate new cases, conduct contact tracing, and introduce laboratory testing and vaccines in affected areas of Africa.

The most prominent feature of the disease is a skin rash, which is associated with painful lesions similar in appearance to those of smallpox. Fever and enlarged lymph nodes are frequently reported. The disease is mild, primarily requiring little or no medical intervention, but some affected people may develop scarring. Nevertheless, the disease can be severe and, in some cases, fatal, particularly in those with immunodeficiencies and comorbidities.(27).

Overall mortality is low; however, morbidity is significant. Pain, eye involvement, and scarring are notable, as well as fear of stigmatisation, and mortalities are reported in young children, pregnant women, and people living with HIV (PLHIV) not on antiretroviral therapy (ARVs).(28)

Diagnosis by PCR on specimens from the lesions is accessible in the public (NICD) and private sectors in South Africa. Treatment is supportive, focusing on pain management, maintaining fluid balance, providing nutritional support, treating secondary infections, and offering psychosocial support. Tecovirimat, a drug developed for smallpox treatment,(29,30) has not been shown to have a significant effect on morbidity or mortality; however, data on its benefit in PLHIV with severe immunosuppression are lacking.(31) The drug is available in South Africa for compassionate use in persons who have extensive lesions, mpox disease-related complications, and those who are immunocompromised. HIV testing should be conducted in all individuals with confirmed mpox, and ARVs should be initiated as soon as possible. The development of immune reconstitution inflammatory syndrome is uncommon in those treated with tecovirimat. Regarding the mpox vaccine,(32) a vaccination program was initiated in South Africa in mid-2025, but only a limited number of at-risk persons have been vaccinated to date.

OTHER HIGHLIGHTS

Crimean-Congo haemorrhagic fever, which typically affects farmers, abattoir workers, animal health workers, and individuals residing in rural areas, presents with fever, myalgia, and headache, followed by bleeding (including epistaxis and haematemesis). A history of tick (*Hyalomma* species) contact, livestock or patient exposure, and residing or visiting a rural area are essential to elicit. A reduced platelet count and raised transaminases are usual. Infection prevention and control measures, as well as special testing, must be followed.

Tick bite fever is common in South Africa. While most infections are mild, severe and fatal cases are reported, usually as a result of infection with *Rickettsia conorii*. Fever, headache, and an eschar (often best located by finding a painful, enlarged lymph node) should prompt treatment with doxycycline (and not macrolides) in all patients. Serology is positive only from the second week of illness, and PCR on blood samples shows low sensitivity; swabs of eschars are more suitable samples for PCR.

Ongoing outbreaks of chikungunya and dengue are being reported from many parts of the world, with the most recent chikungunya outbreaks reported from the Indian Ocean islands.

East African trypanosomiasis, albeit rare, has been confirmed in travellers, expatriates, and residents of game parks in Malawi, Zambia, and Zimbabwe following tsetse fly bites. A characteristic chancre, usually misdiagnosed as a spider bite, cellulitis, or tick bite, is noted in a majority of cases. Careful examination of a peripheral blood smear is critical, and PCR is available (NICD). Specific drugs, including fexinidazole, a new oral treatment, are available in South Africa.

PEARLS

- Reliable and detailed histories: where, when, and what (exposures, occupation/hobby, drugs)
- Knowledge of geography, diseases, and outbreaks
- All the pieces of the 'puzzle' must fit: epidemiology, clinical, and laboratory
- Anything can occur anywhere
- Question and review the diagnosis
- Not all patients with a viral haemorrhagic fever (VHF) bleed, not all patients with bleeding have VHF
- Early recognition and infection control are critical for preventing the spread of VHF
- Rapidly progressive febrile illness in a young person - consider meningococcal disease and treat urgently
- Beware a previously healthy worker (or especially clusters of health workers) who develops febrile, progressive illness. Investigate for infections acquired in the health care setting, as per syndrome, e.g., VHF, coronaviruses
- All needlestick injuries sustained by health workers (or exposures to body fluids) should be investigated beyond HIV and hepatitis, and include appropriate post-exposure monitoring and prophylaxis
- Never miss malaria, as it is rapidly progressive and treatable. Consider malaria in cases of unexplained febrile illness, even in the absence of recent travel. Remember that mosquitoes also sometimes travel!
- Consider rabies in a patient with progressive, fatal encephalitis.

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