WWW.IJRPR.COM

**International Journal of Research Publication and Reviews**

Journal homepage: www.ijrpr.com ISSN 2582-7421

# Review of the Year 2018: Five Hot Topics in Tropical Medicine

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**ABSTRACT**

The field of tropical medicine saw numerous major advancements in 2018, including the approval of unique Transnational outbreaks of both vector-borne and zoonotic diseases, licencing of existing medications for established indications but in novel environments, and pharmaceuticals for novel indications.

Here, we outline the top five tropical medicine news items from 2018 and highlight each one's potentially game-changing development for the field.

**Keywords:-** human African trypanosomiashis lvermectin, monkeypox, Plasmodium vivax, Strongyloidiasis, human African trypanosomiasis

## Review of the Year 2018

Further into the year 2019, consideration of The successes and challenges of 2018 help us better comprehend the complicated environment of tropical medicine, prioritise efforts that can build on 2017's achievements and capitalise on their momentum, and, finally, pinpoint areas that need collectively renewed attention and emphasis. We will highlight five hot topics in tropical medicine that had an impact on our area in the previous year in this review. We try to locate each hot subject within the travel and tropical medicine literature, note its significance, pinpoint what changed in 2018, and interpret how it will change our practise and strategy moving forward.

Hot Topic: Health Canada has approved the use of ivermectin to treat strongyloidiasis.

Regional and North American impact

## Background

Drs. William C. Campbell and Satoshi Mura shared the 2015 Nobel Prize in Physiology or Medicine for their discovery of the avermectin family of compounds, which is where ivermectin (22, 23-dihydroavermectin B1) is derived [1]. Ivermectin, a macrocyclic lactone, predominantly affects invertebrate brain and muscle cells by potentiating glutamate-gated chloride channels, interfering with their polarisation and finally causing paralysis [2]. Ivermectin is well tolerated in humans, with pruritus being the most common side effect. However, caution is advised due to the drug's potential to potentiate GABAergic synapses, which can occasionally result in other neurotoxicity reactions like headaches, seizures, and dizziness.

Ivermectin in relation to Canada The prevalence of imported onchocerciasis in Canada is vanishingly low.

Table 1 First market approvals and current indications of ivermectin by country

| Region | First approval date | Current indications |
|---|---|---|
| France | October 1987 | Onchocerciasis, strongyloidiasis, lymphatic filariasis, human sarcoptic scabies |
| United States | November 1996 | Onchocerciasis, strongyloidiasis |
| Australia | June 1997 | Onchocerciasis, strongyloidiasis, human sarcoptic scabies, crusted scabies |
| Japan | October 2002 | Strongyloidiasis, human sarcoptic scabies, crusted scabies |
| Netherlands | March 2003 | Strongyloidiasis, lymphatic filariasis, human sarcoptic scabies |
| New Zealand | August 2005 | Strongyloidiasis, lymphatic filariasis, human sarcoptic scabies |
| Germany | February 2016 | Strongyloidiasis, lymphatic filariasis, human sarcoptic scabies |
| Canada | September 2018 | Onchocerciasis, strongyloidiasis |

a big referral centre serving a broad catchment population only had 2 occurrences recorded over a 6-year period [7]. Even while imported onchocerciasis is more frequent and requires ivermectin therapy in some non-endemic nations [8],Strongyloidiasis is a disease that is particularly prevalent in immigrants and refugees in Canada, who make up 21.9% of the country's population. 85% of the 7.5 million foreign-born Canadians that make up the nation's ethnocultural variety came from areas where strongyloidiasis is endemic [9]. Strongyloidiasis seroprevalence rates among our immigrant population vary widely, according to research, with up to 77% of Cambodian refugees and 12% of Vietnamese refugees exhibiting serologic reactivity [10, 11]. Additionally, among the top five illnesses in surveillance, strongyloidiasis is consistently seen.

## Prior to 2018, the Ivermectin landscape in Canada prior to 2018

Essential antihelminthic medications are categorically unavailable in Canada. In the country, the great majority of effective treatments are not licenced nor sold.most of the World Health Organization's (WHO) list of neglected tropical diseases (NTDs) [16]. Prior to 2018, clinicians must apply to Health Canada's Special Access Programme (SAP), which grants individual licences for unlicensed pharmaceutical items in the nation, in order to get some of these essential treatment choices, including ivermectin. Accessibility is still restricted, and it frequently takes more than a week to receive medication after submitting a SAP application [17]. Delays in obtaining potentially life-saving medications resulted in high-profile news accounts of deaths connected to dissemination Iatrogenic immunosuppression is increasingly used in the treatment of Canadian patients with a wide range of inflammatory and malignant disorders, and there is a dearth of The availability of ivermectin led to an increase in fatal disseminated strongyloidiasis cases across Canada. In order to lower morbidity and mortality across the nation, these incidents prompted the Committee to Advise on Tropical Medicine and Travel (CATMAT), an outside advisory group to the Public Health Agency of Canada, to create national guidelines on the topic [10].

## What altered throughout 2018?

Ivermectin (marketed under the brand name Stromectol®) received a Notice of Approval after being submitted for review by Merck & Co., Inc.On September 10, 2018, Health Canada, the nation's licencing authority for pharmacologic goods, granted compliance, allowing the medicine to be marketed and kept on pharmacy formularies [24]. Ivermectin use for other conditions that can be treated with the drug, such as human sarcoptic scabies, crusted scabies, lymphatic filariasis, and cutaneous larva migrans, must continue to be done so off-label. Health Canada has approved the use of ivermectin for the indications of strongyloidiasis and onchocerciasis, so this means that it is now legal to use it for those conditions Ivermectin will now be available more quickly for the treatment of both mild and severe strongyloidiasis, which will undoubtedly minimise associated morbidity and death, especially as it might be better integrated.

## Conclusions

Ivermectin, an antiparasitic drug, has significantly reduced the prevalence of NTDs like onchocerciasis on a global scale. Strongyloidiasis, which affects up to 2.5 million foreign-born Canadians nationally, is projected to affect a significant portion of the at-risk population in Canada due to ivermectin's relative inaccessibility. Ivermectin has been approved for licence and marketing, and as of September 2018, clinicians treating patients with strongyloidiasis and other parasite illnesses can now effectively treat these patients. Even though some Canadian patients may face financial obstacles due to a lack of federal, provincial, or private drug coverage, this is a positive step forward for Canadians and could serve as an inspiration for other nations looking to increase access to necessary antihelminthic drugs.

Hot topic number two: overseas tourists exporting yellow fever impact scope: Global

## Background

Aedes and Haemogogus mosquitoes carrying the arbovirus Flavivirus, which causes Yellow Fever (YF), can infect humans and non-human primates. In 13 tropical South American countries and 29 sub-Saharan African nations, YF is endemic, causing an estimated 200,000 infections and 30,000 annual fatalities in endemic populations [26]. There are three different cycles of transmission: the sylvatic cycle, which involves primate-to-human transmission; the intermediate cycle, which involves either primate- or human-to-human transmission; and the urban cycle, which involves both human- and peri-domestic mosquito transmission [26–28]. When people enter the limits of the bush for work or play, transmission frequently happens [26–28].

therapeutic presentation According to estimates, YF infections in endemic or transmission areas result in 80–90% of cases of moderate disease and 15% of cases of severe disease [28–30]. Multiple competing co-endemic flaviviruses influencing the results of serologic tests, poor diagnoses in endemic locations, and varying The scheduling of vaccinations in high-risk locations makes it difficult to determine the true seroprevalence of an infection. Infection symptoms appear suddenly and last for three to six days. These symptoms include fever, chills, headache, myalgia, prostration, nausea, and vomiting. The second stage of the illness may manifest with fever, jaundice, hemorrhagic signs, shock, and multisystem organ failure following a period of remission of several hours to days [28]. 20–50% of hepatorenal insufficiency cases result in death [28–30]. Clinical characteristics, such as febrile jaundice, and travel history are frequently used to make a preliminary diagnosis of YF.

## Prior to 2018, tourists described the YF landscape

Travelers' prevention By staying away from mosquitoes, you can prevent YF and stop its cycle of perpetuation.Cycles of transmission and immunisation work best [33]. All eligible individuals who are 9 months old, travelling to areas where YF transmission occurs, and receiving the vaccination at least 10 days prior to departure are advised to do so [33–37]. Since 2016, the WHO has recommended against booster shots, save in some immunocompromised individuals, as a single dose of the YF vaccine gives lifelong protection [38, 39]. A single dose of the YF vaccine offers long-lasting protection for the majority of visitors [33, 35–38, 40]. If more than 10 years have passed since the last vaccine, people who are going to places where YF outbreaks are occurring may want to consider getting a booster dose [33, 35, 40]. newcomers to travelling should avoid visiting locations where YF is prevalent or is experiencing an outbreak [33, 35, 40, 41]. danger to passengers Travelers are thought to have a low risk of YF, with estimates ranging from 1 per 1,000,000 to 1 per 100,000 people travel each month [34]. In Africa and South America, respectively, the disease rate per number of tourists for a 2-week stay during a high-risk season is predicted to be 50 per 100,000 and 5 per 100,000 travellers, respectively [34]. Risk is frequently influenced by vaccination status, the destination, the time of year, the length of exposure, the occupation, leisure activities, and the local rate of transmission [34]. The case-fatality rate among unimmunized travellers is substantial, approaching 90% [42].

## What altered throughout 2018?

The possibility for brand-new urban cycles of transmission, a growth in the number of cases exported by tourists from risk areas, some of these factors in the year 2018

This culminated in the creation of new public health-level policies and guidelines in non-endemic regions like Canada and the US. whom had fatal outcomes, and the ongoing threat to the YF vaccine supply chain in the context of high demand. worry about fresh urban transmission cycles As YF outbreaks have grown recently, cases have been transferred by visitors to nations where the disease is not prevalent. 11 long-term visitors from Asia contracted YF in 2016 after going to Angola, where one of the biggest urban outbreaks was going on [43]. travellers lacked vaccinations or had received them too late.

This transfer of YF to Asia via international travellers put 1.8 billion people at risk by initiating a potential new urban cycle of transmission due to the urban mosquito vector Aedes aegypti's presence among huge unvaccinated populations.[43]. A total of 1218 confirmed human cases of YF, including 364 fatalities, were noted in Brazil between 1 July 2017 and 24 April 2018 [27, 44]. Over 32 million people live in the heavily crowded metropolises of Rio de Janeiro and Sao Paulo, where this pandemic took place [27, 44]. These locations were considered to pose little risk for the spread of the YF virus up until April 2017 [27, 44]. The WHO modified its YF vaccine guidelines for Brazil in January 2018 to cover all visitors or residents of Brazil.living in: the entire state of Espirito Santo, So Paulo, Rio de Janeiro, Paraná, Santa Catarina, and Rio Grande do State of Sul [44]. Only 53.6% of So Paulo, 55.6% of Rio de Janeiro, and 55% of Bahia states have attained adequate immunisation rates since the vaccination campaign was implemented [44], confirming the possibility of continuous YF transmission.exported cases related to travel Ten travel-related instances of YF, including four fatalities, were recorded between January and March 2018 among overseas tourists leaving Brazil who were all unvaccinated [42]. The Program for Monitoring Emerging Diseases (ProMED) documented five of the cases involving visitors from Argentina and Chile [42].

The other five confirmed cases were reported by GeoSentinel, the global clinician-based sentinel surveillance system for travel-related illness among international travelers and migrants, a first for the surveillance system [42]. All of the cases were acquired via sylvatic transmission and travel time varied between 1 and 4 weeks [42]. As of 24 April 2018, a total of 19 confirmed cases of YF were reported among unvaccinated international travelers in Brazil,Argentina,France,Germany,the Netherlands,Romania,Switzerland, and the United Kingdom [45]. In comparison, from 1970 through 2015, only 10 cases of YF were reported in unvaccinated travelers from the United States and Europe to West Africa and South America[34].a creative solution to the vaccine supply disruption The Sanofi Pasteur-produced YF-Vax is a live-attenuated vaccine that is licenced and commercialised in North America and is efficacious [33, 35, 36]. November 2015 marked the Critical vaccine shortages were felt all over the world as a result of the convergence of increased demand brought on by the Angola outbreak and the relocation of YF-Vax production to a more modern Sanofi Pasteur facility [35].During this time, the US FDA negotiated access to and licensure of Stamaril, a comparable vaccine that has been produced and sold in 70 countries with comparable safety and efficacy by Sanofi Pasteur France since 1986 [35]. Sanofi Pasteur provided a consistent but constrained supply of YF-Vax instead of Stamaril in Canada.

As a result, in spite of being unable to meet IHR requirements, CATMAT created guidelines in 2018 proposing the use of fractional doses as an interim mitigation technique that would grant exemption for at least 12 months.requires a global vaccination certificate [35, 46].With the issuing of a waiver indicating vaccine shortage, fractional dosing of one-fifth the dose (0.1 ml SC) of YF-Vax is advised as an alternative personal protection measure [35].

## Conclusion

The ongoing YF-Vax shortage will continue to challenge our collective ability to prevent new cases both locally and amongst travelers, break known transmission cycles in endemic areas, and issue vaccine certificates that are fully compliant with IHRs. In addition to strengthening vaccine coverage in YF endemic countries, the emphasis remains on ensuring vaccination of individuals crossing borders tobprevent international spread and to protect travelers from disease [37, 43]. Each year millions of travelers depart from YF endemic areas to non-endemic areas that have potential for virus transmission without having to provide proof of vaccination [37, 43, 47]. Rapid global changes in human mobility and urbanization necessitate

reexamination of vaccination policies and practices to prevent urban YF epidemics [37, 43].
IHRs can be circumvented by fabricating YF certificates without administering the vaccine, therefore better laws and practises are urgently needed.The international community will be better positioned to react quickly to new outbreak foci and to produce new knowledge about clinical aspects of disease, such as true incidence and prevalence, which remain elusive, with the help of both increased provider-based surveillance and laboratory capacity [43]. When examining sick returning travellers, clinicians should be on the lookout for YF outbreaks and continued transmission in those places.

**Hot topic Three:**Fexinidazole for treating human African trypanosomiasis (HAT)

Impact scope:primarily on regional, western, and sub-Saharan Africa

## Background

African human Approximately 70 million people in sub-Saharan Africa are afflicted by trypanosomiasis (HAT), sometimes referred to as sleeping sickness. The majority of those who contract the disease reside in rural and isolated locations, where health systems are frequently deficient or nonexistent, even if it can harm travellers returning from endemic areas [48–51].

Untreated illness causes a coma and ultimately death [52].HAT has the potential to impact both humans and animals, posing serious problems for food security, health, economic development, agriculture, and, most importantly, eradication [48].The WHO has set a 2020 deadline for HAT eradication because it is thought to be a serious public health issue [53].

HAT is brought on by parasitic protozoans of the Trypanosoma genus that are spread by tsetse flies [48, 49, 54]. Trypansoma brucei gambiense and T. b. rhodesiense are the two species that can cause the disease, with the former being more common in west and central Africa, causing chronic infection over months to years and being responsible for 97% of known cases. In contrast, T. b.Rhodesiense is only found in 3% of patients, is endemic to south and east Africa, and causes acute illness [48, 52]. HAT is difficult to diagnose and treat, and certain treatment plans have the potential to be lethal or extremely toxic.A promising trial showing the safety and effectiveness of oral fexinidazole for the treatment of late-stage T. b. gambiense was published by Mesu and colleagues in the Lancet in 2018 [55], and it has the potential to change the course of the disease.progression of this deadly condition

.The hemolymphatic (peripheral) and meningoencephalic (central nervous system) clinical stages of HAT are two separate clinical phases [52, 55]. The parasite enters the local lymphatics following an inoculation bite from a tsetse fly, and once in the bloodstream, the hemolymphatic stage starts.A promising trial showing the safety and effectiveness of oral fexinidazole for the treatment of late-stage T. b. gambiense was published by Mesu and colleagues in the Lancet in 2018 [55], and it has the potential to change the course of the disease.progression of this deadly condition.The hemolymphatic (peripheral) and meningoencephalic (central nervous system) clinical stages of HAT are two separate clinical phases [52, 55]. The parasite enters the local lymphatics following an inoculation bite from a tsetse fly, and once in the bloodstream, the hemolymphatic stage starts.HAT diagnosis Poor and labor-intensive diagnostics limit the ability to diagnose HAT accurately, and stage-dependent therapy makes prompt diagnosis extremely difficult and efficient management. Cerebrospinal fluid (CSF) analysis is required for a definitive diagnosis in order to distinguish between early- and late-stage disease and inform treatment choices [56]. In populations exposed to T. b. gambiense, risk-based screening programmes currently use the card agglutination test for trypanosomiasis (CATT).

Patients who have peripheral disease are subjected to systematic staging by lumbar puncture.Patients should ideally be followed up because relapse rates are high.Repeat lumbar punctures may be necessary up to 18–24 months after treatment to confirm the disease's and the parasites' cure [48, 55]. Invasive diagnostic and prognostic procedures won't be necessary thanks to the advancement of the diagnostic approach and the development of newer molecular techniques and non-invasive testing [48].

## Before 2018, the HAT treatment landscape

Pentamidine, suramin, melarsoprol, and eflornithine were the four medications traditionally used to treat HAT. More recently, nifurtimox-eflornithine has been added.combining therapies (NECT). Parenterally administered pentamidine and suramin are still used to treat early stage disease in T. b. gambiense and T. b. rhodesiense, respectively [57]. Melarsoprol, an arsenical that causes a posttreatment reactive encephalopathy and has an associated mortality rate of 5.9% [55–57], is the only treatment for late stage T. b. rhodesiense. It was also used for late stage T. b. gambiense for decades. Melarsoprol's toxicity necessitates parenteral delivery, hospitalisation, and close observation.Eflornithine, a safer alternative to melarsoprol that was approved for the treatment of T. b. gambiense in 1990, still has a high adverse event profile.

Eflornithine, like melarsoprol, necessitates numerous daily infusions, which is frequently challenging in a distant or rural area where HAT is endemic [56–58]. NECT, which combines oral and IV therapy with a simpler and more affordable regimen, was introduced for T. b. gambiense in 2009 [58].NECT was found to be beneficial since it greatly reduced the number of incident cases, but it still calls for hospital admission, sterile lumbar puncture equipment, and qualified medical personnel, all of whom are in limited supply in places where HAT is endemic [56]. (Table 2).

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Table 2 HAT Treatment for Late Stage Disease from 1949 to 2018 [58]

| **Drug** | **Advantages** | **Disadvantages** |
|---|---|---|
| Melarsoprol | Only treatment available for years, can be used for both. g-HATa and r-HATb | Derived from arsenic and can cause reactive encephalopathy,fatal in 3–10% |
| Eflornithine Monotherapy | Less toxic than melarsoprol | Can only be used for the treatment of g-HAT, requires 56 infusions over 14 days, inpatient admission, sterile equipment and trained hospital staff |
| Nifurtimox-EflornithineCombination Therapy (NECT)b | Decreased the overall incidence of disease and relapse rates at 18 months as compared to eflornithine alone, and is less toxic than melarsoprol | Can only be used for the treatment of g-HAT (1st line), requires inpatient admission, sterile equipment and trained hospital staff |

## What altered throughout 2018?

The Drugs for Neglected Diseases project (DNDi) and their affiliate partners rediscovered the antiparasitic medication fexinidazole in 2005.It was considered to be the first medication that was only available orally and was successful in treating T. b. gambiense in both early and late stages, which prompted studies into its clinical applicability in human trials [56, 59]. Results of the multicenter, randomised, non-inferiority trial showing the safety and effectiveness of oral fexinidazole for the treatment of late stage T. b. gambiense were published in January 2018 [55]. Between 2012 and 2016, this study enrolled 394 patients from T. b. gambiense treatment facilities in the Democratic Republic of the Congo (DRC) and the Central African Republic.

Patients underwent lumbar puncture and were randomised to receive either fexinidazole or NECT therapy for 10 days.a component of end-point evaluation. Clinical (mortality, rescue treatment) and parasitologic (trypanosome clearance) outcomes were measured. Success rates were 91.2% for the fexinidazole group and 97.6% for the NECT group at 18 months, which the WHO deemed to be an acceptable margin. In addition, fexinidazole was more tolerated than NECT, and no patients died as a result of the medication. Less people died for any reason than the 5.9% mortality rate associated with melarsoprol, which was recorded. Personality changes, psychosis, and hyponatremia were among the four major side effects of treatment, but generally, the advantages of oral fexinidazole therapy outweighed these concerns [55].

## Conclusions

In sub-Saharan Africa, the deadly neglected tropical disease known as HAT primarily affects rural and isolated areas. Traditional HAT therapies are extremely toxic and may be fatal. Melarsoprol, an arsenic compound, was the sole treatment for T. b. rhodesiense and has been the cornerstone of therapy for late stage HAT since 1949.More current pharmacological regimes, including NECT, have a higher safety profile than melarsoprol but still call for hospitalisation, sterile supplies, and qualified medical personnel. The recent clinical trial for the use of oral fexinidazole in both early and late stages of disease have been ground-breaking for HAT and are expected to change the course of the disease.Moving away from active case detection at primary health centres and toward passive case detection in rural regions are HAT control methods. Additionally, research on anti-tsetse vaccines, molecular target testing, and other vector control Programs have started. The WHO's goal of eradication by 2020 may be aided by the development of new molecular techniques and fexinidazole, even though there is still much work to be done in this area.

**Hot Topic four:**Tafenoquine for Plasmodium vivax malaria .

scope of Impact: global

## Background

When a female Anopheles mosquito carrying the malaria virus bites a person, it spreads the potentially fatal disease known as malaria. It is the most significant parasite illness affecting humans, infecting 200 million individuals globally and contributing to roughly 400,000 fatalities annually [60]. Only six Plasmodium species, including P. falciparum, P. vivax, P. ovale, P. malariae, and the two simian malarias, P. knowlesi and P. simium, have been confirmed to infect humans out of the roughly 100 species of Plasmodium that have been identified [60, 61]. P. vivax, one of these species, accounts for 20% of cases worldwide and nearly half of all malaria cases outside of Africa [60, 62], mostly primarily in Asia and Latin America [61]. Despite having low blood-stage parasitemia in comparison to P. falciparum malaria, P. vivax malaria is not benign. It has been shown to relapse within weeks to months following the primary infection, owing to formation of latent hypnozoites in the liver, which makes it difficult to eliminate and increases the risk of severe infection and fatal outcomes [63]. P. vivax malaria is an important infection of returning travelers associated with significant morbidity and mortality, yet new effective drugs for prevention, treatment and control have been inadequate and deeply neglected [64].

Radical cure and presumed anti-relapse therapy (PART) For many years, the bulk of antimalarial medications focused on P. falciprium and had broader uses that included P. vivax coverage. However, a number of research studies from South America and Asia have revealed a substantial incidence of relapse in P. vivax malaria patients who were solely given chloroquine. Data from Korean War veterans with P. vivax in the 1950s showed that overlapping the blood schizonticide (chloroquine or quinine) with primaquine resulted in significantly lower relapse rates. This led to the use of primaquine as part of the "radical cure," which targets both replicating asexual blood-stages and hypnozoites in the liver.

Primaquine can also be utilised in "presumptive anti-relapse therapy" (PART) for travels to locations with high rates of endemic disease.a protracted duration of P. vivax [65]. In this plan, the final two weeks of chemoprophylaxis are overlapped with 14 days of primaquine treatment.(For instance, doxycycline or mefloquine). Since glucose-6-phosphate dehydrogenase (G6PD) testing is required, post-travel PART is rarely recommended to the typical asymptomatic returned traveller to P. vivax risk areas due to safety, efficacy, and inconvenience concerns [63].Primaquine has been used successfully to prevent P. vivax relapse since 1952 [63], despite the fact that a two-week course of the drug is taxing and can result in potentially fatal hemolytic anaemia in patients with G6PD deficiency.

## What altered throughout 2018?

The development of the hypnozoiticides 8-aminoquinolines A new liver drug was licenced for usage in 2018 by the US Tafenoquine, an 8-aminoquinoline, is schizonticidal and hypnozoiticidal and is used to prevent all malarias as well as relapse from P. vivax and P. ovale [64]. By being approved for use as a chemoprophylactic, requiring weekly dose rather than daily, and having blood schizonticidal activity that reduces the likelihood of malarial infections relapsing, tafenoquine solves a number of the drawbacks of primaquine [64]. Tafenoquine has a half-life of 14 days as opposed to primaquine's half-life of 6 hours, which confers the majority of its advantages over primaquine. The brand names ArakodaTM (60 Degrees Pharmaceuticals) and KrintafelTM (GSK) are used to market tafenoquine [64]. A comparison of the main chemopreventive medications in (Table 3)

Table 3 Comparison of malaria chemoprophylaxis options

| **Agent** | **Meflaquine** | **Doxycycline** | **Atovoquone-proquanil** | Primaquine | Tafenoquine |
|---|---|---|---|---|---|
| Dosing | Weakly | Daily | Daily | Daily | Weakly |
| Radical cure | No | No | No | Yes | Yes |
| P. falciparum active | Yes | Yes | Yes | Yes | Yes |
| Pregnancy | Yes | No | No | No | No |
| G6PD safety | Yes | Yes | Yes | No | No |
| Children | Yes | No | Yes | Yes | ? |
| Resistance | Yes | Yes | Yes | No | Unlikely |
| CYP dependent | No | No | No | Yes | ? |

Tafenoquine's safety and effectiveness as a radical cure have been assessed in a number of randomised controlled trials, and they have shown that it is not inferior than primaquine [64–66]. The All trials included non-pregnant people with G6PD activity levels greater than 70%. All study arms included a 3-day chloroquine treatment period, with primaquine (PQ) being given in 15-mg doses every day for 14 days while tafenoquine (TQ) was given as a single 300-mg dosage (Table 4).

Table 4 Tafenoquine for radical cure of acute vivax malaria [64,66, 80]

| **Trial type** | **Sample size** | **Regions** | **Placebo** | **% Recurrence free** |
|---|---|---|---|---|
| RCT [64] | 161 | Asia,Africa,Americas | Yes | TQ = 89%<br>PQ= 77%<br>Placebo = 54% |
| RCT [66] | 522 | Asia,Africa,Americas | Yes | TQ = 62%<br>PQ= 70% Placebo = 28% |
| RCT [80] | 251 | Asia,Africa,Americas | No | TQ = 73%<br>PQ= 75% |

Additionally, studies assessing tafenoquine's effectiveness as a malaria chemoprophylactic drug are compiled in Table 5.

Table 5 Tafenoquine for malaria chemoprophylaxis [81–84]

| **Trial type/ Duration** | **Sample size** | **Regions/Species** | **Placebo** | **Efficacy** |
|---|---|---|---|---|
| RCT/6 months [81] | 615 soldiers | Timor / Australia P. falciparum and P. vivax | No | N/A – 4 cases in TQ arm |
| RCT/15 weeks [82] | 123Adults | Kenya P. falciparum | Yes | 86% |
| RCT/15 weeks [82] | 231Adults | Ghana P. falciparum | Yes | 87% (equivalent to mefloquine) |

| | | | | |
|---|---|---|---|---|
| Experimental exposure to P.falciparum[84]. | 16 Adults. (4 controls) | Australia P. falciparum | Yes | 100% |

upcoming directions Tafenoquine is now only advised for adults who are 16 years of age or older, and studies are being conducted to determine its safety and the best formulation for usage in youngsters (Nov 2019 - NCT02563496).The process through which tafenoquine is metabolised in people and it is currently unknown whether it needs monoamine oxidases or any of the isotypes of cytochrome P-450. To determine the answer to this crucial mechanistic query, which is crucial for foretelling drug interactions, more research is necessary.

Future clinical trials will need to assess the long-term effects of tafenoquine use because the majority of the safety and efficacy studies reported in the tables above have identified side-effects beyond 6 months of use (Oct 2020 – NCT03320174)

## Conclusions

A long-acting 8-aminoquinoline with wide anti-malarial efficacy, tafenoquine, was recently licenced. One dosage has been When used with chloroquine, it has been demonstrated to be non-inferior to 14 days of primaquine for a radical cure of P. vivax. Tafenoquine, like primaquine, exhibits potential hemolytic toxicity in people with G6PD deficiency, hence such quantitative testing is necessary prior to treatment. Additionally, it should not be used as a preventative measure in women who are pregnant, nursing, or perhaps suffering from mental disorders. Travelers to regions where P. falciparum and P. vivax are co-endemic should take tafenoquine as part of their malaria prophylaxis.

**Hot topic no. 5:** outbreak of monkey pox in Nigeria

Mostly regional (West Africa, Europe) but possibly global in scope

## Background

The monkeypox virus (MPXV), a member of the family Poxviridae's genus Orthopoxvirus, is what causes monkeypox [67]. Smallpox and cowpox are other members of this genus that can infect people [68].After an epidemic at a monkey facility in Copenhagen, Denmark, MPXV was first identified in monkeys in 1958 [69]. The propensity of MPXV to infect a range of different mammals was soon discovered,involving people [70]. In the Democratic Republic of Congo (formerly known as Zaire), the first human case of monkeypox infection occurred in 1970 [69].

Monkey pox's clinical manifestations Despite having a less severe prognosis, monkeypox manifests similarly to the viral disease smallpox [71]. Fever, headache, exhaustion, myalgia, and other vague prodromal symptoms are among the first signs to manifest [72]. an exceptional The disease can be distinguished from smallpox by lymphadenopathy [67]. After one to three days of prodrome, a macular or vesicular rash may develop, frequently on the palms of the hands or the bottoms of the feet [73]. The disease lasts between two and four weeks and typically takes 1-2 weeks to develop [72]. The Central African strain of MPXV may produce more severe disease than the West African strain, according to anecdotal evidence and a dearth of clinical research.

Geographical spread A 9-year-old kid in the DRC, where smallpox was believed to have been eradicated in 1968 [67], was the first person to be infected with MPXV in 1970. Since then, the majority of cases have been documented in remote areas that resemble rainforests Accordingly, MPXV is thought to be endemic to areas of the Congo Basin and western Africa, mainly the DRC ([67]; for a map showing the disease's spread, visit https://www.who.int/news-room/fact-sheets/detail/monkeypox).

Transmission MPXV can be spread through respiratory droplets and direct contact with the fluid from active lesions [73]. It often spreads from animal to human, making it a zoonosis of particular concern to West Africa, but there have also been reports of human-to-human transmission. Human infections in Africa have been linked to handling of animals like monkeys, giant Gambian rats, and squirrels [67].The direct contact with blood, body fluids, the cutaneous or mucosal lesions of an infected animal, or the consumption of undercooked meat from infected animals are the two main ways that zoonotic transmission occurs [67]. The reservoir for transmission is thought to be the rodent population, specifically the dormice and rope squirrels [73].Although the natural path by which animals come into existence is unknown, it probably reflects species specificity [70].

Prevention and treatment There is now no recognised treatment that is regarded as safe or effective, but retrospective investigations have shown that prior smallpox immunisation has shown protective efficacy against the monkeypox development [72]. Although there hasn't been a systematic investigation on the administration of smallpox vaccine after exposure to monkeypox, it has been used in outbreak scenarios and is thought to provide some protection. Although they have been tested in vitro, antiviral medications like cidofovir have never been put through a clinical trial.

## Landscape of monkeypox prior to 2018

Following the importation of an exotic rodent from Ghana to Texas in 2003, monkeypox was spread throughout the US. Mice and squirrels with infection were then given out to a facility in Illinois that sold animals, where some of the cages housing the diseased rodents were next to those housing prairie dogs that were going to be distributed across the US, resulting in an animal-to-animal transmission event that was ultimately suspected to be the cause of

zoonotic transmission that year [74]. This series of importation and interspecific mixing episodes resulted in a total of 37 confirmed cases and 10 suspected cases of monkeypox in 6 states [74].

In the end, all human cases—including those in which the virus recovered from patients who had been infected and that of the pet prairie dogs were both identified as MPXV—were linked to interaction with prairie dogs [75]. Included in the To reduce transmission, the smallpox vaccine was provided as part of an epidemic control plan. Since 2003, there have been a number of minor outbreaks outside of the DRC, with case counts ranging from one to twenty.

## What altered throughout 2018?

Nigerian epidemic 2017–18 In the state of Bayelsa, the first cases in Nigeria appeared in September 2017. At 33 suspected instances were reported at that time in 7 states, with most cases affecting those over the age of 20 [75]. The sickness rapidly spread across the entire nation after that. Transmissions increased in 2018, resulting in 114 suspected cases and 45 confirmed cases of monkeypox. In one case of advanced, untreated HIV, the consequence was death.The Nigeria Centre for Disease Control (NCDC) oversaw activities aimed at controlling monkeypox in the afflicted states, including regional training on the disease, training for wildlife, and increased surveillance [76, 77].Using personal protective equipment and improved infection prevention and control strategies, NCDC made sure that suspected and confirmed cases were managed in designated healthcare facilities in accordance with national guidelines [76, 77].

imported cases - Israel and the UK Three instances were recorded in the UK, with the first two occurrences happening in September 2018. The first instance involved a Nigerian.Visiting Cornwall for a training exercise is an Abuja-based navy officer [68]. The officer was taken to Public Health England for investigation of lymphadenopathy and a rash near the groyne after travelling from London to Cornwall and developing a fever the next day [68]. The guy was given antibiotics after an incorrect staphylococcal infection diagnosis, but within a few days the rash had spread to his body, face, and arms. Diagnostic testing of the lesion fluid was triggered by the reevaluation, and MPXV DNA was found [78]. In the second instance, an Englishman who had just returned from a 22-day trip to After the second instance was presented in the UK in September 2018, an Israeli guy who lived and worked in Port Harcourt fell ill for a week.after his return from Nigeria, showing signs of lymphadenopathy, vesicular rash, and fever [71]. Early October 2018 saw the discovery of the fourth exporting case, a doctor who attended to the second UK case in the hospital. Again, there was no immediate suspicion of monkeypox, therefore full personal protection gear was not worn to guard against infection [68]. Smallpox vaccination was given to stop the spread of the disease after the discovery of the third case.

## Conclusions

In conclusion, monkeypox is an orthopoxvirus like smallpox. Mostly zoonotic, with rodents maybe involved are the main reservoirs, and is spread via respiratory and contact droplets. Due to theoretical and empirical cross-protection advantages, the smallpox vaccination has been adopted as a prevention method, much like how cowpox was discovered to offer protection against smallpox in the days of Edward Jenner. For brief, localised outbreaks, it is acceptable to use smallpox vaccine stocks already on hand. However, reliance on a smallpox-based vaccination control plan in the context of a larger, more prolonged, or global outbreak would be extremely difficult due to the elimination of smallpox and the relatively limited global vaccine stock levels. Similarly, the absence of suitable models hinders the development of new smallpox vaccines.Thus, the development of a particular vaccine for this indication should be given priority in view of recent outbreaks and the exportation of monkeypox. Additionally, disease exportation serves to remind medical professionals that monkeypox is still included in the differential diagnosis in persons.presenting with a widespread vesiculopustular rash, fever, and lymphadenopathy, especially if you have travelled to West or Central Africa, and being aware that local transmissions can essentially happen anywhere due to the globalisation of the exotic animal trade.

## 2018 in review: summary

In summary, the year 2018 in the field of tropical medicine saw important advancements in the areas of The deployment of novel vaccine strategies to influence outbreak control of vector-borne diseases (fractional YF Vax dosing); travel-related globalisation of zoonotic infectious diseases that are theoretically (monkeypox) or empirically (YF) vaccine preventable. Novel drug treatments (tafenoquine, fexinidazole) and novel licensures of existing drugs (ivermectin). These recent developments—both positive and negative—should spur further focus, funding, and, hopefully, innovation in the fight against zoonotic, vector-borne, and neglected tropical diseases.2018 has highlighted how renewed focus on medications already in development (tafenoquine); expansion of markets for orphan drugs is important despite the lengthy and expensive pipeline to new drugs and vaccines for such indications.Drugs that have been rediscovered (fexinidazole), drugs that have been licenced elsewhere (ivermectin), new techniques to stretch a licenced but limited resource (YF Vax), and laterality of vaccine deployment (smallpox vaccine) can all upend conventional methods for treating tropical infectious diseases and advance the field.

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