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Guidelines for Malaria Prevention for New Zealand Travellers when they Travel Abroad

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Sponsored by: Royal New Zealand College of General Practitioners

Background:

International travel by New Zealand residents is increasing, with 2.35 million overseas trips made in the year to July 2015 (Statistics New Zealand 2015). Many of these trips include travel to areas where the risk of exposure to infectious disease is significant, one of these diseases is malaria which is an entirely preventable and treatable mosquito-borne illness. In 2014, 97 countries and territories had ongoing malaria transmission. Globally an estimated 3.3 billion people are at risk of malaria, 1.2 billion of whom are at high risk. In high-risk areas, more than one malaria case occurs per 1000 population.

New Zealand travellers are increasingly travelling to developing country destinations, but in so doing they are putting themselves at increased risk, given that 20% of them will become unwell in some form. General Practitioners, and Practice Nurses, in New Zealand are in a perfect position to provide travel health advice for their registered patients. However, there are no national guidelines surrounding the provision of travel health advice, and especially that relating to malaria prevention, in this country. This is in direct contrast to countries such as the United States, Canada and the United Kingdom all of whom have comprehensive national guidelines on malaria prophylaxis and prevention

Objectives:

The aim of this study is to develop national guidelines for the i) pharmaceutical prophylaxis and ii) the prevention of malaria in NZ travellers. These guidelines would be primarily of use to those general practitioners who practice travel health, and secondarily to those from other disciplines such as public health, tropical medicine, occupational health and school health. It is anticipated that these guidelines will be endorsed by the NZ Ministry of Health and will become the standard for providing ongoing malaria prevention advice for NZ travellers. We hope that these guidelines also bring attention to the global malaria problem to the travelling population by being written to be as user-friendly as possible.

We also set out to become specialised in malaria prevention for countries in the South Pacific, namely Papua New Guinea, Solomon Islands and Vanuatu as they are becoming increasingly popular destinations for New Zealand travellers. No currently published malaria guidelines from the Centre of Disease Control and Prevention (USA), Public Health England, Health Protection Agency of Canada or the World Health Organisation have detailed malaria transmission maps of the above Pacific Island countries. Through this studentship and together with the Malaria Atlas Project, we were able to produce malaria transmission maps for the Pacific.

Methods:

A systematic review was undertaken by consulting the WHO, Public Health England, Centre of Disease Control and Prevention (USA) and Public Health Agency of Canada malaria guidelines. Information was compared between the sources and relevant information was used to write the New Zealand malaria prevention guidelines. The aim was to make the guidelines much simpler and user-friendly compared to other publications while retaining important information for malaria prevention.

Any discrepancies were further researched by consulting peer-reviewed journal articles on the topic required or resolved by advice from my supervisors Dr Marc Shaw and Claire Wong who are specialists in Travel Medicine.

Information included in the 'Guidelines for Malaria Prevention for New Zealand Travellers when they Travel Abroad' comprises of:

-Awareness of malaria risk to New Zealand travellers as well as information on symptoms and sequelae of malaria

-Bite prevention strategies including repellents, insecticides, room protection and fallacies

-Guidelines on prescribing chemoprophylaxis/antimalarial drugs used in NZ

-Advice for travellers with special conditions or co-morbidities (pregnancy, infants and children, liver/kidney/spleen failure, patients on anticoagulant therapy etc)

-Travel destinations around the world which constitute the greatest risk of malaria transmission for the New Zealand population.

- Country Specific Malaria Risk Areas and Recommended Preventative Measures.

This is currently undergoing review by an Australasian consensus group of experts in travel medicine, public health and malaria. This is because many of the malaria endemic countries are described to have different malaria risks between the malaria guidelines of WHO, Public Health England, Centre of Disease Control and Prevention and Health Protection Agency of Canada. Hence each publication recommends different chemoprophylaxis regimens for various countries. The aim of this consensus group review is to come to a standardised approach to malaria chemoprophylaxis advice to every malaria endemic country.

The members of this consensus group are:

Prof Dennis Shanks	Director, Australian Army Malaria Institute
Prof Peter Leggat, AM	College of Public Health, Medical and Veterinary Sciences, Division of Tropical Health and Medicine, James Cook University, Australia
Prof Michael Baker	Professor of Public Health | Department of Public Health, University of Otago, Wellington
Dr Nick Douglas	DPhil, Malaria Research
Snr Travel Nurse Claire Wong	Worldwise Travellers Health Centres of New Zealand

Prof Marc Shaw

College of Public Health, Medical and Veterinary Sciences, James Cook University, Australia

The primary data sources used for the project were:

World Health Organisation – International Travel and Health 2015 update – Malaria Chapter
Accessible from: http://www.who.int/ith/2015-ith-chapter7.pdf?ua=1

Public Health England – Guidelines on the prevention of malaria in travellers from the United Kingdom

Centre of Disease Control and Prevention – CDC Health Information for International Travel – The Yellow Book

Public Health Agency of Canada – Canadian Recommendations for the Prevention and Treatment of Malaria

Malaria Atlas Project (custom malaria transmission maps for the Pacific Islands had to be created for our purpose – to advise in the malaria risk of Pacific Island Countries)
Accessible from: http://www.map.ox.ac.uk/

MEDSAFE Datasheet (for information on antimalarial drug indications, interactions and adverse effects)
Accessible from: http://www.medsafe.govt.nz/profs/datasheet/dsform.asp

Results:

The Guidelines for Malaria Prevention for New Zealand Travellers when they Travel Abroad are included below. After the Australasian consensus group have finalised the recommendations for the country specific malaria prevention advice, the document will be published. There is already a process in place where my supervisor Dr Marc Shaw is aiming to get the document endorsed by the Ministry of Health to be used throughout New Zealand.

2016

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Aims

"The aim of this study is to develop national guidelines for the i) pharmaceutical prophylaxis and ii) the prevention of malaria in NZ travellers. These guidelines would be primarily of use to those general practitioners who practice travel health, and secondarily to those from other disciplines such as public health, tropical medicine, occupational health and school health." We hope that these guidelines also bring attention to the global malaria problem to the travelling population.

General Treatment Principles

The following are a few important points to keep in mind when advising on the use of malaria chemoprophylaxis to travellers. These simple measures can be overlooked by health professionals and travellers and should be followed to minimise the transmission of malaria.

It is essential that a full clinical history is obtained, detailing current medication including those drugs prescribed by hospitals which may not appear on GP's drug lists for repeat prescriptions, significant health problems and any known drug allergies [(1)].

There should be extensive evaluation of travel itinerary to assess length and level of malaria exposure for each country visited to ensure preventative measures and chemoprophylaxis prescribed are appropriate. Specific cities, types of accommodation, season and style of travel should be taken into account [(1,2)].

Lack of knowledge that malaria was a threat; fear of or past experience with adverse effects of antimalarials; the false belief that prior malaria infections have conferred long-term immunity; the cost of medications; confusion arising from contradictory recommendations; forgetfulness; or lack of interest in taking antimalarial medications are all risk factors for non-adherence and should be addressed by a health professional [(3)].

Travellers are advised to only use medication from reputable sources- ideally take prophylactic drugs from New Zealand. One-third to one-half of artesunate tablets in Southeast Asia have been found to have no active ingredient [(3)]. ACMP advises those purchasing antimalarial drugs over the internet to ensure that they are dealing with a bona fide supplier or web site [(1)]. This ensures that travellers are taking medication with proven active ingredients and are protected against malaria transmission.

No regimen is 100% effective, the combination of preventative measures advised will give significant protection against malaria [(1,2,3)]. Travellers should be encouraged to continue chemoprophylaxis despite suffering what they believe to be a malarial illness. If a fever is experienced whilst in a malaria endemic country or up to 12 months after leaving, complete the course of chemoprophylaxis and seek urgent medical attention.

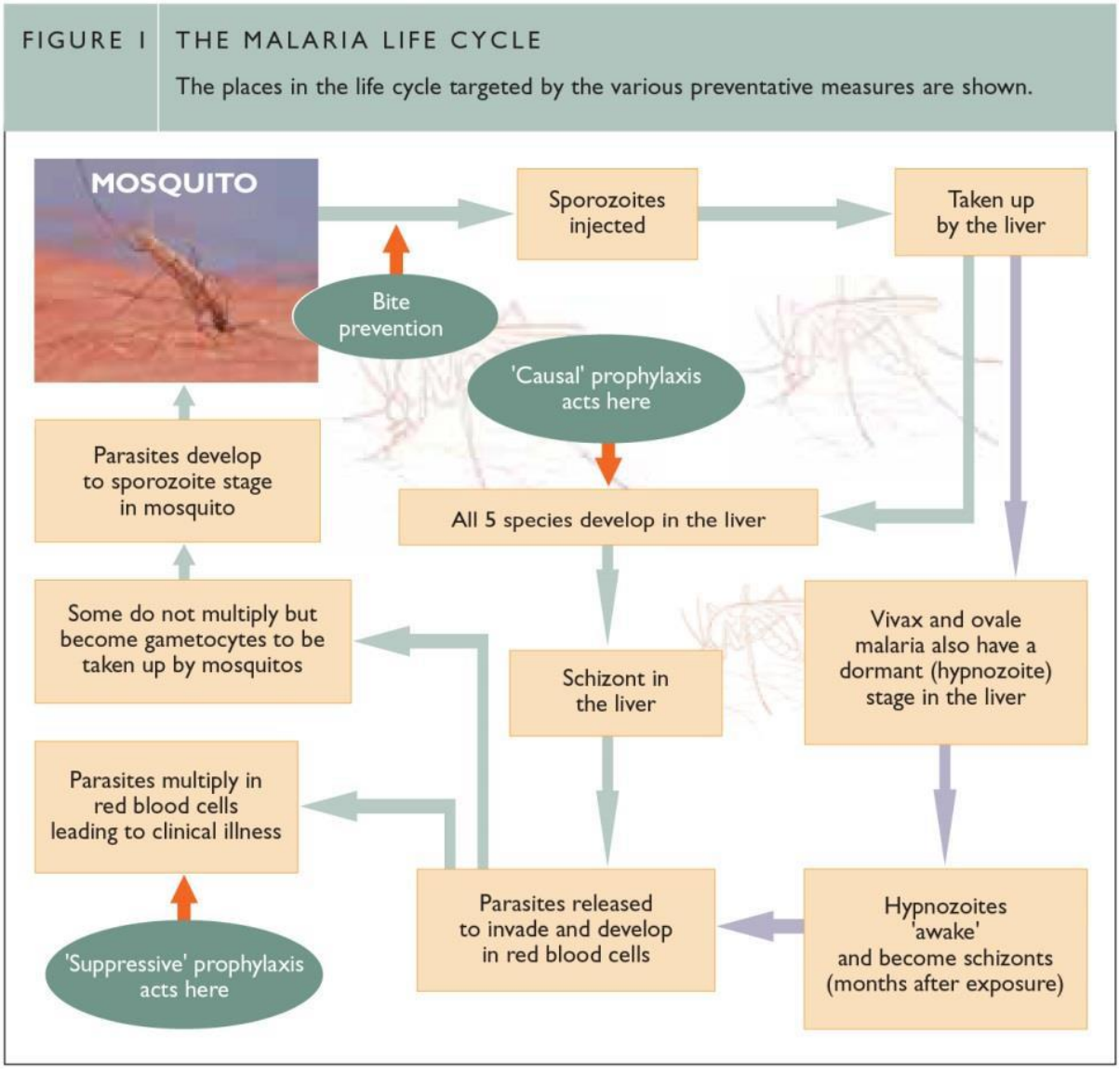
Risk within a country varies according to the regions visited and even between travellers [(2,4,5)]. Travellers should seek advice of malaria risk in specific zones they will be visiting. If this information is not available, take precautions according to the highest level of reported risk [(4)].

1. Awareness of Risk - What is Malaria?

Malaria is a serious febrile illness that is transmitted by infected female *Anopheles* mosquitoes, blood transfusions, organ transplantation, needle sharing or congenitally from mother to foetus. It leads to an infection of the red blood cells with a *Plasmodium* parasite. There are five species of *Plasmodium* parasite but mixed infections are rare but can occur [1,2,3].

While malaria usually occurs within a few weeks of infection, disease can occasionally be delayed for many months [6].

Life Cycle of a *Plasmodium* parasite [1]



1.1 Symptoms

Clinical symptoms of malaria -fever/sweats/chills, malaise (vague discomfort), myalgia (muscle pain, tenderness) headache, diarrhoea, cough [1,2,3,4]. These initial symptoms are nonspecific and cannot be distinguished from other febrile illnesses such as acute respiratory infections, dengue fever and septicaemia [4,5].

Major features of severe or complicated *falciparum* malaria [1,2]

- Impaired consciousness or seizures
- Renal impairment (oliguria < 0.4ml/kg bodyweight per hour or creatinine >265µmol/l))
- Acidosis (pH <7.3)
- Hypoglycaemia (<2.2mmol/l)
- Pulmonary oedema or acute respiratory distress syndrome (ARDS)
- Haemoglobin ≤8g/dL
- Spontaneous bleeding/disseminated intravascular coagulation
- Shock (algid malaria)
- Haemoglobinuria (without G6PD deficiency)
- Severe anaemia
- Jaundice
- Prostration (inability to sit or stand)
- Parasitaemia>2% red blood cells parasitized

1.2 Species of *Plasmodium* that affects Humans

Species	Comment
Plasmodium falciparum	The most dangerous, responsible for the vast majority of malaria deaths worldwide
Plasmodium vivax	A relapsing malaria *See life cycle on page 9*
Plasmodium ovale	A relapsing malaria *See life cycle on page 9*
Plasmodium malariae	May present with late recrudescence after many years
Plasmodium knowlesi	Very rarely imported at present, but capable of producing severe illness

1.3 Conditions of high risk exposure to Malaria

- High humidity and an ambient temperature in the range 20 to 30°. Malaria transmission does not usually occur in temperatures below 15-16°C [1,5]
- Altitudes lower than 2000m [1]
- Seasonal rainfall - increases mosquito breeding, malaria risk can be seasonal in many areas [1,3]
- Malaria incidence is generally higher in rural than in urban areas [1,3,4]. However the risk of malaria in cities and towns of malaria endemic countries must not be discounted.
- The risk of contracting malaria rises proportionally to the length of stay in a malaria endemic area [1]
- The *Anopheles* mosquitoes bite most often in the few hours before dusk and the few hours after dawn. Being outdoors during these times without sufficient bite protection increases the risk [1,2,3].
- Staying in cheap accommodation without proper mosquito protection carries a higher risk of being bitten than in air-conditioned hotels. The use of impregnated bed nets will lower the risk of being bitten during the hours of sleep [1]

1.4 Distribution of drug resistant Malaria

Chloroquine-resistant *falciparum* malaria is now widespread [1,3,6] in all malaria endemic areas of the world except for Mexico, the Caribbean, Central America west of the Panama Canal, and parts of the Middle East [3].

Chloroquine-resistant *P. vivax* is found in the Indonesian archipelago; the Malay Peninsula, including Myanmar, and eastward to Southern Vietnam and may have spread further [1].

Plasmodium species resistant to Mefloquine are reported to be present in some areas of Cambodia, China, Lao People's Democratic Republic, Myanmar, Thailand and Vietnam [2,3,6].

P. vivax with reduced susceptibility to primaquine is found in South-East Asia and Oceania and higher doses of primaquine are required to achieve radical cure of this parasite from those areas. A higher dose may also be required for *P vivax* from India, Pakistan, Afghanistan and South America [1].

Refer to Individual risk assessment and recommended chemoprophylaxis per country for more information (*see page 22*)

2. Bite Prevention

Protection against arthropod bites is best achieved by avoiding infested habitats, wearing protective clothing, and applying insect repellent [7].

2.1 Clothing

Clothing impregnated with permethrin will offer significant protection against mosquito bites [5]. Clothing with lighter colours, tighter weaves and thicker material will reduce the chances of being bitten [5]. Arms, legs and ankles are common areas where mosquitoes bite so covering these or applying insect repellents are important [1,5].

2.2 Repellents

DEET

ACMP and CATMAT recommend DEET (N,N-diethyl-3-methylbenzamide) based insect repellents [1,3]. Concentrations 20-30% or over give a longer duration of protection than currently available formulations of other agents [1,7].

There is a low risk of adverse effects when DEET is applied according to product directions [7] and DEET has a good safety profile [7,8] and shows excellent performance against mosquitoes [1,3,5]

The duration of protection is 1 to 3 hours for 20%, up to 6 hours for 30% and up to 12 hours for 50% DEET. There is no further increase in duration of protection beyond concentrations of 50% [1,5,7,9]

DEET and Sunscreen: Repellent activity will reduce more quickly than that of a sunscreen if reapplying only sunscreen on top. The mean decrease in SPF after the application of insect repellent was 33·5% [10]. Repellent will therefore usually need to be reapplied on top of a sunscreen [1,5].

When both sunscreen and DEET are required, **DEET should be applied after the sunscreen** [1,2]. 30 to 50 SPF sunscreen should be applied to compensate for DEET-induced reduction in SPF [1].

DEET in Pregnancy: DEET may be used at a concentration of up to 50% in pregnancy (including first trimester), breast feeding and for infants and children aged over 2 months. Nursing mothers should wash repellents off their hands and breast skin prior to handling infants [1].

ACMP advice on use of DEET for protection from mosquito bites [1]:

- There is no current evidence that any group (including pregnant women and small children) is at increased risk from using 50% DEET
- Lower concentrations are not suitable for prolonged exposure, such as that encountered by backpackers and expedition travellers
- Concentrations below 20% are inappropriate in almost any circumstances

Icaridin

Icaridin is reported to have repellent properties comparable to those of DEET [1]. If a traveller elects to use icaridin for mosquito bite prevention, ACMP and CATMAT advise the use of at least a 20% preparation [1,3].

Oil of citronella and other plant derivatives

Oil of citronella products offer only short lived protection and as such are not recommended for use by travellers for malaria prevention when travelling to malarious countries [1]. Combinations of plant derivatives of citronella, cedar, verbena, pennyroyal, rosemary, basil, thyme, allspice, garlic,

peppermint, eucalyptus, lantana and neem have been used with varying success. Most of the essential oils tended to give short lasting protection, usually less than 2 hours [5,8]. In addition to being less effective than DEET and Icaridin, natural oils and derivatives have not been extensively tested for efficacy of mosquito bite prevention [5].

Natural oils and derivatives are not recommended for use by travellers as a bite prevention strategy in a malaria endemic area.

2.2 Insecticide treated nets

Insecticide (pyrethroid)-impregnated bed nets improve protection because they help to prevent:

(a) Biting through the net on parts of the body touching the net

(b) Mosquitoes surviving long enough near a net to find any tears in the net which may exist

(c) Diversion of mosquitoes from someone under a net to someone in the same room without a net [1].

Most of the nets now available are long-lasting impregnated nets (LLIN). The pyrethroid is incorporated into the material of the net itself or bound to it with a resin giving it an expected useful life of at least 3 years.

Standard nets will need to be re-impregnated every 6 to 12 months (depending on how frequently the net is washed) to remain effective. The 6 months starts from the date when it starts to be used and washed, as washing and handling are the main factors removing the pyrethroid [1].

A good net for the traveller should i) be from synthetic fibre (nylon, polyester or polythene), ii) be impregnated, iii) have a denier of around 100 and iv) be easy to set up.

2.3 Room protection

Air conditioning reduces the likelihood of mosquito bites as a result of substantial reduction in night time temperature. Ceiling fans reduce mosquito nuisance.
Doors, windows and other possible mosquito entry routes to sleeping accommodation should be screened with fine mesh netting which must be close-fitting and free from tears [1,5].

The room should be sprayed before dusk with a knockdown insecticide to kill any mosquitoes which may have entered the accommodation during the day [1,5].

2.4 Fallacies

Herbal remedies, homeopathy, buzzers (ultrasonic devices), vitamin B [9], vitamin B12, garlic, savoury yeast extract spread, tea tree oil, bath oils, wristbands [7], neckbands, ankle bands etc. are not proven to be effective at preventing bites from mosquitos and subsequently are ineffective bit prevention strategies [1,5,7].

Other insecticide-based approaches such as insecticide coils which are burned, vaporizers, aerosol sprays and insecticide treated bed sheets should not be relied on for protection against mosquitoes for the prevention of malaria [3]. A combination of personal protective measures will give the greatest protection.

3. Chemoprophylaxis

3.1 Choosing an Antimalarial

The following steps should be followed to ensure that the antimalarial prescribed is safe for the traveller and effective against the *Plasmodium* species present in the travel destinations.

- Evaluate the traveller's exact travel itinerary and determine their malaria risk profile by consulting section 4. Country Specific Malaria Risk Areas (*see page 22*). Take into account the type of accommodation the traveller is staying in, how long they will be in each country and the risk levels of the particular regions of the countries they are visiting.
- For many itineraries there will be several chemoprophylaxis options which are effective. The choice of antimalarial will depend on several factors: The traveller's health status (*see section 7. Considerations for patients with special conditions or co-morbidities on page 22*), other medications being taken (prescription, over the counter and herbal medication) to check for potential drug interactions, traveller's tolerances to potential side effects and cost of the regimen.
- Consult the Chemoprophylaxis drug chart (*see page 16*) and choose an antimalarial which can be used safely taking into account a special condition such as a child, a pregnant or breastfeeding traveller as well as any co-morbidities they may have. Check the relevant row for drug interactions with the traveller's other treatments as well as informing and ensuring the traveller is comfortable with the potential side effects which may occur.
- Discuss the importance of bite prevention strategies such as the use of an effective insect repellent (DEET or Icaridin) and sleeping under insecticide treated bed nets where appropriate. The efficacy of chemoprophylaxis is dependent on strict adherence to the dosage regimen of the medication in combination with proper bite prevention strategies [(3)].
- Inform travellers that if they experience a fever or flu-like symptoms within one year of returning from their travel to a malaria endemic country, they should immediately seek medical attention. They should ensure that their health professionals are aware of their recent travel status to consider malaria as a potential cause of sickness [(1,2,3)] (*see page 9*).

There are also rare health risks associated with side-effects and drug interactions of antimalarial drugs. The management of malaria chemoprophylaxis involves balancing these potential risks with the benefit of administering chemoprophylaxis [(3)].

Tolerability can be tested to have a trial of the medication for a couple of weeks before the traveller's departure. This ensures that travellers are prepared for side effects and ensure adherence is maintained [(3)].

3.2 Discontinuing antimalarial drugs

Fatal malaria can occur in travellers who decide to discontinue their malaria prophylaxis without first consulting their health professional [(3)]. Reasons for why travellers may choose to abandon their current regimen are meeting other travellers or health care providers who provide conflicting advice with their travel health doctor. All advice received from sources other than your health professional should at the very least be questioned. Medications available around the world may be less effective, associated with serious adverse effects or may not be manufactured to New Zealand health care standards.

Malaria chemoprophylaxis prescribed by the health professional in New Zealand must be taken for the full course and according to the instructions. The only exception is if a serious adverse effect is

experienced by the traveller in which a health care professional should be urgently consulted and a change of antimalarial is warranted.

3.3 Co-Administration of Antimalarial Drugs and Vaccines

Simultaneous administration of antibiotics may interfere with oral bacterial vaccines.

Doxycycline is an antibiotic and should never be co-administered with live attenuated bacterial oral vaccines [3]. Doxycycline possibly reduces the efficacy of oral typhoid vaccine if given simultaneously [1]. It is cautious to wait at least 3 days after the administration of the oral typhoid vaccine and the first dose of any antimalarial medication – including doxycycline [3].

Chloroquine may suppress the antibody response to pre-exposure intradermal human diploid rabies vaccine [1]. This interaction is not seen when the rabies vaccine is given intramuscularly (the recommended mode of vaccination in the UK) [1], however the vaccine can be given intradermally as long as there is a minimum period of three days before the first dose of antimalarial medication.

3.4 Antimalarial Drug Chart

- Causal prophylaxis - Causal prophylaxis is directed against the liver stage of the malaria parasite, which takes approximately 7 days to develop. Causal prophylactics need to continue for 7 days after leaving a malarious area [1]. The most common causal prophylaxis used in NZ is atovaquone-proguanil combination.
- Suppressive Chemoprophylaxis - Suppressive prophylaxis is directed against the red blood cell stages of the malaria parasite and thus needs to be taken for four weeks after leaving a malarious area to prevent infection [1]. Suppressive chemoprophylaxis drugs used in NZ are Doxycycline, Mefloquine and Chloroquine.

Drug Name	Doxycycline	Mefloquine	Atovaquone and Proguanil	Chloroquine
Trade Name	Doxycycline	Lariam	Malarone	Plaquenil
Approximate Cost per Week	$4	$9	$70	$2
When to start [4]	1-2 days before	1-3 weeks before	1-2 days before	1 week before
Adult Dose [1]	1 tablet (100mg) daily with evening meal	1 tablet (250mg) weekly with food	1 tablet daily (Proguanil 100mg + Atovaquone 250mg) with food	2 tablets (2*155mg) once a week with food
Child Dose (weight is a better guide than age for children and should be used for dosage calculation which should never exceed adult dose) [1,3,4] *For more information on child doses see section 7.6 Infants and Children on page 4*	Adult Dose from 12 years of age. Unsuitable for children <12 years old.	5-9.9kg = 0.25 dose. 10 -15.9kg = 0.25 dose. 16-24.9kg = 0.5 dose. 25-44.9kg = 0.75 dose. 45 kg and over = Adult dose.	5-7.9kg = 0.125 dose 8-8.9kg = 0.188 dose 10-19.9kg = 0.25 dose 20-29.9kg = 0.5 dose 30-39.9kg = 0.75 dose 40kg and over =Adult dose.	<6 kg = 0.125 dose 6-9.9kg = 0.25 dose 10 to 15.9 kg = 0.375 dose 16 to 24.9kg = 0.5 dose 25 to 44.9kg = 0.75 dose 45 kg and over = Adult dose.
When to Finish [4]	28 days after	28 days after	7 days after	28 days after
Effectiveness	92-98%	>90% (PHE)	>90%	High where no resistant strains of *P.falciparum*. Effective against most *P.vivax, P.ovale, P.knowlesi* and *P.malariae* [1]

Drug Name	Doxycycline	Mefloquine	Atovaquone and Proguanil	Chloroquine
Resistance (*See section 4. Country Specific Malaria risk Areas and recommended chemoprophylaxis on page 22 for more information)*	Minimal	Border areas of Thailand with Cambodia and Burma [1]	Minimal	Widespread in Africa and Asia and Pacific. Chloroquine resistant *falciparum* malaria is now reported from all WHO regions except Central America north of the Panama Canal and the Island of Hispaniola (Haiti and the Dominican Republic) [1]
Possible Side Effects	Nausea, vomiting, abdominal pain, heartburn on empty stomach. Oesophagitis, Sunlight sensitivity, Vaginitis, thrush, and Candidiasis [1,3,5]. Headaches or visual disturbance	GI disturbance. Vivid dreams. Headaches. Dizziness. Very rare (1/10,000) risk of psychosis or seizures. Insomnia [4].	Mild and minimal side effects for most patients. Most common are gastrointestinal effects - Nausea, vomiting, diarrhoea [1,3]. Cough. Headache [1]. Mouth Ulcers.	Stomach upset. Rash/itch. Ringing in the ears (Tinnitus). Dizziness. Headache. Eye damage with long-term use. Very rare (1/20,000) risk of psychosis.
Contraindications (*see section 7. Consideration of patients with special conditions or co-morbidities on page 0 for more information)*	Pregnancy and breastfeeding. Kids <12 years. Tetracycline allergy [1,5]. Liver failure - dose adjustment may be required [1,3,5].	Early pregnancy, History of anxiety, depression, epilepsy, fits, psychosis, schizophrenia, Heart rhythm problems or medications, Contraindicated in scuba divers	Pregnancy and breastfeeding, Children <5kg [2], Kidney Failure <30ml/min creatinine clearance [5].	Previous psychosis, Epilepsy [5], Myasthenia Gravis, Retinopathy, G6PD Deficiency, Psoriasis may be exacerbated [5].

Drug Name	Doxycycline	Mefloquine	Atovaquone and Proguanil	Chloroquine
		and airplane pilots. Liver Failure.		
Drug interactions *(For more detailed and specific information on drug interactions, consult MEDSAFE Datasheets which can be found at www.medsafe.govt.nz)*	Warfarin (*see page 0)*, Roaccutane - increases the chance of (benign intracranial hypertension), which can lead to brain injury. Metabolism accelerated by barbiturates, carbamazepine, phenytoin (increase dose to 100mg twice daily if other anti malarials are unacceptable).	Anti-epileptics, cardiac drugs. Mefloquine is metabolised by CYP3A4. Caution if administered with drugs inhibiting CYP3A4 such as ketoconazole or macrolide antimicrobials because mefloquine can be raised above therapeutic concentrations [(3)].	Warfarin. Plasma concentration of Atovaquone is reduced by Rifabutin, Rifampicin, Tetracycline and Metoclopramide. Indinavir, Zidovudine, ritonavir-boosted protease inhibitors and most non-nucleoside reverse transcriptase inhibitors have a reported drug interaction.	Amiodarone, Ciclosporin, Digoxin, Mefloquine, Moxifloxacin [(1)].
Co-administration with vaccines (*see page 15)*	There is a theoretical risk of reduced effectiveness of the oral typhoid vaccine if given concurrently with doxycycline. Doxycycline should therefore not be used within	Vaccination with live, oral typhoid or cholera vaccines should be completed at least three days before the first dose of mefloquine [(5)]	It is advisable to wait at least 3 days after any vaccinations before beginning chemoprophylaxis.	Concurrent use of chloroquine interferes with antibody response to intradermal human diploid cell rabies vaccine.

Drug Name	Doxycycline	Mefloquine	Atovaquone and Proguanil	Chloroquine
	3 days of administration			
Long Term Prophylaxis (*see section 3.5 Long term chemoprophylaxis page 21)*	Doxycycline – Evidence suggests that is safe to use for at least up to two years. Longer term use possible if justified by malaria risk.	Mefloquine – can be used up to three years in the absence of side effects. If used for a prolonged period regular liver and eye function tests should be undertaken.	No evidence of harm in long term use. Can be used confidently for travel up to one year. Longer term use possible if justified by malaria risk.	Chloroquine – safe for long term use, consider 6-12 months ophthalmic examination from 6 years cumulative use
Pregnancy and Breastfeeding (*see section 7.10 Pregnancy and Breastfeeding on page 6)*	Not recommended. If required <15 weeks gestation, should not be withheld if other options unsuitable. Should not be given to women who are breastfeeding.	Safe after 1st trimester and in breastfeeding	Not recommended in pregnancy. Should be avoided in breastfeeding but A/P can be used if there is no other suitable antimalarials [(1)]	Safe
Pros	Cheap. Helps prevent other infections e.g Traveller's diarrhoea, chest infections, some tropical infections. Good for last	Cheap. Ok for infants, children, pregnancy and breastfeeding. Convenient dosage - once weekly. .	Well tolerated. Few side effects. Good for last minute traveller. Short course.	Cheap. OK for infants, children, late pregnancy and breastfeeding. Convenient dosage - once weekly.

Drug Name	Doxycycline	Mefloquine	Atovaquone and Proguanil	Chloroquine
	minute traveller.			
Cons	Anti-biotic. Long Course. Cannot be used by children < 12 years. Increases likelihood of vaginal yeast infections in women.	Not for last minute traveller. Long course. Cannot be used in areas of mefloquine resistance. Cannot be used for patients with psychiatric conditions or cardiac conduction abnormalities.	Expensive. Not in Pregnancy, breastfeeding and children <5kg. Not in severe renal impairment.	Widespread resistance. Not for last minute traveller. May affect psoriasis.

3.5 Long term chemoprophylaxis for adults

Long term travel is defined as travelling to a malarious country for over six months. Licensing criteria for antimalarial drugs often restrict the recommended periods of administration (usually due to a lack of formal trials of long-term administration, rather than from evidence of adverse effects). This leads to uncertainly about the safety of long-term prescribing [1].

Long-term use of some of the currently advised malaria drugs falls outside the terms of their current Marketing Authorisation (Licence) [1].

Possible Options are:

- Switching from one chemoprophylaxis regimen to another as the time limit is reached
- Discontinuing prophylaxis in favour of access to local advice and standby or physician-guided treatment
- Continuing with one prophylactic regimen beyond its licensed length of use

Any change to antimalarial medication should only be done so after consulting with a travel health physician.

Drugs for Long-Term Chemoprophylaxis

Chloroquine – safe for long term use, consider 6-12 months ophthalmic examination [1,3,4] from 5 years cumulative use [1,4].

Mefloquine – can be used up to three years in the absence of side effects. Data indicate no increased risk of serious side-effects with long-term use if the drug is tolerated in the short term [4]. If used for a prolonged period regular liver and eye function tests should be undertaken [1].

Doxycycline – Evidence suggests that is safe to use for at least up to two years. Longer term use possible if justified by malaria risk [1]

Atovaquone/Proguanil – No evidence of harm in long term use. Can be used confidently for travel up to one year. Longer term use is possible if justified by malaria risk.

3.6 Primaquine terminal prophylaxis of *P. vivax* and *P. ovale*

Primaquine is active against hypnozoites (persistent liver stages of the *Plasmodium* parasite present only in *P. vivax* and *P. ovale*) and is used in the treatment of these forms of malaria. Dormant hypnozoites explain why attacks of *vivax* or *ovale* malaria can occur up to 5 years after the end of chemoprophylaxis [1,3]. Primarily primaquine is administered as terminal prophylaxis after the traveller has left a malaria endemic area to decrease the risk of relapsing malaria.

It also has causal prophylactic activity against the liver stage schizonts of all malaria parasites of humans [1].

Primaquine is not currently recommended as a first line agent for malaria prevention in UK and NZ travellers, but may be considered in special circumstances on expert advice. There is a definite risk of haemolysis in G6PD-deficient individuals. The traveller's G6PD level must be checked before primaquine is prescribed. Primaquine is contraindicated for use in individuals with G6PD deficiency and pregnancy [1,2,3,6].

4. Country Specific Malaria Risk Areas and Recommended Preventative Measures

Information is combination from risk assessment by WHO, CDC, Public Health England and Health Protection Canada which has been reviewed by an Australasian Expert Advisory Panel on Malaria.

Country	Malaria Transmission Areas and Risk level	Recommended Chemoprophylaxis for New Zealand travellers in the risk areas of the destinations

Discrepancies

The malaria risk and chemoprophylaxis recommendations per country were written after consulting a review of the WHO, Centre of Disease Control and Prevention – USA, Public Health England and the Public Health Agency of Canada. The New Zealand risk characterizations are generally consistent with most publications; the most obvious differences relate to difference in recommendations for chemoprophylaxis in areas with low endemicity.

Some jurisdictions (e.g. United States) have a very low risk tolerance for malaria in returning travellers, and thus give more weight to chemoprophylaxis. Other jurisdictions emphasize the potential for drug-adverse effects, and are less likely to recommend chemoprophylaxis in low-risk areas. As well, region-specific recommendations are dynamic; thus, some differences arise as a result of the age of the epidemiologic evidence on which the individual recommendation is based. [3]

In areas of chloroquine sensitivity, the antimalarial preferred in NZ is chloroquine because it is safe to use in pregnancy, breastfeeding and for young children as well as for long term use from 6-12 months. Chloroquine needs to be taken only once a week which can be more convenient for travellers and hence increase compliance.

Proguanil alone is recommended as an alternative to chloroquine by Public Health England but there are very few regions in the world where the local *P.falciparum* strains are fully sensitive to proguanil [1]. Proguanil alone as an antimalarial is not recommended by CATMAT, CDC and WHO [3] and is not currently available in NZ as a stand-alone drug for malaria chemoprophylaxis.

Chloroquine-proguanil combination is considered to be significantly less effective than Atovaquone-proguanil, doxycycline and mefloquine and is therefore not recommended by CATMAT [3] and for use in NZ.

5. NZ Specific Considerations

5.1 Regions of the World which constitute the greatest risk for NZ travellers

Although malaria has never been endemic in New Zealand, it is an important cause of severe and potentially fatal illness and, along with dengue fever, the most common notified vector-borne diseases in returned travellers to New Zealand [(11)].

In New Zealand travellers from 1997 to 2009, 666 malaria infections were reported (an average of 51 cases/year), with 410 cases (61.6%) in civilians and 133 (20%) in military personnel. The most common countries from which civilians acquired malaria were Papua New Guinea (24.4%), India (18.6%), the Solomon Islands (8.8%), Indonesia (6.1%), and Vanuatu (5.9%) [(11)]. Most infections (61.6%) occurred in travellers aged 20–39 years.

Compared to a previous malaria report in 1992 there is now a lower percentage of cases acquired from Papua New Guinea and Western Pacific (from 59.2% to 39.3%), and a higher percentage from Africa (from 8.6% to 21.3%) [(11)]

This reflects changing travel patterns of New Zealanders and the origins of visitors and immigrants [(11)].

Travellers with the highest estimated relative risk for infection are those going to West Africa and Oceania [(2)].

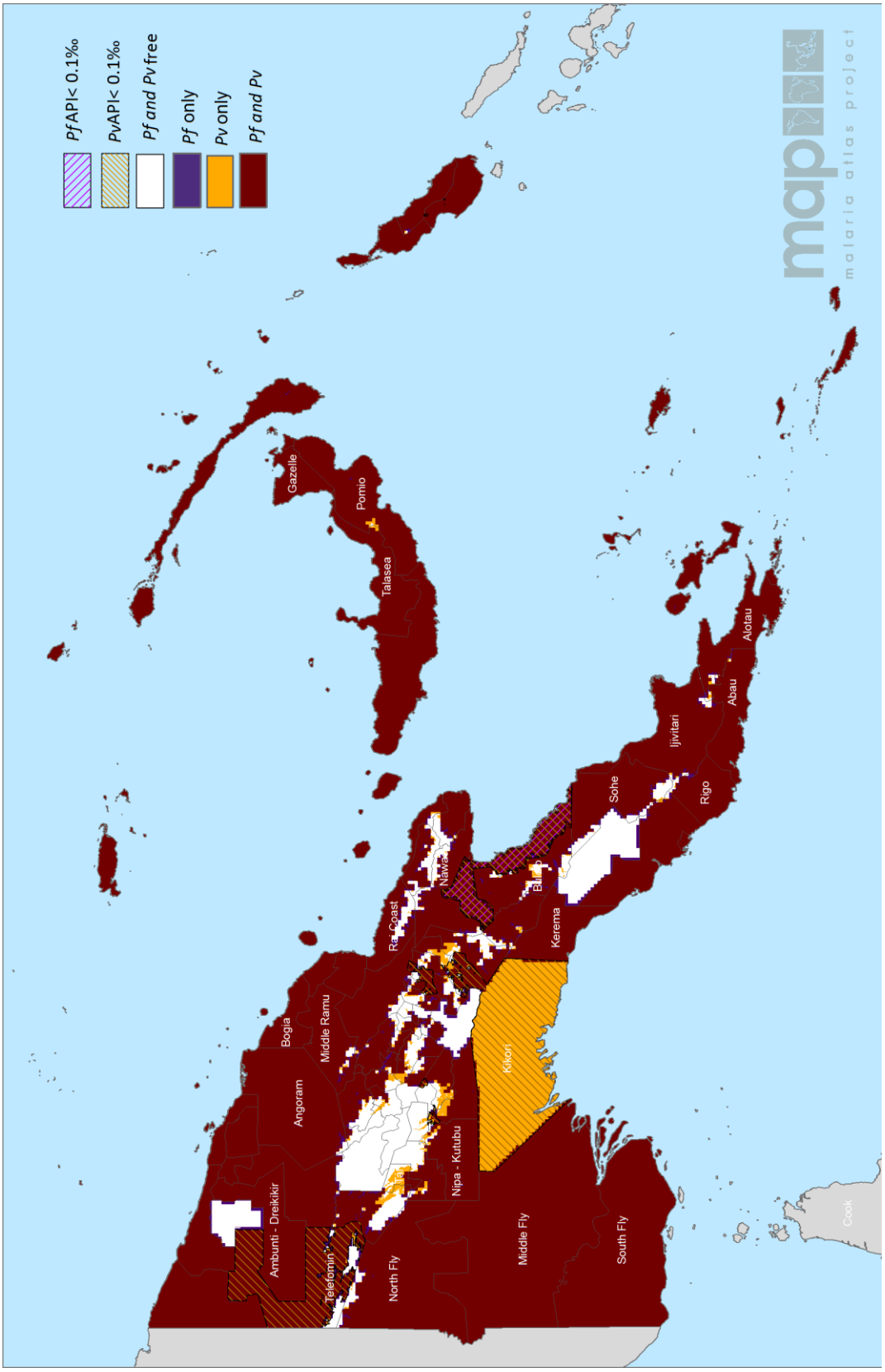
5.2 Visiting Friends and Relatives

First and second generation immigrants living in non-endemic countries who return to their countries of origin to visit friends and relatives (VFRs) are at highest risk. Acquired Immunity is lost quickly and VFRs have the same risk as non-immune travellers [(1,2,3,5)]. According to a recent study on imported malaria cases in NZ from 1997 to 2009 majority of Papua New Guineans acquired malaria from Papua New Guinea, Pacific Islanders from the Western Pacific, Indians and Pakistanis from the Indian subcontinent, other Asians from Southeast Asia, and Africans from Africa [(11)]. Travellers returning to home countries to visit family and friends (VFRs) have a higher risk of malaria and other tropical infections compared to tourists [(11)].

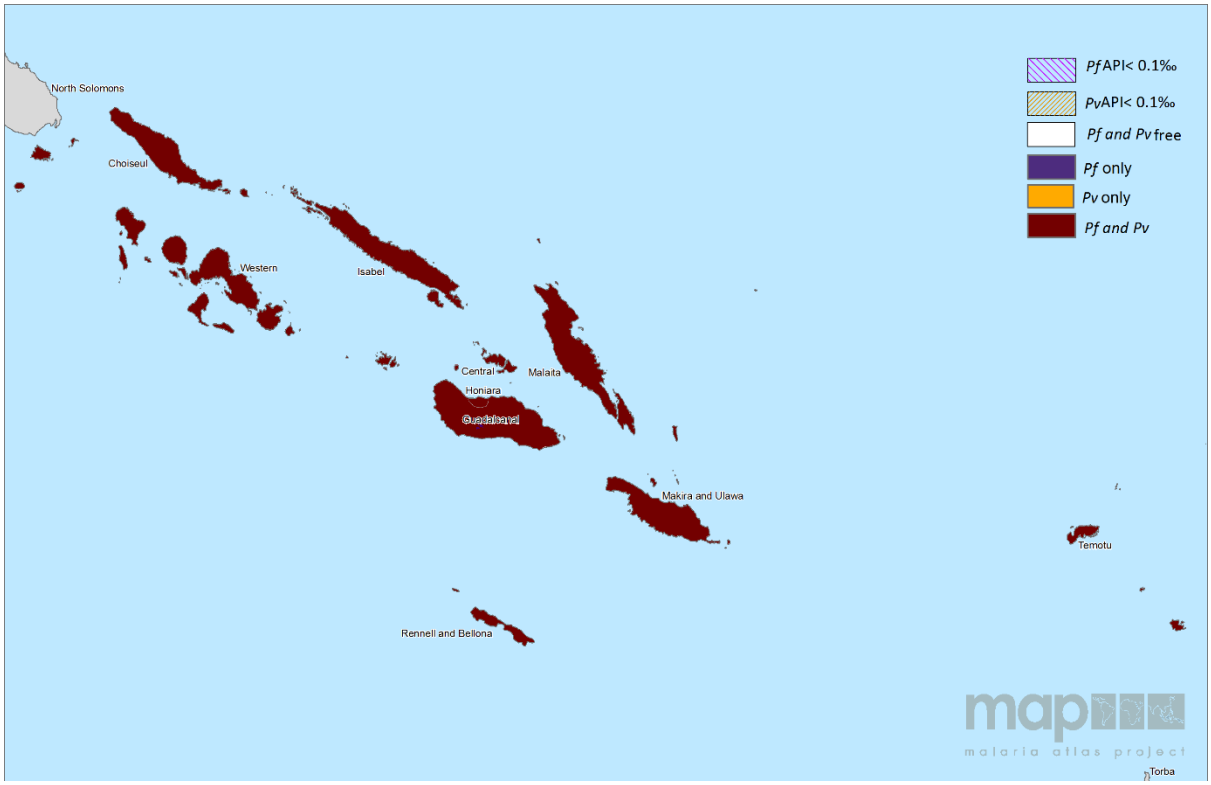
VFRs have a higher risk of malaria as they are less likely to take chemoprophylaxis and more likely to travel to rural areas, villages, and less developed areas where infection risks are higher, stay for extended periods of time, and exposed to local living conditions and hygiene standards [(3,11)]

6. Malaria Transmission Maps of Pacific Island Countries with Malaria

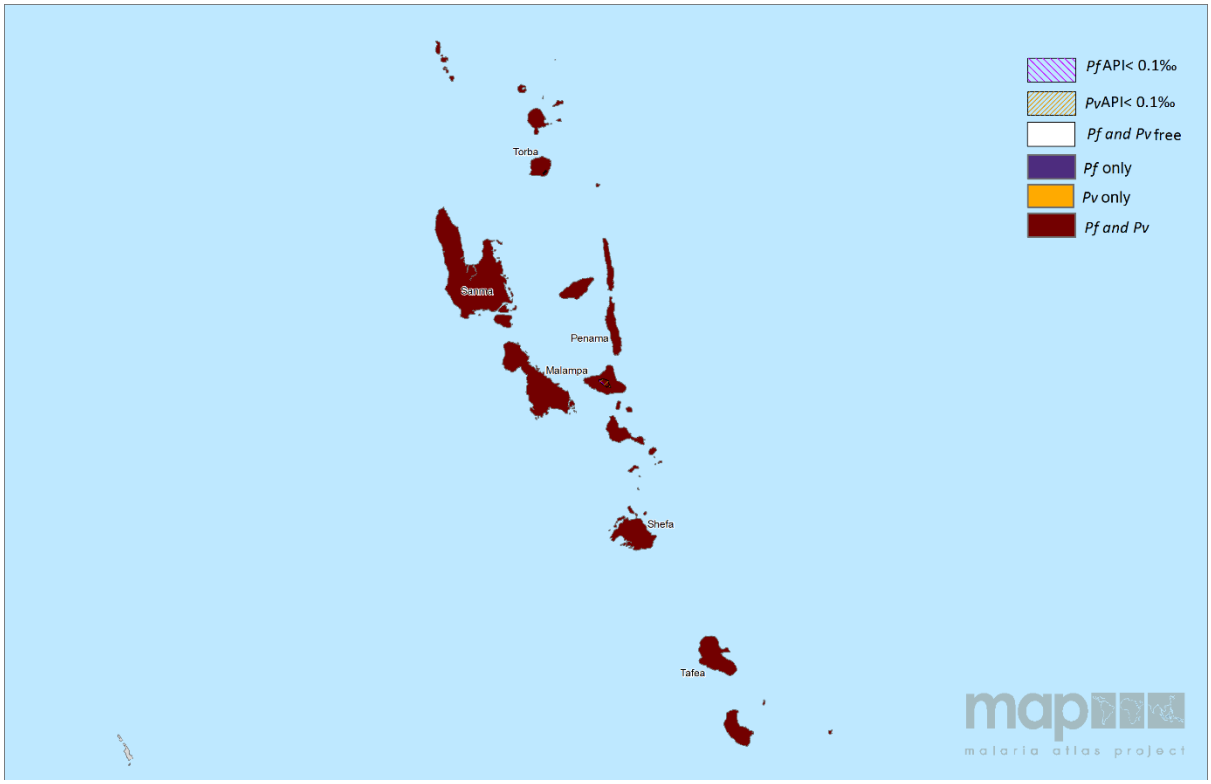
Papua New Guinea



Solomon Islands



Vanuatu



Disclaimer: Please note that any information derived from The Malaria Atlas Project is not an appropriate source for travel advice on malaria risk. Always consult your physician for the latest advice prior to travel. Rights to all maps used in this publication belong to the Malaria Atlas Project

7. Considerations for Patients with Co-morbidities or Special Conditions

7.1 Cardiovascular System

Anticoagulants

The coumarins, including warfarin

Before using antimalarials patients should ensure their INR is stable and in the therapeutic range prior to departure and have adequate anticoagulant for the whole trip. Patients on anticoagulants are likely to have cardiovascular disease and be taking other drugs. An extensive medical history should be obtained to ensure no drug interactions occur with the chemoprophylaxis [(1)]

Chloroquine

No interaction between warfarin and chloroquine documented in the BNF, although there is a caution in the SPC for chloroquine [(1)].

Mefloquine

Not considered to be a problem for those taking warfarin. The manufacturer states that 'although no drug interaction is known with anticoagulants, effects of mefloquine on travellers should be checked before departure.' [(1)] Please see below for how this can be monitored.

Doxycycline

The anticoagulant effect of coumarins (including warfarin) is possibly enhanced by tetracyclines. [(1)]

Atovaquone/proguanil

Unknown whether there are interactions between atovaquone/proguanil and warfarin, although there has been an isolated report of an enhanced effect of warfarin when taken together with proguanil [(1)].

Advice for malaria chemoprophylaxis for patients taking warfarin

Antimalarials should be started 2-3 weeks prior to departure. Baseline INR should be checked prior to and 1 week after taking chemoprophylaxis to determine whether dosage needs to be adjusted [(1,3)]. The INR must be checked with the traveller's anticoagulant clinic to ensure it is appropriate for travel. Monitoring of INR at regular intervals is necessary for longer trips and can be self-tested by experienced patients. Patients are recommended to stay in contact with their anticoagulant clinic for dosage recommendations [(1)].

New Oral Anticoagulants

Darbigatran etexilate, rivaroxaban and apixaban are the most common NOAC. They do not require laboratory management and have a lower potential for drug interactions than coumarins. There is limited experience of antimalarial chemoprophylaxis with NOAC [(1)].

Rivaroxaban and apixaban are substrates of CYP3A4 and p-glycoprotein. Dabigatran is a substrate of p-glycoprotein. [(1)]

Mefloquine inhibits CYP3A4 and p-glycoprotein, so could increase darbigatran, rivaroxaban and apixaban plasma concentrations which might lead to an increased bleeding tendency [(1)].

Atovaquone may produce minor inhibition of CYP3A4 which may increase concentrations of rivaroxaban and apixaban slightly above therapeutic level [1].

The effect of proguanil on this enzyme is unknown. Neither atovaquone nor proguanil inhibits p-glycoprotein [1].

7.2 Gastrointestinal System

Liver Disease

There is a risk of drug accumulation in severe liver impairment due to decreased metabolism.

Doxycycline – may be used for mild and moderate liver impairment, but a dose adjustment may be required [1,3]. A CDC expert meeting concluded that the dose of doxycycline does not have to be adjusted in patients with impaired hepatic function since it is excreted as an inactive chelated product via a process of back diffusion in the small bowel. Note to prescribers: The BNF states that tetracyclines should be avoided or used with caution in patients with hepatic impairment.

Mefloquine - may be used for mild and moderate liver impairment with caution [1,3]

Atovaquone-proguanil combination preparation may be used for mild and moderate liver impairment without a change in dosage [1,3]. The manufacturer of atovaquone-proguanil combination preparation states that although no pharmacokinetic studies have been conducted in severe hepatic impairment, no special precautions or dosage adjustment are anticipated (SPC) [1]. Use with caution in patients with severe hepatic impairment [3].

7.3 Genitourinary System

Renal Impairment

Chloroquine is partially excreted via the kidneys while proguanil is wholly excreted via the kidneys. [1] Dose reduction for prophylaxis is required only in severe renal impairment [1]. Caution for use in renal impairment as dosage adjustment may be required [3].

Atovaquone-proguanil - Not recommended for patients with an eGFR of less than 30mL/minute due to risk of drug accumulation [1,3]. Not to be used in patients receiving renal dialysis [1]

Doxycycline or mefloquine - May be used in severe renal failure. There is no need to reduce the dose of doxycycline or mefloquine in renal dialysis [1,3]

Spleen failure/Splenectomy

Patients whose spleen has been removed or whose splenic function is severely impaired are at particular risk of severe malaria and, where possible, should avoid travel to malarious areas.

If travel is essential, every effort should be made to avoid infection by rigorous use of anti-mosquito precautions and strict adherence to appropriate chemoprophylaxis. If the traveller becomes unwell during or after their visit, medical attention is required as a matter of urgency. Asplenia increases the risk, magnitude and duration of parasitemia, even among partially immune individuals in malaria-endemic countries [3]. Doxycycline for malarial prophylaxis may be preferred over other options due to its antibacterial activity to reduce the risk of postsplenectomy bacterial sepsis.

7.4 Haematopoietic System

Acute porphyria

Apart from atovaquone-proguanil, all of the first line malaria chemoprophylactic agents are considered possibly porphyrinogenic and are recommended for use with precaution and only if no safer alternative exists [3].

Doxycycline is unsafe in porphyria so should not be used for antimalarial chemoprophylaxis in patients with acute porphyria [1].

Mefloquine and Atovaquone-proguanil can be safely used in porphyria [12].

Glucose-6-Phosphate dehydrogenase Deficiency

Absence of G6PD renders the red cell liable to haemolysis in the presence of some drugs.

All G6PD-deficient travellers to malarious areas should take appropriate chemoprophylaxis

Chloroquine

Theoretical risk of haemolysis in some G6PD-deficient individuals. Haemolysis does not appear to be a problem when chloroquine is given in the dose recommended for malaria chemoprophylaxis so there is no need to withhold chloroquine prophylaxis from those known to be G6PD-deficient [1,3]. This risk is acceptable in acute malaria and G6PD levels are not usually checked before using chloroquine in treatment doses [1].

Atovaquone-proguanil, doxycycline or mefloquine

There is no need to withhold any of these agents from those known to be G6PD-deficient. [1]

Primaquine – is used in exceptional circumstances for the treatment of hypnozoite stages of *vivax* and *ovale* malaria is heavily contraindicated for use in patients with G6PD-deficiency [1,3].

HIV/Immunocompromised patients (Organ Transplant)

Acute malaria stimulates HIV-1 replication, resulting in increased viral loads that may hasten disease progression, decrease CD4 counts and increase transmission risk [3,5].

Co-infected pregnant women are at risk from higher parasite density, anaemia and malarial infection of the placenta [1]. Children born to women with HIV and malaria infection have low birth weight and are more likely to die during infancy. Malaria during pregnancy increases the risk of mother-to-child transmission of HIV-1 [1,3].

HIV infection may increase the risk of malaria treatment failure [4] with risk increasing as CD4 counts decline [3].

HIV protease inhibitors as well as the non-nucleoside reverse transcriptase inhibitors (NNRTIs) can either inhibit or induce the same liver enzymes which metabolise most drugs used for malaria prophylaxis and treatment [1,3].

Before prescribing antimalarials to travellers with HIV, please refer to the MEDSAFE datasheets on chloroquine, mefloquine, doxycycline and atovaquone-proguanil to check for significant drug interactions. The datasheets can be found at www.medsafe.govt.nz/profs/datasheet/dsform.asp.

Antimalarial drugs for patients with HIV

Below is a simple guideline to possible interactions with common drugs used in HIV therapy. However as newer treatments arise as well as the variations in drugs used by different countries/treatments, it is wise to check specific interactions with antimalarials and the exact medication being used by travellers with HIV.

General anti-retroviral and antimalarial drug interactions [3]

Chloroquine – No documented significant interactions. Ritonavir – potential increase in chloroquine levels

Mefloquine –Non- nucleoside reverse transcriptase inhibitors (NNRTIs) may decrease mefloquine levels reducing the concentrations below therapeutic levels to prevent malaria. Protease inhibitors (PIs) taken with mefloquine may result in a decrease in protease inhibitor or mefloquine levels.

Doxycycline – No interactions with NNRTIs or PIs. Avoid use with tablets or oral suspensions of Didanosine. No interaction seen with Videx enterocoated capsules.

Doxycycline is the simplest chemoprophylaxis against malaria for most people on antiretrovirals. However, information in this area is accumulating rapidly and the travel health adviser should check the manufacturer's SPC and the BNF on an individual agent basis and discuss the options for chemoprophylaxis with the traveller's own HIV physician who should make the decision on choice of agent [1].

Atovaquone-proguanil – Azidothymidine (AZT) levels are increased but dose adjustment is not required. NNRTIs and PIs – avoid co-administration due to risk of atovaquone levels decreasing below the therapeutic concentration.

Antimalarial drugs for immunocompromised patients

A review on the prevention of infection in adult travellers after organ transplantation recommended that ciclosporine levels should be monitored if chloroquine is co-administered [1].

General anti-rejection drug and antimalarial drug interactions [3]

Antimalarial	Anti-rejection drug	Potential Effect
Chloroquine	Tacrolimus Cyclosporine	Prolonged QT Increased levels of cyclosporine
Mefloquine	Tacrolimus Cyclosporine	Prolonged QT Prolonged QT
Doxycycline	Mycophenolate	Decreased levels of mycophenolate
Atovaquone	No reported interactions with anti-rejection drugs to date	

Sickle cell disease and thalassaemia

Presence of the sickle cell trait confers some protection against malaria, though individuals with the sickle cell trait still require antimalarial prophylaxis.

For those with homozygous sickle-cell disease, malaria is regarded as a significant cause of morbidity and mortality, producing further haemolysis against the background of that due to sickle cell disease itself. Therefore, it is essential that individuals with sickle cell disease travelling to malaria-endemic areas receive rigorous antimalarial protection [1].

Thalassaemia may provide protection against severe malaria, but there is currently no evidence it prevents uncomplicated malaria. Patients with thalassaemia are required to take appropriate chemoprophylaxis when travelling to malaria endemic countries.

7.5 Infants and Children

Children are at high risk for severe and fatal malaria, chemoprophylaxis and rigorous bite prevention strategies in malarious areas are essential. Children must be supervised to ensure the complete course of the medication is completed correctly.

Infants do not receive sufficient medication through breast milk for protection and hence should be prescribed antimalarial drugs even if their mother is taking antimalarials [3,4].

Administering antimalarials to children can be difficult as only Atovaquone-proguanil is available in New Zealand as a paediatric formulation. Chloroquine and Mefloquine tablets will have to be broken down to ensure the correct dosages are given to children. Most antimalarials are foul-tasting and mixing them with jam, banana, sweetened condensed milk or other similar foods will make them easier to swallow for children [1,5].

Weight is a better guide than age for children and should be used for dosage calculation which should never exceed adult dose [1,2,4,5].

<u>Chloroquine</u>

-Preferred chemoprophylaxis drug in areas with chloroquine-sensitive malaria.

Take care to ensure that tablets are actually swallowed, as they have a bitter taste. Sweetened chloroquine syrup is available in some countries. Store safely away from children since an overdose can be fatal [1,2].

<u>Dosages (as a fraction of adult doses):</u>

<6 kg = 0.125 dose , 6-9.9kg = 0.25 dose, 10 to 15.9 kg = 0.375 dose, 16 to 24.9kg = 0.5 dose, 25 to 44.9kg = 0.75 dose, over 45 kg = Adult dose.

Adult dose: 2 tablets (2*155mg) once a week with food beginning 1 week prior to departure and for 28 days after returning from a malaria endemic area.

<u>Mefloquine</u>

Should only be given to infants of more than 5 kg body weight [4,5]. Problem in administering correct dosage because there is currently no suspension available and adult-dose tablets must be broken [1,5] Young children are less likely to suffer major neuropsychiatric side effects from mefloquine but may be more likely to experience vomiting [3].

Dosages (as a fraction of adult doses):

5-9.9kg = 0.25 dose. 10 -15.9kg = 0.25 dose. 16-24.9kg = 0.5 dose. 25-44.9kg = 0.75 dose. 45 kg and over = Adult dose.

Adult dose: 1 tablet (250mg) weekly with food beginning 1-3 weeks prior to departure and for 28 days after returning from a malaria endemic area.

Doxycycline

Only licensed in the UK and NZ for children over the age of 12 years due to its potential to cause bone damage and discolouration of teeth. This age limit varies between countries with some recommendations stating it is safe to use in children >8 years. The standard practice in New Zealand is to only prescribe doxycycline for children >12 years to minimise risk of any adverse effects.

Tablets should be swallowed whole and must not be crushed [(1)]

Adult Dose from 12 years of age. Unsuitable for children <12 years old.

Adult dose: 1 tablet (100mg) daily with evening meal beginning 1-2 days prior to departure and for 28 days after returning from a malaria endemic area.

Atovaquone-proguanil

Paediatric tablets are licensed in the UK for malaria prophylaxis in children from 11 kg upwards. Clinical trials using atovaquone-proguanil to treat malaria in children weighing as low as 5 kg suggest it may be safe for infants of this size when required [(3)]

For children weighing less than 11 kg, ACMP recommends the following dosage regimen:

Weight 5 to 8 kg: half a paediatric tablet daily [(1,2,3)]

Weight >8 to 10 kg: three quarters of a paediatric tablet daily [(1,2,3)]

Paediatric tablets are a quarter of the strength of adult tablets – Proguanil 25mg + Atovaquone 62.5mg

For children weighing less than 10 kg, dosing may be made easier by using paediatric tablets described above.

Dosages (as a fraction of adult doses):

5-7.9kg = 0.125 dose, 8-9.9 kg = 0.188 dose, 10-19.9kg = 0.25 dose, 20-29.9kg = 0.5 dose, 30-39.9kg = 0.75 dose, 40kg and over =Adult dose.

Adult dose: 1 tablet daily (Proguanil 100mg + Atovaquone 250mg) with food beginning 1-2 days prior to departure and for 7 days after returning from a malaria endemic area.

7.6 Integumentary System

Psoriasis

Chloroquine/hydroxychloroquine – reported to trigger acute flares of psoriasis. Chloroquine and its derivatives should be avoided when prescribing chemoprophylaxis for patients with psoriasis [(3,5)].

Mefloquine, atovaquone-proguanil and doxycycline are not shown to exacerbate psoriasis based on current literature [3].

7.7 Neurological System

Epilepsy

In epilepsy [3]:

- doxycycline or atovaquone/proguanil can be used
- chloroquine: unsuitable.
- mefloquine: unsuitable – should not be prescribed for travellers before completing a careful assessment of history of depression, generalised anxiety disorder or psychosis.

Doxycycline: Half-life may be reduced by phenytoin, carbamazepine, and barbiturates as they induce hepatic microsomal enzymes [1,3]. Try to advise another antimalarial. If not possible or acceptable to the traveller, increase the dose of doxycycline to 100mg twice daily and counsel regarding measures to minimise the risk of adverse events [1].

Myasthenia Gravis

Acute infections such as malaria may exacerbate myasthenia gravis. Therefore appropriate bite prevention strategies and malaria chemoprophylaxis should be adhered to.

Chloroquine, mefloquine and doxycycline have all been associated with worsening of myasthenia symptoms and should be avoided [3]. Doxycycline has a less frequent association with worsening myasthenia symptoms than chloroquine and mefloquine. Doxycycline can be used in a trial for stable patients with only ophthalmologic symptoms 1-2 weeks before departure [3].

Atovaquone-proguanil has not been linked with worsening of myasthenia symptoms but proguanil therapy alone has. A trial of therapy before the traveller's departure is recommended [3].

Doxycycline and Atovaquone-proguanil both have short half-lives and if adverse effect do occur, the duration of the worsened symptoms is limited [3]

Because of the risk of severe decompensation with respiratory compromise, travellers with active myasthenia gravis should avoid travelling to areas where tertiary care may be difficult to access in a timely manner and should ensure they carry adequate medical evacuation insurance [3].

7.8 Pregnancy and Breastfeeding

Pregnant women are advised to avoid travel to malarious areas [4,5]. There is an increased risk of developing severe malaria and a higher risk of fatality compared to non-pregnant women [2,5]. Complications, including severe anaemia, hypoglycaemia, jaundice, renal failure, hyperpyrexia and pulmonary oedema, may ensue. The result may be miscarriage, premature delivery, spontaneous abortion and stillbirth [1,2,3,5].

Avoidance of mosquito bites is extremely important in pregnancy as pregnant women are particularly attractive to mosquitoes [1,3]. Ideally, pregnant women should remain indoors between dusk and dawn. If they have to be outdoors at night they should adhere rigorously to bite precautions [1]. Bite prevention strategies recommended for pregnant travellers are the same as for all travellers and include the use of DEET/Icaridin based insecticides, sleeping under

mosquito nets or in air-conditioned rooms and wearing light coloured clothing which minimises skin exposure. *See section 2. Bite Prevention on page 12 for more information.*

Diagnosis of *falciparum* malaria in pregnancy can be particularly difficult as parasites may not be detectable in blood films due to sequestration in the placenta [1,5].

Antimalarial Drugs in Pregnancy

Chloroquine is safe to take in pregnancy in areas where resistance to chloroquine is not reported. For areas with chloroquine resistance, mefloquine is the only drug recommended for use during pregnancy when used at prophylactic doses [1,2,3,5]. It is advised that mefloquine is only prescribed from the second trimester of pregnancy and onwards. If travel to a malaria endemic country with chloroquine resistance cannot be deferred until then, mefloquine may be used after a careful risk assessment by a doctor in the first trimester.

Doxycycline - Contraindicated in pregnancy for risk of adverse effects seen in foetal development with tetracycline – a related drug [2,3,5]. However, under special circumstances, if required before 15 weeks' gestation it should not be withheld if other options are unsuitable. The course of doxycycline, including the 4 weeks after travel, must be completed before 15 weeks' gestation [1].

Atovaquone/proguanil - Lack of evidence on safety in pregnancy. The individual components have shown no effects on parturition or pre- and post-natal development. ACMP and CATMAT advise against the use of atovaquone/proguanil for antimalarial chemoprophylaxis in pregnancy. However, if there are no other appropriate options, its use may be considered in the second and third trimesters after careful risk assessment. Women who have taken atovaquone/proguanil inadvertently just prior to or during the first trimester should be advised that this does not constitute an indication to terminate the pregnancy [1].

Chemoprophylaxis prior to conception

Observe the following time intervals after completing the course, before attempting to conceive:

Mefloquine: 3 months [1,3,4]

Doxycycline: 1 week [4]

Atovaquone/proguanil: 3 weeks [1,4]

Breastfeeding

Chloroquine – safe to use during breastfeeding [2,3,4]

Mefloquine – safe to use during lactation [1,3,4]

Doxycycline - ACMP's view is that doxycycline should not be used in breast feeding unless there is no alternative agent and its use is felt to be essential [1]

Atovaquone/proguanil - Not recommended because of the absence of data however, can be used when breast-feeding if there is no suitable alternative antimalarial [1].

The amount of medication in breast milk will not protect the infant from malaria. Therefore, the breastfeeding child needs his or her own prophylaxis [1,2,3,5].

7.9 Respiratory System

Smoking Cessation

Chloroquine or mefloquine should not be used by patients taking Zyban (bupropion hydrochloride SR) as the chances of seizure may be increased [1].

8. Special Situations

8.1 Cruises

Bite prevention strategies should be used by all travellers on cruises which are expected to pass through or stop over in malaria endemic countries.

Detailed itinerary evaluation should be taken to assess the risk level of malaria exposure. Certain cruises which pass through areas like the Amazon in Brazil, or the Orinoco river in Venezuela will certainly require chemoprophylaxis [1].

8.2 Elderly Travellers

No reduction in antimalarial dosage is required on the basis of advanced age. However elderly travellers are more likely to have underlying conditions such as renal impairment or liver impairment which affects the recommended dosage for antimalarials [1]. Elderly travellers are also more likely to take additional medications for other health conditions such as anti-coagulants [1], so special care should be taken that no drug interactions will occur when prescribing antimalarials.

8.3 Last minute travellers

Mefloquine, doxycycline and atovaquone-proguanil are prescription only medicines in New Zealand.

If a GP appointment is unable to be made at short notice, travellers can attend some commercial travel clinics which cater for walk-in appointments.

Because chloroquine is required to be taken for 1 week prior to travel and mefloquine for 2-3 weeks prior to travel, they are not recommended for last minute travellers. The recommended antimalarials for last minute travellers are doxycycline and atovaquone-proguanil as they need to be started only 2 days prior to travel. *For more information consult the antimalarial drug chart on page 16.*

It is better to start chemoprophylaxis late than not to take it at all as suppressive prophylactics will begin to work by the end of the malaria incubation period [1].

8.4 Multi-trip travel

Some travellers such as expatriates or business persons make regular short trips to malaria endemic countries several times a year. Chemoprophylaxis may be required all year-round when taking into account the periods before and after travel that antimalarials need to be taken for. In this instance, the requirement for chemoprophylaxis should be assessed on the risk level of the areas visited *see page 22.*

If the traveller wishes to not take antimalarials between visits, atovaquone-proguanil is the preferred option because of its short 7 day post-exposure course [1].

8.5 Oil Rigs

People employed in the oil industry may have to make regular trips to oil rigs every 4-6 weeks followed by a similar period of leave back home. The level of malaria risk largely depends on the geographical location of the oil rig and the conditions of accommodation available. It is wise to take chemoprophylaxis for the first trip until the malaria risk is known. Antimalarial chemoprophylaxis is advised for those workers on oil rigs based in river estuaries [(1)].

8.6 Stopovers

Many stopovers for international flights occur in urban or tourist areas. The malaria risk is usually not significant enough to warrant chemoprophylaxis. However if overnight stay is located in a region of a malaria endemic country with high risk such as sub-Saharan Africa or South-East Asia, antimalarial chemoprophylaxis is recommended [(1)].

9. Treatment of suspected cases of malaria in NZ

If flu like symptoms or a fever with an unidentifiable cause occur up to one year post travel from a country known to contain malaria – seek urgent medical advice [(2,3,6)]. Malaria can be fatal if treatment is delayed, regardless if antimalarials were taken or not [(2,3,4)].

Febrile travellers should ensure to provide their medical professionals with their travel history including the fact that they had been to a malaria endemic country in the last 12 months [(3)].

For Health care practitioners – consider malaria in the differential diagnosis if the travel history of the patient and clinical signs are those compatible with malaria. Use a different drug for treatment than was used for the chemoprophylaxis [(1,6)]. A thick and thin blood film should be obtained and examined for parasites as soon as possible. If the blood films are negative initially and the traveller remains symptomatic, repeat the blood films at least twice over the next 12-24 hours [(3)]. A single negative blood film or negative antigen test does not exclude the diagnosis of malaria, particularly if the patient has recently taken antimalarials [(6)]. When laboratory analysis is delayed, physicians should begin treatment if the clinical indicators and travel history suggest malaria [(4)].

Abbreviations

ACMP – Advisory Committee on Malaria Prevention for UK Travellers

BNF – British National Formulary

DEET – N,N-diethyl-3-methylbenzamide, previously N,N – diethyl-m-toluamide (an insect repellent)

CATMAT – The Committee to Advise on Tropical Medicine and Travel (expert advisory body which assists the Public Health Agency of Canada with travel health-related advice for travellers and health care professionals.

CDC – Centre for Disease Control and Prevention (USA)

G6PD – Glucose 6-Phosphate Dehydrogenase (a metabolic enzyme)

HIV – Human Immunodeficiency Virus

INR – International Normalised Ratio

MAP – Malaria Atlas Project

NOAC – New Oral Anti-Coagulant

PI – Protease Inhibitor

PHE – Public Health England

NNRTI – Non-Nucleoside Reverse Transcriptase Inhibitor

NZ – New Zealand

SPC – Summary of Product Characteristics (known as a "datasheet" in NZ for information about medicines produced by MEDSAFE New Zealand)

SPF – Sun Protection Factor

UK – United Kingdom

USA – United States of America

VFR – Visiting Friends and Relatives

WHO – World Health Organisation

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