TRAVEL MEDICINE PHARMAC 2016
PREVENTING MALARIA IN TRAVELLERS

Dr Jenny Visser
Malaria

- Protozoa
- 5 species capable of infecting humans
  - *Plasmodium falciparum*
  - *Plasmodium vivax*
  - *Plasmodium ovale*
  - *Plasmodium malariae*
  - *Plasmodium knowlesi* (zoonosis)
- Vector:
  - *Anopheles spp*
  - Night biting, rural/forested regions
Malaria in Travellers

- Annually approximately 25-30 million international travellers from non endemic areas travel to endemic areas*
- Internationally an estimated 30 000 cases of travel-associated malaria occur**
- Evidence that incidence is reducing in returning travellers, but proportion of falciparum malaria increasing***

*** Schlagenhauf P, Hommel M. (2011) Travellers' malaria-'one shoe does not fit all'. Malaria J. 10(1):129
Figure 20. *Plasmodium* species and country of overseas travel for malaria notifications, 2014

Note: Some cases reported travelling to more than one country during the incubation period for the disease. Those who travelled to Australia also said they have travelled to another malaria-endemic country (Solomon Islands, Uganda and Zambia).
NZ Imported Malaria: 13 years data*

- 666 cases
- 80% (533) non-military: 20% (133) military
- In non-military
  - Average 41 cases/year
  - Acquired in
    - PNG (24.4%)
    - India (18.6%)
    - Solomon Islands (8.8%)
    - Indonesia (6.1%)
    - Vanuatu (5.9%)
    - Uganda (2.9%)
    - Thailand (2.7%)
    - Tanzania (2.7%)
    - Malawi (2.7%)

FIG. 3. *Plasmodium* species by region where malaria was acquired.

**P. vivax**: 72.7%

**P. falciparum**: 27.2%
Imported malaria Auckland 2008-2009*

- 34 cases in 32 individuals
- 24 male & 8 female
- Mean age 21 (6m-75 yrs)
- Background
  - 11/32 NZ residents
  - 21/32 new arrivals
    - 11 refugees
    - 10 migrants

- Of 11/32 NZ residents
  - 8/11 VFRs
  - 3/11 missionaries
  - 6 falciparum malaria
  - 4 vivax malaria
  - 1 both

- “Malaria in Akld is seen in new arrivals and VFR travellers, not in tourist travellers”
Risk of Malaria

- Incidence of malaria in travellers without chemoprophylaxis (per month)*
  - PNG >3%
  - Solomon Islands >3%
  - West Africa 2.4%
  - East Africa 1.2%
  - India 0.35%
  - South-east Asia 0.1%
  - South America 0.05%

PREVENTING MALARIA in Travellers

A Awareness-know the risk

B Bites by mosquitoes-prevent

C Compliance with Chemoprophylaxis

D Diagnose malaria swiftly and treat appropriately
Malaria Chemoprophylaxis

- Malaria chemoprophylactics currently available in New Zealand
  - Chloroquine
  - Mefloquine
  - Doxycycline*
  - Malarone
  - Primaquine**

- * Not licensed as an antimalarial in NZ
- ** Unlicensed medication. Available only under Section 29 of Medicines Act.
Malaria transmission and drug sensitivity across the world.


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Anti-malarial Regimens

- All Regions (no mefloquine resistance)
  - Mefloquine
  - Doxycycline
  - Atovaquone plus Proguanil (Malarone®)

- Regions with chloroquine sensitivity
  - Chloroquine

- Mefloquine resistant areas
  - Doxycycline
  - Malarone®
MALARIA LIFECYCLE
Anti-malarial Regimens

- World wide all *P. falciparum* malaria is chloroquine resistant
- In areas of chloroquine resistance (but no mefloquine resistance) use:
  - Mefloquine or
  - Doxycycline or
  - Malarone®

- This order implies **no hierarchy of choice**.
- Which is chosen will depend on
  - pre-existing conditions
  - concomitant medications
  - personal preference
  - what the traveller can afford.
Chloroquine

- In New Zealand currently only available as Hydroxychloroquine
- (Historically Chloroquine sulphate/phosphate)
- Dose: 400mg (310mg base) once weekly commenced 2 weeks prior to entering malarial area, weekly while there and weekly for 8 weeks after*
  - *

- Only indicated in areas where no chloroquine resistance recorded
- BUT
  - Only in areas with *P. vivax* alone
  - Few destinations, parts of Central America
  - Few travellers go to these areas
  - In chloroquine sensitive *P. vivax* regions, can use doxycycline, mefloquine or Malarone®
  - Hydroxychloroquine costs about the same as mefloquine
  - RARELY used
Mefloquine

- Lariam® in New Zealand
- Various generics available overseas
- **DOSE***: one tablet (250mg) once weekly commencing 2-4 weeks prior to entering malarial zone, once weekly while there and once weekly for 4 weeks after
- Rapid loading dose is licensed (but use with caution)
  - one tablet daily for 3 days and weekly there-after
- **


- **Adverse events**
  - Neuropsychiatric (NP)
    - Prevalence highly variable depending on study population and definitions
    - One review.* Disabling NP AEs reported in 0.008-0.1% of users
    - Recent “Blackbox” warning in USA**
      - Carefully select who you prescribe it to
      - **

        [http://www.fda.gov/drugs/dugsafety/ucm362227.htm](http://www.fda.gov/drugs/dugsafety/ucm362227.htm)
Doxycycline

• Widely prescribed as malaria chemoprophylaxis both in NZ and elsewhere
• Not licensed as such in NZ
• DOSE: 100mg once daily commencing 2 days prior to entering malarial zone, daily while there and daily for 4 weeks after

• Adverse events
  – oesophagitis, oesophageal perforation, indigestion/dyspepsia
  – sun sensitivity/rash
  – Candidiasis
Malarone®

• Combination tablet of Atovaquone 250mg and Proguanil 100mg

• Dose: One tablet once daily commencing one day before entering malarial area, daily while there and daily for 7 days after leaving*

• *  

• Adverse events
  – Low discontinuation rates
  – Commonest adverse events nausea and headache
Primaquine

- Not licensed in NZ
  - Section 29
- Used for **eradication therapy** (of the hypnozoite) in known vivax malaria or in those at increased risk of vivax malaria *
- Must check for **G6PD deficiency**
- A handful of small but well conducted studies show it is also an effective chemoprophylactic agent and it is worth considering for those where all else contraindicated **, *** 

- *
  [http://www.who.int/ith/ITH_chapter_7.pdf?ua=1](http://www.who.int/ith/ITH_chapter_7.pdf?ua=1)
- ***
To prescribe or Not?

• Hospitalisation rate for adverse events due to chloroquine or mefloquine has been measured as 1 per 10,000 users*

• The incidence of malaria in travellers to many destinations (e.g., much of Asia and the Americas) is less than the risk of adverse events due to chemoprophylaxis

• Therefore, prescribing must be tailored taking into account: destination, season, type of travel, length of travel and personality

*Steffen R et al. (1993). Mefloquine compared with other chemoprophylactic regimens in tourists visiting East Africa. Lancet, 341, 1299-1303
<table>
<thead>
<tr>
<th>Medication</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Mefloquine (Lariam®)</td>
<td>Weekly dosing</td>
<td>Real and perceived adverse events</td>
</tr>
<tr>
<td></td>
<td>Long half life</td>
<td>Excess neuropsychiatric side effects</td>
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<td></td>
<td>Good data for long term use</td>
<td>“Mid range” price</td>
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<td>“No” accumulative adverse events</td>
<td>“Black Box” warning USA FDA and European Drug safety authorities considering the same</td>
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<td>Pregnancy?: NZ Medsafe Category B3 and advises against use in first trimester</td>
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<td></td>
<td>Well tolerated and licensed in children (≥5kg)</td>
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<tr>
<td>Doxycycline</td>
<td>Cheap</td>
<td>Compliance with 4 weeks post travel dosing</td>
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<tr>
<td></td>
<td>Widely prescribed</td>
<td>Can’t use in children &lt; 11yrs (?8yrs) and pregnant women (except maybe 1st trimester)</td>
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<tr>
<td></td>
<td>Daily dosing</td>
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<td></td>
<td>Generally well tolerated (but risk of gastrointestinal side effects)</td>
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<tr>
<td>Atovaquone/Proguanil (Malarone®)</td>
<td>Short course/easy compliance</td>
<td>Cost</td>
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<td></td>
<td>Long half life</td>
<td>Limited data on use in pregnancy</td>
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Malarone®

• Most expensive option on daily basis, but is well suited to some travellers
  – Short term trips
    • 5 day safari in sub Saharan Africa
    • 3 day business trip to PNG

• Emergency Standby Treatment (ESTB)*
  – Malarone® only option we have in NZ
Scenario

- 28 year old going on 25 day safari in Tanzania, Kenya, Zambia and Botswana
- Would you recommend malaria chemoprophylaxis?
- If yes, which one?
Areas with malaria: Present in the following districts: Central and North West (including Chobe National Park). None in the cities of Francistown and Gaborone.

**Estimated relative risk of malaria for US travelers:** Very low.

**Drug resistance**: Chloroquine.

**Malaria species**: *P. falciparum* 90%, *P. vivax* 5%, *P. ovale* 5%.

**Recommended chemoprophylaxis**: Atovaquone-proguanil, doxycycline, or mefloquine.