Achieving Consensus on Malaria Recommendations: Is It Possible?

Mary E. Wilson, MD
May 28, 2015
CISTM14 Québec City, Canada
I have no conflicts of interest to disclose.
Questions

- How do guidelines/recommendations differ?
- Why do guidelines differ?
- What are the consequences?
- Can we achieve consensus?
- What can we expect in the future?
Global Burden of Malaria

• **3.3 billion** people, in 97 countries, are at risk of being infected with malaria and developing the disease\(^1\).

• **1.2 billion** are at high risk\(^1\).

• **Millions** travel to these areas annually.

\(^1\)World Malaria Report 2014 WHO
Why do we recommend prophylaxis?

• Protect the individual traveler
  – Disease and death
  – Primarily falciparum

• Protect population
  – Prevent introductions
  – Prevent reintroductions
  – Policy implications
Prevention in travelers

- **Mosquito avoidance measures** / bite avoidance (BA) / personal protective measures (PPM)

- **Chemoprophylaxis**
  - Primary prophylaxis
  - Presumptive anti-relapse therapy (terminal prophylaxis)
Review of current guidelines
The drugs

• Licensing
  – Chloroquine, hydroxychloroquine, proguanil, chloroquine + proguanil

• Availability
  – Supply chain

• Access
  – UK
    • Retail pharmacy/over the counter: chloroquine and/or proguanil
    • Rx only: mefloquine, doxycycline and A/P
The drugs

• Indications for and ease of off-label use; restrictions (mefloquine)
  – Doxycycline
  – Primaquine:
    – Primary prophylaxis and anti-relapse therapy
The drugs

• Recommendations for use (yes/no) based on time and place
  – Geography; intensity of transmission
  – Season, altitude, urban/rural
• Which drug(s)? Recommendations for specific drug based on person or risk group
  – E.g., pregnant, infant, breastfeeding
  – Medical problems, e.g., cardiac, psychiatric
The drugs

- Alternative approach: standby emergency treatment (SBET)
  - Carry a treatment course of antimalarial drug
  - Take medication for suspected malaria
- Specific drugs and areas for which they are recommended vary
Key considerations

• Percentage of falciparum infections
• Local levels of resistance
• Adverse event profile of drugs
• Duration of travel
  – Canada: length of travel used in some cases in making recommendations (e.g. chloroquine for stays >1 week; chloroquine or PPM alone for stays of <1 week)

• Duration the drug can be used
  – UK: Mefloquine
    “[....] mefloquine taken for over 1 year is well tolerated. The SPC states the maximum recommended duration of administration of mefloquine is 12 months. [..], advice from the ACMP indicates that there is no evidence of harm in long term use if the drug is tolerated in the short term, and suggests that mefloquine can be used safely for up to three years and beyond in the absence of significant side effects.”
Risk characterization

- US: “estimated relative risk for US travelers” high, moderate, low, very low, rare cases, no transmission

- UK: characterizes risk as high, low, very low, low to no risk. “level of risk below the threshold for recommending chemoprophylaxis”

- Canada: “threat of malaria”, “minimal risk”
Mefloquine

- 2013 “box warning” by US FDA
- 2014 European Medicines Agency (EMA) mandated a mefloquine communication plan for EU member states
  - Checklist (list of 5 contraindications, yes to any ➔)
- Criticisms on the new restrictions and implications for many travelers
  - VFRs
  - Long-term travelers
  - Pregnant women
  - Young children
Recommendations by the expert committee for travel medicine 2015
Why do guidelines differ?
There are many issues to consider

- % falciparum
- Season
- Use of standby emergency treatment
- Length of travel
- Specific groups and their needs
- Urban/Rural locale
- Availability of drugs
- Region of the country
- Adverse event profile
- Health authority or country guidelines
Additional issues for consideration

- Perception of risk
- Culture; history
- Economics
- Lack of evidence
- Different interpretation of data
- Public opinion and media reports
- Traveler’s preferences
- Health authority or country guidelines
Chemoprophylaxis guidelines for Mexico:


Minimal or no malaria transmission in major resort areas on the coasts, including the [...] Sonora, and Tabasco. No. Use PPM

Moderate risk in parts of the states of Chiapas and Oaxaca. Chloroquine Low risk in rural areas of the states of Nayarit, Sinaloa, Chihuahua, and Durango.

Chloroquine for stays >1 week; Chloroquine or PPM alone for stays of <1 week in low risk rural areas [...].

There is a low risk of malaria in the states of Oaxaca and Chiapas in southern Mexico (C only). There is a very low risk of malaria in the states of Chihuahua, Durango, Nyanat, Quintana, Roo and Sinao and the rest of Mexico BA only.

Malaria risk due almost exclusively to P. Vvax is intermittently present through [...]by tourists.

Low risk in some localities in the states of Chiapas State (Costa) and in localities with very low risk situation in the states of Chihuahua, Durango, Nayarit, Quintana Roo and Sinaloa. Recommended prevention in moderate risk areas: BA only (2013).

No chemoprophylaxis is recommended. Carry artemether/lumer fantrin (ALT) or atovaquone/proguanil (APT) for standby emergency self-treatment.
Chemoprophylaxis guidelines for India:

Areas with malaria: All areas throughout the country, including cities of Bombay (Mumbai) and Delhi, except none in areas >2,000 m (6,561 ft) in Himachal Pradesh, Jammu and Kashmir, and Sikkim. Estimated relative risk of malaria for US travelers: Moderate.


No malaria transmission at [...], Jammu and Kashmir, and Sikkim. No prophylaxis. All other areas- including most urban areas such as Bombay (Mumbai) and Delhi. Risk is lower in most of the southernmost regions of India. Risk is low in central urban areas of Agra and Bangalore. A/P, doxycycline, or mefloquine. PPM alone can be considered for stays of <1 week in central urban areas of Delhi, Agra and Bangalore.

There is a risk of malaria sufficiently high to justify chemoprophylaxis in the states of Assam and Orissa; the districts of East Godavari, Srikakulam, Vishakhapatnam and Vizianagaram in the state of Andhra Pradesh; and the districts of Balaghat, Dindori, Mandla and Seoni in the state of Madhya Pradesh (A/P, D, M).BA plus chemoprophylaxis with mefloquine or Doxycycline or A/P if traveling to specified areas

Malaria risk exists throughout the year in the whole country at altitudes below 2000 m, with overall 40–50% of cases due to P. falciparum and the remainder due to P. vivax. There is no transmission in parts of the states of Himachal Pradesh, Jammu and Kashmir, and Sikkim. Risk of falciparum malaria is relatively higher in the north-eastern states, in the Andaman and Nicobar [...], West Bengal (with the exception of the city of Kolkata).

Bite prevention + A/P or doxycycline or mefloquine.

ECTM/Switzerland

No chemoprophylaxis is recommended. Carry ALT or APT for standby emergency self-treatment.
Additional complexities in malaria chemoprophylaxis
Things change

- Change in malaria epidemiology
- Changes in resistance to antimalarial drugs
- New data about drugs become available
  - Expand or restrict use
Caveats, considerations and complexities

• Travelers’ activities, characteristics, preferences, and behavior vary
• Prevention involves more than prescribing chemoprophylaxis
What are the consequences of lack of consensus?
Impact of Inconsistent Guidelines

• Reduced confidence in recommendations
  – undermine credibility other recommendations?

• Reduced adherence?

• Other?
Increasing number of countries are moving towards elimination.
Consequences of elimination

- More areas with low or minimal risk (or vivax only)
- Risk of reintroduction by travelers or migrants
Malaria Imported to China from Ghana

- Shanglin County, China
- Since 2006, >10,000 local residents have traveled to mine gold, primarily to Ghana
- Regulations in Ghana in 2013 forced many to return abruptly
- 4052 returnees were screened
- 874 had malaria (95% *P. falciparum*)
- No local transmission documented

Li et al. EID May 2015
Can we achieve consensus?
What are realistic goals?

• Shared framework for describing risk; identify key inputs
• Common metrics; shared definitions
  – Thresholds and specific interventions will vary
• Commitment to surveillance in travelers and local populations
• Shared data
Looking forward

• Potential game changers
  – New diagnostics
  – New drugs
Key Conclusions

• Guidelines differ and will likely continue to differ
• There is broad agreement in areas with intense transmission
• Areas with variable recommendations will likely increase
  – Vivax; low/moderate transmission
• We will need consider the role of prophylaxis in preventing introduction
• Guidelines must be responsive to change; should be evidence-based and internally consistent
• We will not achieve consensus until malaria eliminated
• New prophylactic drugs and diagnostics could transform the landscape
• In the meantime, we should work to harmonize definitions and develop shared metrics
Thank you
Acknowledgment:
Farrah Kashfipour
Global health sciences fellow
UCSF