Malaria and Travellers Diarrhea

Manitoba 7th Travel Health Conference

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Objectives - to review

- **MALARIA**
  - Geographic risk of malaria
  - Malaria lifecycle/transmission
  - Methods of prevention
    - Chemoprophylaxis
    - Personal Protection Measures
  - Symptoms and appropriate triage/referral
  - Self-treatment of malaria

- **TRAVELLERS DIARRHEA**
  - Epidemiology
  - Prevention Strategies
  - Prophylaxis
  - Drug Treatment
Counting Malaria Out: April 25 is World Malaria Day, commemorating the date in 2000 when 44 African leaders committed to cutting malaria deaths in half by 2010. Each year, malaria causes approximately 1 million deaths, most in young children in Africa. Recent increases in resources are beginning to result in successes in the fight against this scourge.

How Can Malaria Be Prevented?

- For people living in malaria-endemic areas, an integrated package of effective preventive interventions— insecticide-treated bed nets, intermittent preventive treatment for pregnant women, and indoor residual spraying where appropriate, as well as prompt diagnosis and treatment of malaria illness with artemisinin-based combination therapy—can significantly reduce the impact of malaria.

- Although malaria was eliminated from the United States in 1951, approximately 1,500 travelers from the United States return with malaria each year. On average, five of these travelers will die from this preventable infection.
Prevention and treatment of falciparum malaria

2 February 2009 -- In recent weeks, several European countries have reported unusually high numbers of cases of *P. falciparum* infection in holiday travellers to the Gambia (West Africa) who had not taken adequate protective measures against malaria.
MALARIA
Global Malaria Situation:

- 3.3 billion at risk
  - 109 countries
  - 45 within Africa

- Approximately 250 million cases (86% cases in tropical Africa)
  - 80% in 13 countries
  - >50% Nigeria, DRC, Ethiopia, Tanzania, and Kenya

Outside of Africa
- 80% India, Sudan, Myanmar, Bangladesh, Indonesia, PNG, Pakistan

- 1x10^6 deaths
  - 91% AFR
  - 85% children under 5
  - 15-25% all childhood deaths under 5 years

Above: World malaria situation. Malaria is endemic to tropical and subtropical regions.

WHO World Malaria Report
2008
Malaria in Travellers

- #1 life-threatening infection
- >20 million at risk
- Approx. 30,000 acquire malaria/yr

- Canadian travellers
  - 1 million potentially at risk
  - 350-1000 cases per year
  - 1-2 deaths

- US travelers
  - 1500-2000 cases per year
  - 5 deaths

- Mortality (PF): overall 1-4%
  - >40 yrs 6%
  - >70 yrs 30%
  - severe >20%
Why worry about travellers’ malaria?

- 29 year old lady - 3 week journey to Togo and Ghana
  - No malaria prophylaxis
  - Minimal mosquito prevention measures
- Ill on day of return - in bed? Temp
- Day 3 at home
  - Brother could not get sense from her on the phone
  - Sent RN friend to check things out... called 911
So do we really have to worry about malaria in our travellers?

- **Arrival in ER**
  - confused
  - Hgb 78; plts 32
  - Parasitemia 30%

- **Transfer to tertiary care centre**
- **ICU admission**
- **Exchange transfusion x 3 days**
  - Total 18 units PRBC
Increasing numbers of risk travelers

- Young children
- Pregnant women
- HIV
- Immune suppressed
- Long-term expatriate
- VFR travelers

  - Risk malaria VFR traveller 8 x tourists
**Canadian Malaria Network** Since June 2001

Set up to make IV quinine available readily for treating MD.

About to roll out IV artesunate
12 centers across the country - distribute drug 24 hrs per day.

Surveillance data requested at time of using drug and follow-up day 28 (poor reporting D28)

**Overall Goals**
Ready access to life saving drug
Surveillance data on severe and complicated malaria in Canada

**Limitations**
Number of hospitals feel they should have drug on hand (many sites and satellites just restocking)
Poor adherence to filling out reporting forms – form B

[www.travelhealth.qc.ca](http://www.travelhealth.qc.ca) go to section for professionals - includes list of participating centres
Frequency of Quinine Use
1 June 2001 – 31 May 2008

Overall
Males 57 (48 AFR)
Females 51 (43 AFR)
Birth place
"Cdn" 41 (37.6%)
Endemic 66 (61.1%)
Unknown 1

Children
N = 31 (28.7%)
All from AFR
17 males (54.8%)
Endemic Born 21 (67.7%)
Ave Age 6.4 yr (6mo – 16 y)
Distribution of Cases Acquired in Africa 92/108 (85%)

- Ghana 14
- Nigeria 14
- Ivory Coast 6
- Congo 6
- Mali 4
- Uganda 4
- Burkina Faso 4
- Senegal 4
- Tanzania 4
- Sierra Leone 4
- Guinea 4
- Cameroon 3
- Burundi 3
- Kenya 3

- Benin 2
- Ethiopia 2
- Liberia 2
- Mozambique 2
- Malawi 1
- Gabon 1
- DRC 1
- Zambia 1
- Eritrea 1
- Sudan 1
- “Africa” 1
Distribution of Cases Acquired Outside Africa

- Asia
  Sri Lanka
  India
  Thailand
  Burma
  PNG (2)

- Central America
  Honduras
  Belize (2)

- South America
  Guyana (2)

- Caribbean
  DR
  Haiti (4)
NOTE All sites and satellites will have supply of artesunate
Patient Presentation Across Canada

Appropriate Indication
Yes 97 (89.6%)
IV artesunate

- Being supplied by WRAIR
- In collaboration with Health Canada Special Access Program
- Also help from PHAC and US CDC

Distribution imminent
Summary about severe malaria in Canada

- Cases presenting across country
- Most in foreign born (likely more of VFR)
- Most acquired in AFR (all for Children)
- Need to have supplies across the country
- Need to consider better communication of CMN and particularly the satellite centres
Malaria

- No perfect prophylaxis
  - may alter how and when you present
- Widespread in the tropics, widespread (R)
- 3/4 falciparum present in the first month
  - almost never > 6 months
- Other malarias - 45% first month
  - but, 25% have symptoms > 6 months
5 species infect humans:
- *Plasmodium falciparum*
- *Plasmodium vivax*
- *Plasmodium ovale*
- *Plasmodium malariae*
- *Plasmodium knowlesi*
Anopheles mosquitoes
Female
Bites dusk to dawn
Malaria clinical spectrum

- Most fever or flu-like illness
- **Fatalities** with Pf
  - occasionally with Pv - splenic rupture
  - Cerebral malaria (Pf) - focal or generalized symptoms
  - Hypoglycemia - from disease and treatment
    - quinine leads to insulin release
  - Risk Acute Respiratory Distress Syndrome (Pf)
    - due to capillary leak - need to limit fluids
- Acute renal failure (Pf)
  - Not uncommon complication of severe malaria
Malaria: Problems for North American health care providers

- Not seriously considering the diagnosis
- Not recognizing fever in a returning traveler / recent immigrant as a MEDICAL EMERGENCY
- Not recognizing malaria as a medical emergency
- Not appreciating how quickly a patient can become gravely ill
Multiple Guidelines

- WHO
- European
- UK
- Australian
- US CDC
- CATMAT - Canada
Goals of Malaria Chemosuppression

- Overall prevention of symptomatic malaria
- Main goal - prevention of falciparum malaria, specifically, prevention of falciparum deaths
- Requires an Individual Risk Assessment
  - Benefits must outweigh the risks
**Malaria pills don’t work if you don’t take them**  
*Shanks*

<table>
<thead>
<tr>
<th>Px</th>
<th>US</th>
<th>UK</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/wrong</td>
<td>84.2%</td>
<td>81%</td>
<td>97%</td>
</tr>
<tr>
<td>Recommended</td>
<td>15.8%</td>
<td>4%</td>
<td>3%</td>
</tr>
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</table>

MMWR 2001; Eurosurveillance 1998; Kain et al CID 1998
Four components of malaria prevention should be discussed with the traveller (ABCD):

a. the risk of acquiring malaria
b. personal protective measures to prevent mosquito bites
c. chemoprophylactic drugs (where appropriate)
d. the need to seek early diagnosis and treatment for a febrile illness
MQ

- **Efficacy** PF, PV >90%
  - except Thai borders

- **Adverse Events**
  - GI upset
  - Neuropsychiatric adverse events
    - severe 1/10,000, mod 1/200

- **Discontinuation rate** 1-5%

- **Longterm safety data** available (Lobel)
MQ

- Suicides reported – not related to drug dosing
- Contraindicated if history of psychiatric illness

- Any symptoms of anxiety, poor sleep etc may be harbinger to worse neuropsychiatric adverse events – advise to change

- Conclusions
  - still useful, in selected individuals
  - trial of therapy pre-departure
Doxycycline

- Protective efficacy > 90%
- Contraindicated – pregnancy and kids <8y
- Adverse events:
  - GI upset frequent
  - esophogeal ulceration
  - sun sensitivity
  - candida vaginitis

Daily dosing – concern re effectiveness
Doxycycline – long term use

Extracted from data on minocycline
(Gough BMJ 1996; Gotlieb Lancet 1997)

Serum sickness, drug induced lupus, autoimmune hepatitis and fulminant hepatic necrosis
Malarone (ATV/PG)

- Causal prophylaxis – take 7 days post
- Daily dosing
- Expensive
- Safe in children

- CDC and PHAC say safe to use down to 5 kg – adapted from data on safety for treatment
Non-immune travellers; N=1013 (~80% SSA)
PE 100% for both (secondary endpoint)

<table>
<thead>
<tr>
<th>AEs</th>
<th>ATV/PG</th>
<th>MQ</th>
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<tbody>
<tr>
<td>Any</td>
<td>71%</td>
<td>76%</td>
</tr>
<tr>
<td>Rx rel</td>
<td>30%</td>
<td>42%*</td>
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<tr>
<td>Neuropsych</td>
<td>14%</td>
<td>29%*</td>
</tr>
<tr>
<td>Dreams</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Dizzy</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>D/C rate</td>
<td>1.2%</td>
<td>5%*</td>
</tr>
<tr>
<td>D/C neuro</td>
<td>0.6%</td>
<td>3.9%</td>
</tr>
</tbody>
</table>
ATV/PG vs Doxy vs MQ vs CQ/PG
Schlagenbaugh et al BMJ Nov 2003

RCT non-immune travellers ≤ 4 wks
N = 623
Endpoints – AEs QoL POMs
CQ/PG worst tolerated
MQ moderate tolerated, most neuropsychiatric effects
Best tolerated ATV/PG, followed by Doxycycline
ATV/PG and underlying disease

No adjustment needed for:
- Elderly
- Mild to moderate renal impairment
- Mild to moderate hepatic impairment

Contraindicated in those with severe renal impairment ($\text{CrCl} < 30 \text{ ml/min}$)
**Primaquine**

- Efficacy 85-95% for PF and PV
- Causal prophylaxis
- Adverse effects - GI upset
- Contraindicated – G6PD deficiency, pregnancy
- Alternative for CRPF areas
- Possibly for areas with PV
Malaria Chemoprophylaxis Summary

- Chloroquine sensitive areas (very few areas)
  - CQ
  - Alternative first line agents CRPF areas
- Chloroquine resistant areas
  - ATVPG (Malarone) ≥ 5 kg
  - Doxycycline > 8 years
  - Mefloquine - ≥ 5 kg
  - (alternative Primaquine)
- Areas with predominantly PV
  - Primaquine
- CQ and MQ resistant areas
  - Doxycycline (alternative ATVPG/Malarone)
Standby Treatment

- Means different things in different countries
  - EU recommendations many places no Px, instead SBT
  - North America usually reserved for those who will not take prophylaxis or else will be far from medical care
    - can self-initiate therapy on way to getting care
  - Consider for longer trips
    - safe and effective therapy in case Dx with malaria
Take Home Messages

- Malaria is an important risk for many travelers
- Prevention is key
  - Assessment of risk of exposure
  - Prevention of anopheline bites
  - Assessment of appropriate prophylaxis
  - *** Fast and appropriate medical care in event of malaria
Diarrhea
Gastrointestinal complaints in Ill Travelers
Journal of Travel Medicine, Volume 15, Issue 4, 2008, 221–228

- 6,086 any gastrointestinal infection to seek medical care at a GeoSentinel clinic post travel during 2000 to 2005.
- Regional and country-specific reporting rate ratios (RRRs) in comparison to risk in northern and western Europe.
- Highest risk
  - sub-Saharan Africa (RRR = 282), South America (RRR = 203), and South Asia (RRR = 890)
- Moderate
  - (25 – 142) Oceania, the Middle East, North Africa, Central America, the Caribbean, and Southeast Asia.
- Least
  - (≤28) southern, central, and eastern Europe; North America; Northeast Asia; and Australasia.
- Income level of the country visited was inversely proportional to the RRR for gastrointestinal infection.
**TRAVELERS’ DIARRHEA**

**Areas of Risk**

- **High-risk:** Latin America, Africa, Southern Asia.  
  Attack rate: ~40%

- **Low-risk:** U.S., Europe, Japan, Australia and New Zealand  
  Attack rate: <4%

- **Intermediate-risk:** China, Russia, the Middle East, Caribbean Islands such as Jamaica, South Africa, southern cone of South America and Thailand  
  Attack rate: ~8-15%
• **CLASSIC DISEASE:** > 2 loose stools / day  
  + 1 G.I. symptom

• **MILD DISEASE:** 1–2 loose stools / day  
  +/- 1 G.I. symptom

• **ACUTE DIARRHEA:** 0–14 days

• **PERSISTANT DIARRHEA:** 14–30 days (3%)

• **CHRONIC DIARRHEA:** > 30 days (~1%)
Travelers from industrialized countries to the tropics:

- Two-week incidence: 20–67%
- Hospitalized: 1%
- Confined to bed: 15%
- Alter activities: 25%
- Persisitant diarrhea: 3%
Travelers’ Diarrhea: Incidence

Usually benign and self-limiting

Duration:
Mean = 3-4 days
Median = 2 days
Infectious Etiology of Travelers’ Diarrhea

- **Bacterial**: 60-80%
- **Parasitic**: 5-10%
- **Viral**: 10-20%
UNUSUAL CAUSE OF DIARRHEA IN TRAVELERS


- Description of 6 cases with documented *C. difficile* disease following TD treatment
Travelers’ Diarrhea: the Causes

• Since bacterial enteropathogens are the most common causes of travelers’ diarrhea, antibiotic agents are predictably active in treatment and prevention.

• The prevalence of *Campylobacter* drives choice of antibiotic especially in SE Asia.
Traveler’s Diarrhea
Development of Immunity

Monthly diarrhea rate

- US newly arrived
- US returned from summer vacation
- US 4 mo later
- Mexican National
Risk Factors for Travelers’ Diarrhea

- **Destination**
  - Highest risk in developing countries

- **Country of origin**
  - Persons coming from developed countries at highest risk

- **Previous exposure**
  - Lower risk among those with lots of developing country exposure
Risk Factors for Travelers’ Diarrhea

- **Duration of stay**
  - Longer the stay, lower the risk

- **Socio-economic status**
  - High status = less chance of developing protective immunity

- **Age**
  - Very young: fecal oral
  - Young adult: adventurous
Risk Factors for Travelers’ Diarrhea

- **Season**
  - Highest in summer, rainy or post monsoon seasons
- **Mode of travel**
  - Organized travel may be safer
- **Standard of accommodation**
  - Fairly unpredictable
Travelers’ Diarrhea: Risk Factors

- Other than not traveling, the individual has little control over the known risk factors.

- 5-star travel itineraries might help, but not all travelers can afford this kind of travel and cannot insist on traveling during safer seasons.
RISK FACTOR FOR TRAVELERS’ DIARRHEA: WATER

Dietary Errors

- WATER OFTEN MEETS STANDARDS LEAVING THE CHLORINATION PLANT
- OLD PIPES AND UNHYGIENIC PRACTICES
- CROSS CONTAMINATION IN RAINY SEASON
RISK FACTOR FOR TRAVELERS’ DIARRHEA: FOOD

- Food grown with night soil
- Personal hygiene of food preparer
- Storage of food

Dietary Errors
## RISK FACTOR FOR TRAVELERS’ DIARRHEA: FOOD

### Dietary Errors

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>E. coli</th>
<th>ETEC</th>
<th>Other</th>
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<tr>
<td><strong>Mexican</strong></td>
<td></td>
<td></td>
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<tr>
<td>Restaurants:</td>
<td>162</td>
<td>40</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Homes:</td>
<td>353</td>
<td>72</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td><strong>US</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restaurants:</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
PREVENTION OF TRAVELERS’ DIARRHEA

“Boil it, cook it, peel it, or forget it”

Easy to remember, impossible to do!
Food Consumption – Key Prevention Strategy

- Persons are challenged to select safe foods
- Commonly found buffets may not be safe
- Flight attendants may unwittingly serve an additional challenge
Safe Versus Unsafe Foods During International Travel

- >59°C
- Moist foods at room temperature
- Non-cleaned skins on fruit
- Diluted with local water
- Hot Sauces

- Dry
- Peeled
- High sugar content
- Beverage with seal
- Carbonation
- Milk
Travelers’ Diarrhea: 
Influence of Dietary Errors

98% of travelers made at least 1 alimentary mistake during the first 3 days of stay

Kozicky et al., Int. J. Epidemiol, 1985; 14: 169-72
VACCINATION FOR TRAVELERS' DIARRHEA?

Travelers

- TD: 60%
- ETEC-TD: 25%
- LT-ETEC: 50%
- Protection by WC-rCTB vaccine

TD = travelers' diarrhea
PREVENTION OF TRAVELERS' DIARRHEA

EDUCATION: KEEP IT SIMPLE

FOOD
- HOT
- DRY
- PEELED
- PASTEURIZED
- NOT RAW

WATER
- CARBONATED
- NOT TAP
Travelers’ Diarrhea: Risk Factors

**TAKE HOME MESSAGES**

- Food and beverage risks are ubiquitous.
- Travelers make dietary errors despite education.
- Cooking for oneself is safest but impractical.
- Innovative approaches to education should be tried and outcomes measured.
What About Chemoprophylaxis?
Safety Concerns with Systemic Antibiotics

- Systemic side effects can be serious
  - Occurring in (~1/10,000)
    - Hypoglycemia
    - QT interval concerns
- Tendon rupture
  - Black box warning added to fluoroquinolones
  - Increased risk of tendinitis & tendon rupture 3- to 6-fold

Safety Concerns with Systemic Antibiotics

- Risk of *Clostridium difficile* infection
  - Retrospective case study of 6 travelers previously treated with antibiotics for TD who developed CDI
    - Patients had history of prior fluoroquinolone use
  - New strains of *C. difficile* have become more resistant to fluoroquinolones
    - Exposure to systemic antibiotics (fluoroquinolones and cephalosporins) is a risk factor for developing *C. difficile*

Situations That Might Warrant Chemoprophylaxis for Diarrhea

- Health impairments
  - Inflammatory bowel disease
  - Use of acid-reducing medications
  - Conditions that could not tolerate dehydration
  - Immunocompromised individuals
- Travel itinerary cannot afford a brief illness
  - “Criticality” of travel
- Risk of TD is very high
- Traveler may ask for prophylaxis

## Classic chemoprophylaxis

<table>
<thead>
<tr>
<th>Agent</th>
<th>%Protection</th>
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<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>&lt;60</td>
</tr>
<tr>
<td>Probiotics</td>
<td>0–49</td>
</tr>
<tr>
<td>Bismuth subsalicylate</td>
<td>~65</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>~80</td>
</tr>
</tbody>
</table>
Rifaximin (600 mg) vs Placebo

Time to Onset of Diarrhea

- **Rifaximin**
- **Placebo**

The graph shows the comparison of time to first unformed stool, days, between Rifaximin and Placebo. The y-axis represents the probability of developing TD, %.
Post-infectious Complications of Travelers’ Diarrhea

Reasons to consider chemoprophylaxis?
**Post-infectious Complications**

*Most are rare or uncommon*

- **Guillain-Barré syndrome**
  - 20-40% of cases associated with *Campylobacter* infections

- **Reactive arthritis**
  - *Shigella, Salmonella, Yersinia, and Campylobacter*

- **Acute renal failure**
  - *Salmonella, E. coli*

- **Irritable bowel syndrome**
  - bacterial gastroenteritis

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Occurrence of Post-Travelers’ Diarrhea Irritable Bowel Syndrome (IBS)

Diarrhea in Mexico

Acute Diarrhea: 63%
Post-Diarrhea IBS: 10%

Diarrhea in Asia

Acute Diarrhea: 84%
Post-Diarrhea IBS: 13.60%
Non-Diarrhea IBS: 2.40%

Not prevented despite “early” antibiotic treatment

**TAKE HOME MESSAGES**

- Chemoprophylaxis works.
- Chemoprophylaxis should prevent IBS, a factor not considered in earlier decisions.
- Rifaximin (not yet available in Canada) appears to be safe, resistance development to date has not been a notable problem, and the usefulness of rifaximin is limited to enteric syndromes.
What Do We Have To Treat Travelers’ Diarrhea?
Nonspecific symptomatic therapy

- **Antisecretory agents: Bismuth subsalicylate**
  - Decrease number of stools passed by 16–18%

- **Antimotility agents: Loperamide**
  - Decrease number of stools passed by >50%

- **Clays: Attapulgite**
  - Make stools more formed
  - No effect on duration of disease

**Antimicrobial therapy**

- The only therapy that can cure bacterial diarrheal illness

WHO/CDD/CMT 86.1 (Rev 1, 1988).
Rifaximin vs Ciprofloxacin

Rifaximin is noninferior to ciprofloxacin in Mexico.

Travelers’ Diarrhea: Therapy

• **TAKE HOME MESSAGES**
  • Symptomatic (e.g. loperamide) therapy is effective (and safe).
  • Antibiotics cure the majority of travelers’ diarrhea cases since the cause is bacterial.
The five keys to safer food

- Keep clean
- Separate raw and cooked
- Cook thoroughly
- Keep food at safe temperatures
- Use safe water and raw materials
IMPORTANT RESOURCES:

• Health Canada (www.travelhealth.gc.ca) [CATMAT]
• US CDC (www.cdc.gov)
• World Health Organization (www.who.int)
• International Society of Travel Medicine (www.istm.org)