Fever & other problems in the returned traveller.

Jay S. Keystone & Edward C. Keystone MD
TDU TGH and RDU MSH
• Travel-Associated Illnesses in the Region of Peel

• Presented by: Gregory Kujbida, Student CD Epidemiologist,
  Infection Prevention & Surveillance

• Surveillance and Epidemiology Team Meeting
• July 13, 2011
What makes Peel unique?

20%

49%

28%

Source: Region of Peel, 2008
VFRs

- New Canadians
- Return to homeland
- Spouse or children

Source: CDC, 2010
Why increased risk?

- Poor risk awareness
- No pre-travel health-care encounter
- Higher risk destinations
- “Immunity” misconception

Source: CDC, 2010
Proportion of cases by country

- Unknown
- Other
- Ghana
- Nigeria
- Pakistan
- India
VFR Disease Risk

- Malaria
- Typhoid
- TB
- Hep. A
- STIs
- Paratyphoid

Source: CDC, 2010
Malaria, 2006-2010

Incidence of Malaria, Peel and Ontario, 2006-2010

~2X
Typhoid Fever, 2006-2010

Incidence of Typhoid Fever, Peel and Ontario, 2006-2010

~4X

Peel Health
Paratyphoid Fever, 2006-2010

Incidence of Paratyphoid Fever, Peel and Ontario, 2006-2010

Age-standardized number of cases per 100,000

2006 2007 2008 2009 2010
Year

Peel  Ontario

~4X
GeoSentinel: The Global Surveillance Network of the ISTM and CDC

A worldwide communications and data collection network of travel/tropical medicine clinics
51 travel/tropical medicine clinics globally (since 1996)
Spectrum of Disease and Relation to Place of Exposure among Ill Returned Travelers

David O. Freedman, M.D., Leisa H. Weld, Ph.D., Phyllis E. Zarsky, M.D., Tamara Fisk, M.D.,† Rachel Robins, M.D., Frank von Sonnenburg, M.D., Jay S. Keystone, M.D., Prativa Pandey, M.D., and Martin S. Cetron, M.D., for the GeoSentinel Surveillance Network†
Percent Illness in Returned Travelers
N=17,353
NEJM 2005;354:119-30

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Carib 1,115</th>
<th>CAM1, 326</th>
<th>SAM 1,675</th>
<th>SSA 4,524</th>
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<td>8</td>
<td>7</td>
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<td>6</td>
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</table>
Fever in a Returned Traveler

- A ~50 year old female VFR presents to your office with a 3 day history of fever, headache, and cough after returning from a 3 week stay in Tanzania to
- Her physical examination is unremarkable.

What do you want to know?
What do you want to know?

1. Pre-travel preparation
2. Travel itinerary
3. Exposure history
4. Fever pattern
1. Pre-Travel Preparation

i. immunizations: efficacy:

- yellow fever > 95%
- hepatitis A > 95%
- hepatitis B 80-95%
- typhoid fever 70%
- meningococcal meningitis > 90%
- Japanese encephalitis > 90%
Pre-Travel Preparation (Cont’d)

ii. malaria chemoprophylaxis:
   • drug
   • dose
   • compliance
   • duration
   • iii. other medications
4. Fever pattern

- continuous: typhoid fever
- periodic: malaria
5. Exposure History

What do travelers do to put themselves at risk of infectious diseases?
## 4. Exposure History

<table>
<thead>
<tr>
<th>Activity</th>
<th>Action</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>Unpasteurized cheese</td>
<td>brucellosis, TB</td>
</tr>
<tr>
<td>Fresh water</td>
<td>Swimming</td>
<td>schistosomiasis, leptospirosis</td>
</tr>
<tr>
<td>Blood and body fluids</td>
<td>sex, injections, piercing</td>
<td>HIV, STI</td>
</tr>
<tr>
<td>Insects</td>
<td>Tick bite</td>
<td>rickettsia, borrelia</td>
</tr>
<tr>
<td>Animals</td>
<td>Cattle, sheep, goat ‘Pee’</td>
<td>Q-fever, brucella</td>
</tr>
</tbody>
</table>
Approach to fever in returned traveller

- Immunization and antimalarial drug history
- Epidemiology and exposure history
- Clinical picture including fever pattern
- Complete physical examination
- Laboratory tests according to Diff. Diagnosis
## Percent Fever in Returned Travelers

N=3907  NEJM 2005;354:

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<td>&lt;1</td>
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<td>32</td>
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<td>mono</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>3</td>
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<tr>
<td>rickettsia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Salmon.</td>
<td>2</td>
<td>3</td>
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<td>3</td>
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## Percent Fever from the tropics

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<tr>
<th>Diagnosis</th>
<th>Maclean</th>
<th>Doherty</th>
<th>O’ Brien</th>
<th>Bottieau</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>587</td>
<td>195</td>
<td>232</td>
<td>1842</td>
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<tr>
<td>Malaria</td>
<td>32</td>
<td>42</td>
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<td>28</td>
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<td>Respiratory</td>
<td>11</td>
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<td>24</td>
<td>10.5</td>
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<td>Gastroenter.</td>
<td>4.5</td>
<td>6.5</td>
<td>14</td>
<td>6.2</td>
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<tr>
<td>Dengue</td>
<td>2</td>
<td>6</td>
<td>8</td>
<td>3</td>
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*Bottieau, Arch Int Med 2006;166:1642-8*
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<td>195</td>
<td>232</td>
<td>1842</td>
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<tr>
<td>Hepatitis</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0.6</td>
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<tr>
<td>Urinary tract</td>
<td>4</td>
<td>2.5</td>
<td>--</td>
<td>3.4</td>
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<tr>
<td>Typhoid</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>0.8</td>
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<tr>
<td>Rickettsia</td>
<td>2</td>
<td>6</td>
<td>8</td>
<td>3.3</td>
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<tr>
<td>Undiagnosed</td>
<td>25</td>
<td>24.5</td>
<td>9</td>
<td>24.5</td>
</tr>
</tbody>
</table>

*Bottieau, Arch Int Med 2006;166:1642-8*
Imported Malaria USA 2009 n=582
MMWR 2011; 60:1-15

- VFR: 63.3%
- Missionary: 9.9%
- Business: 6.1%
- Tourism: 4.8%
- Student: 4.2%
Plasmodium knowlesi: The Fifth Human Malaria Parasite

N. J. White
Department of Tropical Medicine, Mahidol University, Bangkok, Thailand; and Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford, United Kingdom

(See the article by Cox-Singh et al. on pages 165–71)

In 1932, when Knowles and Das Gupta [1] succeeded in transmitting to humans the monkey malaria they had discovered, it appeared that a new agent for malaria therapy had been discovered. Since the Nobel Prize-winning research of Julius Wagner-Jauregg, malaria therapy had become widely used for the treatment of general paralysis of the insane (neurosyphilis), one of the main reasons for admission to psychiatric institutions. But it soon became apparent that this infection simian malaria organism to humans (Plasmodium cynomolgi), and in 1967, Chin et al. [3] showed that P. knowlesi could also be transmitted from monkeys to humans. The mosquitoes used were Anopheles balbisiana, which is a member of the Anopheles leucophirus group, which has undergone extensive taxonomic revision in recent years. This is an important vector of human malaria in Southeast Asia, where the natural hosts of P. knowlesi—the long-tailed and pig-tailed macaques—abound.

Fatal cases. There are several important practical lessons from this experience. Humans can and do acquire some monkey malarias if they share the same habitat (the reverse is also true). Molecular techniques are very useful in identifying the infection, in describing the epidemiology, and in characterizing mixed infections, which are otherwise underreported. This discovery resulted from good clinical and laboratory investigation, combined with an efficient malaria-control program. Presumably, the P. knowlesi epidemic could have been prevented had the discovery been recognized at the time.
## Interval between arrival and symptom onset USA 2003 N=1268 MMWR 2005;54:25-39

<table>
<thead>
<tr>
<th>Interval mo.</th>
<th>% <em>P. falciparum</em> N=457</th>
<th>% <em>P. vivax</em> N=135</th>
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<tbody>
<tr>
<td>&lt; 0</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>0-1</td>
<td>99%</td>
<td>73%</td>
</tr>
<tr>
<td>1-2</td>
<td>6%</td>
<td>20%</td>
</tr>
<tr>
<td>3-6</td>
<td>0.4%</td>
<td>14%</td>
</tr>
<tr>
<td>6-12</td>
<td>0.4%</td>
<td>12%</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>0.7%</td>
<td>0.7%</td>
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</table>
## Source of Imported Malaria USA


<table>
<thead>
<tr>
<th>Source</th>
<th>% <em>P. falciparum</em> N=680</th>
<th>% <em>P. vivax</em> N=286</th>
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<tr>
<td>Africa</td>
<td>86</td>
<td>17</td>
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<tr>
<td>Asia</td>
<td>2.7</td>
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<td>C.America</td>
<td>4.1</td>
<td>16</td>
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<tr>
<td>Mexico</td>
<td>&lt; 1</td>
<td>5</td>
</tr>
<tr>
<td>S Asia</td>
<td>&lt; 1</td>
<td>6</td>
</tr>
<tr>
<td>Oceania</td>
<td>&lt; 1</td>
<td>8</td>
</tr>
</tbody>
</table>
Pf Malaria onset according to pre-existing immunity

EID 2008 14 (2)–February

Non-immunes n=197

Semi-immunes n=63

53%
36%
11%
55%
25%
6%
2%
3%
3%
2%

No. cases

<10 d
10–20 d
21–30 d
31–59 d
60–180 d
181–365 d
>1–2 y
>2–3 y
>3–4 y
>4–5 y
>5–6 y
Malaria Clinical: “the flu”

- Fever
- Fever
- Fever

- Headache, chills, period fever abdominal pain, cough
Malaria Diagnosis

- **CBC:** Anemia uncommon
  - WBC $\uparrow$ or $\downarrow$: 95%
  - platelets $\downarrow$: 60-83%
  - LDH $\uparrow$: 70-83%
- **LFT’s:** abnormal: 50%
- Fever pattern $\Rightarrow$ often not helpful
Malaria specific diagnosis

1. thick and thin blood films
   - *thick films* - used to diagnose
   - (5 x more concentrated c/w thin films)
   - *thin films* - used to speciate
   - if neg-repeat films 3 x (12 - 24 hrs. apart)

2. Antigen detection (rapid diagnostic test)
<table>
<thead>
<tr>
<th>Parasite</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. falciparum</td>
<td>99%</td>
<td>94%</td>
</tr>
<tr>
<td>P. vivax</td>
<td>94%</td>
<td>100%</td>
</tr>
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</table>
A sad story

- 25 year old Canadian university student develops fever 7 days after return from voluntourism in Malawi. Goes to ER of ‘Elsewhere General’ where malaria films are negative and he is sent home with a diagnosis of “flu”. No further tests are recommended.

He dies of malaria 3 days later!
4 answers you need to know to manage malaria

1. If malaria, what is the species?
2. If *P.f.* , what is the parasitemia?
3. Is the parasite likely to be chloroquine resistant?
4. Is there evidence for severe malaria
## Treatment of uncomplicated falciparum malaria

<table>
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<tr>
<th>Drug</th>
<th>Advantage</th>
<th>Disadvantage</th>
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<tbody>
<tr>
<td>Chloroquine</td>
<td>Short course,</td>
<td>Limited efficacy</td>
</tr>
<tr>
<td>Atovaquone/prog.</td>
<td>Short course</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Short course</td>
<td>Neuropsych.</td>
</tr>
<tr>
<td>Quinine + doxy.</td>
<td>Long course</td>
<td>Cinchonism</td>
</tr>
<tr>
<td>Quinine + clinda.</td>
<td>Long course</td>
<td>Cinch. C. difficile</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>Short course</td>
<td>Availability</td>
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</table>
Malaria key points

- Fever in the returned traveller is malaria until proven otherwise and is a medical emergency
- 5 malaria species... falciparum kills and kills quickly
- Diagnosis by thick and thin blood films and rapid diagnostic technique
- Atov/proguanil (Malaone) DOC for PF
DENGUE
<table>
<thead>
<tr>
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<th>Carib</th>
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<td>12</td>
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<td>&lt;1</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>mono</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>rickettsia</td>
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<td>0</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>2</td>
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<tr>
<td>Salmon.</td>
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N=3907  NEJM 2005;354:119-30

Reports to WHO
- Cases
- Deaths
- Countries

Cases
- Deaths
- Countries

Year
1970
1975
1980
1985
1990
1995

Cases (in 1000s)
- 1000
- 2000
- 3000
- 4000
- 5000
- 6000

Deaths
- 10
- 20
- 30
- 40
- 50
- 60

Countries
- 60
- 70
- 80
- 90
- 100

WHO/CDS
Dengue

- Flavivirus transmitted by day-biting Aedes mosquitoes (related to YF, West Nile, JE)
- Mostly in Caribbean and SE Asia, rare in Africa
- Mostly urban transmission
- 4 serotypes (Dengue 1-4)
Dengue Fever: clinical

- Fever
- Headache / retro-orbital pain
- Muscle and joint pain 50% ("break-bone fever")
- Nausea/vomiting
- Rash
- Hemorrhagic manifestations

IP: 3 days - 2 weeks
Dengue Fever
Dengue Fever: diagnosis

- **Routine:** leucopenia, thrombocytopenia
- **Specific:** serology: increase IgM,
  - or 4 fold rise in IgG
Dengue Management

- fluid & electrolyte balance
- antipyretics
- avoid salicylates & nsaids
Dengue Key features

- Most frequently from SEAsia, Caribbean, L. America,... *not* Africa
- Short Onset and short duration
- Classical: headache, retro-orbital pain, myalgia, arthralgia
- Diagnosis by serology
Salmonella typhi
## Percent Fever in Returned Travelers

N=3907  NEJM 2005;354:

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<tr>
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Typhoid fever \((Salmonella\ typhi)\) in US travellers 1994-99

Steinberg CID 2004;39:186

- **Source:** 50% of cases from 3 countries
  - India  30%
  - Pakistan  13%
  - Bangladesh  6%

- **Reason for travel:** 77% cases in VFR’s
## Typhoid Fever clinical

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>percent</th>
<th>Signs</th>
<th>percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>prolong. fever</td>
<td>99</td>
<td>apathy</td>
<td>70</td>
</tr>
<tr>
<td>headache</td>
<td>85</td>
<td>hepatomegaly</td>
<td>50</td>
</tr>
<tr>
<td>Abd. pain</td>
<td>50</td>
<td>splenomegaly</td>
<td>35</td>
</tr>
<tr>
<td>constipation</td>
<td>40</td>
<td>rose spots</td>
<td>0-50</td>
</tr>
<tr>
<td>diarrhea</td>
<td>45</td>
<td>Rel. bradycardia</td>
<td>15</td>
</tr>
<tr>
<td>cough</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sore throat</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Typhoid fever: Treatment

- increasing MDRTF; ☑ cipro sens (~30%) South & East Asia

- DOC: fluoroquinolone (ciprofloxacin levofloxacin) or 3rd generation cephalosporin (ceftriaxone)
Typhoid Key Features

• Most frequently from Indian subcontinent
• Most frequently in immigrants or VFRs
• Prolonged fever (> 2 weeks and malaria ruled out = typhoid)
• Classic symptoms: fever, headache, cough, constipation; BUT any fever alone
• Culture everything!
## Percent Fever in Returned Travelers

**N = 3907**

NEJM 2005;354:

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Tick Typhus: Fevre Boutonneuse

- tick-borne Rickettsial infection *R. africae*, *R. conorii*
- Mediterranean, Southern Africa, Indian subcontinent
- fever, regional adenopathy, rash, eschar
- usually mild illness; self-limited over 1-2 wks
Review

Foreign travel, casual sex, and sexually transmitted infections: systematic review and meta-analysis

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Objectives: With increasing international travel it is important to understand how frequent casual travel sex and unprotected intercourse are, and what impact this may have on the risk of acquiring sexually transmitted infections (STIs).

Methods: We conducted a systematic review, and where appropriate meta-analyses, to ascertain the influence of foreign travel on behavior, including new partnerships, unprotected intercourse, and STI acquisition.

Results: The pooled prevalence of travel-associated casual sex was 20.4\% (95\% confidence interval (CI) 14.8–26.7\%), with 49.4\% (95\% CI 38.4–60.5\%) of these having unprotected intercourse. The predominant characteristics of people who had new sexual partners abroad were: young age, male gender, single status, and traveling alone or with friends, with a previous history of multiple sexual partners or an STI. People who travel or stay abroad for longer periods and men who have sex with men are at higher risk of developing new sexual partnerships and having unprotected intercourse. The risk of developing an STI is increased up to 3-fold in people who experience casual travel sex.

Conclusions: New sexual partnerships and unprotected intercourse abroad are relatively common. People who develop new sexual partnerships and have unprotected intercourse abroad have an increased risk of STIs. There is, however, a paucity of information related to strategies to prevent the risk of STI acquisition during foreign travel.
Risk of sexual risk behaviour and variables

- Alcohol/drug use before sex
- Gender: male
- Age < 25, variable
- Education: lower
- Trip duration: 30 days
- Trip purpose: business, study
- No steady partner
- Casual sex at home
- Expectation of sex
- Unexpected 55%
- MSM’s
- Foreign partner: 63-70%
Proportion sexual partners

n=24

20%
Risk of STI with travel-related casual sex

Both sexes

Odds ratio meta-analysis plot [fixed effects]

- Mercer (2007)
  - Odds ratio: 3.11 (2.41, 3.99)

- Bavastrelli (1998)
  - Odds ratio: 2.73 (0.93, 9.05)

- Combined [fixed]
  - Odds ratio: 3.08 (2.43, 3.91)
DRUG-RESISTANT GONORRHEA STRAIN EMERGES

Often called the "clap," the infection had been easily treatable -- until now.

THE GIST

- A new strain of gonorrhea is resistant to antibiotics.
- Since antibiotics were introduced in the 1940s, the bacterium has shown the capacity to develop resistance.
- As many as 700,000 people in the United States are believed to get the disease each year.

For the first time, international researchers have identified a strain of gonorrhea that is resistant to treatment with antibiotics, scientists announced at a sex disease research conference Monday.

The common bacterial infection, often called the "clap," has until now been easily treatable with antibiotics but if left untreated can lead to sterility in men and complications in women.

An electron micrograph of a Neisseria...
Young people are "immortal and invincible"
Travel advice to STI prevention:
post-exposure

• Early post-exposure Tx with risky exposure or genital symptoms eg. azithromycin 1gm for chlamydia

• HIV PEP -83% reduction: Truvada( emtricitabine/tenofovir ) 300/200 OD + Kaletra (lopinavir/ritonavir) 200/50 -2 tabs twice daily x 1 month
A worldwide market

What's called medical tourism – patients going to a different country for either urgent or elective medical procedures – is fast becoming a worldwide, multibillion-dollar industry.

The reasons patients travel for treatment vary. Many medical tourists from the United States are seeking treatment at a quarter or sometimes even a 10th of the cost at home. From Canada, it is often people who are frustrated by long waiting times. From Great Britain, the patient can't wait for treatment by the National Health Service but also can't afford to see a physician in private practice. For others, becoming a medical tourist is a chance to combine a tropical vacation with elective or plastic surgery.

And more patients are coming from poorer countries such as Bangladesh where treatment may not be available.

Medical tourism is actually thousands of years old. In ancient Greece, pilgrims and patients came from all over the Mediterranean to the sanctuary of the healing god, Asklepios, at Epidaurus. In Roman Britain, patients took the waters at a shrine at Bath, a practice that continued for 2,000 years. From the 18th century wealthy Europeans travelled to spas from Germany to the Nile. In the 21st century, relatively low-cost jet travel has taken the industry beyond the wealthy and desperate.
Medical tourism

Practice of travelling across international borders to obtain health care. Wikipedia
Medical tourism

- elective joint surgeries: hip, knee and back
- cardiac surgery
- organ transplantation
- plastic surgery
- dental surgery
- reproductive procedures (fertility tourism)
Heart-valve replacement ~$200,000 or more in the US, costs $10,000 in India—and that includes round-trip airfare and a brief vacation package.

Metal-free dental bridge worth $5,500 in the US costs $500 in India,

Knee replacement: in Thailand with six days of physical therapy costs about one-fifth of what it would in the States

Lasik eye surgery: worth $3,700 in the US is available in many other countries for only $730

Cosmetic surgery: A full facelift that would cost $20,000 in the US runs about $1,250 in South Africa.
Why not participate in medical tourism?

• infectious disease risks (surgical, local)
• quality of surgical care and post-op care
• biological fluids risk (blood, IV fluids etc)
• limited contact with surgeon post-op
• prolonged travel -post op risks
• inadequate complaint system; no legal redress
• ethical issues (diverting care from locals)
Can one reduce the risks?

- Medical tourism organization
- International healthcare accreditation: - ‘joint commission on accreditation of healthcare organizations’ (USA) ;- Accreditation Canada
- Contact ‘survivors’
- Do your homework (internet)
N=33 kidney transplants overseas: (China, Iran, Phillipines)

4 required urgent hospitalization: 3/4 lost transplant
52% had infections (9 hospitalized)
1 died of fulminant hepatitis B
Acute rejection 30% vs 12% UCLA patients
“Mostly in patients who had received care on the Indian subcontinent”: 60% had been admitted to a hospital in India and Pakistan
Fever in the returned traveler summary

- fever from the tropics may not have a tropical cause
- fever from the tropics may not be tropical but is a medical emergency, and malaria until proven otherwise
- the most common tropical causes of fever: malaria, dengue, typhus, typhoid
In an undifferentiated fever, what tests should you order?

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, diff</td>
<td>platelets: malaria, typhoid, dengue</td>
</tr>
<tr>
<td>Malaria</td>
<td>daily x 3</td>
</tr>
<tr>
<td>LFT’s</td>
<td>hepatitis</td>
</tr>
<tr>
<td>cultures</td>
<td>typhoid fever</td>
</tr>
<tr>
<td>urinalysis</td>
<td>UTI</td>
</tr>
<tr>
<td>CXR</td>
<td>pneumonia</td>
</tr>
<tr>
<td>serology</td>
<td>dengue, Rickettsia etc.</td>
</tr>
</tbody>
</table>
Selected References


2. GIDEON website: www.gideononline.com


Selected References, cont.


Selected references con’t

