Advances in Travel Medicine:
A Clinical Vignette-Driven Review

Elizabeth A. Talbot MD
Associate Professor, ID & Int’l Health
Geisel School of Medicine at Dartmouth
Deputy State Epidemiologist, NH DHHS
I have no disclosures or conflicts of interest to declare.
My Charge

• Vignette-driven
  – Ill-returned travelers
  – Drug resistant Enterobacteriaceae

• Recent, relevant, revolutionary literature
Case: A Favor for a Fever

- 34F ID physician colleague pages to ask you to prescribe empiric malaria self treatment
- 20d ago she returned from 6w Sierra Leone
  - Teaching healthcare workers to work in ETC
  - No known Ebola virus disease (EVD) patient contact
  - “Low risk” and just completing DHHS “Direct Active Monitoring” with twice daily fever and symptom checks
    - She doesn’t want to induce chaos by letting them know she has F
- HA, F “exactly like my previous malaria”
  - Sheepishly admits not taking malaria prophylaxis
Question

Regarding risk of ebola virus disease, which is true?

1. This can’t be EVD because she never had any direct patient contact
2. Not EVD because incubation is too long for otherwise healthy adult
3. This is unlikely to be EVD because she does not have any hemorrhagic symptoms
4. EVD must be ruled out and you should contact the public health authorities immediately
Question

Regarding risk of ebola virus disease, which is true?

1. This can’t be EVD because she never had any direct patient contact
2. Not EVD because incubation is too long for otherwise healthy adult
3. This is unlikely to be EVD because she does not have any hemorrhagic symptoms
4. EVD must be ruled out and you should contact the public health authorities immediately
In Phase 1, response necessarily occurred in clinical evidence void

ERT analyzed data on ~4,000 (3,343 confirmed and 667 probable) Ebola patients
- Guinea, Liberia, Sierra Leone, Nigeria
- Through Sept 14th 2014

Specific hemorrhagic symptoms were reported in <1% to 5.7% of patients
- “Unexplained bleeding” in 18%

<table>
<thead>
<tr>
<th>Variable</th>
<th>All Patients</th>
<th>Patients Who Died</th>
<th>Patients Who Recovered</th>
<th>Odds Ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</td>
<td></td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>685/1415 (48.4)</td>
<td>515/1056 (48.8)</td>
<td>170/359 (47.4)</td>
<td>0.93 (0.73–1.19)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;15 yr</td>
<td>190/1378 (13.8)</td>
<td>145/1021 (14.2)</td>
<td>45/357 (12.6)</td>
<td>1.18 (0.83–1.71)</td>
</tr>
<tr>
<td>15–44 yr</td>
<td>838/1378 (60.8)</td>
<td>577/1021 (56.5)</td>
<td>261/357 (73.1)</td>
<td>0.48 (0.36–0.62)</td>
</tr>
<tr>
<td>≥45 yr</td>
<td>350/1378 (25.4)</td>
<td>299/1021 (29.3)</td>
<td>51/357 (14.3)</td>
<td>2.47 (1.79–3.46)</td>
</tr>
<tr>
<td>Health care worker</td>
<td>158/1429 (11.1)</td>
<td>112/1067 (10.5)</td>
<td>46/362 (12.7)</td>
<td>0.86 (0.60–1.27)</td>
</tr>
<tr>
<td><strong>Signs and symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever‡</td>
<td>1002/1151 (87.1)</td>
<td>746/846 (88.2)</td>
<td>256/305 (83.9)</td>
<td>1.34 (0.92–1.95)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>866/1133 (76.4)</td>
<td>633/829 (76.4)</td>
<td>233/304 (76.6)</td>
<td>0.94 (0.68–1.28)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>681/1055 (64.5)</td>
<td>498/778 (64.0)</td>
<td>183/277 (66.1)</td>
<td>0.92 (0.69–1.23)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>753/1114 (67.6)</td>
<td>566/816 (69.4)</td>
<td>187/298 (62.8)</td>
<td>1.19 (0.89–1.59)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>721/1099 (65.6)</td>
<td>555/813 (68.3)</td>
<td>166/286 (58.0)</td>
<td>1.42 (1.06–1.89)</td>
</tr>
<tr>
<td>Headache</td>
<td>553/1035 (53.4)</td>
<td>407/757 (53.8)</td>
<td>146/278 (52.5)</td>
<td>1.03 (0.78–1.36)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>439/992 (44.3)</td>
<td>311/715 (43.5)</td>
<td>128/277 (46.2)</td>
<td>0.85 (0.64–1.13)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>385/990 (38.9)</td>
<td>293/728 (40.2)</td>
<td>92/262 (35.1)</td>
<td>1.24 (0.92–1.67)</td>
</tr>
<tr>
<td>Joint pain</td>
<td>374/950 (39.4)</td>
<td>283/695 (40.7)</td>
<td>91/255 (35.7)</td>
<td>1.32 (0.98–1.80)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>254/686 (37.0)</td>
<td>196/488 (40.2)</td>
<td>58/198 (29.3)</td>
<td>1.53 (1.07–2.20)</td>
</tr>
<tr>
<td>Cough</td>
<td>194/655 (29.6)</td>
<td>150/462 (32.5)</td>
<td>44/193 (22.8)</td>
<td>1.74 (1.18–2.51)</td>
</tr>
<tr>
<td>Difficulty breathing</td>
<td>155/665 (23.3)</td>
<td>123/472 (26.1)</td>
<td>32/193 (16.6)</td>
<td>1.68 (1.10–2.63)</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>169/514 (32.9)</td>
<td>138/375 (36.8)</td>
<td>31/139 (22.3)</td>
<td>2.22 (1.41–3.59)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>137/658 (20.8)</td>
<td>109/465 (23.4)</td>
<td>28/193 (14.5)</td>
<td>2.03 (1.29–3.29)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>102/467 (21.8)</td>
<td>82/339 (24.2)</td>
<td>20/128 (15.6)</td>
<td>1.94 (1.13–3.46)</td>
</tr>
<tr>
<td>Confusion</td>
<td>84/631 (13.3)</td>
<td>68/446 (15.2)</td>
<td>16/185 (8.6)</td>
<td>2.00 (1.14–3.71)</td>
</tr>
<tr>
<td>Hiccups</td>
<td>108/947 (11.4)</td>
<td>91/699 (13.0)</td>
<td>17/248 (6.9)</td>
<td>2.15 (1.27–3.82)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>65/627 (10.4)</td>
<td>52/443 (11.7)</td>
<td>13/184 (7.1)</td>
<td>1.83 (0.99–3.53)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>48/622 (7.7)</td>
<td>39/438 (8.9)</td>
<td>9/184 (4.9)</td>
<td>1.95 (0.95–4.40)</td>
</tr>
<tr>
<td>Rash</td>
<td>37/642 (5.8)</td>
<td>30/453 (6.6)</td>
<td>7/189 (3.7)</td>
<td>1.90 (0.86–4.83)</td>
</tr>
<tr>
<td>Coma or unconsciousness</td>
<td>37/627 (5.9)</td>
<td>34/445 (7.6)</td>
<td>3/182 (1.6)</td>
<td>4.59 (1.61–19.34)</td>
</tr>
<tr>
<td>Unexplained bleeding</td>
<td>168/932 (18.0)</td>
<td>140/693 (20.2)</td>
<td>28/239 (11.7)</td>
<td>1.83 (1.20–2.90)</td>
</tr>
</tbody>
</table>
Clinical Illness and Outcomes in Patients with Ebola in Sierra Leone


- First 106 EVD patients in SL
  - Only one with hemorrhage
Lunsar, Port Loko, Sierra Leone
95% of case patients had symptom onset within 21 days after exposure.

Rapid Response to Ebola Outbreaks in Remote Areas — Liberia, July–November 2014

MMWR; February 20, 2015 / 64(Early Release);1-5

NEJM 2014; 371:1481-95
More to Learn About Ebola

After Nearly Claiming His Life, Ebola Lurked in a Doctor’s Eye

By DENISE GRADY   MAY 7, 2015
Case: GI/Respiratory Illness in Pilgrim

- 70y man with CVD and DM returned from pilgrimage to Medina and Mecca KSA
  - D5 diarrhea, fever
  - D7 reported to local ED
  - D14 en route home cough and SOB
- PE 38.2, otherwise normal
- Laboratory findings
  - Leuko- and lymphopenia
  - Elevated creatinine and CRP
- CXR with bilateral infiltrates
Patient and his 73y symptomatic sister with similar comorbidities tested positive for MERS-CoV

Question

Regarding acquisition of MERS-CoV in travelers, which is most likely?

1. Consumption of unpasteurized dromedary milk
2. Direct contact with bats
3. Visiting the “wet markets” in endemic areas
4. Exposure to coughing people in clinical settings
Question

Regarding acquisition of MERS-CoV in travelers, which is most likely?

1. Consumption of unpasteurized dromedary milk
2. Direct contact with bats
3. Visiting the “wet markets” in endemic areas
4. Exposure to coughing people in clinical settings
Travel-related MERS-CoV cases: an assessment of exposures and risk factors in a group of Dutch travellers returning from the Kingdom of Saudi Arabia, May 2014

Ewout B Fanoë, Marianne AB van der Sande, Marleen Kraaij-Dirkzwager, Kees Dirksen, Marcel Jonges, Wim van der Hoek, Marion PG Koopmans, Douwe van der Werf, Gerard Sonder, Charlie van der Weijden, Jet van der Heuvel, Luc Gelinck, Jolande W Bouwhuis, Arianne B van Gageldonk-Laferber, and on behalf of the members of the MERS-CoV outbreak investigation team of The Netherlands

<table>
<thead>
<tr>
<th>Animal exposure</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Asymptomatic travellers (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit to camel farm</td>
<td>No</td>
<td>No</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Direct contact with camels</td>
<td>No</td>
<td>No</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Indirect contact with camels</td>
<td>No</td>
<td>No</td>
<td>8 (28%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Food exposures</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Asymptomatic travellers (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption of unpasteurized milk</td>
<td>No</td>
<td>No</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>Visit to local market in Medina</td>
<td>Yes</td>
<td>No</td>
<td>21 (72%)</td>
</tr>
<tr>
<td>Consumption of fruits on market</td>
<td>No</td>
<td>No</td>
<td>7 (24%)</td>
</tr>
<tr>
<td>Buying souvenirs on market</td>
<td>No</td>
<td>No</td>
<td>14 (28%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Human exposures</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Asymptomatic travellers (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact with coughing patients (excluding case 1 and 2)</td>
<td>Yes, in waiting room of a hospital</td>
<td>No</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hospital visit (due to other non-MERS related illnesses)</td>
<td>Yes</td>
<td>No</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Minimal social contact with case 1 and/or 2</td>
<td>Case 1 and 2 had daily contact with each other</td>
<td>No</td>
<td>17 (59%)</td>
</tr>
<tr>
<td>Daily contact with case 1 and/or 2</td>
<td>Case 1 and 2 had daily contact with each other and shared hotel rooms</td>
<td>No</td>
<td>12 (41%)</td>
</tr>
</tbody>
</table>
MERS Reservoir?

- Blood, tissue, throat/rectal swabs from 96 bats captured in orchard close to index case's home and work
- Fragment of MERS-CoV genome found
- Most people don’t have contact with bats

Memish ZA et al. EID 2013: 19(11)
• Cross-sectional serosurvey of healthy adults at clinics and in national burden-of-disease study
  – Enriched with shepherds and abattoir workers
  – Screen with ELISA, confirm IF and PRNT
• 15 pos among 10,009 (0.15%; 95% CI 0.09–0.24)
  – 15X in shepherds, 23X in slaughterhouse workers
• Projected 44,951 adults seropositive for MERS-CoV in KSA
South Korea has reported 4 lab-confirmed cases

Index case is South Korean traveler from Bahrain, KSA, UAE
  – May 4 returned
  – May 11 developed symptoms
  – May 18 hospitalized

3 contacts who did not travel also tested positive
  – Spouse, hospital roommate, and daughter of hospital roommate (only several hours)

63 asymptomatic contacts are under quarantine

Global total: 1150 confirmed with 471 deaths
When to Test for MERS CoV?

• [Fever AND pneumonia or ARDS] AND EITHER:
  − History of relevant travel within 14 days before symptom onset
  OR
  − Close contact with symptomatic traveler who developed F and ARI within 14 days after relevant travel
  OR
  − Member of a cluster of patients with severe ARI of unknown etiology in which MERS-CoV is being evaluated, in consultation
  OR
• F AND respiratory illness AND being in healthcare facility within 14 days before symptom onset in relevant geography in which recent healthcare-associated cases of MERS have been identified
  OR
• F OR respiratory illness AND close contact with confirmed case

Case: Cough in VFR Traveler

• 26W with recent VFR travel
  – Immigrated from Nigeria to US Sept 2013
    • Positive tuberculin skin test
    • Calcified granulomas on CXR
    • Given rifampin 300mg qd for 6-7 months

• Jan 2015 presents productive cough, right-sided chest pain, fevers, weight loss
  – CXR right-sided dense consolidation
2 masses, patchy bilateral infiltrates with “cotton wool appearance”
Tree-in-bud bilaterally and small bilateral effusions
Question

Regarding risk of tuberculosis, which is true?

1. This can’t be TB since she was treated correctly for latent TB infection
2. Globally, TB is increasing
3. MDR TB is rare in Nigeria
4. It still takes 6-12 weeks to make the diagnosis of MDR-TB
5. GeoSentinel data suggests TB and LTBI are substantial risk especially in immigrant and VFR travelers
Question

Regarding risk of tuberculosis, which is true?

1. This can’t be TB since she was treated correctly for latent TB infection
2. Globally, TB is increasing
3. MDR TB is rare in Nigeria
4. It still takes 6-12 weeks to make the diagnosis of MDR-TB
5. GeoSentinel data suggests TB and LTBI are substantial risk especially in immigrant and VFR travelers
Global TB Epidemiology 2014

• 9M new TB cases (decrease)
  – India+China 35%, Africa 25%

• 480,000 multi-drug resistant (MDR*) TB cases
  – Half from India, China, Russia
    • 3,600 reported from Nigeria
  – Previously treated: 21%
  – 9% of MDR is XDR-TB**

*MDR=resistance to H+R
**XDR=MDR with resistance to FQ and injectable agents

WHO/HTM/TB/2014.08
Xpert MTB/RIF is a Game Changer

• Automated, real-time PCR
  – 100 mins to TB and rifampin resistance
  – 92% sensitivity overall
• Simple, modular system
  – Cartridges for other diseases
• ‘Should be used instead of AFB smear/culture for MDR, HIV-TB CNS TB suspects’
• This patient’s TB+, rif resistant
  – Days not months to diagnosis
Introduction of Xpert MTB/RIF as initial diagnostic test for TB in India’s public health facilities significantly increased case-notification rates of all bacteriologically confirmed TB by 39% and rifampicin-resistant TB case notification by fivefold.
## TB in Returned Travelers

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Cases, n</th>
<th>Median Age, y</th>
<th>Man–Woman Ratio</th>
<th>Reason for Travel, %*</th>
<th>Top Countries of Exposure†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tourism</td>
<td>Visiting Friends/Relatives</td>
</tr>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rabies PEP after bite or scratch</td>
<td>1249</td>
<td>31</td>
<td>1.0</td>
<td>68.9</td>
<td>17.7</td>
</tr>
<tr>
<td>Cutaneous larva migrans</td>
<td>806</td>
<td>30</td>
<td>0.9</td>
<td>80.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Leishmaniasis (cutaneous or mucocutaneous)</td>
<td>264</td>
<td>23</td>
<td>1.9</td>
<td>49.6</td>
<td>17.0</td>
</tr>
<tr>
<td>Myiasis</td>
<td>174</td>
<td>36</td>
<td>1.3</td>
<td>71.8</td>
<td>6.3</td>
</tr>
<tr>
<td>Tungiasis</td>
<td>87</td>
<td>30</td>
<td>1.1</td>
<td>52.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Gnathostomiasis</td>
<td>12</td>
<td>26.1</td>
<td>1</td>
<td>50.0</td>
<td>8.3</td>
</tr>
<tr>
<td>Leprosy</td>
<td>11</td>
<td>44</td>
<td>4.5</td>
<td>90.9</td>
<td>–</td>
</tr>
<tr>
<td>Cutaneous atypical mycobacteria</td>
<td>6</td>
<td>36.5</td>
<td>2.0</td>
<td>50.0</td>
<td>33.3</td>
</tr>
<tr>
<td>Sporotrichosis</td>
<td>1</td>
<td>14</td>
<td>1 woman</td>
<td>–</td>
<td>100</td>
</tr>
<tr>
<td>Yaws</td>
<td>1</td>
<td>67</td>
<td>1 woman</td>
<td>–</td>
<td>100</td>
</tr>
<tr>
<td><strong>Respiratory or pharyngeal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza</td>
<td>367</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H1N1</td>
<td>176</td>
<td>16</td>
<td>1.2</td>
<td>59.7</td>
<td>10.2</td>
</tr>
<tr>
<td>Influenza A or B</td>
<td>191</td>
<td>36</td>
<td>1.1</td>
<td>59.7</td>
<td>10.5</td>
</tr>
<tr>
<td>MDR or XDR pulmonary TB</td>
<td>3</td>
<td>25</td>
<td>0.5</td>
<td>–</td>
<td>100</td>
</tr>
</tbody>
</table>

TB in Returned Travelers

- In 9,624 US travelers
  - 38 cases of active TB
    - 25 pulmonary
  

- Among 267 immigrants within Europe
  - 46 pulmonary tuberculosis
    - 12 MDR or XDR TB
    - Predominantly in immigrants from Romania and Russia


Case: Pretravel Counsel

• Any patient going anywhere for any reason
• For what diseases is s/he at risk?
GeoSentinel Surveillance Network

Provider based surveillance of international travelers
56 clinics in 24 countries since 1996

http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6203a1.htm
## Recent GeoSentinel Reports

<table>
<thead>
<tr>
<th>First author</th>
<th>Catchment</th>
<th>Cohort</th>
<th>Years</th>
<th>Syndromic</th>
<th>Pretravel?</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schlagenhauf P</td>
<td>EuroTravNet</td>
<td>32,136</td>
<td>2008-12</td>
<td>Malaria, diarrhea high proportionate morbidity (PM)</td>
<td>40% (neg trend)</td>
<td>VBD increasing Utility of pretravel</td>
</tr>
<tr>
<td>Leder K</td>
<td>All GeoSentinel</td>
<td>42,223</td>
<td>2000-10</td>
<td>Top 3 diagnoses malaria, giardia, dengue</td>
<td>-5% (NS)</td>
<td>Tourism decreasing VFR increased Confirms increase in PF and dengue</td>
</tr>
<tr>
<td>Leder K</td>
<td>All GeoSentinel</td>
<td>42,173</td>
<td>2007-11</td>
<td>GI 34% F 23.3% Derm 19.5%</td>
<td>40.5%</td>
<td>VFR pretravel only 18.3%</td>
</tr>
<tr>
<td>Hagmann SHF</td>
<td>US GeoSentinel</td>
<td>9,624</td>
<td>2000-12</td>
<td>GI 58% F 18% Derm 17%</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>Boggild AK</td>
<td>CanTravNet</td>
<td>4,365</td>
<td>2009-11</td>
<td>GI 44% F+resp 16% Derm 15%</td>
<td>34%</td>
<td>Foreign-born 45% 876 (20%) immigration</td>
</tr>
</tbody>
</table>


Leder et al. Trends and Clusters. EID 2013: 19 (7)


Boggild AK et al. Travel-acquired infections and illnesses in Canadians . . . Open Medicine 2014;8(1)e20.
Usefulness of Pre-travel Consult

• Pre-travel consultation was associated with significantly lower proportionate morbidity (PM) for (not TD)
  – *P. falciparum* malaria
    • Controlled for destination, age, purpose
  – Acute hepatitis
  – HIV/AIDS
  – Animal bites requiring rabies PEP
    • Dogs (46%), primates (18%) and cats (13%)

• Validates goals of travel medicine practice

Case: A Savvy Pre-Traveler

- 55y physician with celiac disease planning to respond to Nepal earthquake
- He asks about his risk of infectious diarrhea and strategies to avoid
  - He especially wants to know his risk of acquiring drug resistant enteric bacteria

NYT April 29 2015
Question

Regarding his risk of acquiring drug resistant enteric bacteria, which is true?

1. Clinically significant resistance to nontyphoidal Salmonellae is associated with travel to Asia
2. ESBL producing Enterobacteriaceae (PE) colonization increases from 5% pre- to 30% post-travel
3. Travelers at high risk for resistance might need to be managed using contact precautions because colonization may be prolonged and is transmissible
4. ESBL-PE colonization is more likely in travelers who take antibiotics
Question

Regarding his risk of acquiring drug resistant enteric bacteria, which is true?

1. Clinically significant resistance to nontyphoidal Salmonellae is associated with travel to Asia
2. ESBL producing Enterobacteriaceae (PE) colonization increases from 5% pre- to 30% post-travel
3. Travelers at high risk for resistance might need to be managed using contact precautions because colonization may be prolonged and is transmissible
4. ESBL-PE colonization is more likely in travelers who take antibiotics
NonTyphoidal Salmonella Resistance

- 99% of 2,153 Oregon NTS cases tested for drug susceptibility
  - 347 (16%) isolates had clinically important resistance
  - Proportion resistant increased each year
  - Associated with hospitalization
    - Trend toward invasive disease
- Among 84% interviewed, travel to Asia 5-fold increase

Increasing ESBL-PE Colonization

• ESBL-PE resistant to cephalosporins
  – Genes are $bla_{CTX-M}$, $bla_{TEM}$ and $bla_{SHV}$

• Cohort analyses suggested travel as risk factor for colonization with ESBL-PE

• Prospective study of 262 Swedish travelers
  – Questionnaires and selective fecal culture before and after travel

Risk Factors for ESBL-PE: Sweden

- ESBL-PE from 2.4% before to 30% post travel
  - 90% *Escherichia coli*
  - 73% CTX-M
- Risk for acquisition
  - Asia as destination
  - Diarrhea
    - Not antibiotic use during travel

Risk Factors for ESBL-PE: NLs

- 370 travelers from NLs
- ESBL-PE from 8.6% before to 31% post travel
  - RF travel to S and E Asia
- At 6m, 17% still colonized
  - Not necessarily same
    - Gene transfer?
- 66% of household contacts with clonal strain

Paltansing S et al. ESBL-PE among travelers from the Netherlands. EID Vol. 19, No. 8, Aug 2013
ESBL Risk Increased After Travel

430 Finns questionnaire and stool culture on selective media for ESBL-PE before and after travel

Kantele A et al. Antimicrobials Incr Travelers’ Risk of Colonization by ESBL-PE. CID 2015: Jan 21
21% became colonized by ESBL-PE
- All *E. coli* except 3

Risk factor MVA
- Geographic region
- Increasing age
- TD (aOR 31!)
- Abx for TD (3.0)

Kantele A et al. Antimicrobials Increase Travelers’ Risk of Colonization by ESBL-PE. CID 2015: online Jan 21
The “Gut Resistome”

- Cx-based methods do not capture majority of gastrointestinal microbiota which is not cultivable
- PCR metagenomic approach
- 122 travelers underwent pre- and post-travel measurement of all resistance genes
- ESBL gene $bla_{CTX-M}$ 9 to 33.6%
  - Highest from India 58.1%

von Wintersdorff CJH et al. High Rates of Antimicrobial Drug Resistance Gene Acquisition after International Travel, the Netherlands. EID 2014: 20 (4)
Carbapenems: “The Big Gun”

• Ertapenem, imipenem, meropenem, doripenem
• Active against most
  – ESBL Enterobacteriaceae
  – Streptococci
  – Enterococci
  – Meth-sensitive *Staph aureus*
  – Pseudomonas
  – Anaerobes
Carbapenemase-Producing Enterobacteriaceae

- C-PE are extremely drug resistant
- No decolonization strategy, high mortality rate, resistance can transfer between many Enterobacteriaceae

### Class A (serine)
- SME (*Serratia*)
- IMI (*Enterobacter*)
- GES (*Pseudomonas*)
- KPC (*Klebsiella*)

### Class B (MBL)
- VIM (*Pseudomonas*)
- IMP, SPM, GIM, SIM
- NDM

### Class D
- OXA (*Acinetobacter*)

New Delhi metallo-β-lactamase plasmid-mediated. Resistant to all β-lactams and most other classes
C-PE Endemic in South Asia

- In tap water and sewage in New Delhi, India*
  - 2/50 water
  - 12/170 sewage specimens
  - 20 different bacterial species

- Global spread related to medical tourism**

**Kumarasamy, Lancet Infect Dis 2010
C-PE are Travel Related

India, Pakistan, Bangl
Balkans and Mid East
Unknown

Nordmann et al. Emerg Infect Dis 2011
80% of travelers to South Asia who get TD and take antibiotics to treat will acquire ESBL-PE!

Reaction?
- No antimicrobial prophylaxis
- Mild/mod TD should not be treated
- Vigilance re: subsequent infections
  - e.g., UTI may be ESBL organisms
- Infection control measures on return
- Household contacts?
Summary

• We are steep on the learning curve for
  – Historic Ebola epidemic
  – MERS CoV epidemic

• New tool in the armamentarium for TB suspect management and global control

• GeoSentinel remains an important tool
  – Value of pre-travel counsel

• Resistant NTS, and ESBL- and C-PE are associated with travel, especially to Asia, and diarrhea and use of antibiotics in travel
  – Multiple urgent practice changes suggested
Thank you!
The Power of GeoSentinel

- For the traveler
  - Informs individual risk counseling

- For the travel medicine community
  - Provides evidence for counseling and the spectrum of disease related to human mobility

- For understanding global epidemiology
  - Assumes travelers serve as sentinels
    - Analysis of dengue from GeoSentinel detected increasing trend in travelers before national outbreak recognized*
  - Informs public health authorities on cross-border infection trends and threats


GeoSentinel Limitations

• Cannot derive actual risk of acquiring each infection
  – Lacks numerator (all illnesses)
    • Bias toward specialized clinics
  – Lacks denominator (all travelers)
  – Proportionate morbidity: cases/1,000 ill travelers

• Apparent disease trends might be attributable to trends in travel patterns or diagnostic access/availability

• Some diseases
  – Occur in non-tourist destination countries
  – Occur, are diagnosed and treated in destinations

What About Traveler’s Diarrhea?

<table>
<thead>
<tr>
<th>Total (n)</th>
<th>Cases (n)</th>
<th>Proportionate morbidity per 1000</th>
<th>PMR (95% CI)</th>
<th>Men (n)</th>
<th>Cases (n)</th>
<th>Proportionate morbidity per 1000</th>
<th>PMR (95% CI)</th>
<th>Women (n)</th>
<th>Cases (n)</th>
<th>Proportionate morbidity per 1000</th>
<th>PMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 8865</td>
<td>1880</td>
<td>212.07</td>
<td>Ref</td>
<td>4888</td>
<td>982</td>
<td>200.90</td>
<td>Ref</td>
<td>3973</td>
<td>895</td>
<td>225.27</td>
<td>Ref</td>
</tr>
<tr>
<td>Yes 12870</td>
<td>3620</td>
<td>281.27</td>
<td>1.33 (1.26-1.39)</td>
<td>6007</td>
<td>1523</td>
<td>253.54</td>
<td>1.262 (1.18-1.36)</td>
<td>6852</td>
<td>2093</td>
<td>305.46</td>
<td>1.356 (1.27-1.45)</td>
</tr>
</tbody>
</table>

PMR=proportionate morbidity ratio. No=no pre-travel advice. Yes=pre-travel advice received. Ref=reference value for the groups with no pre-travel advice.

Table 2: Effect of pre-travel consultation on proportionate morbidity and proportionate morbidity ratios of specific diagnoses overall and by sex.

- PM from diarrhea increased in group that received pretravel services
  - Acute and chronic diarrhea, *Giardia, Campylobacter*
  - Consistent with earlier study

- Why this paradoxical finding?
  - Perhaps sensitized to return to care if ill
  - Those who seek pre-travel advice are visiting higher-risk destinations
### Table 4. Nonmalarial illness among travelers returning from Africa who were seen at GeoSentinel clinic sites, March 1997–May 2011*

<table>
<thead>
<tr>
<th>Illness/incident</th>
<th>Total</th>
<th>Central Africa</th>
<th>Eastern Africa</th>
<th>Northern Africa</th>
<th>Southern Africa</th>
<th>Western Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistosomiasis</td>
<td>530</td>
<td>42</td>
<td>278</td>
<td>41</td>
<td>22</td>
<td>147</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>147</td>
<td>9</td>
<td>89</td>
<td>14</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Schistosoma haematobium</td>
<td>118</td>
<td>7</td>
<td>66</td>
<td>5</td>
<td>5</td>
<td>35</td>
</tr>
<tr>
<td>Filaria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongylodes</td>
<td>195</td>
<td>34</td>
<td>78</td>
<td>13</td>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td>Simple intestinal</td>
<td>191</td>
<td>34</td>
<td>78</td>
<td>12</td>
<td>6</td>
<td>61</td>
</tr>
<tr>
<td>Hyperinfection</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Non-Strongylodes</td>
<td>140</td>
<td>102</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Loa loa</td>
<td>86</td>
<td>82</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Onchocerca volvulus</td>
<td>21</td>
<td>12</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>31</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>17</td>
</tr>
<tr>
<td>Wucheria bancrofti</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vaccine-preventable disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>59</td>
<td>3</td>
<td>14</td>
<td>28</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Influenza</td>
<td>24</td>
<td>0</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Measles</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Typhoid fever†</td>
<td>58</td>
<td>6</td>
<td>22</td>
<td>4</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Bite wounds;‡</td>
<td>193</td>
<td>5</td>
<td>47</td>
<td>105</td>
<td>11</td>
<td>25</td>
</tr>
<tr>
<td>Bite wounds necessitating rabies prophylaxis</td>
<td>184</td>
<td>4</td>
<td>38</td>
<td>107</td>
<td>13</td>
<td>22</td>
</tr>
<tr>
<td>Source of bite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td>91</td>
<td>4</td>
<td>17</td>
<td>52</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Cat</td>
<td>46</td>
<td>0</td>
<td>8</td>
<td>36</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other†</td>
<td>66</td>
<td>1</td>
<td>22</td>
<td>17</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Dengue (uncomplicated)</td>
<td>113</td>
<td>6</td>
<td>46</td>
<td>5</td>
<td>8</td>
<td>48</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>86</td>
<td>2</td>
<td>33</td>
<td>16</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>43</td>
<td>2</td>
<td>14</td>
<td>14</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>24</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Miliary, disseminated</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Meningitis</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Multidrug resistant‡</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Sample Findings

• FQ resistance gene *qnrS* 8.2 to 55.7%
  • Highest from SEA 75%
• No evidence for
  – Influence of antibiotic use
  – TD as RF for acquisition

von Wintersdorff CJH et al. High Rates of Antimicrobial Drug Resistance Gene Acquisition after International Travel, the Netherlands. EID 2014: 20 (4)