Yellow Fever

“Yellow fever should be dealt with as an enemy which imperils life and cripples commerce and industry”

Dr Shidan Tosif
Paediatrician
CPMG Travel Clinic
Overview

- History
- Transmission
- Yellow fever disease
- New international recommendations
- Late breaking news...
Yellow Fever Decimates Philadelphia

After 31 years of absence, yellow fever returned to Philadelphia, killing thousands of city residents over a span of several months. As the then-capital and largest city of the United States, Philadelphia was home to both local and federal governments, most of whose members (including President George Washington) fled to escape the disease. The total number of cases was estimated to be approximately 11,000; the final mortality rate for the city was 10%.

Like many others, Philadelphia physician Dr. Benjamin Rush (1745-1813) observed the symptoms and spread of the disease closely, hoping to uncover some definite cause and means of prevention. Rush kept meticulous notes about his individual patients as well as about conditions in the city for many years. His notes ranged from the observation that “A meteor was seen at two o’clock in the morning, on or about the twelfth of September” to several remarks that, curiously, “Moschetoese” were “uncommonly numerous.”
1899

Yellow Fever Plagues Panama Canal Workers

The French officially abandoned efforts to build the Panama Canal and transferred the rights to the project to the United States, in part because of the yellow fever and malaria deaths among the project’s workers.
U.S. Army Researchers Discover the Cause of Yellow Fever

William Crawford Gorgas (1854-1920), a Colonel in the U.S. Army Medical Corps, later described the details of the discovery:

They... found out that [a man], before he had been bitten by the yellow-fever mosquito, could sleep in the bed in which a patient had died of yellow fever, could be covered with a black vomit from a yellow-fever patient, or be exposed to the emanations from yellow fever in any other way, and as long as he was kept safe from the bite of the mosquito he would not have yellow fever; but this same man, after all this exposure, if afterwards bitten by an infected mosquito, would very certainly catch the disease.

...They had a little frame building built in this camp furnished with jars and the necessary simple material for breeding mosquitoes... Eggs of this particular species of mosquito were obtained and hatched in one of the jars. A female mosquito was taken from the...
Max Theiler Develops Yellow Fever Vaccine

Max Theiler and his colleagues developed a live attenuated vaccine for yellow fever using tissue cultures prepared from embryonated chicken eggs. Among the many subcultures of the yellow fever virus in the laboratory, the one designated “17D” was used, giving the vaccine its name. He published results of U.S. vaccine trials in humans in 1937. The vaccine was easily adapted for mass production and became the universal standard.
Present state

- WHO (2007) immunization coverage 51% in countries at risk for outbreaks
- Coverage has increased from 1988 (modern peak of disease) with more than 5 million cases reported globally - immunization coverage of less than 5%.
- WHO target for affected regions 60-80% coverage
- Endemic in tropical sub-Saharan Africa and South America

Annually 84,000–170,000 cases
up to 60 000 deaths
Transmission

• RNA Virus, genus Flavivirus (*flavus* = yellow in latin)
• Arthropod vector - *Aedes aegypti* (also *Haemogogus sp*)

**Sylvatic yellow fever** (also known as “jungle yellow fever”)
**Intermediate yellow fever**: most common type of outbreak in Africa
**Urban yellow fever**: domestic mosquito transmits the virus between humans
Yellow Fever

- Majority infected asymptomatic or only mild illness.
- Incubation period typically 3–6 days
- Viral haemorrhagic disease

- Acute viraemic phase (milder, lasting 3-4 days):
  - Sudden onset high fever and severe headache
  - Chills, back pain, general body aches, nausea, vomiting, fatigue
  - May have Faget’s sign (bradycardia with high fever)
  - Associated with
  - Most improve

- Period of remission
  - Up to 48hrs

- Toxic phase (severe, 48hrs after viraemia)
  - ~15% of cases progress to develop severe form
  - High fever, jaundice, bleeding, and eventually shock, multiple organ failure
Treatment

- No specific treatment - supportive care
- Avoid certain medications, such as aspirin or other NSAIDS
- Yellow fever patients should be protected from further mosquito exposure (staying indoors and/or under a mosquito net) during the first few days of illness – to break transmission cycle
Outcome

• Majority recover
• If severe “toxic” disease case-fatality ratio is 20%-50%
  • Risk factors for death - hypotension, shock, renal failure, severe hemorrhagic disease, coma, and convulsions
  • Convalescence often prolonged, several weeks.
  • Rarely, death can after complete recovery from acute illness thought to be attributable to myocardial damage and cardiac arrhythmia
  • Jaundice has been observed for up to 3 months after recovery
Prevention

• Mosquito avoidance
• Immunisation
“A single dose of yellow fever vaccine is sufficient to confer sustained immunity and life-long protection against yellow fever disease and a booster dose of yellow fever vaccine is not needed.”
Recent Updates

• Since 1965, international health regulations have allowed countries to require YF vaccination within the previous 10 years as criteria for entry
• Proof of vaccination is at the country's discretion
• April 2013, WHO Strategic Advisory Group of Experts (SAGE) concluded that single dose of yellow fever vaccine provided lifelong immunity
• May 2014, WHO Health Assembly adopted an amendment that extends YF vaccine protection to the lifetime of the vaccinated person.
• Legal effective date of this international health regulation is June 2016.
Update on yellow fever vaccination for travellers

The Australian Government is adopting the World Health Organization amendment to the International Health Regulations (2005), that the period of protection afforded by yellow fever vaccination, and the term of validity of the certificate, will change from 10 years to the duration of the life of the person vaccinated. This is based on data demonstrating for the majority of recipients, a single dose of yellow fever vaccine results in life-long immunity.
Summary of GRADE Evidence (SAGE)

• 18 vaccine failures among > 540 million doses
• 2 (11%) of vaccine failures occurred > 10 years from last YF vaccine dose (20 and 27 years)

• Paediatric seroconversion rate 93% (95% CI 88-96%) – 88% when sample size accounted for
• Adult seroconversion rate 98% for all populations, 97% endemic areas
4.23.7 Recommendations

Children aged <9 months
Yellow fever vaccine is contraindicated in infants aged <9 months.

Children aged ≥9 months and adults
A single dose of yellow fever vaccine is recommended for:

- persons ≥9 months of age travelling to, or living in, areas with a risk of yellow fever virus transmission. Information about the risk for specific destinations should be sought from a reputable source, such as the World Health Organization (WHO), prior to travel.
- laboratory personnel who routinely work with yellow fever virus,
It is strongly recommended that all travellers be vaccinated for yellow fever if travelling to or from a yellow fever declared country. Refer to: Where can I get a yellow fever vaccination and vaccination certificate.

People who are one year of age or older will be asked to provide an international vaccination certificate if, within six days before arriving in Australia, they have stayed overnight or longer in a yellow fever declared country. People unable to provide a certificate will still be able to enter Australia.

Will I be allowed to enter Australia, if I do not have a yellow fever vaccination certificate?

If you are arriving in Australia from a yellow fever declared country but do not hold a vaccination certificate you will still be permitted to enter Australia without one. On arrival in Australia, Department of Agriculture, Biosecurity officers will reinforce the seriousness of the disease to you and provide you with a Yellow Fever Action Card. The card provides instructions on what you should do if you develop any symptoms of yellow fever in the six-day period following your departure from a yellow fever declared country.

As part of your travel arrangements it is strongly recommended that you check the yellow fever entry requirements for all the countries you intend entering, including those in which you will transit by contacting their foreign missions in Australia. The quarantine requirements for yellow fever vaccination differ markedly from country to country depending upon their relative risk exposure to the disease. The Department of Foreign Affairs and Trade (DFAT) web site lists contact details for diplomatic representatives of various foreign governments. DFAT’s Smartraveller web site also provides further information.
Traveller Risk

• 1970-2009: nine cases reported in unvaccinated travellers from US and Europe from West Africa (five cases) and South America (four cases)
• Eight of these nine travellers died
• Calculating travellers risk:
  • Immunization status, personal protection measures, location, duration of exposure, occupational and recreational activities and local rate of virus transmission at the time of travel
  • Both West Africa and South America, YFV transmission typically is seasonal and is associated with the mid-to-late rainy season
Traveller Risk

The risk of acquiring yellow fever is difficult to predict because of variations in ecologic determinants of virus transmission.

For a 2-week stay, the risks for illness and death due to yellow fever for an unvaccinated traveller visiting an endemic area in:

- West Africa are 50 per 100,000 and 10 per 100,000, respectively
- South America are 5 per 100,000 and 1 per 100,000, respectively
<table>
<thead>
<tr>
<th>Disease</th>
<th>2007</th>
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<th>2012</th>
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<td>365</td>
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<td>Botulism</td>
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<td>276</td>
<td>564</td>
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<td>Hepatitis E</td>
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<td>68</td>
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<td>71</td>
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<td>Salmonellosis</td>
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<td>8,286</td>
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<td>Shigellosis</td>
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<td>828</td>
<td>616</td>
<td>551</td>
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<td>STEC, VTEC³</td>
<td>105</td>
<td>98</td>
<td>128</td>
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<td>111</td>
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<td>Typhoid</td>
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<td>Cholera</td>
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<td>5</td>
<td>3</td>
<td>6</td>
<td>5</td>
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<td>Highly pathogenic avian influenza in humans</td>
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<td>0</td>
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<td>Plague</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Rabies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Severe acute respiratory syndrome</td>
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<td>0</td>
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<tr>
<td>Viral haemorrhagic fever</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td><strong>Yellow fever</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
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</tbody>
</table>
Vaccine

- *Stamaril* – (live attenuated yellow fever virus [17D strain])
- Dose for children and adults is 0.5 mL, to be given by either IM or SC injection.
- May contain traces of egg proteins, does not contain antibiotics, preservatives or gelatin.
- Vaccination elicits protective levels of neutralising antibodies in approximately 90% of adult vaccine recipients by day 14, and in virtually all by day 28.
Vaccine Side Effects

• Mild headache, muscle ache, and low-grade fever, in addition to redness, pain, and swelling at the injection site

• More serious adverse events (rare)
  • Viscerotropic disease
    • RF: Thymus disease, > 60 years
    • Risk (if >70 years of age) 2.4 cases/ 100,000 vaccine doses
  • Neurotropic disease
    • RF: < 6m, > 60 years
    • Risk 0.13 -0.8 / 100,000 doses
Contraindications

- age < 9 months*
- pregnant women*
- people with severe allergies to egg protein; and
- people with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or in the presence of a thymus disorder.

*Exception during yellow fever outbreak when the risk of infection is high
Booster Recommendations

For individuals whose last dose of yellow fever vaccine was at least 10 years previously if:

• prolonged period in endemic areas
• highly endemic areas (such as rural West Africa) during peak transmission season
• plan to travel where ongoing outbreak
Medical Product Alert N° 2/2016

Falsified AMARIL yellow fever vaccines circulating in South East Asia

This Medical Product Alert relates to the confirmed circulation of falsified versions of “AMARIL stabilised vaccine” in South East Asia.

This vaccine is used to immunise against yellow fever and is a WHO prequalified product. Yellow fever vaccine is on the WHO list of Essential Medicines.

On the 9th of February 2016, the Pasteur Institute in Dakar, Senegal, informed WHO that they had identified a falsified version of their “AMARIL stabilised vaccine” circulating in Bangladesh.
Summary

• Historically a devastating disease
• Vaccine confers high rate of life long immunity
• New recommendation by WHO and adopted by Australia
Thank you for your attention!

Slowly he would cruise the neighborhood, waiting for that occasional careless child who confused him with another vendor.
References

• WHO Yellow Fever Factsheet available at:  
  http://www.who.int/mediacentre/factsheets/fs100/en/

• NATHANC travel advice available at:  
  http://travelhealthpro.org.uk/news-search/?loc=all&dis=492&mnh=6

• DOH available at:  

• REVIEW ARTICLE: Eduardo Gotuzzo, Sergio Yactayo, and Erika Córdova,  
  Efficacy and Duration of Immunity after Yellow Fever Vaccination:  
  Systematic Review on the Need for a Booster Every 10 Years.  

• The United States Army Yellow Fever Commission  
  http://exhibits.hsl.virginia.edu/yellowfever/
Table 9: Seroconversion rates following a primary dose of yellow fever (YF) vaccine in young children

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>YF Vaccine</th>
<th>Other vaccine(s)[1]</th>
<th>Age</th>
<th>Assay Used</th>
<th>Seroconverted[2] No.</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Belmusto-Worn 2005</td>
<td>Endemic</td>
<td>17D-204</td>
<td>None</td>
<td>9 mo-10 yo</td>
<td>LNI</td>
<td>917/981 (93)</td>
<td></td>
</tr>
<tr>
<td>Nascimento 2011[3]</td>
<td>Endemic</td>
<td>17DD/17D-213</td>
<td>None MMR</td>
<td>12-23 mo</td>
<td>PRNT&lt;sub&gt;50&lt;/sub&gt;</td>
<td>718/819 (88) 552/792 (70)</td>
<td></td>
</tr>
<tr>
<td>Yvonnet 1986</td>
<td>Endemic</td>
<td>17D-204</td>
<td>BCG, DTP, HepB, M, Polio</td>
<td>9-36 mo</td>
<td>PRNT&lt;sub&gt;90&lt;/sub&gt;</td>
<td>170/183 (93)</td>
<td></td>
</tr>
<tr>
<td>Coursaget 1995</td>
<td>Endemic</td>
<td>17D-204</td>
<td>HepB, M</td>
<td>9 mo</td>
<td>PRNT&lt;sub&gt;90&lt;/sub&gt;</td>
<td>165/172 (96)</td>
<td></td>
</tr>
<tr>
<td>Lhuillier 1989</td>
<td>Endemic</td>
<td>17D-204</td>
<td>M</td>
<td>6-9 mo</td>
<td>HIA</td>
<td>122/135 (90)</td>
<td></td>
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<tr>
<td>Mouchon 1990</td>
<td>Endemic</td>
<td>17D-204</td>
<td>M</td>
<td>6-10 mo</td>
<td>PRNT&lt;sub&gt;80&lt;/sub&gt;</td>
<td>131/139 (94)</td>
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<td>Stefano 1999</td>
<td>Endemic</td>
<td>17DD</td>
<td>M</td>
<td>9 mo</td>
<td>PRNT&lt;sub&gt;50&lt;/sub&gt;</td>
<td>228/294 (78)</td>
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</tr>
<tr>
<td>Adu 1996</td>
<td>Endemic</td>
<td>17D-204</td>
<td>M</td>
<td>6-12 mo</td>
<td>ELISA</td>
<td>379/400 (95)</td>
<td></td>
</tr>
<tr>
<td>Soula 1991</td>
<td>Endemic</td>
<td>17D-204</td>
<td>M</td>
<td>4-24 mo</td>
<td>PRNT</td>
<td>158/167 (95)</td>
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<tr>
<td>Ruben 1973</td>
<td>Endemic</td>
<td>17D-204</td>
<td>M, DPT, S</td>
<td>6-24 mo</td>
<td>PRNT&lt;sub&gt;90&lt;/sub&gt;</td>
<td>158/165 (96)</td>
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<td>Gateff 1973</td>
<td>Endemic</td>
<td>17D-204</td>
<td>BCG, M, S, T</td>
<td>1-5 yo</td>
<td>HIA</td>
<td>119/139 (86)</td>
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<td>Osei-Kwasi 2001</td>
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<td>17D-204</td>
<td>None</td>
<td>6-9 mo</td>
<td>PRNT</td>
<td>284/289 (98)</td>
<td></td>
</tr>
</tbody>
</table>

Table 9 Footnotes

BCG = Bacillus Calmette-Guérin vaccine; DTP = diphtheria, tetanus, and pertussis combined vaccine; ELISA = enzyme-linked immunosorbent assay; HepB = hepatitis B vaccine; HIA = hemagglutination inhibition assay; LNI = log<sub>10</sub> neutralization index; M = measles vaccine; MMR= measles, mumps, and rubella combined vaccines; mo = months old; PRNT = plaque reduction neutralization test; S = Smallpox; T = tetanus; yo = years old

1. Except for Nascimento, seroconversion rates following concurrent administration of YF vaccine with other vaccines compared to administration alone was not significantly different so the proportion are for all children who received YF vaccine. For Nascimento, a significant difference was seen between seroconversion rates when YF vaccine was co-administered with MMR vaccine versus given 30 days post MMR vaccine; these data are presented individually.
2. Measured 30-90 days post YF vaccination.
3. Percent seroconversion is for per protocol population; numerator and denominator data estimated from total numbers in each cohort.
Work Group conclusions

- Single dose of YF vaccine provides long-lasting protection in most travelers
- No longer recommend booster doses of YF vaccine for most travelers
- Recommend YF vaccine booster doses for persons who immune response to previous dose might have been compromised
- Consider YF vaccine booster doses for persons in higher-risk setting for exposure to YF virus
## Seroconversion rates for children by age groups

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of studies</th>
<th>Estimated seroconversion*</th>
<th>(95% CI)</th>
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<tbody>
<tr>
<td>≥9 months</td>
<td>11</td>
<td>92%</td>
<td>(86%-96%)</td>
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<tr>
<td>&lt;9 months</td>
<td>4</td>
<td>95%</td>
<td>(91%-98%)</td>
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<tr>
<td>≥12 months</td>
<td>4</td>
<td>89%</td>
<td>(78%-96%)</td>
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<tr>
<td>&lt;12 months</td>
<td>7</td>
<td>93%</td>
<td>(87%-97%)</td>
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</table>

*DerSimonian-Laird random effects model using the Freeman-Tukey transformation for proportions*
Immunogenicity of YF vaccine in young children

- 12 studies with immunogenicity data on 4,675 children aged 4 months to 10 years in endemic areas at one to two months post vaccination

- Estimate of seroconversion rate is 93% (95% CI 88%-96%) using random effects model
  - 88% when study size differences and variability between studies was not accounted for
Summary of YF vaccine booster dose data and considerations

- Very few vaccine failures noted following YF vaccine
- Most (92%) vaccine recipients are seropositive at ≥10 years post vaccination
- Serious adverse events are uncommon following booster doses of YF vaccine
- High value placed on preventing serious disease with no treatment and poor outcome
- Current statement in ACIP recommendations will no longer be relevant when IHR updated in June 2016