Dengue and Yellow Fever: The Anatomy of Decline and Emergence

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Dengue and yellow fever: decline and emergence

• Background on epidemiology and clinical
• Yellow fever decline
• Re-emergence of dengue
• Reasons for re-emergence of dengue
• Re-emergence of yellow fever?
• Possible explanations for the lack of yellow fever re-emergence

Yellow fever and dengue viruses

• Family: Flaviviridae
• Genus: Flavivirus
• Yellow fever virus; Prototype flavivirus
• Dengue viruses
• Serotypes: Denv-1
  - Denv-2
  - Denv-3
  - Denv-4

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Flavivirus phylogeny

Nonstructural gene

Mosquito-borne

Tick-borne

No vector

Insect

Yellow fever and dengue virus genome

Kuhn, et al., 2006

Africa

Transmission cycles of yellow fever

Enzootic zone

Ae. africanus

Epidemic zone

Ae. aegypti

Monkey

Human

Ae. aegypti

Ae. africanus

Known part of cycle

Speculative part of cycle

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Yellow fever transmission cycle in the Americas

Transmission and maintenance cycles of dengue viruses

Aedes aegypti
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Principal urban vector of DEN and YF

- Vector: *Aedes aegypti*
- Biology:
  - Urban
  - Day biting
  - Breeds in domestic water
  - Preferentially bites man
  - Highly efficient epidemic vector
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Yellow fever

- Disease: the original viral hemorrhagic fever, a systemic illness with
  - High viremia
  - Hepatic, renal, myocardial injury
  - Hemorrhage
  - Shock syndrome
  - Case fatality, 20%

Dengue hemorrhagic fever

- Fever, or recent history of acute fever
- Hemorrhagic manifestations
- Low platelet count (100,000/mm³ or less)
- Objective evidence of "vascular leakage"
- Case fatality rate: average 5%


Differential diagnosis of dengue and yellow fever

- Influenza
- Measles
- Rubella
- Malaria
- Typhoid fever
- Leptospirosis
- Rickettsial infections
- Bacterial sepsis
- Other viral hemorrhagic fevers

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Yellow fever history

- 1600s - Virus, vector introduced from Africa
- 1648 - Yucatan epidemic, Mayan records
- 1750 - Term 'yellow fever' first used in Barbados
- 18th-19th Centuries - major epidemics, Americas, Europe, West Africa
- 1900 - Reed demonstrates filterable virus transmitted by *Ae. aegypti*; vector control begins
- 1904-1912 - Yellow fever controlled in Cuba and Panama
- 1905 - Last outbreak in U.S. (New Orleans)
- 1927 - Virus isolated in Africa
- 1932 - YF jungle transmission cycle (Brazil, then Africa) sylvatic mosquitoes and non-human primates
- 1936 - Yellow fever vaccine developed
- 1946 - *Aedes aegypti* eradication program in Americas

Importance of the 1890s

- Filterable agent (=virus) as cause of animal disease
- Malaria transmission by mosquito
- Discovery of extrinsic incubation period
- Yellow fever transmission by *Ae. aegypti*
- Spanish-American War
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Urban yellow fever epidemics in the United States 1793-1905

1. Philadelphia, 1793; 5,000 dead
2. New York City, 1793; 730 dead
3. Boston, New York City and Philadelphia; 1798; more than 5,000 dead
4. Baltimore, 1800; 1,200 dead
5. New Orleans, 1853; 8000 or more dead
6. Norfolk, 1855; 2,000 dead
7. Mississippi Valley, 1878; 20,000 dead
8. Cuba, 1898; hundreds dead
9. New Orleans, 1905; more than 900 dead

Currently:
• Rare imported cases with travel history
• No local transmission
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Reported cases of yellow fever 1948-98

WHO Report, 2000

Aedes aegypti distribution in the Americas

Adapted from Gubler, 1998

Dengue: a historical perspective
More important epidemics of dengue-like illness
- China - 992
- Caribbean - 1635
- Panama - 1699
- Spain/Africa - 1700s
- Batavia, Indonesia - 1779
- Cairo, Egypt - 1779
- Philadelphia, PA, USA - 1780
- Spain - 1801
- Cuba - 1828
- Americas and Asia-Pacific - 1800s & early 1900s
- World War II - 1941-45
- Aedes aegypti eradication program in Americas, 1946
- Post war era - 20th Century re-emergence

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Epidemic dengue hemorrhagic fever / dengue shock syndrome emerged as newly recognized disease in Southeast Asia in the 1950s

- At the end of WWII all four serotypes of dengue were widespread in Asia

Expanding geographic distribution of epidemic dengue/dengue hemorrhagic fever in Asia

Adapted from Gubler, 1998

Aedes aegypti distribution in the Americas

Adapted from Gubler, 1998

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The emergence of dengue hemorrhagic fever in the Americas

Re-emergence of dengue in the US 1980

Autochthonous dengue in the United States

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Dengue fever in Africa
Prior to 1980 1981-2010

Areas at risk
Adapted from Gubler, 1998

Epidemic transmission
Areas at risk

The 20th century re-emergence 
of epidemic dengue

- Expanding geographic distribution
- Increased epidemic activity
- Hyperendemicity
- Emergence of DHF

Average annual number of DF/DHF cases reported to WHO, 1955 - 2008

Source: DengueNet 2008 data provisional

Approximate global distribution of dengue and Aedes aegypti, by state/province, 2010

- Areas with recent dengue transmission
- Areas infested with Aedes aegypti

Adapted from Gubler, 1998
Public health impact of dengue

- 2.5-3 billion people live in areas of risk
- 50-100 million cases/infections/year
- Millions hospitalized
- 500,000 cases of dengue hemorrhagic fever
- 20,000 plus deaths
- Incidence and geographic range are increasing
- Economic impact
- No vaccine or antiviral drugs
- Mosquito control has been largely ineffective

Why have we seen such a dramatic increase in epidemic dengue/dengue hemorrhagic fever?

- Complacency, Lack of political will
- Policy changes
- Changes in public health
- Changing life styles/behavior
- Microbial adaptation
- Technology
- Climate change?

Why have we seen such a dramatic increase in epidemic dengue/dengue hemorrhagic fever?

Major drivers

- Demographic changes (Pop. growth and distribution)
  - Environmental change
    - Uncontrolled urbanization
- Modern transportation (Globalization)
  - Increased movement of people, animals, commodities
- Lack of effective mosquito control
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Estimated number of people living in urban areas

Source: UN

The urban and rural population of the world 1950-2030

Source: UN

Urbanization
The case of Dhaka, Bangladesh

Source: UN
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Emergence of dengue/dengue hemorrhagic fever
Uncontrolled urbanization

- Crowding
- Living conditions
- Lack of basic services: inadequate housing, piped water, sewage and waste management

From: PAHO, 1997; Gubler, 1998


Source: UN, World Urbanization Prospects, The 1999 Revision

Urban population growth and reported dengue cases

Population data, UN; Dengue data, WHO, to April, 2008

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Dengue viruses & mosquitoes: hitching a ride on modern transportation

The global airline network

Mean annual number of airline passengers by decade, United States, 1954-2007

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Global movement of dengue (1981-1990)
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Yellow fever: re-emergence?

- Increased global travel
- Encroachment of humans into sylvatic cycle
- Human migration and urbanization
- Reinfestation by *Aedes aegypti* of urban areas threatens major population centers

Low YF vaccine coverage rates

Number of yellow fever cases and deaths reported to WHO, by decade, 1950-1999

- 1950-59: 0 cases, 0 deaths
- 1960-69: 8000 cases, 10000 deaths
- 1970-79: 18000 cases, 16000 deaths
- 1980-89: 14000 cases, 16000 deaths
- 1990-99: 12000 cases, 14000 deaths

*Aedes aegypti* distribution in the Americas

- Adapted from Gubler, 1998

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Potential for urban yellow fever epidemics in the Americas

Imported yellow fever
- Texas – 2002
- Belgium – 2000
- California – 1999
- Germany – 1999
- Switzerland – 1996
- Tennessee – 1996

Urban yellow fever, Santa Cruz, Bolivia  
Dec 1997 - June 1998

Two clusters of transmission
- Six acute cases confirmed
  - Five died
  - (Three cases likely contracted infection in the city)
- Serosurvey - 281
  - 16 (6%) had YF antibody
  - 5 - no previous immunization
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**Epidemiologic distribution of yellow fever, Brazil**

States: 12
Population: 27,014,229

Endemic areas:

- States: 12
- Population: 27,014,229

Epizootic area:

- States: parts of 3
- Population: 10,443,215

YF free area:

- States: 15

Fonte: SUCAM/MS
Vasconcelos, P.F. (1997)

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**Distribution of confirmed cases of yellow fever by date of onset of symptoms, Laurelty, Paraguay, 2008**

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**Hypothesis to explain the absence of urban yellow fever epidemics in the Americas**

- Cross-protective flavivirus immunity
  - Evidence through monkey experiments
- Virus Adaptation
  - Humans
  - *Aedes aegypti*
- Evolutionary exclusion
Hypothesis to explain the absence of yellow fever in Asia

- A matter of logistics
- Cross-protective flavivirus immunity
- Low vector competence of Asian Aedes aegypti
- Geographic and demographic obstacles to spread yellow fever virus
- Evolutionary exclusion

Potential global spread of urban yellow fever

Dengue and yellow fever viruses

Summary

- Both old diseases
- Both effectively controlled
- Dengue re-emerged; yellow fever did not
- Dengue viruses evolved with urbanization
- Yellow fever remained in the jungle
- Current global threat
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