West Nile fever
2nd FAO-OIE-WHO Joint Scientific Consultation: Influenza and other Emerging Infectious Diseases at the Human Animal Interface
Verona, Italy, 27-29 April 2010
Hervé Zeller
European Centre for Disease Prevention and Control, Stockholm, Sweden

West Nile virus: the agent
Positive single strand RNA virus
Enveloped virus

*Flavivirus* genus, *Flaviviridae* family

Identified in humans and horses, birds, mosquitoes, ticks,
as well as during main outbreaks in cattle, sheep, goats, deer, dogs, cats, bats, pigs, squirrels, chipmunks, rabbits….

and in frogs…

Infection induces immune response which can stay for several years
Transmission cycle

- Natural cycle between birds and mosquitoes
- Asymptomatic infections (>70%)
- Mild febrile illness
- Neuroinvasive illness in 1 out of 150-300 cases (mostly in elderly) with fatalities.
- Sporadic disease outbreaks in humans and horses in Africa, Europe, Asia and Australia
- Emergence in North America (1999)

Birds: amplifying host

![Graph showing virus replication in different bird species](image-url)

Cycle of transmission

- Competent mosquitoes able to replicate and transmit the virus
- Susceptible amplifying hosts (birds)
- Bird – mosquito – bird
  Mosquito bite: a complex figure: blood meal on a viremic amplifying host (bird)
  - Extrinsic incubation period: 7-14 days (duration varies according to environmental factors: temperature...)
- Mosquito - humans: Infection by biting infected bridge mosquitoes (multiple blood meals)

WN in mosquitoes: Europe/Mediterranean Basin

<table>
<thead>
<tr>
<th>Mosquito species</th>
<th>Country (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anopheles coustani maculipennis</td>
<td>Israel (1) Portugal, (3), Ukraine (2), Romania (1)</td>
</tr>
<tr>
<td>Aedes cantans</td>
<td>Slovakia (1) Ukraine (1), Bulgaria (2)</td>
</tr>
<tr>
<td>Aedes caspius</td>
<td>Ukraine (1)</td>
</tr>
<tr>
<td>Aedes excrucians</td>
<td>Ukraine (1), Russia (1)</td>
</tr>
<tr>
<td>Culex antennatus*</td>
<td>Egypt (5)</td>
</tr>
<tr>
<td>Culex modestus</td>
<td>France (2), Russia (1)</td>
</tr>
<tr>
<td>Culex pipiens</td>
<td>Israel (2), Egypt (1), Romania (12)</td>
</tr>
<tr>
<td>Culex perexiguus</td>
<td>Czechland, (2), Bulgaria (1) Portugal (2)</td>
</tr>
<tr>
<td>Culex torrentium</td>
<td>Egypt</td>
</tr>
<tr>
<td>Culex univittatus</td>
<td>Egypt (9), Israel (5), Portugal (2)</td>
</tr>
<tr>
<td>Uranoteania</td>
<td>Russia</td>
</tr>
</tbody>
</table>

Adapted from: Hubalek, 2000
Modes of transmission to human

- Mosquito - human:
  but no transmission from human to mosquitoes (low viremia)

- Human - human infection
  - via blood products/organs:
    Numerous asymptomatic cases (up to 80%) with a low viremia for a median of 6.5 days up to 3 weeks
    From June to December 2003, 818 viremic blood donations in 6 million units (Source: MMWR 2004;53:281-4)

Virus phylogeny

- the strains from USA, Israel, Tunisia, France Italy: 1998-2009
- Astrakhan strains, 1999-2005
- Eg-101 and China strains
- the strains from Romania 1996, Volgograd 1999-2003, Astrakhan-2005
- Kunjin strains
  - lineage II isolates, South Africa, Senegal, new Volgograd-2007 and Hungary-2004
  - India strain
  - Knd88-190 strain
  - and Volgograd “Urano” isolates, 2002-2006

lineage I

lineage II
Invasiveness related to avian virulence

Epidemics in northern latitudes consistently associated with proline substitution at NS3-249 position.

Proline mutant imparts high virulence in American crows

Genetic network analysis of E gene region of North American WNV.
Labeled by year of collection from 1998 (Israel) to 2004.
Labeled by time zone.
Multiple lines converging on a single peripheral variant indicate alternative mutational pathways.
Storks, birds of prey, pigeons...

and domestic geese...

Source: M. Malkinson

Israel
1997-98
Bird mortality
Storks, birds of prey, pigeons...

Crows

Blue jays
Arrival in North America… = commotion

USA: West Nile – Neuroinvasive human cases 1999-2009
11657 cases CFR 9.6%

Canada 2001-2009
800 NI cases
Estimates
0.11-0.25 millions human infections

Horses, USA:
More than 27,000 cases since 2001
with a case fatality rate of about 33%

Estimate: 1.6-3.7 millions human infections
**Sustainability of transmission**

**Bird - bird transmission**

Isolation of WNV from a Red-tailed hawk that died in NY during Feb 2000.


**Persistent avian infection:**
Experimentally infected birds positive for WNV RNA at necropsy 6-8 wks post infection

Reisen et al. 2006. JME 43: 344

Predation and/or scavenging: possible mechanism for WNV infection in raptors during winter
WNV probably overwinters by multiple mechanisms:

- Vertical infection of diapausing Culex females
- Vertical transmission in Culex:
  - Cx. pipiens overwintering mosquitoes
    (USA, Czech Republic) (PCR 4, isolation 1 out of 4)
    Virus also isolated from male Cx. pipiens in US, and
    from larvae of Cx. univittatus Kenya
- Chronic avian infections [no evidence for relapse]
- Migrating birds [results mostly negative]


Epidemiological situation in Europe 2000-2009

Human neuro-invasive cases

- Hungary (2003-07) 14 cases
  (2008) 14 cases (August 14 [8], Sept 24 [6])
- France (2003) 4 cases
- Portugal (2004) 2 cases (non NI)
- Spain (2007) 1 case
- Italy (2008) 6 cases (2009) 16 cases
  August - October
- Romania (1997-2007): x cases
  Romania (2008) 2 cases August-Sept ember
  (2008) 2 cases August
Interface aspects affecting evolution, exposure, or transmission

Climate impact: Seasonality for transmission
Mosquitoes activity is dependent on temperature and humidity
Do mosquitoes change host preference habits over the season: switching from birds to mammals?

West Nile virus disease cases (N = 28,961), by week of illness onset --- US, 1999—2008
Cases in Europe from 2006 to 2009 (mid-July to mid-October)

Lindsey NP et al. Surveillance Summaries April 2, 2010 / 59(02):1-17
Epidemiological situation in the Americas

1999  New York
2001  Cayman islands, Canada
2002  Guadeloupe, Dominican Republic, Jamaica
2003  Mexico, Bahamas, Puerto Rico, Cuba
2004  Colombia, Trinidad
2006  Argentina
also reported in Venezuela

Vaccine: for humans

Cost-effectiveness of West Nile Virus Vaccination
Zohrabian A et al EID 12, No. 3, March 2006

“Analysis indicated that universal vaccination against WNV disease would be unlikely to result in societal monetary savings unless disease incidence increases substantially over what has been seen in the past 6 years”
New approaches needed
Uncertainties

West Nile persistence in temperate climate:

In Europe, data collected in wild birds and horses suggest that a recurrent circulation of West Nile virus could exist in some areas.

Whether this circulation is permanent (due to overwintering mechanisms) or not remains unknown?

Climate changes:

Model predictions: example:

“Based on the climatologically characteristic drought occurrence in the past and on climate model predictions for climate change and potentially greater drought occurrence in the future, we suggest that the frequency and relative risk of WNV outbreaks could increase.”.


More Challenges

Yesterday: West Nile

• Lack of resources
• Learning to live with WNV does not mean complacency
• Creative (and cost efficient) strategies needed to mitigate an omnipresent risk

Tomorrow: Usutu?

Saint-Louis Encephalitis may reach the old world?

Imaginative scenario:

to assess the unpredictable and the Public Health impact?

One perspective:

to get a comprehensive approach of the ecology of the environment constantly modified by humans

Environmental and human behaviour “surveillance” is crucial…