

Yellow fever vaccine: new insights into an old immunogen

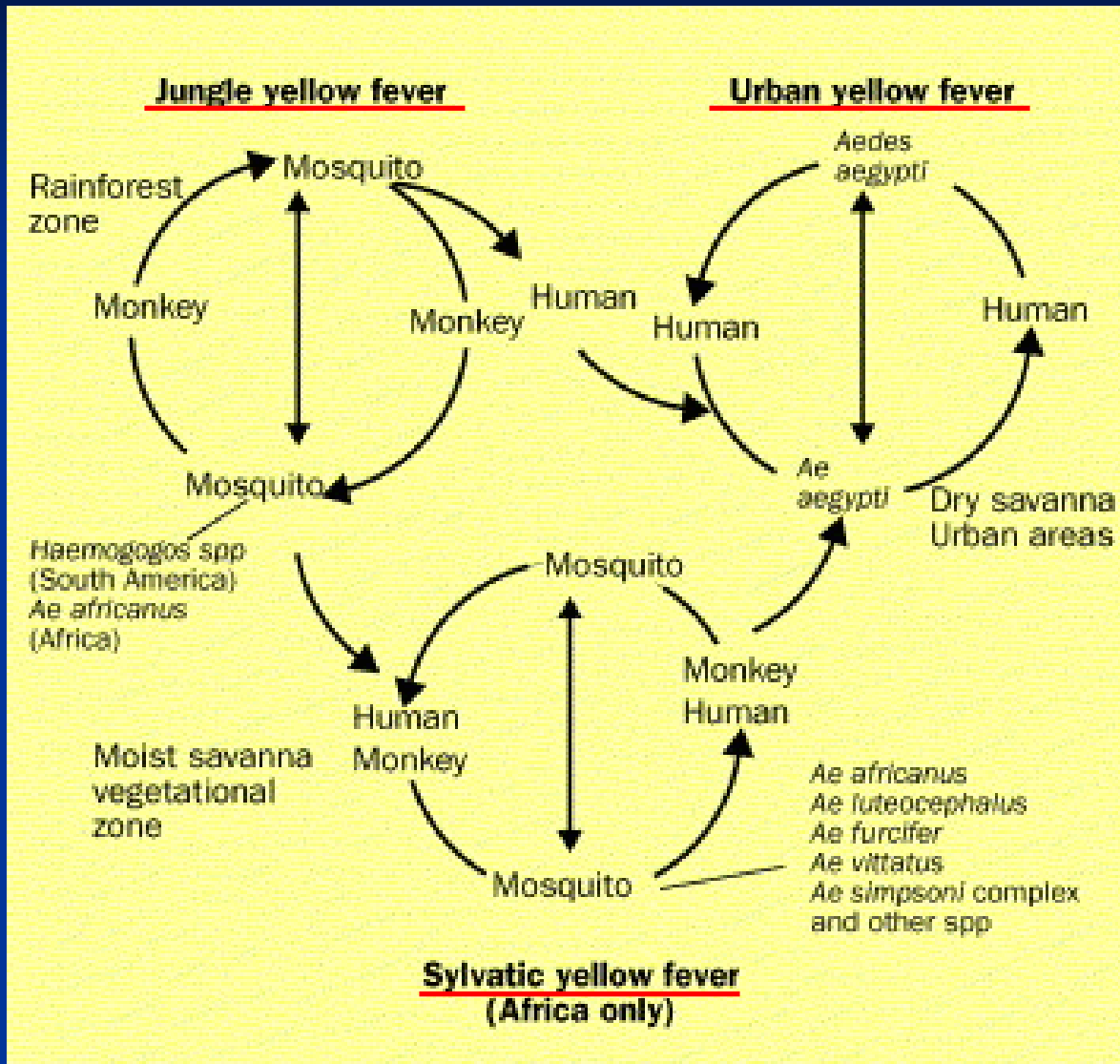
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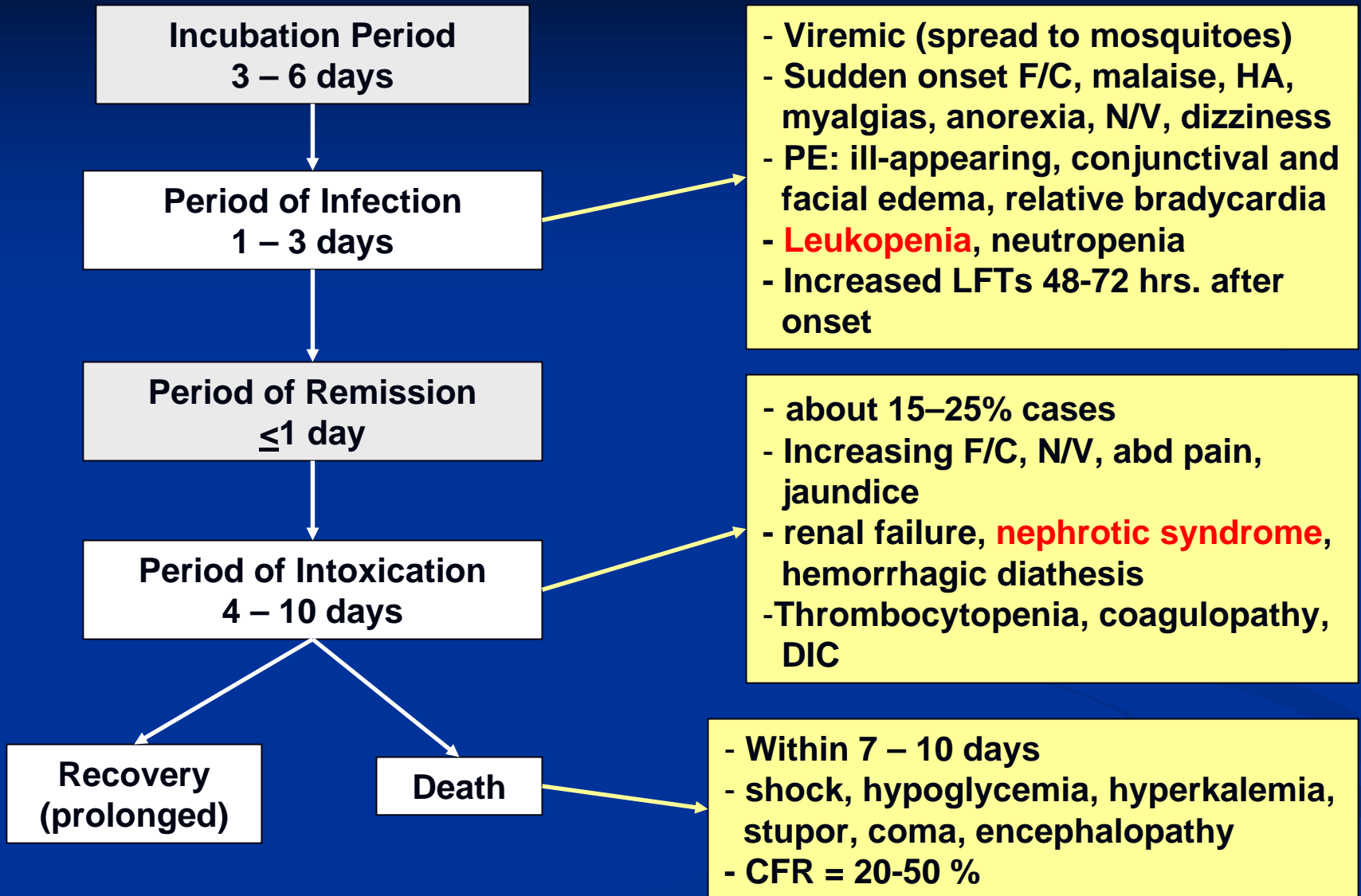
Yellow Fever

- Outbreaks in Africa and New World during eighteenth and nineteenth centuries
- Important dates:
 - 1900: identified mosquito vector
 - 1927: virus first isolated in Africa
 - 1930s: Theiler's 17D vaccine, won Nobel Prize
- Last U.S. case in 1920s; last U.S. outbreak in New Orleans in 1905.
- 3 deaths in U.S. travelers to the Amazon since 1996.

YF Transmission Cycle



YF - Clinical



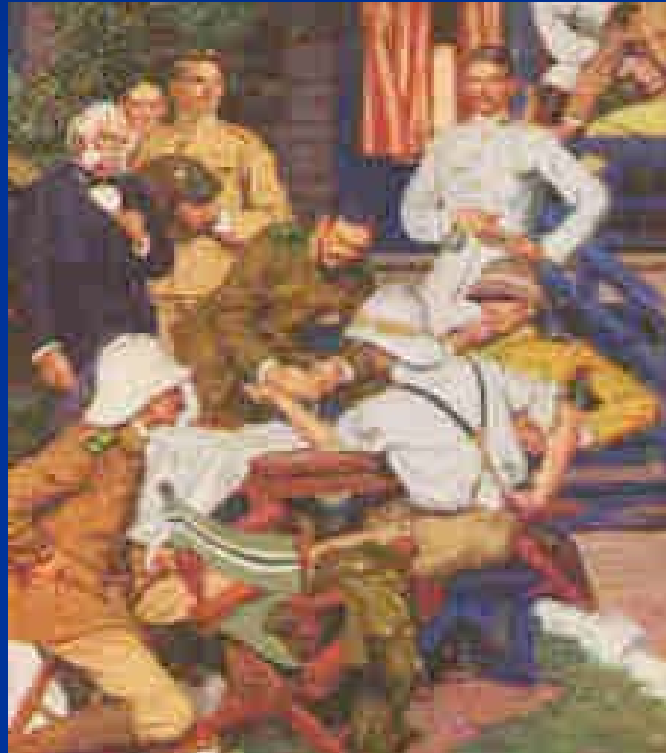
Ddx: other causes of hepatitis or hemorrhagic fevers; Lepto, malaria, typhoid, thyphus, relapsing fever.

Management and Prevention

- Diagnosis:
 - Viral isolation, PCR, IHC
 - Don't do liver biopsy! Hemorrhage risk.
- Management:
 - Supportive
 - Ribavirin
 - IVIG

} Unclear benefit
- Prevention:
 - Mosquito precautions and control
 - Vaccination

Yellow fever vaccine



Vaccination

- The deliberate induction of protective immunity to a pathogen by administration of non-pathogenic forms of the pathogen or its antigens to induce a memory immune response

- For over 65 years, more than 350 million people have been vaccinated with yellow fever vaccine YF 17D

Arroyo, J. et al. *TRENDS In Mol Med.* 2001. 7(8):350-354

**...Yet Little is Known About
YF 17D's Mechanisms of Inducing
Such Long Lasting Protective
Immunity**

The Yellow Fever vaccine

- Live- attenuated vaccine prepared from Asibi wild type wtYF (Nigeria, 1927). Called the 17D strain.
- Sequentially passaged through minced mouse embryo, minced whole chick embryos, minced whole chick embryos-neural tissue, embryonated eggs
- Vaccination results in viral replication, neutralizing antibody, and long-lived immunity
- 3 WHO – approved vaccine sub-strains produced by 6 manufacturers worldwide
- ~300,000 doses sold annually in the U.S to travelers
- ~600,000 doses sold annually to the U.S. military

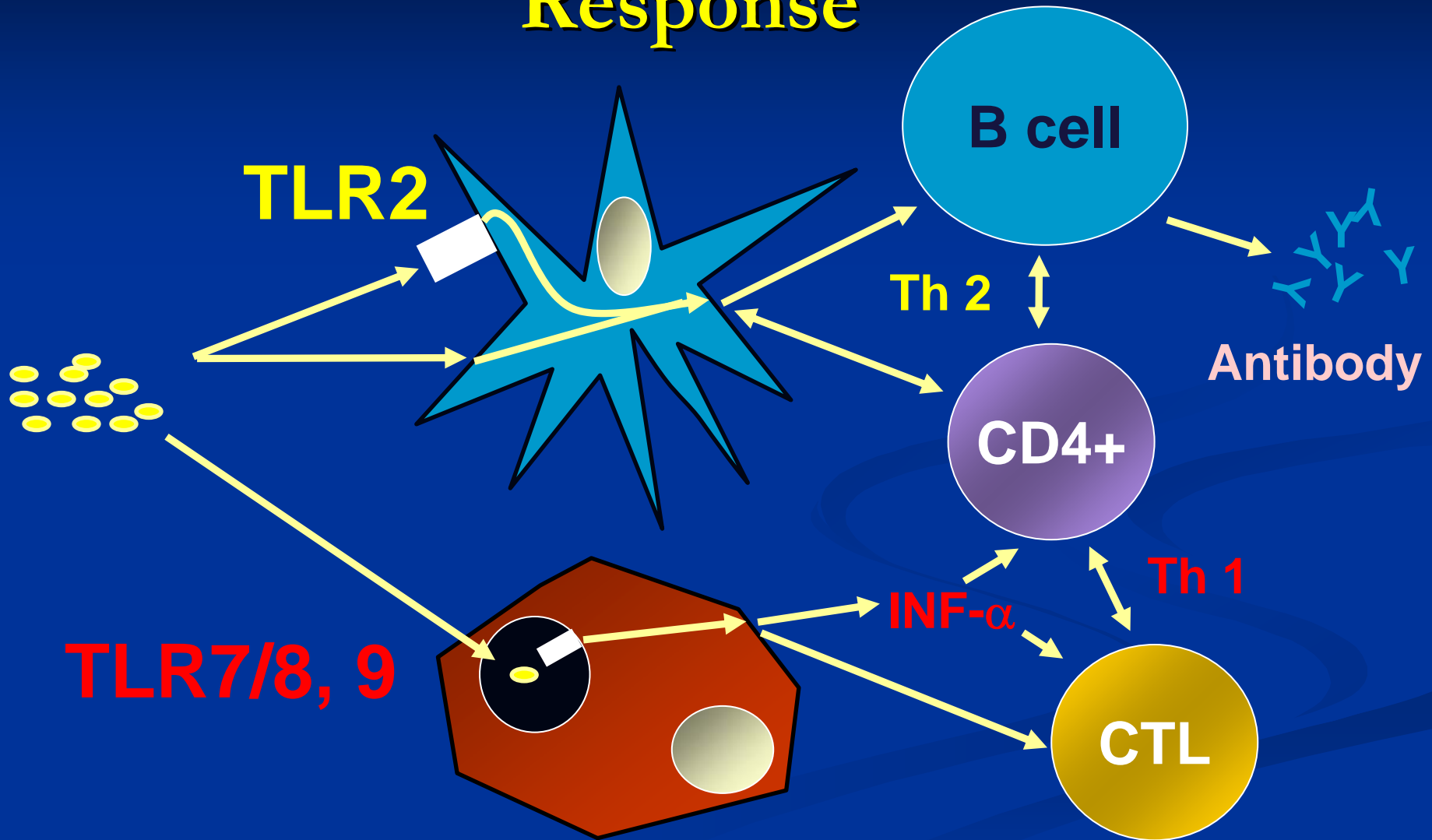
Why Study Immune Responses To The YF Vaccine?

- **Understand the different components of the immune response to a live YF-17D infection**
 - **Basic Immunology**
 - **Adverse events**
 - **Vaccine vector**

Yellow Fever Study Design

- **Yellow Fever Vaccine**
 - 17D-204 strain, live attenuated vaccine
 - Delivered Subcutaneously in the upper arm
- **1° infection of healthy adults age 20-45**
- **Whole blood samples drawn at days -7, 0, 3, 7, 11, 15, 30, 60, 180, 360 post vaccination**
- **Analysis Performed**
 - Phenotypic analysis of CD8 T Cells
 - IFN γ ICC and ELISPOT assays for CD8 T cells
 - Neutralizing antibody titers
 - Assessment of bystander activation
 - CD8 response to boost

YF-17D Generates a Multifaceted Response



Conclusions:

- Two weeks following YFV inoculation, we observed maximum expansion of a well-defined pool of effector CD8 T cells, characterized by the expression of the T cell activation markers, CD38 and HLA-DR.
- At the peak of the CD8 T cell response, 13% of total CD8 T cells expressed CD38 and HLA-DR following YFV inoculation.
- At the peak of the anti-VV CD8 T cell response, all HLA-A2VVCLT tetramer-specific CD8 T cells expressed perforin and granzyme B molecules, implying that all responding T cells pass through an obligate effector phase after infection.
- From two to four weeks post-infection, virus-specific effector populations contracted 5-10 fold and down regulated expression of activation markers, resulting in the formation of long-lived populations of resting memory CD8 T cells.

Conclusions (2):

- The populations of memory CD8 T cells may be further subdivided on the basis of migration patterns and cytotoxic potential.
- Bystander activation does not contribute to the peak of the anti-viral CD8 T cell response, suggesting that the observed T cell responses were primarily virus-specific.
- This study supports a linear model of CD8 T cell differentiation, where naive CD8 T cells undergo massive expansion to generate a pool of effector T cells, that gradually contracts and differentiates to form a long-lasting population of virus-specific memory CD8 T cells.

Yellow Fever Vaccine – Associated Viscerotropic Disease

Adverse Reactions

- Early 1940s: 199 cases of encephalitis (Brazil), change in production standards
- Since 1945: 21 cases of encephalitis
 - 18 cases in children => 16 under 7 months old
 - Contraindicated for children < 6 months old
 - Not recommended for children < 9 months old
- Anaphylactic reactions ~ 1 / 58,000 (gelatin?)
- Egg or chicken hypersensitivity

Serious Adverse Events

Viscerotropic Disease → **Yellow Fever Vaccine-Associated Viscerotropic Disease**

Neurologic Disease → **Yellow Fever Vaccine-Associated Neurologic Disease**

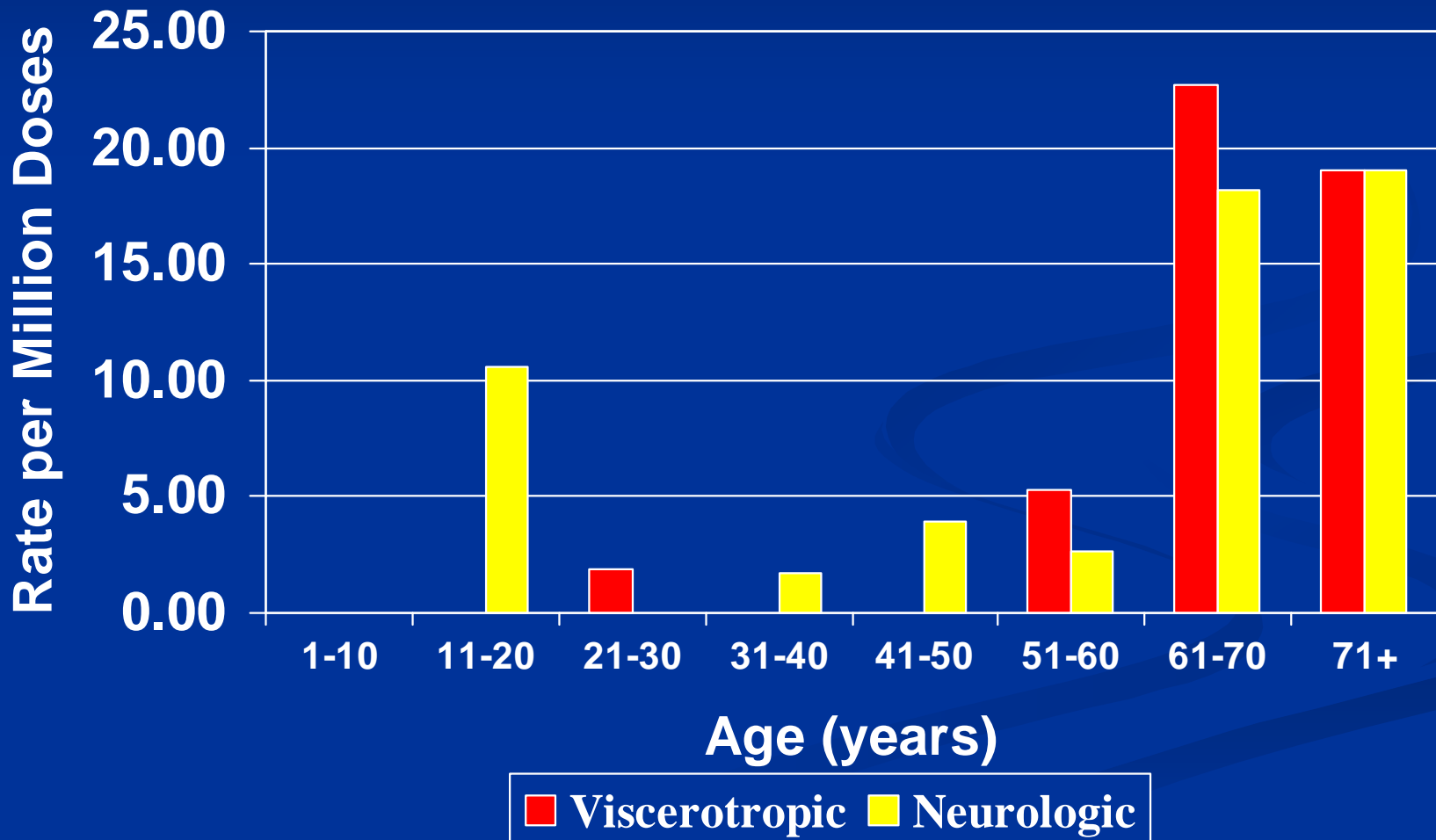
YFV - AVD

- 1996 – 2001: 7 cases of severe multi-organ system failure (now called YFV – AVD)
- 6 of the 7 died (CFR = 85.7%)
- 4 cases from U.S. and 1 from Australia
 - Mean age 68.2 years (56 – 79 years)
- 2 Brazilian cases
 - Ages 5 years and 22 years
- Host dependent risk factors

Risk Factors Identified

- **More serious adverse events in persons > 40, especially in those > 60 years**
 - RRR = 4.4 for those 60-69 years old
 - RRR = 13.4 for those ≥ 70 years old
- **4 of 29 (14%) YFV-AVD cases with history of thymus disease**
- **Careful risk – benefit assessment**
 - **Caution: persons > 60 years old**
 - **Contraindication: history of thymus disease (myasthenia gravis, thymoma, or prior thymectomy), immunosuppression**

Age-Specific Reported Rate of Adverse Events per Million Doses Distributed to U.S. Civilians, 1990-2005



Results

- 11 cases of YFV-AVD were reported between 1996 and 2004.
- All primary YF vaccinees
- Case Status:
 - Definite 5, Probable 1, Suspect 4, UI 1
- Mean age = 59.2 years (22 – 79 years)
- Male 8, Female 3
- 6 deaths (case fatality rate = 54.5%)

Yellow Fever Vaccine-Associated Viscerotropic Disease: Clinical Summary

- All primary vaccinees, 2-5 days post-vaccination
- Fever, myalgia, arthralgia
- Elevated liver enzymes & bilirubin
- Thrombocytopenia, lymphocytopenia
- Rhabdomyolysis
- Hypotension requiring vasopressors
- Renal failure requiring dialysis
- Respiratory failure requiring intubation
- Case Fatality Rate >50%

Evidence supporting causality...

- Temporal association (2-5 days post YEL)
- *17D vtYF* isolated: blood, CSF, muscle, heart, brain, liver
- Compatible YF histopathology associated with large amt of viral antigen in target tissue
- No other pathogens or etiology identified

Evidence supporting causality...

- VAVD syndrome similar to *wt* YF
- Multiple cases (22 + since 1996)
- Nine countries & 4 different vaccine products
- Both vaccine strain subtypes 17D-204 & 17 DD
- Biologic plausibility
 - live attenuated virus vaccine associated *wt* disease syndromes

V_t YF:

Molecular sequencing results

- Brazilian cases:
 - 2 patients w/ 17DD YF viral isolates
 - Serum + liver, spleen, kidney, heart
 - No mutation at E protein
 - Same as vaccine type in vial and seed lot
- U.S. cases:
 - 2 patients w/ 17D 204 YF viral isolates
 - Serum, serum + CSF
 - 1 with mutations at “E” and “M” proteins
 - 1 without any mutations
- Australia sequencing shows *vt* 17D-204

Summary

- **YFV-AVD is rare and risk factors for severe disease are still unknown.**
- **Women with YFV-AVD have a higher fatality rate than men.**
- **The rate of change in AST, ALT, and platelets may predict severity of disease.**

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