

USAMRIID



Vaccines to control emerging infectious diseases

Phillip R. Pittman, MD, MPH
Chief, Division of Medicine
Director, Vaccine Clinical Research Center
USAMRIID
Fort Detrick, MD 21702

28 Jan 2009

Preventing epidemics by vaccination

- **Since George Washington use scarification to vaccinate his troops against smallpox during the Revolutionary War, vaccines, when available, have been used to prevent epidemics in the US and other parts of the world.**
- **There are instances when available vaccines were not used because of various fears with occasional devastating consequences. The alleged association of autism etc with childhood vaccination gave charge to the “Vaccine No Group” in the US**
- **And, of course, there are instances when epidemics have raged and effective vaccines have not become available.**

Preventing epidemics by vaccination

Old viruses, old locales re-emerging

- CHIK
- RVF
- AHF

• Emerging viruses

- H5N1

• Potential for natural spread of old viruses to new location and effect on agriculture, livestock and humans

- WNV, RVF

• Potential of non-natural spread effecting livestock, agriculture and humans.

Variolation of the Troops Helped Win the Revolutionary War



George Washington had all his troops variolated, which protected his army from smallpox but led to media criticism, e.g., 1812 article by UK Anti-Vaccine society



West Nile Virus: Background

- **First isolated in 1937 in Uganda from blood of a febrile woman.**
- **Family: Flaviviridae**
 - Genus: Flavivirus
 - Japanese Encephalitis Antigenic Complex
 - Complex includes: Alfuy, Japanese encephalitis, Kokobera, Koutango, Kunjin, Murray Valley encephalitis, St. Louis encephalitis, Stratford, Usutu, and West Nile viruses.
- **All are transmissible by mosquitoes, many can cause febrile, sometimes fatal, illnesses in humans.**

West Nile Virus: Background

- **First recorded epidemic in Israel in 1950's.**
- **Soon recognized as one of the most widespread Flaviviruses.**
- **Distributed through Africa, West Asia, Europe and the Middle East.**

West Nile Virus: Entomology

- Isolated from over 40 mosquito species
 - Mostly *Culex* species:
 - *Cx. univittatus*, *Cx. perixiguus*, *Cx. pipiens*, *Cx. modestus*, *Cx. quinquefasciatus*, *Cx. tritaeniorhynchus*, and *Cx. vishnui*
 - Other mosquito species in a variety of genera:
 - *Aedes*, *Aedeomyia*, *Anopheles*, *Coquillettidia*, *Mansonia*, *Mimomyia*
 - Isolated from ticks:
 - Soft tick genera: *Argas*, *Ornithodoros*
 - Hard tick genera: *Amblyomma*, *Dermacentor*, *Hyalomma*, *Rhipicephalus*,

West Nile Virus: Reservoir Hosts

- **Isolated from numerous wild birds.**
 - Wetland and terrestrial species.
- **Birds are primary amplifier hosts.**
 - Reservoir status not known.
- **Migratory bird role in distribution and re-introduction of virus into northern latitudes.**
- **Role of other vertebrates not known.**

West Nile Fever: Human Disease

- Febrile, influenza-like illness with abrupt onset
- Moderate to high fever
- Headache, sore throat, backache, myalgia, arthralgia, fatigue
- Rash, lymphadenopathy
- Acute aseptic meningitis or encephalitis
- Most fatal cases >50 years old.

West Nile Virus in the US - Some Possible Pathways of Introduction

- **Infected human host**
- **Human-transported vertebrate host**
 - Legal
 - Illegal
- **Human-transported vector(s)**
- **Storm-transported vertebrate host (bird)**
- **Intentional introduction (terrorist event)**

WNV-related publications

- **Descriptions of outbreak**

MMWR: 1999;48:845-49

MMWR: 1999;48:890-92

MMWR: 1999;48:944-46,55

MMWR: 2000;49:178-79

MMWR: 2000;49:211

Anderson et al., Isolation of West Nile virus from mosquitoes, crows, and a Cooper's hawk in Connecticut. *Science* 1999;286:2331-33.

- **Virus characterization**

Briese et al., Identification of a Kunjin/West Nile-like flavivirus in brains of patients with New York Encephalitis (Letter). *Lancet* 1999;354:1261-62.

Jia et al., Genetic analysis of West Nile New York 1999 encephalitis virus. (Letter). *Lancet* 1999;354:1971-72.

Lanciotti et al., Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern U.S. *Science*. 1999;286:2333-37.

WNV

Status of Human Vaccine

- No human vaccine although several groups working on effort

Status of animal vaccine

- Horse vaccine available.

Argentine Hemorrhagic Fever

- **Clinical Aspects**—AHF is a rodent-borne viral hemorrhagic fever endemic to north-central Argentina. Initial symptoms of fever, headaches, malaise, and loss of appetite occur 1-2 weeks following infection. Symptoms intensify over the 3rd week producing vascular, renal, hematological, and neurological alterations. Left untreated, mortality reaches 15%-30%.
- **Vector**—the primary vector is the rodent, *Calomys musculinus*, which spreads the virus through its saliva and urine. Infection is produced through contact of skin or mucous membranes, or through inhalation of infected particles. 80% of cases are males 15-60 yrs.

Argentine Hemorrhagic fever

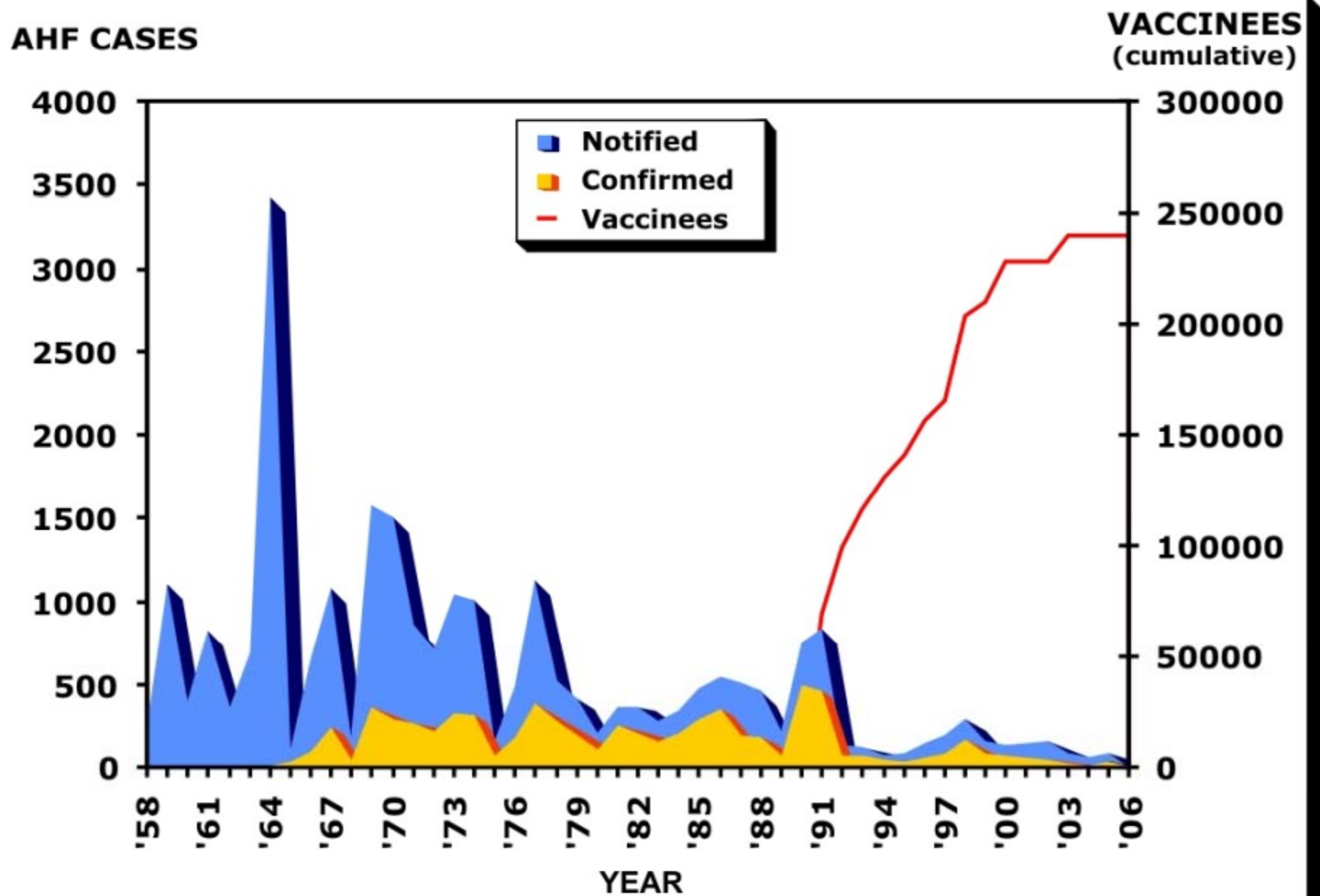
Etiologic agent is the Junin virus, a member of the Tacaribe complex of New World arenaviruses. It is a CDC Class A virus.

Vaccine—the Junin vaccine, Candid #1 is a live-attenuated vaccine developed in 1985 by Dr. Julio Barrera Oro at USAMRIID and made available to Argentina in 1990. This vaccine is currently licensed in Argentina.

Candid #1 was studied in a Phase 3 clinical trial involving an adult high-risk population and was shown to be safe and 95.5% efficacious.

The Junin vaccine has reduced the incidence of disease from 100-800 cases per year to approximately 19 cases as shown in next slide. (courtesy of Drs. Kelly McKee & Dr. Julio Barrera Oro)

AHF Notified and Confirmed Cases (1958 - 2006)



Epidemic of Chikungunya virus

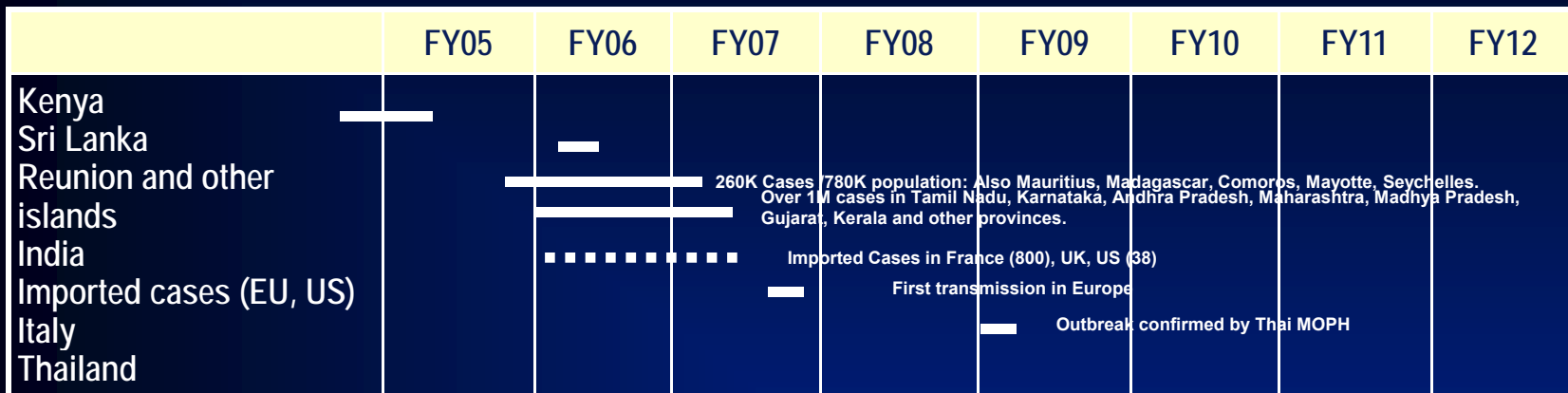
CHIK vaccine developed by USAMRIID cuts at least 5 years off normal development of a vaccine for a virus that is causing a severe epidemic in the Indian Ocean, Asia, and eastern Africa.

CHIK Background

- The Disease.

- Chikungunya virus causes an acute febrile illness characterized by rash and sometimes severe and temporarily crippling joint and muscle pain.
- Virus is highly infectious to laboratory workers.
- In a recent (2005-6) epidemic (Reunion, France), virus caused acute, incapacitating disease in up to 1/3 of persons.
 - Many patients collapse and are unable to walk due to involvement of joints in the legs.
 - Joint symptoms may persist for months.
 - Chikungunya is spreading. The outbreak in Italy is the first in Europe.

Recent Chikungunya Outbreaks



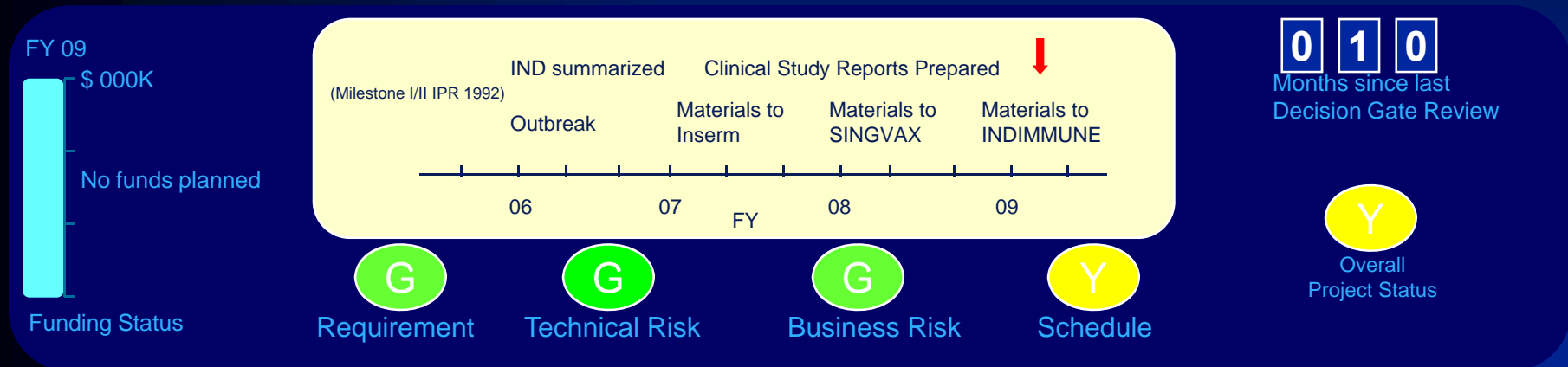
- **Causes of Change in Epidemiology of Chikungunya**

- Virus genome mutations facilitate transmission by *Aedes albopictus*
- *Aedes albopictus* has become world wide
 - Related to international commerce in used tires
 - Infests much of southeastern US

Program Status: Chikungunya Virus Vaccine

(Technology Transfer)

Product: Transfer of Chikungunya Vaccine IND, IND Summary, and Production Seeds to manufacturers with an interest in producing vaccine and completion of sponsor's regulatory responsibilities for completed clinical trials.



- Overall Project Status: 2 MTAs completed. Third is under negotiation.
- Technical Risk: Vaccine has performed well in two clinical trials.
- Business Risk: One company has indicated willingness to file for FDA licensure.

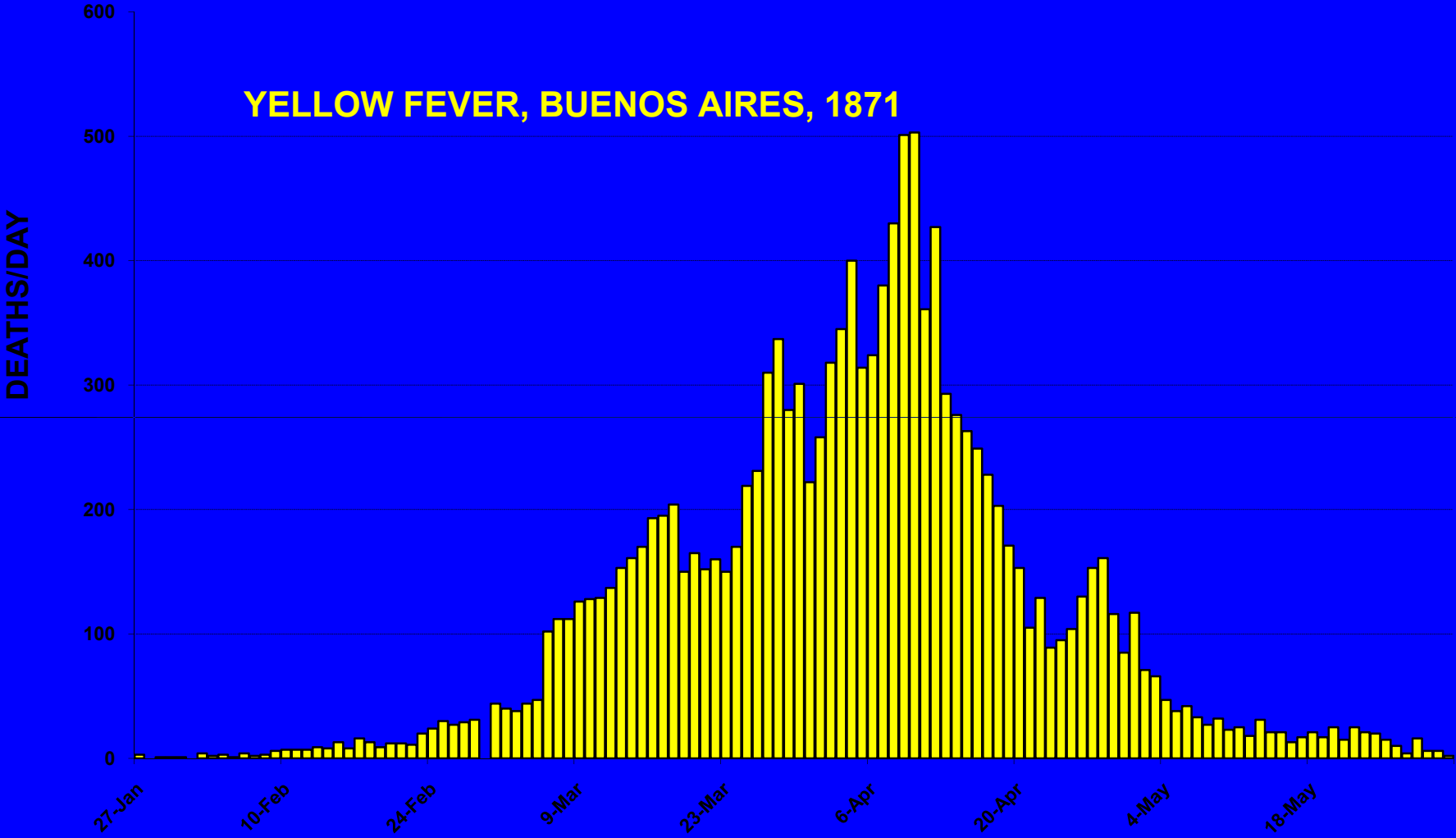
Yellow fever epidemic, 1793

With a population of approximately 55,000 in 1793, Philadelphia was America's largest city, its capital and its busiest port. The summer of that year was unusually dry and hot. The water levels of streams and wells were dangerously reduced, providing an excellent breeding ground for insects. By July the city's inhabitants were remarking on the extraordinary number of flies and mosquitoes that swarmed around the dock area. That same month, a trickle of refugees escaping political turmoil in the Caribbean Islands became a torrent of thousands as ship after ship unloaded its human cargo on Philadelphia's docks. Unbeknownst to the city's inhabitants, all the necessary ingredients for an unprecedented health disaster were now in place.

Philadelphia's ravenous mosquitoes provided the perfect vehicle for spreading the disease by first lurching on an infected victim and then biting a healthy one. The first fatalities appeared in July and the numbers grew steadily. Victims initially experienced pains in the head, back and limbs accompanied by a high fever. These symptoms would often disappear, leaving a false sense of security. Shortly, the disease would announce its return with an even more severe fever and turn the victim's skin a ghastly yellow while he vomited black clots of blood. Death soon followed as the victim slipped into a helpless stupor.

A good portion of the population, along with members of Congress, President Washington and his Cabinet, abandoned the city. The disease subsided and finally disappeared with the arrival of cold weather in November. It is estimated that 2,000 died.

YELLOW FEVER, BUENOS AIRES, 1871



Yellow Fever Disease

- A severe mosquito-borne hemorrhagic fever characterized by hepatitis, renal failure, bleeding and shock.
- Yf is endemic/epidemic in tropical South America and Africa, where up to 200,000 cases occur annually.
- High case fatality rate (20-50%) makes Yf one of the most dreaded infectious diseases. Four deaths occurred recently in unvaccinated tourists from the US and Europe.
- The etiologic agent is an ss-RNA virus of the Flaviviridae family that include dengue, WN, TBE, etc.
- There is an effective vaccine against Yf.

Yellow Fever Vaccine

- **Yf vaccine is a safe, effective prophylactic against yellow fever disease.**
- **Developed in 1936 by Theiler & Smith by attenuating in the wild-type Asibi strain in mouse and chick tissue.**
- **After SQ inoculation, neutralizing antibodies appear by Day 10, and immunity is probably lifelong, although revaccination is recommended every 10 years.**

Yellow Fever Vaccine

- **Adverse Reactions**

- Anaphylactic reactions 1/58,000
- Multisystem and neurologic adverse events was 2.42/100,000 doses (total # doses 1, 440,000).
- 6 fatal cases of fatal rxns reported to date
 - Encephalitis in a child in the US
 - 3 cases of multisystem failure in elderly persons in the US
 - 2 similar cases in a child and a young adult in Brazil
 - The Brazilian cases had a clinicopathological picture resembling wild-type YF and occurred during a campaign in which 34 million doses were given

Yellow Fever Vaccine

- **Adverse Reactions**

- Most AEs appear to be due to an abnormal response of the individual host rather than to mutation in the vaccine virus.
- Mild, transient subclinical elevations in serum transaminases occur in 3.5% of vaccinees in the recent Monath study.
- Recent analysis of VAERS database in the US found the incidence of severe (but not mild) AEs to be significantly higher in elderly compared with younger individuals. In the recent Monath study both were lower in the elderly.
 - Elderly more tolerant and less likely to complain?
 - Elderly have decreased innate immune response and cytokine-mediated syndrome

Vaccines for Rift Valley fever

- **Inactivated RVF vaccine**
 - IND vaccine in use at the USAMRIID for several decades.
 - Effective at preventing infection in laboratory workers and shown to be efficacious in preventing RVF virus infection in animal models.
 - Downside: Initial priming requires 4 doses over 6 months and vast majority of vaccinees require annual boosts.
 - An improved vaccine has been developed at the USAMRIID

RVF MP12, live, attenuated vaccine

- **Derived at USAMRIID in 1980s by 5-FU & serial plaque picking**
- **Protective in sheep, cattle, NHP**
- **Clinically tested in 81 subjects under IND**
- **Single injection**
- **No significant adverse events**
- **Potential human and animal vaccine.**

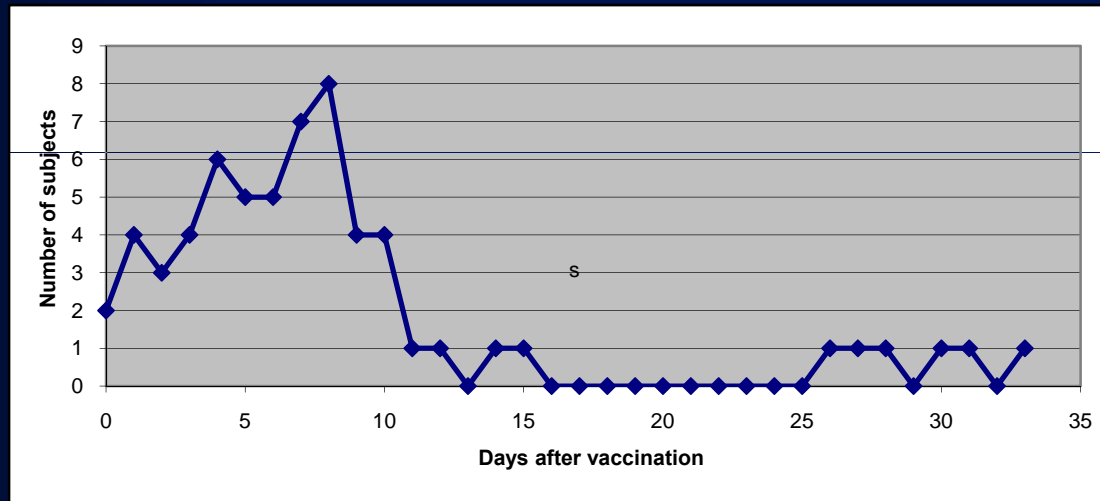
Transient exercise related elevated transaminases and CPK in a few subjects

Adverse Event Frequency \leq 30 Days

Symptom (Medical Term)	N	%
Headache	27	19
Fatigue	10	7.0
Fever	9	6.3
Flu-Like Symptoms	8	5.6
Muscle Pain	6	4.2
Nausea	5	3.5
Sore Throat	4	2.8
Diarrhea	4	2.8
Nasal Congestion	4	2.8
Clammy Skin (Hands)	2	1.4
Cough	2	1.4
Blurred Vision	2	1.4
Runny Nose	2	1.4
Lightheaded And Dizziness	2	1.4
Vomiting	2	1.4
Itching	2	1.4
Stuffy Nose	2	1.4
Feverish	2	1.4

Sign (Medical Term)	N	%
Tenderness	9	6.3
Redness	5	3.5
Induration	3	2.1
Bruise	2	1.4

Rift Valley Fever MP12



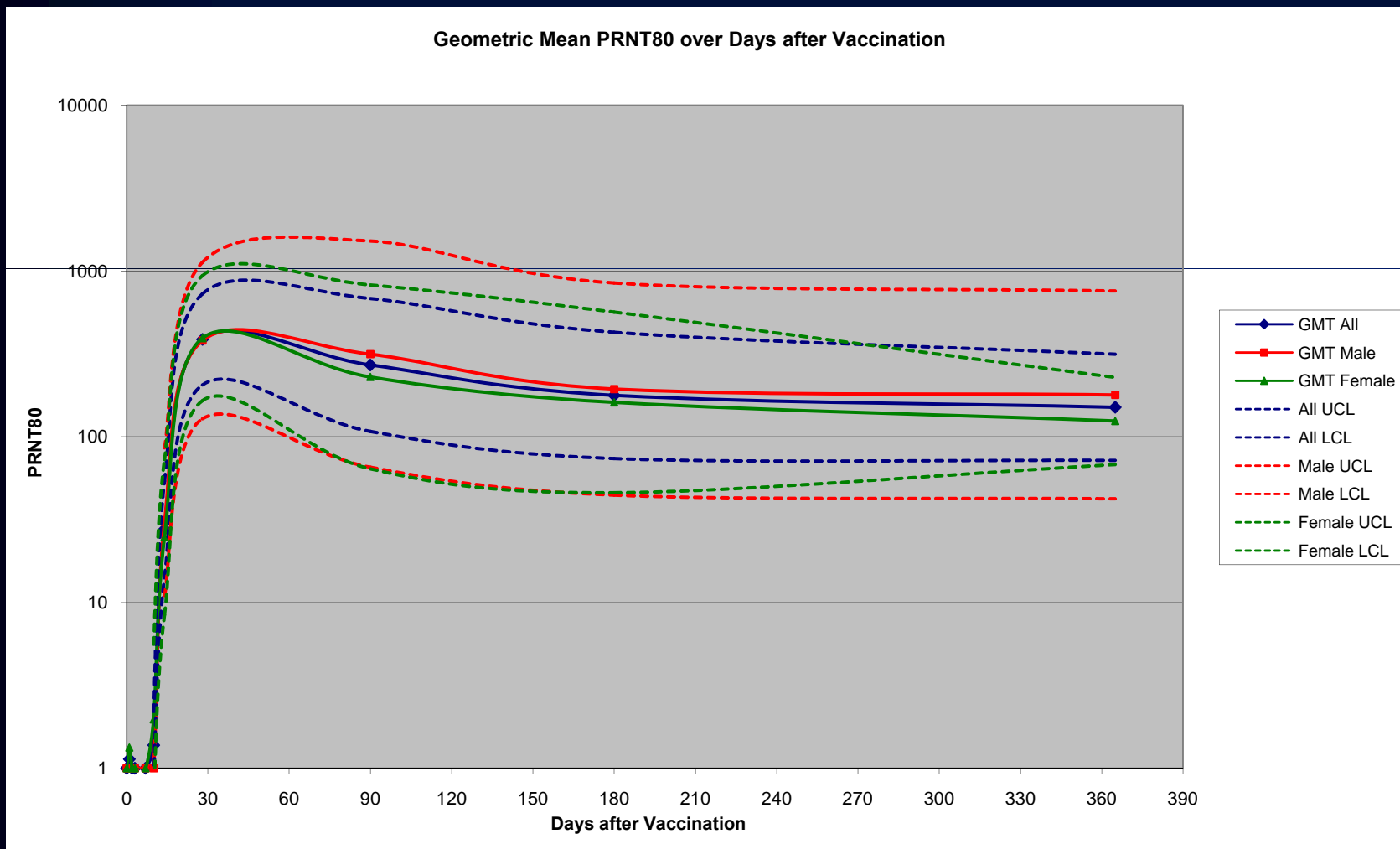
Seroconversion Rate

Seroconversion rate

- 18/19 (95%) had PRNT80 titer $\geq 1:40$ within 30 days after vaccination
- All 18 responders had a titer $\geq 1:40$ at 1 year
- In contrast, of 540 subjects vaccinated with the earlier inactivated vaccine, only 28/540 still had a PRNT80 $\geq 1:40$ at one year.

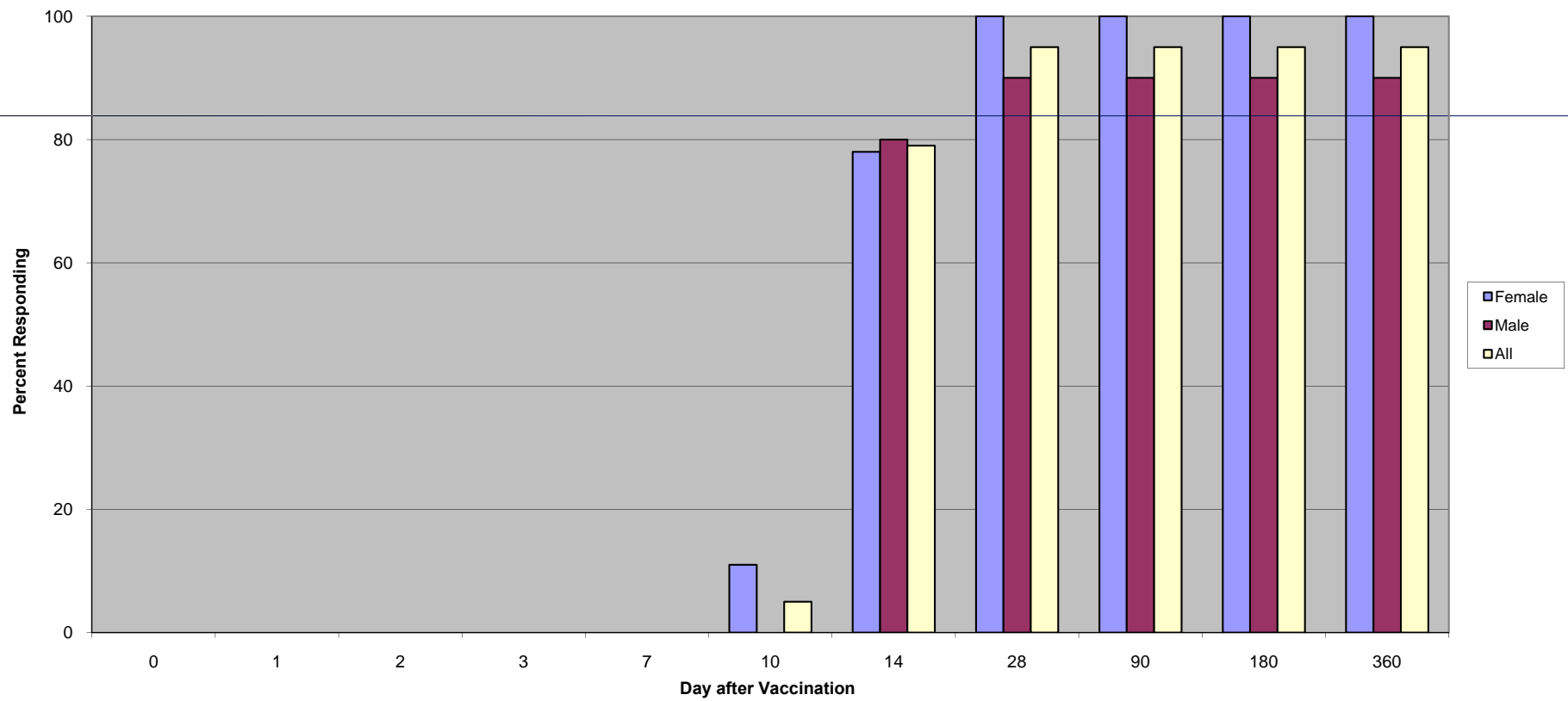
Distribution of mean neutralizing antibody levels for RVF MP12 vaccine over 1 year is shown on next slides.

RVF MP12 PRNT80



PRNT80 Response

Percentage of PRNT80 Responders over Time after Vaccination



SOME PROPERTIES OF MP-12

- **Nine coding mutations plus 23 other mutations; attenuating lesions in L and M viral RNA segments**
- **Attenuated for common laboratory rodent hosts**
- **Low neurovirulence in rhesus monkeys (Morrill, et al)**
- **Attenuated for sheep, cattle, lambs, hamsters, pregnant sheep and cattle, fetal calves (Morrill, et al)**
- **Safe for sheep fetus and provides colostral immunity after born. (One study claims teratogenicity for very early fetus)**
- **Does not revert in serial pass in lambs, mice (Morrill, et al)**

Stable Genetic and Phenotypic Attenuation

- **Passaged in vitro >30 times with only a few mutations but no reversion to parental genotype or increase in virulence in immature mouse model (poster)**
- **Virus recovered from human vaccinees has a few new mutations but no reversion to parental genotype and no increase in virulence for immature (19 day old mice, Morrill, et al) (poster)**
- **Level of viremia in humans, sheep, cattle, mice, and hamsters low and insufficient to infect mosquitoes**
- **Artificially infected mosquitoes can transmit but no reversion in highly sensitive recipient host (Turell, et al)**

FUTURE OF MP-12

- **NIAID has funded for developmental studies, safety studies, production of a new lot of human vaccine and new FDA filing**
- **Estimated 2-3 years until available for widespread testing (could be sooner if US Army chooses to release limited amounts of previous lot of MP-12 to selected high risk populations)**
- **Pfizer Animal Health is producing MP-12 for veterinary use. Will be licensed in USA and for sale generally. (Price, amounts, etc?)**
- **Deletions, insertions being explored with reverse genetics (poster)**

Preventing Epidemics by Human Vaccination

DISCUSSION