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Yellow Fever: 100 Years of Discovery

SUMMARY OF THE ORIGINAL ARTICLE

The Etiology of Yellow Fever: An Additional Note

Walter Reed, MD, Jas. Carroll, MD,
and Aristides Agramonte, MD

JAMA. 1901;36(8):431-440

The article describes a series of experiments conducted to explore how yellow fever is propagated from individual to individual and how the contagium is spread within households. The study was conducted in an experimental sanitary station in Cuba, where exposures and movements could be completely controlled. During the investigation, 12 nonimmune persons underwent different exposures, including mosquitoes that had fed on yellow fever patients, blood from infected patients, and fomites belonging to infected patients.

The study provided the following observations: (1) *Aedes aegypti* mosquitoes transferred the disease from an infected individual to a nonimmune person; (2) at least 12 days were needed for the extrinsic incubation period in the mosquito before it could transmit the infection; (3) yellow fever can be transferred to a nonimmune person from the blood of an infected individual taken during the first 2 days of the illness; (4) a filterable agent was responsible for infection; (5) the incubation period for humans ranged between 2 and 6 days; and (6) yellow fever cannot be transmitted by fomites nor spread in a house without the presence of mosquitoes. The most significant conclusion was that the "spread of yellow fever can be most effectually controlled by measures directed to the destruction of mosquitoes."

See www.jama.com for full text of the original *JAMA* article.

Commentary by J. Erin Staples, MD, PhD,
and Thomas P. Monath, MD

YELLOW FEVER HAS LONG BEEN ONE OF THE MOST LETHAL and feared diseases. Prior to 1900, the etiology and mode of transmission of yellow fever were enigmatic. The first experiments that unlocked these mysteries were performed by Walter Reed and his colleagues at the turn of the last century.¹ Here we briefly review the major discoveries in the field of yellow fever research over the last 100 years and reflect on important gaps remaining.

Yellow fever virus originated in Africa and was brought to the western hemisphere during the slave trade era, with the first epidemic reported in 1648 in the Yucatan.² Over the ensuing 200 years, outbreaks occurred widely in tropical America, the North American coastal cities, and Europe.³ By the 19th century, it was recognized that yellow fever was not communicable person-to-person, but theories wrongly attributed the disease to atmospheric miasmata. In 1881, Carlos Finlay of Cuba significantly advanced the field when he suggested *Culex cubensis* (now known as *Aedes aegypti*) as the mosquito responsible for spreading the disease.⁴ Despite multiple attempts, he was not able to prove his theory but it would serve as the basis for Reed's research.

At the end of the 19th century, the United States invaded Cuba during its war with Spain. For every soldier who died in battle, 13 died of yellow fever.⁴ Surgeon General George Sternberg sent Walter Reed, Aristides Agramonte, James Carroll, and Jesse Lazear to Cuba to investigate the cause of yellow fever. Reed's work proved that *Aedes aegypti* mosquitoes were the primary mode of transmission for the disease and that yellow fever was caused by a filterable agent found in the blood of infected patients.¹

Reed's work led General William Gorgas to institute a campaign in Havana against the urban mosquito vector, eliminating the disease in 1902.³ He accomplished the same task 4 years later in Panama, which allowed the canal to be completed. By 1918, the Rockefeller Foundation formed a Yellow Fever Commission with the ultimate goal of eradicating yellow fever through the elimination of *Aedes aegypti*.³ While these early activities were initially successful against urban (*Aedes aegypti*-borne) yellow fever, the goal of eradication was dispelled with the discovery that yellow fever was

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a zoonosis, maintained by sylvatic mosquito species and non-human primates in the Amazon jungle.⁵

It took more than a quarter of a century after Reed's observation that yellow fever was caused by a filterable agent before the isolation of the causative virus. In 1927, Adrian Stokes isolated the virus from a sick man in Ghana known as Asibi.³ In 1930, Max Theiler was able to identify a more convenient animal model by demonstrating that mice were susceptible to intracerebral inoculation of the virus.³ This led to the development of a test for neutralizing antibodies that was widely deployed for epidemiological and diagnostic studies.

Theiler and colleagues passaged the Asibi virus more than 200 times in cell cultures. Testing of this subculture, designated 17D, revealed that the virus had become attenuated but could still induce a protective immune response in monkeys and humans.³ The 17D strain would serve as the basis of the vaccine still in use today and is responsible for saving untold numbers of lives. For this work, Theiler was awarded the Nobel Prize in 1951. At about the same time a second live attenuated vaccine was developed from a different strain isolated in Dakar in 1927. This virus was attenuated by serial passages in mouse brain yielding the French neurotropic vaccine (FNV). This vaccine was widely used through the 1960s in francophone Africa, leading to the virtual disappearance of the disease.⁶

These early discoveries served as the foundation of subsequent investigations of yellow fever over the ensuing decades. Advances were made in the epidemiology, ecology, diagnostics, etiology, and prevention of yellow fever. The test for neutralizing antibodies developed by Theiler allowed for the delineation of the geographic boundaries of virus transmission. Tropical regions of both Africa and the Americas were found to have endemic virus transmission, but yellow fever was notably absent from Asia.

Ecologic assessments in Africa identified additional sylvatic mosquitoes capable of transmitting the disease.^{7,8} Vertical transmission of the virus in mosquitoes, first reported in 1905, was confirmed in the 1970s, explaining the long-term persistence of the virus in nature.⁸ Considerable field research efforts failed to uncover a role for animals other than nonhuman primates in the circulation of yellow fever virus.³

By 1960, hemagglutination-inhibition and complement fixation tests were available, simplifying the detection of antibodies to yellow fever virus.⁹ These tests also revealed that yellow fever virus was antigenically related to other group B arboviruses (now called Flaviviruses, named after the prototype yellow fever virus, *flavus* meaning yellow in Latin). In the 1970s, viral detection was improved with the development of insect cell cultures and inoculation techniques for mosquitoes. Eventually enzyme-linked immunosorbent assay and reverse transcription-polymerase chain reaction were developed, which further simplified and improved antibody and viral detection.¹⁰ Serological studies

in the late 1980s revealed that only 1 of 7 people infected with yellow fever virus became ill.¹⁰ Understanding of the virus and the molecular basis of virulence was advanced by the sequencing of the vaccine virus and the parent Asibi strain by Charles Rice and colleagues.¹¹

Starting in the 1940s, mass campaigns had been conducted using 17D vaccine in South America and vaccination with FNV was made compulsory in francophone Africa.⁶ In the 1950s and 1960s, concerns were raised regarding the high rate of postvaccinal encephalitis following the use of FNV in children, and the vaccine was abandoned in 1982.¹⁰ Compared with FNV, neurological adverse events with 17D appeared to be rare and confined almost entirely to very young infants, leading to a recommendation for restricted use in children younger than 9 months of age. Various investigations of 17D vaccine showed the immunity following a single dose of the vaccine to be extraordinarily durable, probably lifelong, making it one of the most efficient and effective vaccines.¹⁰ In the 1990s, 17D vaccine was successfully harnessed as a live vector for genes of other flaviviruses, leading to a slate of new vaccines in advanced clinical development, including vaccines to prevent dengue, Japanese encephalitis, and West Nile disease.¹²

The 1950s saw an unprecedented expansion of yellow fever activity in the Americas, with cases in Panama for the first time in 43 years. Before the end of the decade, the disease had spread throughout Central America, finally stopping near the border of Guatemala and Mexico.⁶ In the 1960s, epidemics occurred in both Africa and the Americas, causing thousands of cases in West Africa where vaccine coverage had waned or was absent, and in Ethiopia where the disease had not previously been reported. In the late 1980s, another major expansion of yellow fever activity occurred in Africa and there were an estimated 120 000 cases and 24 000 deaths in Nigeria alone.⁶ Ecological surveillance of sylvatic mosquitoes and monkeys revealed that these expansions had their origins in an amplification of the enzootic transmission cycle, but from a public health perspective the fundamental problem was poor or nonexistent coverage with an available, inexpensive, and cost-effective vaccine.

Since 1988, the World Health Organization (WHO) and the Pan American Health Organization have promoted the use of yellow fever vaccine in routine childhood immunization programs. While this approach will help curb the number of susceptible persons over time, it will result in a large proportion of the at-risk population not being covered in the short-term. To address this issue, WHO has received funding support from the Global Alliance for Vaccines and Immunization to perform preventive catch-up campaigns in the 12 West African countries most at risk for the disease.¹³ Vaccine coverage rates are high in South America and a few African countries, and are increasing in many others.

A different threat arises from the fact that countries in South America contain regions in which jungle yellow fe-

ver occurs and other regions (along the coast) where yellow fever is nonendemic. Vaccination is practiced in the endemic but not in the coastal zones. Prior to the 1970s, the urban mosquito vector (*Aedes aegypti*) had been eradicated from South America, freeing these coastal regions from the threat of introduction and spread of yellow fever from the jungle to the urban transmission cycle. However, with the senescence of mosquito control and the huge expansion of cities along the coast, these regions are increasingly at risk. The ease of international travel also makes the introduction and spread of yellow fever into new areas infested with competent *Aedes* vectors possible, theoretically placing parts of Asia, Australia, Europe, and North America at risk.¹⁴ While outbreaks in many developed areas are likely to be identified and controlled quickly, they would significantly impact public health infrastructure and the medical system as well as tax the limited supply of 17D vaccine.

A major gap in the knowledge about yellow fever is how to manage and treat patients with this disease and with serious vaccine-associated adverse events. Treatment of yellow fever by supportive care is essentially ineffective, and improvements in intensive care have not changed the 50% lethality rate. Efforts to develop antiviral drugs for other flavivirus diseases, such as hepatitis C and dengue, should be expanded to include yellow fever. Rapid, point-of-care diagnostic tests not yet developed will be critical when an antiviral is available. In addition, current serologic tests are unable to differentiate between cross-reactive flaviviral antibodies, thus limiting the utility of the tests to definitively diagnose the disease.

The complex interactions between yellow fever virus, cellular factors that control replication, and the innate and adaptive immune systems are poorly understood. Current work by basic immunologists is focusing on some of these factors, which may be key to understanding why only 1 of 7 people become ill after natural infection and why 1 in 200 000 people develop life-threatening viscerotropic adverse events to 17D vaccine that resemble wild-type yellow fever disease.¹⁰ Just recently, a cluster of viscerotropic adverse event cases occurred in Peru at a previously unprecedented incidence. Despite an intensive investigation, however, the cause remains elusive.¹⁵

Many questions remain about yellow fever disease, the etiological agent, and even about its natural transmission

cycle. The threat of urban outbreaks and long-distance introductions is increasing. It is not understood why upswings in enzootic transmission occur and yet virtually no field research is currently being performed in this area. The 17D vaccine has been associated only recently with fatal adverse events, the pathogenesis of which are poorly known and improvements to the vaccine's safety will be required. There are no specific drugs to treat the disease or severe reactions to the vaccine. While a significant amount has been learned in the last 100 years, clearly there is still much more to be discovered about yellow fever.

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