



Aerial View of Memphis in 1870.

From the Library of Congress (<https://www.loc.gov/resource/g3964m.pm009010/>).

the Great Chicago Fire of 1871, the 1889 Johnstown Flood, and the 1906 San Francisco earthquake. In their 2005 book *Yellow Jack*, J.R. Pierce and J. Writer noted, “There is not a single disease today that can terrorize a community the way yellow fever did. . . . Americans living in seaport cities came to dread the approaching summer. This seasonal anxiety lasted over a hundred years.”

The last major U.S. yellow fever epidemic occurred in New Orleans in 1905 (with an estimated 5000 cases and 1000 deaths), but there are renewed fears that yellow fever could return to the southern United States, especially in Gulf Coast cities, such as Galveston, Corpus Christi, and Houston, Texas; Mobile, Alabama; New Orleans; and Tampa. Such an epidemic could take a greater toll than most modern outbreaks of infectious disease in the United States.

There are new reasons to be concerned about a potential reemergence. First, as noted above, outbreaks in humans of viral infections caused by aedes mosquitoes have already begun to occur in Florida and Texas. Although

these have generally been small, their mere presence, together with new predictions of increases in aedes habitats throughout the South, attributable to climate change and urbanization, suggests that suitable conditions for future epidemics will become prevalent.

In addition, the areas in the Western Hemisphere that are at risk for yellow fever have expanded over the past two decades and now include both Venezuela, where the disease reemerged in 2019, and Brazil’s highly urbanized coastal regions. From late 2016 to 2019, Brazil experienced an epidemic nearly three times the size of any recorded in the previous 36 years, affecting its three most populous states, Minas Gerais, Rio de Janeiro, and São Paulo.³ The Brazilian outbreak paralleled a resurgence of yellow fever in Central and West Africa, including Angola, the Democratic Republic of Congo, and Nigeria. A major concern in Brazil was that the epidemic affected areas distant from the Amazon rainforest where sylvatic or “jungle” yellow fever had historically occurred, and where the virus is


transmitted by nonurbanized mosquitoes not belonging to the aedes genus (haemagogus or sabethes). Although there was no evidence that urbanized *Ae. aegypti* mosquitoes were transmitting yellow fever — the culprit was most likely haemagogus species — the fact that the epidemic occurred far from traditional sylvatic areas could mean that spillovers to urban areas are not far off.³ Another troubling matter is that the virus may have been introduced in Minas Gerais in 2014 and gone unnoticed for 2 years before it accelerated and spread across southeastern Brazil.

Still another reason for concern about reemergence is the role of climate change and the climate oscillations caused by El Niño. The 1878 yellow fever epidemic in the U.S. Mississippi Valley occurred during an El Niño event that began the previous year.⁴ That event created warmer and wetter conditions in the U.S. South, which may have enhanced the survival of *Ae. aegypti* mosquitoes and accelerated virus development and replication in mosquito hosts. A warming climate promotes *Ae. aegypti*-vectored arboviral diseases.⁵ With North America facing record-high temperatures and moisture and accelerated warming of its surrounding waters just ahead of an expected El Niño event, the United States could face similar conditions.

In the 1990s, the Global Program for Vaccines and Immunization and the Regional Office for Africa of the World Health Organization (WHO) expressed concerns about the return of yellow fever outbreaks in the southeastern United States and elsewhere. The combination of regular aedes-associated arbovirus outbreaks in Florida and Texas, an expanding yellow fever risk map

in the Western Hemisphere, and the potential for El Niño to exacerbate the impact of climate change and urbanization should give us pause.

Our ability to respond is unclear. When Zika virus infection emerged in the continental United States in 2016, we learned that mosquito-control capabilities varied considerably among counties in Florida and Texas; this problem has not been corrected. Local dengue transmission has occurred repeatedly in southern states, and dengue is likely to become endemic in the South, highlighting a crucial need for further development and rollout of dengue vaccines. Unfortunately, we have faced a dramatic increase in anti-

 An audio interview with Peter Hotez is available at NEJM.org

vaccine activism during the Covid-19 pandemic that could extend to yellow fever and other critical arboviral immunizations. An effective, albeit expensive, yellow fever vaccine exists, but it's a live-virus vaccine and can have serious, if rare, side effects. Currently, the U.S. population is nearly entirely unvaccinated against yellow fever, and there are no vaccine doses in the U.S. Strategic National Stockpile.

During a sizable epidemic, yellow fever could tear quickly through unimmunized populations across the American South, and it is unlikely that the U.S. government would be prepared to acquire and distribute vaccines in a timely manner, even if there were public demand. In Brazil, fractional dosing of yellow fever vaccines has been used to extend vaccine reach and quickly amplify herd immunity, a strategy approved by the WHO for emergency situations.

Ultimately, we need a comprehensive plan for better coordinating mosquito surveillance and control among counties at risk, with steps for rapidly vaccinating the population (possibly including using fractional dosing if the vaccine is not available in sufficient quantities), along with enhanced vector-control efforts and the possible introduction of innovative vector-control technologies, such as wolbachia or gene delivery, which has the potential to reduce mosquito density and virus infectivity rates (vector competence). We believe yellow fever should be prioritized as part of our national pandemic-preparedness efforts, given that the con-

ditions are now in place for yellow jack to return and sicken many people in southern U.S. cities.

Disclosure forms provided by the authors are available at NEJM.org.

From the Departments of Pediatrics and Molecular Virology and Microbiology, National School of Tropical Medicine, Baylor College of Medicine, Houston (P.J.H.); and the Department of Pediatrics, Stanford University School of Medicine, Stanford, CA (A.D.L.).

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Wedding Websites, Free Speech, and Adverse Drug Effects

Jerry Avorn, M.D.

In its June 2023 decision in *303 Creative L.L.C. v. Elenis*,¹ the U.S. Supreme Court upheld the right of a wedding website designer to refuse to provide services for a same-sex marriage. In its 6-to-3 decision, the Court ruled that the designer's First Amendment rights would be violated by a requirement that she provide such services, since that would represent a form of "compelled speech." This decision could well legiti-

mize denials of services to people who are members of sexual or gender minority groups and potentially to many other marginalized groups. But the principles underlying it could also have surprisingly far-reaching implications, possibly affecting the ability of physicians and patients to learn about the side effects of the drugs we use.

The *303 Creative* case was obviously not about medicine, and

some observers believe it relates only to protecting a company's right to avoid compelled "expressive speech." But it is the latest of several decisions that trace a potentially ominous trend eroding the regulation of corporate statements. The argument is sometimes linked to religious liberty, as was the case in a 2018 Supreme Court decision, *National Institute of Family and Life Advocates v. Becerra*.² There, an antiabortion group suc-