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A Yellow Fever Epidemic: A New Global Health Emergency?

Lawrence O. Gostin

Georgetown University Law Center, gostin@law.georgetown.edu

Daniel Lucey

Georgetown University, drl23@georgetown.edu


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VIEWPOINT

A Yellow Fever Epidemic A New Global Health Emergency?

Daniel Lucey, MD, MPH
O'Neill Institute
for National and
Global Health Law,
Georgetown University
Law Center,
Washington, DC.

Lawrence O. Gostin, JD
O'Neill Institute
for National and
Global Health Law,
Georgetown University
Law Center,
Washington, DC.

The worst yellow fever epidemic in Angola since 1986 is rapidly spreading, including the capital, Luanda. In Angola, the epidemic began in December 2015 and the laboratory-confirmed outbreak was reported to the World Health Organization (WHO) on January 21, 2016.¹ Angola has had 2023 suspected cases and 258 deaths as of April 26, 2016.¹ China, the Democratic Republic of Congo, and Kenya also have reported cases arising from infected travelers from Angola. Namibia and Zambia also share a long border with Angola, with considerable population movement between the countries. Similar to other recent epidemics, quick and effective action to stop the spread of yellow fever is the responsibility of the world's health community.

More than 7 million Angolans have been vaccinated, but supply shortages could potentially lead to a health security crisis if yellow fever spreads within Africa, Asia (which has never experienced a yellow fever epidemic), or the Americas (where *Aedes* mosquito vectors transmit yellow fever as well as Zika, dengue, and chikungunya). The Pan American Health Organization declared an epidemiological alert on April 22, 2016, for yellow fever in Latin America.² The WHO should urgently convene an emergency committee to mobilize funds, coordinate an international response, and spearhead a surge in vaccine production. Prior

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delays by the WHO in convening emergency committees for the Ebola virus, and possibly the ongoing Zika epidemic, cost lives and should not be repeated.³ Acting proactively to address the evolving yellow fever epidemic is imperative.

Epidemiology and Diagnosis of Yellow Fever

The yellow fever virus is an arbovirus that belongs to the flavivirus genus (like Zika, dengue, and West Nile). (Yellow refers to jaundice caused by liver involvement.) The virus is transmitted between humans and from monkeys to humans by mosquitoes, primarily by *Aedes (aegypti)* and *Hemogogus*, in 1 of 3 cycles: (1) urban yellow fever, (2) jungle (sylvatic) yellow fever, and (3) intermediate yellow fever. More than 500 million individuals are at risk in Africa, as are approximately 400 million individuals in Latin America.⁴ Historically, well-described outbreaks occurred in the United States (eg, in 1793 in Philadelphia, Pennsylvania; in 1878 in

Memphis, Tennessee; and in 1905 in New Orleans, Louisiana) and in Europe in 1730 and 1821.

After an incubation period of 3 to 6 days, an acute febrile phase occurs with myalgia, headache, back pain, anorexia, nausea, and sometimes vomiting; symptoms typically resolve within 1 week. In approximately 1 in 7 individuals, a second phase quickly follows with high fever, jaundice, bleeding, and kidney damage, with death occurring in 50% of patients; most of the remaining half fully recover.⁴ Each year, yellow fever causes an estimated 30 000 deaths, mostly in Africa.⁴

Even with knowledge of the typical clinical manifestations and outbreak epidemiology, clinical diagnosis can be difficult because yellow fever can mimic multiple febrile illnesses, including those causing jaundice and bleeding (such as acute viral hepatitis and viral hemorrhagic fevers). Laboratory diagnostic tests can detect the virus and specific antibodies in the blood. No specific antiviral drug or immune therapy exists for yellow fever disease.

The Yellow Fever Vaccine

A licensed, live attenuated, yellow fever vaccine has been available for decades, conferring lifelong protection within 10 days in more than 90% of individuals who received the vaccine.⁴ National border rules currently require a yellow fever card showing proof of vaccination within 10 years for epidemiologically at-risk travelers. Although the yellow fever vaccine is well tolerated, it is not recommended in nonepidemic settings for individuals with severe immunodeficiency, pregnant women, infants, or individuals with severe egg allergies. Individuals older than 60 years are at higher risk for a rare, but serious complication, vaccine-associated viscerotropic disease. The WHO recommends routine vaccination for children living in at-risk countries for yellow fever, with community immunity conferred by vaccination rates of 60% to 80%.⁴

Mass vaccination campaigns in conjunction with mosquito control, surveillance, and coordinated responses are urgently needed in the event of an outbreak. The WHO serves as the Secretariat for the International Coordinating Group for yellow fever vaccine provision, with partners such as the United Nations (UN) Children's Fund, the International Federation of Red Cross and Red Crescent Societies, and Doctors Without Borders (Médecins Sans Frontières).⁴ The International Coordinating Group maintains a vaccine stockpile for rapid response; however, a serious vaccine shortage is anticipated if yellow fever spreads to other countries or regions. Surge capacity is currently limited

Corresponding Author: Lawrence O. Gostin, JD, O'Neill Institute for National and Global Health Law, Georgetown University Law Center, 600 New Jersey Ave NW, Washington, DC 20001 (gostin@law.georgetown.edu).

because specific pathogen-free chicken eggs are needed to produce the vaccine.

On May 2, 2016, the Democratic Republic of Congo announced plans to vaccinate nearly 2 million individuals in Kinshasa and Kongo Central, suspecting local transmission.⁵ This campaign, along with Angola, could be a tipping point in exhausting global vaccine supplies.

The WHO's Emergency Use Assessment and Listing (EUAL) procedures, first introduced for the Ebola virus,⁶ could be adapted to safeguard the yellow fever vaccine supply. International experts have urged using one-fifth of the normal vaccine dose in Angola to avert acute shortages if the virus spreads.⁷ If this suggested practice is carried out, regulatory hurdles would likely be encountered, and there would also be uncertainty regarding the extent and duration of immunity, especially in children. Monath et al⁷ recently recommended "invoking the EUAL [procedures] now, rather than waiting for a major yellow fever vaccine shortage to occur." Stewardship of scarce vaccine supplies is essential, but requires the WHO's director-general to declare a public health emergency of international concern or determine it is "in the best interest of public health."⁶ Given the world's vital health security interests, the WHO's director-general should use EUAL procedures to authorize a reduced vaccine dose to control the epidemic in Angola.

Time to Convene an Emergency Committee

It is only by convening an emergency committee that the WHO's director-general could declare a public health emergency of international concern. Whether this emergency committee recommends declaring a public health emergency of international concern, it would advise the WHO's director-general on responding to ongoing and future yellow fever outbreaks. There are strong reasons to convene an emergency committee now. The looming threat of a severe yellow fever vaccine shortage exists amid epidemics in Africa, and potentially in Latin America and Asia. Even if the emergency committee does not recommend a public health emergency of international concern, it could recommend invoking EUAL procedures for use of a reduced vaccine dose.

Among multiple needed steps, the WHO's director-general (based on the emergency committee's advice) should convene and coordinate stakeholder meetings with yellow fever vaccine manufacturers to catalyze a surge in production; incentivize and coordi-

nate innovation in research and development for non-egg-based yellow fever vaccines; coordinate mosquito vector control for yellow fever, benefitting also prevention measures for the ongoing Zika virus epidemic. Recommendations are already in place to prevent infections by vaccinating travelers to Angola. Convening a yellow fever emergency committee would not require a declaration of a public health emergency of international concern, as demonstrated by 10 Middle East respiratory syndrome committees convened between 2013 and 2015, in which a global health emergency was not declared.

Going Forward: A Standing Emergency Committee

The WHO has responded much more quickly to this yellow fever epidemic than with either the Ebola virus or even the Zika virus. The WHO's director-general traveled to Angola in early April, working with international partners to roll out a mass yellow fever vaccination campaign—expressing the concern that "the whole world could be at risk" of a yellow fever epidemic. Global health advocates should not have to call for convening an emergency committee for each new international health threat. Instead, the WHO should establish a standing emergency committee⁸ to meet regularly to advise the director-general whether to declare an emergency, take necessary steps to avert a crisis, or both. The complexities and apparent increased frequency of emerging infectious disease threats, and the catastrophic consequences of delays in the international response, make it no longer tenable to place the sole responsibility and authority with the WHO's director-general to convene currently ad hoc emergency committees. As the WHO begins the election campaign for a new director-general, it is an opportune moment to strengthen its capacity and leadership in global health security.

The UN's high-level panel on the global health crises called Ebola a "preventable tragedy." If the ongoing panepidemics of Zika-caused neurological syndromes or yellow fever eventually lead to catastrophic consequences, then the panel's admonition could come true: "If the WHO does not successfully reform, the next major pandemic will cause thousands of otherwise preventable deaths. This may be the last opportunity to ensure that the WHO is empowered to build an effective emergency preparedness and response capacity with the necessary political leadership. Another failure to perform may necessitate consideration of alternate UN institutional response mechanisms."⁹

ARTICLE INFORMATION

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