Yellow fever, caused by yellow fever virus, is a mosquito-borne flavivirus disease; it is found in sub-Saharan Africa and tropical South America, where approximately 1 billion people in 46 countries are at risk for it. A live attenuated vaccine (strain 17D) was developed by Max Theiler and colleagues in the 1930s — work that earned Theiler a Nobel Prize. An excellent vaccine, it has been in use since 1937; more than 650 million doses have been distributed in the past 75 years, and 1 dose probably confers lifelong protective immunity. The disease, however, has not been conquered: there are still an estimated 180,000 cases and 78,000 resulting deaths every year.¹

In the past 6 months, we’ve seen a major resurgence of yellow fever disease that has proved difficult to control in multiple African countries. As a result, the World Health Organization (WHO) announced on May 19 that it had convened an emergency committee under the International Health Regulations to review the situation. That committee decided that the current epidemic is a “serious public health concern” but does not, unlike the current Zika virus epidemic, constitute a Public Health Emergency of International Concern.²

How did this situation arise? In December 2015, a yellow fever outbreak was identified in Angola. That outbreak continues, despite distribution of nearly 12 million doses of vaccine in the country, and as of May 20, 2016, a total of 2420 suspected cases, including 298 deaths, had been reported. Alarmingly, the cases are not limited to Angola: the virus has spread, by way of infected travelers from Angola, to the Democratic Republic of Congo (DRC), Kenya, and China, further demonstrating the difficulty of controlling infectious diseases in this era of unprecedented mobility. In addition, cases in Angola and the DRC are found in cities, which suggests that transmission may be occurring through an “urban yellow fever” cycle, in which the virus is transmitted between humans by means of the bite of *Aedes aegypti* mosquitoes, rather than the traditional “jungle yellow fever” cycle of monkey–mosquito–monkey transmission in which humans are incidental hosts. Further complicating the situation, there appears to be a separate outbreak in Uganda concurrent with the Angola-based outbreak.

The identification in China of 11 travelers who returned from Angola with yellow fever infection is also particularly troubling, since yellow fever has never been found in Asia even though laboratory
studies have demonstrated that Asian A. aegypti mosquitoes are vector-competent. The reason for the absence of yellow fever from Asia is unknown and has been a subject of much speculation. Although it is very worrisome that people are returning from Angola with yellow fever, it is somewhat reassuring that China manufactures 17D vaccine for the domestic market and would probably be able to control an outbreak. The importations, however, indicate that there are weaknesses in the current International Health Regulations, which require persons entering a region with potential for yellow fever outbreaks to provide evidence of immunization.

Given that we have a highly effective yellow fever vaccine that confers lifelong immunity with one dose, why is yellow fever still a problem? Much of the answer comes down to vaccine supply and demand.

The 17D vaccine is a “legacy” vaccine produced in embryonated chicken eggs using technology that has changed little since the 1940s, when the seed-lot system was introduced. Three 17D sub-strains (17D-204, 17DD, and 17D-213) are used as vaccines. They have minor differences in genome sequences, but all have proved to be excellent vaccines. Currently, there are only six manufacturers of yellow fever vaccine worldwide, and they collectively produce approximately 50 million to 100 million doses each year; four (Institut Pasteur, Senegal; Bio-Manguinhos/Fiocruz, Brazil; Chumakov Institute of Poliomyelitis and Viral Encephalitides, Russia; and Sanofi Pasteur, France) are “prequalified” by the WHO to distribute vaccine internationally and two (Sanofi Pasteur, United States; and Wuhan Institute of Biological Products, China) make vaccine for domestic markets. Thus, the number of producers and the manufacturing process limit the amount of vaccine available.

Furthermore, there is a requirement for a minimum amount of virus in a dose (10^3.0 IU) but no maximum amount per dose, and some manufacturers’ lots contain 10^6.5 IU per dose (over 1000 times the minimum). Although all vaccines have proved efficacious overall, the potency of the vaccines produced by the six manufacturers varies. Currently, approximately 6 million doses are kept in reserve for emergencies. That quantity is adequate for most years, but occasionally — now, for instance, or during the 2008 epidemic in South America — these reserves are insufficient to meet the demand from large outbreaks, particularly when they affect areas where yellow fever is not seen very often, as in Angola, which had gone decades without an urban outbreak.

Clearly, there is a need to increase the vaccine supply, but a number of approaches could improve the situation in the future. First, we can increase the reserve stockpile kept for emergencies. Second, regulators and the WHO could set a maximum for the amount of vaccine in a dose. Studies have shown that 3000 IU (1/50 of the quantity in a dose of at least one current vaccine) or less is sufficient to stimulate protective immunity. Consequently, vaccine bulk could be diluted in manufacturing freeze-dried vaccine, but studies would be needed to investigate the stability of diluted versus undiluted vaccine and the duration of protective immunity.

Relatedly, a dose-sparing approach has been suggested, in which a fraction of the current dose could be given to vaccinees once a vaccine vial had been opened. This approach would have to be evaluated carefully to ensure that vaccinees received the appropriate quantity of diluted vaccine. In addition, the vaccine is recommended for persons 9 months of age or older (6 months or older in epidemic situations), and studies would be needed to determine whether dose-sparing vaccination was equivalent in children and adults.

Similarly, some experts have suggested using intradermal immunization rather than the traditional intramuscular or subcutaneous route. Although that option seems promising, the limited studies that have been conducted included no comparison between intradermal and conventional subcutaneous immunization with the same dose of vaccine. Moreover, these studies have involved vaccine from only two of the six manufacturers.

A third approach is to shift manufacturing from embryonated chicken eggs to a continuous cell line. This possibility proved unsuccessful when it was investigated in the 1980s, but cell-culture technology has greatly improved in the past 30 years. Notably, Sanofi Pasteur manufactures its chimeric yellow fever 17D-dengue (Dengvaxia) and chimeric yellow fever 17D-Japanese encephalitis (Imojev) vaccines in monkey kidney Vero cells, which suggests that Vero cells could be used to manufacture 17D vaccine. Of course, the immunogenicity and safety profile of such a Vero-cell-derived vaccine would need to be compared with that of currently licensed egg-derived vaccines.

Finally, there have been no systematic studies investigating
the genome sequences of wild-type yellow fever virus strains from outbreaks to elucidate the evolution of the virus and help model the potential for outbreaks. There are 40 genomic sequences of wild-type yellow fever virus isolates in GenBank, of which 12 are from Brazil and 14 from Senegal, though the virus is currently found in 44 other countries. We still have much to learn about wild-type yellow fever virus.

In the short term, there will be difficulties in ensuring that sufficient vaccine is available to fight this major public health problem, but we have the opportunity to avoid vaccine shortfalls in the future. Toward that end, the WHO periodically reviews “Recommendations to Assure the Quality, Safety and Efficacy of Live Attenuated Yellow Fever Vaccines.” Now may be the time to revisit these requirements, which were last reviewed in 2010.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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