The global threat of the emerging epidemic of yellow fever in Angola is underscored by the recent spread of similar Aedes aegypti mosquito-borne viruses including dengue, chikungunya, and now Zika. Since their emergence in the 1950s, dengue virus infection has been reported from more than 128 countries, the chikungunya virus has been reported from over 60 countries,2,3 while yellow fever, first identified as a viral infection in 1900, has been reported from more than 57 countries and is on the move once again.4 Although outbreaks of chikungunya and dengue seem to have case fatality rates of less than 1%, yellow fever outbreaks have case fatality rates as high as 75% in hospitalised cases.5

There has been an effective yellow fever vaccine since the late 1930s, but in 1987 Nigeria had an urban outbreak because the Aedes vector is present and the population is unvaccinated.8 Should yellow fever outbreaks occur elsewhere in Africa, in Latin America, or in Asia, current global supplies of yellow fever vaccine will be inadequate. A blueprint for national yellow fever contingency plans in southeast Asia had been developed in 2011 at a WHO meeting in India.9

In 2000, when there was a global shortage of yellow fever vaccines for outbreak response, an International Coordinating Group (ICG)10—a partnership of WHO, UNICEF, Médecins Sans Frontières—and the International Federation of Red Cross and Crescent Societies—began procurement and stockpiling of yellow fever vaccine that is released to countries reporting yellow fever outbreaks based on agreed criteria for yellow fever vaccine release during outbreaks. The current global stockpile of yellow fever vaccine, however, may demand more attention. To date WHO, through the ICG, has provided 7·3 million doses of yellow fever vaccine to Angola (population about 23 million) and routine immunisation of children in those African countries that have included yellow fever vaccine in their routine childhood immunisation programmes has in some instances been suspended because of diversion of global stocks to Angola.

The global supply of immediately available yellow fever vaccine from all six of the world’s manufacturers is
Comment

Invoking the EUAL now, rather than waiting for a major yellow fever vaccine shortage to occur, and stronger surveillance and vector control, could potentially avoid the need to declare a Public Health Emergency of International Concern (PHEIC), and better ensure our global health security.

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about 5 million doses currently. The annual production is about 80 million doses per year, while the one manufacturer in China produces only 0·3 million doses per year, and the ability of all manufacturers to ramp up production is limited. Overall, supply falls short of demand nearly every year and this is accentuated during emergencies such as that in Angola. The Director-General of WHO recently visited Angola and promised 3 million more doses, but it could be that millions of additional doses will be needed as vaccine demand increases in Angola and in neighbouring countries. If outbreaks were to occur in densely populated areas of Asia, there could be a requirement for very large amounts of vaccine.

The yellow fever vaccine is a live, attenuated vaccine that replicates within the body and produces long-duration (probably lifelong) immunity. We suggest that the most expedient approach to increase yellow fever vaccine supply would be to use a lower dose of vaccine to immunise those at risk. Clinical trials have shown that a one-tenth dose of the vaccine is as effective as full dose vaccine in rapidly stimulating immunity.11,12 Consideration should therefore be given to using the existing formulation by subcutaneous injection of a dose reduced from 0·5 mL to 0·1 mL, expanding the supply by five-fold. The 0·1 mL volume can be accurately given by a 1 mL syringe13 and this strategy would increase the current vaccine stockpiles held globally and in Angola. There is not, however, regulatory acceptance of a dosage change. One important issue is stability and expiration dating, which is determined by virus titre in each of the vaccine manufacturers’ formulations. Another is whether long-term duration of immunity would be affected by the lower dose, although this is not an impediment to emergency use. A third issue is efficacy of the lower dose in children, which has not been determined by clinical testing. In some studies, yellow fever vaccine has been shown somewhat less effective in children than in adults.14

Even so, WHO could consider recommending the use of 0·1 mL of vaccine using the Emergency Use Assessment and Listing (EUAL) procedure,15 which was invoked to allow use of unlicensed products against Ebola during the recent crisis. At the same time, WHO should continue encouraging countries to enhance surveillance and intensify control activities against mosquito-borne viral infections in general.