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Editorial

Yellow Fever: A Neglected Disease and Time to Fractional Dosing Protective Vaccine?

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Yellow fever virus is an ribonucleic-acid (RNA) virus that belongs to the genus "*Flavivirus*". This virus is related to the Japanese encephalitis, St. Louis encephalitis, and West Nile viruses. It is transmitted to humans and mammalians primarily through the bites of infected *Aedes* or *Haemagogus* species mosquitoes. Primates or non-primates are infectious or viremic to mosquitoes shortly before the onset of fever and up to 5 days after the onset. This virus has three transmission cycles; urban, intermediate (savannah), and jungle (sylvatic). The urban cycle involves transmission of the virus between urban mosquitoes, primarily *Aedes aegypti* and humans. The majority of infected individuals have only mild illness or no illness. The incubation period is characteristically 3 - 6 days. The initial clinical presentations include sudden onset of fever, chills, back pain, severe headache, malaise, fatigue, weakness, nausea, and vomiting. Most of the patients improve after the initial clinical presentations. Approximately 15% of symptomatic cases progress to the development of a more severe form after a short remission of hours to a day, usually 48 hours after viremia that is characterized by high fever, bleeding (hematemesis, petechiae, ecchymoses, melana, etc.), jaundice, and finally multiple organ failure with shock.

Preliminary diagnosis is depended on vaccination status, patients' clinical presentations, travel history, including destination, activities, and time of year. Serologic assays to detect virus-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are some accomplished laboratory diagnostic methods. These methods can have serologic cross-reactions with other flaviviruses, such as dengue or West Nile viruses. So, positive results should be confirmed by a more specific methods, such as plaque-reduction neutralization test, etc. Yellow-fever-virus RNA in the serum can be detected by virus isolation or nucleic acid amplification testing, such as reverse-transcriptase-polymerase-chain reaction (RT-PCR) during the first 3 - 4 days of the illness. Nevertheless, the viral RNA is usually undetectable by the time overt symptoms are recognized. Thus, negative RT-PCR and virus isolation results cannot exclude the diagnosis of yellow fever. The diagnosis of yellow fever can be made by the immunohistochemical staining formalin-fixed material that detects the yellow fever virus antigen. No specific treatment for yellow fever are available. The patients should be protected from further mosquito exposure for up to 5 days after the onset of fever. Yellow fever patients should be hospitalized for supportive care and close observation.

The additional doses of yellow fever vaccine should be considered in HIV-infected individuals, travelers who received yellow fever vaccine at least 10 years previously and who will be in a higher-risk setting based on season, activities, location, and duration of their travel, laboratory staff who routinely handle wild-type yellow fever virus, individuals who received a hematopoietic stem cell transplant following their last dose of yellow fever vaccine, and woman who were pregnant when first vaccinated. Precautions to yellow fever vaccination include asymptomatic HIV infection and CD4+ T-lymphocyte count 200 - 499 cells/mm^3 (15 - 24% of total in children aged < 6 years), aged 6 - 8 months, and more than 60 years. Contraindications to yellow fever vaccination include aged < 6 months, symptomatic HIV infection or CD4+ T-lymphocyte count < 200 cells/mm^3 (< 15 % of total in children aged < 6 years), malignant tumors, organ transplantation, primary immunodeficiencies, immunosuppressive and immunomodulatory therapies, thymus disorder associated with abnormal immune function, and allergy to a vaccine component. It is clear that there is a need to increase the yellow fever vaccine. The

World Health Organization and the regulators can set a maximum for the amount of vaccine in a dose to stimulate protective immunity. A dose-sparing approach has been recommended, in which a fraction of the current dose could be administered to vaccines, once a vaccine vial had been opened. Nevertheless, this approach should have to be evaluated carefully to ensure that the vaccines received the suitable quantity of diluted vaccine. A recent study in Angola demonstrated that the fractional dosing of the yellow fever vaccine could provide the largest reduction in infection attack rate if the efficacy of 5-fold fractional-dose vaccines exceeded 20%. In the near-future, we have the opportunity to avoid vaccine shortages in the future and now it is time to revise the "Recommendations to Assure the Quality, Safety and Efficacy of Live Attenuated Yellow Fever Vaccines" that were last reviewed seven years ago.

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