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**A SINGLE SHOT OF 17D VACCINE IS NOT ENOUGH TO PROTECT FOR
LIFETIME AGAINST YELLOW FEVER**

Pedro F. C. Vasconcelos – Director of the Instituto Evandro Chagas, MoH, Ananindeua, Brazil

E-mail: pedrovasconcelos@iec.pa.gov.br

Running title: Two doses of yellow fever vaccine for full protection

Abstract

Yellow fever vaccine is used since the 1930's to prevent yellow fever a severe infectious disease caused by yellow fever virus (YFV) mainly transmitted by Culicidae mosquitoes of the genera *Aedes* and *Haemagogus*. Until 2013, the World Health Organization (WHO) recommended a vaccine dose each ten years. This was changed and a new recommendation of a single shot for life protection against YFV infection was established. Recent evidences published elsewhere suggest that at least a second dose is needed to fully protection against yellow fever disease. In this work we discuss the feasibility of one or two doses, the necessity of a new and modern vaccine and ask for a WHO meeting to a new recommendation on YFV vaccination for people living in or travelling to the endemic areas.

Yellow fever is an infectious disease endemic in sub-Saharan Africa and tropical South America transmitted by Culicidae mosquitoes of the genera *Aedes*, *Haemagogus* and *Sabethes*. *Aedes aegypti* is the urban vector and associated with large epidemics in the past in both sides of the Atlantic Ocean, while sylvatic vectors are different; in Africa many species of *Aedes* are incriminated as jungle vectors including *Ae. africanus*, *Ae. sympsoni*, etc. (WHO, 1985); in South America the species *Haemagogus janthinomys* in northern and central regions and *Hg. leucocelaenus* in Southern Cone are the main vectors, and many *Sabethes* species are secondary vectors (Monath & Vasconcelos, 2015; Vasconcelos & Monath, 2016).

Yellow fever is a severe disease with high case fatality rate (CFR) especially in South America where in general CFR reaches 50% of reported cases, but it ranges from 30% to 80% (Monath & Vasconcelos, 2015). Historically, the urban cycle was responsible for the most severe epidemics observed in the both endemic regions in previous centuries (WHO, 1985).

The development and use of the 17D vaccine virus since the 1930's (Theiler & Smith, 1937) dramatically reduced the incidence of yellow fever, and in the New World stopped transmission in urban settings. For decades the World Health Organization (WHO) recommended vaccination every ten years for all people, including travelers and people living in endemic areas (WHO, 1985; WHO, 2008; Monath, 2001).

The recent epidemics of yellow fever in Angola and Brazil in 2016 and 2017, respectively, brought in the air the question on the number of YF vaccine to protect people against disease, because the occurrence of cases among people previously vaccinated. In 2013, the WHO recommended the single dose of YF vaccine for lifelong protection against YF (WHO, 2013). The decision of the WHO meeting was agreed by everyone; it was based in old studies, and following national discussions, Brazil decided not to adopt the recommendation. However, this was revised by the Brazilian Ministry of Health in 2017 due the largest epidemic in the country since the urban cycle was eliminated in the 1940's, and the country has temporally adopted the single vaccine dose due the shortage of 17D vaccine.

The polemic of a single, two or multiple yellow fever vaccine doses over the lifespan of those in endemic areas is an open question to investigate and the

decision should be scientifically based and preferentially on recent data. Indeed, I think it is necessary to recapitulate some situations in the light of the recent epidemics in the Old World (Angola and Democratic Republic of Congo) and New World (Brazil), in the last two years. In particular, there are logistic and technical problems to produce the necessary quantity of the 17D vaccines.

Below are listed some of difficulties related with 17D vaccine production/shortage:

1. The WHO decision was based in the light of shortage of yellow fever vaccine;
2. The shortage occurs because the 17D vaccine production is limited, laborious and empiric. The price per dose is cheap and therefore, it is not attractive to the industry (producers);
3. The shortage of 17D vaccine resulted in the use of fractioned dose during the 2016 epidemic in Kinshasa city the Democratic Republic of Congo capital;
4. The WHO stockpile of 6 million doses funded by the GAVI alliance is insufficient to guarantee a fast and efficient response to the reemergence of yellow fever globally. The occurrence of several yellow fever imported cases in China highlights this weakness;
5. To increase the production of 17D vaccines it is necessary to improve and modernize the plant of producers;
6. The cost of modernization of the plant of producers is extremely high and is not attractive to the WHO's prequalified producers;
7. Technically it is necessary to develop a new and modern yellow fever vaccine that can be economically attractive to industry, increased safety

against severe adverse viscerotropic disease, and at least as immunogenic as 17D, and;

8. This will take several years, maybe more than a decade, to be available and depending of the approach used will require several doses to guarantee lifelong protection.

On the other side, at least two recent studies developed in Brazil showed that the levels of neutralizing antibodies decrease dramatically in adults and in children, eight years and four years, respectively, after primary vaccination (Caldas et al., 2014; Campi-Azevedo et al., 2016). In addition, between 1980 and 2017, 29 cases of severe frequently fatal sylvatic yellow fever cases were reported among people previously vaccinated in Brazil, not computed yet the cases of the recent epidemic (PAHO, 2016), supporting the above mentioned studies that recommended at least two doses to obtain complete protection against yellow fever. This is especially significant during the reemergence of disease in Brazil and other South American endemic countries (Vasconcelos, 2010).

The persistence of recommendation of a single dose of 17D vaccine as sufficient to protect vaccinees against disease is not feasible anymore and can result in several deaths of people that could be prevented with an additional vaccine dose.

Therefore, I appeal that the WHO urgently convey a meeting with specialists on vaccine, epidemiologists and virologists, together with the WHO prequalified producers of the 17D vaccine to review this topic, and to stimulate the increase

and or modernization of 17D vaccine production in order to allow a more efficient protection of people living in or travelling to endemic areas.

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