“A randomized, blinded non-inferiority trial on the immunogenicity and safety of fractional doses of yellow fever vaccines”

Study summary

Yellow fever (YF) is a mosquito-borne viral disease that is endemic in 34 countries in the African region and 14 in South America. YF virus infection can be asymptomatic or cause a wide spectrum of disease, from mild symptoms to severe, potentially lethal illness with jaundice, renal failure and haemorrhage. The vast majority of reported cases and deaths occur in sub-Saharan Africa where yellow fever is a major health problem occurring in epidemic patterns. There is no specific treatment for yellow fever infection. However, YF vaccine is shown to be very effective for outbreak control as well as for the prevention of outbreaks. YF vaccination confers protection in most vaccinated individuals and this is considered to be life-long.

In 2016, YF outbreaks occurred in Africa (Angola, Democratic Republic of Congo (DRC) and Uganda) as well as in South America (Brazil, Colombia and Peru). Factors such increased urbanization in poor areas without proper water and sanitation systems and population movements, have the potential to contribute to increasing incidence of yellow fever and large epidemics. In July 2016, the demand for yellow fever vaccines in response to the large urban outbreaks occurring concurrently and the risk of further spread through the African continent and even to Asia, was larger than the available supply. In this situation, the World Health Organization (WHO) developed recommendations for the use of fractional-dose of yellow fever vaccine as a dose-sparing strategy. This strategy consisted on delivering 1/5th of the conventional dose and was used to vaccinate over 7 million people in Kinshasa, the capital city of DRC.

The evidence to recommend the use of fractional dosing was based on a limited number of clinical studies. However this was considered sufficient to provide emergency recommendations. In order to broaden and also possibly simplify WHO recommendations of fractional dose use in case of need for emergency campaigns, additional data is needed to respond to the important data gaps. These include the applicability of the fractional dose to all WHO-prequalified vaccines, the persistence of neutralizing antibodies and the performance of the fractional dose in young children and populations in Africa including those with HIV. Following these data gaps, WHO called for research to be conducted.

This study aims to respond to some of the research questions that would allow to broaden the recommendations on the use of fractional doses of yellow fever vaccine in emergency situations. In the first phase of the study, 960 adults were recruited in Mbarara, Uganda and Kilifi, Kenya. Results for the immunogenicity date 28 days post-vaccination and safety data were reviewed by the study Data and Safety Monitoring Board (DSMB) and the results were considered satisfactory. Therefore, the study will continue with the recruitment of 420 children in Mbarara, Uganda and 250 HIV infected adults in Kilifi, Kenya, to assess non-inferiority of the selected WHO prequalified vaccine (Chumakov Institute yellow fever vaccine).

The main objective of the studies in children and HIV+ adults is to assess the non-inferiority is seroconversion 28 days after vaccination of a fractional dose compared to full dose of the yellow fever vaccine produced by Chumakov Institute in these sub-populations. As secondary objectives the study will assess seroprotection 10 days and 1 year after vaccination, to assess rapidity and persistence of protective antibody levels; describe the geometric mean titre and the change in neutralizing antibody on Day 28 after vaccination with fractional and full doses; and assess the occurrence of adverse events and serious adverse events (SAE) during 28 days after administration of fractional and full doses.