Yellow Fever Vaccination

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Yellow fever (YF) remains a threat to global health, with an increasing number of major outbreaks in the tropical areas of the world over the recent past. In light of this, the Eliminate Yellow Fever Epidemics Strategy was established with the aim of protecting one billion people at risk of YF through vaccination by the year 2026. The current YF vaccine gives excellent protection, but its use is limited by shortages in supply due to the difficulties in producing the vaccine. There are good grounds for believing that alternative fractional dosing regimens can produce strong protection and overcome the problem of supply shortages as less vaccine is required per person. However, immune responses to these vaccination approaches are yet to be fully understood. In addition, published data on immune responses following YF vaccination have mostly quantified neutralising antibody titers. However, vaccine-induced antibodies can confer immunity through other antibody effector functions beyond neutralisation, and an effective vaccine is also likely to induce strong and persistent memory T cell responses.

Keywords: yellow fever virus ; yellow fever ; yellow fever vaccine ; humoral immune response ; cell-mediated immune response

1. Introduction

Yellow fever (YF) is a disease caused by YF virus (YFV) which is known to cause death in about 30–60% of those infected [1][2]. The global annual prevalence of YF infection among humans is estimated at 200,000, with most cases reported in sub-Saharan Africa and South America where it is endemic [3]. Over the past five years, there have been outbreaks of YF in Brazil, Angola, Democratic Republic of Congo and Nigeria, with the risk of further spread to other countries and continents [4]. The Eliminate Yellow Fever Epidemics strategy aims to protect one billion people against YF through vaccination by the year 2026 [5].

2. Diversity and Transmission of YFV

Molecular phylogenetic studies have described YFV diversity based on nucleotide sequence analysis of the whole genome as well as different sub-genomic regions [6]. It has been reported that the evolutionary rate of YFV, which is estimated at 2–5 × 10−4substitutions/site/year, is generally consistent across different sub-genomic regions and therefore a representation of that of the entire genome [6][7]. Based on complete genome sequences or sub-genomic sequences, the nucleotide difference between African and South American genotypes is up to 16%, whereas nucleotide difference between African genotypes is approximately 8% and approximately 5% between South American genotypes [6][8]. There are no studies that have investigated the relationship between YFV strains to specific phenotypes such as disease severity, possibly due to the availability of a vaccine that is effective across all strains resulting in limited interest in experimental investigations [6].

YFV is transmitted to humans and non-human primates in tropical areas of Africa and the Americas, via the bite of an infected mosquito [9]. Transmission to humans occurs in three cycles: sylvatic, intermediate, and urban [2][9]. In sylvatic transmission, infection to humans occurs when they enter forests where the virus is enzootically transmitted between non-human primates and mosquitoes. In intermediate (savannah) transmission, humans residing in rural areas become infected when bitten by infected semi-domestic mosquitoes that feed on both humans and non-human primates, and in urban transmission, urban infected mosquitoes (Aedes aegypti) transmit the virus from human to human in densely populated areas [2].

3. Clinical Presentation, Diagnosis and Treatment of YF

Diagnosis of YF remains challenging given the differences in disease severity and symptom presentation in different infected individuals, similarity of clinical symptoms with other endemic diseases, and laboratory diagnosis which requires specialised resources that may not be accessible in areas where YF is endemic [2]. Furthermore, protein similarity of YFV

to other flaviviruses (DENV, WNV, and ZIKV) often results in the production of cross-reactive antibodies thus making serological tests inconclusive [10]. Nevertheless, diagnosis can be made based using reverse transcriptase polymerase chain reaction to asses for YFV genomic RNA in body fluids and /or using serological tests which involve evaluating for the presence of YFV specific Immunologlobulin M (IgM) or Immunologlobulin G (IgG), with a differential diagnosis of DENV, WNV and ZIKV to rule out these viruses [11]. In addition, plaque reduction neutralisation antibody tests (PRNT) add specificity to the serological distinction by using a higher titre threshold (typically fourfold difference in PRNT titres) when comparing responses between flaviviruses [11]. There is no specific antiviral treatment for YF. However, early supportive clinical management of specific symptoms or complications (such as treatment for dehydration, fever, organ failure, and antibiotics for associated bacterial infections) could improve the outcome [2][6].

4. YF Prevention

There is a safe and effective vaccine against YF which was first developed in 1937 using a live attenuated YF virus strain (17D), with the subsequent production of YF vaccine using sub-strains (17D-204, 17DD and 17D-213) of 17D [1][12]. 17D was developed by passaging the virulent strain (Asibi) in rhesus macaques, mouse and chicken embryos causing mutations in genes encoding for both structural and non-structural proteins leading to the loss of its virulence [13]. The E protein of the 17D contains most of the mutations compared to other viral proteins, and given that E protein is responsible for viral attachment, fusion and is considered a major target for antibodies, mutations in this protein play a significant role in the attenuation of 17D [14][13].

The vaccine is administered intramuscularly or subcutaneously to adults travelling to endemic areas or periodically in response to outbreaks, and to children (>nine months of age) through routine childhood immunisation, with 80% and 100% of the vaccinees developing neutralising antibodies (nAbs) 10 days and one month post-immunisation, respectively [9][15]. There has been no difference reported in safety and protective immunity when the vaccine is administered either intradermally or subcutaneously [16]. Given evidence that the single primary dose of YF vaccine can provide lifelong immunity, a booster dose, which was previously given at an interval of 10 years from the primary dose, is no longer needed except among at-risk populations such as those who are immunocompromised or immunosuppressed [1].

Population YF vaccination coverage of >80% is recommended by the WHO to prevent and control outbreaks, however, YF vaccine coverage remains too low to prevent outbreaks especially in highly urbanised areas [5]. With the recent outbreaks, there is an increasing need to expand YF vaccine stocks since the current supply of YF vaccine is insufficient to provide effective coverage during outbreaks [1][4][9]. As a response, the WHO has recommended the use of fractional doses which have been used to control epidemics in Democratic Republic of Congo and South America, and studies have reported equivalent immunogenicity to that of the standard full dose [1][17][18]. However, immune responses to fractional doses of YF vaccine are yet to be fully understood.

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