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Computational modeling of the immune response to yellow fever

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ABSTRACT

Yellow fever (YF) is an infectious disease caused by a type of virus called *flavivirus*. According to the World Health Organization (WHO), 44 countries are endemics, and around 200,000 cases of YF are recorded per year causing 30,000 deaths, mainly in Africa and South America. For this reason, it is very important to understand the behavior of the disease and the associated immune response in order to design better strategies for treating it. To this end, this study describes a mathematical model to represent the human immune response to an infection by YF virus. For the best of our knowledge, this is the first mathematical model of the effects of the YF in the immune system. This is the beginning of a path that will allow us to verify, for example, if a booster dose of YF vaccine is really necessary every 10 years and if a lower dosage could be used to achieve similar protection.

1. Introduction

Yellow fever (YF) is an infectious disease transmitted by blood-sucking vectors of the *Culicidae* family, especially of the gender *Aedes* and *Haemagogus*. The yellow fever virus (YFV) is a flavivirus from the same family of dengue virus. In general, the disease is transmitted when a mosquito, *Haemagogus* (sylvatic) or *Aedes* (urban), bites an infected person or other primate and then bites a healthy person who is not immune. The infection by YFV can be asymptomatic, present only mild symptoms or cause bleeding, jaundice, and in severe cases lead to death. Reactions can vary among individuals taking into account age, sex and where they live. Furthermore, previous infection with certain heterologous flaviviruses, in particular dengue virus, appear to modulate the expression and disease severity [1].

YF has been one of the most dreaded diseases in the world before the development of a vaccine, but there is still 200,000 cases of YF per year causing 30,000 deaths around the world [1]. The major incidence areas are South America and Africa, but those who travel to these areas and are not vaccinated are also at great risk. In South America the disease occurs mainly in the Amazonian regions and affects, in general, men working in the forest or near it. This number may increase because areas that had never reported cases, like India, has favorable conditions for the establishment of the disease: mosquito infestation, low levels of population immunity and large number of travelers.

Control of the disease is of interest to public health agencies, the medical and scientific community and especially the affected population. The only way to prevent outbreaks is mass vaccination of the population living in or traveling to endemic areas. Today the vaccine is given from 9 months of age and should be reinforced every ten years. But, according to

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Table 1
Model variables and initial values.

Variable	Description	Initial Value
H	Uninfected hepatocytes	5×10^5
H^*	Infected hepatocytes	0
V	Virus titer	10
A_P	Immature antigen-presenting cells	10^3
A_P^*	Virus-loaded antigen-presenting cells in tissue	0
T_{KEt}	Effector CD8+ T cells in tissue	0
A_t	Antiviral antibody titer in tissue	0
A_{PL}^*	Virus-loaded antigen-presenting cells in lymphatic compartment	0
A_{PM}	Mature antigen-presenting cells	0
T_{HN}	Naïve CD4+ T cells	10^3
T_{HE}	Effector CD4+ T cells	0
T_{KN}	Naïve CD8+ T cells	10^3
T_{KE}	Effector CD8+ T cells	0
B_N	Naïve B cells	10^3
B_A	Activated B cells	0
B_M	Memory B cells	0
P_S	Short-lived plasma (antibody-secreting) B cells	0
P_L	Long-lived plasma (antibody-secreting) B cells	0
A	Antiviral antibody titer in lymphatic compartment	0

World Health Organization (WHO), the booster dose of YF vaccine is no longer necessary [1]. There are no prospective clinical studies which prove the durability of efficacy of the YF vaccine in humans but distinct studies have shown that there is evidence to support the recommendation of the WHO [2–4].

To better understand the effects of the disease in the body, it is necessary to comprehend the behavior of the human immune system (HIS) when a person is infected. To this end, this work proposes a new mathematical and computational model of the HIS after an infection by the YFV. For the best of our knowledge, this is the first mathematical and computational model of the effects of the YF in the HIS. The new model is based on a previous work [5] that reproduces the effects of infection by the influenza A virus. Some equations were rearranged to better organize the original two-compartment system. In addition, other modifications were necessary to adapt the behavior of the model to the new disease, i.e. the YF.

The infected organism with YFV rapidly develops an immune response. IgM antibodies appear during the first week of illness, reaching its peak during the second week and usually diminish rapidly over the months. Neutralizing antibodies appear at the end of the first week and persist for many years [6]. The neutralizing antibodies are primarily responsible for conferring immunity against re-exposure to the virus. In fact, there are no reported cases of individuals with a second clinical infection of YF.

There are variations in the behavior of the HIS from individual to individual with regard to the presentation and severity of the disease. Previous infections with other flaviviruses can generate cross-protection against YF, as previously stated. The principal is the dengue virus, but other African flaviviruses can also generate a cross-protection, as Zika and Wesselsbron [6].

There is no specific antiviral treatment for YF. Currently the management of the patient is via medications just to ease symptoms such as pain and fever, in the simplest cases. No treatment prevents the natural course of the disease, therefore the importance of better understanding the HIS mechanisms involved in the combat of the YF.

This work is organized as follows. Section 2 presents the new mathematical model; Section 3 presents the numerical results obtained with the proposed model. Finally, the last Section presents our conclusions and plans for future works.

2. Methods

This section presents the new model proposed to represent the immune response to the YFV, the methods used to solve the system of ordinary differential equations (ODEs) and the computing environment used in the simulations.

2.1. New model

The model was based on a previous work [5] which reproduces the effect of influenza A virus infection in humans. Although both diseases are caused by virus, some adjustments were made in order to better represent YF.

The model takes into account some populations that are very important in the infectious disease process. The main populations are infected and uninfected hepatocytes, virus, antigen-presenting cells, cytotoxic or killer (CD8+) T cells, "helper" T cells (CD4+), long-lived and short-lived antibody-secreting cells, B cells and antibodies. These populations, their acronyms and initial conditions in the model can be found in Table 1. Two distinct compartments are present in the model: the tissue and the lymphatic compartment. In this model, we consider only the hepatic tissue since it is the most affected by the YF.

The model used to simulate an infection by YFV is composed by 19 ODEs and many parameters. The full list of parameters with their descriptions is presented in Table 2.