# Introduction

In this project, we are studying the article “On the Role of CD8+ T Cells in Determining Recovery Time from Influenza Virus Infection” published on December 20 of 2016 by Cao P, Wang Z, Yan AWC, McVernon J, Xu J, Heffernan JM, Kedzierska K and McCaw JM in the paper *Frontiers in Immunology*.

The work behind this article was to model and thus better understand the nature and kinetic behaviour of the main actors in the immunologic response to Influenza virus infections. In particular, the researchers take a close look at the role of the effector CD8+ T cells and their influence on the recovery time of the patient.

Understanding the exact mechanism of the viral infection is an important step in order to find the right treatment and even prevention like new vaccines against influenza. The constant evolution of influenza virus requires yearly adaptation of the vaccine to the currently circulating strains, and researchers are actively investigating new ways to produce more broadly applicable vaccines that would cover a maximum of different influenza strains.

In addition to existing clinical data, the research in this context heavily relies on biological models of the virus. While being relatively easy to model in animals due to the fact that certain influenza types affect a range of mammals other than humans, previous models have been insufficient to elucidate the exact implications of CD8+ T cells. Therefore, an accurate mathematical model taking into account the results of the numerous *in vitro* and *in vivo* experiments and recent clinical data, can give noteworthy insights on the subject.

In the specific case of this article, the results suggest that administering the above-mentioned CD8+ T cells may have a significant benefit for infected patients by greatly reducing the recovery time.

# Influenza virus

Influenza viruses are a group of RNA viruses that appear in the form of both seasonal outbreaks and unpredictable pandemics. The resulting disease is commonly known as the flu or influenza Seasonal infections are associated with the typical winter flu, featuring mild as well as severe symptoms, whereas the punctual pandemics are characterised by their large spreading across continents. The respiratory pathogen, while rarely being fatal in otherwise healthy individuals, can be deadly to high-risk groups with pre-existing respiratory troubles. Typically, it counts between 3 and 5 million severe cases per year globally, with up to 500,000 associated deaths. Within the last 140 years however, there have been six major influenza epidemics, the most severe being the 1918 “Spanish flu”, which counted an estimated 500 million infected out of which up to 100 million are believed to have died.

## Characteristics of the influenza viruses

The group of influenza viruses counts four different species, each distinguished by a specific antigenic type: Influenza A virus, Influenza B virus, Influenza C virus and Influenza D virus. Of these four antigenic types, type A is the most dangerous, type B carries fewer risks but can still cause epidemics, and type C is usually associated with minor symptoms. Type D is less common than the others and is not known to cause infections in humans.

The type of influenza virus is usually determined with the help of the matrix protein (M1) and nucleoprotein (NP) antigens. The M1 protein is needed for the assembly of the virus and the nucleoprotein intervenes in transcription and viral replication.

## Replication mechanism

All four types of influenza viruses are negatively polarised, single-stranded RNA viruses, meaning they are unable to replicate on their own but must use their host organism’s cellular replication mechanism for that purpose. They come with a genome composed only of one RNA strand, as well as a range of other molecules implicated in its survival and propagation. The haemagglutinins, a type of surface protein, help the virus cell attach to the target cell’s membrane and infect it. In order for the virus to reproduce, this strand first has to be copied by an RNA polymerase also brought by the virus itself. RNA polymerase creates a positively polarised strand, which can then be used as if it was a messenger RNA and is thus translated into proteins by the host cell’s ribosomes. The resulting proteins drive the production of new virus cells (virions) favouring the propagation of the virus in the host organism as well as the infection of surrounding individuals.

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“Influenza viruses cause annual outbreaks of respiratory tract infection with attack rates of 5-10%. This means that humans are infected repeatedly with intervals of, on average, 10-20 years. Upon each infection subjects develop innate and adaptive immune responses which aim at clearing the infection. Strain-specific antibody responses are induced, which exert selective pressure on circulating influenza viruses and which drive antigenic drift of seasonal influenza viruses, especially in the hemagglutinin molecule. This antigenic drift necessitates updating of seasonal influenza vaccines regularly in order to match the circulating strains. Upon infection also virus-specific T cell responses are induced, including CD4+ T helper cells and CD8+ cytotoxic T cells. These cells are mainly directed to conserved proteins and therefore display cross-reactivity with a variety of influenza A viruses of different subtypes. T cell mediated immunity therefore may contribute to so-called heterosubtypic immunity and may afford protection against antigenically distinct, potentially pandemic influenza viruses. At present, novel viral targets are identified that may help to develop broad-protective vaccines. Here we review the various arms of the immune response to influenza virus infections and their viral targets and discuss the possibility of developing universal vaccines.”

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## Immune responses

Upon encountering a pathogen such as influenza virus, the human immune system produces different types of reactions, known as immune responses, aiming to avoid the pathogen from spreading and eventually removing it entirely. Broadly speaking, there are two main types of immune responses: the generic one which gets triggered upon encountering anything that can roughly be identified as an intruder, called *innate* response; and the specific or *adaptive* one which the body develops by being exposed to a pathogen and that allow it to remember how to fight that specific pathogen, also known as immunity. The adaptive responses are subdivided into *humoral* and *cellular* responses, the first one taking place when the pathogen is still in the intercellular space of the body, and the latter one kicking in once the pathogen has entered a target cell. Here again, the cellular response implies two different types of cells, namely the *T helper cells* and the *T cytotoxic cells*.



The influenza infection implies both innate and adaptive immune responses. The innate response is independent of the type of virus and acts during the early stage of the infection. It involves, among others, type 1 interferons (IFN) and natural killer cells (NK cells) and is provoked by the presence of infected target cells. The effects are numerous, but in the model at hand, it is only considered that they kill infected cells at a certain rate.

Considering an individual with no previous exposure to the virus, the adaptive immune response has its main impact during later stages of the infection, as the cells involved must be developed by the immune system first. Both the humoral and cellular defences start out with so-called *naive* cells of each type, which upon contact with the pathogen differentiate into *effector* cells capable of fighting the specific virus. As mentioned, the humoral response happens outside of the cells, e.g., in the intercellular space of a tissue or the blood. The involved naive cells called *B cells* are stimulated by the presence of virions to proliferate while differentiating into plasma cells which then secrete virus-specific antibodies. These antibodies neutralise the virus cells in either short-lived or long-lived responses depending on the type of antibody produced. The model also considers different rates of production and consumption for each of these antibody types.