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Mathematical modelling of Foot-and-mouth disease virus vaccines

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1 Introduction

Foot-and-mouth is a disease of global socioeconomic importance, with vaccination the principle tool for control in endemic countries. Improvements in vaccines require advances in our understanding of the host immune response, one aspect of which the study group is asked to consider. Major problems limit the capacity of FMDV vaccines to control infections in developing countries. The virus is notoriously unstable which reduces the yield and effectiveness of the vaccine. A FMDV-specific difficulty is that effective vaccination requires the presence of intact inactivated virus or virus-like particles. Individual proteins or peptides have proven to be insufficiently immunogenic for use as vaccine antigen.

To be recognised by T lymphocytes, viral protein must first be converted into short peptide pieces by antigen presenting cells such as dendritic cells (DC), which thereby control the magnitude and character of the immune response. We have evidence to show vaccine produced from viruses of different serotypes can differentially stimulate T cell responses. The principle difference between these virus strains is their capsid stability (see below), which may influence both the uptake of virus capsid by DCs and the subsequent controlled processing of the capsids to produce peptides for presentation to stimulate T-cells (responsible for helping B cells to produce antibodies and clear the virus). Figure 1 shows the decay rate of capsids in a particular assay at 49^oC.

We would like a model of this process to be developed to explore the interplay of uptake and processing of viral capsids and the impact of capsid stability on gross dynamics of the system. If possible, we would like the group to address the specific question of whether it is the virus strains different stability properties that are responsible for the observed differences in system behaviour. We assume this would either be driven by the characteristics that capsid stability (or instability) imparts to an individual virus particle or how the DCs handle virus fragments as opposed to whole virions. Specifically,

1. Is the efficiency of capsid uptake from extracellular environment by specialised antigen presenting cells (dendritic cells) influenced by the stability of the capsids?

2. Is the processing of the capsid proteins into short peptides influenced by the stability of the capsids?

3. Is the magnitude of the T cell response influenced by the period of time antigen is retained in dendritic cells?

4. Overall, does capsid stability result in an increased specific T cell proliferative response in antigen presentation assays?

5. How does antibody mediated uptake of FMDV capsids influence the subsequent B cell and T cell responses?

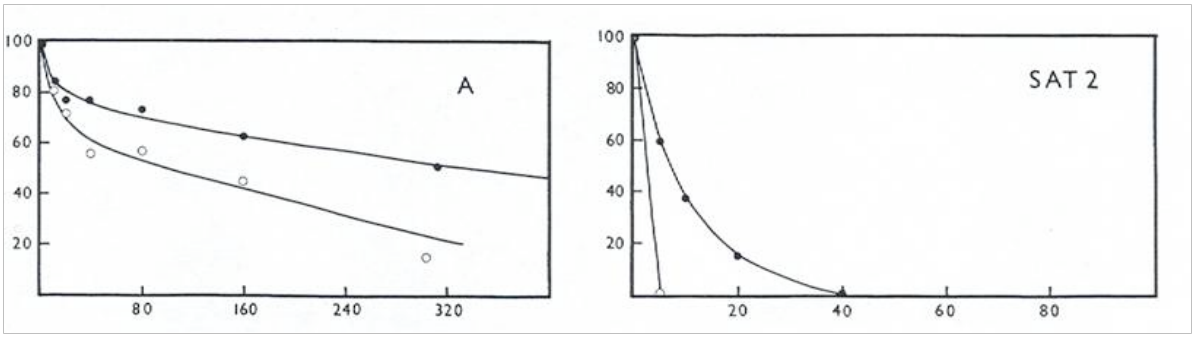

Figure 1: Comparison of the thermal stability of A and SAT2 capsids. The vertical axis shows the percentage of intact capsids remaining after incubation at 49^oC. The horizontal axis shows the incubation time in minutes. Closed circles represent live virus and open circles represent inactivated virus (vaccine antigen). Using this assay, A capsids are approximately 50 fold more stable than SAT2 capsids.

6. Can the model be further developed to predict the response to a second immunisation (booster)?

2 Mathematical model

2.1 Introduction

We aim to construct a model that describes the immediate and long-term immune response to a vaccine introduced into an animal. In simple terms, the vaccine initiates the production of specialist cells (namely B-cells and T-cells) that produce antibodies, which combine with the vaccine capsids and ultimately eliminate them from the system. The success of the vaccination against future FMDV infections requires sufficient levels and sufficiently long occupation time of the antibodies and the cells producing them. The key issue explored in the modelling to come is the effect of the stability of the vaccine, or in more conventional mathematical terms "the vaccine's decay rate", on the resulting immune response. The proposed model goes some way to address the questions in the Introduction, see Section 2.4.

2.2 Modelling of the immune system network

To simplify the modelling we will compartmentalise the system and avoid explicit treatment of the spatial distribution of the model components. Hence, the model variables, listed in Table 1, can be considered to be masses that are functions of time t only. Unlike many pathogens, or other alien agents that the immune system is required to deal with, the vaccine capsid appears not to interfere or inhibit any of the immune response processes. The modelling will therefore describe, in a very simplified way, the "classical" adaptive immune response network. This network consists of two principle pathways, which will be termed the "short-term" and "long-term" pathways; these are illustrated in terms of the variable symbols in Figure **??** and discussed in detail below.

Short-term pathway: The vaccine capsids (V) migrates into the lymphatic system and pass into the lymph nodes. There the antigen markers on the capsid surface will stimulate a cascade of responses that will, in time (τ_1, about 1 day), generate targeted B-cells (B_S) that in turn release into the body specifically-targeted antibodies (immunoglobin IgM,

Variable	Interpretation
V	Vaccine concentration
C	Antigen-Antibody complex concentration
B_S	Short term memory B cell concentration
A_S	Short term memory antibody (IgM) concentration
D_U	Unactivated dendritic cell concentration (assumed constant)
D_M	Activated DC level via macropinocytosis
D_F	Activated DC level via the fc activation process
T	T cell level
B_L	Long term memory B cell level
A_L	Long term memory antibody (IgG) level
Q	Level of T cell activation

Table 1: Table of the model variables

A_s) that binds with the free capsis to form a capsid-antibody complex (C); though this complex is inert, it is involved in the long-term pathway. After the stimulus is removed, the specific B-cell population and consequently antibody production will decline and vanish over a period of a few weeks. This pathway has no in built memory, so that any future insults, either by virus or vaccine, will initiate this process from scratch.

Long-term pathway: The vaccine capsids are delivered to the lymph nodes by DCs, stimulating a different set of responses to that of the short-term pathway. Dendritic cells (D_U) are present throughout the body, and can take up and become activated in two ways. Firstly, by direct uptake of the capsid particles by macropinocytosis ($D_U \to D_M$) and, secondly, by uptake of the capsid-antibody complex via the fc activation process ($D_U \to D_F$). These activated DCs migrate to the lymph-node to present the antigen to naive T-cells, which in time (approximately 3-4 day = τ_2), mature to targeted T-cells (T). The targeted T-cells stimulate development of a new line of differentiated B-cells (B_L), which release more antibodies (A_L, specifically the immunoglobin IgG) into the body. The key difference in this system is that the specific T-cell line is constantly renewed after the presence of the vaccine and hence there is continuous supply of B-cells and IgG long after the inoculation. In the event of a future insult, either by booster vaccine or by FMDV, the specific T-cells divide, in the right circumstances, to a much more enhanced and rapid immune response.

Key to the success of the long-term pathway is the number of T-cells that is generated from the first vaccine inoculation. It will be assumed in the model that the "tick-over" level of T-cells, i.e. the long term level following the inoculation, is a linear function of the total amount of DC activation, i.e. the "memory variable" $Q(t)$.

2.3 Mathematical modelling

We construct the model based on standard mass action laws applied to the pathway shown in Figure 2. The only exceptions to this is the activation rates of DCs, in which it is assume that DCs have only a limited uptake potential of the viral capsid and complex; Michaelis-Menten kinetics being employed to describe this saturation in uptake. It is expected that a very small fraction of the total population of DCs will be involved in the vaccination process and we assume the unactivated DC level, D_U, remains constant. Finally, the period of time for B-cell and T-cell generation will be modelled as simple single time point delays. There are a large

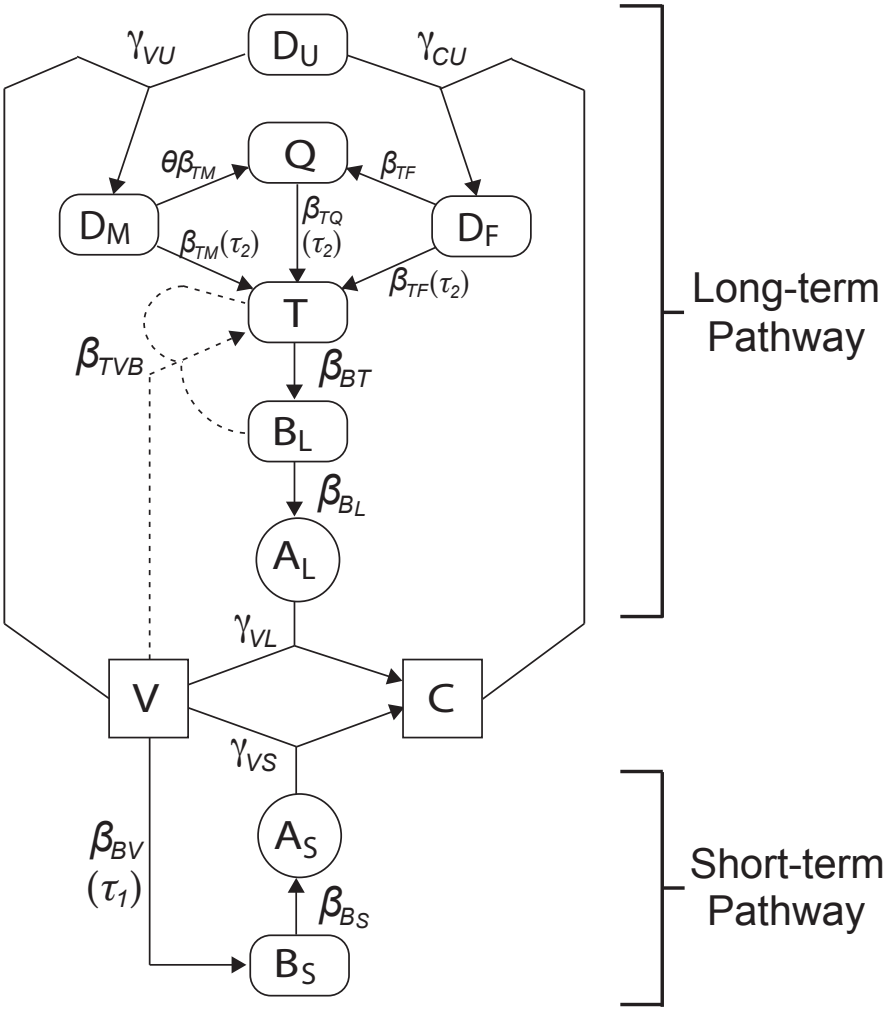

Figure 2: Schematic of the immune response network to the vaccine. The terms in the square boxes are the model's variables (see Table 1) and the arrows labelled with rate constants of the form β_* indicate production and those labelled with rate constants γ_* indicate production via interaction of 2 or more components. The bracketed "τ_*" terms indicates the time delay along the associated path. Natural decay is assumed for all variables except for the memory variable Q.

number of parameters in this system, broadly speaking those starting with β_* are birth rates, γ_* are conversion rates and δ_* are decay rates (see Table 2).

The **evolution of the vaccine** is given by

$$\frac{dV}{dt} = -\boldsymbol{\delta_V} V - \gamma_{VS} V A_S - \gamma_{VU} D_U \left(\frac{V}{V+V_C}\right) - \gamma_{VL} V A_L, \tag{1}$$

which describes the loss rates of V via, in order, natural decay, uptake by IgM, uptake by unactivated DCs and uptake by IgG. The key parameter describing the stability of the vaccine is $\boldsymbol{\delta_V}$, which is decay rate constant of the vaccine, such that the half-life of the vaccine is $\ln(2)/\delta_V$; hence reducing stability corresponds to increasing δ_V.

The modelling of the **short-term pathway** is relatively straightforward and is given by

$$\frac{dB_S}{dt} = \beta_{BV} V(t-\tau_1) - \delta_{B_S} B_S, \tag{2}$$

$$\frac{dA_S}{dt} = \beta_{B_S} B_S - \gamma_{VS} V A_S - \delta_{A_S} A_S. \tag{3}$$

Here, we have implicitly assumed that the level of vaccine in the lymph nodes is proportional to the total level. The output rate of B-cells is dependent on the vaccine levels a time τ_1 ago (about a day) and they die away with half-life $\ln(2)/\delta_{B_S}$. IgM is produced at a rate proportional to B_S, is lost through binding with the vaccine and decays naturally (half-life $\ln(2)/\delta_{A_S}$). We can see that if there is no V, B_S and A_S will decay to zero as expected.

For the **long-term pathway**, the generation of the vaccine–antibody complex is given by

$$\frac{dC}{dt} = \gamma_{VS} V A_S + \gamma_{VL} V A_L - \gamma_{CU} D_U \left(\frac{C}{C + C_C} \right) - \delta_C C, \tag{4}$$

describing rate of C generation via vaccine binding with IgM and IgG, respectively, and loss via uptake by unactivated DCs and natural decay (half-life $\ln(2)/\delta_C$). We note that we have bundled vaccine–IgM and vaccine–IgG complex into a single variable; this seemed reasonable, as properties of the two complexes are very similar. The equations for DC activation are

$$\frac{dD_M}{dt} = \gamma_{VU} D_U \left(\frac{V}{V + V_C} \right) - \delta_{D_M} D_M, \tag{5}$$

$$\frac{dD_F}{dt} = \gamma_{CU} D_U \left(\frac{C}{C + C_C} \right) - \delta_{D_F} D_F, \tag{6}$$

which describe in both cases the rates of generation from unactivated DCs and loss via natural death (half-lives $\ln(2)/\delta_{D_*}$). The memory cells and IgG equations are

$$\frac{dT}{dt} = \beta_{TM} D_M(t-\tau_2) + \beta_{TF} D_F(t-\tau_2) + \beta_{TVB} T V B_L + \beta_{TQ} Q - \delta_T T, \tag{7}$$

$$\frac{dB_L}{dt} = \beta_{BT} T - \delta_{B_L} B_L, \tag{8}$$

$$\frac{dA_L}{dt} = \beta_{B_L} B_L - \gamma_{VL} V A_L - \delta_{A_L} A_L. \tag{9}$$

The first equation descrsibes the net production rate of T-cells via activated DCs (after a delay of time τ_2), division in the presence of V and B_L (the "booster" term), "tick-over" production of T-cells dependent on past activation and natural death. The "booster" term in this equation is at the heart of the long-term immunity response, here, T-cells will more rapidly reproduce in response to any new intake of vaccine or virus; this process also requires the presence of long-term B-cells and we have assumed the simplest kinetics to describe this interaction. We further note, that in the presence of the vaccine and activated DCs, we expect the contribution to T-cell production via the memory term $\beta_{TQ}Q$ to be very much smaller than the first two (first exposure with vaccine) or three (subsequent exposures) terms on the right-hand side. The equations for B_L and A_L are similar to those of the short-term pathway, the only difference being that B_L is generated by T-cells. The variable Q describes is a measure of the total amount of T-cell production via DC activation that has occurred in the past and, assuming a a weighted linear dependence, is defined by

$$Q = \int_{-\infty}^{t} \left(\theta \beta_{TM} D_M(\hat{t} - \tau_2) + \beta_{TF} D_F(\hat{t} - \tau_2) \right) d\hat{t}; \tag{10}$$

Parameter	Interpretation
β_{BV}	Rate of Short-term memory B-cell generation due to vaccine
β_{B_S}	Rate of IgM production by Short-term B-cells
β_{TF}	Rate of T-cell generation via fc activated DCs
β_{TM}	Rate of T-cell generation via macropinocytosis activated DCs
β_{TVB}	Rate of T-cell generation via vaccine presence
β_{TQ}	"Tick-over" rate of T-cell generation
β_{BT}	Rate of Long term memory B-cell generation by T-cells
β_{B_L}	Rate of IgG production by Long-term B-cells
γ_{VS}	Vaccine-IgM uptake rate
γ_{VL}	Vaccine-IgG uptake rate
γ_{VU}	Vaccine uptake rate by micropinocytosis
γ_{CU}	Complex uptake rate by fc activated pathway
$\boldsymbol{\delta_V}$	Decay rate of Vaccine (unstable-3 hrs, stable-6 hrs)
δ_{B_S}	Death rate of Short term memory B cell (1 wk)
δ_{A_S}	Decay rate of Short term memory antibody (IgM) (8 wks)
δ_C	Decay rate of Antigen-Antibody complex (very short time)
δ_{D_M}	Death rate of D_M
δ_{D_F}	Death rate of D_F
δ_T	Death rate of T cell (months)
δ_{B_L}	Death rate of Long term memory B cell
δ_{A_L}	Decay rate of Long term memory antibody (IgG) (8 wks)
θ	Activated DC weight coefficient for tick-over T-call production

Table 2: Table of the model parameters

however, for computational convenience, we take the derivative

$$\frac{dQ}{dt} = \theta\beta_{TM}D_M(t-\tau_2) + \beta_{TF}D_F(t-\tau_2). \tag{11}$$

We observe from (7) that as V vanishes following exposure and eventually $D_M \to 0$ and $D_F \to 0$, Q will become constant, Q_∞ say, and hence in large time the level of T-cells will settle to a "tick-over" level of $T \sim \beta_{TQ}Q_\infty/\delta_T$.

It is assumed that at $t = 0$ the vaccine is introduced and we impose the following initial and past conditions

$$t < 0: \qquad V = B_S = A_S = C = D_F = D_M = T = B_L = A_L = Q = 0, \tag{12}$$

$$t = 0: \qquad V = V_0, \quad B_S = A_S = C = D_F = D_M = T = B_L = A_L = Q = 0. \tag{13}$$

2.4 Key parameters regarding questions 1-6 in the Introduction

Discussing the questions in turn.

1. Is the efficiency of capsid uptake from extracellular environment by specialised antigen presenting cells (dendritic cells) influenced by the stability of the capsids?
   - Efficiency of capsid uptake is dependent on its stability δ_V, i.e. the occupation time of the vaccine, and the DC uptake rate directly (γ_{VU}) and indirectly via the complex pathway (which is governed by all parameters!).
2. Is the processing of the capsid proteins into short peptides influenced by the stability of the capsids?

- This is not considered in the model, at least not in such specific detail. This process is in sense described by assuming that the activated DC decay rate, constants δ_{D_M} and δ_{D_F}, includes the deactivation of DC by processed capsid breakdown.

3. Is the magnitude of the T cell response influenced by the period of time antigen is retained in dendritic cells?
   - The occupation of activated DCs is governed by δ_{D_M} and δ_{D_F}. The effectiveness of these cells to generate T-cells is directly governed by parameters β_{TM} and β_{TF}.
4. Overall, does capsid stability result in an increased specific T cell proliferative response in antigen presentation assays?
   - The parameter δ_V governs vaccine stability and this will have a knock on effect on complex formation and subsequent DC uptake. In these assays, the other parameters are fixed and a survey of the effects of the stability can be investigated from simulations using different values of δ_V.
5. How does antibody mediated uptake of FMDV capsids influence the subsequent B cell and T cell responses?
   - The rates of antibody mediated uptake are governed by parameters γ_{VS} and γ_{VL}.
6. Can the model be further developed to predict the response to a second immunisation (booster)?
   - This is straightforward. Defining $t = T$ to be the time point of the booster, we simulate the model as defined to $t = T$, then impose $V(T) = V(T^-) + V_1$ and continue the simulation assuming continuity of all the other variables at $t = T$. Here $V(T^-)$ is $V(t)$ as $t \to T^-$, though if the booster is administered a few weeks after the initial inoculum, we would expect $V(T^-) \approx 0$, so in effect $V(T) = V_1$.

A further issue which is very straightforward to simulate is the level of the inoculation. Is it possible to offset deficiencies in vaccine stability by injecting more vaccine? If so, how much?

2.5 Nondimensionalization

The customary first step in an analysis of a new model is to non-dimensionalise the system of equations in order to (1) reduce the number of parameters and (2) remove the units of the variables and parameters so that the relative magnitudes of the terms can be compared directly and systematically, which can help identify the important underlying mechanisms that govern the model results. The change in events following inoculation of the vaccine appears to occur over 7 days, which is roughly the half-life of IgM and we rescale time as follows

$$t \;=\; \frac{\hat{t}}{\delta_{B_S}},$$

where the hatted variable here and those that follow are the non-dimensional versions of the original variables. For the dependent variables we write

$$V = \frac{\delta_{B_S}^3}{\beta_{BV}\beta_{B_S}\gamma_{VS}}\hat{V}, \quad C = \frac{\delta_{B_S}^3}{\beta_{BV}\beta_{B_S}\gamma_{VS}}\hat{C}, \quad B_S = \frac{\delta_{B_S}^2}{\beta_{B_S}\gamma_{VS}}\hat{B}_S, \quad A_S = \frac{\delta_{B_S}}{\gamma_{VS}}\hat{A}_S,$$
$$T = \frac{D_U\gamma_{CU}\beta_{TF}}{\delta_{B_S}^2}\hat{T}, \quad B_L = \frac{D_U\beta_{BT}\gamma_{CU}\beta_{TF}}{\delta_{B_S}^3}\hat{B}_L, \quad A_L = \frac{D_U\beta_{B_L}\beta_{BT}\gamma_{CU}\beta_{TF}}{\delta_{B_S}^4}\hat{A}_L,$$
$$D_M \;=\; \frac{D_U\gamma_{VU}}{\delta_{B_S}}\hat{D}_M, \quad D_F \;=\; \frac{D_U\gamma_{CU}}{\delta_{B_S}}\hat{D}_F, \quad Q = \frac{D_U\gamma_{CU}\beta_{TF}}{\delta_{B_S}^2}\hat{Q},$$

and the non-dimensional parameters are defined as follows

$$\delta_1 = \frac{\delta_V}{\delta_{B_S}}, \quad \delta_2 = \frac{D_U \gamma_{VU} \beta_{BV} \beta_{B_S} \gamma_{VS}}{\delta_{B_S}^4}, \quad \delta_3 = \frac{\delta_C}{\delta_{B_S}}, \quad \delta_4 = \frac{\delta_{D_F}}{\delta_{B_S}}, \quad \delta_5 = \frac{\delta_{D_M}}{\delta_{B_S}}, \quad \delta_6 = \frac{\delta_{A_S}}{\delta_{B_S}},$$

$$\delta_7 = \frac{\delta_{B_L}}{\delta_{B_S}}, \quad \delta_8 = \frac{\delta_{A_L}}{\delta_{B_S}}, \quad \delta_9 = \frac{\delta_T}{\delta_{B_S}}, \quad \delta_{10} = \frac{\delta_{B_S}^2 \gamma_{VS}}{\beta_{BV} \beta_{B_S}}, \quad \delta_{11} = \frac{\beta_{TM} \gamma_{VU}}{\beta_{TF} \gamma_{CU}}$$

$$\delta_{12} = \frac{D_U \gamma_{CU} \beta_{BV} \beta_{B_S} \gamma_{VS}}{\delta_{B_S}^4}, \quad \delta_{13} = \frac{D_U \beta_{B_L} \beta_{BT} \gamma_{CU} \beta_{TF} \gamma_{VL}}{\delta_{B_S}^5},$$

$$\delta_{15} = \frac{\gamma_{VL} \delta_{B_S}^2}{\beta_{BV} \beta_{B_S} \gamma_{VS}}, \quad \delta_{16} = \frac{D_U \beta_{BT} \gamma_{CU} \beta_{TF} \beta_{TVB}}{\delta_{B_S} \beta_{BV} \beta_{B_S} \gamma_{VS}}, \quad \delta_{17} = \frac{\beta_{TQ}}{\delta_{B_S}}$$

$$\hat{V}_C = \frac{V_C \beta_{BV} \beta_{B_S} \gamma_{VS}}{\delta_{B_S}^3}, \quad \hat{C}_C = \frac{C_C \beta_{B_{BV}} \beta_{B_S} \gamma_{VS}}{\delta_{B_S}^3}, \quad \hat{\tau}_1 = \delta_{B_S} \tau_1, \quad \hat{\tau}_2 = \delta_{B_S} \tau_2,$$

$$\hat{V}_0 = \frac{V_0 \beta_{BV} \beta_{B_S} \gamma_{VS}}{\delta_{B_S}^3}.$$

Dropping the hats for clarity, the non-dimensional system of equations are

$$\frac{dV}{dt} = -\delta_1 V - V A_S - \delta_2 \left(\frac{V}{V + V_C} \right) - \delta_{13} V A_L \tag{14}$$

$$\frac{dB_S}{dt} = V(t - \tau_1) - B_S \tag{15}$$

$$\frac{dA_S}{dt} = B_S - \delta_6 A_S - \delta_{10} V A_S \tag{16}$$

$$\frac{dC}{dt} = V A_S + \delta_{13} V A_L - \delta_3 C - \delta_{12} \left(\frac{C}{C + C_C} \right) \tag{17}$$

$$\frac{dD_M}{dt} = \left(\frac{V}{V + V_C} \right) - \delta_5 D_M \tag{18}$$

$$\frac{dD_F}{dt} = \left(\frac{C}{C + C_C} \right) - \delta_4 D_F \tag{19}$$

$$\frac{dT}{dt} = \delta_{11} D_M(t - \tau_2) + D_F(t - \tau_2) - \delta_9 T + \delta_{16} T V B_L + \delta_{17} Q(t - \tau_2) \tag{20}$$

$$\frac{dB_L}{dt} = T - \delta_7 B_L \tag{21}$$

$$\frac{dA_L}{dt} = B_L - \delta_8 A_L - \delta_{15} V A_L \tag{22}$$

$$\frac{dQ}{dt} = \theta \delta_{11} D_M + D_F, \tag{23}$$

subject to the dimensionless initial and past conditions

$$t < 0 : \qquad V = B_S = A_S = C = D_F = D_M = T = B_L = A_L = Q = 0, \tag{24}$$

$$t = 0 : \qquad V = V_0, \quad B_S = A_S = C = D_F = D_M = T = B_L = A_L = Q = 0. \tag{25}$$

3 Results

Using the mathematical model it is possible to explore the range of behaviours that it exhibits for a set of biologically plausible parameters. The "standard" set of parameters are given in Table 3. Figure 3 shows the dynamical response of the principal model variables following a single vaccination event at time $t = 0$. Plots are shown for two different vaccine capsid

Parameter	Value	Parameter	Value	Parameter	Value
V_0	10	C_C	0.1	V_C	7
τ_1	0.14	τ_2	0.57	T_{boost}	8
δ_1	10/20	δ_2	1	δ_3	1
δ_4	5000	δ_5	3	δ_6	0.6
δ_7	1	δ_8	4	δ_9	1
δ_{10}	0.007	δ_{11}	0.1	δ_{12}	0.14
δ_{13}	0.14	δ_{15}	0.2	δ_{16}	18000
δ_{17}	0.05	θ	1		

Table 3: Table of dimensionless values used in the simulation that produced the results shown in Figure 6; the values used in Figures 3 and 4 are mostly the same. The two values for δ_1 correspond to the stable ($\delta_1 = 10$) and unstable ($\delta_1 = 20$) cases.

stabilities (red - "stable", blue - "unstable"). Overall, it can be seen from Figure 3 that the model is capable of producing acceptable dynamic behaviours for the variables. Vaccine concentration declines rapidly in the days immediately following the vaccination event whereas the fields corresponding to the immunological variables exhibit longer-time-scale responses.

3.1 Effects of vaccine stability

Some key features are worthy of note:

- Capsid stability has a large impact on the activated dentritic cell levels depending upon the mechanism by which antigen is ingested by the cell. Unstable vaccine is taken up much less efficiently by the fc receptor route, whereas macropinocytosis is less affected by vaccine stability (see plots for D_F and D_M). There is also a corresponding pronounced effect of capsid stability on the antigen-antibody complex concentration (plot for C).

- The short-term and long-term B cell responses behave as expected with the short-term response peaking several days after the vaccination event and the long-term response peaking after weeks have passed (see plots for B_S and B_L).

- Short and long-term antibody responses have the appropriate dynamical responses (see plots for A_S and A_L). Moreover, whereas the short-term antibody response is immediate, the long-term antibody response only begins to take-off at around 4 days after the vaccination event. This delay effect is also seen in the response of the T dependent antibody responses [7]. The model indicates that vaccine stability might not have a pronounced impact on the timing of the T cell response, though it will have an effect on its magnitude.

Each of the above features are supported qualitatively by experimental studies of immune responses to FMD vaccine thereby giving confidence that the basic mathematical model captures the most significant interactions that are generated following vaccination with antigen capsids of differing stability.

In terms of the questions posed in Section 1, we can see in response to question 1 that the efficiency of capsid uptake is quite strongly influenced by the capsid stability. This is evident from the plots of D_F and D_M. Also in response to question 4 it can be seen how capsid stability influences the T cell response from the plot of T.

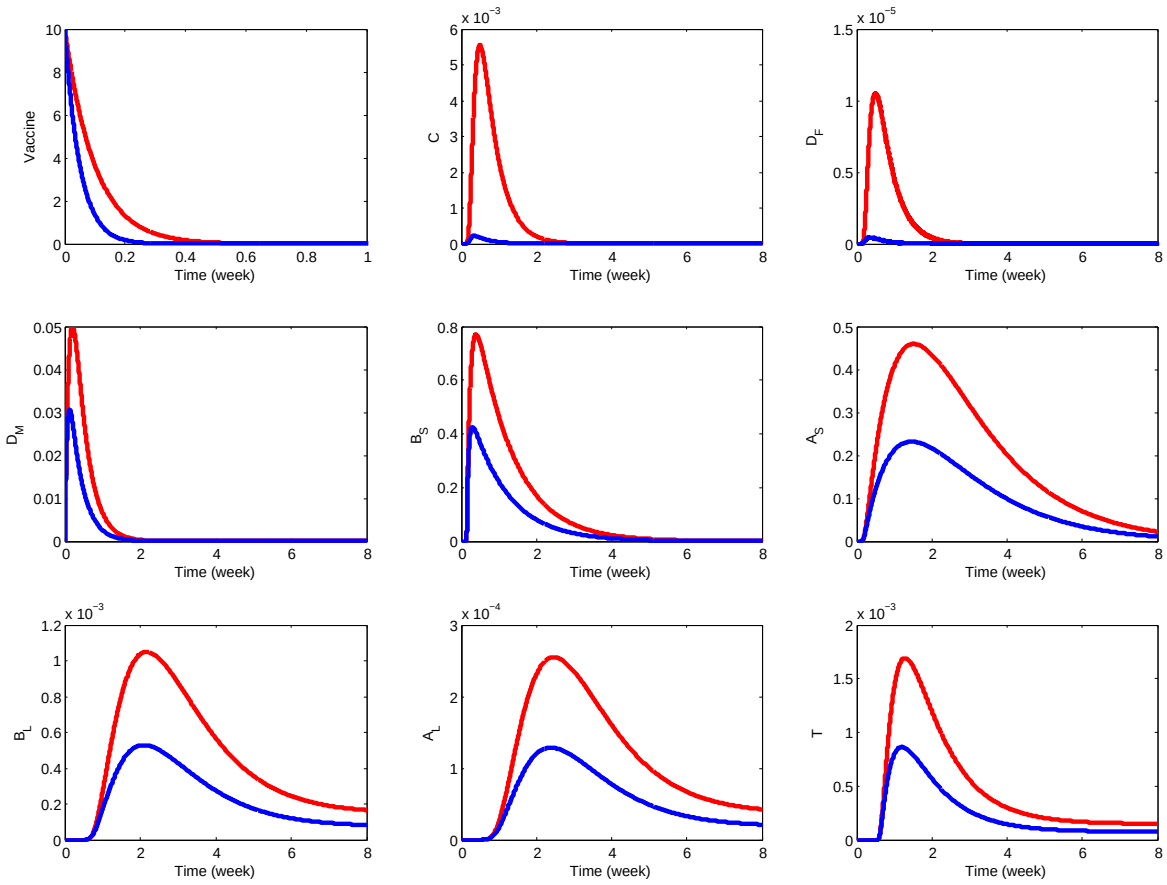

Figure 3: Dynamic behavior of all variables in response to single vaccination at $t = 0$ over the time course of 8 weeks. Stable (red line) and unstable (blue line) vaccine correspond to $\delta_1 = 10$ and $\delta_1 = 20$, respectively. Note different time scale for the Vaccine.

3.2 Effects of higher dose vaccine

As an extension of the basic simulation above, we investigated whether it is possible to mitigate deficiencies in vaccine stability by injecting a higher dose of vaccine. It is a question of some practical importance.

We repeated the simulation for 4 different types of vaccination. Firstly, we did one for stable vaccine ($\delta_1 = 10$) and another for unstable vaccine ($\delta_1 = 20$), exactly as in Fig.1, with dose of $V_0 = 10$. Two further simulations were done for unstable vaccine though now with increased inoculation doses $V_0 = 30$ and 50 to see if this can replicate the responses that are stimulated by the stable vaccine with $V_0 = 10$.

Under the condition of our limited set of parameters, a 3-fold increase in the inoculation dose of unstable vaccine shows similar dynamics as the stable one for B_L, A_L, and T. It shows that the effectiveness of vaccination can be recovered by enhancing the inoculation dose of an unstable vaccine candidate. This mitigation is achieved mainly by higher or similar D_M level for stable (red) and unstable with increased dose (blue dotted and dash dot). On the contrary, higher levels of B_S and A_S for 3-fold more unstable vaccine (blue dash dot) compared to that for stable vaccine (red) does not lead to high C and thus D_F concentration. This means that the unstable but increased dose achieves similar vaccination effect as the stable one by producing more D_M by macropinocytosis. Note also that the difference in scale for D_M and D_F, i.e., the macropinocytosis may play bigger role to attain vaccination effects. The similar

levels of C and D_F as for stable vaccine is attained by 5-fold more inoculation dose for unstable vaccine.

3.3 Booster effect

Motivated by question 6 in Section 1, it is straightforward to extend the above analysis to the case where there is an additional booster vaccination which takes place some weeks after the initial vaccination event. When this happens the vaccine antigen in the booster can immediately interact with the pre-existing T cell population that was generated from the initial vaccination event thereby generating a faster immunological response. (This is essentially the memory effect in immunology). Using the model it is possible to look at the effect of vaccine stability on the response of the immune system to additional vaccination events.

The evolution of the model variables' response to primary and secondary vaccinations are shown in Figure 5 for a stable (red, $\delta_1 = 10$) and unstable (blue, $\delta_1 = 20$) vaccine. The initial vaccination event occurs at $t = 0$ and a second vaccination occurs at a $t = 8$. As expected the immune response to the more stable vaccine is much more pronounced than that of the unstable case, as is illustrated from the experimental data shown in the bottom two graphs of Figure

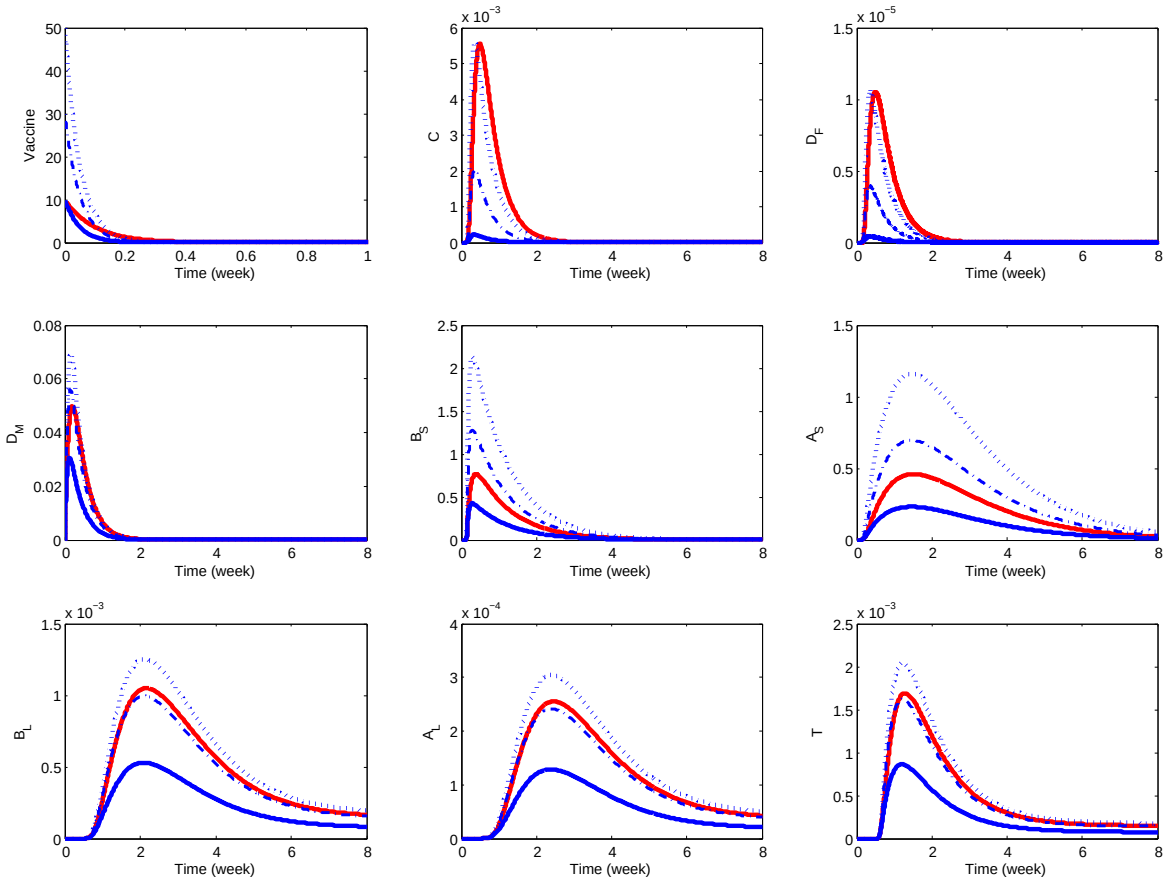

Figure 4: Comparison of system behaviors with different level of inoculation at $t = 0$ over the time course of 8 weeks. Stable (red line) and unstable (blue lines) vaccine correspond to $\delta_1 = 10$ and $\delta_1 = 20$, respectively. Stable vaccine (red) is introduced with $V_0 = 10$. Unstable vaccines (blue) are introduced with $V_0 = 10$ (solid), $V_0 = 30$ (blue dash dot), and $V_0 = 50$ (dotted), respectively.

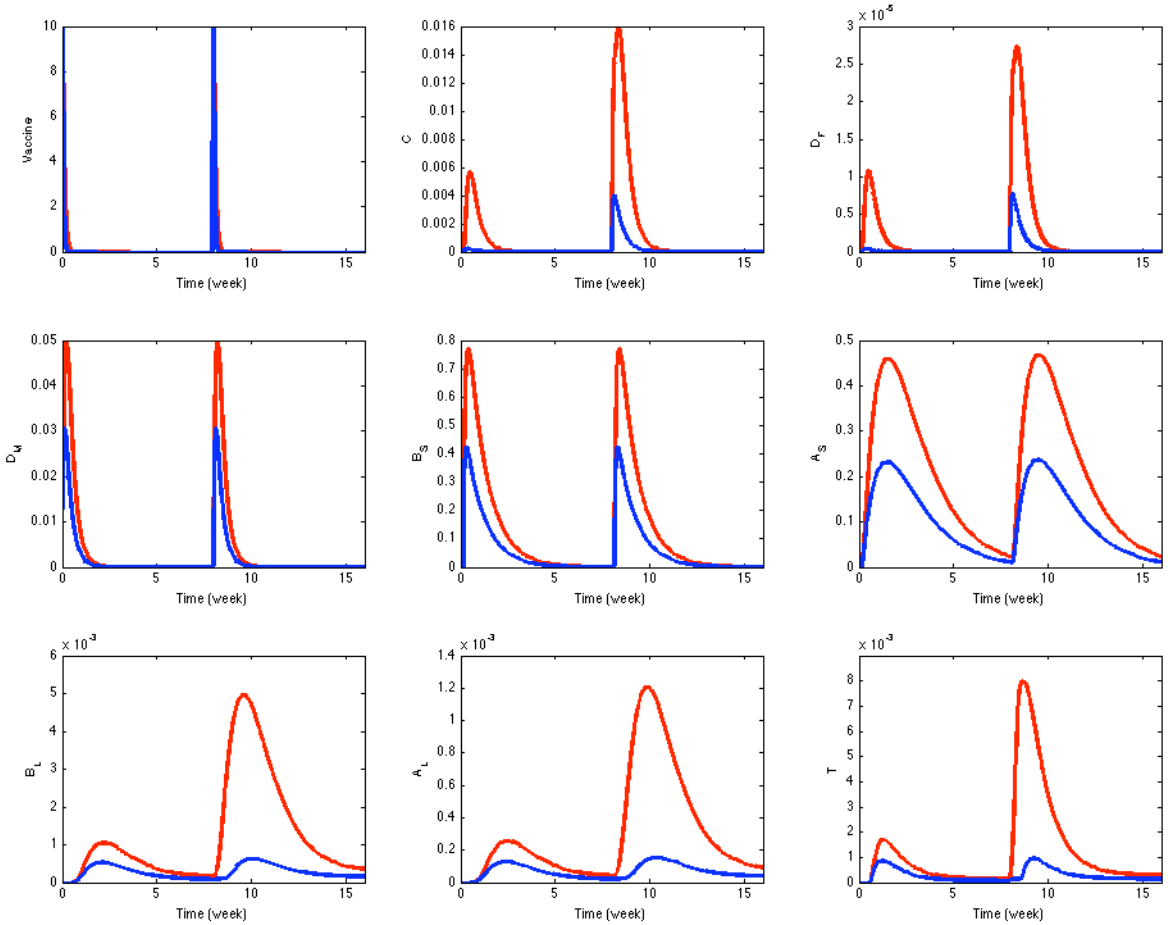

Figure 5: Dynamic behavior of all variables in response to an initial and booster vaccination at $t = 0$ and $t = 8$ over the time course of around 16 weeks. Stable (red line) and unstable (blue line) vaccine correspond to $\delta_1 = 10$ and $\delta_1 = 20$, respectively.

6. The key difference is that there is a much more rapid rise and considerable enhancement in T-cell levels following the booster of the stable vaccine, peaking at approximately 4 times the level of that after the primary vaccination. As a consequence, the levels of long-term B-cells, IgG, vaccine-IgG complex and fc activated DC cells are also significantly enhanced. We note further, that there is relatively little difference in the short-term response to stable vaccine. Examination of the response to the unstable vaccine shows little difference between the primary and secondary vaccinations, though, there is a notable increase in vaccine-IgG complex and fc activated DC cells after the second vaccination, however, the peak is lower than that of the stable case after the first vaccination. Nevertheless, such a rise in levels of C and D_F does indicate that there was a low level of activation of the long-term response following the first vaccination, and further boosts of the unstable vaccine may eventually provide the desired immunity in the animal.

Figure 6 shows a comparison of anti-body levels (IgM = red, IgG $\times 500$ = blue) between the model results (top graphs) and experimental data from 6 month old calves (bottom graphs) in response to two inoculations of stable (left, using $\delta_1 = 10$) and unstable (right, using $\delta_1 = 20$) vaccines. In the experiments, the booster was administered 58 days after the initial inoculum, which is approximately $t = 8$ in simulated time (indicated by the vertical lines in the top graphs). The first observation is that the model agrees qualitatively well with the experimental

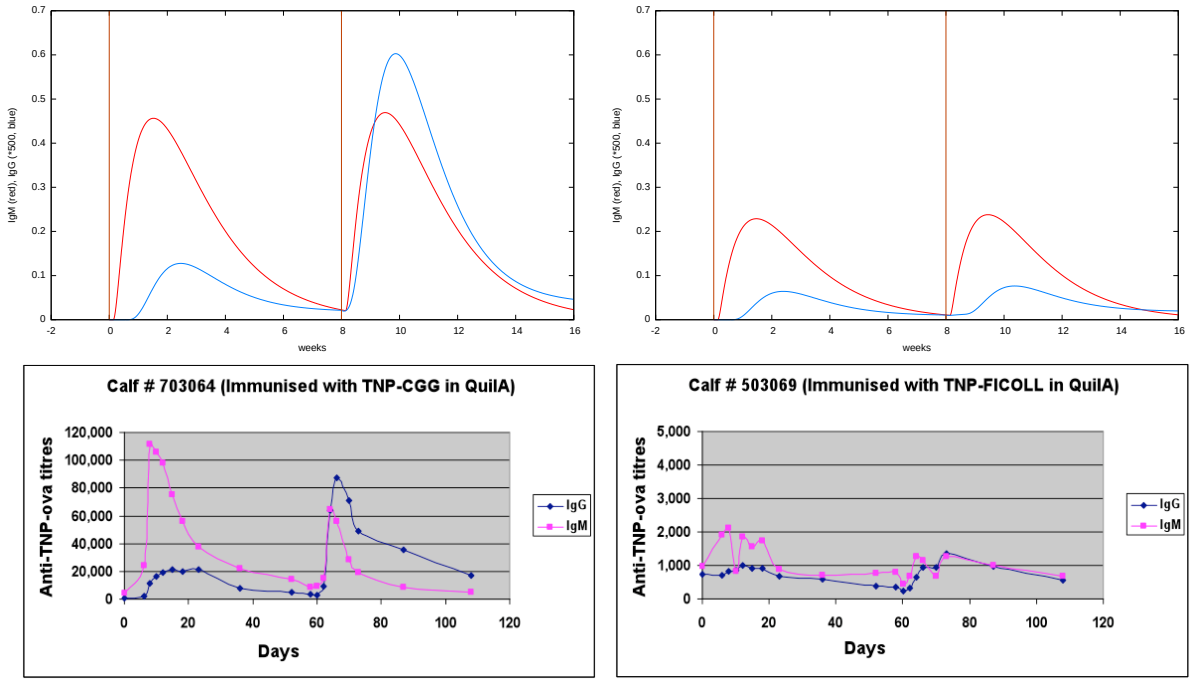

Figure 6: Comparison of the model solutions with experimental data to the first vaccination ($t = 0$) and a booster vaccination at simulated time $t = 8$ and experimental time of about 58 days. In all graphs IgM levels are shown in red and IgG levels in blue; the values of IgG have been multiplied by 500 for clarity. The plots on the left and the right correspond to the stable ($\delta_1 = 10$) and unstable ($\delta_1 = 20$) vaccine cases, respectively. The vertical lines in the top two graphs indicate the time point of inoculation. The data shown in the bottom two graphs were obtained from 6 month old two calves, one immunised with a stable vaccine TNP-CGG in Quill A adjuvant (left) and the other with the unstable form TNP-FICOLL in Quill A adjuvant (right).

data in both the stable and unstable cases. In particular, the desired significant jump in IgG levels following the second vaccination of the stable vaccine is illustrated well by the model. Examining the graphs in more detail, we can see that following the booster vaccination, the model suggests that the IgM is about the same following the initial vaccination. This is in apparent contrast with the experimental data which suggest lower, marginally in the unstable vaccine case, IgM response following the second vaccination. However, in both the model and experiment, IgG levels appear slightly enhanced following the booster, though, once again, very marginal in the unstable case. Further examination shows that the experimental antibody levels are measured to be 20-60 times higher in the stable vaccine case, whilst the model suggests between 2-10 times higher. This may suggest that half-life of the unstable vaccine is somewhat less than half that of the stable one. Nevertheless, the model is largely consistent with these empirical observations, but where our model appears to depart qualitatively from the experimental picture is that (for the albeit limited parameter regime we have explored) the IgM antibody response is generally larger than that seen after the initial vaccination.

4 Discussion

The study group was asked to consider number of different, but related, questions. The development of a model has helped to elucidate some of these as well as offering a clear way

to proceed in the future. In some cases the process of constructing a model, building on physically realistic constructions, has proposed answers, while others have been inferred from the model output and simulations. Implicit in the use of a mass action model is the assumption that responses are influenced by the length of time factors are present. It is perhaps therefore inevitable that capsid stability, as modelled here, has a direct impact on the T cell proliferation response.

The model includes two distinct pathways: short term B-cell production and longer production of target T-cells. Analysis of these produces the behaviour expected from experimental observations, including the timing of the peak in the long and short term responses. The explicit inclusion of clearly identified parameters which governing specific aspects of the system, such as antibody mediated uptake, allow for the influence of each of these to be explored. There was not sufficient time for this during the study group week, but offers a clear and useful way to exploit and extend what has been achieved thus far. Of primary interest is understanding the dynamic response of the system to the decay rate of vaccine capsid δ_V.

Results suggest that vaccine stability may not have a pronounced impact on the timing of the T cell response, but will affect its magnitude. Future work will look in more detail to how these predictions compare with experimental evidence that vaccine produced from different virus serotypes can differentially stimulate T cell responses. The system achieves good qualitative agreement with empirical observations of the system response to booster vaccine doses, and suggests that stable vaccine benefit more from multiple doses.

The model also predicts that high decay rate can be compensated with an increase in dose, but this is perhaps not surprising for mass action model. Here we have studied the effect of vaccine decay rate on its uptake and the subsequent dynamics, and assume that this is representative of vaccine stability. The validity of this assumption will be considered in greater detail in future work. We have not explicitly address antigen processing and presentation, but there is potential for the system to be extended to incorporate this, building on existing work in this area (e.g. [1, 2]).

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