Parameter Estimation of Antibody Control of EIAV in SCID to Stimulate the Immune System

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Abstract: In this paper, we introduce viral dynamic modeling of antibody protection from Equine Infectious Anemia Virus (EIAV) infection in Severe Combined Immunodeficiency (SCID) horses may lead to insights into the FFT (Fast Fourier Transform) simulation of control of infection by antibody vaccination. Circumstances are determined under which wild-type infection is eradicated with the antibody vaccine. Also a three-strain competition model is considered in which a second mutant strain may coexist with the first mutant strain. The conditions that permit viral escape by the mutant strains are determined. This work provides insights into the development of vaccines that stimulate the immune system to control infection effectively.

Key Words: EIAV, SCID, mutant, FFT.

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1. INTRODUCTION

(EIAV) is an RNA virus, a member of the Retroviridae family and of the lentivirus genus infecting equids. It causes a persistent infection characterized by recurring febrile episodes associating viremia, fever, thrombocytopenia and wasting sysmptoms. Among lentiviruses, EIAV is unique in that, despite a rapid virus replication and antigenic variation, most animals progress from a chronic stage characterized by recurring peaks of viremia and fever to an asymptomatic stage of infection[1]. The understanding of the correlates of this immune control is of great interest in defining vaccine strategies. The major challenge to development of a successful human immunodeficiency virus type1(HIV-1) preventive vaccine is an incomplete understanding of the correlates of protective immunity to HIV-1 infection[2]. Lentiviruses are characterized by high rates of mutation, recombination, and replication, resulting in multiple, diverse populations of viral variants that rapidly adapt to changes in the host environment. Understanding virus and host factors that shape the evolution and selection of virus variant in vivo is an essential component of preventive and therapeutic strategies to control lentivirus infections in humans and animals. Equine infectious anemia virus (EIAV) possesses common features of the Lentiviridae subfamily of retroviruses, including a complex genome organization, tropism for cells of the monocyte/macrophage lineage, and establishment of a persistent, life-long infection. The dynamics of clinical disease and immune control make EIAV a good model to study the role of both host and viral mechanisms contributing to lentiviral persistence and pathogenesis [3]. Eventually, most horses exert immunological control over replicating virus and enter a prolonged period of clinical quiescence associated with the presence of cytotoxic T cells and broadly neutralizing antibody (bNAb). Elucidating mechanisms of viral escape from bNAb is important for the design of effective vaccines for EIAV and related lentiviruses, such as HIV-1[4]. The Nab responses broadly significantly during long-term persistent EIAV infection and bNAb play a critical role in EIAV immune control.

Horses with severe combined immunodeficiency (SCID) serve as a useful tool to examine viral dynamics in animals without adaptive immune responses. Infusion of SCID foals with plasma from a long-term EIAV infected immuno competent horse conferred upon them EIAV-specific neutralizing antibodies, which protected them from wild-type EIAV infection. Mathematical modeling

of neutralizing antibody protection from EIAV infection in SCID horses may lead to insights into the mechanisms of control of infection by antibody vaccination [5, 6].

An impulsive mathematical model is used to predict under what conditions we achieve the eradication of the wild-type strain with a finite number of antibody infusions. Also we estimate the antibody neutralization rate and the basic reproductive number R_0. Another study followed up on this work to examine the effect of mutation on CTL vaccine [8, 9]. This is related to the use of pulse vaccination, seasonal skipping in recurrent epidemics, antiretroviral drug treatment and birth pulses in animals [10].

The goal of the study is to understand the role that neutralizing antibody vaccines can play in the control of lentivirus infection with FFT simulation. Conditions are determined under which wild-type infection is eradicated with the antibody vaccine. This work contributes to the understanding of virus control and potentially provides insights into the development of vaccines that stimulate the immune system to control infection [7].

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g	Virus growth rate for wild type in the absence of antibodies
h	Virus growth rate for mutant 1
i	Virus growth rate for mutant 2
B	Virus carrying capacity
p	Wild-type virus neutralization by antibody
q	Mutant 1 virus neutralization by antibody
r	Mutant 2 virus neutralization by antibody
D	antibody decay rate
A^i	Amount of antibody infusion
A_0	Antibody on day 0
W	Number of wild-type viral particles that initiated infection
M	Number of mutant 1 viral particles that initiated infection
N	Number of mutant 2 viral particles that initiated infection
$t_{1/2}$	Half life of virus due to antibody neutralization
c_1, c_2, c_3	Viral clearance rate
f	Antibody magnification factor

2. Mathematical Model

We use ODE model to three strains of the virus and impulsive differential equations to model the behavior of neutralizing antibodies. The effect of vaccinating at times $t_k\,(k=-1,7,14)$. WE assume that virus is removed in proportion to neutralizing antibodies at rates nW,nM,nN, respectively, and also assume that the wild-type has higher replication and is more susceptible to the antibody respone than mutant 1; similarly, assume that mutant 1 has higher replication and is more susceptible to the antibody response than mutant 2 [11].

Then the model is :

$$W = Ke^{-[(pA+c_1)-g(1-\frac{V}{B})]t}$$

$$M = Ke^{-[(qA+c_2)-h(1-\frac{V}{B})]t}$$

$$N = Ke^{-[(rA+c_3)-i(1-\frac{V}{B})]t}$$

$$A = Ke^{-(D+pW+qM+rN)t}$$

$$\Delta A = A^i$$

Here $V = W + M + N$, K= arbitrary constant. We assume the following: $p > q > r, g > h > i$.

The antibodies on day 0 are calculated from A^i on day -1. The value of η is calculated from the half-life of horse IgG. The half-life of virus due to antibody

neutralization , $t_{1/2}$ was estimated using the half-life of SIV in animals that were CD8-depleted. The viral growth rate was calculated by fitting data from EIAV infected SCID horses to the model with antibody neutralization set to zero with the viral clearance rate subtracted. The carrying capacity was also fit to the same data and then adjusted to account and clearance effects. Note that each strain has a different carrying capacity.

(i). Calculating Parameters:

Calculating p

Consider a simplified version of the model without impulses or viral replication:

$$\frac{dW}{dt} = -pWA$$

$$\frac{dA}{dt} = -DA$$

$$A(t) = A_0 e^{-Dt}$$

$$\frac{dW}{dt} = -pWA_0 e^{-Dt}$$

$$\int_0^t \frac{dW}{W} dt = -pA_0 \int_0^t e^{-Dt} dt$$

$$\log\left(\frac{W}{W_0}\right) = \frac{pA_0}{D} e^{-Dt} - \frac{pA_0}{D}$$

$$W = W_0 e^{-pA_0(1-e^{-Dt})/D}$$

Put t = $t_{1/2}$ then

$$-\log 2 = \frac{-pA_0}{D}(1 - e^{-Dt_{1/2}})$$

$$p = \frac{D \log 2}{A_0\left(1 - e^{-Dt_{1/2}}\right)}$$

Calculating A_0

The parameter A_0 was determined from the initial condition A_{-1} by calculating the exponential decay after a single day had elapsed. Thus:

$$A_0 = A_{-1} e^{-D}$$

(ii). **Calculating g and B:**

This is calculated by fitting the data from EIAV infected control SCID horses A2245, A2247, H707 and H713 [5], to the D.E. for wild-type virus with antibody neutralization set to zero. After fitting the total growth rate, the clearance rate was subtracted to determine g . The virus growth rate for mutant 1, h was determined equivalently by fitting data from infected EIAV specific antibody infused SCID horses A2239 and A2240 [5], and subtracting the clearance rate. To calculate g , we allowed the difference($g - c_1$) to range from -0.1 to 9.1 and then recovered g from the viral clearance rate in each Mont Carlo simulation. The carrying capacity in the absence of antibody neutralization was similarly fitted to EIAV infected SCID horses and found to be $\tilde{B} = 2.9 \times 10^6$ (range $1.9 \times 10^6 - 9.7 \times 10^6$). These values were then scaled to $B = \tilde{B}(1 - \frac{c_1}{g})$ to account for viral growth and clearance.

We analyzed the non-impulsive system there are four equilibria (i) the disease-fre equilibrium, (ii) an equilibrium with mutant 1 alone, (iii) an equilibrium with mutant 2 alone (iv) and a coexistence equilibrium, where all three viral strains coexist. Also we calculated the basic reproduction number. This is a threshold condition that determines whether the disease will persist or be eliminated. We determined that the disease will persist if $R_0 = \frac{g}{c_1} > 1$. R_0 is a composite, consisting of five threshold values($R_1, R_2, R_{E1}, R_{E2}, R_{E3}$) that are derived from bifurcation properties of the existence of endemic equilibria.

We aimed to determine whether, according to the model, a finite number of impulses could lead to virus elimination. A finite number of impulsive effects cannot fundamentally alter the long-term stability properties of equilibria. However , if the viral load falls below the eradication threshold of one viral particle in the horse, then the virus will be eradicated. With 3000 ml of plasma in the horse, this corresponds to an eradication threshold of one particle per 3000ml.

(iii). The Non-Impulse System:

The non-impulsive system is equivalent to the impulse model with $A^i = 0$.

If $A \neq 0$ at equilibrium, then $pW + qM + rN = -D < 0$. It follows that any equilibrium has $A = 0$. If $W = 0$, then either $M = 0$ or $h(1-\frac{V}{B}) = c_2$. In the former case, either $N = 0$ or $i(1-\frac{N}{B}) = N$, $N = B(1-\frac{c_2}{i})$

Assuming $R_2 = \frac{i}{c_3} > 1$. In the latter case,

$iN\frac{c_2}{h} = c_3 N$, $N = 0$ similarly, $h(1-\frac{M}{B}) = c_2$,

$M = B(1-\frac{c_2}{h})$ assuming $R_1 = \frac{h}{c_2} > 1$ or $N = 0$.

If $W \neq 0$, then, $g(1-\frac{V}{B}) = c_1$,

$hM\frac{c_1}{g} + W = c_2 M$ assuming $R_{E1} = \frac{c_2 g}{h c_1} > 1$.

$iN\frac{c_1}{g} + W = c_3 N$ $IN = \frac{gW}{dNgW - gNdW} IW$

assuming $R_{E2} = \frac{c_3 g}{i c_1} > 1$ then W satisfies :

$$\hat{W} = \frac{B(g-c_1)}{g(1+\frac{g}{c_2 g - h c_1} + \frac{g}{c_3 g - i c_1})}$$ assuming

$R_{E3} = \frac{g}{c_1} > 1$. Hence the equilibria of the non-impulsive system are :

$(W, M, N, A) = (0,0,0,0), (0, D(1-\frac{c_2}{h}), 0, 0), (0, 0, D(1-\frac{c_3}{i}), 0)$

and $(\hat{W}, \frac{g}{c_2 g - h c_1}\hat{W}, \frac{g}{c_3 g - i c_1}\hat{W}, 0)$

If the wild type exists at equilibrium, then do both mutants. If ther's no wildtype at equilibrium, then one or the other mutant exists alone or not at all.

Jacobian

The Jacobian is J = [J_1 | J_2], where :

$$J_1 = \begin{bmatrix} -pA + g(1-\frac{V}{B}) - \frac{gW}{B} - c_1 & -\frac{gW}{B} \\ \frac{-hM}{B} & -qA + h(1-\frac{V}{B}) - \frac{hM}{B} - c_2 \\ \frac{-iN}{B} & \frac{-iN}{B} \\ -pA & -qA \end{bmatrix}$$

$$J_2 = \begin{bmatrix} -\frac{gW}{B} & -pW \\ \frac{-hM}{B} & -qM \\ -rA + i(1-\frac{V}{B}) - \frac{iN}{B} - c_3 & -rN \\ -rA & -D - pW - qM - rN \end{bmatrix}$$

then

$$J|_{(0,0,0,0)} = \begin{bmatrix} g-c_1 & 0 & 0 & 0 \\ 0 & h-c_2 & 0 & 0 \\ 0 & 0 & i-c_3 & 0 \\ 0 & 0 & 0 & -D \end{bmatrix}$$

This equilibrium is unstable if $R_{E3} > 1$, or $R_1 > 1 or R_2 > 1$. It follows that the disease-free equilibrium is always unstable. Evaluating J at $(0, M, 0, 0)$, we have:

$$\begin{bmatrix} g(1-\frac{M}{B}) - c_1 & 0 & 0 & 0 \\ \frac{-hM}{B} & h(1-\frac{M}{B}) - \frac{hM}{B} - c_2 & \frac{hM}{B} & -qM \\ 0 & 0 & i(1-\frac{M}{B}) - c_3 & 0 \\ 0 & 0 & 0 & -D - qIM \end{bmatrix}$$

The eigen values are :

$$\lambda_{1,2,3,4} = g(1-\frac{M}{B}) - c_1, h(1-\frac{M}{B}) - \frac{ghM}{B} - c_2, i(1-\frac{M}{B}) - c_3, -D - qM$$

$$= g\frac{c_2}{h} - c_1, h\frac{c_2}{h} - \frac{hM}{B} - c_2, i\frac{c_2}{h} - c_3, -D - qM$$

$$= \frac{1}{h}(c_2 g - hc_1), -\frac{hM}{B}, \frac{c_2 i - c_3 h}{h}, -D - qM$$

This equilibrium is unstable if $R_{E1} > 1$ or if:

$$c_2 i - c_3 h > 0$$

Finally, evaluating J at (0,0, N ,0) we have

$$\begin{bmatrix} g(1-\frac{N}{B}) - c_1 & 0 & 0 & 0 \\ 0 & h(1-\frac{N}{B}) - c_2 & 0 & 0 \\ -\frac{iN}{B} & -\frac{iN}{B} & i(1-\frac{N}{B}) - \frac{hM}{B} - c_3 & -rN \\ 0 & 0 & 0 & -D - rN \end{bmatrix}$$

$$\lambda_{1,2,3,4} = g(1-\frac{N}{B}) - c_1, h(1-\frac{N}{B}) - c_2, i(1-\frac{N}{B}) - \frac{iN}{B} - c_3, -D - rN$$

$$= g\frac{c_3}{i} - c_1, h\frac{c_3}{i} - c_2, \frac{ic_3}{i} - \frac{ic_3}{B} - c_3, -D - rN$$

$$= \frac{1}{i}(c_3 g - ic_1, \frac{c_3 h - c_2 i}{i}, \frac{iN}{B}, -D - rN)$$

This equilibrium is unstable if $R_{E2} > 1$.

Calculating R_0

Using the existence of the endemic equilibrium method [12], the disease is endemic if :

$\max\{R_1, R_2, R_{E1}, R_{E2}, R_{E3}\} > 1$ however, note that $R_{E3} > R_1 > R_2$ & $R_{E3} > R_{E2} > R_{E1}$. Thus the condition for the disease to persist is :

$$R_0 = R_{E3} > 1$$

C. Stabilizing the Mutant 1 Equilibrium

We can write $g = c_1 + \gamma$, where

$\gamma = 0.5$. Then $R_{E3} = \frac{c_1 + \gamma}{c_1} > 1$ suppose

$h = g - 0.01$. Then $R_{E1} = \frac{c_2 g}{(g - 0.01)c_1} = 1$

solving we have $c_1 = \frac{c_2 g}{(g - 0.01)} = 0.0097997$

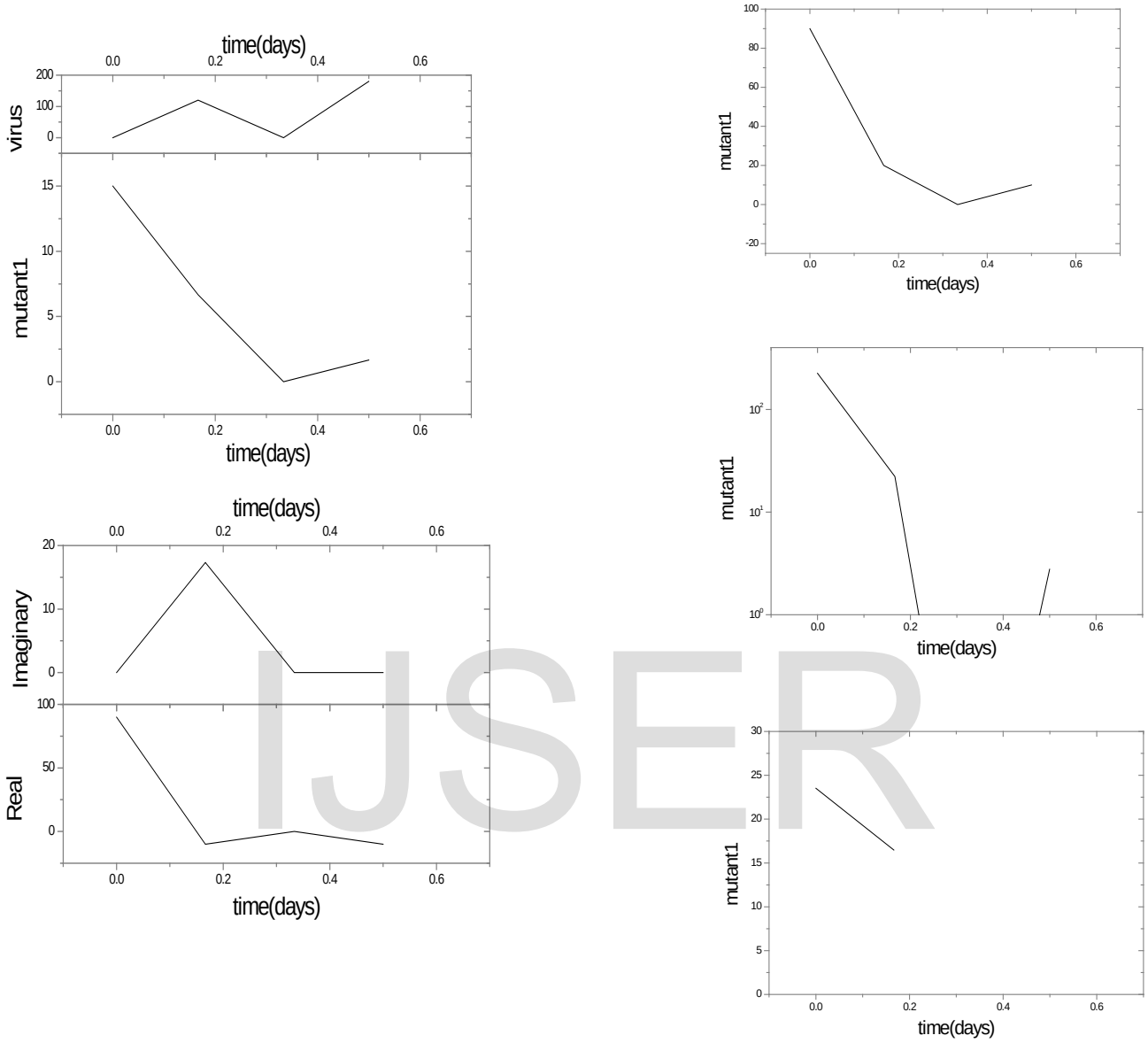
3. Results

Using the sample values in Table 1, to examine the transient and long-term behavior of the system. To investigate the effect of antibody control, we increased both the antibody infusion, and the neutralization ability, by a magnification factor m, where m = 1,10, 50. The value m = 10 means antibodies are ten times greater when infused and are 10 times more effective at neutralizing the virus. The magnification factor thus accounts for theoretical improvements on the vaccine. Also we examine the relative effectiveness of viral neutralization of mutants using three scenarios : (i) the neutralization rates for both mutants are identical to the neutralization rate of the wild-type virus; (2) mutant 1 has 10-fold resistance and mutant 2 has 100-fold resistance; and (3) both mutants have 100 – fold resistance. The results are summarized in table 1.

Table 1. The outcomes from changing antibody infusion and relative effectiveness.

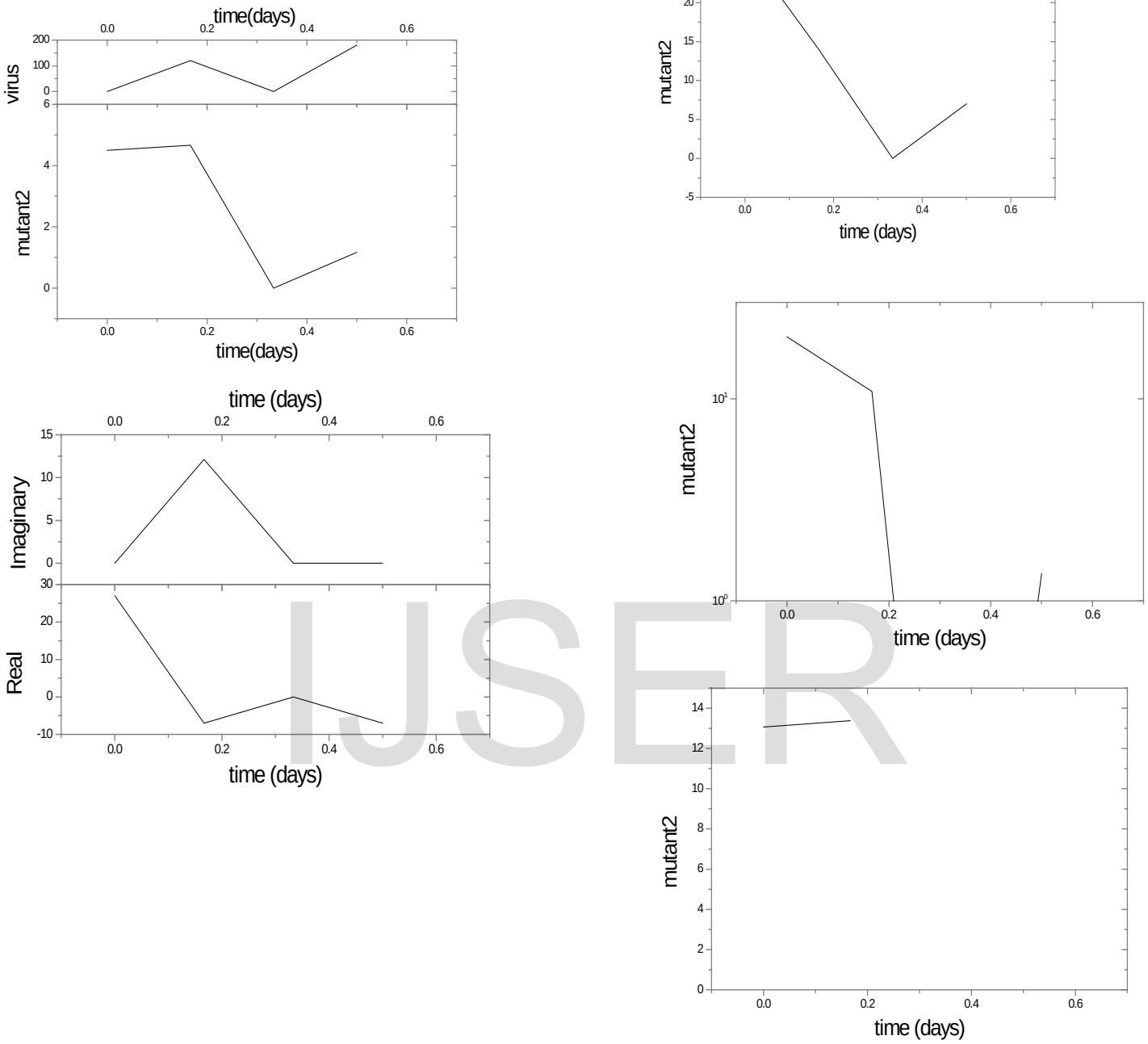
Relative effectiveness	**Antibody Magnification factor f**			
q r	**1**	**10**	**50**	Figure
p p	coexistence	wild-type last	exponentially fast	1
0.1 p 0.01 p	Coexistence	wild-type &Mutant 1 eradicated	Mutant2 last	2
0.01 p 0.01 p	Coexistence	wild-type eradicated	mutant 1 escape or eradication	3

Figure 1. FFT simulation of mutant1



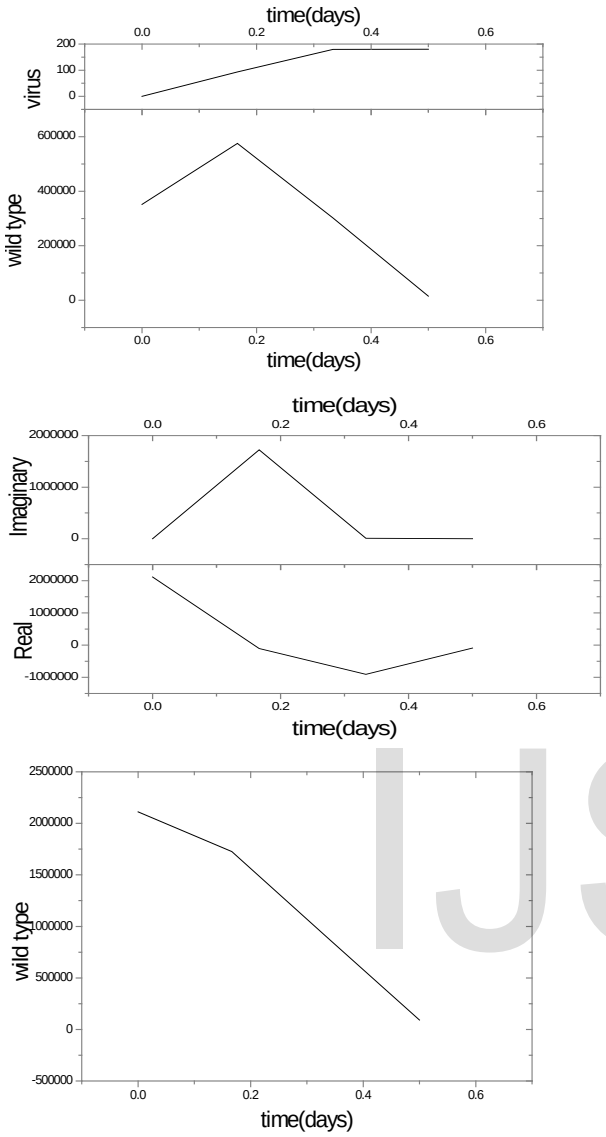
In figure 1 To examine the case when the antibody neutralization rates for all three strains we use FFT simulation .The antibody rates for all three strains are equal. When antibody magnification is f=1, all three strains coexist, but the wild-type dominates. Both 10-fold and 50-fold antibody magnifications eventually control all three strains of the virus. In the case of 10-fold antibody magnification corresponds to the first antibody boost on Day 7, which accelerates the eradication process. Eradication occurs exponentially quickly in the case of 50-fold magnification.

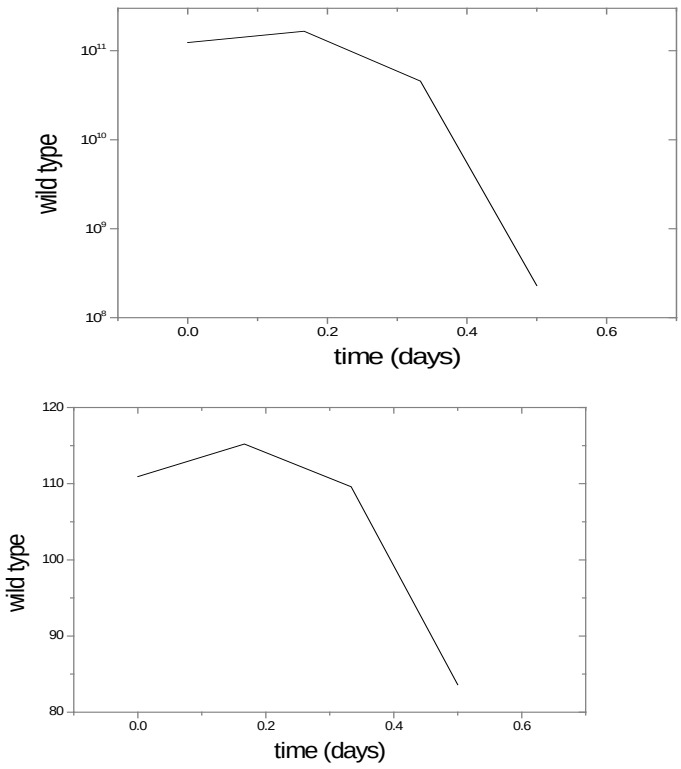
Figure 2. FFT simulation of mutant2



In Figure 2 We examined the case when Mutant 1 had 10-fold resistance and Mutant 2 had 100-fold resistance When antibody magnification is f=1, all three strains coexist, but the wild-type dominates. 10-fold antibody magnification controls the wild-type and mutant1, but allows Mutant2 to escape However,50-fold antibody magnification eventually controls all three strains of the virus. Mutant 2 is eradicated before the antibodies have decayed to zero.

Figure 3. FFT simulation of wild type





In figure 3 We examined the case when both mutants had 100-fold resistance. When f=1 all three strains coexist, but the wild-type dominates. 10-fold antibody magnification controls the wild-type and reduces mutant2, but allows mutant 1 to escape; note that there are no antibodies after about 40 days, so mutant 2 will eventually be out-competed by mutant1. 50-fold antibody magnification still allows mutant 1 to escape, but controls mutant 2 ; in this case, mutant 1 is reduced, but not eradicated, when the antibodies decay to zero, allowing it to bounce back.

4. Discussion

Mathematically, we identified the steady states of the model; we calculated the basic reproduction number and we demonstrated the stability of the steady states. We used an impulsive differential equation model to investigate the scenarios that can theoretically give rise to the outcomes observed in viral infections with antibody vaccination [12]. Our model determined under which conditions the impulses could eradicate infection or could result in mutant escape. This study shows the effects of magnification of the antibody effect. This illustrates the range of effectiveness of different vaccination strategies. If we had a vaccine that was more effective than the baseline vaccine, then different outcomes could occur, including mutant escape. Our model can compare the results found when mutants are equally susceptible to antibody neutralization with the

results found when mutants are differentially susceptible to antibody neutralization. Finally, our modeling results suggest how the escape of a mutant strain can emerge in the presence of a second weaker mutant strain. We calculated the virus neutralization rate by antibodies from the initial amount of antibody infusion, the half-life of virus due to neutralizing antibody and the antibody decay rate. Also we calculated the overall growth rates of wild-type and mutant virus strains by fitting data from EIAV infected SCID horses to our model. To develop an effective neutralizing antibody-eliciting vaccine, it is essential to have an understanding of the conditions that allow virus persistence in the face of neutralizing antibodies. The model shows which conditions can lead to the control of all strains, which conditions lead to the escape of all mutant strains, and which conditions lead to control of some strains but escape of others. This indicates the importance of the dosage and neutralization rate needed by passive immunization to control infection.

5. Conclusions

In the studies the infusion of broadly neutralizing antibodies protected some horses from EIAV infection, and other horses from wild-type EIAV infection but not from a neutralization resistant EIAV variant. The current study indicates which conditions can theoretically give rise to these two outcomes, as well as others. Furthermore, our results quantify the high antibody magnification, resulting in eradication of wild-type and mutant strains, is important for developing an effective vaccine.

Appendix

Parameter	Description	Value	Range	Units
g	Virus growth rate for wild type in the absence of antibodies	23.60	0-46	day^{-1}
h	Virus growth rate for mutant 1	23.23	0-46	day^{-1}
i	Virus growth rate for mutant 2	23.09	0-46	day^{-1}
B	Virus carrying capacity	$1.14x10^{8}$	$7.47x10^{8}$-$3.82x10^{8}$	virus ml^{-1}
p	Wild-type virus neutralization by antibody	$1.462x10^{-2}xm$	$(1.21X10^{-2}$-$2.67X10^{-2})m$	$mlmg^{-1}day^{-1}$
q	Mutant 1 virus neutralization by antibody	(varied)	-	$mlmg^{-1}day^{-1}$
r	Mutant 2 virus neutralization by antibody	(varied)	-	$mlmg^{-1}day^{-1}$
D	antibody decay rate	0.0315	0.0277-0.0365	day^{-1}
A^i	Amount of antibody infusion	38.4Xm	(25.6-51.2)Xm	$mgml^{-1}$
A_0	Antibody on day 0	37.2	24.9-49.4	$mgml^{-1}$
W	Number of wild-type viral particles that initiated infection	224	175-350	virus ml^{-1}
N	Number of mutant 2 viral particles that initiated infection	1	-	virus ml^{-1}
M	Number of mutant 1 viral particles that initiated infection	9	-	virus ml^{-1}
$t_{1/2}$	Half life of virus due to antibody neutralization	1.3	0.7-1.8	day
c_1, c_2, c_3	Viral clearance rate	23	9.1-3.6	day^{-1}
f	Antibody magnification factor	{1,10,50}	_	-

6. References

1. Leroux C, Cadore JL, Montelaro RC (2004). Equine Infectious Anemia Virus (EIAV): What has HIV's country cousin got to tell us? *Vet Res*. 35, 485-512.

2. Liu P, Overman RG,Yates NL, Alam SM, Vandergrift N, Chen Y, Graw F, Freel SA, Kappes JC,Ochsenbauer C, Montefiori DC, Gao F, Perelson AS, Cohen MS, Haynes BF, Tomaras GD (2011). Dynamic Antibody Specificities and Virion Concentrations in Circulating Immune Complexes in Acute to Chronic HIV-1 infection. *J Virol*. 85(21):11196.

3. Carpenter S, Chen WC, Dorman KS (2011). Rev Variation during Persistent Lentivirus Infection. *Viruses*. 3, 1-11; *doi: 10.3390/v3010001*

4. Wu W, Blythe DC, Loyd H, Mealey RH, Tallmadge RL, Dorman KS, Carpenter S (2011). Decreased Infectivity of a Neutralization-Resistant Equine Infectious Anemia Virus Variant Can Be Overcome by Efficient Cell-to-Cell Spread. *J Virol.* 85 (19), 10421-10424.

5. Taylor SD, Leib SR, Carpenter S, Mealey RH (2010). Selection of a Rare Neutralization-Resistant variant following Passive Transfer of Convalescent Immune Plasma in Equine Infectious Anemia Virus-Challenged SCID Horses. *J Virol*. 84 (13), 6536-6548.

6. Taylor SD, Leib SR ,Wu W, Nelson R, Carpenter S, Mealey RH (2011). Protective Effects of Broadly Neutralizing Immunoglobulin against Homologous and Heterologous Equine Infectious Anemia Virus Infection in Horses with Severe Combined Immunodeficieny. *J Virol.* 85(13), 6814 – 6818.

7. Schwartz JE, Smith RJ (2014). Identifying the Conditions Under Which Antibodies Protect Against Infection by Equine Infectious Anemia Virus. *Vaccines*. 2, 397-421.

8. Schwartz EJ, Pawelek KA, Harrington K, Cangelosi R, Madrid S (2013). Immune control of equine infectious anemia virus infection by cell- mediated and humoral responses. *Applied Mathematics*, 4, 171-177.

9. Konrad BP, Vaidya NK, Smith RJ. (2011). Modelling Mutation to a Cytotoxic T-Lymphocyte HIV Vaccine. *Mathematical Population Studies*. 18, 122-149.

10. Miron RE, Smith RJ (2010). Modelling imperfect adherence to HIV induction therapy. *BMC Infectious Diseases*. 10, 6.

11. Arydah MA, Smith RJ, Lutscher F (2012). Modeling Gender-Structured Wildlife Diseases with Harvesting: Chronic Wasting Disease as an Example. *ISRN Biomathematics*. Vol. 2012. Doi. 10.5402/2012/ 802450.

12. Li J, Blakeley D, Smith RJ (2011). The Failure of R_0. *Computational and Mathematical Methods in Medicine.* Vol. 2011, doi: 10.1155/ 2011/ 527610.