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Global dynamics for discrete-time analog of viral infection model with nonlinear incidence and CTL immune response

Jianpeng Wang, Zhidong Teng* and Hui Miao

*Correspondence:
zhidong_teng@sina.com
College of Mathematics and
Systems Science, Xinjiang
University, Urumqi, 830046, People's
Republic of China

Abstract

In this paper, a discrete-time analog of a viral infection model with nonlinear incidence and CTL immune response is established by using the Micken non-standard finite difference scheme. The two basic reproduction numbers R_0 and R_1 are defined. The basic properties on the positivity and boundedness of solutions and the existence of the virus-free, the no-immune, and the infected equilibria are established. By using the Lyapunov functions and linearization methods, the global stability of the equilibria for the model is established. That is, when $R_0 \leq 1$ then the virus-free equilibrium is globally asymptotically stable, and under the additional assumption (A_4) when $R_0 > 1$ and $R_1 \leq 1$ then the no-immune equilibrium is globally asymptotically stable and when $R_0 > 1$ and $R_1 > 1$ then the infected equilibrium is globally asymptotically stable. Furthermore, the numerical simulations show that even if assumption (A_4) does not hold, the no-immune equilibrium and the infected equilibrium also may be globally asymptotically stable.

MSC: 37M99; 39A11; 92D30

Keywords: viral infection model; CTL immune response; NSFD scheme; basic reproduction number; local and global stability

1 Introduction

As is well known, viruses have caused the abundant types of epidemics and are alive almost everywhere on Earth, infecting people, animals, plants, and so on. There are a large number of diseases, which are caused by viruses for example: influenza, hepatitis, HIV, AIDS, SARS, Ebola, MERS. Therefore, it is important to study viral infection, which can supply theoretical evidence for controlling a disease to break out. In the past years, many authors have studied continuous time viral infection models which are described by the differential equations. See, for example, [1–28] and the references cited therein.

In [1], Hattaf *et al.* proposed the following continuous time viral infection model:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda - dx - f(x, y, v)v, \\ \frac{dy(t)}{dt} = f(x, y, v)v - ay, \\ \frac{dv(t)}{dt} = ky - uv, \end{cases} \quad (1)$$

where x , y , and v denote the densities of uninfected cells, infected cells and virus cells, respectively, λ is the rate of production of uninfected cells, d is the death rate of uninfected cells, $f(x, y, v)$ is the rate of uninfected cells to become infected by virus, a is the rate of disappearance of infected cells, k is the rate that virus produces by infected cells, and u is the rate of virus died. The dynamic behaviors of the model are studied. Although model (1) is simple, model (1) is very important in viral epidemiology, which can show ample viral behaviors. Then, based on continuous model (1), Shi and Dong in [22] proposed a discrete-time analog for the special case $f(x, y, v) = \beta x$ of model (1) by using Mickens's non-standard finite difference (NSFD) scheme. The authors studied the local and global stability of the equilibria and the permanence of the model. In [26], Hattaf and Yousfi proposed the following discrete-time analog directly for model (1) by using the NSFD scheme:

$$\begin{cases} x_{n+1} = x_n + h(\lambda - dx_{n+1} - f(x_{n+1}, y_n, v_n)v_n), \\ y_{n+1} = y_n + h(f(x_{n+1}, y_n, v_n)v_n - ay_{n+1}), \\ v_{n+1} = v_n + h(ky_{n+1} - uv_{n+1}), \end{cases} \tag{2}$$

where $n \in N$, and N denotes the set of all non-negative integers. The global asymptotic stability of the disease-free equilibrium and the chronic infection equilibrium is established by constructing the suitable Lyapunov functions. In [28], the authors extended model (2) to the delayed case. By using the method of Lyapunov functions, the authors established the global asymptotic stability of the disease-free equilibrium and the chronic infection equilibrium with no restriction on the time-step size.

In general, our target is to eliminate and control the virus and infected cells. For all this, many authors have noted that the immune response takes great effect to eliminate and control the virus and infected cells because CTL (cytotoxic T lymphocyte) cells affect the virus load. Therefore, a four dimension continuous time virus dynamical model with Beddington-DeAngelis incidence rate and CTL immune response was studied by Wang, Tao and Song in [2]. The model proposed is as follows:

$$\begin{cases} \frac{dx(t)}{dt} = \lambda - dx - \frac{\beta xv}{1+mx+nv}, \\ \frac{dy(t)}{dt} = \frac{\beta xv}{1+mx+nv} - ay - pyz, \\ \frac{dv(t)}{dt} = ky - uv, \\ \frac{dz(t)}{dt} = cyz - bz. \end{cases} \tag{3}$$

The authors established the global stability of the disease-free equilibrium, the immune-free equilibrium, and the endemic equilibrium.

Motivated by the above works, in this paper we consider a discrete-time analog of a class of continuous time virus dynamical models with nonlinear incidence and CTL immune response which is established by using NSFD scheme. The model is proposed in the following form:

$$\begin{cases} \frac{x_{n+1}-x_n}{\phi} = \lambda - dx_{n+1} - f(x_{n+1}, y_n, v_n)v_n, \\ \frac{y_{n+1}-y_n}{\phi} = f(x_{n+1}, y_n, v_n)v_n - ay_{n+1} - py_{n+1}z_{n+1}, \\ \frac{v_{n+1}-v_n}{\phi} = ky_{n+1} - uv_{n+1}, \\ \frac{z_{n+1}-z_n}{\phi} = cy_{n+1}z_{n+1} - bz_{n+1}, \end{cases} \tag{4}$$

where x_n, y_n, v_n and z_n denote the densities of uninfected cells, infected cells, virus cells, and CTL cells at time n , respectively. The parameters $\lambda, d, a, k,$ and u have the same biological meanings as in model (1), p is the removed rate for the infected cells by the CTL immune response, c is the proliferated rate for the CTL cells by contact with infected cells, b is the disappearance rate for the CTL cells, and the function ϕ is a denominator function (see [29, 30]), which is defined by

$$\phi = \phi(h) = \frac{e^{dh} - 1}{d}.$$

It is well known that the non-standard scheme satisfies the following important rules: the standard denominator h in standard discrete derivative is replaced by a denominator function $0 < \phi(h) < 1$, where $\phi(h) = h + o(h^2)$ and h is the time-step size of numerical integration, and the nonlinear terms are approximated in a nonlocal way using more than one mesh point (see [31, 32]).

Particularly, when $f(x, y, v) = \frac{\beta x}{1+mx+nv}$, we can get the corresponding discrete-time analog of continuous model (3) as follows:

$$\begin{cases} \frac{x_{n+1}-x_n}{\phi} = \lambda - dx_{n+1} - \frac{\beta x_{n+1}}{1+mx_{n+1}+nv_n} v_n, \\ \frac{y_{n+1}-y_n}{\phi} = \frac{\beta x_{n+1}}{1+mx_{n+1}+nv_n} v_n - ay_{n+1} - py_{n+1}z_{n+1}, \\ \frac{v_{n+1}-v_n}{\phi} = ky_{n+1} - uv_{n+1}, \\ \frac{z_{n+1}-z_n}{\phi} = cy_{n+1}z_{n+1} - bz_{n+1}. \end{cases} \tag{5}$$

In this paper, our main purpose is to study the threshold dynamics of model (4). The two basic reproduction numbers R_0 and R_1 are defined. The basic properties on the positivity and boundedness of solutions and the existence of the virus-free equilibrium, the no-immune equilibrium and the infected equilibrium are established. By using the Lyapunov functions and linearization methods, we will establish a series of criteria to ensure the stability of the equilibria for model (4). That is, we will prove that when $R_0 \leq 1$ then model (4) only has the virus-free equilibrium and it is globally asymptotically stable, when $R_0 > 1$ and $R_1 \leq 1$ then model (4) has only the virus-free and the no-immune equilibria, the virus-free equilibrium is unstable and under the additional assumption (A_4) (see Section 3) the no-immune equilibrium is globally asymptotically stable, and lastly when $R_0 > 1$ and $R_1 > 1$ then model (4) has three equilibria: the virus-free equilibrium, the no-immune equilibrium, and the infected equilibrium; the virus-free and the no-immune equilibria are unstable and under the additional assumption (A_4) the infected equilibrium is globally asymptotically stable. Furthermore, numerical simulations are given. It is shown that even if assumption (A_4) does not hold, the no-immune equilibrium may be globally asymptotically stable only when $R_0 > 1$ and $R_1 < 1$, and the infected equilibrium may be globally asymptotically stable only when $R_0 > 1$ and $R_1 > 1$.

This paper is organized as follows. In Section 2, we will first introduce some assumptions for nonlinear incidence function $f(x, y, v)$. Next, we will state and prove some basic results on the existence, uniqueness, positivity and ultimate boundedness of solutions with positive initial conditions for model (4). Furthermore, the existence of the virus-free, the no-immune, and the infected equilibria also is obtained. The stability of the virus-free, the no-immune, and the infected equilibria is presented in Section 3. The numerical simulations are presented in Section 4. Lastly, some concluding remarks are presented in Section 5.

2 Preliminaries

As the epidemiological background of model (4), we assume that any solution (x_n, y_n, v_n, z_n) of model (4) satisfies the following initial condition:

$$x_0 > 0, \quad y_0 > 0, \quad v_0 > 0, \quad z_0 > 0. \tag{6}$$

We also require that the function $f(x, y, z)$ satisfies the following assumptions:

- (A₁) $f(0, y, v) = 0$ for all $y \geq 0$ and $v \geq 0$,
- (A₂) $\frac{\partial f(x, y, v)}{\partial x} > 0$ for all $x > 0, y \geq 0$ and $v \geq 0$,
- (A₃) $\frac{\partial f(x, y, v)}{\partial y} \leq 0$ and $\frac{\partial f(x, y, v)}{\partial v} \leq 0$ for all $x \geq 0, y \geq 0$ and $v \geq 0$.

Specially, when $f(x, y, v) = \frac{\beta x}{1+mx+nv}$ and $f(x, y, v) = \frac{\beta x}{1+nv^q}$, where $\beta > 0, m \geq 0, q \geq 0$, and $n \geq 0$ are constants, by simple calculation we know that such $f(x, y, v)$ satisfies the above assumptions (A₁)-(A₃).

Lemma 1 *Let (A₁) and (A₂) hold. Then the solution (x_n, y_n, v_n, z_n) of model (4) with initial value (6) exists uniquely and is positive for all $n \in N$. In addition, $0 < y_n < \frac{1+b\phi}{c\phi}$ for $n = 1, 2, \dots$*

Proof We know that model (4) is equivalent to the following form:

$$\begin{cases} x_{n+1} = \frac{1}{1+\phi d}(x_n + \phi(\lambda - f(x_{n+1}, y_n, v_n)v_n)), \\ y_{n+1} = \frac{y_n + \phi f(x_{n+1}, y_n, v_n)v_n}{1+\phi(a+pz_{n+1})}, \\ v_{n+1} = \frac{v_n + \phi ky_{n+1}}{1+\phi u}, \\ z_{n+1} = \frac{z_n}{1+\phi(b-cy_{n+1})}. \end{cases} \tag{7}$$

When $n = 0$, we prove that (x_1, y_1, v_1, z_1) exists uniquely and is positive.

We first consider x_1 . According to the first equation of model (7), we have

$$\varphi(x_1) \triangleq x_1 + \phi[d x_1 + f(x_1, y_0, v_0)v_0 - \lambda] - x_0 = 0.$$

Owing to $\varphi(0) = -x_0 - \phi\lambda < 0, \lim_{x_1 \rightarrow \infty} \varphi(x_1) = \infty$ and from (A₂),

$$\varphi'(x_1) = 1 + \phi \left[d + \frac{\partial f}{\partial x_1}(x_1, y_0, v_0)v_0 \right] > 0.$$

Hence, there is a unique $x_1 > 0$ such that $x_1 = x_0 + \phi[\lambda - dx_1 - f(x_1, y_0, v_0)v_0]$.

Next, we consider z_1 . According to the second and fourth equations of model (7), we have

$$z_1 = z_0 + \phi \left[c \frac{y_0 + \phi f(x_1, y_0, v_0)v_0}{1 + \phi(a + pz_1)} z_1 - bz_1 \right]. \tag{8}$$

Let

$$\begin{aligned} \varphi(z_1) \triangleq & \phi p(1 + \phi b)z_1^2 + (1 + \phi[a - pz_0 - cy_0 \\ & - \phi cv_0 f(x_1, y_0, v_0) + b(1 + \phi a)])z_1 - z_0(1 + \phi a). \end{aligned}$$

This is a quadratic function. Since $\varphi(0) = -z_0(1 + \phi a) < 0$ and $\lim_{z_1 \rightarrow \infty} \varphi(z_1) = \infty$, there is a unique $z_1 > 0$ such that $\varphi(z_1) = 0$. That is, (8) holds.

In the following, we consider y_1 . According to the second and last equations of model (7), we have

$$y_1 = y_0 + \phi \left[f(x_1, y_0, v_0)v_0 - ay_1 - py_1 \frac{z_0}{1 + \phi(b - cy_1)} \right]. \tag{9}$$

Let

$$\begin{aligned} \varphi(y_1) \triangleq & \phi [c(1 + \phi a)y_1^2 - (b + cy_0 + \phi cf(x_1, y_0, v_0)v_0 + a \\ & + \phi ab + pz_0)y_1 + y_0b + (1 + \phi b)f(x_1, y_0, v_0)v_0] + y_0 - y_1. \end{aligned}$$

Owing to $z_1 > 0$, from the last equation of model (7) we have $y_1 < \frac{1+\phi b}{\phi c}$. Then we have

$$\begin{aligned} \varphi(0) &= y_0 + \phi [y_0b + (1 + \phi b)f(x_1, y_0, v_0)v_0] > 0, \\ \varphi\left(\frac{1 + \phi b}{\phi c}\right) &= -\frac{pz_0 + \phi pbz_0}{c} < 0. \end{aligned}$$

Since $\varphi(y_1)$ is a quadratic function, there is a unique $y_1 \in (0, \frac{1+\phi b}{\phi c})$ such that $\varphi(y_1) = 0$. That is, (9) holds.

Finally, we consider v_1 . According to the third equation of model (7), we have $v_1 = \frac{v_0 + \phi ky_1}{1 + \phi u}$. Hence, we know that v_1 uniquely exists and is positive. Therefore, (x_1, y_1, v_1, z_1) exists uniquely and is positive.

When $n = 1$, by a similar argument to the above, we can prove that (x_2, y_2, v_2, z_2) exists uniquely and is positive. Owing to $z_2 > 0$, we also have $y_2 < \frac{1+\phi b}{\phi c}$. Using the mathematical induction, for any $n \geq 0$, we know that (x_n, y_n, v_n, z_n) exists uniquely and is positive. Furthermore, we also have $y_n < \frac{1+\phi b}{\phi c}$. This completes the proof. \square

Let us consider the region

$$\Gamma = \left\{ (x, y, v, z) : 0 < x, y, v, z \leq \frac{\lambda}{\xi} \right\},$$

where $\xi = \min\{d, \frac{a}{2}, u, b\}$. We have the following result.

Lemma 2 Any solution (x_n, y_n, v_n, z_n) of model (4) with initial condition (6) converges on Γ as $n \rightarrow \infty$, and Γ is positive invariable for model (4).

Proof Define a sequence M_n as follows:

$$M_n = x_n + y_n + \frac{a}{2k}v_n + \frac{p}{c}z_n.$$

We have

$$\begin{aligned} M_{n+1} &= x_{n+1} + y_{n+1} + \frac{a}{2k}v_{n+1} + \frac{p}{c}z_{n+1} \\ &= x_n + y_n + \frac{a}{2k}v_n + \frac{p}{c}z_n + \phi[\lambda - dx_{n+1} - ay_{n+1} - py_{n+1}z_{n+1}] \\ &\quad + \phi\left[\frac{a}{2}y_{n+1} - \frac{au}{2k}v_{n+1} + py_{n+1}z_{n+1} - \frac{pb}{c}z_{n+1}\right] \\ &= M_n + \phi\left[\lambda - dx_{n+1} - \frac{a}{2}y_{n+1} - \frac{au}{2k}v_{n+1} - \frac{pb}{c}z_{n+1}\right] \\ &\leq M_n + \phi[\lambda - \xi M_{n+1}]. \end{aligned}$$

Hence,

$$M_{n+1} \leq \frac{1}{1 + \phi\xi}M_n + \frac{\phi\lambda}{1 + \phi\xi}. \tag{10}$$

By using the induction, we have

$$M_n \leq \left(\frac{1}{1 + \phi\xi}\right)^n M_0 + \frac{\lambda}{\xi}\left[1 - \left(\frac{1}{1 + \phi\xi}\right)^n\right].$$

Consequently, $\limsup_{n \rightarrow \infty} M_n \leq \frac{\lambda}{\xi}$. Owing to the positivity of solution (x_n, y_n, v_n, z_n) , we see that (x_n, y_n, v_n, z_n) converges on Γ as $n \rightarrow \infty$. Furthermore, from Lemma 1 and (10), we easily see that Γ is positive invariable for model (4). This completes the proof. \square

The basic reproductive numbers for model (4) are given by

$$R_0 = \frac{kf(\frac{\lambda}{a}, 0, 0)}{au}, \quad R_1 = \frac{c}{b}y_1^*,$$

where y_1^* is given in the following conclusion (ii) of Lemma 3. R_0 is defined as the average number of secondary infected cells generated by a single infected cell put in an uninfected cell (or free virus) population, R_1 is defined as the average number of killed infected cells by a single CTL cell contacting the infected cells. Based on these basic reproductive numbers, we give the following lemma.

Lemma 3 *Let (A₁)-(A₃) hold.*

- (i) *Model (4) always has a virus-free equilibrium $E_0(\frac{\lambda}{a}, 0, 0, 0)$.*
- (ii) *If $R_0 \leq 1$, then model (4) has only a virus-free equilibrium E_0 , and if $R_0 > 1$, then model (4) has a no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$, except for equilibrium E_0 .*
- (iii) *If $R_0 > 1$ and $R_1 \leq 1$, then model (4) has only the virus-free equilibrium E_0 and the no-immune equilibrium E_1 , and if $R_0 > 1$ and $R_1 > 1$, then model (4) has an infected equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$, except for equilibria E_0 and E_1 .*

Proof It is clear that the equilibrium of model (4) satisfies the following equation:

$$\begin{cases} \lambda - dx - f(x, y, v)v = 0, \\ f(x, y, v)v - ay - pyz = 0, \\ ky - uv = 0, \\ cyz - bz = 0. \end{cases} \tag{11}$$

Obviously, (11) has a solution $(\frac{\lambda}{d}, 0, 0, 0)$. Hence, model (4) always has a virus-free equilibrium $E_0(\frac{\lambda}{d}, 0, 0, 0)$. This shows conclusion (i).

Let $z = 0$, from (11) we have $y = \frac{\lambda - dx}{a}$, $v = \frac{k(\lambda - dx)}{au}$, and $f(x, y, v)v = ay$. Hence,

$$g_1(x) \triangleq f\left(x, \frac{\lambda - dx}{a}, \frac{k(\lambda - dx)}{au}\right) - \frac{au}{k} = 0.$$

We have $g_1(0) = -\frac{au}{k} < 0$ and $g_1(\frac{\lambda}{d}) = \frac{au}{k}(R_0 - 1)$. Based on (A_2) and (A_3) , we know that $g_1(x)$ is monotonously increasing for all $x \in (0, \frac{\lambda}{d})$. When $R_0 > 1$, then $g_1(\frac{\lambda}{d}) > 0$. Hence, $g_1(x) = 0$ has a unique solution $x_1^* \in (0, \frac{\lambda}{d})$. This shows that model (4) has a unique no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ with $y_1^* = \frac{\lambda - dx_1^*}{a}$ and $v_1^* = \frac{k(\lambda - dx_1^*)}{au}$. When $R_0 \leq 1$, then $g_1(\frac{\lambda}{d}) \leq 0$. Hence, $g_1(x) = 0$ has no solution in $(0, \frac{\lambda}{d})$. This shows that model (4) has only equilibrium E_0 . Therefore, conclusion (ii) is true.

Let $z \neq 0$, from (11) we have $y = \frac{b}{c}$, $v = \frac{kb}{uc}$, and the following equation:

$$g_2(x) \triangleq f\left(x, \frac{b}{c}, \frac{kb}{uc}\right) - \frac{uc}{kb}(\lambda - dx) = 0.$$

We have $g_2(0) = -\frac{uc\lambda}{kb} < 0$. When $R_0 > 1$ and $R_1 > 1$, we know $y_1^* > \frac{b}{c}$. Owing to $y_1^* = \frac{\lambda - dx_1^*}{a}$, by simply calculating we can obtain $x_1^* < \frac{\lambda}{d} - \frac{ab}{dc}$. Hence,

$$g_2\left(\frac{\lambda}{d} - \frac{ab}{dc}\right) = f\left(\frac{\lambda}{d} - \frac{ab}{dc}, \frac{b}{c}, \frac{kb}{uc}\right) - \frac{ua}{k} > f(x_1^*, y_1^*, v_1^*) - \frac{ua}{k} = 0.$$

From (A_2) , we know that $g_2(x)$ is monotonously increasing for $x > 0$. Hence, there is a unique $x_2^* \in (0, \frac{\lambda}{d} - \frac{ab}{dc})$ such that $g_2(x_2^*) = 0$. This shows that model (4) has a unique infected equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$ with $y_2^* = \frac{b}{c}$, $v_2^* = \frac{kb}{uc}$ and

$$z_2^* = \frac{1}{py_2^*}(\lambda - dx_2^* - ay_2^*) > \frac{1}{py_2^*}\left[\lambda - d\left(\frac{\lambda}{d} - \frac{ab}{dc}\right) - \frac{ab}{c}\right] = 0.$$

When $R_0 > 1$ and $R_1 \leq 1$, similarly to above discussion we can see that if $g_2(x) = 0$ has a positive solution x_2^* , then $x_2^* > \frac{\lambda}{d} - \frac{ab}{dc}$. But, if model (4) has a positive equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$, then $z_2^* = \frac{1}{py_2^*}(\lambda - dx_2^* - ay_2^*) > 0$. Hence, we must have $x_2^* < \frac{\lambda}{d} - \frac{ab}{dc}$, which leads to a contradiction. Therefore, conclusion (iii) is true. This completes the proof. \square

3 Stability of equilibria

First of all, we introduce the following assumption:

$$\left(1 - \frac{f(x, y, v)}{f(x, y_i^*, v_i^*)}\right)\left(\frac{f(x, y_i^*, v_i^*)}{f(x, y, v)} - \frac{v}{v_i^*}\right) \leq 0, \quad i = 1, 2, \tag{A_4}$$

for all $(x, y, v, z) \in \Gamma$, and (x_i^*, y_i^*, v_i^*) is the coordinate of equilibrium E_i for $i = 1, 2$, respectively.

Specially, when $f(x, y, v) = \frac{\beta x}{1+mx+nv}$, by simple calculation we know that $f(x, y, v)$ satisfies assumption (A_4) .

However, when $f(x, y, v) = \frac{\beta x}{1+mv^2}$, in Section 4, we will give the numerical examples to indicate that assumption (A_4) may not be satisfied.

Theorem 1 *Suppose that (A_1) - (A_3) hold. If $R_0 \leq 1$, then the virus-free equilibrium $E_0(\frac{\lambda}{d}, 0, 0, 0)$ of model (4) is globally asymptotically stable.*

Proof Let $x^* = \frac{\lambda}{d}$ and (x_n, y_n, v_n, z_n) be any solution of model (3) with initial condition (6). Choosing a Lyapunov function as follows:

$$W_n = x_n - x^* - \int_{x^*}^{x_n} \frac{f(x^*, 0, 0)}{f(s, 0, 0)} ds + y_n + \frac{a(1 + \phi u)}{k} v_n + \frac{p}{c} z_n,$$

we let

$$m(x) \triangleq x - x^* - \int_{x^*}^x \frac{f(x^*, 0, 0)}{f(s, 0, 0)} ds.$$

According to (A_2) , we easily obtain $m(x) \geq m(x^*) = 0$ for all $x \geq 0$. Therefore, $W_n \geq 0$ for all $x_n \geq 0, y_n \geq 0, v_n \geq 0$, and $z_n \geq 0$. In addition, $W_n = 0$ if and only if $x_n = x^*, y_n = 0, v_n = 0$ and $z_n = 0$. Computing ΔW_n , we have

$$\begin{aligned} \Delta W_n &= x_{n+1} - x_n - \int_{x_n}^{x_{n+1}} \frac{f(x^*, 0, 0)}{f(s, 0, 0)} ds + y_{n+1} - y_n \\ &\quad + \frac{a(1 + \phi u)}{k} (v_{n+1} - v_n) + \frac{p}{c} (z_{n+1} - z_n) \\ &\leq \left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)}\right) (x_{n+1} - x_n) + y_{n+1} - y_n \\ &\quad + \frac{a(1 + \phi u)}{k} (v_{n+1} - v_n) + \frac{p}{c} (z_{n+1} - z_n). \end{aligned}$$

Substituting model (4), we have

$$\begin{aligned} \Delta W_n &\leq \phi \left[\left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)}\right) (\lambda - dx_{n+1} - f(x_{n+1}, y_n, v_n)v_n) + f(x_{n+1}, y_n, v_n)v_n \right. \\ &\quad \left. - ay_{n+1} - py_{n+1}z_{n+1} + \frac{a(1 + \phi u)}{k} (ky_{n+1} - uv_{n+1}) + \frac{p}{c} (cy_{n+1}z_{n+1} - bz_{n+1}) \right] \\ &= \phi \left[\left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)}\right) (\lambda - dx_{n+1}) - f(x_{n+1}, y_n, v_n)v_n \right. \\ &\quad \left. + \frac{f(x_{n+1}, y_n, v_n)}{f(x_{n+1}, 0, 0)} f(x^*, 0, 0)v_n + f(x_{n+1}, y_n, v_n)v_n - ay_{n+1} - py_{n+1}z_{n+1} \right. \\ &\quad \left. + ay_{n+1} + \phi au y_{n+1} - \frac{au(1 + \phi u)}{k} v_{n+1} + py_{n+1}z_{n+1} - \frac{pb}{c} z_{n+1} \right]. \end{aligned}$$

Substituting $\lambda = dx^*$ and $v_{n+1} = \frac{v_n + \phi ky_{n+1}}{1 + \phi u}$ from model (7), we further obtain

$$\begin{aligned} \Delta W_n &\leq \phi \left[dx^* \left(1 - \frac{x_{n+1}}{x^*} \right) \left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)} \right) + \frac{f(x_{n+1}, y_n, v_n)}{f(x_{n+1}, 0, 0)} f(x^*, 0, 0) v_n \right. \\ &\quad \left. + \phi au y_{n+1} - \frac{au(1 + \phi u)}{k} \frac{v_n + \phi ky_{n+1}}{1 + \phi u} - \frac{pb}{c} z_{n+1} \right] \\ &= \phi \left[dx^* \left(1 - \frac{x_{n+1}}{x^*} \right) \left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)} \right) \right. \\ &\quad \left. + \frac{au}{k} \left(\frac{f(x_{n+1}, y_n, v_n)}{f(x_{n+1}, 0, 0)} R_0 - 1 \right) v_n - \frac{pb}{c} z_{n+1} \right]. \end{aligned}$$

Based on (A₃), we have

$$\Delta W_n \leq \phi \left[dx^* \left(1 - \frac{x_{n+1}}{x^*} \right) \left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)} \right) + \frac{au}{k} (R_0 - 1) v_n - \frac{pb}{c} z_{n+1} \right].$$

According to (A₂), we know

$$\left(1 - \frac{x_{n+1}}{x^*} \right) \left(1 - \frac{f(x^*, 0, 0)}{f(x_{n+1}, 0, 0)} \right) \leq 0.$$

Therefore, when $R_0 \leq 1$ and $z_n > 0, v_n > 0$, we get $\Delta W_n \leq 0$. It is obvious that $\Delta W_n = 0$ if and only if $x_n = x^*, y_n = 0, v_n = 0$ and $z_n = 0$. Based on LaSalle’s invariance principle (see [33]), we finally see that the virus-free equilibrium $E_0(x^*, 0, 0, 0)$ is globally asymptotically stable. This completes the proof. \square

Theorem 2 *Suppose that (A₁)-(A₃) hold. If $R_0 > 1$, then the virus-free equilibrium $E_0(\frac{\lambda}{d}, 0, 0, 0)$ of model (4) is unstable.*

Proof By calculating, we can see that the linearization system of model (4) at equilibrium E_0 is

$$\begin{cases} X_{n+1} = \frac{1}{1 + \phi d} X_n - \frac{\phi f(\frac{\lambda}{d}, 0, 0)}{1 + \phi d} V_n, \\ Y_{n+1} = \frac{1}{1 + \phi a} Y_n + \frac{\phi f(\frac{\lambda}{d}, 0, 0)}{1 + \phi a} V_n, \\ V_{n+1} = \frac{\phi k}{(1 + \phi a)(1 + \phi u)} Y_n + \frac{1 + \phi [a + f(\frac{\lambda}{d}, 0, 0)]}{(1 + \phi a)(1 + \phi u)} V_n, \\ Z_{n+1} = \frac{1}{1 + \phi b} Z_n. \end{cases} \tag{12}$$

By calculating we can obtain the characteristic equation of system (12),

$$\begin{aligned} f(\lambda) &\triangleq \left(\lambda - \frac{1}{1 + \phi d} \right) \left(\lambda - \frac{1}{1 + \phi b} \right) \left[(1 + \phi a)(1 + \phi u) \lambda^2 \right. \\ &\quad \left. - \left(2 + \phi \left[a + u + \phi kf \left(\frac{\lambda}{d}, 0, 0 \right) \right] \right) \lambda + 1 \right] = 0. \end{aligned}$$

Solving this equation, we get $\lambda_1 = \frac{1}{1 + \phi d}, \lambda_2 = \frac{1}{1 + \phi b}, \lambda_3$ and λ_4 are determined by the following equation:

$$g(\lambda) \triangleq (1 + \phi a)(1 + \phi u) \lambda^2 - \left(2 + \phi \left[a + u + \phi kf \left(\frac{\lambda}{d}, 0, 0 \right) \right] \right) \lambda + 1 = 0.$$

Since when $R_0 > 1$, we have $g(1) = \phi^2 au(1 - R_0) < 0$ and $\lim_{\lambda \rightarrow \infty} g(\lambda) = \infty$, there exists an $\eta \in (1, +\infty)$ such that $g(\eta) = 0$. This shows that λ_3 or λ_4 is greater than 1. Therefore, the virus-free equilibrium $E_0(\frac{\lambda}{a}, 0, 0, 0)$ is unstable. This completes the proof. \square

For model (5), by calculating, we see that the basic reproductive numbers R_0 and R_1 are given by

$$R_0 = \frac{k\beta\lambda}{au(d + m\lambda)}, \quad R_1 = \frac{\lambda\beta kc + a^2 umb}{aduc + adbk n + a\beta bk + au\lambda mc}.$$

As a consequence of Theorem 1 and Theorem 2 we have the following result for model (5).

Corollary 1 *If $R_0 \leq 1$, then the virus-free equilibrium $E_0(\frac{\lambda}{a}, 0, 0, 0)$ of model (5) is globally asymptotically stable. Otherwise, if $R_0 > 1$, then equilibrium E_0 is unstable.*

Theorem 3 *Suppose that (A_1) - (A_3) and (A_4) for $i = 1$ hold. If $R_0 > 1$ and $R_1 \leq 1$, then the no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ of model (4) is globally asymptotically stable.*

Proof Let (x_n, y_n, v_n, z_n) be any solution of model (4) with initial condition (6). From Lemma 2, we can assume $(x_n, y_n, v_n, z_n) \in \Gamma$ for all $n \geq 0$. Define a Lyapunov function as follows:

$$L_n = x_n - x_1^* - \int_{x_1^*}^{x_n} \frac{f(x_1^*, y_1^*, v_1^*)}{f(s, y_1^*, v_1^*)} ds + y_n - y_1^* - y_1^* \ln \frac{y_n}{y_1^*} + \frac{a(1 + \phi u)}{k} \left(v_n - v_1^* - v_1^* \ln \frac{v_n}{v_1^*} \right) + \frac{p}{c} z_{n+1}.$$

According to (A_2) , we easily obtain

$$m(x) \triangleq x - x_1^* - \int_{x_1^*}^x \frac{f(x_1^*, 0, 0)}{f(s, 0, 0)} ds > 0$$

for all $x \geq 0$ and $x \neq x^*$. Hence, $L_n \geq 0$ for all $x_n \geq 0, y_n \geq 0, v_n \geq 0$ and $z_n \geq 0$. Obviously, $L_n = 0$ if and only if $x_n = x_1^*, y_n = y_1^*, v_n = v_1^*$, and $z_n = 0$. Computing ΔL_n , we have

$$\begin{aligned} \Delta L_n &= x_{n+1} - x_n - \int_{x_n}^{x_{n+1}} \frac{f(x_1^*, y_1^*, v_1^*)}{f(s, y_1^*, v_1^*)} ds + y_{n+1} - y_n - y_1^* \ln \frac{y_{n+1}}{y_n} \\ &\quad + \frac{a(1 + \phi u)}{k} (v_{n+1} - v_n) - \frac{a(1 + \phi u)}{k} v_1^* \ln \frac{v_{n+1}}{v_n} + \frac{p}{c} (z_{n+1} - z_n) \\ &\leq \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)} \right) (x_{n+1} - x_n) + y_{n+1} - y_n - y_1^* \ln \frac{y_{n+1}}{y_n} \\ &\quad - \frac{a(1 + \phi u)}{k} v_1^* \ln \frac{v_{n+1}}{v_n} + \frac{p}{c} (z_{n+1} - z_n) + \frac{a(1 + \phi u)}{k} (v_{n+1} - v_n). \end{aligned}$$

From $\ln x \leq x - 1$ for $x > 0$, we further have

$$\begin{aligned} \Delta L_n &\leq \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)} \right) (x_{n+1} - x_n) + \left(1 - \frac{y_1^*}{y_{n+1}} \right) (y_{n+1} - y_n) \\ &\quad + \frac{a}{k} \left(1 - \frac{v_1^*}{v_{n+1}} \right) (v_{n+1} - v_n) + \frac{\phi au}{k} \left(v_{n+1} - v_n + v_1^* \ln \frac{v_n}{v_{n+1}} \right) + \frac{p}{c} (z_{n+1} - z_n). \end{aligned}$$

Substituting model (4), owing to x_1^* , y_1^* , and v_1^* satisfying the equations

$$\begin{cases} 0 = \lambda - dx_1^* - f(x_1^*, y_1^*, v_1^*)v_1^*, \\ 0 = f(x_1^*, y_1^*, v_1^*)v_1^* - ay_1^*, \\ 0 = ky_1^* - uv_1^*, \end{cases}$$

we obtain

$$\begin{aligned} \Delta L_n &\leq \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right)(x_{n+1} - x_n) + \left(1 - \frac{y_1^*}{y_{n+1}}\right)(f(x_{n+1}, y_n, v_n)v_n \\ &\quad - ay_{n+1} - py_{n+1}z_{n+1})\phi + \frac{a}{k}\left(1 - \frac{v_1^*}{v_{n+1}}\right)(ky_{n+1} - uv_{n+1})\phi \\ &\quad + \frac{\phi au}{k}(v_{n+1} - v_n) + \frac{\phi au}{k}v_1^* \ln \frac{v_n}{v_{n+1}} + \frac{p}{c}(cy_{n+1}z_{n+1} - bz_{n+1})\phi \\ &= \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right)(x_{n+1} - x_n) + ay_1^* \left(1 - \frac{y_1^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_1^*, y_1^*, v_1^*)}\right)\phi \\ &\quad + ay_1^* \left(1 - \frac{y_{n+1}}{v_{n+1}} \frac{v_1^*}{y_1^*} - \frac{v_n}{v_1^*}\right)\phi + f(x_{n+1}, y_n, v_n)v_n\phi \\ &\quad + \frac{\phi pb}{c}(R_1 - 1)z_{n+1} + \frac{\phi au}{k}v_1^* \ln \frac{v_n}{v_{n+1}}. \end{aligned}$$

Since $\lambda = dx_1^* + ay_1^*$, the first equation model (4) becomes

$$x_{n+1} = x_n + \phi[dx_1^* + ay_1^* - dx_{n+1} - f(x_{n+1}, y_n, v_n)v_n].$$

We have

$$\begin{aligned} \Delta L_n &\leq \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right)(dx_1^* + ay_1^* - dx_{n+1} - f(x_{n+1}, y_n, v_n)v_n)\phi \\ &\quad + ay_1^* \left(1 - \frac{y_1^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_1^*, y_1^*, v_1^*)}\right)\phi + ay_1^* \left(1 - \frac{y_{n+1}}{v_{n+1}} \frac{v_1^*}{y_1^*} - \frac{v_n}{v_1^*}\right)\phi \\ &\quad + \phi f(x_{n+1}, y_n, v_n)v_n + \frac{\phi pb}{c}(R_1 - 1)z_{n+1} + \frac{\phi au}{k}v_1^* \ln \frac{v_n}{v_{n+1}} \\ &= \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right)(dx_1^* - dx_{n+1})\phi + ay_1^* \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right. \\ &\quad \left. + \frac{f(x_{n+1}, y_n, v_n)}{f(x_{n+1}, y_1^*, v_1^*)} \frac{v_n}{v_1^*}\right)\phi + ay_1^* \left(1 - \frac{y_1^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_1^*, y_1^*, v_1^*)}\right)\phi \\ &\quad + ay_1^* \left(1 - \frac{y_{n+1}}{v_{n+1}} \frac{v_1^*}{y_1^*} - \frac{v_n}{v_1^*}\right)\phi + \frac{\phi pb}{c}(R_1 - 1)z_{n+1} + \frac{\phi au}{k}v_1^* \ln \frac{v_n}{v_{n+1}} \\ &= \phi dx_1^* \left(1 - \frac{x_{n+1}}{x_1^*}\right) \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right) + \phi ay_1^* \left(4 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right. \\ &\quad \left. - \frac{y_1^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_1^*, y_1^*, v_1^*)} - \frac{y_{n+1}}{y_1^*} \frac{v_1^*}{v_{n+1}} - \frac{f(x_{n+1}, y_1^*, v_1^*)}{f(x_{n+1}, y_n, v_n)} - \ln \frac{v_{n+1}}{v_n}\right) \\ &\quad + \phi ay_1^* \left(-1 - \frac{v_n}{v_1^*} + \frac{f(x_{n+1}, y_1^*, v_1^*)}{f(x_{n+1}, y_n, v_n)} + \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_{n+1}, y_1^*, v_1^*)}\right) + \frac{\phi pb}{c}(R_1 - 1)z_{n+1}. \end{aligned}$$

Let $g(x) = x - 1 - \ln x$, then $g(x) \geq 0$ for all $x > 0$. Hence, we can get

$$\begin{aligned}
 & 4 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)} - \frac{y_1^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_1^*, y_1^*, v_1^*)} \\
 & \quad - \frac{y_{n+1}}{y_1^*} \frac{v_1^*}{v_{n+1}} - \frac{f(x_{n+1}, y_1^*, v_1^*)}{f(x_{n+1}, y_n, v_n)} - \ln \frac{v_{n+1}}{v_n} \\
 & = -g\left(\frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right) - g\left(\frac{y_1^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_1^*, y_1^*, v_1^*)}\right) \\
 & \quad - g\left(\frac{y_{n+1}}{y_1^*} \frac{v_1^*}{v_{n+1}}\right) - g\left(\frac{f(x_{n+1}, y_1^*, v_1^*)}{f(x_{n+1}, y_n, v_n)}\right) \leq 0.
 \end{aligned} \tag{13}$$

According to (A₂), we know

$$\left(1 - \frac{x_{n+1}}{x_1^*}\right) \left(1 - \frac{f(x_1^*, y_1^*, v_1^*)}{f(x_{n+1}, y_1^*, v_1^*)}\right) \leq 0. \tag{14}$$

Since (A₄) holds for $i = 1$, we further have

$$-1 - \frac{v_n}{v_1^*} + \frac{f(x_{n+1}, y_1^*, v_1^*)}{f(x_{n+1}, y_n, v_n)} + \frac{v_n f(x_{n+1}, y_n, v_n)}{v_1^* f(x_{n+1}, y_1^*, v_1^*)} \leq 0. \tag{15}$$

Therefore, when $R_1 \leq 1$, from (13), (14), and (15) we finally obtain $\Delta L_n \leq 0$ and $\Delta L_n = 0$ if and only if $x_n = x_1^*$, $y_n = y_1^*$, $v_n = v_1^*$ and $z_n = 0$. Based on LaSalle’s invariance principle, we see that the no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ is globally asymptotically stable. This completes the proof. \square

Theorem 4 *Suppose that (A₁)-(A₃) hold. If $R_0 > 1$ and $R_1 > 1$, then the no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ of model (4) is unstable.*

Proof By calculating, we easily see that the linearization system of model (4) at equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ is

$$\left\{ \begin{aligned}
 X_{n+1} &= \frac{1}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} X_n - \frac{\phi \frac{\partial f}{\partial y} v_1^*}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} Y_n - \frac{\phi(\frac{\partial f}{\partial v} v_1^* + f(x_1^*, y_1^*, v_1^*))}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} V_n, \\
 Y_{n+1} &= \frac{\phi \frac{\partial f}{\partial x} v_1^*}{(1+\phi(d+\frac{\partial f}{\partial x} v_1^*))(1+\phi a)} X_n + (1 - \phi^2 \frac{\frac{\partial f}{\partial x} v_1^* \frac{\partial f}{\partial y} v_1^*}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} + \phi \frac{\partial f}{\partial y} v_1^*) \\
 &\quad \times \frac{1}{1+\phi a} Y_n + \frac{1}{1+\phi a} [-\phi \frac{\partial f}{\partial x} v_1^* \frac{\phi(\frac{\partial f}{\partial v} v_1^* + f(x_1^*, y_1^*, v_1^*))}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} \\
 &\quad + \phi \frac{\partial f}{\partial v} v_1^* + \phi f(x_1^*, y_1^*, v_1^*)] V_n - \frac{\phi p y_1^*}{1+\phi(b-cy_1^*)} \frac{1}{1+\phi a} Z_n, \\
 V_{n+1} &= \frac{\phi \frac{\partial f}{\partial x} v_1^*}{(1+\phi(d+\frac{\partial f}{\partial x} v_1^*))(1+\phi a)} \frac{\phi k}{1+\phi u} X_n + (1 - \phi^2 \frac{\frac{\partial f}{\partial x} v_1^* \frac{\partial f}{\partial y} v_1^*}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} \\
 &\quad + \phi \frac{\partial f}{\partial y} v_1^*) \frac{1}{1+\phi a} \frac{\phi k}{1+\phi u} Y_n + [\frac{1}{1+\phi a} \frac{\phi k}{1+\phi u} (-\phi \frac{\partial f}{\partial x} v_1^* \\
 &\quad \times \frac{\phi(\frac{\partial f}{\partial v} v_1^* + f(x_1^*, y_1^*, v_1^*))}{1+\phi(d+\frac{\partial f}{\partial x} v_1^*)} + \phi \frac{\partial f}{\partial v} v_1^* + \phi f(x_1^*, y_1^*, v_1^*) + \frac{1}{1+\phi u}] V_n \\
 &\quad - \frac{\phi p y_1^*}{1+\phi(b-cy_1^*)} \frac{1}{1+\phi a} \frac{\phi k}{1+\phi u} Z_n, \\
 Z_{n+1} &= \frac{1}{1+\phi(b-cy_1^*)} Z_n,
 \end{aligned} \right. \tag{16}$$

where

$$\frac{\partial f}{\partial x} = \frac{\partial f}{\partial x}(x_1^*, y_1^*, v_1^*), \quad \frac{\partial f}{\partial y} = \frac{\partial f}{\partial y}(x_1^*, y_1^*, v_1^*), \quad \frac{\partial f}{\partial v} = \frac{\partial f}{\partial v}(x_1^*, y_1^*, v_1^*).$$

By calculating we obtain the characteristic equation of equation (16),

$$f(\lambda) \triangleq \left(\lambda - \frac{1}{1 + \phi(b - cy_1^*)} \right) (\lambda^3 + m\lambda^2 + n\lambda + l) = 0,$$

where

$$\begin{aligned} m &= -(1 + \phi d) \frac{\phi^2 k \left(\frac{\partial f}{\partial v} v_1^* + f(x_1^*, y_1^*, v_1^*) \right)}{(1 + \phi(d + \frac{\partial f}{\partial x} v_1^*))(1 + \phi u)(1 + \phi a)} - \frac{1}{1 + \phi u} \\ &\quad - \frac{\phi \frac{\partial f}{\partial y} v_1^* + 1}{1 + \phi a} + \frac{\phi^2 \frac{\partial f}{\partial x} v_1^* \frac{\partial f}{\partial y} v_1^*}{(1 + \phi(d + \frac{\partial f}{\partial x} v_1^*))(1 + \phi a)} - \frac{1}{1 + \phi(d + \frac{\partial f}{\partial x} v_1^*)}, \\ n &= \frac{\phi^2 k \left(\frac{\partial f}{\partial v} v_1^* + f(x_1^*, y_1^*, v_1^*) \right)}{(1 + \phi(d + \frac{\partial f}{\partial x} v_1^*))(1 + \phi u)(1 + \phi a)} + \frac{1}{(1 + \phi(d + \frac{\partial f}{\partial x} v_1^*))(1 + \phi u)} \\ &\quad + \left(\frac{1}{1 + \phi(d + \frac{\partial f}{\partial x} v_1^*)} + \frac{1}{1 + \phi u} \right) \frac{\phi \frac{\partial f}{\partial y} v_1^* + 1}{1 + \phi a} \\ &\quad - \frac{\phi^2 k \frac{\partial f}{\partial x} v_1^*}{(1 + \phi(d + \frac{\partial f}{\partial x} v_1^*))(1 + \phi u)^2(1 + \phi a)}, \\ l &= - \frac{\phi \frac{\partial f}{\partial y} v_1^* + 1}{(1 + \phi(d + m))(1 + \phi u)(1 + \phi a)}. \end{aligned}$$

Let λ_i ($i = 1, 2, 3, 4$) be the roots of $f(\lambda) = 0$, then $\lambda_1 = \frac{1}{1 + \phi(b - cy_1^*)}$ and λ_2, λ_3 and λ_4 satisfy the equation $\lambda^3 + m\lambda^2 + n\lambda + l = 0$. From $Z_n > 0$, we know $\frac{1}{1 + \phi(b - cy_1^*)} > 0$. By $R_1 > 1$, we have $\frac{b}{c} < y_1^*$. Hence, we get $\frac{1}{1 + \phi(b - cy_1^*)} > 1$. This shows that when $R_1 > 1$, the no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ is unstable. This completes the proof. \square

As a consequence of Theorems 3 and 4 we have the following result for model (5).

Corollary 2 *If $R_0 > 1$ and $R_1 \leq 1$, then the no-immune equilibrium $E_1(x_1^*, y_1^*, v_1^*, 0)$ of model (5) is globally asymptotically stable. Otherwise, if $R_0 > 1$ and $R_1 > 1$, then equilibrium E_1 is unstable.*

Theorem 5 *Suppose that (A₁)-(A₃) and (A₄) for $i = 2$ hold. If $R_0 > 1$ and $R_1 > 1$, then the infected equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$ of model (4) is globally asymptotically stable.*

Proof Let (x_n, y_n, v_n, z_n) be any solution of model (4) with initial condition (6). We can assume by Lemma 2 $(x_n, y_n, v_n, z_n) \in \Gamma$ for all $n \geq 0$. Define a Lyapunov function as follows:

$$\begin{aligned} L_n &= x_n - x_2^* - \int_{x_2^*}^{x_n} \frac{f(x_2^*, y_2^*, v_2^*)}{f(s, y_2^*, v_2^*)} ds + y_n - y_2^* - y_2^* \ln \frac{y_n}{y_2^*} \\ &\quad + \frac{(a + pz_2^*)(1 + \phi u)}{k} \left(v_n - v_2^* - v_2^* \ln \frac{v_n}{v_2^*} \right) + \frac{p}{c} \left(z_n - z_2^* - z_2^* \ln \frac{z_n}{z_2^*} \right). \end{aligned}$$

Obviously, we know $L_n \geq 0$ for all $x_n \geq 0, y_n \geq 0, v_n \geq 0$ and $z_n \geq 0$, and $L_n = 0$ if and only if $x_n = x_2^*, y_n = y_2^*, v_n = v_2^*$, and $z_n = z_2^*$. Computing ΔL_n , we have

$$\begin{aligned} \Delta L_n &= x_{n+1} - x_n - \int_{x_n}^{x_{n+1}} \frac{f(x_2^*, y_2^*, v_2^*)}{f(s, y_2^*, v_2^*)} ds + y_{n+1} - y_n - y_2^* \ln \frac{y_{n+1}}{y_n} \\ &\quad + \frac{(a + pz_2^*)(1 + \phi u)}{k} \left(v_{n+1} - v_n - v_2^* \ln \frac{v_{n+1}}{v_n} \right) + \frac{p}{c} \left(z_{n+1} - z_n - z_2^* \ln \frac{z_{n+1}}{z_n} \right) \\ &\leq \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) (x_{n+1} - x_n) + y_{n+1} - y_n + y_2^* \ln \frac{y_n}{y_{n+1}} \\ &\quad + \frac{(a + pz_2^*)(1 + \phi u)}{k} \left(v_{n+1} - v_n - v_2^* \ln \frac{v_{n+1}}{v_n} \right) + \frac{p}{c} \left(z_{n+1} - z_n - z_2^* \ln \frac{z_{n+1}}{z_n} \right). \end{aligned}$$

Using $\ln x \leq x - 1$ for $x > 0$, we further have

$$\begin{aligned} \Delta L_n &\leq \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) (x_{n+1} - x_n) + \left(1 - \frac{y_2^*}{y_{n+1}} \right) (y_{n+1} - y_n) \\ &\quad + \frac{(a + pz_2^*)(1 + \phi u)}{k} (v_{n+1} - v_n) - \frac{(a + pz_2^*)(1 + \phi u)}{k} v_2^* \ln \frac{v_{n+1}}{v_n} \\ &\quad + \frac{p}{c} \left(1 - \frac{z_2^*}{z_{n+1}} \right) (z_{n+1} - z_n). \end{aligned}$$

Since equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$ satisfies the equations

$$\begin{cases} \lambda - dx_2^* - f(x_2^*, y_2^*, v_2^*)v_2^* = 0, \\ f(x_2^*, y_2^*, v_2^*)v_2^* - ay_2^* - py_2^*z_2^* = 0, \\ ky_2^* - uv_2^* = 0, \\ cy_2^*z_2^* - bz_2^* = 0, \end{cases}$$

we have

$$\begin{aligned} \Delta L_n &\leq \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) (x_{n+1} - x_n) + \left(1 - \frac{y_2^*}{y_{n+1}} \right) (y_{n+1} - y_n) \\ &\quad + \frac{(a + pz_2^*)(1 + \phi u)}{k} (v_{n+1} - v_n) - \frac{(a + pz_2^*)(1 + \phi u)}{k} v_2^* \ln \frac{v_{n+1}}{v_n} \\ &\quad - \phi (ay_2^* + py_2^*z_2^*) \ln \frac{v_{n+1}}{v_n} + \frac{p}{c} \left(1 - \frac{z_2^*}{z_{n+1}} \right) (z_{n+1} - z_n) \\ &= \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) (x_{n+1} - x_n) + \left(1 - \frac{y_2^*}{y_{n+1}} \right) (y_{n+1} - y_n) \\ &\quad + \frac{(a + pz_2^*)}{k} \left(v_{n+1} - v_n - v_2^* \ln \frac{v_{n+1}}{v_n} \right) + \frac{ay_2^* + py_2^*z_2^*}{v_2^*} (v_{n+1} - v_n) \phi \\ &\quad - \phi (ay_2^* + py_2^*z_2^*) \ln \frac{v_{n+1}}{v_n} + \frac{p}{c} \left(1 - \frac{z_2^*}{z_{n+1}} \right) (z_{n+1} - z_n). \end{aligned}$$

Substituting model (4) and $\lambda = dx_2^* + ay_2^* + py_2^*z_2^*$, we have

$$\begin{aligned}
 \Delta L_n &\leq \phi \left[\left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) (dx_2^* + ay_2^* + py_2^* z_2^* - dx_{n+1} - f(x_{n+1}, y_n, v_n)v_n) \right. \\
 &\quad + \left(1 - \frac{y_2^*}{y_{n+1}} \right) (f(x_{n+1}, y_n, v_n)v_n - ay_{n+1} - py_{n+1}z_{n+1}) \\
 &\quad + \frac{(a + pz_2^*)}{k} \left(1 - \frac{v_2^*}{v_{n+1}} \right) (ky_{n+1} - uv_{n+1}) + \frac{ay_2^* + py_2^* v_2^*}{v_2^*} (v_{n+1} - v_n) \\
 &\quad \left. - (ay_2^* + py_2^* z_2^*) \ln \frac{v_{n+1}}{v_n} + \frac{p}{c} \left(1 - \frac{z_2^*}{z_{n+1}} \right) (cy_{n+1}z_{n+1} - bz_{n+1}) \right] \\
 &= \phi \left[dx_2^* \left(1 - \frac{x_{n+1}}{x_2^*} \right) \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) + (ay_2^* + py_2^* z_2^*) \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) \right. \\
 &\quad + \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_{n+1}, y_2^*, v_2^*)} + (ay_2^* + py_2^* z_2^*) \left(2 - \frac{v_n}{v_2^*} - \frac{y_{n+1}}{y_2^*} \frac{v_2^*}{v_{n+1}} \right) \\
 &\quad \left. - (ay_2^* + py_2^* z_2^*) \frac{y_2^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_2^*, y_2^*, v_2^*)} - (ay_2^* + py_2^* z_2^*) \ln \frac{v_{n+1}}{v_n} \right] \\
 &= \phi \left[dx_2^* \left(1 - \frac{x_{n+1}}{x_2^*} \right) \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) + (ay_2^* + py_2^* z_2^*) \left(4 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) \right. \\
 &\quad - \frac{y_2^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_2^*, y_2^*, v_2^*)} - \frac{y_{n+1}}{y_2^*} \frac{v_2^*}{v_{n+1}} - \frac{f(x_{n+1}, y_2^*, v_2^*)}{f(x_{n+1}, y_n, v_n)} - \ln \frac{v_{n+1}}{v_n} \left. \right) \\
 &\quad \left. + (ay_2^* + py_2^* z_2^*) \left(-1 - \frac{v_n}{v_2^*} + \frac{f(x_{n+1}, y_2^*, v_2^*)}{f(x_{n+1}, y_n, v_n)} + \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_{n+1}, y_2^*, v_2^*)} \right) \right].
 \end{aligned}$$

Let $g(x) = x - 1 - \ln x$, we have

$$\begin{aligned}
 &4 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} - \frac{y_2^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_2^*, y_2^*, v_2^*)} \\
 &\quad - \frac{y_{n+1}}{y_2^*} \frac{v_2^*}{v_{n+1}} - \frac{f(x_{n+1}, y_2^*, v_2^*)}{f(x_{n+1}, y_n, v_n)} - \ln \frac{v_{n+1}}{v_n} \\
 &= -g \left(\frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) - g \left(\frac{y_2^*}{y_{n+1}} \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_2^*, y_2^*, v_2^*)} \right) \\
 &\quad - g \left(\frac{y_{n+1}}{y_2^*} \frac{v_2^*}{v_{n+1}} \right) - g \left(\frac{f(x_{n+1}, y_2^*, v_2^*)}{f(x_{n+1}, y_n, v_n)} \right) \leq 0. \tag{17}
 \end{aligned}$$

According to (A_2) , we know

$$\left(1 - \frac{x_{n+1}}{x_2^*} \right) \left(1 - \frac{f(x_2^*, y_2^*, v_2^*)}{f(x_{n+1}, y_2^*, v_2^*)} \right) \leq 0. \tag{18}$$

Since (A_4) holds for $i = 2$, we further obtain

$$-1 - \frac{v_n}{v_2^*} + \frac{f(x_{n+1}, y_2^*, v_2^*)}{f(x_{n+1}, y_n, v_n)} + \frac{v_n f(x_{n+1}, y_n, v_n)}{v_2^* f(x_{n+1}, y_2^*, v_2^*)} \leq 0. \tag{19}$$

Therefore, when $R_1 > 1$, from (17), (18), and (19) we finally have $\Delta L_n \leq 0$. Obviously, $\Delta L_n = 0$ if and only if $x_n = x_2^*$, $y_n = y_2^*$, $v_n = v_2^*$, and $z_n = z_2^*$. Based on LaSalle’s invariance principle, we finally see that the infected equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$ is globally asymptotically stable. This completes the proof. \square

As a consequence of Theorem 5 we have the following result for model (5).

Corollary 3 *Let $R_1 > 1$. Then the infected equilibrium $E_2(x_2^*, y_2^*, v_2^*, z_2^*)$ of model (5) is globally asymptotically stable.*

4 Numerical examples

In this section, we give the numerical examples to discuss assumption (A_4) . In model (4), we choose a nonlinear incidence $f(x, y, v) = \frac{\beta x}{1 + nv^2}$. Furthermore, $h = 1$ in the denominator function ϕ . The mortality rate of the CTL response b in model (4) is chosen as a free parameter. All remaining parameters in model (4) are chosen as in Table 1.

We first take the mortality rate of CTL response $b = 0.75$. By calculating, we see that the basic reproduction numbers $R_0 \doteq 75 > 1$ and $R_1 \doteq 0.5216 < 1$. Furthermore, we also have $\frac{\lambda}{\xi} = 100$. Hence, model (4) has only the virus-free equilibrium $E_0(100, 0, 0, 0,)$ and the no-immune equilibrium $E_1(21.745, 39.127, 39.127, 0)$.

Consider assumption (A_4) . By calculating we obtain

$$\left(1 - \frac{f(x, y, v)}{f(x, y_i^*, v_i^*)}\right) \left(\frac{f(x, y_i^*, v_i^*)}{f(x, y, v)} - \frac{v}{v_i^*}\right) = \left(1 - \frac{1 + nv_i^{*2}}{1 + nv^2}\right) (v - v_i^*)(nvv_i^* - 1). \tag{20}$$

For $i = 1$, since $n\frac{\lambda}{\xi}v_1^* - 1 \doteq 38.127 > 0$, where $v_1^* \doteq 39.127$, from (20) we see that assumption (A_4) for $i = 1$ is not satisfied.

However, the numerical simulations given in Figure 1 show that equilibrium E_1 is globally asymptotically stable.

We next take the mortality rate of CTL response $b = 0.15$. By calculating, we see that the basic reproduction numbers $R_0 \doteq 75 > 1$ and $R_1 \doteq 2.608 > 1$. Furthermore, we also have $\frac{\lambda}{\xi} = 100$. Hence, model (4) has the virus-free equilibrium $E_0(100, 0, 0, 0)$, the no-immune equilibrium $E_1(21.746, 39.127, 39.127, 0)$, and the infected equilibrium $E_2(12.621, 15, 15, 0.383)$.

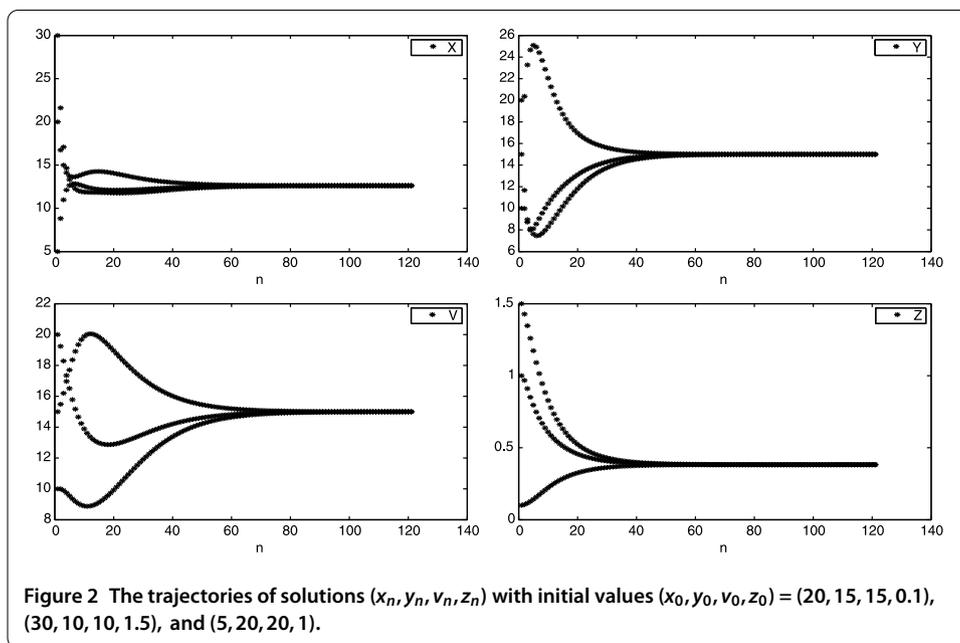
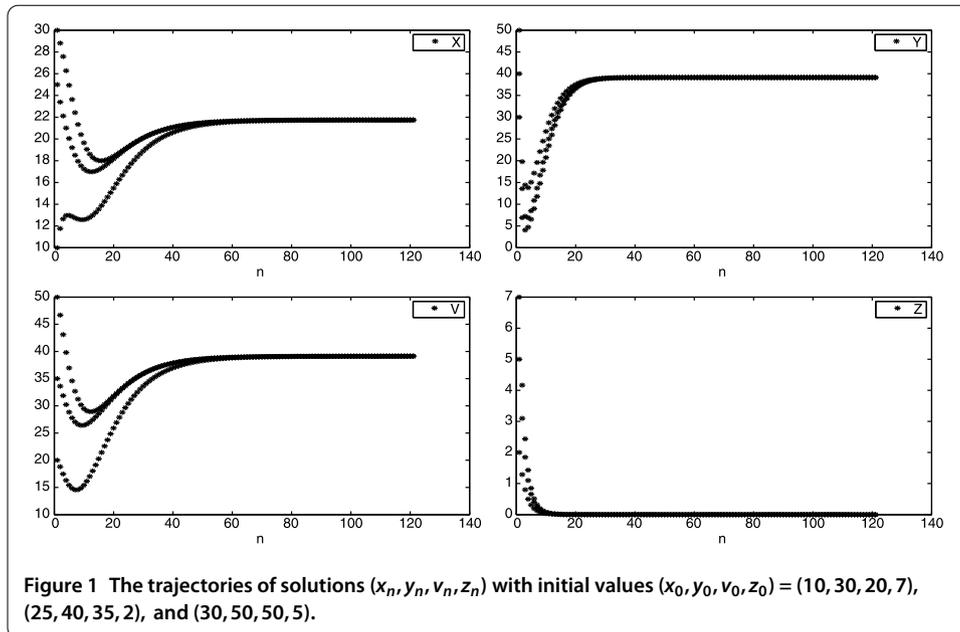
Consider assumption (A_4) . Since $n\frac{\lambda}{\xi}v_2^* - 1 \doteq 14 > 0$, where $v_2^* \doteq 15$, from (20) we see that assumption (A_4) for $i = 2$ is not satisfied.

However, the numerical simulations given in Figure 2 show that equilibrium E_2 is globally asymptotically stable.

The above numerical examples show that even if assumption (A_4) does not hold, the no-immune equilibrium may be globally asymptotically stable only when $R_0 > 1$ and $R_1 < 1$, and the infected equilibrium may be globally asymptotically stable only when $R_0 > 1$ and $R_1 > 1$.

Table 1 List of parameters

Parameter	Definition	Value	Source
λ	Production rate of uninfected cells	10	References [31, 32]
d	Death rate of uninfected cells	0.1	References [31, 32]
β	Infection rate	0.15	References [31, 32]
a	Death rate of infected cells	0.2	References [19, 31]
p	CTL effectiveness	1	References [19, 31]
n	Saturation coefficient	0.01	Reference [7]
k	Production rate of free virus	0.1	References [19, 31]
u	Clearance rate of free virus	0.1	References [19, 30]
c	Proliferation rate of CTL response	0.01	References [19, 30]



5 Discussions

In this paper, we studied a four dimensional discrete-time virus infected model (4) with general nonlinear incidence function $f(x, y, v)v$ and CTL immune response obeying Micken's non-standard finite difference (NSFD) scheme. Assumptions (A_1) - (A_4) for nonlinear function $f(x, y, v)$ are introduced and two basic reproduction numbers R_0 and R_1 also are defined. The basic properties of model (4) on the existence of the virus-free equilibrium E_0 , the no-immune equilibrium E_1 , and the infected equilibrium E_2 , and the positivity and ultimate boundedness of the solutions are established. Under (A_1) - (A_4) , the global stability and instability of the equilibria are completely determined by the basic reproduction numbers R_0 and R_1 . That is, if $R_0 \leq 1$ then E_0 is globally asymptotically stable,

if $R_0 > 1$ and $R_1 \leq 1$ then E_0 is unstable and E_1 is globally asymptotically stable and if $R_0 > 1$ and $R_1 > 1$ then E_0 and E_1 are unstable and E_2 is globally asymptotically stable.

We see that (A_1) - (A_3) are basic for model (4). Particularly, when $f(x, y, v) = \frac{\beta x}{1+mx+nv}$ and $f(x, y, v) = \frac{\beta x}{1+mv^q}$ then (A_1) - (A_3) naturally hold. But (A_4) is a mathematical assumption. It is only used in the proofs of theorems on the global stability of the no-immune equilibrium E_1 and the infected equilibrium E_2 to obtain $\Delta L_n \leq 0$ for the Lyapunov function L_n (see the proofs of Theorem 4 and Theorem 5). However, we also see that when $f(x, y, v) = \frac{\beta x}{1+mx+nv}$, (A_4) naturally hold. Furthermore, the numerical simulations given in Section 4 show that even if (A_4) does not hold, the no-immune equilibrium E_1 may be globally asymptotically stable only when $R_0 > 1$ and $R_1 < 1$, and the infected equilibrium E_2 may be globally asymptotically stable only when $R_0 > 1$ and $R_1 > 1$.

Generally, we expect that the global stability of the equilibria for model (4) can be completely determined only by the basic reproduction numbers R_0 and R_1 . Therefore, an open problem is whether (A_4) can be thrown off in Theorem 4 and Theorem 5. Furthermore, we also do not obtain the local asymptotic stability of the infected equilibrium E_2 only under (A_1) - (A_3) . The cause is that the characteristic equation of linearized system of model (4) at equilibrium E_2 is very complicated.

When the incidence function $f(x, y, v) = \frac{\beta x}{1+mx+nv}$, we know that (A_1) - (A_4) are satisfied. The global stability of the equilibria of the discrete model (5) only depends on the basic reproduction numbers R_0 and R_1 . This shows that the global stability of the equilibria for the discrete model (5) is equal to the corresponding continuous model (3). This implies that the NSFD scheme preserves the stability of the continuous model.

As is well known, in our body the immune response is made up of both a cellular response and a humoral response. The cellular response is that T cells kill the infected cells, the humoral response is that B cells produce an antibody to neutralize the virus. In this paper, we only consider the cellular response. In the future, our work will focus on the idea that the two kinds of immune response simultaneously play a role.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed equally to the writing of this paper. All authors read and approved the final manuscript.

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