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An age-structured epidemic model of rotavirus with vaccination

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Abstract The recent approval of a rotavirus vaccine in Mexico motivates this study on the potential impact of the use of such a vaccine on rotavirus prevention and control. An age-structured model that describes the rotavirus transmission dynamics of infections is introduced. Conditions that guarantee the local and global stability analysis of the disease-free steady state distribution as well as the existence of an endemic steady state distribution are established. The impact of maternal antibodies on the implementation of vaccine is evaluated. Model results are used to identify optimal age-dependent vaccination strategies. A convergent numerical scheme for the model is introduced but not implemented. This paper is dedicated to Prof. K. P. Hadeler, who continues to push the frontier of knowledge in mathematical biology.

Keywords rotavirus · age-structure · vacccination

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1 Introduction

The discovery of rotavirus ([4]) as the major etiologic agent of diarrhea in infants and young children has had a dramatic impact on public health policy programs geared towards the reductions of diarrhea morbidity and mortality over the last three decades. 95% of children worldwide have experienced a rotavirus infection with most infections in the 3 to 5 year age-range [24]. The highest rate of infection occurs in infants between 6 and 24 months of age [18]. Mortality from rotavirus diarrhea is quite low but morbidity is still high. In the United States rotavirus infections affect approximately 2.7 million children under 5 years of age and result in the hospitalization of $55,000$ children every year [24]. The direct costs on U.S. medical care have been estimated to be around $274 million [24]. The overall cost associated with rotavirus infections has been estimated at more than $1 billion per year, in the United States alone [24]. Over $600,000$ children die annually worldwide [7].

The primary mode of rotavirus transmission is fecal-oral [15]. Reported low titers of virus in respiratory tract secretions and other body fluids represent (less common) secondary transmission routes. Rotavirus can survive for months at room temperature and it is resistant to chloroform, ether, fluorocarbons, CsCl, non-ionic detergents and pH 4-9 [27]. Rotavirus can be passed from one person to another through a set of contaminated hands with the virus or by touching a contaminated surface or object. The virus enters the body through the mouth. Children can spread rotavirus before and after they develop symptoms [25].

Rotaviruses infect the mature absorptive villous epithelium of the upper two thirds of the small intestine and replicate in the cells that line the inside of the upper small intestine [24]. Infectious particles are released into the intestinal lumen and replicate more in the distal areas of the small intestine [24]. The replication rate decreases with the ability of the intestine to absorb salts and water [25]. Once infection occurs, the incubation period for rotavirus disease is about 2 days [21]. Most primary rotavirus infections are associated with acute diarrhea and may lead to dehydration and occasionally to death. Common symptoms involve vomiting and diarrhea for 3-8 days, frequent fever and abdominal pain. Immunity after infection is incomplete but recurrent infections tend to be less severe [3].

Many studies about rotavirus immunity have found that maternal antibodies protect younger infants [31]. Adults appear to be able to build up some level of immunity from recurrent infections [19]. Rotavirus disease is rare among infants younger than three months old as maternal antibodies protect them [24]. Newborns may be protected against infection for several months just from maternal antibodies [3]. Some studies suggest that long-lasting partial natural immunity may be possible [2]. In fact, some have shown that children who are infected more than once tend to have less severe symptoms in subsequent reinfections [34]. The highest rates of illness occur among infants and young children age 6 months to 2 years of age albeit adults can also be infected but their symptoms tend to be generally mild. Seropositive adults may develop rotaries diarrhea from interactions with their sick chil-

dren or from traveling in endemic areas [14]. In summary, immunity from natural infection is not complete or permanent.

This paper is organized as follows: Section 2 introduces an age-structured model that describes the transmission dynamics of rotaries infections in the presence of maternal antibodies and vaccination; The basic reproductive number $\Re_0$ and the vaccination reproductive number $\Re(.)$ (when the individuals are vaccinated at the age-specific vaccination rate $\phi(a)$) are computed and conditions for the local stability of the infection-free steady state distribution are identified in Section 3; In Section 4 the global stability of the infection-free steady state distribution and conditions that guarantee the existence of an endemic steady state distribution are established; Section 5 applies the prior results to the study of optimal vaccination policies; Section 6 introduces a convergent discretization of the age-structured model of Section 2; and, Section 7 collects final thoughts and conclusions.

2 Age-structured model of rotavirus infection with age-dependent parameters

Mothers with antibodies due to prior infection protect their breast-fed infants against infections. The infection rate of infants younger than 6 months of age is much lower than that of those with ages in the 6 to 24 month range [18]. Early studies of rotavirus immunity has found that incomplete natural immunity is acquired from prior infections. Here, it is assumed that in general treated or recovered individuals can become re-infected while infants are assumed to be totally protected by maternal antibodies while they are being breast-fed.

The population under consideration is divided into six age-dependent classes: breast-fed infants, susceptible, latent, infectious, recovered and vaccinated. $X(a,t)$, $S(t,a)$, $L(t,a)$, $I(t,a)$, $J(t,a)$ and $V(t,a)$ denote their respective age densities. Λ denotes the birth rate (assumed constant); q the proportion of infants who breast-feed (gaining temporary immunity against rotavirus infections); $\omega(a)$ the per capita rate of departure from the breast-feeding class into the susceptible class; and, $\mu(a)$ the age-specific per-capita natural death rate. Contacts between individuals are age-dependent and assumed to be driven by age-class activity levels and age-densities. The age-dependent mixing contacts structure is modeled via the mixing density, $p(t,a,a')$, which gives the proportion of contact that individuals of age a have with individuals of age a' given that they had contacts with somebody at time t. $\beta(a)$ is the age-specific probability of becoming infected per contact (with an infectious individuals); $c(a)$ is the age-specific per-capita contact/activity rate; and, $\phi(a)$ is the per-capita rate at which susceptible individuals are vaccinated. σ and δ denote the reductions in risk from prior exposure to a rotavirus or a vaccine ($0 \leq \sigma \leq 1$, $0 \leq \delta \leq 1$); k is the per-capita rate of progression from the latent to the infectious class; and, r is the per-capita treatment rate. The resulting age-structured model can be formulated as the

following initial boundary value problem:

$$\begin{aligned}
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)X(t,a) &= -\omega(a)X(t,a)-\mu(a)X(t,a)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)S(t,a) &= \omega(a)X(t,a)-\beta(a)c(a)B(t)S(t,a)-\phi(a)S(t,a)\\
&\quad -\mu(a)S(t,a)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)V(t,a) &= \phi(a)S(t,a)-\delta\beta(a)c(a)B(t)V(t,a)-\mu(a)V(t,a)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)L(t,a) &= \beta(a)c(a)B(t)[S(t,a)+\sigma J(t,a)+\delta V(t,a)]\\
&\quad -[k+\mu(a)]L(t,a)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)I(t,a) &= kL(t,a)-[r+\mu(a)]I(t,a)\\
\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)J(t,a) &= rI(t,a)-\sigma\beta(a)c(a)B(t)J(t,a)-\mu(a)J(t,a)\\
B(t) &= \int_0^\infty \frac{I(t,a')}{n(t,a')}p(t,a,a')da' \qquad (1)
\end{aligned}$$

where

$$\begin{aligned}
&p(t,a,a')\geq 0, \qquad \int_0^\infty p(t,a,a')=1,\\
&c(a)n(a,t)p(a,a',t)=c(a')n(a',t)p(a',a,t),\\
&X(t,0)=q\Lambda, \qquad S(t,0)=(1-q)\Lambda,\\
&V(t,0)=L(t,0)=I(t,0)=J(t,0)=0,\\
&X(0,a)=X_0(a), \qquad S(0,a)=S_0(a), \qquad V(0,a)=V_0(a),\\
&L(0,a)=L_0(a), \qquad I(0,a)=I_0(a), \qquad J(0,a)=J_0(a),\\
&n(t,a)=X(t,a)+S(t,a)+V(t,a)+L(t,a)+I(t,a)+J(t,a).
\end{aligned}$$

In the above formulation we could have assumed that k and r are functions of age but do not to keep the notation slightly less cumbersome. We assume that $\lim_{a\to\tilde{A}^-} w(a)=\infty$ and that $\omega\equiv 0$ for $a\geq\tilde{A}>0$. The initial age densities are known and zero beyond a fixed maximal age. From the approach in [5], we know that the only separable mixing solution is proportional mixing, that is, $p(t,a,a')\equiv p(t,a')\equiv\frac{c(a')n(t,a')}{\int_0^\infty c(a)n(t,a)da}$. Explicit formulae for the basic reproductive number $\Re_0$ and the vaccination-dependent reproductive number $\Re(\cdot)$ are derived later. The effectiveness of control policies is typically determined from their impact on the basic reproductive number, $\Re_0$. The effectiveness of vaccine policies on disease dynamics is tested from their impact on population whose individuals are vaccinated prior to an outbreak. Typically, $\Re_0<1$ guarantees the local stability of the infection-free distribution while $\Re_0>1$ implies its instability. $\Re_0>1$ often guarantees the existence of an endemic non-uniform distribution. Control is considered here in situations when $\Re_0>1$.

3 Calculation of $\Re(\phi)$

The population under consideration can be assumed to be at a demographic steady states since $n(t,a)$ satisfies the following initial boundary problem:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)n(t,a) = -\mu(a)n(t,a),$$
$$n(t,0) = \Lambda,$$
$$n(0,a) = n_0(a) = X_0(a)+S_0(a)+V_0(a)+L_0(a)+I_0(a)+J_0(a),$$

which when solved, using the method of characteristic, gives

$$n(t,a) = n_0(a-t)\frac{\mathcal{F}(a)}{\mathcal{F}(a-t)}H(a-t)+\Lambda\mathcal{F}(a)H(t-a),$$

where

$$\mathcal{F}(a) = exp\left(-\int_0^a \mu(s)ds\right),$$
$$H(s) = 1, s\geq 0; \qquad H(s) = 0, s<0.$$

Hence,

$$\lim_{t\to\infty} n(t,a) = \Lambda\mathcal{F}(a) := n^*(a),$$
$$\lim_{t\to\infty} p(t,a) = \frac{c(a)\mathcal{F}(a)}{\int_0^\infty c(b)\mathcal{F}(b)db} := p_\infty(a).$$

In the following analysis we assume that the host population has already reached the stationary age distribution, i.e. $n(t,a) = n^*(a)$. The use of the re-scaled variables,

$$x(t,a) = \tfrac{X(t,a)}{n(t,a)}, \qquad s(t,a) = \tfrac{S(t,a)}{n(t,a)}, \qquad v(t,a) = \tfrac{V(t,a)}{n(t,a)},$$
$$l(t,a) = \tfrac{L(t,a)}{n(t,a)}, \qquad i(t,a) = \tfrac{I(t,a)}{n(t,a)}, \qquad j(t,a) = \tfrac{J(t,a)}{n(t,a)},$$

leads to the following equivalent system:

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)x(t,a) = -\omega(a)x(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)s(t,a) = \omega(a)x(t,a)-\beta(a)c(a)B(t)s(t,a)-\phi(a)s(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)v(t,a) = \phi(a)s(t,a)-\delta\beta(a)c(a)B(t)v(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)l(t,a) = \beta(a)c(a)B(t)[s(t,a)+\sigma j(t,a)+\delta v(t,a)]-kl(t,a),$$
$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right)i(t,a) = kl(t,a)-ri(t,a),$$

$$\left(\frac{\partial}{\partial t}+\frac{\partial}{\partial a}\right) j(t,a) = ri(t,a) - \sigma\beta(a)c(a)B(t)j(t,a),$$
$$B(t) = \int_0^\infty i(t,a)p_\infty(a)da,$$
$$p_\infty(a) = \frac{c(a)\mathcal{F}(a)}{\int_0^\infty c(b)\mathcal{F}(b)db}, \tag{2}$$

$$\begin{aligned} x(t,0) &= q, \qquad s(t,0) = 1-q,\\ v(t,0) &= l(t,0) = i(t,0) = j(t,0) = 0,\\ x(0,a) &= x_0(a), \qquad s(0,a) = s_0(a), \qquad v(0,a) = v_0(a),\\ l(0,a) &= l_0(a), \qquad i(0,a) = i_0(a), \qquad j(0,a) = j_0(a). \end{aligned}$$

System (2) supports the infection-free non-uniform steady state distribution given by:

$$\begin{aligned} x^*(a) &= q\Pi(0,a),\\ s^*(a) &= q\Phi(0,a)\int_0^a \left[-\frac{d}{dh}\Pi(0,h)\right][\Phi(0,h)]^{-1}dh + (1-q)\Phi(0,a), \quad (3)\\ v^*(a) &= \int_0^a \phi(h)s^*(h)dh,\\ l^*(a) &= 0, \qquad i^*(a) = 0, \qquad j^*(a) = 0, \end{aligned}$$

where

$$\Phi(a,b) = e^{-\int_a^b \phi(\tau)d\tau}, \qquad \Pi(a,b) = e^{-\int_a^b \omega(\tau)d\tau}. \tag{4}$$

Also we assume that $\omega(a)\Pi(0,a)$ is bounded for $a \le \tilde{A}$ from where it follows that $\Pi(0,a)$ is absolutely continuous for $a \le \tilde{A}$. One can note that $\Pi(0,a) = e^{-\int_0^a \omega(\tau)d\tau}$ for $a < \tilde{A}$ and $\Pi(0,a) = 0$ otherwise.

The local stability of the infection-free non-uniform steady state distribution (3) is tested using the perturbations:

$$\begin{aligned} x(a,t) &= \hat{x}(a)e^{\lambda t} + x^*(a), \qquad s(a,t) = \hat{s}(a)e^{\lambda t} + s^*(a),\\ v(a,t) &= \hat{v}(a)e^{\lambda t} + v^*(a), \qquad l(a,t) = \hat{l}(a)e^{\lambda t},\\ i(a,t) &= \hat{i}(a)e^{\lambda t}, \qquad j(a,t) = \hat{j}(a)e^{\lambda t}, \qquad B(t) = B_0 e^{\lambda t} \end{aligned}$$

where

$$B_0 = \int_0^\infty \hat{i}(a)p_\infty(a)da. \tag{5}$$

Linearization and a little algebra leads to the following eigenvalue problem

$$\begin{aligned} \hat{l}_a(a) + \lambda\hat{l}(a) &= \beta(a)c(a)B_0[s^*(a) + \delta v^*(a)] - k\hat{l}(a),\\ \hat{i}_a(a) + \lambda\hat{i}(a) &= k\hat{l}(a) - r\hat{i}(a),\\ \hat{j}_a(a) + \lambda\hat{j}(a) &= r\hat{i}(a). \end{aligned} \tag{6}$$

Solving for $\hat{i}(a)$ gives

$$\hat{i}(a) = \int_0^a B_0 \frac{k}{r-k}[e^{(k+\lambda)(h-a)} - e^{(r+\lambda)(h-a)}]\beta(h)c(h)[s^*(h)+\delta v^*(h)]dh, \quad (7)$$

where $s^*(a)$ and $v^*(a)$ are as given in (3). Combining Eqs. (5) and (7) gives

$$\begin{aligned} B_0 = B_0 \int_0^\infty \int_0^a & \frac{k}{r-k} p_\infty(a)[e^{(k+\lambda)(h-a)} - e^{(r+\lambda)(h-a)}]\beta(h)c(h) \\ & [s^*(h) + \delta v^*(h)]dhda. \end{aligned}$$

Dividing both sides of an equation by B_0 (assuming $B_0 \neq 0$) and changing the order of integration result in the corresponding Lotka characteristic equation,

$$\begin{aligned} 1 \; = & \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau+h)[e^{-(k+\lambda)\tau} - e^{-(r+\lambda)\tau}]\beta(h)c(h) \\ & [s^*(h) + \delta v^*(h)]dhd\tau \\ := & \; G(\lambda), \end{aligned} \quad (8)$$

where $s^*(h)+\delta v^*(h) = q\Phi(0,h)\int_0^h \left[-\frac{d}{d\tau}\Pi(0,\tau)\right][\Phi(0,\tau)]^{-1} d\tau + (1-q)\Phi(0,h) + \delta\int_0^h \phi(\tau)s^*(\tau)d\tau$ and $\Pi(a,b)$ and $\Phi(a,b)$ as given in (4).

The control adjusted reproductive number is defined as $\Re(\phi,q,\omega) \equiv G(0)$, where

$$\Re(\phi,q,\omega) = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau+h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)[s^*(h)+\delta v^*(h)]dhd\tau,$$

with $s^*(h)+\delta v^*(h) = q\Phi(0,h)\int_0^h \left[-\frac{d}{d\tau}\Pi(0,\tau)\right][\Phi(0,\tau)]^{-1} d\tau + (1-q)\Phi(0,h) + \delta\int_0^h \phi(\tau)s^*(\tau)d\tau$ and $\Pi(a,b)$ and $\Phi(a,b)$ as given in (4).

The basic reproductive number (i.e., $\phi(a) \equiv 0$) $\Re(0,q,\omega) = \Re_0(q,\omega)$ is given by

$$\Re_0(q,\omega) = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau+h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)[1-q\Pi(0,h)]dhd\tau.$$

$\Re(\phi,q,\omega)$ behaves as expected in special cases, for example,

$$\frac{\partial \Re}{\partial q} < 0, \qquad \Re_0(1,\omega) \leq \Re_0(q,\omega), \qquad q \in [0,1].$$

That is, as the proportion of newborns who are breast-fed increases we see reductions on $\Re_0(q,\omega)$. Furthermore $\Re_0(q,\omega)$ increases as $\omega(a)$ increases. We now establish the following result:

Theorem 1 *The infection-free non-uniform steady state distribution given by (3) is locally asymptotically stable (l.a.s.) if* $\Re(\phi,q,\omega) < 1$ *and unstable if* $\Re(\phi,q,\omega) > 1$.

Proof Eq. (8) has a unique negative real solution λ^* if and only if $G(0) < 1$ (i.e. $\Re(\phi, q, \omega) < 1$) and has a unique positive real solution λ^* if and only if $G(0) > 1$ (i.e. $\Re(\phi, q, \omega) > 1$) since $G'(\lambda) < 0$ for all λ, $\lim_{\lambda\to\infty} G(\lambda) = 0$ and $\lim_{\lambda\to-\infty} G(\lambda) = \infty$. λ^* is a dominant root, that is, if $\lambda = x + iy$ is a complex root then $x \le \lambda^*$. This follows from the observations that

$$1 = G(\lambda) = |G(x + iy)| \le G(x),$$

and that $x \le \lambda^*$. The fact that the unique real root is dominant guarantees the local asymptotic stability of the infection-free non-uniform steady state distribution is locally asymptotically stable if $\Re(\phi, q, \omega) < 1$ and unstable if $\Re(\phi, q, \omega) > 1$.

4 Endemic non-uniform steady state distribution

The following theorem establishes the conditions for the existence of an endemic non-uniform steady state distribution.

Theorem 2 *There exists an endemic non-uniform steady state distribution of System (2) when* $\Re(\phi, q, \omega) > 1$.

Proof A non-uniform age-distribution is a solution of the following nonlinear system.

$$\begin{aligned}
\tfrac{dx^*(a)}{da} &= -\omega(a)x^*(a),\\
\tfrac{ds^*(a)}{da} &= \omega(a)x^*(a) - \beta(a)c(a)B^*s^*(a) - \phi(a)s^*(a),\\
\tfrac{dv^*(a)}{da} &= \phi(a)s^*(a) - \delta\beta(a)c(a)B^*v^*(a),\\
\tfrac{dl^*(a)}{da} &= \beta(a)c(a)B^*[s^*(a) + \sigma j^*(a) + \delta v^*(a)] - kl^*(a),\\
\tfrac{di^*(a)}{da} &= kl^*(a) - ri^*(a),\\
\tfrac{dj^*(a)}{da} &= ri^*(a) - \sigma\beta(a)c(a)B^*j^*(a),
\end{aligned} \tag{9}$$

where

$$B^* = \int_0^\infty i^*(a)p_\infty(a)da, \qquad p_\infty(a) = \frac{c(a)n^*(a)}{\int_0^\infty c(u)n^*(u)du},$$
$$x^*(0) = q, \qquad s^*(0) = 1 - q, \qquad v^*(0) = l^*(0) = i^*(0) = j^*(0) = 0.$$

Solving for l^* and i^* in Eq. (9) gives

$$l^*(a) = B^*\int_0^a e^{-k(a-h)}\beta(h)c(h)G(h, B^*)dh,$$
$$i^*(a) = k\int_0^a l^*(h)e^{-r(a-h)}dh,$$

where

$$G(h, B^*) = s^*(h, B^*) + \sigma j^*(h, B^*) + \delta v^*(h, B^*),$$

and

$$
\begin{aligned}
x^*(a) &= qe^{-\int_0^a \omega(\tau)d\tau}, \\
s^*(a) &= qe^{-\int_0^a \beta(\tau)c(\tau)B^*+\phi(\tau)d\tau} \int_0^a \omega(h)e^{\int_0^h \beta(\tau)c(\tau)B^*+\phi(\tau)-\omega(\tau)d\tau}dh \\
&\quad +(1-q)e^{-\int_0^a \beta(\tau)c(\tau)B^*+\phi(\tau)d\tau}, \\
v^*(a) &= \int_0^a e^{-\int_h^a B^*\delta\beta(\tau)c(\tau)d\tau}\phi(h)s^*(h)dh, \\
j^*(a) &= \int_0^a ri^*(h)e^{-\int_h^a B^*\sigma\beta(\tau)c(\tau)d\tau}dh \\
&\equiv \frac{1}{\sigma}\int_0^h g(h,a,B^*)G(a,B^*)da
\end{aligned}
$$

$G(h,B^*)$ can be expressed as the following Volterra integral equation with parameter B^*

$$G(h,B^*) = f(h,B^*) + \int_0^h g(h,a,B^*)G(h,B^*)dh,$$

where $f(h,B^*) = s^*(h,B^*) + \delta v^*(h,B^*)$ and

$$
\begin{aligned}
g(h,a,B^*) \equiv \sigma B^*\beta(a)c(a)\tfrac{rk}{r-k}\textstyle\int_a^h (e^{k(a-s)} - e^{r(a-s)}) \\
exp\left[-B^*\int_s^h \sigma\beta(u)c(u)du\right]ds.
\end{aligned}
$$

The definitions of $g(h,a,B^*)$ follows from

$$
\begin{aligned}
\sigma j^*(h,B^*) &= \sigma B^* rk \int_0^h e^{-\int_s^h B^*\sigma\beta(\tau)c(\tau)d\tau}\int_0^s e^{-r(s-u)}\int_0^u e^{-k(u-a)}\beta(a)c(a) \\
&\quad G(a,B^*)da\,du\,ds \\
&= \sigma B^*\frac{rk}{r-k}\int_0^h e^{-\int_s^h B^*\sigma\beta(\tau)c(\tau)d\tau}\int_0^s [e^{k(a-s)} - e^{r(a-s)}]\beta(a)c(a) \\
&\quad G(a,B^*)da\,ds \\
&= \int_0^h \sigma B^*\beta(a)c(a)\frac{rk}{r-k}\int_a^h e^{-\int_s^h B^*\sigma\beta(\tau)c(\tau)d\tau} \\
&\quad [e^{k(a-s)} - e^{r(a-s)}]ds\,G(a,B^*)da \\
&= \int_0^h g(h,a,B^*)G(a,B^*)da.
\end{aligned}
$$

All known functions are continuous in $[0,A]\times(0,\infty]$ and $f \in C([0,A)\times \Re^+\cup\{0\};\Re^+\cup\{0\})$ is continuously differentiable with respect to B^*. Furthermore, for each $B^*\in\Re^+\cup\{0\}$, the function $g(\cdot,\cdot,B^*)$ is a Volterra kernel of continuous type on $[0,A)$ (see Ref. [11]). It follows that for each $B^*>0$,

there is unique solution $G(h, B^*)$ defined on the maximal interval of existence $[0, A_{max})$, and that $G(h, B^*)$ depends continuously on B^*, [11]. Furthermore since $x+s+v+l+j = 1$, $G(h, B^*)$ is bounded, which implies that $A_{max} = \infty$ [11].

Using $l^*(a)$ and i^* equations, after changing the order of integration, gives

$$i^*(a) = B^* \int_0^a \frac{k}{r-k}[e^{k(\tau-a)} - e^{r(\tau-a)}]\beta(\tau)c(\tau)G(\tau, B^*)d\tau.$$

We substitute this last expression for $i^*(a)$ into the equation for B^* in Equation (9), divide by B^* ($B^* > 0$), change variables ($\nu = a - \tau$) in order to arrive at the following equation for $H(B^*)$:

$$\begin{aligned} 1 &= \int_0^\infty \int_0^\infty \frac{k}{r-k}[e^{-k\nu} - e^{-r\nu}]\beta(\tau)c(\tau)G(\tau, B^*)p_\infty(\tau+\nu)d\nu d\tau \\ &:= H(B^*). \end{aligned} \tag{10}$$

The case $B^* = 0$ corresponds to the solution:

$$\begin{aligned} x^*(a) &= qe^{-\int_0^a \omega(\tau)d\tau}, \\ s^*(a) &= qe^{-\int_0^a \phi(\tau)d\tau} \int_0^a \omega(h)e^{\int_0^h \phi(\tau)-\omega(\tau)d\tau}dh + (1-q)e^{-\int_0^a \phi(\tau)d\tau}, \\ v^*(a) &= \int_0^a \phi(h)s^*(h)dh, \\ l^*(a) &= 0, \qquad i^*(a) = 0, \qquad j^*(a) = 0. \end{aligned} \tag{11}$$

If we define $H(0) = \Re(\phi)$ and assume that $H(0) > 1$ then $i^*(a) < 1$ since $x^*(a) + s^*(a) + v^*(a) + l^*(a) + i^*(a) + j^*(a) = 1$. Therefore

$$B^* \int_0^a \frac{k}{r-k}[e^{k(\tau-a)} - e^{r(\tau-a)}]\beta(\tau)c(\tau)G(\tau, B^*)d\tau < 1.$$

Thus it follows from Eq. (10) that

$$\begin{aligned} B^*H(B^*) &= \int_0^\infty p_\infty(a)B^* \int_0^a \frac{k}{r-k}[e^{k(\tau-a)} - e^{r(\tau-a)}]\beta(\tau)c(\tau)G(\tau, B^*)d\tau da \\ &< \int_0^\infty p_\infty(a)da = 1. \end{aligned} \tag{12}$$

Hence $H(1) < 1$ and since by assumption $H(0) > 1$. The continuity of $H(B^*)$ implies that $H(B^*)$ must have at least one solution in $(0, 1)$. Thus there exists an endemic steady state distribution (satisfying Eq. (9)) whenever $\Re(\phi, q, \omega) > 1$.

Hence, $\Re(\phi, q, \omega) > 1$ provides a sufficient condition for the existence of a non-trivial non-uniform endemic steady state age-distribution while $\Re(\phi, q, \omega) < 1$ guarantees the local stability of the infection-free non-uniform distribution. The possibility of the existence of multiple endemic equilibria when $\Re(\phi, q, \omega) < 1$ cannot be ruled out here (see [16], [20]). However, it can be shown that in the absence of any type of vaccination, this distribution is globally stable.

Theorem 3 *The infection-free non-uniform distribution of Eq. (2) is globally asymptotically stable whenever* $\Re_0 < 1$.

Proof Let $\mathcal{J}$ denote the rate at which uninfected individuals of age a are infected at time t. Since $s(t,a) + j(t,a) + v(t,a) \leq 1$, $\sigma \leq 1$ and $\delta \leq 1$, it follows that

$$\begin{aligned}\mathcal{J}(t,a) &= \beta(a)c(a)B(t)[s(t,a) + \sigma j(t,a) + \delta v(t,a)] \\ &\leq \beta(a)c(a)B(t)[1 - x(t,a)],\end{aligned} \tag{13}$$

where $B(t)$ is given in Eq. (2). Integrating Eq. (2) along characteristic lines gives

$$\begin{aligned}x(a,t) &= qe^{-\int_0^a \omega(\tau)d\tau}, \qquad a < t \\ l(t,a) &= \int_0^a e^{-ks}\mathcal{J}(t-s,a-s)ds, \qquad a < t \\ i(t,a) &= k\int_0^a e^{-rs}l(t-s,a-s)ds, \qquad a < t\end{aligned} \tag{14}$$

Replacing l by the integral in Eq. (14) we get that, for $a < t$,

$$\begin{aligned}i(t,a) &= k\int_0^a e^{-rs}\int_0^{a-s} e^{-k\lambda}\mathcal{J}(t-s-\lambda,a-s-\lambda)d\lambda ds, \qquad a < t \\ &= k\int_0^a\int_0^{a-s} e^{-rs}e^{-k(a-s-\alpha)}\mathcal{J}(t-a+\alpha,\alpha)d\alpha ds, \qquad (\alpha = a-s-\lambda) \\ &= \frac{k}{r-k}\int_0^a (e^{-k(a-\alpha)} - e^{-r(a-\alpha)})\mathcal{J}(t-a+\alpha,\alpha)d\alpha.\end{aligned} \tag{15}$$

If we let $W(a) = \limsup_{t\to\infty}\mathcal{J}(t,a)$ then by making use of Eqs. (13), (14) and (15) we arrive at the following inequality

$$\begin{aligned}\mathcal{J}(t,a) \leq \beta(a)c(a)[1 - qe^{-\int_0^a \omega(\tau)d\tau}]\int_0^\infty \frac{k}{r-k}p_\infty(a)\int_0^a (e^{-k(a-\alpha)} - e^{-r(a-\alpha)}) \\ \mathcal{J}(t-a+\alpha,\alpha)d\alpha da.\end{aligned}$$

Making use of Fatou's Lemma gives

$$\begin{aligned}W(a) \;\leq\; &\beta(a)c(a)[1 - qe^{-\int_0^a \omega(\tau)d\tau}]\int_0^\infty \frac{k}{r-k}p_\infty(a)\int_0^a (e^{-k(a-\alpha)} - e^{-r(a-\alpha)}) \\ &W(\alpha)d\alpha da \\ :=\; &C\beta(a)c(a)[1 - qe^{-\int_0^a \omega(\tau)d\tau}].\end{aligned} \tag{16}$$

If we multiply out some parameters and integrate, we get that

$$C \leq C\int_0^\infty\int_0^a \frac{k}{r-k}p_\infty(a)(e^{-k(a-\alpha)} - e^{-r(a-\alpha)})\beta(\alpha)c(\alpha)[1 - qe^{-\int_0^\alpha \omega(\tau)d\tau}]d\alpha da. \tag{17}$$

Changing the order of integration and letting $\tau = a - \alpha$ leads to the inequality $C \leq C\Re_0$. Hence if $\Re_0 < 1$ then $C \equiv 0$. That is, $W(a) \equiv 0$ or $\limsup_{t\to\infty}\mathcal{J}(t,a) \equiv 0$. From Eqs. (14) and (15) it follows that

$$\lim_{t\to\infty} l(t,a) = 0, \qquad \lim_{t\to\infty} i(t,a) = 0.$$

5 Optimal vaccination strategies

The goal of the vaccination program is either to reduce disease prevalence to a predetermined level at a minimal cost or to design a vaccination program that uses resources as effectively as possible, that is, a program that reduces prevalence in the most under a fixed budget. Here it is implicitly assumed that lowering the reproductive number reduces the disease prevalence (see [10]).

There are a multiple set of strategies that can be used to reduce prevalence. Here we follow in "spirit" the approach used by Rorres and Fair [28], an approach that has been extended and refined to a multitude of settings (including epidemiology) by Hadeler and Müller [12]. This approach focuses on the minimization of the functional $F(\phi, a, \omega) = \Re_0(q, \omega) - \Re(\phi, q, \omega)$ which in our case is explicitly given by

$$F(\phi, q, \omega) = \int_0^\infty \int_0^\infty \frac{k}{r-k} p_\infty(\tau + h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)(1-\delta) \int_0^a \phi(z) s_\phi(z) dz dh d\tau. \tag{18}$$

Since the vaccination policy is implemented a priori, that is, on a disease-free populations, we let $s_\phi(a)$ denote susceptible age-distribution in a disease-free population as defined in Eq. (3):

$$s_\phi(a, q, \omega) = q\Phi(0, a) \int_0^a \left[-\frac{d}{dh} \Pi(0, h) \right] [\Phi(0, h)]^{-1} \, dh + (1-q)\Phi(0, a).$$

We now proceed under the assumption that it is nearly impossible to eliminate an established (endemic) disease from a population, that is, we assume that $\Re(\phi, q, \omega) > 1$ (but see [12]). Following the approach in ([12], [13]) we study two problems. In the first, a prevalence reduction goal is set a priori and the policy ($\phi(a)$, q, ω) that minimizes the cost of implementing it is found. In the second situation, it is assumed that we have a fixed budget (here measured in "dollars" or "euros") and the policy ($\phi(a)$, q, ω) that minimizes $\Re(\phi, q, \omega)$ is determined.

We let $C(\phi, q, \omega)$ denote the total cost associated with the implementation of the vaccination strategy (ϕ, q, ω). It is assumed that $C(\phi, q, \omega)$ depends on the vaccination rate in the following way

$$C(\phi, q, \omega) = \int_0^\infty \kappa(a)\phi(a) S_\phi(a, q, \omega) da, \tag{19}$$

where

$$S_\phi(a, q, \omega) = \Lambda e^{-\int_0^a \mu(s) ds} s_\phi(a, q, \omega) \tag{20}$$

and $\kappa(a)$ is the age-specific vaccination cost. We can now reformulate the optimization problems describe before in precise terms:
(I) Find a vaccination strategy $(\phi(a), q, \omega)$ that minimizes $C(\phi, q, \omega)$ constrained by $\Re(\phi, q, \omega) \leq \Re_*$,

(II) Find a vaccination strategy $(\phi(a), q, \omega)$ that minimizes $\Re(\phi, q, \omega)$ constrained by $C(\phi, q, \omega) \leq C_*$,
where $\Re_*$ and C_* are specified constant values. Problem I and II can be moved into the realm of linear optimization theory ([12]). In fact, the transformation

$$\begin{aligned}\psi(a) &:= -\frac{d}{da}\left(s_\phi(a,q,\omega) + qe^{-\int_0^a \omega(\tau)d\tau}\right)\\ &= \phi(a)s_\phi(a,q,\omega),\end{aligned}$$

works. Hence, if we let

$$\begin{aligned}&\bar{F}(\psi, q, \omega) = F(\phi, q, \omega),\\ &\bar{C}(\psi, q, \omega) = C(\phi, q, \omega),\\ &(1-\delta)\int_0^a \phi(z,q,\omega)s_\phi(z,q,\omega)dz = \int_0^a (1-\delta)\psi(z,q,\omega)dz\end{aligned}$$

and

$$\begin{aligned}\bar{F}(\psi) &= \int_0^\infty \int_0^\infty \frac{k}{r-k}p_\infty(\tau+h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)(1-\delta)\\ &\qquad \int_0^a \psi(z)dzdhd\tau\\ &= \int_0^\infty \left[\int_a^\infty \int_0^\infty \frac{k}{r-k}p_\infty(\tau+h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)(1-\delta)dhd\tau\right]\\ &\qquad \psi(a)da\end{aligned}$$

then their use on Eqs. (18) and (19) leads to the re-formulation of the optimization problem in term of the following linear functionals:

$$\begin{aligned}\bar{F}(\psi, q, \omega) &= \int_0^\infty K(a)\psi(a,q,\omega)da,\\ \bar{C}(\psi, q, \omega) &= \int_0^\infty M(a)\psi(a,q,\omega)da,\end{aligned}$$

where

$$\begin{aligned}K(a) &= \int_a^\infty \int_0^\infty \frac{k}{r-k}p_\infty(\tau+h)[e^{-k\tau} - e^{-r\tau}]\beta(h)c(h)(1-\delta)dhd\tau,\\ M(a) &= \Lambda e^{-\int_0^a \mu(\tau)d\tau}\kappa(a),\end{aligned}$$

and $Q(a) := \int_0^\infty \psi(a)da \leq 1$.

Problem I now reads as follows: minimize $\bar{C}(\psi)$ subject to $f(\psi) \leq 0$ and $\psi \geq 0$ where

$$f(\psi) = \begin{pmatrix} f_1(\psi) \\ f_2(\psi) \end{pmatrix} = \begin{pmatrix} \rho - \bar{F}(\psi) \\ Q(\psi) - 1 \end{pmatrix}, \tag{21}$$

$f(\psi) \leq 0$ ($f_i(\psi) \leq 0$ $(i = 1, 2)$) and $\rho = \Re_0 - \Re_*$, and apply the main Theorem in ([12], [13]).

Remark 1 The results in ([12],[13]) guarantee that there are two possible optimal vaccination strategies for Problem (I): (i) one-age strategy, that is, vaccinate the susceptible population at exactly age Ω or (ii) two-age strategy, that is, vaccinate a fraction of the susceptible population at age $\Omega_1$and a second fraction of susceptible at age Ω_2 where Ω_1 and Ω_2 are functions of q and ω.

Explicit information on the nature of Ω_1 and Ω_2 can be derived. Problem (II) has similar solution and we refer the interested readers to the work in ([12],[13]).

6 A numerical method: discretization

Professor K.P. Hadeler received his Ph.D. from Professor Lothar Collatz (1910-1990), a prominent numerical analyst. Hence, it is not surprising to see that the numerical implementation of theoretical models has also been one of his interests. Here, we include a convergent numerical scheme that can be used to simulate our age-structured rotavirus model. In order to show that the scheme converges, we discretize System (1) using the finite difference method along the characteristic lines of our hyperbolic system [1], [22]. We take identical time and age steps and assume that a and t are bounded ($a \in [0, A]$ and $t \in [0, T]$) and consequently, the computational mesh is rather simple. We divide the intervals $[0, A]$ and $[0, T]$ into subintervals of step length h,

$$a_i = ih \quad (i = 1, \ldots, M), \qquad t_j = jh \quad (j = 1, \ldots, N) \tag{22}$$

and approximate the derivatives by

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) x(t,a) \approx \frac{[X(t_j, a_i) - X(t_{j-1}, a_i)] + [X(t_{j-1}, a_i) - X(t_{j-1}, a_{i-1})]}{h}$$
$$= \frac{X(t_j, a_i) - X(t_{j-1}, a_{i-1})}{h} = \frac{X_i^j - X_{i-1}^{j-1}}{h}. \tag{23}$$

We linearize the term

$$\beta(a_i)c(a_i)B(t_j)S(t_j, a_i)$$

using the following approximation

$$\beta(a_i)c(a_i)B(t_{j-1})S(t_j, a_i) = \beta_i c_i B_{j-1} S_i^j.$$

The discretized system becomes

$$\begin{aligned}
\frac{X_i^j - X_{i-1}^{j-1}}{h} &= -(\omega_i + \mu_i)X_i^j, \\
\frac{S_i^j - S_{i-1}^{j-1}}{h} &= \omega_i X_i^j - \beta_i c_i B_{j-1} S_i^j - \mu_i S_i^j - \phi_i S_i^j, \\
\frac{V_i^j - V_{i-1}^{j-1}}{h} &= \phi_i S_i^j - \mu_i V_i^j - \delta\beta_i c_i B_{j-1} V_i^j,
\end{aligned}$$

$$\begin{aligned}
\frac{L_i^j - L_{i-1}^{j-1}}{h} &= \beta_i c_i B_{j-1}[S_i^j + \sigma J_i^j + \delta V_i^j] - [k+\mu_i]L_i^j,\\
\frac{I_i^j - I_{i-1}^{j-1}}{h} &= kL_i^j - [r+\mu_i]I_i^j,\\
\frac{J_i^j - J_{i-1}^{j-1}}{h} &= rI_i^j - \sigma\beta_i c_i B_{j-1} J_i^j - \mu_i J_i^j. \qquad (24)
\end{aligned}$$

Summing up, one can obtain

$$\frac{n_i^j - n_{i-1}^{j-1}}{h} = -\mu_i n_i^j.$$

Integrals are approximated via the trapezoidal rule, that is, using the formula

$$\int_0^\infty c(u)n(t,u)du \approx \frac{1}{2}c_0 n_0^j h + \Sigma_{i=1}^{M-1} c_i n_i^j h + \frac{1}{2}c_M n_M^j h.$$

Thus

$$p(t,a) = \frac{c_i n_i^j}{\frac{1}{2}c_0 n_0^j h + \Sigma_{i=1}^{M-1} c_i n_i^j h + \frac{1}{2}c_M n_M^j h}$$

and

$$B^j = \frac{1}{2}\frac{I_0^j}{n_0^j}p_0^j h + \sum_{i=1}^{M-1}\frac{I_i^j}{n_i^j}p_i^j h + \frac{1}{2}\frac{I_M^j}{n_M^j}p_M^j h.$$

Solving System (24) leads to

$$\begin{aligned}
X_i^j &= \frac{X_{i-1}^{j-1}}{1+(\omega_i+\mu_i)h},\\
S_i^j &= \frac{S_{i-1}^{j-1} + \omega_i h X_i^j}{1+\beta_i c_i h B_{j-1} + \mu_i h + \phi_i h},\\
V_i^j &= \frac{h\phi_i S_i^j + V_{i-1}^{j-1}}{1+\delta\beta_i c_i h B_{j-1} + \mu_i h},\\
I_i^j &= \frac{I_{i-1}^{j-1} + khL_i^j}{1+rh+\mu_i h},\\
J_i^j &= \frac{J_{i-1}^{j-1} + rhI_i^j}{1+\sigma h\beta_i c_i B_{j-1} + \mu_i h}\\
&= \frac{J_{i-1}^{j-1}}{1+\sigma h\beta_i c_i B_{j-1} + \mu_i h} + \frac{rh(I_{i-1}^{j-1} + khL_i^j)}{(1+rh+\mu_i h)(1+\sigma h\beta_i c_i B_{j-1} + \mu_i h)},\\
L_i^j &= \frac{L_{i-1}^{j-1} + \beta_i c_i h B_{j-1}[S_i^j + \sigma J_i^j + \delta V_i^j]}{1+kh+\mu_i h} \qquad (25)
\end{aligned}$$

where the correct expansion for S_i^j, J_i^j and V_i^j are put in the L_i^j equation. Initial conditions are set as follows:

$$\begin{aligned}
&X_0^j = q\Lambda, \qquad S_0^j = (1-q)\Lambda,\\
&V_0^j = L_0^j = I_0^j = J_0^j = 0,\\
&X_i^0 = X_0(a_i), \qquad S_i^0 = S_0(a_i), \qquad V_i^0 = V_0(a_i),\\
&L_i^0 = L_0(a_i), \qquad I_i^0 = I_0(a_i), \qquad J_i^0 = J_0(a_i).
\end{aligned}$$

Alternatively, one can limit the change in the L equation in order to be able to solve directly for J (after having solved for X, S and V). This is accomplished by approximating L by

$$\frac{L_i^j - L_{i-1}^{j-1}}{h} = \beta_i c_i B_{j-1}[S_i^j + \sigma J_i^{j-1} + \delta V_i^j] - [k+\mu_i]L_i^j.$$

From this last expression, L_i^j can be directly computed since since J_i^{j-1} is known from the previous time step. Thus,

$$\begin{aligned}
L_i^j &= \frac{L_{i-1}^{j-1} + \beta_i c_i h B_{j-1}[S_i^j + \sigma J_i^{j-1} + \delta V_i^j]}{1 + kh + \mu_i h},\\
I_i^j &= \frac{I_{i-1}^{j-1} + khL_i^j}{1 + rh + \mu_i h},\\
J_i^j &= \frac{J_{i-1}^{j-1} + rhI_i^j}{1 + h\sigma\beta_i c_i B_{j-1} + h\mu_i}.
\end{aligned} \tag{26}$$

This last approach is a little "iffy" but easier to program. Our analysis will be restricted to the first approach. To approximate the error, we set

$$\begin{aligned}
X(t_j,a_i) - X_i^j &= \xi_{i,j}, \qquad S(t_j,a_i) - S_i^j = \eta_{i,j},\\
V(t_j,a_i) - V_i^j &= \zeta_{i,j}, \qquad L(t_j,a_i) - L_i^j = \chi_{i,j},\\
I(t_j,a_i) - I_i^j &= \vartheta_{i,j}, \qquad J(t_j,a_i) - J_i^j = \varepsilon_{i,j}.
\end{aligned}$$

We compute the derivatives at (t_j, a_i) using (22) and subtract the corresponding terms from (25). We arrive at the following expression for the error estimates

$$\begin{aligned}
\frac{\xi_{i,j} - \xi_{i-1,j-1}}{h} &= -(\omega_i + \mu_i)\xi_{i,j} + O(h),\\
\frac{\eta_{i,j} - \eta_{i-1,j-1}}{h} &= \omega_i\xi_{i,j} - \beta_i c_i[B(t_j) - B(t_{j-1})]S(a_i,t_j) - \mu_i\eta_{i,j} - \phi_i\eta_{i,j}\\
&\quad -\beta_i c_i B_{j-1}\eta_{i,j} + \beta_i c_i[B_{j-1} - B(t_{j-1})]S(a_i,t_j) + O(h),\\
\frac{\zeta_{i,j} - \zeta_{i-1,j-1}}{h} &= \phi_i\eta_{i,j} - \mu_i\zeta_{i,j} - \delta\beta_i c_i[B(t_j) - B(t_{j-1})]V(a_i,t_j)\\
&\quad -\delta\beta_i c_i[B(t_{j-1}) - B_{j-1}]V(a_i,t_j) - \delta\beta_i c_i B_{j-1}\zeta_{i,j} + O(h),\\
\frac{\chi_{i,j} - \chi_{i-1,j-1}}{h} &= \beta_i c_i[B(t_j) - B(t_{j-1})][S(a_i,t_j) + \sigma J(a_i,t_j) + \delta V(a_i,t_j)]\\
&\quad +\beta_i c_i[B(t_{j-1}) - B_{j-1}][S(a_i,t_j) + \sigma J(a_i,t_j) + \delta V(a_i,t_j)]
\end{aligned}$$

$$
\begin{aligned}
&\quad -[k+\mu_i]\chi_{i,j} + \beta_i c_i B_{j-1}[\eta_{i,j} + \sigma\varepsilon_{i,j} + \delta\zeta_{i,j}] + O(h),\\
\frac{\vartheta_{i,j} - \vartheta_{i-1,j-1}}{h} &= k\chi_{i,j} - [r+\mu_i]\vartheta_{i,j} + O(h),\\
\frac{\varepsilon_{i,j} - \varepsilon_{i-1,j-1}}{h} &= r\vartheta_{i,j} - \sigma\beta_i c_i[B(t_j) - B(t_{j-1})]J(a_i,t_j) - \mu_i\varepsilon_{i,j}\\
&\quad +\sigma\beta_i c_i[B_{j-1} - B(t_{j-1})]J(a_i,t_j) - \sigma\beta_i c_i B_{j-1}\varepsilon_{i,j} + O(h).
\end{aligned}
$$

This system is equipped with initial and boundary conditions which are all equal to zero, that is $\xi_0^j = 0$, $\eta_0^j = 0$, $\zeta_0^j = 0$, $\chi_0^j = 0$, $\vartheta_0^j = 0$, $\epsilon_0^j = 0$ for all j, and similarly, $\xi_i^0 = 0$, $\eta_i^0 = 0$, $\zeta_i^0 = 0$, $\chi_i^0 = 0$, $\vartheta_i^0 = 0$, $\epsilon_i^0 = 0$ for all i. Solving for $\xi_{i,j}$, $\eta_{i,j}$, $\zeta_{i,j}$, $\chi_{i,j}$, $\vartheta_{i,j}$ and $\varepsilon_{i,j}$ gives

$$
\begin{aligned}
\xi_{i,j} &= \frac{\xi_{i-1,j-1}}{1+h(\omega_i+\mu_i)} + O(h^2),\\
\eta_{i,j} &= \frac{h\omega_i\xi_{i,j} - h\beta_i c_i[B(t_j) - B(t_{j-1})]S(a_i,t_j)}{1+h(\mu_i+\phi_i+\beta_i c_i B_{j-1})}\\
&\quad -\frac{h\beta_i c_i[B(t_{j-1}) - B_{j-1}]S(a_i,j_t) - \eta_{i-1,j-1}}{1+h(\mu_i+\phi_i+\beta_i c_i B_{j-1})} + O(h^2),\\
\zeta_{i,j} &= \frac{h\phi_i\eta_{i,j} - h\delta\beta_i c_i[B(t_j) - B(t_{j-1})]V(a_i,t_j)}{1+h(\mu_i+\delta\beta_i c_i B_{j-1})}\\
&\quad -\frac{h\delta\beta_i c_i[B(t_{j-1}) - B_{j-1}]V(a_i,t_j) - \zeta_{i-1,j-1}}{1+h(\mu_i+\delta\beta_i c_i B_{j-1})} + O(h^2),\\
\chi_{i,j} &= \frac{p_1}{q_1} + O(h^2),\\
\vartheta_{i,j} &= \frac{hk\chi_{i,j} + \vartheta_{i-1,j-1}}{1+hr+h\mu_i} + O(h^2),\\
\varepsilon_{i,j} &= \frac{\varepsilon_{i-1,j-1} + hr\vartheta_{i,j} - h\sigma\beta_i c_i[B(t_j) - B(t_{j-1})]J(a_i,t_j)}{1+h\sigma\beta_i c_i B_{j-1} + h\mu_i}\\
&\quad +\frac{h\sigma\beta_i c_i[B_{j-1} - B(t_{j-1})]J(a_i,t_j)}{1+h\sigma\beta_i c_i B_{j-1} + h\mu_i} + O(h^2),
\end{aligned}
$$

where

$$
\begin{aligned}
p_1 &= h\beta_i c_i[B(t_j) - B(t_{j-1})][S(a_i,t_j) + \sigma J(a_i,t_j) + \delta V(a_i,t_j)]\\
&\quad +h\beta_i c_i[B(t_{j-1}) - B_{j-1}][S(a_i,t_j) + \sigma J(a_i,t_j) + \delta V(a_i,t_j)]\\
&\quad +h\beta_i c_i B_{j-1}[\eta_{i,j} + \sigma\varepsilon_{i,j} + \delta\zeta_{i,j}] + \chi_{i-1,j-1},
\end{aligned}
$$

and

$$
q_1 = 1 + h(k+\mu_i).
$$

Following Iannelli et al. [17] we make use of the norm

$$
\|f_n\| = \sum_{j=1}^{N} f_i h,
$$

on the error estimates

$$|\xi_{i,j}| \le |\xi_{i-1,j-1}| + O(h^2).$$

Multiplying both sides by h and summing from $i = 1, \dots M$ gives

$$||\xi_j|| \le h\xi_{0,j-1} + ||\xi_{j-1}|| + O(h^2),$$

that is, $||\xi_j|| \le O(h)$. Next we observe that

$$\begin{aligned}|\eta_{i,j}| \le\ & h\omega_i|\xi_{i,j}| + h|\beta_i c_i[B(t_j) - B(t_{j-1})]S(a_i,t_j)| \\ & + h|\beta_i c_i[B(t_{j-1}) - B_{j-1}]S(a_i,t_j)| + |\eta_{i-1,j-1}| + O(h^2). \quad (27)\end{aligned}$$

In order to look at convergence of $(|B(t_j) - B(t_{j-1})| + |B(t_{j-1}) - B_{j-1}|)$. We observe that

$$B(t_j) = \int_0^\infty \frac{I(t_j,a')}{n(t_j,a')} \frac{c(a')n(t_j,a')}{\int_0^\infty c(u)n(t_j,u)du} da' = \frac{\int_0^\infty c(a')I(t_j,a')da'}{\int_0^\infty c(u)n(t_j,u)du}$$

which can be approximated using the trapezoidal rule. In fact,

$$\begin{aligned}B(t_j) \ &\approx \ \frac{\frac{1}{2}c(0)I(a,t_j)h + \sum_{i=1}^{M-1} c(a_i)I(a_i,t_j)h + \frac{1}{2}c(a_M)I(a_M,t_j)h + O(h^2)}{\frac{1}{2}c(0)n(a,t_j)h + \sum_{i=1}^{M-1} c(a_i)n(a_i,t_j)h + \frac{1}{2}c(a_M)n(a_M,t_j)h + O(h^2)} \\ &:= \frac{\mathbf{I(t_j)} + O(h^2)}{\mathbf{N(t_j)} + O(h^2)}.\end{aligned}$$

Similarly B_j in the numerical scheme can be written as

$$B_j = \frac{\frac{1}{2}c_0 I_0^j h + \sum_{i=1}^{M-1} c_i I_i^j h + \frac{1}{2}c_M I_M^j h}{\frac{1}{2}c_0 n_0^j h + \sum_{i=1}^{M-1} c_i n_i^j h + \frac{1}{2}c_M n_M^j h} := \frac{\mathbf{DI_j}}{\mathbf{DN_j}}. \quad (28)$$

Hence,

$$\begin{aligned}B(t_j) - B_j &= \frac{\mathbf{I(t_j)} + O(h^2)}{\mathbf{N(t_j)} + O(h^2)} - \frac{\mathbf{DI_j}}{\mathbf{DN_j}} \\ &= \frac{[\mathbf{I(t_j)} + O(h^2)]\mathbf{DN_j} - \mathbf{DI_j}[\mathbf{N(t_j)} + O(h^2)]}{[\mathbf{N(t_j)} + O(h^2)]\mathbf{DN_j}} \\ &= \frac{[\mathbf{I(t_j)} + O(h^2)]\mathbf{DN_j} - [\mathbf{I(t_j)} + O(h^2)][\mathbf{N(t_j)} + O(h^2)]}{[\mathbf{N(t_j)} + O(h^2)]\mathbf{DN_j}} \\ &\quad + \frac{[\mathbf{I(t_j)} + O(h^2)][\mathbf{N(t_j)} + O(h^2)] - \mathbf{DI_j}[\mathbf{N(t_j)} + O(h^2)]}{[\mathbf{N(t_j)} + O(h^2)]\mathbf{DN_j}} \\ &= \frac{[\mathbf{I(t_j)} + O(h^2)][\mathbf{DN_j} - \mathbf{N(t_j)} + O(h^2)]}{[\mathbf{N(t_j)} + O(h^2)]\mathbf{DN_j}} + \frac{\mathbf{I(t_j)} - \mathbf{DI_j} + \mathbf{O(h^2)}}{\mathbf{DN_j}}.\end{aligned}$$

Furthermore

$$\frac{\mathbf{I(t_j)} + \mathbf{O(h^2)}}{\mathbf{N(t_j)} + \mathbf{O(h^2)}} \le 1$$

since

$$\begin{aligned}\mathbf{I(t_j)} + \mathbf{O(h^2)} &= \textstyle\int_0^\infty c(a)I(t_j,a)da,\\ \mathbf{N(t_j)} + \mathbf{O(h^2)} &= \textstyle\int_0^\infty c(u)n(t_j,u)du,\\ \textstyle\int_0^\infty I(a,t)da &\le \textstyle\int_0^\infty n(a,t)da.\end{aligned}$$

We now make use of the solution for $n(a,t)$ introduced in Section 3. That is, we take

$$n(t,a) = n_0(a-t)\frac{\mathcal{F}(a)}{\mathcal{F}(a-t)}H(a-t) + \Lambda\mathcal{F}(a)H(t-a),$$

where

$$\begin{aligned}&\mathcal{F}(a) = exp\left(-\int_0^a \mu(s)ds\right),\\ &H(s) = 1, s \ge 0; \qquad H(s) = 0, s < 0.\end{aligned}$$

$\mathbf{DN_j} - \mathbf{N(t_j)} = 0$ since we know the exact values of $n(t,a)$ and $n(t_j,a_i) \approx n_i^j$. The error in the approximation comes from the use of the trapezoidal rule only. Hence

$$\begin{aligned}|B(t_j) - B_j| &\le \frac{|\mathbf{DN_j} - \mathbf{N(t_j)} + O(h^2)|}{\mathbf{DN_j}} + \frac{|\mathbf{I(t_j)} - \mathbf{DI_j} + O(h^2)|}{\mathbf{DN_j}}\\ &\le \frac{O(h^2)}{\mathbf{DN_j}} + \frac{|\mathbf{I(t_j)} - \mathbf{DI_j}|}{\mathbf{DN_j}} + O(h)\\ &= \frac{|\mathbf{I(t_j)} - \mathbf{DI_j}|}{\mathbf{DN_j}} + O(h)\\ &= \frac{1}{\mathbf{DN_j}}\left[\frac{1}{2}c_0\vartheta_0^j h + \sum_{i=1}^{M-1} c_i\vartheta_i^j h + \frac{1}{2}c_M\vartheta_M^j h\right] + O(h)\\ &\le \frac{1}{\mathbf{DN_j}}||\vartheta_j|| + O(h).\end{aligned}$$

Also,

$$\begin{aligned}B(t_j) - B(t_{j-1}) &= \frac{\mathbf{I(t_j)} + O(h^2)}{\mathbf{N(t_j)} + O(h^2)} - \frac{\mathbf{I(t_{j-1})} + O(h^2)}{\mathbf{N(t_{j-1})} + O(h^2)}\\ &= \frac{[\mathbf{I(t_j)} + O(h^2)][\mathbf{N(t_{j-1})} + O(h^2)]}{[\mathbf{N(t_j)} + O(h^2)][\mathbf{N(t_{j-1})} + O(h^2)]}\\ &\quad - \frac{[\mathbf{N(t_j)} + O(h^2)][\mathbf{I(t_{j-1})} + O(h^2)]}{[\mathbf{N(t_j)} + O(h^2)][\mathbf{N(t_{j-1})} + O(h^2)]}\\ &= \frac{\mathbf{I(t_j)N(t_{j-1})} - \mathbf{I(t_{j-1})N(t_j)} + [\mathbf{I(t_j)} + \mathbf{N(t_{j-1})}]O(h^2)}{[\mathbf{N(t_j)} + O(h^2)][\mathbf{N(t_{j-1})} + O(h^2)]}\\ &\quad - \frac{[\mathbf{I(t_{j-1})} + \mathbf{N(t_j)}]O(h^2) + O(h^4)}{[\mathbf{N(t_j)} + O(h^2)][\mathbf{N(t_{j-1})} + O(h^2)]}\end{aligned}$$

$$\leq \frac{\mathbf{I(t_{j-1})[N(t_{j-1}) - N(t_{j-1})] + N(t_{j-1})[I(t_j) - I(t_{j-1})]}}{\mathbf{N(t_j)N(t_{j-1})}}$$
$$+\frac{O(h^2) + O(h^4)}{\mathbf{N(t_j)N(t_{j-1})}}$$
$$\leq \frac{O(h)}{\mathbf{N(t_j)}}.$$

We add $|\xi_{i,j}|$ to both sides of inequality (27) to obtain:

$$|\xi_{i,j}| + |\eta_{i,j}| \leq (1 + h\omega_i)|\xi_{i,j}| + h\beta_i c_i |B(t_j) - B(t_{j-1})| S(a_i, t_j)$$
$$+h\beta_i c_i |B(t_{j-1}) - B_{j-1}| S(a_i, t_j) + |\eta_{i-1,j-1}| + O(h^2)$$

Using the expression for $\xi_{i,j}$ in terms of $\xi_{i-1,j-1}$ and the estimates for $|B(t_j) - B(t_{j-1})|$ and $|B(t_j) - B_j|$ we find:

$$|\xi_{i,j}| + |\eta_{i,j}| \leq \frac{(1 + h\omega_i)|\xi_{i-1,j-1}|}{1 + h(\omega_i + \mu_i)} + \frac{h\beta_i c_i S(a_i, t_j) \cdot Ch}{\mathbf{N(t_j)}}$$
$$+\frac{h\beta_i c_i S(a_i, t_j) \cdot ||\vartheta_j||}{\mathbf{DN_j}} + |\eta_{i-1,j-1}| + O(h^2)$$
$$\leq |\xi_{i-1,j-1}| + |\eta_{i-1,j-1}| + \frac{Ch^2 \beta_i c_i S(a_i, t_j)}{\mathbf{N(t_j)}}$$
$$+\frac{h\beta_i c_i S(a_i, t_j) \cdot ||\vartheta_j||}{\mathbf{DN_j}} + O(h^2),$$

which leads to

$$||\xi_j|| + ||\eta_j|| \leq ||\xi_{j-1}|| + ||\eta_{j-1}|| + C_1 h||\vartheta_j|| + O(h^2) \tag{29}$$

Similarly,

$$||\zeta_j|| \leq ||\zeta_{j-1}|| + \hat{C}h||\eta_j|| + C_2 h||\vartheta_j|| + O(h^2). \tag{30}$$

Since $B_j \leq 1$ for all $j's$ it follows that

$$||\chi_j|| \leq ||\chi_{j-1}|| + C_3 h||\vartheta_j|| + C_4 h(||\eta_j|| + ||\varepsilon_j|| + ||\zeta_j||) + O(h^2)$$
$$||\vartheta_j|| \leq ||\vartheta_{j-1}|| + kh||\chi_j|| + O(h^2)$$
$$||\varepsilon_j|| \leq ||\varepsilon_{j-1}|| + C_5 h||\vartheta_j|| + O(h^2)$$

where C_1 through C_5 and $\hat{C}$ are appropriate constants that depend on the upper bounds of the parameter functions but not on h, i or j. Now we let $\Gamma_j = |\xi_j| + |\eta_j| + |\zeta_j| + |\chi_j| + |\chi_j| + |\vartheta_j| + |\varepsilon_j|$ and adding above inequalities leads to

$$||\Gamma_j|| \leq ||\Gamma_{j-1}|| + Ch||\Gamma_j|| + O(h^2),$$

i.e.

$$(1 - Ch)||\Gamma_j|| \leq ||\Gamma_{j-1}|| + O(h^2),$$

which leads to

$$\begin{aligned}
||\Gamma_j|| &\leq \frac{1}{1-Ch}||\Gamma_{j-1}|| + \frac{1}{1-Ch}O(h^2) \\
&\leq \frac{1}{(1-Ch)^j}||\Gamma_0|| + \left[\frac{1}{(1-Ch)^j} + \cdots + \frac{1}{1-Ch}\right] O(h) \\
&= \frac{1}{1-Ch}\frac{1-(\frac{1}{1-Ch})^j}{1-\frac{1}{1-Ch}} \\
&\quad \frac{1-Ch}{Ch}\left[(\frac{1}{1-Ch})^j - 1\right] O(h^2) \\
&\leq \left[(\frac{1}{1-CT/N})^N - 1\right] O(h) \\
&\leq [e^{CT} - 1]O(h) \leq O(h).
\end{aligned}$$

Thus each component in Γ_j satisfies $\Gamma_{i,j} \leq \Gamma_{i-1,j-1} + O(h^2)$ and by iteration it follows that $\Gamma_{i,j} \leq O(h)$ for all $i's$ and $j's$. Now the convergence of the numerical scheme has therefore been established.

7 Discussion

The oral vaccine, Rotarix, by GlaxoSmithKline was launched in Mexico in January, 2005. A successful experience by Mexico would likely influence the licensing of Rotarix in other Latin American countries and possibly in the U.S. It is the existence of a viable rotavirus vaccine in Mexico that motivates the work in this article. First, we formulate an age-structured model and use it to study the dynamics and control under vaccination against rotavirus infections. This policy is tested in a population where some infants are assumed to be protected by maternal antibodies. We calculate the basic reproduction number, $\Re_0$ and the control reproductive number, $\Re(\phi, q, \omega)$. It is shown that a vaccine can help to reduce rotavirus prevalence through the analysis of $\Re_0$ and $\Re(\phi, q, \omega)$.

Several researchers have claimed that the use of the current vaccine may indeed provide the best hope of controlling the yearly rotavirus outbreaks [9]. Their reasons include the fact that it has been well documented that maternal immunity acquired from breast-feeding or partial natural immunity acquired from previous rotavirus infections do provide protection against rotavirus infection. Furthermore, it is believed that a vaccine may stimulate "herd" immunity [8]. Here, we have not included the impact of temporary or partial natural immunity.

In some developing countries, even treatment to re-hydrate children experiencing severe rotavirus diarrhea is unavailable [29]. Studies showed that the impact of improved hygiene on rotavirus transmission rates is not significant. The ability of rotavirus to survive at room temperature for long periods of time contributes to its high infection morbidity rate. Previous studies have shown that the vaccine, Rotarix, 73% protection against any and 90% protection against severe rotavirus (mostly G1) gastroenteritis [33]. It has also

been shown that this vaccine reduces hospital admissions by 70% [26]. GlaxoSmithKline has concluded that the vaccine provides an overall efficacy of 48% against a first episode of rotavirus diarrhea [26]. The pentavalent vaccine containing 5 reassorted rotaviruses, RotaTeq, is reported to provide to 68% to 75% protection against all rotavirus gastroenteritis regardless of severity while reducing severe symptoms in all (100%) vaccinated cases [32]. Before "Rotashield" (an alternative vaccine) was withdrawn it was scheduled to be applied at 2, 4 and 6 months of age. Whether or not this would be the optimal vaccine strategy in developing countries needs to be addressed. Here, our theoretical work on the role of such a policy ($\phi(a)$) on $\Re(\phi, q, \omega)$ when cost is included suggests a different policy but our model may not have included all the relevant epidemiology.

The reproductive number of rotavirus depends on parameters and functions, all of which can influence its magnitude. In particular, when all parameters fixed, we see that $\Re(\phi, q, \omega)$ increases with higher mixing rate or activity rate. We also see that higher breast-feeding or vaccination rates result in decreases on $\Re(\phi, q, \omega)$. Maternal antibodies are known to provide protection against infection for infants and they decay with time [30]. However it is well known that maternal antibodies have the inhibitory effect on infant immune responses after immunization [23]. This work and proposed vaccine schedule have now motivated us to look at a caricature of immune response model that will help finding the "optimal" protection window conferred by maternal antibodies in the case of rotavirus infection. Furthermore it is believed that contaminated food or water may serve as a "vector" that passes rotavirus to humans. These and other possible alternate transmission routes have not been taken explicitly into account. Whether or not non-vaccine policies (like education) can reduce infections is unclear and was not tested here.

Our model is based on a previous Tuberculosis model ([6]). It has been modified to incorporate vaccination in a population where some infants are temporarily protected by maternal antibodies. That is, our model explicitly addresses the supporting role of breast feeding (maternal antibody) on rotavirus control. We have followed the approach in [12] when formulating the optimization problem, that is in identifying optimal age-dependent vaccination strategies. The work of K.P. Hadeler and his lectures on epidemiology have been invaluable in this and many projects throughout our lives. We have introduced a convergent discretization of our age-structured model as computer simulations are important. This work hopes to increase the understanding of rotavirus infection. The model proposed here may be further expanded to incorporate the factors mentioned in this sections as well as the observed seasonal variation in transmission rates.

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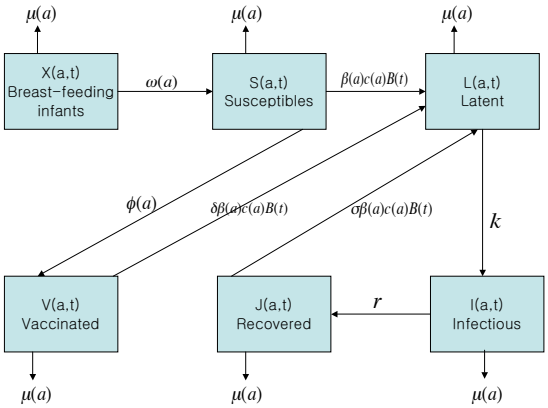

Fig. 1 Infants with breast feeding are protected against infection and younger aged children are more prone to get infected. Repeated infection is possible but symptom are less severe in such cases. Vaccination is the best way to prevent Rotaries infection and can be applied differently among age groups.

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