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An age-structured model of human papillomavirus vaccination

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Abstract

Recently, a vaccine for human papillomavirus was introduced, but made available only for girls and adult women aged 13–26. Since rates of sexual activity vary by age and gender, vaccinating only an age-limited subset of one cohort may be insufficient to control the disease across all age groups and genders. We develop an age-dependent two-sex mathematical model to describe the HPV vaccination program for a vaccine targeting HPV types 16 and 18 in both childhood and adult stages. A stability analysis is performed to determine the stability of the disease-free and endemic equilibria for different vaccination programs. The basic reproduction number is derived for perfect childhood vaccination, perfect adult vaccination and childhood–adult vaccination. We show that the effects of age dependency are complex, but that vaccinating a single age cohort in one gender, as current programs do, can result in eventual control of the disease across all age groups. We also support our theoretical analysis with numerical simulations. This provides a framework for future research and public-health policy to determine the dependence of HPV vaccination programs on age and sexual behaviour, as well as how the vaccine can reduce the number of infections and deaths due to cervical cancer.

Keywords: Human papillomavirus; Age dependence; Mathematical model; Cervicalcancer; Vaccine

1. Introduction

Human papillomavirus (HPV) is the name of a group of viruses that includes more than 100 different strains or types; more than 30 of these viruses are sexually transmitted. Persistent infection with high-risk types of HPV is the most important risk factor for cervical cancer; the development of cervical cancer is always preceded by infection with one of these viruses. However, the opposite is not always true; infection can occur without it leading to cancer [1].

As the infection is necessary for cancer to develop, vaccination that prevents HPV infection could potentially also prevent cervical cancer. Several such vaccines have already been developed and tested [1]. A vaccine against HPV types 6, 11, 16 and 18 is now licensed for use in Canada and many other countries [4].

With promising efficacy results from HPV vaccines, policymakers are being asked to make recommendations and decisions regarding optimal strategies to reduce HPV infection and disease. Such decisions are increasingly being made with significant input from mathematical and economic models. The demand for modelling has resulted in the development of numerous mathematical and economical models examining the best strategies and the cost effectiveness of vaccination [1,3,6,8–11,13,16,18,20].

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Age structure in epidemic models has been considered by many authors, because of the recognition that transmission dynamics of certain diseases (such as sexually transmitted diseases) vary by age cohort. For diseases with long transmission periods, the duration of infection, probability of transmission and natural death rate will all depend on age. Despite the dependence of the transmission rates and the rates of sexual activity on age class, there have been few age-structured mathematical models of HPV. Sexual contact varies by age and gender, and the vaccine is only available for women aged 13–26. However, partnerships between older men and younger women versus older women may facilitate disease transmission. Conversely, the effects of vaccinating a targeted age group may result in a general reduction of viral prevalence.

Here, we develop a partial differential equation (PDE) model to study the effect of HPV vaccination for HPV types 16 and 18 (which are responsible for more than 70% of cervical cancers [10]), using a time- and age-dependent system of PDEs, in order to evaluate a vaccination program and find parameters that play a major role in controlling the disease. This is a generalization of [20], extending our time-dependent model to incorporate age-dependent effects.

Although age-structure could be approximated by a number of discrete classes (see, for example, [2]), these would divide the population into mutually exclusive sexual profiles corresponding to different groups of sexual activity, defined by their average number of different partnerships formed each year. Each group would further contain gender and disease status, as well as vaccination status. Such a model would be extremely complex. Conversely, a continuous model, such as the one we develop here, allows a range of age effects to be examined simultaneously and incorporates the variation in disease and vaccination status in an elegant way.

We are interested in using our model to address the following question: can vaccinating in one age cohort and one gender control the disease across different ages and genders? This paper is organized as follows. In Section 2, we introduce the problem as a system of PDEs with initial and boundary conditions. In Section 3, we determine steady-state equilibria and calculate the reproduction number. In Section 4, we study the stability of all the possible equilibria. In Section 5, we support our results with numerical simulations. We conclude with a discussion.

2. The model

We extended the model in [20] to include sexually active women and men from all ages. The system of PDEs that describe the dynamics of adult women and men due to birth, death and vaccination is a generalized system to the system of ordinary differential equations in [20]. In addition to the model assumptions found in [20], we assume that women enter the model as children at age 13, women cannot be vaccinated after age 26 and the vaccine may not confer 100% protection. The model classifies the adult population into eight classes: vaccinated susceptible adult women (A_v), unvaccinated susceptible adult women (A_u), vaccinated infected adult women (I_v), unvaccinated infected adult women (I_u), recovered women (R_w), susceptible adult men (M), infected adult men (N) and recovered men (R_m). A childhood vaccine results in a proportion (p) of adult women initially being vaccinated. Unvaccinated adult women (A_u) can either be vaccinated when they are in the age range 13–26 (represented by $\chi_{[13,26]}$) or become infected (I_u), with rate β_m depending on age and time, when they meet an infected man N. Vaccinated adult women (A_v) can also become infected (I_v) with rate $(1-\psi)\beta_m$, where ψ is the efficacy of the vaccine. Unvaccinated men (M) become infected upon contact with infected women (I_u or I_v), with a rate β_w or $\eta\beta_w$ depend on age and time. Infected women (I_u and I_v) recover at rates r_u and r_v, while infected men recover with a rate r_m. Since we are interested in studying the effect of vaccination for HPV types 16 and 18, we assume that recovering from these HPV types means immunity to these types [12,17]. The age-dependent natural death rate is μ and the age-dependent disease death rate for unvaccinated females is d_u, for vaccinated females is d_v and for males is d_m. The model is illustrated in Fig. 1. Parameters can be found in Table 1.

The reported number of annual partners per year is given in Fig. 2.

The system of PDEs is

$$\partial_t A_u + \partial_a A_u = -(\mu(a) + \beta_m(t,a))A_u - \left(\frac{1}{13}a - 1\right)\chi_{[13,26]} f(\overline{p})A_u \tag{1}$$

$$\partial_t I_u + \partial_a I_u = \beta_m(t,a)A_u - (\mu(a) + d_u(a) + r_u(a))I_u \tag{2}$$

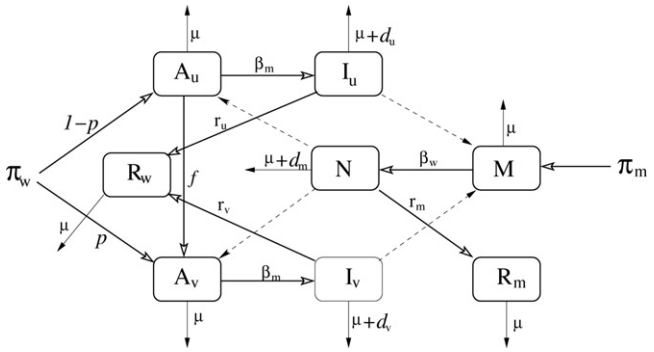

Fig. 1. The mathematical model. Men can be susceptible (M), infected (N) or recovered (R_m). Women can be susceptible and unvaccinated (A_u), infected and unvaccinated (I_u), susceptible and vaccinated (A_v), infected and vaccinated (I_v) or recovered (R_w).

Table 1
Variables and parameters.

Variable	Definition
$A_u(t,a)$	Unvaccinated susceptible adult women of age a at time t
$A_v(t,a)$	Vaccinated susceptible adult women of age a at time t
$I_u(t,a)$	Infected unvaccinated adult women of age a at time t
$I_v(t,a)$	Infected vaccinated adult women of age a at time t
$R_w(t,a)$	Recovered adult women of age a at time t
$M(t,a)$	Susceptible adult men of age a at time t
$N(t,a)$	Infected adult men of age a at time t
$R_m(t,a)$	Recovered adult men of age a at time t
π_w	Rate of appearance of new adult females
π_m	Rate of appearance of new adult males
p	Proportion of female children successfully vaccinated
$\overline{p}$	Proportion of adult females successfully vaccinated
β_{wm}	Probability of transmission to a man by an infected woman
β_{mw}	Probability of transmission to a woman by an infected man
ψ	Vaccine efficacy
$\mu(a)$	Natural death rate as a function of age a
$d_u(a)$	Unvaccinated female disease death rate as a function of age a
$d_v(a)$	Vaccinated female disease death rate as a function of age a
$d_m(a)$	Male disease death rate as a function of age a
$r_u(a)$	Unvaccinated female recovery rate from disease as a function of age a
$r_v(a)$	Vaccinated female recovery rate from disease as a function of age a
$r_m(a)$	Male recovery rate from disease as a function of age a
γ	Maximal possible rate of adult vaccination
c	Attentuation constant
η	Modification parameter

$$\begin{aligned}\partial_t A_v + \partial_a A_v = \; & -(\mu(a) + \beta_m(t,a)(1-\psi))A_v \\ & + \left(\frac{1}{13}a - 1\right)\chi_{[13,26]} f(\overline{p}) A_u \end{aligned} \tag{3}$$

$$\partial_t I_v + \partial_a I_v = \beta_m(t,a)(1-\psi)A_v - (\mu(a) + d_v(a) + r_v(a))I_v \tag{4}$$

$$\partial_t R_w + \partial_a R_w = r_u(a)I_u + r_v(a)I_v - \mu(a)R_w \tag{5}$$

$$\partial_t M + \partial_a M = -(\mu(a) + \beta_w(t,a))M \tag{6}$$

$$\partial_t N + \partial_a N = \beta_w(t,a)M - (\mu(a) + d_m(a) + r_m(a))N \tag{7}$$

$$\partial_t R_m + \partial_a R_m = r_m(a)N - \mu(a)R_m \tag{8}$$

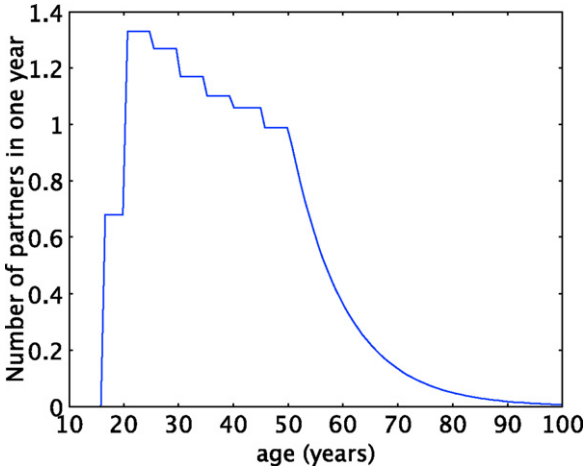

Fig. 2. The number of reported partners for men and women as a function of age in the last 12 months

with the boundary conditions

$$\begin{aligned} &A_u(t,13) = (1-p)\pi_w \quad I_u(t,13) = 0 \quad A_v(t,13) = p\pi_w \\ &I_v(t,13) = 0 \quad R_w(t,13) = 0 \quad M(t,13) = \pi_m \\ &N(t,13) = 0 \quad R_m(t,13) = 0 \end{aligned} \tag{9}$$

and the initial conditions

$$\begin{aligned} &A_u(0,a) = A_u^0(a) \quad I_u(0,a) = I_u^0(a) \quad A_v(0,a) = A_v^0(a) \\ &I_v(0,a) = I_v^0(a) \quad R_w(0,a) = R_w^0(a) \quad M(0,a) = M^0(a) \\ &N(0,a) = N^0(a) \quad R_m(0,a) = R_m^0(a) \end{aligned} \tag{10}$$

Here,

$$\beta_m(t,a) = \beta_{mw} \int_{13}^{\infty} K_m(a,b)N(t,b)db \tag{11}$$

$$\beta_w(t,a) = \beta_{wm} \int_{13}^{\infty} K_w(a,b)(I_u(t,b) + \eta I_v(t,b))db \tag{12}$$

are called the forces of infection. $K_m(a,b)$ is the rate at which an infective man of age b comes into a contact with a susceptible woman of age a, $K_w(a,b)$ is the rate at which an infective woman of age b comes into contact with a susceptible man of age a and η is a modification parameter that represents the reduction in transmissiblity due to vaccine, where $0 < \eta \leq 1$. For men of a fixed age b, the infection rate of females at any time is $\beta_{mw}K_m(a,b)N(t,b)$ where β_{mw} is the transmission rate from infected males to susceptible females if contact occurs, $K_m(a,b)$ is the probability at which an infective man of age b comes into a contact with a susceptible woman of age a. Then we integrate over all men ages above 13. Note that the integral is zero when b exceeds a man's maximum age.

For simplicity, we will assume that both $K_m(a,b)$ and $K_w(a,b)$ are separable; that is,

$$K_m(a,b) = c_w(a)c_N(b)$$
$$K_m(a,b) = c_m(a)c_I(b)$$

We thus have

$$\beta_m(t,a) = \beta_{mw}c_w(a)\lambda(t) \tag{13}$$

$$\beta_w(t,a) = \beta_{wm}c_m(a)\omega(t) \tag{14}$$

where

$$\lambda(t) = \int_{13}^{\infty} c_N(b)N(t,b)db \tag{15}$$

$$\omega(t) = \int_{13}^{\infty} c_I(b)(I_u(t,b) + \eta I_v(t,b))db \tag{16}$$

and $c_i(a) > 0$, for $i = w, I, m, N$.

As in [20],

$$f(\overline{p}) = \frac{c\overline{p}}{(1 - \overline{p} + \gamma)} \tag{17}$$

where c is the attenuation constant and γ is the maximum possible rate of adult vaccination; see [20] for more discussion. (Note that here we have incorporated the immunogenicity into p and $\overline{p}$.)

The vaccine is given in two stages: the childhood vaccine for age $a < 13$ and the adult vaccine for age $13 < a \leq 26$. The childhood vaccine is free and the chance of getting the vaccine does not depend on age, while the adult vaccine costs CAN$400. Consequently, we assume that the likelihood of paying for the vaccine increases with age, since adult women will earn more money the older they get, as well as gain more awareness of the need for the vaccine as they gain more sexual experience.

We use χ, the characteristic function, to determine vaccine eligibility, where

$$\left(\frac{1}{13}a - 1\right)\chi_{[13,26]} = \begin{cases} \frac{1}{13}a - 1 & a \in [13, 26] \\ 0 & \text{otherwise} \end{cases}$$

3. Steady-state solution

In this section, we analyze the large time behaviour of solutions for the system (1)–(10) in order to determine the long-term effects of age distribution. Let $t \to \infty$ in the system (1)–(10). Then we have the following steady-state system of ordinary differential equations (ODEs):

$$\frac{d\overline{A}_u}{da} = -(\mu(a) + \beta_{mw}c_w(a)\lambda_\infty)\overline{A}_u - (\frac{1}{13}a - 1)\chi_{[13,26]}f(\overline{p})\overline{A}_u \tag{18}$$

$$\frac{d\overline{I}_u}{da} = \beta_{mw}c_w(a)\lambda_\infty\overline{A}_u - (\mu(a) + d_u(a) + r_u(a))\overline{I}_u \tag{19}$$

$$\frac{d\overline{A}_v}{da} = -(\mu(a) + \beta_{mw}c_w(a)\lambda_\infty(1 - \psi))\overline{A}_v + (\frac{1}{13}a - 1)\chi_{[13,26]}f(\overline{p})\overline{A}_u \tag{20}$$

$$\frac{d\overline{I}_v}{da} = \beta_{mw}c_w(a)\lambda_\infty(1 - \psi)\overline{A}_v - (\mu(a) + d_v(a) + r_v(a))\overline{I}_v \tag{21}$$

$$\frac{d\overline{R}_w}{da} = r_u(a)\overline{I}_u + r_v(a)\overline{I}_v - \mu(a)\overline{R}_w \tag{22}$$

$$\frac{d\overline{M}}{da} = -(\mu(a) + \beta_{wm}c_m(a)\omega_\infty)\overline{M} \tag{23}$$

$$\frac{d\overline{N}}{da} = \beta_{wm}c_m(a)\omega_\infty\overline{M} - (\mu(a) + d_m(a) + r_m(a))\overline{N} \tag{24}$$

$$\frac{d\overline{R}_m}{da} = r_m(a)\overline{N} - \mu\overline{R}_m \tag{25}$$

with boundary conditions

$$\begin{aligned} &\overline{A}_u(13) = (1-p)\pi_w \quad \overline{I}_u(13) = 0 \quad \overline{A}_v(13) = p\pi_w \\ &\overline{I}_v(13) = 0 \quad \overline{R}_w(13) = 0 \quad \overline{M}(13) = \pi_m \\ &\overline{N}(13) = 0 \quad \overline{R}_m(a) = 0. \end{aligned} \tag{26}$$

Here,

$$\lambda_\infty = \int_{13}^{\infty} c_N(b)\overline{N}(b)db \tag{27}$$

$$\omega_\infty = \int_{13}^{\infty} c_I(b)(\overline{I}_u(b) + \eta\overline{I}_v(b))db \tag{28}$$

Define

$$P_i(a) = \exp\left(-\int_{13}^{a}(\mu(s) + d_i(s) + r_i(s))ds\right) \tag{29}$$

for $i = u, v, m$ to be the probabilities of remaining in the infected classes I_u, I_v and N respectively until age a. Also, define

$$Q_i(a) = \exp\left(\int_{13}^{a}(r_i(s) + d_i(s))ds\right) \tag{30}$$

such that $Q_i^{-1}(a)$, for $i = u, v, m$, are the probabilities of remaining in the infected classes I_u, I_v and N respectively until age a, if no natural death occurs.

Note that if any of the classes is empty, then the probability of remaining in this class is zero.

The implicit solution for this system is the following

$$\overline{A}_u(a) = (1-p)\pi_w \exp\left(-\int_{13}^{a}\left[\mu(s) + \beta_{mw}c_w(s)\lambda_\infty + \left(\frac{1}{13}s - 1\right)\chi_{[13,26]}f(\overline{p})\right]ds\right) \tag{31}$$

$$\begin{aligned} \overline{A}_v(a) = \quad & \exp\left(-\int_{13}^{a}[\mu(s) + \beta_{mw}(1-\psi)c_w(s)\lambda_\infty]\,ds\right) \\ & \times\left(p\pi_w + (1-p)\pi_w\chi_{[13,26]}f(\overline{p})\int_{13}^{a}\left[\left(\frac{1}{13}s - 1\right)\right.\right. \\ & \left.\left.\times\exp\left(-\int_{13}^{s}\left(\psi\beta_{mw}c_w(k)\lambda_\infty + \left(\frac{1}{13}k - 1\right)\chi_{[13,26]}f(\overline{p})\right)dk\right)ds\right]\right) \end{aligned} \tag{32}$$

$$\begin{aligned} \overline{I}_u(a) = \quad & (1-p)\pi_w\beta_{mw}\lambda_\infty P_u(a) \\ & \times\int_{13}^{a}\left[c_w(s)Q_u(s)\exp\left(-\int_{13}^{s}\left(\beta_{mw}c_w(k)\lambda_\infty + \left(\frac{1}{13}k - 1\right)\chi_{[13,26]}f(\overline{p})\right)dk\right)\right]ds \end{aligned} \tag{33}$$

$$\begin{aligned} \overline{I}_v(a) = \quad & \beta_{mw}(1-\psi)\lambda_\infty P_v(a) \\ & \times\int_{13}^{a}\left[c_w(s)Q_v(s)\exp\left(-\beta_{mw}(1-\psi)\lambda_\infty\int_{13}^{s}c_w(k)dk\right)\right. \\ & \times\left(p\pi_w + (1-p)\pi_w\chi_{[13,26]}f(\overline{p})\right. \\ & \left.\left.\times\int_{13}^{s}\left(\left(\frac{1}{13}k - 1\right)\exp\left(-\int_{13}^{k}(\psi\beta_{mw}c_w(h)\lambda_\infty + \left(\frac{1}{13}h - 1\right)\chi_{[13,26]}f(\overline{p}))dh\right)\right)dk\right)\right]ds \end{aligned} \tag{34}$$

$$\overline{M}(a) = \pi_m\exp\left(-\int_{13}^{a}(\mu(s) + \beta_{wm}c_m(s)\omega_\infty)\,ds\right) \tag{35}$$

$$\overline{N}(a) = \beta_{wm}\pi_m\omega_\infty P_m(a)\int_{13}^{a}\left[c_m(s)Q_m(s)\exp\left(-\omega_\infty\beta_{wm}\int_{13}^{s}c_m(k)dk\right)\right]ds \tag{36}$$

The implicit solutions for $\overline{R}_w$ and $\overline{R}_m$ are not written here because they are irrelevant to our work. From Eqs. (27) and (28), and the solution above, we have

$$\lambda_\infty = \beta_{wm}\pi_m\omega_\infty\int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}\left[c_m(s)Q_m(s)\exp\left(-\beta_{wm}\omega_\infty\int_{13}^{s}c_m(k)dk\right)\right]ds\right)db \tag{37}$$

and

$$\begin{aligned}\omega_\infty = \;& \pi_w\beta_{mw}\lambda_\infty\int_{13}^{\infty}c_I(a)\left[(1-p)P_u(a)\int_{13}^{a}c_w(s)Q_u(s)\right.\\
&\times\exp\left(-\int_{13}^{s}\left(\beta_{mw}c_w(k)\lambda_\infty+\left(\frac{1}{13}k-1\right)\chi_{[13,26]}f(\overline{p})\right)dk\right)ds\\
&+\eta(1-\psi)P_v(a)\int_{13}^{\infty}c_w(s)Q_v(s)\exp\left(-\beta_{mw}\lambda_\infty(1-\psi)\int_{13}^{k}c_w(k)dk\right)\\
&\times\left(p+(1-p)\chi_{[13,26]}f(\overline{p})\int_{13}^{s}\left(\left(\frac{1}{13}k-1\right)\right.\right.\\
&\left.\left.\left.\times\exp\left(-\int_{13}^{k}\left(\psi\beta_{mw}c_w(h)\lambda_\infty+\left(\frac{1}{13}h-1\right)\chi_{[13,26]}f(\overline{p})\right)dh\right)\right)dk\right)ds\right]da\end{aligned} \tag{38}$$

Substituting (37) into (38), we have

$$\begin{aligned}\omega_\infty = \;& \pi_w\pi_m\beta_{wm}\beta_{mw}\omega_\infty\\
&\times\int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}\left[c_m(s)Q_m(s)\exp\left(-\beta_{wm}\omega_\infty\int_{13}^{s}c_m(k)dk\right)\right]ds\right)db\\
&\times\int_{13}^{\infty}c_I(a)\left[(1-p)P_u(a)\int_{13}^{a}c_w(s)Q_u(s)\right.\\
&\times\exp\left(-\int_{13}^{s}\left(\beta_{mw}c_w(k)\lambda_\infty+\left(\frac{1}{13}k-1\right)\chi_{[13,26]}f(\overline{p})\right)dk\right)ds\\
&+\eta(1-\psi)P_v(a)\int_{13}^{\infty}c_w(s)Q_v(s)\exp\left(-\beta_{mw}\lambda_\infty(1-\psi)\int_{13}^{k}c_w(k)dk\right)\\
&\times\left(p+(1-p)\chi_{[13,26]}f(\overline{p})\int_{13}^{s}\left(\left(\frac{1}{13}k-1\right)\right.\right.\\
&\left.\left.\left.\times\exp\left(-\int_{13}^{k}\left(\psi\beta_{mw}c_w(h)\lambda_\infty+\left(\frac{1}{13}h-1\right)\chi_{[13,26]}f(\overline{p})\right)dh\right)\right)dk\right)ds\right]da\end{aligned} \tag{39}$$

This equation will be used for the analysis of the following three vaccination cases.

3.1. All females are vaccinated before age 13

In this case, we have $p = 1$, which implies $\overline{A}_u = 0$. Also, we have $\overline{p} = 0$, which implies $f(\overline{p}) = 0$; see (17). Therefore, (39) becomes

$$\begin{aligned}\omega_\infty = \quad & \pi_w\pi_m\beta_{wm}\beta_{mw}\eta(1-\psi)\omega_\infty \\ & \times \int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}[c_m(s)Q_m(s)H(s)]ds\right)db \\ & \times \int_{13}^{\infty}\left(c_I(a)P_v(a)\int_{13}^{a}[c_w(s)Q_v(s)G(s)]ds\right)da\end{aligned} \tag{40}$$

where

$$H(s) = \exp\left(-\beta_{wm}\omega_\infty\int_{13}^{s}c_m(k)dk\right) \tag{41}$$

and

$$\begin{aligned}G(s) = \quad & \exp\left(-\beta_{mw}\lambda_\infty(1-\psi)\int_{13}^{s}c_w(k)dk\right) \\ = \exp\,(& -\beta_{wm}\beta_{mw}\pi_m\omega_\infty \\ & \times\int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}\left[c_m(s)Q_m(s)\exp\left(-\beta_{wm}\omega_\infty\int_{13}^{s}c_m(k)dk\right)\right]ds\right)db \\ & \times(1-\psi)\int_{13}^{s}c_w(k)dk\Bigg)\end{aligned}$$

where we have used (37).

Rearranging (40), we have

$$\begin{aligned}\omega_\infty \quad & (1-\pi_w\pi_m\beta_{wm}\beta_{mw}\eta(1-\psi) \\ & \times\int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}[c_m(s)Q_m(s)H(s)]ds\right)db \\ & \times\int_{13}^{\infty}\left(c_I(a)P_v(a)\int_{13}^{a}[c_w(s)Q_v(s)G(s)]\,ds\right)da\Bigg) = 0\end{aligned} \tag{42}$$

This implies either the disease goes to extinction ($\omega_\infty = 0$) or the disease will persist ($\omega_\infty > 0$), which implies $G(s)$, $H(s) < 1$ and

$$R_{v0} \equiv \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \int_{13}^{\infty} \left(c_N(b) P_m(b) \int_{13}^{b} c_m(s) Q_m(s) ds \right) db \times \int_{13}^{\infty} \left(c_I(a) P_v(a) \int_{13}^{a} c_w(s) Q_v(s) ds \right) da > 1 \tag{43}$$

Conversely, if $G(s)$, $H(s) < 1$, then $\omega_\infty, \lambda_\infty > 0$, which implies $R_{v0} > 1$.

Note that if $\omega_\infty = 0$ then (37) implies $\lambda_\infty = 0$. Also, making (27) and (28) equal zero implies $\overline{I}_v(a) = \overline{N}(a) = 0$ for all a, because $c_N(a)$, $c_I(a) > 0$ for all a. We have thus proved the following theorem.

Theorem 3.1. *If $R_{v0} < 1$, then we have only the disease-free equilibrium*

$$(\overline{A}_u(a), \overline{I}_u(a), \overline{A}_v(a), \overline{R}_w, \overline{I}_v(a), \overline{M}(a), \overline{N}(a), \overline{R}_m) = \left(0, 0, \pi_w \exp\left(-\int_{13}^{a} \mu(s) ds\right), 0, 0, \pi_m \exp\left(-\int_{13}^{a} \mu(s) ds\right), 0, 0\right)$$

If $R_{v0} > 1$, then there exists a unique positive endemic equilibrium.

Remark. Note that there is at most one endemic equilibrium. In other words, if an endemic equilibrium exists, then it is unique. To prove this claim, assume that $\omega_\infty \neq 0$ exists. Note that $H(s)$ and $G(s)$ are also functions of ω_∞. Define

$$K(\omega_\infty) = \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \times \int_{13}^{\infty} \left(c_N(b) P_m(b) \int_{13}^{b} [c_m(s) Q_m(s) H(s, \omega_\infty)] ds \right) db \times \int_{13}^{\infty} \left(c_I(a) P_v(a) \int_{13}^{a} [c_w(s) Q_v(s) G(s, \omega_\infty)]\, ds \right) da$$

Note that the function K is a strictly decreasing function of ω_∞ and $K(0) = R_{v0}$, so we have

(1) If $R_{v0} > 1$, then we have exactly one $\omega_\infty > 0$ (the endemic equilibrium) satisfying $K(\omega_\infty) = 1$ (Eq. (42)).
(2) If $R_{v0} \leq 1$, then $K(\omega_\infty) = 1$ has only the solution $\omega_\infty = 0$ (the disease-free equilibrium).

This implies that a unique endemic equilibrium exists iff $R_{v0} > 1$.

Remark. Note that if c_N, c_m, c_I, c_w, μ and d_u are constant functions, then we have

$$R_{v0} \equiv \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) c_w c_N c_m c_I \frac{1}{\mu^2 (\mu + d_v)^2}$$

which is equivalent to what we have in [20], when $d_u = 0$ and with $\beta_N = \beta_{mw} c_w c_N$ and $\beta_M = \beta_{wm} c_m c_I$. For the definition of β_N and β_M see [20].

3.2. All females are vaccinated after age 13

In this section, we deal with the non-practical case that is perfect adult vaccine ($\psi = 1$). This is an extreme case that will aid us in the next section. In this case, we have $p = 0$ and $\overline{p} = 1$. Therefore, (39) implies

$$\begin{aligned}\omega_\infty = \; & \pi_w\pi_m\beta_{wm}\beta_{mw}\omega_\infty \\ & \times \int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}[c_m(s)Q_m(s)H(s)]\,ds\right)db \\ & \times \int_{13}^{\infty}\left\{c_I(a)P_u(a)\int_{13}^{a}[c_w(s)Q_u(s) \right. \\ & \left. \times \exp\left(-f(\overline{p})\chi_{[13,26]}\int_{13}^{s}\left(\frac{1}{13}k-1\right)dk\right)\tilde{G}(s)\right]ds\right\}da\end{aligned}$$

Here

$$\tilde{G}(s) = \exp\left(-\beta_{mw}\lambda_\infty\int_{13}^{s}c_w(k)dk\right)$$

As above, we have

$$\begin{aligned}R_{u0} \equiv \; & \pi_w\pi_m\beta_{wm}\beta_{mw}\int_{13}^{\infty}c_N(b)P_m(b)\int_{13}^{b}c_m(s)Q_m(s)dsdb \\ & \times \int_{13}^{\infty}c_I(a)P_u(a)\int_{13}^{a}c_w(s)Q_u(s)\exp\left[-f(\overline{p})\chi_{[13,26]}\int_{13}^{s}\left(\frac{1}{13}k-1\right)dk\right]dsda\end{aligned}$$

The following theorem is analogous to Theorem 3.1.

Theorem 3.2. *If $R_{u0} < 1$, then we have only the disease-free equilibrium*

$$\begin{aligned}&(\overline{A}_u(a), \overline{I}_u(a), \overline{A}_v(a), \overline{R}_w(a), \overline{I}_v(a), \overline{M}(a), \overline{N}(a), \overline{R}_m(a)) \\ &\quad = \left(\pi_w\exp\left\{-\int_{13}^{a}\left[\mu(s)-\left(\frac{1}{13}s-1\right)\chi_{[13,26]}f(\overline{p})\right]ds\right\}, 0, 0, 0, \pi_m\exp\left\{-\int_{13}^{a}\mu(s)ds\right\}, 0\right).\end{aligned}$$

If $R_{u0} > 1$, then there exists a unique positive endemic equilibrium.

3.3. General vaccination

We now examine vaccination in both children and adults. From Eq. (39) and under the condition $\omega_\infty > 0$, we have

$$
\begin{aligned}
1 < \quad & \pi_w\pi_m\beta_{wm}\beta_{mw} \\
& \times \int_{13}^{\infty} \left(c_N(b)P_m(b) \int_{13}^{b} [c_m(s)Q_m(s)]ds \right) db \\
& \times \int_{13}^{\infty} c_I(a) \left[(1-p)P_u(a) \int_{13}^{a} c_w(s)Q_u(s) \exp\left(-f(\overline{p})\chi_{[13,26]} \int_{13}^{s} \left(\frac{1}{13}k - 1 \right) dk \right) ds \right. \\
& + \eta(1-\psi)P_v(a) \int_{13}^{\infty} c_w(s)Q_v(s) \left(p + (1-p)f(\overline{p})\chi_{[13,26]} \right. \\
& \left. \left. \times \int_{13}^{s} \left(\left(\frac{1}{13}k - 1 \right) \exp\left(-f(\overline{p})\chi_{[13,26]} \int_{13}^{k} (\frac{1}{13}h - 1)dh \right) \right) dk \right) ds \right] da \\
= \quad & \pi_w\pi_m\beta_{wm}\beta_{mw} \\
& \times \int_{13}^{\infty} \left(c_N(b)P_m(b) \int_{13}^{b} [c_m(s)Q_m(s)]ds \right) db \\
& \times \int_{13}^{\infty} c_I(a) \left[(1-p)P_u(a) \int_{13}^{a} c_w(s)Q_u(s) \exp\left(-f(\overline{p})\chi_{[13,26]} \int_{13}^{s} \left(\frac{1}{13}k - 1 \right) dk \right) ds \right. \\
& + \eta(1-\psi)P_v(a) \int_{13}^{\infty} c_w(s)Q_v(s) \left(p + (1-p) \right. \\
& \left. \left. \times \left(1 - \exp\left(-f(\overline{p})\chi_{[13,26]} \int_{13}^{s} \left(\frac{1}{13}h - 1 \right) dh \right) \right) ds \right] da \\
= \quad & \pi_w\pi_m\beta_{wm}\beta_{mw} \\
& \times \int_{13}^{\infty} \left(c_N(b)P_m(b) \int_{13}^{b} [c_m(s)Q_m(s)]ds \right) db \\
& \times \int_{13}^{\infty} c_I(a) \left[(1-p)P_u(a) \int_{13}^{a} c_w(s)Q_u(s) \exp\left(-f(\overline{p})\chi_{[13,26]} \int_{13}^{s} \left(\frac{1}{13}k - 1 \right) dk \right) ds \right. \\
& + \eta(1-\psi)P_v(a) \int_{13}^{\infty} c_w(s)Q_v(s) \left(1 - (1-p) \right. \\
& \left. \left. \times \exp\left(-f(\overline{p})\chi_{[13,26]} \int_{13}^{s} \left(\frac{1}{13}h - 1 \right) dh \right) \right) ds \right] da \\
\leq \quad & (1-p)R_{u0} + R_{v0}
\end{aligned}
$$

Now define

$$R_0 \equiv (1-p)R_{u0} + R_{v0}$$

Note that for $p = 1$, we have $R_0 = R_{v0}$. Also, for $p = 0$ (which implies $P_v(a) = 0$) and $\overline{p} = 1$, we have $R_0 = R_{u0}$, which are the two cases considered above. Note also that

$$R_0 \leq R_{v0} + R_{u0} \tag{44}$$

Therefore, we have the following corollary.

Corollary 3.3. *If $R_{v0} + R_{u0} < 1$, then $R_0 < 1$, and we have only the disease-free equilibrium*

$$\begin{aligned}
\overline{A}_u(a) = &\quad (1-p)\pi_w \exp\left(-\int_{13}^{a}\left(\mu(s)+\left(\frac{1}{13}s-1\right)\chi_{[13,26]}f(\overline{p})\right)ds\right)\\
\overline{A}_v(a) = &\quad \exp\left(-\int_{13}^{a}\mu(s)ds\right)\\
&\quad \times\left(p\pi_w+(1-p)\pi_w\left(1-\exp\left(-\int_{13}^{a}\left(\frac{1}{13}k-1\right)\chi_{[13,26]}f(\overline{p})dk\right)\right)\right]ds\right)\\
\overline{M}(a) = &\quad \pi_m \exp\left(-\int_{13}^{a}\mu(s)ds\right)
\end{aligned}$$

and $\overline{I}_u(a) = \overline{I}_v(a) = \overline{R}_w(a) = \overline{N}(a) = \overline{R}_m(a) = 0$.

Note that we have used integration by substitution to simplify $\overline{A}_v(a)$.

In general, we have the following.

Theorem 3.4. *If $R_0 < 1$, then we have only the disease-free equilibrium and if $R_0 > 1$, then there exists a unique positive endemic equilibrium.*

As a result, we have a formula for the reproduction number [15] in three vaccination cases. The reproduction number depends mainly on birth rates, death rates, probability of transmission, vaccine efficacy and the proportions of people vaccinated. Moreover, we have shown the importance of the basic reproduction number in determining the existence of the endemic equilibrium.

4. Stability of equilibria

In this section, we study the stability of the steady states for the system (1)–(10) as given by the results in Section 3. In order to linearize the system around the equilibrium, we make a small perturbation around equilibrium (see [14]). This implies

$$A_u(t,a) = \overline{A}_u(a) + \exp(zt)\xi_u(a) \tag{45}$$

$$I_u(t,a) = \overline{I}_u(a) + \exp(zt)\zeta_u(a) \tag{46}$$

$$A_v(t,a) = \overline{A}_v(a) + \exp(zt)\xi_v(a) \tag{47}$$

$$R_w(t,a) = \overline{R}_w(a) + \exp(zt)\xi_w(a) \tag{48}$$

$$I_v(t,a) = \overline{I}_v(a) + \exp(zt)\zeta_v(a) \tag{49}$$

$$M(t,a) = \overline{M}(a) + \exp(zt)\xi_M(a) \tag{50}$$

$$N(t,a) = \overline{N}(a) + \exp(zt)\zeta_N(a) \tag{51}$$

$$R_m(t,a) = \overline{R}(a) + \exp(zt)\xi_r(a) \tag{52}$$

From this and (9), we conclude

$$\begin{aligned}
&\xi_u(13) = 0 \quad \zeta_u(13) = 0 \quad \xi_v(13) = 0\\
&\zeta_v(13) = 0 \quad \xi_w(13) = 0\\
&\xi_M(13) = 0 \quad \zeta_N(13) = 0 \quad \xi_r(13) = 0.
\end{aligned}$$

Note that, under these assumptions, we have

$$\begin{aligned}
\lambda(t) &= \lambda_\infty + \theta_N \exp(zt)\\
\omega(t) &= \omega_\infty + \theta_I \exp(zt)
\end{aligned}$$

where

$$\lambda_\infty = \int_{13}^{\infty} c_N(b)\overline{N}(b)db$$
$$\omega_\infty = \int_{13}^{\infty} c_I(b)(\overline{I}_u(b) + \eta\overline{I}_v(b))db$$

and

$$\begin{aligned}\theta_N &\equiv \int_{13}^{\infty} c_N(b)\zeta_N(b)db \\ \theta_I &\equiv \int_{13}^{\infty} c_I(b)(\zeta_u(b) + \eta\zeta_v(b))db\end{aligned} \tag{53}$$

For the disease-free equilibrium, we have $\overline{I}_u = \overline{I}_v = \overline{N} = 0$, which implies $\omega_\infty = \lambda_\infty = 0$.

The equilibrium is locally stable if $(A_u, I_u, A_v, I_v, R_w, M, N, R_m) \to (\overline{A}_u, \overline{I}_u, \overline{A}_v, \overline{I}_v, \overline{R}_w, \overline{M}, \overline{N}, \overline{R}_m)$ as $t \to \infty$ and unstable otherwise.

4.1. Stability of the disease-free equilibrium for childhood-only vaccination

In this case, we have a simplified system. Since $p = 1$ and $\overline{A}_u = 0$ in (1)–(10), the system becomes

$$\partial_t A_v + \partial_a A_v = -(\mu(a) + \beta_m(t,a)(1-\psi))A_v \tag{54}$$
$$\partial_t I_v + \partial_a I_v = \beta_m(t,a)(1-\psi)A_v - (\mu(a) + d_v(a) + r_v(a))I_v$$
$$\partial_t R_w + \partial_a R_w = r_v(a)I_v - \mu(a)R_w$$
$$\partial_t M + \partial_a M = -(\mu(a) + \beta_w(t,a))M \tag{55}$$
$$\partial_t N + \partial_a N = \beta_w(t,a)M - (\mu(a) + d_m(a) + r_m(a))N$$
$$\partial_t R_m + \partial_a R_m = r_m(a)N - \mu(a)R_m$$

with the boundary conditions

$$A_v(t,13) = \pi_w \quad I_v(t,13) = 0 \quad R_w(t,13) = 0$$
$$M(t,13) = \pi_m \quad N(t,13) = 0 \quad R_m(t,13) = 0$$

and the initial conditions

$$\begin{aligned} A_v(0,a) &= A_v^0(a) \quad I_v(0,a) = I_v^0(a) \quad R_w(0,a) = R_w^0(a) \\ M(0,a) &= M^0(a) \quad N(0,a) = N^0(a) \quad R_m(0,a) = R_m^0(a)\end{aligned} \tag{56}$$

Note that we consider $I_u = 0$, since $A_u = 0$ and the convergence is exponential.

Substituting (47) into (54), we have

$$\begin{aligned}(z\xi_v + \xi_v')\exp(zt) + \overline{A}_v'(a) = \quad & -(\mu(a) + \beta_{mw}c_m(a)\theta_N \exp(zt)(1-\psi)) \\ & \times(\overline{A}_v(a) + \exp(zt)\xi_v(a)) \\ \xi_v(13) = \quad & 0\end{aligned}$$

Simplifying, we have

$$\begin{aligned} z\xi_v + \xi_v' &= -\beta_{mw}c_m(a)\theta_N(1-\psi)\overline{A}_v - \mu(a)\xi_v \\ \xi_v(13) &= 0\end{aligned} \tag{57}$$

Note that we ignored the term that contains the product $\theta_N\xi_v$, because we consider only a small perturbation around the equilibrium and this term is extremely small.

The solution of (57) is

$$\xi_v(a) = -\beta_{mw}\theta_N(1-\psi)\pi_w \exp\left(-\int_{13}^{a}[z + \mu(s)]ds\right)\int_{13}^{a}[c_m(k)\exp(zk)]dk \tag{58}$$

In the same way,

$$z\zeta_v + \zeta_v' = \beta_{mw} c_m(a)\theta_N(1-\psi)\overline{A}_v - (\mu(a) + d_v(a) + r_v(a))\zeta_v$$
$$\zeta_v(13) = 0$$

with the solution

$$\zeta_v(a) = \beta_{mw}\theta_N(1-\psi)\pi_w P_v(a)\exp(-z(a-13)) \times \int_{13}^{a} [c_m(s)Q_v(s)\exp(z(s-13))]ds$$

Furthermore,

$$z\xi_M + \xi_M' = -\beta_{wm} c_w(a)\theta_I \overline{M} - \mu(a)\xi_M$$
$$\xi_M(13) = 0$$

with the solution

$$\xi_M(a) = -\beta_{wm}\theta_I\pi_m \exp\left(-\int_{13}^{a}[z+\mu(s)]ds\right)\int_{13}^{a}[c_w(k)\exp(zk)]dk \tag{59}$$

and

$$z\zeta_N + \zeta_N' = -\beta_{wm} c_w(a)\theta_I \overline{M} - (\mu(a) + d_m(a) + r_m(a))\zeta_N$$
$$\xi_M(0) = 0$$

with the solution

$$\zeta_N(a) = \beta_{wm}\theta_I\pi_m P_m(a)\exp(-z(a-13)) \times \int_{13}^{a}[c_w(s)Q_m(s)\exp(z(s-13))]ds$$

Note that we did not evaluate ξ_w and ξ_r because they are irrelevant to our work.

We have

$$\theta_N = \beta_{wm}\theta_I\pi_m \int_{13}^{\infty}\left[c_N(a)P_m(a)\exp(-z(a-13)) \times \int_{13}^{a}(c_m(s)Q_m(s)\exp(z(s-13)))ds)\right]da \tag{60}$$

$$\theta_I = \beta_{mw}\theta_N\eta(1-\psi)\pi_w \int_{13}^{\infty}\left[c_I(a)P_v(a)\exp(-z(s-13)) \times \int_{13}^{a}(c_w(s)Q_v(s)\exp(z(s-13))ds\right]da \tag{61}$$

Substituting (60) in (61), we have

$$\theta_I = \pi_w\pi_m\beta_{wm}\beta_{mw}\eta(1-\psi)\theta_I \times \int_{13}^{\infty}\left[c_N(a)P_m(a)\exp(-za)\int_{13}^{a}(c_m(s)Q_m(s)\exp(zs))ds\right]da \times \int_{13}^{\infty}\left[c_I(a)P_v(a)\exp(-za)\int_{13}^{a}(c_w(s)Q_v(s)\exp(zs))ds\right]da \tag{62}$$

Then, under the assumption $\theta_I \neq 0$, we have

$$\begin{aligned} 1 = \quad & \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \\ & \times \int_{13}^{\infty} \left[c_N(a) P_m(a) \exp(-za) \int_{13}^{a} (c_m(s) Q_m(s) \exp(zs)) ds \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a) \exp(-za) \int_{13}^{a} (c_w(s) Q_v(s) \exp(zs)) ds \right] da \end{aligned} \tag{63}$$

We now introduce the function

$$F : \mathbb{R} \to [0, \infty) \tag{64}$$

$$\begin{aligned} F(z) \equiv \quad & \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \\ & \times \int_{13}^{\infty} \left[c_N(a) P_m(a) \exp(-za) \int_{13}^{a} (c_m(s) Q_m(s) \exp(zs)) ds \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a) \exp(-za) \int_{13}^{a} (c_w(s) Q_v(s) \exp(zs) ds \right] da. \\ = \quad & \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \\ & \times \int_{13}^{\infty} \left[c_N(a) P_m(a) \int_{13}^{a} (c_m(s) Q_m(s) \exp(-z(a-s))) ds \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a) \int_{13}^{a} (c_w(s) Q_v(s) \exp(-z(a-s)) ds \right] da \end{aligned}$$

which, under the substitution $r = a - s$, can be written as

$$\begin{aligned} F(z) = \quad & \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \\ & \times \int_{13}^{\infty} \left[c_N(a) P_m(a) \int_{0}^{a-13} (c_m(a-r) Q_m(a-r) \exp(-zr)) dr \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a)) \int_{0}^{a-13} (c_w(a-r) Q_v(a-r) \exp(-zr)) dr \right] da \end{aligned}$$

For z real, F satisfies the following properties:

- F is continuous in z
- $F(0) = R_{v0}$
- $\lim_{z \to \infty} F(z) = 0$
- $\lim_{z \to -\infty} F(z) = \infty$.

As a result, we have the following theorem.

Theorem 4.1. *1. If $R_{v0} < 1$, then there exists $z = z_0 < 0$ such that (63) holds and the disease-free equilibrium is locally stable. 2. If $R_{v0} > 1$, then there exists $z = z_0 > 0$ such that (63) holds and the disease-free equilibrium is unstable.*

Proof. The existence of z in both cases follows from the properties of F and the Intermediate Value Theorem. When $z = z_0 > 0$, $(A_v, I_v, M, N) \to \infty$ as $t \to \infty$ (see (45)–(51)) and hence the equilibrium is unstable. When $z = z_0 < 0$, $(A_v, I_v, M, N) \to (\overline{A}_v, \overline{I}_v, \overline{M}, \overline{N})$ and thus the equilibrium is locally stable. □

The same holds if z is complex. If we write $z = \rho + i\theta$ for some numbers $\rho > 0$ and $0 \le \theta < 2\pi$, then

$$\begin{aligned} 1 = \quad & \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \\ & \times \int_{13}^{\infty} \left[c_N(a) P_m(a) \int_0^{a-13} (c_m(a-r) Q_m(a-r) \cos(\rho\theta) \exp(-\rho r)) dr \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a)) \int_0^{a-13} (c_w(a-r) Q_v(a-r) \cos(\rho\theta) \exp(-\rho r)) dr \right] da \\ & - \int_{13}^{\infty} \left[c_N(a) P_m(a) \int_0^{a-13} (c_m(a-r) Q_m(a-r) \sin(\rho\theta) \exp(-\rho r)) dr \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a) \int_0^{a-13} (c_w(a-r) Q_v(a-r) \sin(\rho\theta) \exp(-\rho r)) dr \right] da. \end{aligned} \tag{65}$$

which follows from (62) by considering $z = \rho + i\theta$, then taking the real part of both sides and dividing by θ_I.

Now, (65) implies

$$\begin{aligned} 1 < \quad & \pi_w \pi_m \beta_{wm} \beta_{mw} \eta (1-\psi) \\ & \times \int_{13}^{\infty} \left[c_N(a) P_m(a) \int_0^{a-13} (c_m(a-r) Q_m(a-r) \exp(-\rho r)) dr \right] da \\ & \times \int_{13}^{\infty} \left[c_I(a) P_v(a)) \int_0^{a-13} (c_w(a-r) Q_v(a-r) \exp(-\rho r)) dr \right] da \\ & \equiv F(\rho) \end{aligned} \tag{66}$$

where F still satisfies the same properties above.

As a result, if $R_{v0} > 1$ we still have $\rho > 0$ such that (65) holds and if $R_{v0} < 1$ there exists $\rho < 0$ such that (65) holds.

4.2. Stability of the disease equilibrium for childhood-only vaccination

We can repeat the same process for the endemic equilibrium, in which $\overline{I}_v, \overline{N} > 0$. We have

$$\begin{aligned} z\xi_v + \xi_v' &= -\beta_{mw} c_w(a) \theta_N (1-\psi) \overline{A}_v - (\mu(a) + \beta_{mw} c_w(a) \lambda_\infty (1-\psi)) \xi_v \\ \xi_v(13) &= 0 \end{aligned}$$

with the solution

$$\begin{aligned} \xi_v(a) = \quad & -\beta_{mw} \theta_N (1-\psi) \pi_w \exp\left(- \int_{13}^{a} [z + \mu(s) + \beta_{mw} c_w(s) \lambda_\infty (1-\psi)] \, ds \right) \\ & \times \int_{13}^{a} [c_w(k) \exp(zk)] dk \end{aligned} \tag{67}$$

Here, we have used (32) (with $p = 1$). Next,

$$\begin{aligned} z\zeta_v + \zeta_v' = \quad & \beta_{mw} c_w(a) \theta_N (1-\psi) \overline{A}_v + \beta_{mw} c_w(a) \lambda_\infty (1-\psi) \xi_v \\ & -(\mu(a) + d_v(a) + r_v(a)) \zeta_v \\ \zeta_v(13) = \quad & 0 \end{aligned}$$

with the solution

$$\begin{aligned}\zeta_v(a) = \quad & \beta_{mw}\theta_N(1-\psi)\pi_w P_v(a)\exp(-z(a-13)) \\ & \times \int_{13}^{a}\left[\exp\left(\int_{13}^{s}(d_v(k)+r_v(k)-\beta_{mw}c_w(k)\lambda_\infty(1-\psi))dk\right)\right. \\ & \left.\times\left(-\lambda_\infty(1-\psi)\beta_{mw}\int_{13}^{s}c_w(k)\exp(zk)dk + c_w(s)\exp(zs)\right)\right]ds\end{aligned}$$

Furthermore,

$$\begin{aligned}& z\xi_M + \xi_M' = -\beta_{wm}c_m(a)\theta_I\overline{M} - (\mu(a)+\beta_{wm}c_m(a)\omega_\infty)\xi_M \\ & \xi_M(13) = 0\end{aligned}$$

with the solution

$$\xi_M(a) = -\beta_{wm}\theta_I\pi_m\exp\left(-\int_{13}^{a}[z+\mu(s)+\beta_{wm}c_m(s)\omega_\infty]\,ds\right)\int_{13}^{a}[c_m(s)\exp(zs)]ds \tag{68}$$

Finally,

$$\begin{aligned}z\zeta_N + \zeta_N' \quad &= \beta_{wm}c_m(a)\theta_I\overline{M} + \beta_{wm}c_m(a)\omega_\infty\xi_M - (\mu(a)+d_m(a)+r_m(a))\zeta_N \\ \zeta_N(0) \quad &= 0\end{aligned}$$

with the solution

$$\begin{aligned}\zeta_N(a) = \quad & -\beta_{wm}\theta_I\pi_m\exp(-za)P_m(a) \\ & \times\int_{13}^{a}\left[c_w(s)\exp\left(\int_{13}^{s}(d_m(k)+r_m(k)-\beta_{wm}c_m(k)\omega_\infty)dk\right)\right. \\ & \left.\times\left(-\omega_\infty\beta_{wm}\int_{13}^{s}(c_m(k)\exp(zk))dk + c_m(s)\exp(zs)\right)\right]ds\end{aligned}$$

We now have

$$\begin{aligned}\theta_N = \quad & -\beta_{wm}\theta_I\pi_m\int_{13}^{\infty}(c_N(a)\exp(-za)P_m(a) \\ & \times\int_{13}^{a}\left[c_w(s)\exp\left(\int_{13}^{s}(d_m(k)+r_m(k)-\beta_{wm}c_m(k)\omega_\infty)dk\right)\right. \\ & \left.\times\left(-\omega_\infty\beta_{wm}\int_{13}^{s}(c_m(k)\exp(zk))dk + c_m(s)\exp(zs)\right)\right]ds\Bigg)da\end{aligned} \tag{69}$$

$$\begin{aligned}\theta_I = \quad & \eta(1-\psi)\beta_{mw}\theta_N\pi_w\int_{13}^{\infty}(c_I(a)\exp(-za)P_v(a) \\ & \times\int_{13}^{a}\left[c_w(s)\exp\left(\int_{13}^{s}(d_v(k)+r_v(k)-(1-\psi)\beta_{mw}c_w(k)\lambda_\infty)dk\right)\right. \\ & \left.\times\left(-\lambda_\infty(1-\psi)\beta_{mw}\int_{13}^{s}(c_w(k)\exp(zk))dk + c_w(s)\exp(zs)\right)\right]ds\Bigg)da\end{aligned} \tag{70}$$

Substituting (69) into (70), then taking into account $\lambda_\infty, \omega_\infty, \theta_I > 0$, we have

$$
\begin{aligned}
1 < \quad & \pi_w\pi_m\beta_{wm}\beta_{mw}\eta(1-\psi)\int_{13}^{\infty}(c_N(a)\exp(-za)P_m(a)\\
& \times\int_{13}^{a}\left[c_m(s)\exp\left(\int_{13}^{s}(d_m(k)+r_m(k))dk\right)\right.\\
& \left.\times\left(-\omega_\infty\beta_{wm}\int_{13}^{s}c_m(k)\exp(zk)dk+c_m(s)\exp(zs)\right)\right]ds\Bigg)da\\
& \times\int_{13}^{\infty}\left(c_I(a)\exp(-za)P_v(a)\int_{13}^{a}\left[c_w(s)\exp\left(\int_{13}^{s}(d_v(k)+r_v(k))dk\right)\right.\right.\\
& \left.\left.\times\left(-\lambda_\infty(1-\psi)\beta_{mw}\int_{13}^{s}c_w(k)\exp(zk)dk+c_w(s)\exp(zs)\right)\right]ds\right)da\\
< \quad & \pi_w\pi_m\beta_{wm}\beta_{mw}\eta(1-\psi)\int_{13}^{\infty}(c_N(a)\exp(-za)P_m(a)\\
& \times\int_{13}^{a}\left[c_w(s)\exp\left(\int_{13}^{s}(d_m(k)+r_m(k))dk\right)\exp(zs)\right]ds\Bigg)da\\
& \times\int_{13}^{\infty}\left(c_I(a)\exp(-za)P_v(a)\int_{13}^{a}\left[c_w(s)\exp(zs)\exp\left(\int_{13}^{s}(d_v(k)+r_v(k)\right)dk\right)\right]ds\right)da\\
< \quad & \pi_w\pi_m\beta_{wm}\beta_{mw}\eta(1-\psi)\\
& \times\int_{13}^{\infty}\left[c_N(a)P_m(a)\int_{13}^{a}(c_m(s)Q_m(s)\exp(-z(a-s)))ds\right]da\\
& \times\int_{13}^{\infty}\left[c_I(a)P_v(a)\int_{13}^{a}(c_w(s)Q_v(s)\exp(-z(a-s))ds\right]da.\\
& \equiv F(z)
\end{aligned}
\tag{71}
$$

Theorem 4.2. *For $R_{v0} > 1$, there exists $z = z_0 < 0$ such that (71) holds and the endemic equilibrium is locally stable.*

We have proved the following.

Remark. The same results can be proved for the case of adult-only vaccination.

4.3. Stability of disease-free and endemic equilibria for general vaccination

We now examine stability of equilibria when both children and adults are vaccinated. The method of Sections 4.1 and 4.2 can be repeated here to get the following main result.

Theorem 4.3.

1. *The disease-free equilibrium is locally stable when $R_0 < 1$ and unstable when $R_0 > 1$.*
2. *The endemic equilibrium exists only when $R_0 > 1$. Moreover, they are locally stable.*

Table 2
Sample values.

Variable	Sample value used	Reference
π_w	17, 000 year^{-1}	Assumed
π_m	17, 000 year^{-1}	Assumed
p	0.77	[20]
$\overline{p}$	0.392	[20]
β_{wm}	0.7 year^{-1}	[9]
β_{mw}	0.8 year^{-1}	[9]
ψ	0.87	Assumed
$\mu(a)$	$0.0003\exp(0.0735a)$	[5]
$r_u(a)$	1/1.5 year^{-1}	[12]
$r_v(a)$	1 year^{-1}	[7]
$r_m(a)$	1/1.25 year^{-1}	[12]
γ	0.1 year^{-1}	[20]
c	0.15	[20]
η	0.9	Assumed

Note that the proof is exactly as in the previous two subsections, but with

$$\begin{aligned}\tilde{F}(z) = \;& \pi_w\pi_m\beta_{wm}\beta_{mw}\\ & \times\int_{13}^{\infty}\left(c_N(b)P_m(b)\int_{13}^{b}[c_m(s)Q_m(s)\exp(-z(a-s))]ds\right)db\\ & \times\int_{13}^{\infty}c_I(a)\left[(1-p)P_u(a)\int_{13}^{a}c_w(s)Q_u(s)\exp(-z(a-s))\right.\\ & \times\exp\left(-f(\overline{p})\chi_{[13,26]}\int_{13}^{s}\left(\frac{1}{13}k-1\right)dk\right)ds\\ & +\eta(1-\psi)P_v(a)\int_{13}^{\infty}c_w(s)Q_v(s)\exp(-z(a-s))\,(1-(1-p)\\ & \left.\times\exp\left(-f(\overline{p})\chi_{[13,26]}\int_{13}^{s}\left(\frac{1}{13}h-1\right)dh\right)\right)ds\Bigg]da\end{aligned}$$

As a result, we have proved that disease-free equilibrium is locally stable when the reproduction number is less than one and unstable otherwise. Also, we have proven that the endemic equilibrium is locally stable whenever it exists. Thus, the disease goes extinct only when the reproduction number is less than one and there are no backward bifurcations. Hence R_0 is a threshold parameter (see [19] for more discussion). This proves the importance of reducing the value of some parameters (such as β_{mw} and β_{wm}) in order to control the disease.

5. Numerical simulations

In this section, we will use the system (1)–(10) and initial data for Toronto, Canada, 1996, to approximate the number of HPV cases in Toronto after 20 years. Parameters are listed in Table 1. The initial number of women and men are given in Table 2. The average number of sex partners is given in Table 3. It is important to recognize that the methodology used to collect the data presented in Table 3 excludes youth who are at greatest risk of sexually transmitted disease. These include aboriginal youth and youth on the streets [21].

Now, take

$$c_N = S_p/N_w \quad c_m(a) = 1/N_m$$
$$c_I = S_p/N_m \quad c_w(a) = 1/N_w$$

Table 3
Population by age (≥ 15) and sex, Toronto, 1996 [22].

Age group	Female	Male
15–19	65,000	68,700
20–24	83,800	79,100
25–29	109,600	102,200
30–34	117,600	117,000
35–39	106,400	103,100
40–44	93,900	86,000
45–49	86,100	78,100
50–54	66,000	59,600
55–59	59,100	51,700
60–64	56,400	50,800
65–74	105,200	85,200
75+	81,900	74,500
Total	1,031,000	929,000

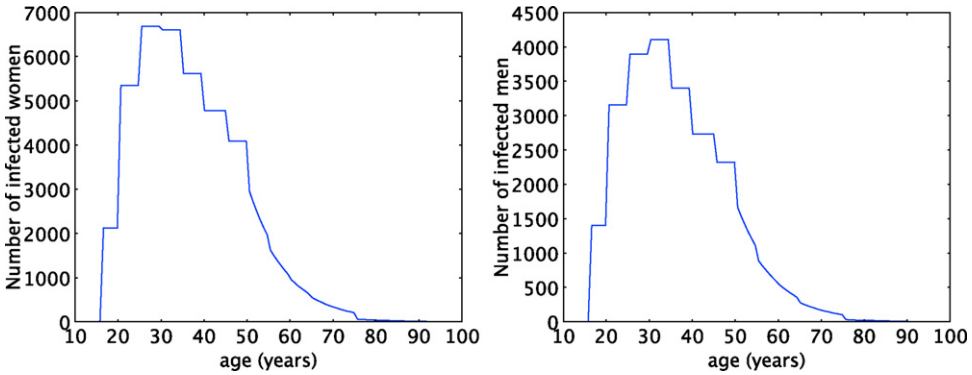

Fig. 3. Initial number of infected women and men as a function of age.

Then we take

$$I_u^0(a) = 0.24 \times pS_p(a)N_w(a)$$
$$A_u^0(a) = p(N_w(a) - I_u^0(a) - I_v^0(a))$$
$$I_v^0(a) = 0.24 \times (1-p)S_p(a)N_w(a)$$
$$A_v^0(a) = (1-p)(N_w(a) - I_u^0(a) - I_v^0(a))$$
$$N^0(a) = 0.15 \times S_p(a)N_m(a)$$
$$M(a) = N_m(a) - N^0(a)$$

Note that

$$A_u^0(a) + I_u^0(a) + A_v^0(a) + I_v^0(a) = N_w(a)$$
$$N^0(a) + M^0(a) = N_m(a)$$

The graphs of $I_u^0 + I_v^0$ and N_0 are shown in Fig. 3. The death rate $\mu(a)$ is taken to be the Gompertz function [5] shown in Fig. 4.

The disease death rate is illustrated in Fig. 5, while the average number of sex partners is given in Table 4.

The finite element method is used here to find the solution. Since the accuracy of this method depends on how small the mesh is, we used different small meshes, but the outcome was unchanged (results not shown).

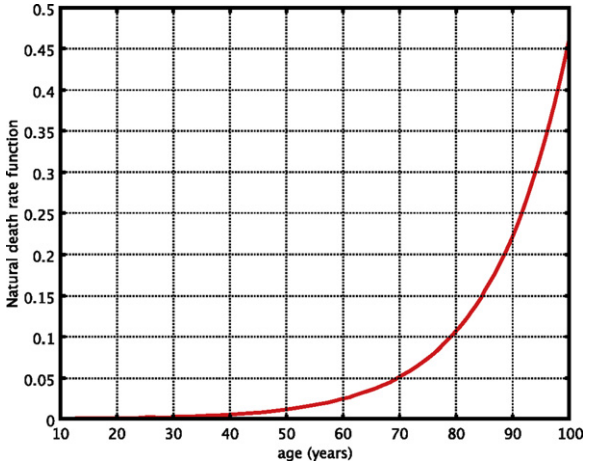

Fig. 4. The natural death rate as a function of age can be represented by the Gompertz function.

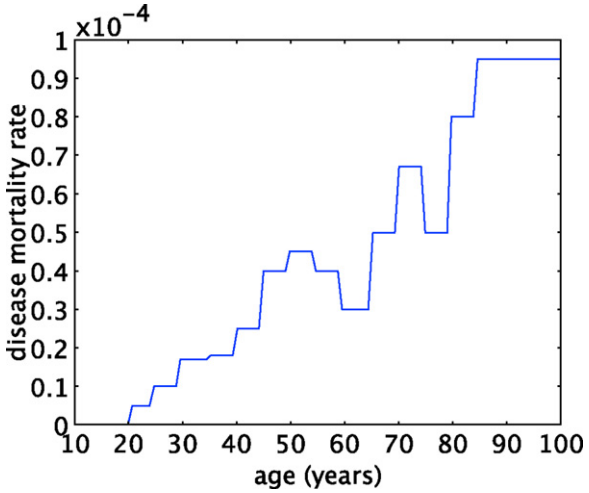

Fig. 5. The disease death rate as a function of age.

Table 4
Average number of sex partners in the last 12 months, Canada, 1996 [21].

Age group	16.5–19	20–24	25–29	30–34	35–39	40–44	45–49
Number of partners	0.68	1.33	1.27	1.17	1.1	1.06	0.99

In Fig. 6, we have the number of infected women and men after 100 years when nobody is vaccinated. Note that $R_0 > 1$ in this case and the disease persists. In Fig. 7, we have the number of infected women and men during 20 years when 77% of children and 40% of adult women are vaccinated. $R_0 < 1$ in this case and the disease goes to extinction.

6. Discussion

We introduced an age-dependent model for HPV to represents the different rate of transmission for different ages. Rates of sexual activity vary by age class and gender, while the vaccine is only available for women aged 13–26. We solved the steady-state system in the limit and found an explicit value for the basic reproduction number for perfect childhood vaccination, perfect adult vaccination and childhood–adult vaccination. The value of the reproduction number

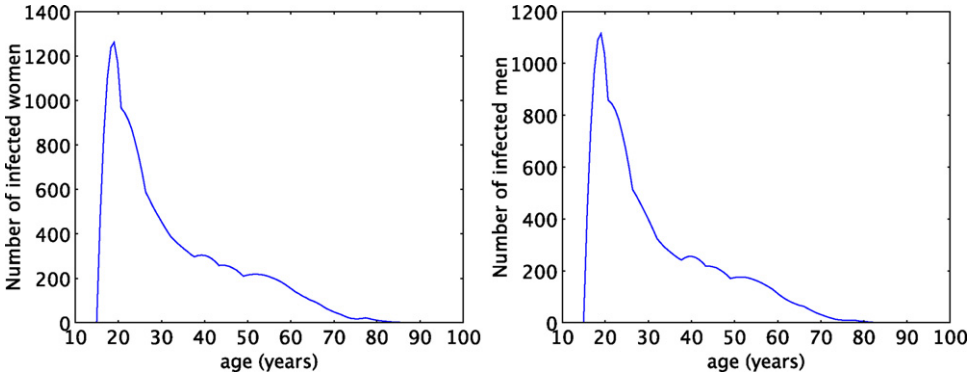

Fig. 6. The number of infected women and men as age-dependent functions after 100 years when no one is vaccinated.

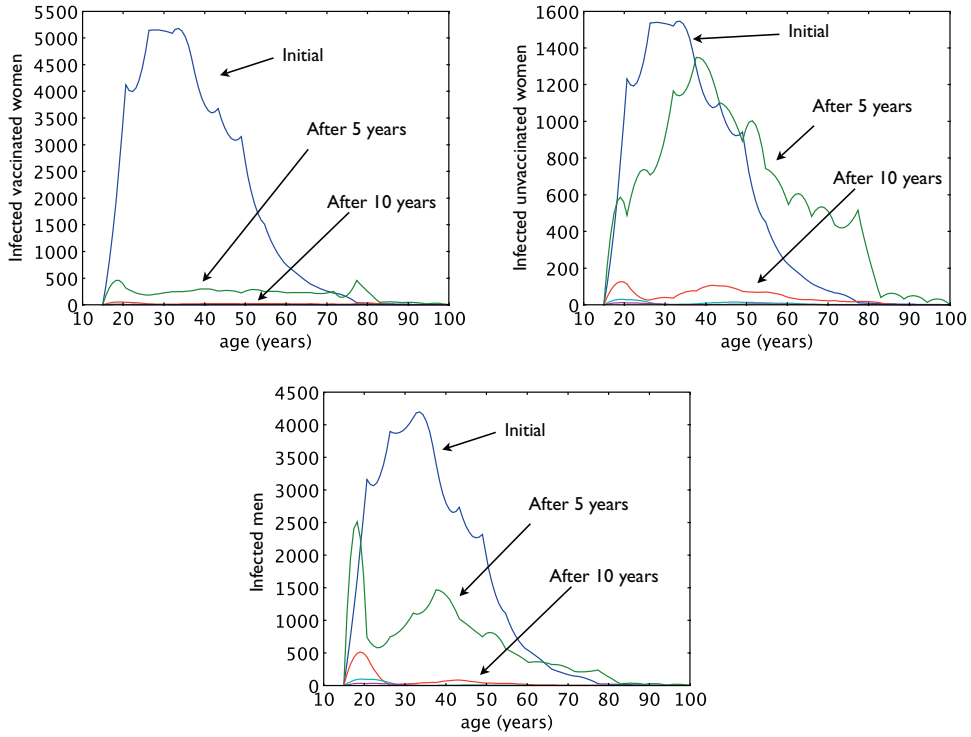

Fig. 7. The number of infected vaccinated women, infected unvaccinated women and infected men as time and age-dependent functions during 20 years when 77% of children and 40% of adults are vaccinated. Note that the infecteds are decreasing with time.

determines the stability of the disease-free equilibrium. For R_0 less than one, the disease-free equilibrium is the only equilibrium. For R_0 greater than one, the disease-free and endemic equilibria coexist.

We examined two limiting cases: (i) vaccinating all children but no adults and (ii) vaccinating all adults but no children, in order to derive the basic reproduction numbers and stability for these cases; we then showed that general vaccination was a composite of these limiting cases. We used the reproduction number to determine the stability of the equilibria and we found that, for R_0 less than one, we have a locally stable, disease-free equilibrium and for R_0 greater than one, we have a non-stable disease-free equilibrium and a locally stable endemic equilibrium. This demonstrates the threshold nature of the reproduction number and hence its utility in disease control [19].

The basic reproduction number depends mainly on birth rates, death rates, transmission probabilities, vaccine efficacy and the proportions of people vaccinated. To ensure eradication of the targeted types, we need not only vaccinate with high efficacy, but we need to increase the number of women vaccinated, both as children and as adults. Note that, unlike

many simple vaccination models, a backward bifurcation (multiple equilibria coexisting when $R_0 < 1$) does not exist for our model. This agrees with Elbasha et al. [10].

We have used data from other studies to estimate the solution numerically using the Finite Element Method. We approximated the solution after 20 years for the 1996 Toronto population. Furthermore, we calculated the value of the reproduction number and the approximated solution after 100 years to check our stability results.

Our model has several limitations, which should be noted. We only consider vaccination for types 16 and 18, since these are the types targeted by Cervarix, the most recent approved HPV vaccine. Future work will adapt the model to include other HPV types, such as the non-cancerous types targeted by Gardasil. In addition, we assume that infected individuals are asymptomatic and that sexual activity is consequently unaffected (which may not be the case for other HPV types, due to the external appearance of genital warts). The model focused on heterosexual transmission and assumed that individuals had fewer sexual contacts as they aged, and that recovery was permanent, in both men and women. Furthermore, we did not explicitly model cervical cancer.

To the best of our knowledge, this is the first age-dependent PDE model of HPV. It is an extension of the ODE model in [20] in which results were limited to specific age ranges and their age-linked partners. Here, we investigated the age-dependent impact of vaccination on HPV types 16 and 18, which will consequently reduce the number of deaths due to cervical cancer. We considered a childhood vaccination program supported by adult vaccination program for women only. The analysis and the numerical simulations show that this strategy is effective in reducing the number of infected and the number of deaths due to disease. Note that we consider the case that the number of vaccinated women infected initially is relatively large. This is because the vaccine is imperfect and because many adult women may already be infected. Our results demonstrate that the vaccine is effective even in this extreme case.

Thus, although the effects of age dependency are complex, we have shown that vaccinating a single age cohort can result in eventual control of the disease in all age groups and genders. Although this model was developed specifically for HPV types 16 and 18, the results could extend to other types and even other viruses. The important priorities for future research and public-health policy include understanding the effect of vaccination, and how the prevalence of HPV depends on both age and sexual behaviour.

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