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Vaccine impact in homogeneous and age-structured models

F.M.G. Magpantay

Department of Mathematics, University of Manitoba, Winnipeg, MB, Canada R3T 2N2 Tel.: +1-204-474-9701

Abstract

A general model of an imperfect vaccine for a childhood disease is presented and the effects of different types of vaccine failure on transmission were investigated using models that consider both homogeneous and age-specific mixing. The models are extensions of the standard SEIR equations with an additional vaccinated component that allows for five different vaccine parameters: three types of vaccine failure in decreasing susceptibility to infection via failure in degree (“leakiness”), take (“all-or-nothingness”) and duration (waning of vaccine-derived immunity); one parameter reflecting the relative reduction in infectiousness of vaccinated individuals who get infected; and one parameter that reflects the relative reduction in reporting probability of vaccinated individuals due to a possible reduction in severity of symptoms. Only the first four parameters affect disease transmission (as measured by the basic reproduction number). The reduction in transmission due to vaccination is different for age-structured models than for homogeneous models. Notably, if the vaccine exhibits waning protection this could be larger for an age-structured model with high contact rates between young children who are still protected by the vaccine and lower contact rates between adults for whom protection might have already waned. Analytic expressions for age-specific “vaccine impacts” were also derived. The overall vaccine impact is bounded between the age-specific impact for the oldest age class and that of the youngest age class.

Keywords

age-structure; disease ecology; imperfect vaccines; mathematical modeling

1 Introduction

Childhood infectious diseases are diseases that are usually contracted at a young age, and often only once. This occurs because it is possible to develop an immune response that the pathogen cannot circumvent. Vaccination has been one of our most successful tools in the battle against such diseases [12]. There have been many studies concerned with the effect of different types of infection- and vaccine-derived immunity on disease transmission [3,6,7,9–11,13]. McLean and Blower [11] introduced a quantity called the vaccine impact (here denoted by ϕ), as a measure of the effectiveness of imperfect vaccines. This quantity is related to the basic reproduction number R_p in the presence of constant vaccination of a fraction p of the population,

$$R_p = R_0(1 - \varphi p). \quad (1)$$

Here, R_0 is the basic reproduction number of the disease in the absence of vaccination ($p = 0$). Solving for φ in (1), we derive the vaccine impact

$$\varphi = \left(\frac{R_0 - R_p}{R_0} \right) \frac{1}{p}, \quad (2)$$

the relative reduction in transmission within a population per unit of vaccination. This definition coincides with the vaccine efficacy $VE = \frac{PE}{p}$ in Farrington [3] where $PE = 1 - \frac{R_p}{R_0}$ is the projected effectiveness of the vaccine.

Another way to look at vaccine impact is to consider the critical vaccination coverage p_c . This is defined to be the value of vaccine coverage p such that $R_p = 1$ (if this is attainable.)

From this we derive $\varphi = \left(1 - \frac{1}{R_0} \right) \frac{1}{p_c}$. The inverse relationship between the vaccine impact and critical vaccine coverage means that the vaccine impact can be thought of as a measure of the so-called herd immunity effects due to vaccination.

The vaccine impact is a measure that can be used to compare models of imperfect vaccines that include different modes of vaccine failure. There have been many studies on the effects of modes of vaccine failure to the epidemiology of diseases [6,10,11]. In [9] we considered the following aspects of vaccine protection:

1. **Immunity against infection.** Three modes by which vaccines might fail to protect vaccinated individuals against infection are: (a) **Leakiness.** A vaccine is said to be leaky when it reduces, but does not eliminate, the potential for infection [7]. The leakiness of a vaccine is measured by the probability of infection upon exposure for a vaccinated individual relative to the same probability for an unvaccinated individual, here denoted by ε_L . (b) **Primary vaccine failure or “all-or-nothingness.”** A vaccine exhibits primary vaccine failure if it fails to provide any protection to some fraction ε_A of vaccinated individuals. Primary vaccine failure is quantified by the fraction of vaccinated individuals for whom the vaccine fails. (c) **Waning.** Vaccine protection is said to wane if it ceases after some time. The amount of vaccine failure due to waning is quantified by the rate at which immunity is lost, denoted by α . Here, as in [10], we also quantify this by the probability that an individual loses vaccine protection over their lifetime, denoted by ε_W .
2. **Reduction in infectiousness and symptoms.** Even if a vaccine fails to protect an individual against infection, it might still have an effect on the manifestation of the disease. We consider the following parameters: (a) **Relative infectiousness,** also called the relative transmissibility, is the ratio of the transmission rate of a vaccinated person to that of an unvaccinated person, here

denoted by θ , and (b) **relative reporting probability**, the ratio of the reporting probability of a vaccinated person relative to that of an unvaccinated person. This can reflect the degree to which infections in vaccinated individuals produce milder disease symptoms. By itself, this parameter affects the reported number of cases, but it does not actually affect the level of disease transmission.

Only the first four parameters described above (leakiness, primary vaccine failure, waning and relative infectiousness) are involved in the overall transmission of the disease (as measured by the basic reproduction number). The fifth parameter (relative reporting probability) is important to include when fitting models to data, however it only affects the reporting of the disease and not the overall transmission of the disease. In [9] it was shown that the vaccine impact for an homogeneous model involving the five parameters is

$$\varphi = (1 - \varepsilon_A)[(1 - \theta) + \theta(1 - \varepsilon_L)(1 - \varepsilon_W)]. \quad (3)$$

As expected, the relative reporting probability is not part of this expression. When $\theta = 1$ the vaccine impact measures the protection a vaccinated individual receives relative to an unvaccinated individual. This was discussed in [10] where it was also shown that in this special case, this vaccine impact is the same as the vaccine impact defined by McLean and Blower [11]. Expression (3) enables us to compare the overall reduction in transmission implied by different models of the acellular pertussis vaccine that were found to be most consistent with the data. Different amounts of primary vaccine failure were combined with leakiness and waning, and the best parameter fits for each model were mostly found to be consistent with a sizeable reduction in transmission [10].

In this paper we derive the vaccine impact for models that incorporates the four parameters that affect disease transmission: leakiness, primary vaccine failure, waning and relative infectiousness. Much of the existing literature on vaccine impact only include a subset of these parameters, and these usually focus on its effect on transmission in homogeneous models of diseases. However it is known that in models accounting for structured populations and heterogeneous contacts, measures of transmission such as the basic reproduction number can be very different from what would be derived using homogeneous models [4]. Thus the vaccine impact φ , as defined in (1), will also be different when taking into account heterogeneous contacts. Here we show that the vaccine impact for age-structured models can also be very different from those derived for homogeneous models if distinct age-structured contacts are taken into account. While the homogeneous model vaccine impact (3) only depends on the vaccine and demographic parameters (and not on the parameters governing disease transmission), we show that the age-structured model vaccine impact depends on the contact rates and coverage p (refer to Proposition 4 and Figure 3). In particular, if the vaccine exhibits waning protection the overall impact can be larger for age-structured models if the contact rates between children are higher than those between adults. This is because if vaccine protection does not wane for most individuals until they become adults subject to lower contact rates, then these individuals are at lower risk for both infection and transmission of the disease.

This paper is divided into four sections. In Section 2 we review the model presented in [10] which involves all the modes of vaccine failure introduced. In Section 3 we extend the simple model to an age-structured model and derive analytic expressions for age-specific vaccine impact values for such a model. We also prove, using the Perron-Frobenius theorem for irreducible matrices, that the overall vaccine impact is bounded between the impact for the youngest and oldest age classes. In Section 4 we conclude with a summary of our results and a short discussion of extension of the results to models consisting of systems of partial differential equations with continuous age structure, and models including other modes of vaccine failure.

2 Homogeneous model

We begin with a brief discussion of the homogeneous model of an imperfect vaccine that was used in [9]. The model diagram is shown in Figure 1. The compartments and parameters of the model are defined in Tables 1–2. The model is composed of a system of ordinary differential equations given in Definition 1. In this model, the leakiness ε_L , primary vaccine failure ε_A , waning probability ε_W and relative infectiousness θ parameters are called the vaccine parameters sometimes referred to as a tuple $(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta)$. Since the relative reporting probability η does not affect transmission, we do not include it in this model. However, as has already been noted, this parameter should be taken into account when fitting models to data [9].

Definition 1

The homogeneous imperfect vaccine model is given by the following system of ordinary differential equations,

$$\begin{aligned}
 \frac{dV}{dt} &= (1 - \varepsilon_A)p\mu - \alpha V - \varepsilon_L \lambda V - \mu V, \\
 \frac{dS_1}{dt} &= (1 - (1 - \varepsilon_A)p) \mu - \lambda S_1 - \mu S_1, \\
 \frac{dE_1}{dt} &= \lambda S_1 - \sigma E_1 - \mu E_1, \\
 \frac{dI_1}{dt} &= \sigma E_1 - \gamma I_1 - \mu I_1, \\
 \frac{dS_2}{dt} &= \alpha V - \lambda S_2 - \mu S_2, \\
 \frac{dE_2}{dt} &= \varepsilon_L \lambda V + \lambda S_2 - \sigma E_2 - \mu E_2, \\
 \frac{dI_2}{dt} &= \sigma E_2 - \gamma I_2 - \mu I_2, \\
 \frac{dR}{dt} &= \gamma I_1 + \gamma I_2 - \mu R, \\
 \lambda &= \beta(I_1 + \theta I_2).
 \end{aligned} \tag{4}$$

for $t \geq 0$ where $\alpha = \frac{\mu \varepsilon_W}{1 - \varepsilon_W}$ and the initial conditions satisfy

$$V(0)+S_1(0)+E_1(0)+I_1(0)+S_2(0)+E_2(0)+I_2(0)+R(0)=1. \quad (5)$$

This model is based on the standard susceptible-exposed-infected-recovered (SEIR) models with additional compartments and connections to accommodate the different modes of vaccine failure (leakiness, primary vaccine failure, waning and relative infectiousness) added in. For all $t \geq 0$, a fraction p of the newborns are vaccinated. Of this fraction, a proportion ε_A exhibit primary vaccine failure and go instead to the S_1 class, while the remaining proportion go to the V class. The V class has a reduced probability of getting infected upon exposure relative to the S_1 or S_2 classes, given by the leakiness parameter ε_L . Vaccine protection is also assumed to wane and the rate at which transitions from the V class to the S_2 class occur is α . An individual in the V or S_2 classes that gets infected enters the exposed (E_2) then infectious (I_2) classes, which is separate from the exposed (E_1) and infectious (I_1) classes for unvaccinated individuals or those that have experienced primary vaccine failure. The vaccinated infected individuals (I_2) are only a fraction θ as infectious as an unvaccinated infected individual in the I_1 compartment.

This model of vaccination makes the assumption that vaccination is administered immediately after birth. Such a simplifying assumption is often used to model childhood vaccination that occurs at a very young age [5,8–11], before children reach ages that are associated with higher contact rates such as when they start going to school or daycare.

As noted in the introduction, instead of using α we use the parameter ε_W , defined by

$$\varepsilon_W = \frac{\alpha}{\alpha + \mu}. \quad (6)$$

Thus ε_W is the probability that the vaccine protection of individuals in the V class wanes within one's lifetime given that they do not get infected first. Further discussion on this choice of parametrizing the amount of waning is discussed in [10]. In the appendix of [9], the basic reproduction number R_p as a function of the vaccination coverage p of the system (4) was derived using the next-generation matrix method of [2] and [1]. For convenience, these results are also presented here as item 3 of Proposition 1. In this section we use $X = (V, S_1, E_1, I_1, S_2, E_2, I_2, R)$ to refer to the state of the system. Superscripts of 0 are used to refer to the disease-free equilibrium and * for the endemic equilibrium.

Proposition 1

The model in Definition 1 has the following properties.

1. *The system of equations is well-posed and invariant in the set $\mathcal{D} = \{X \in [0, 1]^8 : V + S_1 + E_1 + I_1 + S_2 + E_2 + I_2 + R = 1\}$.*
2. *The disease free equilibrium of the system is $X^0 = (V^0, S_1^0, E_1^0, I_1^0, S_2^0, E_2^0, I_2^0, R^0)$ where,*

$$\begin{aligned}
 V^0 &= \frac{p(1-\varepsilon_A)\mu}{\mu+\alpha} = p(1-\varepsilon_A)(1-\varepsilon_W), \\
 S_1^0 &= 1 - (1-\varepsilon_A)p, \\
 S_2^0 &= \frac{p(1-\varepsilon_A)\alpha}{\mu+\alpha} = p(1-\varepsilon_A)\varepsilon_W, \\
 E_1^0 &= I_1^0 = E_2^0 = I_2^0 = R^0 = 0.
 \end{aligned} \tag{7}$$

3. The basic reproduction number associated with the homogeneous model (4) is

$$R_p = R_0(1-\varphi p),$$

where $R_0 = \frac{\beta}{\gamma+\mu} \frac{\sigma}{\sigma+\mu}$ is the basic reproduction number in the absence of vaccination ($p=0$) and φ , the vaccine impact, is given by

$$\varphi = (1-\varepsilon_A)(1-\theta + \theta(1-\varepsilon_L)(1-\varepsilon_W)). \tag{8}$$

4. If $R_p < 1$, the disease-free equilibrium X^0 is the only equilibrium of the system in $\mathcal{D}$. If $R_p > 1$ then there are two steady states in $\mathcal{D}$, the disease-free equilibrium X^0 and the endemic equilibrium $X^* = (V^*, S_1^*, E_1^*, I_1^*, S_2^*, E_2^*, I_2^*, R^*)$ where,

$$\begin{aligned}
 V^* &= \frac{(1-\varepsilon_A)p\mu}{\alpha+\varepsilon_L\lambda^*+\mu} = \frac{(1-\varepsilon_A)(1-\varepsilon_W)p\mu}{\mu+\varepsilon_L(1-\varepsilon_W)\lambda^*}, \\
 S_1^* &= \frac{(1-(1-\varepsilon_A)p)\mu}{\lambda^*+\mu} \\
 E_1^* &= \frac{\lambda^*}{\sigma+\mu} S_1^* \\
 I_1^* &= \frac{\sigma}{\gamma+\mu} E_1^* \\
 S_2^* &= \frac{\alpha(1-\varepsilon_A)p\mu}{(\alpha+\varepsilon_L\lambda^*+\mu)(\lambda^*+\mu)} = \frac{(1-\varepsilon_A)\varepsilon_W p\mu^2}{(\mu+\varepsilon_L(1-\varepsilon_W)\lambda^*)(\lambda^*+\mu)}, \\
 E_2^* &= \frac{\lambda^*}{\sigma+\mu} (S_2^* + \varepsilon_L V^*) \\
 I_2^* &= \frac{\sigma}{\gamma+\mu} E_2^* \\
 R^* &= 1 - V^* - S_1^* - E_1^* - I_1^* - S_2^* - E_2^* - I_2^*
 \end{aligned} \tag{9}$$

and λ^* is found by substituting (9) into the following expression,

$$1 = R_0 [S_1^* + \theta(S_2^* + \varepsilon_L V^*)], \tag{10}$$

and solving for the unique $\lambda^* \in (0, \infty)$.

5. If $R_p < 1$ the disease-free equilibrium X^0 is locally asymptotically stable. If $R_p > 1$ then the disease-free equilibrium X^0 is unstable and only initializations with $E_1(0) = I_1(0) = E_2(0) = I_2(0) = 0$ will approach this equilibrium.

Proof—The proof of items 1–2 are standard. The proof of item 3 (derivation of the formula for R_p is provided in the supplementary information of [9]. The expressions for V^* , S_1^* and S_2^* in (9) can be derived by setting $\lambda^* = \beta(I_1^* + \theta I_2^*)$ and solving for the equilibria of (4) in terms of λ^* . In terms of these expressions we can derive expressions for E_1^* and E_2^* , and from these we derive I_1^* and I_2^* . Substituting these expressions back to $\lambda^* = \beta(I_1^* + \theta I_2^*)$, we derive

$$\lambda^* = \lambda^* \frac{\beta}{\gamma + \mu} \frac{\sigma}{\sigma + \mu} [S_1^* + \theta(S_2^* + \varepsilon_L V^*)] = \lambda^* R_0 [S_1^* + \theta(S_2^* + \varepsilon_L V^*)].$$

The solution $\lambda^* = 0$ corresponds to the disease-free equilibrium. If we set $\lambda^* = 0$, we derive (10). Set the function $s(\lambda^*)$ equal to the expression $S_1^* + \theta(S_2^* + \varepsilon_L V^*)$. This yields,

$$1 = R_0 s(\lambda^*).$$

We observe that $s(\lambda^*)$ is decreasing for $\lambda^* \in (0, \infty)$, $s(0) = S_1^0 + \theta(S_2^0 + \varepsilon_L V^0) = 1 - \varphi p$ and $\lim_{\lambda^* \rightarrow \infty} s(\lambda^*) = 0$. It follows from this that if $R_p = R_0(1 - \varphi p) < 1$ then there is no solution to (10) with $\lambda^* > 0$ (and therefore no endemic equilibrium in $\mathcal{D}$.) If $R_p > 1$ then there exists a unique solution $\lambda^* > 0$ to (10), and in this case the expression X^* corresponds to a unique endemic equilibrium in $\mathcal{D}$. This completes the proof of item 4.

The proof of item 5 follows from the theory on the next-generation matrix and the basic reproduction number [1,2].

Proposition 2

All combinations of vaccine parameters (ε_L , ε_A , ε_W , θ) with the same vaccine impact φ and $\varepsilon_L = 0$ have the same force of infection $\lambda^ = \mu(R_p - 1) = \mu[R_0(1 - \varphi p) - 1]$ at the endemic equilibrium X^* .*

Proof—By substituting (9) into (10), we derive

$$\begin{aligned}
\frac{1}{R_0} &= [S_1^* + \theta(S_2^* + \varepsilon_L V^*)], \\
&= \left[\frac{(1 - (1 - \varepsilon_A)p)\mu}{\lambda^* + \mu} + \theta \left(\frac{(1 - \varepsilon_A)\varepsilon_W p \mu^2}{(\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*)(\lambda^* + \mu)} + \varepsilon_L \frac{(1 - \varepsilon_A)(1 - \varepsilon_W)p\mu}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} \right) \right], \\
&= \frac{\mu}{\mu + \lambda^*} \left[(1 - (1 - \varepsilon_A)p) + \theta \left(\frac{(1 - \varepsilon_A)\varepsilon_W p \mu}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} + \varepsilon_L \frac{(1 - \varepsilon_A)(1 - \varepsilon_W)p(\mu + \lambda^*)}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} \right) \right], \\
&= \frac{\mu}{\mu + \lambda^*} \left[1 - (1 - \varepsilon_A)p \left(1 - \theta \frac{\varepsilon_W \mu + \varepsilon_L(1 - \varepsilon_W)(\mu + \lambda^*)}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} \right) \right], \\
&= \frac{\mu}{\mu + \lambda^*} \left[1 - (1 - \varepsilon_A)p \left(1 - \theta + \theta \frac{(1 - \varepsilon_L)(1 - \varepsilon_W)\mu}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} \right) \right]. \tag{11}
\end{aligned}$$

If $\varepsilon_L = 0$, this last equation simplifies to a linear equation for λ^* ,

$$\frac{1}{R_0} = \frac{\mu}{\mu + \lambda^*} (1 - \varphi p).$$

Solving for λ^* yields the required expression $\lambda^* = \mu(R_p - 1)$.

Proposition 3

Suppose that the vaccine impact φ is fixed such that $R_p > 1$.

1. Let $\theta = 1$. The vaccine parameter set $(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta)$ that has the highest value of the force of infection at endemic equilibrium (λ^*) is,

$$(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta) = (1 - \varphi, 0, 0, 1).$$

This is the model with fixed φ that has the highest leakiness.

2. Let $\theta = 0$. In this case the vaccine impact must satisfy $\varphi = 1 - \varepsilon_A$ and any set $(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta)$ has the same force of infection at endemic equilibrium given by $\lambda^* = \mu(R_p - 1)$.
3. Let $\varepsilon_A \in [0, 1)$ and $\theta \in (0, 1)$ be fixed. This means ε_L and ε_W are allowed to vary but are required to satisfy the following expression

$$(1 - \varepsilon_L)(1 - \varepsilon_W) = \frac{\varphi - (1 - \theta)(1 - \varepsilon_A)}{\theta(1 - \varepsilon_A)}.$$

The vaccine parameter set $(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta)$ that satisfies these conditions and has the highest value of the force of infection at endemic equilibrium (λ^*) is,

$$(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta) = \left(1 - \frac{\varphi - (1 - \theta)(1 - \varepsilon_A)}{\theta(1 - \varepsilon_A)}, \varepsilon_A, 0, \theta \right).$$

This is the model with fixed φ , ε_A and θ that has the highest leakiness and zero waning.

Proof—The proofs of the items in this proposition are similar to proofs given in [10] for a simpler model. The proofs of items 1–2 are omitted. To prove item 3, we go back to (11) and derive,

$$\begin{aligned} 1 &= \frac{\mu}{\mu + \lambda^*} R_0 \left[1 - (1 - \varepsilon_A) p \left(1 - \theta + \theta(1 - \varepsilon_L)(1 - \varepsilon_W) \frac{\mu}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} \right) \right], \\ &= \frac{\mu}{\mu + \lambda^*} R_0 \left[1 - (1 - \varepsilon_A) p \left(1 - \theta + \theta(1 - \varepsilon_L)(1 - \varepsilon_W) \left(1 - \frac{\varepsilon_L(1 - \varepsilon_W)\lambda^*}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} \right) \right) \right], \\ &= \frac{\mu}{\mu + \lambda^*} R_0 \left[1 - \varphi p - \frac{\theta \varepsilon_L(1 - \varepsilon_A)(1 - \varepsilon_L)(1 - \varepsilon_W)^2 \lambda^*}{\mu + \varepsilon_L(1 - \varepsilon_W)\lambda^*} p \right]. \end{aligned}$$

From this we can derive the following quadratic expression in λ^* ,

$$\frac{\varepsilon_L(1 - \varepsilon_W)}{\mu} \lambda^{*2} + [1 + \varepsilon_L(1 - \varepsilon_W) - R_0 \varepsilon_L(1 - \varepsilon_W)(\theta(1 - \varepsilon_L)(1 - \varepsilon_A)(1 - \varepsilon_W)p + (1 - \varphi p))] \lambda^* + \mu(1 - R_0(1 - \varphi p)) = 0.$$

Using $\theta(1 - \varepsilon_L)(1 - \varepsilon_A)(1 - \varepsilon_W) = \varphi - (1 - \varepsilon_A)(1 - \theta)$ and $R_p = R_0(1 - \varphi p)$ yields,

$$\frac{x}{\mu} \lambda^{*2} + [1 + x - x R_0(1 - q p)] \lambda^* + \mu(1 - R_p) = 0,$$

where $q = (1 - \varepsilon_A)(1 - \theta)$ is fixed and $x = \varepsilon_L(1 - \varepsilon_W) \in [0, 1]$. Solving for a positive solution λ^* yields

$$\lambda^* = \frac{\mu}{2} \left[R_0(1 - q) - 1 - \frac{1}{x} + \sqrt{\left(R_0(1 - q p) - 1 - \frac{1}{x} \right)^2 + \frac{4}{x}(R_p - 1)} \right]. \quad (12)$$

Define $\Lambda^*(x)$ to be this expression,

$$\Lambda^*(x) = \frac{\mu}{2} \left[R_0(1 - q) - 1 - \frac{1}{x} + \sqrt{\left(R_0(1 - q p) - 1 - \frac{1}{x} \right)^2 + \frac{4}{x}(R_p - 1)} \right]. \quad (13)$$

Since we are keeping φ , ε_A and θ fixed, R_p and q are also fixed. Taking the derivative with respect to x ,

$$\frac{d}{dx} \Lambda^*(x) = \frac{\mu}{2x^2} \left[1 + \frac{R_0(1-qp) - 1 - \frac{1}{x} - 2(R_p - 1)}{\sqrt{(R_0(1-qp) - 1 - \frac{1}{x})^2 + \frac{4}{x}(R_p - 1)}} \right] = \frac{\mu}{2x^2} \left[1 + \frac{a-b}{\sqrt{a^2+c}} \right]. \quad (14)$$

where $a = R_0(1-qp) - 1 - \frac{1}{x}$, $b = 2(R_p - 1)$ and $c = \frac{4}{x}(R_p - 1)$. We claim that $\frac{d}{dx} \Lambda^*(x) \geq 0$ for all $x > 0$. When $a \geq b$ this is clearly true so consider the case when $a < b$. Since $c > b > 0$,

$$1 + \frac{a-b}{\sqrt{a^2+c}} \geq 0, \iff \frac{a^2 - 2ab + b^2}{a^2 + c} \leq 1 \iff b^2 - 2ab - c \leq 0.$$

The expression

$$\begin{aligned} b^2 - 2ab - c &= 2(R_p - 1) \left[2(R_p - 1) - 2 \left(R_0(1-qp) - 1 - \frac{1}{x} \right) \right] - \frac{4}{x}(R_p - 1), \\ &= 4(R_p - 1) [R_p - R_0(1-qp)], \\ &= 4(R_p - 1)R_0(q - \varphi)p, \\ &= -4(R_p - 1)R_0\theta(1 - \varepsilon_A)(1 - \varepsilon_L)(1 - \varepsilon_W)p, \\ &\leq 0. \end{aligned}$$

Thus it follows that the value of the endemic steady state increases with x . This means the maximum value for Λ^* occurs at the maximum value of ε_L .

3 General case with multiple age-classes

In this section we extend the model to include age-structure. The population is split into M age groups labeled $N^{(i)}$ for $i = 1, \dots, M$. The rate of transfer from $N^{(i)}$ to $N^{(i+1)}$ is $\nu^{(i)}$ as shown in Figure 2. All age groups are assumed to have a death rate of μ , thus the average

age of group $N^{(i)}$ is $\sum_{j=1}^i \frac{1}{\mu + \nu^{(j)}}$. Each group $N^{(i)}$ is also divided into $V^{(i)}$,

$S_1^{(i)}, E_1^{(i)}, I_1^{(i)}, S_2^{(i)}, E_2^{(i)}, I_2^{(i)}$ and $R^{(i)}$ components corresponding to the eight different compartments of the model in Definition 1. The equations describing the extension of this model to an age-structured model are given in Definition 2.

To keep the focus on the disease dynamics, we assume that the demographics of the population remains fixed, i.e. $N^{(i)}$ is fixed at its steady state values for $i = 1, \dots, M$. The total population remains constant at one so standard incidence and mass action incidence are equivalent. The steady state values (summarized in Table 3) can be found by adding up the derivatives for each component and solving for the equilibrium. Thus,

$$N^{(1)} = \frac{\mu}{\mu + \nu^{(1)}}, \quad N^{(i)} = \frac{\nu^{(i-1)} N^{(i-1)}}{\mu + \nu^{(i)}}. \quad (15)$$

This can be written in simpler notation by defining $\zeta^{(i)}$ to be the probability that an individual goes from the i th age class to the $(i+1)$ st age class. For $i = 2, \dots, M$,

$$\zeta^{(i)} = \frac{\nu^{(i)}}{\mu + \nu^{(i)}}. \quad (16)$$

Thus,

$$N^{(i)} = (1 - \zeta^{(i)}) \prod_{j=1}^{i-1} \zeta^{(j)}. \quad (17)$$

We also introduce the following notation: The probability of vaccine immunity waning at the i th age group is,

$$\varepsilon_w^{(i)} = \frac{\alpha}{\alpha + \mu + \nu^{(i)}}. \quad (18)$$

These additional parameters for the age-structured model with M age groups are summarized in Table 3. In this table we also define the age-specific vaccine impacts $\phi^{(i)}$, and the effective vaccine impact $\phi^*(p)$. The effective vaccine impact $\phi^*(p)$ is defined to be consistent with the use of vaccine impact in (1), as the relative change in reproduction number per vaccinated individual. For an age-structured model this is now a function of the vaccine coverage p .

Definition 2

The imperfect vaccine model with M age classes is given by the following system of ODEs:

$$\begin{aligned}
\frac{dV^{(i)}}{dt} &= (1 - \varepsilon_A) p \mu \delta_{i,1} - \alpha V^{(i)} - \varepsilon_L \lambda V^{(i)} - \mu V^{(i)} + \nu^{(i-1)} V^{(i-1)} - \nu^{(i)} V^{(i)}, \\
\frac{dS_1^{(i)}}{dt} &= (1 - (1 - \varepsilon_A) p) \mu \delta_{i,1} - \lambda^{(i)} S_1^{(i)} - \mu S_1^{(i)} + \nu^{(i-1)} S_1^{(i-1)} - \nu^{(i)} S_1^{(i)}, \\
\frac{dE_1^{(i)}}{dt} &= \lambda^{(i)} S_1^{(i)} - \sigma E_1^{(i)} - \mu E_1^{(i)} + \nu^{(i-1)} E_1^{(i-1)} - \nu^{(i)} E_1^{(i)}, \\
\frac{dI_1^{(i)}}{dt} &= \sigma E_1^{(i)} - \gamma I_1^{(i)} - \mu I_1^{(i)} + \nu^{(i-1)} I_1^{(i-1)} - \nu^{(i)} I_1^{(i)}, \\
\frac{dS_2^{(i)}}{dt} &= \alpha V^{(i)} - \lambda S_2^{(i)} - \mu S_2^{(i)} + \nu^{(i-1)} S_2^{(i-1)} - \nu^{(i)} S_2^{(i)}, \\
\frac{dE_2^{(i)}}{dt} &= \varepsilon_L \lambda^{(i)} V^{(i)} + \lambda^{(i)} S_2^{(i)} - \sigma E_2^{(i)} - \mu E_2^{(i)} + \nu^{(i-1)} E_2^{(i-1)} - \nu^{(i)} E_2^{(i)}, \\
\frac{dI_2^{(i)}}{dt} &= \sigma E_2^{(i)} - \gamma I_2^{(i)} - \mu I_2^{(i)} + \nu^{(i-1)} I_2^{(i-1)} - \nu^{(i)} I_2^{(i)}, \\
\frac{dR^{(i)}}{dt} &= \gamma I_1^{(i)} + \gamma I_2^{(i)} - \mu R^{(i)} + \nu^{(i-1)} R^{(i-1)} - \nu^{(i)} R^{(i)}.
\end{aligned} \tag{19}$$

where $\delta_{i,j}$ is the Kronecker delta function and the force of infection is given by,

$$\lambda^{(i)} = \sum_{j=1}^M \beta_{i,j} (I_1^{(j)} + \theta I_2^{(j)}). \tag{20}$$

for $t = 0$ and $i = 1, \dots, M$. The initial conditions are assumed to satisfy

$$V^{(i)}(0) + S_1^{(i)}(0) + E_1^{(i)}(0) + I_1^{(i)}(0) + S_2^{(i)}(0) + E_2^{(i)}(0) + I_2^{(i)}(0) + R^{(i)}(0) = N^{(i)}, \tag{21}$$

for $i = 1, \dots, M$.

Before we present our results on this model, we first present some notation for dealing with this system.

Definition 3

The state of the system will be referred to as $X = (X^{(i)})_{i=1}^M$ where

$$X^{(i)} = (V^{(i)}, S_1^{(i)}, E_1^{(i)}, I_1^{(i)}, S_2^{(i)}, E_2^{(i)}, I_2^{(i)}, R^{(i)}),$$

for $i = 1, \dots, M$. In this section we also use the notation $V = (V^{(i)})_{i=1}^M$, i.e. V represents an $M \times 1$ vector of the vaccinated component for all age classes in order. Similar notation will be

used for the other disease states. In addition, adding a superscript of 0 to a symbol will denote its disease-free steady state and a superscript of * denotes the endemic steady state.

We use e_k denote the vector with one in its k th entry and zeroes everywhere else. Throughout this section we will use boldface or script fonts to denote matrices. The notation $\mathbf{I}_k$ denotes a $k \times k$ identity matrix. We also define the following functions: for $k \in \{0, \dots, M\}$, $\mathbf{L}_k: \mathbb{R}^{M-k} \rightarrow \mathbb{R}^{M \times M}$, where

$$\mathbf{L}_k(\{a_1, \dots, a_{M-k}\}) = [\delta_{i,j+k}]_{i,j=1}^M \begin{bmatrix} a_1 \\ a_2 \\ \vdots \\ a_{M-k} \\ 0 \\ \vdots \\ 0 \end{bmatrix} \quad (22)$$

Here, $[\delta_{i,j+k}]_{i,j=1}^M$ is the shift matrix which consists of ones in the k th subdiagonal and zeros everywhere else. For example, $\mathbf{L}_0(\{a_1, \dots, a_M\}) = \text{diag}(\{a_1, \dots, a_M\})$. Also,

$$\mathbf{L}_1(\{a_1, \dots, a_{M-1}\}) = \begin{bmatrix} 0 & 0 & 0 & \dots & 0 & 0 \\ a_1 & 0 & 0 & \dots & 0 & 0 \\ 0 & a_2 & 0 & \dots & 0 & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \ddots & 0 & 0 \\ 0 & 0 & 0 & \dots & a_{M-1} & 0 \end{bmatrix}. \quad (23)$$

In the next proposition we prove some results on the equilibria of the general age-structured model and derive analytic bounds on the effective vaccine impact.

Proposition 4

The model in Definition 2 has the following properties.

1. The system of equations is well-posed and invariant in the set $\mathcal{D}$ where

$$\mathcal{D} = \left\{ (X^{(i)})_{i=1}^M \in [0, 1]^{8M} : V^{(i)} + S_1^{(i)} + E_1^{(i)} + I_1^{(i)} + S_2^{(i)} + E_2^{(i)} + I_2^{(i)} + R^{(i)} = N^{(i)}, i=1, \dots, M \right\}.$$

2. The disease-free equilibrium of this model is given by $X^0 = (X^{0(i)})_{i=1}^M$ where

$$X^{0(i)} = (V^{0(i)}, S_1^{0(i)}, E_1^{0(i)}, I_1^{0(i)}, S_2^{0(i)}, E_2^{0(i)}, I_2^{0(i)}, R^{0(i)}),$$

and for $i = 1, \dots, M$,

$$\begin{aligned}
V^{0(i)} &= N^{(i)}(1-\varepsilon_A)p \prod_{j=1}^i (1-\varepsilon_W^{(j)}), \\
S_1^{0(i)} &= N^{(i)}(1-(1-\varepsilon_A)p), \\
S_2^{0(i)} &= N^{(i)}(1-\varepsilon_A)p \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1-\varepsilon_W^{(j)}), \\
E_1^{0(i)} &= I_1^{0(i)} = E_2^{0(i)} = I_2^{0(i)} = R^{0(i)} = 0.
\end{aligned} \tag{24}$$

3. The basic reproduction number associated with the homogeneous model (4) can be written as

$$R_p = R_0(1-\varphi^*(p)p), \tag{25}$$

where R_0 is the basic reproduction number in the absence of vaccination ($p=0$) and $\varphi^*(p)$ is the overall vaccine impact. For $i=1, \dots, M$ we define the vaccine impact associated with age class i to be,

$$\varphi^{(i)} = (1-\varepsilon_A) \left[(1-\theta) + \theta(1-\varepsilon_L) \prod_{j=1}^i (1-\varepsilon_W^{(j)}) \right]. \tag{26}$$

The overall vaccine impact $\varphi^*(p)$ satisfies $\varphi^*(p) \in [\varphi^{(M)}, \varphi^{(1)}]$ for all $p \in (0, 1]$.

4. The endemic equilibrium of this model is given by $X^* = (X^{*(i)})$ where

$$X^{*(i)} = (V^{*(i)}, S_1^{*(i)}, E_1^{*(i)}, I_1^{*(i)}, S_2^{*(i)}, E_2^{*(i)}, I_2^{*(i)}, R^{*(i)}),$$

and for $i=1, \dots, M$,

$$\begin{aligned}
V^{*(i)} &= e_i \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}(1-\varepsilon_W^{(i)})}{\mu + \nu^{(i)} + \varepsilon_L(1-\varepsilon_W^{(i)})} \right\}_{i=2}^M \right) \right]^{-1} \begin{bmatrix} \frac{(1-\varepsilon_A)(1-\varepsilon_W^{(1)})p\mu}{\varepsilon_L(1-\varepsilon_W^{(1)})\lambda^{*(1)} + \mu + \nu^{(1)}} \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \\
S_1^{*(i)} &= e_i \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\lambda^{*(i)} + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} \begin{bmatrix} \frac{(1-(1-\varepsilon_A)p)\mu}{\lambda^{*(1)} + \mu + \nu^{(1)}} \\ 0 \\ \vdots \\ 0 \end{bmatrix}, \\
S_2^{*(i)} &= e_i \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\lambda^{(i)} + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} V^*, \\
E_1^{*(i)} &= e_i \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\sigma + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} \frac{\lambda^{*(i)}}{\sigma + \mu + \nu^{(i)}} S_1^*, \\
E_2^{*(i)} &= e_i \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\sigma + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} \frac{\lambda^{*(i)}}{\sigma + \mu + \nu^{(i)}} (S_2^* + \varepsilon_L V^*), \\
I_k^{*(i)} &= e_i \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\gamma + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} \frac{\sigma}{\gamma + \mu + \nu^{(i)}} E_k^*, \quad \text{for } k=1, 2, \\
R^{*(i)} &= N^{(i)} - (V^{*(i)} + S_1^{*(i)} + E_1^{*(i)} + I_1^{*(i)} + S_2^{*(i)} + E_2^{*(i)} + I_2^{*(i)}),
\end{aligned}
\tag{27}$$

and $\lambda^{*(i)}$ is found by substituting (27) into the following system of equations,

$$\begin{aligned}
\begin{bmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{bmatrix} &= [\beta_{i,j}]_{i,j=1}^M \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\gamma + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} \mathbf{L}_0 \left(\left\{ \frac{\sigma}{\sigma + \mu + \nu^{(i)}} \right\}_{i=1}^M \right) \\
&\cdot \left[\mathbf{I}_M - \mathbf{L}_1 \left(\left\{ \frac{\nu^{(i-1)}}{\sigma + \mu + \nu^{(i)}} \right\}_{i=2}^M \right) \right]^{-1} \mathbf{L}_0 \left(\left\{ \frac{1}{\gamma + \mu + \nu^{(i)}} \right\}_{i=1}^M \right) [S_1^* + \theta(S_2^* + \varepsilon_L V^*)],
\end{aligned}$$

and solving this system for solutions such that $\lambda^{*(i)} > 0$ for $i = 1 \dots M$. Note that in the notation above, the $\cdot$ indicates regular matrix multiplication

5. If $R_p < 1$ then the disease-free equilibrium X^0 is locally asymptotically stable. If $R_p > 1$ then the disease-free equilibrium X^0 is unstable and only initializations with $E_1^{(1)}(0) = I_1^{(1)}(0) = E_2^{(1)}(0) = I_2^{(1)}(0) = E_1^{(2)}(0) = I_1^{(2)}(0) = E_2^{(2)}(0) = I_2^{(2)}(0) = 0$ will approach this equilibrium.

Proof—The proof of item 1 is standard and is omitted. We also omit the proof to show that for the first age group,

$$\begin{aligned} V^{0(1)} &= \frac{\mu}{\mu + \nu^{(1)}} (1 - \varepsilon_A) p (1 - \varepsilon_W^{(1)}), \\ S_1^{0(1)} &= \frac{\mu}{\mu + \nu^{(1)}} (1 - (1 - \varepsilon_A) p), \\ S_2^{0(1)} &= \frac{\mu}{\mu + \nu^{(1)}} (1 - \varepsilon_A) p \varepsilon_W^{(1)}, \\ E_1^{0(1)} &= I_1^{0(1)} = E_2^{0(1)} = I_2^{0(1)} = R^{0(1)} = 0. \end{aligned} \quad (28)$$

This is consistent with the formula in item 2 for $i = 1$. We now prove that the formula holds for $i = 2, \dots, M$ by induction. For some i , assume that (24) holds. By setting $\frac{dV^{(i+1)}}{dt} = 0$ we derive,

$$\begin{aligned} V^{0(i+1)} &= \frac{\nu^{(i)} V^{0(i)}}{\alpha + \mu + \nu^{(i+1)}}, \\ &= \frac{\nu^{(i)}}{\alpha + \mu + \nu^{(i+1)}} N^{(i)} (1 - \varepsilon_A) p \prod_{j=1}^i (1 - \varepsilon_W^{(j)}), \\ &= \frac{\mu + \nu^{(i+1)}}{\alpha + \mu + \nu^{(i+1)}} \frac{\nu^{(i)}}{\mu + \nu^{(i+1)}} N^{(i)} (1 - \varepsilon_A) p \prod_{j=1}^i (1 - \varepsilon_W^{(j)}), \\ &= (1 - \varepsilon_W^{(i+1)}) N^{(i+1)} (1 - \varepsilon_A) p \prod_{j=1}^i (1 - \varepsilon_W^{(j)}), \\ &= N^{(i+1)} (1 - \varepsilon_A) p \prod_{j=1}^{i+1} (1 - \varepsilon_W^{(j)}). \end{aligned}$$

This verifies the formula for $V^{0(i)}$. Next we set $\frac{dS_1^{(i+1)}}{dt} = 0$ and derive,

$$\begin{aligned} S_1^{0(i+1)} &= \frac{\nu^{(i)} S_1^{(i)}}{\mu + \nu^{(i+1)}}, \\ &= \frac{\nu^{(i)}}{\mu + \nu^{(i+1)}} N^{(i)} (1 - (1 - \varepsilon_A) p), \\ &= \frac{\mu}{\mu + \nu^{(i+1)}} \frac{\nu^{(i)}}{\mu} N^{(i)} (1 - (1 - \varepsilon_A) p), \\ &= N^{(i+1)} (1 - (1 - \varepsilon_A) p). \end{aligned}$$

This verifies the formula for $S_1^{0(i)}$. Next we set $\frac{dS_2^{(i+1)}}{dt} = 0$ and derive,

$$\begin{aligned}
S_2^{0(i+1)} &= \frac{\alpha V^{(i+1)} + \nu^{(i)} S_2^{(i)}}{\mu + \nu^{(i+1)}} \\
&= \frac{\alpha}{\mu + \nu^{(i+1)}} N^{(i+1)} (1 - \varepsilon_A) p \prod_{j=1}^{i+1} (1 - \varepsilon_W^{(j)}) + \frac{\nu^{(i)}}{\mu + \nu^{(i+1)}} N^{(i)} (1 - \varepsilon_A) p \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}), \\
&= \frac{\alpha + \mu + \nu^{(i+1)}}{\mu + \nu^{(i+1)}} \frac{\alpha}{\alpha + \mu + \nu^{(i+1)}} N^{(i+1)} (1 - \varepsilon_A) p \prod_{j=1}^{i+1} (1 - \varepsilon_W^{(j)}) + \frac{\mu}{\mu + \nu^{(i+1)}} \frac{\nu^{(i)}}{\mu} N^{(i)} (1 - \varepsilon_A) p \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}), \\
&= \frac{1}{1 - \varepsilon_W^{(i+1)}} \varepsilon_W^{(i+1)} N^{(i+1)} (1 - \varepsilon_A) p \prod_{j=1}^{i+1} (1 - \varepsilon_W^{(j)}) + N^{(i+1)} (1 - \varepsilon_A) p \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}), \\
&= N^{(i+1)} (1 - \varepsilon_A) p \varepsilon_W^{(i+1)} \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) + N^{(i+1)} (1 - \varepsilon_A) p \prod_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}), \\
&= N^{(i+1)} (1 - \varepsilon_A) p \sum_{k=1}^{i+1} \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}).
\end{aligned}$$

This completes the induction for the formula for $S_2^{0(i)}$.

To prove item 3, we require an expression for $S_1^{0(i)} + \theta(S_2^{0(i)} + \varepsilon_L V^{0(i)})$. We first consider the general form of $S_2^{0(i)} + \varepsilon_L V^{0(i)}$,

$$\begin{aligned}
S_2^{0(i)} + \varepsilon_L V^{0(i)} &= N^{(i)} (1 - \varepsilon_A) p \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \varepsilon_L N^{(i)} (1 - \varepsilon_A) p \prod_{j=1}^i (1 - \varepsilon_W^{(j)}), \\
&= N^{(i)} (1 - \varepsilon_A) p \left[\sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \varepsilon_L \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right].
\end{aligned}$$

Thus,

$$\begin{aligned}
&S_1^{0(i)} + \theta(S_2^{0(i)} + \varepsilon_L V^{0(i)}) \\
&= N^{(i)} [1 - (1 - \varepsilon_A) p] + \theta N^{(i)} (1 - \varepsilon_A) p \left[\sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \varepsilon_L \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right], \\
&= N^{(i)} \left[1 - (1 - \varepsilon_A) p \left[1 - \theta \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) - \theta \varepsilon_L \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right] \right].
\end{aligned}$$

Define $\phi^{(i)}$, the vaccine impact on age class i so that $S_1^{(i)} + \theta(S_2^{(i)} + \varepsilon_L V^{(i)}) = N^{(i)} (1 - \phi^{(i)} p)$. Then,

$$\begin{aligned}
\varphi^{(i)} &= (1 - \varepsilon_A) \left[1 - \theta \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) - \theta \varepsilon_L \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right], \\
&= (1 - \varepsilon_A) \left[1 - \theta + \theta \left(1 - \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) - \varepsilon_L \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right) \right]. \quad (29)
\end{aligned}$$

We will prove that this is the same as the expression given in item 3. We do this by first showing for any $q \in \{2, \dots, M\}$ we have the following property,

$$\begin{aligned}
&\sum_{k=1}^q \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \prod_{j=1}^q (1 - \varepsilon_W^{(j)}) \\
&= \sum_{k=1}^{q-1} \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \varepsilon_W^{(q)} \prod_{j=1}^{q-1} (1 - \varepsilon_W^{(j)}) + \prod_{j=1}^q (1 - \varepsilon_W^{(j)}) \\
&= \sum_{k=1}^{q-1} \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \varepsilon_W^{(q)} \prod_{j=1}^{q-1} (1 - \varepsilon_W^{(j)}) + (1 - \varepsilon_W^{(q)}) \prod_{j=1}^{q-1} (1 - \varepsilon_W^{(j)}) \\
&= \sum_{k=1}^{q-1} \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \prod_{j=1}^{q-1} (1 - \varepsilon_W^{(j)}).
\end{aligned}$$

Since this is true for all $q \in \{2, \dots, M\}$ it follows that,

$$\begin{aligned}
&\sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) = \sum_{k=1}^1 \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) + \prod_{j=1}^1 (1 - \varepsilon_W^{(j)}) \\
&= \varepsilon_W^{(1)} + (1 - \varepsilon_W^{(1)}) \\
&= 1
\end{aligned}$$

Thus, $1 - \sum_{k=1}^i \varepsilon_W^{(k)} \prod_{j=1}^{k-1} (1 - \varepsilon_W^{(j)}) = \prod_{j=1}^i (1 - \varepsilon_W^{(j)})$. Using this in (29), we derive

$$\begin{aligned}
\varphi^{(i)} &= (1 - \varepsilon_A) \left[1 - \theta + \theta \left(\prod_{j=1}^i (1 - \varepsilon_W^{(j)}) - \varepsilon_L \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right) \right] \\
&= (1 - \varepsilon_A) \left[1 - \theta + \theta (1 - \varepsilon_L) \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right].
\end{aligned}$$

This is the formula given in item 2.

To prove item 3, we need the basic reproduction number of the system with vaccination. To find this we solve for the next generation matrix following the steps in [2]. Let Y be the $4M \times 1$ vector that includes all of the compartments with infections,

$$Y = (E_1^{(1)}, I_1^{(1)}, E_1^{(2)}, I_1^{(2)}, \dots, E_1^{(M)}, I_1^{(M)}, E_2^{(1)}, I_2^{(1)}, E_2^{(2)}, I_2^{(2)}, \dots, E_2^{(M)}, I_2^{(M)}).$$

Let Z be all other components of the model. We can then rewrite the equations in (19) as,

$$\frac{dY}{dt} = f(Y, Z), \quad \frac{dZ}{dt} = g(Y, Z).$$

We linearize the system of equations for Y about the disease-free equilibrium X^0 . This yields,

$$\frac{dY}{dt} = \mathcal{M}Y,$$

where the matrix $\mathcal{M} \in \mathbb{R}^{4M \times 4M}$. We can split this matrix into four blocks that are each $2M \times 2M$ in size. The structure of the matrix and its blocks are shown below.

$$\mathcal{M} = \begin{bmatrix} \frac{\partial f_1}{\partial E_1^{(1)}} & \frac{\partial f_1}{\partial I_1^{(1)}} & \cdots & \frac{\partial f_1}{\partial E_1^{(M)}} & \frac{\partial f_1}{\partial I_1^{(M)}} & \frac{\partial f_1}{\partial E_2^{(1)}} & \frac{\partial f_1}{\partial I_2^{(1)}} & \cdots & \frac{\partial f_1}{\partial E_2^{(M)}} & \frac{\partial f_1}{\partial I_2^{(M)}} \\ \frac{\partial f_2}{\partial E_1^{(1)}} & \frac{\partial f_2}{\partial I_1^{(1)}} & \cdots & \frac{\partial f_2}{\partial E_1^{(M)}} & \frac{\partial f_2}{\partial I_1^{(M)}} & \frac{\partial f_2}{\partial E_2^{(1)}} & \frac{\partial f_2}{\partial I_2^{(1)}} & \cdots & \frac{\partial f_2}{\partial E_2^{(M)}} & \frac{\partial f_2}{\partial I_2^{(M)}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \frac{\partial f_{2M}}{\partial E_1^{(1)}} & \frac{\partial f_{2M}}{\partial I_1^{(1)}} & \cdots & \frac{\partial f_{2M}}{\partial E_1^{(M)}} & \frac{\partial f_{2M}}{\partial I_1^{(M)}} & \frac{\partial f_{2M}}{\partial E_2^{(1)}} & \frac{\partial f_{2M}}{\partial I_2^{(1)}} & \cdots & \frac{\partial f_{2M}}{\partial E_2^{(M)}} & \frac{\partial f_{2M}}{\partial I_2^{(M)}} \\ \hline \frac{\partial f_{2M+1}}{\partial E_1^{(1)}} & \frac{\partial f_{2M+1}}{\partial I_1^{(1)}} & \cdots & \frac{\partial f_{2M+1}}{\partial E_1^{(M)}} & \frac{\partial f_{2M+1}}{\partial I_1^{(M)}} & \frac{\partial f_{2M+1}}{\partial E_2^{(1)}} & \frac{\partial f_{2M+1}}{\partial I_2^{(1)}} & \cdots & \frac{\partial f_{2M+1}}{\partial E_2^{(M)}} & \frac{\partial f_{2M+1}}{\partial I_2^{(M)}} \\ \frac{\partial f_{2M+2}}{\partial E_1^{(1)}} & \frac{\partial f_{2M+2}}{\partial I_1^{(1)}} & \cdots & \frac{\partial f_{2M+2}}{\partial E_1^{(M)}} & \frac{\partial f_{2M+2}}{\partial I_1^{(M)}} & \frac{\partial f_{2M+2}}{\partial E_2^{(1)}} & \frac{\partial f_{2M+2}}{\partial I_2^{(1)}} & \cdots & \frac{\partial f_{2M+2}}{\partial E_2^{(M)}} & \frac{\partial f_{2M+2}}{\partial I_2^{(M)}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ \frac{\partial f_{4M}}{\partial E_1^{(1)}} & \frac{\partial f_{4M}}{\partial I_1^{(1)}} & \cdots & \frac{\partial f_{4M}}{\partial E_1^{(M)}} & \frac{\partial f_{4M}}{\partial I_1^{(M)}} & \frac{\partial f_{4M}}{\partial E_2^{(1)}} & \frac{\partial f_{4M}}{\partial I_2^{(1)}} & \cdots & \frac{\partial f_{4M}}{\partial E_2^{(M)}} & \frac{\partial f_{4M}}{\partial I_2^{(M)}} \end{bmatrix}$$

(30)

This matrix can be written as $\mathcal{M} = \mathcal{F} - \mathcal{V}$ where the $\mathcal{F}$ matrix represents the new infections and $\mathcal{V}$ represents the progression of the disease [2]. For this model,

$$\mathcal{F} = \begin{bmatrix} \mathcal{F}_*(S_1^0) & \theta \mathcal{F}_*(S_1^0) \\ \mathcal{F}_*(S_2^0 + \varepsilon_L V^0) & \theta \mathcal{F}_*(S_2^0 + \varepsilon_L V^0) \end{bmatrix}.$$

Here we define the matrix-valued function $\mathcal{F}_* : \mathbb{R}^M \rightarrow \mathbb{R}^{2M \times 2M}$ as,

$$\mathcal{F}_*(X) = \begin{bmatrix} 0 & \beta_{1,1}X_1 & 0 & \beta_{1,2}X_1 & \cdots & 0 & \beta_{1,M}X_1 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & \beta_{2,1}X_2 & 0 & \beta_{2,2}X_2 & \cdots & 0 & \beta_{2,M}X_2 \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & \beta_{M,1}X_M & 0 & \beta_{M,2}X_M & \cdots & 0 & \beta_{M,M}X_M \\ 0 & 0 & 0 & 0 & \cdots & 0 & 0 \end{bmatrix}.$$

This can also be written as,

$$\mathcal{F}_*(X) = \underbrace{\left(\mathbf{I}_M \otimes \begin{bmatrix} 1 \\ 0 \end{bmatrix} \right)}_{\text{resize } 2M \times M} \underbrace{\mathbf{L}_0(X)}_{\text{"susceptible" } M \times M} \underbrace{[\beta_{i,j}]_{i,j=1}^M}_{\text{transmission } M \times M} \underbrace{\left(\mathbf{I}_M \otimes \begin{bmatrix} 1 & 0 \end{bmatrix} \right)}_{\text{resize } M \times 2M}.$$

The matrix $\mathcal{V}$ has the following block-diagonal form,

$$\mathcal{V} = \begin{bmatrix} \mathcal{V}_* & \mathbf{0} \\ \mathbf{0} & \mathcal{V}_* \end{bmatrix}.$$

Here the matrix-valued function $\mathcal{V}_* : \mathbb{R}^M \rightarrow \mathbb{R}^{2M \times 2M}$ is,

$$\mathcal{V}_* = \underbrace{\text{diag} \left(\left\{ \mathcal{P}^{(i)} \right\}_{i=1}^M \right)}_{\text{progression } 2M \times 2M} + \underbrace{[\delta_{i,j+2}]_{i,j=1}^{2M}}_{\text{shift down } 2M \times 2M} \underbrace{\text{diag} \left(\left\{ \mathcal{A}^{(i)} \right\}_{i=1}^M \right)}_{\text{aging } 2M \times 2M} \quad (31)$$

where,

$$\mathcal{P}^{(i)} = \begin{bmatrix} \sigma + \mu + \nu^{(i)} & 0 \\ -\sigma & \gamma + \mu + \nu^{(i)} \end{bmatrix}, \quad \mathcal{A}^{(i)} = - \begin{bmatrix} \nu^{(i)} & 0 \\ 0 & \nu^{(i)} \end{bmatrix}.$$

Note that we use diag in (31) instead of $\mathbf{L}_0$, because in this case we are referring to placing block 2×2 matrices in the diagonal. The next generation matrix is given by,

$$\mathcal{K} = \mathcal{F} \mathcal{V}^{-1} = \begin{bmatrix} \mathcal{F}_*(S_1^0) \mathcal{V}_*^{-1} & \theta \mathcal{F}_*(S_1^0) \mathcal{V}_*^{-1} \\ \mathcal{F}_*(S_2^0 + \varepsilon_L V^0) \mathcal{V}_*^{-1} & \theta \mathcal{F}_*(S_2^0 + \varepsilon_L V^0) \mathcal{V}_*^{-1} \end{bmatrix} \in \mathbb{R}^{4M \times 4M}.$$

Each submatrix in this expression is $\mathbb{R}^{2M \times 2M}$ with non-negative entries. The matrix function $\mathcal{F}_*(X)$ is as given above and $\mathcal{V}_*^{-1}$ can be shown to have the following form,

$$\mathcal{V}_*^{-1} = \left[\begin{matrix} (-1)^{i+j} P^{(i)-1} \prod_{k=j}^{i-1} \mathcal{A}^{(k)} \mathcal{P}^{(k)-1} \\ i, j=1 \end{matrix} \right]^M$$

Here $\mathcal{A}^{(k)}$ and $\mathcal{P}^{(k)}$ are 2×2 matrices. This notation means that $\mathcal{V}_*^{-1}$ is composed of $M \times M$ blocks of 2×2 matrices. The factors in $\mathcal{V}_*^{-1}$ correspond to probabilities and sojourn times

$$\mathcal{P}^{(i)-1} = \begin{bmatrix} \frac{1}{\sigma + \mu + \nu^{(i)}} & 0 \\ \frac{1}{\gamma + \mu + \nu^{(i)}} \frac{\sigma}{\sigma + \mu + \nu^{(i)}} & \frac{1}{\gamma + \mu + \nu^{(i)}} \end{bmatrix}, \quad \mathcal{A}^{(k)} \mathcal{P}^{(k)-1} = \begin{bmatrix} \frac{\nu^{(k)}}{\sigma + \mu + \nu^{(k)}} & 0 \\ \frac{\nu^{(k)}}{\gamma + \mu + \nu^{(k)}} \frac{\sigma}{\sigma + \mu + \nu^{(k)}} & \frac{\nu^{(k)}}{\gamma + \mu + \nu^{(k)}} \end{bmatrix}.$$

The form of $\mathcal{F}$ leads to all even-numbered rows of $\mathcal{K}$ to consist of all zeros. This yields $2M$ zero eigenvalues. Thus, the following smaller matrix $\tilde{\mathcal{K}} \in \mathbb{R}^{2M \times 2M}$ has the same nonzero eigenvalues as $\mathcal{K}$.

$$\tilde{\mathcal{K}} = \begin{bmatrix} \mathbf{L}_0(S_1^0) \mathcal{Q} & \theta \mathbf{L}_0(S_1^0) \mathcal{Q} \\ \mathbf{L}_0(S_2^0 + \varepsilon_L V^0) \mathcal{Q} & \theta \mathbf{L}_0(S_2^0 + \varepsilon_L V^0) \mathcal{Q} \end{bmatrix}$$

Here recall that in our notation, $\mathbf{L}_0(X) = \text{diag}(X)$. The matrix $\mathcal{Q}$ is given by,

$$\mathcal{Q} = [\beta_{i,j}]_{i,j=1}^M [(\mathcal{V}_*^{-1})_{2i,j}]_{i,j=1}^M$$

From the assumption that $\beta_{i,j} > 0$ for all i and j it follows easily that $\mathcal{Q}$ is irreducible.

To determine bounds on the eigenvalues of $\tilde{\mathcal{K}}$, we look at the determinant of $\tilde{\mathcal{K}} - x \mathbf{I}_{2M}$ for some dummy variable x and notice that this does not change under certain row and column operations,

$$\begin{aligned} |\tilde{\mathcal{K}} - x \mathbf{I}_{2M}| &= \begin{vmatrix} \mathbf{L}_0(S_1^0) \mathcal{Q} - x \mathbf{I}_M & \theta \mathbf{L}_0(S_1^0) \mathcal{Q} \\ \mathbf{L}_0(S_2^0 + \varepsilon_L V^0) \mathcal{Q} & \theta \mathbf{L}_0(S_2^0 + \varepsilon_L V^0) \mathcal{Q} - x \mathbf{I}_M \end{vmatrix}, \\ &= \begin{vmatrix} \mathbf{L}_0(S_1^0) \mathcal{Q} - x \mathbf{I}_M & \theta x \mathbf{I}_M \\ \mathbf{L}_0(S_2^0 + \varepsilon_L V^0) \mathcal{Q} & -x \mathbf{I}_M \end{vmatrix}, \\ &= \begin{vmatrix} \mathbf{L}_0(S_1^0 + \theta(S_2^0 + \varepsilon_L V^0)) \mathcal{Q} - x \mathbf{I}_2 & 0 \\ \mathbf{L}_0(S_2^0 + \varepsilon_L V^0) \mathcal{Q} & -x \mathbf{I}_M \end{vmatrix} \\ &= |\mathbf{L}_0(S_1^0 + \theta(S_2^0 + \varepsilon_L V^0)) \mathcal{Q} - x \mathbf{I}_2| | -x \mathbf{I}_M |, \\ &= |\mathbf{L}_0(S_1^0 + \theta(S_2^0 + \varepsilon_L V^0)) \mathcal{Q} - x \mathbf{I}_M| (-x)^M. \end{aligned}$$

This implies that there are M zero eigenvalues of $\tilde{\mathcal{H}}$ and the spectral radius can be given by,

$$R_p = \rho \left(\mathbf{L}_0 (S_1^0 + \theta (S_2^0 + \varepsilon_L V^0)) \mathcal{Q} \right).$$

Let the age-specific vaccine impact $\varphi^{(i)}$ be defined such that,

$$S_1^{0(i)} + \theta (S_2^{0(i)} + \varepsilon_L V^{0(i)}) = (1 - \varphi^{(i)} p) N^{(i)}.$$

Solving for $\varphi^{(i)}$ yields the following expression in item 3,

$$\varphi^{(i)} = (1 - \varepsilon_A) \left[(1 - \theta) + \theta (1 - \varepsilon_L) \prod_{j=1}^i (1 - \varepsilon_W^{(j)}) \right].$$

By Perron-Frobenius theorem for irreducible matrices,

$$\rho \left((1 - \varphi^{(M)} p) \mathbf{L}_0(N) \mathcal{Q} \right) \leq R_p \leq \rho \left((1 - \varphi^{(1)} p) \mathbf{L}_0(N) \mathcal{Q} \right).$$

Since $R_0 = \rho(\mathbf{L}_0(N) \mathcal{Q})$ this yields,

$$(1 - \varphi^{(1)} p) R_0 \leq R_p \leq (1 - \varphi^{(M)} p) R_0,$$

Applying (25) yields,

$$\varphi^{(M)} \leq \varphi^*(p) \leq \varphi^{(1)}.$$

This completes the proof of item 3.

To prove item 4, we first observe that $\beta_{ij} > 0$ means that if $\lambda^{(i)} > 0$ for some i , then $\lambda^{(i)} > 0$ for all i . The formula in item 4 can be derived by solving the equilibrium system of (19) under assumption that $\lambda^{(i)} = \lambda^{*(i)} > 0$ for $i = 1, \dots, M$. The system of equations for $\lambda^{*(i)}$ can be derived by substituting the equations for the endemics states to the equation

$$\lambda^{*(i)} = \sum_{j=1}^M \beta_{i,j} (I_1^{*(j)} + \theta I_2^{*(j)}),$$

and canceling out $\lambda^{*(i)}$ to derive the given system of equations in item 4.

The proof of item 5 follows from the theory on the next-generation matrix and the basic reproduction number [2,1].

We note that in item 4 of Proposition 4, we did not prove either the existence or uniqueness of the endemic steady state in the case $R_p > 1$. This is a subject for future study.

The age-specific vaccine impact $\phi^{(i)}$ reflect the relative reduction in the number of “effective” susceptibles within the age class $\mathcal{M}^{(i)}$. It is clear that the vaccine impact for the younger age classes are always higher than that for adults if there is any waning of the vaccine. We also note that the homogeneous vaccine impact, given in (8), is a better lower bound when it is known that the contact rates for older age classes for whom vaccine protection might wane is less than that between young children who are still protected by the vaccine. In Figure 3 we present an example plot of the vaccine impact and the derived bounds for $M=3$ using a contact rate that has the following form:

$$[\beta_{i,j}]_{i,j=1}^3 = b \begin{bmatrix} 0 & \chi_1 & \chi_1 \\ \chi_1 & 1 & \chi_1 \\ \chi_1 & \chi_1 & \chi_2 \end{bmatrix}. \quad (32)$$

If a vaccine does not exhibit any waning ($\alpha = 0$), we easily derive from Proposition 4 part 3 that $\phi^{(i)} = (1 - \epsilon_A)(1 - \theta + \theta(1 - \epsilon_L))$ for $i = 1, \dots, M$ and thus $\phi^*(p) = (1 - \epsilon_A)(1 - \theta + \theta(1 - \epsilon_L))$ for all p . If the vaccine does wane over time ($\alpha > 0$) this affects $\phi^{(i)}$ for $i = M$ (the oldest age class) the most. In Figure 4 we present plots illustration how the age distribution of the infected classes at endemic steady state ($I_1^{*(i)} + I_2^{*(i)}$) for different types of vaccines vary with coverage p . Here we see that in the waning vaccine model, the oldest age class form the largest fraction of the infected class at high levels of vaccine coverage.

4 Conclusions

Vaccine impact is defined to be the reduction in disease transmission per unit of vaccinated individual [11]. It can also be thought of as a measure of herd immunity due to its inverse relation to critical vaccination coverage. It is a robust measure of the effect of vaccination on disease transmission, which may be measured even if the exact mode of vaccine failure is unidentifiable [9].

In this paper we derived the vaccine impact using an imperfect vaccine model that accommodates five different modes of vaccine protection, four of which affect transmission (leakiness, primary vaccine failure, waning and relative infectiousness). The homogeneous version of this model has been fitted to pertussis incidence data from different regions of Italy in a previous paper [9]. Here we presented a mathematical analysis of both the homogeneous model and the age-structured extension. We first derived an analytic expression for the vaccine impact under the assumption of homogeneous contacts. We also proved that if there is zero leakiness, all combinations of the other vaccine parameters that lead to the same vaccine impact have the same force of infection at endemic equilibrium. This homogeneous model was extended to accommodate age structure and we derived

analytic expressions for the “age-specific vaccine impacts.” The overall vaccine impact was proven (Proposition 4, part 3) to be bounded between the age-specific impact for the oldest age class ($\phi^{(M)}$) and that for the youngest age class ($\phi^{(1)}$). This result is independent of the structure of the contact matrix. Compared to a homogeneous model, the impact of vaccination is larger in an age-structured model if the vaccine wanes and the contact rates between children is higher than that between adults.

An extension of the model in Definition 2 with continuous age structure and continuous waning rate can be considered. If instead of a constant waning rate, we have $\alpha = \alpha(a)$, a function of age, we can derive the vaccine impact for individuals at age a to be,

$$(1 - \varepsilon_A) [(1 - \theta) + \theta(1 - \varepsilon_L)(1 - \varepsilon_W(a))],$$

where $\varepsilon_W(a) = e^{-\int_0^a \alpha(s) ds}$. This is a natural extension of the expressions in (26). The analysis of such a model is a subject for future study. An additional therapeutic effect of vaccination that has not been considered is a possible increase in the recovery rate of infected vaccinated individuals. If the recovery rate from the I_2 compartment to the R compartment is increased from γ to $\bar{\gamma}$ while the transition rate from I_1 to R remains at γ , we can define

$$\varepsilon_p = \frac{\frac{1}{\mu + \bar{\gamma}}}{\frac{1}{\mu + \gamma}} = \frac{\mu + \gamma}{\mu + \bar{\gamma}}, \quad (33)$$

and the vaccine impact for the homogeneous model (8) becomes

$$\varphi = (1 - \varepsilon_A) [1 - \theta \varepsilon_p + \theta \varepsilon_p (1 - \varepsilon_L)(1 - \varepsilon_W)]. \quad (34)$$

This parameter ε_p has the same effect on steady-state dynamics as the relative infectiousness θ . Its effect on age-structured models could be included in future studies and may have interesting consequences in models that involve long infectious periods (small γ). Additionally, disease-induced mortality may be considered in future studies in order to include disease that may significantly alter the demographics of a population.

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Fig. 1.

A model of imperfect vaccine immunity incorporating three possible modes of failure in susceptibility: leakiness (blue), primary vaccine failure (green) and waning (red). The reduction in infectiousness of infected, vaccinated individuals are also taken into account (orange).

Fig. 2.
Model of imperfect vaccine immunity from Figure 1 extended to have multiple age classes.

Fig. 3.

Sample plot of the vaccine impacts for the homogeneous model and the age-structured model with three age classes ($M=3$). As proven in Proposition 4, the vaccine impact for the age-structured model is bounded between the impacts for the youngest age class ($\phi^{(1)}$) and that for the oldest age class ($\phi^{(M)}$). Here we set all transmission rates between age classes $i=1$ to 3 to be the same except for that within the oldest age class which we allow to vary (transmission matrix is given by (32) with $\chi_1 = 1$ and χ_2 changing). When $\chi_2 = 1$ the age-structured model is equivalent to the homogeneous model and the two models have the same vaccine impact. The values of both the age-structured and homogeneous vaccine impacts do not depend on b . In the standard case when the contact rates between children is assumed to be larger than those between adults ($\chi \in (0, 1)$) the age-structured vaccine impact is higher than the homogeneous vaccine impact. The parameters used in this plot are

$$\mu = \frac{1}{60} \text{ yr}^{-1}, \sigma = \frac{365}{8} \text{ yr}^{-1}, \gamma = \frac{365}{14} \text{ yr}^{-1}, \nu^{(1)} = \frac{1}{4.29} \text{ yr}^{-1} \text{ (mean age of } \mathcal{N}^{(1)} \text{ is 4 yrs),}$$

$$\nu^{(2)} = \frac{1}{15} \text{ yr}^{-1} \text{ (mean age of } \mathcal{N}^{(2)} \text{ is 16 yrs), } \theta = 0.9, \varepsilon_L = 0.1, \varepsilon_A = 0.1 \text{ and } \alpha = 0.01 \text{ yr}^{-1}.$$

This yields $\varepsilon_W^{(1)} = 0.039$, $\varepsilon_W^{(2)} = 0.11$ and $\varepsilon_W^{(3)} = 0.38$.

Fig. 4.

Sample plot of how age distribution of the infectious classes at endemic steady state

($I_1^{*(i)} + I_2^{*(i)}$ for age classes $i = 1, \dots, 3$) as a proportion of the total infected change with vaccine coverage. These plots were generated using the transmission matrix (32) with $\chi_1 = \chi_2 = 0.5$. The proportions are shown for three different types of vaccines: (a) purely leaky, (b) purely all-or-nothing and (c) purely waning, all with the same vaccine impact $\phi^*(p) = 0.8$. The parameters used in this plot are $b = 500 \text{ yr}^{-1}$,

$\mu = \frac{1}{60} \text{ yr}^{-1}$, $\sigma = \frac{365}{8} \text{ yr}^{-1}$, $\gamma = \frac{365}{14} \text{ yr}^{-1}$, $\nu^{(1)} = \frac{1}{4.29} \text{ yr}^{-1}$ (mean age of the first age class is 4 yrs), $\nu^{(2)} = \frac{1}{15} \text{ yr}^{-1}$ (mean age of the second age class is 16 yrs) and $\theta = 1$.

Table 1

Notation for the compartments of the homogeneous model.

Symbol	Compartment
V	Vaccinated individuals that have not been infected and whose protection has not waned
S_1	Susceptible individuals who (i) were never vaccinated or (ii) had experienced primary vaccine failure
E_1	Individuals in the latent stage who (i) were never vaccinated or (ii) were vaccinated but experienced primary vaccine failure
I_1	Individuals in the infectious stage who (i) were never vaccinated or (ii) were vaccinated but experienced primary vaccine failure
S_2	Vaccinated individuals whose protection has waned
E_2	Individuals in the latent stage who were vaccinated and did not experience primary vaccine failure
I_2	Individuals in the infectious stage who were vaccinated and did not experience primary vaccine failure
R	Individuals in the recovered stage
X	$(V, S_1, E_1, I_1, S_2, E_2, I_2, R)$

Table 2

Description of parameters and list of default values used for simulations. The parameters ε_L , ε_A , ε_W and θ are called the vaccine parameters and will often be considered as the tuple $(\varepsilon_L, \varepsilon_A, \varepsilon_W, \theta)$.

Symbol	Parameter	Range
μ	Birth and death rate	$[0, \infty)$
σ	Incubation rate	$[0, \infty)$
γ	Recovery rate	$[0, \infty)$
β	Transmission rate	$[0, \infty)$
θ	Relative infectiousness	$[0, 1]$
ε_L	“Leakiness,” the factor by which the probability that an individual will get infected after exposure is reduced after vaccination	$[0, 1)$
ε_A	“All-or-nothing probability,” the probability of not getting protected after vaccination	$[0, 1)$
ε_W	“Waning probability,” Probability that protection wanes in the case given that one does not get infected first	$[0, 1)$
a	Waning rate of vaccine-derived immunity, equal to $\frac{\mu\varepsilon_W}{1-\varepsilon_W}$	$[0, \infty)$
φ	Vaccine impact	$(0, 1]$
p	Constant fraction of newborns vaccinated used in steady state analysis	$[0, 1]$

Table 3

Description of the additional notation for the model with M age classes.

Symbol	Parameter	Range or Value
M	Number of age classes	$\mathbb{Z}^+$
$\beta_{i,j}$	Transmission rate between age classes i and j	$(0, \infty)$
$\nu^{(i)}$	Aging rate from age class i to $i + 1$	$(0, \infty)$
$\nu^{(M)}$	Aging rate from the last age class M , fixed at zero	0
$\varepsilon_W^{(i)}$	Probability of vaccine immunity waning in the i th age class, $\varepsilon_W^{(i)} = \frac{\alpha}{\alpha + \mu + \nu^{(i)}}$	$[0, 1]$
$\zeta^{(i)}$	Probability of aging from age class i to $i + 1$.	Equation (16)
$N^{(i)}$	Fraction of population in i th age class at steady state.	Equation (17)
$\phi^{(i)}$	Age-specific vaccine impact.	Equation (26)
$\phi^*(p)$	Effective vaccine impact.	$\frac{1}{p} \frac{R_0 - R_p}{R_0}$