Assessing the potential impact of *Salmonella* vaccines in an endemically infected dairy herd

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ABSTRACT

*Salmonella* spp. in cattle contribute to bacterial foodborne disease for humans. Reduction of *Salmonella* prevalence in herds is important to prevent human *Salmonella* infections. Typical control measures are culling of infected animals, vaccination, and improved hygiene management. Vaccines have been developed for controlling *Salmonella* transmission in dairy herds; however, these vaccines are imperfect and a variety of vaccine effects on susceptibility, infectiousness, *Salmonella* shedding level, and duration of infectious period were reported. To assess the potential impact of imperfect *Salmonella* vaccines on prevalence over time and the eradication criterion, we developed a deterministic compartmental model with both replacement (cohort) and lifetime (continuous) vaccination strategies, and applied it to a *Salmonella* Cerro infection in a dairy farm. To understand the uncertainty of prevalence and identify key model parameters, global parameter uncertainty and sensitivity analyses were performed. The results show that imperfect *Salmonella* vaccines reduce the prevalence of *Salmonella* Cerro. Among three vaccine effects that were being considered, decreasing the length of the infectious period is most effective in reducing the endemic prevalence. Analyses of contour lines of prevalence or the critical reproduction ratio illustrate that, reducing prevalence to a certain level or zero can be achieved by choosing vaccines that have either a single vaccine effect at relatively high effectiveness, or two or more vaccine effects at relatively low effectiveness. Parameter sensitivity analysis suggests that effective control measures through applying *Salmonella* vaccines should be adjusted at different stages of infection. In addition, lifetime (continuous) vaccination is more effective than replacement (cohort) vaccination. The potential application of the developed vaccination model to other *Salmonella* serotypes related to foodborne diseases was also discussed. The presented study may be used as a tool for guiding the development of *Salmonella* vaccines.

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1. Introduction

*Salmonella* spp. are a leading cause of bacterial foodborne disease, known to affect both humans and animals. In the United States, human salmonellosis results in an estimated 1.4 million illnesses and 550 deaths annually (Mead et al., 1999). Cattle were recognized as a reservoir of many of the more than 2500 *Salmonella* serotypes (Baumler, 2004). Human infections are usually associated with the consumption of contaminated meat (especially poultry and pork), eggs, milk, water, dairy products, fresh produce, or direct contact with infectious animals and their environment (el-Gazzar and Marth, 1992; Cody et al., 1999; Gupta et al., 2003; Olsen et al., 2004; Dechet et al., 2006; Leedom, 2006). Although only five serotypes account for approximately 60% of the human cases, all *Salmonella* serotypes are potentially considered pathogenic (Baumler, 2004; van Kessel et al., 2007). Foodborne *Salmonella* outbreaks are often associated with contaminated eggs and poultry products, but unpasteurized milk, dairy products, and ground beef from dairy herds also have a significant contribution (Troutt and Osburn, 1997; Dechet et al., 2006; van Kessel et al., 2007).

*Salmonella* transmission in dairy herds is via direct horizontal fecal-oral route, vertical transmission from an adult to its offspring, and indirect transmission through the contaminated environment (Baumler, 2004). To lower the risk of *Salmonella* infections, reducing the prevalence in dairy cattle through preventing key transmission routes within and between herds is necessary. It is, however, difficult to control *Salmonella* infection in herds. A broad spectrum of epidemiological transmission patterns...
have been observed among various *Salmonella* serotypes, from transient epidemics to long term endemic persistence (Wray et al., 1989; Anderson et al., 2001; Humphrey, 2004; Xiao et al., 2005).

Intervention strategies typically implemented in dairy herds, aimed at reducing the prevalence of *Salmonella* infection, are culling of infectious animals, vaccination, and improved hygiene management. Vaccination, as a control measure, has been extensively studied and applied for preventing the invasion and transmission of many human infectious diseases, and has resulted in a better control or elimination of these infectious diseases (Anderson and May, 1991; Keeling and Rohani, 2008). Commercial *Salmonella* vaccines, such as killed bacterins and a number of attenuated *Salmonella* strains, have been developed for preventing *Salmonella* transmission and clinical salmonellosis in cattle (Wray et al., 1977; Smith et al., 1984; Stocker, 1988). Various studies indicate that available *Salmonella* vaccines are imperfect (i.e., vaccines provide partial protection on individual animals and/or their protection wanes over time), and the effects of vaccines are different (Smith et al., 1980; Weber et al., 1993; Steinbach and Meyer, 1994; House et al., 2001; House and Smith, 2004; Denagamage et al., 2007; Heider et al., 2008). Some *Salmonella* vaccines were found to decrease susceptibility to infection, while others decreased disease-induced mortality or shortened the infectious period. Still other vaccines were found to reduce infectiousness, either directly or by reducing *Salmonella* shedding level. The impact of vaccines on prevalence ranged from good to ineffective.

This study aimed to assess the potential impact of imperfect *Salmonella* vaccines with single or multiple vaccine effects on the dynamics of *Salmonella* infection in a dairy herd using a modeling approach. Recently, a few compartmental models have been developed to understand the dynamics of *Salmonella* infection in dairy herds (Xiao et al., 2005, 2006; Chapagain et al., 2007; Lanzas et al., 2008). However, these models, to date, have been confined to describing the dynamics without vaccination. In addition, a comprehensive assessment of model dynamics, as discussed by Marino et al. (2008), should include the analysis of global parameter uncertainty and sensitivity, while previous *Salmonella* models focused on using a set of baseline values of model parameters.

As understanding of infection dynamics with vaccination is critical for designing and deploying efficient control measures, modeling of *Salmonella* transmission with imperfect vaccines in dairy herds will be valuable. In this study, we developed a deterministic compartmental model for imperfect *Salmonella* vaccines with two types of vaccination strategies, replacement (cohort) and lifetime (continuous) vaccination. This model was built on the previous models proposed by Xiao et al. (2005) and Chapagain et al. (2007). Because the results of whole-herd diagnostic tests were available, the model was parametrized using field data from an outbreak of *Salmonella* Cerro infection in a Pennsylvania dairy farm. Several recent publications have shown *Salmonella* Cerro to be among the more prevalent serovars in cattle (Morrow et al., 2005; Kunze et al., 2008; Pandya et al., 2009). The farm under study, participating in a cooperative Pennsylvania dairy farm. Several recent publications have shown modeling of parameter uncertainty and sensitivity, while previous Marino et al. (2008), should include the analysis of global to describing the dynamics without vaccination. In addition, a criterion were affected by various effects of imperfect vaccines, and to find which vaccine effect was most effective in reducing prevalence. Secondly, we wanted to offer some insights for guiding the development of imperfect *Salmonella* vaccines, when two or more vaccine effects simultaneously protected individual animals. Finally, using global parameter uncertainty and sensitivity analyses, we wanted to examine the uncertainty of prevalence, and to identify the most influential model parameters for designing effective control measures.

### 2. Materials and methods

#### 2.1. Farm description

The dairy farm where the outbreak of *Salmonella* Cerro occurred is located in Pennsylvania. The milking herd consisted of approximately 100 dry and lactating cows that were housed in a free stall barn. Heifers on this farm were transferred at 6–8 months of age to a contract heifer grower and, as replacement animals, they returned to the milking herd prior to their first calving.

To monitor the dairy farm for a number of zoonotic and animal health pathogens, a longitudinal study including quarterly blood sampling and bi-annual fecal sampling started in March 2004. After initially detecting *Salmonella* Cerro infection on the farm, a more intensive sampling program was implemented, with fecal samples for all cows and environmental samples collected every 6–8 weeks for 2 years. The results of fecal sample testing indicated a widespread outbreak of *Salmonella* Cerro in this farm (van Kessel et al., 2007). The prevalence after the outbreak persisted at a relatively high level due to the unusually long infectious period of *Salmonella* Cerro, ~7.16 months (Chapagain et al., 2007). No apparent clinical symptoms were associated with the high prevalence of *Salmonella* Cerro in this herd. To reduce the high prevalence, a vaccination program was initiated. During the approximate annual cycle of cows (an annual cycle consists of dry period—non-lactating, ~45 days, and giving birth followed by a lactating period, ~320 days), every second unvaccinated cow in the dry period was vaccinated before returning to the lactation period, while vaccinated cows were re-vaccinated when entering the dry period again. In addition, every second replacement animal was vaccinated.

#### 2.2. Model formulation

Fig. 1 illustrates a compartmental vaccination model of *Salmonella* Cerro transmission in a milking herd. According to the infection and vaccination status, animals were divided into six compartments: susceptible animals (S), infectious animals (I), recovered animals (R), susceptible vaccinees (X), infected vaccinees (Y), and recovered vaccinees (Z). The contaminated environment (W) represented a source of the indirect transmission. As shown in the previous work by Chapagain et al. (2007), the infectious period of *Salmonella* Cerro follows a gamma distribution rather than the usual exponential distribution. The gamma distribution function of infectious periods was modeled by subdividing the infectious compartment into n infectious stages $I_k$ ($k = 1, 2, \ldots, n$), where the average duration for each stage is $1/\gamma^k$ (Lloyd, 2001a,b; Chapagain et al., 2007). For simplicity, we assumed that the infectious period of infected vaccinees in the compartment Y also follows a gamma distribution.

The vaccination program implemented on the farm was simulated by both replacement (cohort) and lifetime (continuous) vaccination strategies. In replacement cohort vaccination, a proportion $p_1$ of replacement animals was vaccinated and moved to the compartment of susceptible vaccinees (X). In lifetime
(continuous) vaccination, animals were vaccinated when passing through the dry period. A proportion $p_2$ of unvaccinated animals entering the dry period in compartments $S$, $I_k$, and $R$ was vaccinated and moved to corresponding vaccinated compartments $X, Y_k,$ and $Z$, respectively, at effective rate $p_2 \psi$, where $\psi$ denotes the rate at which animals enter and exit the dry period. The vaccination process occurred through the dry period, and vaccinated animals acquired on average their vaccine-induced immunity in 20 days after vaccine was injected. However, because animals in the dry period were housed in a free stall under one roof with the lactating animals, we did not explicitly model the dry and lactating periods and only quantified net movements in and out of compartments. The duration of animals acquired their vaccine-induced immunity is relatively short, ~20 days = 0.677 months, compared to the duration of infection-induced immunity loss, ~4.5 months (see Table 1). Therefore, the rate $\psi$ is the rate of animals entering and exiting the dry period and should not be understood as the rate of lifetime (continuous) vaccination. The remaining animals $(1 - p_2)$ not vaccinated in the dry period in compartments $S, I_k,$ and $R$ returned to compartments $S, I_k,$ and $R$, respectively. Vaccinated animals in compartments $X, Y_k,$ and $Z$, entering and exiting the dry period at rate $\psi$, were revaccinated and returned to compartments $X, Y_k,$ and $Z$, respectively. In addition, we have assumed that the rate of loss of vaccine-induced immunity is smaller than the rate at which animals enter and exit the dry period; thus, vaccinees were revaccinated before the vaccine-induced immunity was lost.

Animals in the susceptible compartment $S$ were either infected at the rate of force of infection, $\lambda$, or moved to the vaccinated compartment $X$ at effective rate $p_2 \psi$. The susceptible animals ($S$), upon infection, entered the infectious compartment ($I_1$) (here, we assumed no latent period). Animals in infectious compartments $I_k$ ($k = 1, 2, \ldots, n$) shed *Salmonella* Cerro in feces at rate $\sigma$. Infectious animals entered the recovered compartment ($R$), when infection-induced immunity provided a temporal protection from *Salmonella* infection. Animals in the recovery compartment ($R$) lost their immunity at rate $\phi_1$ and moved back to the susceptible compartment ($S$).

*Salmonella* vaccination on dairy cows may induce a biological response in a vaccinee, reducing susceptibility, the degree of infectiousness, shedding level, and/or infectious period. In this study, the vaccine effect (VE) was defined as 1 minus some measure of relative risk (RR) in the vaccinated group compared with the unvaccinated group, i.e., $VE = 1 - RR$ (Halloran et al., 1997, 1999). Because vaccine effects of imperfect *Salmonella* vaccines were assumed to range from 0 to 1, the RR in this study cannot be greater than 1. The vaccine effect on susceptibility ($q$) denotes the ratio of the reduced transmission probability through decreasing susceptibility of vaccinated susceptibles over the transmission probability associated with unvaccinated susceptibles. The vaccine effect on infectiousness ($g$) denotes the transmission probability ratio of vaccinated and unvaccinated infecteds, as well as the proportional reduction in the *Salmonella* shedding level in vaccinated infecteds, because infectiousness and pathogen shedding levels are proportional. The vaccine effect on the infectious period ($h$) denotes the ratio of the duration of vaccinated over unvaccinated infectious animals. All values of vaccine effects range from 0 to 1, with 0 indicating no effectiveness and 1 representing perfect protection.

**Table 1** Parameters used in the model.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu$</td>
<td>Average recruitment or death rate (per day)</td>
<td>0.001</td>
<td>Chapagain et al. (2007)</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Transmission rate (per animal per day)</td>
<td>0.0187</td>
<td>Estimated</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>Recovery rate (per day)</td>
<td>0.0047</td>
<td>Chapagain et al. (2007)</td>
</tr>
<tr>
<td>$n$</td>
<td>number of stages of infectious compartment</td>
<td>128</td>
<td>Chapagain et al. (2007)</td>
</tr>
<tr>
<td>$\phi_1$</td>
<td>Rate of immunity-loss ($R$) (per day)</td>
<td>0.0073</td>
<td>Chapagain et al. (2007)</td>
</tr>
<tr>
<td>$\eta$</td>
<td>Indirect transmission rate (per infectious unit per day)</td>
<td>$1.3 \times 10^{-11}$</td>
<td>Xiao et al. (2005, 2006)</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Shedding rate (per day)</td>
<td>$1.3 \times 10^8$</td>
<td>Xiao et al. (2005, 2006)</td>
</tr>
<tr>
<td>$\delta$</td>
<td>Rate of removing pathogen from environment (per day)</td>
<td>0.99</td>
<td>Xiao et al. (2005, 2006)</td>
</tr>
<tr>
<td>$\phi_2$</td>
<td>Rate of immunity-loss ($Z$) (per day)</td>
<td>0.0073</td>
<td>Assumed</td>
</tr>
<tr>
<td>$\psi$</td>
<td>Rate of animals entering and exiting the dry period (per day)</td>
<td>0.0028</td>
<td>Estimated</td>
</tr>
<tr>
<td>$p_1$</td>
<td>Proportion of vaccinated replacement animals</td>
<td>0–1</td>
<td></td>
</tr>
<tr>
<td>$p_2$</td>
<td>Proportion of vaccinated animals during dry period</td>
<td>0–1</td>
<td></td>
</tr>
<tr>
<td>$q$</td>
<td>Vaccine effect on susceptibility</td>
<td>($e - 0$)</td>
<td></td>
</tr>
<tr>
<td>$g$</td>
<td>Vaccine effect on infectiousness/shedding level</td>
<td>($e - 0$)</td>
<td></td>
</tr>
<tr>
<td>$h$</td>
<td>Vaccine effect on infectious period</td>
<td>($e - 0$)</td>
<td></td>
</tr>
</tbody>
</table>
Susceptible vaccinees (X) were infected at rate \((1 - q)\lambda\), where the susceptibility of susceptible vaccinees was reduced by a factor \(1 - q\). Infected vaccinees in the compartment \(Y_i\) \((i = 1, 2, \ldots, n)\) reduced infectiousness and *Salmonella* shedding level by a factor \(1 - g\). The infectious period of an infected vaccinee was reduced by a factor \(1 - h\). Infected vaccinees entered the compartment \(Z\) when infection-induced immunity provided a temporal protection and became recovered vaccinees. Recovered vaccinees \((Z)\) moved back to the compartment of susceptible vaccinees \((X)\) at rate \(\phi_2\). We thereby distinguished infection-induced immunity and vaccine-induced immunity.

The force of infection, \(\lambda\), includes direct transmission from infectious animals \((I_k)\) and infected vaccinees \((Y_i)\), and indirect transmission from the contaminated environment \((W)\). The shedding rate of infectious material to the environment is denoted by \(W\). The contaminated environment \((W)\) infected susceptible animals \((S\) and \(X)\) at rates \(\eta\) and \((1 - q)\eta\), respectively. All animals were subject to the same average death (or culling) rate \(\mu\). To maintain the constant population \(N\) (sum of animals in each compartment), the animal replacement rate was also assumed to be \(\mu\).

### 2.3. The system of nonlinear ordinary differential equations

The system of nonlinear ordinary differential equations describing the dynamics of *Salmonella* Cerro infection with vaccination in Fig. 1 are

\[
\frac{dS}{dt} = (1 - p_1)\mu N + \phi_1 R - (\lambda + p_2\psi + \mu)S, \tag{1}
\]

\[
\frac{dX}{dt} = p_1\mu N + \phi_2 Z + p_2\psi S - ((1 - q)\lambda + \mu)X, \tag{2}
\]

\[
\frac{dY_l}{dt} = \lambda S - (\eta\gamma + \mu + p_2\psi)Y_l, \tag{3}
\]

\[
\frac{dY_k}{dt} = \eta\gamma Y_{k-1} - (\eta\gamma + \mu + p_2\psi)Y_k, \quad 2 \leq k \leq n, \tag{4}
\]

\[
\frac{dY_1}{dt} = (1 - q)\lambda X + p_2\psi Y_1 - \left(\frac{\eta\gamma}{1 - h} + \mu\right)Y_1, \tag{5}
\]

\[
\frac{dY_i}{dt} = \frac{\eta\gamma}{1 - h} Y_{i-1} + p_2\psi Y_i - \left(\frac{\eta\gamma}{1 - h} + \mu\right)Y_i, \quad 2 \leq i \leq n, \tag{6}
\]

\[
\frac{dR}{dt} = \eta\gamma I_n - (\phi_1 + \mu + p_2\psi)R, \tag{7}
\]

\[
\frac{dZ}{dt} = \eta\gamma Y_n + p_2\psi R - (\phi_2 + \mu)Z, \tag{8}
\]

\[
\frac{dW}{dt} = \sigma I + (1 - g)\sigma Y - (\delta + \eta)W, \tag{9}
\]

where \(I, Y, \lambda\), and \(N\) are

\[
I = \sum_{i=1}^{n} I_i, \quad Y = \sum_{i=1}^{n} Y_i, \tag{10}
\]

\[
\lambda = \beta \frac{X + (1 - g)Y}{\lambda + \eta W}, \tag{11}
\]

\[
N = S + I + R + X + Y + Z. \tag{12}
\]

The analytical solutions of the dynamic system (Eqs. (1)–(9)) of *Salmonella* Cerro infection were not available; thus, numerical approaches were applied. In mathematical epidemiology a threshold quantity governing the system dynamics is the basic reproduction ratio \(R_0\). The \(R_0\) is the number of secondary cases infected by a primary infectious individual during the whole infectious period in a fully susceptible population. For many epidemiological models, \(R_0 > 1\) implies that the pathogen will invade and persist in the population, while \(R_0 < 1\) indicates that the pathogen will die out. Exceptions to this \(R_0\) dogma, however, exist for certain vaccination model systems, in which backward bifurcation occurs (Krbić-Zaleta and Velasco-Hernandez, 2000; Arino et al., 2003; Elbasha and Gumel, 2006; Sharomi et al., 2007). For the present model, given the parameters in Table 1, only forward bifurcation was found numerically.

The reproduction ratio \(R(p_1, p_2)\) under vaccination with proportion parameters \(p_1\) and \(p_2\) for the dynamic system (Eqs. (1)–(9)) is the largest eigenvalue of the next generation matrix (Diekmann and Heesterbeek, 2000; van den Driessche and Watmough, 2002; Xiao et al., 2005). For the gamma distribution of infectious periods, the analytical expression of \(R(p_1, p_2)\) is tedious. For simplicity and without loss of general understanding, we illustrated the reproduction ratio using a simpler expression of \(R(p_1, p_2)\) for a special case \((n = 1)\) of the gamma distribution. A detailed derivation of the general \(R(p_1, p_2)\) for the gamma distribution of infectious periods was given in Appendix A. All numerical calculations presented in the results section were based on the gamma distribution of infectious periods with \(n = 128\).

The reproduction ratio \(R(p_1, p_2)\) for \(n = 1\), i.e., exponential distribution of infectious periods, is (see Appendix B):

\[
R(p_1, p_2) = \frac{b + \eta\sigma}{p_2\psi + \gamma + \mu} + \frac{(1 - q)g}{\gamma(1 - h) + \mu}, \tag{13}
\]

In the case of replacement (cohort) vaccination \((p_2 = 0)\), the reproduction ratio was further simplified:

\[
R(p_1, p_2 = 0) = R_0(1 - p_1) \left(1 - \frac{R_0}{R_0}\right) = R_0(1 - p_1) \Phi, \tag{14}
\]

\[
= R_0(1 - p_1) \left(1 - (1 - q)(1 - g)\frac{\gamma + \mu}{\gamma(1 - h) + \mu}\right), \tag{15}
\]

where \(R_0\) and \(R_0\) are the basic reproduction ratios for the cases of non-vaccination and fully vaccinated populations, respectively (see Appendix C). The overall population-level vaccine efficacy \(\Phi\) was defined as \(1 - R_0/R_0\) and it is a function of vaccine effects \(q, g,\) and \(h\). Therefore, if \(\Phi > 0\), vaccines will have a beneficial effect in reducing the reproduction ratio. Otherwise, vaccines may have zero (the reproduction ratio does not change) or even negative effects (the reproduction ratio increases).

For the case of lifetime (continuous) vaccination \((p_1 = 0)\), however, as seen from expression (13), the overall vaccine efficacy \(\Phi\) cannot be written as a simple expression with an intuitive explanation. Nonetheless, the first term of \(R(p_1 = 0, p_2)\) in expression (13) is the number of secondary infections caused by a primary infectious animal \((I)\) plus the number of secondary infections caused by the same primary infectious animal who was vaccinated \((Y)\) at any point in the infectious period. The second term of \(R(p_1 = 0, p_2)\) in expression (13) is the number of secondary infections caused by a primary infected vaccinee \((Y)\). For the case of both replacement (cohort) and lifetime (continuous) vaccination \((p_1 \neq 0, p_2 \neq 0)\), the same explanation still applies. In the present study, we simulated the implemented vaccination program with the same coverage of replacement (cohort) and lifetime (continuous) vaccination, i.e., \(p_1 = p_2 = p = 0.5\).

The baseline values of parameters used in the model are summarized in Table 1. The epidemiological and demographic parameters, such as \(\gamma, \phi_1,\) and \(\mu\), were estimated from fecal culture data (Chapagain et al., 2007). The transmission rate \(\beta\) was
estimated by fitting the predicted prevalence to the observed prevalence. The rate of pathogen removal from the environment (δ = 0.99 per day) represented relatively strict hygiene management on the farm (Xiao et al., 2005, 2006).

To evaluate how imperfect Salmonella vaccines with single or multiple vaccine effects impact the prevalence of Salmonella Cerro and the eradication criterion, we numerically solved the dynamic system (Eqs. (1)–(9)) and evaluated the reproduction ratio \( R(p_1 = p, p_2 = p) \). The simulated vaccination program was initiated when Salmonella Cerro infection reached the approximated (asymptotically) endemic equilibrium. Here, we assumed that vaccination was initiated at the 48th month.

2.4. Parameter uncertainty and sensitivity analyses

Parameters in Table 1 may be grouped into three types: epidemiological, demographic and vaccination-related. The baseline

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**Fig. 2.** Simulated prevalence (solid line) fitted to the observed prevalence of Salmonella Cerro without vaccination.

**Fig. 3.** Transient prevalence at 3 months (I) and 1 year (II), and long term prevalence at 16 years (III) by single vaccine effect after initiation of the vaccination program. Square: \( g \), vaccine effect on infectiousness/shedding level; circle: \( q \), vaccine effect on susceptibility; triangle: \( h \), vaccine effect on infectious period.
values of epidemiological and demographic parameters were estimated from longitudinal fecal culture data; for other unknown parameters related to the environment, sensible assumptions were used (Xiao et al., 2005, 2006). Accuracy of baseline values of model parameters depends on methods used for estimation and quality of data; thus, parameters are inevitably associated with uncertainty to some extent. Vaccine effects, represented by \( q \), \( g \), and \( h \), are more difficult to estimate accurately, as imperfect Salmonella vaccines may have multiple vaccine effects. Analyses of parameter uncertainty and sensitivity are, therefore, critical to assess the impact and identify the key parameters of Salmonella vaccination on the dynamics of infections.

In this study we used the Latin-Hypercube sampling (LHS) technique to create parameter samples. The uncertainty of prevalence was evaluated, and the model parameter sensitivity was measured by partial rank correlation coefficient (PRCC) (Helton and Davis, 2002, 2003; Helton et al., 2006, 2007; Saltelli et al., 2000; Saltelli, 2002, 2004; Marino et al., 2008). Most model parameters were varied within the ranges of \( \pm 25\% \) of their baseline values, while vaccine effects, \( q \), \( g \), and \( h \), were varied in the range of 0.2–0.8. Parameter sample size for global parameter uncertainty and sensitivity analyses was 1000. The uncertainty of the prevalence over time was obtained by numerically evaluating the dynamic system (Eqs. (1)–(9)) 1000 times and each with a different set of input parameter values created by LHS. The curve of PRCC over time for each model parameter was obtained by connecting PRCC at all specified time points.

3. Results

3.1. Prevalence of Salmonella Cerro without vaccination

When \( p_1 = p_2 = 0 \), no vaccination was implemented. In Fig. 2, we reproduced the results of the previous study by Chapagain et al. (2007). The simulated prevalence using baseline values of model parameters in Table 1 was fitted to the observed prevalence of Salmonella Cerro. After the outbreak, the model showed that an asymptotically endemic state was established in five years.

3.2. Vaccine effects in reducing prevalence

Fig. 3 shows that prevalence is reduced when increasing any single vaccine effect, \( q \), or \( g \), or \( h \), alone. Transient prevalence at 3
months and 1 year after vaccination program initiated was plotted in groups I and II, respectively, while the long term prevalence was given in group III at 16 years (in our numerical simulations, 16 years was long enough to obtain a new asymptotically stable prevalence). In each group, there were three different prevalences. It is clear that vaccine effect on infectious period \((h)\) had largest impact on the reduction of endemic prevalence. In the case of groups I and II, the vaccine effect on susceptibility \((q)\) had larger impact on the reduction of endemic prevalence than the vaccine effect on infectiousness/shedding level \((g)\); while in the case of group III, when \(q\) or \(g\) were greater than 0.90, vaccine effect on infectiousness/shedding level \((g)\) had a larger impact than that of vaccine effect on susceptibility \((q)\) in the reduction of endemic prevalence.

To show Salmonella vaccines with two effects \((q\text{ and }g)\) together, contour plots of prevalence at 1 and 16 years after the initiation of vaccination were given in Figs. 4(a) and (b). On each contour line, the same prevalence was conserved, but vaccine effects on susceptibility and infectiousness/shedding level, \(q\) and \(g\), were varied. From Figs. 4(a) and (b), we observed that to reduce prevalence to a desired level (on a contour line) at a specified time point (1 year) or at the long term (16 years), there were many combinations of vaccine effects, \(q\) and \(g\), available. The impact of three vaccine effects \((q, g, \text{ and } h = 0.5)\) together on prevalence was shown by contour plots of prevalence in Figs. 4(c) and (d).

### 3.3. Vaccine effects on the eradication criterion

In Fig. 5(a), the critical surface of \(R(q, g, h) = 1\) as a function of three vaccine effects, \(q, g, \text{ and } h\), was plotted at \(p_1 = p_2 = p = 0.5\).

Any point formed by \((q, g, h)\) above the \(R = 1\) surface indicates that vaccination will eradicate the pathogen in the long term, while at any point below this critical surface, vaccination will not eliminate the pathogen from herds. In the latter case, vaccination still reduces the asymptotically endemic Salmonella prevalence to a certain level if the reproduction ratio with vaccination is less than that without vaccination, i.e., \(R(q, g, h) < R(0, 0, 0)\). When vaccine effect on infectious period was zero, i.e., \(h = 0\), the critical surface in Fig. 5(a) became a simple critical curve in Fig. 5(b). In the case of only two vaccine effects being considered \((q \neq 0, g \neq 0, h = 0)\), when increasing the proportion \(p\) of vaccinated animals both in replacement (cohort) and lifetime (continuous) vaccination, the series of critical curves \(R(q, g) = 1\) moved toward the origin. In the case of three vaccine effects, when vaccine effect on infectious period was fixed, for example, \(h = 0.7\), Fig. 5(d) shows that the same series of critical curves \(R(q, g) = 1\) moved closer to the origin when compared to Fig. 5(c).

### 3.4. Uncertainty of prevalence

Fig. 6 shows the uncertainty of prevalence with the description of summary statistics. A relatively broad range of prevalence was observed from the 10th percentile to the 90th percentile. The mean values and medians were almost overlapped. The dynamics of Salmonella Cerro infection with no vaccination, only replacement (cohort) vaccination, only lifetime (continuous) vaccination, and both vaccination strategies, were simulated and plotted in Figs. 6(a), (b), (c), and (d), respectively. The trend of prevalence in Figs. 6(b)–(d) went down over time.
3.5. Parameter sensitivity analysis

In Fig. 7(a), model parameter sensitivities measured by PRCC are given. The shaded area representing PRCC values that were not significantly correlated to the model prevalence. The significance of PRCC values was tested using a $t$ statistic. Here, we applied Bonferroni method for multiple PRCC value corrections (after correction, PRCC values within the shaded area having their $p$-value $> 0.05$).

Because the values of PRCC for each model parameter were time-dependent, key model parameters were different at different time points. In the early phase of the outbreak, for example, the 4th month (see Fig. 7(b)), the most influential model parameters for prevalence were transmission rate ($\beta$), indirect transmission rate ($\eta$), Salmonella shedding rate ($\alpha$), the rate of pathogen removal from the environment ($\delta$), and general replacement rate ($\mu$). All other model parameters were insignificant. The effect of direct transmission rate ($\beta$) was positively correlated with prevalence, which suggests that if we increase direct transmission rate ($\beta$) prevalence increases.

When prevalence approached its asymptotically endemic state, for example, the 46th month (see Fig. 7(c)), the most influential model parameters were recovery rate ($\gamma$), transmission rate ($\beta$), and rate of loss of infection-induced immunity ($\phi_1$). All other...
parameters were also significantly related to the model prevalence, but the correlation was relatively weak. The effect of recovery rate ($\gamma$, infectious period is $1/\gamma$) was negatively correlated with prevalence, which indicates that if we increase recovery rate ($\gamma$, or decrease infectious period) prevalence decreases. In addition, some model parameters, such as transmission rate ($\beta$) and the general replacement rate ($\mu$), changed their signs over the time course, indicating that the impact of them at different stages of the outbreak varied.

After vaccination initiated at the 48th month, the impact of vaccine effects, $q$, $g$, and $h$, on prevalence can be seen in Fig. 7(a). For a vaccine with multiple vaccine effects on susceptibility, infectiousness/shedding level, and infectious period, all vaccine effects were statistically significant. However, during the early stage of vaccination, vaccine effect on infectious period was more important than the other two vaccine effects, while four years after vaccination started (96th months), these three vaccine effects were similar.

Fig. 7. Global parameter sensitivity analyses for prevalence over time with a simulated vaccination program. The gray area represents PRCC values that are not significantly different from zero. (a) Model parameter sensitivities measured by PRCC over time; (b) and (d) snapshots of model parameter sensitivities in the early outbreak of Salmonella Cerro (at the 4th month) and the asymptotically endemic state (at the 46th month).
4. Discussion

4.1. Effects of imperfect Salmonella vaccines

The results have shown that prevalence decreases as vaccine effects increase. However, the impacts of different vaccine effects on prevalence and the eradication criterion were different. Among three vaccine effects that were being considered, reduction of the infectious period was most effective in reducing the endemic prevalence. This finding was supported both by studies of single vaccine effect alone (Fig. 3) and global parameter sensitivity analysis (Fig. 7(a)).

Although reduction of susceptibility alone was more effective at decreasing prevalence than reduction of infectiousness/shedding level alone, this may not be true when the value of a vaccine effect ($g$ or $q$) is greater than 0.9 for a long term (16 years in group III of Fig. 3). This indicates that, for the purpose of reducing the prevalence in the short term, vaccines that reduce susceptibility would be a better choice, but for the purpose of long term elimination, vaccines that reduce infectiousness/shedding level would be a better choice. This point is valid only when either vaccine effect is relatively high, $>0.9$.

4.2. Development and selection of vaccines with multiple effects

Figs. 4 and 5 provided a useful illustration for guiding the development and selection of imperfect vaccines. Any point on the plane of vaccine effects, $q$ and $g$, in Fig. 4, represents a possible vaccine which reduces susceptibility and infectiousness/shedding level. Along a single contour line of prevalence (prevalence is the same on each contour line), potential vaccines may be selected. For example, if our goal is to reduce the asymptotically endemic prevalence (50% without vaccination) to 35% in one year, we may find the contour line of prevalence of 35.5% in Fig. 4(a), and then examine the possible values of vaccine effects ($q$ and $g$) along this contour line. The vaccines chosen could reduce only susceptibility (i.e., $q = 0.72$, $g = 0$) or infectiousness/shedding level (i.e., $q = 0$, $g = 0.97$), or both together (i.e., $q = 0.52$, $g = 0.60$). Similarly, if our goal is to eradicate the infection in the long term, we may use Figs. 4(b) and 5(b) to guide the selection of potential vaccines. From the contour lines of prevalence and the eradication criterion, we noticed that a vaccine with a higher value of vaccine effect reducing susceptibility or infectiousness/shedding level alone can be replaced by a vaccine with lower values in both vaccine effects. This vaccine could be developed by a combination of two independently functioning vaccines, one with a single vaccine effect on susceptibility and the other reducing infectiousness/shedding level.

The coverages $p_1$ and $p_2$ of animals vaccinated in both replacement (cohort) and lifetime (continuous) vaccination also have an important role to the selection of potential vaccines. If the proportion $p$ ($= p_1 = p_2$) of animals vaccinated in replacement (cohort) and lifetime (continuous) vaccination increases ($p > 0.5$), the range of choosing effective vaccines is enlarged (see Fig. 5(c)). This means that, for the same effort of eradication, higher proportions of animals vaccinated require relatively lower effectiveness of vaccines. Extension of the above discussion to vaccines with three vaccine effects is straightforward. Figs. 4(c) and (d), and Fig. 5(d) illustrated contour plots of prevalence and a series of eradication criterion curves, respectively, when the vaccine effect on the infectious period was halved ($h = 0.5$). These figures show that, for vaccine selection, the range of vaccine effects on susceptibility ($q$) and infectiousness/shedding level ($g$) are further enlarged.

4.3. Design of effective control strategies

As shown in Fig. 7(a), model parameter sensitivity was time-dependent. Accordingly, this suggests that effective control measures at different stages of Salmonella Cerro infection should be adjusted. In the early phase of outbreak, as shown in Fig. 7(b), the most influential parameters were direct transmission rate ($\beta$) and indirect transmission rate ($\eta$); thus, control measures aimed at reducing direct and indirect transmissions were most effective in reducing prevalence. This implies that, if vaccination was considered, vaccines having effects in reducing susceptibility and infectiousness/shedding level would be most effective in the early outbreak. Of course, improving hygiene management was also capable of reducing Salmonella transmission rates ($\beta$ and $\eta$). In contrast, in the asymptotically endemic state at the 46th month, the most important parameter (see Fig. 7(c)) was the recovery rate ($\gamma$; infectious period is 1/\gamma$). Therefore, if vaccination was a desired control measure, vaccines targeted to the reduction of infectious period would be most effective in an endemically infected herd.

In the simulated vaccination program, we used the same proportion ($p_1 = p_2 = p = 0.5$) of vaccinated animals for both replacement (cohort) and lifetime (continuous) vaccination. However, we may release this constraint in the simulation study. As shown in Figs. 6(a)–(d), it is obvious that lifetime (continuous) vaccination alone (Fig. 6(c)) was more effective than replacement (cohort) vaccination alone (Fig. 6(b)). Of course, the most effective vaccination was to apply these two types of vaccination strategies simultaneously (Fig. 6(d)).

4.4. Modeling approach

Mathematical modeling approaches help us not only understand the dynamics of many infectious diseases, but also evaluate the effectiveness of various control methods; however, several limitations exist in the deterministic compartmental model as applied in this study. The compartmental model based on the biology of infection status assumes homogeneous individuals in each compartment, and individual heterogeneity is ignored. The deterministic method can only provide us average results; the highly variable prevalence and fadeout phenomena observed in field data cannot be addressed. Therefore, the developed deterministic vaccination compartmental model is only an approximated and simplified description of a real dairy farm with Salmonella Cerro infection. As illustrated in Fig. 2, there is a disparity between observed and simulated prevalences after the initial period. To understand this disparity, we have to consider a number of potential sources. Firstly, the simulated prevalence in Fig. 2 was calculated using the deterministic compartmental model and a single set of baseline parameter values given in Table 1, thus the average simulated prevalence may not be fitted well to the observed prevalence. Secondly, model parameters are associated with uncertainties. For example, the transmission rate has a relatively large range based on field data (Chapagain et al., 2007). We therefore applied global parameter uncertainty and sensitivity analyses for prevalence. The uncertainty analysis of prevalence demonstrated in Fig. 6 shows that the difference between the observed prevalence and the simulated prevalence from 10th to 90th percentile becomes smaller. Thirdly, the quality of the observed prevalence is subject to test methods with different test sensitivities and specificities. Imperfect test sensitivity and specificity may influence the accuracy of the observed prevalence. Finally, stochasticity may have an effect on the observed prevalence, and a stochastic vaccination model may be more appropriate to account for the observed prevalence. However, in this study, we focused on the potential impact of imperfect
Salmonella vaccines on the dynamics of prevalence and eradication criterion, so the disparity shown in Fig. 2 would not affect the quality of the present deterministic compartmental model and all derived analyses, or the impact is minimal.

Although a few number of interesting findings were discovered by applying the present vaccination model to studying the potential impact of Salmonella imperfect vaccines on a dairy herd infected by Salmonella Cerro, the model developed in this work is flexible to accommodate other Salmonella serotypes—because a susceptible-infected-recovered-susceptible compartmental model (SIRS) was developed as a general framework to understand the dynamics of Salmonella serotypes related to foodborne diseases (Xiao et al., 2005). Extensions of the present vaccination model can be made in the following a number of ways. Firstly, the developed vaccination model with imperfect vaccines can be applied to other Salmonella serotypes more related to foodborne diseases such as serotypes DT104 and Newport. When epidemiological and demographic parameters can be estimated from field data, we may re-parametrize the vaccination model and investigate the effect of imperfect vaccines on dynamics and eradication criterion of these serotypes. Because imperfect Salmonella vaccines may also reduce clinical cases related to foodborne diseases, a vaccine effect on the reduction of disease-induced mortality rate can be introduced. Inclusion of such a vaccine effect is fairly easy; however, prevalence may increase due to vaccinated infectious animals staying longer in the herd (i.e., the average infectious period may increase because Salmonella vaccines lower the disease-induced mortality rate). Secondly, the present vaccination model did not consider animal population structures explicitly. A multiple-group structure consisting of calves, heifer, dry, and lactation groups should be considered, with birth (cohort) vaccination for calves, and lifetime (continuous) vaccination for dry cows (Xiao et al., 2005), if the structure of a studied herd is an important consideration. Both vaccination strategies can be utilized separately or combined in a real life situation. Thirdly, the waning rate of imperfect Salmonella vaccines was assumed smaller than the rate of animals entering the dry period. This assumption seems to be plausible for the present model; however, if the vaccine-induced immunity is lost quickly before animals entering the next dry period, the waning rate of vaccines should be reflected in the model. The present model would be still applicable after explicitly adding the waning of vaccine effectiveness. Finally, in the present model, we considered the mechanisms of vaccine-induced immunity and infection-induced immunity different. If no difference is assumed for these two resistance mechanisms, then modification of the present vaccination model is necessary. Moreover, the developed vaccination model in this study may also be applicable for other animal herds, such as pig herds infected with Salmonella.

5. Summary

We have developed a Salmonella vaccination model for assessing the potential impact of imperfect Salmonella vaccines on the dynamics of Salmonella infection. In this model, a gamma distribution of infectious periods and vaccine effects on susceptibility, infectiousness/shedding level, and infectious period were modeled explicitly. We then parametrized the model for Salmonella Cerro infection in a dairy herd, and evaluated how these vaccine effects impacted prevalence and the eradication criterion. To assess how model parameters influence prevalence, we performed global parameter uncertainty and sensitivity analyses using a sampling-based Latin-Hypercube Monte Carlo method and a partial rank correlation coefficient method, respectively.

Our results show that imperfect Salmonella vaccines reduce prevalence but the impacts differ depending on the vaccine effect. Among three vaccine effects under consideration, reduction of the length of the infectious period was most effective in reducing the endemic prevalence. Analyses of contour lines of prevalence or the critical reproduction ratio illustrate that, reducing prevalence to a certain level or zero can be achieved by choosing vaccines that have either a single vaccine effect at relatively high effectiveness, or two or more vaccine effects at relatively low effectiveness. Parameter sensitivity analysis suggests that effective control measures through applying Salmonella vaccines should be adjusted at different stages of infection. In addition, lifetime (continuous) vaccination was more effective than replacement (cohort) vaccination. The potential application of the developed vaccination model to other Salmonella serotypes related to foodborne diseases was also discussed. The presented study may be used as a tool for guiding the development of imperfect Salmonella vaccines.

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Appendix A. Derivation of the reproduction ratio \( R(p_1, p_2) \)

The reproduction ratio \( R(p_1, p_2) \) for the dynamical system in Appendix A was derived using the next generation matrix method developed by Diekmann and Heesterbeek (2000), van den Driessche and Watmough (2002) and Xiao et al. (2005). The \( R(p_1, p_2) \) is the largest eigenvalue of the next generation matrix, which is a product of two \((2n + 1) \times (2n + 1)\) matrices, \( F \) and \( V^{-1} \). The matrix \( F \) was defined by the new infections via direct transmission and indirect transmission through the contaminated environment, while the matrix \( V \) was defined by moving infectious individuals in other means. The reproduction ratio \( R(p_1, p_2) \) was obtained by solving the characteristic equation: The matrices \( F \) and \( V \) are

\[
R(p_1, p_2) = \max(A_{eg}; |FV^{-1} - A_{eg}| = 0),
\]

\[
F = \begin{pmatrix}
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 \\
\end{pmatrix},
\]

\[
V = \begin{pmatrix}
v_1 & \cdots & v_3 & \cdots & v_4 & \cdots & v_6 & \cdots & v_8 \\
v_3 & v_1 & \cdots & v_3 & \cdots & v_4 & \cdots & v_6 & \cdots & v_8 \\
v_5 & v_3 & v_1 & \cdots & v_5 & \cdots & v_4 & \cdots & v_6 & \cdots & v_8 \\
v_5 & v_4 & v_2 & \cdots & v_5 & \cdots & v_4 & \cdots & v_6 & \cdots & v_8 \\
v_6 & v_4 & v_2 & \cdots & v_6 & \cdots & v_4 & \cdots & v_6 & \cdots & v_8 \\
\end{pmatrix},
\]

\[
L = \begin{pmatrix}
\lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda \\
\lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda \\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
\lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda \\
\lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda & \cdots & \lambda \\
\end{pmatrix}.
\]
The elements in the matrices $F$ and $V$ were defined as

$$f_1 = \beta' \frac{S'}{N},$$

$$f_2 = (1 - g)\beta' \frac{S'}{N},$$

$$f_3 = \eta \frac{S'}{N},$$

$$f_4 = (1 - q)\eta \frac{X'}{N},$$

$$f_5 = (1 - q)(1 - g)\eta \frac{X'}{N},$$

$$f_6 = \eta X'.$$

$$v_1 = n_1' + \mu + p_2 \psi,$$

$$v_2 = \frac{n_2'}{(1 - h)} + \mu,$$

$$v_3 = -n_1',$$

$$v_4 = -\frac{n_1'}{1 - h},$$

$$v_5 = -p_2 \psi,$$

$$v_6 = -\sigma,$$

$$v_7 = -(1 - g)\sigma,$$

$$v_8 = \delta + \eta,$$

where $S'$ and $X'$ denote disease free solutions for susceptibles and susceptible vaccinees, respectively,

$$S' = \frac{(1 - p_1)\mu}{p_2 \psi + \mu}, \quad (A.4)$$

$$X' = \frac{p_2 \psi + p_2 \psi}{p_2 \psi + \mu} \quad (A.5)$$

To find the largest eigenvalue of the next generation matrix $FV^{-1}$, matrices $F$ and $V$ can be rewritten as

$$F = \begin{pmatrix} F_A & F_B \\ 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} V_A & 0 \\ V_B & V_C \end{pmatrix},$$

where $F_A$ and $V_A$ are $2n \times 2n$ matrices; $F_B$ and $V_B$ denote a $2n \times 1$ column vector and a $1 \times 2n$ row vector, respectively; $V_C$ represents the scalar $v_8$. The next generation matrix $FV^{-1}$ is written as

$$FV^{-1} = \begin{pmatrix} F_A & F_B \\ 0 & 0 \end{pmatrix} \begin{pmatrix} V_A^{-1} & 0 \\ -v_8^{-1} V_B V_A^{-1} & v_8^{-1} \end{pmatrix}
= \begin{pmatrix} F_A - F_B v_8^{-1} V_B V_A^{-1} & F_B v_8^{-1} \\ 0 & 0 \end{pmatrix}.$$  

(A.8)

Because all elements of the last row (the $2n + 1$th row) of $FV^{-1}$ are zero, the characteristic equation (Eq. (A.1)) can be reduced to (the trivial solution $A_{eg} = 0$ was discarded):

$$R(p_1, p_2) = \max(A_{eg}, |\tilde{F}_A V_A^{-1} - A_{eg}|) = 0.$$  

(A.9)

where $\tilde{F}_A = F_A - F_B v_8^{-1} V_B$. The $2n \times 2n$ matrix $F_B v_8^{-1} V_B$ is

$$F_B v_8^{-1} V_B = \begin{pmatrix} f_3 v_6^2 & \cdots & f_3 v_6 & f_3 v_7^2 & \cdots & f_3 v_7 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \vdots & 0 & \vdots & 0 & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \vdots & 0 & \vdots & 0 & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \vdots & 0 & \vdots & 0 & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix}.$$  

To evaluate eigenvalues of Eq. (A.9), we define $\tilde{F}_A$ and $V_A$ as

$$\tilde{F}_A = \begin{pmatrix} \tilde{F}_{A1} & \tilde{F}_{A2} \\ \tilde{F}_{A3} & \tilde{F}_{A4} \end{pmatrix}.$$  

(A.10)

$$V_A = \begin{pmatrix} V_{A1} & 0 \\ V_{A2} & V_{A3} \end{pmatrix}.$$  

(A.11)

where $\tilde{F}_{Ai}$ ($i = 1, 2, 3, 4$) and $V_{Ai}$ ($i = 1, 2, 3$) represents $n \times n$ matrices. The matrix $\tilde{F}_A V_A^{-1}$ in Eq. (A.9) can be rewritten as

$$\tilde{F}_A V_A^{-1} = \begin{pmatrix} \tilde{F}_{A1} & \tilde{F}_{A2} \\ \tilde{F}_{A3} & \tilde{F}_{A4} \end{pmatrix} \begin{pmatrix} V_{A1}^{-1} & 0 \\ -V_{A3}^{-1} V_{A2} V_{A1}^{-1} & V_{A3}^{-1} \end{pmatrix}
= \begin{pmatrix} (\tilde{F}_{A1} - \tilde{F}_{A2} V_{A3}^{-1} V_{A2}) V_{A1}^{-1} & \tilde{F}_{A2} V_{A3}^{-1} \\ (\tilde{F}_{A3} - \tilde{F}_{A4} V_{A3}^{-1} V_{A2}) V_{A1}^{-1} & \tilde{F}_{A4} V_{A3}^{-1} \end{pmatrix}.$$  

(A.12)

We notice that in each $n \times n$ matrix $\tilde{F}_{Ai}$ all elements except the first row are zero, therefore, the $\tilde{F}_{Ai} V_{Ai}^{-1}$ can be expressed as

$$\tilde{F}_{Ai} V_{Ai}^{-1} = \begin{pmatrix} R_{11} & R_{12} & \cdots & R_{1n} & R_{1,n+1} & R_{1,n+2} & \cdots & R_{1,2n} \\ \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ R_{n+1,1} & R_{n+1,2} & \cdots & R_{n+1,n} & R_{n+1,n+1} & R_{n+1,n+2} & \cdots & R_{n+1,2n} \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \\ \vdots & \vdots & \cdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & \cdots & 0 & 0 & 0 & \cdots & 0 \end{pmatrix}.$$  

(A.13)

Because elements of the first and ($n+1$)th rows of the matrix $\tilde{F}_{Ai} V_{Ai}^{-1}$ are nonzero and elements of all other rows are zero, i.e.,

$$R_0 = \delta_0 + \delta_{0,1} R_0, \quad (i = j = 0),$$

the reduced characteristic equation (Eq. (A.9)) can be further reduced to (the trivial solution $A_{eg} = 0$ was discarded):

$$R(p_1, p_2) = \max(A_{eg}, |\tilde{F}_A V_A^{-1} - A_{eg}| = 0).$$  

(A.14)

Letting $R_{11} = R_1$, $R_{1,n+1} = R_2$, $R_{n+1,n+1} = R_3$, and $R_{n+1,n+1} = R_4$, the characteristic equation (Eq. (A.14)) was rewritten as a quadratic equation of $A_{eg}$:

$$(A_{eg} - R_1)(A_{eg} - R_4) - R_2 R_3 = 0.$$  

(A.15)

To find the reproduction ratio, we have to find the $R_1$, $R_2$, $R_3$, and $R_4$. The $R_1$ is the first element of the first row of the $n \times n$ matrix $(\tilde{F}_A - \tilde{F}_{A2} V_{A3}^{-1} V_{A2}) V_{A1}^{-1}$. Letting $a = v_1$ and $b = -v_3$, the $n \times n$ matrix $V_{A1}$ is

$$V_{A1} = \begin{pmatrix} a & -b & a \\ -b & a & \cdots \\ \vdots & \cdots & \cdots \\ -b & a \end{pmatrix}.$$  

(A.16)
The inverse of the matrix $V_{A1}^{-1}$ can be found:

$$V_{A1}^{-1} = \begin{pmatrix}
\frac{1}{a} & b \\
\frac{b}{a} & 1 \\
\vdots & \vdots \\
\left(\frac{b}{a}\right)^{n-1} & \frac{b}{a} \\
\end{pmatrix}.$$  

(A.17)

Similarly, letting $c = v_2$ and $d = -v_4$, the $n \times n$ matrix $V_{A3}^{-1}$ is

$$V_{A3} = \begin{pmatrix}
c & -d & c \\
-d & c & -d \\
\vdots & \vdots & \vdots \\
\left(\frac{d}{c}\right)^{n-1} & \frac{d}{c} & \left(\frac{d}{c}\right)^{n-2} \\
\end{pmatrix}. 

(A.18)

The inverse of the matrix $V_{A3}^{-1}$ is

$$V_{A3}^{-1} = \frac{1}{c} \begin{pmatrix}
\frac{1}{d} & -c & \frac{1}{c} \\
\frac{d}{c} & 1 & \frac{d}{c} \\
\vdots & \vdots & \vdots \\
\left(\frac{d}{c}\right)^{n-1} & \frac{d}{c} & \left(\frac{d}{c}\right)^{n-2} \\
\end{pmatrix}.$$  

(A.19)

After a few steps of algebra, the $R_1$ is

$$R_1 = \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N} \left(\frac{1}{a - b} \sum_{i=1}^{n} \left(\frac{b}{a}\right)^{i-1}\right)$$

$$+ \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N^2} p_2 \psi(1 - g)$$

$$\times \frac{1}{ac} \left(\sum_{i=1}^{n} \left(\frac{b}{a}\right)^{i-1} \left(\sum_{i=1}^{n+1} \left(\frac{d}{c}\right)^{j-1}\right)\right).$$

(A.20)

Finally, the $R_1$ may be written as

$$R_1 = \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N} \frac{1}{a - b} \left(1 - \frac{b}{a}\right)^n$$

$$+ \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N^2} p_2 \psi(1 - g)$$

$$\times \frac{1}{c - d} \left(\frac{1 - b}{a - b} - \frac{d}{c} \left(1 - \frac{b}{a}\right)^n\right) - \frac{c}{c - d} \left(1 - \frac{b}{a}\right)^n. 

(A.21)

Similarly, $R_2$, $R_3$, and $R_4$ are

$$R_2 = (1 - g) \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N} \frac{1}{c - d}. 

(A.22)

$$R_3 = (1 - q) \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{X^1}{N} \frac{1}{a - b}$$

$$+ (1 - q) \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{X^1}{N^2} p_2 \psi(1 - g)$$

$$\times \left(1 - \frac{b}{a}\right)^n$$

$$\times \left(\frac{1}{c - d} \left(\frac{1 - b}{a - b} - \frac{d}{c} \left(1 - \frac{b}{a}\right)^n\right) - \frac{c}{c - d} \left(1 - \frac{b}{a}\right)^n\right). 

(A.23)

$$R_4 = (1 - q)(1 - g) \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{X^1}{N} \frac{1}{c - d}. 

(A.24)

Because $R_1 R_2 = R_3 R_4$, the nonzero solution of the quadratic equation of $A_{1g}$ is the reproduction ratio $R(p_1, p_2)$:

$$R(p_1, p_2) = \max(A_{1g}) = R_1 + R_4. 

(A.25)

Appendix B. The reproduction ratios for the special cases of the gamma distributed infectious periods: exponentially distributed infectious periods ($n = 1$) and the constant infectious period ($n \to \infty$)

Using the expression of the reproduction ratio $R(p_1, p_2)$ (Eq. (A.25)), we let $n = 1$ and $n \to \infty$ to obtain the reproduction ratios for the exponentially distributed infectious period and the constant infectious period, respectively.

When $n = 1$, Eq. (A.25) becomes

$$R(p_1, p_2) = \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N} \frac{1}{1 - \frac{b}{a} - \frac{d}{c} \left(1 - \frac{b}{a}\right)^n}\left(1 - \frac{c}{c - d} \left(1 - \frac{b}{a}\right)^n\right).$$

(B.1)

When $n \to \infty$, Eq. (A.25) becomes

$$R(p_1, p_2) = \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{S^1}{N} \frac{1}{1 - \frac{b}{a} - \frac{d}{c} \left(1 - \frac{b}{a}\right)^n}\left(1 - \frac{c}{c - d} \left(1 - \frac{b}{a}\right)^n\right).$$

(B.2)

Appendix C. The overall vaccine efficacy for replacement (cohort) vaccination only

If we let $p_2 = 0$, i.e., no lifetime (continuous) vaccination, then the reproduction ratio has a simple expression on which the overall vaccine efficacy was defined (Halloran et al., 1997, 1999; Longini et al., 1998; Becker and Starczak, 1998; Farrington, 2003). Eq. (A.25) is now rewritten as

$$R(p_1) = (1 - p_1)R_0 + p_1R_v = R_0 \left(1 - p_1 \left(1 - \frac{R_v}{R_0}\right)\right).$$ 

(C.1)

where $R_0$ and $R_v$ are the reproduction ratios for the cases of non-vaccination and fully vaccinated populations, respectively.

$$R_0 = R(p_1) = 0 \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{1}{\mu} \left(1 - \left(\frac{n \gamma}{n \gamma + \mu}\right)^n\right).$$

(C.2)

$$R_v = R(p_1 = 1)$$

$$= (1 - q)(1 - g) \left(\beta + \frac{\eta \sigma}{\eta + \delta}\right) \frac{1}{\mu} \left(1 - \left(\frac{n \gamma}{n \gamma + \mu}\right)^n\right).$$

(C.3)

The overall vaccine efficacy was defined as

$$\phi = 1 - \frac{R_v}{R_0} = 1 - (1 - q)(1 - g) \left(1 - \left(\frac{n \gamma}{n \gamma + \mu}\right)^n\right).$$

(C.4)

The $\phi$ is a monotonically increasing function of vaccine effects, $q, g$, and $h$. This means that the overall vaccine efficacy is always
positive, i.e., $\Phi - 0$, and thus the reproduction ratio $R_P(1)$ is less than $R_0$. The overall vaccine efficacy $\Phi$ for two limitation cases, i.e., the exponentially distributed infectious periods and the constant infectious period, was obtained by letting $n = 1$ and $n \to \infty$ in Eq. (C.4), respectively.

When $n = 1$,

$$\Phi = 1 - \left(1 - q\left(1 - g \right)^{\gamma + \mu} \right) / (1 - h) + \mu.$$  

(C.5)

and when $n \to \infty$,

$$\Phi = 1 - \left(1 - q\left(1 - g \right)^{1 - \mu} \right) / 1 - e^{-\mu h}.$$  

(C.6)

The eradication criterion for the coverage of replacement (cohort) vaccination was derived using Eq. (C.1):

$$p_1 \geq p_{c_1} = \frac{1 - \left(1 - \frac{1}{R_0} \right)}{\Phi} (C.7)$$

If the vaccine has effects only on both susceptibility and infectiosity, then the known critical vaccination coverage $p_{c_1}$ was reproduced (Longini et al., 1998):

$$p_{c_1} = \frac{q + h - qg}{1 - \frac{1}{R_0}} (C.8)$$

References


