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WANING HERD IMMUNITY: A CHALLENGE FOR ERADICATION OF MEASLES

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ABSTRACT. Since eradication of smallpox, many vaccine-preventable diseases such as measles, polio, and whooping cough have been targeted for global elimination. Despite aggressive vaccination programs, this goal has not been achieved and large outbreaks continue to occur, even in populations in which these diseases were once wiped out. In this study, we investigate the principal reason for recurrent outbreaks by analyzing the dynamics of immunity to measles, acquired by transfer of maternal antibodies, natural infection or vaccination, in both the individual and the population. In particular, we discuss the effect of maternal protection on the incidence of infection, and provide a biological explanation for the alterations in patterns of measles epidemics. The results show that the presence of herd immunity above a critical threshold is paramount in preventing large outbreaks of measles. The maintenance of such immunity, however, may not be achievable only by increasing the vaccination coverage, since it reduces the pathogen circulation and consequent boosting of immunity. This requires a combination of high primary vaccine coverage and timely revaccination for boosting of immunity. Due to its high reproductive number, measles eradication would require vaccine coverage above 95 percent, a target that has so far been difficult to achieve.

1. Introduction. Many infectious pathogens, such as measles, mumps, rubella, chickenpox, and influenza viruses and the bacterium *Bordetella Pertussis*, can be effectively controlled by the adaptive immune response generated in immunocompetent individuals. The development of this response depends on the nature of interaction between the pathogen and the immune system, which governs the *within-host* "micro-dynamics" of the infectious process [**38**]. The underlying complex dynamical process involves several steps, including recognition and

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subsequent elimination of the pathogen, and retains a memory in the form of specific T and B cells and antibody molecules for future responses to the same pathogen. These cells and antibodies are subject to decay at rates that vary with the pathogen. Upon re-exposure to the pathogen, a much more rapid and efficient (secondary) immune response evolves that often prevents replication of the pathogen and its subsequent clinical indicators [**24, 28, 38**]. Although adaptive immunity is a self-protection mechanism, its protective effects often extend well beyond the individual, since the existence of such immunity greatly influences the transmission dynamics of the pathogen in the population as a whole.

The presence of adaptive immunity among individuals is essential for the creation and maintenance of population immunity, referred to as "herd immunity" [**12**]. It can be influenced by natural infection, natural and public health vaccination and the immunological status of individuals in the population [**12, 15, 16, 28, 38**]. Raising herd immunity may interrupt pathogen circulation in the population, which reduces the chance of recurrent exposure and boosting of immunity. In the absence of such boosting, however, the adaptive immunity of individuals decays gradually, causing a decline in the herd immunity [**24**]. It is therefore important to draw out the interplay between pathogen dynamics, individual immunity and herd immunity, that could elucidate fundamental principles for disease control in a population.

The dynamics of appearance and loss of adaptive immunity may also provide a biological explanation for the observed transitions in epidemic patterns of several infectious diseases, such as influenza and some childhood infections [**10, 11, 23**]. While interpandemic influenza epidemics occur almost annually [**10**], epidemics of measles showed annual, biennial and triennial cycles before mass vaccination was adopted and irregular behavior with longer interepidemic periods within the vaccination era ([**11**] and references therein). Such oscillatory behavior of infectious disease epidemics may arise from the interplay between three confounding factors: (i) the rate of loss of individuals' immunity; (ii) the proportion of immune individuals in the population and (iii) the rate of evolution of the pathogen to a point that it escapes the herd immunity. An understanding of the dynamical interactions between these factors may enable one to predict the occurrence of epidemics and to disrupt the patterns of disease oscillation by maintaining

an adequate level of herd immunity through public health vaccination programs. Although a number of derivatives of susceptible-infected-recovered (SIR) models exists, none has the inherent ability to provide a broad understanding of such interactions.

This study undertakes to provide an understanding of the relationship between immunity and epidemics of vaccine-preventable diseases, with particular emphasis on childhood infections. A modeling approach is followed to link the immune-dynamics at the individual level to the dynamics of disease transmission and control at the population level. We illustrate the results for measles as an example of a serious childhood disease, which remains a major cause of morbidity and mortality worldwide, accounting for almost 1,000,000 deaths annually [**14, 29**]. We chose to study measles infection, in part due to the availability of high quality epidemiological and clinical data, and the absence of rapid mutations and recombination events in the present-day measles virus sequences which limit the generation of quasi-species and strain turnover [**26, 34**]. In the following, we describe the biological foundation and structure of the models considered in this paper.

2. Natural vaccination. In addition to natural infection or vaccination, immunity to a pathogen may also be conferred by mother-to-child transmission of pathogen-specific antibodies *in utero* and through breastfeeding [**38**]. Such transfer depends on the level of adaptive immunity of the mother, which is greatly affected by her nutritional and immune status. The maternal antibodies may reduce the risk of infection during infancy, a period known for ongoing maturation of the immune system. These antibodies attenuate many pathogens that get past the innate immunity barriers of newborns and infants, by binding and setting up the pathogen for phagocytosis by macrophages or dendritic cells. This indirectly triggers the onset of a suboptimal adaptive immune response to the pathogen in the child since, once the pathogen is phagocytosed, its proteins are broken into an array of small antigen peptides that become presentable to T cells. This in turn causes clonal expansion of pathogen specific T cells and ensuing processes. This is referred to as "natural vaccination," in which maternal antibody-pathogen complexes serve as vaccinating antigens [**24, 38**]. Inadequate transfer of maternal antibodies may not prevent infection, but lead to subclinical infection and induction of immunity by natural vaccina-

tion [**7, 32**]. The robustness of such immunity negatively correlates with the level of protection conferred by maternal antibodies (maternal protection), which is generally lower among infants whose mothers acquired immunity by vaccination [**22**]. This immunity may influence the transmission dynamics of the pathogen in the population as well as its epidemic patterns. Here, we develop a model that explains these phenomena by incorporating a biological parameter to account for the degree of protection afforded by maternal antibodies.

The model presented in Appendix A incorporates two classes of susceptible individuals, comprising newborns with maternal antibodies (B_M) and individuals in whom maternal antibodies have waned (S). We distinguish between classes of infected individuals with severe (clinical: I_c) and mild (subclinical: I_s, B_s) forms of infection. Clinical infection can occur upon contact with clinically or subclinically infected individuals [**28**]; however, newborns with subclinical infection (B_s) are unlikely to contribute significantly to the transmission of disease due to their very low number of contacts with the non-immune population during the relatively short period of infectiousness. Both clinically and subclinically infected individuals recover to form a class of individuals (R) whose immunity is governed by the antibody dynamics. The recovered individuals may experience a subclinical infection when their antibodies decay over time below a critical mass. The model is schematically depicted in Figure 1, with the associated parameters described in Table 1.

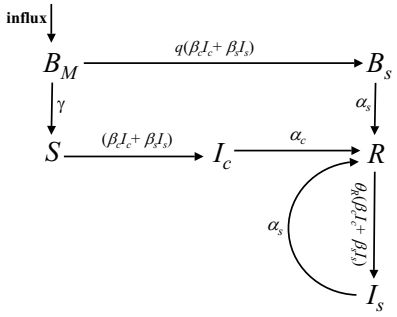


FIGURE 1. Model diagram for transitions between subpopulations without vaccination during disease progression and recovery. Clinical and subclinical infections in which maternal antibodies have waned are denoted by I_c and I_s, respectively. The label on the arrow $B_M \to B_s$ represents the rate of natural vaccination in newborns during maternal protection.

TABLE 1. Description of the model parameters with estimated ranges for measles infection [**4, 15, 16, 20, 29, 30, 31, 37**].

Parameter	Description	Estimated range
β_c	transmission rate of clinical infection	≥ 200 (people year)$^{-1}$
β_s	transmission rate of subclinical infection	$\sim 0.1\beta_c$ (people year)$^{-1}$
$1/\alpha_c$	infectious period of clinical infection	5 (day)
$1/\alpha_s$	infectious period of subclinical infection	0.5–1 (day)
$1-q$	degree of maternal protection	0–1
$1/\gamma$	duration of maternal protection	6–15 (month)
$1/\mu$	average life time	50 (year)
δ	decay rate of infection-induced antibody	variable (year^{-1})
η	decay rate of vaccine-induced antibody	variable (year^{-1})
ξ	vaccination coverage of newborns	0–1
$\kappa_{\min}$	minimum antibody level	0
σ_c	maximum antibody level induced by clinical infection	1
σ_s	maximum antibody level induced by subclinical infection	0.5
σ_v	maximum antibody level induced by vaccination	0.9

2.1. Antibody dynamics. Neutralizing antibodies provide the principal protective mechanism against infections caused by re-exposure to pathogens [**38**]. The underlying dynamical process involves activation of pathogen-specific helper T and B cells, differentiation of B cells into plasma and memory cells and production of antibodies from activated B and plasma cells [**24, 38**]. The levels of neutralizing antibody may be affected by preexisting factors such as nutritional or immune deficiencies, and re-exposure to the pathogen. While the former reduce the antibody levels, the latter is important in boosting antibody titres and maintaining them at protective levels [**15, 16, 24, 38**]. The level of antibody titre decreases in the absence of re-exposure to the pathogen. Laboratory measurements indicate that clinical infection confers considerably higher levels of antibody titre than subclinical infection [**4, 28, 30, 31**]. Taking into account a simplified mechanism for boosting antibody levels through pathogen re-exposure [**15**], the dynamics of the population-mean level of neutralizing antibodies (κ_R) may be expressed in terms of clinical, subclinical, and recovered classes

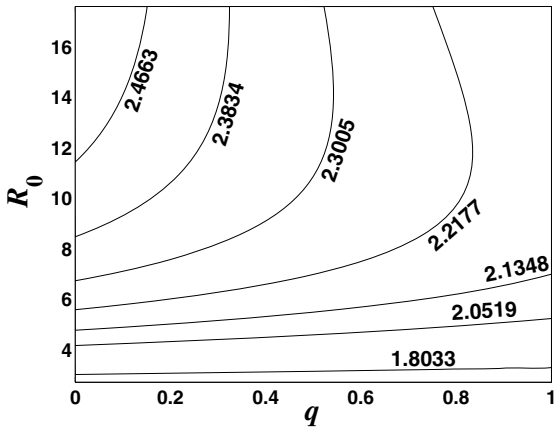


FIGURE 2. Contour plots of the equilibrium states showing the proportion of clinical infection in units of 10^{-4}, with a slow rate of antibody decay $\delta = 0.05$, for $\mathcal{R}_0$ versus q. Parameter values are: $\alpha_c = 73$, $\alpha_s = 500$, $\gamma = 1.35$ and $\mu = 0.02$.

as

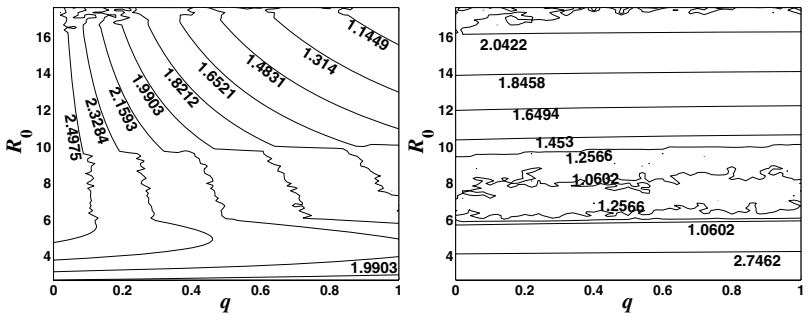
$$\kappa_R' = \delta(\kappa_{\min} - \kappa_R) + \alpha_s(\sigma_s - \kappa_R)\frac{B_s + I_s}{R} + \alpha_c(\sigma_c - \kappa_R)\frac{I_c}{R}, \tag{1}$$

where κ_R' is the derivative of κ_R with respect to the time, and the parameters are described in Table 1.

The risk of re-infection (θ_R) is largely dependent on two critical factors: (i) the individual's immunity, as determined by the level of antibodies and (ii) the incidence of infection in the population. As antibodies decay over time, their level passes through a region, below which an individual may develop a high risk of subclinical infection. This represents a transition from full to suboptimal protection, and we describe it by the function

$$H_\varepsilon(x) = (1 + \exp(-x/\varepsilon))^{-1}, \tag{2}$$

where ε characterizes the width of the transition region. Away from this region, $H_\varepsilon \approx 0$ ($x < -\varepsilon$) or $H_\varepsilon \approx 1$ ($x > \varepsilon$). The desired form of the risk θ_R can then be specified as $\theta_R(\kappa_R) = H_\varepsilon(L - \kappa_R)$, where L is the mean level of neutralizing antibodies in the transition region, so that $\theta_R(L) = 1/2$. Therefore, in a first approximation, $\theta_R = 0$ ($\theta_R = 1$) for sufficiently high (low) levels of antibody titre.



(a) (b)

FIGURE 3. Contour plots corresponding to equilibrium states showing the proportion of: (a) clinical infection in units of 10^{-4}; and (b) subclinical infection in units of 10^{-3}, with fast rate of antibody decay $\delta = 1.2$ for $\mathcal{R}_0$ versus q. Parameter values are: $p = 0.9$, $\alpha_c = 73$, $\alpha_s = 500$, $\gamma = 1.35$ and $\mu = 0.02$.

2.2. Simulations and results. The model has an infection-free equilibrium E_0 (see Appendix A) independent of the level of antibody. A simple analysis of the linearized model in the vicinity of E_0 shows that it is stable if the basic reproductive number ($\mathcal{R}_0$) is less than unity, where

$$\mathcal{R}_0 = \frac{\gamma}{\mu + \gamma} \frac{\beta_c}{\mu + \alpha_c}. \tag{3}$$

The basic reproduction number is defined as the number of new infectious cases generated by a single infected individual introduced into a wholly susceptible population during the course of infection [**3**]. While the disease is expected to be eradicated if $\mathcal{R}_0$ is less than one, it will persist within the population whenever $\mathcal{R}_0$ exceeds one.

The persistence of a disease may manifest itself as an endemic state, or as intermittent or periodic epidemics with oscillations in disease dynamics. The endemicity of the disease in the population can be described by analyzing the endemic equilibria of the model (see Appendix B). These endemic states depend on the risk of infection that is governed by the antibody dynamics in the population. Analysis of the model, as well as simulations using parameters estimated for measles infection (Table 1), reveal that subclinical infection disappears when

protective antibodies rise to sufficiently high levels; this occurs when the rate of antibody formation exceeds that of its loss. Simulations presented in Figure 2 for a slow rate of antibody loss show the existence of an equilibrium with clinical infection whose prevalence decreases as the incidence of natural vaccination increases. The reduction is more pronounced for higher values of $\mathcal{R}_0$, corresponding to higher transmission intensities. In contrast, the model may exhibit endemic equilibria at which both clinical and subclinical infections are present, provided that the antibody level plateaus at a value below protective levels in the population (Figure 3). This occurs when the rate of antibody decay is sufficiently higher than that of its formation.

Since measles is characterized as a seasonal disease [**11, 23**], we consider an extension of the model to include time-varying transmission rates between susceptible and infected individuals, given by the sinusoidal function $\beta_c(t) = \beta_c[1 + \beta_0 \sin(2\pi t)]$, where $0 \leq \beta_0 \leq 1$ measures the amplitude of the seasonal variation in transmission. Simulations with the same parameter values as those used for constant transmission rates show similar consequences of natural vaccination for the incidence of clinical infection. We used $\beta_0 = 0.1$, which is within the estimated range for the optimum level of seasonality with the standard exponential distribution of infectious periods in SIR-type models [**23**].

One of the most important dynamical features of the model appears in the interplay between the rate of natural vaccination (regulated by parameter q) and the periodicity of disease epidemics. Simulations of the profile of clinical infection show a lengthening of the interepidemic periods as the incidence of natural vaccination increases: annual cycles when $q = 0.1$, biennial cycles at $q = 0.5$ and 4-year cycles with $q = 0.9$ (Figure 4). These simulations reveal that variation in the level of maternal protection can lead to different patterns of disease oscillation, without changing the amplitude of seasonal fluctuation in transmission intensities.

Transitions in patterns of disease epidemics can also be described through diagrams showing the period doubling bifurcations that the model undergoes. Alterations in these patterns are illustrated in Figure 5 for upper and lower branches of the period doubling bifurcation diagrams of clinical infection. The results demonstrate that epidemics of severe disease occur less frequently and with smaller magnitude when a higher fraction of newborns with maternal protection experiences sub-

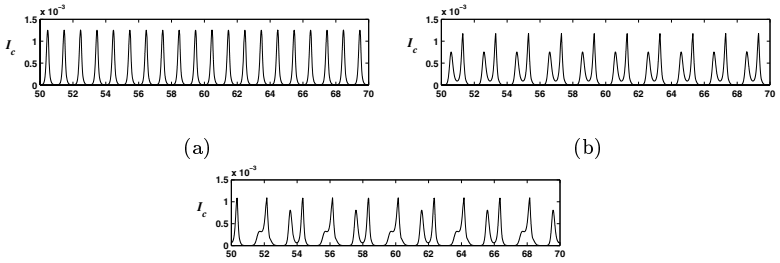


FIGURE 4. Epidemic patterns of disease oscillations for clinical infection: (a) $q = 0.1$ with annual cycles; (b) $q = 0.5$ with biennial cycles; (c) $q = 0.9$ with 4-year cycles. Parameter values (in units of year^{-1}) are: $\alpha_c = 73$, $\alpha_s = 500$, $\gamma = 1.35$, $\mu = 0.02$, $\delta = 1.2$, $\mathcal{R}_0 = 16.89$ and $\beta_0 = 0.1$ for the amplitude of seasonal variation. Higher values of q correspond to lower levels of maternal protection.

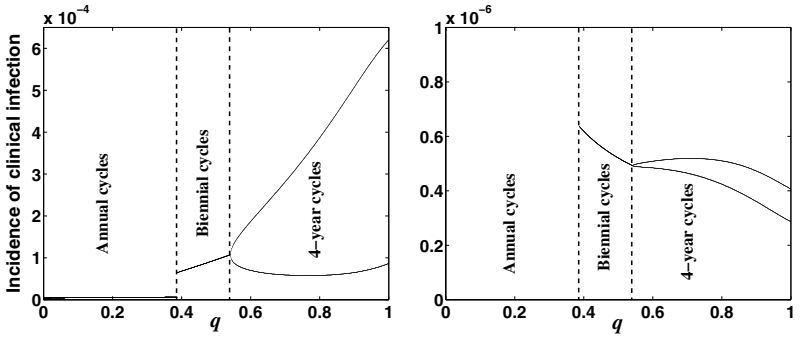


FIGURE 5. Bifurcation diagrams of clinical infection for $0 \leq q \leq 1$. Parameter values (in units of year^{-1}) are: $\alpha_c = 73$, $\alpha_s = 500$, $\gamma = 1.35$, $\mu = 0.02$, $\delta = 1.2$, $\mathcal{R}_0 = 16.9$ and $\beta_0 = 0.1$, and transmission rates are seasonal. Figures (a) and (b) illustrate, respectively, upper and lower branches of period doubling bifurcations.

clinical infection, especially in areas where transmission intensities are greatest. This is indeed well documented by clinical and epidemiological studies [**17, 35**] and has recently been studied for pertussis [**1**]. Thus, not only can the phenomenon of natural vaccination alter the patterns of disease epidemics but also provide a biological explanation

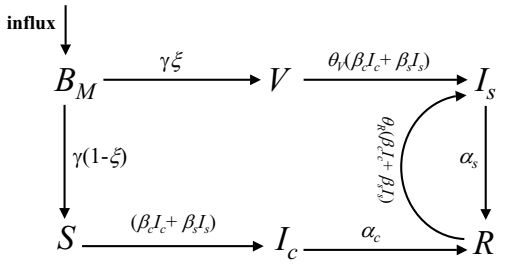


FIGURE 6. Model diagram for transitions between subpopulations of individuals with vaccination, during disease progression and recovery.

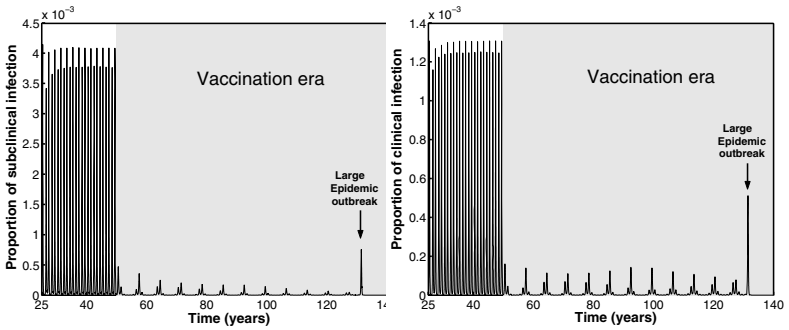
for varying severity of childhood infections in diverse population demographics.

3. Public health vaccination. One of the major successes of modern medicine has been the use of vaccines to induce immunity to pathogens without experiencing natural infection [**24**]. Vaccination campaigns have dramatically reduced the incidence of several infections, including measles, polio and whooping cough; yet, eradication of these diseases remains an elusive target [**14, 16, 33**]. The recurrence of their epidemics is thought to be due to a temporal decline in the individuals' immunity afforded by vaccination [**2, 18, 20, 21, 29, 31**].

Here, we modify the model described in Figure 1 to include vaccination as a public health control measure, in the absence of natural vaccination. Consistent with the current vaccination policy, the model assumes that the vaccine is administered to newborns in synchronization with the loss of maternal protection. The transition diagram of the modified model is given in Figure 6, which incorporates a class of vaccinated individuals (V) who may experience subclinical infection due to decay of protective antibodies over the time elapsed since vaccination.

The dynamics of antibody level following natural exposure to the pathogen can be described by equation (1), where $B_s \equiv 0$. Similarly, the dynamics of the population-mean vaccine-induced antibody level (κ_V) may be expressed by:

$$\kappa_V' = \eta(\kappa_{\min} - \kappa_V) + (\sigma_v - \kappa_V)\frac{\xi\gamma B_M}{V},$$



(a) (b)

FIGURE 7. Profiles of (a) subclinical and (b) clinical infection for 50 years without vaccination (white region) followed by 90 years of vaccination with 90% coverage (shaded region). Parameter values (in units of year^{-1}) are: $\alpha_c = 73$, $\alpha_s = 500$, $\gamma = 1.35$, $\mu = 0.02$, $\delta = 0.7$, $\eta = 0.08$ and $\beta_0 = 0.1$. Before the vaccination era, $q = 0.5; \xi = 0$ (corresponding to $\mathcal{R}_0 \approx 16.89$), and within the vaccination era $q = 0; \xi = 0.9$ (corresponding to $\mathcal{R}_v \approx 1.91$).

with the parameters given in Table 1. An argument similar to the one made earlier in the natural vaccination model can be applied to the risk functions $\theta_R(\kappa_R) = H_\varepsilon(L - \kappa_R)$ and $\theta_V(\kappa_V) = H_\varepsilon(L - \kappa_V)$ which allow both recovered and vaccinated individuals to become subclinically infected when antibody levels fall below those needed for complete protection. Some general results, concerning the existence of the endemic equilibria for β_s and β_c not seasonally varying, are given in Appendix B.

3.1. Simulations and results. In the presence of vaccination, eradication is feasible if the effective reproductive number ($\mathcal{R}_v$) is less than unity. This threshold quantity involves the vaccination coverage of newborns (ξ) as a control parameter and depends on the saturation level of vaccine-induced antibody. The analysis of the infection-free equilibrium yields the expression

$$\mathcal{R}_v = \mathcal{R}_0\big(1 - \xi(1 - \theta_V B)\big), \tag{4}$$

where $\mathcal{R}_0$ is given by (3), $\theta_V \equiv \theta_V(\kappa_V^*) = H_\varepsilon(L - \kappa_V^*)$ and

$$\kappa_V^* = \frac{\eta\kappa_{\min} + \mu\sigma_v}{\eta + \mu},$$

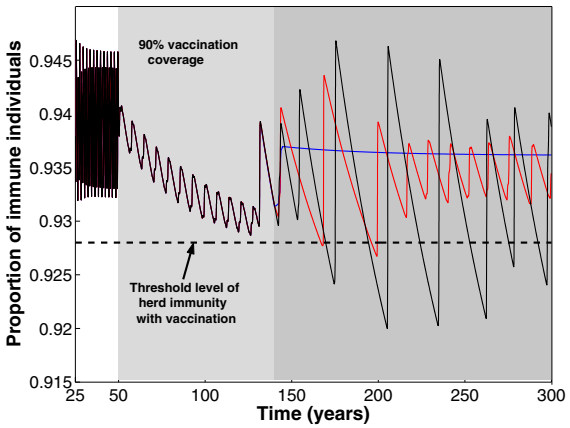


FIGURE 8. The proportion of immune individuals (herd immunity) for 50 years' pre-vaccination, followed by two vaccination eras: 50–140 years of 90% coverage (light grey region); 140–300 years of vaccination with coverage of 90% (black curve), 92% (red curve), and 95% (blue curve) in the dark grey region. At the onset of vaccination, the threshold of herd immunity is reduced from $\mathcal{H}_c \approx 94.1\%$ to $\mathcal{H}_c^v \approx 92.7\%$; this is accompanied by a drastic reduction in the amplitude of disease oscillations and a lengthening of their period, which lead to a gradual overall decline in the herd immunity. Within the second vaccination era (dark grey region) epidemic outbreaks become less frequent as the coverage increases even marginally, and the level of herd immunity is sustained above its threshold for $\xi = 0.95 > \xi_0 = 0.9407$, where ξ_0 is defined in the text.

$$B = \frac{\beta_s}{\beta_c}\frac{\mu + \alpha_c}{\mu + \alpha_s}$$

The expression for $\mathcal{R}_v$ provides the critical vaccine coverage required for disease eradication, which is derived from setting the threshold $\mathcal{R}_v = 1$ and λ is given by

$$\xi_c = \frac{1}{1 - \theta_V B}\left(1 - \frac{1}{\mathcal{R}_0}\right) \approx \begin{cases} 1 - (1/\mathcal{R}_0) & \text{if } \kappa_V^* > L + O(\varepsilon) \\ 1/(1 - 1/\mathcal{R}_0)/(1 - B) & \text{if } \kappa_V^* < L - O(\varepsilon). \end{cases}$$

In previous work [**2**], we have shown that eradication of infection by paediatric vaccination in the absence of re-exposure is feasible only if the fraction of vaccinated individuals' life during which they are protected from infection exceeds the threshold $1 - 1/\mathcal{R}_0$. This establishes a relationship between the basic reproductive number, coverage of primary vaccination, and the duration of immunity induced by vaccination.

To illustrate the impact of a vaccination program, we have simulated the model in Figure 1 for 50 years prior to vaccination, followed by 90 years of vaccination with 90 percent coverage using the model in Figure 6. Simulations for the profile of clinical and subclinical infections show a dramatic decrease in the incidence of infection following the onset of vaccination (Figure 7). This is supported by documented data [**6, 8, 9**] and is referred to as a "honeymoon" period [**25**]. The pattern of epidemics predicted by the model is remarkably similar to that observed epidemiologically [**36**], which serves to validate the tenets of the models described here. With these parameter values (Table 1), a vaccine coverage of $\xi_c \approx 0.955$ is required to eliminate the pathogen from the population. Under a slightly lower coverage ($\xi = 90\%$), the magnitude of epidemics of subclinical infection undergoes a steady decline, but eventually large epidemic outbreaks of both subclinical and clinical infections occur. This is clearly due to a decrease in the proportion of immune individuals in the population, i.e., waning herd immunity, as depicted in Figure 8. The proportions of susceptible, vaccinated and recovered individuals undergo sudden changes when large outbreaks occur within the vaccination era (Figure 9). The interval between two large outbreaks is significantly extended by boosting individuals' immunity due to the persistence of the pathogen in the population. This fact is crucial in planning for global eradication of vaccine-preventable diseases.

The results of simulations in Figure 9 reveal that increasing the proportion of vaccine-protected individuals offsets the proportion of individuals acquiring immunity by natural infection. Consequently, increasing vaccine coverage does not necessarily raise the herd immunity. This is further demonstrated by comparing the level of herd immunity before and within the vaccination eras (Figure 8). The threshold of herd immunity before vaccination is given by $\mathcal{H}_c = 1 - 1/\mathcal{R}_0$ [**12**], which is approximately 0.941, with the parameter values used in our simulations. However, the proportion of the immune class (recovered individuals) is generally below this threshold, and therefore no reduction in the incidence of infection is observed. Following the onset of vaccination, the threshold of herd immunity is reduced to

$$(5)\quad \mathcal{H}_c^v = \mathcal{H}_c\left(\frac{\text{lifetime} - \text{age at vaccination}}{\text{lifetime}}\right) = \left(1 - \frac{1}{\mathcal{R}_0}\right)\left(\frac{\gamma - \mu}{\gamma}\right),$$

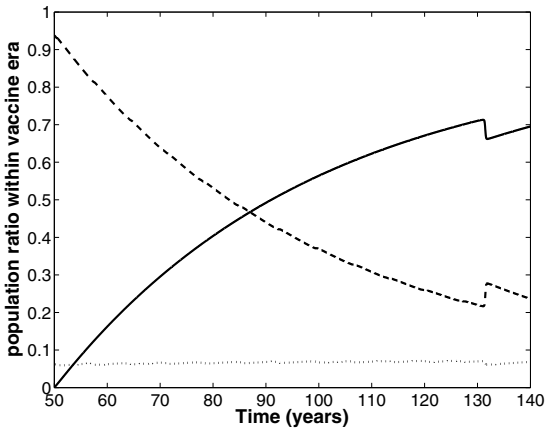


FIGURE 9. Population ratio of vaccinated (solid-curve), recovered (dashed-curve) and susceptible (dotted-curve) individuals over 90 years within the vaccination era with 90% coverage. Parameter values (in units of year^{-1}) are: $\alpha_c = 73$, $\alpha_s = 500$, $\gamma = 1.35$, $\mu = 0.02$, $\delta = 0.7$, $\eta = 0.08$, $\beta_0 = 0.1$, $q = 0$ and $\xi = 0.9$ (corresponding to $\mathcal{R}_v \approx 1.91$). These curves undergo a sudden change at the time of occurrence of large epidemic outbreaks.

which evaluates to $\mathcal{H}_c^v \approx 0.927$. Although the proportion of immune individuals is above the threshold $\mathcal{H}_c^v$, no rise in the level of herd immunity is observed by such high vaccination coverage (light grey region in Figure 8). In fact, this proportion shows a decrement over time due to the loss of individuals' immunity caused by antibody decay in both recovered and vaccinated classes. This is a direct consequence of the reduction in the incidence of disease within the vaccination era that lowers the rate of re-exposure and subsequent boosting of immunity [**37**]. When the proportion of immune individuals falls below the threshold $\mathcal{H}_c^v$, large epidemic outbreaks of both clinical and subclinical infections occur, as exemplified in Figure 7. This highlights the importance of maintaining protective levels of individuals' immunity through revaccination programs [**2, 36**].

4. Discussion. This study offers a theoretical framework that couples the transmission dynamics of vaccine-preventable diseases with immunity at the individual level. The model developed here considers the evolution of adaptive immunity conferred by natural vaccination, natural infection and public health vaccination. From a dynam-

ical standpoint, it incorporates a parameter to represent the degree of maternal protection that controls the rate of natural vaccination in newborns. The results show that epidemics of the clinical form of disease occur less frequently when newborns acquire suboptimal immunity upon exposure to the pathogen and provide a biological explanation for transitions between oscillatory patterns in epidemics of measles in the absence of vaccination.

In the presence of public health vaccination, the model assumes that natural exposure to the pathogen during infancy is negligible due to diminution of the incidence of infection by vaccination programs. While establishing a relationship between the individual's immunity and herd immunity, the model yields a critical threshold of vaccine coverage needed for disease eradication. Furthermore, it demonstrates that the effects of public health vaccination on the dynamics of infection are similar to those arising from natural vaccination, in terms of reducing both the amplitude and frequency of epidemics. However, these effects are much more pronounced for public health vaccination than for natural vaccination (Figures 4 and 7). The threshold of vaccine coverage and the age at which a primary vaccine is administered are shown to be critical parameters that determine the threshold of herd immunity. It is evident from (5) that increasing vaccine coverage has no effect on the herd immunity threshold, but it prolongs the duration of herd immunity above its threshold. In other words, the herd immunity wanes over a longer period of time as the vaccine coverage increases (Figure 8). Further analysis reveals that the level of herd immunity eventually saturates at $\xi\gamma/(\mu+\gamma)$ in the absence of pathogen. Therefore, to prevent the recurrence of an epidemic outbreak by reintroduction of the pathogen, the saturation level must stay above the herd immunity threshold, and this requires $\xi > \mathcal{H}_c^v(\mu+\gamma)/\gamma \equiv \xi_0$. This prediction concerning herd immunity is illustrated in Figure 8 for vaccination coverage below and above ξ_0 and corroborates recent epidemiological findings of a measles outbreak in the Republic of the Marshall Islands in 2003, which suggest a 95 percent level of herd immunity to prevent recurrence of outbreaks [**21**]. The need for such a high level of immunity to measles inspired us to evaluate the threshold of herd immunity for smallpox that was eradicated in 1977 [**20**]. With the estimated $\mathcal{R}_0$ from 3.5 to 6 [**13**], the threshold of herd immunity for smallpox ranges from 70 percent to 83 percent, which is nearly

10–20 percent below the corresponding range for measles. As a result, eradication of smallpox was feasible with even lower vaccine coverage than what is required for eradication of measles.

The preceding two decades have witnessed the occurrence of measles epidemic outbreaks, in spite of industrious efforts in mounting vaccination programs [**2, 18, 20, 21, 29, 36**]. The present study shows that waning of herd immunity is the principal mechanism responsible for such events, even in highly vaccinated populations. Recent epidemiological observations of measles outbreaks [**20, 21, 29, 36**] and an unexpected increase in chlamydia infection reported in British Columbia, Canada [**5**], substantiate the findings of this paper.

In the absence of global eradication of a pathogen, the threat of epidemic outbreaks still exists in populations in which the disease has been wiped out. Such outbreaks may occur when a high level of population immunity is not sustained, as was the case in the Republic of the Marshall Islands in 2003 [**20**]. The findings of this study signal a global health warning that attention must be paid to maintaining high levels of herd immunity for measles, and other persistent vaccine-preventable diseases, large epidemic outbreaks of which have not occurred in recent years. This would require an international surveillance of populations' immunity to particular pathogens, which could guide the implementation of public health booster vaccination programs. To achieve global eradication, it is essential to combine high primary vaccine coverage with timely revaccination for boosting individuals' immunity.

APPENDIX

A. The general model is given by the following deterministic system of differential equations

$$B_M' = \mu - q(\beta_s I_s + \beta_c I_c)B_M - \mu B_M - \gamma B_M, \tag{6}$$

$$B_s' = q(\beta_s I_s + \beta_c I_c)B_M - (\mu + \alpha_s)B_s, \tag{7}$$

$$S' = (1-\xi)\gamma B_M - (\beta_s I_s + \beta_c I_c)S - \mu S, \tag{8}$$

$$I_s' = (\beta_s I_s + \beta_c I_c)(\theta_R R + \theta_V V) - (\mu + \alpha_s)I_s, \tag{9}$$

$$I_c' = (\beta_s I_s + \beta_c I_c)S - (\mu + \alpha_c)I_c, \tag{10}$$

$$R' = \alpha_s(B_s + I_s) + \alpha_c I_c - \theta_R(\beta_s I_s + \beta_c I_c)R - \mu R, \tag{11}$$

$$V' = \xi\gamma B_M - \theta_V(\beta_s I_s + \beta_c I_c)V - \mu V, \tag{12}$$

where B_M, B_s, S, I_s, I_c, R and V represent classes of newborns with maternal antibodies, newborns with subclinical infection, susceptible, subclinical infected, clinical infected, recovered and vaccinated individuals, respectively, and the parameters are described in Table 1. The natural vaccination model in Figure 1 is obtained when $\xi \equiv 0$ (i.e., $V \equiv 0$) and $0 \leq q \leq 1$; and the model with public health vaccination in Figure 5 is derived when $q \equiv 0$, i.e., $B_s \equiv 0$, and $0 \leq \xi \leq 1$. The model has an infection-free equilibrium of the form

$$E_{0,\xi} = (B_M^0, B_s^0, S^0, I_s^0, I_c^0, R^0, V^0) = \left(\frac{\mu}{\mu+\gamma}, 0, \frac{(1-\xi)\gamma}{\mu+\gamma}, 0, 0, 0, \frac{\xi\gamma}{\mu+\gamma}\right),$$

which reduces to E_0 in the absence of vaccination, given by

$$E_0 = (B_M^0, B_s^0, S^0, I_s^0, I_c^0, R^0) = \left(\frac{\mu}{\mu+\gamma}, 0, \frac{\gamma}{\mu+\gamma}, 0, 0, 0\right).$$

B. In order to find the equilibria $(B_M, B_s, S, I_s, I_c, R, V) \in \mathbf{R}_+^7$ of the model (6)–(12) with β constant, it is convenient to define $K = \beta_s I_s + \beta_c I_c$. Then, an infection-free equilibrium (endemic equilibrium) corresponds to a solution $K = 0$ ($K > 0$), when they exist. After straightforward but tedious substitutions into (6)–(12), and expressing the variables in terms of K, we obtain the equation $KP(K) = 0$, where P is the degree-4 polynomial

$$P(K) = a_4 K^4 + a_3 K^3 + a_2 K^2 + a_1 K + a_0.$$

Therefore, the infection-free equilibrium always exists, and the endemic equilibria are the positive solutions, if they exist, of $P(K) = 0$, where the coefficients of P are given by the following expressions

$$a_4 = \mu\,\theta_R\,q\,\theta_V,$$

$$a_3 = \left(-\frac{q\,\mu\,\alpha_s\,\beta_s}{\mu+\alpha_s} + \mu\,(\mu+\gamma) + \mu^2 q\right)\theta_V\theta_R + \mu^2\,q\theta_R\,\theta_R + \mu\,(\mu+\alpha_s)\,q\,\theta_V,$$

$$a_2 = \left(\left(-\frac{(1-\xi)\,\mu\,\gamma\,(\mu\,\beta_c + \alpha_c\,\beta_s)}{\mu+\alpha_c} - \frac{q\,\mu^2\,\alpha_s\,\beta_s}{\mu+\alpha_s} + \mu^2\,(\mu+\gamma) - \mu\,\gamma\,\xi\,\beta_s\right)\theta_V - \frac{q\,\mu^2\,\alpha_s\,\beta_s}{\mu+\alpha_s} + (\mu\,(\mu+\gamma) + \mu^2\,q)\,\mu\right)\theta_R$$

$$
\begin{aligned}
&+ (\mu(\mu+\alpha_s)(\mu+\gamma) + \mu^2(\mu+\alpha_s)q)\theta_V + \mu^2(\mu+\alpha_s)q,\\
a_1 =&\left(-\frac{(1-\xi)\mu^2\gamma(\mu\beta_c+\alpha_c\beta_s)}{\mu+\alpha_c} + \mu^3(\mu+\gamma) - \frac{q\mu^3\alpha_s\beta_s}{\mu+\alpha_s} - \mu^2\gamma\xi\beta_s\theta_V\right)\theta_R\\
&+\left(-\frac{(1-\xi)\mu^2\gamma\beta_c(\mu+\alpha_s)}{\mu+\alpha_c} - \mu^2\gamma\xi\beta_s + \mu^2(\mu+\alpha_s)(\mu+\gamma)\right)\theta_V\\
&+ (\mu(\mu+\alpha_s)(\mu+\gamma) + \mu^2(\mu+\alpha_s)q)\mu,\\
a_0 =& \mu^3(\mu+\alpha_s)(\mu+\gamma)(1-\mathcal{R}_v).
\end{aligned}
$$

It should be noted that, in the above solution procedure, we are tacitly regarding θ_R and θ_V as fixed parameters. This is justified as long as the solutions derived do not lie within a distance $O(\varepsilon)$ of the transition regions separating their sub- and supra-threshold antibody level (L) at their respective equilibrium concentrations (κ_R^*, κ_V^*), which are given by

$$
\begin{aligned}
\kappa_R^* &= \frac{\delta\kappa_{\min} + \alpha_s\sigma_s(B_s + I_s/R) + \alpha_c\sigma_c(I_c/R)}{\delta + \alpha_s(B_s + I_s/R) + \alpha_c(I_c/R)},\\
\kappa_V^* &= \frac{\eta\kappa_{\min} + \sigma_V(\gamma\xi B_M/V)}{\eta + (\gamma\xi B_M/V)}.
\end{aligned}
$$

Furthermore, the following consistency conditions must be satisfied:

$$
\begin{aligned}
\theta_R = 0 \Longleftrightarrow \kappa_R^* > L, \qquad \theta_R = 1 \Longleftrightarrow \kappa_R^* < L,\\
\theta_V = 0 \Longleftrightarrow \kappa_V^* > L, \qquad \theta_V = 1 \Longleftrightarrow \kappa_V^* < L.
\end{aligned}
$$

The endemic equilibria are then given in terms of K by

$$
\begin{aligned}
B_M &= \frac{\mu}{qK+\mu+\gamma}, \qquad B_s = \frac{qK\mu}{(\mu+\alpha_s)(qK+\mu+\gamma)},\\
S &= \frac{(1-\xi)\gamma\mu}{(K+\mu)(qK+\mu+\gamma)},
\end{aligned}
$$

$$
\begin{aligned}
I_c &= \frac{K(1-\xi)\mu\gamma}{(\mu+\alpha_c)(K+\mu)(qK+\mu+\gamma)}, \qquad I_s = \frac{K-\beta_s I_s}{\beta_s},\\
V &= \frac{\xi\mu\gamma}{(\mu+\theta_V K)(qK+\mu+\gamma)}, \qquad R = \frac{(\mu+\alpha_s)I_s - \theta_V KV}{\theta_R K}.
\end{aligned}
$$

Special case 1. $\theta_R = \theta_V = 0$ (both κ_R^* and κ_V^* are supra-threshold L). In this case, $P(K)$ reduces to a quadratic with $a_1, a_2 > 0$. Therefore, there exists a unique endemic equilibria if and only if $a_0 < 0$, or equivalently $\mathcal{R}_v > 1$.

Special case 2. $\theta_R = 0$, $\theta_V = 1$ (κ_R^* is supra-threshold L). Thus, $P(K)$ reduces to a cubic where $a_3, a_2 > 0$. If $\mathcal{R}_v > 1$, then $a_0 < 0$ and there is again a unique endemic equilibrium. Otherwise, there are either a unique or three endemic equilibria. In this case, the existence of three equilibria may lead to the dynamical phenomenon of backward bifurcation which is beyond the scope of this paper, and we refer to [**27**] for a general reference citing related studies.

In the general case, when neither $\theta_R = 0$ nor $\theta_V = 0$, we are obliged to find the roots of the general fourth-order polynomial. However, except near the transition regions, if either κ_R^* or κ_V^* are supra-threshold, then the corresponding θ_R or θ_V will be very close to zero. This gives rise to a singular perturbation of the polynomial equation $P(K) = 0$ since, as we observe from the above expressions for the polynomial coefficients, a_4 is proportional to $\theta_R \theta_V$.

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