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Too Much of a Good Thing? When to Stop Catch-Up Vaccination

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Abstract

During the 20th century, deaths from a range of serious infectious diseases decreased dramatically due to the development of safe and effective vaccines. However, infant immunization coverage has increased only marginally since the 1960s, and many people remain susceptible to vaccine-preventable diseases. “Catch-up vaccination” for age groups beyond infancy can be an attractive and effective means of immunizing people who were missed earlier. However, as newborn vaccination rates increase, catch-up vaccination becomes less attractive: the number of susceptible people decreases, so the cost to find and vaccinate each unvaccinated person may increase; additionally, the number of infected individuals decreases, so each unvaccinated person faces a lower risk of infection. This paper presents a general framework for determining the optimal time to discontinue a catch-up vaccination program. We use a cost-effectiveness framework: we consider the cost per quality-adjusted life year gained of catch-up vaccination efforts, as a function of newborn immunization rates over time and consequent disease prevalence and incidence. We illustrate our results with the example of hepatitis B catch-up vaccination in China. We contrast results from a dynamic modeling approach with an approach that ignores the impact of vaccination on future disease incidence. The latter approach is likely to be simpler for decision makers to understand and implement because of lower data requirements.

Keywords

vaccine; epidemic control; hepatitis B

1. Introduction

During the 20th century, deaths from a range of serious infectious diseases such as smallpox, measles, polio, diphtheria, pneumococcal disease, and bacterial meningitis decreased dramatically due to the development of safe and effective vaccines against these pathogens. However, infant immunization coverage has increased only marginally since the 1960s, and many people remain susceptible to vaccine-preventable diseases.[1] The World Health Organization (WHO) reports that almost 20% of children born in 2007 did not receive complete routine vaccination.[2] Newborns and young children may not receive recommended vaccinations because they lack access to health care, face social barriers, or

have parents who are unaware of or unmotivated about vaccination.[3] Vaccine price may also be an impediment, especially in the developing world.[4, 5]

Because infant immunization is incomplete, there may be a need for recurring annual campaigns to reach children missed in infancy. The WHO recommends expanding immunization to every eligible person, including those in age groups beyond infancy.[1] Such "catch-up vaccination" can be an attractive and effective means of immunizing people who were missed earlier.[6–8] Although newborn vaccination is the most cost-effective strategy for preventing disease,[9, 10] catch-up vaccination for individuals missed by newborn vaccination can be highly cost-effective (e.g.,[10]). Many successful catch-up vaccination programs have been implemented around the globe, including immunization programs for measles,[11, 12] haemophilus influenza type B (which causes bacterial meningitis),[13] and polio.[14] An ongoing program in China aims to provide catch-up vaccination for hepatitis B virus to at least 500,000 children.[8]

For many vaccine-preventable diseases, newborn vaccination rates are increasing.[4, 15, 16] This affects the cost-effectiveness of catch-up vaccination: the number of susceptible individuals decreases, so the cost to find and vaccinate each unvaccinated person may increase; additionally, the number of infected individuals decreases, so each unvaccinated person faces a lower risk of infection. This paper presents a general framework for determining the optimal time to discontinue catch-up vaccination programs. We focus specifically on control of chronic diseases (as opposed to diseases such as influenza where patients either recover or die[17]). We consider an ongoing catch-up vaccination program where individuals of any given age(s) who missed newborn vaccination are vaccinated each year. We use a cost-effectiveness framework: we consider the cost per quality-adjusted life year (QALY) gained[18] of catch-up vaccination efforts, as a function of newborn immunization rates over time and consequent disease prevalence and incidence. Much previous theoretical research on controlling vaccine-preventable diseases has focused on disease eradication.[19–24] However, disease eradication can be extremely costly and, for most vaccine-preventable diseases, is not a realistic goal for the foreseeable future. Other studies focus on levels of vaccination to achieve herd immunity.[25–27] However, it may still be valuable from a public health perspective to vaccinate even if coverage levels to achieve herd immunity are not possible, and it may also be valuable to vaccinate *beyond* levels required for herd immunity in order to hasten the decline in the epidemic. We thus focus on achieving various levels of disease control, rather than eradication, and we use cost-effectiveness of these levels of control as our outcome measure; such a framework makes the implicit assumption that funds not spent on a particular vaccination program could be spent on another health intervention.[18] Other research has examined the long-term impact of infection reduction for chronic diseases, but has focused on newborn vaccination only and has not used a cost-effectiveness framework.[28–30]

Many studies that evaluate the cost-effectiveness of vaccination use simple Markov cohort models that do not take into account the dynamics of the epidemic,[10, 31–36] yet studies have shown that the impact of vaccination on herd immunity can be important, particularly when the vaccination program can affect a substantial fraction of the population.[37–40] However,

studies of the impact of herd immunity often focus on mass infant vaccination for diseases such as measles and varicella that have relatively short infectious periods.[38, 39]

We solve the catch-up vaccination problem with an approach that captures the dynamics of infection transmission, and then contrast results from this approach with an approach that ignores the impact of vaccination on disease incidence. We allow for age dependency (as opposed to a homogeneous population[17]) to account for the fact that younger children may receive more benefits from the intervention and/or harms from infection. Age is often an important inclusion criteria for catch-up vaccination guidelines.[41] Finally, unlike previous research which assumes constant marginal costs of immunization,[19–21, 23, 24, 42, 43] we allow for increasing marginal costs.

In Section 2 we formulate our model. In Section 3 we focus on a single age group and ask, "What should our vaccination coverage goal be this year for each age group?" This can help establish the upper age limit at which one would want to start catch-up vaccination. In Section 4 we look over time and ask, "When should we stop catch-up vaccination programs for different age groups?" We illustrate our results in Section 5 with the example of hepatitis B catch-up vaccination in China. Section 6 concludes with discussion.

2. Model Formulation

We consider a population of individuals stratified by age and disease state. All notation is shown in Table 1. We define a set of mutually exclusive, collectively exhaustive age groups $a = 0, 1, \ldots, A$, indexed by increasing age (where $a = 0$ represents newborns), and disease groups $d \in D$, where $d = S$ denotes a susceptible individual, $d = I$ denotes an infected individual, and $d = R$ denotes an individual who is immune (either from vaccination or previous infection that has resolved itself). We consider a time horizon with discrete time increments $t = 0, 1, \ldots, T$. We set the time increment t to be the same as the time units for age (e.g., years).

We consider the decision of whether to perform catch-up vaccination among eligible individuals in age group $a > 0$ in any time period t, and the fraction of such individuals $x_a(t)$ who should be vaccinated. We assume that $0 \leq x_a(t) \leq x_a^{\max}$, where $x_a^{\max} \leq 1$ is the upper limit on the fraction of age group a that can feasibly be vaccinated. Vaccine-eligible individuals include all susceptible individuals as well as infected or immune individuals who are unaware of their disease status. Vaccine recordkeeping may be imperfect and some individuals who have already been vaccinated may be unaware of their protection. Moreover, for many catch-up vaccination programs, individuals are not tested for infection or immunity prior to vaccination, as such tests are too expensive. (For most vaccines, revaccination does not harm the patient.) Thus, infected and immune individuals may be unnecessarily vaccinated during a catch-up campaign. We assume that the newborn vaccination rate $x_0(t)$ is known and is determined exogenously.

To model the dynamics of infection transmission, we use an age-structured deterministic SIR (Susceptible, Infected, Recovered) epidemic model with homogeneous mixing.[22] This model is similar to others used to predict long-term prevalence of chronic infectious diseases.[28] (An SICR model incorporating an additional Carrier state could also be used, but

because the infectious state can be short, we elected to use an SIR model). In this model, the infection rate at time t is proportional to the number of infected and susceptible individuals, taking the form $\beta S(t)I(t)/N(t)$, where β is the so-called "sufficient contact rate" (it is a function of the number of contacts per unit time, and the chance of infection transmission per contact), $S(t)$ is the number of susceptible individuals, $I(t)$ is the number of infected individuals, and $N(t)$ is the total population size.[22] In our age-structured model, the infection rate for individuals in age group a at time t is

$$\beta_a S_a(t) \left[\sum_{k=0}^{A} I_k(t)\right] / \left[\sum_{k=0}^{A} N_k(t)\right] = \beta_a S_a(t) \left[\sum_{k=0}^{A} I_k(t)\right] / N(t).$$

The dynamics of the model are as follows. We distinguish between newborns ($a = 0$) and all other age groups ($a > 0$). All equations are for $t = 0, 1, 2, \ldots, T$.

$$S_0(t) = \sum_{a=1}^{A} \phi_a \left(S_a(t) + I_a(t)\left(1-p_0\right) + R_a(t)\right)\left(1-ex_0(t)\right) \quad (1)$$

$$I_0(t) = \sum_{a=1}^{A} \phi_a I_a(t) p_0 \left(1-ex_0(t)\right) \quad (2)$$

$$R_0(t) = \sum_{a=1}^{A} \phi_a \left(S_a(t) + I_a(t) + R_a(t)\right) ex_0(t) \quad (3)$$

$$S_{a+1}(t+1) = S_a(t)\left[1-\mu_{a,S} - \left(1-\mu_{a,S}\right) ex_a(t) - \left(1-\mu_{a,S}\right)\left(1-ex_a(t)\right)\beta_a \left[\sum_{k=0}^{A} I_k(t)\right] / N(t)\right], a \geq 0 \quad (4)$$

$$I_{a+1}(t+1) = I_a(t)\left(1-\mu_{a,I} - \left(1-\mu_{a,I}\right)\nu\right) + S_a(t) p_a \left(1-\mu_{a,S}\right)\left(1-ex_a(t)\right)\beta_a \left[\sum_{k=0}^{A} I_k(t)\right] / N(t),\ a \geq 0 \quad (5)$$

$$\begin{aligned} R_{a+1}(t+1) = {} & R_a(t)\left(1-\mu_{a,R}\right) \\ & + S_a(t)\left(1-\mu_{a,S}\right) ex_a(t) \\ & + I_a(t)\left(1-\mu_{a,I}\right)\nu \\ & + S_a(t)\left(1-p_a\right)\left(1-\mu_{a,S}\right)\left(1-ex_a(t)\right)\beta_a \left[\sum_{k=0}^{A} I_k(t)\right] / N(t),\ a \geq 0 \end{aligned} \quad (6)$$

We assume that initial compartment sizes are known for non-newborns ($a > 0$): $S_a(0) = S_{a,0}$, $I_a(0) = I_{a,0}$, $R_a(0) = R_{a,0}$. Equations (1) – (3) describe the entry of newborns into the system as susceptible, infected, or recovered (immune) and equations (4) – (6) describe disease

progression among individuals age 1 or older. Susceptible individuals (those not successfully vaccinated) acquire infection through contact with an infected person. Individuals enter the immune states either by developing natural immunity (they become infected and their immune system resolves the infection, with probability $1-p_a$, or by being successfully vaccinated). We assume that the vaccine has the same efficacy in preventing mother-to-child transmission as it has in conferring immunity to future infections, similar to many vaccines.[44]

The model is illustrated schematically in Figure 1. In any time period t, every individual in the population is in a compartment distinguished by age (a = 0, 1, …, A) and infection status (susceptible (S), Infected (I), or Immune (R)). At the end of any time period t, newborn children enter the population as either susceptible, infected, or immune (due to newborn vaccination). Additionally, at the end of the time period, susceptible newborns (who are now age a=1) can remain susceptible (thus entering compartment $S_1(t+1)$), become infected (entering compartment $I_1(t+1)$), become immune (due to vaccination, thus entering compartment ($R_1(t+1)$), or die (thus leaving the population). Infected newborns can remain infected (entering compartment $I_1(t+1)$), become immune (due to recovery from the infection, thus entering compartment ($R_1(t+1)$), or die. Immune newborns can remain immune (entering compartment $R_1(t+1)$) or die. Similarly, individuals of any age a progress to age $a+1$ at the end of the time period, with analogous transitions between infected, susceptible, and recovered compartments. All of these transitions occur for every time period t = 0, 1, …, T.

We solve the optimal vaccination problem by decomposing it. We first solve the problem for a single age group in a single time period (Section 3) and then consider the long-term problem of catch-up vaccination target coverage levels for different age groups over time and when to discontinue such efforts (Section 4).

3. Single-Period Decision Problem

3.1 Single-Period Problem

We first focus on a single time period and single age group $a > 0$ and ask, “What should our vaccination coverage goal be this year for each age group?” Answering this question can help determine how much effort to expend on different age groups and can determine the upper age limit at which one would want to institute catch-up vaccination. We assume that the newborn vaccination rate $x_0(t)$, t = 0, 1, …, T, is known. To determine the optimal level of catch-up vaccination, we use a cost-benefit analysis: we value health benefits in monetary terms. The value of the catch-up vaccination program equals the net present value of incremental health benefits generated by the vaccination program (calculated in monetary terms), minus the associated change in healthcare costs, minus the cost of the vaccination program (Drummond[45] and Gold[18] provide details on the appropriateness of this as a value measure). We assign a monetary value λ to each QALY experienced; this value represents the decision maker’s willingness to pay for an incremental QALY.[18, 45] There is not always agreement on what this value of λ should be. However, the WHO suggests that a reasonable amount to pay for a disability-adjusted life year averted (which is slightly different from, but very similar to a QALY gained[46, 47]) is one to three times a country’s per capita GDP.[48, 49]

The problem of maximizing the net present monetary benefit of vaccinating a fraction $x_\alpha(0)$ of individuals in age group $\alpha > 0$ can be written as:

$$\mathrm{P1}: \max_{x_\alpha(0)} \sum_{t=0}^{T} \left(\frac{1}{1+r}\right)^t \left[\sum_{a=0}^{A} \lambda \left(q_{a,S} S_a(t) + q_{a,I} I_a(t) + q_{a,R} R_a(t)\right) - \left(c_{a,S} S_a(t) + c_{a,I} I_a(t) + c_{a,R} R_a(t)\right)\right] - CV_\alpha\left(x_\alpha(0)\right) \quad (7)$$

$$s.t.\ (1)-(6)$$
$$0 \le x_\alpha(0) \le x_\alpha^{\max} \quad (8)$$

$$x_\alpha(t) = 0,\ t = 1, 2, \ldots, T \quad (9)$$

The first term in (7) is the net present monetary value of total health benefits (QALYs experienced) in the population. The second term is the net present value of total healthcare costs in the population. The final term is the total cost to vaccinate a fraction $x_\alpha(t)$ of all eligible individuals in age group α (those who are susceptible and those who are infected or immune but unaware of their disease status). We define this function as

$$CV_a(x_a) = \begin{cases} 0 & x_a = 0 \\ F + \left(c_v x_a + f_a\left(x_a\right)\right)\left(S_a + I_a u_{I,a} + R_a u_{R,a}\right) & 0 < x_a \le 1 \end{cases} \quad (10)$$

where for simplicity we have dropped the argument t. The first term in (10) represents the fixed cost of the vaccination program. The second term represents the cost per person vaccinated; this is proportional to the number of susceptible individuals plus the number of infected and immune individuals who do not know their disease status. The per person vaccination cost comprises the constant per person cost of vaccination, c_v, plus the incremental cost of vaccination above baseline, which is given by the function $f_a(x_a)$. We assume that f_a is a nonnegative, nondecreasing, convex function of x_a; thus $CV_a(x_a)$ is also a nonnegative, nondecreasing, convex function of x_a, reflecting the possibility that per person costs rise as the number of people to be found and vaccinated declines.

Research on vaccine program size suggests that the average cost of vaccinating individuals begins to rise when vaccination coverage reaches high levels[50] because the last individuals requiring vaccination may be very difficult to find and reach.[51, 52] A systematic review found that average costs of vaccination programs operating from fixed facilities initially decline with the scale of vaccination programs because of high fixed costs, but costs may later increase when the programs expand outside of dense urban areas into more rural and remote regions.[53] Another review found that the average cost per immunized child is often minimized at a coverage level of about 50–60% and then increases noticeably at about 80% population coverage.[50]

P1 is a complex nonlinear problem (the objective function is governed by the nonlinear dynamics of the epidemic, (1) – (6)). The problem can be solved using numerical methods: for any level of catch-up vaccination, one can use (1) – (6) to calculate $S_a(t)$, $I_a(t)$, and $R_a(t)$ for $a = 0, \ldots, A$, $t = 1, \ldots, T$, and thus the objective function value. However, instantiation of

the model requires significant demographic and epidemiological data that decision makers may not have (e.g., the number of susceptible, infected, and immune individuals of each age, the disease sufficient contact rate for each age group, etc.). In the following section we develop a simple approximation of this model that can be used by decision makers more readily than the exact dynamic model.

3.2 Approximate Single-Period Problem

To simplify P1, we assume that future incidence (the chance that an unvaccinated, susceptible person acquires the infection in the future) does not depend on $x_\alpha(0)$ (the fraction of individuals of a particular age α who are vaccinated this year). This will cause us to slightly understate the benefits of vaccination since vaccination leads to fewer susceptible individuals and thus decreased incidence. This assumption is likely to be reasonable for situations where the vaccination of a single age group in one year has little impact on disease prevalence in the entire population.

The only interactions between age cohorts in equations (4) – (6) are related to incidence. The assumption that $x_\alpha(0)$ does not affect future incidence means that the only people affected by the catch-up vaccination program are those who receive vaccination. Thus, instead of tracking the nonlinear dynamic constraints (1) – (6) for all age groups in P1, in the approximate problem we need only look at differences in costs and health benefits for susceptible individuals in the age cohort who become immune through catch-up vaccination.

Given the above assumption, and letting $H_{a,d}$ and $C_{a,d}$ denote, respectively, the expected present value of lifetime health outcomes and health care costs for a person starting at age a in disease state d at time 0, we approximate (P1) as:

$$\text{P2:} \max_{x_\alpha(0)} S_\alpha(0) e x_\alpha(0) \left[\lambda \left(H_{\alpha,R} - H_{\alpha,S} \right) - \left(C_{\alpha,R} - C_{\alpha,S} \right) \right] - CV_\alpha \left(x_\alpha(0) \right) \quad (11)$$

$$s.t. \quad 0 \leq x_\alpha(0) \leq x_\alpha^{\max} \quad (8)$$

$$x_\alpha(t) = 0, \; t = 1, 2, \ldots, T \quad (9)$$

The first term in the objective function is the net present monetary value of the health benefits minus changes in health care costs accruing from successfully vaccinated individuals. The second term is the vaccination cost. To solve P2, we must know $H_{a,R}$, $H_{a,S}$, $C_{a,R}$, and $C_{a,S}$. The quantities $H_{a,R}$ and $C_{a,R}$ can be calculated using Markov models or other models of health progression.[10, 54] The quantities $H_{a,S}$ and $C_{a,S}$ depend on the future incidence of the disease which, in general, will change over time (i.e., $i_a(t) \neq i_a(t+1)$). Equations (1) – (6) can be used to estimate incidence, or future incidence can be estimated more simply; in Section 3.3 we discuss several ways to estimate incidence. Given estimated future incidence, Markov models of infection and disease progression can be used to calculate $H_{a,S}$ and $C_{a,S}$.

It is straightforward to find the optimal level of vaccination $x^*_\alpha(0)$, for P2. In the Appendix we derive and characterize this solution.

3.3. Estimating Infection Risk

In the approximate single-period problem P2, the infection risk (incidence) is a determinant of the expected health effects and health care costs for susceptible individuals, $H_{a,S}$ and $C_{a,S}$. Estimates of future incidence are thus needed for solving P2.

The risk of infection for a susceptible individual of age a in time period t is

$$i_a(t) = \frac{\beta_a \sum_{k=0}^{A} [I_k(t)]}{\sum_{k=0}^{A} N_k(t)}. \quad (12)$$

In this section we discuss four ways of estimating (12). In Section 5, we test these estimates with a numerical example of hepatitis B in China.

Dynamic Model—The risk of infection (12) can be determined by numerically solving the system of equations (1) – (6) to determine $I_a(t)$ and $N_a(t)$ for $t = 1, \ldots, T$. However, because such calculations may be complex (and instantiating the epidemic model requires estimation of many parameter values), we now discuss three simpler ways of estimating future disease incidence.

Constant Incidence—One simple estimate of future incidence is to assume that it is the same as current incidence; that is, $i_a(t) = i_a(0)$ for all t. Although infant vaccination and catch-up vaccination efforts can decrease disease incidence over time, for a large population it may take many years before incidence decreases appreciably, so the estimate of constant incidence may be reasonable. If infant and catch-up vaccination rates are no lower than previous rates (with mixing patterns and other epidemiological parameters unchanged), then current incidence is an upper bound on future incidence.

Cut-off Estimate—Another estimate of future incidence can be obtained by assuming that the current age-infection distribution remains the same over time, except for assuming that individuals born at time 0 and afterward will not become infected (as though 100% of newborns are vaccinated with a 100% effective vaccine):

$$\sum_{k=0}^{A} N_k(t) \cong \sum_{k=0}^{A} N_k(0); I_a(t) \cong \begin{cases} 0 & a \le t \\ I_a(0) & a > t \end{cases}, \text{for } t \ge 0, 0 \le a \le A \quad (13)$$

This estimate is similar to “cutting off” the tail of (or zeroing-out) the age-infection distribution corresponding to younger ages. This may be reasonable if the age-infection distribution is in a steady state to begin with and, except for vaccination of the young, it is expected that the steady-state infection distribution will continue.

Age-out Estimate—Another estimate of future incidence can be obtained by assuming no new infections or resolved infections, and also assuming that individuals born at time 0 and afterward will not become infected (as though 100% are vaccinated with a 100% effective vaccine). This takes the current population of infected individuals with their current infection prevalence and "ages them out". This implies, for example, that the infection prevalence for age a=10 at t=7 is equal to the infection prevalence for age a=3 at t=0. For some incurable chronic diseases, the infection reservoir can only be eliminated through mortality of those with the infection.[55] If we assume Type I survivorship[22] (everyone lives exactly A time units), then the cohort of infected people ages one time unit for every unit of time that passes. With this assumption, the annual risk of infection for a susceptible individual can be estimated as:

$$\sum_{k=0}^{A} N_k(t) \cong \sum_{k=0}^{A} N_k(0); I_a(t) \cong \begin{cases} 0 & a \le t \\ I_{a-t}(0) & a > t \end{cases}, \text{for } t \ge 0, 0 \le a \le A \quad (14)$$

4. When to Stop Catch-Up Vaccination

We now examine the problem of when to stop catch-up vaccination in each age group a. The vaccination levels are denoted by a vector of values, $x_a(t)$, for all ages $a > 0$ and time periods t:

$$X = (x_1(0), x_1(1), \ldots, x_1(T), x_2(0), x_2(1) \ldots x_2(T), \ldots, x_A(0), x_A(1), \ldots x_A(T)).$$

We assume that catch-up vaccination at the level determined at time 0 for each age group, $x_a^*(0)$, will be continued until it is no longer cost-effective to do so, and then no catch-up vaccination will be performed in that age group. Determining the optimal time to stop catch-up vaccination for each age group a is equivalent to determining at what time t, $x_a^*(t)=0$. As before, the goal is to maximize the net monetary benefit of catch-up vaccination.

The problem can be written as:

$$\text{P3:} \max_X \sum_{t=0}^{T} \left(\frac{1}{1+r}\right)^t [\sum_{a=0}^{A} \lambda \left(q_{a,S} S_a(t) + q_{a,I} I_a(t) + q_{a,R} R_a(t)\right)] - \left(c_{a,S} S_a(t) + c_{a,I} I_a(t) + c_{a,R} R_a(t)\right) - CV_a(x_a(t))] \quad (15)$$

s.t. (1) – (6)

$$x_a(t) = \{x_a^*(0), 0\}, \quad \begin{matrix} s.t. \quad (1)-(6) \\ 1 \le a \le A,\ 0 \le t \le T \ (\text{where } x_a^*(0) \text{ solves P1}) \end{matrix} \quad (16)$$

$$x_a(t+1) \le x_a(t), \quad 1 \le a \le A,\ 0 \le t \le T \quad (17)$$

This formulation allows us to consider catch-up vaccination in any subset of age groups; for age groups not considered for catch-up vaccination, we can set $x_a^{\max}=0$.

We can solve P3 using numerical methods. To do so, we start at time $t = 0$ and determine the optimal fraction of each age group a to vaccinate by solving P1 (or we can solve P2 to obtain an approximate solution). Then, given these values, we project the dynamic model (1) – (6) forward one period. With the updated values of $S_a(1)$, $I_a(1)$, and $R_a(1)$ for all a, we then determine whether to continue with the previous vaccination level for each age group a (i.e., whether $x_a^*(1)=x_a^*(0)$) or whether catch-up vaccination for age group a should be discontinued (i.e., $x_a^*(1)=0$). We continue this process until we find $\tilde{t}$ such that $x_a^*(\tilde{t})=0$ for all ages $a > 0$ or until $t = T$.

5. Example: Hepatitis B in China

We illustrate our models with the example of hepatitis B catch-up vaccination for children and adolescents in China. Approximately one-third of the world's 350 million cases of hepatitis B infection occur in China,[56, 57] where the disease is a generalized epidemic and an estimated 7.4% of the population is chronically infected.[56, 58] Approximately 1% of those under 5 are infected, 2.5% of those between 5 and 14 are infected, and 8.5% of those 15 and older are infected.[58] The most common routes of transmission are neonatal infection and horizontal transmission during early childhood.[56, 59]

The Chinese government recommended hepatitis B vaccination in 1992, and in 2002 the vaccine was made free for newborns. These policy changes helped newborn vaccination coverage rise from 70.7% in 1997 to 89.8% in 2003.[59] However, even with recent dramatic increases in newborn vaccination rates, an estimated 150 million children in China are still unprotected from hepatitis B.[4, 58] Infection in children is a particular problem because the younger the age at infection, the more likely it is that the infection will become chronic (lifelong).[60] Left untreated, approximately one in four chronically infected individuals will die from liver disease related to hepatitis B.[44, 61, 62] Because it is effective and cost-effective (and likely to be cost-saving[10]), hepatitis B catch-up vaccination for school-age children was made free by the government in 2009.[63] At the same time, extensive public health efforts have led to steady increases in newborn vaccination rates across the country.[4] Given the increases in newborn vaccination rates, when is catch-up vaccination for different age groups no longer cost-effective?

Parameter values for the model (Table 2 and Appendix Table 1) were drawn from a study on the cost-effectiveness of catch-up vaccination for children and adolescents in China;[10] that study modeled the effects of chronic hepatitis B infection, but only considered the cost-effectiveness of current catch-up vaccination efforts (without considering when to stop catch-up vaccination), and did not consider costs of vaccination above baseline (thus, the optimal catch-up vaccination level for any age group was either 0% or 100%). To model the epidemic, we used a slightly more sophisticated model of disease than the model given by (1) – (6): we subdivided the infected state $I(\cdot)$ into multiple states in order to more accurately represent the costs and health effects of hepatitis B infection (Appendix Figure 1).[10] In this model of hepatitis B, the basic reproductive number is calculated to be 1.1 which is similar to that found in other studies of hepatitis B.[64, 65] We used this model of disease when solving both P1 and P2. We used a health system perspective and included all lifetime health care costs for individuals in the population. The current per capita GDP in China is about

$4500,[66–68] so an incremental cost-effectiveness ratio between $4,500 and $13,500would be considered cost-effective, and a ratio less than $4500 would be considered highly cost-effective according to WHO criteria.[48, 49] In our base case analyses we assumed λ = $4500; in sensitivity analysis we considered λ = $13,500 and λ = $0. We considered ages a = 0, 1, …, 100 years old and considered a time horizon of T = 100 years. We considered possible catch-up vaccination for ages a = 1, …, 19 years old (thus, $x_a^{\max}=0$ for a = 20, …, 100).

5.1 How Many People to Vaccinate Now

Figure 2 shows the net monetary benefit (net value of health benefits minus net health care costs) under different willingness-to-pay thresholds for a single individual of age a = 1, …, 19 calculated using the different incidence estimates described in Section 3; this is the first term in the objective function of P2. The net monetary benefit estimates are remarkably similar in this example, indicating that a simple estimate of future incidence is sufficient for evaluating current catch-up vaccination policies. We note that the net monetary benefits of hepatitis B vaccination in China are predicted to be higher using models with static incidence than using models with dynamically calculated incidence. China's hepatitis B epidemic is not in a steady state: recent increasing levels of newborn vaccination are expected to cause prevalence to drop in the future. Since the dynamic model would capture this anticipated lower long-term infection risk to those vaccinated, the dynamic model will predict less value to a vaccinated individual than a model using a static prediction of long-term incidence. Although a static model of incidence may underestimate the value of vaccination because it does not incorporate the benefit of preventing secondary infections, a static model in this case will overestimate the value of vaccination because it may overestimate the infection risk to individuals in the future when prevalence declines. Appendix Figures 2a and 2b illustrate this counterintuitive situation by comparing a disease with constant prevalence to a disease with declining prevalence such as hepatitis B in China.

Figure 3 shows the optimal fraction of each age group to vaccinate for hepatitis B in China as calculated by solving P1 and by solving P2 using the assumption of constant incidence. The results are very similar. The optimal solution, obtained by solving P1, is 100% catch-up vaccination for all ages 1 through 19. The solution to P2 also calls for 100% catch-up vaccination through age 14.In this example, P2 is a good approximation of P1. This is because China has a large number of infected individuals who cannot be cured – and thus an "infection reservoir" that will remain in the population for a long time.

Figure 4 shows how age and prior vaccination coverage combined can affect the cost-effectiveness of catch-up vaccination. Values were obtained by solving P2 with each of the four different incidence estimates. Each line represents the prior vaccination coverage level such that catch-up vaccination costs $4500/QALY gained (Figure 4a), $13,500/QALY gained (Figure 4b), or $0/QALY gained (Figure 4c). Figure 4 shows that as the cohort age increases, the prior vaccination coverage must be lower for a program to be cost-effective; this is because of reduced catch-up vaccination benefit for older individuals. Moreover, for a higher willingness to pay per QALY gained (Figure 4b), catch-up vaccination is cost-effective for higher levels of prior vaccination; and for a lower willingness to pay per QALY gained (Figure 4c), catch-up vaccination is cost-effective at lower levels of prior

vaccination. As figures 4 and 2 show, for a variety of willingness-to-pay thresholds, the policy recommendations about the target level of coverage to provide are invariant to the infection risk estimates.

We conducted sensitivity analysis on the recovery rate to see how these general conclusions might apply for diseases with shorter infectious periods. If the length of infection is much shorter (2–10 years) the results using a static model of incidence versus a dynamic model diverge (Appendix Figure 4). Under these conditions, using a dynamic model may be more important.

5.2 When to Stop Catch-Up Vaccination

We now examine the problem of how many years into the future to perform catch-up vaccination. We first consider programs that would vaccinate children at school entry, either at age 5 when entering kindergarten or at age 12 when entering middle school. We assumed 90% newborn vaccination coverage each year. We assumed different maximum feasible levels of catch-up vaccination, ranging from 50% to 100%. We solved P3 with $x_a^*(t)$ as calculated by P1 (exact numerical solution) and then as calculated by P2 (approximate numerical solution). The solutions obtained using these two methods were identical, and called for the maximum feasible level of catch-up vaccination each year until it is no longer cost-effective. Figure 5a shows that, if just 5-year-olds are vaccinated, catch-up vaccination must continue for about 71 years if 100% catch-up coverage can be achieved, and for 77 years if only 50% coverage can be achieved. Similarly, if just 12-year-olds are vaccinated, catch-up vaccination must continue for 67 years if 100% coverage can be achieved, and for 73 years if only 50% coverage can be achieved.

We next consider a program that would provide catch-up vaccination to children at both points of school entry, ages 5 and 12. Figure 5b shows that the number of years for which catch-up vaccination of 5-year-olds is cost-effective is unchanged, but catch-up vaccination for 12-year-olds is discontinued sooner than when there was no 5-year-old vaccination. When 5-year-olds also receive catch-up vaccination, catch-up vaccination of 12-year-olds continues for 11 years if 100% coverage can be achieved, and for 66 years if only 50% coverage can be achieved.

The model can also be used to determine the “best case” scenario for catch-up vaccination among children, which would occur if all eligible children were to receive 100% catch-up vaccination. Figure 6a shows the solution to P3 assuming that all eligible children ages 1 through 19 can be reached by catch-up vaccination, and that the current newborn vaccination level of 90% continues each year. Those solutions call for 100% vaccination coverage for most ages until catch-up vaccination is no longer cost-effective. At older ages, the catch-up vaccination program covers many of the children in the first few years, so further catch-up vaccination is no longer cost-effective because the program creates high levels of immunity in the population (and thus more wasted re-vaccinations). However, for children age 1, the catch-up vaccination program is still cost-effective because newborn coverage still leaves many susceptible children (with fewer wasted re-vaccinations), and younger children still have much to benefit from vaccination. Figure 6a also shows the cases in which the maximum feasible catch-up vaccination coverage in any year is at most 75% or

50%. With these lower coverage levels, catch-up vaccination must be continued for several more years for children of school age, and for many more years for preschool age children.

In China, remote rural regions have significantly lower birth-dose vaccination coverage than urban areas.[4, 58] Figure 6b shows the solution to the catch-up vaccination problem for a region in which only 75% newborn vaccination coverage is achieved, and for the cases of 50%, 75%, and 100% maximum achievable catch-up vaccination coverage in each age group. Compared to the case of 90% newborn coverage, it is cost-effective to provide catch-up vaccination for more years in the future and for older children.

We conducted sensitivity analysis on the rate of disease transmission, the awareness of serostatus, the discount rate, length of infection, and threshold cost-effectiveness ratio. If the rates of disease transmission are significantly lower, the catch-up vaccination program becomes less valuable and would not be continued as long, but the different infection risk estimates would still lead to similar conclusions (Appendix Figure 5). If more individuals are aware of their serostatus, a catch-up vaccination program would be more valuable because unnecessary vaccination would not be performed (Appendix Figure 6), and if the discount rate used were lower (higher), the program would be more (less) valuable and would be continued a longer (shorter) time in the future (Appendix Figure 7). If the average length of infection were shorter than 10 years and if catch-up vaccination were given to all children ages 1–19, then it would not be valuable to continue catch-up vaccination as long because the disease could be more quickly controlled (Appendix Figure 8). Finally, if the threshold cost-effectiveness ratio is higher (lower), the length of time in the future to continue catch-up vaccination is slightly longer (shorter) (Appendix Figure 9).

6. Discussion

Catch-up vaccination can be a cost-effective (or even cost-saving) health intervention, but catchup vaccination programs can become less cost-effective as newborn vaccination rates increase. Our models can be used to determine the optimal fraction of each age group to vaccinate, and when to stop such catch-up vaccination. Such information can help decision makers make the best use of limited health care resources now, and can assist with future public health planning.

We have shown that simple analyses, which ignore changes in future disease incidence caused by catch-up vaccination, can provide good solutions to the catch-up vaccination problem. This is particularly true for diseases such as hepatitis B; that is, incurable diseases with long infectious periods for which there is a stable infection reservoir in the population. Our simple model of when to stop catch-up vaccination (P3 with the approximate subproblem P2 and a simple estimate of constant future disease incidence) could be readily used by decision makers, as such a model requires significantly less data than a full dynamic model and can easily be implemented in a spreadsheet. The simple model requires estimates of vaccination cost as a function of how many people are vaccinated ($CV_a(x_a)$); net present health costs and QALYs for susceptible and immune individuals of a given age ($H_{a,R}$, $H_{a,S}$, $C_{a,R}$, and $C_{a,S}$, which can be estimated from a Markov or other model); the number of infected people in the population by age ($I_a(0)$); the total population size ($N(0)$); and current

disease incidence in different age groups ($i_a(0)$). Data to support estimation of these quantities are typically available to public health decision makers. The simple model provides insights which are likely to also hold when more detailed models of disease are used.

These results complement prior research examining vaccination programs using static and dynamic models of infection. Edmunds et al.[38] and Brisson and Edmunds[39] note that constant-force-of-infection models may be appropriate if mass immunization does not substantially alter herd immunity. We have found this to be the case for catch-up vaccination for a disease with a large, stable infection reservoir.

We illustrated our ideas using the example of hepatitis B catch-up vaccination in China. We showed that, even with 90% newborn vaccination coverage, it is still cost-effective to provide catch-up vaccination to preschool age children for decades into the future, particularly if the catch-up vaccination programs cannot reach all susceptible children. If only selected groups can be reached by catch-up vaccination, or if newborn vaccination coverage is lower than 90%, it is cost-effective to perform catchup vaccination even longer.

Our analysis has several limitations. Our dynamic model of infection (which we calibrated to observed hepatitis B incidence in the Chinese population for our example) assumes homogenous mixing. Since this is unlikely to be the case, the quantitative results should be interpreted with caution if used to inform decision making. For some diseases such as hepatitis B, there is little hard evidence on how population mixing affects disease spread other than in limited instances such as transmission from mother to child. However, it may be possible that a population exhibits preferential mixing patterns where certain age groups have higher infectious contact with certain other age groups: for example, young adults could preferentially transmit an infection through sexual contact with other young adults, or young children could preferentially transmit a bloodborne infection to other children through childhood cuts and scrapes. It is straightforward to modify our dynamic model given by (1) – (6) to incorporate preferential mixing and it is straightforward to write an expression for incidence in each age group (similar to (12)). If individuals mix preferentially with similar age groups, catch-up vaccination programs that target younger high-risk individuals could reduce the epidemic prevalence more quickly because these young individuals will be the most important reservoir infecting other young individuals in the future. The cutoff and age-out incidence estimates in Section 3.3 can be modified for the case of preferential mixing by replacing the assumption that the total population size is constant with the assumption that the number of people in each age group is constant. Additionally, our mathematical presentation in equations (1) – (6) used an SIR model, with the Infected state representing all infected individuals. A more detailed SICR model incorporating an additional Carrier state could also be used if it is desired to explicitly model transient versus chronic infection. Finally, our model does not include waning vaccine immunity. Although the assumption of lifelong immunity is likely appropriate for hepatitis B,[69, 70] waning immunity may be important to incorporate for other diseases. Waning immunity would lead to a longer continuation of catch-up vaccination efforts. Future analyses could incorporate waning immunity into the model.

Many countries also face a high burden of disease from hepatitis B. For example, Vietnam has chronic hepatitis B prevalence and death rates that are approximately twice as high as in China.[62, 71] Our models could be used to determine cost-effective catch-up vaccination levels for these settings. Our methods may also be applicable to other long-term chronic infectious diseases. For example, human papillomavirus (HPV) is an incurable, vaccine-preventable infection that may have a long infectious period. Thus, as for hepatitis B, a catch-up vaccination program is unlikely to have a major impact on the number of people currently infected, which means that it is unlikely to have a major impact on the infection risk. However, because the major mode of transmission of HPV is sexual, a dynamic transmission model with preferential mixing patterns might be more accurate than the model given by (1) – (6).

Our sensitivity analyses suggest that static models may be acceptable for evaluating catch-up vaccination programs that are supplemental and unlikely to have a large impact on the course of the epidemic. For an epidemic that is not in a steady state or when the catch-up vaccination program is likely to have an appreciable impact on the overall course of the epidemic, then a dynamic model may be needed to provide more accurate results.

No vaccines currently exist for human immunodeficiency virus (HIV) and hepatitis C virus although a number of trials for potential vaccines against these diseases are currently underway.[72, 73] If and when vaccines are developed for these diseases, the dissemination of these vaccines would likely follow a path similar to that of the hepatitis B vaccine: first to high-risk groups, then to young age groups and, finally, catch-up vaccination. If the disease spread is generalized (not concentrated in certain risk groups), then an analysis such as ours might be helpful once vaccine production levels are sufficient to allow for catch-up vaccination.

Newborn vaccination rates are insufficient to protect children from many diseases, making catchup vaccination an important and cost-effective health intervention. We have shown that simple models may be sufficient to give policymakers insight into the appropriate levels of catch-up vaccination and guidance as to how long catch-up vaccination should be continued. Such models can be especially helpful for diseases such as hepatitis B that are endemic and have a large infection reservoir.

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APPENDIX

Calculation of Optimal Vaccination Level

We characterize the optimal level of vaccination $x_\alpha^*(0)$, for P2, and show how it varies as a function of the newborn vaccination level, cohort age, disease incidence, and vaccination cost. The first two terms in (11) are positive (by assumption, catch-up vaccination generates an incremental health benefit to the person vaccinated, and reduces that person’s future health care costs) and increasing linearly in x_a, and the term $CV_a(x_a)$ is nonnegative, convex, and nondecreasing in x_a. Thus, the objective function of P2 is concave in x_a and has the following optimal solution:

$$x_\alpha^*(0)=\begin{cases} \hat{x}_\alpha(0) & 0<\hat{x}_\alpha(0)<x_\alpha^{\max}, S_\alpha(0)\left[\lambda\left(H_{\alpha,R}-H_{\alpha,S}\right)-\left(C_{\alpha,R}-C_{\alpha,S}\right)\right]\hat{x}_\alpha(0)e-CV_\alpha\left(\hat{x}_\alpha(0)\right)>0 \\ x_\alpha^{\max} & \hat{x}_\alpha(0)\geq x_\alpha^{\max}, S_\alpha(0)\left[\lambda\left(H_{\alpha,R}-H_{\alpha,S}\right)-\left(C_{\alpha,R}-C_{\alpha,S}\right)\right]\hat{x}_\alpha(0)e-CV_\alpha\left(\hat{x}_\alpha(0)\right)>0 \\ 0 & \text{otherwise} \end{cases}$$

where

$$\hat{x}_\alpha(0)=f'^{-1}\left(\frac{S_\alpha(0)e\left(\lambda\left(H_{\alpha,R}-H_{\alpha,S}\right)-\left(C_{\alpha,R}-C_{\alpha,S}\right)\right)-c_v\left(S_\alpha(0)+I_\alpha(0)u_{I,\alpha}+R_\alpha(0)u_{R,\alpha}\right)}{\left(S_\alpha(0)+I_\alpha(0)u_{I,\alpha}+R_\alpha(0)u_{R,\alpha}\right)}\right).$$

The optimal vaccination level may be zero, $x_a^{\max}$, or an interior point solution, $0<x_\alpha^*(0)<x_a^{\max}$. We note that if $f_a(x_a)=0$ (no costs above baseline), then $x_\alpha^*(0)=0$ or $x_a^{\max}$. Appendix Figure 3 shows the case of an interior solution.

Given the above expression for the optimal vaccination level, it is straightforward to establish the following.

Optimal Vaccination Level

The optimal vaccination level obtained by solving P2 is:

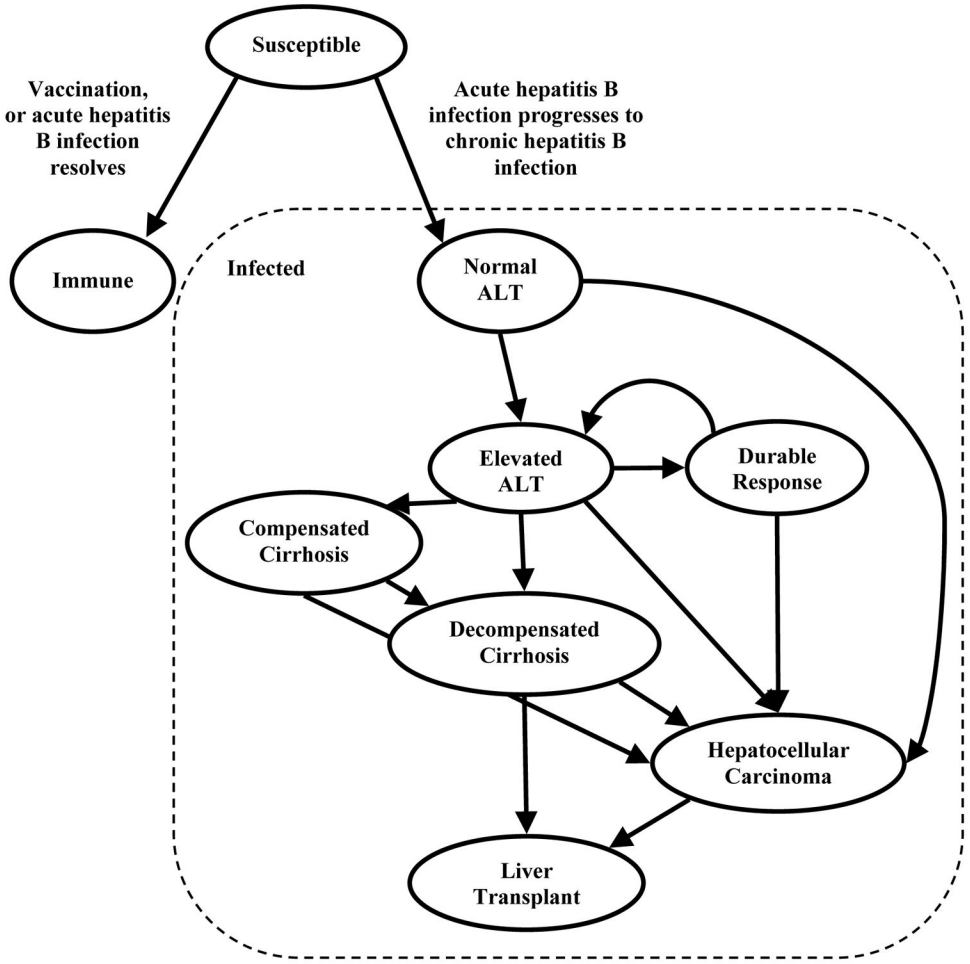
- **i.** nonincreasing in the newborn vaccination level $x_0(\cdot)$ (i.e., the level of prior immunity);
- **ii.** nonincreasing in cohort age α;
- **iii.** nondecreasing in the disease incidence $i_a(t)$; and
- **iv.** nonincreasing in vaccination cost $CV_a(x_a)$.

As the newborn vaccination level $x_0((\cdot)$ increases, the number of individuals who are immune but unaware of their immunity $R_a(0)$ $u_{R,a}$ will increase (because of our assumption that a constant fraction of immune individuals are unaware of their disease status); thus, for any given vaccination level, the fraction of vaccinations given to individuals who do not need it will increase. The benefits of catch-up vaccination are driven by the risk of infection and age. Benefits of catch-up vaccination are nonincreasing with the age of those vaccinated because younger children will live longer and will be exposed to more opportunities to become infected than adults: $(H_{a,R} - H_{a,S})$ and $(C_{a,R} - C_{a,S})$ will have nonincreasing differences with age. Thus, the optimal vaccination level is higher (or at least not lower) for younger age groups than for older age groups. A higher risk of infection will increase the monetary benefits of a vaccination program by increasing health benefits that accrue to successfully vaccinated individuals $(H_{a,R} - H_{a,S})$ and increasing the health savings for those individuals $(C_{a,R} - C_{a,S})$; thus, a higher risk of infection leads to a higher cost-effective level of catch-up vaccination. Finally, if the vaccination cost $CV_a(x_a)$ increases, the optimal vaccination level cannot increase.

Hepatitis B Model for China

The model of hepatitis B used in our example analysis includes additional health states for the "infected" health state, as shown in Appendix Figure 1. Appendix Table 1 provides values for parameters used in the model.

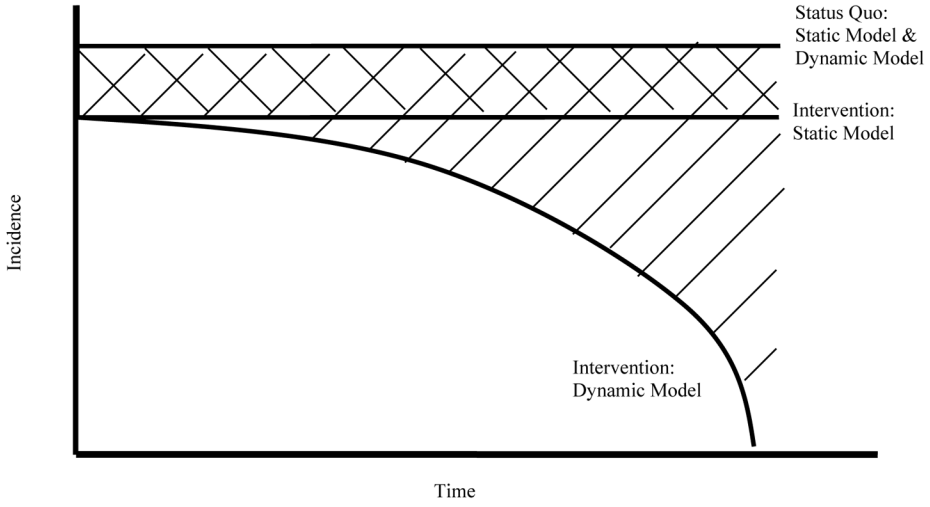
To estimate incidence of acute hepatitis B infection in unprotected individuals, we evaluated how prevalence has evolved over time in the population of children in China. We first calculated what we would expect prevalence of chronic disease to be at birth given expected chronic disease prevalence of 5% at birth without vaccination[85] and using observed birth-dose vaccination coverage and vaccine efficacy. We then used this along with information about the likelihood of acute infections becoming chronic to estimate the number of chronic infections and probability of immunity to hepatitis B in early childhood (ages 1–4 and 5–14). By varying the incidence of acute infection, we could see what incidence level would most closely match the observed prevalence of chronic infection and immunity. Knowing the incidence of acute infection and current prevalence in the entire population of China (7.4%) enabled us to calculate the rate of contact that is sufficient to transmit the infection, β. These calculations matched disease prevalence and immunity observed in the Chinese population approximately but not exactly, so we varied the value of β widely in sensitivity analysis.



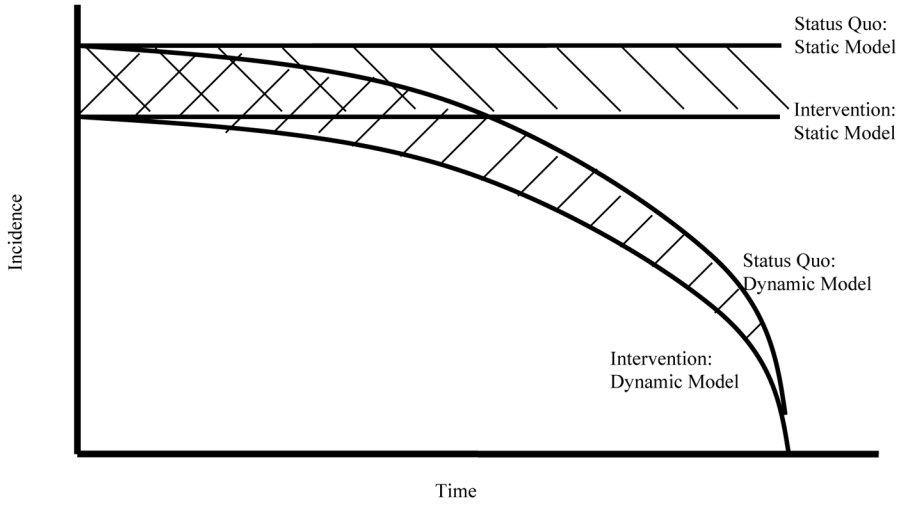
Appendix Figure 1.

Diagram of model of hepatitis B infection and progression*. This model is used in both P1 and P2. It is used to calculate the dynamic health effects and costs in P1 and used to calculate the long-term health effects and costs, $H_{a,d}$ and $C_{a,d}$ for P2.

* ALT = alanine aminotransferase. Circles represent health states. Lines represent transitions between those states. Although not shown, individuals with decompensated cirrhosis can also have other complications such as variceal bleeding, ascites, or encephalopathy. Additionally, the model is age-structured, so each disease state is indexed by age $a = 1, \ldots, A$ and at each time step individuals of age a transition to a disease state for individuals age $a+1$.



Appendix Figure 2a



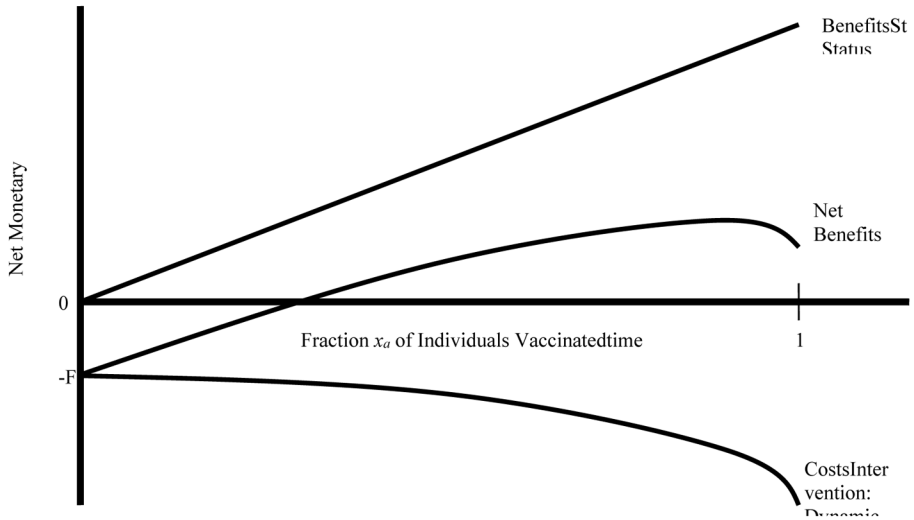
Appendix Figure 2b

Appendix Figure 2.

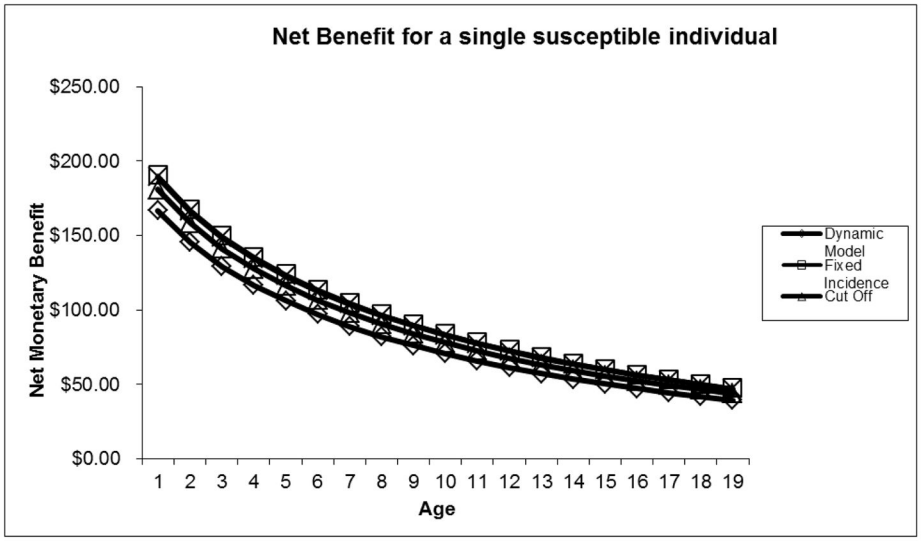
Projected incidence starting in a steady state epidemic (Appendix Figure 2a) and a declining epidemic (Appendix Figure 2b), under the status quo and in the presence of catch-up vaccination. The “northwest-southeast” diagonal lines represent the benefit projected using a static model. The “northeast-southwest” diagonal lines represent the benefit projected using the dynamic model.

Appendix Figure 2a: Projected incidence starting in a steady state epidemic. The reduction in incidence projected using the dynamic model is greater than that projected using a static model.

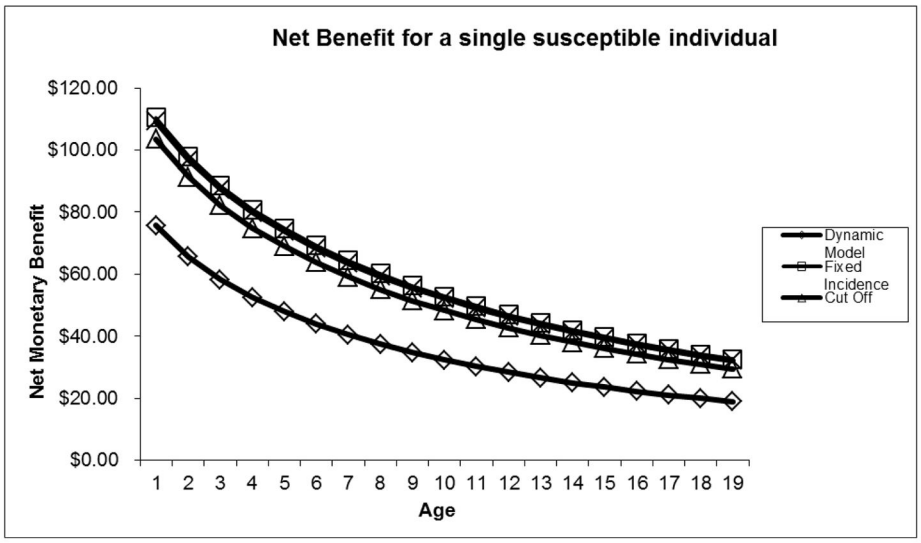
Appendix Figure 2b: Projected incidence starting in a declining epidemic. The reduction in incidence projected using the dynamic model is smaller than that projected using a static model.



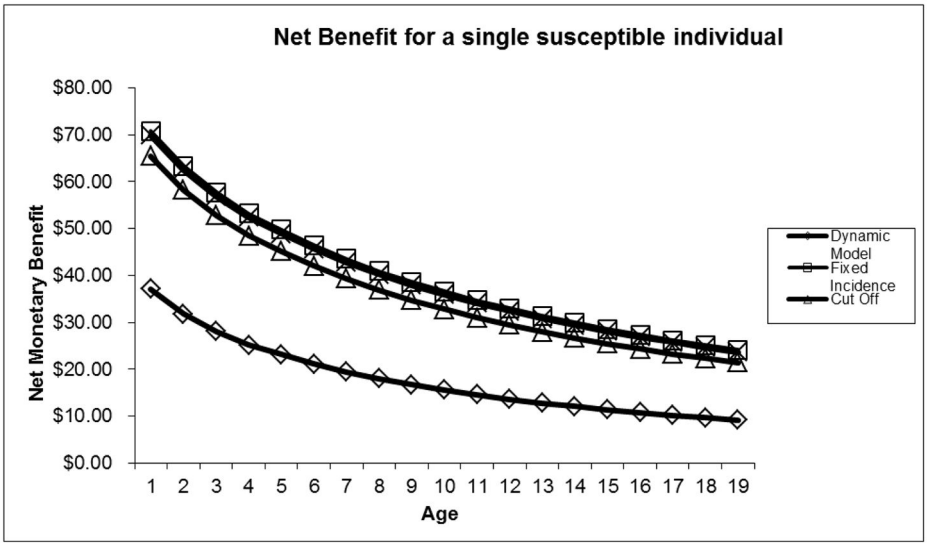
Appendix Figure 3.
Example of the form of the benefits, costs and net monetary benefit of vaccinating a fraction x_a of individuals in age group a.



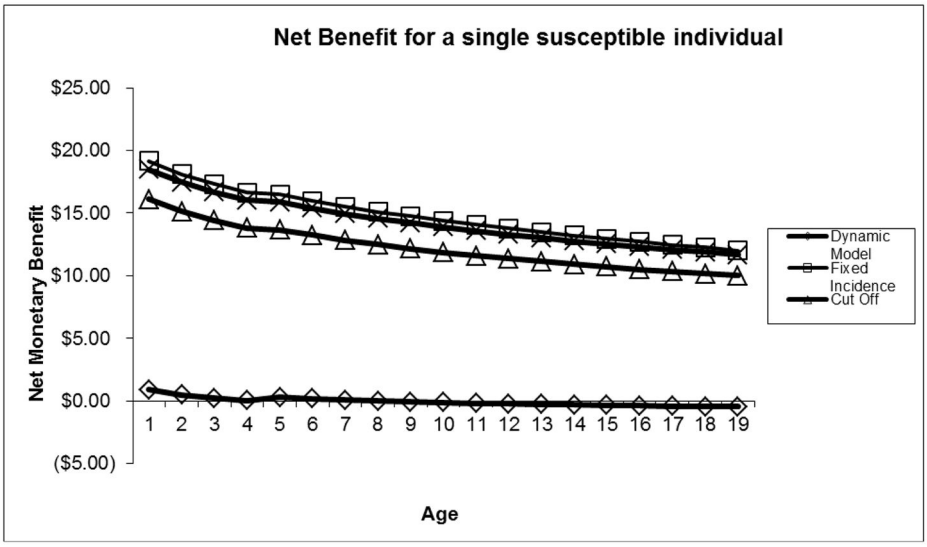
Appendix Figure 4a



Appendix Figure 4b



Appendix Figure 4c



Appendix Figure 4d

Appendix Figure 4.

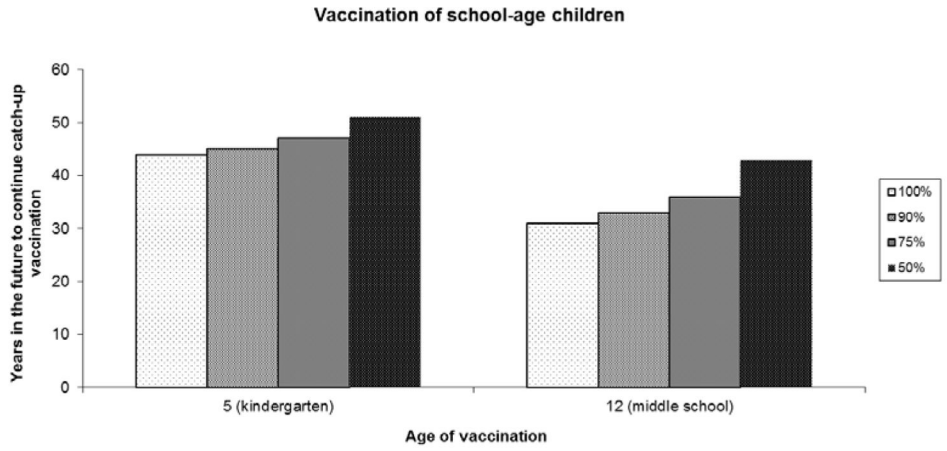
Hepatitis B example: Sensitivity analysis of net monetary benefit for a single susceptible individual as a function of rate of recovery from chronic hepatitis B infection.

Appendix Figure 4a: 1% annual recovery (and immunity) from chronic infection.

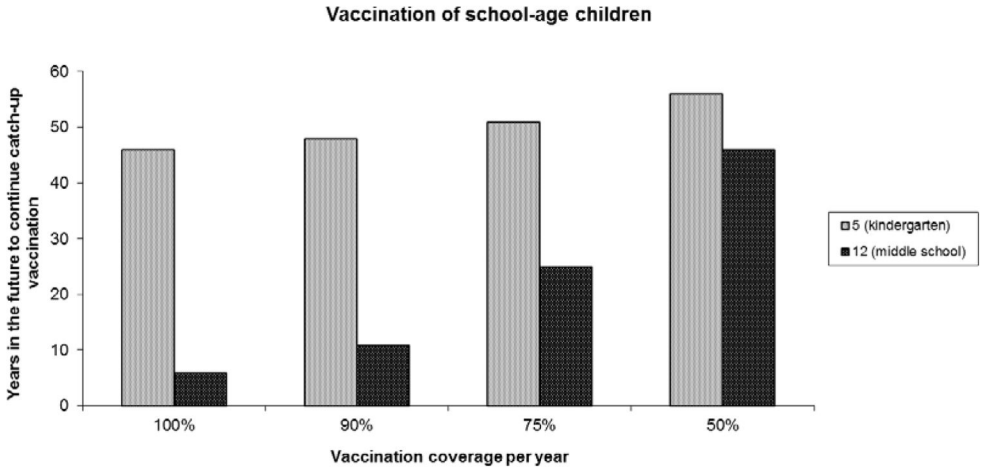
Appendix Figure 4b: 5% annual recovery (and immunity) from chronic infection.

Appendix Figure 4c: 10% annual recovery (and immunity) from chronic infection.

Appendix Figure 4d: 50% annual recovery (and immunity) from chronic infection.



Appendix Figure 5a



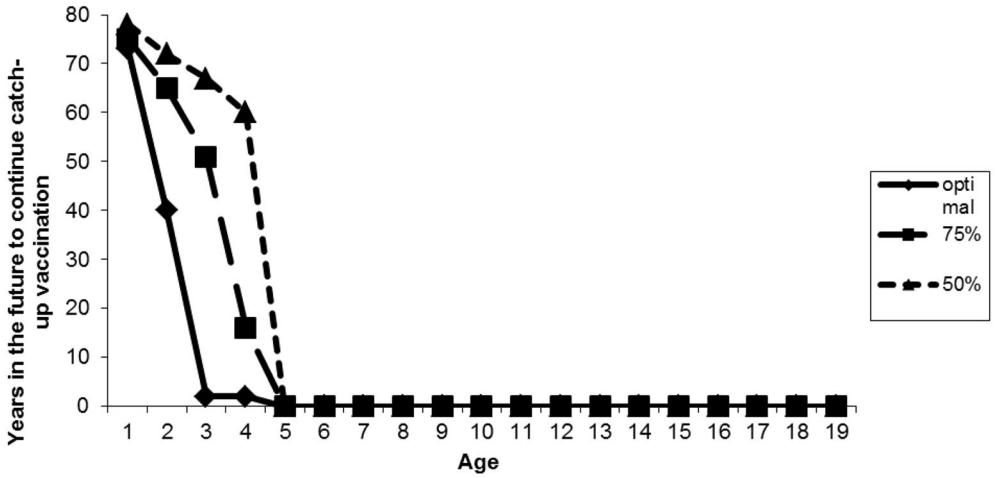
Appendix Figure 5b

Appendix Figure 5.

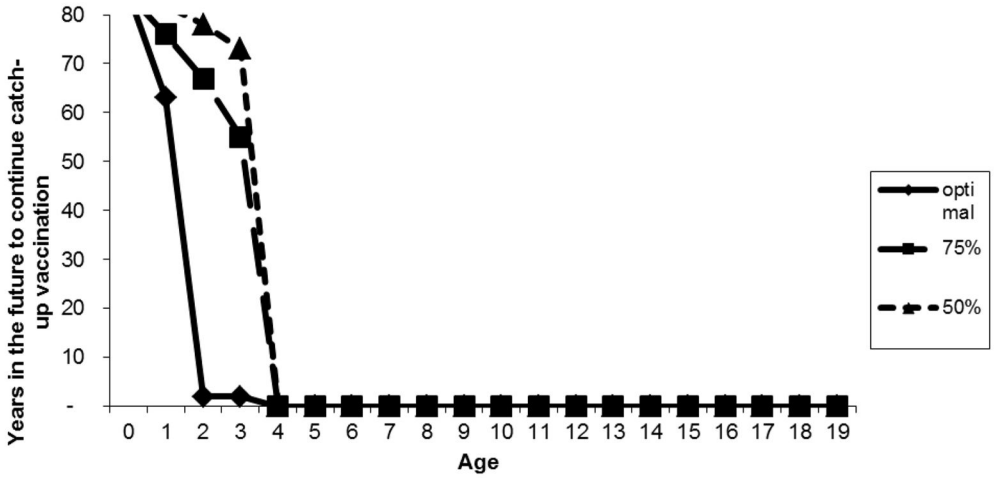
Hepatitis B example: Results for a lower transmission scenario (β at 1/10 of its initial value and the risk of mother-to-child transmission halved).

Appendix Figure 5a: Vaccination of 5-year-olds or 12-year-olds

Appendix Figure 5b: Vaccination of both 5-year-olds and 12-year-olds



Appendix Figure 6a



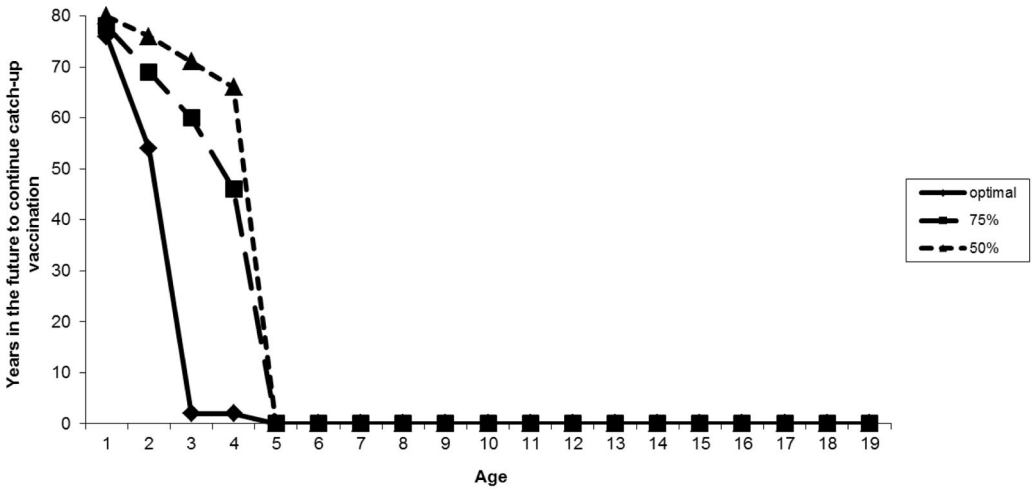
Appendix Figure 6b

Appendix Figure 6.

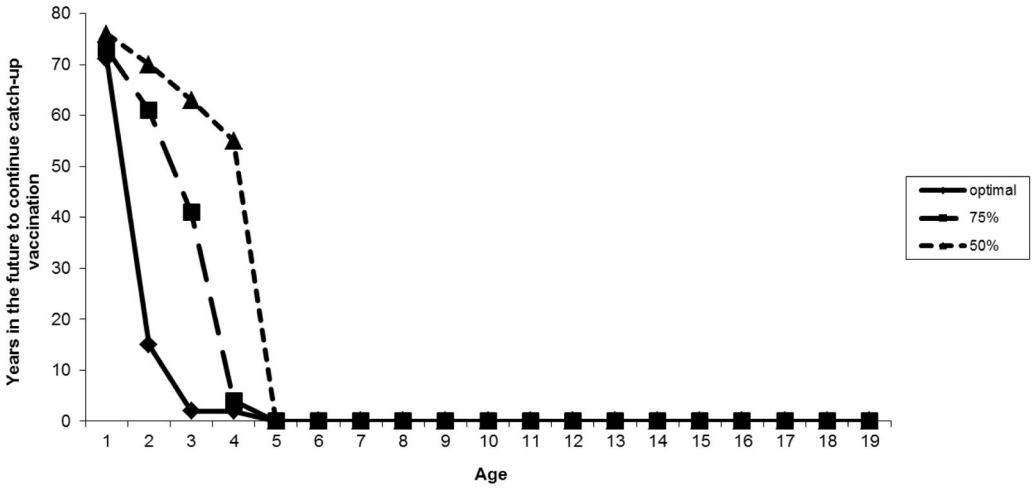
Hepatitis B example: Sensitivity to changes in awareness of hepatitis B serostatus.

Appendix Figure 6a: 90% birth coverage, with 50% aware of infection and 75% aware of serostatus

Appendix Figure 6b: 90% birth coverage, with 95% aware of infection and 95% awareness of serostatus

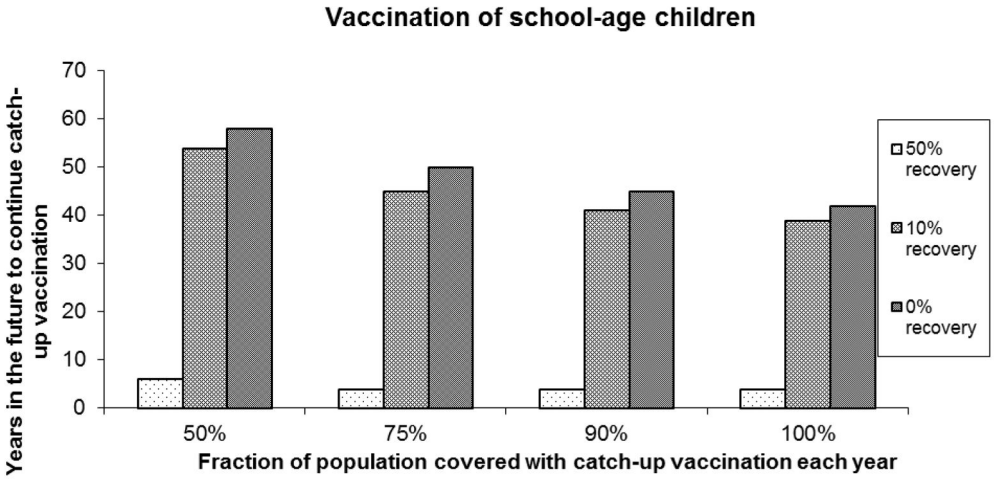


Appendix Figure 7a



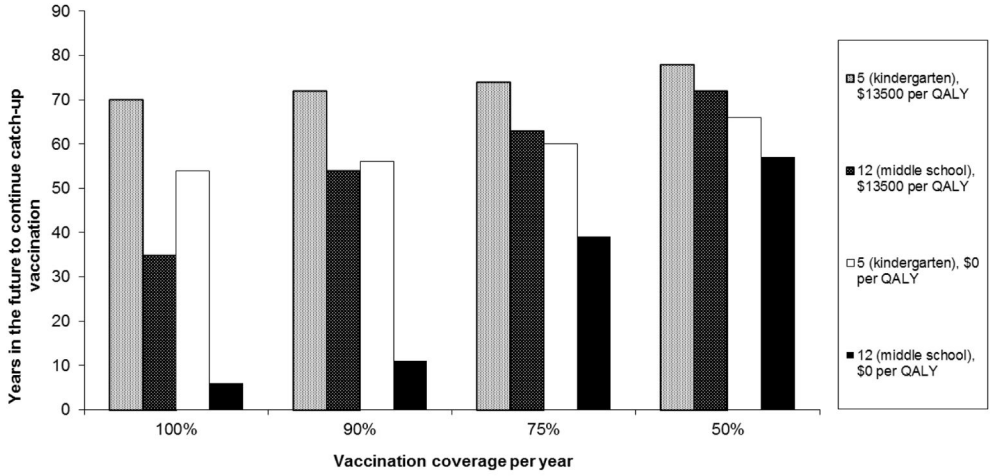
Appendix Figure 7b

Appendix Figure 7.
Hepatitis B example: Sensitivity to changes in discount rate.
Appendix Figure 7a: 90% birth coverage, with 0% discount rate
Appendix Figure 7b: 90% birth coverage, with 5% discount rate



Appendix Figure 8.

Hepatitis B example: Impact of rate of recovery from chronic hepatitis B infection on length of time to continue a catch-up vaccination program for all children ages 1–19.



Appendix Figure 9.

Hepatitis B example: Impact of willingness-to-pay threshold on the length of time to continue a vaccination program for both 5-year-olds and 12-year-olds.

Appendix Table 1

Hepatitis B model parameters.

Parameter	Value	Source
Probabilities		
Starting Population		
Compliance with vaccine intervention	70%	Assumed
Percent chronically infected who are aware of infection[1]	50%	[83, 84]
Percent aware who receive medical management	50%	Assumed

Parameter	Value	Source
Chronic infections that have elevated ALT	2.0%	Assumed
Already immune (given no chronic infection)	50%	Assumed
Aware of immunity (previous vaccination)	75%	Assumed
Protected by three doses of HBV vaccine	95%	81, 82, 86
Annual voluntary vaccination	0.5%	Assumed
Acute Infection		
Annual acute HBV infection incidence	1000/100,000	56, 87–91
Asymptomatic acute infections	90%	80, 92–95
Symptomatic acute infections that require hospitalization	12%	80, 92, 93
Hospitalized cases that are fulminant	4%	80, 92, 93
Fulminant cases that result in death	70%	80, 92, 93
Disease Progression parameters (annual probabilities)		
Normal ALT to elevated ALT[2]	0.15%	96
Normal ALT to HCC	0.34%	98
Durable virologic response while on treatment	15%	79, 99–102
Chronic HBV infection with elevated ALT to compensated cirrhosis	3.8%	76, 79
Chronic HBV infection with elevated ALT to HCC	1.5%	76, 79
Durable response relapse to elevated ALT	7%	79, 103, 104
Durable response to HCC	0.34%	98
Compensated cirrhosis to decompensated cirrhosis	7%	76, 79
Mortality from compensated cirrhosis	4.8%	76, 79
Mortality from decompensated cirrhosis	17.3%	76, 79
Cirrhosis to HCC	3.3%	76, 79, 105
Cirrhosis to cirrhosis with ascites	68%	79
Cirrhosis to cirrhosis with variceal bleeding	14.6%	79
Cirrhosis to cirrhosis with encephalopathy	10%	79
Receiving a liver transplant while in decompensated cirrhosis	1.5 %	76, 79, 106–108
Mortality from HCC	40.0%	76, 79, 109, 110
Mortality from HCC while on medical management (due to early detection)	20%	110
Receiving a liver transplant while in HCC	0.1%	76, 79, 108, 111–115
Mortality first year after liver transplantation	15%	76, 79
Mortality second and subsequent years after liver transplantation	1.5%	76, 79
Costs ($)		
Vaccine costs		
Vaccine (per dose)	0.34	15, 74, 1163
Vaccine administration (per dose)	0.60	116
Liver transplantation cost	30,000	76, 77
Annual treatment costs		
Fraction of patients on drug therapy while in durable response4	50%	Assumed
Drugs	2000	76, 78
Regular health monitoring	250	75, 77
Cirrhosis	2000	75–77

Parameter	Value	Source
Ascites	2500	75–77
Encephalopathy	2500	75–77
Variceal hemorrhage	2500	75–77
HCC	5000	75–77
Transplantation followup	3000	76
Annual normal health care costs	118	117
Discount rate	3%	118
Quality Multipliers		
Acute HBV infection	0.94	80
Chronic HBV infection, normal ALT	1.00	80, 99
Chronic HBV infection, elevated ALT	0.99	76, 80, 99
Durable response	1.00	79
Compensated cirrhosis	0.80	76, 79, 99
Decompensated cirrhosis	0.60	76, 79, 99
HCC	0.73	76, 79, 99
Liver transplant	0.86	76, 79, 99

HBV – hepatitis B virus; ALT – alanine aminotransferase

1 Percentage of all chronically infected individuals who are aware of their infection

2 This value was estimated from 96, and then calibrated to yield approximately 25% mortality from untreated liver disease 86, 97.

3 Personal communication with physicians in China

4 Some therapies are discontinued if the therapy suppresses the virus. This parameter is the fraction of patients who continue on drug therapy after the therapy has suppressed the virus into a “durable response.”

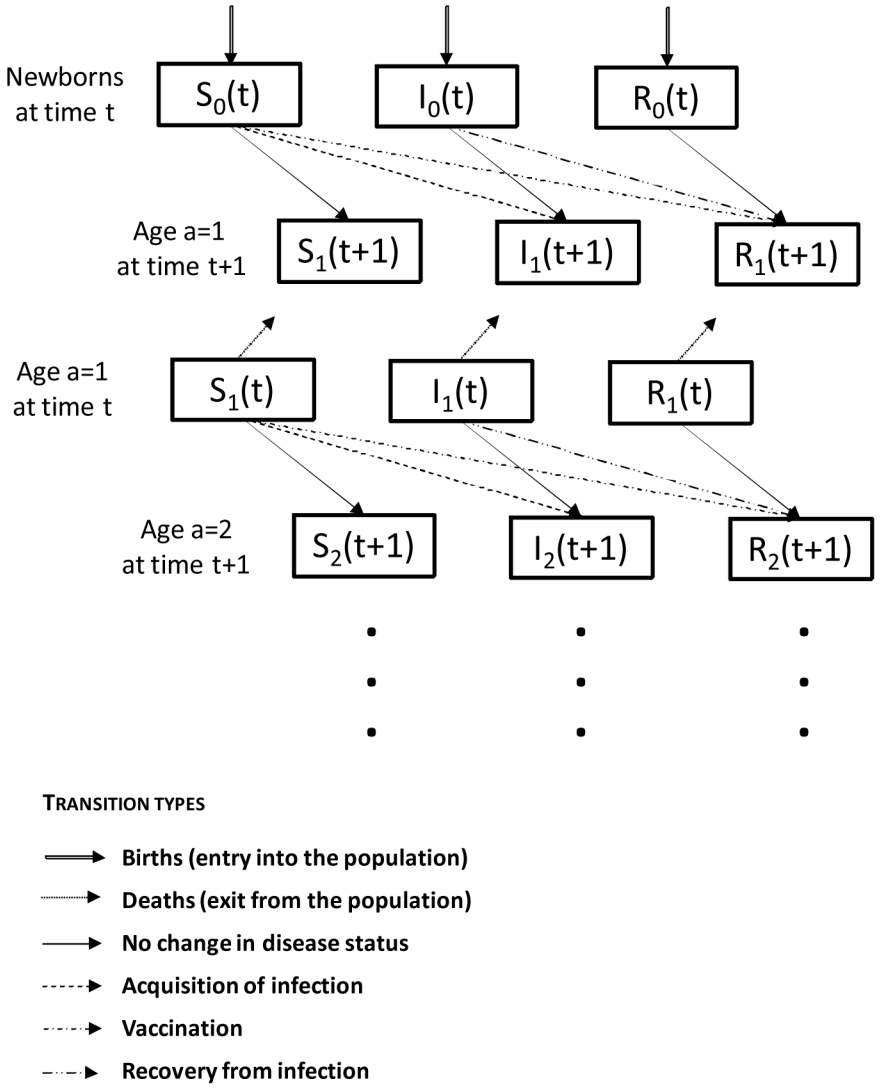


Figure 1.

Schematic of age-structured SIR model, showing transitions that occur from time period *t* to time period *t*+1. The model incorporates ages $a = 0, 1, \ldots, A$ and time periods $t = 0, 1, \ldots, T$.

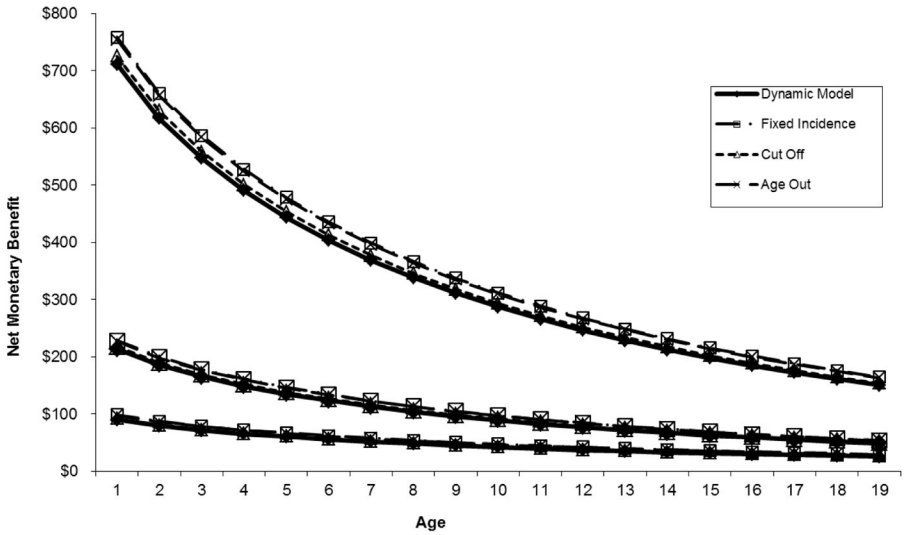


Figure 2.

Hepatitis B example: Effect of different incidence estimates on the net monetary benefit of vaccinating a single susceptible individual, the first two terms in the objective function of P2 (which excludes secondary infections). The top sets of lines are for willingness-to-pay values of $13500 per QALY, the second set of lines are for willingness-to-pay values of $4500 per QALY, and the bottom set of lines are for willingness-to-pay values of $0 per QALY.

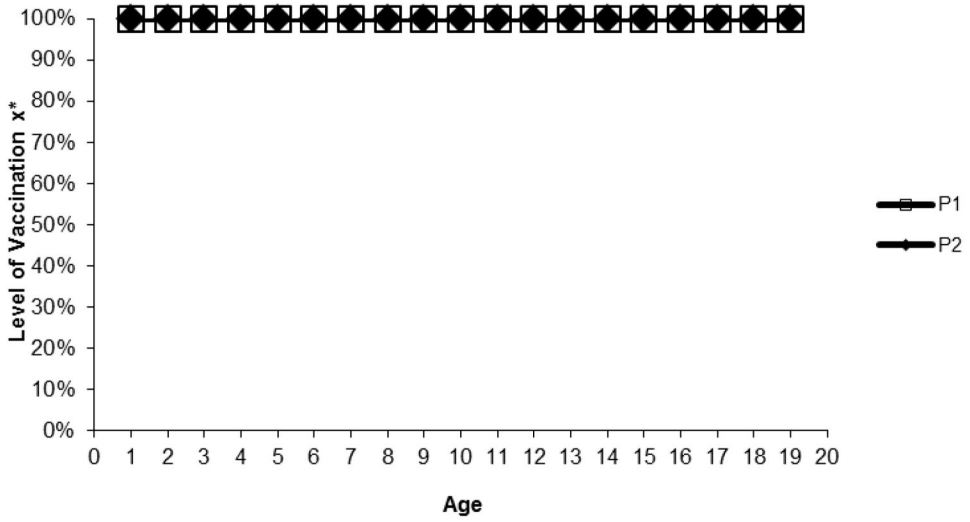


Figure 3.

Hepatitis B example: Optimal fraction of each age group to vaccinate, obtained by solving P1 (which includes secondary infections) and P2 (which excludes secondary infections) using the assumption of constant incidence and assuming λ = \$4500/QALY.

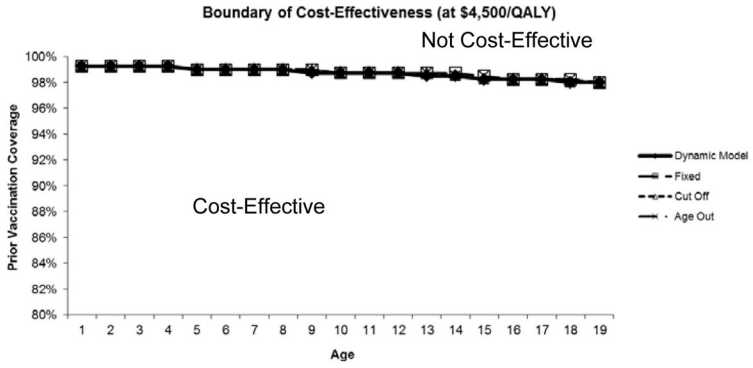


Figure 4a

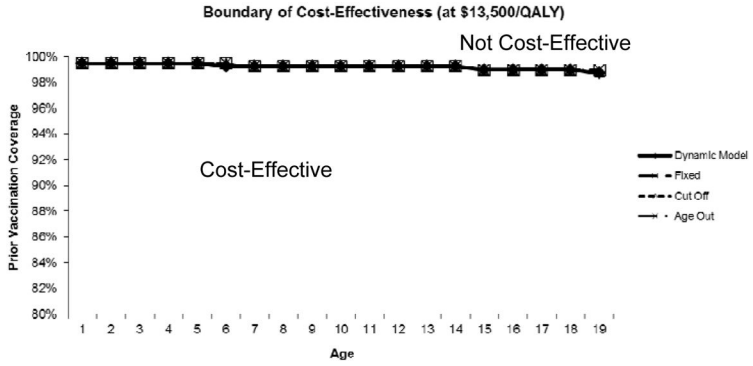


Figure 4b

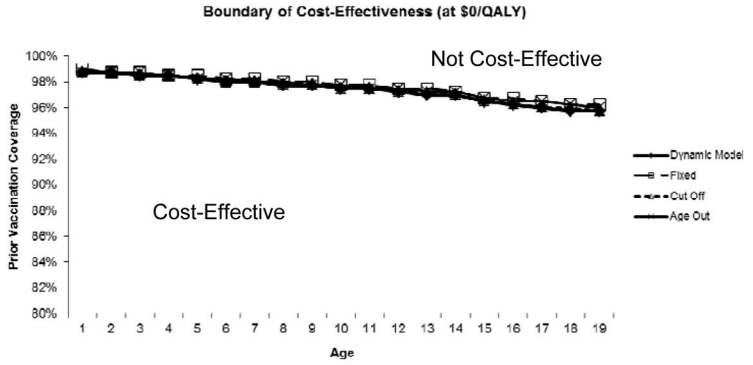


Figure 4c

Figure 4.

Hepatitis B example: Policy space of cost-effectiveness for various ages and levels of prior vaccination coverage for different incidence estimates, obtained by solving P2 (which excludes secondary infections) with λ = \$4500/QALY (Figure 4a), \$13,500/QALY (Figure 4b), and \$0/QALY (Figure 4c). Each line represents the prior vaccination coverage level such that catch-up vaccination costs \$4500/QALY gained (Figure 4a), or \$13,500/QALY gained (Figure 4b), or \$0/QALY gained (Figure 4c). Areas above the lines are regions in which the catch-up vaccination intervention is not cost-effective and areas below the lines are regions in which the intervention is cost-effective.

Figure 4a: Willingness-to-pay $4500/QALY gained
Figure 4b: Willingness-to-pay $13500/QALY gained
Figure 4c: Willingness-to-pay $0/QALY gained

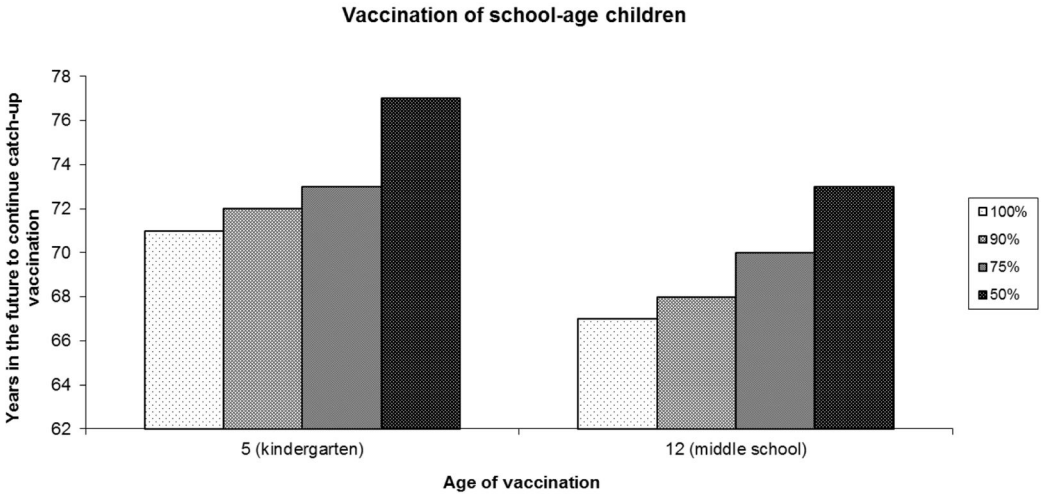


Figure 5a

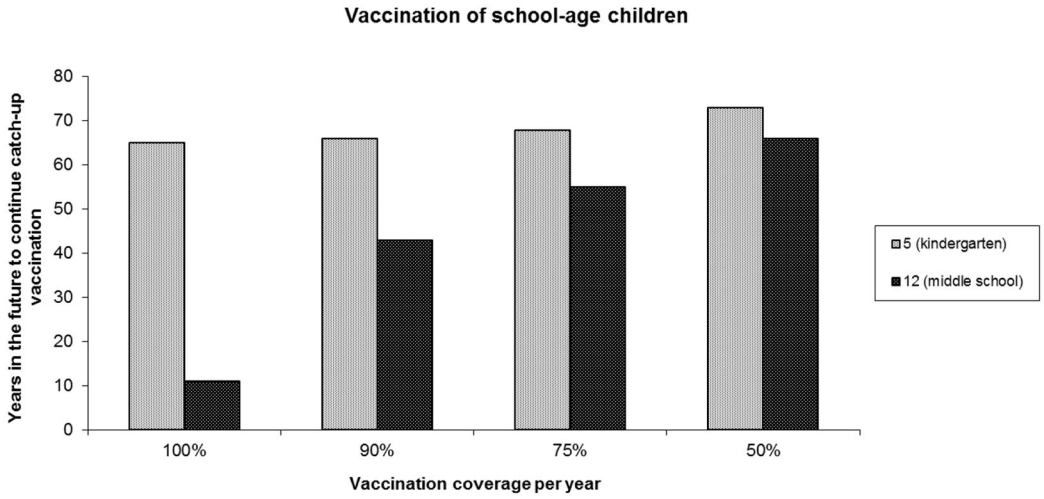


Figure 5b

Figure 5.

Hepatitis B example: Number of years for which it is cost-effective to perform catch-up vaccination for hepatitis B in children ages 5 and 12, obtained by solving P3, and assuming λ = \$4500/QALY. The newborn vaccination rate is assumed to be 90%. The optimal solution is the maximum allowable level of catch-up vaccination each year until it is no longer cost-effective. We consider 50%, 75%, 90%, and 100% maximum achievable vaccination coverage. Figure 5a shows two cases, 5-year-olds vaccinated or 12-year-olds vaccinated, and Figure 5b shows the case of a joint vaccination program that vaccinates both 5-year-olds and 12-year-olds.

Figure 5a: Vaccination of 5-year-olds or 12-year-olds

Figure 5b: Vaccination of both 5-year-olds and 12-year-olds

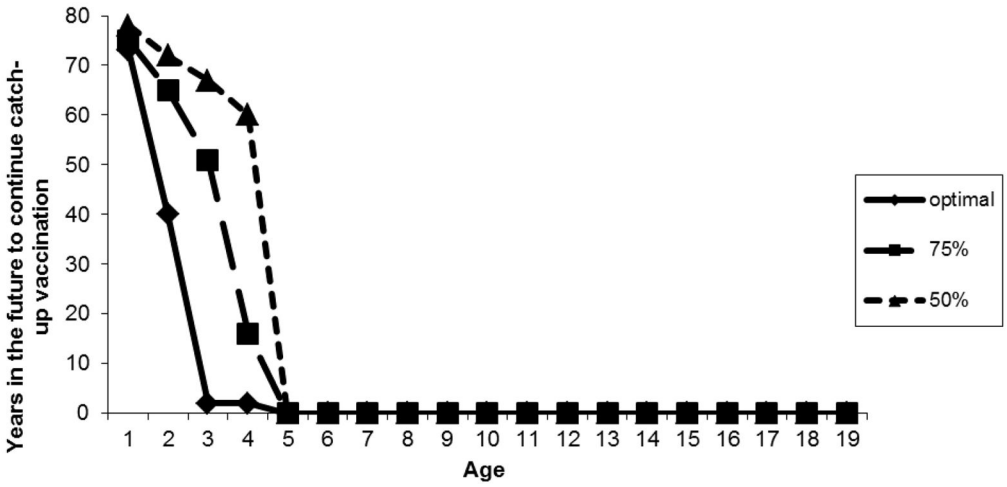


Figure 6a

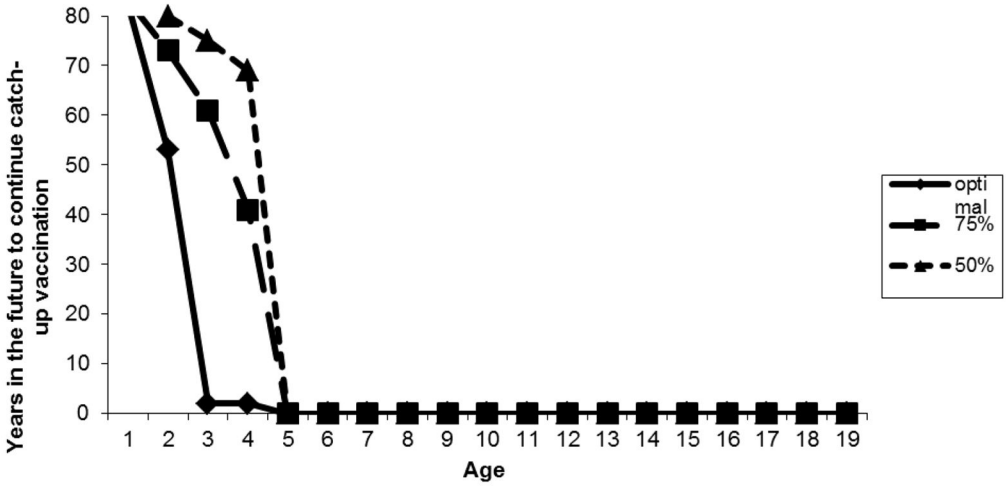


Figure 6b

Figure 6.

Hepatitis B example: Number of years for which it is cost-effective to perform catch-up vaccination for hepatitis B in children age 19 and younger, obtained by solving P3, and assuming λ = \$2500/QALY. The newborn vaccination rate is assumed to be 90% in Figure 6a, and 75% in Figure 6b. Each line represents a different possible x* (fraction vaccinated each year): the optimal solution is 100% catch-up vaccination of age groups each year until it is no longer cost-effective; the figure also shows the case of lower vaccination levels (50% and 75%).

Figure 6a: 90% newborn vaccination coverage

Figure 6b: 75% newborn vaccination coverage

Table 1

Model notation.

Variable	Description
t	Time index; $t = 0, 1, \ldots, T$
a	Index for age groups; $a = 0, 1, \ldots, A$; $a = 0$ represents newborns
$x_a(t)$	Fraction of eligible individuals of age a vaccinated during time period t, $0 \le x_a(t) \le x_a^{\max}$; $x_0(t)$ represents vaccination at birth
$S_a(t)$	Number of susceptible individuals in age group a in time period t; $S_a(0) = S_{a,0}$, $a > 0$
$I_a(t)$	Number of infected individuals in age group a in time period t; $I_a(0) = I_{a,0}$, $a > 0$
$R_a(t)$	Number of immune individuals in age group a in time period t; $R_a(0) = R_{a,0}$, $a > 0$
$N_a(t)$	Total number of individuals in age group a in time period t; $N_a(t) = S_a(t) + I_a(t) + R_a(t)$
$N(t)$	Total number of individuals in the population in time period t; $N(t) = \sum_{a=0}^{A} N_a(t)$
β_a	Disease sufficient contact rate for individuals of age a (rate of contact between susceptible individuals of age a and infected individuals that is sufficient to transmit the infection)
$i_a(t)$	Risk of infection to a susceptible individual of age a in time period t, $0 \le i_a(t) \le 1$
φ_a	Fertility rate for individuals in age group a (averaged across males and females)
p_0	Chance that an unvaccinated child is infected perinatally and develops chronic infection
p_a	Chance that an acute infection in a person of age $a > 0$ will become a chronic infection
ν	Rate of recovery from the chronic infection, $\nu \ge 0$
$\mu_{a,d}$	Fraction of individuals of age a in disease state d who die in any time period
e	Effectiveness of the vaccine at inducing immunity in a susceptible individual
$u_{I,a}$	Fraction of infected individuals in age group a who are unaware of their infection
$u_{R,a}$	Fraction of immune individuals in age group a who are unaware of their immunity
c_{ad}	Health care cost per unit time for a person of age a in disease state d
q_{ad}	Quality-of-life multiplier for a person of age a in disease state d
$C_{a,d}$	Expected net present health care costs for a person of age a in disease state d
$H_{a,d}$	Expected net present health effects measured in quality-adjusted life years (QALYs) for a person of age a in disease state d
F	Fixed cost of the catch-up vaccination program; $F \ge 0$
c_v	Baseline marginal cost to vaccinate one person
$f_a(x_a(t))$	Cost above baseline per person vaccinated, as a function of the fraction $x_a(t)$ of age group a vaccinated; assumed to be nonnegative, nondecreasing, and convex in $x_a(t)$
$CV_a(x_a(t))$	Total cost of vaccinating a fraction $x_a(t)$ of individuals in age group a
λ	Monetary value of health effects
r	Discount rate for costs and health benefits

Table 2

Key parameter values for numerical example of hepatitis B in China.

Parameter	Base Value	Source
Newborn vaccination coverage, x_0 (t)	90%	[4, 58]
Maximum allowable catch-up vaccination level, $x_a^{\max}$, a = 1, …, 19	1	Assumed
Fixed cost of vaccination program, F	$0	Assumed
Baseline marginal cost of vaccination, c_v	$2.82	[10, 74]
Cost of vaccination above baseline, $f_a(x_a)$	0 for x_a <0.5 $c_v(2x_a-1)$ for $x_a \geq 0.5$	[50–53]
Monetary value of a year of full health, λ	$4500/QALY	Based on per capita GDP[66–68]
Population size, $N(0)$	1.3 billion	[68]
Health care cost per year, $c_{a,d}$	$118–$5,000*	[10, 75–78]
Quality multiplier for health states, $q_{a,d}$	0.6–1.0*	[10, 33, 76, 79, 80]
Vaccine effectiveness, e	0.95	[10, 44, 81, 82]
Fraction of infected who are unaware of their infection, $u_{I,a}$	50%	[10, 83, 84]
Fraction of immune who are unaware of their immunity, $u_{R,a}$	25%	[10]
Sufficient contact rate, β_a	0.135	Based on calculations from [10, 58]
Discount rate, r	3%	[18]

* Costs vary by disease state (see Appendix Figure 1), from $118 for healthy individuals to $5,000 for those with liver cancer. Quality multipliers vary from 0.6 for those with decompensated cirrhosis to 1.0 for healthy individuals. Details are provided in Appendix Table 1.