Eradicating a Disease: Lessons from Mathematical Epidemiology

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> *But perhaps we will attain more surely the end that we propose, if we add here an evaluation of the ravage of natural smallpox, & of that which one can gain in procuring it artificially.* —Daniel Bernoulli, 1760 [**2**, p. 4].

May 8, 1980, smallpox was declared dead. Over its brutal run this scourge took hundreds of millions of lives—mostly children—and left billions more sickened, scarred, or blinded. The global eradication of smallpox was a stunning achievement, a wondrous, chilling, solemn triumph for medicine, mathematics, and the will of a world to look after its own.

Three decades later, smallpox remains, however, the only human infectious disease eradicated. How can we repeat this success? The science of mathematical epidemiology has evolved into a rich discipline committed to this question. New mathematical models are promisingly agile and robust, while twenty-first century computational firepower provides the leverage for their analysis. Moreover, the ranks of those working in the field of mathematical epidemiology have swelled in the post-smallpox years. Compartmental models, like the classic *susceptible–infected–removed* (SIR) model, for example, are now a key component of many undergraduate differential equations classes; articles written to help integrate the field into collegiate mathematics have appeared in this JOURNAL [**17, 18, 19**], and elsewhere. (See also the article by Ronald Mickens in this issue.)

How then can we best use new resources, interest, and commitment to address the fundamental questions of mathematical epidemiology? In the classroom, perhaps the place to begin is with a re-examination of the central ideas of the field through the lens of some of their earliest incarnations.

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Daniel Bernoulli and variolation

Daniel Bernoulli (1700–1782) was not the first mathematical epidemiologist, but few would dispute the magnitude of his contribution to the science. In his fifties, already established as a respected physician, professor of anatomy, physiology, botany, physics and mathematics, Bernoulli turned his attention to the problem of smallpox.

Smallpox (*Variola major* and its less virulent cousin, *Variola minor*) is a viral disease spread from person to person by face-to-face or direct contact with bodily fluids or contaminated objects. Following a one- to two-week incubation period, infected persons generally develop fevers, rashes, and eventually the pustules which give the disease its name. Bernoulli estimated that approximately three quarters of all persons alive in the eighteenth century had been infected with smallpox [**5**, p. 275]. It has been subsequently noted in [**1**, p. 458] that "at times, in certain cities, the smallpox mortality was not less than one-sixth of the birth rate." Those infected either die, or recover with immunity to the disease.

It is this immunity that made the idea of eradication feasible. "Artificial immunity" against smallpox could be induced via inoculation—a process in Bernoulli's time that was achieved by *variolation*. Variolation involved deliberately infecting a patient with the less deadly *Variola minor* strain of smallpox when he or she was in good health. In eighteenth-century Europe this was typically done by rubbing material from a smallpox pustule into a scratch on the patient's hand or arm. As a result, the patient would develop a localized, less deadly form of the virus. Under the best circumstances, he or she would recover with acquired immunity to smallpox.

In [**3**] Bernoulli attempted to quantify the rewards of universal inoculation against smallpox. He cited expected survival rates from an actuarial "life table" constructed by Edmund Halley (discoverer of the eponymous comet). With this data as a baseline survival curve for a population subject to smallpox mortality, Bernoulli calculated, for each age from birth to twenty-five years, the fraction of each population never before infected by smallpox (and hence susceptible to it). In his calculations, Bernoulli assumed that the risk of contracting smallpox for any susceptible individual at any age was constant: 12.5%. Further, he assumed an age-independent case fatality rate, also 12.5%. Tracking a hypothetical cohort of 1,300 newborns inoculated at birth, Bernoulli was able to compare Halley's baseline survival table with one for a population in which smallpox had been completely eradicated. Table 1 shows that in the absence of death due to smallpox, seventy-nine more newborns of Bernoulli's hypothetical cohort of 1,300 would survive to see their twenty-fifth birthday. This calculation, he stated, could also be viewed as an increase in life expectancy: from twenty-six years, seven months, to twenty-nine years, nine months.

Bernoulli's paper was first presented at the Royal Academy of Science in Paris in 1760, and published in 1766. In crafting his argument for universal inoculation against smallpox, Bernoulli made a tremendous contribution to mathematical epidemiology; he created what is thought to be the very first compartmental model of an infectious disease. The definitive source on his mathematical approach is Dietz and Heesterbeek [**8**]. Within their rich treatment, they translate Bernoulli's model into the language of modern mathematics, and express the dynamics between two disjoint, age-dependent classes, the *susceptible* and the *immune*.

Bernoulli's paper is notable for its decidedly political and economic tone; he argued that a "Civil Life" begins at seventeen, "the age at which one is beginning to be useful to the State" [**5**, p. 287], and points to an additional 25,000 civil lives produced by the end of smallpox mortality. This is perhaps why, in contrast to more modern compartmental models, Bernoulli chose to use *age*, rather than time, as the independent

Table 1. This Table enables us to see at a glance how many out of 1,300 children, supposed born at the same time, would remain alive from year to year up to the age of twenty-five, supposing them liable to smallpox; and how many would remain if they were all free from this disease; with the comparison and the difference of the two states—D.B. [**5**, pp. 276–278].

Ages by years	Natural state with smallpox	State without smallpox	Difference or gain
0	1,300	1,300	0
1	1,000	1,017.1	17.1
2	855	881.8	26.8
3	798	833.3	35.3
4	760	802.0	42.0
5	732	779.8	47.8
6	710	762.8	52.8
7	692	749.1	57.2
8	680	740.9	60.9
9	670	734.4	64.4
10	661	728.4	67.4
11	653	722.9	69.9
12	646	718.2	72.2
13	640	714.1	74.1
14	634	709.7	75.7
15	628	705.0	77.0
16	622	700.1	78.1
17	616	695.0	79.0
18	610	689.6	79.6
19	604	684.0	80.0
20	598	678.2	80.2
21	592	672.3	80.3
22	586	666.3	80.3
23	579	659.0	80.0
24	572	651.7	79.7
25	565	644.3	79.3

variable in his model. From [**8**, pp. 5–6], let $u(a)$ represent the proportion of newborns who will remain alive and susceptible (i.e., never infected) at age a, and $w(a)$ the proportion of those at age a, who are alive with immunity to smallpox acquired through recovery from infection. In this model, the proportion of those actively infected is discounted due to the relatively brief duration of the illness with respect to the length of the average life.

At any age a, let $\lambda(a)$ be the rate of infection of susceptibles; $s(a)$ the rate of recovery among the infected; and $\mu(a)$ the rate of death unrelated to smallpox. One arrives at the differential equations:

$$\frac{du}{da} = -\left[\lambda(a) + \mu(a)\right] u(a), \tag{1}$$

and

$$\frac{dw}{da} = \lambda(a)s(a)u(a) - \mu(a)w(a). \tag{2}$$

Since all newborns begin life in the susceptible class, we can take as initial conditions $u(0) = 1$ and $w(0) = 0$. Equation (1) can be solved via an integrating factor $\delta_u(a)$:

$$\delta_u(a) = \exp\left[\int_0^a \lambda(\tau) + \mu(\tau)\, d\tau\right],$$

to give

$$u(a) = \exp\left[-(\Lambda(a) + M(a))\right], \tag{3}$$

where

$$\Lambda(a) = \int_0^a \lambda(\tau)\, d\tau,$$

and

$$M(a) = \int_0^a \mu(\tau)\, d\tau.$$

Substituting (3) into (2) with integrating factor

$$\delta_w(a) = \exp\left[\int_0^a \mu(\tau)\, d\tau\right]$$

gives

$$w(a) = \exp\left[-M(a)\right] \int_0^a s(\tau)\lambda(\tau)\, e^{-\Lambda(\tau)}\, d\tau.$$

The probability of survival through age a is given then by the *survival function* $l(a)$:

$$l(a) = u(a) + w(a). \tag{4}$$

Notice that we can model a population without smallpox via $\lambda(a) = 0$; the quantities $\Lambda(a)$ and $w(a)$ vanish, returning the survival function $l_0(a) = \exp\left[-M(a)\right]$.

In practice, of course, it is impossible to eliminate smallpox infectivity among the susceptible class. Bernoulli's analysis led him to propose, in effect, the opposite: universal inoculation of all susceptibles. Yet variolation was not without risk—this 'artificial smallpox' could be (unintentionally) contagious or fatal. In adjusting his model to include the dangers of variolation, Bernoulli began with the following philosophical question:

> It is, then, only the risk which is attributed to inoculation which should keep us undecided... 'What would be the state of the human race if, at the price of a certain number of victims, we could procure for it freedom from natural smallpox?' [**5**, p. 284]

This question was a difficult one for many, as the risks of inoculation were poorly quantified at that time; variolation was alternately advocated and scorned in Bernoulli's day. In the American colonies, for example, George Washington's troops were inoculated before the siege of Boston in 1775, yet after the Revolutionary War, many American cities prohibited the practice entirely [**1**, p. 466]. Additional scientific advances would be required to forward the cause of smallpox eradication.

Milkmaids, cowpox and the birth of vaccine

Some thirty years after Bernoulli's paper, an English doctor named Edward Jenner became the first to document *vaccination*, a significant medical improvement to variolation, scientifically. "Country lore" had long suggested that milkmaids were disproportionately spared the scourge of smallpox, having gained immunity via exposure to cowpox among the herd. In 1796, Jenner inoculated his gardener's eight-year-old son James Phipps, with material from a cowpox lesion on the hand of local milkmaid Sarah Nelmes. Seven weeks later, Jenner "challenged" Phipps by injecting him with variolated smallpox material; the injection site showed no immunological response, demonstrating the boy's newly acquired immunity. The experiment was repeated some twenty times throughout Phipps's life, again with no response [**1**]. While Jenner's treatment did not mark the first human cowpox inoculation, he was the first to document its success scientifically. Jenner coined the term "vaccination" to describe the procedure, from the Latin *vacca* for cow. The safer practice of vaccination eventually replaced variolation, and its role is central in the discussion of the eradication of smallpox.

Modern compartmental models

Much has been written about compartmental epidemiological models. Those proposed by Kermack and McKendrick in 1927 [**14**] are often credited as the first modern models of disease dynamics; their approach has proven both flexible and robust. Here we describe briefly some of the features of these models insofar as they shed light on eradication. For greater depth, consider the treatments found in [**6, 9, 15**] and elsewhere.

The path of many viral epidemics, including smallpox, can be described by counting the fraction of a population in each of four disjoint subsets, or compartments: *susceptible*, *exposed* (infected, but not yet infectious), *infectious*, and *removed* (that is, vaccinated, recovered with immunity, or dead from the disease). Together, the four compartments comprise the modern SEIR model; combining the *exposed* and *infectious* compartments into a single *infected* compartment, we arrive at the even better known SIR model (see Figure 1).

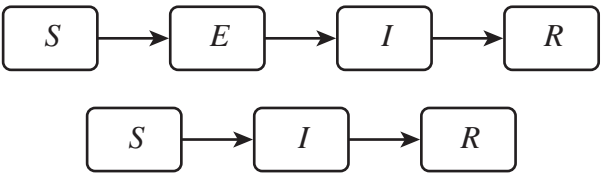


Figure 1. The *Susceptible–Exposed–Infectious–Removed* (SEIR) model and the simpler *Susceptible–Infected–Removed* (SIR) model.

The SEIR and SIR models share much in terms of qualitative behavior, and for ease of discussion we focus here on the SIR model. This model incorporates four basic assumptions. While certainly not exact in describing any real epidemic, these assumptions offer a mathematically useful, if naive, simplification of epidemiological behavior. These assumptions are:

- The population in question is uniformly mixed; that is, every pair of individuals is equally likely to interact;

- with respect to a transmission rate β, the law of mass action holds: in a population of size N, an average infected I makes contact sufficient to transmit infection to βN susceptibles S per unit time;
- the length of the infectious period is exponentially distributed with a mean of α^{-1}:

$$\int_0^\infty \alpha s e^{-\alpha s}\, ds = \int_0^\infty e^{-\alpha s}\, ds = \frac{1}{\alpha};\ \text{and}$$

- there is no entry into or out of the population with the possible exception of death through disease.

This final assumption restricts the SIR model to the analysis of outbreaks which occur over a short timespan so that births, and deaths unrelated to the disease, may be disregarded. Fortunately for our analysis, smallpox is one such virus. Combining these assumptions leads to the following differential system [**14**]:

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= \beta SI - \alpha I, \\ \frac{dR}{dt} &= \alpha I. \end{aligned} \tag{5}$$

Notice from the first two equations in (5) that the growth of the susceptible and infected classes is independent of the size of the removed class R. We can therefore simplify the system:

$$\frac{dS}{dt} = -\beta SI, \tag{6a}$$

$$\frac{dI}{dt} = (\beta S - \alpha)\, I, \tag{6b}$$

and recover an expression for R once S and I are known. Dividing (6b) by (6a) gives

$$\frac{dI}{dS} = -1 + \frac{\alpha}{\beta S},$$

which we can integrate with respect to S:

$$I = -S + \frac{\alpha}{\beta} \ln S + C, \tag{7}$$

obtaining a family of curves in S, I-solution space defined up to a constant of integration.

Equation (7) is special in that it observes its own type of conservation law, yielding another way to describe the orbits of the epidemic curve. The quantity $H(S, I)$:

$$H(S(t), I(t)) = S(t) + I(t) - \frac{\alpha}{\beta} \ln S(t)$$

is conserved in the sense that $\frac{d}{dt} H(S, I)$ is identically zero. From this it follows that the solution curves to equation (7) always lie on the level curves $H(S, I) = k$, for some real k.

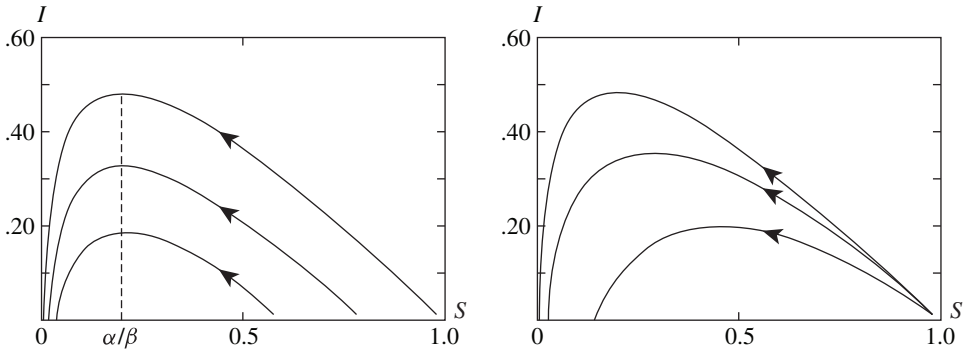
Substituting $S(0) = S_0$ and $I(0) = I_0$ into equation (7) and eliminating the constant of integration, we attain a final expression for the epidemic curve:

$$I(t) = -S(t) + S_0 + I_0 + \frac{\alpha}{\beta} \ln \frac{S(t)}{S_0}. \tag{8}$$

Observe that the derivative $\frac{dI}{dS}$ in equation (6b) vanishes at $S = \alpha/\beta$; substituting this into equation (8) immediately gives the peak of an epidemic at

$$I_{\max} = S_0 + I_0 + \frac{\alpha}{\beta}\left(\ln \frac{\alpha}{\beta} - \ln S_0 - 1\right).$$

Typical epidemic trajectories are given in Figures 2(a) and 2(b). The vertical line $S = \alpha/\beta$ in Figure 2(a) is one component of the I-nullcline—the set of points (S, I) at which $\frac{dI}{dt} = 0$. To the right of this line, $\frac{dI}{dt} > 0$, as in the beginning of an outbreak. To the left of $S = \alpha/\beta$, $\frac{dI}{dt} < 0$; this downward pressure on the proportion of infected individuals is typical in a population which has already outlasted the worst of an epidemic.



(a) fixed paramter value α/β (b) fixed initial value (S_0, I_0)

Figure 2. Typical epidemic curves.

Control strategies, geometrically interpreted

The expression $\frac{\alpha}{\beta} \ln \frac{S(t)}{S_0}$ in equation (8) is nonpositive for all time. One strategy then to control the size of an epidemic might be to *increase* α/β, either by reducing the transmission parameter β, or increasing the infectious constant α. Each tactic makes real-world sense. Reducing β, in effect, makes a disease less easily transmitted. Prevention and education measures are pointed to directly by this as they attempt to make the *susceptible less susceptible*. Increasing the α parameter, on the other hand, is equivalent to *reducing* the mean infectious period α^{-1}, corresponding to finding a treatment that makes the *infectious infectious for a shorter period of time*.

Geometrically, any epidemiological tactic that leads to an increase in α/β can be described as a rightward translation of the line $S = \alpha/\beta$. See curves (a) and (b) in Figure 3. Any such rightward translation reduces the expected maximum number of new infections. But while any increase in the parameter α/β is worth pursuing, epidemiological realities make eradication via adjustments to α and β alone too great a hurdle. Successful eradication requires simultaneously the reduction of the number of initially susceptible individuals through immunization. This is the most effective strategy. See curve (c) in Figure 3.

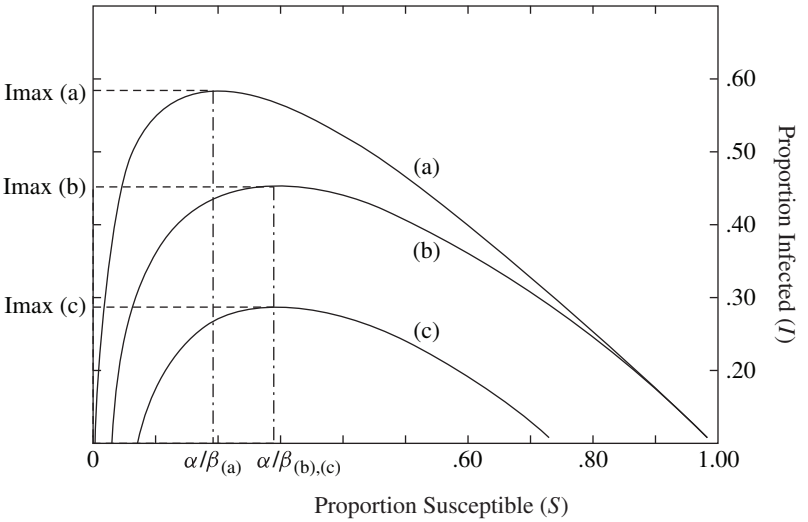


Figure 3. (a) epidemic curve in the absence of control strategies; (b) increase in α/β leads to a reduction in the epidemic peak $I_{\max}$; (c) further reduction in $I_{\max}$ by reducing the initial susceptible population through immunization.

Herd immunity leads to eradication

Recall equation (6b):

$$\frac{dI}{dt} = (\beta S - \alpha)\, I,$$

and notice that $\frac{dI}{dt}$ is strictly negative if $\frac{\beta S}{\alpha} < 1$. From equation (6a) we have that $\frac{dS}{dt}$ is strictly negative for all positive S and I, so that any initial condition satisfying $\frac{\beta S_0}{\alpha} < 1$ will continue to satisfy $\frac{\beta S}{\alpha} < 1$, and hence, $\frac{dI}{dt} < 0$ for all forward time. The quantity $\frac{\beta S_0}{\alpha}$ is called the *basic reproduction number* of the disease, and is typically denoted R_0. It determines, for a given disease and population, whether the introduction of a small number of infected individuals will lead to an epidemic or not. When $R_0 > 1$, there is an epidemic. When $R_0 < 1$, we say *herd immunity* has been attained, and the outbreak quickly dies out. Smallpox is believed to have an R_0 of about five [**13**, p. 612], although estimates vary wildly. In [**10**, p. 748], a search of the literature found values for R_0 in smallpox cited from as low as 1.5 to greater than 20. Such uncertainty is part of the very fabric of mathematical biology.

Can a reproductive number be reduced five fold via immunization? For each vaccine-preventable virus we can compute the required immunized population proportion based on no more than the basic reproductive number of the disease. We denote this required proportion p, the *herd immunity threshold*, and replace the basic reproductive number R_0 with an *effective* reproductive number $\tilde{R}_0 = (1 - p)\, R_0$. Note that at the herd immunity threshold $(1 - p)\, R_0 < 1$, or equivalently, $p > 1 - \frac{1}{R_0}$.

So, in order to eradicate a vaccine-preventable infectious disease, greater than $((1 - \frac{1}{R_0}) * 100)$ percent of the population must be immunized. A simple calculation shows that the smallpox virus has a herd immunity threshold near $p = 0.8$.

In 1967, the World Health Organization launched the *Intensified Global Smallpox Eradication Programme*, undertaking exactly this lofty goal: vaccination of at least eighty percent of the world's at-risk population [**7**]. Millions were vaccinated over the

subsequent decade. In 1977, a twenty-three-year-old cook and volunteer vaccinator, Ali Maow Maalin, was diagnosed with *Variola minor* at the hospital in the town of Merca, Somalia—the very last case of naturally occurring smallpox [**16**]. Maalin subsequently recovered.

The next eradication?

With the lessons learned from the eradication of smallpox, surely it should be possible to eradicate other human infectious diseases. Which? Most bacterial infections confer at best limited immunity, and a standard SIR-type control strategy is inappropriate. The simplest models have also proved inadequate to capture the complicated heterogeneity at work behind most sexually transmitted diseases. In addition, viruses with a non-human reservoir or with a non-human transmission vector, operate with dynamic complexities that makes eradication a tremendous challenge. Yet while every disease folds its own complications into modeling efforts, several viral diseases may still prove viable candidates for eradication. Table 2 gives the basic reproductive numbers R_0 and corresponding herd immunity thresholds p for several diseases [**13**, p. 612]. These permit only very rough comparisons as precise methods for calculating R_0 differ among diseases and approximations for any one disease vary by region and/or time period.

Table 2. Approximate values for R_0 and p for five viral infectious diseases.

Disease	Approximate Basic Reproductive Number R_0	Approximate Herd Immunity Threshold p
Polio	5	.80
Rubella (German measles)	7	.86
Chicken pox	11	.91
Mumps	12	.92
Measles	16	.94

With a basic reproduction number similar to that of smallpox—roughly five—polio is the most attractive target for eradication. Following the eradication of smallpox, the *Global Polio Eradication Initiative* was launched in 1988 with the goal of greater than eighty percent immunization. So far, the effort has made huge strides; the number of paralytic cases of wild poliovirus worldwide has fallen by greater than ninety-nine percent throughout the world [**11**]. Today polio remains endemic in only four countries: Afghanistan, Pakistan, India and Nigeria, and, despite poverty, war and natural disaster, the end may be in sight. In the calendar year 2010, the number of wild poliovirus cases fell to 1,349 worldwide [**12**].

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Summary. Smallpox remains the only human disease ever eradicated. In this paper, we consider the mathematics behind control strategies used in the effort to eradicate smallpox, from

the life tables of Daniel Bernoulli, to the more modern *susceptible-infected-removed* (SIR)-type compartmental models. In addition, we examine the mathematical feasibility of the eradication of polio and certain other infectious diseases.

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