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Disease elimination and re-emergence in differential-equation models

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Abstract

Traditional differential equation models of disease transmission are often used to predict disease trajectories and evaluate the effectiveness of alternative intervention strategies. However, such models cannot account explicitly for probabilistic events, such as those that dominate dynamics when disease prevalence is low during the elimination and re-emergence phases of an outbreak. To account for the dynamics at low prevalence, i.e. the elimination and risk of disease re-emergence, without the added analytical and computational complexity of a stochastic model, we develop a novel application of control theory. We apply our approach to analyze historical data of measles elimination and re-emergence in Iceland from 1923 to 1938, predicting the temporal trajectory of local measles elimination and re-emerge as a result of disease migration from Copenhagen, Denmark.

Keywords

infectious-disease modeling; eradication; migration; dynamic modeling; control theory

1. Introduction

The ultimate goal of public health is the eradication of disease. A major challenge to this goal is that even when disease elimination can be achieved in a local population, there often

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remains a risk of re-emergence from other locations. Differential equation models have been employed to predict the trajectories of outbreaks and to evaluate the effectiveness of public health policies targeting disease elimination (Anderson et al., 1992; Hethcote and Van den Driessche, 2000; Keeling and Rohani, 2007). However, differential equation models do not accurately capture the dynamics of disease elimination and risk of re-emergence when disease prevalence is low. Instead, arbitrary thresholds of incidence have been used as a proxy for disease elimination in differential equation models (Andrews et al., 2012; Dowdy, 2009; Duintjer Tebbens et al., 2014; Maude et al., 2012; Silal et al., 2014; White et al., 2009). Alternatively, stochastic models have been adopted to accurately incorporate disease dynamics at low prevalence (Keeling and Rohani, 2007). However, stochastic models are significantly more computationally, analytically, and conceptually challenging (Dimitrov and Meyers, 2010).

Here we propose applying control theory (Brogliato et al., 2007; Doyle et al., 2009; Kailath, 1980; Luenberger, 1979) to model the elimination and re-emergence of an infectious disease. Typically, a control theory model combines differential equations that represent the state of the system with external factors that impact the system. Following this approach, we modeled the transmission of infection in a community at risk for re-emergence from surrounding communities. From our model, we determined parameter conditions for the elimination of an outbreak, and forecast the times until elimination and re-emergence. We used time series data of measles elimination and re-emergence events in Iceland to illustrate the application of our model.

2. The control theory model

To model the elimination and re-emergence of infection in a community, we developed a control system of the form

$$\frac{dx}{dt} = f(x, \sigma),$$

where the output variables $x(t) \in \mathbb{R}^n$ the state and evolution of the system, and input variables $\sigma(t) \in \mathbb{R}^m$ influence the evolution of the output variables, but are not themselves impacted by the state variables. In our model, the output variables x correspond to the state of an outbreak within a community, and the input variables σ are the external factors that impact re-emergence from other communities.

2.1 The local transmission of infection

We considered a population divided into the proportion of people susceptible (s), infected (i) and recovered (r), with $s + i + r = 1$ which follow a standard SIR-type model:

$$\begin{aligned} \frac{ds}{dt} &= b - \lambda s - bs, \\ \frac{di}{dt} &= \lambda s - \gamma i - bi, \\ r &= 1 - s - i, \end{aligned} \quad (1)$$

where λ is the force of infection, γ is the recovery rate, and b is the rate of demographic turnover (i.e. b is both the per capita birth rate and the per capita death rate).

In SIR-type models there are many possible reasons for choosing a nonstandard force of infection: for instance, modeling such effects as the crowding of infected individuals, positive measures taken by susceptible individuals to avoid infection, the effects of behavioural changes, or disease elimination (Alexander and Moghadas, 2005; Liu et al., 1987, 1986; Ruan and Wang, 2003; Van den Driessche and Watmough, 2000). We consider a nonstandard force of infection (Guldborg and Waage, 1864; Hethcote and Van den Driessche, 1991; Liu et al., 1987, 1986),

$$\lambda = \beta i^\alpha, \text{ where } \alpha \geq 0.$$

Here, λ includes an interaction coefficient α , and as a special case, reduces to the standard mass action when the interaction coefficient $\alpha = 1$ (Hethcote and Van den Driessche, 2000). The inclusion of $\alpha \neq 1$ interaction coefficient allows for nonlinearities in contact rates that may arise due to spatial substructuring (Bjørnstad et al., 2002). Spatial substructuring, from a region-wide perspective could account for hot spots of measles transmissions, such as within and between schools. In particular, if measles transmission within a school is greater on average than other schools, the result is spatial substructuring, and consequently motivates the selection of $\alpha \neq 1$ (Bjørnstad et al., 2002). In addition, taking βi^α with an interaction coefficient $\alpha \neq 1$ directly parallels multi-order reaction kinetics from chemical reaction theory (Savageau, 1969a, 1969b). Thereby, α can be interpreted as the order of interaction, and controls how the rate of newly infected (βi^α) scales with the proportion of infected i . In addition, our formulation of λ also satisfies the basic physical principles underlying transmission dynamics (Korobeinikov and Maini, 2005), such that transmission cannot occur in the absence of infection ($\lambda(0) = 0$) and transmission increases as the

proportion of the infectious population increases ($\frac{d\lambda}{di} \geq 0$).

The recovery rate γ can also be more generally assumed to be proportional to i^ξ , with interaction coefficient ξ . The standard choice $\xi = 1$ implies that the per capita rate at which people leave the infected compartment (γ) is constant throughout the entire population, in contrast to the different durations of infection that naturally occur. Consequently, the recovery rate is taken to be:

$$\gamma = \eta i^{\xi-1}, \text{ with } \xi \geq 0.$$

The inclusion of interaction coefficient $\xi \neq 1$, in a similar fashion to α in the force of infection, allows for nonlinearities in the duration of infection that may arise due to the different rates at which people recover from infection. Once again, a way to conceptualize ξ is to think of schools as hot spots for measles transmission. Schools that exhibit higher transmission levels, are more likely to have a higher magnitude of exposure, which often leads to longer recovery times. In addition, one could also conceptualize ξ through measles

transmission amongst and between similar age groups and the potential impact of age-related effects on recovery.

2.2 The reproduction numbers

The basic reproduction number, R_0 , is the number of new infections caused by a single infectious person in an otherwise wholly susceptible population (Diekmann et al., 1990). The next-generation method (Diekmann et al., 1990; Heffernan et al., 2005; Liu et al., 1987; Van den Driessche and Watmough, 2002, 2000) is a standard technique to determine the R_0 for differential equation models of disease transmission. For example, under the assumption that $\alpha = \xi = 1$ in system (1), the next-generation method linearizes the flow of newly infected people, $\mathcal{F} = \beta i s$, and the flow from the infected compartments, at $\mathcal{V} = \eta i + b i$ at the disease-free equilibrium $E_0 = \{s = 1, i = 0, r = 0\}$:

$$F = \frac{d}{di} \mathcal{F} \Big|_{E_0} = \beta \text{ and } V = \frac{d}{di} \mathcal{V} \Big|_{E_0} = \eta + b$$

The next-generation matrix is the rate of production of new infected $F = \beta$, multiplied by the duration of infection $V^{-1} = \frac{1}{\eta + b}$, giving $G = \frac{\beta}{\eta + b}$. In general, the R_0 is then the largest eigenvalue of G , but since G here is scalar, $R_0 = \frac{\beta}{\eta + b}$.

However, system (1) is not linearizable (i.e. differentiable) at $i = 0$ when $\alpha < 1$ or $\xi < 1$, so the standard next-generation method cannot be used directly. Instead, since there is only one infected compartment, we can directly compute the effective reproduction number:

$$R_e(i, s) = \frac{\mathcal{F}}{\mathcal{V}} = \frac{\beta i^\alpha s}{\eta i^\xi + b i} = \frac{\beta i^{\alpha-1} s}{\eta i^{\xi-1} + b}$$

and

$$R_0 = R_e(i, s) \Big|_{s=1} = \frac{\beta i^{\alpha-1}}{\eta i^{\xi-1} + b}. \quad (2)$$

Importantly, R_0 depends on i in general, unlike in the case when the system is linearizable. The behavior of R_0 can be characterized by the dependency on i through the interaction coefficients. It follows that

$$R_0 \approx \begin{cases} \frac{\beta}{\eta} i^{\alpha-\xi} & \text{if } \xi < 1, \\ \frac{\beta}{\eta+b} i^{\alpha-1} & \text{if } \xi = 1, \\ \frac{\beta}{b} i^{\alpha-1} & \text{if } \xi > 1. \end{cases} \quad (3)$$

If the exponent of i in (3) is negative, transmission accelerates as $i \rightarrow 0^+$, with $R_0(0) = \infty$. Conversely, if the exponent of i is positive, transmission decelerates as $i \rightarrow 0^+$, and terminates at, i.e. $R_0(0) = 0$. Finally, if the exponent of i is exactly in (3), then $0 < R_0 < \infty$ becomes constant as $i \rightarrow 0^+$ (Table 2.1).

2.3 The absence of infection

If a disease in a community is eliminated, the gradual accumulation of susceptible people via birth/immigration and removal of immune people through death/emigration, as well as potentially waning immunity, drive the potential for disease re-emergence. The time until the population is at risk of re-emergence (i.e. the population has sufficient susceptible to sustain transmission) can be obtained from system (1) under the conditions that elimination has occurred (i.e. $i = 0$):

$$\frac{ds}{dt} = b(1 - s), \quad (4)$$

Supposing t_e is the time when the infection is eliminated, the proportion of susceptible exponentially approaches 1, as given by:

$$s(t) = 1 - (1 - s_e)\exp(-bt), \quad (5)$$

where $s(t_e) = s_e$.

2.4 Risk of re-emergence

In the hypothetical case of a completely isolated community, i.e. equation (4), re-emergence cannot occur. Otherwise, re-emergence can occur from another location, which we accounted for by allowing the input variables σ of the control system to depend on the disease incidence in other communities $\hat{i}$:

$$\sigma = \max(\hat{i} - i^c, 0), \quad (6)$$

The rare event of disease emergence increases with the incidence in other communities. Thus, i^c is taken as the proportion of incidence required for migration to occur. In essence, σ represents contact between susceptible in the community of interest and infected in other communities, and thus we can consider a non-standard force of infection with external community effects as:

$$\lambda_\sigma = \beta(i + \sigma)^\alpha s. \quad (7)$$

By replacing λ with (7) in system (1), the re-emergence of an eliminated disease could be modelled with appropriate knowledge of σ and the proportion of susceptible within the community of interest. For the re-emergence of an eliminated disease to occur, it is

necessary that $\frac{di}{dt} \geq 0$. Such a condition requires that R_e crosses the critical threshold value

of 1. With this information we can approximate the time when a community becomes at risk of re-emergence, t_{risk} , from manipulating the functional form of R_e . By evaluating R_e at $i = 0$ and at $s(t)$ in the absence of infection (5), it follows that:

$$R_e(0, s(t)) = R_0(0)s(t) = R_0(0)(1 - (1 - s_e)\exp(-bt)).$$

To determine t_{risk} from the above expression, we need to determine when $R_e(0, s(t))$ reaches the critical threshold value of 1, that is:

$$R_0(0)(1 - (1 - s_e)\exp(-bt_{risk})) = 1. \quad (8)$$

Isolating for t_{risk} yields,

$$t_{risk} = \frac{1}{b} \ln \left(\frac{1 - s_e}{1 - \frac{1}{R_0(0)}} \right). \quad (9)$$

The time t_{risk} is proportional to the logarithm of the proportion immune, $1 - s_e$, relative to the critical proportion of the population that must be immune for elimination to be attained,

$$1 - \frac{1}{R_0(0)} \quad (\text{Anderson et al., 1992}).$$

3. Elimination

We demonstrate whether elimination can occur for four different regions of the interaction coefficients α and ξ (Table 3.1). We derive lower bounds on the duration of time that $\frac{di}{dt} < 0$ and then determine whether i decreases fast enough to achieve elimination. Here we outline the framework for projecting elimination (please see derivation in the Webappendices).

3.1 Interaction coefficient $\xi > 1$

We demonstrate that elimination cannot occur when $\xi > 1$:

3.1.1 When $\xi > 1$, the inequality

$$\frac{di}{dt} > -\eta i^\xi - bi,$$

has the solution (Webappendix S.1.1):

$$i^{\xi-1} \geq \frac{b}{-\eta + (bi_0^{1-\xi} + \eta) \exp(-b(1-\xi)t)}.$$

Consequently, $i^{\xi-1}$ for all $t < \infty$, and thus elimination cannot occur.

3.1.2 Interaction coefficient $\xi = 1$ —When $\xi = 1$, solving the inequality

$$\frac{di}{dt} > -\eta i - bi,$$

yields the solution (Webappendix S.1.1):

$$i \geq i_0 \exp(-(\eta+b)t).$$

For all $t < \infty$, > 0 , such that elimination cannot occur.

3.2 Interaction coefficients $\alpha < 1$, $\xi > \alpha$ and $\xi < 1$

The behaviour of the system around the disease-free equilibrium indicates that elimination cannot occur (Webappendix S.2). When $\alpha < 1$ and $\xi < 1$, we cannot directly linearize the system $i = 0$ at because $\alpha < 1$ or $\xi < 1$ lead to a singular Jacobian at the disease-free equilibrium. Instead, linearizing $i^{1-\alpha} \frac{di}{dt}$ shows that near the disease-free equilibrium

$$i(t) \approx (\beta(1-\alpha)t + i_0^{1-\alpha})^{\frac{1}{1-\alpha}},$$

which implies elimination does not occur (Webappendix S.2).

3.3 Interaction coefficients $\alpha < 1$ and $\xi = \alpha$

When $\alpha < 1$ and $\xi = \alpha$ there are two subcases to determine elimination criteria: the case

when $\frac{\beta}{\eta} < 1$ and the case when $\frac{\beta}{\eta} \geq 1$. In both cases, the possibility of elimination hinges on $\frac{di}{dt} < 0$. We denote t_0 as the first instant where $\frac{di}{dt}|_{t_0} < 0$ with the added condition that $s(t_0) < \frac{\eta}{\beta}$ (i.e. the value of s that guarantees $R_e < 1$). After time t_0 , $\frac{di}{dt}$ is negative if $R_e < 1$, which occurs as long as either $R_0(i) \leq \frac{\beta}{\eta} < 1$, or if $s < \frac{\eta}{\beta}$.

3.3.1 Interaction coefficients $\alpha < 1$, $\xi = \alpha$ and $\frac{\beta}{\eta} < 1$ —Here elimination is demonstrated through finding a function $\bar{i}$ that bounds the infected compartment i , so that 0

$i(t) < \bar{i}(t)$ is squeezed to zero at some time $t^* < \infty$. For this case, because $\frac{\beta}{\eta} < 1$ necessarily $R_0(i) < 1$. Furthermore, $R_0(i) < 1$ implies $\beta i^\alpha - \eta i^\alpha - bi < 0$, and consequently,

$$\frac{di}{dt} = \beta i^\alpha s - \eta i^\alpha - bi < \beta i^\alpha - \eta i^\alpha - bi < 0. \quad (12)$$

Using an integrating factor technique (Webappendix S.1.2), the proportion of infected is bounded above by,

$$i^{1-\alpha} < \frac{\beta - \eta}{b} + \frac{(\eta - \beta + bi_0^{1-\alpha})\exp(-b(1-\alpha)(t-t_0))}{b} := \bar{i}^{1-\alpha}. \quad (13)$$

Setting the right-hand side of (13) to zero and solving for t gives a bound on the time it will take for the infected to converge to the disease-free equilibrium,

$$t \leq t_0 + \frac{1}{b(1-\alpha)} \ln \left(\frac{\eta - \beta + bi_0^{1-\alpha}}{\eta - \beta} \right) := t^*. \quad (14)$$

The finite time convergence is necessary because $0 < i^{1-\alpha} < \bar{i}^{1-\alpha}$ and at t^* , the upper bound $\bar{i}(t^*)^{1-\alpha} = 0$.

3.3.2 Interaction coefficients $\alpha < 1$, $\xi = \alpha$, and $\frac{\beta}{\eta} < 1$ —To demonstrate elimination

criteria for this case, it is necessary to determine how long $s(t) < \frac{\eta}{\beta}$, and thus, when $\frac{ds}{dt}$ changes signs after the peak of the epidemic. Thus, we denote t_1 as the moment when $\frac{ds}{dt}$ becomes positive.

Because $s(t_0) < \frac{\eta}{\beta}$, $\frac{di}{dt}|_{t=t_0} < 0$ and $\frac{ds}{dt} < 0$, we know $\frac{di}{dt} < 0$ at least until time t_1 . From t_1 we determine a lower bound on how long $R_e < 1$. With the initial conditions $s(t_1) = s_1$ and $i(t_1) = i_1$, the integral of the inequality $\frac{ds}{dt} \leq b(1-s)$ over (t_1, t) is:

$$s(t) \leq 1 - (1 - s_1)\exp(-b(t - t_1)) := \tilde{s}(t). \quad (15)$$

By solving $\tilde{s}(t) = \frac{\eta}{\beta}$ for t we have that $R_e < 1$ provided that:

$$t < t_1 + \frac{\ln(\beta(1 - s_1)) - \ln(\beta - \eta)}{b} := \tilde{t}. \quad (16)$$

It follows that $\frac{di}{dt} < 0$ over the interval $(t_1, \tilde{t})$. We also show that $\frac{di}{dt}$ decreases fast enough for elimination to be possible. Given that $R_e(s, i) < 1$ and $\frac{di}{dt} < 0$ we have that,

$$\frac{di}{dt} = \beta i^\alpha s - \eta i^\alpha - bi < \beta i^\alpha \tilde{s}(t) - \eta i^\alpha - bi < 0 \text{ for } t \in (t_1, \tilde{t}).$$

Using an integrating factor technique (Webappendix S.1.3), the proportion of infected is bounded by:

$$i^{1-\alpha} < \frac{\beta - \eta}{b} + \exp(-b(t-t_1)) \frac{\beta(1-\alpha)(1-s_1)}{\alpha b} + \left(i_0^{1-\alpha} - \frac{\beta - \eta}{b} - \frac{\beta(1-\alpha)(1-s_1)}{\alpha b} \right) \exp(-b(1-\alpha)(t-t_1)) := \tilde{t}^{1-\alpha} \quad (17)$$

Thus, if t exists such that the right-hand side of (17) is zero and $t < \tilde{t}$, elimination occurs.

3.4 Interaction coefficients $\xi < \alpha$ and $\xi < 1$

From the inequality,

$$\frac{di}{dt} = \beta i^\alpha s - \eta i^\xi - bi \leq \beta i^\xi s - \eta i^\xi - bi,$$

one can obtain elimination criteria by following the same procedures as in Section 3.3 with α relabelled as or ξ vice-versa.

4. Application of methodology: Elimination and re-emergence of measles in Iceland

To illustrate model predictions, we model measles outbreaks based on time series of measles incidence in Reykjavik, Iceland from 1924 to 1938 (Cliff et al., 1981). Because Denmark is historically a primary source of measles migration to Iceland (by way of fishing boats) (Cliff et al., 1981), we take into account a primary source of re-emergence to Reykjavik based on measles incidence in Copenhagen, Denmark (Metcalf et al., 2009) from 1928 to 1938 (Figure S1).

From our data-driven analysis of the measles incidence in Reykjavik, we estimated, $\alpha = 0.9$,

$\xi = 0.9$ and $\frac{\beta}{\eta} = 2.65$ (Webappendix S.3.1-S.3.2). The time series data from Copenhagen was used to determine the rate of infection re-emergence σ (Webappendix S.3.3). Additional parameter values were determined from Icelandic demographic data, and the literature (Table 4.1).

We apply our methodology to illustrate predictions regarding the time until elimination and the risk of re-emergence of measles in Reykjavik from July 1924 until June 1928. We further incorporate the rate of infection re-emergence σ calculated from Copenhagen time series data, to demonstrate the model predictions of measles re-emergence specifically from Copenhagen to Reykjavik from July 1928 to June 1938.

4.1 Measles in Reykjavik from July 1924 to June 1928

Using the parameter estimates of ξ , α , and $\frac{\beta}{\eta}$ (Table 4.1) and procedure of Section 3.3.2, we determine $t_1 = 164$ days is the first time after the peak of infection when $\frac{ds}{dt} > 0$. Substituting $s(t_1) = s_1 = 0.2527$ and $i(t_1) = i_1 = 0.0015$, into (16) yields $R_e < 1$ provided that:

$$t < t_1 + \frac{\ln(\beta(1 - s_1) - \ln(\beta - \eta))}{b} := \tilde{t} = 1177 \text{ days.}$$

From (17), we know that the infected proportion i is bounded by $\bar{i}$. The function $\bar{i}$ when $t^* = 361$ days, meaning that elimination is predicted to occur within 361 days. This model prediction is consistent with the observed 1924-1925 Reykjavik measles outbreak (Figure 4.1), which was recorded to have been eliminated after 304 days (Figure 4.2).

After the 1924 measles epidemic is eliminated in May 1925, our model predicts (by evaluating (9), or solving (8) for $R_e > 1$) that the next measles outbreak is likely to occur after 1177 days (October 1927) which is shortly before Reykjavik's next measles epidemic in August 1928 (Figure 4.3).

4.2 The re-emergence of measles in Reykjavik from August 1928 to March 1937

The re-emergence of measles in Reykjavik from Copenhagen is unlikely when the proportion of infected in Copenhagen (i) (Figure S1) is below some critical threshold. Consequently, we consider the rate of infection re-emergence (6) as:

$$\sigma_{Copenhagen} = \max(\hat{i} - i^c, 0),$$

where i^c is the proportion of incidence required for migration from Copenhagen to Reykjavik (Table 4.1).

When $i^c = 0.0004$, our model incorporating the force of infection with external community effects λ_σ fits well with the measles epidemics in Reykjavik from August 1928 to March 1937 (Figure 3). When to $i^c = 0.0001$ to 0.0003, re-emergence of measles occurs more frequently (Figures 4.4), which prevents an accumulation of the susceptible population, thereby reducing both the R_e (Figures 4.5) and the predicted size of the 1936 outbreak.

5. Discussion

We developed a deterministic method for investigating disease elimination and risk of re-emergence. Our methodology extends the formulation of deterministic epidemic models to include interaction coefficients that could account for factors such as behavioral reaction to disease spread, and intervention measures that curtail disease transmission. We demonstrated, through differential inequalities and linearization-type techniques, a procedure through which it can be determined whether values of the interaction coefficients

permit or exclude disease elimination. We also demonstrated the use of our methodology to estimate both the time until elimination (when possible) and the time until re-emergence becomes possible through replenishment of susceptible in the population. Importantly, our methods for determining whether disease elimination can occur in finite time and estimating the times of elimination and re-emergence are data-driven and do not require computational simulations.

A requirement of our model, akin to chemical reaction dynamics, is the estimation of interaction coefficients from observed data. However, unlike their estimation in chemical reaction dynamics, interaction coefficients can be estimated from different data sources. For instance, beyond incidence time series data, estimates of interaction coefficients could be obtainable from seroprevalence levels, data on the duration of infectiousness, or other measures that appropriately capture population substructuring relevant to disease transmission or recovery.

We illustrated the applicability of our novel approach by comparing its predictions to historical data of measles elimination and re-emergence in Reykjavik, Iceland. Using time series data from 1924 to 1928 from Reykjavik (Cliff et al., 1981), our estimation method predicted measles elimination would occur within 361 days, while validation with a full simulation of the model estimated elimination time to be 278 days, both of which are similar to the observed elimination time of 304 days.

Our model predictions suggest that it takes 3.2 years for the susceptibles to be replenished through birth in Reykjavik, after an epidemic. Thus, our predictions indicate that Reykjavik was unlikely to experience another sustained measles epidemic before October 1927. This model prediction is corroborated by the actual surveillance data that reveal a rapid fade out of measles following a re-emergence in late 1925. In addition, the occurrence of Reykjavik's next measles epidemic in Reykjavik during the middle of 1928 is in line with our model predictions of re-emergence risk. Subsequent to the 1928 outbreak, our model predicts that by 1936 more than enough susceptibles had accumulated in Reykjavik to sustain a large outbreak, consistent with the 1936 epidemic that did ensue.

Previous deterministic methods for evaluating disease elimination generally use an arbitrary threshold of incidence or prevalence below which the outbreak is deemed eliminated (Andrews et al., 2012; Dowdy, 2009; Duintjer Tebbens et al., 2014; Maude et al., 2012; Silal et al., 2014; White et al., 2009). Here, we proposed a methodology for evaluating disease elimination that avoids the necessity of such thresholds. Instead, we used a generalized force of infection and recovery term to permit disease elimination. We also permit disease re-emergence by applying a control theory modification to the force of infection that allows for external perturbations to the system. A particular advantage of using such a control theory modification to the force of infection, is that it can naturally be extended to reflect the impact of multiple external communities on multiple communities of interest. Thereby, our modifications to the force of infection could permit the study of disease elimination and re-emergence on a broader scale. Furthermore, our methodology to determine the duration of time until elimination could be extended to systems where the force of infection also includes a multiple of the susceptible proportion. In addition, our methodology of solving

differential inequalities to obtain estimates of the times until disease elimination and re-emergence is pertinent to many other compartmental models, including those with an incubation period, mass vaccination, and age structure. For example, our methodology is applicable to infectious diseases currently targeted for eradication, including polio and leprosy or outbreaks of emerging diseases, such as Ebola.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We developed a novel framework to analyze disease elimination and re-emergence.
- We provide a simulation free method to determine if disease elimination is possible.
- We model measles eliminations and re-emergences in Iceland from 1924 to 1938.
- Iceland was likely to experience a measles re-emergence shortly after October 1927.
- Undocumented measles re-emergences in Iceland were unlikely from 1930 to 1936.

Figure 4.1.
Reykjavik measles time series (blue) and fitted model (black).

Figure 4.2.

Elimination of infection. i^{1-a} (blue), upper bound function i^{1-a} (green), proportion of susceptible (red), maximum proportion $i(t_0)^{1-a}$ (x), and minimum proportion of susceptible required to sustain transmission $s(t_1)$ (o). Numerical simulation estimated that elimination would occur on day 278, the inequality (17) estimated elimination would occur before 361 days, and the actual outbreak was recorded to have been eliminated on day 304.

Figure 4.3.
Effective reproduction number, R_e (blue) with critical threshold $R_e = 1$ (blue).

Figure 4.4.
Proportion of Reykjavik infected with measles for different levels of migration between Reykjavik and Copenhagen.

Figure 4.5.
 R_e with different proportion of incidence required for migration in Reykjavik, Iceland.

Table 2.1

$R_0(i)$ for given interaction coefficients.

$\lim_{i \rightarrow 0^+} R_0(i)$	Condition
$\frac{\beta}{b}$	$\alpha = 1$ and $\xi > \alpha$
∞	$\alpha < 1$ and $\xi > \alpha$
$\frac{\beta}{\eta}$	$\alpha < 1$ and $\xi = \alpha$
0	$\alpha > 1$ or $\xi < \alpha$
$\frac{\beta}{\eta + b}$	$\alpha = 1$ and $\xi = \alpha$

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Table 3.1

Conditions of α and ξ for elimination.

Condition	Elimination possible	Section
$\alpha = 1$ and $\xi > \alpha$	False	3.1
$\alpha < 1$ and $\xi > \alpha$	False	3.1 (if $\xi = 1$) 3.2 (if $\xi < 1$)
$\alpha < 1$ and $\xi = \alpha$	True	3.3
$\alpha > 1$ or $\xi < \alpha$	true if $\xi < 1$, and false if $\xi = 1$	3.1 (if $\xi = 1$) 3.4 (if $\xi < 1$)
$\alpha = 1$ and $\xi = \alpha$	False	3.1

Table 4.1
Parameter values for transmission model

Symbol	Parameter	Base	Ref
b	Rate of demographic turnover	0.027/yr	Statistics Iceland
β	Contact parameter	0.23 proportion ⁻¹ /day	(Grenfell et al., 2001)
γ	Recovery rate	0.125 / day	(Cliff et al., 1981)
η	Recovery coefficient	0.087 proportion ^{1-ξ} /day	Webappendix S.3.1
i^c	proportion of incidence required for migration	0.0001 – 0.0004	Webappendix S.3.2
α	Interaction coefficient	0.9	Webappendix S.3.3
ξ	Interaction coefficient	0.9	Webappendix S.3.3