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Effect of Vaccination in Environmentally Induced Diseases

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Abstract

Along with the constant improvement in hygiene in the last few decades there has been a continuous increase in the incidence of particular diseases, mainly of autoimmune or allergic etiology, but also of diseases caused by infectious agents, such as listeriosis. We here present a model for the effect of exposure to agents causing or inducing the disease on the incidence of morbidity. The proposed model is an expansion of the SIR model to non-contagious diseases and aims to estimate the balance between immunization and disease probability. The model results indicate that, paradoxically in a wide range of parameters, a decrease in exposure to the disease inducing agent results in an increase in disease incidence. This can occur if: (a) the probability of developing disease, given an exposure to the agent increases with age, (b) immunity to the agent is long. The inverse relation between exposure and disease incidence results from a decrease in the adult immunized population following a previous decrease in the exposure rate. Therefore, a lower exposure can lead to lower incidence in the short term but to higher incidence in the long term.

Keywords

Hygiene model; Linear SIR; Immunity; Listeriosis

1 Introduction

Early exposure to infectious disease agents and the resulting development of protective immunity affect diseases incidence. In adult diseases, a balance exists between the immunization obtained at younger ages and the extent of exposure to the disease agent at older ages. Theoretical results and epidemiological observations suggest that in cases of contagious diseases like measles and rubella, for which seriousness of illness increases with age of infection, weakening in the force of infection (e.g. due to immunization) can actually increase the incidence of serious cases due to an increase in the mean age of infection (Anderson and May 1983).

A different argument may explain a similar observation in non-infectious diseases. Recently, an increase was observed in some non-contagious food-borne illness or non-infectious morbidity like allergies and autoimmune diseases. For the latter, it was observed that improvement of hygiene is associated with an increase in morbidity. One possible explanation for this observation is that exposure to the inducing agent early in life is not associated with morbidity and provides immunization that may protect from morbidity due to later exposure. Therefore, a decrease in the exposure can lead on the one hand to a lower probability of morbidity per susceptible person, but on the other hand to an increase in the susceptible population. The increased susceptible population would be the direct result of a reduction of the immunized population. We here discuss the mathematical details of such a situation and show that indeed a reduction in the exposure rate can lead to a higher incidence of environmentally induced diseases (e.g. auto-immune diseases, food-borne diseases or vector borne diseases for which human are considered dead-end hosts). Such an inverse correlation exists only if there is a significant time lag between the initial immunization and disease induction. A second necessary condition is that the immunity obtained at the immunization stage would be long lasting.

The classical SIR model (Anderson and May 1983) contains a non-linear infection probability based on the combined fraction of susceptible and infected populations, since most studied cases were of contagious diseases. We here analyze the simpler linear system, where the probability that a susceptible should be affected is not proportional to the fraction of the population already affected. Linear ODE can describe the case of non-contagious diseases. Such models were previously studied in a more limited context (e.g. McBride and French 2006; Coleman et al. 2001). In contrast with contagious diseases, in environmentally induced diseases, the balance leading to the disease is between the immunization and the disease induced by the same agent. In the following analysis, we will discuss the effect of a generic “disease agent”. Such a disease agent can be a food-borne bacterium, an allergen, or any agent that induces both disease and immunity to the disease. An allergen, for example, can obviously induce allergy but it can also induce immunization through the induction of immune regulation.

2 Results

We introduce here a population model incorporating the: age (T) of each subject and the chronological/historical (t) time. We initially assume that the population ($N(T, t)$)—the fraction of people of age T at a chronological time t) has a uniform and constant distribution and that all subjects die at the age of 80:

$$N(T, t) = \begin{cases} N, & T \leq 80, \\ 0, & T > 80. \end{cases}$$

We then further relax these assumptions to show that their effect is limited. We also assume that the disease probability ($\lambda(T, t)$) does not change as a function of the chronological time (t) $\lambda(T, t) = \lambda(T)$.

Let us first consider a population divided into three compartments: Susceptible, Sick and Immunized (Fig. 1). We denote by x , y , and z the probability of each individual being susceptible, sick or immunized (z), respectively. Note that the sum of x , y , and z may be lower than 1, since some individuals may die from the disease. Each susceptible person can be infected with an age dependent probability $\lambda(T)$ (representing the force of infection). We divide $\lambda(T)$ into a constant λ multiplied by an age dependent function $\sigma(T)$ multiplied by a

transition probability $P([susceptible \rightarrow disease]|\tilde{\lambda})$, where T is the age and $\sigma(T)$ is normalized to be between 0 and 1. $\tilde{\lambda}$ is defined as the probability of encountering the disease agent. $\sigma(T)$ represents the normalized susceptibility to infection given an encounter. Each naive can also be immunized by the encounter with a low dose of disease agent, with a probability of $\tilde{\lambda}P([susceptible \rightarrow immune]|\tilde{\lambda})$. Thus, the naive compartment has a transition rate of $\tilde{\lambda}P([susceptible \rightarrow immune]|\tilde{\lambda})$ to the immunized compartment and of $\tilde{\lambda}\sigma(T)P([susceptible \rightarrow sick]|\tilde{\lambda})$ to the sick compartment. Recovery takes place with a rate of ψ . Immunity may wane and thus an immunized can become naive again with a transition rate of β . If immunity is life-long, we set $\beta = 0$. A low probability of μ that sick persons would die as a result of the disease can also be taken into account. As for natural mortality, type I survivorship function is assumed in the generic model. That is, 100% of the population survives until the age of 80 and then everyone promptly dies. We will relax this last assumption in the next sections. This model (Fig. 1) can be expressed by the following set of equations:

$$\begin{aligned}\frac{dx}{dT} &= -\tilde{\lambda}\sigma(T)P([susceptible \rightarrow sick]|\tilde{\lambda})x \\ &\quad -\tilde{\lambda}P([susceptible \rightarrow immunized]|\tilde{\lambda})x + \beta z, \\ \frac{dy}{dT} &= \tilde{\lambda}\sigma(T)P([susceptible \rightarrow sick]|\tilde{\lambda})x - (\psi + \mu)y, \\ \frac{dz}{dT} &= \tilde{\lambda}P([susceptible \rightarrow immunized]|\tilde{\lambda})x - \beta z + \psi y.\end{aligned}\quad (1)$$

Let us denote:

$$\lambda = \tilde{\lambda}P([susceptible \rightarrow sick]|\tilde{\lambda}), \quad \lambda_v = \tilde{\lambda}P([susceptible \rightarrow immunized]|\tilde{\lambda})$$

and

$$\varepsilon = P([susceptible \rightarrow immunized]|\tilde{\lambda})/P([susceptible \rightarrow sick]|\tilde{\lambda})$$

to obtain:

$$\begin{aligned}\frac{dx}{dT} &= -\lambda\sigma(T)x - \lambda\varepsilon x + \beta z, \\ \frac{dy}{dT} &= \lambda\sigma(T)x - (\psi + \mu)y, \\ \frac{dz}{dT} &= \lambda\varepsilon x - \beta z + \psi y.\end{aligned}\quad (2)$$

These equations are solved for the lifetime of a patient from birth to death ($0 \rightarrow T_{\text{End}}$).

We first simplify the problem and set $\sigma(T)$ to be a uniform step function after T_{Start} years,

$$\sigma(T) = \begin{cases} \sigma & T_{\text{Start}} < T < T_{\text{End}}, \\ 0 & \text{else.} \end{cases}$$

We also set $\lambda \ll 1$, as happens in most diseases. The total probability of a person to be sick during his lifetime, independent of the outcome of the disease, is $L(\lambda) = \int_{T \in [\text{Start}, \text{End}]} \lambda x(\lambda)$,

$T)dT$. For this simple case, we compute $L(\lambda)$ analytically and numerically, and show that for large regions in the parameter space $L(\lambda)$ does not monotonically increase as a function of λ .

2.1 Immunization and disease

Immunization and disease are both affected by the disease agent encounter probability. We have previously defined

$$\varepsilon = \frac{P([susceptible \rightarrow immunized] | \tilde{\lambda})}{P([susceptible \rightarrow sick] | \tilde{\lambda})}.$$

This requires the assumption that increasing or decreasing the amount of disease agent in the environment (λ) increases and decreases the immunization and infection probabilities ($\tilde{\lambda}$) by similar factors. We here show that if all exposure events are independent and the values of λ and λ_v are much lower than one, this assumption holds. Formally, we claim the following lemma.

Lemma 1 Assuming all exposure events are independent, and that the disease and immunization probability are low, one can approximate: $\varepsilon = \lambda/\lambda_v \approx \text{const}$, $\{0 \leq \lambda \ll 1, 0 \leq \lambda_v \ll 1\}$.

Proof Let us define the number of events per period where a person is exposed to k agents as S_k , and the risk of diseases of a susceptible after a single exposure to a disease agent as r .

Assuming that each exposure event is independent, the probability of getting sick is one minus the probability of not getting sick in any of the exposures. The probability of not getting sick in a single exposure to k disease agents is e^{-kr} . The probability of not getting sick after S_k encounters is e^{-krS_k} . The total disease probability is thus:

$$\begin{aligned} \lambda &= 1 - P(\text{not getting sick}) \\ &= 1 - \prod_{\text{Number of agents encountered} = k} P(\text{encountering } k \text{ agents})^{\text{Number of such encounters}} \\ &= 1 - \prod_{k=1}^{\infty} e^{-krS_k}. \end{aligned}$$

Note that if a small number of agents cannot induce a disease, the low values of S_k can be set to zero. The probability of getting immunized per exposure to the disease agent (r_v) can be used to compute the total immunization probability: $\lambda_v = 1 - \prod_{k=1}^{\infty} e^{-kr_v S_k}$. The multiplication can be transformed to a sum in the exponent: $\lambda = 1 - e^{-\sum_{k=1}^{\infty} krS_k}$. Since λ is a very small number, this can be approximated by: $\lambda \approx r \sum_{k=1}^{\infty} kS_k$, assuming S_k decreases rapidly enough to zero. Similarly $\lambda_v \approx r_v \sum_{k=1}^{\infty} kS_k$, leading to a constant ratio between the two values.

2.2 Effect of exposure rate

Given the constant value of:

$$\varepsilon = \frac{P([susceptible \rightarrow immunized] | \tilde{\lambda})}{P([susceptible \rightarrow sick] | \tilde{\lambda})},$$

we show that decreasing the agent encounter probability (as defined by λ) can actually increase the disease incidence ($L(\lambda)$). In other words, the observed increase in disease incidence can actually be the direct result of the reduction in the exposure probability to the disease agent. Formally, this can be stated as the following lemma.

Lemma 2 $L(\lambda)$ is not always a monotonic function.

Proof Let us assume that

$$\mathbf{A.} \quad N(T, t) = \begin{cases} N, & T \leq 80, \\ 0, & T > 80. \end{cases}$$

$$\mathbf{B.} \quad \lambda(T, t) = \lambda(T).$$

$$\mathbf{C.} \quad \text{The fraction of the population killed by the disease is negligible: } \mu \int_T y(T) dT \ll 1.$$

Given these assumptions, $L(\lambda)$ can be computed using the solution of (2) that can be posed in a matrix form as

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix}'_T = \begin{pmatrix} -\lambda(\sigma + \varepsilon) & 0 & \beta \\ \lambda\sigma & -\psi & 0 \\ \lambda\varepsilon & \psi & -\beta \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix}. \quad (3)$$

There are a few general domains in the parameter space where $L(\lambda)$ is not a monotonic function. We here show two such cases.

One case of non-monotonic $L(\lambda)$ is for long-lived immunity ($\beta = 0$). Ignoring the negligible effect of disease induced mortality (μ) on y , the sum of x , y , and z can be approximated to 1.

The number of variables can be reduced to obtain: $y = 1 - x - z$.

Equation (3) can be written as

$$\begin{pmatrix} x \\ z \end{pmatrix}'_T = A \begin{pmatrix} x \\ z \end{pmatrix} + b,$$

where

$$A = \begin{pmatrix} -\lambda(\sigma + \varepsilon) & \beta \\ \lambda\varepsilon - \psi & -\psi - \beta \end{pmatrix}, \quad b = \begin{pmatrix} 0 \\ \psi \end{pmatrix}. \quad (4)$$

The solution before T_{Start} (when $\sigma = 0$) is:

$$\begin{pmatrix} x(T) \\ z(T) \end{pmatrix} = A^{-1}b + \sum_{i=1}^2 C_i v_i e^{\gamma_i T},$$

where

$$v = \begin{pmatrix} \frac{-\lambda(\sigma+\varepsilon)+\psi}{-\lambda\varepsilon+\psi} & 0 \\ 1 & 1 \end{pmatrix} \text{ and } \gamma = [-\lambda(\sigma+\varepsilon), -\psi]$$

are the eigenvectors and eigenvalues and $C = [2, -1]$.

For $T > T_{\text{Start}}$ ($\sigma \neq 0$) the solution is

$$\begin{pmatrix} x(T) \\ z(T) \end{pmatrix} = \begin{pmatrix} 0 \\ -1 \end{pmatrix} + D_1 \begin{pmatrix} 0 \\ 1 \end{pmatrix} e^{-\psi T} + D_2 \begin{pmatrix} -\frac{\lambda(\sigma+\varepsilon)-\psi}{\lambda\varepsilon-\psi} \\ 1 \end{pmatrix} e^{-\lambda(\sigma+\varepsilon)T}, \quad (5)$$

$$\begin{aligned} D_1 &= \left[2 - \frac{\lambda\sigma}{\lambda(\sigma+\varepsilon)-\psi} e^{(-\lambda\varepsilon+\psi)T_{\text{Start}}} \right], \\ D_2 &= - \left[\frac{\lambda\varepsilon-\psi}{\lambda(\sigma+\varepsilon)-\psi} \right] e^{\lambda\sigma T_{\text{Start}}}, \\ y(T) &= 1 - x(T) - z(T). \end{aligned} \quad (6)$$

The resulting disease frequency is

$$L(\lambda) = \int_{T_{\text{Start}}}^{T_{\text{End}}} \lambda \sigma x(T) dT = - \frac{\sigma e^{\lambda\sigma T_{\text{Start}}}}{\sigma + \varepsilon} \left[e^{-\lambda(\sigma+\varepsilon)T_{\text{End}}} - e^{-\lambda(\sigma+\varepsilon)T_{\text{Start}}} \right]. \quad (7)$$

This function is a non-monotonous. It has a maximum at the finite value of

$$\begin{aligned} \lambda^* &= \frac{\ln\left(\frac{(\sigma+\varepsilon)T_{\text{End}} - \sigma T_{\text{Start}}}{\varepsilon T_{\text{Start}}}\right)}{(\sigma+\varepsilon)(T_{\text{End}} - T_{\text{Start}})}, \\ \frac{d^2(L(\lambda))}{d\lambda^2} \Big|_{\lambda=\lambda^*} &< 0 \text{ for } \frac{1}{(T_{\text{End}} - T_{\text{Start}})} < \varepsilon. \end{aligned} \quad (8)$$

Note that this result spans a wide range of the parameter space. In other words, as one decreases the encounter probability toward the critical value (λ^*), the disease rate will increase (Fig. 2A).

To summarize, if immunity is lifelong ($\beta = 0$), then beyond a given value of λ , increasing λ will reduce disease incidence and vice versa.

Interestingly, the transition value decreases as T_{Start} increases. Note that if T_{Start} is very low, the transition rate will be so high that it will not be observed in realistic situations (Fig. 2B). Formally, if T_{Start} is zero, a transition will never occur as explained in Lemma 3.

A second case for which a clear maximum in the disease frequency occurs for finite values of λ is when $\psi = 0$ and β is small enough. In such a case, again ignoring the mortality, one obtains

$$\begin{pmatrix} x \\ z \end{pmatrix}'_T = \begin{pmatrix} -\lambda(\sigma+\varepsilon) & \beta \\ \lambda\varepsilon & -\beta \end{pmatrix} \begin{pmatrix} x \\ z \end{pmatrix} \quad (9)$$

with a general solution for $T > T_{\text{Start}}$ of

$$\begin{pmatrix} x(T) \\ z(T) \end{pmatrix} = D_1 \begin{pmatrix} \frac{\beta}{\lambda(\varepsilon+\sigma)+\omega_1} \\ 1 \end{pmatrix} e^{\omega_1(T-T_{\text{Start}})} + D_2 \begin{pmatrix} \frac{\beta}{\lambda(\varepsilon+\sigma)+\omega_2} \\ 1 \end{pmatrix} e^{\omega_2(T-T_{\text{Start}})} \quad (10)$$

where

$$\omega = \frac{1}{2} \left(-\beta - \lambda(\sigma+\varepsilon) \pm \sqrt{(\beta+\lambda(\sigma+\varepsilon))^2 - 4\beta\lambda\sigma} \right)$$

and

$$V_1 = \begin{pmatrix} \frac{\beta}{\lambda(\varepsilon+\sigma)+\omega_1} \\ 1 \end{pmatrix}, \quad V_2 = \begin{pmatrix} \frac{\beta}{\lambda(\varepsilon+\sigma)+\omega_2} \\ 1 \end{pmatrix}.$$

And the values of D solve the following equations:

$$\begin{cases} D_1 + D_2 = \frac{\lambda\varepsilon}{\lambda\varepsilon+\beta} (1 - e^{-(\lambda\varepsilon+\beta)T_{\text{Start}}}), \\ \frac{\beta}{(\lambda(\varepsilon+\sigma)+\omega_1)} D_1 + \frac{\beta}{(\lambda(\varepsilon+\sigma)+\omega_2)} D_2 = \frac{(\lambda\varepsilon e^{-(\lambda\varepsilon+\beta)T_{\text{Start}}+\beta})}{\lambda\varepsilon+\beta}. \end{cases} \quad (11)$$

$L(\lambda)$ is thus

$$\begin{aligned} L(\lambda) &= -\frac{\lambda\beta}{(\lambda\varepsilon+\beta)(\omega_2-\omega_1)\omega_1} \left[e^{-(\lambda\varepsilon+\beta)T_{\text{Start}}} \left(\frac{-\lambda\varepsilon\omega_1}{\beta} \right) + \lambda\sigma + \omega_2 \right] \times [1 - e^{\omega_1(T_{\text{End}}-T_{\text{Start}})}] \\ &\quad - \frac{\lambda\beta}{(\lambda\varepsilon+\beta)(\omega_1-\omega_2)\omega_2} \left[e^{-(\lambda\varepsilon+\beta)T_{\text{Start}}} \left(\frac{-\lambda\varepsilon\omega_2}{\beta} \right) + \lambda\sigma + \omega_1 \right] \times [1 - e^{\omega_2(T_{\text{End}}-T_{\text{Start}})}] \\ &= \frac{1}{\sigma} + \frac{e^{\omega_1(T_{\text{End}}-T_{\text{Start}})}}{\sigma(\lambda\varepsilon+\beta)(-\sqrt{(\beta+\lambda(\sigma+\varepsilon))^2-4\beta\lambda\sigma})} \times \{ [-\sigma\lambda^2\varepsilon e^{-(\lambda\varepsilon+\beta)T_{\text{Start}}} + \omega_2(\lambda\sigma+\omega_2)] - [-\sigma\lambda^2\varepsilon e^{-(\lambda\varepsilon+\beta)T_{\text{Start}}} + \omega_1(\lambda\sigma+\omega_1)] e^{(\omega_2-\omega_1)(T_{\text{End}}-T_{\text{Start}})} \}. \end{aligned} \quad (12)$$

One can examine the values of $\frac{d}{d\lambda}(L(\lambda))$ at the boundaries ($\lambda \rightarrow 0, \lambda \rightarrow 1$).

For the left boundary ($\lambda \rightarrow 0$): $\frac{d}{d\lambda}(L(\lambda))$ is a positive value for all parameters in the studied regime, while, for the right boundary ($\lambda \rightarrow 1$): $\frac{d}{d\lambda}(L(\lambda)) < 0$ only for $\beta \ll 1$. Thus, if $\psi = 0$ and $\beta \ll 1$, $L(\lambda)$ has at least one maximum for a finite values of λ .

The transition from a monotonic to a non-monotonic function based on $\frac{d}{d\lambda}(L(\lambda))$ and $L(\lambda)$ as a function of λ for various parameter sets can be observed in Fig. 3.

2.3 Effect of historical changes in exposure rate

A direct conclusion from Lemma 1 is that if the force of infection (λ) is a decreasing function over chronological time (t), the total disease frequency ($L(t)$) can increase in time. In order to compute the total disease frequency $L(t)$, we slightly modify the definition of L . In the previous section, L represented the total disease probability over the lifetime of an individual. The total incidence in the population was simply NL , since both L and N were constant in time (t). We now relax these assumptions, and the total disease incidence at a given time has to be computed as

$$L(t) = \int_{T \in [\text{Start}, \text{End}]} N(T, t) \lambda(t) x(T, t) dT, \quad (13)$$

where $N(T, t)$ is the total number of persons of age T at time t , $\lambda(t)$ is the force of infection at time t and $x(T, t)$ is the fraction of susceptible people of age T at time t (see Fig. 4 for a descriptive scheme). The total disease incidence is the combined disease incidence over people of all ages. For the sake of clarity, we will denote the disease incidence as computed in previous sections as $L_0(\lambda)$, and the time varying incidence as $L(t)$. Formally, we claim the following corollary.

Corollary 1 If $\lambda(t)$ is a decreasing function: $\lambda(t_1) > \lambda(t_2)$, where $t_1 < t_2$ are chronological time points, the total disease incidence at a given time (t), as defined by (13) can be a decreasing function.

Proof In the simplest case, where the disease agent encounter probability is fixed for a period longer than the maximal lifespan at a value of $\lambda(t_2)$ and the population is fixed:

$$L(t_2) = \lambda(t_2) \int_{T \in [\text{Start}, \text{End}]} N x(T) dT = L_0(\lambda(t_2)). \quad (14)$$

Similarly, before any change occurred in $\lambda(t)$, $L(t_1) = L_0(\lambda(t_1))$. Given Lemma 2, for some values of λ : $\lambda(t_2) < \lambda(t_1)$ and $L_0(\lambda(t_2)) > L_0(\lambda(t_1))$. Thus, the increase in the disease occurrence rate, following a decrease in the disease agent encounter probability, can be translated into a chronological increase in the disease frequency accompanied by a chronological decrease in the encounter rate as indeed observed.

2.4 Effect of minimal disease age

Lemma 3 For a constant population structure ($N(T, t)$), if the minimal disease age is similar to the minimal age for immunization, a decrease in the disease agent encounter rate will always lead to a decrease in the disease probability.

Proof We show that if $T_{\text{Start}} = 0$ then $L(\lambda)$ is always monotonic.

Let us set $T_{\text{Start}} = 0$ in (7) (Lemma 2). The resulting disease frequency is now

$$L(\lambda) = \int_0^{T_{\text{End}}} N \lambda \sigma x(T) dT = - \frac{N^2 \sigma}{\sigma + \varepsilon} \left[e^{-\lambda(\sigma + \varepsilon) T_{\text{End}}} - 1 \right]. \quad (15)$$

The resulting derivative is

$$\frac{d(L(\lambda))}{d\lambda} = N^2 \sigma T_{\text{End}} e^{-\lambda(\sigma + \varepsilon) T_{\text{End}}} \geq 0. \quad (16)$$

Since the derivative is positive for all λ , decreasing the encounter probability will decrease λ and subsequently the disease probability. Note that this is the extreme case of the situation discussed in Fig. 2B, where we have shown that as the initial disease age decrease, the critical value (λ^*) increases. When the initial disease age is 0, the critical value is simply infinity.

2.5 Realistic situations

Lemma 4 If the disease is incurable ($\psi = 0$) and rare ($y \ll 1$), the increase in disease frequency following an increase in the disease agent encounter rate can be expanded to realistic values of $\sigma(T)$, $N(T, t)$ and $\lambda(t)$. Note that most environmentally induced diseases are indeed rare and incurable.

Proof The total number of persons infected in a given year (independently of the disease result—death or immunity) can be computed as

$$L(t) = \int_T N(T, t) \sigma(T) \lambda(t) x(T, t) dT. \quad (17)$$

If y is small enough, one can ignore the effect of y on x and obtain

$$\begin{aligned} \frac{dx(T, t)}{dT} &= -\lambda(t) \varepsilon x(T, t) + \beta z(T, t), \\ \frac{dz(T, t)}{dT} &= \lambda(t) \varepsilon x(T, t) - \beta z(T, t) \end{aligned} \quad (18)$$

which leads to

$$\frac{dx(T, t)}{dT} = -\lambda(t) \varepsilon x(T, t) + \beta(N(T, t) - x(T, t)). \quad (19)$$

This equation can be transferred to the T space, defining, $t = T_{\text{birth}} + T$ leading to

$$\frac{dx(T, T_{\text{birth}})}{dT} = \beta N(T, T_{\text{birth}} + T) - (\lambda(T_{\text{birth}} + T)\varepsilon + \beta) x(T, T_{\text{birth}}). \quad (20)$$

The solution to (18) is:

$$x(T, T_{\text{birth}}) = N(T, T_{\text{birth}} + T) \left[\beta e^{-f(T, T_{\text{birth}})} \int_0^T e^{f(T', T_{\text{birth}})} dT' + e^{-f(T, T_{\text{birth}})} \right] \quad (21)$$

$$\text{where } f(T, T_{\text{birth}}) := \int_0^T (\lambda(T_{\text{birth}} + T')\varepsilon + \beta) dT'.$$

The first term in x represents the effect of immunity loss and the second term represents the direct reduction in the susceptible population following immunization.

The total disease incidence then is

$$L(t) = \lambda(t) \int_T N(T, t) \sigma(T) e^{-f(T, t-T)} \left[1 + \beta \int_0^T e^{f(T', t-T')} dT' \right] dT = \lambda(t). \quad (22)$$

The integral over all people of age T at the chronological time t can be replaced by an integral over the birth year of each person— T_{birth}

$$L(t) = \lambda(t) \int_{T_{\text{Birth}}=t}^{t-T_{\text{End}}} N(0, t-T_{\text{Birth}}) \sigma(t-T_{\text{Birth}}) e^{-f(t-T_{\text{Birth}}, T_{\text{Birth}})} \left[1 + \beta \int_0^T e^{f(t-T_{\text{Birth}}, T')} dT' \right] dT_{\text{Birth}} = \lambda(t) S(t). \quad (23)$$

For low enough values of β , one can ignore the immunization loss term, and the disease incidence simply represents the balance between the reduction in the susceptible population ($S(t)$) and the probability of getting sick ($\lambda(t)$). Thus, if the integral of $e^{-f(T)}$ increases faster than the decrease in a given time of $\lambda(t)$, then $L(t)$ will increase. The disease incidence rate is the combined effect of the previous exposure rates leading to immunization and current exposure rate. A simple example would be where $\lambda(t) = Ae^{-\alpha t}$, N is constant and $\beta \approx 0$. In such a case, the derivative of $L(t)$ is positive when

$$\begin{aligned} \frac{dL(t)}{dt} &= N \frac{d\lambda(t)}{dt} \int_T \sigma(T) e^{-f(T, T_{\text{Birth}})} dT \\ &+ \lambda(t) \sigma(T) e^{-f(T, T_{\text{Birth}})} > 0 \Rightarrow \\ &- \alpha A e^{-\alpha t} e^{-\frac{\varepsilon}{\alpha} A e^{-\alpha T_{\text{Birth}}}} \int_{T \in [\text{Start}, \text{End}]} e^{\frac{\varepsilon}{\alpha} A e^{-\alpha(T_{\text{Birth}} + T)}} dT \\ &+ A e^{-\alpha t} \sigma(T) e^{-\frac{\varepsilon}{\alpha} A e^{-\alpha T_{\text{Birth}} [1 - e^{-\alpha T}]}} > 0. \end{aligned} \quad (24)$$

Thus, if α fulfills the follows condition, the disease probability will actually increase:

$$- \left[Ei \left(1, -\frac{\varepsilon}{\alpha} A e^{-\alpha(T_{\text{Birth}} + T_{\text{End}})} \right) - Ei \left(1, -\frac{\varepsilon}{\alpha} A e^{-\alpha(T_{\text{Birth}} + T_{\text{Start}})} \right) \right] + \sigma(T) e^{\frac{\varepsilon}{\alpha} A e^{-\alpha(T_{\text{Birth}} - T)}} > 0.$$

2.6 Listeria Model

A recent case of an increase in disease coupled with a decrease in the exposure rate to the factor inducing the disease is listeriosis. Listeriosis is a highly fatal, yet quite rare disease. Its case fatality can reach 60% (Vazquez-Boland et al. 2001). It is caused by the intracellular bacteria, *Listeria monocytogenes*. This pathogen is known as a psychrotrophic bacterium. *L. monocytogenes* is primarily spread by food, and transmission from human to human plays a negligible role in its epidemiology (Sauders et al. 2005). Adaptive immunity to *L. monocytogenes* is mainly mediated by cellular response and is dominated by CD8+ T-cells (Pamer 2004), though CD4+ T-cells are required for the development of adequate memory response (Sun and Bevan 2003; Pamer 2004). As listeriosis might be highly fatal, there is no experimental knowledge regarding the longevity of the human immune response to *L. monocytogenes*. However, infection of mice by *L. monocytogenes* has been shown to induce long-term and even life-long protective immunity (Lara-Tejero and Pamer 2004; Pamer 2004). This acquired immunity is not related to the induction of clinical signs by infection with *L. monocytogenes* (Goossens and Milon 1992; Darji et al. 2003). T-cells specific for *L. monocytogenes* are also frequently present in healthy humans (Munk and Kaufmann 1988), which suggests that prior exposures to *L. monocytogenes* via food stimulated specific immune response against the bacteria.

Several European studies recently described a sharp and steady increase in the incidence of listeriosis amongst the elderly population. This increase was described in England and Wales (Gillespie et al. 2006). A similar increase was also observed in Germany, Denmark and Norway during the last few years (Koch and Stark 2006; Antal et al. 2007) though in the latter increase was also apparent in people aged 40–59 years.

In view of this rise in the incidence of listeriosis, and taking into account the above-mentioned characteristics of *L. monocytogenes*, we recently hypothesized that the upsurge of listeriosis incidence may originate from a decrease in the overall population immunity to *L. monocytogenes* infection (Lavi et al. 2008). We here apply the above-mentioned formalism to Listeriosis. Even if immunity is not for life, only cases in which $\beta \ll 1$ are considered, since it is assumed that immunity for *L. monocytogenes* lasts many years (Lara-Tejero and Pamer 2004; Pamer 2004). Based on a recent population estimates for England and Wales, we determine $N(T, t) = N(T)$ as a decay linear function: $N(T) = 400 - 20(T - T_{\text{Start}})$. We assume for the sake of simplicity that $\lambda(t)$ is first a constant, then a decreasing linear function until it reaches the transition time; then it stabilizes again at the value of λ_b :

$$\lambda(t) = \begin{cases} \lambda_a, & t < t_1, \\ (\lambda_b - \lambda_a) \frac{t - t_0}{t_1 - t_0} + \lambda_a, & t_0 \leq t < t_1, \\ \lambda_b, & t_1 \leq t. \end{cases} \quad (26)$$

Finally, we assume that

$$\sigma(T) = \begin{cases} 1 & 60 < T < 80, \\ 0 & \text{else.} \end{cases}$$

The optimal values of λ_a , λ_b , t_1 , ε , and t_0 were computed using the observed listeriosis frequencies (Fig. 5) (Koch and Stark 2006; Goulet et al. 2008). In order to find the parameter set to fit the data we minimized the “mean square error” (MSE). The MSE is defined as the difference between the actual observations and the response predicted by the model:

$$\min(\text{Error}) = \min \left(\sum (L(t, \vec{\theta}) - \text{RealDate})^2 \right), \quad \vec{\theta} = [\varepsilon, \lambda_a, \lambda_b, t_0, t_1].$$

The results (Table 1 and Fig. 5) show similar values for λ_a and λ_b in England and in Germany. The interesting difference relates to the timing of the decrease in the exposure rate. In England the best fit describes a rapid decrease from the 40s to the 50s of the twentieth century, probably when refrigeration was introduced. In Germany a much slower process is observed, spanning 20 years and starting 10 years later. We currently have no clear historical model explaining these differences. Moreover, the fit is based on a simplistic linear model of the exposure probability decrease. Such a model is obviously not very realistic, and its results should be taken more as a proof of concept than a direct claim on the estimated start and end of the decrease in the exposure rate.

To summarize, beyond the conceptual claim that reducing exposure can lead to an increase in disease frequency, the model presented here can actually directly fit observed data.

3 Discussion

We have here presented a generic model for the effect of the exposure rate to non-infectious disease inducing agents on disease incidence rate. This model shows that paradoxically the decrease in the exposure frequency can actually lead to an increase in the disease incidence, with two important limiting conditions: (a) long lived immunity following early exposure to the disease inducing agent, (b) a delay between the age in which immunity can be acquired and the age at which exposure might result in a disease. The apparent paradox is the direct result of the balance between the smaller fraction of the susceptible population that is immunized and the lower probability of each susceptible person being sick. Such a result can be expected in all environmentally induced diseases with no person to person transmission.

The precise numerical results from the model depend on the age distribution of the population, the morbidity to immunity probability ratio and the precise time evolution of the disease agent encounter probability.

The time difference between the minimal age for immunity and disease acquisition may actually be appropriate for a large number of diseases. A large number of diseases are significantly more dangerous in adults. In these diseases, the time interval before they become dangerous can be enough to induce immunity in a large part of the population if the exposure rate is high enough. If on the other hand, the disease can affect newborns, the advantage of having a large part of the population immunized does not balance the higher incidence in non-immunized children. Similarly, if immunization is short-timed, a continuous exposure to the pathogen (or disease inducing factor, such as allergen) is required. Our model shows that this continuous exposure will induce a higher disease incidence rate than would be obtained in the non-immunized population at low exposure rates. Quite surprisingly, many modern diseases may enter the scope of the presented model. Beyond the effect of food-borne pathogens, autoimmune diseases and allergies are continuously rising in the western world. A hygiene model that has been proposed for these

diseases suggests that lack of exposure to pathogenic and non-pathogenic organisms prevents the regulation of the immune system (Lack 2008; Cooke 2009). However, another suggested explanation for this observation may be that exposure to the actual inducing agent early in life is not associated with morbidity and provides a sort of immunization that may protect from morbidity due to later exposure. As suggested by our model, paradoxically, an increase in exposure to the agent may result in reduction of disease incidence. If the hygiene model is to be applied as is, the two conditions mentioned above of long lived immunity and a delay in the minimal age for disease should apply. These conditions now remain to be checked in each specific disease.

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Fig. 1.

The Linear SIR Model for non-contagious disease. The proposed model has three compartments. The first (X) is a naïve compartment of people potentially susceptible to the disease that were never exposed to a high enough dose of *L. monocytogenes* to develop an immune response. The second compartment (Y) is the immunized population. The third compartment (Z) is the sick population. A naïve can become immunized with a probability λ_v if he was ever exposed to a high enough *L. monocytogenes* dose. A naïve can also become sick with a probability of λ if he is exposed to an appropriate dose of *L. monocytogenes* at the appropriate age. Immunity might wane with time. Thus, each immunized has a chance, β , of becoming “naïve” again. Finally, a sick person may die with a probability of μ or recover and become immunized with a probability of ψ . Additionally, immunized have a low chance λ' of becoming ill. The chance of becoming sick is time dependent and designed as a constant multiplied by a time dependent function, $\sigma(T)$

Fig. 2. Parameters space for evaluating $L(\lambda)$ where $\beta = 0$ (4). First example where $L(\lambda)$ is not a monotonic function, for any ε , ψ and $\beta = 0$. A numerical evaluation of $L(\lambda)$ was plotted using the Maple program. $L(\lambda)$, described by (7), is the solution of the system described by (8) plotted in the z axis; while λ and ε are in x and y axis, respectively. A clear maximum in the disease frequency occurs for finite values of large parameters space (λ, ε)

Fig. 3.

Parameters space for evaluating $L(\lambda)$ where $\psi = 0$ (9). Second example where $L(\lambda)$ is not a monotonic function, for most ε values, $\beta \ll 1$ and $\psi = 0$. $L(\lambda)$, described by (12), is the

solution of the system described by (9). Since $0 \leq \lambda \leq 1$, we examine the value of $\frac{d}{d\lambda}(L(\lambda))$

in its boundaries ($\lambda \rightarrow 0, \lambda \rightarrow 1$). For the right boundary ($\lambda \rightarrow 0$): $\frac{d}{d\lambda}(L(\lambda))$ can be determined to be a positive value, for all parameters, while, for the left boundary

($\lambda \rightarrow 1$): $\frac{d}{d\lambda}(L(\lambda)) < 0$ only for $\beta \ll 1$. We evaluate $\frac{d}{d\lambda}(L(\lambda))$ as a function of the variable λ and

the parameters β and ε . Using the parameters: $T_{\text{Start}} = 60$, $T_{\text{End}} = 80$, $\sigma = 1$, the function $L(\lambda)$ (**A**) and its derivative (**B**) were plotted at $\lambda \rightarrow 1$

Fig. 4.

Descriptive scheme of effect leading to high disease incidence. The *lower right drawing* represents the exposure rate as a function of the chronological time (t). The lower left figure represent $\sigma(T)$ as a function of the year of birth of each member of the population and the chronological time, since Listeriosis occurs mainly at old age, people with later birth years (y axis) can get sick only later in chronological time (x axis). The main drawing represents the fraction of the susceptible population as a function of the year of birth (y axis) and chronological time (x axis). Each person is assumed to live no more than 80 years. Thus, all values beyond a 80-year layer along the diagonal are 0. The parameter set that we used is: $T_{\text{Start}} = 60$, $T_{\text{End}} = 80$, $\varepsilon = 70$, $\psi = 0$, $\beta = 0$, $\mu = 0$, $\lambda_a = 0.001$, $\lambda_b = 0.0001$, $t_0 = 1960$, $t_1 = 1980$. As the exposure rate decreases, a larger part of the population becomes susceptible. The balance between these two effects determines the disease incidence

Fig. 5.

Observed increase in $L(\lambda, t)$ following the decrease in λ in Listeriosis in a few European countries, and the best fit model. The *gray stars* represent the Listeriosis incidence in England from 2001 to 2005 (Koch and Stark 2006) and the *black squares* for England and Wales from 1990 to 2004 (Gillespie et al. 2006). We assumed this increase results from the mechanism proposed in this paper and checked which parameter produced the best fit (*fitting lines*). The *black* and *gray lines* represent the least square fits of the respective models. The fitting parameters are described in Table 1

Table 1

Parameters	Listeriosis incidence in England and Wales from 1990 to 2004 (Gillespie et al. 2006)	Listeriosis incidence in Germany from 2001 to 2005 (Koch and Stark 2006)
t_1	1952.8148	1963.9222
t_0	1932.8148	1944.1369
λ_a	0.001075	0.000804
λ_b	0.000138	9.301e-05
ε	156.8006	81.466
β	0.00187	1.82e-15
Min(error)	5863.51	24313