A New Linear Analytical *SIR* Model For Age-Dependent Susceptibility and Occupation-Dependent Immune Status

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Abstract: - A new form of a linear *SIR* model (Susceptible-Infected-Recovered) is posed and analytical solutions are presented. It is motivated by a desire to mimic illness patterns for particular zoonotic microorganisms. In cases where person-to-person transmission of a zoonosis is generally considered to be rare (e.g., campylobacteriosis), an interaction term between Susceptible and Infected groups is not necessary, enabling a linear model to be posed. Immunity losses and gains are accounted for, and also the possibility that infection may occur in the absence of any illness symptoms. Under realistic values of its parameters, the solutions are able to mimic two patterns often inferred from clinical trial and outbreak data: (i) that children are more susceptible to zoonotic pathogens than adults, (ii) that people in regular contact with farm animals may attain greater immunity than the ordinary public.

Key-Words: - Dose-response, differential group immunity, turning points, immunity loss, analytical solutions.

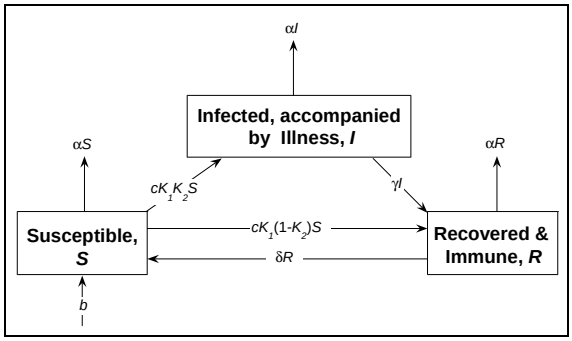
1 Introduction

Quantitative microbial risk assessment (QMRA) demands information on dose-response, typically obtained from a clinical trial in which volunteers are split into groups, each receiving different doses of a particular pathogen [1]. In some cases (e.g., *Giardia* cysts, adenoviruses), the dose-response relationship appears to conform to a single-hit model in which each pathogen particle has a constant probability in any human host of surviving the body's defences to reach an infection site. The resulting model has a simple decreasing exponential or binomial form. For other pathogens (such as *Campylobacter*) there is clear evidence of differential susceptibility between the individuals participating in the trial. To account for this, the pathogen survival probability is replaced by a beta-distribution. The resulting model (which has a more complex form—beta-Poisson or beta-binomial) therefore accounts for differential immunity *within* the group of people participating in the trial [2]. However, in applications of QMRA to larger populations, one may be faced with the need to account for differential immunity *between* groups. For example, rural workers in regular contact with livestock have a greater and more frequent exposure to zoonotic pathogens, and so may develop and maintain a greater immunity than the bulk of the population. Conversely, a city person may develop immunity after illness, but lose it thereafter. A study of the risk of campylobacteriosis in the New Zealand population has indicated that dose-response models do need to account for this feature. Furthermore, there is evidence that children are more susceptible than adults [3], and it should be noted that, for ethical reasons, clinical trials generally do not include children. Therefore, there is a need to account for both the age-dependence of susceptibility, and also the differential immunity status of subgroups in a population.

We develop a linear model for these features, based on the Susceptible-Infected-Recovered (*SIR*) framework. Its linearity arises because the human population can be regularly exposed to zoonotic pathogens such as *Campylobacter jejuni* through both food and environmental routes; person-to-person transmission is generally considered to be rare. Dose-response data enters the model via probability terms accounting for infection-given-dose and for illness-given-infection.

2 Problem Formulation

The basic SIR model is shown below.



In this diagram:

b = immigration rate of susceptibles (#/T^{-1});
c = specific rate of contact with pathogen (T^{-1});
K_1 = probability of infection given contact;
K_2 = probability of illness given infection;
γ = 1/shedding period (T^{-1});
α = specific death rate in population (T^{-1});
δ = specific immunity loss rate (T^{-1}).

2.1 Assumptions

The following assumptions are made in developing the solutions to the model: (i) static conditions prevail, so that *S*, *I* and *R* change with age (*a*), but not with time; (ii) the population is of constant size (*N*); (iii) all persons are born susceptible, so the initial conditions are $S_{a=0} = N$, $I_{a=0} = 0$ and $R_{a=0} = 0$; (iv) α is the same for all *S*-*I*-*R* classes; (v) the model parameters γ and δ are also constant; (vi) person-to-person transmission can be ignored; (vii) individuals may become infected and ill and then recover to become immune, or, on exposure, they may pass directly into the immune class.

Assumption (i) recognizes that some zoonoses (e.g., campylobacteriosis) seldom appear as large outbreaks. Assumption (iv) is permissible because many zoonotic pathogens, and *Campylobacter* in particular, cause much more mild illness than death. Assumption (vi) dictates a linear model, whereas much of the *SIR* literature is concerned with nonlinear models, including an *SI* interaction term [4]. Analytical solutions to the *SIR* equations may therefore be obtained. Assumption (vii) mimics a pattern sometimes found in clinical trials [5].

With these assumptions, this model represents two extensions of the basic static linear model presented elsewhere [6]: firstly, by including immunity losses and gains and secondly, by allowing individuals to pass directly from the *S* to the *R* class [via assumption (vii)].

2.2 Differential Equations

The equations that result from this *SIR* structure and the assumptions stated above are:

$$\frac{\mathrm{d}S}{\mathrm{d}a} = b - \alpha S - cK_1K_2S - cK_1(1-K_2)S + \delta R \qquad (1)$$

$$\frac{\mathrm{d}I}{\mathrm{d}a} = cK_1K_2S - (\alpha+\gamma)I \qquad (2)$$

$$\frac{\mathrm{d}R}{\mathrm{d}a} = \gamma I + cK_1(1-K_2)S - (\alpha+\delta)R \qquad (3)$$

$$N = S + I + R \qquad (4)$$

where *S*, *I* and *R* are functions of age (*a*), and all other terms are independent of age.

Doses enter the model via the probability terms K_1 and K_2. In so doing it is appropriate to use a simple single-hit decreasing binomial or exponential model, because immunity is already catered for in the *SIR* model. In that case we have

$$K_{1,2} = 1 - \mathrm{e}^{-r_{1,2}d_{\mathrm{ave}}} \quad \text{or} \quad K_{1,2} = 1 - (1-r_{1,2})^d \qquad (5)$$

where *r* is a pathogen survival probability in any host to be determined for infection (r_1) and for illness-given-infection (r_2). Note that the first equation is typically used in analyzing clinical trial data, in which d_{ave} is the *average* dose given to subgroups in the trial, whereas the second equation may be used in risk calculations, in which *d* is the particular dose assigned to an individual [2].

3 Problem Solution

By differentiating (4) with respect to age, we obtain

$$b = \alpha(S + I + R) = \alpha N \qquad (6)$$

which removes *b* from (1). *N* may also be removed from (1–4) by making use of the dimensionless proportions $s = S/N$, $i = I/N$ and $r = R/N$. The full equation set is derived using standard (albeit tedious) analytical methods [7], and are given in the Appendix. Their analytical forms have all been checked in detail, using Mathematica® [8], and calculations made from them have been checked against results from an ordinary differential equation solver [9].

The solutions can be used to calculate the proportions of ill people for any group of people

with similar immunity profiles, and for any given age group. They all consist of an age-progression toward *Methuselah* states (old age). For example, the ultimate (*Methuselah)* illness proportion is

$$i_\infty = \frac{(\alpha+\delta)\,cK_1K_2}{(\alpha+\gamma)(\alpha+\delta+cK_1)+\delta cK_1K_2} \qquad (7)$$

3.1 Illness turning points

It is instructive to consider the special case where the determinant of the auxiliary equation for equations (1–3) vanishes. The solutions are then of simpler form (i.e., the $\Delta = 0$ case in the Appendix). This shows that illness proportions can peak before the *Methuselah* state (7) is attained. To see that, note that setting the first differential of the equation for illness (16) to zero gives an extremum at

$$a\big|_{i_{\text{extremum}}} = \frac{1}{\mu}\left[1+\frac{2(\alpha+\delta)}{cK_1+\gamma-\delta}\right] = \frac{2}{cK_1+\gamma-\delta} \qquad (8)$$

where $\mu = \alpha + (\gamma + \delta + cK_1)/2$ is the system's time constant. The second derivative of the i equation is

$$\frac{\mathrm{d}^2 i}{\mathrm{d}a^2} = -(\delta-\gamma+cK_1)^2 \mathrm{e}^{-\mu a} \times \frac{4(\gamma+cK_1)+2\alpha[2+a(\delta-\gamma-cK_1)]+a\left[\delta^2-(\gamma+cK_1)^2\right]}{16\delta} \qquad (9)$$

For a maximum to occur, a takes the value given by (8), in which case the right-hand-side of (9) must be negative. This requires that the numerator of the fraction term in that equation is positive. This can be shown to give the requirement that

$$\delta < \gamma + cK_1 \qquad (10)$$

If $\delta = \gamma + cK_1$, then we have $\mu = \alpha + \gamma + cK_1$, and the general solution for $i(a)$ is simply

$$i(a) = \frac{(cK_1)^2}{\mu\delta}\left(1-\mathrm{e}^{-\mu a}\right) \qquad (11)$$

which has its maximum as $a \to \infty$. For $\delta > \gamma + cK_1$, there is no positive-age maximum illness proportion before the *Methuselah* state is reached [although (7) then admits a negative-age maximum].

Criteria for turning points for the general cases ($\Delta > 0$ and $\Delta < 0$) are more complex. Nevertheless, early-age maxima can still occur.

3.2 Example predictions

Consider typical data for campylobacteriosis, for which New Zealand has a reported rate well over 300 cases per 100,000 people per year [10], representing many more actual cases. This burden implies a relatively high rate of annual contact with *Campylobacter*. Ignoring available dose data, for the normal population we take $c = 1$ per annum and $K_1 = K_2 = 0.5$. For a typical shedding period (a month) we take $\gamma = 12$ per annum. The overall death rate can be taken as $1/80 \approx 0.0125$ per annum. Now consider immunity loss rates for two distinct groups: 0.9 per annum for the normal population and 0.05 per annum for rural workers in regular contact with animals (e.g., in milking sheds), in which case three revised parameter values must be supplied: $c = 10$, $K_1 = 0.1$, $\delta = 0.05$ per annum. The predictions made by the analytical model presented here for these two cases are shown on Figure 1: part (a) displays results for the high immunity loss rate; part (b) shows results for the low immunity loss rate.

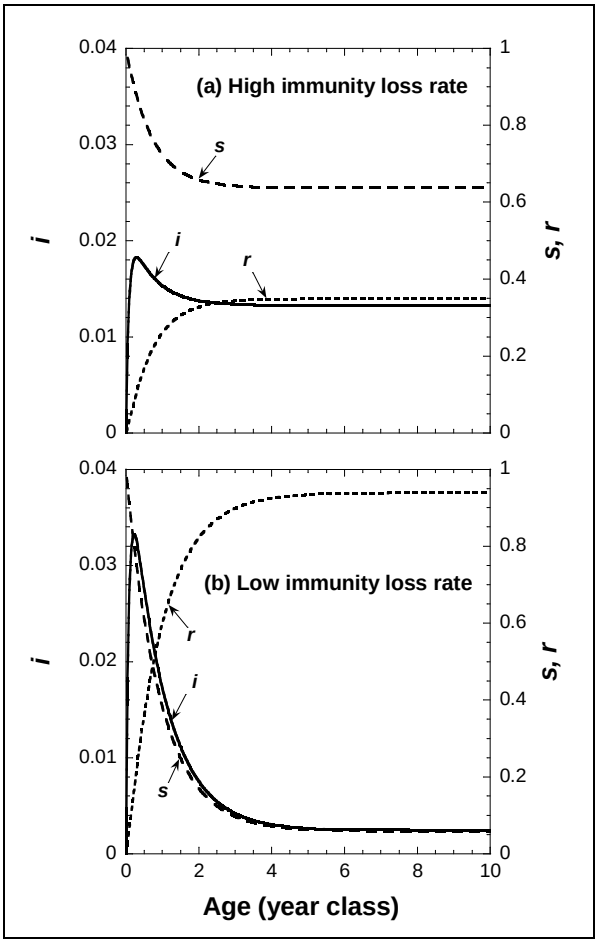


Fig. 1. Parameters values: (a) $c = 1$, $K_1 = K_2 = 0.5$, $\gamma = 12$, $\alpha = 0.0125$, $\delta = 0.9$, (b) K_2, α same as for (a) but with $c = 10$, $K_1 = 0.1$, $\delta = 0.05$.

Both sets of results show that the illness proportion is highest in early years of exposure, in line with inferences elsewhere [3]. Adjusting the immunity loss rate reduces the *Methuselah* illness proportions by a factor more than five-fold (from approximately 0.013 to 0.0024). Notably, the proportions of susceptibles and recovered individuals reverse on this large change in immunity loss rates.

4 Discussion and Conclusion

The solutions to the *SIR* model presented here are of course considerably more complex than the age-independent forms in routine use—though their computation is direct and straightforward. However they do hold some promise in explaining two patterns sometimes inferred from dose-response data and from outbreak data: (i) that children are more susceptible to zoonotic pathogens than adults, (ii) that people in regular contact with farm animals may attain greater immunity for longer periods than the ordinary public (this may also be the case for general rural population frequently exposed to low doses).

The model is of course idealistic, in particular in its use of constant coefficients. This may be overcome by use of numerical methods to solve Equations (1–3); analytical solutions are not generally attainable in such cases. Nevertheless, the analytical solutions shown here serve a valuable purpose in explaining overall features of the behaviour of the model. In any event, mere consideration of the *Methuselah* states is likely to be informative when performing QMRA studies.

This work appears to be the first attempt to incorporate infectious disease dynamics and immunity into dose-response modelling of zoonotic pathogens. It thus represents a shift in thinking to allow for intermixing between hosts, pathogens and the environment. We hope that it will spawn both theoretical and empirical studies, so that microbial risk analyses will be put into a better position to inform policy/interventions in food and environmental safety. Currently the uncertainty in dose-response models (both model and parameter uncertainty) hinders our ability to extend exposure assessments into meaningful assessments of the impact of interventions on public health. The *SIR* approach reported here therefore points to a whole new area of research, clarifying data the need for new data, and identifying differential immunity groups and age classes that may need to be separately considered.

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Appendix: Full List of Analytical Solutions

In the following equation set, Δ is the determinant of the auxiliary equation for the system of Equations (1–3).

General case: $\Delta > 0$

$$s(a) = \left[1 - \mathrm{e}^{-(\zeta+\mu)a}\right] s_\infty + \left[\mathrm{e}^{-\zeta a} + (1+\phi_L)\left(\frac{g}{2\zeta}\right)\left(\mathrm{e}^{\zeta a} - \mathrm{e}^{-\zeta a}\right)\left(\phi_M i_\infty - r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{12}$$

$$i(a) = \left[1 - \mathrm{e}^{-(\zeta+\mu)a}\right] i_\infty - \left[\left(\frac{g}{2\zeta}\right)\left(\mathrm{e}^{\zeta a} - \mathrm{e}^{-\zeta a}\right)\left(\phi_M i_\infty - r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{13}$$

$$r(a) = \left[1 - \mathrm{e}^{-(\zeta+\mu)a}\right] r_\infty - \left[\phi_L\left(\frac{g}{2\zeta}\right)\left(\mathrm{e}^{\zeta a} - \mathrm{e}^{-\zeta a}\right)\left(\phi_M i_\infty - r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{14}$$

Special case: $\Delta = 0$ (so $\zeta = 0$, and $\phi_M = \phi_L = \phi$)

$$s(a) = \left[1 - \mathrm{e}^{-\mu a}\right] s_\infty + \left[1 + (1+\phi) g a \left(\phi i_\infty - r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{15}$$

$$i(a) = \left[1 - \mathrm{e}^{-\mu a}\right] i_\infty - \left[g a \left(\phi i_\infty - r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{16}$$

$$r(a) = \left[1 - \mathrm{e}^{-\mu a}\right] r_\infty - \left[\phi\, g a \left(\phi i_\infty - r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{17}$$

General case: $\Delta < 0$

$$s(a) = \left[1 - \cos(\zeta a)\,\mathrm{e}^{-\mu a}\right] s_\infty + \left[\cos(\zeta a) + \left(\frac{\nu}{\zeta}\right)\sin(\zeta a)\left[\left(\frac{\psi - g\eta}{g\nu}\right) i_\infty + r_\infty\right]\right] \mathrm{e}^{-\mu a} \tag{18}$$

$$i(a) = \left[1 - \cos(\zeta a)\,\mathrm{e}^{-\mu a}\right] i_\infty + \left[\left(\frac{g}{\zeta}\right)\sin(\zeta a)\left(\frac{\eta}{g} i_\infty + r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{19}$$

$$r(a) = \left[1 - \cos(\zeta a)\,\mathrm{e}^{-\mu a}\right] r_\infty - \left[\left(\frac{\eta}{\zeta}\right)\sin(\zeta a)\left(\frac{\psi}{g\eta} i_\infty + r_\infty\right)\right] \mathrm{e}^{-\mu a} \tag{20}$$

where the *Methuselah-states* are:

$$s_\infty = \frac{p\,(\alpha+\delta)}{pq + y},\ \ i_\infty = \frac{g(\alpha+\delta)}{pq + y},\ \text{and}\ \ r_\infty = \frac{pcK_1 - \alpha g}{pq + y},\ \text{with} \tag{21}$$

$$g = cK_1K_2,\ \ p = \alpha + \gamma,\ \ q = \alpha + \delta + cK_1,\ \ y = \delta g,\ \ \mu = \frac{p+q}{2},\ \ \nu = \frac{p-q}{2},$$

$$\Delta = \nu^2 - y,\ \ \zeta = \sqrt{|\Delta|},\ \ \eta = v + g,\ \ \phi_L = -\left(\frac{\zeta+\eta}{g}\right),\ \ \phi_M = \frac{\zeta-\eta}{g},\ \ \psi = \zeta^2 + \eta^2.$$