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The use of a formal sensitivity analysis on epidemic models with immune protection from maternally acquired antibodies

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Abstract

This paper considers the outcome of a formal sensitivity analysis on a series of epidemic model structures developed to study the population level effects of maternal antibodies. The analysis is used to compare the potential influence of maternally acquired immunity on various age and time domain observations of infection and serology, with and without seasonality. The results of the analysis indicate that time series observations are largely insensitive to variations in the average duration of this protection, and that age related empirical data are likely to be most appropriate for estimating these characteristics.

Keywords: SIR Epidemic Models; Maternal Antibodies; Sensitivity Analysis; PDE Systems; Age Dependency; Serological Survey.

1. Introduction

During early life the immature neonate immune system is highly dependent on the accumulated immunologic experience of the mother. For exam-

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ple, in the case of human respiratory syncytial virus (hRSV), which has a particularly low average age at primary infection, studies such as those by Ogilvie et al. [1] and Hacimustafaoglu et al. [2] have shown a strong correlation between high levels of maternal antibodies (MAb) and reduced risk of infection and severity of disease among young infants. Maternal immunity is only acquired passively in the specific form of immunoglobulin isotopes IgA and IgG [3], where IgA is transferred after birth through breast feeding and remains predominantly within mucosal secretions in the digestive and respiratory tracts of the infant. The majority of IgG transfer occurs during the final four weeks of pregnancy, where antibodies actively enter foetal circulation via the placenta. As a result MAb are short lived and following birth, concentrations of IgG in the newborn decay exponentially with a typical half life of around 35-40 days [4]. Many seroepidemiological surveys have shown that most infants become seronegative within 6-9 months of age (see the work by Cox et al. [5] and Hacimustafaoglu et al. [2] for hRSV, Williams et al. [6] for measles and Nicoara et al. [4] for measles, mumps and rubella (MMR)).

The focus of this paper is not on the individual, however, but on the analysis of epidemic models developed to investigate the potential influence of MAb on wider, population level infection dynamics. In this case it is not individual MAb decay (typically estimated using mixed effects modelling techniques and longitudinal serological data) that is directly considered, but the resulting population immunity. The most common approach to deterministic modelling of this type is through a compartmental representation of the various stages of the natural history of infection, written as a system of

ordinary differential equations (ODE). This method was first developed by Kermack and McKendrick [7], in the form of a fundamental SIR (Susceptible-Infective-Recovered) type model structure, which was intended to approximate epidemic evolution within large constant size populations (for general examples see the texts by Jacquez [8] and Capasso [9], and for specific examples see the work by Weber et al. [10] and White et al. [11] for hRSV, and Keeling and Grenfell [12] for measles).

Postulated models of this type are often fitted to time series data corresponding to the prevalence (current number of infective cases) or incidence (current rate of emerging cases) of infection, typically recorded from observations of clinical disease. This process is performed in order to estimate parameter values within the model and make inferences about various characteristics of the real system. However, epidemic data are also often collected with respect to age, for example, in the form of age serological surveys where samples of serum are tested for the presence of disease specific antibodies. It is the objective of this work to use a formal sensitivity analysis, applied to a general partial differential equation (PDE) model structure, in order to compare a number of prospective age and time domain output structures, corresponding to observations of infection and serology. The intention is to establish how well parameters associated with maternally acquired immunity might be determined by various observations of the real system and also to consider the potential influence of these processes on various aspects of system behaviour. The analysis is performed according to the work by Vajda et al. [13] on models residing at endemic equilibrium, where analytic results are derived for systems without seasonal forcing and numerical results obtained

for those that include annual variation with time.

2. SIR Framework Models

The general SIR model [7] is used to characterise epidemic systems where the natural history of infection can be approximated into three distinct stages. The total population is therefore divided into non-overlapping classes that represent subpopulations of individuals with a specific state of disease: Susceptible (S), Infective (I) or Recovered (R). The susceptible class includes all individuals who are able to contract the disease and become infectious; the infective class represents only individuals who are currently infected and infectious to susceptibles, and the recovered class contains all individuals who have recovered from infection and consequently acquired some form of immunity.

The fundamental SIR model can be readily extended to incorporate any number of different epidemiological characteristics such as incomplete immunity (see Gomes et al. [14]), altered secondary infection (see Glass and Grenfell [15], and White et al. [11]) and multiple-strain variants (see White et al. [16]) etc. The potential effects of maternally derived protection can be explored with an additional state compartment $M(t)$, see Figure 1, that corresponds to newborn individuals protected by MAb [17]. Individuals are born into either the maternally protected or susceptible class depending on the previous infection experience of the mother. The total inflow of newborns into the population occurs at a net birth rate equal to μN , where μ (yr^{-1}) is a combined fertility/mortality coefficient and N is the total population size. The parameter ω (yr^{-1}) describes the rate at which maternally

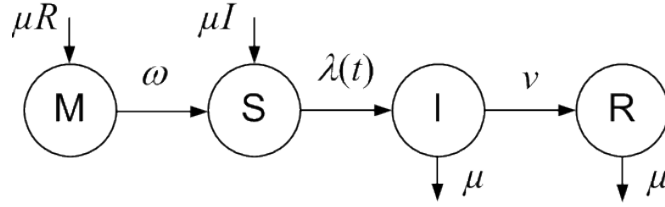


Figure 1: MSIR Compartmental Model

protected newborns become fully susceptible, and ν (yr^{-1}) denotes the rate at which infective individuals recover from infection. It is assumed that the average duration of infection, ν^{-1} , is small with respect to the average life expectancy, μ^{-1} , so that the net mortality rate $\mu(M(t) + S(t) + I(t) + R(t))$ can be assumed to equal μN , hence maintaining a constant size population.

Assuming there is an average contact rate c (yr^{-1}) between all individuals within a particular population, then the rate at which infective individuals $I(t)$ make contact with individuals from the susceptible proportion, $S(t)/N$, can be shown to be $cS(t)I(t)/N$. For each contact between infective and susceptible individuals there is a finite probability ρ that the infectious agent will be successfully transmitted. Therefore the incidence of disease (i.e. the rate at which susceptible individuals become infected) can be modelled as $\beta S(t)I(t)/N$, where $\beta = c\rho$, and $\lambda(t) = \beta I(t)/N$ is often used to represent the force of infection [8]. A system of ordinary differential equations (ODEs)

can then be defined:

$$\frac{dM(t)}{dt} = \mu R(t) - \omega M(t), \quad M(0) = M_0, \quad (1)$$

$$\frac{dS(t)}{dt} = \mu I(t) + \omega M(t) - \frac{\beta(t)}{N} S(t) I(t), \quad S(0) = S_0, \quad (2)$$

$$\frac{dI(t)}{dt} = \frac{\beta(t)}{N} S(t) I(t) - (\mu + \nu) I(t), \quad I(0) = I_0, \quad (3)$$

$$\frac{dR(t)}{dt} = \nu I(t) - \mu R(t), \quad R(0) = R_0. \quad (4)$$

If necessary the system (1)-(4) can be reduced to a set of three state equations given that $R(t) = N - M(t) - S(t) - I(t)$.

Given that both the effects of human behaviour, c , and the contagiousness of the infectious agent, ρ , are potentially governed by recurring seasonal trends, it is common to include a periodic function of time within the transmission parameter $\beta(t)$. For example, seasonality in measles is primarily driven by the annual school term-time pattern of increased contact between individuals in the classroom [18], and prolonged survival of many pathogens outside the host is significantly affected by varying climatic conditions, such as temperature and humidity [19]).

3. PDE Framework Models

In order to compare both time and age domain output structures, the MSIR model framework is required to include variation in the states of disease with respect to age. Age dependency can be included within SIR type epidemic model structures either discretely, as additional state compartments that represent key age/risk groups (see the HIV transmission model by Jacquez [8]), or as in this work, continuously as a system of partial differential equations (PDEs) (see the book by Anderson and May [17]). The

ODE based MSIR model structure, described by equations (1)-(4), is therefore extended so that the system state variables vary with respect to a second independent variable corresponding to age a . In this instance, the functions $M(t, a)$, $S(t, a)$ and $I(t, a)$ represent time varying age distributions of individuals who are maternally protected, susceptible and infective respectively. Since it is the intention of this work to directly compare equivalent age and time domain models of the same MSIR structured system, additional complexities arising from age dependency in other model parameters such as fertility, mortality and heterogeneous social mixing are neglected. Therefore, the full PDE system is defined as follows:

$$\frac{\partial M(t, a)}{\partial t} + \frac{\partial M(t, a)}{\partial a} = -(\omega + \mu)M(t, a), \quad (5)$$

$$\frac{\partial S(t, a)}{\partial t} + \frac{\partial S(t, a)}{\partial a} = \omega M(t, a) - (\lambda(t) + \mu)S(t, a), \quad (6)$$

$$\frac{\partial I(t, a)}{\partial t} + \frac{\partial I(t, a)}{\partial a} = \lambda(t)S(t, a) - (\nu + \mu)I(t, a), \quad (7)$$

where

$$\lambda(t) = (\beta(t)/N) \int_0^\infty I(t, a) da, \quad (8)$$

$$\beta(t) = \beta_0(1 + \beta_1 \cos(2\pi(t - \phi))), \quad (9)$$

with boundary conditions given by:

$$M(t, 0) = \mu \int_0^\infty (N - S(t, a) - I(t, a)) da, \quad (10)$$

$$S(t, 0) = \mu N - M(t, 0), \quad I(t, 0) = 0. \quad (11)$$

Seasonality is included in the transmission parameter as a simple sinusoidal function of time, as shown in equation (9), where β_0 is the average

level of transmission, β_1 represents the magnitude of the annual variation and ϕ corresponds to the phase.

Integrating the PDE model equations with respect to age (i.e. finding the total number of individuals residing in each state of disease for time t) gives rise to a time domain model structure equivalent to the ODE system previously discussed in Section 2 (equations (1)-(4)):

$$\frac{dM(t)}{dt} = M(t, 0) - (\omega + \mu) \int_0^\infty M(t, a) da, \quad (12)$$

$$\frac{dS(t)}{dt} = S(t, 0) + \omega \int_0^\infty M(t, a) da - (\lambda(t) + \mu) \int_0^\infty S(t, a) da, \quad (13)$$

$$\frac{dI(t)}{dt} = \lambda(t) \int_0^\infty S(t, a) da - \nu \int_0^\infty I(t, a) da. \quad (14)$$

Consequently this means that in this simple case the time dynamic behaviour of the model is identical to that of the original ODE model and hence during numerical simulation of the PDE system the integral components within the boundary conditions and the force of infection $\lambda(t)$, can be calculated separately (more easily) from the original ODE system.

If instead the PDE model equations are integrated with respect to time, for example over τ complete annual cycles (to find the annual average number of individuals residing in each state of disease for a given age a) then the following system of age domain integro-differential equations can be derived:

$$\frac{dM(a)}{da} = \frac{\delta(a)}{\tau} \int_0^\tau M(t, 0) dt - (\omega + \mu) \frac{1}{\tau} \int_0^\tau M(t, a) dt, \quad (15)$$

$$\frac{dS(a)}{da} = \frac{\delta(a)}{\tau} \int_0^\tau S(t, 0) dt - \frac{1}{\tau} \int_0^\tau (\lambda(t) + \mu) S(t, a) dt, \quad (16)$$

$$\frac{dI(a)}{da} = \frac{1}{\tau} \int_0^\tau \lambda(t) S(t, a) dt - \frac{\nu}{\tau} \int_0^\tau I(t, a) dt, \quad (17)$$

where the Dirac delta function, $\delta(a)$, terms replace the boundary conditions given by (10)-(11) and ensure that all newborns are born at age zero.

However, given that the incidence age profile is calculated as:

$$\frac{1}{\tau} \int_0^{\tau} \beta(t) S(t, a) I(t) dt, \quad (18)$$

then for seasonal systems there is inevitably some residual time dependency in the age profile hence requiring the full PDE system (5)-(11) to be solved.

The epidemiological measures considered in this study are:

- **Prevalence** - the number of individuals within a population currently presenting the infection, defined by $y = I(t, a)$.
- **Incidence** - the current rate of emerging cases, e.g. recorded as the number of new cases within a 4 week period, $y = \lambda(t, a) S(t, a)$.
- **Serology** - a qualitative serological survey of disease specific antibodies, implemented as $y = M(t, a) + R(t, a)$.

It should be noted that all of these measures can, in principle, be recorded with respect to both time and age. For simplification it is assumed that observable disease is directly correlated with infection, and the presence or absence of antibodies with complete immunity or susceptibility.

4. Structural Identifiability

An important prerequisite to sensitivity analysis is the *a priori* determination of structural identifiability; that is the theoretical problem of whether or not the unknown parameters, $p = (p_1, p_2, \dots, p_m)^T$, of a postulated model

structure can be uniquely determined from a particular set of input/output relations [20, 21]. Global identifiability indicates that a given parameter (or model structure, should all parameters be globally identifiable) can be uniquely determined from the considered observation. However, should a model structure prove not to be globally identifiable, a number of alternative parameterisations, denoted $\tilde{p} = (\tilde{p}_1, \tilde{p}_2, \dots, \tilde{p}_m)^T$, may exist that give rise to identical input/output behaviour, i.e. parameter vectors \tilde{p} and p are indistinguishable. Therefore, unidentifiable parameters are not uniquely determined by the chosen input/output structure and hence cannot be estimated with confidence from even perfect, noise-free and continuous data, regardless of their sensitivity.

Epidemic models of the type described by (1)-(4) tend to be uncontrolled (free or autonomous) and nonlinear, requiring more complex methods of analysis over typical linear systems [22]. A brief overview on techniques for nonlinear identifiability is provided by Boubaker and Fourati [23], but see also the work by Godfrey and Fitch [24] for the use of a Taylor series expansion on examples in pharmacokinetics, publications by Ljung and Glad [25], and Saccomani et al. [26] regarding computational approaches using differential algebra, and Evans et al. [27] for a method based on the existence of a general nonlinear state transformation.

The papers by Evans et al. [28] and Chapman et al. [29] show how the latter of these techniques [27], can be successfully applied to time domain ODE SIR type epidemic models with seasonal forcing, incomplete immunity and birth targeted vaccination. The analyses show that the general SIR, from which the MSIR is extended, is structurally globally identifiable from

a prevalence observation provided the population size, N , is a known parameter. Applying the same analysis to the time domain ODE MSIR model (1)-(4) yields two sets of relations corresponding to indistinguishable parameter vectors, $\tilde{p} \sim p$, given by

$$\{\tilde{\omega} = \omega, \tilde{\mu} = \mu, \tilde{\beta} = \beta, \tilde{N} = N, \tilde{\nu} = \nu, \tilde{M}_0 = M_0, \tilde{S}_0 = S_0, \tilde{I}_0 = I_0\}$$

and

$$\begin{aligned} \{\tilde{\omega} = \mu, \tilde{\mu} = \omega, \tilde{\beta} + \tilde{\omega} = \beta + \omega, \frac{\tilde{\beta}}{\tilde{N}} = \frac{\beta}{N}, \\ \tilde{\nu} = \nu, \tilde{M}_0 \tilde{\omega} = M_0 \omega, \tilde{S}_0 \frac{\tilde{\beta}}{\tilde{N}} + \tilde{\omega} = S_0 \frac{\beta}{N} + \omega, \tilde{I}_0 = I_0\}. \end{aligned} \quad (19)$$

It can be seen from the second set of relations that the model is found to be unidentifiable, since an infinite number of parameter value combinations may be generated that give rise to identical observable behaviour of the system. However, provided that the parameters ω and μ are clearly distinguishable in magnitude (i.e. duration of immunity from MAb is significantly less than average life expectancy) or any one of the unidentifiable parameters is known, then the second set of relations reduce to that of the first. In this instance, the model can be considered to be globally structurally identifiable since the only indistinguishable parameter vector, \tilde{p} , that exists is $\tilde{p} = p$.

Since the general MSIR PDE structure (5)-(11) is homogeneous, model parameters may be estimated using only the time or age domain realisations. Therefore, from the results given by (19), it can be said that the full PDE system is structurally globally identifiable via a prevalence observation of infection recorded with respect to time. Unfortunately, the inclusion of further model complexity arising from epidemiological characteristics such as

altered secondary infections, heterogeneous age dependency, and alternative observations of incidence and serology, lead to excessively intensive symbolic computation using any of the aforementioned analytical methods. Numerical methods such as that described by Batzel et al. [30] may be performed instead, however, these approaches provide only a local analysis for a particular set of parameter values.

5. Sensitivity Analysis Methods & Application

The structural identifiability results (19) of the previous section indicate that all model parameters, including those associated with the duration of MAb protection, are uniquely determined by a prevalence observation and have at least an analytical influence on the corresponding output of a fundamental time domain MSIR type system. However, a positive structural identifiability analysis does not provide a quantitative indication of how well parameters are defined by the output, and hence, does not guarantee robust estimation of parameter values when fitting to empirical data. In contrast, sensitivity based methods are concerned with the quantitative responses of models to the perturbation of inputs and parameters, and are therefore often used as the basis for model reduction and experimental design [31].

In describing the derivation of parametric sensitivities we consider the standard nonlinear system:

$$\Sigma(p) = \begin{cases} \frac{dx(t,p)}{dt} = f(x(t,p), p), \\ y(t,p) = h(x(t,p), p), \\ x(0,p) = x_0(p), \end{cases} \quad (20)$$

where $x(t, p)$ is a vector of state variables and $y(t, p)$ denotes the structure of the output. It should be noted that both $x(t, p)$ and $y(t, p)$ may be defined as functions of either time or age.

For a given function of time (or age), $y(t, p)$, which is also a differentiable function of some parameter vector $p = (p_1, p_2, \dots, p_m)^T$, the point or local sensitivities indicate the rate of change of $y(t, p)$ with respect to p , evaluated at some nominal point in parameter space, p_0 [8]. In this case, the sensitivity functions correspond to partial derivatives of the form:

$$S_i(t, p) = \frac{\partial y(t, p)}{\partial p_i}, \quad (21)$$

which are considered as gradients about p_0 in a m -dimensional parameter space, given as a function of time.

In simple examples it may be possible to evaluate sensitivity derivatives analytically from tractable solutions of the system equations, thus allowing for general results to be obtained. However, in most cases, increasing model complexity inhibits the direct calculation of these functions and a more numerical approach must be adopted instead. In this instance, parametric sensitivity is estimated from manual manipulation (perturbation) of the individual model parameters and observation of the resulting deviation in the output (see the book by Tomovic [32]). Subsequently, this approach yields only a local analysis about the point p_0 , whereby an initial estimate for a nominal set of parameter values is required prior to evaluation.

The generalisation of local analyses over wider regions of parameter space has been attempted through a number of statistical techniques using Monte Carlo simulation [33, 34]. However, numerical based global evaluation of non-monotonic systems remains a challenging task since adjacent sample points

in p may only coincidentally yield similar behaviour of $y(t, p)$. Computation also becomes increasingly intensive with larger numbers of parameters.

5.1. Formal Derivation

The sum of squares deviation of an output function, $y(t, p)$, from some nominal point, $y(t, p_0)$, due to a variation Δp in p , can be expressed in the form:

$$Q(p) = \sum_{j=1}^n [y(t_j, p) - y(t_j, p_0)]^2, \quad (22)$$

for the selected time points $\{t_1, t_2, \dots, t_n\}$. The function $Q(p)$ is an analytic function of p , which has a Taylor series expansion about the point p_0 given by

$$Q(p) \approx Q(p_0) + (\Delta p)^T G(p_0) + \frac{1}{2} (\Delta p)^T H(p_0) \Delta p, \quad (23)$$

where the variation Δp is sufficiently small such that terms of $O(\|\Delta p\|^3)$ can be considered negligible. Since p_0 is assumed to minimise $Q(p)$, the gradient vector, $G(p_0)$, defined by $[G]_i = \partial Q / \partial p_i$, and the term $Q(p_0)$ are both equal to zero. Therefore, the expression given by (23) can be further reduced to:

$$Q(p) \approx \frac{1}{2} (\Delta p)^T H(p_0) \Delta p, \quad (24)$$

where $[H]_{ij} = \partial^2 Q / \partial p_i \partial p_j$ is the Hessian matrix of Q (matrix of second derivatives with respect to p). The m by n sensitivity matrix, S , where $2S^T S = H(p_0)$, can then be constructed according to the selected time points $\{t_1, t_2, \dots, t_n\}$ in the following manner:

$$S = \begin{pmatrix} \frac{\partial y(t_1, p)}{\partial p_1} & \cdots & \frac{\partial y(t_1, p)}{\partial p_m} \\ \vdots & \ddots & \vdots \\ \frac{\partial y(t_n, p)}{\partial p_1} & \cdots & \frac{\partial y(t_n, p)}{\partial p_m} \end{pmatrix}. \quad (25)$$

hence allowing (24) to be rewritten as:

$$Q(p) \approx (\Delta p)^T S^T S \Delta p. \quad (26)$$

Alternatively, following the work of Vajda et al. [13], a normalised parameter vector, α , where $\alpha_i = \ln p_i$ for $i = 1, 2, \dots, m$, may be defined. The resulting normalised sum of squares deviation of the output function $y(t, \alpha)$, from a nominal point, $y(t, \alpha_0)$, to a change $\Delta \alpha$ in α , can then be expressed by:

$$Q(\alpha) = \sum_{j=1}^n \left[\frac{y(t_j, \alpha) - y(t_j, \alpha_0)}{y(t_j, \alpha_0)} \right]^2, \quad (27)$$

hence replacing the response equation in (36). This results in the generation of a normalised sensitivity matrix with elements of the form:

$$S_{ij} = \frac{\partial \ln y(t_j, p)}{\partial \ln p_i}. \quad (28)$$

In cases where analytic solutions to (20) are not obtainable practically, the partial derivatives of the sensitivity matrix are calculated numerically using either finite differencing [35] or direct differential methods [36]. The latter of these techniques involves solving an augmented system of equations derived by differentiating $h(x(t, p), p)$ in (20) with respect to p and switching the order of differentiation:

$$\frac{dS(t, p)}{dt} = \frac{\partial h(x(t, p), p)}{\partial x} S(t, p) + \frac{\partial h(x(t, p), p)}{\partial p}. \quad (29)$$

The state variables, $S_i(t, p)$, corresponding to the sensitivity derivatives given by(21), are then found using a suitable ODE integrator such as `ode15s` in MATLAB. The other derivative components in (29) can be calculated using automatic differentiation methods based on repeated application of the chain rule. These can be implemented using additional MATLAB modules such as `myAD` [37] or `MAD` [38].

6. Sensitivity Analysis of Non-Seasonally Forced Models

All analyses described in this work are performed on models residing at endemic equilibrium. In cases where the transmission function, β , is not subjected to annual variation, state variables described by the PDE system (5)-(11) vary in age profile but remain constant with respect to time. In this instance, algebraic solutions may be found for both the steady state values of the time domain MSIR model (12)-(14), and the state trajectories described by the linear age domain model (15)-(17). This allows for general sensitivity functions to be derived, according to expressions (21) and (28) in Section 5.

6.1. Static Time Domain Analysis

Provided that annual variation, $\beta_1 = 0$, and the basic reproduction number, $R_0 > 1$, where $R_0 = \beta/(\mu + \nu)$, the homogeneous time domain MSIR model, defined by the differential equations (12)-(14) and shown in Figure 1, has the following stable endemic fixed point equilibrium:

$$M^* = \frac{N\nu\mu(\beta - (\mu + \nu))}{\beta(\mu\omega + \nu(\mu + \omega))}, \quad S^* = \frac{N(\mu + \nu)}{\beta}, \quad I^* = \frac{\omega}{\nu}M^*. \quad (30)$$

For a time domain prevalence type observation, where $y(t, p) = I(t, p)$, the magnitude and normalised sensitivities of the output equilibrium point, $y^*(p) = I^*$, to the MAb parameter ω , are found respectively to be given by:

$$\frac{\partial y^*(p)}{\partial \omega} = \frac{N\nu\mu^2(\beta - (\mu + \nu))}{\beta(\mu\omega + \nu(\mu + \omega))^2}, \quad \frac{\partial \ln y^*(p)}{\partial \ln \omega} = \frac{\mu\nu}{\mu\nu + \omega(\mu + \nu)}. \quad (31)$$

Alternatively, for an incidence observation, where $y^*(p) = \beta S^* I^* / N$, given that S^* is not a function of ω , the normalised sensitivity function is identical to that of a prevalence output and the absolute (non-normalised) sensitivity function is simply scaled by a factor of $\beta S^* / N = \mu + \nu$.

Finally, if the output structure corresponds to a serological type observation, where $y^*(p) = N - S^* - I^*$, since again S^* is not a function of ω , the non-normalised sensitivity function is the same as for $y^*(p) = -I^*$ (prevalence). The normalised sensitivity function is then found to be of the form:

$$\frac{\partial \ln y^*(p)}{\partial \ln \omega} = \frac{\mu^2 \omega}{(\mu + \omega)(\mu \nu + \omega(\mu + \nu))}. \quad (32)$$

Given that for almost all SIR type infections $\nu \gg \mu$ (i.e. duration of infection is considerably less than average life expectancy), the following parameter combination (a scaling between normalised prevalence and serological sensitivity functions) adheres to the inequality:

$$\frac{\mu \omega}{\nu(\mu + \omega)} < 1. \quad (33)$$

Hence, the normalised sensitivity values for prevalence and incidence outputs will be greater than that of a serological type output, and by a factor of approximately ν/μ .

Subsequently, the normalised sensitivity functions for all three observations are only dependent on the parameters μ , ν and ω , and are hence independent of the transmission parameter β and the population size N . Furthermore, if $\nu \gg \mu$, it is shown, by dividing the second expression in (31) through by ν , that the normalised sensitivity functions for incidence and prevalence type outputs have only a negligible dependence on the rate of recovery.

Evaluating the function at typical values of $\nu = 73\text{yr}^{-1}$ (average duration of 5 days) and $\mu = 0.010, 0.014$ and 0.028yr^{-1} (life expectancy of 100, 71 and 36 years respectively) from a set of nominal parameter values for pre-vaccine

measles in the UK:

$$\mu = 0.014 \text{ yr}^{-1}, \quad N = 5.7 \times 10^7, \quad \nu = 73 \text{ yr}^{-1}, \quad R_0 = 18, \quad \omega = 4 \text{ yr}^{-1}, \quad (34)$$

the normalised sensitivity functions for an incidence or prevalence type observation can be plotted against varying ω_M (see Figure 2).

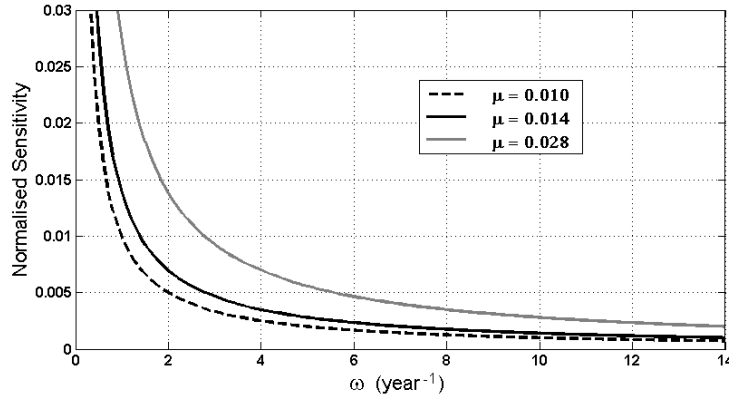


Figure 2: Static normalised sensitivity functions corresponding to an incidence or prevalence type observation of a fundamental MSIR system at endemic equilibrium; computed for varying ω and discrete values of μ .

From the graph it can be seen that higher birth/mortality rates (i.e. lower life expectancy) and higher duration of maternal immunity (i.e. lower ω) result in a heightened sensitivity to ω . This suggests that any influence of ω on population infection levels only occur indirectly as a result of the subsequent death of maternally protected individuals before they experience an infection. This influence is therefore dependent on the population density age profile, which is governed in the heterogeneous case by an age dependent mortality function. Given that typical infant mortality rates (under 1 year of age) are less than 1% for most developed regions, it seems likely that

Table 1: Normalised sensitivity values for all MSIR model parameters evaluated at nominal values corresponding to pre-vaccine measles in the UK.

Parameter	μ	N	ν	β	ω
Prevalence	0.9963	1.0000	-1.0586	0.0588	0.0035
Incidence	0.9965	1.0000	-0.0588	0.0588	0.0035
Serological	-0.0020	1.0000	-0.0586	0.0588	-6.7×10^{-7}

the system transmission function is necessarily inhomogeneous to support a significant static influence of MAb on the endemic prevalence of infection. It should be noted that these conditions are often accentuated in developing populations where there are likely to be higher birth and infant mortality rates, and subsequently an age distribution skewed toward the infant age classes.

For completeness, Table 1 contains the normalised sensitivities of all system parameters in the MSIR model for each of the considered output structures, at the nominal values given in (34).

6.2. Static Age Domain Analysis

For a non-seasonally forced system (i.e. $\beta_1 = 0$), residing at a fixed point endemic equilibrium (in time) a linear purely age dependent system can be derived from the system equations (15)-(17), which has the following analytic solution for an incidence observation:

$$y(a, p) = \frac{\lambda e^{-a\mu} (\omega M_0 e^{-a\omega} - (\mu N \omega - \lambda S_0) e^{-a\lambda})}{\lambda - \omega}, \quad (35)$$

where the initial conditions are $M_0 = \mu S^*$ and $S_0 = \mu M^*$, and the force of infection is given by $\lambda = \beta I^*/N$.

The normalised sensitivity function (squared), with respect to ω , for all three observation types can then be found and plotted with respect to increasing age (see Figure 3), using the same nominal values given in (34) for measles in the UK. Figures 4 and 5 then illustrate how the three sensitivity curves change with varying basic reproduction number ($R_0 = 8$ and $R_0 = 80$, respectively).

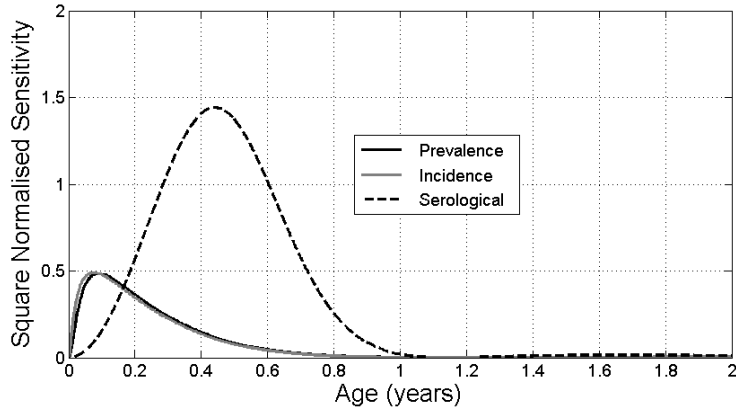


Figure 3: Age profile normalised sensitivity functions for incidence, prevalence and serological outputs of a fundamental MSIR system at endemic equilibrium. Sensitivities are evaluated with respect to ω at nominal parameter values for pre-vaccine measles in the UK (i.e. $R_0 = 18$).

It can be seen from the results that increasing infectivity (subsequently lowering average age of infection) reduces the peak age of sensitivity for all observation types, but has contrasting effects on their magnitude. For low values of R_0 the peak sensitivity for the serological observation is notably larger than that of prevalence and incidence. However, while the latter two output sensitivities increase with higher R_0 the serological sensitivity decreases.

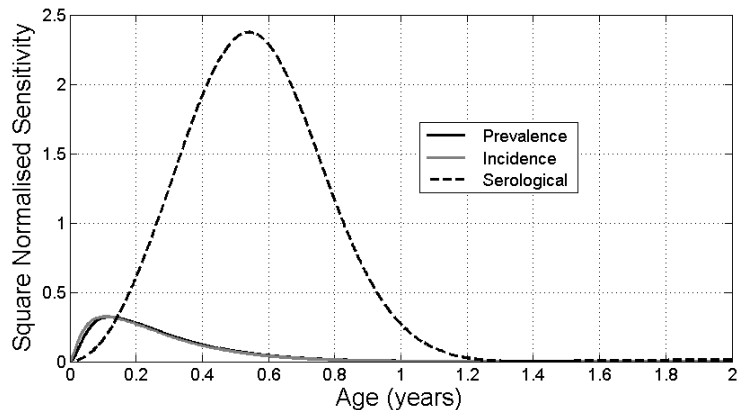


Figure 4: Prevalence, incidence and serological output age profile normalised sensitivity functions corresponding to changes in $\ln \omega$, for $R_0 = 8$.

Figures 6 and 7 show the resulting sensitivity curves for various values of ω corresponding to an average duration of immunity (ω^{-1}) of 12 months and 1 month respectively. The results show that the peak sensitivity for the serological observation varies considerably more than the maximum value for prevalence and incidence outputs.

In all five examples there is no significant difference between the sensitivity characteristics of incidence and prevalence type outputs. However, it does appear that the peak sensitivity for serological type observations occur consistently later in age. This result may prove to be significant in cases where there are age dependent limitations on the observation of clinical disease or the collection of serological samples.

In addition to peak values in normalised sensitivity, it should also be noted that there are key points in age for all output types where the sensitivity of ω is equal to zero. Interestingly the peak age of sensitivity (0.075 and 0.45

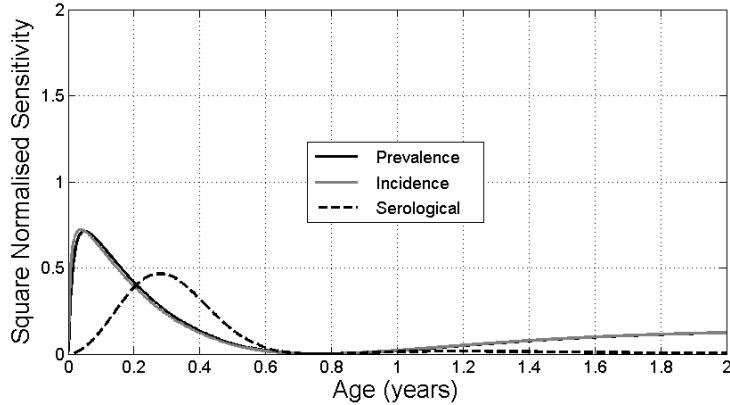


Figure 5: Prevalence, incidence and serological output age profile normalised sensitivity functions corresponding to changes in $\ln \omega$, for $R_0 = 80$.

years) for all output types is well below the average age at primary infection, which can be calculated in the measles case to be 3.97 years. In all cases the sensitivity is significantly greater than that for the time domain observations in Section 6.1.

7. Sensitivity Analysis of Seasonally Forced Models

Many common infections such as Measles, Mumps and Rubella (MMR), Influenza and hRSV tend to display large (seasonal) recurrent epidemics at endemic equilibrium rather than settling to a constant level of transmission. In this instance, parameter sensitivities are determined through the dynamic analysis of epidemic models that include temporal variation. However, since there are no convenient analytic solutions to the MSIR framework models when allowed to vary dynamically with time, the analysis must resort to more numerical based methods, as outlined in Section 5.

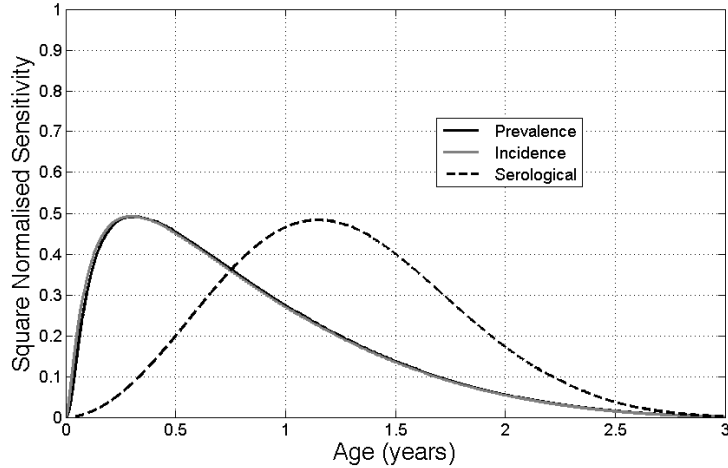


Figure 6: Prevalence, incidence and serological output age profile normalised sensitivity functions corresponding to changes in $\ln \omega$, at $\omega = 1$.

7.1. Homogeneous MSIR

In order to perform a dynamic sensitivity analysis on the seasonally forced MSIR, an augmented system of differential equations are derived according to (29). In this instance, the dependent variables correspond to the dynamic sensitivity functions described by (21). The system of sensitivity equations are then solved numerically, for each of three output structures, using the `ode15s` ODE integrator, and the `myAD` automatic differentiation module [37] in MATLAB version R2009b. The computation is performed on an RM desktop machine with a Pentium D 3.4GHz CPU and 1Gb of RAM, using a maximum step size of 0.001 years.

Prior to analysis, the simulation is run for a suitable length of settling time (i.e. 250 years) in order to allow the system solutions to converge satisfactorily close to their endemic limit cycle. The normalised sensitivity

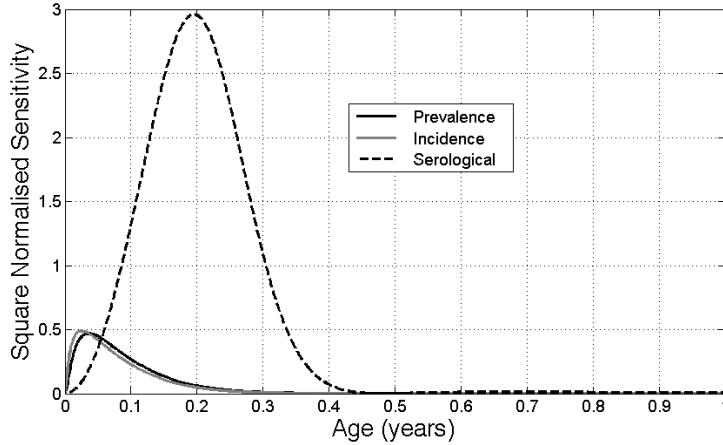


Figure 7: Prevalence, incidence and serological output age profile normalised sensitivity functions corresponding to changes in $\ln \omega$, at $\omega = 12$.

matrix, given by (28), is then generated for all 7 model parameters (i.e. $p = (\mu, N, \beta_0, \beta_1, \phi, \nu, \omega)^T$), with sample points taken at uniform time intervals of 0.01 years, for ten complete annual cycles. Figures 8 and 9 show the resulting deviation in the normalised sum of squares function, $Q(\alpha)$, to a unit change in $\ln \omega$, i.e. normalised sensitivity squared, for incidence or prevalence and serological outputs respectively.

The system is seen to exhibit biennial epidemic behaviour in accordance with documented observations of pre-vaccine measles in the UK [12], where the normalised sensitivity of ω is found also to be periodic with a time period of 2 years. Near identical results were obtained for both prevalence and incidence observations, with normalised sensitivity to ω varying between -0.037 and 0.032 throughout the biennial cycle. In contrast, the normalised sensitivity for a serological type observation varies only between -5.26×10^{-5} and 2.41×10^{-4} .

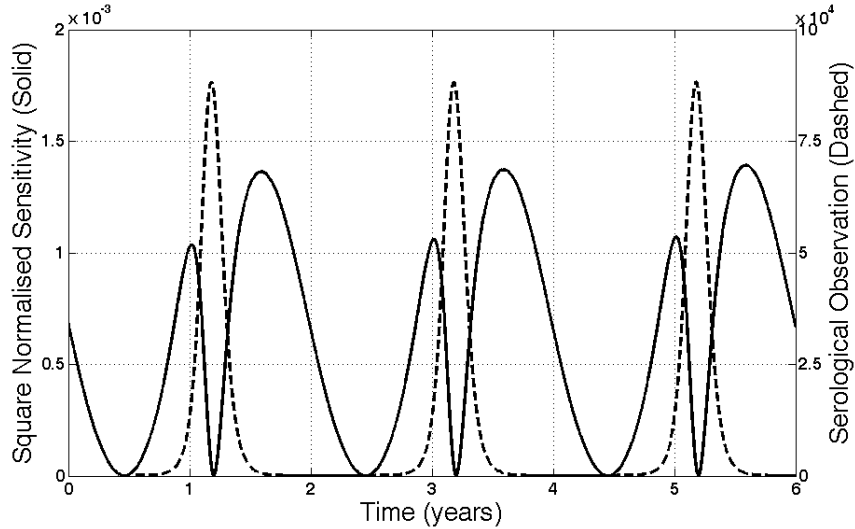


Figure 8: Sum of squares deviation to a unit change in $\ln \omega$ (normalised sensitivity squared), for an MSIR model with seasonal forcing and a prevalence or incidence output; evaluated with nominal parameter values for measles in the UK.

Figures 10 and 11 show the resulting dynamic sensitivity functions for a prevalence/incidence observation where $\omega = 1$ and 6 yr^{-1} respectively (i.e. average duration of maternally acquired immunity of 12 and 2 months).

In this instance the normalised sensitivity functions are found to be amplified with decreasing ω (increasing duration of protection). It can be seen from the outputs of the two simulations that the peak sum of squares deviation to a unit change in normalised ω is more than 10 times greater for an average duration of 12 months than for 2 months.

In all cases the point of maximum (magnitude) normalised sensitivity does not necessarily align with the biennial peak in the corresponding observation. This is an interesting result as it suggests, for example, that prevalence or

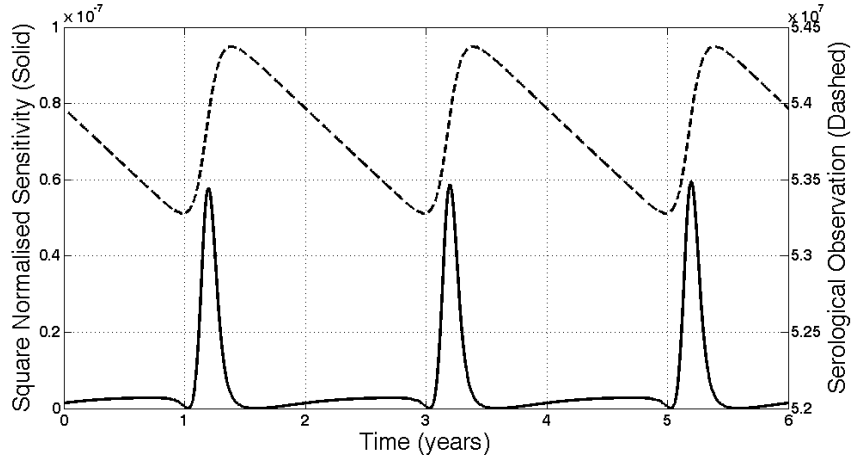


Figure 9: Sum of squares deviation to a unit change in $\ln \omega$ (normalised sensitivity squared), for a seasonally forced MSIR model with a serological type output structure; evaluated with nominal parameter values for measles in the UK.

incidence data collected for validating this particular characteristic of the MSIR model, would not be optimally sampled around the time of maximum epidemic behaviour. It can also be seen that there are regions for all output types where the sensitivity to changes in normalised ω is positive and negative, and hence two points during each biennial cycle where this is also equal to zero.

For completeness, the relative influences of all the MSIR model parameters can be examined through a principal component analysis (PCA) according to the work by Vajda et al. [13]. The analysis is performed by means of an eigenvalue-eigenvector decomposition of the matrix $S^T S = U \Lambda U^T$, where S is typically the normalised sensitivity matrix given by (28), such that U denotes the matrix of normalised eigenvectors, u_i , for $i = 1, 2, \dots, m$, and Λ corresponds to a diagonal matrix of eigenvalues, λ_i . The normalised re-

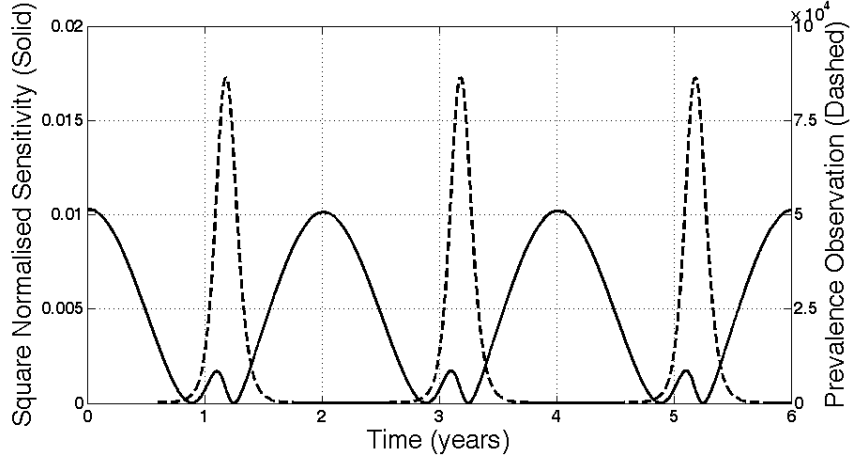


Figure 10: Normalised sensitivity (squared) with respect to $\ln \omega$, for a prevalence or incidence observation of a seasonally forced MSIR model, computed with the nominal UK measles parameter set and $\omega = 1 \text{ yr}^{-1}$

sponse function, $Q(\alpha) \approx (\Delta\alpha)^T S^T S \Delta\alpha$, can then be redefined in terms of the principal components $\Psi = U^T \alpha$,

$$Q(\Psi) = \sum_{i=1}^m \lambda_i \|\Delta\Psi_i\|^2, \quad (36)$$

given that $\Delta\Psi_i = u_i^T \Delta\alpha = (u_{i,1}\Delta\alpha_1 + \dots + u_{i,m}\Delta\alpha_m)$. Consequently, the function Q is most sensitive to changes in α along the principal axis corresponding to the largest eigenvalue and is least sensitive to changes in α along the principal axis corresponding to the smallest eigenvalue.

If λ_i is not small, hence the corresponding principal component is a significant one, a small value for a particular $\|u_{i,j}\|$ indicates that the corresponding parameter α_i contributes little to the component. It is suggested by Vajda et al. [13] that any element of u_i with magnitude less than 0.2 can be excluded from consideration, given that they contribute less than 4% to the sum of

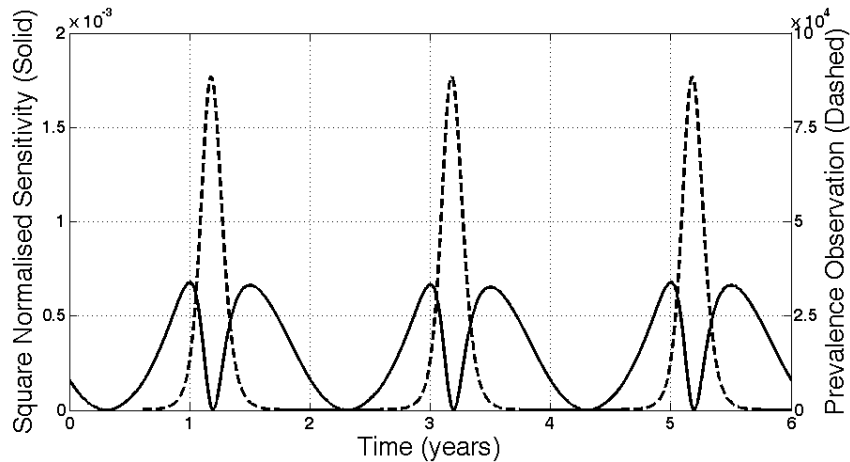


Figure 11: Normalised sensitivity (squared) with respect to $\ln \omega$, for a prevalence or incidence observation of a seasonally forced MSIR model, computed with the nominal UK measles parameter set and $\omega = 6 \text{ yr}^{-1}$

squares of relative changes in $y(t, \alpha)$ as the parameters vary in the direction of the principal component. Table 2 shows the magnitude of the resulting principle components for the MSIR model and the relative contributions of each individual model parameter.

It can be seen that the magnitude of the principal components range between 5.4×10^{-4} and 5.6×10^5 . The parameter ω is clearly the least influential parameter in the model, making significant contributions (i.e. absolute value greater than 0.2 [13]) to only the two smallest components. In this instance an elemental value of 0.002 corresponds to a 0.0004% contribution to the sum of squares deviation in normalised output, in the direction of the largest eigenvalue. It can also be noted that despite a tenfold increase in the peak sum of squares deviation for $\omega = 1 \text{ yr}^{-1}$, see Figure 11, the resulting PCA reveals no greater contribution to all but the smallest principal component.

Table 2: Principal component analysis of the normalised sensitivity matrix corresponding to a MSIR model with seasonal forcing. Computed at nominal parameter values for pre-vaccine measles in the UK and sampled at 0.01 year intervals over a 10 year period.

No.	Eigenvalue	μ	N	β_0	β_1	ϕ	ν	ω
1	561135	0.236	-0.022	0.270	-0.044	-0.927	-0.095	0.002
2	312054	0.560	-0.115	0.710	0.108	0.323	0.230	0.001
3	7952.76	0.366	0.395	-0.009	-0.306	0.174	-0.766	0.003
4	1074.88	0.300	0.594	-0.269	0.672	-0.065	0.170	-0.002
5	32.7887	-0.187	-0.423	0.146	0.662	0.032	-0.567	0.064
6	0.07314	-0.378	0.309	0.357	0.048	0.001	-0.047	-0.794
7	0.00054	0.479	-0.451	-0.450	0.003	-0.000	-0.002	-0.605

In contrast, all other model parameters appear to be well defined by the chosen outputs, with significant influence over at least one of the three major components.

7.2. MSEIRS₄ Model with Incomplete Immunity

An additional example of a seasonally forced epidemic model with a maternally protected state variable is the 17 compartment MSEIRS₄ structure, as described by Weber et al. [10]. The model has been developed as a more realistic compartmental representation of the complex mechanisms associated with reinfection and accumulating acquired immunity observed with hRSV. It has been chosen for analysis in this work because it has been previously fitted to four separate sets of empirical data, corresponding to hRSV infec-

tion in Finland, Florida, Singapore and The Gambia [10]. This means that a formal sensitivity analysis can be performed using fitted nominal values, in order to study the influence of maternally acquired immunity on observations of primary infection, and hence, the determinability of ω .

This is not intended as a critique of the work published by Weber et al. [10], given that the flow rate coefficient ω (denoted ξ in [10]) is not a fitted parameter in their parameter estimation, and the influence of maternal immunity was not the focus of their study, or the subject of any inference from the results.

The set of system equations corresponding to the MSEIRS4 model are provided in Appendix A. The first four infections in the natural history of the disease are distinguished by separate state variables (i.e. $S_i(t)$, $E_i(t)$, $I_i(t)$ and $R_i(t)$ for $i = 1, \dots, 4$), where $E_i(t)$, for $i = 1, \dots, 4$, represents a latent incubation period prior to infected individuals becoming infectious, with corresponding elimination parameter σ . In this instance, an individual's 'baseline' susceptibility ultimately decreases upon recovery from each infection, following a temporary period of full immunity, with duration determined by γ^{-1} .

The analysis is performed using the nominal set of fitted parameter values corresponding to hRSV in The Gambia [10]. In a similar manner to the MSIR example, the sensitivity matrix is generated numerically once the simulation has satisfactorily converged to a stable endemic limit cycle. Sample points are again taken at uniform 0.01 year intervals, for 10 complete annual cycles. Figures 12 and 13 show the resulting deviation in the normalised sum of squares function, $Q(\alpha)$, due to a unit change in $\ln \omega$, for primary preva-

lence or incidence and serological type outputs respectively. The dynamic sensitivity functions are given with respect to time, and presented against their corresponding output functions.

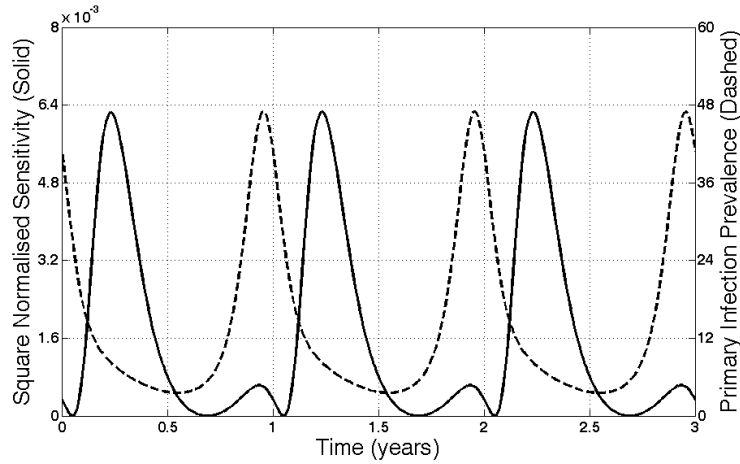


Figure 12: Resulting sum of squares deviation, $Q(\alpha)$, in a prevalence/incidence observation of a seasonally forced MSEIRS4 model, to a unit change in $\ln \omega$ (normalised sensitivity squared); evaluated at nominal values for hRSV in The Gambia.

It is found that the sensitivity of ω for all output types is periodic with a time period of 1 year. Near identical results are obtained for prevalence and incidence outputs (peak absolute value of 0.078), however, the normalised sensitivity of ω for a serological observation is found to be significantly smaller in magnitude (peak absolute value of 0.005) and peaked at slightly different points in time. There are again also two points during each epidemic period where the sensitivity of $y(t, p)$ with respect to ω is equal to zero. The point of maximum sensitivity for all outputs does not necessarily align with the annual peak in the corresponding observation, although their position relative to the annual epidemic cycle is comparable to that of the measles example

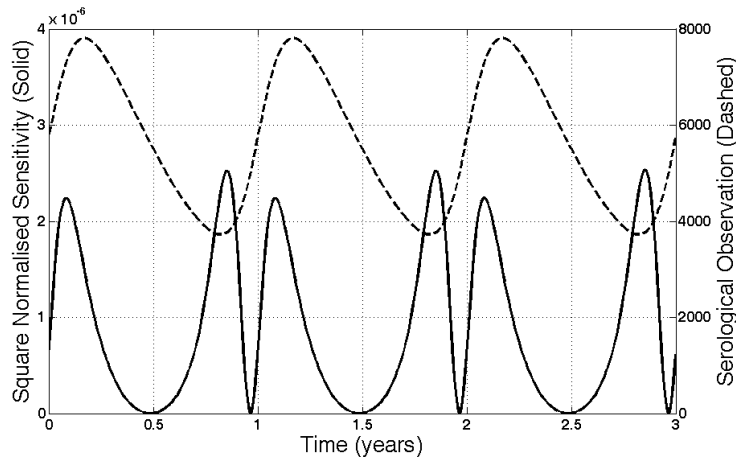


Figure 13: Sum of squares deviation to a unit change in $\ln \omega$ (normalised sensitivity squared), for a serological observation of a MSEIRS4 model; evaluated with nominal parameter values for hRSV in The Gambia.

shown in Figures 8 and 9.

It can also be noted that by removing seasonal forcing from the model (i.e. setting $\beta_1 = 0$ and forcing the system to converge to a fixed point endemic equilibrium) a steady state normalised sensitivity value in the region of 0.0014 is found for a prevalence or incidence observation of primary infection, which is comparable with the MSIR results shown in Figure 2.

A singular value decomposition of $S^T S$, shows that ω is again poorly defined by time series infection dynamics. It can be seen from Table 3, which shows the individual parameter contributions to the resulting principal components of $Q(\alpha)$, that ω is again the least influential parameter in the model structure, making significant contributions to only the latter three principal components.

Similar results were obtained for parameter sets estimated using epidemic

Table 3: Principal component analysis of the normalised sensitivity matrix corresponding to a MSEIRS4 model with nominal values for hRSV in The Gambia. Evaluated using a 0.01 year sampling interval over ten complete annual cycles.

No.	Eigenvalue	μ	β_0	β_1	v	ω
1	30952	0.093	0.599	-0.172	-0.651	-0.001
2	7336.2	-0.172	0.741	0.443	0.367	-0.009
3	335.12	-0.712	0.105	-0.493	0.061	0.016
4	98.965	0.451	0.268	-0.583	0.549	0.017
5	4.0005	-0.481	-0.053	-0.093	0.168	-0.117
6	1.9346	0.048	0.074	-0.344	-0.302	-0.320
7	0.29622	0.119	-0.031	-0.086	0.129	-0.668
8	0.027825	0.061	-0.002	-0.236	0.002	0.662

data from Finland, Florida and Singapore [10], suggesting that the regional variation in parameter values observed in these cases does not have a significant impact on sensitivity.

For comparison, the original MSEIRS4 model, presented by Weber et al. [10], is extended to a simple homogeneous PDE structure in an identical manner to that demonstrated in Section 3, in order to assess equivalent sensitivities in the age domain.

The system equations are solved using an explicit third order backwards difference scheme, where any integral (with respect to age) components are taken directly from a numerical solution of the original time domain model (obtained using fourth order variable step Runge-Kutta). The PDE solution is integrated (with respect to time) using a Romberg (Richardson extrapolation) integration method, over 10 complete annual cycles, in order to find an

average age profile. The normalised sensitivity matrix, S , described in (28), is then constructed using finite differencing for each of the three output types considered. The resulting response functions, $Q(\alpha)$, are shown in Figure 14.

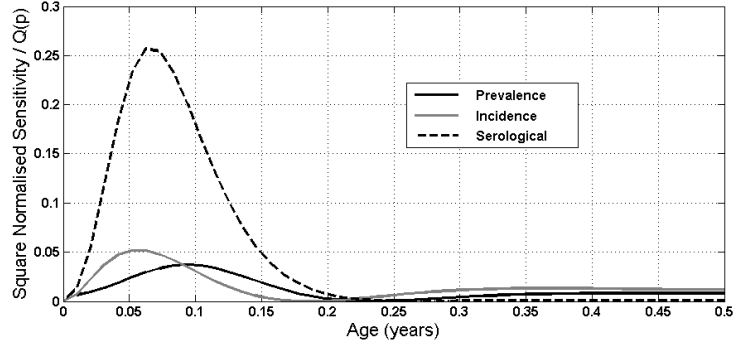


Figure 14: Age profile normalised sensitivity functions for incidence, prevalence and serological outputs of a MSEIRS4 model with respect to $\ln \omega$; computed using finite differencing at nominal parameter values for hRSV in The Gambia.

It can be seen for this example that all three sensitivities peak in a similar region of the age profile, but also that the serological observation is significantly greater. Comparing these results to those in Figures 12 and 13 shows that the margin between squared normalised sensitivities corresponding to age and time domain observations for the MSEIRS4 model is smaller than for the measles example, but still in favour of the age domain.

For comparison, the key sensitivity results for each of the three analyses documented in Sections 6 and 7, and the two example model structures are summarised in Table 4.

Table 4: Comparison of the peak magnitude normalised sensitivities of the considered output structures to changes in $\ln \omega$, for the MSIR (UK measles) and MSEIRS4 (hRSV in The Gambia) model structures, from each of the three equilibrium analyses.

	Static Time		Static Age		Dynamic Seasonal	
	MSIR	MSEIRS4	MSIR	MSEIRS4	MSIR	MSEIRS4
Prevalence	0.0035	0.0014	0.71	0.20	0.036	0.079
Incidence	0.0035	0.0014	0.71	0.22	0.036	0.079
Serological	6.7×10^{-7}	0.00033	1.2	0.51	0.024	0.0016

8. Conclusions

A formal sensitivity analysis has been applied to a set of contrasting epidemic models, with various observation structures, for two common viral diseases. The objective has been to assess the determinability of parameters associated with passive immunity from MAb, and hence, also estimate the magnitude of their influence over the static, dynamic and seasonal characteristics of system behaviour. The results have indicated that the corresponding sensitivity of community-wide transmission levels is potentially increased by processes associated with a greater duration of maternally acquired protection and higher fertility/mortality rates. It has also been shown for homogeneous cases that changes in the rate that maternally protected neonates become fully susceptible has a much greater influence on epidemiological measures recorded with respect to age than with respect time.

A comparison of results corresponding to equilibrium observations of systems with constant and seasonally varying transmission suggests that changes in ω can potentially have a more significant impact on seasonal dynamics

than on static levels of infection. This is likely to be a result of epidemic behaviour being primarily driven by the rate of susceptible supply, which is directly influenced by changes in maternally acquired immunity. However, in all dynamic time domain examples, ω was still clearly found to be the least sensitive parameter in the model. This would seem to be a reasonable result since the maternally protected population represents only a very small proportion of the total population, although, in developing countries where birth and mortality rates are much higher, the influence of MAb may be greater. Consequently, MSIR framework models with time domain output structures are likely to be inappropriate for estimating characteristics associated with maternally acquired immunity, especially for populations in more developed regions. Moreover, in many cases, these models may be acceptably reduced by omitting the immunising effects of MAb if the purpose of the model is to achieve reasonable estimates for other parameters such as those associated with transmission.

All worked examples have consistently shown near identical normalised sensitivity results, corresponding to changes in ω , for observations of incidence and prevalence in either domain. This suggests that it is not critical which of the two data types are used with respect to parameter estimation within these model structures. In addition, no examples were found where it may be beneficial to utilise a serological type observation recorded with respect to time. In all dynamic and static age domain analyses it has been shown that there are key regions, both in the annual epidemic cycle (i.e. with respect to time) and in the average age profile, that correspond to peak, and conversely, zero sensitivity to variation in all unknown model parameters.

This indicates that the use of prior experimental design and optimal sampling could be of great benefit in maximising confidence during parameter estimation and potentially minimising unnecessary data collection. In the age domain, analysis of the considered models has shown comparable peak values in normalised sensitivity for serological and prevalence/incidence outputs. However, these peaks tend not to occur at the same points in age, and have contrasting dependencies on the basic reproduction number and nominal value of ω . Similarly in the time domain, output sensitivity to ω appears in all cases not to coincide with the annual or biennial epidemic peak in infection and differs again between observations of prevalence/incidence and serology.

It should be noted that a potential limitation of the analysis in this work has arisen from the consideration of only homogeneous processes for transmission, immunity and fertility etc. The analysis of heterogeneous PDE based systems is found to be substantially more difficult using techniques associated with automatic differentiation and the accuracy of most numerical methods do not permit the implementation of finite differencing given that time domain sensitivities are found to be in the region of 10^{-3} . However, it is possible that greater output sensitivity may be generated from small perturbations in ω if, for example, the peak age of transmission occurs close to that of the average duration of waning maternal antibody.

Acknowledgements

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Appendix A. MSEIRS4 Model Equations

$$\begin{aligned}
 \dot{M}(t) &= \mu R(t) - (\omega + \mu)M(t), \\
 \dot{S}_1(t) &= \mu(1-R(t)) + \omega M(t) - \mu S_1(t) - \lambda_1(t)S_1(t), \\
 \dot{E}_i(t) &= \lambda_i(t)S_i(t) - (\sigma + \mu)E_i(t), \quad i = 1, \dots, 4, \\
 \dot{I}_i(t) &= \sigma E_i(t) - (\nu + \mu)I_i(t), \quad i = 1, \dots, 4, \\
 \dot{R}_i(t) &= \nu I_i(t) - (\gamma + \mu)R_i(t), \quad i = 1, \dots, 4, \\
 \dot{S}_j(t) &= \gamma R_{j-1}(t) - \mu S_j(t) - \lambda_j(t)S_j(t), \quad j = 2, 3, \\
 \dot{S}_4(t) &= \gamma(R_3(t) + R_4(t)) - \mu S_4(t) - \lambda_4(t)S_4(t),
 \end{aligned}$$

where

$$\begin{aligned}
 R(t) &= \sum_{i=1}^4 R_i(t), & I(t) &= \sum_{i=1}^4 I_i(t), \\
 \lambda_1(t) &= \beta_0(1 + \beta_1 \cos(2\pi t + \phi))I(t), & \lambda_2(t) &= 0.50 \lambda_1(t) \\
 \lambda_3(t) &= 0.35 \lambda_1(t), & \lambda_4(t) &= 0.25 \lambda_1(t),
 \end{aligned}$$