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Age-Structured Models and Optimal Control in Mathematical Epidemiology: A Survey.

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INTRODUCTION

In this chapter we shall discuss the use of both optimal control theory and age-structured epidemic models in mathematical epidemiology. We use a very broad definition of optimal control, for example mathematical models for control by vaccination, as well as applications of optimal control theory. This is a wide area and we have had to be selective. In terms of applications a lot of the models which we present are applicable to the spread of common childhood diseases as that is an area in which age-structured models have been shown to fit data well and are most commonly applied in practice. This is because vaccination programs are often age-dependent targeting children of a given age and so they need age-structured models. The first section of this chapter discusses age-structured epidemic models including the question of optimal vaccination in them.

Then we move on to the optimal control in “stage-structured” (rather than age-structured) epidemic models, in which the individuals are grouped into susceptible, infected, and so on, depending on their relation to the epidemic. This gives a survey of how the ideas of optimal control theory, in particular the Maximum Principle and dynamic programming have been applied in the past to determine optimal control strategies for an epidemic, for example by immunization or removal of infected individuals. We finish this section with a few papers which apply optimal control theory to drug epidemics. We next survey some articles which give applications of optimal control to age-structured epidemic models. Much of this work concerns the existence and structure of optimal age-dependent vaccination strategies for common childhood diseases but we cover some other applications too. This is followed by a short section on spatial models used to determine optimal epidemic control policies. A brief summary and discussion conclude.

EPIDEMIC MODELS WITH AGE-STRUCTURE

We start by discussing epidemic models with age-structure. First we shall describe early work on age-structured epidemic data, much of which was purely descriptive, but showed the need for age-structure to be included in the models. Next we look at some simple age-structured epidemic models. The following subsection discusses numerical work on age-structured models for vaccination programs for common childhood diseases. Much of this has been done by Anderson and May and co-workers and has had a very substantial impact on UK vaccination policy. The final subsection discusses more mathematical threshold and stability results on age-structured epidemic models and some practical

applications. Some of the first two following subsections draw on the literature review of Sfikas (1999).

Early Work on Age-Structured Epidemic Data

The first person to mathematically study the spread of infectious diseases was Bernoulli (1760). This work was intended to evaluate the effectiveness of smallpox variolation and hence influence public health policy. He shows that if smallpox provides permanent protection against getting smallpox a second time then the fraction of individuals of age *a* who will have experienced smallpox is

$$\frac{[1-\exp(-\lambda a)](1-q)}{1-q[1-\exp(-\lambda a)]}.$$

Here *a* is the current age of an individual, and *q* is the probability of dying from an episode of smallpox. λ is the constant rate at which a susceptible is infected (sometimes called the force of infection).

We next describe some statistical work which attempts to fit age-structured mathematical models to data. This was important as by showing that age-structured models can describe realistic epidemic data better it influenced later mathematical modeling work on infectious diseases. The age-related incidence of several common childhood diseases was analyzed by Collins (1929). These included whooping cough, mumps, scarlet fever and chickenpox. Collins fitted age-parametric curves to the age-related incidence of these diseases. Muench (1934) used this data to fit catalytic curves, which were also fitted to case reports for yellow fever and tuberculosis. In those curves if *k* is the fraction of the

population who are susceptible to the disease and λ is the constant infection rate per unit time then at time t a proportion $k[1-\exp(-\lambda t)]$ of individuals will have had the disease.

Griffiths (1974) fitted a catalytic model with an age-dependent force of infection to measles data. A linear rather than a constant force of infection fitted over the age range 0 to 10 years where most cases of measles occurred fitted the data much better. Farrington (1990) used a parametric model fitted to age-structured data to model age-dependent forces of infection for UK mumps, rubella and measles data. This showed that the homogeneously mixing models used previously were inadequate.

Simple Age-Structured Models

Driven by the fact that age-structured models are a better fit to the data for common childhood diseases they began to be used increasingly. We shall now discuss some of the first models used. A major advance was due to Dietz (1981) who used age-structured models to compare vaccination strategies for rubella (German measles) in the UK and the USA. This was stimulated by Knox (1980) who compared alternative rubella vaccination programs by using an equilibrium analysis and simulations based on a dynamic model. However Dietz improves Knox's modeling of the costs of vaccination. One of the major problems with rubella is the implications for a pregnant woman who experiences the disease in the first three months of pregnancy. There is then a risk of Congenital Rubella Syndrome (CRS) for the unborn infant when the child is usually born deaf and may have other complications. At that time the UK strategy was to allow the disease to spread

naturally so that most children achieved natural immunity. To supplement this there was vaccination of 12 to 15 year old girls to mop up the remaining susceptible girls in advance of them becoming pregnant. In contrast the USA strategy was to attempt to immunize all children near birth (after the effects of maternal antibodies had faded). The current UK policy is different as now all infants are vaccinated near birth with a triple MMR (measles, mumps, rubella) immunization. Because girls can get pregnant only after puberty and the fertility of a woman depends on her age an age-structured model must be used to answer the important public health question of what is the best policy.

Dietz used an age-structured model, but assumed homogeneous mixing. Using the equilibrium equations he derived the equilibrium incidence for different vaccination strategies under different assumptions of the boosting effects of the wild virus. He concluded that the USA vaccination strategy used at that time (vaccinate boys and girls at 2 years old) was inferior to the strategy then used by the UK and other European countries (vaccinate girls at 14 years old) for the actual reproductive rate. However vaccination of 2 year old girls might also be best, depending on the costs of different vaccination strategies and achievable coverage.

Schenzle (1984) used an age-structured mathematical deterministic model which took account of increased transmission infectivity within schools to model the spread of measles in England and Wales. The regular opening and closing of schools was modeled and the children were divided into age classes corresponding to the school class which

they attended. This model accurately predicted the real seasonal fluctuations in measles incidence data.

For a generic model the basic reproduction number R_0 for an infectious disease is defined as the expected number of secondary cases caused by a single newly infectious case entering a disease-free population at equilibrium. $R(\psi)$, the basic reproduction number with age-dependent vaccination campaign ψ is the corresponding number in the presence of a steady state vaccination campaign ψ. This can be used to study the control of an epidemic. If $R(\psi) < 1$ then the vaccination campaign is not sufficient to control the epidemic whereas if $R(\psi) \geq 1$ then the vaccination campaign is adequate. So for example we can use this result to find the minimum proportion of children of a given age who must be vaccinated to eliminate the disease in a population using herd immunity.

Dietz and Schenzle (1985) looked at an age-dependent epidemic model for a viral disease in the presence of vaccination. The population is divided into n age classes $I_1, I_2, \ldots I_n$ and the disease transmission rate between age class I_i and age class I_j is $b_i b_j$. Here $b_1, b_2, \ldots b_n$ are constants. This mixing assumption is called proportional mixing. Assuming that the disease lasts only a short time Dietz and Schenzle show that

$$R(\psi) = \frac{\int_0^\infty \exp[-M(a)]\lambda_0(a)\int_0^a \lambda_0(a-c)f(c)\exp[-\Psi(a-c)-\Gamma(c)]dcda}{\int_0^\infty \exp[-M(a)]\lambda_0(a)\int_0^a \lambda_0(a-c)f(c)\exp[-\Lambda_0(a-c)-\Gamma(c)]dcda}.$$

Here $\Psi(a) = \int_0^a \psi(u)du$, $\Lambda_0(a) = \int_0^a \lambda_0(u)du$ and $M(a) = \int_0^a \mu(u)du$. $\mu(a)$ is the death rate at age a and $\lambda_0(a)$ is the equilibrium force of infection at age a if there is no

immunization**.** The force of infection at age a is defined as the total rate at which a single susceptible individual of age a is attacked by the disease. $\psi(a)$ is the vaccination rate. $f(c)$ is the probability that an individual who has been infected for time c is still infectious.

In particular setting $\psi \equiv 0$,

$$R_0 = \frac{\int_0^\infty \exp[-M(a)]\lambda_0(a)\int_0^a \lambda_0(a-c)f(c)\exp[-\Gamma(c)]dcda}{\int_0^\infty \exp[-M(a)]\lambda_0(a)\int_0^a \lambda_0(a-c)f(c)\exp[-\Lambda_0(a-c)-\Gamma(c)]dcda}.$$

Assuming that the disease lasts only a short time

$$R(\psi) \approx \frac{\int_0^\infty \exp[-M(a)]\ \lambda_0^2(a)\exp[-\Psi(a)]\ da}{\int_0^\infty \exp[-M(a)]\lambda_0^2(a)\exp[-\Lambda_0(a)]\ da}$$

and $$R_0 \approx \frac{\int_0^\infty \exp[-M(a)]\ \lambda_0^2(a)\ da}{\int_0^\infty \exp[-M(a)]\lambda_0^2(a)\exp[-\Lambda_0(a)]\ da}.$$

Using the approximate formula for $R(\psi)$ we can show that if vaccination takes place at age V then p, the minimum proportion who must be vaccinated to eliminate the disease in the population is

$$p \approx \left(1-\frac{1}{R_0}\right)\frac{\int_0^\infty \exp[-M(a)]\ \lambda_0^2(a)da}{\int_V^\infty \exp[-M(a)]\ \lambda_0^2(a)da}.$$

Age-Structured Simulation Models to Determine Optimal Vaccination Strategies

Anderson and May and co-workers (Anderson, 1982, Anderson and May, 1983, 1984, 1985, Anderson and Grenfell, 1986, Anderson and May, 1991, see Anderson and May, 1991 for a more comprehensive list of references) have done an enormous amount of work on modeling the spread of common childhood diseases and vaccination programs against them using age-structured mathematical models, often using numerical simulation. This work has had a tremendous impact on UK public health policy and the practical application of mathematical modeling of infectious diseases and we shall now describe some of it as well as work by Roberts and Tobias (2000) for New Zealand.

Anderson (1982) examined age-structured models for common childhood infections where again the force of infection was linear between 0 and 10 years. This fitted measles and whooping cough data well. This idea was extended by Anderson and May (1982). They demonstrated that in order to eliminate a disease a proportion p of the population needs to be vaccinated where $p > 1-(1/R_0)$. If there is a constant per capita death rate μ and a proportion p of the population are immunized at constant rate c then the reproduction number is

$$R_0\,(1-(cp/(c+\mu))).$$

Again this enables us to estimate the minimum vaccination proportion and rate necessary to eliminate the disease in the population.

Anderson and May (1983) considered an age-dependent epidemic model for measles and rubella. The model was age-dependent but assumed homogeneous mixing. They performed simulations and from these estimated the number of measles encephalitis and CRS complications under differing immunization strategies. This is a similar problem to that discussed by Knox and Hethcote. They approximated the USA strategy by immunizing a given fraction of boys and girls at 1 year of age. Their conclusion is that at low levels of vaccine coverage the UK policy was best to prevent CRS but once the coverage level exceeds 85 per cent the USA policy was best. This gives the reassuring conclusion that at that time the UK policy was best for the UK and the USA policy was optimal for the USA.

In a later paper (Anderson and May, 1984) they supposed that the disease transmission coefficient $\beta(a,a')$ depends on both a, the age of the susceptible, and a', the age of the infectious, individuals between whom the disease spreads. They use an age-structured partial differential equation model. In this model $X(a,t)$, $H(a,t)$, $Y(a,t)$, $Z(a,t)$ and $N(a,t)$ denote respectively the densities with respect to age of the number of susceptible, incubating, infected, immune and the total number of individuals of age a at time t. This means for example that the total number of susceptible individuals between ages between ages A_1 and A_2 at time t is given by

$$\int_{A_1}^{A_2} X(a,t)da\ .$$

The partial differential equations which describe the progress of the disease are

$$\frac{\partial X(a,t)}{\partial a} + \frac{\partial X(a,t)}{\partial t} = -(\mu(a) + \lambda(a,t))X(a,t),$$

$$\frac{\partial H(a,t)}{\partial a} + \frac{\partial H(a,t)}{\partial t} = \lambda(a,t)X(a,t) - (\mu(a) + \sigma)H(a,t),$$

$$\frac{\partial Y(a,t)}{\partial a} + \frac{\partial Y(a,t)}{\partial t} = \sigma H(a,t) - (\mu(a) + \gamma)Y(a,t),$$

and

$$\frac{\partial Z(a,t)}{\partial a} + \frac{\partial Z(a,t)}{\partial t} = \gamma Y(a,t) - \mu(a)Z(a,t).$$

$(1/\sigma)$ and $(1/\gamma)$ represent respectively the average latent and infectious periods. The term $\mu(a)$ represents age-dependent mortality where $\mu(a) = 0$ up to the expected lifetime L of the individual and $\mu(a) = \infty$ thereafter. The boundary conditions are

$$X(0,t) = \mu^* \overline{N}\,,\ H(0,t) = 0,\ Y(0,t) = 0 \text{ and } Z(0,t) = 0.$$

Here μ^* is the per capita birth rate and $\overline{N}$ is the constant total number of individuals in the population. For births to balance deaths we must have $\mu^* = (1/L)$. The per capita force of infection $\lambda(a,t)$ experienced by an individual of age a at time t is

$$\lambda(a,t) = \int_0^L \beta(a,a')Y(a',t)da'.$$

The population was divided into age classes $I_1, I_2, \ldots, I_n$ and the disease transmission contact structure was given by a matrix, called the who-acquires-infection-from-whom (WAIFW) matrix, so that for $i,j = 1,2, \ldots, n$, $\beta(a,a') = \beta_{ij}$ when $a \in I_i$ and $a' \in I_j$. Different patterns for this matrix were introduced based on different biological assumptions about social and disease transmission contacts. Both disease case reports and age-serological data were used to calculate the force of infection at equilibrium with no vaccination, and from this the WAIFW matrix. The β_{ij} must all be positive as they are the disease contact

rates. Anderson and May discuss a theoretical two age class epidemic model and a practical illustration of a five age class epidemic model applied to measles data in the UK. They calculate various quantities including p_c, the minimum vaccination proportion required to eliminate the disease in the population assuming vaccination at birth. Their conclusion is that age-related heterogeneity in disease transmission rates can result in higher or lower minimum vaccination coverage levels than those predicted by models which assume homogeneous mixing, depending on the details of the age-structured mixing matrix assumed. In practice the difference is small. For an illustrative example for measles they obtain 89 per cent minimum vaccination coverage for heterogeneous and 94 per cent for homogeneous mixing. For measles heterogeneous mixing usually gives a lower estimate of p_c. Anderson and May recommend that public health authorities take the higher prediction as a guide to be safe.

Anderson and May (1985) used an age-structured mathematical model to discuss UK vaccination policies for measles. The predictions for the critical levels of eradication vaccination coverage are relatively insensitive to the choice of the WAIFW matrix, but they do depend significantly on the estimate of the pre-vaccination force of infection in older age classes. Vaccination policies for rubella in the UK are discussed further by Anderson and Grenfell (1986) using an age-structured numerical simulation model with an age-dependent mixing matrix.

This is just a small selection of the work done by Anderson and May and co-workers on the practical application of age-structured mathematical models to vaccination against

common childhood diseases. Other applications involve modeling diseases such as measles, mumps, rubella and pertussis (Anderson and May, 1991).

Roberts and Tobias (2000) describe how an age-structured mathematical model, with a symmetrical disease transmission matrix, for the dynamics of measles in New Zealand was developed and used to compare the likely effects of different potential vaccination strategies. Measles is particularly difficult to eradicate as it spreads very quickly. In the absence of vaccination R_0 is around 15 and roughly 95 per cent of newborns must consistently be vaccinated to eliminate the disease (Anderson and May, 1991). This is difficult to achieve as the vaccine efficacy is only roughly 95 per cent, so practically everyone needs to be vaccinated.

Four different vaccination schedules each involving two vaccinations were tested in the model. The model was fitted to data and successfully predicted an epidemic in 1997, which was controlled by mass vaccination. The results show that the then current two stage vaccination policy was not adequate to control measles in New Zealand and that it was necessary to bring forward the second dose of vaccine to between approximately 3 to 6 years of age to prevent further measles epidemics. Moreover additionally the first dose needs coverage of at least 90 per cent.

Theoretical Threshold and Stability Results on Age-Structured Epidemic Models and Applications

We have established that we must include age-structure in our models for them to be biologically realistic. Thus we must use partial integro-differential equations to model the spread of the disease. These are mathematically more complicated than using ordinary differential equations. Intuitively we might expect similar threshold results to be true, namely that there is a critical threshold parameter R_0. For $R_0 \leq 1$ we might conjecture that only the disease-free equilibrium (DFE) exists which is globally asymptotically stable (GAS). For $R_0 > 1$ as well as the DFE there is a unique endemic equilibrium. We might expect that provided that it starts away from the DFE the system would tend to the endemic equilibrium.

In this subsection we discuss a sequence of progressively more complex mathematical models attempting to show this. The essential difference in the models is the assumptions which they make about the form of the mixing matrix from complete homogeneous mixing to a general age-structured mixing function. We describe the first model in detail as most of the later papers build on this. In the general case there is a threshold value but it is given by the spectral radius or largest eigenvalue of a positive linear operator. We conclude this section with two practical papers which apply these results to real data to find minimum one and two stage elimination vaccination programs for hepatitis A in Bulgaria and mumps and rubella in the UK.

Greenhalgh (1987) discusses equilibrium and stability properties of simple mathematical models for the transmission of infectious diseases such as measles, rubella and mumps. $X(a,t)$, $Y(a,t)$, $Z(a,t)$ and $N(a,t)$ denote respectively the densities with respect to age of the number of susceptible, infected, immune and the total number of individuals of age a at time t. Similarly to Anderson and May (1984) the partial differential equations which describe the progress of the disease are

$$\frac{\partial X}{\partial a}+\frac{\partial X}{\partial t}=-\lambda X-\mu(a)X, \quad \frac{\partial Y}{\partial a}+\frac{\partial Y}{\partial t}=\lambda X-(\gamma+\mu(a))Y,$$

$$\frac{\partial Z}{\partial a}+\frac{\partial Z}{\partial t}=\gamma Y-\mu(a)Z \quad \text{and} \quad \frac{\partial N}{\partial a}+\frac{\partial N}{\partial t}=\mu(a)N,$$

where the force of infection is defined by

$$\lambda(t)=\beta\int_0^\infty Y(a,t)da.$$

Here the average infectious period is $(1/\gamma)$ and $\mu(a)$ is the death rate at age a. The boundary conditions are

$$X(0,t)=\mu^*\overline{N},\ Y(0,t)=0,\ Z(0,t)=0 \text{ and } N(0,t)=\mu^*\overline{N},$$

where again μ^* is the per capita birth rate and $\overline{N}$ is the constant total number of individuals in the population. For the population to be in equilibrium births must balance deaths and we must have

$$1=\mu^*\int_0^\infty \pi(a)da, \qquad \text{where } \pi(a)=\exp\left(-\int_0^a \mu(\xi)d\xi\right).$$

$\pi(a)$ is the fraction of newborn individuals who survive up to age a.

There is a non-zero positive root for λ, the force of infection at equilibrium if and only if β is greater than β^* given by the unique positive root of the equation

$$\int_0^\infty \frac{\beta\mu^* \overline{N}\pi(a)}{\gamma}\left[1-\exp(-\gamma a)\right]da = 1.$$

Greenhalgh demonstrates that if $\beta<\beta^*$ then there is only the DFE and this equilibrium is locally asymptotically stable (LAS). If $\beta>\beta^*$ then there are two possible equilibria, the DFE and another equilibrium with disease present. The DFE is unstable and a criterion for stability of the second equilibrium is derived. Applications to the case of a constant death rate and a more realistic step death function are discussed. Then the model is extended to introduce an incubating class and newborns protected by maternal antibodies.

Greenhalgh (1988) considers the same basic model with no vaccination but with an age-dependent transmission term $\beta(a,a')$ which represents the rate at which a single susceptible individual of age a comes into contact and is infected by a single infected individual of age a' so that the force of infection is given by

$$\lambda(a,t) = \int_0^\infty \beta(a,a')Y(a',t)da'.$$

He discusses first the proportional mixing case where $\beta(a,a') = f(a)g(a')$. The equilibrium and stability properties are the same as when β was a constant. He extends the proof to the case where

$$\beta(a,a') = f_1(a)g_1(a')+f_2(a)g_2(a')+ \ldots +f_n(a)g_n(a')$$

but can no longer show uniqueness of the endemic equilibrium.

Li and Gupur (2004) consider an age-structured SIRS epidemic model with a vaccination program. In an SIRS epidemic model a typical individual starts off susceptible and at some stage catches the disease. After a short infectious period he or she becomes temporarily immune, and after a relatively long immune period the individual becomes susceptible again. This differs from the models discussed above where the immunity was permanent, called SIR models. $\beta(a,a') = f(a)g(a')$ is separable as in Greenhalgh (1988). There is age-dependent fertility and individuals in the temporarily immune class can be infected at a reduced rate. The rate of loss of immunity $\gamma(a)$ and the vaccination rate $\psi(a)$ are age-dependent. Li and Gupur obtain similar results for their model.

Greenhalgh (1990, 1993) discusses his work further for a general positive transmission coefficient $\beta(a,a')$ integrable with respect to a'. Immunity is again assumed to be permanent. There is a maximum lifetime L beyond which it is not possible to live. He finds that the threshold value is the spectral radius, or largest positive eigenvalue, of a linear operator Φ on $L^2[0,L]$ given by

$$\Phi(x) = \int_0^L \varphi(a,\xi)x(\xi)d\xi ,$$

where $$\varphi(a,\xi) = \int_\xi^L \beta(a,a')\mu * N\pi(a')\exp\left[-\gamma(a'-\xi) - \int_0^\xi f(\eta)d\eta\right]da'.$$

$f(a)$ is the age-dependent vaccination rate at age a. He shows that for $\rho(\Phi)\leq 1$ there is only the DFE, whilst for $\rho(\Phi)>1$ there is at least one non-zero positive solution for $\lambda(a)$. Greenhalgh derives conditions for the stability of the DFE. The results are again extended to the model containing classes of incubating and newborn individuals protected by maternal antibodies. The paper continues by discussing some special cases including the

practically important case of multi-stage vaccination programs and $\beta(a,a')$ given by a matrix.

Inaba (1990) studies a mathematical model for an epidemic spreading in an age-structured population with age-dependent transmission coefficient. He formulates the model as an abstract Cauchy problem in a Banach space and shows the existence and uniqueness of solutions. Then he derives conditions which guarantee the existence and uniqueness of the non-trivial steady state of the model. Finally local and global stability of the steady states are examined.

For technical reasons we suppose that there is some fixed lifetime L such that no-one can survive beyond age L. With notation as above for a, $\xi > 0$ define

$$\varphi(a,\xi) = \int_{\xi}^{L} \beta(a,a')\mu * N\pi(a') \exp\left[-\gamma(a'-\xi)\right] da'.$$

Consider the vector space V of all Lebesgue measurable functions from $[0,L]$ to R such that for x in V

$$\int_{0}^{L} |x|^2 d\xi < \infty .$$

This is a countably infinite-dimensional vector space (Curtain and Pritchard, 1977). The operation

$$T(x) = \int_{0}^{L} \varphi(a,\xi) x(\xi) d\xi$$

defines a positive linear transformation T on this vector space.

Inaba proves conjectures made in Greenhalgh (1988) for an age-structured epidemic model, namely:

(1) there exists a threshold value $r(T)$ given as the spectral radius of the above positive linear operator T;

(2) the DFE is always possible and it is GAS if $r(T) <1$ and unstable for $r(T) >1$;

(3) the endemic equilibrium state is possible if and only if $r(T)>1$;

(4) under appropriate conditions the endemic steady state is unique and LAS.

Diekmann and Heesterbeek (2000) describe a general mathematical framework for calculation of R_0 in structured populations including age-structured populations. In general R_0 is the spectral radius of the next generation operator K on positive age-distributions φ given by

$$(K\varphi)(a) = \int_0^\infty k(a,\alpha)\varphi(\alpha)d\alpha, \text{ where } k(a,\alpha) = \int_0^\infty h(\tau,\alpha)c(a,\alpha+\tau)N(a)\ \frac{F_d(\alpha+\tau)}{F_d(\alpha)}\,d\tau.$$

Here $h(\tau,\alpha)$ is the probability of transmission of the disease given a contact between a susceptible individual of arbitrary age τ and an individual that was itself infected at age α. $c(a,\alpha)$ is the contact coefficient, so that an individual of age α has $c(a,\alpha)N(a)$ contacts per unit of time with individuals of age a. $F_d(\alpha)$ is the cohort survival function, giving the probability that an arbitrary newborn individual will survive up to age a

$$F_d(a) = \exp\left[-\int_0^a \mu(\alpha)d\alpha\right]$$

where $\mu(\alpha)$ is the age-dependent death rate. $N(a)$ is the normalized limiting stable age distribution given by $N(a) = Ce^{-ra}F_d(a)$ where r is the limiting rate of population size increase and

$$C = \left(\int_0^\infty e^{-ra} F_d(a) da \right)^{-1}.$$

There are many other age-structured models in the literature. We cannot give a fully comprehensive survey of these due to lack of space. Moreover the focus of this article is on control in age-structured epidemic models, not on age-structured epidemic models per se. However we shall give a brief sample of some other age-structured epidemic models.

Thieme (2001) examines characterization of R_0 in age-structured SEIR models. In an SEIR model a typical individual starts off susceptible, at some stage catches the disease, then undergoes a relatively short incubation period followed by a relatively short infectious period, then is permanently immune. Li, Gupur and Zhu (2001) also examine threshold and stability results in age-structured SEIR models with a general disease transmission function. They use a semigroup approach to pose the disease dynamics as an abstract Cauchy problem. They show that the conjectures in Greenhalgh (1988) for an age-structured SIR-type model are still valid for an age-structured SEIR model.

Hethcote (2000) surveys mathematical models for infectious diseases. In particular he looks closely at age-structure MSEIR models. In these models a typical newborn individual starts off protected by maternal antibodies. After a short period he or she becomes susceptible. When the individual catches the disease he or she enters the exposed or incubating class. This relatively short incubation period is followed by an infectious period which is also relatively short. At the end of the infectious period the

individual becomes permanently immune. Hethcote formulates the MSEIR model using a separable mixing assumption so that the contact rate between individuals of ages a and $\tilde{a}$ is of the form $b(a)b(\tilde{a})$. The per capita force of infection $\lambda(a,t)$ experienced by a susceptible individual of age a at time t is

$$\frac{\int_0^\infty b(a)b(\tilde{a})I(\tilde{a},t)d\tilde{a}}{\int_0^\infty U(a,t)da}.$$

Here $I(\tilde{a},t)$ and $U(a,t)$ are respectively the density with respect to age of the number of infected and the total number of individuals of ages $\tilde{a}$ and a at time t. Thus $\lambda(a,t)$ is independent of the population size. Hethcote then derives an expression for R_0 and shows using Lyapunov methods that if there is a finite maximum age then the DFE is GAS for $R_0 < 1$ and unstable for $R_0 > 1$. Then he derives expressions for the average age at infection A. The next section looks at expressions for R_0 and A when the death rate is age-independent. This is followed by examining the age-structured MSEIR model with constant coefficients and vaccination at age A_v. He derives a condition on the minimum vaccination proportion g at age A_v to eliminate the disease in the population. Hethcote then looks at R_0 and A for a step death function where everyone survives up to age L and then dies instantaneously. At the end of the paper he applies the MSEIR model with 16 age groups to measles in Niger.

Inaba (2007) develops a new approach to deal with asymptotic behavior of age-structured homogeneous epidemic systems and discusses its application to the MSEIR epidemic model. For the homogeneous system there is no attracting non-trivial equilibrium, instead

he has to examine existence and stability of persistent solutions. Assuming that the host population dynamics can be explained by the stable population model Inaba rewrites the basic system into the system of ratio age distribution which is the age profile divided by the stable age profile. If the host population has the stable age profile the ratio age distribution system is reduced to the normalized system. Then Inaba proves that the local stability or instability of the steady states of the normalized system implies that of the corresponding persistent solutions of the original homogeneous system. In the second half of the paper Inaba shows threshold and stability results for the normalized system.

Another aspect of disease transmission which we have not mentioned is vertical transmission of disease from mother to child. This can be important. For example AIDS, Chagas Disease and hepatitis B are vertically as well as horizontally transmitted. Busenburg and Cooke (1993) survey mathematical models for vertically transmitted diseases and their dynamics.

In an SI model a typical individual starts off susceptible, at some stage catches the disease and becomes permanently infectious. An SIS model is similar to an SI model except that infectious individuals are no longer permanently infectious but return to the susceptible class at the end of a finite infectious period. El-Doma (1999) describes an age-dependent SIS model of a vertically and horizontally transmitted disease when the fertility, mortality and recovery rates all depend on age and there is proportional mixing. He determines the steady states and then obtains an explicitly computable threshold condition. Then he performs a stability analysis. He also studies the time-dependent

solutions of the model and examines the long-term behavior. El-Doma (2003) further examines similar SIS models.

Finally another aspect of some diseases which we have not mentioned is that some diseases can significantly affect mortality. Louie, Roberts and Wake (1994) discuss the regulation of an age-structured population by a fatal disease. A model describing the effect of a fatal disease on an age-structured population which would otherwise grow is presented and analyzed. If the disease is capable of regulating host numbers then there is an endemic steady age distribution (SAD) for which an expression is obtained under some simplifying assumptions. The ability of the disease to regulate the population depends on a parameter $R(\alpha)$ which is defined in terms of the given age-dependent birth and death rates, and α is the age-dependent disease-induced death rate. If $R(\alpha) < 1$ the SAD is attained, whilst $R(\alpha) > 1$ means that the disease cannot control the size of the population. $R(0)$ is the expected number of offspring produced by an individual in the absence of disease so that $R(0)>1$ for a growing population. A stability analysis is also performed and it is conjectured that the endemic SAD is LAS when it exists. This is demonstrated explicitly for a simple example where all the rates are constant.

El-Doma (2004) discusses an SI model for a vertically as well as horizontally transmitted disease, when the fertility, natural mortality and disease-induced mortality rates depend on age, with proportional mixing. He determines the steady states, proves the threshold results and then performs a stability analysis. He shows that there is a parameter $R(\alpha)$, where $\alpha(a)$ is the age-dependent disease-induced mortality rate which determines the

existence of a unique steady state if $R(\alpha) < 1 < R(0) = R_0$. A trivial steady state is also possible and if $R_0 < 1$ then this is unique. Under suitable conditions the endemic steady state is LAS whenever it exists and the trivial steady state is GAS if $R_0 < 1$ and unstable if $R(\alpha) < 1 < R_0$. El-Doma also shows that if $qR(\alpha)>1$ where q is the probability of vertically transmitting the disease or if $q=0$ and $R(\alpha) > 1$ then the only steady state is the trivial steady state. However if $R(\alpha) > 1$ but $qR(\alpha) < 1$ then an endemic steady state is possible as well. In this case the endemic steady state may not be unique. In addition with extra conditions imposed on the epidemiological and demographic parameters then the model could give rise to a continuum of non-trivial steady states. Other assumptions lead to the total population consisting of infectives or susceptibles only.

This finishes our survey of theoretical equilibrium and stability results on age-structured epidemic models. In the general case where the mixing matrix is a general positive integrable bivariate function the threshold value is given as the spectral radius of a positive linear operator. We now discuss some applications of these results to calculating minimum one and two stage vaccination programs for the elimination of hepatitis A in Bulgaria and mumps and rubella in the UK.

Greenhalgh and Dietz (1994) examine the above models from a different point of view. They assume that we are given the age-serological profile of a disease with a given vaccination program (usually with no vaccination) and examine the consequences of different mixing assumptions on R_0 and minimum elimination immunization strategies. The work is applicable to common childhood infections such as chickenpox, measles,

mumps and also to hepatitis A. These are all viral diseases where an individual typically starts off susceptible, at some stage catches the disease and after a short infectious period becomes permanently immune. Homogeneous, proportional, assortative and symmetric mixing assumptions are discussed. Assortative mixing maximizes $R(\psi)$ when a steady state age-dependent vaccination campaign ψ is used. A non-symmetric mixing pattern which minimizes $R(\psi)$ and a lower bound in the important symmetric mixing case are found. In the usual case where we are given the age-serological profile in the absence of vaccination we have bounds for R_0. These results are illustrated with an application to vaccination against hepatitis A in Bulgaria. Numerical evaluations of the effect of different elimination vaccination strategies are examined. These concentrate on the important single and two stage vaccination strategies which vaccinate given proportions of individuals at one and two fixed ages respectively.

Sfikas (1999) applies these methods to age-structured serological data for mumps and rubella in the UK. Kernel smoothing is used to estimate the age-dependent force of infection. As well as the effect of different mixing assumptions Sfikas numerically investigates the effect of different kernel smoothers, bandwidths and age class divisions. Sfikas concludes that a variable bandwidth is best with a smaller bandwidth at smaller ages, because more cases occur there. Bootstrap methods are used to estimate confidence and percentile intervals for R_0 and the minimum elimination vaccination proportions using single and two stage vaccination strategies. This is applied to pre-vaccination mumps and rubella data for the UK and hepatitis A data from Bulgaria.

This concludes our survey of epidemic models with age-structure. Most of these implicitly include vaccination so are relevant to optimal control of an epidemic. Vaccination is one way to control infectious diseases and mathematical models can tell us how many individuals we must vaccinate to eradicate a disease in a population using herd immunity. Both analysis and simulation are useful tools. We have seen that realistic epidemic models must include age-structure. We have concentrated on age-structured epidemic models for the spread and control of common childhood diseases but many other age-structured models exist in the literature. Finally we looked at analytical threshold and stability results and their use in describing optimal vaccination strategies. In the next section we shall look at applications of control theory.

OPTIMAL CONTROL APPLIED TO EPIDEMICS

There have been many previous attempts to apply optimal control theory, particularly the Maximum Principle (MP) and dynamic programming (DP), to epidemic modeling. In this section we shall summarize some of these. We start with infectious disease epidemics and finish with a short section on epidemics of drug use.

Optimal Control of Infectious Disease Epidemics

Wickwire (1977) surveys mathematical models for the control of pests and infectious diseases and some models described in this section draw from this. We first discuss a series of papers which apply optimal control theory to either the deterministic or

stochastic Kermack-McKendrick (KMcK) model, or a slight modification of it (see Kermack and McKendrick, 1927). In the KMcK model there are $x(t)$ susceptibles, $y(t)$ infected individuals and $z(t)$ people isolated and removed from the epidemic. Provided that there are infected people present then these people will be removed at a constant rate. The equations are

$$\frac{dx}{dt} = -\beta xy, \quad \frac{dy}{dt} = \beta xy - \gamma y \text{ and } \frac{dz}{dt} = \gamma y,$$

provided that $y(t) \geq 0$. Here β is the disease transmission coefficient and γ is the removal rate. The epidemic is controlled either by immunization of susceptibles or removal of infected individuals.

Hethcote and Waltman (1973) study optimal vaccination applied to a deterministic epidemic model. A deterministic SIR epidemic model with no births or deaths is modified to allow vaccination. We vaccinate susceptibles at rate $\alpha(t)$. $w(t)$, $x(t)$, $y(t)$ and $z(t)$ are respectively the numbers of vaccinated, susceptible, infected and removed individuals at time t. The equations are:

$$\frac{dx}{dt} = -\beta xy - \alpha, \frac{dy}{dt} = \beta xy - \gamma y, \frac{dz}{dt} = \gamma y \text{ and } \frac{dw}{dt} = \alpha.$$

It is supposed that a vaccination policy α has associated cost $C(\alpha)$. It is proposed to control the epidemic in the time interval $[0,T]$ so that:

(i) no more than A of the population succumbs to the disease by time T and

(ii) no more than B of the population is infective at any one time.

A solution to this problem is found using the DP method. This method is used to construct optimal vaccination schedules for some theoretical epidemics.

Gupta and Rink (1973) consider a mathematical model for optimum control of epidemics. This paper presents an application of a dynamic optimization procedure to finding the most economical use of active and passive immunization to control an infectious disease in a closed population. Active immunization by attenuated pathogen acts after a time delay τ_c, passive immunization acts instantaneously. The model is based on the KMcK model and takes into account the latent and infectious periods, assumed normally distributed. The cost is taken to be a sum of terms $Au+Bu^2$ where u is the amount of vaccine and A and B are constants. There is one such term for each type of vaccine. Conditions for cost optimization are obtained from Pontryagin's Minimum Principle and numerical solutions of the problem for postulated parameter values obtained by using a specialized algorithm.

Abakuks (1973) considers the deterministic KMcK model controlled by removals. He assumes that we always know x, the number of susceptibles and y, the number of infected individuals. At any time we can isolate any number of infectives at cost K each. Abakuks shows that the optimal policies either (i) isolate all of the infectives at (x,y) or (ii) never isolate any of the infectives. He finds that we can draw a curve $x = \tilde{x}(y)$ such that for $x > \tilde{x}(y)$ the best policy removes all the infectives whereas if $x < \tilde{x}(y)$ no infectives should be isolated. The curve $x = \tilde{x}(y)$ is given by $\tilde{x} - \xi(\tilde{x}, y) = Ky$ where $\xi(x,y)$ is the final number of susceptibles in an uncontrolled epidemic with x susceptibles and y infectives at the start. $\xi(x,y)$ is the unique root in $(0,x)$ of the equation

$$\xi - \rho \log \xi = x + y - \rho \log x$$

where $\rho=(\gamma/\beta)$ is the relative removal rate.

In a later paper (Abakuks, 1974) he considers the stochastic KMcK model controlled by immunization. Again he assumes that we always know x and y. At each stage (x,y) we may either stop the epidemic by immunizing all the susceptibles at cost $A+Bx$ or allow the epidemic to continue. A and B are positive constants not both zero. Each infection incurs unit cost. Abakuks shows that an optimal policy either immediately immunizes all susceptibles or never immunizes anyone and finds an expression for when which is the best policy.

Wickwire (1975a) considers optimal policies for control of the deterministic and stochastic KMcK models by isolation. Infected individuals (y) are isolated and become effectively non-infectious at a rate $f(x,y)v$ where x is the number of susceptibles, f is a given function of x and y and $v\in[0,1]$ is the control. Both x and y are known exactly at all times. We wish to minimize the cost function

$$\int_0^T (y + hfv)dt$$

where h is a positive constant. This represents the man-hours lost due to infections plus the cost of isolation. In a class of deterministic problems it is shown that the cost of an admissible policy is determined by the number of infectives $x(T) = \xi_v(x, y)$ at the end of the control period. If $x_0 = \rho(h\gamma - 1)/h\gamma$ then the optimal v minimizes $x_0 \log(\xi_v / x) - \xi_v$. Wickwire then demonstrates that an optimal policy will always either isolate no-one or isolate as many people as possible in $[0,T]$. Some similar partial results are obtained for

the stochastic case. These are combined with numerical results computed by DP methods to provide a guide to the optimal policies.

Morton and Wickwire (1974) use Hethcote and Waltman's model for the spread of a disease controlled by immunization. The cost of the epidemic is taken to be

$$\int_0^\infty (y(s) + \kappa\alpha(s))ds$$

where $\alpha(s)$ is the vaccination rate and $y(s)$ is the number of people infected at time s. κ is a positive constant called the cost rate. The immunization rate $\alpha(t)$ lies in [0,1]. They show that the optimal policy is bang-bang. Amongst policies with only finitely many discontinuities the best policy applies full treatment up to a given time and then applies none. The switch happens when x=0 or the trajectories reach a switching curve $y = \tilde{y}(x)$ which is explicitly determined.

Wickwire (1979) considers both the deterministic and stochastic versions of Morton and Wickwire's problem modified so that infected individuals can also recover naturally and return to the susceptible class at per capita rate θ. The epidemic dynamics are given by

$$\frac{dx}{dt} = -\beta xy + \theta y - \alpha,\ \frac{dy}{dt} = \beta xy - \gamma y - \theta y \text{ and } \frac{dz}{dt} = \gamma y + \alpha,$$

where $z(t)$ is the removed class (both isolated and vaccinated individuals). In the deterministic case a complete analysis of an optimal bang-bang control can be obtained using the same DP methods. In the stochastic case a description of the optimal policy is given.

Weiss (1965) has proposed a simple model for the dynamics of epidemics for diseases like typhoid spread by carriers in which infections can be located and removed as soon as they occur. Wickwire (1977) takes this model where susceptibles are immunized at rate $f(x(t))u(t)$ where $f(x)$ is positive and differentiable, $x(t)$ is the number of susceptibles at time t and $u(t) \in [0,1]$ is a control function. If $y(t)$ is the number of individuals infected at time t then

$$\dot{x} = -\beta xy - f(x)u, \quad u \in [0,1], \qquad \dot{y} = -\gamma y,$$

where β is the disease transmission term and γ is the disease removal rate. The cost of an epidemic starting at (x,y) is

$$V(x, y : u) = \int_0^\infty [ay + c\beta xy + g(x)u]dt$$

where $a, c > 0$ are constants. g usually includes the cost of estimating how many susceptibles and carriers are present at any one time.

We wish to control the epidemic to minimize the cost. An optimal control exists and is usually bang-bang. Wickwire shows that if singular control can be ruled out and if the relative cost rate

$$-\frac{d}{dx}\left[x\left(\frac{g(x)}{f(x)}\right) - c \right]$$

is non-decreasing and non-vanishing then there is at most one switch in an optimal control. In particular this is true when $g(x) = k$ = constant > 0 and $f(x) = 1$ or x. By using DP Wickwire shows that optimal controls switch (if at all) from 1 to 0 when the trajectory crosses the switching curve

$$c\left[1-\exp\left(-\frac{y}{\rho}\right)\right]f(x)=g(x),$$

where $\rho = (\gamma/\beta)$ is the relative removal rate. Similar results are obtained if the cost function is discounted. Wickwire also examines a stochastic version of this problem and obtains similar results using DP methods. Numerical studies are performed using the stochastic model.

In a series of other papers Wickwire studies optimal control applied to variants of the basic KMcK model. Wickwire (1976) controls the deterministic KMcK model by immunization so as to minimize the cost of immunization plus the maximum number of individuals infected, namely

$$\int_0^\infty g(x)u\,dt + \max\{y(t) : t \geq 0\}.$$

The epidemic dynamics are given by

$$\frac{dx}{dt} = -\beta xy - f(x)u \text{ and } \frac{dy}{dt} = \beta xy - \gamma y.$$

Here $f(x)$ and $g(x)$ are positive differentiable functions and the measurable function $u \in [0,1]$ is a control. $y(t)$ is maximized at time $t_f = \inf\{t \geq 0 : x(t) \leq \rho\}$. In particular if $x(0) \leq \rho$ then $t_f = 0$. An optimal control is zero for $t > t_f$. For a wide variety of immunization and control cost rates $f(x)$ and $g(x)$ Wickwire shows that optimal controls never immunize near $t=t_f$ and either never immunize, or immunize fully until they cross a switching curve and then never immunize. The switching curve is given in terms of x by

$$\left(1-\frac{\rho}{x}\right)f(x) = g(x).$$

Wickwire (1977) considers optimal control in the stochastic KMcK model with immunization so as to minimize the expected value of the total amount of time lost due to individuals being infected plus a term representing the cost of the immunization effort over the epidemic. Some results on optimal immunization policies are found but because of their complexity Wickwire concentrates on simpler suboptimal policies which can be a good approximation to the best policies. Wickwire (1975b) considers a modification of the basic deterministic KMcK model adopted for a carrier-borne epidemic. A fraction (1-*p*) of infections are detectable and these infections are isolated as soon as they occur. This epidemic model is controlled by immunization so as to minimize the total cost of individuals becoming infected plus detectable infections plus the immunization program. The equations which describe the spread of the disease are

$$\frac{dx}{dt} = -\beta xy - u, \frac{dy}{dt} = p\beta xy - \gamma y \text{ and } \frac{dz}{dt} = (1-p)\beta xy + \gamma y + u,$$

where $u \in [0,1]$ is the immunization rate and x, y and z denote the numbers of susceptibles, infectives and removed individuals (those who have been isolated, immunized or have naturally recovered). The cost is

$$\int_0^\infty (c_1 y + c_2(1-p)\beta xy + ku)dt$$

where c_1, c_2 and k are positive constants. Wickwire shows that the optimal controls are bang-bang, can have at most one switch and gives a formula for the switching curve. Further details of some of Wickwire's models discussed above are given in Wickwire (1977).

Greenhalgh (1986a) considers a theoretical epidemic model for a disease spreading in a heterogeneously mixing community with control by immunization of susceptibles and removal of infected people. The underlying model is due to Cane and McNamee (1982) and assumes proportional mixing. DP methods and stochastic dominance arguments are used. The situation is discussed first when controlled only by immunization so as to minimize the expected number of people infected at some terminal time *T* and then to maximize the expected number of people immunized at time *T*. The optimal policy is to immunize the most susceptible individuals for both objectives. For control by removals minimizing the expected number of people infected, minimizing the expected number of people who have ever caught the disease and maximizing the expected number of people removed, at time *T*, are discussed. Some partial results are obtained. Counterexamples are discussed to illustrate why the simplifying assumptions are needed. The paper concludes with some applications.

This concludes our description of optimal control methods applied to infectious disease models. In the next subsection we shall discuss epidemics of drug use.

Optimal Control of Drug Use Epidemics

Behrens et al. (1999) present a continuous-time dynamical control model (the LH model) for the cocaine epidemic in the USA. The model is

$$\frac{dL}{dt} = I(L,H) - (a+b)L \text{ and } \frac{dH}{dt} = bL - gH, \text{ where } I(L,H) = \tau + sL\exp\left[-q\frac{H}{L}\right],$$

subject to $L(0)=L_0$, $H(0)=H_0$. Here $L(t)$ and $H(t)$ are the number of light drug and heavy drug users respectively at time t. $I(L,H)$ is the initiation into light use. s is the average rate at which light users attract non-users, τ is the number of innovators and q is a constant measuring the deterrent effects of heavy drug use. a is the rate at which light users quit, b the average rate at which light users escalate to heavy use and g is the average rate at which heavy users quit.

Prevention is modeled as cutting initiation to a certain percentage ψ of its uncontrolled value. Prevention spending w has a diminishing return given by

$$\psi(w) = h + (1-h)\exp[-mw]$$

where h and m are positive constants. The rehabilitative effect of treatment is captured by the parameter β which denotes the increase above baseline g in the rate at which heavy users exit. In particular

$$\beta(H,u) = c\left(\frac{u}{H+\delta}\right)^d$$

where u is the amount spent on treatment and c, d and δ are positive constants with $d<1$.

They use this model to find the optimal allocations of treatment and prevention spending with an objective function

$$J = \int_0^\infty e^{-rt}\big(kQ(t) + u(t) + w(t)\big)dt$$

to minimize the costs of controls and of drug use to society. $Q(t)$ denotes the consumption rate in grams per year. It is a weighted sum ($\mu_L L + \mu_H H$) of L and H according to the average annual consumption rates of light (μ_L) and heavy (μ_H) users respectively. K is the

social cost per gram of consumption and r is the discount rate. It is assumed that the drug control budget for prevention and treatment is proportional to the total consumption i.e. $u(t)+w(t)=\gamma Q(t)$ where γ is a constant.

Behrens et al. consider three different cases: (i) constant-fraction budget allocation, (ii) optimal mix of prevention and treatment and (iii) optimal control without financial limitations on the interventions. In case (i) we have a constant fraction f of the budget going to treatment and 1-f going to prevention throughout the entire epidemic. Hence $u(t) = f\gamma Q(t)$ and $w(t)=(1-f)\gamma Q(t)$. The problem is to choose a fixed f to minimize the total cost. In case (ii) the mixture of treatment and prevention can vary over time. Here the best control policy is bang-bang and requires the proportion of treatment and prevention in the budget to switch sharply from 0 per cent to 100 per cent and vice-versa. Behrens et al. investigate optimal control problems numerically for realistic parameter values for all three problems.

Behrens et al. (2002) extend this model to examine cycles of drug use epidemics through the use of an optimal control model that incorporates an endogenous initiation function, models the reputation of a drug as being determined by memories of past use and finds the optimal drug treatment strategy. The drug's reputation is governed by the relative number of light users and a decaying memory of people who have ever been heavy users ($E(t)$). The flow into this state is the same as the flow into the number of current heavy users bL. The outflow is a simple exponential decay governed by a memory parameter δ.

The differential equations which describe the progress of the disease are

$$\frac{dL}{dt} = I(L,E) - (a+b)L, \frac{dH}{dt} = bL - (g + \beta(H,u))H \text{ and } \frac{dE}{dt} = bL - \delta E$$

with $L(0)=L_0$, and $H(0)=E(0)=H_0$. Using the notation introduced in Behrens et al. (1999) the initiation function is

$$I(L,E) = \tau + sL\exp\left[-q\frac{E}{L}\right]$$

and the rehabilitative effect of treatment $\beta(H,u)= \sigma u^{\zeta}H^{\zeta}$ where σ and ζ are positive constants ($0< \zeta< 1$). There is no explicit prevention spending. Instead memory of the adverse effects of previous epidemics is regarded as a prevention strategy. The cost function of previous drug epidemics is the same as in Behrens et al. (1999).

The MP is used to find the optimal control strategy. Unless the societal discount rate is quite low, if memories of past users decay moderately quickly the optimal strategy is cyclic. Hence "individuals who forget the past are condemned to repeat it" and "for those who forget the past and overvalue the present it may be optimal to have their future recreate the past". Define $p = \exp[-qb/\delta]$ to be the equilibrium reputation of the drug and $\chi = sp(1+qb/\delta)-a-b$. Assume that $\chi-\delta \geq 0$ and $4spqb \geq (\delta+\chi)^2$. Under these conditions a chain of cyclic drug epidemics may occur when

$$r \geq \frac{1}{2}(sp(1+qb/\delta)-a-b-\delta).$$

In other words cyclic drug epidemics can occur if decision-makers are not far-sighted enough (r is too large). The overall findings are supported by numerical analysis based on the 2002 USA cocaine epidemic.

Baveja et al. (2000) present a budget-constrained optimal control model aimed at finding the optimal enforcement profile for a street-level, illicit crackdown operation. The objective is minimizing the number of dealers dealing at the end of the crackdown operation using this as a surrogate measure of residual criminal activity. The problem is posed as an optimal control problem namely to minimize

$$\exp[-rT]\, N(T)$$

subject to $$\frac{dN}{dt} = c_1\left[\pi\alpha N^{\beta-1} - \left(\frac{E}{N}\right)^{\gamma} - \omega_0\right],\ N(0) = N_0 \text{ and } \int_0^T E(t)dt \le B.$$

Here $N(t)$ is the number of drug dealers at time t, r is the discount rate, T is the finite time horizon and $\pi > 0$ is the generalized profit per unit of sales in the market. If there are N dealers then the number of sales per day is αN^{β} where $\alpha > 0$ and $\beta \in [0,1]$ are constants. $E(t)$ is the enforcement cost associated with crackdown at time t and $\gamma > 0$ is a constant parameter associated with the per dealer cost of enforcement. ω_0 is the equilibrium level of generalized profit. It is assumed that $\pi\,\alpha > \omega_0$, otherwise there will be no drug market. $c_1 > 0$ is a speed of adjustment parameter and B is the total budget available for crackdown.

Optimal control methods are used to show that it is always optimal to spend the whole budget. For $\gamma < 1$ (risk-seeking dealers) when $\gamma+\beta \le 1$ then $dE/dt > 0$ if $N > N_{min}$ and $dE/dt < 0$ if $N < N_{min}$ where

$$N_{\min} = \left(1 - \frac{1-\beta}{\gamma}\right)^{\frac{1}{1-\beta}}.$$

For $\gamma \geq 1$ (risk-neutral or risk-avoiding dealers) the unconstrained optimal strategy could suggest the use of unrealistic infinite values of the enforcement E. Hence we assume that the enforcement effort is constrained by $0 \leq E(t) \leq \overline{E}$ for $t \in [0,T]$.

Mathematical analysis supports Behrens et al.'s conjecture that there are two candidates for the optimal policy:

(i) apply no enforcement effort (E=0) until time t_0 and then apply full enforcement effort ($E=\overline{E}$) in $[t_0,T]$. Usually

$$\int_{t_0}^{T} \overline{E}\,dt = B.$$

(ii) apply full enforcement effort ($E=\overline{E}$) until time t_1 and then apply no enforcement effort.

The model of Behrens et al. (1999) motivated Kaya (2004) to look at the problem of bringing the size of the epidemic down to a target level in the minimum possible time, find the necessary number of switchings between treatment and prevention and when these switches happen. He performs a numerical study for both the early and late action scenarios, where controls begin in 1967 and 1990 respectively. He looks at the minimum process time, the cost of control and the target ratio of heavy users. In both cases the best strategy is to prevent first then treat. Also surprisingly if we wish to reach the target as quickly as possible, the ratio of heavy users at the target should be as low as it can be. This also gives the lowest cost. The results are then discussed further.

Almeder et al. (2004) introduce a model for drug initiation that extends traditional models for the spread of drug-use by considering explicitly the age-distribution of the users. Building on a model with the two groups (users and non-users) a continuous age-distribution model is shown to give more detailed results and new results. Moreover prevention programs are often targeted at particular age groups (for example school-based programs). If death rates are neglected then the model reduces to a one group model which is still accurate enough to predict some of the observed behaviors of drug epidemics, for example recurrent cycles. The authors formulate and solve optimal control problems to decide how best to allocate resources to prevention programs.

In this section we have looked at optimal control applied to epidemic models, both infectious disease epidemics and epidemics of drug use. Both deterministic and stochastic models were considered. The major mathematical tools used were the MP and DP. For infectious disease epidemics the control methods were normally immunization of susceptibles and removal of infected individuals, for the drug use epidemic models the controls were prevention and treatment. The optimal controls were usually bang-bang. A common theme was that usually if one was trying to minimize some economic cost of an epidemic, or build up immunity in the population the optimal policy is to remove or immunize as many people as possible up to a switching time and then let the epidemic run its course. Thus removal or immunization effort applied early on in the epidemic is usually more effective as these people left alone would have infected more people than someone removed or immunized later.

MODELS WITH AGE-STRUCTURE AND OPTIMAL CONTROL

In this section we shall examine applications of optimal control in age-structured epidemic models. We start off with two papers which address the optimal age of vaccination in the presence of maternal antibodies. This is followed by a discussion of some papers which give some theoretical results on the structure of optimal vaccination policies for age-structured epidemic models. Finally we discuss an application of the MP to determine the optimal control strategy in a heterogeneous epidemic model.

Optimal Vaccination in the Presence of Maternal Antibodies

Katzmann and Dietz (1984) use an age-structured deterministic mathematical model to examine the effect of maternal antibodies on disease elimination programs. Most newborns are protected by antibodies in their bloodstream from their mother for many viral childhood diseases. This effect fades after six to nine months, but vaccination is ineffective until after this period. Katzmann and Dietz find the optimal vaccination age for an individual to eliminate the infection in the population using herd immunity. They also look at the case where immunity is only temporary.

In their model $X(t,a)$, $U(t,a)$, $V(t,a)$, $W(t,a)$, $Z(t,a)$ and $N(t,a)$ are the densities with respect to age of the numbers of individuals of age a at time t who are respectively protected by maternal antibodies, susceptible, infectious, permanently immune, vaccinated, and the total number of individuals. $\mu(a)$ is the per capita death rate of an individual of age a, the

same for all disease classes. $\pi(a)$ is the per capita vaccination rate. δ is the per capita rate of loss of immunity of vaccinated individuals and σ is the per capita rate of loss of protection by maternal antibodies. Infectious individuals become naturally immune at per capita rate γ and β is the disease contact rate. $\lambda(t)$ the per capita force of infection at time t is given by

$$\lambda(t) = \frac{\beta \int_0^\infty V(t,a)da}{\int_0^\infty N(t,a)da}.$$

The partial differential equations which describe the spread of the disease are

$$\frac{\partial X}{\partial a} + \frac{\partial X}{\partial t} = -(\sigma + \mu(a))X, \qquad \frac{\partial U}{\partial a} + \frac{\partial U}{\partial t} = \sigma X + \delta Z - (\lambda(t) + \pi(a) + \mu(a))U,$$

$$\frac{\partial V}{\partial a} + \frac{\partial V}{\partial t} = \lambda(t)U - (\gamma + \mu(a))V, \quad \frac{\partial W}{\partial a} + \frac{\partial W}{\partial t} = \gamma V - \mu(a)W,$$

and $$\frac{\partial Z}{\partial a} + \frac{\partial Z}{\partial t} = \pi(a)U - (\delta + \mu(a))Z,$$

where $N(t,a) = X(t,a) + U(t,a) + V(t,a) + W(t,a) + Z(t,a)$. The boundary conditions when $a = 0$ are

$$X(t,0) = N_0\left[1 - \frac{U(t,B)}{N(t,B)}\right], \quad U(t,0) = N_0 \frac{U(t,B)}{N(t,B)}$$

and $V(t,0) = W(t,0) = Z(t,0) = 0$. Here B is the average age at childbearing and N_0 is the total birth rate.

If a two-age vaccination policy immunizes a coverage q_i at age T_i for i=1,2 and the death rate $\mu(a) = \mu$ is constant then the average proportion $\bar{u}$ of susceptible individuals in the population at equilibrium is given by

$$\bar{u} = 1 - \frac{z^* \mu}{\mu + \sigma} - \frac{q_1 \mu \left(1 - z^* \exp[-\sigma T_1]\right) \exp\left[-\mu T_1\right]}{\mu + \delta} - \frac{q_2 \mu}{\mu + \delta} \left(1 - z^* \exp[-\sigma T_2]\right) \exp\left[-\mu T_2\right]$$
$$+ \frac{q_1 q_2 \mu}{\mu + \delta} \left(1 - z^* \exp[-\sigma T_1]\right) \exp\left[-\mu T_2 - \delta\left(T_2 - T_1\right)\right].$$

Here z^* is given by

$$z^* = \frac{\left[q_1 (1 - q_2) \exp\left[-\delta\left(B - T_1\right)\right] + q_2 \exp\left[-\delta (B - T_2)\right]\right]}{\left[1 - \exp\left[-\sigma B\right] + q_1 (1 - q_2) \exp\left[-\delta\left(B - T_1\right) - \sigma T_1\right] + q_2 \exp\left[-\delta (B - T_2) - \sigma T_2\right]\right]}.$$

For σT_i, i=1,2 and σB large we have

$$z^* \approx q_1 (1 - q_2) \exp[-\delta (B - T_1)] + q_2 \exp[-\delta (B - T_2)].$$

If there is only one vaccination and $\sigma >> \delta$ then $\bar{u}$ is minimized when $T_1 \approx [\ln(q_1 \sigma / \mu) - \delta B] / \sigma$. The condition $\sigma >> \delta$ is likely to be true in practice as it says that the average period of protection by natural immunity (at least twenty to thirty years) exceeds the average period of protection by maternal antibodies (at most 9 months).

Hethcote (1988) examines optimal ages of vaccination for measles. A mathematical modeling approach is used to theoretically estimate the lifetime expected risk due to measles in a population for some given age-dependent risk function. An age-structured mathematical model is used with homogeneous mixing. Protection by maternal antibodies is considered. One and two stage vaccination policies which vaccinate respectively a fraction V_1 of the population at age A_1 months for i = 1 and i=1,2 are

discussed. Resources for vaccination are limited so there are a limited number of vaccine doses available, this models the situation in developing countries.

Optimal one stage vaccination strategies are considered numerically for various countries (in particular Kenya, parts of South Africa and the USA). The age-dependent risk function is first taken to be infection and second death. Hethcote's calculations for the two stage vaccination strategies when the risk function is either infection or death shows that the optimal two stage vaccination strategy always occurs when the two stages are given at ages as close together as possible. The optimal single stage vaccination strategies are always significantly better than the optimal two stage strategies in which half of the doses are given at one age and the other half at a later age. Hence a strict two stage policy cannot be exactly optimal.

The Structure of Optimal Age-dependent Vaccination Policies

In this subsection we look at two optimization problems: first to find the vaccination strategy that minimizes the cost subject to a constraint on the effect and second to find the vaccination strategy that minimizes the effect subject to a given cost. We find that for a wide variety of problems the optimal policies have the simple one, two (and possibly three) stage forms which are often used in practice.

Hadeler and Müller (1996a,b) develop a theory of vaccination strategies using age-structured epidemic models. Susceptibility and infectivity are assumed to depend on the

age of the susceptible and infected individual respectively and proportional mixing is used. As this model has a variable population size the transmission coefficient is taken to be inversely proportional to the population size. Vaccinated individuals have reduced susceptibility. Both susceptible and vaccinated individuals have age-dependent fertility and mortality. Infected individuals have a separate reduced age-dependent fertility and a decreased age-dependent mortality. The loss of immunity $\gamma(a)$ is also assumed to be age-dependent as is the vaccination rate $\psi(a)$. Hadeler and Müller derive an expression for $R(\psi)$. An expression for the reduction from R_0 to $R(\psi)$ is calculated. Hadeler and Müller (1996b) relate these models to age-dependent vaccination costs. They point out that there is an essential difference between the case where susceptibles can be recognized and only susceptibles vaccinated (Scenario 1) and the case where susceptibles, vaccinated and infected individuals cannot be distinguished, and so all of them must be vaccinated (Scenario 2).

The costs of the vaccination program are denoted $C(\psi)$. These are defined as the per capita weighted number of vaccinations, with weight function $\kappa(a)$:

$$C(\psi) = \int_0^L \kappa(a)\psi(a)u(a)\,da \quad \text{for Scenario 1}$$

and $$C(\psi) = \int_0^L \kappa(a)\psi(a)[u(a)+w(a)+v(a)]\,da \quad \text{for Scenario 2.}$$

Here $u(a)$, $v(a)$ and $w(a)$ are respectively the equilibrium densities with respect to age of the numbers of susceptible, vaccinated and infected individuals at age a. L is the maximum lifetime of an individual.

They define two optimization problems:

P1) Achieve a prescribed effect at minimum costs, i.e. prescribe a level R^* for $R(\psi)$ and minimize $C(\psi)$ under the condition $R(\psi) \leq R^*$;

P2) Achieve an optimum effect at given expenses, e.g. prescribe the maximal expenses $\tilde{\kappa}$ and minimize $R(\psi)$ under the condition $C(\psi) \leq \tilde{\kappa}$.

They use the Kuhn-Tucker theorem to obtain their results. First consider the problem P1 where the immunity is permanent. Hadeler and Müller show that under either Scenario 1 or 2 the optimal vaccination strategy is either a single stage vaccination strategy with vaccination at exactly one age A, or it is a two stage strategy with vaccination at ages A_1 and A_2. Moreover for each scenario they give algorithms for determining the optimal strategy. Some partial results are also obtained for P2 under Scenario 1.

They discuss P2 in the case where immunity can be lost ($\gamma(a) \equiv \gamma > 0$). They assume constant expenses ($\kappa \equiv 1$), an infinite potential lifetime ($L \equiv \infty$) and also that the death rate $\mu(a)$ has a strictly positive lower bound. Under Scenario 1 and additional technical assumptions they show that there exists a unique optimal vaccination strategy. Of course for Scenario 1 to be realistic it must be possible to observe the loss of immunity. The optimal strategy has the special form that in one closed age interval everybody is vaccinated. This interval may shrink to a point and then only part of the population may need to be vaccinated. Thus in general there is an age interval $[A_1,A_2]$ with optimally chosen A_1 and A_2. Everybody who reaches the age A_1 will be vaccinated as well as everyone who loses immunity during the age interval $[A_1,A_2]$. Individuals older than age A_2 who lose immunity will not be revaccinated.

Castillo-Chavez and Feng (1998) consider an age-structured proportional mixing model for the transmission of tuberculosis with age-dependent vaccination. The population is divided into susceptible, vaccinated, exposed, infectious and treated classes and vaccinated and treated individuals may become infected as well as susceptibles. They first show that the DFE is GAS if R_0 is less than one and that an endemic steady state exists when $R(\psi)$, under age-dependent vaccination strategy ψ, strictly exceeds one. Using the same cost function and optimization problems as Hadeler and Müller (1996a,b) they show that the same results hold for their model in Scenario 1 (only susceptibles are vaccinated) and describe how to calculate the optimal policies.

Müller (1998) considers a similar problem for an SIR model but uses different methods. The model differentiates between natural immunity from experiencing the disease and immunization and considers a general age-dependent contact function as well as separable mixing. Two optimization problems are again considered: first to find the vaccination strategy ψ with the smallest $R(\psi)$ at given costs and second to find the vaccination strategy ψ with the smallest costs for a given $R(\psi)$. The two problems are dual in the sense that a solution to one problem is, for appropriate parameters, also a solution to the other problem. Individuals who have been vaccinated receive a vaccination certificate so we do not vaccinate them again, also we do not vaccinate infected people. Müller argues that it is more reasonable to take the number of vaccinations per capita as the cost because as the population grows so does its economic power. There is no limit on the maximum lifetime.

Using the notation of Hadeler and Müller (1996b) the cost function is taken as

$$C(\psi) = \int_0^\infty \frac{\psi(a)[u(a) + \tilde{v}(a)]\, da}{N}.$$

Here $\tilde{v}(a)$ represents the equilibrium density with respect to age of the number of individuals who have not yet been vaccinated but are immune because of the disease. *N* is the total population size. Again for a wide class of mixing patterns optimal immunization strategies vaccinate at most two ages. The ideas of this work can be carried over to the situation with loss of immunity (Müller, 1994).

It is also possible to consider endemic situations. Then the aim of a vaccination strategy will be to minimize the prevalence or the risk cases. Again optimal vaccination policies are concentrated at discrete ages. Müller (2000) looks at optimal vaccination strategies in an age-structured epidemic model. Again he considers two optimization problems, first to find the strategy with minimal costs at a given effect and second to find the strategy with a given effect at minimal costs. Hadeler and Müller (1996b) and Müller (1998) choose the reproduction number as the effect. The more difficult endemic case is discussed by Müller (2000). He takes a simple age-structured SIR model with separable mixing. Again each person who is vaccinated receives a "vaccination certificate". We then vaccinate every non-vaccinated person with the same vaccination strategy. The costs are taken as the number of vaccinations per unit time weighted by age and whether the vaccinated individual is susceptible, infected or immune. The effect is taken to be the reduction of the, possibly age-weighted, prevalence of the disease. This age-weighting reflects

diseases like rubella where different ages have different risks and we wish to reduce the number of risk cases. Müller proves the existence of optimal vaccination strategies and shows that there is an optimal vaccination rate that is non-zero for at most three discrete age classes.

This concludes our discussion of the form of the best vaccination policies in age-structured epidemic models. We considered two problems: to find the vaccination strategy that minimizes the cost subject to a given constraint on the effect and the second to find the vaccination strategy that minimizes the effect subject to a given constraint on the cost. If the effect is taken as the reproduction number or an age-weighted average of the number of cases then a one, two or three stage vaccination strategy will be optimal. This is reassuring as these vaccination policies are used in practice. It is nice to know that the most cost-efficient policies are also of this form.

We thus finish our section on applications of optimal control in age-structured epidemic models. We have looked at determining the optimal age of vaccination to take into account the protective effect of maternal antibodies, then the use of linear programming results to show that for a wide class of problems the single, two or three age vaccination policies include the optimal policy.

SPATIAL CONTROL MODELS

We next briefly describe two models with geographical structure which determine optimal vaccination policies in spatially structured populations. Greenhalgh (1986b) considers optimal control of an epidemic by ring vaccination. This paper deals with the control of disease spread within a community and focuses on whether it is better to attempt to stop the disease by immunizing a large or small ring around the infected area. This tactic has been used in the control of smallpox and rabies. The population is spread out on a two-dimensional geographical lattice and two mechanisms for the spread of the disease are considered corresponding to the Greenwood and Reed-Frost Chain Binomial models. Monte-Carlo simulation shows that there is a threshold result for the probability of whether the disease breaks through the immunizing ring with a threshold value of roughly $8\lambda=\mu$ where λ is the infection rate between a neighboring susceptible and infected individual and μ is the immunization rate. Then the paper looks at controlling the epidemic so as to minimize the expected number of individuals ever infected. Both partial analytical results and Monte-Carlo simulation suggest that, for this objective, policies which always treat one of the susceptible individuals (or populations) immediately at risk are better than those which first attempt to immunize a ring around the infected area.

Tildesley et al. (2006) discuss optimal reactive vaccination strategies for a foot-and-mouth disease (FMD) outbreak in the UK. Using the data from the 2001 epidemic they consider the optimal deployment of limited vaccination capacity in a complex heterogeneous environment. They use a model of FMD spread to investigate the optimal

deployment of reactive annular ring vaccination of cattle constrained by logistical resources. The predicted optimal ring size is highly dependent upon logistical constraints but is more robust to epidemiological parameters. Other ways of targeting reactive vaccination can significantly reduce the epidemic size; in particular ignoring the order in which infections are reported and vaccinating those farms closest to any previously reported case can substantially reduce the epidemic. This is supported by theoretical results for a two-dimensional spatial model of disease spread studied by Greenhalgh (1989). This strategy has the advantage that it rapidly targets new foci of infection and that determining an optimal ring size is unnecessary.

Russell et al. (2006) address the problem of spatial control of rabies in heterogeneous landscapes. In addition to direct oral rabies vaccine (ORV) delivery to protect wildlife in natural habitats, vaccine corridors have been constructed to control the spread. These corridors are often developed around natural barriers, such as rivers, to enhance the effectiveness of vaccine deployment. This paper uses spatially heterogeneous mathematical models to simulate how to distribute vaccine optimally around the barrier. These models are age-structured as adults and juveniles are modeled separately. The model focuses on rabies in raccoons. The key finding is that the vaccine should always be deployed behind the barrier to minimize the recurrence of subsequent epidemics. When the vaccination is in front of the barrier it creates a demographic refuge and seasonal dispersal from the vaccine corridor into an endemic region sustains epidemic oscillations of raccoon rabies.

Arino et al. (2007) discuss the role of quarantine in a multi-species epidemic model with spatial dynamics. A motivation is provided for the development of infectious disease models that incorporate the movement of individuals over a wide range of spatial scales. A general model is formulated for a disease that can be transmitted between different species and multiple patches and the behavior of the system is investigated when the spatial component consists of a ring of patches. The influence of various parameters on R_0 is studied numerically, with particular focus on the role of quarantine in the form of travel restriction. An application to avian influenza is briefly discussed.

SUMMARY AND DISCUSSION

In this chapter we have looked at age-structured epidemic models, and surveyed the use of optimal control theory applied to epidemic models, in particular age-structured models. We have interpreted the term optimal control broadly to include for example calculating the best vaccination policies to control diseases. Age-structure is an important concept in epidemiology as for many diseases commonly made homogeneous mixing assumptions are unrealistic. Our discussion has ranged from the very theoretical, finding the threshold value in an age-structured epidemic model as the spectral radius of a positive linear operator, to the very practical. An example of the latter is simulation models of different vaccination policies for measles and rubella in the UK and New Zealand. We have also included discussions of optimal control theory applied to epidemic models, typically controlled by immunization of susceptibles or removal of infectives. We found that bang-bang policies switching from one extreme to another are

commonly the best ones. For many of these epidemic control problems the optimal policy had at most one switch, from applying full control effort to applying none. Moreover theoretical optimization methods applied to age-structured epidemic models show that the single, two and three stage vaccination policies commonly used in practice include the optimal policy. Spatial simulation models can guide us how to control diseases such as smallpox and rabies. This interesting and ongoing area is one which is not only mathematically interesting but also one where results have been used in practice to guide public health policy.

REFERENCES

Abakuks, A. (1973) An optimal isolation policy for an epidemic, *Journal of Applied Probability*, 10:247-262.

Abakuks, A. (1974) Optimal immunisation policies for epidemics, *Advances in Applied Probability*, 6:494-511.

Almeder, C., Caulkins, J.P., Feichtinger, G. and Tragler, G. (2004) An age-structured single-state drug initiation model – cycles of drug epidemics and optimal prevention programs, *Socio-Economic Planning Sciences*, 38:91-109.

Anderson, R.M. (1982) "Directly transmitted viral and bacterial infections of man" in R.M. Anderson (ed.) *Population Dynamics of Infectious Disease Agents: Theory and Applications*, London: Chapman and Hall.

Anderson, R.M. and Grenfell, B.T. (1986) Quantative investigation of different vaccination policies for the control of congenital rubella syndrome (CRS) in the UK, *Journal of Hygiene*, 96:305-333.

Anderson, R.M. and May, R.M. (1982) Directly transmitted infectious diseases: control by vaccination, *Science*, 215:1053-1060.

Anderson, R.M. and May, R.M. (1983) Vaccination against rubella and measles: quantitative investigations of different policies, *Journal of Hygiene*, 90:259-325.

Anderson, R.M. and May, R.M. (1984) Spatial, temporal and genetic heterogeneity in host populations and the design of immunization programmes. *IMA Journal of Mathematics Applied in Medicine and Biology*, 1:233-266.

Anderson, R.M. and May, R.M. (1985) Age-related changes in the rate of disease transmission: implications for the design of vaccination programs, *Journal of Hygiene*, 94:365-436.

Anderson, R.M. and May, R.M. (1991) *Infectious Diseases of Humans: Dynamics and Control*, Oxford: Oxford University Press.

Arino, J., Jordan, R. and van den Driessche, P. (2007) Quarantine in a multi-species epidemic model with spatial dynamics, *Mathematical Biosciences*, 206:46-60.

Baveja, A. Feichtinger, G. Hartl, R.F. Haunschmied, J.L. and Kort, P.M. (2000) A resource-constrained optimal control model for crackdown on illicit drug markets, *Journal of Mathematical Analysis and Applications*, 249:53-79.

Behrens, D.A., Caulkins, J.P., Tragler, G. Haunschmeid, J.L. and Feichtinger, G. (1999) A dynamic model of drug initiation : implications for treatment and drug control, *Mathematical Biosciences*, 159 :1-20.

Behrens, D.A., Caulkins, J.P., Tragler, G. and Feichtinger, G.A. (2002) Why present-oriented societies undergo cycles of drug epidemics, *Journal of Economic Dynamics and Control*, 26:919-936.

Bernoulli, D. (1760) Essai d'une nouvelle analyse de la mortalité causée par la petite vérole et des advantages de l'inoculation pour la prévenir, *Mémoires de Mathématique et de Physique presentés à l'Académie Royale des Sciences, Paris*, 1-45.

Busenburg, S.N. and Cooke, K.L. (1993) *Vertically Transmitted Diseases: Models and Dynamics*, Lecture Notes in Biomathematics, 23, Berlin:Springer-Verlag.

Cane, V.R. and McNamee, R. (1982) The spread of an epidemic in a heterogeneous population, *Journal of Applied Probability*, 19A:173-184.

Castillo-Chavez, C. and Feng, Z. (1998) Global stability of an age-structure model for TB and its applications to optimal vaccination strategies, *Mathematical Biosciences*, 151:135-154.

Collins, S.D. (1929) Age incidence of the common communicable diseases of children, *United States Public Health Reports*, 44:763-828.

Curtain, R.F. and Pritchard, A.J. (1977) *Functional Analysis in Modern Applied Mathematics*, London:Acadmic Press.

Diekmann, O. and Heesterbeek, J.A.P. (2000) *Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation*, Wiley Series in Mathematical and Computational Biology, Chichester:John Wiley & Sons Ltd.

Dietz, K. (1981) "The evaluation of rubella vaccination strategies", in R.W. Hiorns and K. Cooke (eds.) *The Mathematical Theory of the Dynamics of Biological Populations, Volume II*, London: Academic Press.

Dietz, K. and Schenzle, D. (1985) Proportionate mixing for age-dependent infection transmission, *Journal of Mathematical Biology*, 22:117-120.

El-Doma, M. (1999) Analysis of an age-dependent SIS epidemic model with vertical transmission and proportionate mixing assumption, *Mathematical and Computer Modelling*, 29:31-43.

El-Doma, M. (2003) Stability and disease persistence in an age-structured SIS epidemic model with vertical transmission and a proportionate mixing assumption, *Mathematical Sciences Research Journal*, 7:430-445.

El-Doma (2004) Analysis of an age-dependent SI epidemic model with disease-induced mortality and proportionate mixing assumption: The case of vertically transmitted diseases, *Journal of Applied Mathematics*, 3:235-253.

Farrington, C.P. (1990) Modelling forces of infection for measles, mumps and rubella, *Statistics in Medicine*, 9:953-967.

Greenhalgh, D. (1986a) Control of an epidemic spreading in a heterogeneously mixing population, *Mathematical Biosciences*, 80:23-45.

Greenhalgh, D. (1986b) Optimal control of an epidemic by ring vaccination, *Stochastic Models*, 2:339-363.

Greenhalgh, D. (1987) Analytical results on the stability of age-structured recurrent epidemic models, *IMA Journal of Mathematics Applied in Biology and Medicine*, 4:109-144.

Greenhalgh, D. (1988) Threshold and stability results for an epidemic model with an age-structured meeting rate, *IMA Journal of Mathematics Applied in Medicine and Biology*, 5:81-100.

Greenhalgh, D. (1989) Simple two-dimensional models for the spread of a disease, *Stochastic Models*, 5:131-159.

Greenhalgh, D. (1990) Vaccination campaigns for common childhood diseases, *Mathematical Biosciences*, 100:201-240.

Greenhalgh, D. (1993) Existence, threshold and stability results for an age-structured epidemic model with vaccination and a non-separable transmission coefficient, *International Journal of Systems Science*, 24:641-688.

Greenhalgh, D. and Dietz, K. (1994) Some bounds on estimates for reproductive ratios derived from the age-specific force of infection, *Mathematical Biosciences*, 124:9-57.

Griffiths, D. (1974) A catalytic model of infection for measles, *Applied Statistics*, 23:330-339.

Gupta, N.K. and Rink, R.E. (1973) Optimum control of epidemics, *Mathematical Biosciences*, 18:383-396.

Hadeler, K.P. and Müller, J. (1996a) "Optimal vaccination patterns in age-structured populations I: the reproduction number ", in V. Isham and G.F. Medley (eds.) *Models for Infectious Human Diseases: Their Structure and Relation to Data*, Cambridge:Cambridge University Press.

Hadeler, K.P. and Müller, J. (1996b) "Optimal vaccination patterns in age-structured populations II: optimal strategies", in V. Isham and G.F. Medley (eds.) *Models for Infectious Human Diseases: Their Structure and Relation to Data*, Cambridge:Cambridge University Press.

Hethcote, H.W. (1988) Optimal ages of vaccination for measles, *Mathematical Biosciences*, 89:29-52.

Hethcote, H.W. (2000) The mathematics of infectious diseases, *SIAM Review*, 42:599-653.

Hethcote, H.W. and Waltman, P. (1973) Optimal vaccination schedules in a deterministic epidemic model, *Mathematical Biosciences*, 18:365-381.

Inaba, H. (1990) Threshold and stability results for an age-structured epidemic model with vaccination, *Journal of Mathematical Biology*, 28:411-434.

Inaba, H. (2007) Age-structured homogeneous epidemic systems with application to the MSEIR epidemic model, *Journal of Mathematical Biology*, 54:101-146.

Katzmann, W. and Dietz, K. (1984) Evaluation of age-specific vaccination strategies, *Theoretical Population Biology,* 25:125-137.

Kaya, C.Y. (2004) Time-optimal switching control for the US cocaine epidemic, *Socio-Economic Planning Sciences*, 38:57-72.

Kermack, W.O. and McKendrick, A.G. (1927) A contribution to the mathematical theory of epidemics, *Proceedings of the Royal Society Series A*, 115:700-721.

Knox, E.G. (1980) Strategy for rubella vaccination, *International Journal of Epidemiology*, 9:13-23.

Li, X.-Z. and Gupur, G. (2004) Global stability of an age-structured SIRS epidemic model with vaccination, *Discrete and Continuous Dynamical Systems – Series B*, 4:643-652.

Li, X.-Z., Gupur, G. and Zhu, G. (2001) Threshold and stability results for an age-structured SEIR epidemic model, *Applied Mathematics and Computation*, 42:883-907.

Louie, K., Roberts, M.G. and Wake, G.C. (1994) The regulation of an age-structured population by a fatal disease, *IMA Journal of Mathematics Applied in Medicine and Biology*, 11:229-244.

Morton, R. and Wickwire, K.H. (1974) On the optimal control of a deterministic epidemic, *Advances in Applied Probability*, 6:622-635.

Muench, H. (1934) Derivation of rates from summation data by the catalytic curve, *Journal of the American Statistical Association*, 29:25-38.

Müller, J. (1994) "Optimal vaccination patterns in age-structured populations", unpublished thesis, University of Tübingen, Germany.

Müller, J. (1998) Optimal vaccination patterns in age-structured populations, *SIAM Journal of Applied Mathematics*, 59:222-241.

Müller, J. (2000) Optimal vaccination patterns in age-structured populations: endemic case, *Mathematical and Computer Modelling*, 31:149-160.

Roberts, M.G. and Tobias, M.I. (2000) Predicting and preventing measles epidemics in New Zealand: application of a mathematical model, *Epidemiology and Infection*, 124:279-287.

Russell, C.A., Real, L.A. and Smith, D.L. (2006) Spatial control of rabies on heterogeneous landscapes. PLoS ONE 1(1): e27. Online. Available HTTP: <www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000027> (accessed 30 September 2008).

Schenzle, D. (1984) An age-structured model of pre- and post-vaccination measles transmission, *IMA Journal of Mathematics Applied in Medicine and Biology*, 1:169-191.

Sfikas, N. (1999) “Mathematical models for vaccination programs and statistical analysis of infectious diseases of humans”, unpublished thesis, University of Strathclyde.

Sfikas, N, Greenhalgh, D. and Lewis, F.I. (2007) The basic reproduction number and the vaccination coverage required to eliminate rubella from England and Wales, *Mathematical Population Studies*, 14:3-29.

Thieme, H.R. (2001) Disease extinction and disease persistence in age-structured epidemic models, *Nonlinear Analysis*, 47:6181-6194.

Tildesley, M.J., Savill, N.J., Shaw, D.J., Deardon, R. Brooks, S.P., Woolhouse, M.E.J., Grenfell, B.T. and Keeling, M.J. (2006) Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK, *Nature*, 440:83-86.

Weiss, G.H. (1965) On the spead of epidemics by carriers, *Biometrics*, 21:481-490.

Wickwire, K.H. (1975a) Optimal isolation policies for deterministic and stochastic epidemics, *Mathematical Biosciences*, 26:325-346.

Wickwire, K.H. (1975b) A note on the optimal control of carrier-borne epidemics, *Journal of Applied Probability*, 12:565-568.

Wickwire, K.H. (1976) Optimal control policies for reducing the maximum size of a closed epidemic, I, *Mathematical Biosciences*, 30:129-137.

Wickwire, K.H. (1977) Mathematical models for the control of pests and infectious diseases: a survey, *Theoretical Population Biology*, 11:182-238.

Wickwire, K.H. (1979) Optimal immunisation rules for an epidemic with recovery, *Journal of Optimization Theory and Applications*, 27:549-570.