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A Statistical Method for Modelling Hepatitis A Vaccination in Bulgaria

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Abstract: - In this paper we examine an age-structured partial differential equation compartmental model to predict minimal vaccination strategies to eliminate hepatitis A in Bulgaria. We describe the mathematical model and briefly summarise previous theoretical results. The basic reproduction number is a key parameter of the model. We consider proportional, assortative and symmetric mixing. Using pre-hepatitis A vaccination Bulgarian age-serological data we derive estimates for the basic reproduction number and minimum proportions of susceptibles to be vaccinated to eliminate hepatitis A in Bulgaria using single and double stage vaccination campaigns. 95 percentile confidence intervals are also given.

Key-Words: - Hepatitis A, partial differential equations, basic reproduction number, mixing, vaccination, bootstrap method.

1 Introduction

This paper is concerned with mathematical modelling of vaccination programs against hepatitis A using age-structured serological data for hepatitis A in Bulgaria. A mathematical and statistical modelling method is used to evaluate minimum elimination vaccination proportions and bootstrap 95 percentile intervals for them using single stage and double stage vaccination campaigns. A similar method is used to examine rubella vaccination in the UK in [1]. More recently Farrington, Kanaan and Gay [2] review methods of estimation of R_0 from age-structured serological survey data.

Newborn children are born protected from hepatitis A by maternal antibodies but after this wears off they will be susceptible to hepatitis A. At some stage they catch the disease and after an infectious period they become permanently immune. In developing countries adults are usually immune and epidemics of hepatitis A are uncommon. However improved sanitation in many parts of the world is leaving many young adults susceptible, and outbreaks are increasing. In developed countries, disease transmission is frequent in day-care centres enrolling diapered children, in household and sexual contacts of acute cases, intravenous drug abusers and travellers to countries where disease is endemic [3].

Hepatitis A is spread person to person by the faecal-oral route. The infectious agent is found in faeces, reaching peak levels the week or two before the onset of symptoms, and diminishing rapidly after liver dysfunction or symptoms appear, which is concurrent with the appearance of circulating antibodies to hepatitis A virus. Direct transmission occurs amongst male homosexuals. Common source outbreaks have been related to contaminated water and food contaminated by infected foodhandlers.

2 Mathematical Model

The basic mathematical model used is a compartmental partial differential equation model, originally due to Dietz and Schenzle [4]. $x(a,t)$ denotes the density with respect to age of the number of susceptible individuals of time t. Thus the total number of susceptible individuals between ages A_1 and A_2 is

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

Similarly $y(a,t,c)$ denotes the density with respect to age a and duration of infectiousness c of the number of infecteds at time t. Thus the total number of infected individuals between ages A_1 and A_2 and durations of infectiousness c_1 and c_2 at time t is

$$\int_{A_1}^{A_2}\int_{c_1}^{c_2} y(a,t,c)dcda.$$

The spread of the disease is described by the following partial differential equations:

$$\frac{\partial x}{\partial a}+\frac{\partial x}{\partial t}=-\left[\lambda(a,t)+\varphi(a)+\mu(a)\right]x(a,t), \quad (1)$$

and

$$\frac{\partial y}{\partial a}+\frac{\partial y}{\partial t}+\frac{\partial y}{\partial c}=-\left[y(c)+\mu(a)\right]y(a,t,c), \quad (2)$$

where $x(0,t) = v$, $y(0,t,c) = 0$, and $y(a,t,0) = \lambda(a,t)x(a,t)$. Here

$\varphi(a)$ = per capita vaccination rate of susceptibles of age a;

$\mu(a)$ = per capita death rate of individuals of age a;

N = the total population size;

v = the total birth rate;

$\gamma(c)$ = the rate at which an infectious individual who has had the disease for time c becomes immune;

and

$\frac{\kappa b(a,a')}{N}$ = total rate at which an infected individual of age a' transmits the infection to a susceptible of age a.

These equations are explained by Dietz and Schenzle [4]. Usually $\kappa b(a,a')/N$ is given by a matrix $\{\beta_{ij} : i,j = 1,2, \ldots n\}$ on n age classes called the 'who-acquires–infection–from-whom' (WAIFW) matrix. In this paper we examine proportional, assortative and symmetric mixing. Proportional mixing is when $\beta_{ij} = b_i b_j$ for some $b_1, b_2, \ldots b_n$. Assortative mixing is when individuals mix only with their own age group so $\beta_{ij} = 0$ for $i \neq j$. Symmetric mixing is when $\beta_{ij} = \beta_{ji}$ for $i,j = 1,2, \ldots,n$. Due to lack of space we do not look at homogeneous mixing which is examined in [5].

$$\pi(a)=\exp\left\{-\int_0^a \mu(\xi)d\xi\right\} \quad (3)$$

is the fraction of individuals surviving to age a. The model assumes a constant population size. If L is the maximum lifetime births must balance deaths so

$$N = v\int_0^L \pi(a)da. \quad (4)$$

$\lambda(a,t)$ is the 'force of infection' suffered by individuals of age a at time t. This is given by

$$\frac{\kappa}{N}\int_0^L\int_0^{a'} b(a,a')f(c)y(a',t,c)dcda'.$$

Here $f(c)$ denotes the probability that an individual who has been infected for time c is still infectious.

If $\varphi(a)$ is an age-dependent vaccination campaign R_φ is the basic reproduction number when φ is used. This is the expected number of secondary cases caused by a single infected case entering a disease-free population at equilibrium. We expect that the vaccination campaign φ will eradicate hepatitis A if $R_\varphi < 1$ but not if $R_\varphi > 1$. For an age-structured model R_φ is given as the spectral radius of an age-structured matrix [6].

We use age-structured pre-hepatitis A vaccination serological data from 850 school-children and blood donors in Bulgaria, collected by Professor G. Frösner, Munich and published by Keiding [7]. We use Keiding's non-parametric maximum likelihood method to estimate $\lambda_0(a)$, the age-dependent force of infection in the absence of vaccination. We smooth the estimate using the Epanechnikov kernel. The tail problems are handled as in [6] by using a truncated Epanechnikov kernel.

A variable kernel smoothing bandwidth was used of 5 years up to age 15 years and 15 years at older ages. As a larger number of cases occur at younger ages and fewer cases occur at larger ages it is sensible to use a smaller bandwidth at smaller ages and a larger bandwidth at larger

ages to ensure more even percentile confidence intervals.

The matrix β_{ij} is then estimated using the equations (1)-(2) at equilibrium and mortality data for Bulgaria taken from [8]. For symmetric mixing this results in n^2 equations in n unknowns. Assumptions are made about the form of the WAIFW matrix to reduce the number of unknowns to n. Sometimes these assumptions result in infeasible negative elements of the WAIFW matrix. If so we must go back and examine other possible assumptions on the matrix $\{\beta_{ij}\}$ to find feasible ones. Then for a given mixing assumption and proposed vaccination campaign $\varphi(a)$, R_φ is calculated using formulae given in [1] and [6].

For proportional mixing

$$R_\varphi = \frac{\int_0^L \hat{\lambda}_0^2(\xi) e^{-\Phi(\xi)-M(\xi)} d\xi}{\int_0^L \hat{\lambda}_0^2(\xi) e^{-\hat{\Lambda}_0(\xi)-M(\xi)} d\xi}. \quad (5)$$

Here $\hat{\lambda}_0(\xi)$ is the estimated force of infection in the absence of vaccination and

$$\hat{\Lambda}_0(\xi) = \int_0^\xi \hat{\lambda}_0(u) du. \quad (6)$$

For proportional mixing the results do not depend on the age class division used.

For assortative or symmetric mixing R_φ is the spectral radius of the nxn matrix

$$\hat{\beta}_{\varphi,ij} = \hat{\beta}_{ij} \frac{\kappa v D}{N} A_j^*(\varphi) \qquad i, j = 1,2,...n \quad (7)$$

where

$$A_i^*(\varphi) = \int_{I_i} \exp[-\Phi(\xi) - M(\xi)] d\xi, \quad (8)$$

I_i is the i'th age interval and if τ is the length of the infectious period,

$$D = \int_0^\tau f(c) dc. \quad (9)$$

D is the length of the infectious period weighted by the infectiousness $f(c)$.

For assortative and proportional mixing two age class divisions were used:

(A) 0-5, 6-15, 16-35, and 36-87 years,

representing pre-school children, schoolchildren, younger adults and older adults respectively, and

(B) 0-15, 16-20, 21-35 and 36-87 years,

representing children, older teenagers, young adults and older adults respectively.

3 Method

We can use this method to estimate statistics of interest. A critical elimination vaccination program is one which reduces R_φ to one. We are particularly interested in R_0, the basic reproduction number in the absence of vaccination and p_c, the minimum critical immunisation proportion of newborns necessary to be vaccinated to eliminate the disease. Single stage and double stage vaccination campaigns which target children at a given age and two given ages respectively are of special interest as these are often used in practice. We are interested in estimating $p_c(a)$, the proportion of children (or adults) who must be vaccinated, using a single stage vaccination program with vaccination at age a, in order to eradicate hepatitis A in Bulgaria and $p_1(A_1)$ and $p_2(A_2)$, the critical proportions of children (or adults) who must be vaccinated in order to eradicate hepatitis A in Bulgaria using a double stage vaccination program with vaccinations at ages A_1 and A_2. It is straightforward to use the bootstrap resampling method to estimate percentile confidence intervals for these quantities. Further details are given in [1] and [5].

4 Results

For symmetric mixing we considered the following five symmetric mixing matrices:

Matrix A

$$\begin{pmatrix} \beta_1 & \beta_1 & \beta_3 & \beta_4 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 \\ \beta_3 & \beta_3 & \beta_3 & \beta_4 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 \end{pmatrix},$$

Matrix B

$$\begin{pmatrix} \beta_1 & \beta_2 & \beta_3 & \beta_2 \\ \beta_2 & \beta_2 & \beta_2 & \beta_2 \\ \beta_3 & \beta_2 & \beta_4 & \beta_4 \\ \beta_2 & \beta_2 & \beta_4 & \beta_4 \end{pmatrix},$$

Matrix C

$$\begin{pmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_4 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 \\ \beta_1 & \beta_3 & \beta_3 & \beta_4 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 \end{pmatrix},$$

Matrix D

$$\begin{pmatrix} \beta_1 & \beta_1 & \beta_1 & \beta_1 \\ \beta_1 & \beta_2 & \beta_2 & \beta_2 \\ \beta_1 & \beta_2 & \beta_3 & \beta_4 \\ \beta_1 & \beta_2 & \beta_4 & \beta_4 \end{pmatrix},$$

and Matrix E

$$\begin{pmatrix} \beta_1 & \beta_4 & \beta_4 & \beta_4 \\ \beta_4 & \beta_2 & \beta_4 & \beta_4 \\ \beta_4 & \beta_4 & \beta_3 & \beta_4 \\ \beta_4 & \beta_4 & \beta_4 & \beta_4 \end{pmatrix}.$$

Of these only configurations C and D gave feasible results and the results for C and D were very similar. Because of space limitations we present the results only for matrix configuration D.

Mixing Assumption	Age Class Division	R_0	95 P.C.I.
Prop.		5.00	(3.87,6.93)
Assort.	A	9.97	(7.08,16.93)
Assort.	B	9.38	(6.16,16.99)
Symm.	A	3.40	(1.77,10.65)
Symm.	B	3.93	(2.80,6.73)

Table 1. Estimates of R_0 and associated 95 P.C.I. for different mixing assumptions (proportional, assortative and symmetric) and age class divisions.

Table 1 gives the values of R_0 and associated 95 percentile confidence interval (P.C.I.) for the different mixing assumptions used. For assortative and symmetric mixing the results depend upon the age class division used so two results are given, one for age class division A and one for age class division B.

The values of p_c, the minimum elimination vaccination proportions under different mixing assumptions, assuming vaccination at birth are given in Table 2.

Mixing Assumption	Age Class Division	p_c	95 P.C.I.
Prop.		0.80	(0.74,0.86)
Assort.	A	0.90	(0.86,0.94)
Assort.	B	0.89	(0.84,0.94)
Symm.	A	0.70	(0.44,0.91)
Symm.	B	0.75	(0.65,0.85)

Table 2. Estimates of p_c and associated 95 P.C.I. for different mixing assumptions and age class divisions.

A_0, the maximum age of vaccination at which hepatitis A can be eliminated using a single stage vaccination campaign was also calculated under the different mixing assumptions, but this time the 95 P.C.I.'s were not calculated. The results are given in Table 3.

Mixing Assumption	Age Class Division	A_0
Prop.		14.01
Assort.	A	5.21
Assort.	B	5.71
Symm.	A	22.32
Symm.	B	19.28

Table 3. Estimates of A_0 for different mixing assumptions and age class divisions.

The solid line in Fig. 1a shows the estimated minimum steady-state critical vaccination proportion $p_c(a)$ of susceptible individuals of age a who must be immunised to eliminate hepatitis A in Bulgaria under proportional mixing. Thus a steady state single stage vaccination strategy with vaccination of susceptibles of age a is used. The associated 95 P.C.I. is also given (the dashed lines). Figs 1b and 1c show the corresponding minimum steady state critical vaccination proportions under assortative and symmetric mixing respectively.

The solid line in Fig. 2a shows the estimated minimum steady state critical vaccination proportion p_2 of susceptibles of age $A_2 = 5$ years who must be successfully immunised together with a steady state proportion p_1 of

susceptibles of age $A_1 = 2$ years to eliminate hepatitis A in Bulgaria under proportional mixing. Thus a steady state two stage vaccination strategy with vaccination of susceptibles at ages A_1 and A_2 is used. Again the dashed lines show the associated 95 P.C.I. Fig. 2b and Fig. 2c are the corresponding figures for assortative and symmetric mixing.

a)

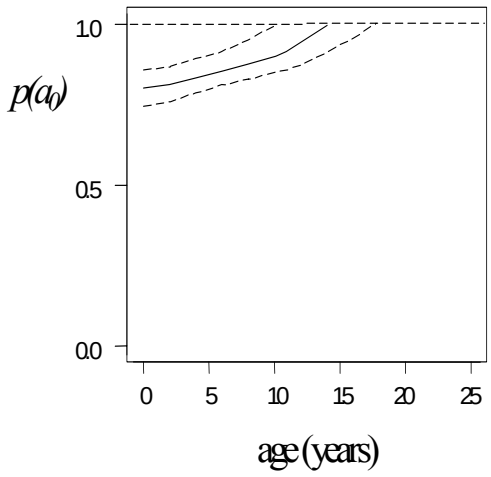

Fig. 1a Estimated minimum elimination vaccination proportion (solid line) and 95 P.C.I. (dashed lines) assuming vaccination of a proportion $p_c(a)$ of susceptibles of age a: proportional mixing.

b)

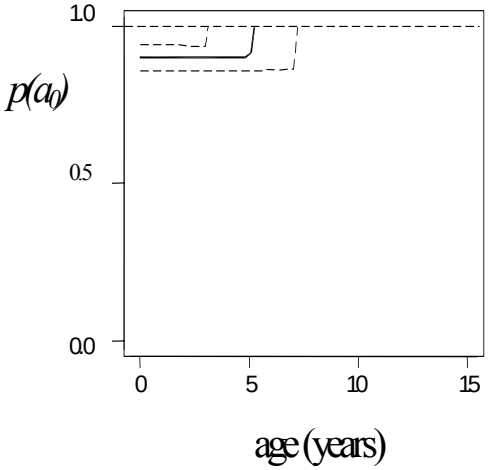

Fig. 1b Estimated minimum elimination vaccination proportion (solid line) and 95 P.C.I. (dashed lines) assuming vaccination of a proportion $p_c(a)$ of susceptibles of age a: assortative mixing.

c)

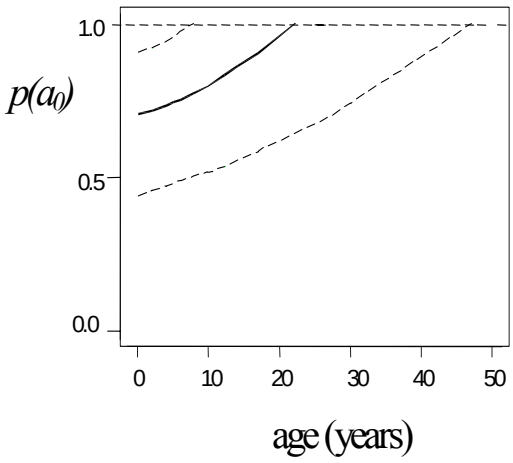

Fig. 1c Estimated minimum elimination vaccination proportion (solid line) and 95 P.C.I. (dashed lines) assuming vaccination of a proportion $p_c(a)$ at a fixed age a: symmetric mixing.

a)

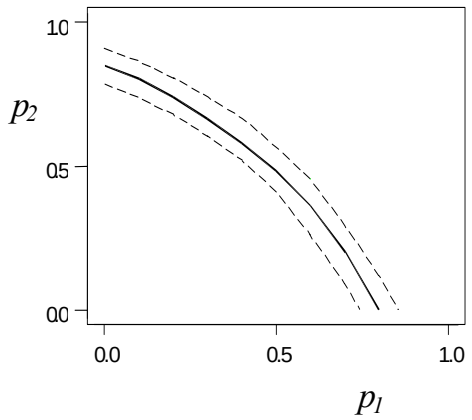

Fig. 2a. Estimated minimum elimination vaccination proportion p_2 at the age of $A_2 = 5$ years and 95 P.C.I. (dashed lines) when a proportion p_1 of susceptibles were vaccinated at age $A_2 = 2$ years: proportional mixing.

b)

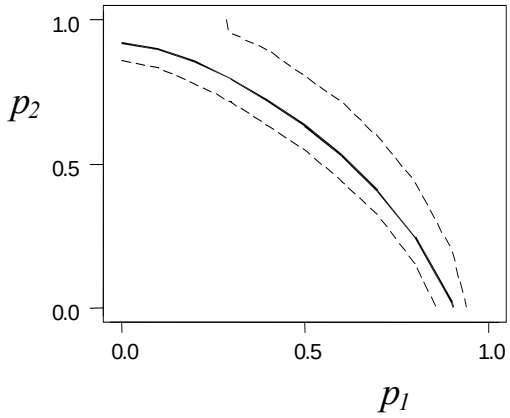

Fig. 2b. Estimated minimum elimination vaccination proportion p_2 at the age of $A_2 = 5$ years and 95 P.C.I. (dashed lines) when a proportion p_1 of susceptibles were vaccinated at age $A_2 = 2$ years: assortative mixing.

c)

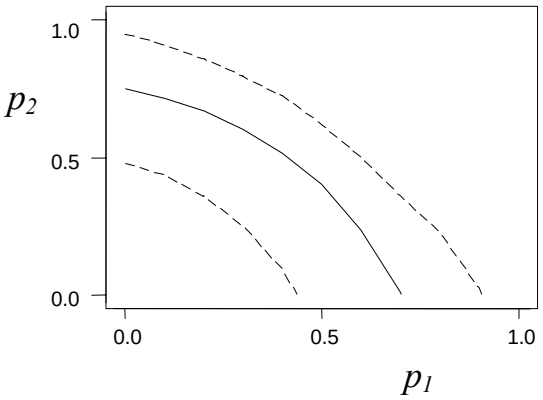

Fig. 2c. Estimated minimum elimination vaccination proportion p_2 at the age of $A_2 = 5$ years and 95 P.C.I. (dashed lines) when a proportion p_1 of susceptibles were vaccinated at age $A_2 = 2$ years: symmetric mixing.

5 Summary and Conclusions

In this paper we have used a mathematical method to examine minimum elimination vaccination strategies for hepatitis A in Bulgaria. 95 percentile confidence intervals were also given. Both R_0 and the minimum elimination vaccination proportions were much higher for assortative than symmetric or proportional mixing, but assortative mixing has been shown to be always the worst mixing assumption [3]. Our most realistic estimate is perhaps symmetric mixing with age class division A, which gives R_0 as 3.40 (95 P.C.I. 1.77 to 10.65) and p_c as 0.70 (95 P.C.I. 0.44 to 0.91).

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