m*umps, immunization, R_0, one stage vaccination policy, two stage vaccination policy.*

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VACCINATION PROGRAMS AGAINST MUMPS IN THE UNITED KINGDOM

This paper deals with minimum elimination vaccination programs for mumps in the UK. A partial differential equation compartmental model is used to describe the spread of the disease. Pre-vaccination age-structured serological data is used to estimate the force of infection in the absence of immunization. Homogeneous, proportional and symmetric mixing are considered. Using the equilibrium equations, for each mixing assumption estimates of the basic reproduction number R_0 and the minimum elimination immunization proportions for single age and two age vaccination programs are presented.

1. INTRODUCTION

Mumps is an acute viral disease characterized by fever, swelling and tenderness of one or more salivary glands, usually the parotid and sometimes the sublingual or sub maxillary glands. Orchitis, which is inflammation of the testicles characterized by pain and a sensation of weight, usually unilateral, occurs in 20-30% of post pubertal males and oophoritis (inflammation affecting an ovary) in about 5% of females after puberty, sterility is an extremely rare sequel. Mumps is recognized less regularly than other common diseases of childhood, such as measles and chicken-pox, although serological studies show that in the absence of immunization more than 85% of people will have had mumps by the time that they reach adulthood. About one-third of exposed susceptible persons have in apparent infections. Most cases in children less than two years of age are sub clinical. The majority of infections occur in winter and spring [2].

Mumps is spread by direct contact with the saliva of an infectious person and by droplet spread. The incubation period is about 12 to 25, commonly 18, days. The virus has been isolated from saliva from 6 to 7 days before overt parotitis to up to 9 days after, exposed non-immune persons should be considered as infectious from the 12'th to the 25'th day after exposure. Maximum infectiousness occurs about 48 hours before the onset of illness [2]. Susceptibility is general. Immunity is generally lifelong and develops after in apparent as well as clinical infection. To the best of our knowledge the strength of immunity developed is the same after in apparent as after clinical infection and our models will assume this. Most adults, particularly those born before 1957, are likely to have been infected naturally and may be considered immune even if they did not have recognized disease. Live attenuated vaccine is available either as a single vaccine, or in

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combination with rubella and measles live virus vaccines (MMR). At the moment mumps is an endemic disease in the UK with generally small seasonal outbreaks [8].

2. MATHEMATICAL MODEL

Recall that mumps is not recognized as consistently as other common childhood diseases. Consequently case notifications are not very reliable and should not be used. The way in which the incidence of serious symptoms of the disease change with age can affect the accuracy of case report notification. Generally speaking for most childhood diseases there is under-reporting of cases, especially at larger ages and this strengthens the decision not to use case report notifications as data for our model. If an infant or young child has a mild dose of infection they are more likely to be taken to see a doctor than school-age children or adults who have daytime commitments.

Farrington [4] gives a large sample of age-structured serological data for mumps. This serological data was collected in five public health laboratories (Ashford, Bristol, Leeds, Manchester and Preston). Serum samples from 8,924 persons aged 1 to 99 were tested for antibodies to measles, mumps and rubella. Serological status, age and sex were recorded for each person. The samples were obtained from residues of specimens submitted for routine diagnostic examination. An updated version of this data is used for the estimation of the age-dependent force of infection in the absence of vaccination $\lambda_0(a)$. This improved version was sent to us by Farrington [5] and is shown in Table 1. In the improved dataset the samples had been retested in order to eliminate the inaccuracies in the original dataset. The methods used are based on Keiding's non-parametric model [9] rather than Farrington's parametric model [4] for the force of infection. In our basic age-structured model for the spread of disease the population amongst whom the infection spreads is divided into classes of susceptible, infected and immune individuals. Every individual is born into the susceptible class. At some stage he or she catches the infection and passes through a short infectious period before becoming permanently immune.

Since we consider that the problem is age-structured, partial differential equations must be used to describe the spread of the disease. Let $x(t,a)$ denote the density with respect to age of the number of susceptible at time t. This means that

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

is the actual number of susceptible individuals between ages A_1 and A_2 at time t. Similarly let $y(t,a,c)$ denote the density with respect to age a, and elapsed time since infection, c, of the number of infected individuals at time t.

Tab.1. Age-serological data: Age of individuals, number tested at that age and number seropositive at that age (Farrington, [5]).

AGE (YEARS)	NUMBER TESTED	SERO-POSITIVE	AGE (YEARS)	NUMBER TESTED	SERO-POSITIVE
1	407	47	50	33	29
2	292	43	51	24	23
3	332	129	52	29	26
4	368	189	53	20	19
5	421	276	54	25	21
6	330	245	55	23	21
7	292	231	56	29	25
8	257	206	57	19	18
9	312	271	58	31	29
10	304	260	59	17	14
11	282	239	60	12	10
12	320	281	61	9	8
13	313	280	62	18	16
14	366	323	63	16	15
15	116	104	64	12	12
16	121	102	65	21	20
17	148	135	66	21	20
18	196	173	67	9	8
19	210	190	68	9	8
20	159	147	69	13	13
21	160	146	70	9	7
22	204	188	71	13	12
23	170	155	72	7	6
24	170	155	73	13	13
25	180	176	74	12	10
26	177	164	75	11	9
27	179	168	76	19	15
28	150	131	77	7	6
29	147	129	78	8	6
30	120	104	79	8	7
31	122	108	80	13	9
32	104	91	81	13	10
33	95	89	82	10	7
34	82	73	83	7	5
35	78	71	84	6	5
36	67	63	85	8	5
37	65	58	86	3	3
38	72	59	87	7	6
39	47	46	88	1	1
40	62	59	89	1	0
41	55	53	90	1	1
42	43	41	91	2	2
43	37	34	92	0	0
44	40	35	93	0	0
45	45	40	94	1	1
46	33	31	95	2	1
47	32	30	96	0	0
48	30	28	97	0	0
49	38	37	98	1	1
			99	1	0

This means that the actual number of infected individuals between ages A_1 and A_2 with elapsed times since infection between C_1 and C_2 at time t is

$$\int_{A_1}^{A_2}\int_{C_1}^{C_2} y(t,a,c)dadc.$$

Also $\lambda(t,a)$ denotes the force of infection which depends on the time t and the age a of the susceptible individual.

If we assume that the contact rate (more accurately the contact rate pertaining to potential infection transmission) $\beta(a,a')$ between a susceptible of age a and an infective of age a' is of the form $\kappa b(a,a')/N$ where N is the total population size and κ denotes an average contact rate, then the partial differential equations which describe the spread of the disease are:

$$\frac{\partial x}{\partial a}+\frac{\partial x}{\partial t}=-[\lambda(t,a)+\phi(a)+\mu(a)]x(t,a) \qquad (1)$$

and

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

where $\varphi(a)$, $\gamma(c)$ and $\mu(a)$ denote respectively, the age-dependent vaccination rate, the rate at which an individual who has been infectious for time c becomes immune and the age-dependent death rate. The boundary conditions for these equations are

$$x(t,0) = \nu,\ y(t,0,c) = 0 \text{ and } y(t,a,0) = \lambda(t,a)x(t,a).$$

Let $f(c)$ denote the probability that an individual who has had the disease for time c is still infectious. Then $\lambda(t,a)$ is given by the equation

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

L is life expectancy at birth and the model assumes that individuals live up to age L and then die at this fixed age. Here ν is the total birth rate which is assumed to be constant. The model is explained further in [3] and used to evaluate UK rubella vaccination programs in [7]. Similar models are discussed in [1].

We divided the population into four age classes roughly corresponding to pre-school children, young schoolchildren, elder schoolchildren and adults. After that we estimated the basic reproduction number R_0 for the different mixing assumptions and the possible divisions of the population into age classes. When estimating the elimination vaccination proportions we simply set $R_\varphi = 1$, since this is the critical value of R_φ which must be exceeded for the disease to persist in the population. These proportions depend on the age at which susceptible individuals are vaccinated, the vaccine efficacy and whether a one stage or two stage vaccination campaign is used. A one stage vaccination campaign means that we are continuously vaccinating a constant proportion φ of the population at a fixed age a. A two stage vaccination campaign means that we vaccinate a

proportion φ_1 at age A_1 and a proportion φ_2 at age A_2. We shall examine both cases since both one and two stage vaccination campaigns are commonly used [6].

The age-dependent force of infection $\lambda_0(a)$ in the absence of vaccination was estimated by Keiding's non-parametric likelihood method. A problem which arises is the fact that our data are discrete points and so they produce a discrete probability distribution whereas we need to have a smooth density in order to differentiate it and so estimate the pre-vaccination force of infection. A smoothing technique needs to be introduced to overcome this problem. Greenhalgh and Dietz [6], Keiding [9] and Groeneboom (discussion of [9]) also deal with this issue. As many cases of the disease occur in childhood and far fewer in adults it is desirable to use a variable bandwidth small at small ages, but large for larger ages. We experimented with several bandwidths and chose 5 years up to the age of 15 years and 15 years thereafter which appeared to be the best. The age-dependent death rate $\mu(a)$ was estimated from data taken from Preston, Keyfitz and Schoen [10].

3. NUMERICAL RESULTS

3.1. HOMOGENEOUS MIXING

Homogeneous mixing means that $\beta(a,a') = \beta$, independent of a and a'. Although homogeneous mixing does not represent the real situation of how mumps spreads it is still useful to have some results for homogeneous mixing, in order to compare them with the results from other mixing assumptions. Table 2 gives some indicative values of the basic reproduction number R_0 when we use different variable bandwidths.

Tab.2. Estimated value of R_0 for variable bandwidths used.

Case	b_1 (years)	b_2 (years)	Age of division	$\hat{R}_0$
A	1	15	15	5.534
B	5	15	15	5.018
C	5	15	25	4.845

R_ϕ is estimated using the formula

$$R_\phi = \frac{\int_0^L e^{-\Phi(\xi)-M(\xi)}d\xi}{\int_0^L e^{-\bar{\lambda}_0\xi-M(\xi)}d\xi},$$

where $\Phi(\xi)=\int_0^\xi \phi(u)du$ and $M(\xi)=\int_0^\xi \mu(u)du$ [6]. $\bar{\lambda}_0$ is the mean pre-vaccination force of infection in $[0,L]$. To estimate R_0 we set $\varphi = 0$. We can use R_φ to estimate the minimum elimination vaccination proportions for mumps in the UK using a one stage and a two stage vaccination strategy. The results are shown in Figure 1. For the two stage strategy we take the ages A_1 = 2 years

and A_2 = 5 years. A_1 = 2 years is good as individuals are not then protected by maternal antibodies and A_2 = 5 years as children start school then and so it is easy to vaccinate at this age.

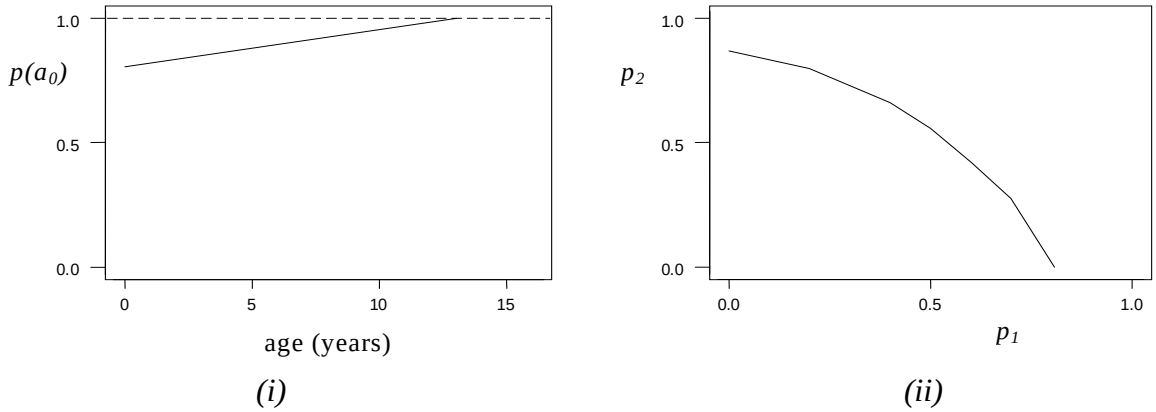


Fig.1. Variable bandwidth Case B. Estimated minimum coverage proportions: *(i)* $p(a_0)$ assuming vaccination at a fixed age a_0, *(ii)* p_2 at age A_2 = 5 years given a coverage p_1 at age A_1 = 2 years.

3.2. PROPORTIONAL MIXING

A commonly used mixing assumption is proportional mixing. This means that $\beta(a,a') = \beta_i\beta_j$ for $a \in I_i$ and $a' \in I_j$. Table 3 gives some indicative values of R_0 with different variable bandwidths.

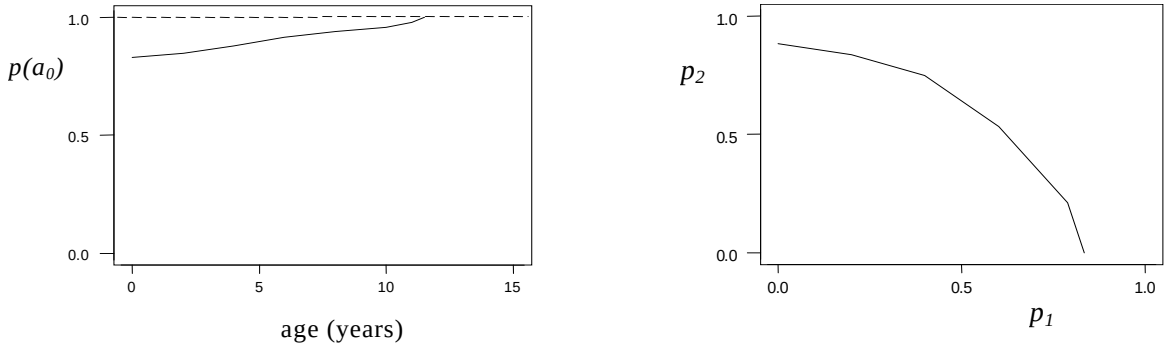
Tab.3. Estimated value of R_0 for bandwidths used.

Case	b_1 (years)	b_2 (years)	Age of division	$\hat{R}_0$
A	5	15	25	5.412
B	5	15	15	5.733
C	10	15	15	5.235

This time R_ϕ is estimated using the equation

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

$\hat{\lambda}_0(\xi)$ is the estimated pre-vaccination force of infection and $\hat{\Lambda}_0(\xi) = \int_0^\xi \hat{\lambda}_0(u)du$. In Figure 2 we present the minimum eradication coverage proportions for bandwidth Case B for a one stage and a two stage vaccination campaign respectively.



(i) *(ii)*

Fig.2. Variable bandwidth Case B. Estimated minimum coverage proportions: *(i)* $p(a_0)$ assuming vaccination at a fixed age a_0, *(ii)* p_2 at age $A_2 = 5$ years given a coverage p_1 at age $A_1 = 2$ years.

3.3. SYMMETRIC MIXING

Symmetric mixing means that $\beta(a,a') = \beta(a',a)$ for all a and a'. If we have n age classes I_1, I_2, … I_n then $\beta(a,a')$ is given by an nxn matrix $\beta(a,a') = \beta_{ij}$ for $a \in I_i$ and $a' \in I_j$. (β_{ij}) is called the who-acquires-infection-from-whom (WAIFW) matrix. Symmetric mixing means that $\beta_{ij} = \beta_{ji}$ for all i and j. In general we estimate β_{ij} from the equilibrium equations for the spread of disease before immunization. This gives n equations in n^2 unknowns so we make some assumptions about the elements of the WAIFW matrix to reduce the number of unknowns to n. This choice is usually justified on social or biological grounds. We look at the following 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

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

Matrix E

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

If we define

$$A_i^*(\phi) = \int_{I_i} e^{-\Phi(\xi) - M(\xi)} d\xi ,$$

then R_ϕ is the spectral radius of the nxn matrix $(\hat{\beta}_{\phi,ij})$ where

$$\hat{\beta}_{\phi,ij} = \beta_{ij} \frac{\kappa \nu D}{N} A_j^*(\phi).$$

Table 4 gives values of R_0 for three different age class divisions and bandwidth Case B (5 years up to age 15 years and then 15 years thereafter).

Tab.4. Value of the basic reproduction number for different age divisions and for the different configurations of the WAIFW matrix.

	Matrix				
Age Division	A	B	C	D	E
0-4, 5-10, 11-15, 16-99	4.876	4.773	xxxxx	4.525	xxxxx
0-4, 5- 9, 10-15, 16-99	4.877	4.775	xxxxx	4.365	xxxxx
0-3, 4- 6, 7 -10, 11-99	4.609	4.609	xxxxx	xxxxx	xxxxx

In the table a 'xxxxx' means that the given mixing matrix and age class division was infeasible and gave a negative estimate for one of the β_{ij} terms. Again we can use the formula for R_ϕ to estimate the minimum elimination vaccination proportions for mumps in the UK using a one stage and a two stage vaccination strategy. The results for Matrix B with a variable bandwidth b_1 = 5 years up to age 15 years and b_2 = 15 years thereafter with age division 0-5, 6-10, 11-15 and 16-99 are shown in Figure 3.

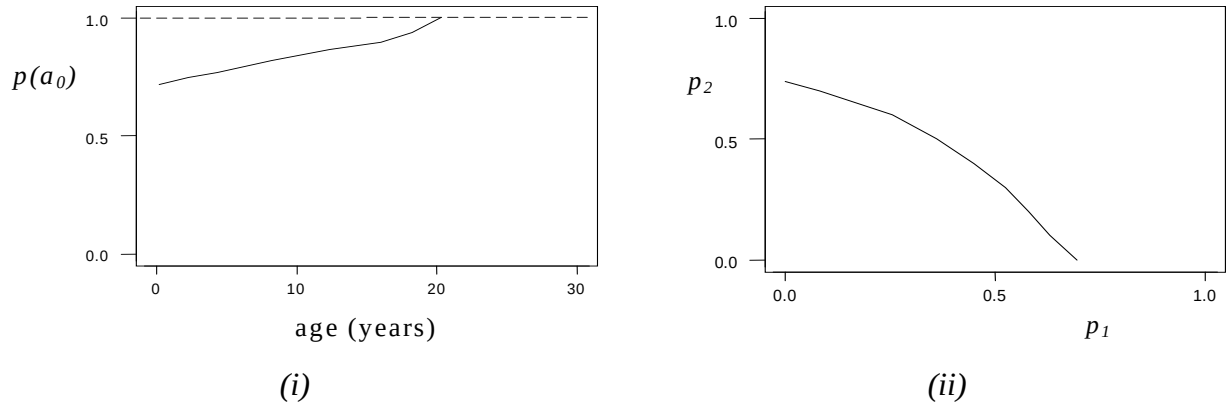


Fig.3. Estimated minimum coverage proportions: *(i)* $p(a_0)$ assuming vaccination at a fixed age a_0, *(ii)* p_2 at age A_2=5 years given a coverage p_1 at age A_1 = 2 years.

4. SUMMARY AND CONCLUSIONS

In this paper we have discussed critical elimination immunization programs for mumps in the UK. We described a compartmental mathematical model based on partial differential equations. Age-structured serological data was used to estimate the pre-vaccination force of infection. The equilibrium versions of the partial differential equations were used to estimate R_ϕ, the reproduction number with constant vaccination program ϕ, under homogeneous, proportional and symmetric mixing assumptions. For each mixing assumption illustrative values for R_0, the basic reproduction number with no immunization, and the minimum elimination vaccination proportions for one stage

and two stage immunization policies were estimated. For symmetric mixing further assumptions about the form of the mixing matrix were needed. These results can help us plan and evaluate the practical problem of eradicating mumps in the UK by vaccination.

BIBLIOGRAPHY

[1] ANDERSON, R.M. and MAY, R.M., Infectious diseases of humans: dynamics and control, Oxford University Press, Oxford, 1991.
[2] BENENSON, A.S., Control of communicable diseases in man, Sixteenth Edition, American Public Health Association, Washington D.C., 1990.
[3] DIETZ, K. and SCHENZLE, D., Proportionate mixing for age-dependent disease transmission, Journal of Mathematical Biology, Vol. 22, pp.117-120, 1985.
[4] FARRINGTON, C.P., Modelling forces of infection for measles, mumps and rubella, Statistics in Medicine, Vol. 9, pp.953-967, 1990.
[5] FARRINGTON, C.P., Private Communication, 1995.
[6] GREENHALGH, D. and DIETZ, K., Some bounds on estimates for reproductive ratios derived from the age-specific force of infection. Mathematical Biosciences, Vol. 124, pp.9-57, 1994.
[7] GREENHALGH, D. and SFIKAS, N., Mathematical modelling of UK rubella vaccination programs. Journal of Medical Informatics and Technologies, Vol. 3, pp.MI-3-MI-11, 2002.
[8] GOVERNMENT STATISTICAL SERVICE, OPCS Monitor: Infectious diseases, 1992, MB2 93, 1993.
[9] KEIDING, N., Age-specific incidence and prevalence: a statistical perspective, Journal of the Royal Statistical Society, Series A, Vol. 154, pp.371-412, 1991.
[10] PRESTON, S.H., KEYFITZ, N. and SCHOEN, R., Causes of Death, Lifetables for National Populations. Studies in Population Series, Seminar Press, London/New York, 1972.