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Infectious diseases: epidemiology, mathematical models and immunization policies

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Foreword

The present report collects several materials on the transmission dynamics of HBV discussed while J.R. Williams was visiting the Department of Statistics and Applied Mathematics of the University of Pisa during July 1996.

It collects also materials from recent research experience of J.R. Williams on the transmission dynamics of measles and the problem of the eradication of measles virus on a world scale, which were the object of a seminar held at the Department of Statistics and Applied Mathematics in the same period.

HBV: mathematical models

P. Manfredi, J.R. Williams, F. Tarini, A. Carducci

Abstract

In this paper several mathematical models for the transmission dynamics of HBV are discussed. In the first part of the paper the emphasis is posed on highly stylized properties of carrier models (possibly the more relevant feature of HBV), by working on basically simple, and so tractable, mathematical formulations. Our interest is essentially on the form of the specific threshold criteria. Viceversa in the second part we discuss some relevant "realistic" HBV model appeared in the literature, namely the "old WHO" model and the CEID model.

HBV: mathematical models

1. Mathematical models for HBV: introduction

The following flow diagram, which represents the sequence of stages characterizing the individual behaviour in HBV (in absence of vaccination), constitute the starting point for the mathematical modelling of the disease.

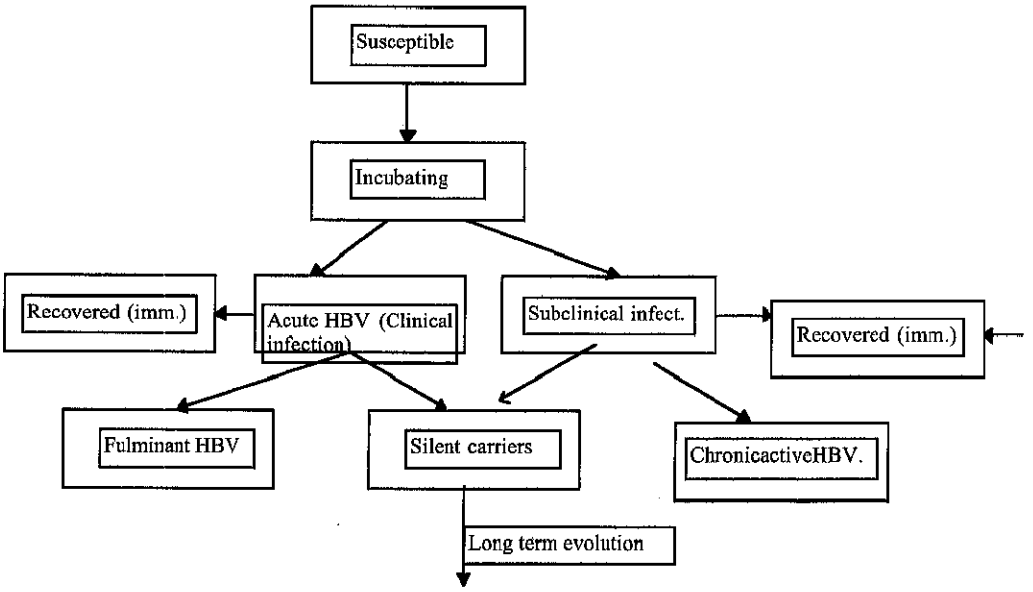


Fig. 1: flow diagram of possible individual states in HBV

The high degree of epidemiological complexity of HBV makes it particularly difficult to picture its fundamental features by means of a simple and clear-cut mathematical representation. Among these features there are:

a)coexistence of practically all routes of transmission, from sexual and IVU transmission (with connected problems of heterogeneities in social behaviours plus inhomogenous mixing) to environmental risk (horizontal transmission between individuals in absence of sexual contacts), vertical transmission, transmission via parenteral exposure to contaminated blood products, and so on

b) coexistence with the acute "infectors" of silent source of infections, such as "subclinical" HBV and (silent) carrier states

c)age dependent force of infection (fundamentally as a consequence of age-dependent contact patterns).

d)age-dependent probabilities of developing the state of chronic carriage

f)(long term) disease induced mortality for carriers due to the previously mentioned complications and so on. These characteristics have been embodied for short in the compartment of "long term" evolution in fig. 1.

This complexity makes practically unavoidable to resort to quite large systems to keep into account all this entanglement of factors. Nonetheless oversimplified mathematical models have still proven to be quite useful to highlight specific aspects of the disease, in particular the role of long-term asymptomatic carriers, which, compared to other STD is possibly the more relevant distinctive feature of HBV. In the sequel some results on basic deterministic epidemiological models with carriers, mainly stated in terms of the comparative effects on endemic thresholds, obtained through highly stylized mathematical models are surveyed, whereas the last section is devoted to more specific aspects concerning large ("reasonable") HBV system modelling.

This paper is organized as follows: after a short recall (in the first section) of some basic aspects of HBV epidemiology relevant for mathematical modelling, we briefly discuss (second paragraph) the basic model for genetic heterogeneity used for HBV by Anderson and May, and then enlarge it to explicitly introduce the role played by sexual activity heteogeneities, a crucial factor in the sexually transmitted HBV.

Then, motivated by basic ideas of the general CEID model, we provide (section 4) a decomposition of it in basically simple ingredients, to study, more realistically the effects of the carrier state when this is strictly sequential to the the infectious one. We introduce so a simple homogenously mixing SEICR (Susceptible $\rightarrow$ exposed $\rightarrow$ infective $\rightarrow$ carrier$\rightarrow$removed) model and ground its "threshold" properties against those possessed by the corresponding SEIR (the properties of which are well known) and SICR models. These threshold criteria are then extended to the more general case with sexual heterogeneities and vertical transmission.

Finally, in the last section a discussion of the main features and results, mainly concerned with the impact of several immunization programs, obtained by two "realistic" HBV models, the "old WHO" model and the CEID model, is made.

2. Pure carrier models: basic facts and genetic heterogeneity

Some results concerning models with carrier, essentially in stochastic settings, are covered by Bailey (1975), but without paying too much attention to substantive interpretations. Hethcote (1976) used an extremely simplified extension of the basic SIR model with constant vital dynamics to take into account of the possibility of carrier state. By assuming that the number C of carriers actually participating to the epidemic process is constant over time, he could show very easily the quite remarkable result, preserved by more refined models, by which in a disease with carriers, even if recovery gives permanent immunity, the disease always remains endemic. In fact in this SIRCC ("SIR with constant number of carriers") model, the presence of the constant C term forces the system to loose its threshold character to possess only one endemic state which is GAS.

Anderson and May (1991, 219-225; 1984) have examined more carefully the role of carriers, by setting the problem of HBV in their general

framework of "genetic heterogeneities". The basic idea is that, essentially due to unknown, possibly genetical, reasons, the host population can be splitten into two groups: "normal individuals", in a fraction (1-f), who recover from infection and are immune since then, and "potential carriers", who once infected have a much longer (in case lifelong) recovery time. So the dynamics of the disease can be represented by means of the following (one-sex) two-groups SIR model (enhanced to permit vertical transmission in the carrier status as well):

$$\begin{aligned} \dot{X}_1 &= \mu N_1 - (\mu+\lambda)X_1 & \dot{X}_2 &= \mu N_2 - \nu\mu Y_2 - (\mu+\lambda)X_2 \\ \dot{Y}_1 &= \lambda X_1 - (\mu+v_1)Y_1 & \dot{Y}_2 &= \lambda X_2 - (\mu+v_2)Y_2 \\ \dot{Z}_1 &= v_1 Y_1 - \mu Z_1 & \dot{Z}_2 &= v_2 Z_2 - \mu Z_2 \end{aligned} \qquad (1)$$

where as usual X_i and Y_i denote the number of susceptible and infective individuals in the two groups, μ denotes at the same time the birth and the death rate prevailing in the population (so ensuring its stationarity), v_i are the recovering rates, ν defines the rate of vertical transmission, while finally λ is the FOI defined as:

$$\lambda(t) = \beta_1 Y_1 + \beta_2 Y_2 \qquad (2)$$

based on a classical bilinear mass action (BMA) incidence. The formulation (2) can be made consistent with the flow diagram of fig. 1, where potentially three categories of infectives which can play a role in the transmission chain coexist: acute infectives, "subclinical" infectives and carriers, by assuming for instance that the epidemiological role of acute and subclinical infectious individuals can be homologated. In fact there is no clear evidence about this: more likely seems the possibility that acute infections reach higher peaks of infectivity while having a much shorter time of infectivity, possibly due to isolation. The opposite should happen for subclinical infections.

The usual criteria of persistence and eradication[1], based on the basic reproduction rate (BRR) actually results to be (approximately) a weighted average of the BRRs which would experience the two subpopulations if they were isolated and of the same amplitude:

$$R_0 = \frac{\beta_1 N}{\mu + v_1}(1-f) + \frac{\beta_2 N}{\mu(1-\nu)+v_2} f = R_0^1(1-f) + R_0^2 f \qquad (3)$$

Equivalently we can give to (3) a more direct interpretation, as the sum of the contribution in terms of new infectives due to one infectious individual, a fraction (1-f) of which is initially introduced into group one and the other fraction (f) into group two, under the assumption that the two groups are completely unconnected.

The formulation (3) highlights a series of typical difficulties connected with policies against diseases characterized by genetic

[1] Standard analysis show that model (1)-(2) always possesses a disease free equilibrium, which is globally stable/unstable below a specific threshold, and a unique endemic equilibrium, which appears above the given threshold and it is, in that case, globally stable. Properties of a quite similar system are studied in Cooke (1982).

heterogeneities and the direct role of vertical transmission in raising the BRR (Anderson and May 1991, 222-224). In particular, compared to the limit situation without VT ($\nu=0$)[2] the existence of vertical transmission raise the BRR of the carrier group, so raising also, coeteris paribus, the overall BRR

Finally, for what concerns the full epidemics dynamics, this will in general be different from the well know traditional SIR damped oscillations in that the very long carrier state, the time scale of which is quite close to the typical demographic ones, can sterilizise fluctuations, so generating a nonoscillatory convergence to a long term endemic state. This fact can be understood quite well from the limit case in which all the infected individuals become carrier forever. The absence of recovering would modify the SIR structure in a SI model with constant population, which has nomore oscillations but simply a logistic type convergence to the endemic state.

3. Sexually transmitted HBV: introducing heterogeneities in sexual activity

The study of the social mechanisms underlying the spread of STD, initiated by the Gonorrhoea group of Hethcote,Yorke and coworkers (Hethcote and Yorke 1984 and references therein), and strongly accelerated in the last years by the blow up of HIV/AIDS epidemics, has produced quite a broad and rich theory, which, even if mainly developed for the study of HIV transmission dynamics, can be quite straightforwardly applied to most STD, not last to HBV, at least as long as we are concerned with sexually transmitted HBV. For references see Anderson and May (1991, ch. 11 and references therein), but also the more theoretical developments by Busenberg, Blythe, Castillo-Chavez and coworkers (Busenberg and Castillo Chavez (1991a,b), Blythe et al. (1991), Blythe et al. (1995)).

The formal introduction of heterogeneities in the level of SAL amounts to assume that the host population, wich is assumed for simplicity one sex, is subdivided in n groups on the basis of their levels of sexual activity, as quantified by the average number c(i) of new sexual partner per unit time, and that these individuals mix among them on the basis of some social "mixing rule", synthesized by a so called mixing function p_{ij}, assigning the proportion of partners in group j held per unit time by "type" i individuals. Under these assumption the basic model (1) with genetic heterogeneity modifies to the following system of 6n equations:

$$\begin{cases} \dot{X}_{1,i} = \mu N_{1,i} - (\mu + \lambda_i) X_{1,i} & \dot{X}_{2,i} = \mu N_{2,i} - \nu\mu Y_{2,i} - (\mu + \lambda_i) X_{2,i} \\ \dot{Y}_{1,i} = \lambda_i X_{1,i} - (\mu + \nu_1) Y_{1,i} & \dot{Y}_{2,i} = \lambda_i X_2 + \nu\mu Y_{2,i} - (\mu + \nu_2) Y_{2,i} \\ \dot{Z}_{1,i} = \nu_1 Y_{1,i} - \mu Z_{1,i} & \dot{Z}_{2,i} = \nu_2 Y_{2,i} - \mu Z_{2,i} \end{cases} \qquad (4)$$

which now embodies, say, two kind of heterogeneities, the social heterogeneity which stratifies individuals in n different groups on the basis

[2] In this case (3) is exact and not approximate.

of their levels of sexual activity, and the genetic heterogeneity inherited from the basic model (1). It is assumed that:

$$N_1 = \sum_{i=1}^{n} N_{1,i} = (1-f)N \qquad N_2 = \sum_{i=1}^{n} N_{2,i} = fN$$
$$N_{1,i} = p(i)N_1 = p(i)(1-f)N \;;\; N_{2,i} = p(i)N_2 = p(i)fN \tag{5}$$

where the p(i)'s denote the proportions of individuals of the various SAL, which, as stated by (5) are assumed uniformly distributed among the two distinct genetical groups (in other words: we exclude correlations between genetic status and SAL).

The structure of the FOI is assumed of the type:

$$\lambda_{1,i}(t) = \lambda_{2,i}(t) = \lambda_i(t) = c(i)\lambda(t) \tag{6}$$

where:

$$\lambda(t) = \left[\sum_{j=1}^{n} \beta_{1,j} p_{ij}^1 \frac{Y_{1,j}}{N_{1,j}} + \sum_{j=1}^{n} \beta_{2,j} p_{ij}^2 \frac{Y_{2,j}}{N_{2,j}} \right] \tag{7}$$

where c(i) is the previously mentioned average number of new sexual partner per unit time (put) per an i individual, $\beta_{1,j}, \beta_{2,j}$ simply extend to this heterogeneous case the transmission probabilities (it seems clearly reasonable to put: $\beta_{1,j} = \beta_1 \;;\; \beta_{2,j} = \beta_2$) of the previous chapter, while p_{ij}^1, p_{ij}^2 denote the proportions in which these sexual partners are allocated: the former is the proportion of partner in group j and of type 1 of a sexually active individual in group i, while the latter is the proportion of partner in group j but type 1. Clearly this simplified form is permitted by the assumed absence of correlation between genetical status and SAL. The mixing probabilities are nonnegative and:

$$\sum_{j=1}^{n} (p_{ij}^1 + p_{ij}^2) = \sum_{j=1}^{n} p_{ij}^1 + \sum_{j=1}^{n} p_{ij}^2 = (1-f) + f = 1 \tag{8}$$

since by cumulating over all groups the two types of probabilities we obtain the "marginal" probabilities to find a random partner in the genetic statuses 1 and 2.

By assuming (Anderson and May 1991, ch. 11) proportionate mixing in the form:

$$p_{ij}^1(t) = \frac{jN_{1,j}}{\sum_{j=1}^{n} jN_j} = p_j^1(t) \;;\; p_{ij}^2(t) = \frac{jN_{2,j}}{\sum_{j=1}^{n} jN_j} = p_j^2(t) \tag{8'}$$

and that c(i)=i, we have:

$$\lambda = \left[\sum_{j=1}^{n} \beta_{1,j} \frac{jN_{1,j}}{\sum jN_j} \frac{Y_{1,j}}{N_{1,j}} + \sum_{j=1}^{n} \beta_{2,j} \frac{jN_{2,j}}{\sum jN_j} \frac{Y_{2,j}}{N_{2,j}} \right] \tag{9}$$

By temporarily neglecting vertical transmission, the following equilibrium relation on the FOI easily follows:

$$\lambda = \sum_{j=1}^{n} j^2 \frac{\beta_{1,j}}{\mu+v_1} \frac{N_{1,j}}{\sum jN_j} \frac{\mu\lambda}{\mu+j\lambda} + \sum_{j=1}^{n} j^2 \frac{\beta_{2,j}}{\mu+v_2} \frac{N_{2,j}}{\sum jN_j} \frac{\mu\lambda}{\mu+j\lambda}$$

ie:

$$1 = \sum_{j=1}^{n} j^2 \frac{\beta_{1,j}}{\mu+v_1} \frac{N_{1,j}}{\sum jN_j} \frac{\mu}{\mu+j\lambda} + \sum_{j=1}^{n} j^2 \frac{\beta_{2,j}}{\mu+v_2} \frac{N_{2,j}}{\sum jN_j} \frac{\mu}{\mu+j\lambda} \qquad (10)$$

By letting λ tending to zero we obtain the appropriate persistence criterion, which is expressible in a particular simple form if the transmission probabilities are not correlated with SAL. In this case we get:

$$R_0 = \frac{\beta_1}{\mu+v_1} \sum_{j=1}^{n} j^2 \frac{N_{1,j}}{\sum jN_j} + \frac{\beta_2}{\mu+v_2} \sum_{j=1}^{n} j^2 \frac{N_{2,j}}{\sum jN_j} =$$
$$= \frac{\beta_1}{\mu+v_1} \sum_{j=1}^{n} j^2 \frac{(1-f)N_j}{\sum jN_j} + \frac{\beta_2}{\mu+v_2} \sum_{j=1}^{n} j^2 \frac{fN_j}{\sum jN_j} = \frac{\beta_1 c}{\mu+v_1}(1-f) + \frac{\beta_2 c}{\mu+v_2} f \qquad (11)$$

Expression (11) is, exactly as in the non-heterogeneous case, a weighted average of the BRR of the two genetically distinct groups 1 and 2, which in this case depend (Anderson and May 1991) not on the total population size, but on the parameter c, which is a special indicator connected with the distribution of SAL. Exactly speaking c is the average number of sexual partners per unit time augmented by the ratio of the variance of the same distribution divided by its mean:

$$c = \sum_{j=1}^{n} j^2 \frac{N_j}{\sum jN_j} = \sum_{j=1}^{n} j^2 \frac{N_j}{\sum N_j} \frac{\sum N_j}{\sum jN_j} = \frac{1}{\sum jN_j / \sum N_j} \sum_{j=1}^{n} j^2 \frac{N_j}{\sum N_j} = \frac{m_2}{m} \qquad (12)$$

a well known result in epidemic theory (May 1990, Anderson and May 1991).

So definitively, under the special circumstances considered here, the introduction of heterogeneities in SAL does not modify the substance of the basic result (3)[3], with the difference that the eradication consideration have now to be made in terms of threholds wich are not expressed in terms of numbers of individuals, as it was in the highly simplistic model of the previous section, but in terms of the levels of sexual activity. In other terms: under the "especially tractable assumption of proportionate mixing, it has been possible to show that, to eradicate the disease, we should be able to reduce the average SAL, ie the average number of partners per year below a defined theshold. These results are particularly suggestive even if care has to be taken, since they are valid under a very special assumption (proportionate mixing), while to have informations on a given concrete situation we should need precise information on what the true mixing pattern actually is.[4]

[3] It is in fact easy to verify that the explicit consideration of VT does not modify the result (3).

[4] At present not so many results are available on "specialised" mixing patterns.

We notice lastly that the explicit consideration of vertical transmission gives rise to a modified persistence criterion which is nothing but (under reasonable approximations) the combination of (12) with (3).

4. Chronic carriage as sequential to the infectious state

Rather than assuming, as in the previous models, that individuals lifecourses as "potential carriers" rather than "normal" are already planned at birth by some supreme authority, as an alternative modelling strategy we may assume that the state of carriage is sequential to the infectious one (so being more adherent to the basic flow diagram of HBV), possibly (as before) as a consequence of a flaccide response of the immune system to the aggression of the parasite.

In this event a heterogeneous representation of the disease embodying the exposed state as well (denote by H the number or density of exposed individuals), is given by the following aggregate SEICR system with vertical transmission from both the infected and the carrier state:

$$\begin{aligned}
\dot{X}_i &= \mu(N_i - \nu_1 Y_i - \nu_2 C_i) - (\mu + \lambda_i)X_i \\
\dot{H} &= \lambda_i X_i + \mu(\nu_1 Y_i + \nu_2 C_i) - (\mu + \sigma)H_i \\
\dot{Y}_i &= \sigma H_i - (\mu + \nu)Y_i \qquad (13) \\
\dot{C}_i &= qvY_i - (\mu + \theta)C_i \\
Z_i &= (1-q)vY_i + \theta C_i - \mu Z_i
\end{aligned}$$

Here in particular q is the proportion of individuals who develop chronic carriage from the infectious state; furthermore the births from infected/carriers mothers are assumed to take place all in the exposed state. This system constitutes a simplified aggregate version of the more general model developed by Anderson et al. (1991,1995), discussed in the next section.

To get insight from the use of models is quite useful a "comparative hierarchical" strategy aimed to contrast sequentially the properties of new, usually more rich and complex, models, against those of the old ones, in order to appreciate the role played by the respective differences and/or modifications.

So, let us start for simplicity from the "aggregate" version (ie without heterogeneities) of model (13), which, assuming the further simplification of absence of vertical transmission, looks as (using a bilinear type mass action) the following homogeneous SEICR model with extended BMA:

$$\begin{aligned}
\dot{X} &= \mu N - (\mu + \lambda)X \\
\dot{H} &= \lambda X - (\mu + \sigma)H \\
\dot{Y} &= \sigma H - (\mu + \nu)Y \qquad \lambda = \beta_1 Y + \beta_2 C \qquad (14) \\
\dot{C} &= q\nu Y - (\mu + \vartheta)C \\
\dot{Z} &= (1-q)\nu Y + \vartheta C - \mu Z
\end{aligned}$$

It is possible to show that properties of (14) are quite similar to those of simpler models without return to susceptibility (as the basic SEIR models), ie it exist a unique endemic equilibrium which appears when a suitable threshold condition is satisfied and which is, in this event, GAS. It is quite useful in this sense to ground the persistence criterion exhibited by model (14) against those of the basic SEIR model, without carriers, and of the SICR derivable from (14) by eliminating the exposed state. Both such models are "one step hierarchically simpler" of our SEICR formulation, so making comparisons quite sharp and easy. Usual equilibrium/persistence calculations give the threshold parameters:

$$\begin{aligned}
&\text{SEIR:} && R_0 = \frac{\beta N}{\mu + \nu}\frac{\sigma}{\mu + \sigma} \\
&\text{SICR:} && R_0 = \frac{\beta_1 N}{\mu + \nu} + \frac{\beta_2 N}{\mu + \theta}\cdot\frac{q\nu}{\mu + \nu} \qquad (15a,b,c) \\
&\text{SEICR:} && R_0 = \left(\frac{\beta_1 N}{\mu + \nu} + \frac{\beta_2 N}{\mu + \vartheta}\cdot\frac{q\nu}{\mu + \nu}\right)\cdot\frac{\sigma}{\mu + \sigma}
\end{aligned}$$

The actual interpretation of the threshold parameter relevant to model (14), given by (15c), is so quite clear. Interpreting sequentially we see that, compared to the usual threshold for SIR models: $R_0=\beta N/(\mu+\nu)$, the introduction of the exposed state (see (15a), which basically acts as a "delayer" in the transmission process, introduces the (true) probability $\sigma/(\mu+\sigma)$, to enter the state of infectious from the latent state. In turn this probability multiplies the special SICR threshold to give the SEICR one. The interpretation of the SICR thresholds in only a bit more involved of the basic $R_0=\beta N/(\mu+\nu)$ but completely natural.

The explicit consideration of vertical transmission involves only slight modifications. It is possible to show that the entire hierarchy of results (15) is mantained (always under some completely reasonable approximations). So, in the SICR model with births from both the infectious and carrier state in the infective state we get:

$$R_0 = \frac{\beta_1 N}{\mu^* + \nu} + \frac{q\nu}{\mu + \theta}\frac{\beta_2 N}{\mu^* + \nu} \qquad (16)$$

where μ^* is modified to take into account of VT, as already observed in (3). In particular:

$$\mu^* = \mu(1 - B_1) \quad \text{where:} \quad B_1 = \nu_1 + \nu_2 \frac{q\nu}{\mu + \vartheta} \qquad (17)$$

Direct comparison with (3) show that the basic result (3) is preserved since expression (17) is nothing but a total probability of vertical transmission due to an HBV individual during his total infectious period to be intended as the sum of the sejour time in the state of acute infection plus the sejour time in the state of carrier

For what concerns the general dynamical properties of the basic SICR and SEICR models considered here it is possible to show that they give, under reasonable parameter values, to qualitative results which are in general very similar to those of the corresponding simple SEIR model, even if the qualitative predictions can be somewhat different.

Passing to the more general case (13) with SAL heterogeneities the persistence criterion modifies quite straightforwardly, with the obvious new of the appearance of the special "c" parameter. The appropriate force of infection is of the form:

$$\Lambda_i(t) = c(i)\lambda_i(t) = c(i)\left[\sum_{j=1}^{n} p_{ij} \frac{\beta_1 Y_j + \beta_2 C_j}{N_j}\right] \qquad (18)$$

where the quantity:

$$\frac{\beta_1 Y_j + \beta_2 C_j}{N_j}$$

represents the total probability to get the infection from a partner randomly chosen in group j. By making the already made assumptions that c(i)=i and that moxing behaviours be of the proportionate mixing type, rapid calculation (see the appendix for details) show that, neglecting VT, the relevant threshold is:

$$BRR = R_0 = \left[\frac{\beta_1}{\mu+\nu} + \frac{\beta_2}{\mu+\nu}\frac{q\nu}{\mu+\theta}\right]\frac{\sigma}{\mu+\sigma}c \qquad (19)$$

The expression directly extends the corresponding quantity (15c) for the nonheterogeneous case, by simply introducing, as already seen before, a different threshold principle expressed in terms of numbers of sexual contacts rather than of population levels. The role of VT is derivable from simple combination of previous results.

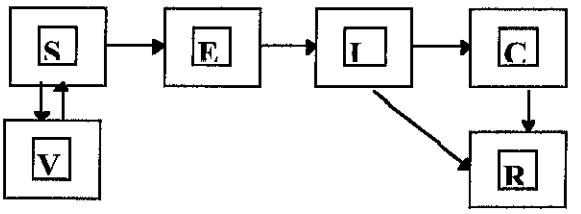
5. Realistic models for HBV dynamics and control

For what concerns more general (compared to those of the past sections) mathematical models for HBV, essentially two "families" are available. The first one is the WHO model developed by Cvjetanovic and coworkers (Cvjetanovic et. al. 1978, Delimar et al. 1985, Pasquini et al. 1987). The second one is the CEID model developed in recent years by Anderson et al. (1992,1995). We termed such models as "realistic" simply because they embed quite a lot of epidemiological details, compared to the highly stylised models discussed in the past sections: a most apparent consequence of this is of course the fact that strong clearcut results are quite more difficult. They have common features but also several relevant differences: the CEID model is SAL structured, while WHO is not (possibly depending on the fact

that it was developed before the "heterogeneity revolution" in epidemic models was developed). The WHO is more faithful to the "full HBV flow" depicted in fig. 1 and so contains a larger number of distinct epidemic compartments. Finally, the CEID model is "fully age structured" (FAS), ie age is treated as a continuous variable by means of the VonFoerster PDE formalism, whereas the WHO is an ODE model in which age is modeled through a sequence of discrete age stages (DAS). These constitute the two possble age structure "modelling philosophies" in epidemiological models (Tudor 1985 is an instance of the mathematical analusis of the DAS approach in SIR models). We start from the CEID model in that it is to be regarded as an outcome of the various models presented in the past sections, and then say just few things on the WHO model.

5.1 The CEID model

With the main goal to compare the impact of several sets of different immunization strategies in a cost-effectiveness setting, Anderson et al (1991, 1995, 1996) have developed a quite general model for sexually transmitted HBV plus vertical transmission, the flow diagram of which is represented below:



In effect the problem of HBV control is by no means an easy one, mostly due to the existence of silent forms of infection (carriers plus subclinical HBV). This fact seriously questions, at least in principle, the effectiveness of strategies such as selective immunization of high risk individuals (keeping into account the difficulty to identify high risk individuals).

In this section we briefly expose the main features of the background model used and its basic predictions on the impact of different immunization strategies, leaving aside the cost-effectiveness results. The CEID model, developed both for homosexual and heterosexual transmission, is a fully age/SAL structured model which generalizes the SAL heterogeneous SEICR model with vertical transmission previously introduced. In the more updated version of the model (1995) the demographic side has recruitment via births plus type 1 mortality (the population is, as usual stationary). Allowance is made for vaccination (V state) and vaccination waning immunity.

Further ingredients which generalise the models considered up to now are:

a)age-dependent vaccination schedules, to take into account not only of vaccination at birth, as in the oversimplified models of the previous section, but also of adolescent and other explicit possibilities such as targeted immunization of possible superspreeders, ie highly sexually active individuals.

b)explicit allowance is made for keeping into account the effects of several relevant parameters connected with HBV immunisation, among which: i)administration of multiple vaccine doses (up to three doses), ii)different level of vaccine acceptance (defined as the proportions ρ_i[5] of individuals who actually received the i-th dose of vaccine), in particular of vaccine compliance (the proportion ρ_1 of individuals who actually received the first dose of vaccine), iii)different levels of efficacy (q_i, the proportions of individuals actually immunised conditionally to the number of doses received). In this way the proportion of the given group under a specified immunisation program which is actually immunised is defined as:

$$Q=\rho_3 q_3+(\rho_2-\rho_3)q_2+(\rho_1-\rho_2)q_1$$

c)age-dependent probabilities q=q(a) of developing the state of chronic carriage

d)screening of pregnant woman is performed, with vaccination plus HB immunoglobuline given to new born individuals at risk of HBV (this guarantees a quite high probability to avoid infection)

e)age-sex-SAL dependent contact patterns. In case of heterosexual contacts (it is completely analogous in the homosexual case) these are described by means of suitable functions of age $c_{gs}(a)$, denoting the average number of new sexual partners per unit time per a male individual (male sex=g) aged a and in SAL s, and $c_{hr}(a)$, denoting the average number of new sexual partners per unit time per a female individual (female sex=h) aged a' and in SAL group r. In particular every individual is assigned since birth to his (her) sexual activity class in which he (she) will remain for the whole sexually active period (no migrations -possibly due to behavioural changes among activity groups - are permitted). Of course his/her sexual activity level is permitted to vary as the individual ages.

This assumption gives rise to an age dependent FOI, the structure of which is the following (obtained by generalising (6.7):

$$\lambda_{gs}(a,t)=c_{gs}(a,t)\sum_{r=1}^{n}\left[\int_F \beta_1 p_{gs,hr}(a,a')\frac{\beta_1 Y_{hr}(a',t)+\beta_2 C_{hr}(a',t)}{N_{hr}(a',t)}da'\right] \quad (1)$$

where F is the sexual activity age span, and all other ingredient can be seen to constitute direct generalisations of the previously introduced formula (18). In particular for what concerns the mixing functions $p_{gs,hr}$ (satisfying: $\sum_{r=1}^{n}\int_F p_{gs,hr}(a,a')da'=1$), an assumption of proportionate mixing among individuals of different sexes is made, in the form:

$$p^1_{gs,hr}(a,a')=\frac{c_{hr}(a',t)N_{hr}(a',t)da}{\sum_{r=1}^{n}\int_F c_{hr}(a',t)N_{hr}(a',t)da'}=p^2_{gs,hr}(a,a')$$

[5] By denoting with p(0),p(1),p(2),p(3) the "exclusive" proportions of individuals who received exactly "i" doses, we obviously have: $p(3)=p_3$, $p(2)=p_2-p_3$, $p(1)=p_1-p_2$.

f) Highly specific to the model (Anderson et a. 1996) is the treatment of possible superspreeders. These are "identified" through their rates of attending GU clinical treatments, which are in turn assumed to be functions of their SAL. Vaccination is then applied to the numbers of attenders to GU services estimated (by suitable regressions) from real data. Allowance is made for compliances and acceptances parameters of GU attenders to depend on SAL and age as well.

The model is used to assess the impact of several different immunisation strategies (separately studied for homosexual and heterosexual communities) on the basis of available UK data. This is obtained mainly through simulation[6] and long term equilibrium analysis, ie by identifying the equilibrium state[7] of the HBV system in absence of immunization policies and then studying the predicted impact on this equilibrium state of various assumptions on the structure of the vaccination program, during a given immunization period of fixed lenght (50 years in the simulations performed).

The immunization programs considered are basically reconducible to two main "extreme" categories, ie *mass immunization* (both infants and adolescents mass vaccination programs are considered) and *targeted immunization*, aimed at highly at risk individuals. Among these highly sexually active individuals plus babies born from infected mothers are considered.

The main results basically show (Anderson et al. 1991, Anderson et al. 1996) that (obviously these conclusions are conditional to the utilised parameters values, some of which are subject to a high degree of uncertainty):

a)within the general (heterosexual) population mass vaccination and targeted vaccination aimed to individuals in the most sexually active classes, seem to be equally effective in significantly reduce HBV, an intuitive explanation being that the average rate of sexual partner change is, on average, quite low. Of course the two programs have quite different time scales, the targeted program being obviously the faster. A compliance level of 90% achieved eradication.

b)within the homosexual community (considered as an independent population) the effects of mass immunization are in general better of those of targeted programs, the reason for this difference lying in the different shapes of the distributions of SAL in the population. In fact in the homosexual "part" of the model the proportion of highly sexually active individuals (ie: with a number of new partner per year above a given threshold) is much greater than in the heterosexual counterpart. This means that, coeteris paribus, a same targeted program will be more effective when applied on the heterosexual part of the population. The effects of the two different policies become comparable only once the number of "targeted" groups in the homosexual population become sufficiently high. Very uptodate results (Williams et al. 1996) seem to suggest that, at least in low-endemic situations, such as the UK, then targeted vaccination can have

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[6] In the simulations parameters assignments are made by using data from NATSSAL for what concerns sexual activity, and several sources for other parameters.

[7] Typically used variables are the equilibrium prevalences of acute infections and carriers (totals and stratified by age and SAL).

"...a much greater potential than at present realised, particulrly if it were possible to improve compliances of clinic attendees" (Williams et al 1996)

c)Antenatal screening, though guaranteeing non negligible effects, is the poorest policy, since only a very small proportion of mothers are chronic carriers.

5.2 The WHO model

We just say very few words on the WHO "eighty years" model, just to point out its main characteristics and differences with respect to the CEID model. In principle the WHO encompasses all the possible relevant individual epidemiological states in HBV development. For instance it includes the period of maternal antibodies protection, sublinical silent HBV, and several states connected with the long terms developments of HBV. In fact the development of HBV following the infectious state is a bit more complicated than we discussed in the previous pages: the states of carriers or removed are not the only possible outcomes: another possibility is the development of the so called state of "chronic active" HBV and so on (see for instance a basic text on the HBV epidemiology). So, possibly combining such a faithful description with more specific formulations, such as the CEID one, which recognizes and concentrates on specific risks factors (sexual rather than due to IVU or transmission via infected blood products, neglected by the WHO model) and on the central role of the stratification in levels of activity, it would be possible in principle to take into account all the relevant biological detail and so all the possible nonlinearities of the transmission dynamics of HBV (possibly with an explosion in the difficulty of interpreting the results of such gigantic model).

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Appendix

Let us first rapidly show how to derive the basic results used in the comparison between the three aggregate models SEIR, SICR, SEICR used in the text. The properties of the basic SEIR model are very well known (Capasso 1993, Anderson and May 1991). Viceversa for the aggregate SICR (SIR model with carriers) model without vertical transmission (VT):

$$\begin{aligned} \dot{X} &= \mu N - (\mu + \lambda)X \\ \dot{Y} &= \lambda X - (\mu + v)Y \\ \dot{C} &= qvY - (\mu + \vartheta)C \\ \dot{Z} &= (1-q)vY + \vartheta C - \mu Z \end{aligned} \qquad \lambda = \beta_1 Y + \beta_2 C \qquad \text{(A.1)}$$

it is easy to show the existence of only one endemic state, obtainable as follows:

$$X=\frac{\mu N}{\mu+\lambda}\quad Y=\frac{\lambda X}{\mu+v}\quad C=\frac{qvY}{\mu+\theta}\quad Z=N-(X+Y+C)\qquad (A.2)$$

from which the equilibrium FOI gives:

$$\lambda=\beta_1 Y+\beta_2 C=\left(\beta_1+\beta_2\frac{qv}{\mu+\theta}\right)Y=\mu\left[\left(\frac{\beta_1 N}{\mu+v}+\frac{\beta_2 N}{\mu+v}\cdot\frac{qv}{\mu+\theta}\right)-1\right]\qquad (A.3)$$

and so:

$$R_0=\frac{\beta_1 N}{\mu+v}+\frac{\beta_2 N}{\mu+\theta}\cdot\frac{qv}{\mu+v}\qquad (A.4)$$

Result (A.4) extends the threshold of the basic model without VT exactly in the same way as it was happening for the basic SIR model. By combining the SEIR and SICR formulations without VT we arive at the SEICR model:

$$\begin{aligned}
\dot{X}&=\mu N-(\mu+\lambda)X\\
\dot{H}&=\lambda X-(\mu+\sigma)H\\
\dot{Y}&=\sigma H-(\mu+v)Y \qquad \lambda=\beta_1 Y+\beta_2 C\\
\dot{C}&=qvY-(\mu+\vartheta)C\\
\dot{Z}&=(1-q)vY+\vartheta C-\mu Z
\end{aligned}\qquad (A.5)$$

Usual equilibrium calculations give the only endemic state :

$$X=\frac{\mu N}{\mu+\lambda}\quad H=\frac{\lambda X}{\mu+\sigma}\quad Y=\frac{\sigma H}{\mu+v}\quad C=\frac{qvY}{\mu+\vartheta}\quad \lambda=\beta_1 Y+\beta_2 C\qquad (A.6)$$

The FOI equation is:

$$\lambda=\beta_1 Y+\beta_2 C=\left[\beta_1+\beta_2\frac{qv}{\mu+\vartheta}\right]Y=\left[\beta_1+\beta_2\frac{qv}{\mu+\vartheta}\right]\frac{\sigma}{\mu+v}\frac{\mu N}{\mu+\sigma}\frac{\lambda}{\mu+\lambda}$$

which gives:

$$\lambda=\mu\left[\left(\frac{\beta_1 N}{\mu+v}+\frac{qv\beta_2 N}{(\mu+v)(\mu+\vartheta)}\right)\cdot\frac{\sigma}{\mu+\sigma}-1\right]\qquad (A.7)$$

and the threshold parameter:

$$R_0=\left(\frac{\beta_1 N}{\mu+v}+\frac{qv\beta_2 N}{(\mu+v)(\mu+\vartheta)}\right)\cdot\frac{\sigma}{\mu+\sigma}\qquad (A.8)$$

The threshold parameter (A.8) combines the features of both previous cases SEIR and SICR and is used in the comparison in the main text:

SEIR: $$R_0 = \frac{\beta N}{\mu + \nu}\frac{\sigma}{\mu + \sigma}$$

SICR: $$R_0 = \frac{\beta_1 N}{\mu + \nu} + \frac{\beta_2 N}{\mu + \theta}\cdot\frac{q\nu}{\mu + \nu}$$

SEICR: $$R_0 = \left(\frac{\beta_1 N}{\mu + \nu} + \frac{q\nu\beta_2 N}{(\mu + \nu)(\mu + \vartheta)}\right)\cdot\frac{\sigma}{\mu + \sigma}$$

The explicit introduction of VT in the SICR model, by assuming that a fraction of all births from the infective and carrier state are infectious give the model:

$$\begin{aligned}
\dot{X} &= \mu(N - \nu_1 Y - \nu_2 C) - (\mu + \lambda)X \\
\dot{Y} &= \lambda X + \mu(\nu_1 Y + \nu_2 C) - (\mu + \nu)Y \\
\dot{C} &= qvY - (\mu + \vartheta)C \\
\dot{Z} &= (1 - q)\nu Y + \vartheta C - \mu Z
\end{aligned} \qquad \lambda = \beta_1 Y + \beta_2 C \qquad (A.9)$$

Equilibrium calculations are more involved. We have:

$$\lambda = \beta_1 Y + \beta_2 C \quad \text{where:} \quad C = \frac{q\nu}{\mu + \vartheta} Y = A_1 Y \quad \Rightarrow \quad \lambda = (\beta_1 + A_1\beta_2)Y$$

$$X = \frac{\mu N - \mu(\nu_1 Y + \nu_2 C)}{\mu + \lambda} = \frac{\mu[N - (\nu_1 + \nu_2 A_1)Y]}{\mu + \lambda} = \frac{\mu[N - B_1 Y]}{\mu + \lambda}$$

$$\Rightarrow \quad Y = \frac{\lambda X}{\mu(1 - B_1) + \nu} = \frac{\lambda X}{\mu^* + \nu} \quad \frac{\lambda}{\mu^* + \nu}\frac{\mu[N - B_1 Y]}{\mu + \lambda} \quad \text{and: } \mu^* = \mu(1 - B_1) \ :$$

so that:

$$Y = \frac{\lambda}{\mu^* + \nu}\frac{\mu[N - B_1 Y]}{\mu + \lambda} = \frac{\mu\lambda}{(\mu^* + \nu)(\mu + \lambda)}[N - B_1 Y] = B_2[N - B_1 Y]$$

$$\Rightarrow \quad Y = \frac{B_2 N}{1 + B_1 B_2} \quad \text{where:} \quad B_2 = \frac{\mu\lambda}{(\mu^* + \nu)(\mu + \lambda)}$$

$$\Rightarrow \quad \lambda = (\beta_1 + \beta_2 A_1)Y = (\beta_1 N + \beta_2 N A_1)\frac{B_2}{1 + B_1 B_2}$$

where:

$$\frac{B_2}{1 + B_1 B_2} = \frac{\dfrac{\mu\lambda}{(\mu^* + \nu)(\mu + \lambda)}}{1 + B_1\dfrac{\mu\lambda}{(\mu^* + \nu)(\mu + \lambda)}} = \frac{\mu\lambda}{(\mu^* + \nu)(\mu + \lambda) + B_1\mu\lambda}$$

The last result gives:

$$\lambda = \frac{(\beta_1 N + A_1\beta_2 N)\mu\lambda}{(\mu^* + \nu)(\mu + \lambda) + B_1\mu\lambda}$$

obtaining the equation:

$$1=\frac{(\beta_1 N + A_1\beta_2 N)\mu}{(\mu^*+\nu)(\mu+\lambda)+B_1\mu\lambda}$$

Let us now observe that in those cases in which the term $B_1\mu\lambda$ is small we simply have:

$$\lambda=\mu\left[\frac{(\beta_1 N+A_1\beta_2 N)}{(\mu^*+\nu)}-1\right] \Rightarrow R_0=\frac{(\beta_1 N+A_1\beta_2 N)}{(\mu^*+\nu)} \qquad (A.10)$$

$$R_0=\frac{\beta_1 N}{\mu^*+\nu}+\frac{q\nu}{\mu+\theta}\frac{\beta_2 N}{\mu^*+\nu} \qquad (A.13)$$

which clearly mirrors the simpler case without VT by replacing μ wit $\mu^*=\mu(1-B_1)$, exactly as in the basic SIR model. The extension to the SEICR case is tedious but straightforward.

The case of heterogeneities in sexual activity

Let us now prove some facts concerning the SEICR models with SAL heterogeneities by using the basic treatment developed in Anderson and May (1991, 1983,1984,1989) for heterogeneous epidemic models. The basic model with discrete SAL stratification is:

$$\begin{aligned}
\dot{X}_i &= \mu(N_i-\nu_1 Y_i-\nu_2 C_i)-(\mu+\Lambda_i)X_i \\
\dot{H}_i &= \Lambda_i X_i+\mu(\nu_1 Y_i+\nu_2 C_i)-(\mu+\sigma)H_i \\
\dot{Y}_i &= \sigma H_i-(\mu+\nu)Y_i \\
\dot{C}_i &= q\nu Y_i-(\mu+\theta)C_i \\
Z_i &= (1-q)\nu Y_i+\theta C_i-\mu Z_i
\end{aligned} \qquad (A.11)$$

with:

$$\Lambda_i(t)=c(i)\lambda_i(t)=c(i)\left[\sum_{j=1}^{n} p_{ij}\frac{\beta_1 Y_j+\beta_2 Y_j}{N_j}\right] \qquad (A.12)$$

where in particular the quantity:

$$\frac{\beta_1 Y_j+\beta_2 Y_j}{N_j}$$

represents the probability to get the infection from a partner which has been chosen in group j. By temporarily neglecting vertical transmission and performing usual equilibrium calculations we get:

$$X_i=\frac{\mu N_i}{\mu+\lambda_i} \quad H_i=\frac{\lambda_i X_i}{\mu+\sigma} \quad Y_i=\frac{\sigma H_i}{\mu+\nu} \quad C_i=\frac{q\nu Y_i}{\mu+\theta} \qquad (A.13)$$

Combining (A.3) with the already made assumption c(i)=i and the assumption of proportionate mixing: $p_{ij}=p_j$, which makes the λ_i quantities independent from i (and so $\lambda_1=\lambda_2=\ldots=\lambda_n=\lambda$), we obtain:

$$\lambda = \sum_{j=1}^{n} p_j \frac{1}{N_j}\left[\beta_1 + \beta_2 \frac{qv}{\mu+\theta}\right] Y_j = \\ = \sum_{j=1}^{n} p_j \frac{1}{N_j}\left[\beta_1 + \beta_2 \frac{qv}{\mu+\theta}\right] \frac{\sigma}{\mu+v} \frac{j\lambda}{\mu+\sigma} \frac{\mu N_j}{\mu+j\lambda} \qquad (A.14)$$

By dividing both members of (A.14) by λ:

$$1 = \sum_{j=1}^{n} j p_j \frac{1}{N_j}\left[\beta_1 + \beta_2 \frac{qv}{\mu+\theta}\right] \frac{\sigma}{\mu+v} \frac{N_j}{\mu+\sigma} \frac{\mu}{\mu+j\lambda} \qquad (A.15)$$

so that, by letting λ go to zero we obtain a threshold criterion in the form:

$$BRR = R_0 = \sum_{j=1}^{n} j p_j \frac{1}{N_j}\left[\beta_1 + \beta_2 \frac{qv}{\mu+\theta}\right] \frac{\sigma}{\mu+v} \frac{N_j}{\mu+\sigma} = \\ = \left[\beta_1 + \beta_2 \frac{qv}{\mu+\theta}\right] \frac{\sigma}{(\mu+v)(\mu+\sigma)} \sum_{j=1}^{n} j p_j \qquad (A.16)$$

Remembering that the average of the distribution in levels of sexual activity under PM assumption is simply c, (16) simplifies to:

$$BRR = R_0 = \left[\frac{\beta_1}{\mu+v} + \frac{\beta_2}{\mu+v}\frac{qv}{\mu+\theta}\right] \frac{\sigma}{\mu+\sigma} c \qquad (A.17)$$

which is the result (19) of the main text.

DATA AND DATA SOURCES ON HEPATITIS B EPIDEMIOLOGY IN ITALY

1. Introduction

The study of hepatitis B epidemiology in Italy is mainly based on two kinds of data: the incidence of clinical cases and the prevalence of infection markers (HB_sAg, anti-HB_sAb, anti-HB_cAb). Incidence data derive from notifications as hepatitis B belongs to the 2nd class of notifiable diseases. More complete information on reported cases, and possible ways of trasmission, are collected by SEIEVA (Integrated Epidemiological System for Acute Viral Hepatitis), which operates since 1984 within the Laboratory of Epidemiology and Biostatistics at Istituto Superiore di Sanità and to which about 260 Local Health Units $(USL)_s$ over a total of about 650 (involving about 40% of Italian population) partecipate. Spatial distribution of the USL_s adhering to the system provide a quite complete picture of hepatitis epidemiology most regions of Italy, but some regions, like Calabria and Sicily are poorly represented and some other (Liguria, Lazio and Basilicata) are absent at all.

Data deriving from this system can be considered reliable as diagnosises are controlled, but they are probably underestimated because of underreporting.

2. Recent trends in incidences

From Seieva aggregate data the dynamics of HBV in Italy during the period 1985-1994 appears very far from an equilibrium dynamics: we observe a quick monotonic decrease in total incidences, from 12 over 100.000 to about 3.5 over 100.000, which seems somewhat slower only in the very last period.

Such decaying trend is of course confirmed at other "levels" even if it appears, in some cases, less clear.

Trends in incidence by age. The somewhat rough age classes stratification (0-14,15-24,25+) shows a quite striking structural change during 1985-1994: in 1985 HBV was, essentially a disease of young adult (ie: (15,24)) with an incidence of more than 40 per 100.000, and only around 7 per 100.000 in the other age classes. During the period considered the incidence in the (15,24) age class undergone a rapid decay (more or less linear), from 40 over 100.000 in 1985 to 6 in 1994. This last datum is about the same of the same as the older age class (25+). Finally the incidence in the younger age class fell, during the period considered, to a very low level (1 per 100.000).

Sex patterns of incidence are characterised by essentially the same qualitative decreasing behaviour during the involved period, with a strong male superincidence: male incidence, even if varying over time, always remains more than twice of female incidence. Given the very high degree of uncertainty which surrounds risk factors of italian HBV transmission dynamics (see later on), the reason of such superincidence are unclear. From a purely theoretical point of view the existence of male superincidence is an indicator of a bias, in the transmission dynamics, toward factors favouring male infections: for instance toward typically male risks such as core effects due to female prostitution and/or IVU (in which there is male bias in frequency) and so on.

Regional trends: incidence was relatively higher in the South (S) (about 15 over 100000) compared to North and Center (11 over 100000) at 1985. Since 1985 incidence in S has fallen down quite rapidly while in NC this has happened sometimes later with the result that North experienced a higher incidence from 1986 to 1992. At present incidences behaviours are quite close together and close to the national average of 3.5, but this quite similar outcome seem rather to be the result of quite complex balancement between fully different effects.

Risk factors: the SEIEVA system data collects informations on the possible ways of transmission through questionaries to infectious individuals. A typical problem is that the same subject very often declares multiple possible factors of expositions. Then, for a more precise assessment of the quantitative importance of every risk factor it is necessary to perform case-control studies and multivariate statistical analysis on incident cases. A study carried out in 1987 on the three first years of SEIEVA activity (Mele e coll, 1990) estimated the relative and attributable risk for hospitalization (Odds Ratio: 1.86; Attributable Risk: 11%), surgical intervention (OR: 2.27; AR: 4%), dental therapy (OR: 1.73; AR: 9%), barber shop shaving (OR: 1.65; AR: 2%), other percutaneous exposure (OR: 2.09; AR: 4%), i.v. drug abuse (OR: 6.55; AR: 0.4%), and household or sexual contact with HBsAg positive carrier (OR: 9.30; AR: 18%). The role of heterosexual transmission was more specifically investigated using both SEIEVA and case-control studies data (Pasquini e coll. 1990): the risk associated with exposure to two or more heterosexual partners was estimated with multiple logistic regression compared to one or none, obtaining Odds Ratios of 1.5 for males and 2.0 for females. For subjects under 25, a trend was observed: the risk of hepatitis B increases with the number of heterosexual partners in the previous year (Mele et al. 1995). Other case-control studies evaluated the importance of beauty treatments and healthcare working in the HBV transmission: tattooing (OR: 2.12) and ear piercing (OR: 2.20) were significantly associated with hepatitis.

Trends (in reported frequencies) of risk factors during 1986-1994 in all the several items previously mentioned show rather steady behaviours

with the exceptions of: i)"other types of parenteral exposures" ii)sexual transmission whose incidences experienced an increasing trend, iii)IVU which experienced a strong peak in 1990.

Anyhow these data appear to be quite unreliable. Apart the unavoidable problem of the declaration of multiple risk factors, the fact that interviews to infectious individuals are not anonymous obviously takes important bias. Furthemore no distinction is made between homosexual and heterosexual transmission and this is a serious drawback as well.

3. Seroprevalence data and trends

Incidence data deriving only from clinical cases can give a poor picture of the actual structure of the disease at a given point in time: they are at best the observed footprint of the existing distribution of HBV silent carriers in the population. The reconstruction of the carriers distribution in the population can only be made via seroepidemiological surveys aimed at the reconstruction of the serological profile of the population, ie of the prevalences of the so called markers of infections. By markers of infection (or serological markers) we mean the several antigens and antibodies that are detectable in a patient's serum throughout the clinical course of hepatitis B. Testing for their presence is necessary to determine the stage of infection and to assess a patient's infectivity. The three major antigens are: i)HB_sAg,the *surface* antigen, ii)HB_eAg, the *e* antigen, and iii)HB_cAg, the *core* antigen, which unfortunately cannot be detected in plasma and, thus, it is not a useful marker of clinical infection. The antibodies specific to these antigens, anti-HB_s , anti-Hb_e and anti-HB_c appear at different stages of the disease. HB_sAg is the first marker to appear in the blood after hepatitis B infection. It appears approximately six weeks after exposure to the virus and persists for 4-14 weeks. Anti-HB_s appears during the recovery phase and is associated with immunity, which is probably life-long. The failure to clear HB_sAg and the development of anti-HB_s within six months of initial infection gives the serological evidence of a chronic carrier state for HBV. The first antibody to appear is anti-HB_c. It is usually related to HBV replication and is present in the serum of acute and chronic HBV cases and also of individuals who have recovered from HBV. HB_eAg appears after HB_sAg and disappears sometimes before the clearance of HB_sAg. Thus for a while they can be present simultaneously. The presence of HB_eAg indicates viral replication and high infectivity. Its detectability for more than ten weeks reveals progression to chronic active hepatitis. The appearance of anti-Hb_e denotes a reduction in the level of infectivity of the patient. If both HB_sAg and anti-HB_s are absent, the contemporaneous presence of anti-HB_e and anti-HB_c are witnesses of a recent infection. Anti-HB_e normally persists

for one or more years after the resolution of HBV infection (Smithkline Beecham 1991).

At present screening for HB_sAg is compulsory in Italy for blood-donors and pregnant women after 6th mounth of pregnancy. The epidemiological picture on hepatitis B, in Italy should be completed with serological data on anti-HB_sAb indicating an occurred infection.

Unfortunately seroepidemiological surveys often relate to limited geographical areas or to particular groups like military recruits, children, sexually trasmitted diseases clinic patients, health-care workers so that results of different studies are difficult to compare. Table 1 summarize, the most important surveys carried out in Italy on HBV markers: their results confirm the data from incidence studies. In fact the markers seroprevalence seems to be decreased more or less regularly from 1981 to 1991, as showed by repeated surveys on military recruits: the adjusted prevalence of Anti-HB_c antibodies dropped from 16.8% to 5.8% in 9 years (D'Amelio, 1992). Variables associated with serological markers prevalence were: age, region of birth, father's education, number of siblings, and HBsAg positive household members (Stroffolini et al 1991, D'Amelio 1992). Health care employment does not seem significantly related with a higher risk of infection (Antoniello, 1989).

4. Vaccine coverage

Since 1991 vaccination against HBV has been made compulsory in Italy for all infants of 3 months and adolescents of 12 years of age without charge. Furthermore vaccination is offered, again without charge, to everyone in specified risk groups acknowledged by law (Dec. Italian Min. of Health 4/10/91).

At present HBV vaccination coverage in Italy appears to be quite high among infants, possibly due to the fact they are submitted to multiple vaccination shedules at the same age. For instance a survey on mandatary vaccination coverage in seven Italian Region carried out in 1993 showed that the anti-HBV vaccine was administered to between 53% (in Tuscany) and 92% (in Lombardia), but in 1995 other studies shown coverages in between 93.3% (in Puglia) and 97% (in Tuscany),.

On the contrary it seems that a quite high number of 12 year old people escape from vaccination, especially in the South Italy, but this number is difficult to evaluate. For instance in Tuscany between 1992 and 1995 the 99.6% of twelve years old people were vaccinated (Bonanni 1996), whereas in the province of Sassari such frequency decreased to 93.9% (Maida 1996).

It is more difficult to obtain data on vaccination of special risk cathegories (such as health workers and so on): among the few available data

the frequency of health care workers vaccinated against HBV ranged from 61.6% in Lombardia in 1992 (Auxilia 1992) to 8.3% in Sardinia in 1993 (Murru 1994).

5. Long term effects

Pasquini et al. (1990), estimate to around 9000 the number of yearly deaths occurring every year in our country due to the long term consequences of the carrier state of HBV, cirrhosis and hepatocellular carcinoma. This figure as well appears to be decreased in the very last period.

6. Suggested explanations

What are the reasons of the quick decrease of the HBV impact in our country, keeping in mind that certainly the national immunization policy, only started in 1991, is a minor responsible?

The Seieva explanation individuates (but witout any use of data) three basic arguments:

a)the "considerable" improvement of socio-economic conditions

b)the decreased family size (see also Mele et al. 1990)

c)the widespread use of disposable syringes over the recent years

but foreshadow the possibility that a role has been played as well from complex effects of the social alarm induced by AIDS blow-up (information programs, behavioural change and so on; this effect could have for instance amplified the c) effect). Let us call this the d) argument.

Prevalence of HBV markers in Italy: data from several serological surveys

Geog. District	Obs. period	Age range	samp. size	Population	HB_sAg	HB_sAb	HB_cAb	anti-HBV	Any Markers	Ref.
Nord	1981	18-26	1207	military	2.4%				10.6%	Pasquini '83
Centro		18-26	1026	recruits	2.2%				10.3%	
Sud		18-26	1527		4.3%				25.2%	
Isole		18-26	1245		4.3%				21.5%	
Nord	1981	18-26	2233	military	2.3%		9.7%			D'Amelio '92
Nord	1990	18-26	3392	recruits	0.8%		3.0%			
Sud e Isole	1981	18-26	2772		4.3%		22.6%			
Sud e Isole	1990	18-26	1586		2.0%		8.6%			
Nord	pub.'84	24-33	108	dentists	2.8%			20.4%		Ribero '84
		34-43	43		2.3%			51.2%		
		44-53	67		1.5%			53.7%		
		54-72	62		3.2%			72.6%		
Italia	1986	18-65	107	blood	1.98%					Giusti '89
Sud				donors	2.69%					
Nord					1.78%					
Centro					0.83%					
Sardegna	1987	0-11	1826		0.2%				1.7%	Stroffolini '89
Nord e Sud	1987-89	3-5	819		0.4%				1.7%	Stroffolini '91
		6-8	1592		0.2%				1.5% (1.3%Nord, 1.6% Sud)	
		10-11	2095		0.5%				2.9% (1.3%Nord, 3.7% Sud)	
		14-16	1533		0.9%				2.9% (1.3%Nord, 4% Sud)	
		17-19	1366		0.9%				4.5% (3.1%Nord, 5.8% Sud)	
Napoli	1980	7-12	393		2.1%				11.7%	D'Argenio '89
Napoli	1988	7-12	484		0.8%				6.8%	
Palermo	1988	6-13	490		1.4%				3.9%	Stroffolini '89
Bari	1989	3-11	1426		3.9%				3.4%	Stroffolini '90
Padova	1989	6-10	1016		0.1%				1.3%	Chiaramonte '91

Sardegna	1989	14-16 17-19	1357 "	students "	1.1% 1.1%			3.6% 5.7%		Stroffolini '90
Palermo	1989	0-9 10-19 20-29 30-39 40-49 50-59	1001	healthy persons	3.3% 2.0% 2.1% 4.3% 2.9% 1.6%				10.8% 10.0% 15.6% 34.3% 38.9% 35.7%	Intonazzo '91
Padova	1979 1989	6-15 6-14	500 1635	students	0.06%			1.3%	16%	Chiaramonte '91
Siena	pub.'89	30-60	350	health workers	2%	0.3%	4%	15.1%	21.4% (22% per 30-40 anni, 19.7% 41-50 anni, 26.8% 50-60 anni)	Almi '89
Piemonte	pub.'89		976	health workers				17.52%		Verani '89
Napoli	pub.'89		339 786	health workers in hospitals.	4.8% 4.0%				2.2% 2.8%	Antoniello '89
Sud-Isole	pub.'90	12-20	204		3.4%			13.2%		Di Ciommo '90
Genova	1990		1395	ecological operators	2.9%	13.8%	1%			Poli'90
Roma	1990	44*	2080	ecological operators	7.4%					Messineo'90
Trieste	1990	40.6*	427	ecological operators	5.1%	18.5%	1.8%		25.5%	Rieppi'90
Roma	1991	43.7*	3668	ecological operators	4.8%		13.7%		24.6%	Messineo'91
Valtellina	pub.'91	17-39 22-73	40 40	IVU alcoholists					68% 10%	Marioni '91
Catania	pub.'92	0->50	152	blood polytrasnf.	8%			55%		Cacopardo '92
Veneto	1985-92		1797	IVU	15%	57%	28%			Mezzelani '94
Rieti " " " Centro-sud	1993 " " " "	20-25 26-35 36-45 46-57 22-55	35 48 13 6 34	jail. populations " " " Penit.Police					48.6% 58.3% 38.5% 83.3% 11.8%	Bonaventura '96

Rieti	"	20-59	244	Police.					14.8%	
Roma	pub.'95		360	health workers in hospitals.				16.3%		Di Ciommo '95

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Perspectives on the global eradication of measles

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Models of transmission dynamics of infectious diseases

A fundamental characteristic of transmission dynamics models of infectious disease is that they are based on populations and are not individual-based. They are closely related to types of models that are used in the field of population biology or population ecology, for example, to consider interacting effects in an ecosystem of numbers of predators and numbers of prey on which they feed. In epidemiology in general this type of model is used to consider the flow of infection in populations and the proportion of a population that may be susceptible to infection, or be infectious, or immune from infection (Anderson & May, 1991). In contrast to other approaches to epidemiological modelling they tend to be deterministic in nature rather than stochastic, and for large populations the state variables in such models can be considered to represent means of distributions of the possible values of such variables that may arise in stochastic modelling. In structure transmission dynamics models are designed to represent the essential processes of transmission of infection in a population, for example patterns of contact, infection, recovery etc. This structure can be thought of as a series of flows between compartments (Figure 1) representing, in the case of measles (= *morbillo*), the proportions of the population concerned which are susceptible, infected but not infectious, infectious and immune. Such a structure can be expressed as a system of ordinary or partial differential equations (ODE's or PDE's)(Figure 2) describing the population flows between compartments. The formulations of such models are intentionally simple so that their behaviour is understandable and consequently can be related to the reality of the processes involved in transmission of infectious diseases. The parameters used in the models are estimated from epidemiological data using standard statistical methods. In general such models are not solvable analytically so, instead, numerical methods are used: the models are described by computer programs whose outputs are trends in the values of the state variables (compartments M, X and so on in Fig. 1) over time.

Role of transmission dynamics models

The main roles of transmission dynamics models are: to aid interpretation of epidemiological trends; to establish what data needs to be collected to increase understanding about patterns of transmission; and, importantly to assist in the design of programmes for control of infection and disease by using model projections of their effects in place of a large series of trials (which may be of many years duration, and which it may be impracticable to perform). It should be noted that results from the use of transmission dynamics models can demonstrate that the behaviour of systems of infectious diseases in populations can be contrary to intuitive expectations, and also, in some circumstances, that programmes of vaccination can cause more harm, in terms of disease, than benefit (Anderson & May, 1991).

Using transmission dynamics models

It is important to make clear that projections produced by this type of model represent trends, not precise predictions. They are useful to compare the effects of different control measures and to give insights into trends in the absence of control. Individual models are tools which are generalisable to many epidemiological environments. The epidemiological environments themselves are characterised by the particular parameter estimates used in running the model.

Before going on to consider an example of the use of such models, it should be emphasised that transmission dynamics models should not be considered as replacements for the various statistical models used in epidemiology. Both approaches to modelling have their own part to play in epidemiological work, and each should be seen as complementary to the other.

Why model measles?

Why is the modelling of measles of particular interest? First, it is a very common infection of childhood and before the commencement of vaccination programmes, the great majority of the population of any country would have experienced measles infection at some time in their lives. Measles also shares many characteristics with other childhood infections. It is an acute infection of relatively short duration (typically less than 2 weeks), and there is no chronic infection; after recovery from infection an individual's immunity to further infection is long lasting (often for the remainder of the individual's lifetime). There is also a large amount of epidemiological data available relating to case notifications of infection and mortality, serology, rates of infection and recovery etc. Most importantly however, in developing countries measles still causes high numbers of deaths and severe morbidity.

In developing countries it has been estimated that 3%-6% of all who are infected with measles die as a result (i.e. the case mortality rate is 3%-6%)(Halsey & Job, 1989). In some situations, in some countries, it can be much higher, with case mortality rates of more than 30% for children under 1 year of age in some areas (Halsey & Job, 1989). The World Health Organisation (WHO ≡ OMS) has estimated that global measles mortality in 1995 is in the region of 1million (WHO, 1996)(it is estimated that measles mortality prior to the start of their Expanded Programme on Immunisation (EPI) was more than 8 million per year (WHO, 1994)). In addition to high levels of mortality, serious morbidity often occurs in children who are infected with measles (Halsey & Job, 1989): in malnourished children blindness can occur; measles can give rise to a certain level of continuing immunosuppression following recovery which contributes to increased mortality for up to 9 months, and probably longer; the physical development of children can also be retarded for up to 12 months after infection.

Measles vaccination

A number of effective measles vaccines have been developed and typically vaccines will immunise effectively 90%-95% of people who are vaccinated. However vaccination is not usually effective if it is given before the loss of the antibodies that a baby receives from its mother during its development *in utero*; on average in developed countries this may take 5-9 months; in developing countries the duration of maternal antibody is somewhat shorter. Vaccination gives immunity of long duration but it is not yet known whether vaccine based immunity will endure for the lifetime of the individual concerned (Ramsey, 1994); it is also not clear how the level of maternal antibody that babies receive will be affected by the fact that their mothers' immunity may derive from past vaccination rather than past infection. Since 1974 vaccination against measles has been included in the WHO's Expanded Programme on Immunisation and WHO estimates that nearly 80% of children in the world are now being vaccinated against measles (WHO, 1994). This figure however conceals a large variation in coverage (i.e. the proportion of those eligible for vaccination who actually receive it) especially in Africa. For example, in the capital of Ethiopia 70% of children are currently vaccinated, but in rural areas only 12% are vaccinated (unpublished data) Although there is a substantial amount of data concerning levels of vaccination coverage in different countries there is no simple relationship between coverage and occurrence of infection, and this is an important justification for the use of transmission dynamics models in making projections of the results of different vaccination policies and different levels of vaccination coverage.

Measles in the world

Figure 3 shows the global reported numbers of measles cases for each year since the start of the EPI in 1974 until 1995. There is a clear decline in reported cases, but it should be emphasised that Figure 3 shows reported cases only and that many countries do not have an adequate reporting system. Estimates for the total numbers of cases for the period 1988-1995 (Figure 4) are more than an order of magnitude greater than reported cases and the trend over time is less clear (NB there was an unspecified change in the estimation methodology in 1992)

The EPI target for measles vaccination coverage has been for 90% of children under 1 year old to be vaccinated by 1995. Figure 5 shows data from WHO which suggests that many countries in the north are achieving this target, but that the lowest levels of vaccination are in sub-Saharan Africa where a number of countries have less than 50% coverage. The majority of Africa and South America have relatively low levels of vaccination although these are the countries with highest levels of morbidity and mortality (it should be noted however that recently a number of countries in South America have had success in increasing the level of vaccination through campaigns of vaccination 'campaigns').

Assessment of progress towards global measles control and EPI goals

As part of the WHO's process of examination of progress towards the goals set for the EPI, the Centre for Epidemiology of Infectious Diseases (CEID) in Oxford was asked to make projections of the likely effects of existing levels of vaccine coverage. An existing model of measles transmission dynamics was used to carry out an individual simulated vaccination programme for each country in the world (Nokes, Williams & Butler, 1995). Information on vaccination coverage over time was provided by WHO for each country, supplemented by information from published sources. The model also required information about age-related fertility and mortality rates for each country, but for many countries this information was not available. Therefore a procedure was adopted involving the use of *k*-means cluster analysis on a number of demographic variables (Table 1)with the intention of characterising the demography of each country as belonging to one of several broad demographic groupings. Four groupings were found to be sufficient to allow adequate demographic diversity without introducing a degree of differentiation between countries that would have been unjustified bearing in mind that such modelling exercises are concerned with trends rather than precise predictions. Three of the four groupings could be characterised as being 'developing' countries and the remaining grouping could be characterised as one of 'developed' countries (Figure 6). The mean growth and death rates for each cluster were used in conjunction with standard life tables to provide an appropriate set of age-related fertility and mortality rates for the cluster. The parameters for each model run therefore included a vaccination

coverage profile for the country concerned and age-related fertility and mortality rates for the cluster to which the country belonged.

An additional demographic factor was that populations with high growth rates have a high proportion of very young children with the result that the average ages of measles infection in such populations are much lower. This in turn means that the optimum age for vaccination is also much lower as vaccination must necessarily be carried out well before the average age of infection. Accordingly for the countries in the 'developed' group the realistic average age of infection was set at 5 years with an age of vaccination of 15 months; for the 'developing' countries group the corresponding time points were 2.5 years and 9 months.

Figure 7 shows the results of the modelling projections. The WHO EPI targets related to reductions from pre-immunisation levels but this basis of assessing performance was misleading because in a growing population even if incidence (e.g. cases of infection/100000 population/year) is constant the number of cases would increase as the population grew. It was decided therefore to adopt the alternative approach of comparing at the same moment in time the results of projections with and without vaccination. The major points to note from the results are that the majority of sub-Saharan Africa is projected to achieve a reduction of below 50% by year 2000; also that the projections for Venezuela and the countries of the Andes Region countries which had quite high levels of vaccination in 1995 (Fig 5) show a relatively low reduction in projected numbers of cases (note however that this modelling work does not take into account the effect of recent campaigns of vaccination in Central and South America).

Global progress towards elimination of measles

The results of this work suggest that much improvement is needed to approach EPI targets even by the year 2000. To consider how this may be achieved it is necessary to consider the dynamics of infection in individual countries. Here the dynamics of measles infection in England & Wales are used as an example of measles in the developed world. Although measles causes higher mortality in the developing world, the considerations are less complex in developed countries; also there is much epidemiological data available relating to England & Wales which can be used to highlight aspects of measles epidemiology.

Measles in individual countries

A striking feature of time series data on measles case notifications is the marked periodicity that is shown over different time scales. On the time scale of 1 year there is a distinctive seasonal pattern that is associated with children of around the age of 5 years starting their first period of schooling (Figure 8)(Ramsey, Gay et al, 1994). Most

children in England & Wales start their school lives either at the beginning of the school year (in September) or at the beginning of the following term (in January). During a few days in September and January therefore some 600,000 children in England & Wales begin their first experience of school, and this also involves a sudden increase in the number of individuals with whom they have direct contact each day, and consequently in the opportunities for the transmission of infection.

On a slightly longer time scale there is also a striking periodicity in the occurrence of epidemics. Figure 9a shows a very marked biennial pattern for measles epidemics in England & Wales with persistence of the infection at much lower levels in the periods between epidemics (endemic persistence). In contrast the occurrence of epidemics in the much smaller population of Iceland is less frequent (figure 9b), typically at 4-yearly intervals and notifications of infections fall to zero in the years between epidemics. This marked periodicity is typical of measles infection, and the time interval between epidemics and the existence of endemic persistence between epidemic years is largely determined by the size of the population concerned

Measles notification data for England & Wales after the introduction of vaccination in 1968 shows a marked decline in incidence as vaccine coverage increases to 92% in 1993 (Figure 10). As well as a sudden reduction in the peaks of the epidemics after the introduction of vaccination there is a small but noticeable increase in the period between epidemics. This can be explained by considering that the action of vaccination as far as the infection is concerned is to reduce the population available for infection (in a sense, in this example, to give England & Wales the characteristics of a smaller country). The data for the period 1989 to 1993 shown in Figure 10 raises the possibility that measles infection might be moving towards extinction in England & Wales. However an extended version of this last set of data (Figure 11) tells a different story(Ramsey, Gay et al, 1994). In the year after 1993 there is a sudden increase in measles notifications in Scotland which is mirrored by a smaller increase in notifications for England & Wales; this sudden increase gave rise to concern that a measles epidemic might be imminent in England & Wales.

Basic reproductive number

Why should there have been this concern when there was a vaccination rate of around 92%? One approach to this problem is to consider an epidemiological measure known as the 'basic reproductive rate' (more correctly 'basic reproductive number') known as R_0. In simple terms R_0 is a measure of the intrinsic potential rate of increase of an infection and is defined as the number of secondary infections that would arise from direct contact with one primary infection introduced into a population in which nobody in the population is immune (Anderson & May, 1991). Theory describes a simple relationship between R_0 and the proportion of the population that it is necessary to vaccinate in order to eradicate an infection. As may be seen from Figure 12 measles is

estimated to have a high R_0 value which in turn implies that around 95% of the population needs to be effectively vaccinated to eliminate the infection. As measles vaccine itself has an efficacy of around 95% (i.e. 95% of those vaccinated receive effective immunity) it appears that it may be necessary to vaccinate 100% of the population if eradication of measles is the objective.

An alternative way of achieving an insight into the danger of resurgence of measles in England & Wales is to consider the way in which the proportion of the population who are immune changes with age, in other words the age-seroprevalence profile of the population. The immunity in the form of antibodies that babies receive from their mothers is lost over the period of a few months (Figure 13a) so by around 9 months of age most babies are susceptible to infection. After this age more and more children will have experienced infection, with their immunity to further infection being reflected in the presence in their blood of their own antibody to measles. By the average age of infection, perhaps around 5 years in developed countries, half will show evidence of seropositivity for measles antibody, and the majority of the population reaching adulthood will show immunity. Figure 13b shows a seroprevalence profile about 2 years after the introduction of vaccination, with the age cohorts who have been vaccinated covering the age range from about 1 year to 3 years old. As the proportion of the population vaccinated increases there are fewer people infected with the virus. Consequently fewer of the unvaccinated population will have contact with infected individuals, and fewer will become infected. Because the increase in numbers of individuals immune as a result of vaccination tends to be balanced by a reduction in numbers immune as a result of infection, the proportion of the population who are susceptible to infection changes little, although their age distribution does change. This effect will result in a characteristic depression in the seroprevalence levels of measles antibody in the population just too old to have been vaccinated; this depression is often known as a 'valley of susceptibility'. Figure 14 contains data for rubella (= rosolia) from Finland which shows a typical profile for antibody seroprevalence (immunity) and the evolution of just such a valley of susceptibility in the years after the start of a vaccination programme (Ukkonen, 1996). In general, unless the level of vaccination is high enough to eradicate the infection altogether (Figure 12), simple theory predicts that, on average, the combination of the proportion of the eligible population that fails to be vaccinated and the valley of susceptibility amongst those too old to have been vaccinated will reach the same proportion as that which existed before vaccination began, so a another epidemic becomes possible. A further consequence of this change in the age distribution of susceptibility is that there will be an increase in the average age at which people in the population are infected.

In order to investigate the reasons for the sudden increase in cases shown in Figure 11 and the potential for an epidemic of measles, Babad et al used a different type of measles model to consider the dynamics of measles in England & Wales(Babad et al, 1995). The model used for that work is known as a realistic age structured (RAS) model, a type of model originally used by Schenzle (1984), and later Bolker & Grenfell

(1993). The main point to note about this model is that it is a cohort model based on the school year; in the model the proportion of the population of school age experiences an increased contact rate during the period of school terms. Also all children in the 5th age cohort begin school at same moment in time (i.e. there is a 12 month range in the age of children starting school; and the date of starting at school is not distributed evenly throughout the year as groups of children achieve the age of 5 years).

RAS model validation

The projections produced by the RAS model provided a good match for both the age-seroprevalence profiles (Figure 15) and age-stratified numbers of cases, although somewhat less good for total time series notification data.

R: Effective reproductive number

Before considering the projections produced as a result of this modelling work it is necessary to say something about the effective reproductive rate which is a measure closely related to R_0. The effective reproductive number (or 'effective reproductive rate'), R, describes the potential for an infection to spread in a particular community without assuming that all in the population are susceptible to infection. R is therefore the number of secondary infections arising from direct contact with one primary infection in a particular epidemiological environment at a particular moment. In other words R is the product of R_0 and the proportion of the population which is susceptible to infection at that particular time. If it happens that no one in the population has immunity to infection R, the effective reproductive rate, is equivalent to R_0 the basic reproductive rate. If, in a particular set of circumstances, $R < 1$, an infection cannot propagate; if $R \geq 1$ an epidemic is possible. In the work with the RAS model R was used as measure of the potential for an epidemic to spread.

RAS model projections

Figure 16 shows the model outputs in the form of the effective reproductive rate, R, against time for various strategies of vaccination. It is clear from these projections that the policy existing at that time in England & Wales, a single vaccination against measles at age 15-24 months, would have been inadequate to prevent a future measles epidemic. Although the ability of the infection to propagate was projected to fall until 1994, it would increase again after this, even though vaccination over the whole period is maintained at the level of 92% of eligible children. One possible alternative was to vaccinate at 2 different ages, so that those who missed the earlier vaccination (or those in whom vaccination was not effective) could have a second chance to be vaccinated. The

model projections show that if the second vaccination is delayed until 11 years of age it would be too late to make much difference to R. There is a high level of susceptibility already among 11-16 year olds, and vaccination at age 11 does not help to fill in the valley of susceptibility amongst those too old to have received the first vaccine at 15-24 months until these have reached the age of 11, some 9 years or so after that first vaccination (it would take a lifetime of 60/70 years for this 'valley' to have moved through all age groups). A policy of second vaccination at 4 years of age should be more successful according to the model projections. R falls below 1 so an epidemic cannot propagate. Such a policy of vaccinating twice, at 15-24 months and at a later age (about 4 years), is soon to be adopted in the UK. This decision has in part been made on the basis of the work carried out by Babad et al (1995); this demonstrates that projections resulting from the use of transmission dynamics models can indeed have an impact on the formulation of policy. It should not be forgotten however that it remains necessary to monitor immunity in the population (i.e. levels of the seroprevalence of measles antibody) to ensure that reality conforms to model projections and to continue the process of validation of model outputs.

Change in age distribution

As remarked upon earlier, one effect of vaccination is to change the average age of infection and Figure 17 shows an example from measles vaccination in China. Is such a change a problem? The answer is, yes, it can be a problem. If a child is very young there is a much higher risk of dying as a result of measles infection. However there is also a steeply increasing chance of death from measles after age 10 (Figure 18), and there are other examples of the risks from infection changing according to age such as with mumps, rubella, or poliomyelitis. Thus by vaccinating a population and increasing the average age of infection, the risks to the individual resulting from infection may be greater. There is a 'trade off' between reduced number of cases and the increased risk of morbidity or mortality from the fewer number of cases that do occur. This effect depends on epidemiological circumstances, including demography, overall health of the population, and level and targeting of vaccine coverage. Figure 19 shows for mumps infection the results of a simple theoretical calculation of the relationship between, on one hand, the ratio of numbers of cases of complications after and before vaccination and, on the other hand, the level of vaccination (Anderson, Crombie & Grenfell, 1987). This simple piece of theory shows for example that the number of cases of orchitis in males in the population could be greater as a result of a vaccination programme unless levels of vaccination approach 70%; compared with the little more than 85% vaccination coverage which is required for elimination of mumps infection. Such simple calculations are not intended as precise predictions. Their role is to warn of the theoretical possibility of such perverse effects arising from vaccination programmes and to emphasise the need for careful planning taking such possible effects into account and

also the need for subsequent monitoring to be carried out. The possible risk of adverse effects of vaccination programmes needs particularly careful consideration in relation to developing countries where elimination of infection may be difficult to achieve and where for a variety of reasons it is also difficult to maintain high levels of vaccine coverage on a long term basis.

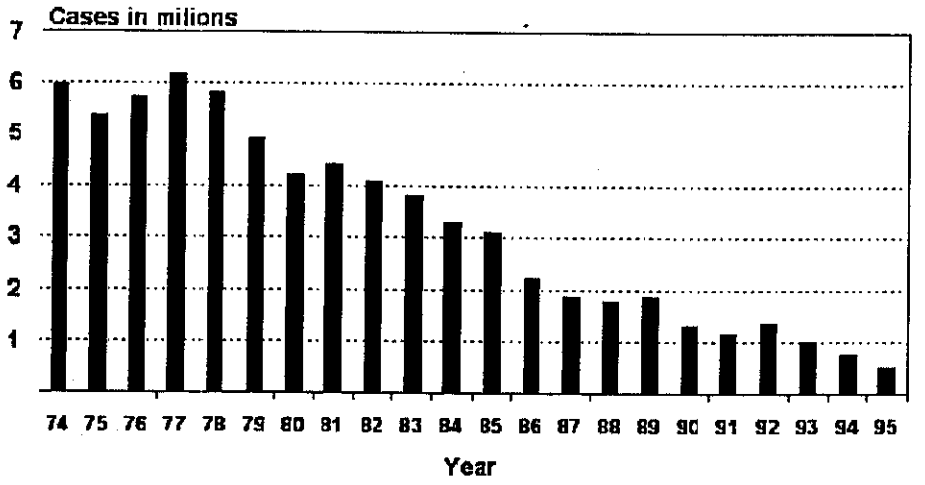
Vaccination window

Another particular problem for developing countries problem concerns the age at which young children can be effectively vaccinated. As noted previously in a low growth population with a uniform age distribution the average age of measles infection may be of the order of 5 years of age. In a high growth population there is a high proportion of the very young in the population and the average age of infection is much lower, perhaps 2.5 years of age. When the average age of infection is as low as this, at an age before many children have lost their maternal antibody a significant proportion of the children of the same age will have already lost their maternal antibody and been infected by measles (Figure 20). It is not possible to vaccinate children effectively if there are significant levels of maternal antibody remaining, and to delay too long allows many to be infected prior to vaccination. It may be therefore that either there is no single age at which vaccination can be carried out when the great majority of children in a cohort can be protected by vaccine or that there is a very small time window (vaccination window) in which to vaccinate effectively (Fig 20). It is therefore much more important to vaccinate children at the correct time in developing countries otherwise many vaccinations may fail, and valuable health resources will be wasted. Presently the vaccine efficacy of measles is about 95% but even if efficacy is 100%, given this problem of a narrow window for effective vaccination, theory suggests that complete (i.e.100%) coverage of a vaccine may be insufficient to eliminate measles in developing countries if vaccination occurs only at one age (Anderson & May, 1991)

Pulse vaccination

As described earlier one approach to increasing the effect of vaccination is to implement a strategy of vaccinating at two different ages, but this makes even more demands on a poorly resourced health infrastructure, and it can be difficult to maintain continuing programmes. Resource problems, political and economic instability and malnutrition make the implementation of effective vaccination programmes much more difficult. One alternative is a policy of 'pulse vaccination'; first tried in The Gambia, later in India and Cuba, and at the present time widely practised throughout Central and South America. Simply, pulse vaccination involves vaccinating as many as possible of the population in a wide range of age groups (perhaps all age groups) at a single point in time. This can either be carried out once only as a vaccination campaign, or repeated at intervals of a

Global annual reported measles cases, 1974-1995



EPI Information System
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Fig 3: Global annual reported measles cases since the start of the WHO Expanded Programme on Immunisation in 1974. Note that the existence and comprehensiveness of reporting systems vary between countries (Source: WHO).

Graphs and Figures

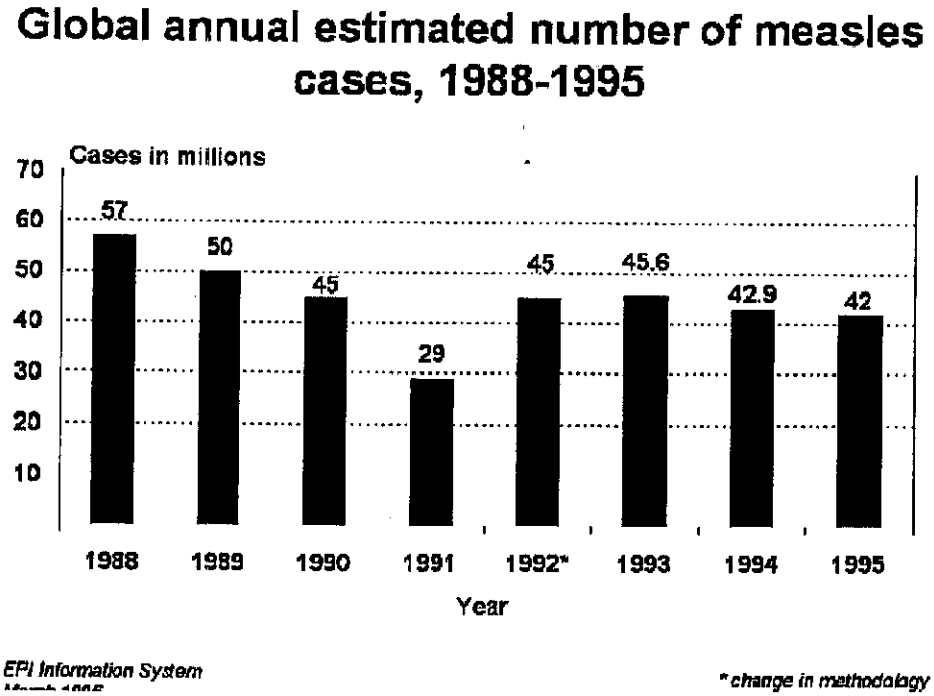


Fig 4: Estimated global numbers of measles cases from 1988 to 1995. Note that there was a change in the methodology of estimation in 1992 (Source: WHO).

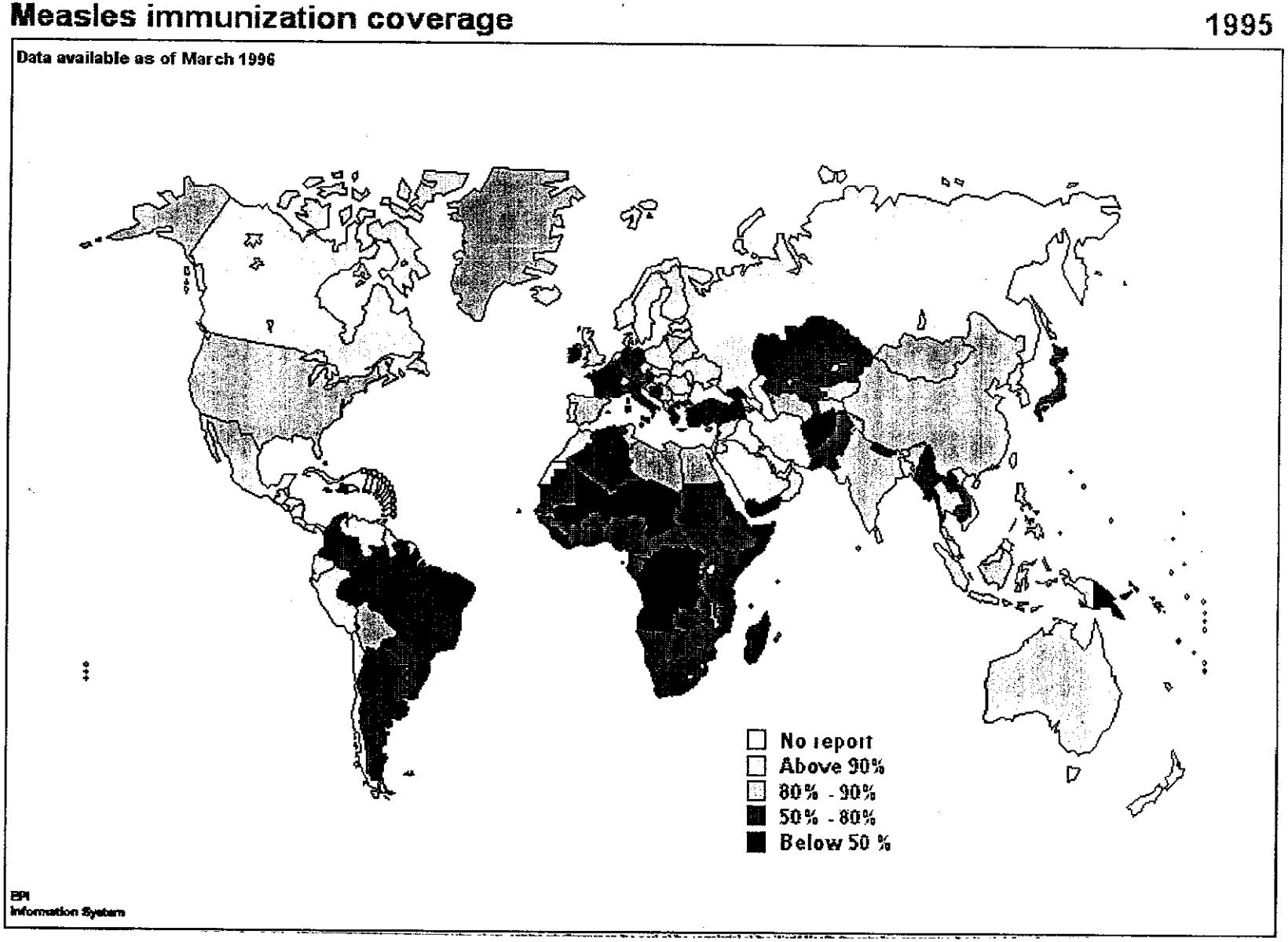


Fig 5: Percentage of eligible population vaccinated against measles. (Source: WHO; from data available in March 1996)

Fig 6: Map showing clustering of countries of the world derived from cluster analysis (Nokes, Williams & Butler, 1995)

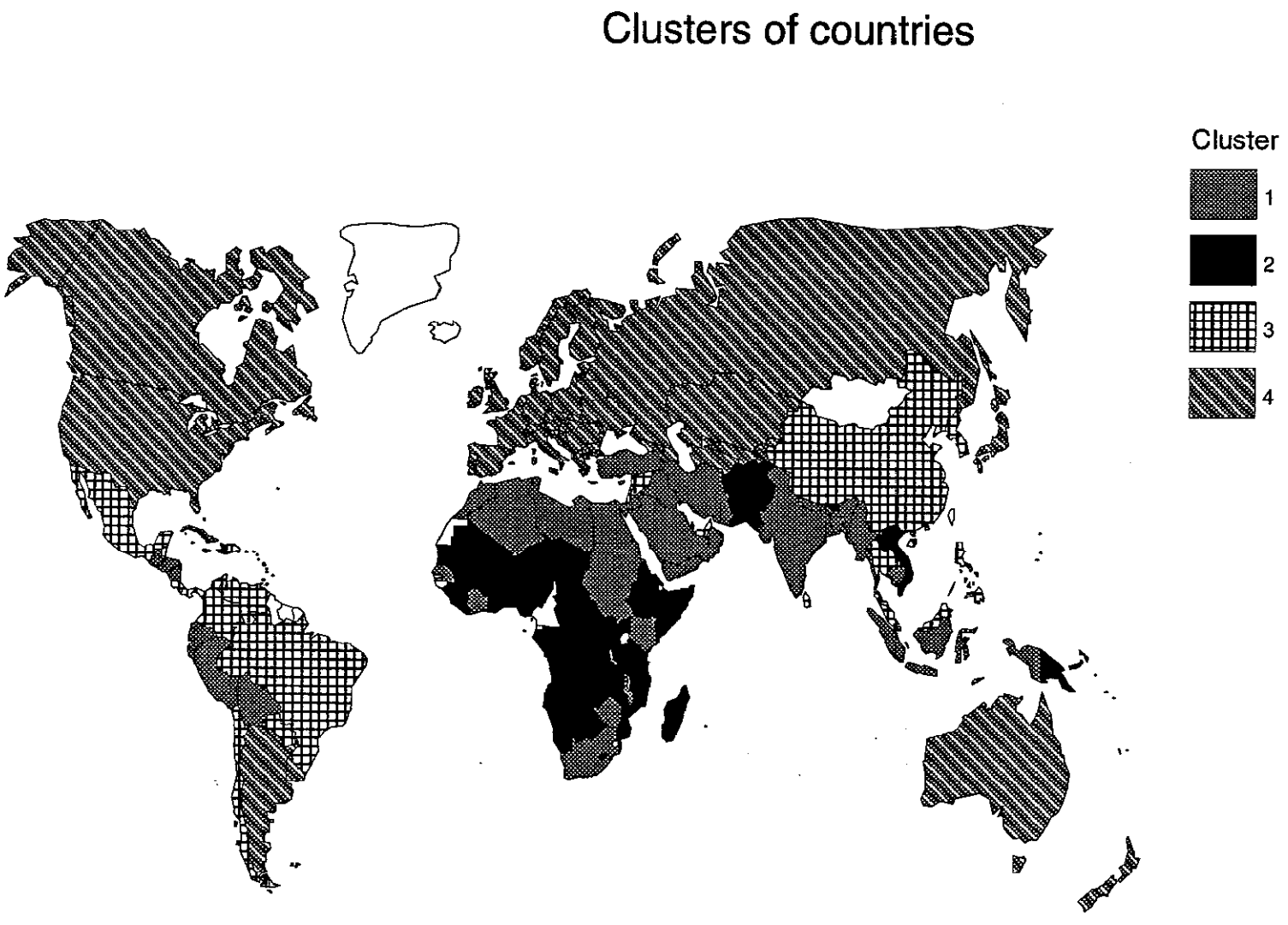


Fig 7: Projections of global reduction in numbers of measles cases as a result of vaccination by year 2000 as a percentage of projected measles incidence in the absence of vaccination (Nokes, Williams & Butler, 1995).

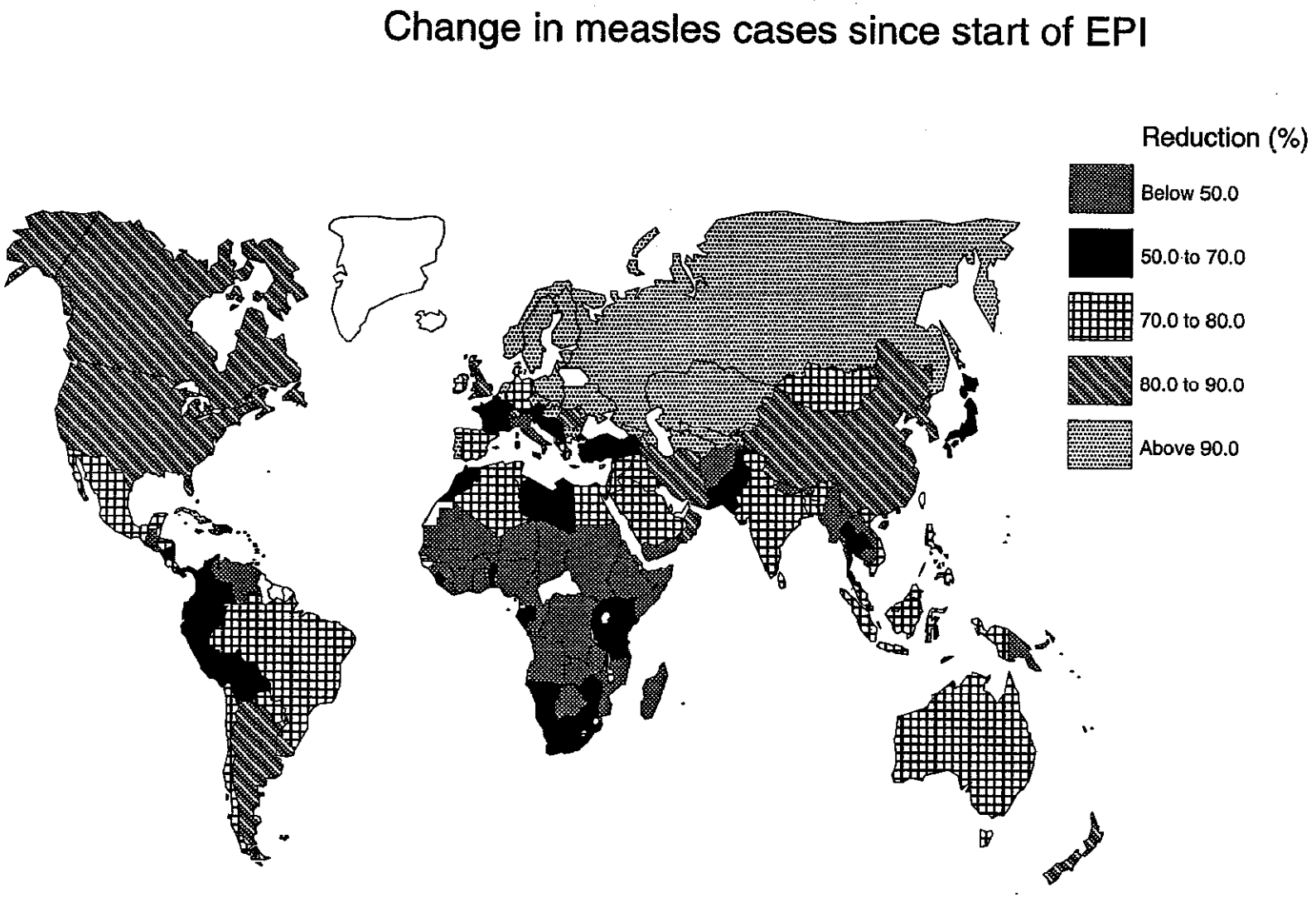
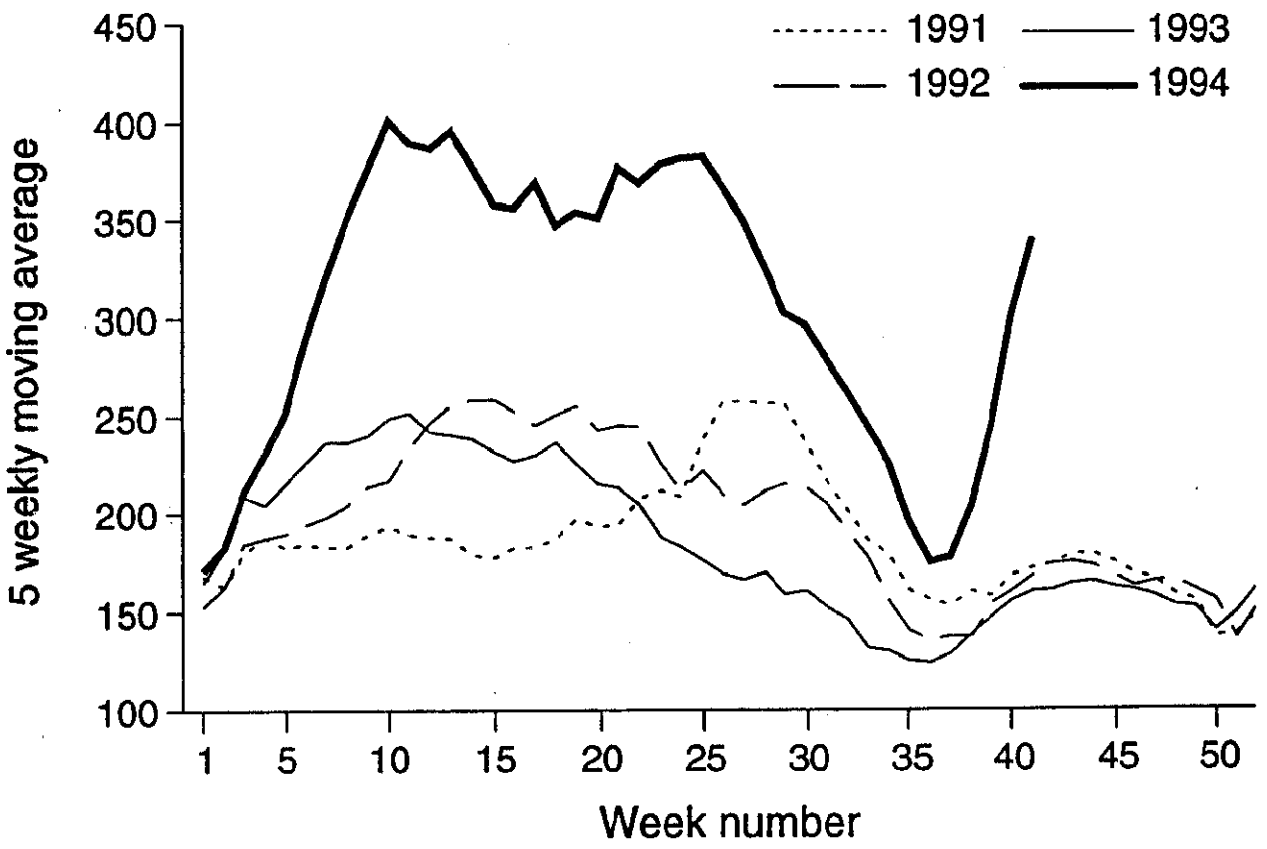


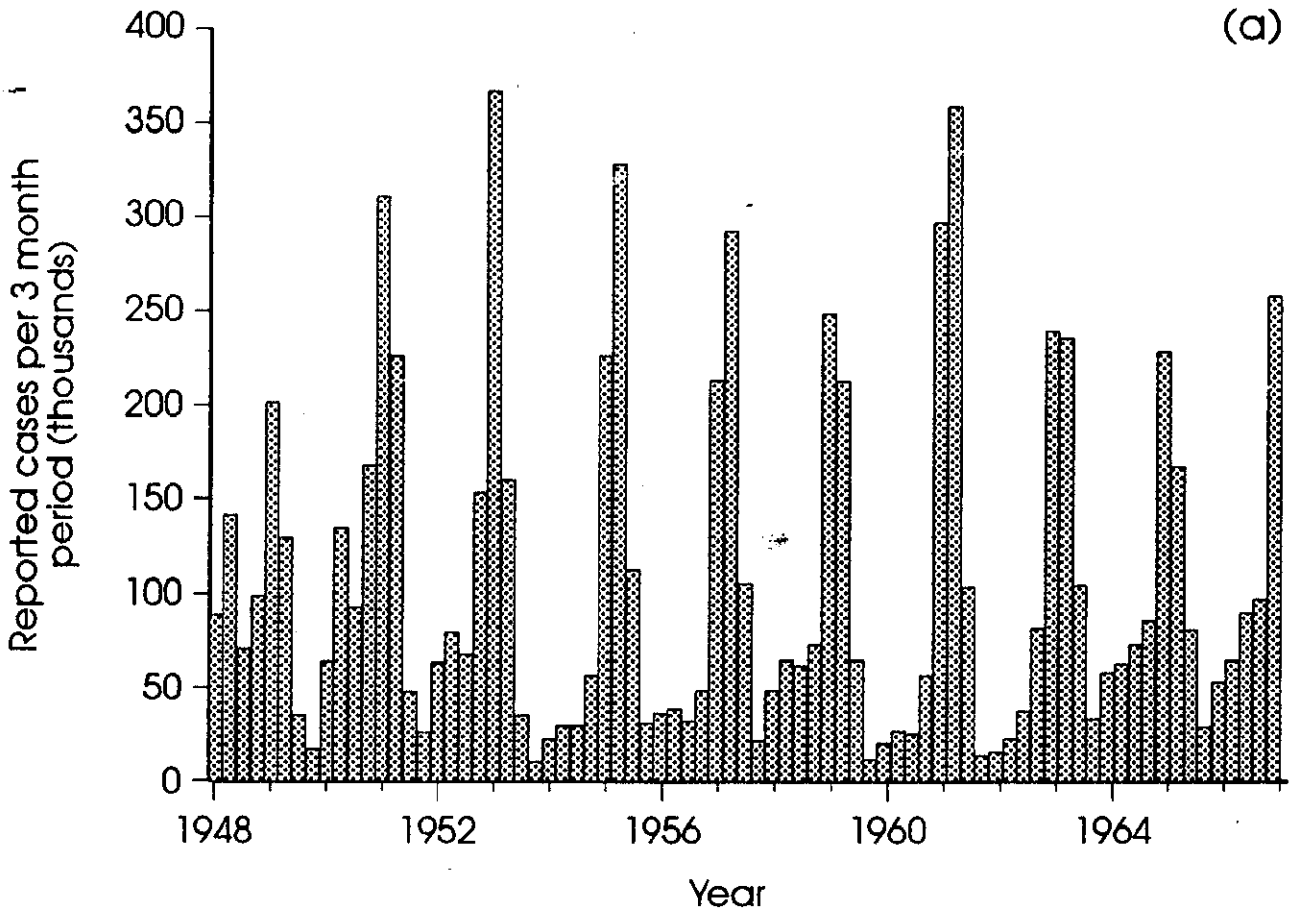
Fig 8: Measles notifications in England & Wales for 1991 to 1994 for each week in the year (Ramsay, Gay et al, 1994)

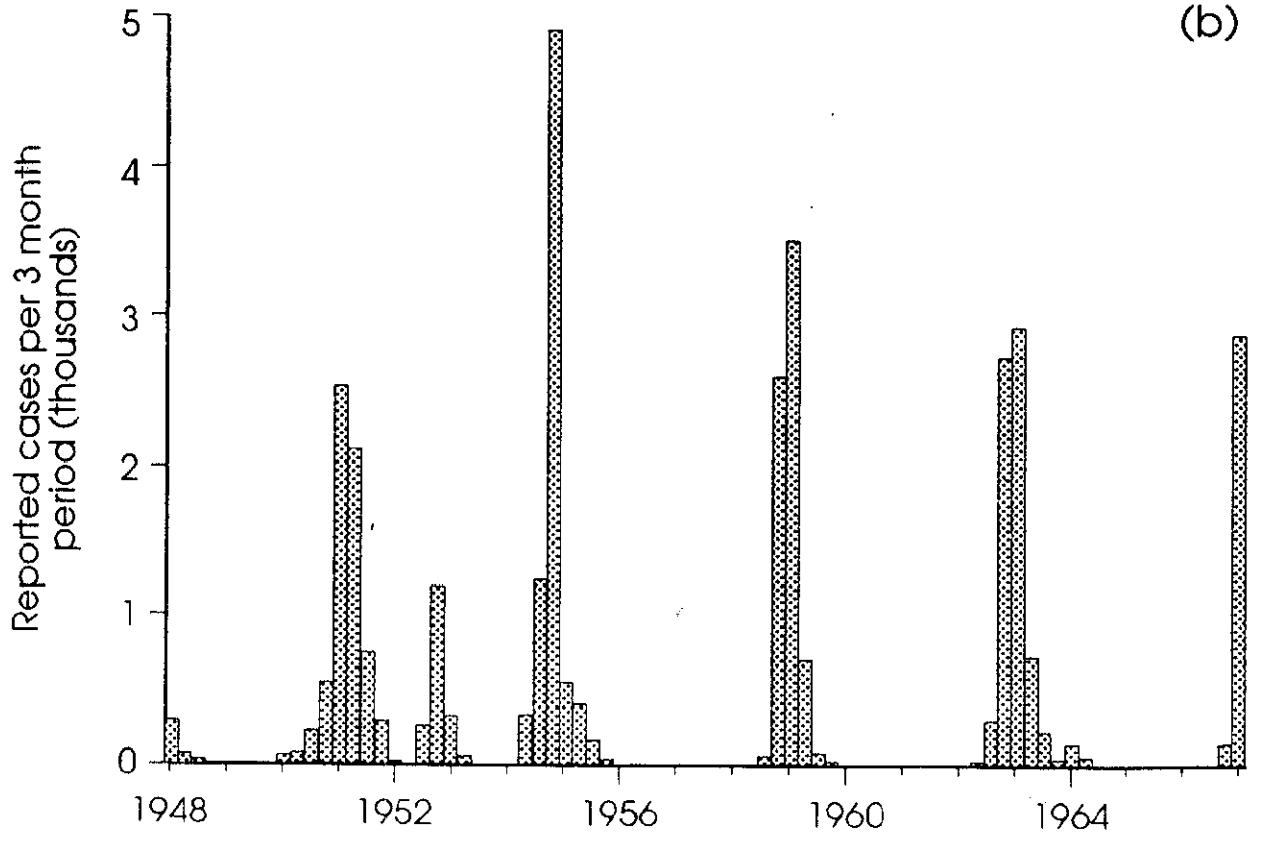


Up to and including week 41
Data for 1992 week 53 not plotted

* Notifications to Office of Population Censuses and Surveys. The five weekly moving average is calculated weekly, in arrears. The week for which it is expressed is the third of five weeks and the quoted average is the sum of notifications in those five weeks, divided by five.

Fig 9: Measles notification data for (a) England & Wales and (b) Iceland (cases per 3 month period) (Source: Fig 4.10 in Anderson & May, 1991; data from (a) Registrar-General's Statistical Review for England & Wales and (b) Cliff, Haggett et al, 1981)





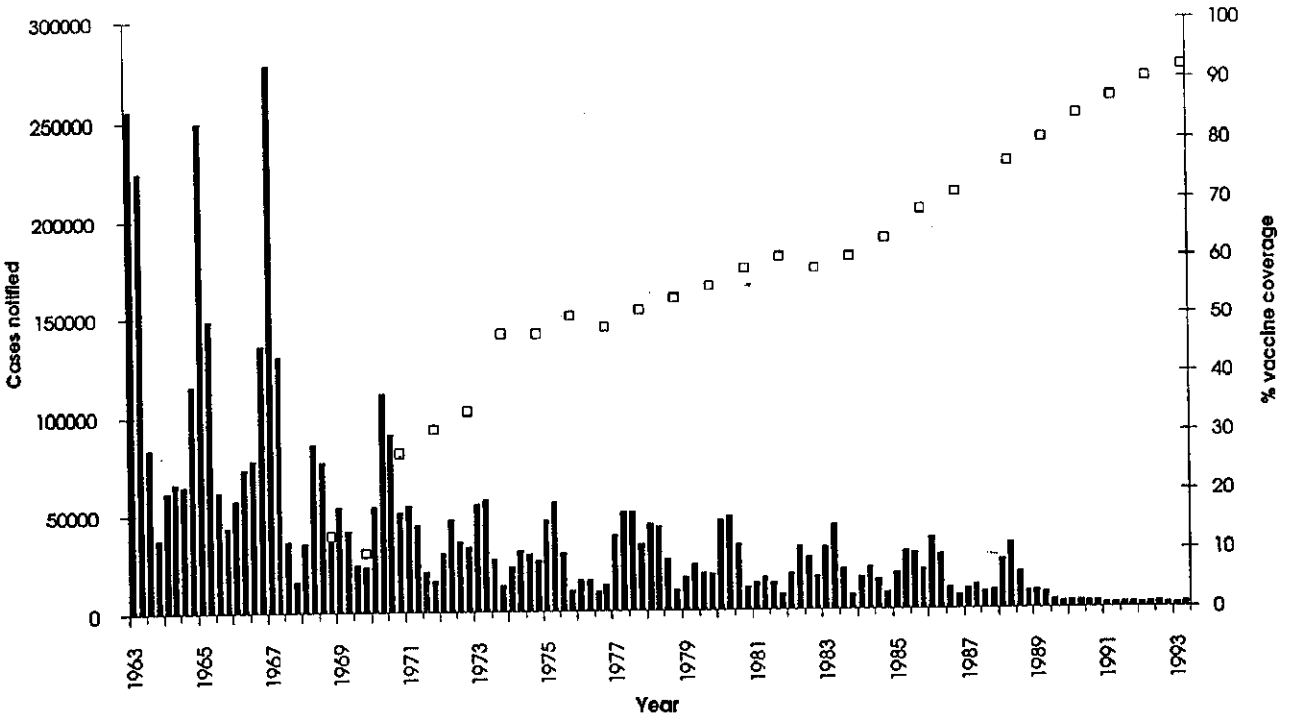
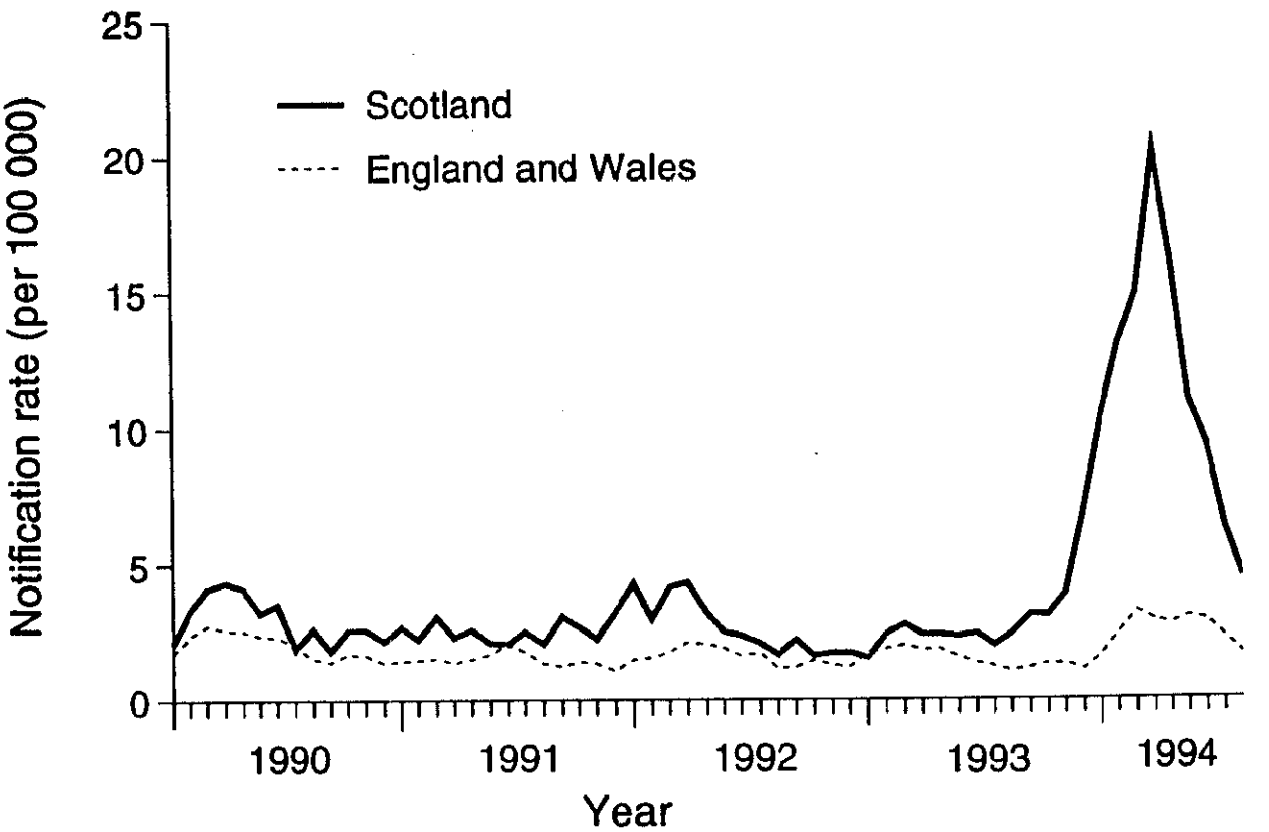


Fig 10: Measles notification data for England & Wales 1963-1993 and vaccine coverage by 2 years of age 1968-1993 (Nokes, Williams & Butler, 1995)

Fig 11: Measles notification data for England & Wales, and Scotland for 1990 to 1994 (cases per 4 week period)(Ramsay Gay et al, 1994)



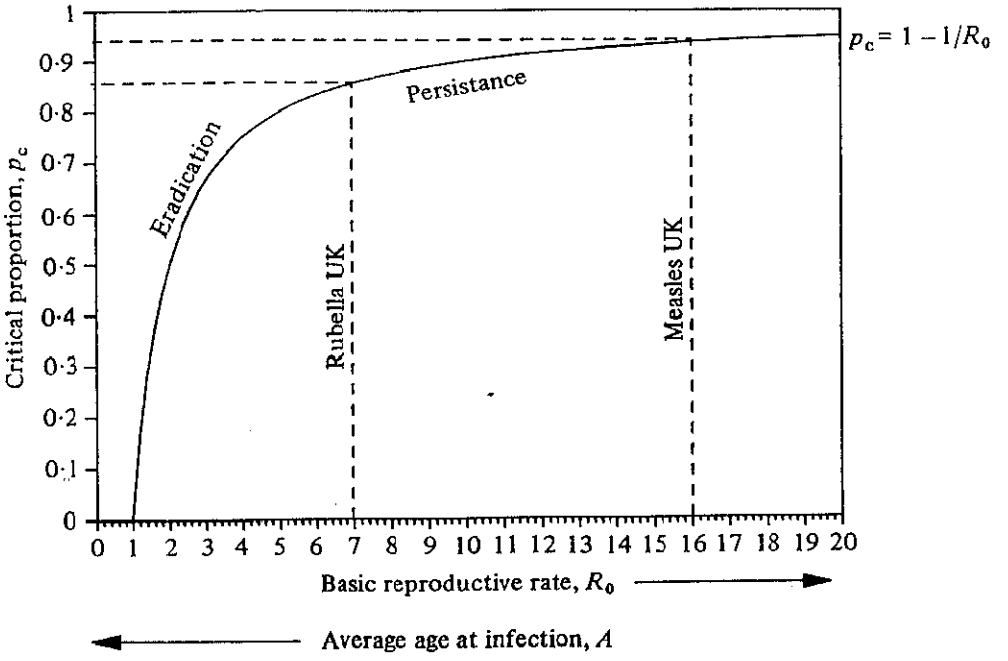
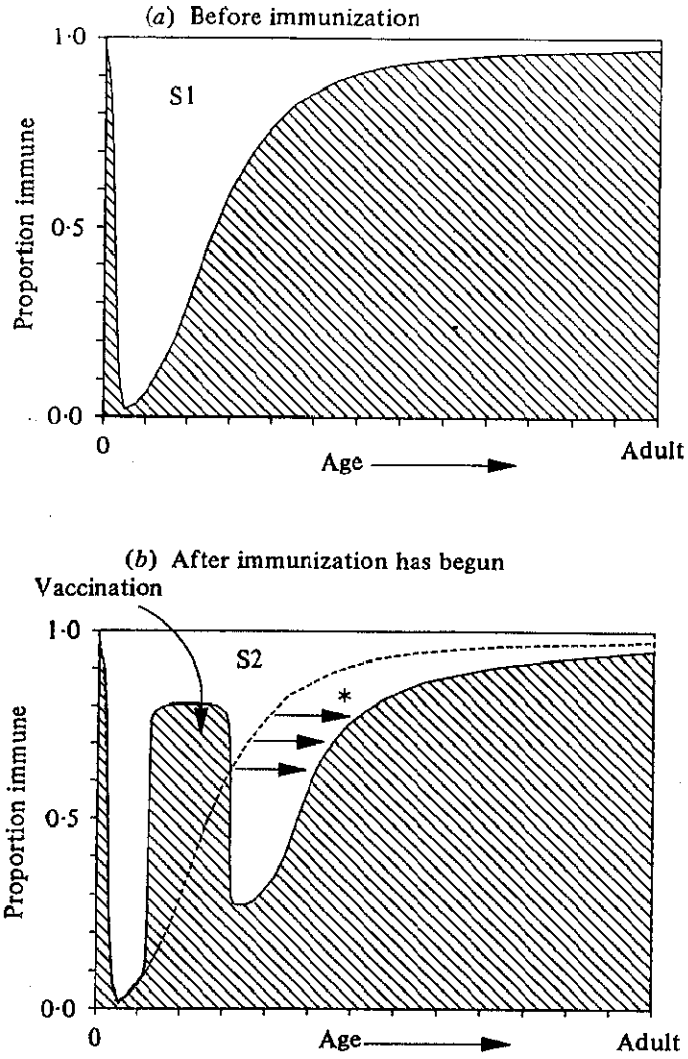


Fig 12: Relationship between R_0 (the basic reproductive rate) and the critical proportion of the population that must be effectively vaccinated (as near birth as possible) to achieve eradication of an infection over time (Nokes and Anderson, 1988)



Schematic illustration of the predicted impact of mass immunization (against a typical childhood viral or bacterial infection) on the distribution of the ages of susceptible individuals. Before immunization (graph *a*) there is a 'valley' of susceptibles (S1) in the young age classes. Attempts to fill in this 'valley' by vaccination (graph *b*) reduces the rate of transmission of the infection in the population, thus lowering the probability of unvaccinated susceptible individuals being infected. As a consequence there is an upward shift in the age-distribution of susceptibles (indicated by the arrows marked *), from that pertaining prior to vaccination (shown by the dotted line). This gives the surprising result that the number or proportion of susceptibles after immunization has begun (area S2) is roughly unchanged from that which existed before immunization (area S1). However, the average age of the susceptibles has increased.

Fig 13: Schematic illustration of the change in the proportion of a population immune to a childhood infection (i.e. the age-seroprevalence profile) (a) before vaccination, and (b) after about 2 years of mass vaccination (Nokes and Anderson, 1988)

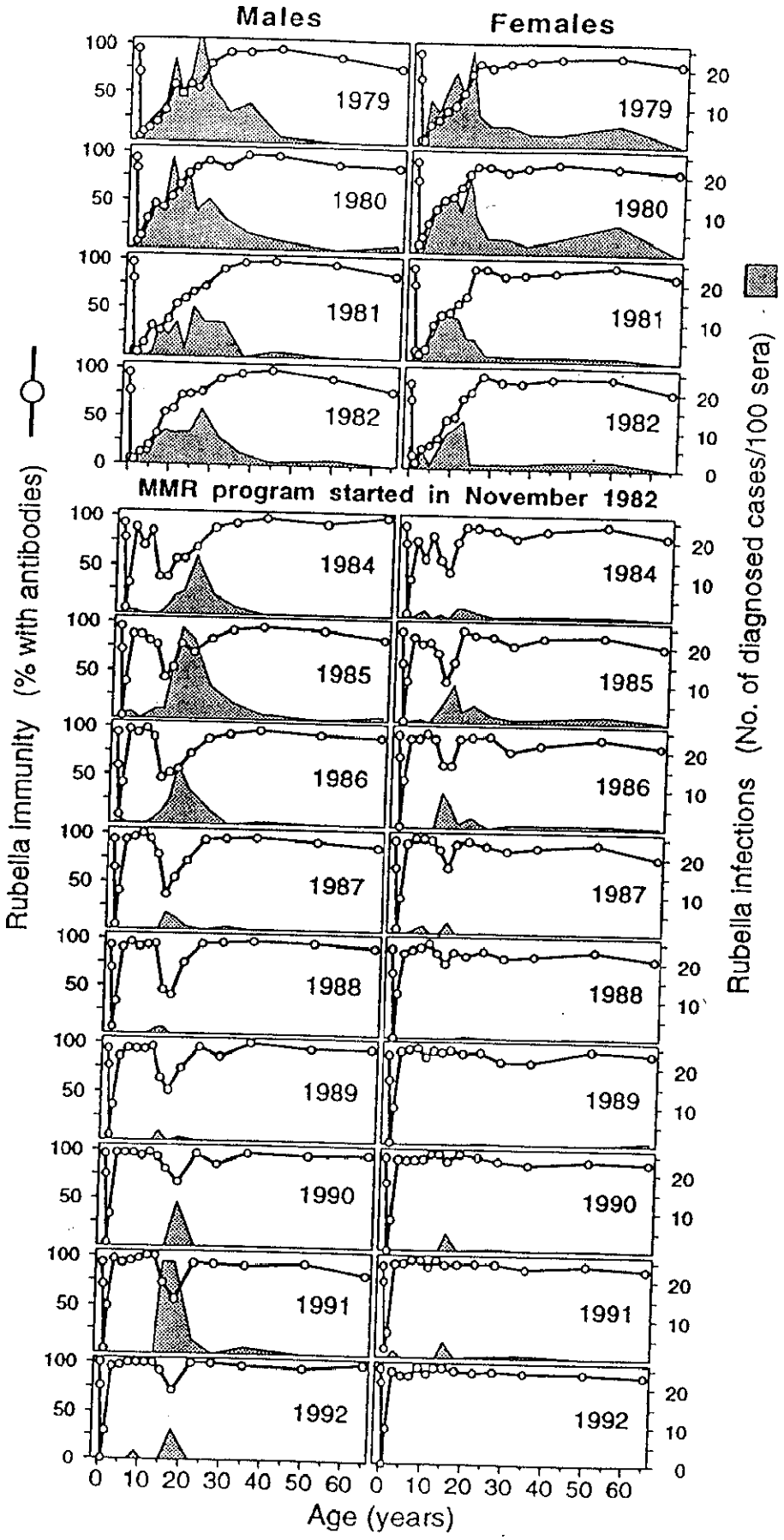


Fig 14: Age stratified seroprevalence data for rubella in Finland (rubella = rosolia); there is no vaccination between 1979 and 1982. By the second year of vaccination in 1984 a valley of susceptibility is clearly apparent and the bottom of this 'valley' occurs at older and older ages as time goes by (Ukkonen, 1996)

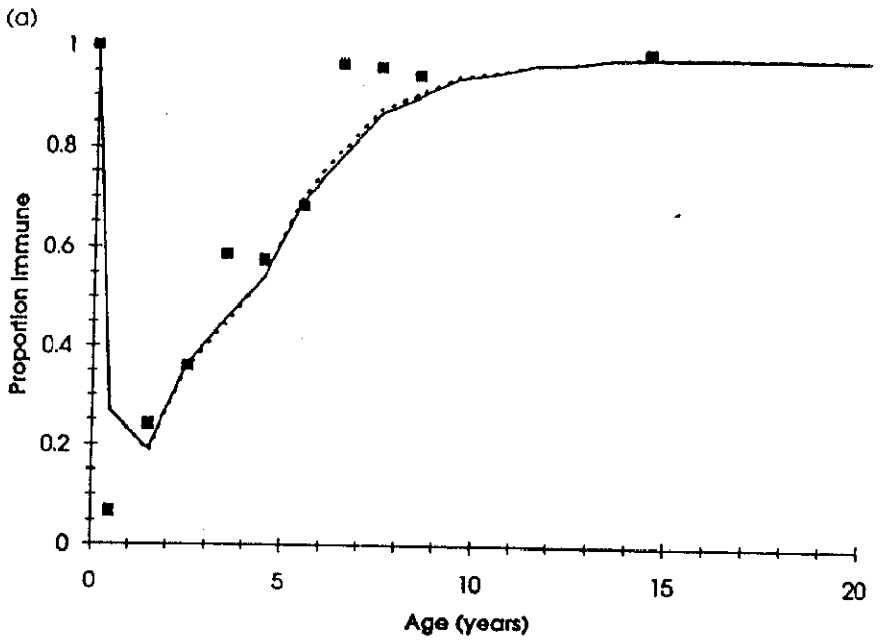
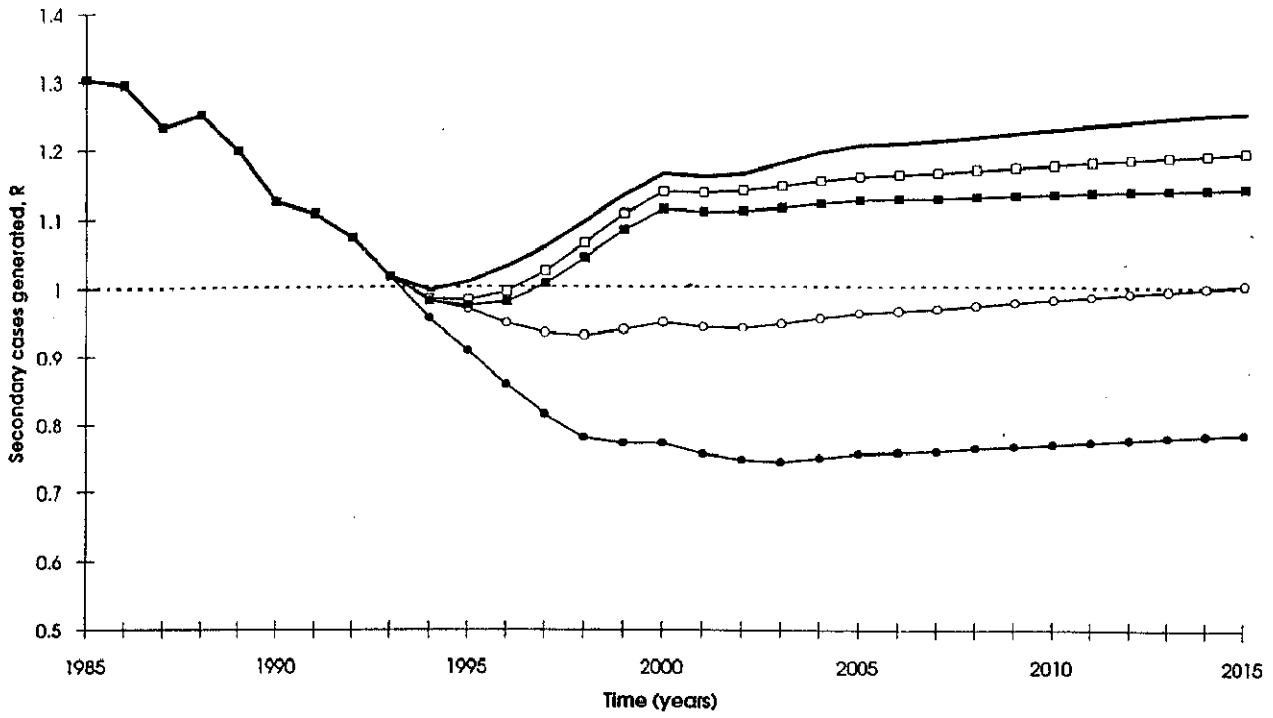


Fig 15: Comparison of serological data from surveys in 1969 with age-seroprevalence results predicted by the realistic age structure (RAS) model for that year (NB Dashed and solid lines represent different model assumptions about rates of contact between infectious and susceptible members of population) (Babad, Nokes et al, 1995)



The predicted impact of different measles immunization policies in England and Wales over the period 1985 to 2015. The relative benefit of each policy is measured by the effective reproductive rate, R (the average number of secondary cases generated per primary case) calculated at the start of each new school year (September) when there is greatest potential for an epidemic. The thick solid line describes the projected impact of the current (baseline) single dose measles immunization policy, with coverage, from 1994 onwards, of 92% of infants before their second birthday. Other lines give the predicted results of modifying this policy to include a second dose of vaccine, from 1994 onwards, either at 11 years of age (squares) or at 4 years (circles), delivered either selectively (open markers) or irrespective of vaccination history (solid markers). (From Babad et al., 1995, with permission from the Editors of Epidemiology and Infection).

Fig 16: Predicted impact of differing measles immunisation policies in England & Wales over the period 1985 to 2015 in terms of R, the effective reproductive rate, which is a measure of the potential of an infection to propagate in the population. Vaccination at a single age is replaced by vaccination at two ages from 1994 onwards (Babad, Nokes et al, 1995).

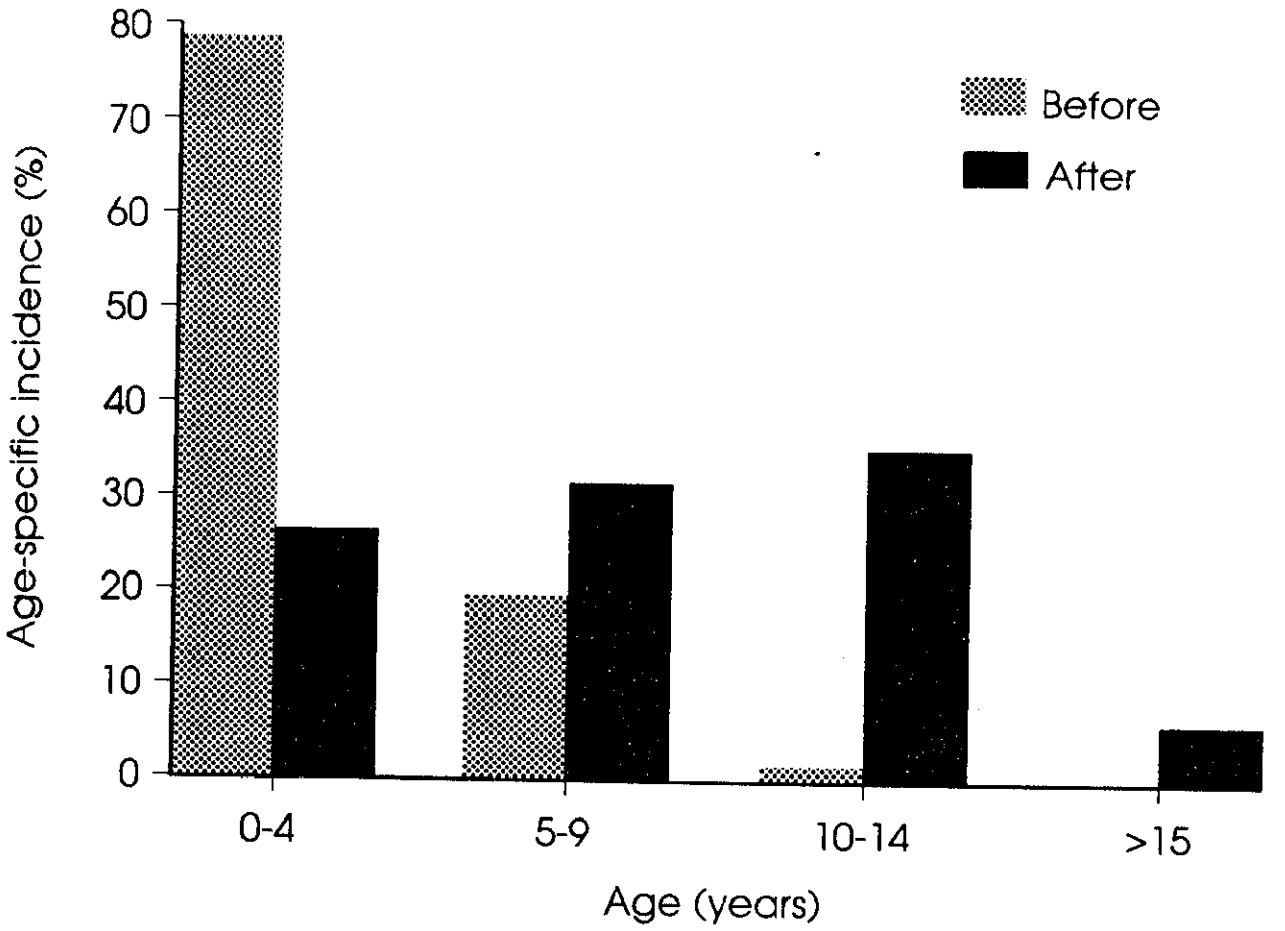


Fig 17: Changes in the age distribution of measles infection in People's Republic of China following the start of mass vaccination. (Source: Fig 13.9 in Anderson & May, 1991; data from Yihao & Wannian, 1983)

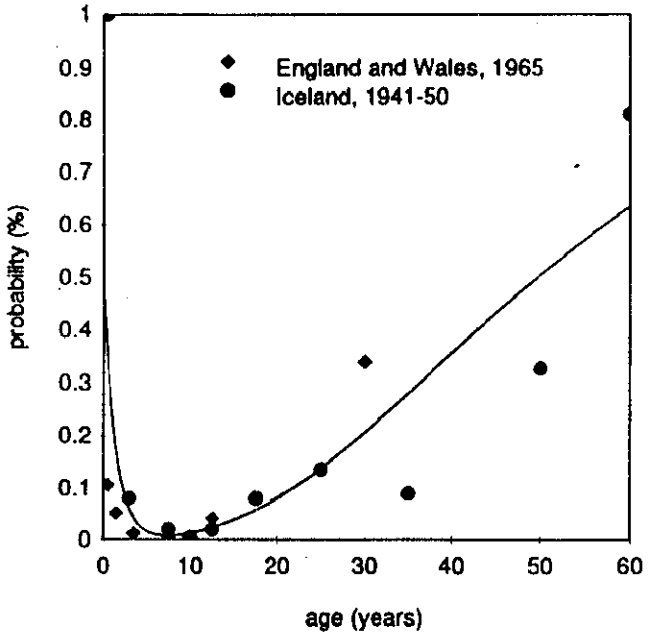


Fig 18: Percentage probability of dying as a result of measles infection (case fatality rate) according to age (Eichner, Zehnder and Dietz, 1996)

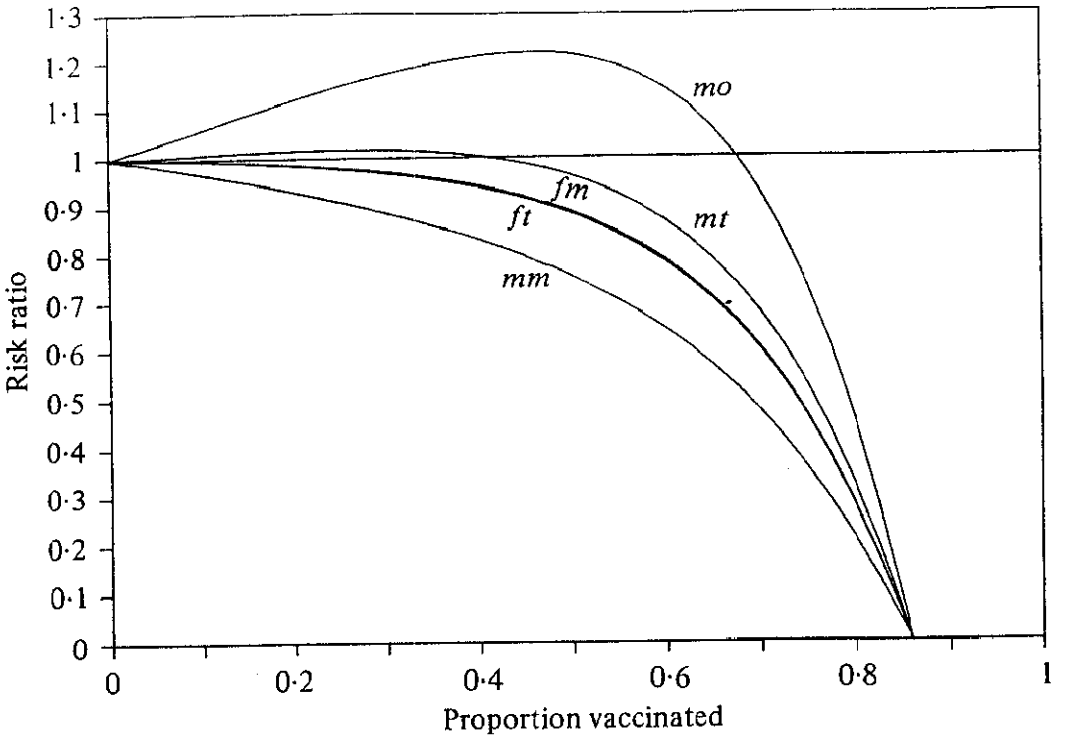


Fig 19: The equilibrium ratio of risk of serious disease after the introduction of mumps vaccination to the risk of serious disease in the absence of vaccination as a function of the proportion of 2-year old children vaccinated each year (mo = male orchitis, mt = total male complications, fm = female meningitis ≡ total female complications = ft, mm = male meningitis) (Anderson, Crombie and Grenfell, 1987)

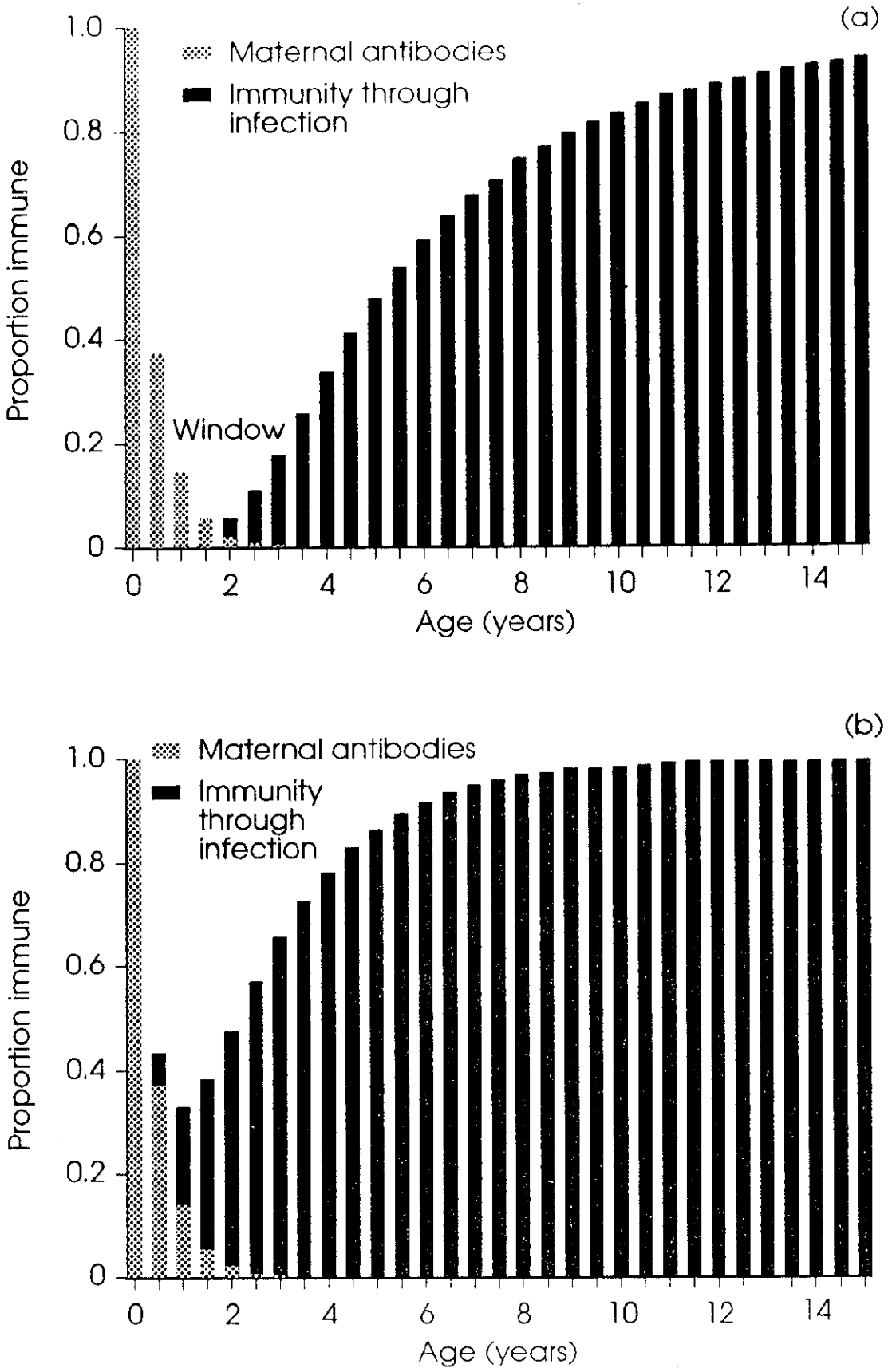


Fig 20: Schematic illustration of the 'vaccination window' problem. (a) With an average age of infection typical of the developed world there is a period during the second year of life when almost all children are susceptible to measles infection and hence can be vaccinated effectively. (b) With a lower average age of infection of about two and a half years there may be no age at which the vast majority of children are either susceptible to infection or can be vaccinated effectively.(Anderson & May, 1991)

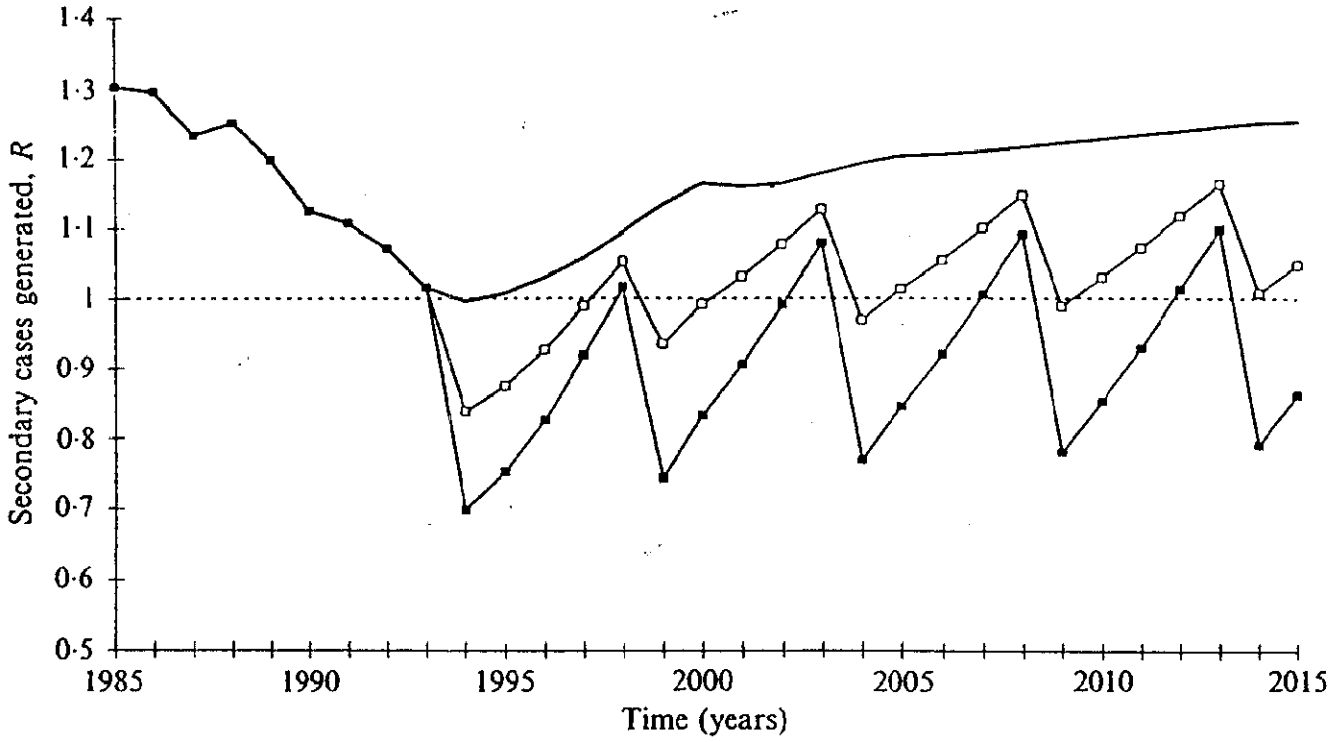


Fig 21: As in Fig 16, predicted impact of differing measles immunisation policies in England & Wales over the period 1985 to 2015 in terms of R, the effective reproductive rate. In addition to a vaccination at a single age, pulse vaccination of all children between ages 5-11 years begins in 1994 at 5 year intervals (Babad, Nokes et al, 1995).

few years (true pulse vaccination). Some countries notably in Latin America have a system of National Vaccination Days which are a good vehicle for this pattern of vaccination. For measles such campaigns are more effective if vaccination is given irrespective of previous vaccination history because of the likelihood of primary vaccine failures in at least 5% of those who are vaccinated. Typically vaccine efficacy has been poorer in developing countries because of the necessity to maintain the vaccine at a cold temperature from the moment of manufacture to the moment of vaccination; the recent development of freeze-dried vaccines will help in the future to eliminate the problem of maintaining this vaccine 'cold chain'.

As an example, the projections using the RAS model of the effects of pulse vaccination in England & Wales are shown in Figure 21. This shows the effect of vaccination pulses every 5 years (at 50% coverage) combined with a single dose at age 15-24 months at 92% coverage. In this case pulse vaccination is sufficient to reduce the possibility of an epidemic in most years. Reducing the interval will improve performance still further but clearly increases demands on resources. Although results are only shown for England & Wales, pulse vaccination or vaccination campaigns can be very effective in developing countries, as has been shown recently by the success in eliminating poliomyelitis in Latin America; such campaign approaches to vaccination have however achieved much lower levels of vaccination in countries of Africa.

Conclusions

This has been a very brief overview of some of the issues relating to the possibilities of using vaccination to eradicate measles, and how transmission dynamics models may be used to provide insights into the likely effects of such policies. There are a number of other issues and complexities which have not been addressed here, and Fig 22 (Dietz, 1995) shows a list of some of the problems and issues that are particularly relevant to developed and developing countries and which are amenable to consideration using the transmission dynamics modelling approach which has been described.

In conclusion it should be mentioned that transmission dynamics models may also be used in investigating a vast range of infections other than the characteristic childhood infections typified by measles. Examples include sexually transmitted diseases (e.g. human immunodeficiency virus), insect vector borne diseases (e.g. malaria, yellow fever or dengue), and parasitic worm infections (e.g. schistosomiasis, ascaris). All these diseases cause high levels of morbidity or mortality in many regions of the world (Warren and Mahmoud, 1989), and transmission dynamics models are one of the most suitable approaches used to identify the most important parts of often complex transmission cycles to project trends in incidence of infection and to explore the likely effects of a wide range of approaches to prevention or control.

Acknowledgements

I would like to thank Piero Manfredi of the Dipartimento di Statistica e Matematica applicata all'Economia and Fabio Tarini of the Dipartimento di Informatica for inviting me to visit the University of Pisa in order to give this seminar in the Facoltà di Economia di Pisa and for giving me the opportunity to meet and discuss our work on infectious disease transmission dynamics. I would also like to take this opportunity to thank my colleagues in Oxford, James Nokes, Ailsa Butler and María Gloria Basáñez, for their thoughts and assistance in the preparation of this seminar and the transcript.

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Table 1

Variables used in cluster analysis:

Child mortality rate 1975
(probability of dying by age 5)
Natural population increase per 1000 1970-75
Crude death rate per 1000 population 1970
Change in child mortality 1975to 1990
Change in rates of natural population increase
(change from rate for 1970-75 in relation to that for 1985-90)

Characteristics of clusters arising from cluster analysis:

Cluster number	Growth rate	Death rate (10^{-3})
1	0.0284	16.7
2	0.0236	21.5
3	0.0275	8.5
4	0.0076	9.3

Figure Legends

Fig 1: Flow chart of a deterministic model showing population flows between different serological compartments as a result of processes of infection. The compartments represent the state variables of the model. (NB In this case deaths from disease are not included in the model).

Fig 2: Partial differential equation system representing a transmission dynamics model of measles infection.

Fig 3: Global annual reported measles cases since the start of the WHO Expanded Programme on Immunisation in 1974. Note that the existence and comprehensiveness of reporting systems vary between countries (Source: WHO).

Fig 4: Estimated global numbers of measles cases from 1988 to 1995. Note that there was a change in the methodology of estimation in 1992 (Source: WHO).

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Fig 15: Comparison of serological data from surveys in 1969 with age-seroprevalence results predicted by the realistic age structure (RAS) model for that year (NB Dashed and solid lines represent different model assumptions about rates of contact between infectious and susceptible members of population) (Babad, Nokes et al, 1995)

Fig 16: Predicted impact of differing measles immunisation policies in England & Wales over the period 1985 to 2015 in terms of R, the effective reproductive rate, which is a measure of the potential of an infection to propagate in the population. Vaccination at a single age is replaced by vaccination at two ages from 1994 onwards (Babad, Nokes et al, 1995).

Fig 17: Changes in the age distribution of measles infection in People's Republic of China following the start of mass vaccination. (Source: Fig 13.9 in Anderson & May, 1991; data from Yihao & Wannian, 1983)

Fig 18: Percentage probability of dying as a result of measles infection (case fatality rate) according to age (Eichner, Zehnder and Dietz, 1996)

Fig 19: The equilibrium ratio of risk of serious disease after the introduction of mumps vaccination to the risk of serious disease in the absence of vaccination as a function of the proportion of 2-year old children vaccinated each year (mo = male orchitis, mt = total male complications, fm = female meningitis ≡ total female complications = ft, mm = male meningitis) (Anderson, Crombie and Grenfell, 1987)

Fig 20: Schematic illustration of the 'vaccination window' problem. (a) With an average age of infection typical of the developed world there is a period during the second year of life when almost all children are susceptible to measles infection and hence can be vaccinated effectively. (b) With a lower average age of infection of about two and a half

years there may be no age at which the vast majority of children are either susceptible to infection or can be vaccinated effectively.(Anderson & May, 1991)

Fig 21: As in Fig 16, predicted impact of differing measles immunisation policies in England & Wales over the period 1985 to 2015 in terms of R, the effective reproductive rate. In addition to a vaccination at a single age, pulse vaccination of all children between ages 5-11 years begins in 1994 at 5 year intervals (Babad, Nokes et al, 1995).

Fig 22: A list of problems relating to vaccination strategies which are amenable to mathematical modelling. (Compiled by RT Chen, CDC, Atlanta, reported by Dietz, 1995).

Fig 1: Flow chart of a deterministic model showing population flows between different serological compartments as a result of processes of infection. The compartments represent the state variables of the model. (NB In this case deaths from disease are not included in the model).

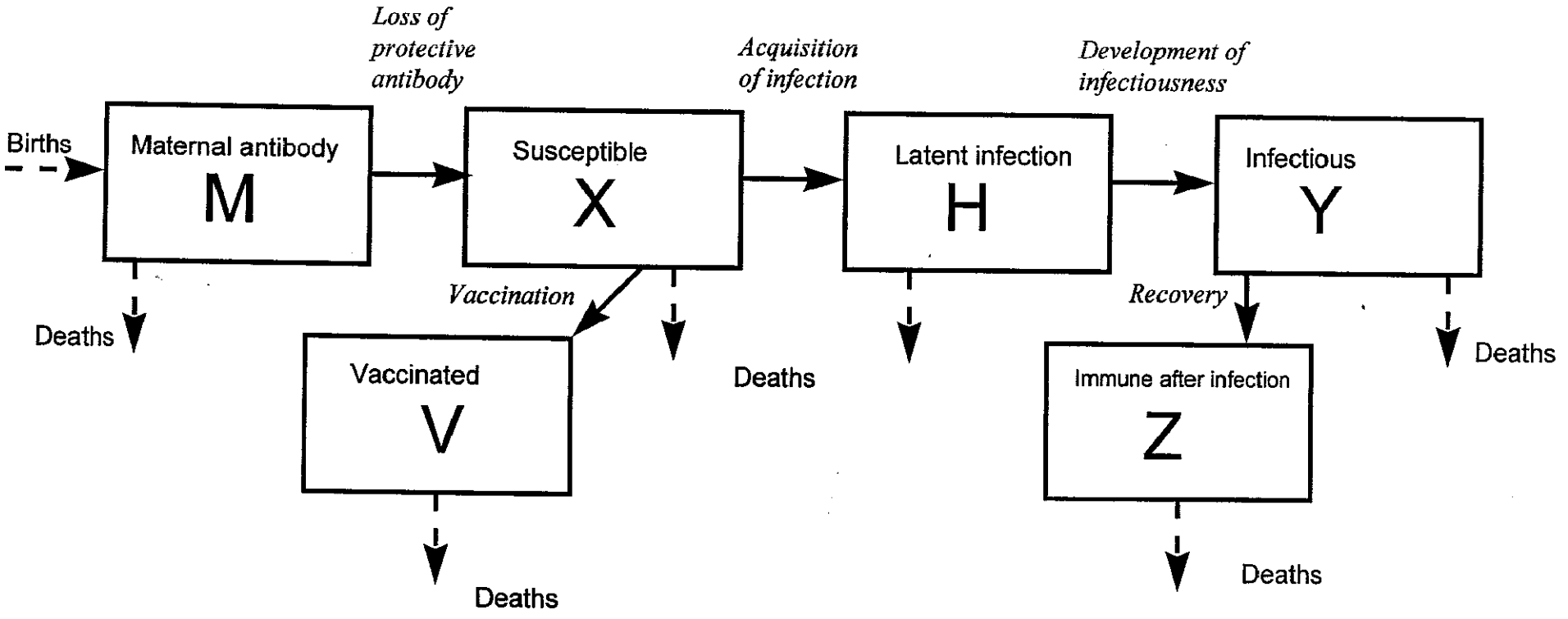

Fig 2: Partial differential equation system representing a transmission dynamics model of measles infection.

MODEL EQUATIONS

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

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

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

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

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

$$\frac{\partial V}{\partial t} + \frac{\partial V}{\partial a} = uX(a,t) - \mu(a)V(a,t)$$

KEY

State Variables:

M :- Immune because of maternal antibody
X :- Susceptible
H :- Latently infected but not yet infectious
Y :- Infectious
Z :- Immune following infection
V :- Immune through vaccination

Parameters:

d :- rate of loss of maternal antibody
u :- rate of effective vaccination in absence of maternal antibody
μ :- age related mortality rate
λ :- force of infection
σ :- incubation rate
γ :- rate of recovery from infection