



UK Vaccination Programme Risk and Reward

UK Vaccination Programme Working Party:
Monica Cornall
Margaret Chan
Jan Sparks

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Contents

1.	Introduction	4
1.1.	Introduction to the UK Vaccination Programme Working Party and this report	4
1.2.	Terms of reference	4
1.3.	Acknowledgements	4
1.4.	Executive summary	5
2.	Introduction to vaccines	6
2.1.	Natural immunity	6
2.2.	Incubation, latent and infectious periods	6
2.3.	How does immunisation work?	6
2.4.	For how long does the vaccination provide immunity?	7
2.5.	Does the vaccine provide neo-natal immunity?	7
2.6.	Breakthrough infections	7
3.	Dynamics and control of disease	8
3.1.	Theory of herd immunity	8
3.2.	Basic reproductive number, R_0	9
3.3.	Effect of immunisation programmes on disease complication rates	10
4.	Models	12
4.1.	Introduction	12
4.2.	Dynamic and static models	12
4.3.	Model 1 - modelling chickenpox and shingles	13
4.4.	Model 2 - The average cost of measles cases and adverse events following vaccination in industrialised countries	16
4.5.	Simplifying assumptions	17
4.6.	Models – commentary	17
5.	Data	18
5.1.	Key sources of data	18
5.2.	Data issues	19
6.	The psychology of immunisation choices	20
6.1.	The risk reward dilemma	20
6.2.	Research into the psychology of making immunisation choices	22
6.3.	The MMR controversy	22

7.	Vaccination programmes in practice	24
7.1.	Who assesses risk and reward?	24
7.2.	Global view	25
7.3.	Control cycle	25
8.	Case Studies	27
8.1.	Case Study 1: Poliomyelitis (Polio)	27
8.2.	Case Study 2: Measles	30
9.	Conclusions	34
9.1.	Summary	34
9.2.	Is there a role for actuaries?	35
10.	Glossary	36
11.	References	38
11.1.	General references & data sources	38
11.2.	Useful websites	39
11.3.	Epidemiological references	39
11.4.	Other sources of interest	39
11.5.	Related to MMR	39

1. Introduction

1.1. Introduction to the UK Vaccination Programme Working Party and this report

There is no shortage of news coverage on the safety of vaccines. Whether it is MMR or the cocktail of jabs administered to combatants in the Gulf War, questions are being raised over whether the right balance is being reached between risk and reward in vaccination programmes. As the political and professional stakes are high the opinions presented in the debate tend to be polarised. It was the apparent lack of an independent voice, and particularly a statistically-informed one, that led to the formation of the Working Party in 2001.

Our initial work focused on understanding how the vaccination programme is delivered and monitored in the UK, how the data is collected, and the basics of epidemiology. In October 2001 we presented a “learner workshop” summarising what we had discovered along with case studies which illustrated the key points of interest. More recently we have concentrated our efforts on searching the existing literature on vaccinations, particularly concentrating on the mathematical models currently in use in the field. The main aim of this has been to assess whether and where actuarial skills may be able to add value.

1.2. Terms of reference

The terms of reference of the working party are set out below.

“To investigate, and hence stimulate informed debate and possible further studies, on the balance between risk and reward inherent in the current UK vaccination programme from an independent statistically informed viewpoint. We do not aim to carry out any new investigations or studies but to interpret and assimilate existing data and studies. As part of our fact-finding we will try to discover whether any organisation currently monitors the trade-off between risk and reward, and what mathematical or statistical models are used.”

1.3. Acknowledgements

The Working Party would like to thank Dr Araceli Busby, Anita Barker and Paula Francombe for their invaluable help in compiling and reviewing the report. We would also like to thank Swiss Re for meeting the costs of printing this report. The views in this paper are entirely those of the authors and not those of any organisation, society or professional body. Any errors are solely the authors’ responsibility.

1.4. Executive summary

The paper summarises the work to date of the UK Vaccination Programme Working Party.

The paper begins with introductions to vaccines and to the dynamics and control of infectious disease in sections 2 and 3 respectively. The fundamental concept of herd immunity is introduced.

In section 4 some examples of mathematical models currently being used in the field are considered. An overview of each model is given and a brief commentary on the models from an actuarial viewpoint is included. The availability of data to allow model assumption sets to be derived is covered in Section 5. Here the limitations of data are also discussed.

The next section (section 6) relates to the psychology of vaccination programmes, introducing the concept of a dynamic risk-reward matrix for vaccination decisions. The discussion brings into the frame the recent SARS outbreak, as well as the on-going MMR and autism debate.

Section 7 looks at how vaccination programmes are organised. The initial focus is on the UK programme – how it is delivered, current rates of uptake, how it is monitored – the view is then broadened to consider the global nature of infectious disease. The concept of a vaccination control cycle is also introduced here.

Section 8 is devoted to two case studies (relating to polio and measles) which highlight the key ideas brought out in the earlier sections of the report.

Section 9 contains the conclusions of the paper in terms of what the members of the Working Party have learnt from their research and potential areas of further research for actuaries. The key conclusions are:

- There is a complex and dynamic interaction between individual and herd immunity. It is essential to pay attention to parental psychology as poor take-up rates of vaccinations can be more risky for the population than having no programme at all.
- Epidemiologists are using sophisticated mathematical models to consider many different aspects of disease transmission and control. The methodology, including sensitivity testing, would be familiar to any actuary.
- There is potential for beneficial co-operation between actuaries and epidemiologists in the future. Actuaries would be able to assist epidemiologists to refine the modelling of mortality. By the same token, actuaries have much to learn from epidemiologists in terms of modelling infectious disease, for example the impact of SARS-type epidemics or the effect of bio-terrorism on insurable events.

2. Introduction to vaccines

2.1. Natural immunity

Under the threat of infection, the immune system attacks the invader and produces antibodies to destroy the organism. The immune system “remembers” this destruction process, so that if the invader returns a repeat attack can be mounted faster.

The duration of human immunity against many viral infections appears to be lifelong though the mechanism by which this is achieved is not completely clear at present.

Maternal antibodies are acquired during foetal development. In the absence of infection, the protection afforded by maternal antibodies decays to zero over a period of approximately one year.

2.2. Incubation, latent and infectious periods

The ‘latent period’ is the time from initial infection to the point at which the individual becomes infectious to others. The ‘incubation period’ denotes the time from initial infection to the point where symptoms of disease appear. During the ‘infectious period’ the patient is infectious to other people. These dynamics vary between different diseases and can help define how a disease spreads in the community. The most difficult diseases to control are those which allow the host to continue to mix in the community and infect many other people before symptoms appear.

2.3. How does immunisation work?¹

Immunity can be induced, either actively (which provides long term protection) or provided by passive transfer (which provides short term protection). Vaccine stimulates the immune system to produce its own antibodies.

Active immunity is induced by using inactivated, or attenuated (weakened²) live organisms or their products. Live attenuated vaccines include those for poliomyelitis (OPV), MMR, and BCG vaccine. Bacterial vaccines such as pertussis and inactivated poliomyelitis (IPV) vaccines contain inactivated organisms.

¹ Source: The Green Book

² eg for OPV the viruses are attenuated by growing successive generations of the virus under special conditions that select for mild, non-virulent strains – Polio Vaccine Factsheet, DoH, 1997

In the passive form, ready-made human antibodies are injected into the human body. This gives immediate protection. However, the protection only lasts a few weeks. An example is hepatitis A vaccine.

2.4. For how long does the vaccination provide immunity?

This is an unknown quantity because vaccination programmes have not been in existence long enough. Surveys of the population take place to assess this. However although individuals can be tested for immunity to a particular disease, it is not possible to tell whether someone is immune because they have had the vaccination or because they have had the disease – they just test positive for the antibodies.

Natural infection by the virus induces higher antibody levels than those induced by vaccines, so it is possible that vaccines do not provide lifelong immunity. It is also possible that natural ‘boosters’ occur when an immune person encounters the disease in the community. This opportunity disappears when a successful immunisation programme is in place.

To date surveys have not shown any indication of rapidly waning immunity after vaccination for rubella³ or measles.

2.5. Does the vaccine provide neo-natal immunity?

If a mother had acquired natural immunity to a disease then she will pass on that immunity to her young baby. This immunity is understood to last for around the first year of life, when the baby is most vulnerable. It is possible that children of mothers with only vaccine-induced immunity will have shorter duration and lower level of maternal antibodies.⁴

2.6. Breakthrough infections

Breakthrough infections are vaccine failures - some vaccinated people will not develop an immune reaction to the vaccine leaving them vulnerable to the disease.

Immunisation provides protection for around 90% of recipients for measles and mumps and over 95% for rubella.⁵ This is why a two dose system of MMR is used in the UK.

³ Prevalence of antibodies against rubella virus in the Netherlands after changing from selective to mass vaccination, De Haas et al, *Epidemiology and Infection*, 1999

⁴ Reduced measles immunity in infants in a well-vaccinated population, Pabst et al, *Pediatr Infect Dis J*, 1992;11

⁵ The Green Book

3. Dynamics and control of disease

3.1. Theory of herd immunity

There are two main effects of an immunisation programme:

- 1) Direct effect: those successfully immunised move into the immune class.
- 2) Indirect effect: more immune individuals means fewer candidates for spreading infection so the force of infection is weakened.

A consequence of the indirect effect is that it is not necessary to immunise everyone in order to eradicate an infection. Once the vaccination coverage has reached some critical level the infection will be unable to maintain itself. This is what is meant by *herd immunity*.

Define:

p proportion successfully immunised
R reproductive rate of parasite in the population
R₀ basic reproductive number (fully susceptible population), ie the average number of secondary infections produced when one infected individual is introduced into a host population where everyone is susceptible

$$R \leq R_0(1-p)$$

If $R < 1$ the infection cannot maintain itself

$$p_c = 1 - (1/R_0)$$

Where p_c is the critical proportion of the population successfully immunised to prevent spread of disease

Figure 3.1 : Overall criterion for eradication ⁶

Figure 3.1 sets out a simple model for the overall criterion for eradication of an infection. The effective reproductive rate of the parasite in the population, R , will be less than $R_0(1-p)$ when part of the population is immune following natural infection. For eradication R needs to be less than 1 because then the disease cannot maintain itself in the long run. Hence setting R to 1 allows the calculation of the critical proportion of the population requiring immunisation for eradication of the disease, denoted by p_c . The relationship between p_c and R is illustrated in Figure 3.2.

⁶ Infectious Diseases of Humans, Anderson and May

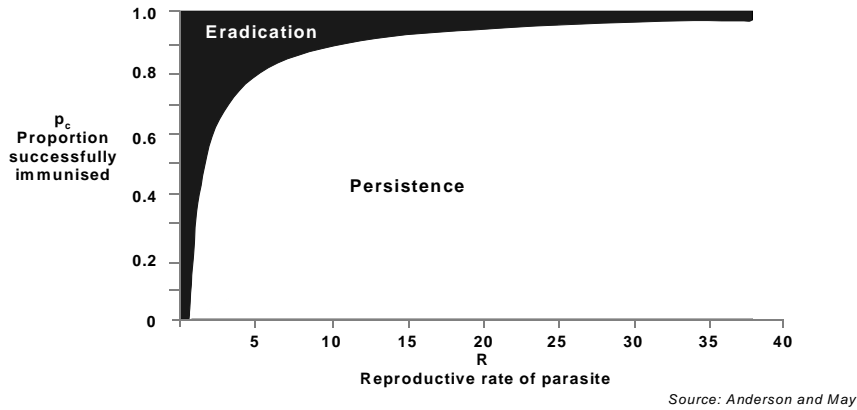


Figure 3.2: Herd immunity achieved when proportion immunised, $p \geq p_c$

3.2. Basic reproductive number, R_0

R_0 can be estimated by studying how early in life individuals succumb to the disease in an un-immunised population.

Define:

λ force of infection - instantaneous per capita rate of acquisition of infection

L life expectancy

A average age at which infection is acquired

$R_0 \approx \lambda L$ and $A \approx 1/\lambda$, so

$R_0 \approx L/A$

R_0 for measles has been estimated to be 16-18, i.e. each infected individual will infect 16 to 18 others in a fully susceptible population. For chickenpox R_0 is 10-12 and for smallpox R_0 is 4-7. The relatively low R_0 and p_c values for smallpox helps to explain the huge success of the smallpox immunisation programme throughout the world.

	R_0 Basic reproductive number	p_c Critical proportion of the population be immunised for eradication
Malaria		99%
Measles	16 -18	90 – 95%
Whooping Cough	16 -18	90 – 95%
Chicken Pox	10 -12	85 – 90%
Mumps	11 -14	85 – 90%
Rubella	6 - 7	82 – 87%
Poliomyelitis	6 - 7	82 – 87%
Smallpox	4 - 7	70 – 80%

Source: Anderson and May

Figure 3.3: Relationship between R_0 and p_c

3.3. Effect of immunisation programmes on disease complication rates

3.3.1. The importance of age at infection

If deaths or serious complications are more likely at older ages, it is possible that an immunisation programme could actually increase the incidence of serious cases in the years between the introduction of an immunisation programme and eradication of the disease. This is because pools of susceptibles (either people for whom the vaccine was not successful or people who were not vaccinated) build up over time and eventually an epidemic breaks out. However the susceptibles catch the disease at a more advanced age than they would have done under pre-immunisation program conditions.

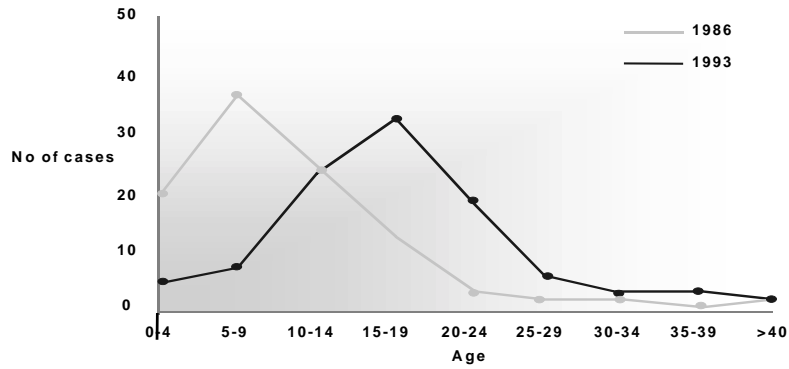
This is illustrated by a poorly implemented vaccination programme for rubella in Greece. Although rubella is usually a mild disease, it poses a serious risk to unborn children if contracted by the mother during the first few months of pregnancy.⁷ In Greece, a programme commenced to give MMR to one year-old children in the late 1970s, mainly via the private sector which meant a fairly low coverage rate (less than 50%). There was no parallel policy to protect adolescents and young women, so as the average age of infection increased so did the proportion of pregnant women susceptible to rubella. In 1993 the incidence of rubella in young adults was the highest ever recorded. The epidemic of Congenital Rubella Syndrome (CRS) that followed was the largest in Greece since 1950.⁸

⁷ In the first 8 to 10 weeks the chance of fetal damage is up to 90%, declining to 10-20% by 16 weeks. Infection can cause spontaneous abortion, stillbirth and congenital rubella syndrome (CRS) which includes cataracts, mental retardation, deafness and cardiac defects.

⁸ Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review, Panagiotopoulos, BMJ 1996

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Age distribution of patients with rubella attending outpatient departments of general hospitals in greater Athens 1986 and 1993



Source: Panagiotopoulos et al 1996

Figure 3.6: Age distribution of patients with rubella attending outpatient departments of general hospitals in Greater Athens 1986 and 1993

4. Models

4.1. Introduction

Epidemiological models require expertise in areas with which actuaries are highly familiar, including age-related morbidity and mortality effects. In addition to these however there are other factors which need to be taken into consideration in modelling the impact of immunisation programmes, particularly the herd immunity effect.

The use of mathematical models is of great importance for epidemiologists, as it can enable them to consider the optimum immunisation strategy before implementation.

This section will look at two epidemiological models in order to demonstrate the level of model available. Firstly a dynamic model, used for modelling chickenpox and shingles, is examined. This is interesting because it takes into account the herd immunity effect and the interaction of immunity between the two diseases. Secondly a paper is analysed describing the cost-benefits of adopting a vaccination policy for measles. This is interesting because it looks at the benefits, in terms of deaths and morbidity prevented by the vaccine, and the costs, in terms of adverse reactions to the vaccine.

4.2. Dynamic and static models

The key factor governing the transmission of infection within a given population is the force of infection. This is defined as the instantaneous per capita rate at which susceptibles acquire infection. Since patterns of contact are age dependent the force of infection is a function of age.

Models which calculate the health benefits of vaccines can be divided into two groups – static models which assume a constant force of infection and dynamic models where the force of infection at time t is a function of the number of infectious individuals in the population at that time. In constant force of infection models the per-susceptible rate of infection is not altered whereas in dynamic models mass immunisation results in fewer infectious individuals in the community and thus a lower force of infection acting on those who are not immunised.

Only dynamic models are able to capture the decline in the rate of infection following mass vaccination (and thus herd-immunity effects).⁹

⁹ Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective, Edmunds, Medley and Nokes, *Statistics in Medicine* 18, 1999

4.3. Model 1 - modelling chickenpox and shingles

There have been a number of recent papers looking at the effects of introducing chickenpox vaccinations. This is a particularly interesting area to model, as it looks at the long term effects of a vaccination programme, taking into account possible age shifts in the prevalence of the disease and the possibility of increased cases of shingles.^{10,11}

Background

Varicella zoster virus (VZV) is a herpes virus that produces two distinct diseases: varicella (chickenpox) and herpes zoster (shingles). Chickenpox results from a first time infection with VZV. The illness tends to be mild but severity increases with age. The lifetime risk of acquiring VZV is over 95%.

After chickenpox, VZV becomes latent in the body and can reactivate, generally after a long period, to cause shingles. Reactivation occurs in 15-20% of individuals over 70% of whom are adults. Shingles is associated with severe morbidity (4% of cases hospitalised) and significant case fatality (.07% of cases). The precise relationship between chickenpox and shingles incidence is unclear. Shingles is infectious and can transmit chickenpox. It has been suggested that shingles may occur more frequently in adults who have not been boosted by chickenpox contacts during their adult life. If so, reduction of chickenpox incidence after mass vaccination could reduce the likelihood of such boosting and thus increase the incidence of shingles.

Routine childhood immunisation was introduced in the US in 1995. The primary concern with introducing such a programme in this country is that by reducing exposure to infection, vaccination could lead to an increase the average age at infection, with a corresponding increase in the complication rate. If vaccination could increase shingles this would also be of concern since it is a more serious disease than chickenpox.

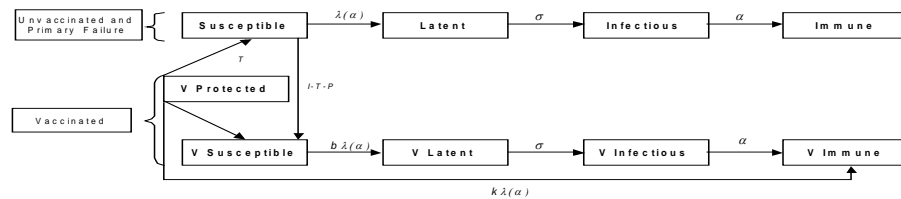
The Model - Description¹²

This study used two models. Model 1 assesses the impact of chickenpox transmission before and after vaccination. Model 2 investigates the potential impact of vaccination on shingles. For simplicity Model 1 only is discussed here.

¹⁰ Modelling the impact of immunisation on the epidemiology of varicella zoster virus, Brisson, Edmunds, Gay et al, *Epidemiology and Infection* 2000.

¹¹ The effect of vaccination on the epidemiology of varicella zoster virus, Edmunds and Brisson, *Journal of Infection*, 2002

¹² Modelling the impact of immunisation on the epidemiology of varicella zoster virus, Brisson, Edmunds, Gay et al, *Epidemiology and Infection* 2000.



Source: Brisson et al

Figure 4.1: Modelling the impact of immunisation on the epidemiology of VZV

Model 1 is illustrated by the flow diagram in figure 4.1. At 6 months of age, once maternal antibodies to chickenpox have waned, children enter the susceptible class (*Susceptible*) and if infected pass through the latent (*Latent* ie infected but not infectious) and infectious (*Infectious*) periods before acquiring lifelong immunity (*Immune*). Following vaccination, individuals either remain in the fully susceptible class (*Susceptible*) because of complete vaccine failure or pass into one of two mutually exclusive classes ((1) a temporary protection class (*V Protected*) in which individuals are immune from infection but may lose protection over time; or (2) a modified susceptible class (*V Susceptible*) in which individuals retain some degree of partial protection (1-b) and if infected are likely to experience a less severe infection. Vaccinated individuals can also become permanently immune (*V Immune*) by having an effective contact with an infectious individual.

Mixing Patterns – the Who-Acquired- Infection-From-Whom matrix (WAIFW)

The WAIFW matrix represents the effective contact rate between age groups ie the rate at which an infective of age X will infect a susceptible of age Y. This can have a significant effect on the impact of transmissions. Because of the difficulty of setting the matrix, sensitivity testing is performed.

Parameters

Parameters are estimated from clinical studies. The force of infection is age and time dependent, and depends on the number of susceptible people in the population ie this is a dynamic model as explained above, so takes into account the effect of herd immunity.

In model 1 the age and time dependant force of chickenpox infection is defined as:

$$\lambda(a,t) = \lambda_v(a,t) + \lambda_z$$

$$= \sum_{a'=0}^L \beta(a',a) (I(a',t) + m VI(a',t)) + \lambda_z$$

where $\lambda_v(a,t)$ is the force of infection due to chickenpox, λ_z is the force of infection due to shingles, $\beta(a',a)$ is the rate at which an infective of age a' will infect a susceptible of age a , L is life expectancy, and m is the rate of chickenpox infectiousness of vaccinees compared to non-vaccinees.

$I(a',t)$ is the number of individuals of age a' at time t who are infectious

$VI(a',t)$ is the number of individuals of age a' at time t who are vaccinated infectious

The model was run for four different strategies of vaccination.

Commentary

Although the overall conclusion of the paper is that the incidence of infection and morbidity will be reduced by mass vaccination, the sensitivity testing produces some interesting results. For example the most effective programmes at reducing the incidence of chickenpox result in the biggest increase in shingles cases, if exposure to chickenpox prevents or delays the development of shingles.

Only the situation of coverage between 40% and 70% (and random age mixing) resulted in a long-term increase in chickenpox morbidity. The authors state that this is unlikely, but given the current reluctance of parents to give MMR, and the fact that chickenpox is seen as a mild disease, this scenario could turn out to be the most likely.

The model shows that the higher the vaccine efficacy the more mass vaccination reduces the incidence of chickenpox infection. On the other hand lower vaccine efficacy reduces the shift in the average age at natural infection by allowing a certain number of cases to occur every year. Thus, paradoxically, for intermediate levels of coverage, lower efficacy vaccines could be better at reducing morbidity than better vaccines, particularly if exposure to chickenpox does boost the immune response to shingles.

4.4. Model 2 - The average cost of measles cases and adverse events following vaccination in industrialised countries ¹³

Background

The objective of this study was to estimate the average cost per measles case and per adverse event following immunisation. Section 8.2 gives more explanation of the disease and its complications.

Model - Description

A decision tree (see Appendix I) was built to represent the complications associated with measles cases and adverse events following immunisation. Distributions are defined for the parameter estimates. The model is run 10,000 times and on each occasion, a new set of parameter values for all the uncertain parameters are randomly selected according to their distribution using Monte Carlo sampling. This provides an outcome distribution for the cost of an average measles case and allows the authors to report a mean and 95% credibility intervals.

Commentary

The paper aims to give a cost-benefit analysis of the vaccine compared to the disease. The sensitivity testing showed that the three most influential variables on costs per measles case were:

- Average number of work days lost by the mother for a non-hospitalised case
- Proportion of cases not seeking medical attention (22.5% assumed), and
- Proportion of encephalitis cases developing sequelae leading to residential care.

The authors noted that it was most sensitive to some everyday assumptions, which affect a large number of the patients modelled, such as the number of parental days off work for caring for a child with measles, and their lost salary. However the paper did not seem to take into account the corresponding cost of time off work to get children vaccinated. Similarly the cost of Calpol for treating measles was counted, but not the corresponding cost of dosing every vaccinated child with Calpol, which is recommended practice to counteract fever. The fourth major sensitivity might be whether the MMR vaccine causes some other (unproven) side-effects such as autism and the cost of caring for those patients.

¹³ The average cost of measles cases and adverse events following vaccination in industrialised countries, Carabin, Edmunds et al, BMC Public Health, 2002]

4.5. Simplifying assumptions

4.5.1. Simplified mortality assumptions

A common simplifying assumption made by epidemiologists is that everyone lives for their life expectancy. This is known as Type I mortality. Type II mortality assumes a constant force of mortality rate of μ and results in an exponential decline in the number surviving. If a disease with significant mortality was being modelled the simplification of using Type I mortality could make a significant difference to the results.

4.5.2. Lack of understanding of the immune system

Many of the models assume that the vaccines provide lifelong immunity. This is obviously a critical assumption, particularly for a disease like rubella where the complications are much more serious at child bearing ages.

Most of the models assume immunity in the first year of life. It is not yet known to what extent a mother who is vaccine immune would pass on immunity to her baby. If the transmission of immunity is weak then this would provide a window of risk until the child is immunised.

4.6. Models – commentary

Although the paper presents only two models here, these are indicative of the type of models which epidemiologists are using to assess the risks and rewards of vaccination strategies.

Many of these models are very sensitive to the assumptions made in them, and it can be difficult to assess what these input assumptions should be. Actuaries are aware of the importance of sensitivity testing and refining the quality of the data for those assumptions to which the model is most sensitive. Actuaries also know that models are an excellent way of looking at problems, and testing scenarios, even those as unlikely as an unproven reaction to a vaccine.

5. Data

Models are only as good as the data used to populate them. This was never more relevant than for models of disease, where there are immense problems in finding relevant up-to-date and usable information.

5.1. Key sources of data

We examined the main primary sources of data:

Disease incidence and complication rates

These are collected by the PHLS, which now comes under the Health Protection Agency. See Appendix III for more information on the key bodies involved in vaccination delivery and monitoring.

Number of vaccinations administered

These are available from the child health service which forms part of the NHS.

Adverse reactions - Yellow card scheme

The yellow card system is a voluntary reporting of adverse drug reactions (ADRs) by medical personnel including doctors, coroners and nurses. The yellow card system was introduced in 1964 after thalidomide highlighted the need for routine post-marketing surveillance of medicines.

Reports are collected on serious reactions to established drugs, or any suspected ADR related to 'black triangle' drugs. Virtually all new drugs will carry the black triangle until fully tested for safety.

The yellow card system is a collaboration between the Medicines Control Agency (MCA), the Medical Research Council (MRC) and the Committee of Safety of Medicines (CSM).

5.2. Data issues

5.2.1. Finding relevant and up-to-date data on the disease complication rates

Disease complication rate data needs to be relevant to current UK conditions. However the success of vaccination programmes in eradicating disease means that up-to-date, credible data is no longer available. This leaves modellers with the choice of using UK data which is several decades old (which may not be relevant because of medical advances in treatment or social conditions) or more recent overseas data (which may not be relevant because of different medical systems, or social conditions). Recent data on epidemics needs to be handled very carefully due to small sample sizes. Care is also needed in comparing data from pre and post vaccination periods as the post-vaccination era data will show an age-shift in the cases and hence a resulting increase in complication rates might be expected. See the case study on measles for a specific example of the difficulties.

5.2.2. Assessing Adverse Drug Reactions (ADRs)

This is even more problematic, as the current debate on autism and MMR shows. It can be very difficult to prove causality. Although there is a relatively sophisticated yellow card reporting system, it is dependent on the individual judgement of the GP. The yellow card returns can be difficult to assess because of the lack of grading of clinical seriousness of the ADRs.

6. The psychology of immunisation choices

6.1. The risk reward dilemma

This section introduces the idea of the immunisation risk-reward dilemma, and how different parties (policy-makers and parents) may make different decisions based on the same information.

6.1.1. What is in the balance?

On one hand there is the cost (in terms of money and human suffering) of complications of the natural disease (e.g. paralysis for polio, encephalitis for measles, birth defects for rubella), or death from that disease.

On the other hand there is the risk of adverse reactions to the vaccine. These include contracting the natural disease from the vaccine, side-effects of the vaccine and, rarely, death caused by the vaccine.

Logically if the complications of disease outweigh the adverse reactions and unwanted effects, then vaccination should go ahead. However there are a number of complicating factors:

- the risks associated with natural disease are dynamic, being affected by improved treatment, average age of infection, and so on;
- the epidemic nature of disease makes it difficult to assess risk at any point in time;
- the perception of risk can be different from the actuality.

Another complicating factor, and a particularly fascinating one, is considering how the position will be different for an individual compared to the population as a whole. This framework is used to consider the balance between risk and reward in the context of our case studies in Section 8.

6.1.2. Vaccination risk reward matrix

A 2 x 2 matrix is used (as shown in Figure 6.2) to weigh up the risk-reward balance and consider changes over time.

Vaccination risk reward matrix

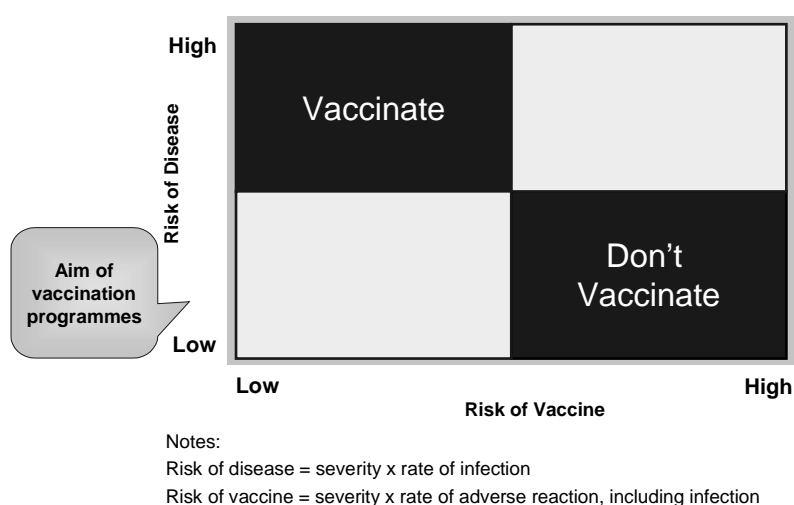


Figure 6.2: Vaccination risk reward matrix

On the vertical axis is risk of the natural disease, taking account of both frequency of infection and severity of symptoms. Typically as a vaccination programme is introduced risk decreases as infection rates decline. However, some increase may occur if the resulting average age at infection causes more serious complications.

The horizontal axis represents risks associated with the vaccine, again looking at severity and rate. Movement along this axis may result from such things as changes in the vaccine type and age at which it is administered.

The label of two of the blocks is obvious: vaccinate if risk of disease is high and adverse reactions low. Don't vaccinate if the reverse is true.

In a high-high or low-low position, the decision is less obvious and other factors need to come into play, such as whether effective treatment exists for a certain condition.

6.2. Research into the psychology of making immunisation choices

A recent report¹⁴ on parental perception of immunisation risk, identified that parents who immunise their children have significant concerns about associated risks. Vaccine risk acceptability is not simply balanced against the risk posed by the infection. Importantly, this interacts with parental attitude to the immunisation process and with their trust in the risk managers (government and health professionals). The survey showed that BSE had badly dented confidence in the honesty of official sources. The paper suggests parents should not feel pressurised to immunise as this increases their feeling of lack of control. It also concludes that more open research into MMR in particular would increase confidence in the scientific knowledge of vaccine risk.

This research appears to show that our model should include a third dimension of 'trust in the process'.

6.3. The MMR controversy

The theory behind the controversy is that MMR vaccine might damage the bowel and as a result chemicals which occur naturally in the bowel might gain access to the brain and affect development.

Researchers at the Royal Free Hospital under Andrew Wakefield¹⁵ suggested that there might be a link between measles vaccine and inflammatory bowel disease and autism. This was based on research which showed that measles viruses could be detected in inflammatory bowel tissues affected by Crohn's disease.¹⁶ The report showed that developmental regression occurred soon after MMR vaccination. 8 out of 12 children had an onset of behavioural problems from 24 hours to 2 months after receiving MMR.

There have been various follow up studies which have sought to refute the suggested link.

Taylor et al published a paper in 1999¹⁷ which investigated the history of all 498 known autistic children born since 1979 in North Thames covering the period before and after the introduction of MMR vaccine in 1988. It concluded there was no link between MMR and autism.

¹⁴A qualitative investigation of vaccine risk perception amongst parents who immunise their children: a matter of public health concern, Raithatha et al, Journal of Public Health Medicine, 2003

¹⁵ Ileal lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children, Wakefield et al, The Lancet, 1998

¹⁶ Evidence of persistent measles virus infection in Crohn's disease, Wakefield et al, Journal of virology, 1993

¹⁷ Autism and MMR vaccine: no epidemiological evidence for a causal association. Lancet 1999

Another paper published in 2001¹⁸ reanalysed the data from the 1999 study to show that there is still no association even if a longer onset period is analysed.

There is little doubt that diagnosed autism has been increasing, but there is no proven explanation for this. A time-trend analysis of autism between 1988 and 1993 ¹⁹(post MMR introduction) showed that the incidence in 2-5 year old boys increased four-fold over this period. The report concludes that there is some other reason for the onset of autism because if MMR were the cause you would expect the risk of autism to stop rising within a few years of the vaccine being in full use. It concludes that either the rise is due to better diagnosis, or a different environmental factor, so the results provide evidence against a causal relationship between MMR vaccination and the risk of autism.

Many parents have been seeking to give their children the single measles vaccine, rather than MMR, but there is not one available under the NHS in this country. The DoH insist that MMR is safe and that the single vaccine puts children at risk because of the prolonged immunisation schedule, and because it is not licensed in the UK. In the meantime the uptake of MMR vaccine has fallen to low levels in some parts of the country with a number of outbreaks in South London in particular where vaccine take-up is low. (See section 7.1 for figures on current MMR coverage).

¹⁸ MMR and autism: further evidence against a causal association, Farrington, Miller and Taylor, Vaccine, 2001

¹⁹ MMR vaccine and the incidence of autism recorded by general practitioners: a time trend analysis, Kaye et al, BMJ, February 2001

7. Vaccination programmes in practice

Appendix II shows the current UK vaccination schedule.²⁰

The current coverage for polio vaccine is 94%²¹, which compares favourably to the required coverage level of 82% to 87% for eradication.

The coverage for MMR in the UK is 84%, with coverage as low as 73%²² in certain London Boroughs. The MMR vaccine is estimated to be 90-95% effective, meaning the immunised population is falling well short of the critical level of coverage of over 90%. This highlights the potential for a measles epidemic. There have been recent outbreaks of the disease with 195 confirmed cases in England and Wales in 2002 (compared to 28 in 2001).²³

7.1. Who assesses risk and reward?

The Department of Health is ultimately responsible for determining the immunisation policy for the UK. However, in reaching its views it will take advice from all the various interested parties including:

- The Joint Committee on Vaccines and Immunisations (JCVI);
- The World Health Organisation (WHO);
- The various public health, epidemiological and medical bodies such as the Royal Colleges.

There are also many bodies involved in the delivery and monitoring of the vaccination programme in the UK. Further details on the role of these bodies can be found in Appendix III.

²⁰ 'The Green Book', Immunisation against infectious disease 1996

²¹ DoH immunisation statistics division (2nd birthday in 2001/2)

²² DoH immunisation statistics

²³ Source: PHLS – Measles Notifications Confirmed Cases

7.2. Global view

Even within Europe the incidence rate for measles varies widely. For example there were 5049 reported cases of measles in Italy and 4664 reported cases in Germany, compared to 327 in the UK in 2002.²⁴

Similarly for rubella low levels of immunity are reported in France (88%), Italy (90%), and Germany (92%) compared with only 97-99% in the UK, Netherlands and Finland.²⁵

SARS

A recent example of the global nature of disease was Severe Acute Respiratory Syndrome (SARS). An epidemic broke out in China in early 2003, and quickly spread to other countries including Hong Kong, Canada and the UK. The fear and disruption caused was immense and the case fatality rate was estimated to be around 11%. During the outbreak, some countries adopted measures such as isolating patients, quarantining people and imposing airport screening to bring the SARS outbreak under control. There is still no vaccine for SARS and the origin of the virus remains unclear.

7.3. Control cycle

A control cycle is a commonly used business tool. The different aspects of an immunisation programme can be placed into a control cycle as illustrated in figure 7.7.

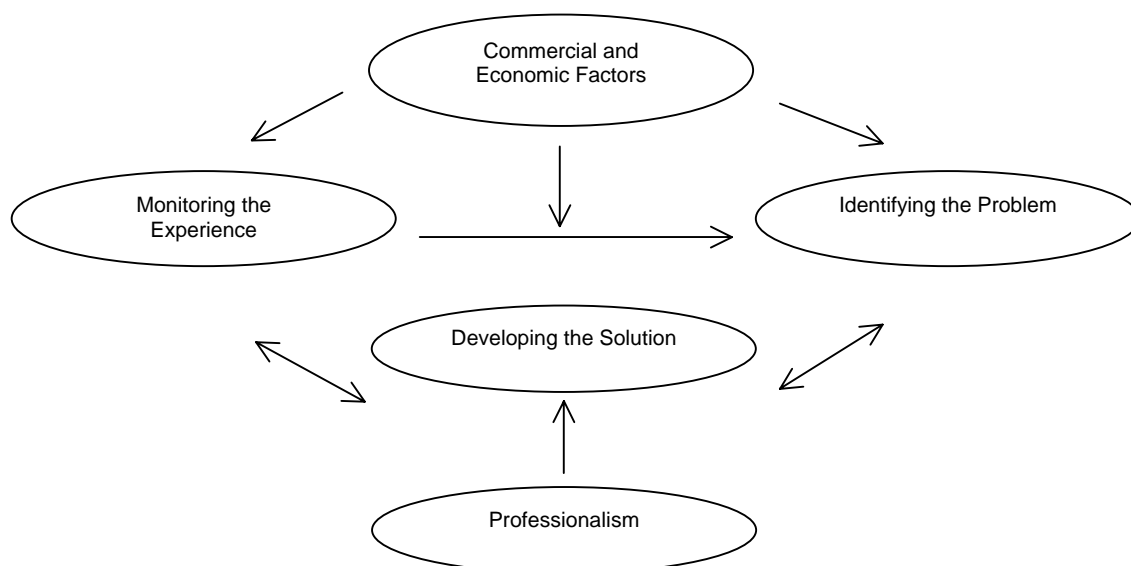


Figure 7.7: Control cycle

²⁴ Eurosurveillance

²⁵ Pebody, Edmunds et al, the seroepidemiology of rubella in Western Europe, *Epidemiol Infect* 2000

It is worth noting that the control cycle is dynamic in that there is no fixed direction in terms of movement between the different stages.

Commercial and Economic Factors relates to the environment in which the programme operates. This includes looking at what the public needs and the choices that are available. This can also extend to how the vaccination policy is set and communicated to the public. It also considers who the key players are, how vaccines are controlled and regulated and how experience is recorded and monitored. More generally, factors that have contributed to the evolution of vaccination policy (such as increases in global mobility) are also included.

Identifying the Problem looks at how risks, benefits and costs of the vaccination program are assessed (see Section 6.2 on the risk reward dilemma). This typically involves the identification and quantification of the risks and rewards of vaccinating versus not vaccinating. The benefits received from fewer cases of disease must outweigh the cost of implementing the vaccination, including adverse reactions.

Developing the Solution is concerned with identifying potential solutions to the problem via the use of modelling. Different options can be modelled to see how effectively they reduce risk and at what financial cost they can be implemented. Sensitivity testing will be needed to test the robustness of a particular strategy. Stochastic modelling may be used as an additional tool to form a range of feasible outcomes. Greater understanding of the interaction between the model parameters and their outcome can help in the assessment of effectiveness of the policy being modelled.

Monitoring the Experience aims to analyse the data captured from the vaccination program. This data can be used to update the model assumptions as part of the feedback process. Any problems with the current vaccination policy may also be identified, such as the risk of coverage being lower than the level required for eradication or frequency of adverse reactions being higher than expected.

Professionalism is important in the immunisation control cycle, since the formulating of an effective vaccination programme requires the specialist skills of epidemiologists and statisticians. It also requires doctors and other medical practitioners in terms of delivering and monitoring the effectiveness of policy.

8. Case Studies

Here two case studies are presented so that the theory of vaccination can be put into context. They illustrate how risk-reward assessments may be made in practice.

The first case study is polio. This was chosen because it illustrates the dilemma that the more successful a vaccine programme is, the higher the relative risk of the vaccine appears compared to the very slight risk of catching the disease.

The second case study is measles. This has been included because of the controversy surrounding the MMR vaccine today.

8.1. Case Study 1: Poliomyelitis (Polio)

8.1.1. The disease

Polio is an acute illness which is caused by one of three types of polio virus. Although nowadays polio is thought of as a serious disease the infection can be clinically unapparent, and can range in severity from a non-paralytic fever to aseptic meningitis or paralysis which can be fatal. The paralysis can be mild, but it can be very severe. One in a thousand infected adults and one in 75 infected children will be paralysed.²⁶ If the respiratory muscles are paralysed, there is a higher risk of death. The disease is extremely infectious with some households having a 100% infection rate. Incubation is 3 to 21 days. The disease is most infectious 7 to 10 days before and after the onset of symptoms.²⁷

8.1.2. The vaccine

There are two main types of vaccine. OPV (Oral Polio Vaccine) is a live vaccine, and is the vaccine used in the UK vaccination programme. It is a live vaccine and in rare cases (around one in a million) it can lead to vaccine-associated poliomyelitis.²⁸ IPV (Inactive Polio Vaccine) is used in the United States.

8.1.3. Current risk versus reward

As Figure 8.1 shows the vaccination programme has been successful in effectively eliminating the disease from the UK. Whereas there were several thousand cases of polio in the UK each year in the 1950s, there are none today, other than those few caused by the vaccine or brought in from abroad. The annual number of cases caused by the vaccine in the UK is on average one recipient and one contact case in relation to over two million doses of vaccine per annum.

²⁶ The Green Book

²⁷ The Green Book

²⁸ Polio Vaccine Factsheet, DoH, 1997

Notified cases of paralytic Poliomyelitis to ONS England and Wales (1940-1995)

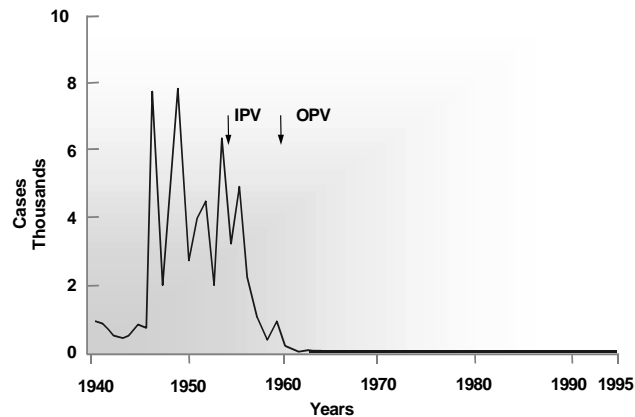


Figure 8.1: Notified cases of paralytic poliomyelitis to ONS England and Wales (1940–1995)²⁹

Between 1985 and 1995 there were 28 reported cases of polio. Of these 19 were vaccine associated (14 recipients and 5 contacts), 6 were imported and in 3 cases the cause was not known.³⁰ The current vaccination coverage is 94%.³¹

It is interesting to note that the USA currently uses IPV whereas the UK uses OPV. Although OPV is more risky in terms of actually causing the disease the reason it is used in the UK is because it is more effective in covering the types of virus likely to be imported from those countries where polio is still endemic. OPV is also a cheaper vaccine and simpler to administer than IPV. Since OPV is a live vaccine it can produce some immunity to the disease in people who have not been vaccinated but encounter it from being in contact with vaccinated people.

8.1.4. Adverse reactions

Figure 8.2 shows the number of adverse reactions to the polio vaccine reported under the yellow card system, and the number of DSS compensation claims.

²⁹ The Green Book

³⁰ The Green Book

³¹ NHS Immunisation Statistics, 2001-2002).

Polio - adverse reactions

Yellow card (1/7/63 - 10/9/01)	
Total reactions	2,554 (serious 676)
Total reports	1,270 (serious 555)
Total fatalities	35 (27 SIDS)
Total Polio	17
DSS compensation scheme - Polio*	
Claims	1675
Success	277
* Scheme started 1979, claims go back to NHS inception implies 80% disability	

Figure 8.2: Polio – adverse reactions

8.1.5. Dynamic risk reward matrix

The decision as to whether to have your child vaccinated against polio in the 1950s was not difficult. The risk of the disease was very real; with several thousand cases a year. The relative risk of a one in a million chance of an adverse reaction from the vaccine was low. The decision process for an individual and the population as a whole was the same.

Forty years on, the disease has effectively been eradicated in the UK, so for an individual deciding whether to have their child vaccinated the decision is not clear cut. The odds of either catching polio, or contracting it from the vaccination are relatively similar – though both are extremely unlikely. On the other hand, the decision for the population as a whole is in favour of having the vaccine. If a large proportion of people decide not to have the vaccine leading to a reintroduction of the disease then it could rapidly become an epidemic.

This begs the question of when to call a halt in a vaccination programme. From the analysis above it is not when the risk of vaccination outweighs the reward for an individual, because there is the herd immunity case to consider. On the other hand it seems rather extreme to continue a vaccination programme when there is effectively no chance of catching the disease, because there is always an inherent risk in vaccination programmes both in terms of the measurable risks and those which are less certain (eg long term unknown or non measurable risks in terms of damaging the immune system). A meeting of the JCVI in 2002 agreed that ‘the move from OPV to IPV in primary immunisation should be made as soon as is practicable’³², which would suggest that the policymakers now view the vaccine risk with OPV as unacceptably high. The situation also suggests that directing resources towards global eradication of polio epidemics should be a high priority.

³² www.doh.gov.uk/jcvi/mins25jan02.htm

8.2. Case Study 2: Measles

8.2.1. The disease

Measles is a highly infectious acute viral illness transmitted via droplet infection. Prior to mass vaccination there were bi-annual epidemics.

Measles can cause complications including otitis media (infection of the middle ear), bronchitis, pneumonia, convulsions and, rarely, encephalitis. Complications are more common and severe in poorly nourished and chronically ill children. Encephalitis has a 15% mortality rate on average, though this increases steeply with age. In 20-40% of encephalitis cases there is brain damage.³³ In addition late onset Subacute Sclerosing PanEncephalitis (SSPE) is a rare but fatal late complication of measles infection.

8.2.2. The MMR vaccination

The MMR (combined measles, mumps and rubella vaccine) was introduced in 1988, and is the only measles vaccine licensed in the UK. There has been considerable controversy over potential side effects as described in section 6.3.

8.2.3. Current risk versus reward

Figure 8.4 shows that measles notifications have dropped considerably since the 1950s (when virtually 100% of children had measles), to a few thousand cases a year now, due to the introduction of the vaccine.

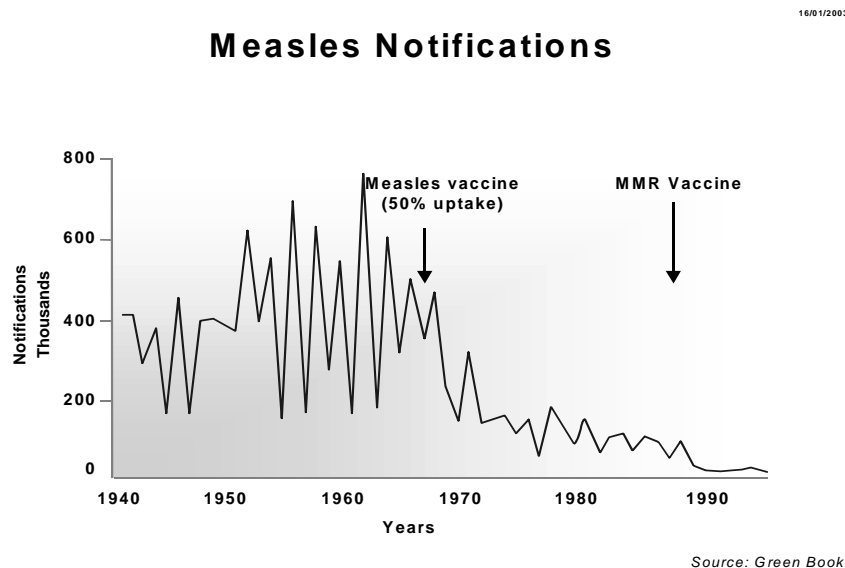


Figure 8.4: Measles notifications

³³ The Green Book

Between 1996 and 1988 there were eleven deaths in England and Wales due to measles, four of these were due to acute measles illness rather than complications. In the previous decade there were an average of 13 acute measles deaths each year.³⁴ This compared to around 100 deaths a year in the 50s when measles affected most children.

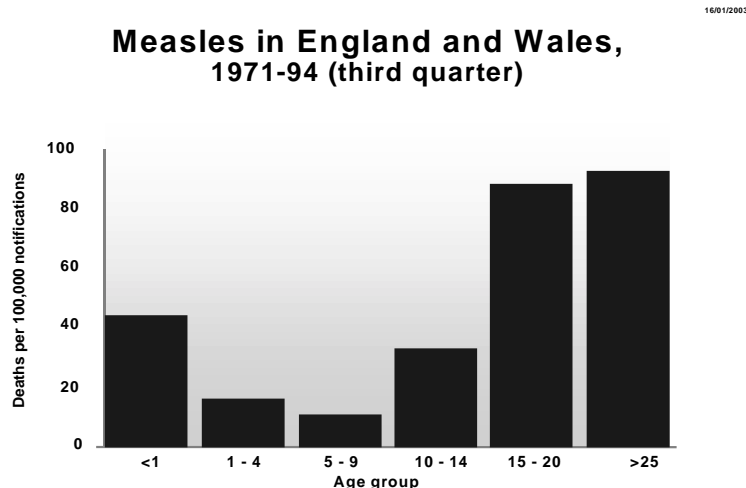


Figure 8.5: Measles in England And Wales, 1971 – 94 (third quarter)

Figure 8.6 shows the complication rates for people with measles in the HPE immunisation fact sheet.

We sought to verify these figures from original source data but found that this is difficult. UK data of large sample size is now quite old. Overseas data may not be relevant. The complication rates vary immensely:

In 1964 a large survey was carried out in the UK prior to the vaccination. A further survey was carried out in 1978 in the UK.³⁵ The 1978 survey was based on 9000 cases of measles out of 55000 notifications in that year. The 1964 survey was based on 53000 cases. The rates for deaths (0.2/1000), admission to hospital (1%) and respiratory complications (4%) were the same in 1963 and 1976. More neurological complications and otitis media were reported in 1976 – 0.6% and 5% compared to .4% and 2.5%.

In a more recent outbreak in the Netherlands³⁶ (2961 confirmed cases followed up) the complication rates were higher. Deaths (1/1000), hospitalisations (2.3%), respiratory 7.6% and otitis media 5.7%. It is not clear why the effects were more severe, though it could be age effects. The age distribution was 19% aged 10 or more compared to 5% in the UK survey. Even worse was an outbreak in Catalonia, which showed a 10.2% hospitalisation rate. In this cases two-thirds

³⁴ The Green Book, 1996

³⁵ Severity of notified measles, Miller, BMJ, May 1978

³⁶ Measles outbreak – Netherlands, April 1999-January 2000, MMWR, Vol 49

were aged 10 or over, with an epidemic in the army being a major part of the outbreak.³⁷

Measles in malnourished people can cause high case fatality rates: 34% in Somali refugees, 33% in Ethiopian refugees, and 15-21% in Mozambican refugee children.³⁸

1601/2003

The complications

	Complication Rate 1 in
Ear infection	20
Pneumonia / bronchitis	25
Convulsion	200
Diarrhoea	6
Meningitis / encephalitis	1000
Late onset SSPE	1,000,000
Death	2,500 – 5,000

Source: HPE, Immunisation factsheet 1997

Figure 8.6: Measles complications

8.2.4. Adverse reactions

Figure 8.7 shows the yellow card reports for MMR vaccine and the DSS compensation claims. It would be interesting to see these as a percentage of exposed to risk but unfortunately these figures are not available.

³⁷ Measles epidemiology in Catalonia (Spain): implications for a regional vaccination programme, Godoy et al, International Journal of Epidemiology, 1999

³⁸ Measles in Vietnamese refugee children in Hong Kong, Epidemiology and Infection, 1999

ADRS - MMR

1/6/1/2003

Yellow card	
(1/7/63 - 10/9/01)	
Total reactions	5,838 (serious 1462)
Total reports	3,528 (serious 1271)
Total fatalities	10 (2 SIDS)
DSS	
Claims	579
Success	12

Figure 8.7: Adverse reactions for MMR & DSS compensation claims

8.2.5. Dynamic risk reward matrix

The risk reward matrix shows an interesting dilemma for measles. Measles is a relatively low risk disease for well nourished children. So long as the vaccine risk is very small an individual would probably decide to have the vaccine. However if the individual perceives the risk of the vaccine to be relatively high they may well decline the vaccine, as a substantial number of parents are doing at present. The accumulation of these individual decisions alters the risk equation for the population as a whole. If the percentage of children being vaccinated falls below the critical proportion to achieve elimination of the disease, the risk of an epidemic and catching the disease increases. Furthermore, the epidemic may not happen for some time, and then there will be a substantial number of older people at risk who have no natural immunity because they have not been exposed to the disease, some of whom will have either not been vaccinated or the vaccine will not have been effective for them. These older people are considerably more at risk of serious side effect so overall, the effect on public health of introducing the vaccine program could be negative.

9. Conclusions

9.1. Summary

The theory behind immunisation is complex and considerable depth of epidemiological study is available, though not often communicated to the public. The UK surveillance system is sophisticated, with detailed statistics collected on a regular basis. Study of these statistics and existing epidemiological models and academic papers gives some understanding of the relative risks of disease and vaccination as they stand today in the UK.

There is a complex interaction between individual and herd immunity. The risk-reward dilemma is played out at an individual level as individuals perceive the relative risks to themselves or their children of disease and vaccination. If sufficient people are vaccinated then the disease can be effectively wiped out, protecting those individuals who are not vaccinated for whatever reason. However if the vaccinated percentage falls below the critical proportion epidemics can break out and alter the risk reward balance for the population as a whole.

From immunisation theory, and from the Greek rubella experience, a poorly implemented immunisation programme can be dangerous. Diseases tend to have more serious side effects as people get older. If populations are not properly immunised, but not given the chance to acquire natural immunity as young children, they become more susceptible to epidemics.

The risk reward balance is dynamic. For a parent in the 1950's the vaccination decision was easy, high risk of disease compared to low vaccination risk led to the individual decision to vaccinate, and high population coverage. For the millennium baby, perceived low risk of disease compared to the possible risks of vaccination may lead to the individual decision not to vaccinate. Unless the herd immunity decision is considered there is an inevitable pull towards lower vaccination rates which will in turn increase the chance of epidemics in the population.

This illustrates the importance of the current MMR debate and why the effect it is having on vaccination levels matters. Ongoing high vaccination coverage will be required to prevent epidemics. Partial coverage will mean that some people tend to be infected at an older age when serious complications are more likely.

The UK does have a thorough surveillance system. Regular surveys take place to check whether the population is immune to specific diseases. Adverse reactions to the vaccine, and disease notifications, deaths and complication rates are compiled.

There are a significant number of scientific papers written by epidemiologists looking at most aspects of vaccination risk and reward. The mathematical models used were sophisticated, and the techniques used would be of interest to actuaries

wanting to model disease. The way in which the modelling was carried out, including sensitivity testing, would be familiar to any actuary.

9.2. Is there a role for actuaries?

Because of the similarity in skills used for modelling there will be opportunities for future collaboration between actuaries and epidemiologists. Actuaries can learn from the experience of epidemiologists in modelling disease, but also add something in terms of the modelling of mortality. Actuaries are well placed to make robust critical analysis of epidemiological models and vice-versa.

In the future, with the threat of epidemics of diseases like SARs or even biological terrorism, infectious disease modelling is likely to become rather more important in the traditional actuarial fields than it is today. For those diseases where the mortality rate is important (eg for a disease like SARs where the disease affects the mortality rate) then more explicit modelling of mortality will need to be incorporated into epidemiological models. There would be a role for actuaries here.

It is likely that some actuarial modelling software may have advantages over the standard packages used by epidemiologists.

The disciplines used by actuaries such as sensitivity testing are also used in epidemiological models, and are indeed important as the models can be highly sensitive to the assumptions made. There does appear to be a particular problem with availability of useful and credible data, which could be fundamentally affecting the validity of the models used eg data on how long vaccines last and the effect of maternal immunity. Some form of 'control cycle' of regularly assessing data and reviewing assumptions for models is an actuarial discipline which could be adopted by the relevant health authorities.

Perhaps the biggest area for improvement is in the communication of the principles to those outside the medical and epidemiological professions. The current public debate about vaccinations is very low level and is highly simplified in both the press coverage and the official leaflets on each vaccine. There is evidently a dilemma here for policymakers who are trying to communicate at all levels. The actuarial community is one in which an independent statistically informed debate could take place on this issue.

In conclusion, the epidemiological field is a close cousin to actuarial study and there are many opportunities for the two professions to co-operate more closely in future.

10. Glossary

ADR	Adverse Drug Reaction
Attenuated	Weakened (see section 2.3)
Autism	Behavioural disorder, emotional deficit and general learning disability with particular reference to communication difficulties – there is a spectrum of autistic disorder (See section 6.3)
BCG	Bacillus Galmette-Guerin vaccine (against tuberculosis)
Breakthrough infection	See section 2.6
Calpol	Over-the-counter liquid paracetamol for infants
CDC	Center for Disease control (US equivalent of the PHLS)
Critical proportion (p_0)	See section 3.2
Crohns disease	an inflammatory condition of the intestine
CRS	Congenital rubella syndrome (see 3.3.1)
DTP	Diphtheria, Tetanus, Polio vaccine
Encephalitis	Inflammation of the lining of the brain
Epidemiology	‘The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control of health problems’ ³⁹
Green Book	1996 Immunisation against infectious disease, Jenner (Standard reference book used by health visitors)
Herd immunity	See Section 3.1 for explanation
HPE	Health Promotion England – see Appendix III
IPV	Inactivated Polio Vaccine – see section 8.1.2
JCVI	Joint Committee on Vaccines – See Appendix III
Live vaccine	See Section 2.3

³⁹ Basic Epidemiology, Beaglehole, Bonita, WHO

MMR	Mumps, measles, rubella vaccine – see section 8.2.2
MRC	Medical Research council – see Appendix III
NICE	National Institute for Clinical Excellence – see App III
OPV	Oral Polio Vaccine – see section 8.1.2
Otitis media	Infection of the middle ear – can cause deafness
PHLS	Public Health Laboratory – see Appendix III
Reproductive number (R)	See section 3.2
Rubella	German measles
SARS	See section 7.2
Seropositive	Possessing antibodies specific to a particular microparasite’s antigens – indicating either a subject has had the disease or been successfully vaccinated.
SSPE	Subacute Sclerosing PanEncephalitis, a rare but fatal late complication of measles infection.
Pertussis	Whooping cough
VAERS	Vaccine Adverse Event Reporting System (US)
Varicella	Chickenpox
VZV	Varicella Zoster Virus (causes chickenpox and shingles)
WHO	World Health Organisation - see Appendix III
Yellow Cards	UK system for reporting adverse events for vaccines
Zoster	Shingles

11. References

11.1. General references & data sources

Immunisation against infectious disease 1996 – Salisbury & Begg (Department of Health) HMSO **The Green Book**

MMR Factsheet – DoH 1997

MMR Factsheet 2 – HEA 1998

MMR Factsheet 3 – DoH and HPE 2001

MMR Factsheet 4

MMR The facts – brochure – NHS/HPE

Measles, mumps and rubella Vaccines – What you need to know – CDC (Center for disease control – US)

Polio Vaccine Factsheet – DOH/HEA 1997

Deaths from selected infectious disease – Series MB2

Notifications of certain infectious diseases – Series MB2

Measles notifications rates per 100,000

Morbidity: Notification of selected infectious diseases (89-99)- PHLS/CDSC

Causes of Death – Series DH2 no 26

Adverse Drug Reactions Online Information Tracking (Yellow Card Reports) – MCA

Vaccine Damage Payments Scheme - DSS

Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy – Gay, Hesketh, Morgan-Capner and Miller – Feb 1995

Predicting the impact of measles vaccination in England and Wales : model validation and analysis of policy options – Babad, Nokes, Gay, Miller, Morgan-Capner and Anderson 1994

NHS Immunisation Statistics 1997-98 – DoH

Vaccine Adverse Even Reporting System (VAERS) – US FDA

Monitoring the safety and quality of medicines: The Yellow Card Scheme - MCA

Immunisation and vaccination activity KC50 – ONS – National Assembly for Wales

11.2. Useful websites

www.immunisation.org

www.mca.gov.uk

www.thelancet.com

www.DoH.gov.uk/hpsss

<http://bmj.com>

www.phls.co.uk

www.fda.gov/cber/vaers

11.3. Epidemiological references

Infectious diseases of humans – dynamics and control – Roy Anderson and Robert May

Epidemiology in medicine – Charles H Hennekens

Modern infectious disease epidemiology – Johan Giesecke

11.4. Other sources of interest

Immunisation – Harriet Griffey

Vaccination and immunisation – what does your child need – Anne Charlish

Vaccination and immunisation – dangers, delusions and alternatives – Leon Chaitow

Plague, pox, and pestilence – disease in history – Kenneth F Kiel

11.5. Related to MMR

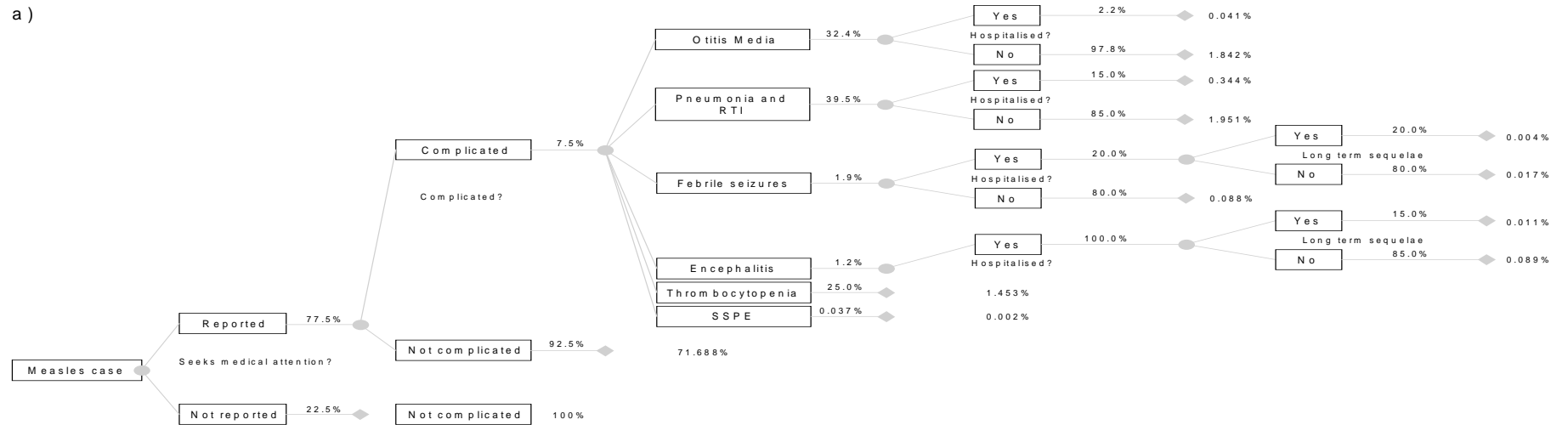
Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal association – Brent Taylor, Elizabeth Miller, C Paddy Farrington et al - The Lancet June 12, 1999

MMR and autism: further evidence against a causal association – Farrington, Miller, Taylor – Vaccine 19 (2001)

A response to ‘Measles, mumps, and rubella vaccine: Through a glass, darkly’ by Drs AJ Wakefield and SM Montgomery and published reviewers’ comments – P Arlett and P Bryan Post-Licensing Division, UK Medicines Control Agency

Appendix I Cost-benefit model for measles

a)



b)

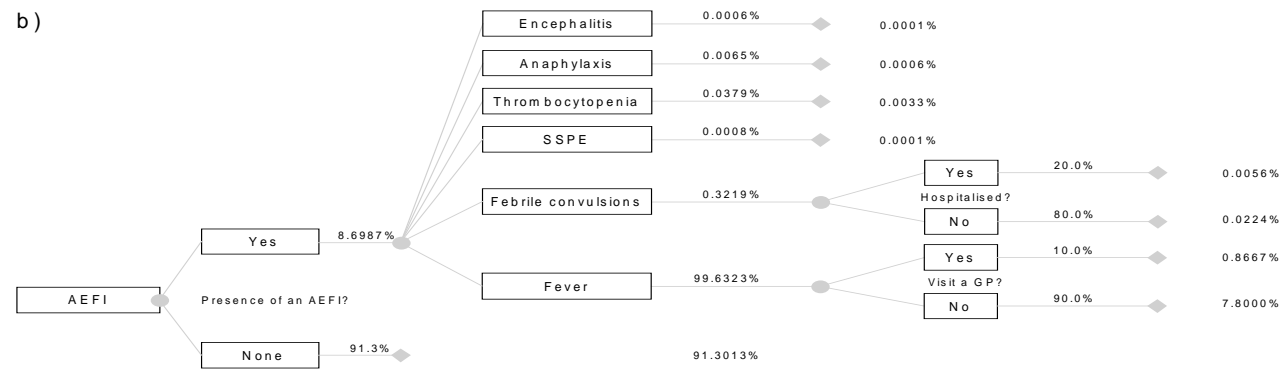


Figure 1.

Decision trees. a) measles cases and b) Adverse Event Following Immunisation (AEFI) with measles vaccines.

Legend: This graph shows the proportion of cases with each symptom, complication, sequelae or hospitalisation. A circle corresponds to a chance node (defined by the probability of the event occurring), a diamond represents an end node. The number at the top of each branch shows the proportion of each event occurring at that point in the tree. The total proportion of cases in each group per measles case is written at the right of each branch.

Appendix II The UK vaccination schedule

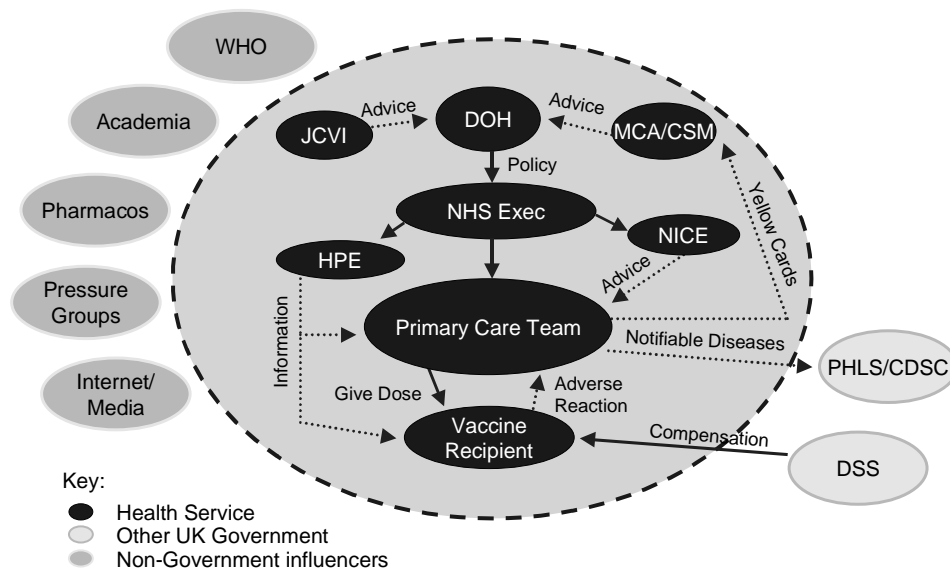
Current UK vaccination schedule

Immunisation Schedule

Vaccine	Age	Notes
D/T/P and Hib Polio	1st dose (2 months) 2nd dose (3 months) 3rd dose (4 months)	Primary course
Measles/mumps/rubella (MMR)	12-15 months	Can be given at any age over 12 months
Booster DT and polio, MMR second dose	3-5 years	Three years after completion of primary course
BCG	10-14 years or infancy	
Booster tetanus diphtheria and polio	13-18 years	

Source: Green Book

Appendix III – Key Players in the UK Vaccination Programme



Overview of some key players

The Department of Health (DoH)

The DoH is the government department responsible for health *policy* and *delivery* in England. It has three main areas of responsibility:

The National Health Service (NHS)

The NHS is not actually part of the Department of Health, but is managed by the NHS Executive which is part of the DoH. In other words, the NHS is the delivery mechanism for healthcare, which is both publicly run and publicly funded.

The NHS Executive is responsible for setting policy for the NHS, as well as its operational management. Policy decisions are identified by the Minister for Health, and his/her advisors within the DoH.

Each regional office and strategic health authority has a Director of Public Health. This individual would be charged with the oversight and direction of the immunisation programme within that area, as well as responsibility for other public health issues. The childhood vaccination programme is therefore administered by the NHS and involves many different parties including health visitors, GPs, and the school health service.

Health Promotion England

Health Promotion England is a non-statutory body within the NHS, managed through Lambeth, Southwark and Lewisham Health Authority.

It is a small team comprising professionals in health education, with expertise in its main programme areas, as well as specialist staff working in advertising, publishing, marketing and communications.

The HPE disseminates information about immunisations to the public and to health professionals, in support of government policy.

Joint Committee on Vaccines and Immunisations (JCVI)

The Joint Committee on Vaccines and Immunisations is a statutory standing advisory committee whose role it is to give independent advice to UK health departments on immunisation. This includes giving direction to the childhood immunisation programme. However, the JCVI does not have any operational responsibility for the programme, and its members are not DoH civil servants, but rather the great and the good from academia and medicine.

Medicines Control Agency (MCA)

The MCA is an executive agency of the Department of Health. It is the UK body responsible for licensing drugs in the UK.

The Medicines Control Agency's primary objective is to safeguard public health by ensuring that all medicines on the UK market meet appropriate standards of safety, quality and efficacy. Safety aspects cover potential or actual harmful effects; quality relates to development and manufacture; and efficacy is a measure of the beneficial effect of the medicine on patients.

In other words, the MCA is charged with ensuring that vaccines are safe and do what they should do.

The National Institute of Clinical Excellence (NICE)

NICE was set up as a Special Health Authority for England and Wales on 1 April 1999. It is part of the NHS, and its role is to provide patients, health professionals and the public with authoritative, robust and reliable guidance on current “best practice” in medicine. The guidance covers both individual health technologies (including medicines, medical devices, diagnostic techniques, and procedures) and the clinical management of specific conditions.

NICE’s relationship with the JCVI is not entirely clear, though it seems that NICE would rely on JCVI advice in all immunisation matters and would simply disseminate that advice.

The Public Health Laboratory Service (PHLS)

The role of the PHLS was to protect the population from infection by detecting, diagnosing, and monitoring communicable diseases. From 1 April 2003 its role has been taken over by the Health Protection Agency (HPA), described below.

The PHLS has been the key source of UK data on the incidence and complication rates of the diseases the vaccination programme is aiming to eradicate. The evidence comes from expert analysis and assessment of data generated from the PHLS's own microbiological and epidemiological investigations and from many other sources.

The Health Protection Agency (HPA)

The HPA is a new national organisation covering England and Wales. It is dedicated to protecting people's health by providing an integrated approach to health protection and reducing the impact of infectious diseases, poisons, chemicals, biological and radiation hazards. It brings together a number of organisations including

- PHLS including CDSC and Central Public Health Laboratory;
- NHS staff responsible for infectious disease control, emergency planning etc.

The idea of the HPA is to allow the skills and expertise of a number of organisations to work in a more co-ordinated way, to reduce the burden and consequences of health protection threats or disease.

The HPA's role includes:

- advising government on public health protection policies and programmes;
- providing an impartial and authoritative source of information and advice to professionals and the public;
- improving knowledge of health protection through research, development, education and training.

The Medical Research Council (MRC)

The MRC aims to improve health by promoting research into all areas of medical and related science. It supports medical research in three main ways:

- Through its research establishments.
- Grants to individual scientists.
- Support for postgraduate students.

The MRC supports the NHS by focusing on research relevant for the UK, but tries not to overlap with the work of the NHS's own R&D activities.