# VACCINATION

LE VACCIN DE LA DIPHTÉRIE. L'inoculation.

# VACCINATION

**Office of Health Economics**
162 Regent Street London W1R 6DD

No. 50 in a series of papers on current health problems published by the Office of Health Economics. Copies are available at 25p postage free.
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Printed in England by White Crescent Press Ltd, Luton

# Introduction



During the past century the life expectancy at birth of the average Englishman has risen from 40 to around 70 years. Whereas it is likely that in 1870 only 60 per cent or less of children born alive in this country survived their first five years 98 per cent did so in 1970.

A major factor in these dramatic changes in mortality has been the virtual eradication, in the economically 'developed' world, of infectious disease as a significant cause of death. This was accomplished primarily by environmental improvements and public health measures such as adequate sanitation, clean water supplies and better nutrition and housing. Through these the sources of many infections have been eliminated and the resistance of the population to communicable illness has been raised.

Pharmaceutical developments since the 1930s have also aided in the reduction of such ill health, as has the introduction of new vaccines and their use in national and international programmes of disease control. This paper is concerned with questions relating to the latter sphere, looking in particular at the significance of current immunising techniques in social and economic as well as in medical terms.

On a world-scale vaccination is still at a stage where its major contributions to the welfare of mankind are probably yet to be made, although the current WHO smallpox eradication programme based on vaccination already ranks as one of the major achievements of preventative medicine in modern times. Between 1967 and 1973 the estimated true incidence of the disease (as opposed to the notified incidence) fell to about one twentieth of its former level and it is thought possible that the target of the global elimination of smallpox may be achieved by the end of 1975, despite its continued endemic presence in the Indian subcontinent and Ethiopia.

There is also good reason to believe that there will shortly be new additions and improvements to the vaccines currently available for human use, listed in Table 1. Promising areas for further research include the control of infectious and serum hepatitis (jaundice) and the development of a vaccine against cytomegalovirus disease, which is the main viral cause of severe mental retardation.

Yet in countries like Britain where health standards in the area of communicable diseases are already high the scope for extending the application of existing immunising methods are to a degree

**Table 1** *Available vaccines for the prevention of human diseases*

| *Vaccine/Disease* | *Comments* |
|---|---|
| **Viral Vaccines** | |
| Adenovirus infections | There exist both live and killed vaccines against adenovirus infections which effect the respiratory tract, an example being the common cold. Because of the variety of pathogens involved and the usual mildness of such infections in otherwise healthy individuals the development prospects for these vaccines are very limited. |
| German measles (rubella) | Until vaccination was introduced in Britain in 1971 rubella caused about 200 congenitally abnormal children to be born here each year. Selective vaccination (live) now gives long lasting protection to women during their child bearing years and should prevent all but a few children being damaged. |
| Influenza | The killed vaccines now available give good protection for up to a year, the period of immunity being limited by changes in the wild virus. They are of particular value amongst the elderly and others, such as the chronically ill, who are at special risk although recent improvements in vaccine purity have made them safe for use throughout the adult population. |
| Measles | Introduced into the NHS in 1968 measles vaccination using live attenuated pathogens gives long lasting protection. In view of measles possible link with multiple sclerosis (Field 1973) epidemiological surveillance of possible effects of vaccination on the incidence of that condition would be of interest. |
| Mumps | A live, long-lasting immunisation first developed in 1949. It is not available through the NHS although it can be purchased privately in Britain. Currently epidemiologists are trying to define more accurately the hazards associated with complications stemming from mumps. |
| Poliomyelitis | Salk (killed) vaccine lasts for two to four years whilst the Sabine live oral vaccine gives indefinite long-term protection. It establishes colonies of attenuated virus in the intestines of the vaccinee which may be passed on to other individuals, so extending protection throughout the community. There is a slight risk of the attenuated strain causing symptomatic attacks of polio as it circulates in the population, three such cases occuring in 1972 in Britain. |
| Rabies | Whether live or killed rabies vaccines give only short-lived protection. Up until recently there had been little significant improvement on Pasteurs original vaccine. Fourteen consecutive daily injections into the stomach wall are used to give immunity. However, work at the Wistar Institute has led to the production of a safer, more effective and easier to use vaccine. Given in Britain only when exposure to rabies is feared. |
| Smallpox | The live vaccine is usually considered to give between three and five years' protection. See text for the history of smallpox vaccination. No longer used routinely in Britain. New vaccine based on an attenuated smallpox strain will probably soon be available. |
| Yellow fever | A live vaccine giving about ten years' protection. Of particular value in semi-tropical climates it is one of the most successful of all vaccines. Used by travellers who may obtain it from authorised centres in Britain. |

**Bacterial vaccines**

| | |
|---|---|
| Anthrax | A killed vaccine suitable for man was developed in 1948. It is only recommended for agricultural and other workers such as butchers who may be at special risk. Reinforcing doses should be given yearly. |
| Bubonic plague | Both killed and live vaccines give only about six months' protection. The use of the vaccines is therefore limited to the prevention of epidemics. |
| Cholera | A killed vaccine giving only six months' protection. Recent work has indicated that it is of relatively little use in epidemics and it is hoped that improved vaccines may be produced. In the meantime better sanitation is the best control over cholera, although vaccination is valuable for travellers. Research is being conducted on vaccine improvements. |
| Diphtheria | The toxoid (ie the partly denatured but still strongly antigenic bacterial toxin) gives long lasting immunity. Anti-toxin may also be used in certain circumstances. |
| Meningococcal meningitis | Vaccines have recently been made available for both types A and C meningococcal infection. These cause considerable mortality and morbidity in areas of the developing world (e.g. The Sudan, Brazil and Central Asia) and have become increasingly resistant to medicines. However, the strain found in Britain (type B) is milder and is responsive to chemotherapy. |
| Tetanus | The toxoid is used as with diphtheria. Recent work indicates that the living conditions of the vaccinee may vary the length of protection received (Meira 1973) although this usually lasts for at least three to five years between boosters. |
| Tuberculosis | BCG vaccination gives long lasting cellular immunity against tuberculosis. It is normally given to those aged between 10 and 13 years in Britain. |
| Tularemia | A plague-like disease transmitted by rodents. Inactivated and attenuated vaccines have been used to protect those at special risk although chemotherapy is now usually relied on. Not known in Britain. |
| Typhoid and para-typhoid fevers | TAB killed vaccine or separate typhoid vaccines are used for travellers although they are not recommended for use in Britain because they do not give immediate protection (in epidemics) and may disguise the disease. Therefore available chemotherapy is employed. Boosting is needed about once every three years. |
| Whooping cough | Normal childhood vaccination (killed) may give lifelong protection. See text. Improved vaccine may become available in the relatively near future. |

**Rickettsial vaccines**

| | |
|---|---|
| Typhus | Killed vaccines highly effective against both louse-borne and scrub-typhus are available. In Britain its only use is for those travelling to areas where it is widespread such as Ethiopia or the Sudan. Protection lasts for about one year. |
| Rocky mountain spotted fever | A number of other vaccines for rickettsial infections exist, notably that for rocky mountain spotted fever. Although effective their use is limited because of the rarity of the disease concerned. |

**Anti-allergy vaccines**

Allergies stem from an unusual form of immune response to the presence of foreign matter in the body, for instance the

plant proteins of pollen. Whilst most people can tolerate such material fairly easily some suffer a marked reaction characterised by histomine release. This stems from a unique antigen antibody reaction involving an immunoglobulin only recently identified (IgE). If the allergen (antigen) involved can be isolated it may be used, by repeated vaccination, to build up normal antibodies in the blood stream which will subsequently compete with IgE to react with further allergen so relieving the hypersensitive allergic response. Some authorities believe that T cell tolerance is also induced. The process of isolating the precise allergens involved may be laborious and expensive but the gains to the individuals affected can be considerable.

**Animal vaccines** Many vaccines are available for protecting agricultural and domestic animals. Some of these, such as those against brucellosis, are of direct potential importance with regard to human health. The remainder are of value in that they may raise or maintain food production whilst obviating the need for any use of medicines more desirably reserved for treatment of the human population. They may have a particularly valuable contribution to make in areas of the developing world where human health suffers considerably as a result of food scarcity. Here the costs and impracticality (because of problems such as disease transmission through wildlife) of alternative policies for controlling the spread of infections like foot and mouth disease, such as the slaughter of all affected animals within a quarantined area, make prevention through vaccination especially worthwhile.

limited. Indeed, some of the epidemiological changes which vaccination programmes have helped to promote have led to questioning of their continued value within communities such as our own. An important objective of this paper is therefore to examine to what degree and in what areas the future use of vaccines in this country is to be encouraged or restricted.

# Immunity and vaccination

Our bodies possess a number of defences against the numerous disease causing micro-organisms in the world about us. Some of these act generally against any form of invading pathogen and others more specifically against particular types of organism. The latter kind of immunity, when established, provides a full defence against many diseases but the biological mechanisms underlying it are such that attacks must be suffered before an individual can become immune.[1] Although in many, perhaps most, cases protection may be derived from unnoticed sub-clinical illness more severe conditions will often cause discomforting, damaging and/or potentially fatal symptoms before immunity can be generated.

1 A more detailed explanation of immunity is given in the appendix.

The significance of vaccination as a preventive technique is that its use may avoid the chance of people having to suffer such an episode. It elicits from non-immune individuals a primary response during which the cells responsible for the development of specific immunity 'learn' to produce antibody to the antigen (antibody inducing material) which has been introduced. A vaccinated person is thus protected by the initially induced immunity and also primed to meet an attack of the illness concerned, should this occur, with a strong secondary response.

The usual initial symptoms are avoided because the pathogen injected has either been weakened (attenuated) or killed and the appropriate antigenic matter extracted from it. This process may sometimes carry with it the slight disadvantage of reducing the period of immunity given by the vaccine as opposed to a full episode of the disease although this may be compensated for by subsequent 'booster' injections. However, it would be dangerous to generalise too much in this context in that vaccines such as those for measles or polio probably give just as long a protection as do the diseases themselves and tetanus toxoid confers immunity even though a symptomatic attack of tetanus itself will usually fail to do so. Similarly there are no firm rules as to duration of immunity given by viral as opposed to bacterial vaccines even though attenuated viral ones tend to have longer lasting effects than do killed bacterial products.

The advantages of active immunisation may be employed in a number of differing ways. For instance, mass vaccination campaigns can be aimed at the eradication of illnesses within communities in certain circumstances although generally orderly long-term programmes of basic immunisation are more effective. And strategic and/or 'ring' vaccination (the selective immunisation of possible contacts) can be used to control outbreaks in non-immune or partially immune populations and so close off possible routes of transmission for the disease concerned.

The following sections of this paper discuss the applications and implications of such approaches to immunisation in the context of both the conditions existing in modern Britain and those prevailing in the developing countries. The remainder of this one and the chronology presented in Table 2 provide an introductory history of the development of the immunising techniques now available.

## Smallpox inoculation and vaccination

In both ancient Greece and China it was observed that adults who were pockmarked from a previous attack of smallpox did not usually contract the disease a second time. Various sources also

**Table 2** *A chronology of vaccination*

| | |
|---|---|
| ?BC–1000AD | Greek and Chinese medicine recognises the protective effective of an attack of smallpox on the survivors. Forms of variolation practised |
| 1683 | Van Leeuwenhoek's microscope. Bacteria discovered |
| 1721 | Variolation introduced into Britain from Turkey (although it had previously been practised to a limited degree in areas such as the Scottish Highlands) |
| 1765 | Thesis regarding the role of cowpox infection in protecting humans against smallpox reported to the Medical Society of London by Fewster |
| 1798 | Jenner publishes 'An inquiry into the causes and effects of Variolae Vaccinae'. Vaccination swiftly supersedes variolation |
| 1840 | Variolation illegal in Britain |
| 1853 | Vaccination universally available and compulsory in Britain |
| 1876 | Koch identifies anthrax bacillus |
| 1880 | Pasteur develops fowl cholera vaccine, Eberth identifies typhoid bacillus |
| 1881 | Pasteur Roux and Chamberland develop their anthrax vaccine |
| 1882 | Koch identifies tubercule bacillus |
| 1883 | Koch identifies cholera vibrio |
| 1884 | Klebs and Loeffler identify diphtheria bacillus and Nicolaier that of tetanus |
| 1885 | Pasteur develops his rabies vaccine |
| 1888 | Roux and Yersin describe diphtheria toxin |
| 1890 | Koch introduces tuberculin (which is unsuccessful but leads ultimately to an understanding of cell-mediated immunity) |
| 1891 | Behring and Kitasato papers on diphtheria and tetanus antitoxins |
| 1892 | Haffkine begins his work on cholera vaccines in India |
| 1897 | Ehrlick's paper on the standardisation of diphtheria antitoxin. Haffkine extends his activities to the use of plague vaccines |
| 1898 | Almroth Wright develops typhoid vaccine (and works on his theory of opsonins). Monckton and Copeman introduce glycerated calf-lymph for vaccination |
| 1908 | Metchnikoff shares a Nobel prize with Ehrlick for his work on immunity, particularly the development of the concept of phagocytosis (which dates back to the 1880s) |
| 1910 | Ehrlick pioneers chemotherapy with the introduction of salvarson '606' for the treatment of syphilis |
| 1913 | Behring introduces toxin/antitoxin immunisation against diphtheria. Schick test for diphtheria immunity |
| (1914–18) | Tetanus antitoxin used prophylactically in European armies. Large scale diphtheria immunisation in New York |
| 1921 | Calmette and Guerin – BCG vaccination for tuberculosis |
| 1923 | Ramon uses diphtheria toxoid (i.e. the denatured but antigenic toxin) for human immunisation |
| 1927 | Ramon and Zoeller introduce tetanus toxoid for immunisation |
| 1933 | Typhus vaccine (Weigl) and early pertussis vaccine (Sauer) |
| 1935 | Value of Sulphonamides in humans established |
| 1937 | Early influenza vaccines. '17D' yellow fever vaccine (Theiler) |
| 1938 | Tetanus toxoid used widely in British army. Chemotherapy firmly established for the treatment of pneumonia etc |
| 1941 | Florey and Chain use penicillin (discovered by Fleming in 1928) in humans. It is not used on a wide scale until 1944, after the intervention of United States military and commercial interests |
| 1943 | Streptomycin used for the treatment of tuberculosis |
| 1948 | Compulsory smallpox vaccination ended in Britain. Start of NHS |
| 1949 | Mumps vaccine developed. Enders and Weller culture polio virus in human tissues |

| | |
|---|---|
| 1954 | Salk vaccine for polio first used in America |
| 1957 | Sabin live oral polio vaccine used in the Congo. Isaacs and Lindenmann describe interferon |
| 1960 | Enders develops measles vaccine. Use of multi-valent vaccines extended. Burnet and Medawar receive a Nobel prize for their work on immunology |
| 1962 | Weller reports a successful rubella vaccine |
| 1968 | Type C meningitis vaccine developed |
| 1971 | Smallpox vaccination no longer routine in Britain |
| 1972 | Type A meningitis vaccine begins field trials in Egypt and the Sudan. |
| 1974 | Elek and Stern report preliminary findings on a vaccine to protect against cytomeglo virus infection |

*Note:* It was nearly a century between the first responsible reports of smallpox prevention via infection with cowpox and the introduction of widespread vaccination in Britain. In our own century 20 years elapsed between the use of diphtheria toxoid for immunisation and the introduction of a full scale programme of immunisation in Britain. Indeed toxin/antitoxin mixtures had been available since the first world war. Similar delays may be observed with regard to tetanus and BCG vaccines. In the related world of chemotherapy nearly two decades passed between Fleming's first paper on penicillin and that drug's widespread use.

More recently measles and rubella vaccines were introduced within a decade of their development and polio vaccine was employed three years after its production. Even so the use of vaccines has been in general marked by caution rather than excess haste. Although isolated examples such as the Lubech disaster with BCG (subsequently shown not to be a result of infection by the attenuated strain) may apparently justify such considerable hesitation it did result in the loss of many thousands of lives.

attribute to the Chinese the discovery that dry crusts from a smallpox victim's pustules, powdered and inhaled via the nose, would often promote an episode of illness mild enough to be risked yet which would confer subsequent immunity.

But despite this early knowledge techniques for the prevention of smallpox were not to be found in Britain on any significant scale until the eighteenth century. The method of variolation adopted at that time was based on the then current Turkish practice of introducing material from smallpox pustules into an incision made in the arm of the person to be protected. It was termed inoculation by the physician responsible for its introduction, Emmanuel Timoni. Under the patronage of influential figures such as Lady Mary Wortley Montagu this technique soon became fashionable, despite its dangers. Although the illness it caused was sometimes both severe and contagious, thus causing epidemics, the fear of smallpox at that time was so great that the practice was generally found to be acceptable.

Yet throughout the eighteenth century there were occasional suggestions that a more desirable alternative to inoculation existed. As early as 1713 it had been noted that an attack of cowpox might immunise against smallpox (Bowers 1973). The advantages of this finding lay in the fact that the risks associated

with cowpox in man are negligible compared to those of smallpox. It was not, however, until the publication of Edward Jenner's *Inquiry into the causes and effects of Variolae Vaccinae* in 1798 that the potential of inoculation with cowpox (vaccination)[1] became fully publicised. Once this occurred variolation rapidly became obsolete. Vaccination became compulsory in Bavaria in 1807, in France in 1809 and in Denmark in 1810 although it was not until 1840 that variolation became illegal in Britain and 1853 that vaccination became obligatory.

Early state involvement with vaccination has characterised much of the subsequent development of immunisation programmes throughout the world. This is understandable in that the benefits of any preventive technique are never directly visible so that it may be felt there is a greater need to encourage their use amongst the population than there is in the case of curative medicine. And during the nineteenth century, when there were very few effective therapies available in any sphere of medicine, the potential benefits of smallpox vaccination for the community were so great that no government could have afforded to ignore them. The latter is still true of many forms of immunisation today.

### The further development of immunising techniques

Improvements in smallpox vaccination in the nineteenth century centred on refinements of the production of the vaccine itself and on the more rigorous application of standards relating to its use. Innovations in the latter area included, by the end of the nineteenth century, awareness of the need for an as far as was then possible standardised product and the use of glycerolated calf lymph which to an extent prevented the vaccine from becoming contaminated by bacteria and losing its potency in storage. Regarding the methods of immunisation practices such as 'arm to arm' vaccination, which involved the transfer of potentially infectious material from individual to individual, had been generally abandoned by the beginning of the twentieth century.

More far-reaching developments in the history of artificial immunisation were generated by the work of Louis Pasteur. His most outstanding contributions to medical science were made during the 1880s when he developed immunising techniques against anthrax in farm animals and rabies (which he identified as a 'virus' disease) in man and animals. Pasteur also discovered that virulent viruses or bacteria could be attenuated by being grown in unfavourable conditions such as by 'passaging' them through the bodies of animals normally unaffected by the disease concerned

1 It was nearly a century later that Pasteur suggested that vaccination should be used to refer to all immunising techniques as a tribute to Jenner.

or by growing them in the laboratory in appropriate media. However, it is somewhat ironic that rabies is, in this context, an exceptional case.

It was largely due to the impetus provided by Pasteur's school in Paris and the competition which built up between that centre and that of Robert Koch and his colleagues in Germany that increased world-wide interest in the potential of immunising techniques built up and the developments of the early twentieth century, indicated in Table 2, occurred. These were followed by the spur to development resulting from the problems of the First World War and the emergence of interest in the commercial mass production of vaccines. It was during the inter-war period, with the work of men such as Dale and Hartley in Britain, that a full awareness of the need for strict biological standards relating to vaccine use emerged.

The growth in more recent years of the science of immunology, that is of the study of the body's capacity for self defence and hence for self recognition in general, may be attributed to earlier work on immunisation coupled with research on the problems revealed during transplant surgery. But any detailed discussion of this area would involve subject matter beyond the frame of reference of this paper. However, the topic is touched on in the appendix to this study.

## The present use of vaccines in Britain

The National Health Services Act of 1946, which came into force in 1948, made the arrangements for infant and other vaccination the responsibility of Local Authority health departments. They were required to ensure that facilities for immunisation against smallpox and diphtheria were available for voluntary use by the public and they could also, with ministerial direction or approval, make similar provisions for protection against any other disease.

The extention of vaccination programmes proceeded swiftly. In 1948 several Authorities were already offering immunisation against whooping cough (pertussis). During 1949 arrangements for tuberculin testing and BCG vaccination for persons in known contact with tuberculosis were introduced and in 1953 routine BCG vaccination for secondary school children was established. The period 1956–58 saw the development of the polio vaccination campaign which proved to be spectacularly successful. By 1957 all Local Authorities were offering whooping cough vaccination and

during the 1950s the provisions for tetanus vaccination were also progressively extended. Hence by 1962 state provisions for immunisation against poliomyelitis, diphtheria, smallpox, tetanus, tuberculosis and pertussis existed nationwide. Developments since that date have included the commencement of a measles campaign in 1968 and a selective rubella vaccination programme in 1971. The current levels of vaccine usage are shown in Table 3.

Programmes of immunisation vary between different countries in accordance with demographic, epidemiological, economic and related social and medical factors although the British schedule (shown in Table 4) differs from that of the other developed countries only in relatively minor ways. For instance in Sweden (and much of Eastern Europe) BCG vaccination is given to newborn babies, mainly for the sake of administrative ease and the resultant high rates of immunisation within the population (Lundbeck 1973) whilst in Britain the usual age for BCG vaccination is between 10 and 13 years. This latter pattern was established because at the time of the introduction of vaccination it was believed that young adults, particularly females, were most at risk from tuberculosis in Britain and there was uncertainty regarding the period of immunity given by vaccination. Another, more general, difference between the British vaccination programmes and those of many other European nations is this country's emphasis on voluntary acceptance.

This may be thought to influence the value of immunisation where very high rates of vaccination are needed to promote 'herd immunity' although the British record so far appears to be as good as that of most other countries.

The services delivered by the NHS during the period 1948–74 have met with a considerable degree of success. For example, in England and Wales in 1948, 748 people, 70 per cent of them children aged less than 1 year, died of whooping cough. A further 327 died from measles, 241 from polio and 156 rom diphtheria. By contrast only two children, both less than six months old, died of whooping cough in 1972. No deaths were recorded as resulting from either diphtheria or polio. And the number of measles deaths stood at 29 (M of H 1950, DHSS 1973).

However, as a result of the recent health service re-organisation the responsibility for maintaining the vaccination programmes has now been transferred from the local authorities to (in England and Wales) the new Area Health Authorities, working through the Area Medical Officers and their staffs and the District Community Physicians. The long term advantages of this could include improved statistical records regarding the uptake and eventual epidemiological significance of the immunisation services avail-

**Table 3** *Numbers vaccinated (England) 1966–72*

| | *Disease* | *1966* | *1967* | *1968* | *1969* | *1970* | *1971* | *1972* |
|---|---|---|---|---|---|---|---|---|
| Number under age 16 who completed a primary course (1000s) | Diphtheria | 733·6 | 755·4 | 672·4 | [1] 490·9 | 645·2 | 678·8 | 657·4 |
| | Whooping cough | 659·2 | 676·4 | 596·6 | [1] 433·4 | 587·1 | 608·5 | 600·9 |
| | Poliomyelitis | 825·4 | 786·1 | 691·2 | [1] 523·3 | 660·1 | 674·4 | 662·9 |
| | Tetanus | 794·4 | 807·0 | 716·3 | [1] 530·2 | 685·7 | 713·1 | 689·7 |
| Numbers under age 16 vaccinated (1000s) | Measles | | | [2] 688·1 | [3] 379·4 | 601·5 | 519·8 | 497·1 |
| | Rubella | | | | | 112·2 | 366·3 | [4] 278·2 |
| Total vaccinated (BCG) | Tuberculosis | 456·4 | 460 | 478·5 | 484·9 | 479·8 | 551·1 | 544·5 |
| Number vaccinated by end of stated year as a percentage of total born in second previous year. | Diphtheria | 76 | 78 | 79 | 83 | 81 | 80 | 81 |
| | Whooping cough | 74 | 76 | 77 | 81 | 79 | 78 | 79 |
| | Tetanus | 76 | 78 | 79 | 83 | 81 | 80 | 81 |
| | Poliomyelitis | 73 | 75 | 77 | 80 | 79 | 80 | 80 |
| | Measles | | | | | [2,3] 34 | 47 | 52 |

*Source* DHSS 1974

[1] Low figures are due to changes in the recommended schedule of vaccination and immunisation
[2] Figures for nine months only
[3] There was a temporary reduction in the supply of vaccine after March 1969 when the use of one manufacturer's product was suspended
[4] Refers to girls between 11th and 14th birthdays

**Table 4** *Schedule of vaccination and immunisation procedures*

| *Age* | *Vaccine* | *Interval* | *Notes* |
|---|---|---|---|
| During the first year of life | Diph/Tet/Pert and oral polio vaccine (first dose) | | The earliest age at which the first dose should be given is three months, but a better general immunological response can be expected if the first dose is delayed to 6 months of age |
| | Diph/Tet/Pert and oral polio vaccine (second dose) | Preferably after an interval of six to eight weeks | |
| | Diph/Tet/Pert and oral polio vaccine (third dose) | Preferably after an interval of four to six months | |
| During the second year of life | Measles vaccine | After an interval of not less than three weeks | Although measles vaccination can be given in the second year of life delay until the age of three years or more will reduce the risk of occasional severe reactions to the vaccine which occur mainly in children under the age of three years |
| At 5 years of age or school entry | Diph/Tet and oral polio vaccine or Dip/Tet/ Polio vaccine | | These may be given, if desired, at three years of age to children entering nursery schools, attending day nurseries or living in children's homes |
| Between 10 and 13 years of age | BCG vaccine | | For tuberculin-negative children |
| All girls aged 11 to 13 years | Rubella vaccine | There should be an interval of not less than three weeks between BCG and rubella vaccination | All girls of this age should be offered rubella vaccine whether or not there is a past history of an attack of rubella |
| At 15 to 19 years of age or on leaving school | Polio vaccine (oral or inactivated) and tetanus toxoid | | |

*Source* DHSS 1972 (b)

able in the country as a whole. This would be valuable in the process of evaluating the balance of wellbeing and hazard associated with the use of any vaccine on a large scale, aspects of which are discussed below.

Some fears have been voiced to the effect that the health service re-organisation may have endangered the ability of the NHS to react quickly in a crisis situation such as that created by an outbreak of a dangerous disease such as smallpox. Responsibility and legal powers in the field of environmental health are now split between the local authority Directors of Environmental Health and the NHS Community Physicians and Area Medical Officers.

However, in the case of such an outbreak executive power would be effectively held by the NHS and contingency plans designed to ensure effective epidemiological control should have been drawn up. Thus, as in some other areas, doubts about the wisdom of the 1974 re-organisation and/or predictions of its ill effects may prove to have been unfounded.

## The risks and benefits of vaccination

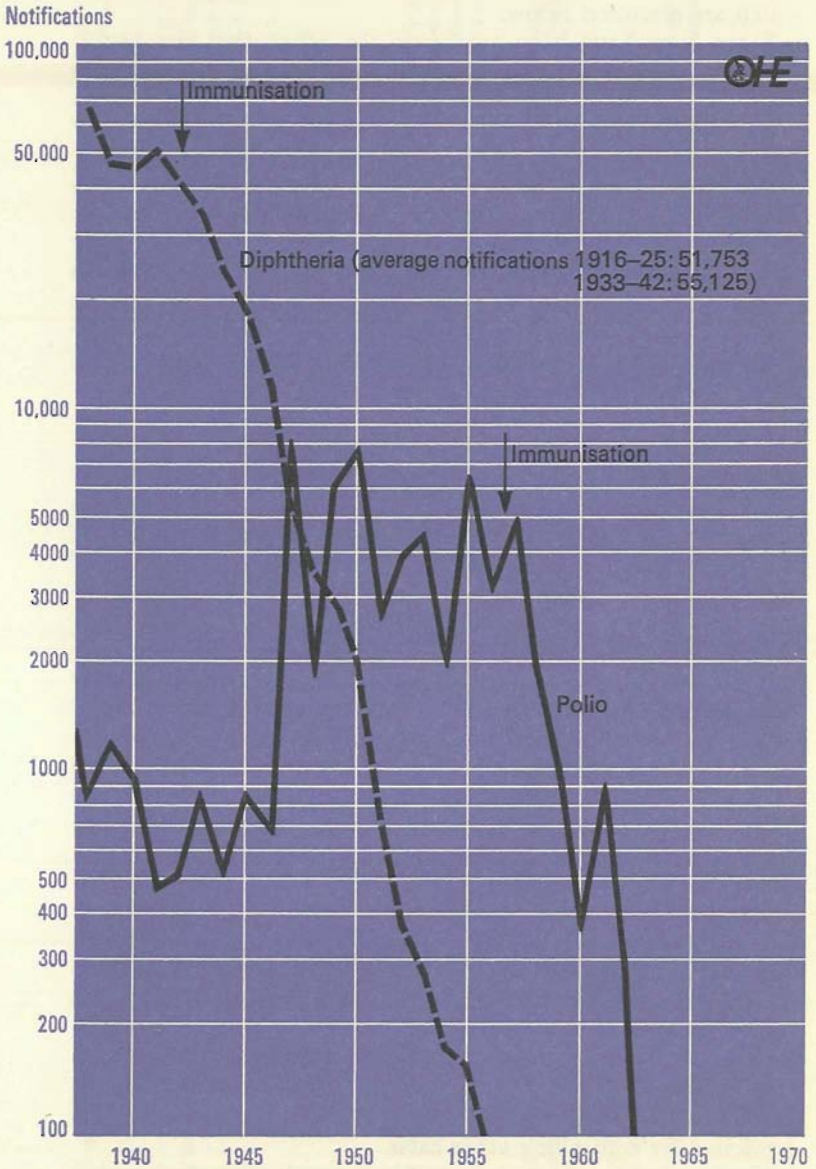
The dramatic success of vaccination programmes like those against diphtheria or poliomyelitis (illustrated in Figure 1) has been widely and rightly recognised. Yet it is possible to form an over-optimistic picture of the significance of certain forms of vaccination. An illustration of this point may be drawn from the records of the BCG vaccination programme in the United Kingdom.

Although its commencement around 1950 was apparently associated with a marked fall in the mortality (and incidence) associated with tuberculosis (see Figure 2) the near simultaneous effect of chemotherapy in controlling the spread of the disease as well as in treating those suffering it was almost certainly the most important medical factor in this drop. Improved housing and related environmental factors which came with the economic growth after the Second World War were also very important.

The relevance of BCG vaccination to the health of the nation today is even more doubtful. It has been estimated that it now probably results in less than one case of tuberculosis per 1,000 vaccinations being prevented and that soon this proportion could fall to one in 10,000 (Springett 1972). Hence in the future it may well be preferable, on economic grounds at least, to vaccinate only those at special risk such as those who work in hospitals dealing with TB cases or immigrants from Asia and rely on medicines for controlling other cases.

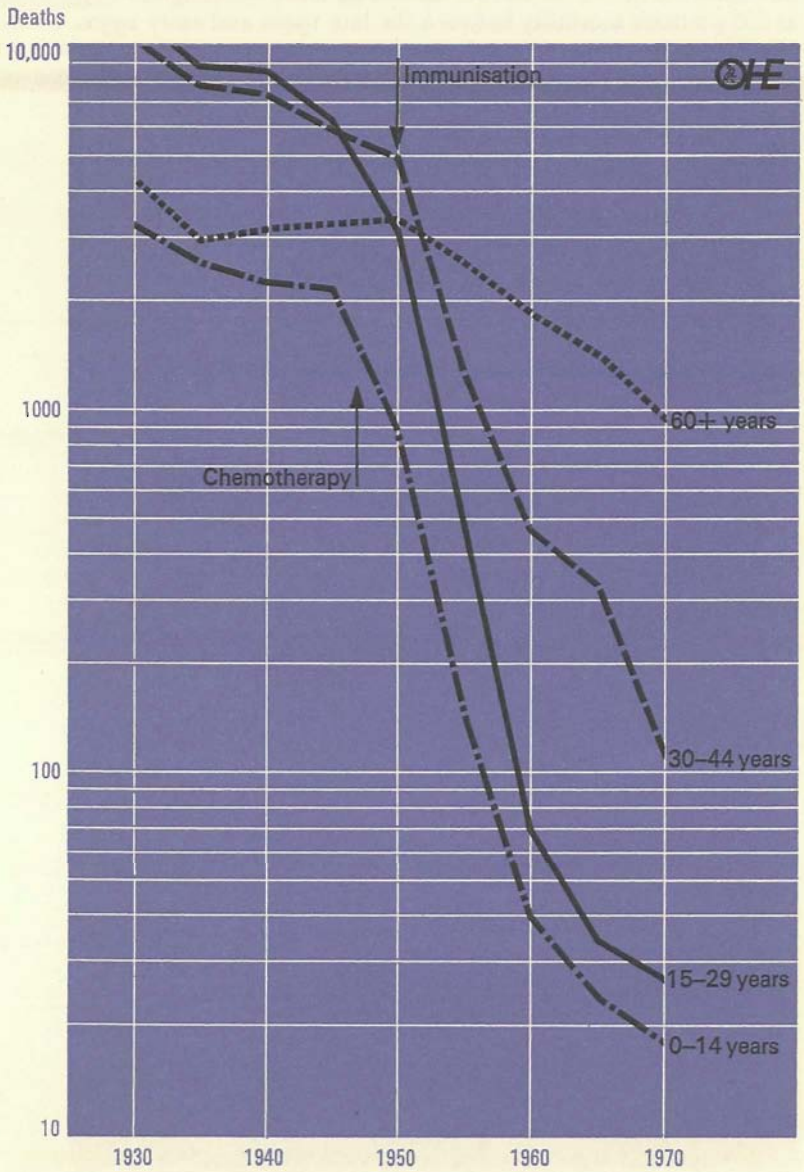
Similar considerations play a role in the evaluation of whooping cough (pertussis) vaccination although the question here is

**Figure 1** *Poliomyelitis and diphtheria notifications 1940–70 (England and Wales)*




*Source* Annual Reports of the Chief Medical Officer of the MOH/DHSS

**Figure 2** *Deaths from tuberculosis, 1930–70, various age groups (England and Wales)*




*Source* Registrar-General

complicated by the risks associated with this immunisation and by some questioning of the efficacy of vaccination. Whooping cough incidence fell before the start of the full national campaign in 1957 as did pertussis mortality between the late 1940s and early 1950s. The latter trend was due to improvements in treatment such as the introduction of antibiotics which prevented intercurrent infections as well as the improvements in the nutrition and living conditions of the population, although as Figure 3 shows the fall in incidence starting around 1950 was most probably due to individual local authority immunisation programmes. During the last 10–15 years the fatality ratio associated with whooping cough has remained constant, suggesting that the disease has probably not grown milder due to spontaneous changes. It may thus be misleading to compare it with a condition such as scarlet fever which over the course of the past century has become far less of a health hazard because of both natural attenuation and the direct effects of antibiotics on the illness (see Table 5).

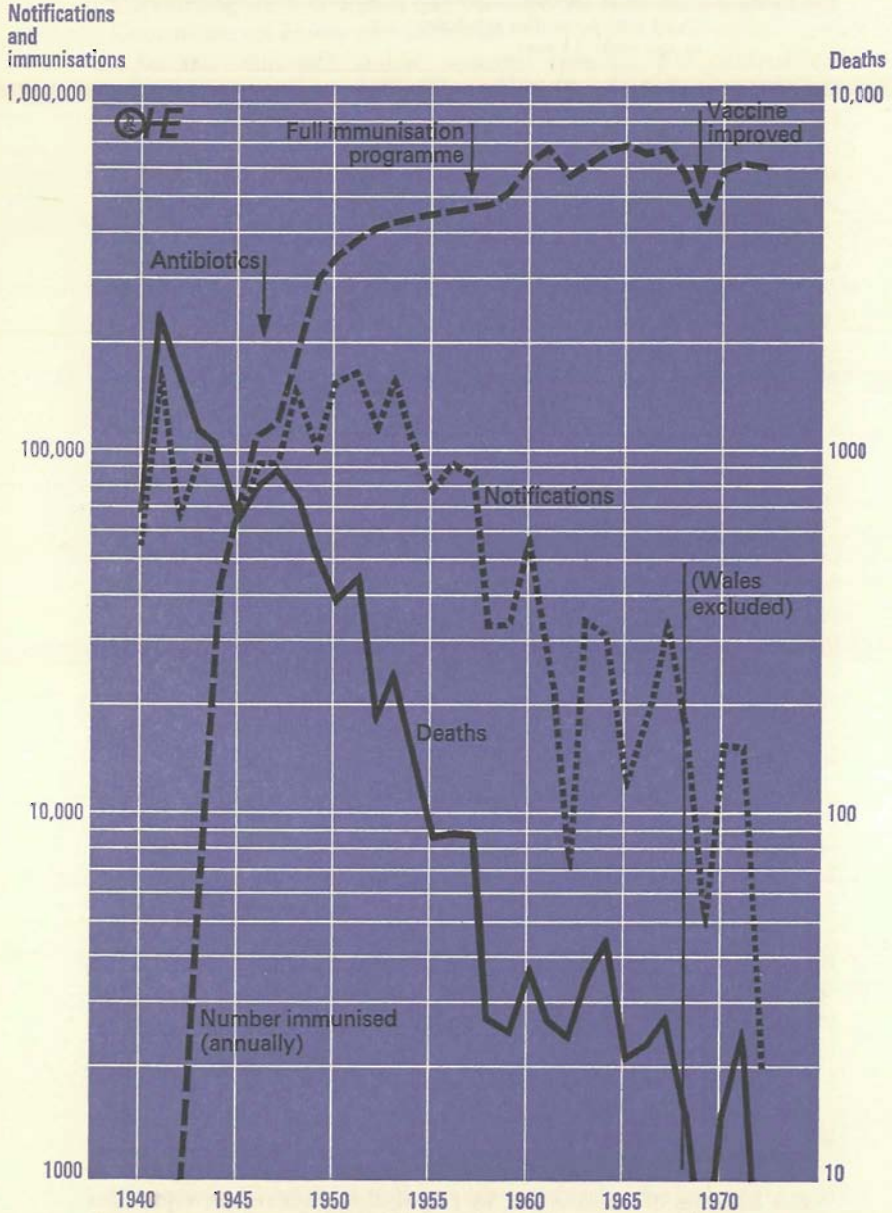
The fluctuations in the number of whooping cough cases in the 1960s have also led to doubts regarding the value of immunisation. Work done by the Public Health Laboratory Service indicates that towards the end of that decade some of the vaccines used were only 20 per cent efficient[1] (PHLS 1969). But recently a marked fall in the annual number of reported cases, to the region of 2,000 to 2,500, has followed improvements in the vaccine's antigenicity and potency.

Against this background it has to be remembered both that pertussis can cause brain damage or death amongst children, mainly those aged under six months, and also that the use of the vaccine itself involves similar hazards. In this country both Wilson and Dick have highlighted such risks, the latter estimating that, on the basis of certain localities experience, 70–80 children a year in Britain may receive significant nervous system damage as a result of immunisation against whooping cough (Dick 1972). The experimental halting of this vaccine's use, as for example by Ehrengut in Hamburg, does not appear to have resulted in any increase in the numbers of whooping cough cases.

However, it may be that these risks have been significantly over-stated (Perkins 1974, Griffith 1974). The estimate of the number of children harmed by pertussis vaccine quoted above has not been substantiated by published material and could possibly include cases of epilepsy, convulsions or mental retarda-

1 That is only about 20 per cent of those likely to catch whooping cough in a vaccinated as opposed to an unvaccinated population were protected. The pertussis vaccines have now been more effectively standardised so that probably 80 per cent of vaccinees are protected.

**Figure 3** *Whooping cough. Notifications, immunisations and deaths 1940–73 (England and Wales)*




*Sources* Annual Reports of the Chief Medical Officer of the MOH/DHSS. Griffith A H 1973.

**Table 5** *Death rates per million for children, selected diseases (England and Wales)*

| Period | Death rates per million population at ages under 15 years | | | | |
|---|---|---|---|---|---|
| | *Scarlet fever* | *Diphtheria* | *Whooping cough* | *Acute poliomyelitis* | *Measles* |
| 1851–1855 | | | 1,338 | | 1,047 |
| 1856–1860 | 1,919 | 1,347 | 1,300 | | 1,114 |
| 1861–1865 | 2,307 | 1,389 | 1,336 | | 1,189 |
| 1866–1870 | 2,258 | 871 | 1,405 | | 1,109 |
| 1871–1875 | 1,760 | 788 | 1,282 | | 962 |
| 1876–1880 | 1,575 | 709 | 1,349 | | 988 |
| 1881–1885 | 1,012 | 826 | 1,180 | | 1,070 |
| 1886–1890 | 572 | 781 | 1,163 | | 1,234 |
| 1891–1895 | 434 | 875 | 1,070 | | 1,104 |
| 1896–1900 | 331 | 872 | 1,003 | | 1,184 |
| 1901–1905 | 319 | 653 | 874 | | 955 |
| 1906–1910 | 224 | 491 | 756 | | 874 |
| 1911–1915 | 161 | 434 | 633 | 14 | 1,043 |
| 1916–1920 | 84 | 439 | 473 | 12 | 625 |
| 1921–1925 | 79 | 302 | 448 | 11 | 420 |
| 1926–1930 | 48 | 294 | 360 | 12 | 357 |
| 1931–1935 | 50 | 293 | 223 | 11 | 270 |
| 1936–1939 | 27 | 287 | 163 | 11 | 149 |
| 1940–1944 | 11 | 192 | 140 | 7 | 78 |
| 1945–1949 | 3 | 30 | 81 | 16 | 47 |
| 1950–1954 | 1 | 2 | 29 | 14 | 19 |
| 1955–1959 | 0 | 0 | 6 | 5 | 8 |
| 1960–1964 | 0 | 0 | 3 | 1 | 7 |
| 1965–1969 | 0 | 0 | 2 | 0 | 6 |

*Source* Registrar-General

tion resulting from other causes. The 36 examples of vaccine damage seen by Wilson at the Great Ormond Street Hospital for Sick Children over a period of 11 years (Kulenkampff *et al* 1974) were comprised mainly of children vaccinated rather below the ideal minimum age of six months and who in 12 cases had histories involving factors such as previous convulsions, recent intercurrent infection and reactions to previous DPT immunisations. And it is also to be noted that the danger of whooping cough cases re-occurring in large numbers is probably much greater if an entire community is left un-immunised rather than just the children in one town or region.

These points underline the delicate balance between the risks and benefits of vaccination in populations where the equations of these two facets involves relatively small hazards and gains on

either side, factors which are in themselves extremely difficult to quantify. Improved surveillance in this area is needed, despite the existing work of bodies like the Adverse Reactions Unit of the Committee on Safety of Medicines.

In fact although public concern recently has centred on pertussis immunisation there is an element of risk in any vaccination. As well as the possibility of allergic responses they may, in the case of live vaccines, cause symptomatic illness. This may be serious in the case of conditions such as polio (where there is around a one in a million chance of contracting the disease from the attenuated vaccine depending on the virus type involved). And there may also be a risk of vaccine contaminants, such as the monkey virus sv40 in early polio vaccines, although modern production controls ensure that known hazards are minimal. Some of the complex issues involved in the evaluation of immunisation programmes are illustrated below in the context of the prevention of measles.

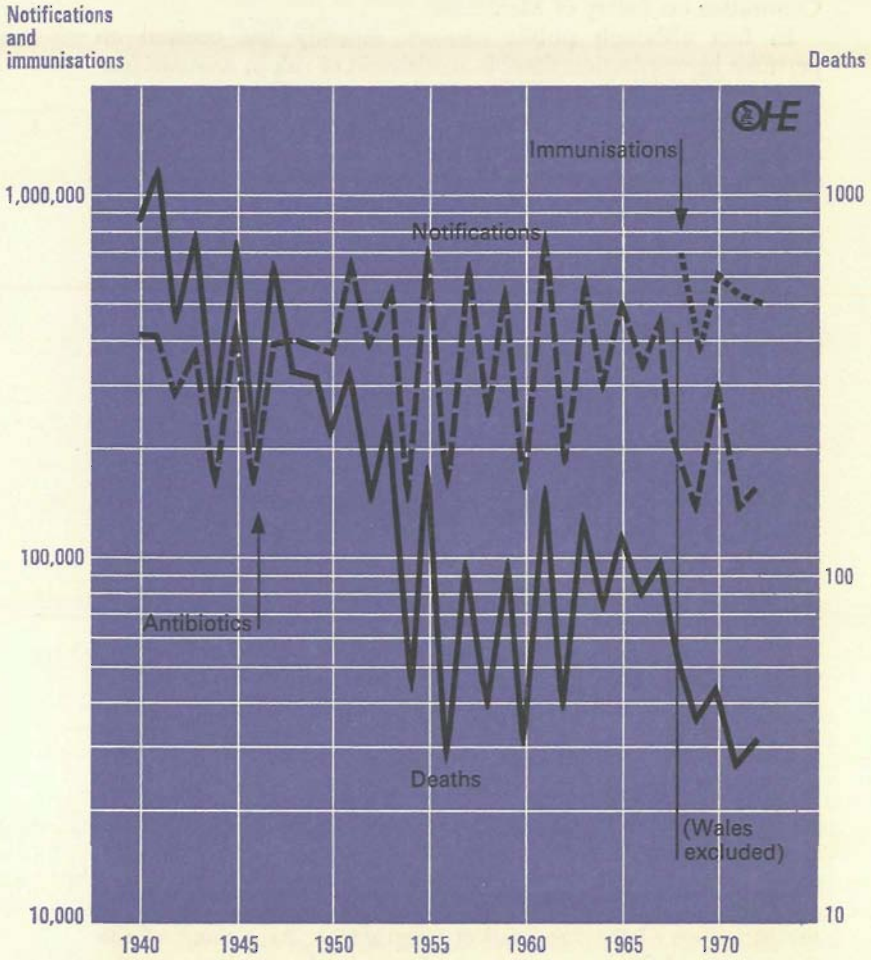
### A specific example – measles vaccination

During the 1960s the number of annual cases ranged between 300 and 700 thousand (measles tends to occur in biennial epidemics) causing 50 to 150 deaths and an average of around 500 possible cases of encephalitis which could leave the children affected permanently brain damaged (DHSS 1971). In all about one in every 15 persons suffering from measles experiences a potentially serious complication (DHSS 1967). Hospital and other medical care for those suffering from measles complications cost about £1,500,000 each year in the 1960s (1974 prices).

Thus the burden to society of even what is generally considered to be a mild illness is considerable. In 1968 a nationwide vaccination programme was commenced, although this was slowed at the start because of shortages of vaccine associated with the withdrawal of the 'Beckenham 31' strain vaccine after reported reactions to it. However, vaccination against measles is still received by only about half the child population, six years after the inception of the vaccination programme. As a result of this there were about 150,000 cases of measles in the last year for which statistics are available despite the existence of a 95 per cent+ effective vaccine. Around 30 deaths and a greater number of cases of brain damage and other complications occurred as a result.

Even so, as Figure 4 shows, the start of immunisation reduced mortality considerably. This had remained a relatively stable proportion of the total number of cases during the late 1950s and the 1960s, after the fall in the fatality ratio caused by improve-

**Figure 4** *Measles. Notifications, immunisations and deaths 1940–72 (England and Wales)*




*Source* Annual Reports of the Chief Medical Officer of the MOH/DHSS

ments in treatment and better living conditions.

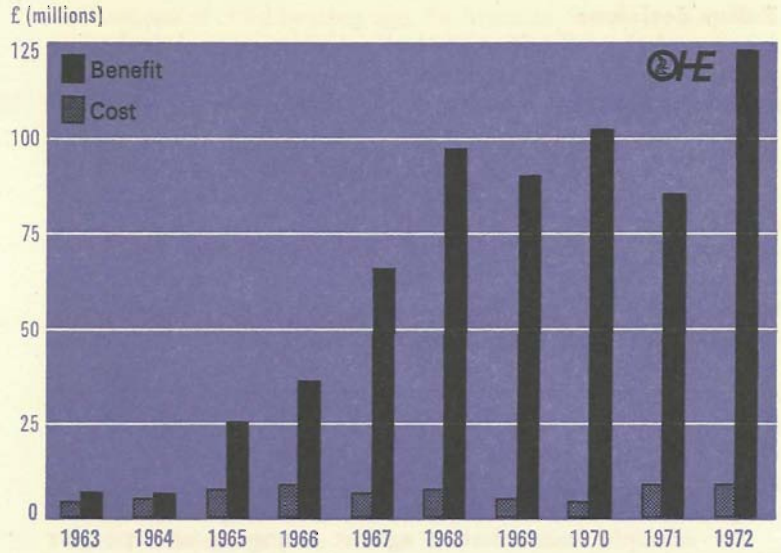
Studies of the risks associated with measles vaccination are encouraging although not absolutely conclusive. In America, where over 50 million doses have been used in the past decade, epidemiologists have found little evidence of vaccine complications in comparison to those found in connection with measles

itself (Jabbour *et al* 1972). On the other hand the estimated benefits have included the prevention of nearly 8,000 cases of mental retardation and 2,400 deaths. Spencer and Axnick (1973) have estimated that over £500 million have been saved in the United States as a result of measles vaccination[1] during the 1960s. (See Table 6 and Figure 5)

**Table 6** *Summary of health and resource savings due to immunisation against measles, United States, 1963–72*

| | |
|---|---|
| Cases averted | 23,707,000 cases |
| Lives saved | 2,400 lives |
| Cases of mental retardation averted | 7,900 cases |
| Additional years of normal and productive life gained by preventing premature death and retardation | 709,000 years |
| School days saved | 78,000,000 days |
| Physician visits saved | 12,182,000 visits |
| Hospital days saved | 1,352,000 days |

**Figure 5** *Costs and benefits of measles immunisations in the USA, 1963–72*




*Source* Spencer and Axnick 1974

1 In some other areas the economic benefits attributable to immunisation have been even greater. For example, it has been estimated that about £2,500 million was saved in America as a result of polio vaccination between 1955 and 1961 (Fudenberg 1974).

This evidence certainly suggests that vaccination is desirable. However, the fact that measles is a more serious condition amongst adults than children underlines the unsatisfactory nature of the present situation in which probably only half the child population is immunised. Measles remains endemic but its incidence could be sufficiently reduced to enable many unvaccinated people to avoid infection by it until the end of their childhood or early adulthood. Hence the long-term risk of ill effects in the population as a whole may so far have remained virtually constant because of the poor acceptance rates of the British programme.

Even if measles ceases to be endemic certain important problems will remain. A minority of the population will always be non-immune and hence particularly vulnerable in adulthood. Thus in the future the success of vaccination against measles may mean that any outbreak of the disease will have to be met by stringent epidemiological controls, as in the case of smallpox at the present time, if the benefits of the reduced incidence in children due to immunisation are to be retained for the entire community.

## Policy decisions

In view of the difficulties involved in planning and evaluating vaccination campaigns it appears desirable that expert analysis should be used to calculate the risks involved, working as freely as possible from the influence of public and political sentiment. In this context the recent formation of a special sub-committee of the Joint Committee on Vaccination and Immunisation, which advises the DHSS on policy, to review the available information on the risks of immunisation is a welcome step.

Yet it appears unlikely that any major changes in policy (with a possible exception regarding pertussis) will be made in the next few years. At the present time a clearer understanding of the natural history of the common infectious diseases coupled with an improved epidemiological record of their effects and those of vaccines is probably the first priority although the need for the careful setting and control of vaccine standards (e.g. for instance with regard to potency and antigenic selection) is a key issue at both national and international levels.

For example, immunisation against mumps is now possible and widely used in the United States. But the harmful effects of this disease are rare and the vaccine is unlikely to become available through the NHS until or unless new figures indicating particular at-risk groups or times are produced.

Similarly no further policy changes with regard to smallpox

vaccination are likely, even though the decision to abandon routine smallpox immunisation in 1971 was widely criticised. It is interesting to note with regard to this issue that between 1951 and 1970 there were 101 deaths from smallpox vaccination as opposed to only 47 from smallpox and that it is improbable that the community immunity resulting from vaccination exceeded 10 per cent during that period (Dick 1972). Yet it is still sometimes argued that the advisability of the withdrawal of vaccination to some extent hinges on the success of the current world smallpox eradication programme. For example, it is said that should individuals who have reached maturity require primary smallpox vaccination for travelling abroad then the risks involved might be greater than those for children. This factor has, however, been exaggerated in the past (Henderson 1973) and is now thought to be insignificant.

A third example of immunisation policy which will probably remain unchanged despite some questioning of its value is the case of rubella (german measles). Britain pursues a policy of selective vaccination for females in adolescence because virtually the only significant health hazard this illness represents is that of foetal malformation.[1] Prevention of this demands immunity for all women of child bearing age. In America, however, a total immunisation programme has been launched, designed at eradicating the disease from the entire community. It has been suggested in the USA that with the latter approach the risks to pregnancies amongst non-immune females are smaller than is the case with the British programme.

Yet selective immunisation minimises any risk associated with vaccination itself and may also be justified to some extent on the grounds of cost savings although this was not a factor in the British decision. The authorities in this country believe that the circulation of rubella in the community will 'boost' the immunity of vaccinated women rather than put pregnancies at risk and have therefore opted for the 'target' use of the vaccine. They point out that it is unlikely that rubella could actually be eliminated in either America or Britain by a total immunisation policy and that the restricted circulation of the disease which would ensue in a partially immunised population would most probably be more dangerous than the free circulation allowed by the selective British policy.

The only other important question regarding vaccine use at present relates to the influenza vaccines which are now available. These are discussed in detail later in this paper but the most

1 Caution must be exercised with regard to possible teratogenic effects of the vaccine (Vaheri *et al* 1972).

important point to be made about them in the context of this section is that they too are suitable for selective usage. Groups such as the elderly or chronically ill are at particular risk from influenza and hence even though these vaccines may not at present be thought to be as valuable for use amongst the young and healthy they should certainly be supplied to individuals in the former categories. At present this is not usually the case and large numbers of elderly people are unprotected and so stand in danger of long spells of sickness or premature death.

A final point is that it has been suggested that under the reorganised NHS it may be possible to amalgamate the vaccination programme further into the family doctor service (in some areas family doctors already give 50 per cent of vaccinations) and/or to ensure that any clinics or health centres giving vaccinations have full knowledge of the medical histories of the individuals concerned and their relatives. Advocates of this approach believe that it would enable those at special risk of side effects to avoid unnecessary immunisation and danger. But all too often damaging reactions are unpredictable and more knowledge of their causes is needed before improvements in services such as those outlined above can ever become particularly effective. For the moment perhaps the most beneficial organisational development would be the complete computerisation of all vaccination records which could result in more effective efforts to ensure high acceptance rates and fuller community immunity coupled with the more efficient identification of any subsequent ill effects via an adequate system of record linkage.

## Vaccination in developing countries

In many of the areas of the emergent nations of Africa, Asia and Latin America around half of all recorded deaths are still amongst children aged under five years from a combination of malnutrition and multiple infections. Whilst the value of immunisation in developed countries may now sometimes be questioned because the risks of infectious diseases are so low the rewards of extending vaccination programmes in the poorer areas of the world would be immense, although they must be accompanied by attempts to reduce fertility and improve nutrition and environmental factors such as housing and sanitation.

Arguments which suggest that vaccination against conditions like measles (which causes widespread distress, death and disable-

ment amongst populations living in poor environments) in the developing countries are a misallocation of resources serving only to increase the population and thus the overall level of distress are too simplistic. Relief from some of the multiplicity of infections suffered by the children who survive to adulthood would probably increase their overall vitality and ability to improve their own situation. And a fall in the death rate amongst populations has been shown normally to lead to a corresponding fall in the birth rate. This probably stems from changes in the nature of the relationship between children and their mothers as well as in the family structure, coupled with the rational awareness of parents that they need have fewer offspring to ensure the survival of some adulthood if effective medical care is available. It is in the area of highly sophisticated care in hospitals that major economic savings may be achieved, not in failing to establish vaccination programmes which benefit the entire population.

Despite the advisory services and other resources made available by the WHO many nations still have inadequate vaccination programmes. An important factor limiting progress in this area is the general lack of adequate rural health services. The extension of training of medical auxiliaries capable of carrying out immunisation independently as part of a simple permanently established medical system would seem essential if services are to be effective.

Technical advances which may be of particular value in the developing world include the production of safe and effective vaccines with up to six separate antigens in them. The use of these may save considerable time and money by avoiding the duplication of effort in immunising communities. However, the uptake of useful innovations may not be as swift as might be hoped. For example, the employment of jet injection apparatus, which could also lead to marked economic and operational savings, is still relatively limited although this may in part be due to factors such as a shortage of vaccines in suitable containers or the apparent preference within some cultures for immunisation via syringe injection and the physical penetration this involves.

Other problems facing vaccination programmes include the difficulty of storing certain vaccines (e.g. yellow fever vaccine) in warm climates although this has been to some extent overcome by techniques such as freeze drying. Even when this type of difficulty is solved it should not be assumed that approaches which have proved successful in the context of the temperate, economically developed nations are necessarily going to be of similar value in developing countries. For instance in the case of poliomyelitis, which is of increasing significance in the third

world, the live vaccine may be of diminished efficiency in semi-tropical regions. This is in part at least because the establishment of the attenuated polio virus in the vaccines may be impaired by the presence of enteric infections.

It also has to be remembered that many of the diseases which are still major health hazards in the poorer parts of the world, such as malaria, cannot as yet be prevented by vaccines. And with some others, such as cholera, the present vaccine gives protection only over a very limited period. Although suitable for use by travellers the value of such vaccines in preventing epidemics is relatively small and environmental control is more important. Immunisation programmes alone cannot, therefore, solve all the health problems of the developing world. But they can do much to alter the balance of illness against vitality and in doing so open the way to more satisfactory answers.

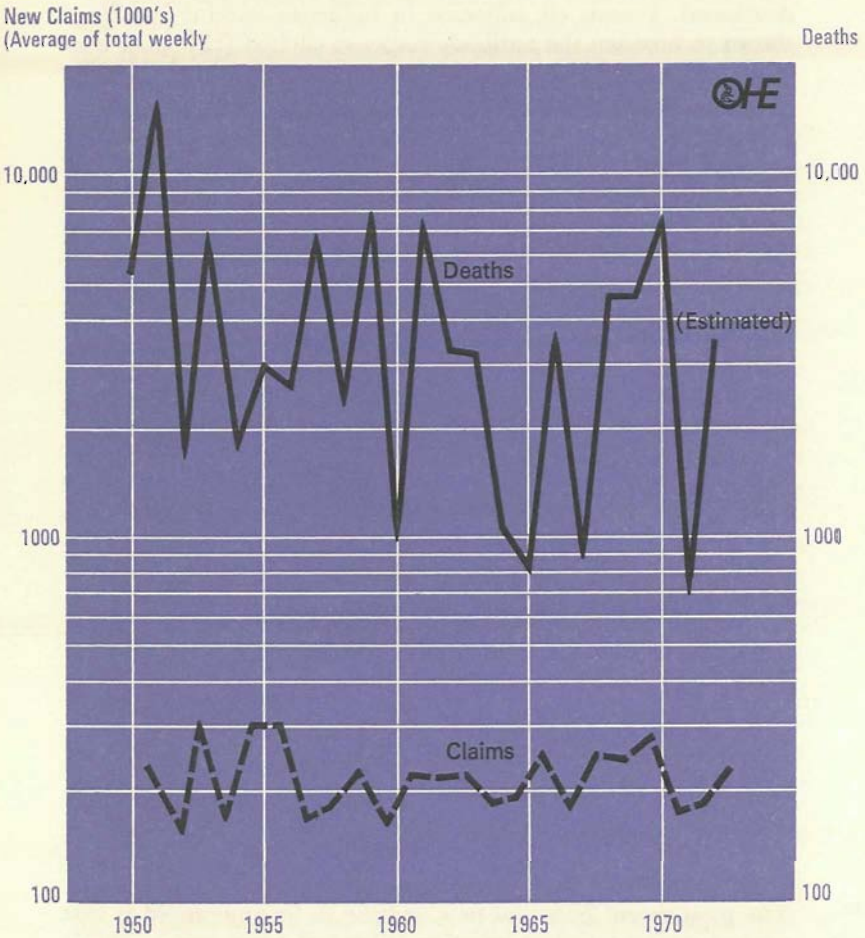
# Future developments

Progress in the field of vaccination depends on both the improvement of existing products and on the development of immunising antigens against diseases for which they were hitherto unavailable. Examples of current activity in the former area include efforts to strengthen the efficiency and duration of cholera vaccines (possibly through the production of a toxoid) and the development of a new rabies vaccine. One which is safer and easier to use should soon be generally available (Wiktor *et al* 1973). And most importantly of all considerable research effort is being devoted towards the improvement of influenza vaccines. This section examines the latter topic in further detail before surveying the possibilities regarding completely new vaccines.

## Influenza vaccines

Influenza represents a world-wide threat to health, causing considerable mortality and morbidity in developed and developing countries. The elderly and those suffering from chronic illnesses are at particular risk from the disease although in an epidemic year between 25 and 30 million working days may be lost as a result of the infection amongst the employed population in the UK (see Figure 6). The control of influenza is therefore a very worthwhile aim but this has proved difficult mainly due to the fact that the virus is subject to marked and rapid variations in its antigenic properties both between and within its various strains. Because of this influenza vaccines are often only of limited

**Figure 6** *Influenza. Deaths and new sickness benefit claims 1950–72 (England and Wales)*




*Source* Annual Reports of the Chief Medical Officer of the MOH/DHSS

efficiency in practical use and the duration of the protection they give usually lasts only for one year. Some trials, such as one recently carried out by the PHLS on post office workers, have proved disappointing (PHLS 1974).

However, several new techniques offer the prospect of further improvements. One of these is the use of adjuvants, additives to the vaccine which increase the production of antibodies in

response to the antigen. Aluminium hydroxide has been used for this purpose in vaccines such as triple antigen (diph/tet/pert) and more recently adjuvants derived from vegetable oils have been developed. Peanut oil adjuvant in influenza vaccine has been shown to broaden the antibody response elicited (Hilleman *et al* 1973), a property which could increase the length of time for which immunisation remains effective.

In recent years attempts to increase the purity of influenza vaccine, which would decrease the risk of reactions to it and so allow greater antigenic concentration, have been made. The most successful of the techniques so far employed has proved to be zonal centrifuging. The use of this method has not only allowed the potency of influenza vaccines to be raised but their improved safety has considerably increased the numbers of people within the population who stand to benefit by their use.

Research is also being conducted in techniques which may reduce the problems created by antigenic changes on the part of the virus. It has been suggested that these may be predicted (Fazekas de St Groth *et al* 1973) but this appears improbable. More encouraging is the development of recombinant influenza strains. These are the result of hybridising a laboratory-developed, rapidly-growing virus strain with new ones as they appear. It is subsequently possible to select out suitable mutants with the required antigenic properties (i.e. those of the new strain) and the growth potential for culturing in sufficient quantities and concentration for full scale vaccine manufacture (of killed vaccine).

In this context the role of the WHO in the world-wide surveillance of influenza and the rapid identification of new strains is particularly important. Only through an effective 'early warning' system can the manufacturers gain sufficient time to produce vaccines in quantity before outbreaks become uncontrollable.

## New vaccines

The most recent potential new vaccine to be announced is that against cytomegalovirus infection (Elek and Stern 1974). This is the most important viral cause of mental retardation, affecting the children born to mothers infected during pregnancy. As many as 4–500 such cases may occur annually in this country, over twice as many as were on average attributed to german measles before the introduction of vaccination.

A number of problems exist in relation to the new vaccine and it has been suggested that it may possibly be oncogenic or cause a latent infection which may recrudesce at some stage. Further cautious research is therefore needed but it should be realised that

the potential economic and other social and personal returns to a successful vaccine would be immense.

Another area where the development of a vaccine is needed and now seems possible is that of infectious and serum hepatitis.[1] In the latter case the discovery of Australia antigen in association with type B (serum) hepatitis has lead to much research activity. This has recently been complemented by the identification of a virus associated with type A (infectious) hepatitis in patients' faeces (Feinstone *et al* 1973). Infectious hepatitis alone caused 137 deaths in England in 1972 (out of 11,690 notifications) and thus it would be desirable to prevent it. The growth of the use of blood products in medicine and the development of kidney machines and allied technologies has resulted in serum hepatitis becoming increasingly common and a vaccine, if feasible, would be of great value especially to those employed in health care.

A number of other potential areas for the development of new vaccines exist. For example, it is conceivable that immunisation against gonococcal infection will become possible although where there is no risk of mortality associated with a condition and effective chemotherapy is available the use of any preventive technique involving even a minute risk to life is questionable.

Perhaps the most interesting future possibility is that some forms of human cancer may be caused by viruses and be preventable by appropriate immunisation. Certain vaccines, such as BCG, are already used as non specific immunostimulants in some forms of cancer therapy. One example of an animal cancer which may be controlled by vaccination has already been found (Mareks disease in chickens) and commercially employed. In humans there is still no fully proven link between viruses and oncogenesis although it is probable that herpes viruses are in part at least responsible for some cancers (e.g. of the bladder or cervix). The argument for Epstein-Barr virus infection being responsible for Burkitt's lymphoma is particularly strong (Epstein *et al* 1973). EB virus, which is commonly associated with glandular fever and has probably infected the majority of the population at some time, may also play a role in the genesis of some human leukaemias (Zorbala-Mallois *et al* 1974).

However, this does not necessarily mean that successful immunisation will ever be possible. For instance as with some parasitic diseases[2], there is a possibility that the pathogenesis

1 Human gamma globulins may be used in the prevention or treatment of hepatitis.

2 The body mounts a weak immune response to most parasitic diseases and so vaccines may perhaps be developed although this possibility appears remote. Immunisation already exists for one form of human leishmaniasis.

of cancer in at least some forms depends on an inadequate immune response which may stimulate the tumour cells (or damage the host in the case of the parasitic conditions). Thus treatment or prevention in this field may well depend on fundamental advances in immunology rather than on the development of a vaccine.

## Social and economic influences

The application of new or existing knowledge of immunising techniques is frequently affected by social and economic factors. As well as hard considerations of cost or acceptability in terms of personal hazard these may also include aspects of evaluation nearer to the world of fashion. George Bernard Shaw made this point at the turn of this century when he used the character of Sir Colenso Ridgeon (modelled on his friend Almroth Wright) in *The Doctor's Dilemma* to ridicule what he termed the vaccination craze. Although Shaw's views on this question lacked adequate foundation it is true that in early decades of this century it was a popular belief that immunisation was a potential cure for all human ills. By contrast pharmaceutical research was considered to be of relatively little importance.

But the advent of sulphonamides in the mid-1930s and the antibiotics in the early 1940s caused a general reversal of this situation. Commercial losses at that time on vaccines which the new medicines made obsolete to some extent undermined industrial and government confidence in further vaccine development. And public interest swiftly centred on the new 'wonder drugs'.

Today any dichotomy between the supporters of vaccination as opposed to those of chemotherapy has largely died away and it is unlikely that research in either field suffers from interest concentrating excessively on the other. But a number of economic and social considerations continue to affect the production and use of vaccines, both nationally and internationally. For example, the return on capital employed in the manufacture of vaccines is, except in the case of pioneering new products, far lower than the average for the pharmaceutical industry or manufacturing industry as a whole. (Some vaccines, such as that against pertussis, may even be being produced at a loss by certain British companies.) This is due to a number of factors including the multiplicity of state owned or aided and private manufacturers throughout the world offering similar vaccines. Although this duplication of productive capacity may seem wasteful it has the advantage to society of maintaining manufacturing skills and

permitting large variations in the volume of production in the face of epidemics.[1]

However, where national pride has led some developing countries to embark on the production of their own vaccines rather than buying as economically as possible on the open market this has involved them in considerable unnecessary expenditure. Another factor affecting the world market in vaccines is that they have been supplied as part of foreign aid programmes. This too has had the generally desirable effect of keeping prices low although some of these programmes have been aimed at providing 'tied aid'. This means that a principal objective has been the stimulation of industry in the donor country. Others have been mounted as political exercises aimed at propaganda and the socio-economic penetration of developing nations. Thus medical and social considerations regarding immunisation have sometimes been overlooked.

Nevertheless vaccines such as smallpox, cholera, typhoid, yellow fever or triple antigen are supplied at WHO negotiated prices in the region of 1–2p per dose. When it is remembered that many vaccines will in only a few properly spaced doses confer life-long immunity the economics of vaccine use from the consumer viewpoint are often extremely attractive. Even in Britain, which uses relatively expensive vaccines such as rubella selectively on a nationwide scale, the total identifiable vaccine cost to the NHS was in the region of only £4 million in 1972 (DHSS 1973–74).

Yet it may be that, because the economic returns on existing vaccines are low, resources are concentrated to too great a degree on creating new vaccines rather than improving those already in use. However, if this criticism is correct it would apply to the various state-financed vaccine research centres throughout the world as well as to private industry. Thus the key problems may be ones relating to non-economic pressures affecting research policy and a rational approach to the establishment of standards rather than the system of finance. In qualification it should be pointed out that many experts do not accept this argument and also that once a safe vaccine has been produced there may be reasons for not trying to improve on it with another product (except in ways like increasing the purity) unless there is very good evidence that marked advantages might accrue. The trials of any new vaccine carry risks to the vaccinees and should not be entered upon lightly.

1 For example, in the cholera pandemic at the start of this decade over 36 million doses of vaccine were used in a year. Last year demand dropped to around 4 million doses.

## Vaccine-damaged people

The small yet finite hazards associated with the use of vaccines are justified to the community as a whole by the relief from damaging and killing diseases which they bring. Naturally these dangers should be minimised by vigorous policies designed to ensure production standards and monitor the epidemiological signifi cance of vaccination programmes. In Britain the work of bodies such as the National Institute of Biological Standards and Control and the Public Health Laboratory Services help to ensure this even though there are still gaps in the statistical sources necessary for calculating the true cost/benefit ratios (in terms of human suffering and death rather than economic substitution) of vaccine use.

Yet there remains an important problem, that of people damaged by vaccines and who in particular may suffer neurological illness as a result. The numbers of cases involved are difficult to assess and it is feared that the available official records are inadequate. This is not unduly surprising in that serious reactions to vaccines occur very rarely and it is obviously difficult for the medical profession to record such reactions as being certainly due to vaccine use. It may thus be impossible to demonstrate clearly vaccine damage even when it is suspected. Publicly repeated estimates such as that there have been around 2,000 cases of brain damage as a result of vaccination since the start of the NHS are thus largely speculative rather than scientifically proven.

Even so they have successfully drawn attention to an important element in the profit and loss equation relating to vaccine use in societies such as ours. Although in the last century it is very probable that a far higher incidence of serious reactions were caused by smallpox vaccination alone the problem of vaccine-damaged people has become more serious today than it was even in the relatively near past because the risks of damage from other causes have fallen so greatly.

Recently public attention has been drawn to the argument that compensation should be paid to these individuals, both by the formation of an association for parents of vaccine-damaged children and by the work of individual MPs and doctors. In several European countries and Japan the state already ensures against the risks of damage caused by its vaccination programmes.[1] Although it may be argued that for a national health service it is more important to ensure that all handicapped people receive adequate help and care, whatever the cause of their

1 In West Germany, for example, there was an annual average of 34 accepted claims during the 1960s for damage other than that resulting from smallpox vaccination.

condition, it could be that such a system of compensation would prove beneficial in this country. For example, it might help to maintain vaccination acceptance rates and so minimise the overall burden of handicap resulting from infectious diseases. And large payments to the few hundred children suffering vaccine damage could well help to underline the poverty of the services currently provided by the community for the 50,000 severely handicapped children alive today whose condition is attributed to chance rather than an identifiable cause.

The entire question of liability and compensation is currently being studied by a Royal Commission (the 'Pearson' Commission) whose report should help to clarify this difficult problem in relation to health care and linked areas. But its recommendations will not necessarily apply retrospectively and so may not prove to be of any great value to those people who have already suffered as a result of vaccine reactions. As awareness of this problem will doubtless lead to improved safety standards and so a reduction in the number of future cases it is to be hoped that the attention of the public and the media will not be drawn away from the plight of the families and individuals currently facing the problems of such handicap.

# Conclusion

The medical advances of the twentieth century and allied social developments in areas like the quality of housing have succeeded in protecting the people of countries such as Britain from many of the ill effects of the infectious diseases. Although this group of illnesses were only a century ago the major cause of death today they represent a relatively insignificant health care problem as compared with the chronic, degenerative conditions of later life. In the sheltered conditions of the modern world the speed and radical nature of this progress is often overlooked. Vaccination is frequently thought of as being simply a means of avoiding the relatively minor symptomatic discomforts of 'childhood' complaints rather than as a vital defence against life endangering hazards.

It is true that changes in the epidemiology of the communicable diseases have brought the value of some immunisation programmes in the developed world nearer to a 'threshold of transition' situation in which the ill health they cause may balance that which they prevent. The severity of smallpox vaccination reactions and the small risk of encountering the disease in Europe and North America is one example of such a case. The debate

surrounding the use of pertussis vaccine is another even though in this instance it is possible that immunisation may still provide net benefits to the community and particularly to children aged under six months (who may be too young to be vaccinated themselves). However, public and to some extent medical confidence in whooping cough vaccination has been shaken and it may prove desirable for this form of immunisation to be withdrawn from the NHS schedule in the near future, if only to maintain public trust in and uptake of the remainder of the immunisations available. Within a decade BCG vaccination may become a third case of an immunisation programme suitable for withdrawal, although here the argument would rest on grounds of cost rather than safety.

The value of other vaccines employed in Britain appears to be without question considerable although the future development of new medicines (such as anti-virals) could eventually decrease the relative productivity of all forms of immunisation. But for the present it would be entirely misleading to suggest that there is any benefit to be gained for individuals through the avoidance of the vaccinations at present available and unwise to believe on the current evidence that diseases such as diphtheria would not again become prevalent or be just as hazardous to life as they were in the past if routine vaccination were to be withdrawn.

In some areas of England 30 or 40 per cent of children may fail to receive polio or tetanus immunisation whilst nearer 50 per cent over the country as a whole may not be immunised against measles. Figures such as these, together with those showing the underutilisation of influenza vaccine even amongst those groups who stand to benefit by it to a considerable degree, should be seen as being as disturbing as any which relate to the possible ill effects of vaccines.

Although public discussion of vaccination must point out that, as with any other effective medical intervention, there are risks involved, this aspect of the issue should not be dwelt on for too long or to the exclusion of others. There seems to be no reason to doubt that the individuals responsible for the formation of policy regarding immunisation in this country are fully aware of, and are carrying out, their duty to balance hazard with gain. Although the public should always press for stringent safety measures and full access to information regarding the dangers to which they may be exposed by state policy individuals seeking to ensure their own health or that of their families should realise that as far as immunisation is concerned their best interests are to be served by a willing acceptance of the vaccinations offered through the National Health Service.

# Appendix



**The mechanisms of specific immunity**

Resistance to infection is achieved in humans through a number of distinct mechanisms, as shown in Table 7. Those involved directly in the process of immunisation by vaccination are the specific responses, which are stimulated to give active immunity. (The injection of antibody containing serum from a donor into the body of a person who may have, or have been exposed to, a given disease should not be confused with vaccination in that it promotes only passive immunity. The recipient's immune responses are not 'primed' to meet the disease concerned and protection lasts only as long as does the introduced antibody.)

There are two main types of specific immune response. The first is the production and release of free (humoral) antibody into the blood and other body fluids. This may act directly by, for example, neutralising toxins or binding foreign substances or bodies together and/or rendering them more vulnerable to attack by phagocytes or the complement system.[1] The second involves the production of sensitised lymphocytes (white cells formed in the lymph system) which have antibody 'bound' to their surface and which secrete biologically active materials known as mediators which may stimulate non-specific immune responses, such as a concentration of phagocytic inflammatory cells in invaded tissue. The second type of immune response is known as cell mediated immunity and is the basis both of the body's ability to reject tissue transplants and to resist diseases such as tuberculosis.

In both types of response the key cell involved has been found to be the small lymphocyte. These cells actually produce antibody and also retain the ability to do so indefinitely after an initial exposure to given antigen. In birds it may be clearly shown that there is a division within the small lymphocyte population between those whose maturation occurs mainly within the Thymus and those whose immunocompetence develops in the Bursa of Fabricus. The latter eventually become the source of humoral antibody whereas the Thymus cells are concerned largely with cell-mediated immunity. Although there is not such a clear differentiation in mammalian physiology there are firm grounds

**Table 7** *Mechanisms of resistance to infection*

| *Type* | | *Examples* |
|---|---|---|
| Non-specific immunity | | Phagocytosis—lysozyme—interferon |
| Specifically acquired immunity | | |
| Passive | Natural | Maternally derived Ig in baby |
| | Induced | Protection by preformed heterologous antibody or homologous $\gamma$-globulin |
| Active | Natural | Exposure to infection |
| | Induced | Immunisation with toxoid, or killed or attenuated organisms |

From Riott (1971)

1 Complement activity depends on the operation of nine protein complements which act in sequence and can eventually punch a 'functional hole' through the cell membrane on which they have become fixed.

for believing a similar separation of function exists within our own lymphocyte population. Hence a distinction is drawn between B cells and T cells.

However, the respective roles of B and T lymphocytes should not be over-simplified and it should not be thought that they are the only cells involved in the overall process of an immune response. In the case of cell-mediated immunity it has been established that initial macrophage (large phagocytes produced by the reticulo-endothelial system) activity rendering the substances involved more antigenic is a necessary prelude to a T lymphocyte immune response. Although no evidence exists to indicate that similar macrophage intervention is needed to stimulate B lymphocyte production of humoral antibody (Riott 1971) it is believed that T cells specifically help B cells to function even though the two types of immune defence are probably capable of some degree of independent function. Also antibody produced by B cells can subsequently enhance or inhibit the responses of T cells and other cells. Recent work has indicated specific synergistic interaction between sub-populations of T cells.

The response to the first introduction of an antigen is termed primary and is characterised by the predominate production of IgM (immuno-globulin M) type antibodies. This is probably a relatively early form of antibody in evolutionary terms which has a mainly agglutinating role. In time the primary immune responses fades. If the antigen concerned continues to be presented or is represented to the host a secondary response ensues. This involves a greatly increased production of antibody belonging to the IgG (gamma-immuno-globulin) type and usually allows the host organism protection from any symptomatic illness.

It has been shown that during the primary response an early delayed allergic response to the antigen is elicited. This has a localising effect and may be a valuable preliminary to the later synthesis of antibody involved in the secondary response in that the spread of antigen is delayed until the body is prepared. However, a delayed allergic response is probably not in itself an essential pre-requisite to humoral antibody synthesis.

**The nature of antibodies (immunoglobulins)**

Immunoglobulins are complex proteins with a basic structure of two heavy and two light peptide chains. They are large, with molecular weights ranging from 150,000 (IgG) to 900,000 (IgM). In humans variations in the structure of the heavy chains give rise to five main types of immunoglobulin. These are IgG, IgM, IgA, IgE and IgD.

Antibodies do not enter into simple chemical reactions with antigens but should be regarded as fitting together with them, like irregularly shaped building blocks. Receptor sights on the surface of the antigen molecules correspond closely to mirror-image formations on the surface of the antibody molecules. Antigen and antibody complexes are held together by forces which can effect all macro-molecules such as hydrogen bonding, coulombic forces or the fitting together of hydrophobic surfaces. Antibodies act on antigens or antigen-bearing bodies in a number of ways. For instance, they may bind antigens together so preventing their spread and increasing the ease of phagocytic attack. A similar effect is seen when micro-organisms are opsonised. That is when they become coated with antibody which renders them 'tasty' for phagocytes. Antibody may also have a cytotoxic effect by activating the complement system by fixing components of it, which circulate freely in the extracellular fluids, to the surface of cells.

**Hypersensitivity**

An important aspect of the capacity for specific immune response is that when

an individual has been immunologically primed further contact with antigen can lead not only to secondary boosting of antibody production but can also cause tissue damaging reactions. Probably the best known examples of such hypersensitive responses are allergies such as hay-fever. Others include prolonged reactions to insect bites, serum sickness, contact dermatitis, rhesus incompatibility and reactions against medicines. An understanding of these phenomena is useful in any discussion of the more complex aspects of immunology. With regard to a simple understanding of vaccination it is of less importance although excessive exposure to antigen, which may be the result of over frequent re-vaccinations, can cause hypersensitivity reactions.

**The role of the immune responses**

It is improbable that the immune responses mechanisms evolved primarily as a means of bodily defence against external attack. One suggestion is that they stem from the need to remove cellular breakdown products and dead tissues. Another, put forward by Burnet amongst others, is that their key role is to act as a bodily surveillance system through which the functional need to recognise mutating cells (as in cancer) and eliminate them may be fulfilled. In all the roles mentioned above one essential property is shared. This is that the immunity system can differentiate between acceptable 'self' tissues and unacceptable dead, mutating or foreign material. Such an ability is obviously beneficial to any organism and is essential for the survival of the higher, complex, forms of life. But in assessing the value of our natural immune responses to medicine it should be remembered that they do not always have desirable effects and nor are they always particularly efficient. Although evolution favours that which is in net terms advantageous to a species there is no reason why any such development should not have associated drawbacks. Thus the body's attempts to defend itself can sometimes provide the most damaging effects of certain diseases in that auto-immune responses occur, as in rheumatic heart disease or possibly in rheumatoid arthritis. And some cancers may actually be stimulated by weak attempts to resist them.

Thus it is not necessarily true that our bodies naturally possess the means of defending themselves against every ailment and that all that medicine has to do is discover how to stimulate the appropriate immune response to order. Progress in immunology likely to lead to major human benefits will probably stem from a fuller understanding of the body's limited capabilities for defence coupled with the intelligent use of discoveries in fields such as pharmacology. Thus the chance advantages of evolution may be supplemented by the intentions of human reason.

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