VACCINES AND PUBLIC HEALTH

- *Implications of research for vaccine development in the UK.*
- *Safety, efficacy and public concerns.*
- *Barriers to future developments.*

POST **66**
REPORT SUMMARY **July 1995**

This is a summary of a 40-page report available from the PARLIAMENTARY OFFICE OF SCIENCE AND TECHNOLOGY (extension 2840).

Vaccines have been a critical part of the fight against disease both in the developed and developing world. In the last 20 years, scientists have gained unprecedented insights into the immune system and how vaccines work, yet innovation is still slow and public concerns over vaccine use remain.

Against the backdrop of the recently-opened Jenner Institute for Vaccine Research, POST has released a study of vaccines and their future role in public health. This note summarises the findings of the full report [1].

BACKGROUND

The first vaccine was tried by a Dorset farmer in 1774 who inoculated his family with cowpox to protect them against smallpox. In 1796, Edward Jenner was the first to use vaccination in medical practice. Some 200 years later (in 1980), the World Health Organisation (WHO) announced the global eradication of smallpox as a result of a world-wide vaccination programme.

Vaccines have thus transformed public health worldwide; yet suitable vaccines have proved difficult to develop for some long-established diseases such as malaria, and for new diseases such as HIV / AIDS. New vaccines are also needed because disease-causing organisms adapt to current drug treatments, and because diseases are more easily disseminated as a result of increasing migration and world population pressures.

Recent scientific developments give much cause for optimism. Molecular biology offers new and powerful tools in the development of novel vaccines, and has underpinned many of the recent leaps forward in our understanding of how the immune system works. These advances raise the prospect of new and more effective vaccines, not only for infectious diseases but possibly also for cancer and auto-immune disorders. However, there are obstacles to these opportunities being realised; there are also concerns over how to enable the development of new vaccines for developing countries unable to pay for them, as well as the recent ethical concerns in the UK over the use of rubella vaccine cultured in cells originating from aborted foetal tissue. POST's study addresses these and other issues.

1. The full report "Vaccines and their future role in public health" (40pp) is available (free to Parliamentarians; £12 otherwise) from POST (0171-219-2840).

HOW DO VACCINES WORK?

The principle behind vaccines is very simple - namely to stimulate our immune system to combat an infectious agent (bacteria, virus, etc.) without suffering the disease itself. The full report describes the ways in which our immune system 'remembers' infectious agents and the various types of vaccine which can be used (**Table 1**), and how they work by stimulating humoral, cell-mediated or mucosal immunity.

Table 1 DIFFERENT TYPES OF VACCINES

APPROACH	EXAMPLE
Antigens attached to whole organisms	
Live, closely related organisms	Smallpox / Cowpox
Live, attenuated (weakened) organisms	Tuberculosis
Killed, whole organisms	Pertussis
Free Antigens	
Modified toxins (toxoids)	Diphtheria
Killed, disrupted organisms	Influenza
Antigens purified from organisms	Hepatitis B
Purified, modified antigens (conjugates)	Anti-H. influenza
Genetically engineered antigens	Hepatitis B

The full report also reviews in detail the UK routine immunisation schedule (**Table 2**), and the ways in which high uptake rates of over 90% are maintained by the Department of Health (DH) and the medical profession. In addition, current policy is reviewed on vaccines applied more selectively, i.e. those against hepatitis A and B virus, influenza, meningococcal and pneumococcal infections, rabies, anthrax, typhoid, cholera and yellow fever.

Table 2 SCHEDULE FOR ROUTINE IMMUNISATION

CONDITION /VACCINE	DOSE	AGE
Diphtheria, tetanus, pertussis (DTP), polio and Hib infection		
DTP + polio + Hib vaccines	1st	2 months
	2nd	3 months
	3rd	4 months
Diphtheria, tetanus + polio vaccines	1st booster	4-5 years
	2nd booster	15-18 years
Measles, mumps and rubella (MMR)		
MMR vaccine		12-18 months
Tuberculosis		
BCG		10-14 years (or infancy)

The global picture is also described - in particular the progress made in delivering a primary immunisation package (diphtheria, tetanus, pertussis, measles, poliomyelitis and BCG vaccines), where the proportion of children immunised worldwide has risen from 5% in

Table 3 EFFECTS ON PUBLIC HEALTH OF UK IMMUNISATION PROGRAMMES

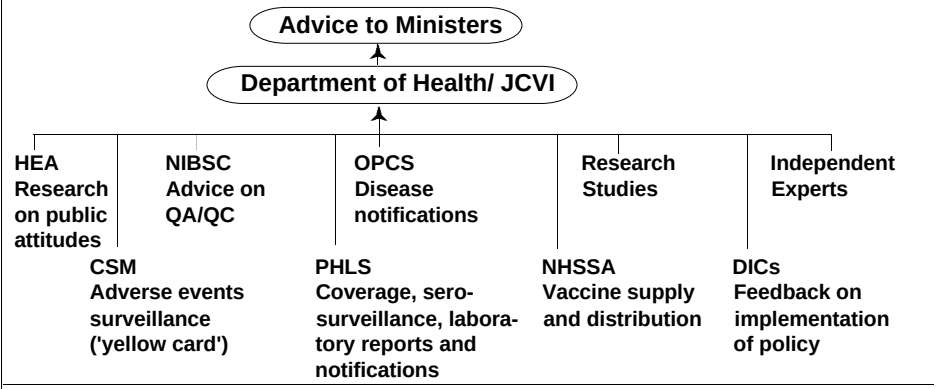
VACCINE	TYPICAL ANNUAL NUMBER OF CASES PRIOR TO VACCINE	TYPICAL ANNUAL NUMBER NOW
Pertussis	> 100,000 (early 1950s)	around 2,000
Diphtheria	> 45,000 (1940)	around 5 (all imported)
Tetanus	around 20 (early 1970s)	5-10
Poliomyelitis	> 6,000 (1955)	1-2 (all vaccine associated)
Measles	160,000-800,000	virtually eliminated in recent campaign
Rubella	20-30 cases of CRS* (1970-85)	< 5 cases of CRS*
BCG (tuberculosis)	around 50,000 (early 1950s)	around 6,000
Hib (invasive Hib disease)	> 1,200	95% or more reduction

** CRS: congenital rubella syndrome*

Table 4 SAFETY CONCERNS ASSOCIATED WITH SOME VACCINES

VACCINE	MAIN CONCERN
Pertussis	Suggested as cause of severe neurological conditions, including permanent brain damage. Risk too small to be quantified.
Poliomyelitis	Vaccine-associated poliomyelitis. Risk estimated at 1-2 cases per million doses of vaccine.
MMR	Measles component may cause feverish convulsions in 1 in 1000 children.
Diphtheria	Neurological reactions have been reported but risk is too small to quantify.
BCG	Severe injection site reactions occur, usually associated with faulty vaccination technique.
All	Severe anaphylactic reactions are very rare. Overall risk estimated at less than 1 in 200,000 vaccinations.

Figure 1 REGULATORY AND ADVISORY BODIES



(See full report for acronyms)

the 1970s to over 80% in 1991, partly as a result of WHO and UNICEF's **Expanded Programme on Immunisation (EPI)**, launched in 1985.

BENEFITS AND RISKS

Vaccines differ fundamentally from treatment in that they are given to large numbers of people who are generally well, in order to prevent a much smaller number of cases of disease. Consequently, the benefits and risks are spread rather differently than in conventional treatment where an individual accepts the personal risk of treatment in the expectation that he/she will benefit personally. With vaccinations, all accept the risk, while the benefit is probabilistic (i.e. it reduces the chances of catching the disease), or altruistic (i.e. it benefits society as a whole to reduce the incidence of the disease). The full report looks at the balance of benefits and risks in more detail. On the benefit side, there has been a great reduction in disease as a result of vaccination (**Table 3**).

Because vaccines are given on such a large scale, and because the people receiving them are 'healthy', the risks associated with a vaccine's use have to be extremely low. Local reactions at the site of injection or symptoms such as a slight fever are the most common side-effects, but the most serious general vaccine-related risk is **anaphylaxis** - an abnormal immune reaction to some component of the vaccine. Fortunately, severe anaphylactic reactions are extremely rare - between 1978 and 1989, only 118 such reactions were reported (none of them fatal), from 25 million childhood vaccinations - less than 1 in every 200,000 vaccinations. Other risks associated with immunisation are specific to the vaccine in question and are summarised in **Table 4** and reviewed in more detail in the full report.

The full report reviews the regulatory and advisory bodies (**Figure 1**) and the roles of the European Medicines Agency (EMA), the UK Medicines Control Agency (MCA), the DH, PHLS and the DH's Joint Committee on Vaccination and Immunisation (JCVI). The systems used for monitoring for potential problems (largely achieved through the 'yellow card' system, where doctors report any adverse events to the Committee on the Safety Medicines (**CSM**)) is also described, as well as the ways in which epidemiological factors, public attitudes etc., are taken into account in informing decisions on vaccine use - for instance, in the decision to undertake a mass immunisation campaign against measles in 1994.

The importance of public perception is also discussed - in particular lessons to be learnt from public fears over the safety of the pertussis vaccine in the late 1970s and the recent controversy (again over the rubella vaccine) over the fact that the rubella vaccine involves a cell line originally derived from an aborted foetus.

NEW VACCINE RESEARCH

Recent advances across a wide range of scientific disciplines have enhanced the prospects for developing new and better vaccines. These include the application of new technologies such as molecular biology to vaccine research, advances in our understanding of the immune system (particularly of the importance of mucosal immunity), and an increasing understanding

of the diseases themselves. Important developments are reviewed in the full report with particular focus on:

- Sub-unit Vaccines
- Attenuated Vaccines
- Vector Vaccines
- DNA Vaccines
- Conjugate Vaccines
- Improving Stability
- Mucosal Immunity
- Cancer Vaccines

In the UK, future research priorities include developing new vaccines against:-

- encapsulated bacteria such as *Neisseria meningitidis*, and *Streptococcus pneumoniae*;
- sexually transmitted diseases, particularly gonorrhoea and chlamydia;
- gastroenteritis caused by food-borne *Salmonella*.

The full report examines prospects in these areas as well as for the development of effective vaccines against globally significant diseases including:

- vaccines that are heat-stable, can be given orally, contain novel combinations, are suitable for use in infants shortly after birth, and protect against a wide range of diseases;
- new (sub-unit) vaccines against the most serious forms of malaria;
- vaccines against HIV / AIDS, where scientists are trying to stimulate cell-mediated (e.g. killer T cell) responses to attack cells **after** they have become infected.

ISSUES

How should Vaccines be Used?

The full report discusses factors which may lead to changes to current immunisation practice. The main candidate for **reducing** the scope of vaccination is the BCG vaccine for tuberculosis (TB). Here, the disease is becoming increasingly concentrated among high-risk groups such as the homeless, travellers to or from certain countries, and certain ethnic groups, etc., and the question is whether immunisation targeted at these groups would be more effective than the current school immunisation programme.

As far as **expanding** the immunisation programme is concerned, policy on **hepatitis B** vaccine is under review, but universal vaccination is unlikely to be justified unless carrier rates increase significantly, or vaccine prices fall and safe, effective combination vaccines (e.g. hepatitis B in combination with DTP) become available.

Another target for expanded immunisation is against the bacteria responsible for **meningitis** and other **serious infections** (e.g. of the blood). Although the threat from *Haemophilus influenza* bacterium (Hib) has been dramatically reduced by the Hib vaccine, *Neisseria meningitidis* is still a significant cause of illness and death. The full report points out however the obstacles which remain in the way of a vaccine effective against the main disease type in the UK. Although both DH and MRC are funding work in this area, a commercial vaccine is unlikely in the next 5-10 years.

Streptococcus pneumoniae is also of concern because infections are rising (particularly amongthe very young and the elderly), and because the spread of antibiotic resistance is making infections more difficult to treat[2]. Research is underway to develop new, conjugate versions effective in young children, and **the case is also being evaluated for extending routine vaccination** against *S. pneumoniae* **to include healthy people over 65 years old.**

The adequacy of immunisation against **influenza** is also a matter of debate, with rates of vaccination for persons at special risk varying markedly from one area to another. Public health specialists argue that **more could be done to increase uptake of the vaccine among people within the 'special risk' groups, and one option would be to adopt supplementary strategies in inner city districts** and other areas where the vaccines are needed most.

The full report also looks at the importance of ensuring that epidemiological information continues to be provided while hospital Pathology Services undergo market testing. One option is **to ensure that pathology contracts explicitly mention the need to continue to report to PHLS/CDSC, data and samples relevant to the epidemiology of infectious disease**.

Public Acceptance and Perception

The vast majority of the public appear to accept the need for continued immunisation and the DH targets of 95% of children receiving the main vaccines is likely to be met this year. Nevertheless, research by the HEA highlights the following parental concerns:

- concerns over vaccine safety;
- perception that some diseases are not (or are no longer) a serious threat;
- difficulty over access to services;
- loss of commitment after the first-born child.

Some parents may also have ethical objections to vaccines, as illustrated by concerns over the origin of the rubella vaccine. The full report examines some of these potential obstacles to increasing vaccine uptake rates in more detail.

On safety, recent concerns are examined in detail over measles and rubella vaccine as a possible cause of the rare neurological condition Guillain Barre syndrome,

2. See POST report 'Diseases Fighting Back'.

recent experience with the Urabe strain of MMR vaccine (one of a number of new strains of mumps virus developed in response to increasing demand in the 1980s), and questions over the possible longer-term effects of measles vaccine on rates of inflammatory bowel disease later in life.

The Urabe experience was exacerbated by the failure of the yellow card surveillance system to detect the scale of the problem, and ways of improving it are reviewed in the full report. **Improving the existing surveillance system is seen as a priority by the DH and other public health specialists, particularly in view of the recent introduction of the Hib vaccine, and the likelihood of new vaccine antigens being introduced in the not-too-distant future**.

No medical intervention is risk-free, and vaccines are no exception. Consequently, each year a few suffer serious adverse effects as the result of immunisation, and it has been Government policy for many years to provide some payment under the **Vaccine Damage Payments Scheme**. Settlements are limited to a maximum 'one-off' payment of £30,000 - last revised in 1991. Typically around 50 people apply each year under this scheme with fewer than 5 receiving payment at an annual average cost of around £50,000. The full report reviews arguments for changing the current 80% disability threshold and the maximum payment. However, the Government recently made it clear that it has no plans to review the Scheme, stating that it "*operates fairly and effectively in its present form*".

As vaccines become more successful at reducing levels of disease, parents may question **whether it is worth exposing their child** to even the very low risks of immunisation, given that the risk of contracting the disease has become so small. Such attitudes do not mesh with the public health case that immunisation should continue until the disease has been completely eradicated on a global scale, since withdrawing a vaccine prematurely creates an opportunity for infectious disease to bounce back. The full report describes the importance of targeted promotional campaigns which have ensured that immunisation rates are in excess of 95% in most areas, and that only 3% of parents explicitly refused consent in the recent measles campaign.

Obstacles to the Development of New Vaccines

Despite the recent technical advances outlined, there are many hurdles which limit the extent to which scientific research is translated into new vaccines. The biggest obstacles are economic - vaccines are used on such a wide scale that there is considerable pressure on manufacturers to keep prices very low, even in developed countries, yet vaccines may take as long and cost as much to develop as conventional medicines. These economic 'facts of life' do not rule out the commercial development of new vaccines completely, but mean that companies will tend to 'play safe' - e.g. only develop those products for which there is a big demand in the developed world. **Persuading companies to take a less selective view of product development** - e.g. to develop vaccines for the third world or to protect against rare diseases - will require a greater co-operation between researchers, industry and the main purchasers of vaccines (Governments and international bodies such as UNICEF).

The full report examines moves in this area which have led to the establishment of the Edward Jenner Institute to provide a UK focus for vaccine research. Initial costs (£10M) involved in establishing, building and equipping the new Institute will be met by Glaxo Wellcome, with running costs over the first ten years being met jointly by Glaxo Wellcome (£3M p.a.) and the public sector (MRC £1.5M, BBSRC £1M and DH £0.5M). The Edward Jenner Institute will be sited alongside the Institute for Animal Health in Berkshire, and aims to:

- develop a better understanding of the immune response to different diseases, by applying new techniques (particularly molecular biology);
- provide better models for the assessment of candidate vaccines protecting against human diseases;
- develop new insights into vaccine formulation and the role of adjuvants.

While setting up the Institute is clearly a positive step for vaccine research in the UK, there are still questions over the extent to which the relatively small UK vaccines industry is able to capitalise on this knowledge to develop new vaccines, and the full report suggests that **exploitation of new opportunities for vaccine development will be affected by progress in a number of key areas:**

- rationalisation of regulatory systems;
- greater co-operation with policy-makers;.
- changes in public and media attitudes;
- agreements on pricing, including rates of return and the question of **dual pricing** whereby manufacturers subsidise vaccine sales to developing countries by charging higher prices in the developed world.

Overall, vaccines will remain a primary weapon in the fight against disease and there are also long-term benefits for developed countries in encouraging more effective vaccines in developing countries, since the eventual cessation of current immunisation programmes in the UK and elsewhere will only be possible once the diseases have been eradicated world-wide.