

Immunization against the classic infectious diseases of childhood

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Immunization has caused massive reductions in childhood sickness and mortality over the past 50 years. Liz Miller explores current practice and describes the impact of the anti-vaccine lobby.

● What has immunization achieved over the last 50 years?

The development of vaccines for the prevention of infectious diseases is without doubt one of the most significant achievements of medical science. Over 80% of the world's children now receive immunizations against one or more of the killer diseases of childhood, with an estimated prevention of over 3 million unnecessary deaths each year. In countries such as North America and Western Europe, deaths from vaccine-preventable infections such as polio, measles, diphtheria and tetanus are now virtually unknown. The reduction in the burden of suffering from the common childhood infections achieved in England and Wales since the 1940s as a result of immunization is shown in Table 1.

Table 1. Reduction in the incidence of vaccine-preventable diseases in England and Wales

Diseases	Before vaccination		After vaccine use (1997)	
	Baseline year	No. of cases	No. of cases	Reduction (%)
Measles	1940	409,521	186	>99
Mumps	1989	20,713	175	>99
Rubella	1989	24,570	99	>99
Congenital Rubella	1971	73	0	100
Diphtheria	1940	46,281	4	>99
Polio	1940	1,066	0	100
Hib	1989	655	30	95
Pertussis	1940	53,607	2996	94

Note: cases of measles, mumps and rubella in 1997 include only laboratory confirmed cases.

One of the most important factors in determining the success of an immunization programme is achieving high vaccine coverage. For highly infectious diseases such as measles and pertussis, coverage rates of around 90% must be attained before a reduction of virus transmission between unvaccinated members of the population (i.e. herd immunity) is achieved. Following the national measles-rubella vaccination campaign in 1994, endemic measles transmission has been interrupted in England and Wales (Fig. 1) and confirmed cases are now only seen in association with outbreaks spread in unvaccinated communities which decline vaccination. However, unless coverage rates are sustained, these achievements may be rapidly reversed as we saw with whooping cough in the 1970s (Fig. 2).

● Old and new methods for vaccine production

The success of our current immunization programmes has been largely accomplished with vaccines produced by simple technologies without the benefit of our present-day understanding of immunology and molecular biology. The vaccines which are now routinely offered to all children in the UK are made by one of the following four techniques:

Diphtheria and tetanus – inactivated extract of the toxin responsible for the disease symptoms

Whooping cough – killed suspension of whole *Bordetella pertussis* organisms

Measles, mumps, rubella, oral polio – naturally occurring virus which has been attenuated by growing it in tissue culture

***Haemophilus influenzae* b (Hib) and meningococcus C** – conjugation of the protective polysaccharide antigen with a protein

The diphtheria and tetanus toxoid vaccines are among the simplest yet most successful vaccines, although the requirement for repeated doses to ensure adequate priming and maintenance of protective antibody levels in the individual is a drawback. Methods for sustained slow release of antigen by its encapsulation in microspheres which are broken down by the body at different rates according to their size are now being developed and offer the prospect of delivering the full priming course in a single shot.

Use of killed suspensions of the organism, although now regarded as a rather crude approach, has also had some outstanding successes, such as the whole-cell pertussis vaccines developed in the 1940s and 1950s, the killed polio vaccine of the 1950s made by Salk (Fig. 3) and more recently the killed hepatitis A vaccines. Attempts to develop improved pertussis vaccines by incorporating only those antigens which are important for protection while excluding unnecessary toxins has met with varied success. Although generally less reactogenic, most acellular pertussis have failed to match the protection afforded by the best whole-cell vaccines due to the lack of key protective antigens.

The technique of attenuating a pathogenic organism by adapting it to grow under altered environmental conditions was pioneered by Pasteur over 100 years ago with the development of the first rabies vaccines, produced by serial passage of the virus in rabbit spinal cord. This empirical approach to viral attenuation was further developed by Sabin in the 1950s, with the production of live oral polio vaccine – the instrument now being used to achieve global eradication of polio. The development of polio vaccines benefited greatly from the tissue culture technique for viral propagation pioneered by the American virologist Enders and his colleagues in the late 1940s, as did the development of the three other live viral vaccines which have proved so successful in combating the classical diseases of childhood – measles, mumps and rubella. The application of molecular biology to the identification of virulence genes has now allowed a detailed understanding of the basis of microbial pathogenesis and the important antigenic epitopes. It has opened the way for a more rational and less empirical approach to vaccine design.

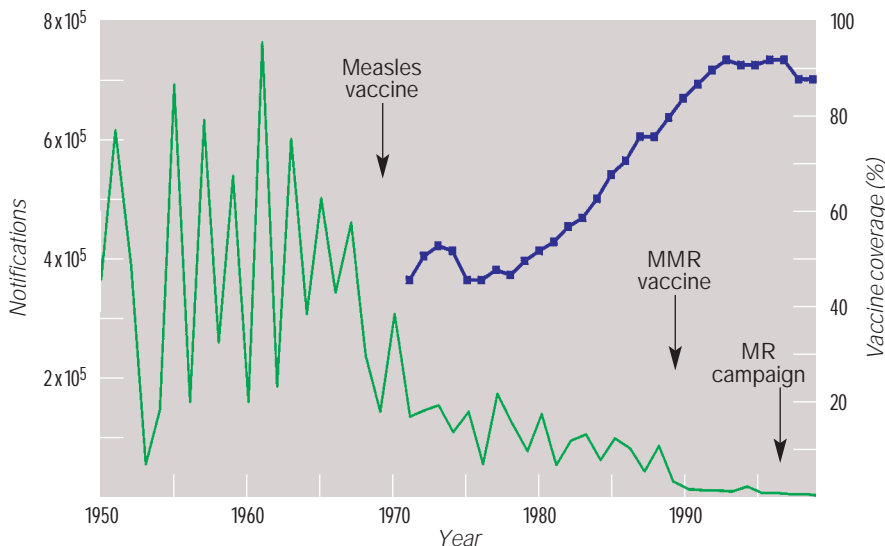
One of the most promising advances in vaccine technology in recent years has been the use of glyco-conjugation to protect against some of the common invasive bacterial infections such as Hib, *Neisseria meningitidis* and *Streptococcus pneumoniae*. All these organisms possess a polysaccharide capsule which is normally a poor immunogen, particularly in young children, and, being T-cell-independent, fails to induce immunological memory even in older age groups. By covalently coupling the polysaccharide to a carrier protein such as tetanus toxoid these deficiencies can be overcome and a T-cell-dependent antibody response achieved even in the very young infant. Because conjugate vaccines reduce carriage as well as protecting the individual against invasive disease, herd immunity can be generated which protects infants too young to be vaccinated.

Conjugation technology has now been used to develop vaccines against meningococcal serogroup C disease and early surveillance data for the UK, the first country to introduce these vaccines into routine, suggests that they will be just as successful as Hib vaccines. The first cohorts to be offered the vaccine were adolescents aged 15–17 years (in November 1999) and infants under 1 year (from December 1999) and a reduced incidence of serogroup C disease is already apparent within a few weeks of the introduction of the vaccine (Fig. 4). Unfortunately, the similarity between group B polysaccharide and human tissue antigens has resulted in a reluctance to develop conjugate B vaccines. Other protective antigens based on outer-membrane proteins, which are highly variable between strains, are being explored as potential vaccine candidates. The application of conjugation technology to the pneumococcus has also presented problems as protection against the different capsular polysaccharide serotypes (currently numbering nearly 90) is serotype-specific. A seven-valent conjugate vaccine has recently been shown to be highly effective against invasive pneumococcal disease, pneumonia and otitis media caused by serotypes represented in the vaccine in trials in California and Finland. The serotypes in this vaccine comprise about 88% of the invasive pneumococcal isolates typed by the England and Wales Central Public Health Laboratory Service in the first 6 months of 1999. Nine- and eleven-valent vaccines, which cover 90 and 92%, respectively, of the prevalent serotypes in England and Wales are now under evaluation.

● The anti-vaccine lobby

Despite, or possibly because of, the outstanding success of our immunization programmes, they have recently become the target of organized and vocal criticism from a minority group which questions the wisdom of universal immunization against diseases, some of which currently pose no public health threat, precisely because they are well controlled by vaccination. Such opposition is not

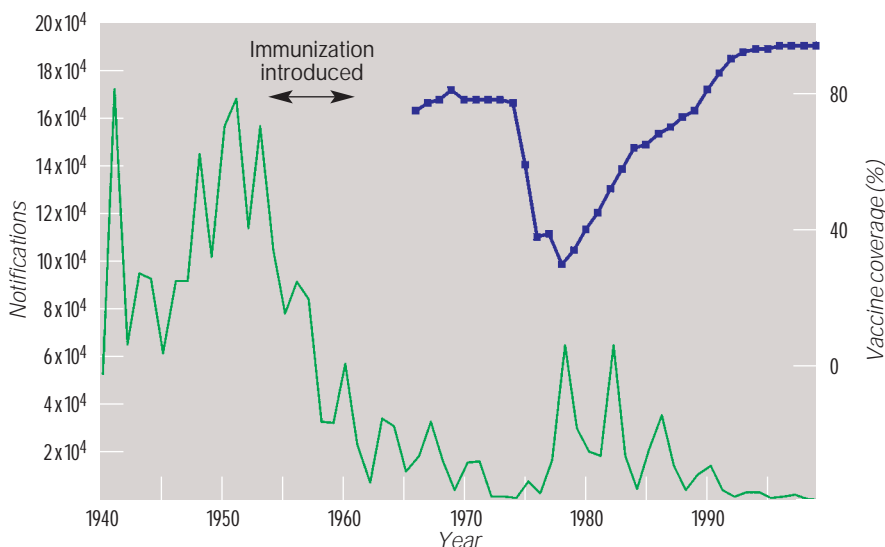
Fig. 1. Annual measles notifications and vaccine coverage (England and Wales 1950–1999*)



*Provisional data

Source: Office for National Statistics and Department of Health

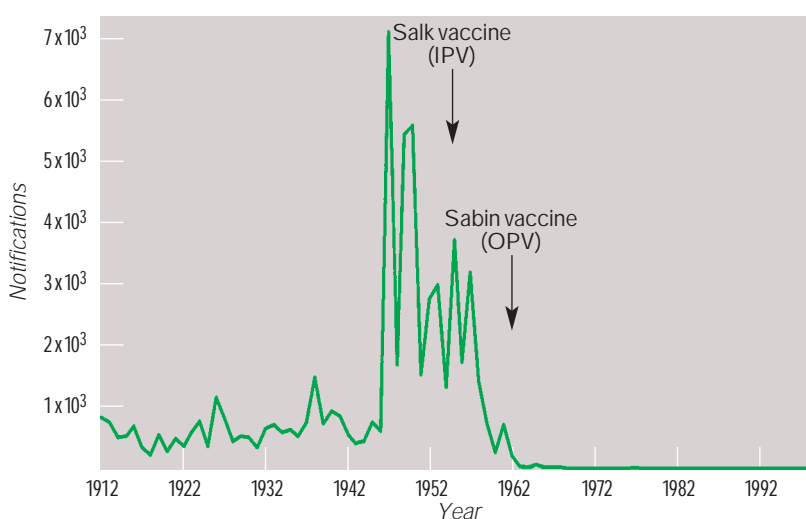
Fig. 2. Whooping cough cases and vaccine coverage (England and Wales 1940–1999*)



*Provisional data

Source: PHLS Communicable Disease Surveillance Centre, Department of Health, ONS

Fig. 3. Acute paralytic poliomyelitis (England and Wales 1912–1999*)



*Provisional data

Source: Notifications to ONS 1984; cases ascertained from any source after 1985

new as evidenced by the famous cartoon of 1802 which depicted individuals growing cow-like parts after smallpox vaccination. However, with the rapid access to material through the internet, myths and unfounded allegations about vaccine safety can now be propagated rapidly around the globe.

The focus of the anti-vaccine lobby varies between countries and in the UK was centred on whole-cell pertussis vaccines in the 1970s and more recently on MMR vaccines, the unfounded allegation for the latter's safety encompassing such diverse disorders as autism and inflammatory bowel disease. Although there is no scientific evidence in support of these concerns, MMR coverage rates have recently declined (Fig. 1) and one in four children is not taking up the pre-school MMR booster. Unless reversed, this trend could lead to outbreaks of disease in school-age children in the future. Such resurgences can have devastating consequences, even for those living in developed countries such as Holland which recently experienced three deaths from measles as

a result of an outbreak in a religious group with an objection to immunization. In France vaccine safety concerns have focused on hepatitis B vaccine and multiple sclerosis, while in the US diabetes and immunization in general have received attention. In New Zealand, anxiety has been raised over a possible link between atopic disorders and early immunization.

The diseases currently receiving attention as alleged vaccine reactions have a number of features in common. First, the diseases in question are of unknown aetiology and usually of increasing incidence. Second, the postulated association is championed by one investigator/group but is not confirmed by peers or subsequent research. Third, these rebuttals often fail to attract the publicity of the original claim alleging a link. For example, a paper by workers at the Royal Free Hospital reporting

an apparent increase in Crohn's disease in a cohort exposed to measles vaccine received considerable media attention (despite the numerous flaws in its design pointed out in the many letters to *The Lancet* that followed its publication), whereas the subsequent negative study from the same group was merely published as a conference abstract and largely ignored.

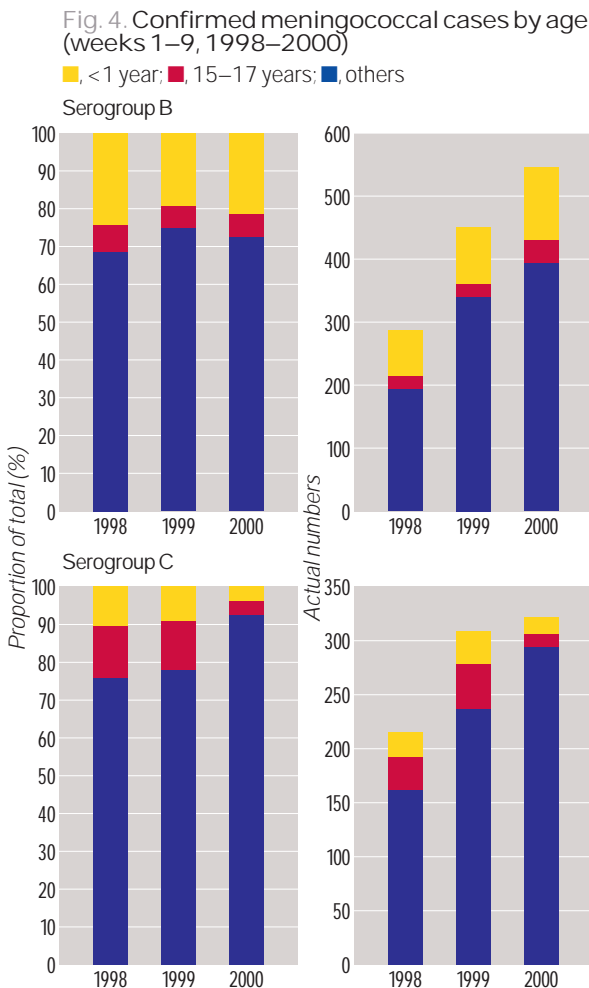
The literature put out by the anti-vaccine lobby often plays on parental fears of the alleged unknown effects of vaccines and seeks to endorse its views by misquoting the work of others. For example, when the new meningococcal C conjugate vaccination programme was recently introduced, the November edition of the anti-vaccination publication entitled *What Doctors Don't Tell You* (WDDTY) ran an article in which the PHLS was quoted as saying that 'The old vaccine doesn't work – and neither does the new one'. In fact the PHLS had pointed out via its website that neither the old plain AC polysaccharide nor the new C conjugate vaccines would protect against B disease and that continued vigilance was necessary as meningococcal B infection would still occur. I was subsequently contacted for advice by one parent who said that his child was about to be vaccinated with the C conjugate vaccine but he was now reluctant to go ahead having read the article from WDDTY. Fortunately, I was able to give this parent the correct information but I wonder how many others were dissuaded by this irresponsible article from letting their child have the life-saving vaccine.

For those who are concerned about having their child vaccinated as a result of reading material from groups opposed to vaccination it may be useful to apply the following criteria when judging its credentials:

- Do the authors have any medical or relevant scientific qualifications?
- Have their views been subjected to the normal peer review process achieved via publication in a journal?
- Do the authors have any professional accountability?

The last point is particularly telling. What would the position be with respect to liability of the author of the WDDTY piece if a child had died of meningococcal C disease having refused vaccine as a result of this article? A medical practitioner giving unsound advice would, of course, be professionally accountable.

It is perhaps encouraging that, despite the considerable media attention given to the safety of MMR vaccine in the UK in recent years, coverage has only fallen by a few percentage points. The robust, evidence-based defence of the vaccine organized in a timely manner by the Department of Health, plus a refusal to bow to the irrational and dangerous demands to provide single antigen vaccines in place of MMR vaccine, has undoubtedly helped to sustain coverage rates. The painful lessons learnt with pertussis vaccine in the 1970s may now be paying dividends.



Source: Laboratory confirmed cases – PHLS Meningococcal Reference Unit (MRU)

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Further reading

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