REVIEW

Childhood immunisation: what is the future?

Andrew J Pollard

Arch Dis Child 2007;**92**:426–433. doi: 10.1136/adc.2006.095760

Improved immunisation programmes and the development of new vaccines provide unprecedented opportunities to improve and sustain the health of our children. There are major challenges ahead in communicating the benefits of immunisation to all populations and in delivering vaccines to those in greatest need. In this review on immunisation, I have asked international opinion leaders to comment on the present and the future of immunisation to provide signposts for the narrative.

Immunisation is the key to the health of our children.

> Apart from the provision of clean water, vaccines have had a more profound effect on world health, especially of children, than any other public health measure.
> *E Richard Moxon, Action Research Professor of Child Health, University of Oxford, UK*

Almost all febrile children seen in emergency departments in the UK this weekend will have a minor viral infection, the vast majority of those who are admitted will go home well after a day or two, and death from an infectious disease is unlikely. I can be this complacent because child mortality has fallen 100-fold in the UK in the past century through improvements in nutrition, water quality, sanitation, healthcare and education, and significantly because of immunisation. Most child deaths in the UK are from accidents or malignancy, and even these are rare. Indeed, parents now rightly do not expect any of their children to die, and the introduction of the new immunisation schedule in the UK in September 2006 further defends the health of our children with the addition of a vaccine that will have a major impact on invasive pneumococcal disease and pneumonia. To put this in a global context, the World Health Organization (WHO) estimates that the lives of more than 2 million children were saved by immunisation in 2003 alone, demonstrating the incredible value of immunisation for child health.[1] This global impact of immunisation was recognised in the opening comments in the first edition of the major textbook *Vaccines* in 1988[2]:

> The impact of vaccination on the health of the world's people is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth.
> *Susan Plotkin and Stanley Plotkin*

Correspondence to:
Dr Andrew J Pollard, Department of Paediatrics, University of Oxford, Level 2, Children's Hospital, Oxford OX3 9DU, UK; andrew.pollard@paediatrics.ox.ac.uk

Accepted 4 November 2006

COMMUNICATING THE VALUE OF IMMUNISATION

> The value of immunisation for child health is not known to most physicians, and to the population in general.
> *Heinz-Josef Schmitt, Professor of Paediatric Infectious Diseases, Epidemiology and Vaccine Development, Johannes Gutenberg University, Germany*

In industrialised nations, such as the UK, immunisation has transformed the practice of paediatrics. Smallpox is eradicated, indigenous polio has disappeared, and tetanus, diphtheria, *Haemophilus influenzae* type b (Hib) and meningococcal serogroup C (MenC) disease are almost never seen (table 1). Yet we take vaccines for granted. Ask the paediatric senior house officer (resident) what they mean when they write "immunisations up to date" in their admission notes and you will meet uncertainty. Ask parents about the importance of a vaccine such as measles or mumps for child health and many will wonder why it is so important since "we all had it as children".

> In contrast to the United States, paediatricians in both the UK and Australia are relatively uninvolved with day to day issues in immunisation, which is largely the responsibility of general practitioners. Nevertheless, they are frequently called upon for expert comment both professionally and to local media and may be ill-equipped.
> *Peter McIntyre, Director, National Centre for Immunisation Research and Surveillance, Australia*

Paediatricians in the UK have little to do with immunisation because most vaccines are administered in the community and usually by practice nurses. Since this area of medical practice (immunisation) is not a major part of our specialty, many of us do not feel confident to defend the benefits of immunisation and knowledgeably discuss and balance the real and the mythical risks. If paediatricians disengage from vaccines, the most important of child health interventions, then there is a risk that we will passively contribute to a further decline in confidence in vaccines and fail in our role as promoters of child health.

Abbreviations: DTP, diphtheria, tetanus, pertussis; Hib, *Haemophilus influenzae* type b; HPV, human papilloma virus; MenC, meningococcal serogroup C; WHO, World Health Organization

Table 1 Mortality and morbidity of vaccine preventable diseases in England and Wales

	Annual cases in the pre-vaccine era	Annual mortality in the pre-vaccine era	Current estimates of number of cases	Current estimates of mortality
Diphtheria	61 000 cases in 1940	1 in 20 (mortality rates up to 1 in 5 have been reported in epidemics)	56 cases from 1986–2002	Only 2 deaths between 1986 and 2002
Tetanus	Not available	1–9 out of 10	Approx 186 cases from 1984–2002. 8 cases reported in 2003	No cases or deaths in children under 5 years. No deaths of any age reported in 2003
Pertussis	120 000 cases per year (1950s) Incidence rate of 150/100 000	1 in 500 babies with pertussis	1000 cases in 2002	0–9 deaths per year
Polio	8000 cases of paralysis during epidemics (early 1950s) Incidence of 2–30/100 000	1 in 1000 affected children develop paralysis. 1 in 20 hospitalised patients die	No endemic cases since 1984. 41 cases from 1985–2002	Nil
Haemophilus influenzae type b	803 cases in 1991 (20/100 000 children under 5 years)	1 in 20 with Hib meningitis (about 30 deaths per year)	21 cases in 1998 (0.65/100 000 children under 5 years of age)	Not available
Serogroup C *Neisseria meningitidis*	1500 reported cases in 1998–9 (extrapolated from laboratory confirmed cases)	150 deaths (5–10% of cases)	120 cases in 2002–2003	20 deaths in 2002–2003
Streptococcus pneumoniae	Currently 5000–6000 cases of invasive disease per year 250–350 cases of meningitis per year	10% mortality from pneumococcal meningitis under 2 years of age	Vaccine introduced in late 2006	Not available
Measles	160 000–800 000 cases per year in 1960s	1 in 2500 deaths (100 deaths per year) and 1 in 1000 with encephalitis and 20 cases of SSPE per year (rate of 1 in 25 000)	191 cases confirmed in 2004	1 death since 1992 and 1 or 2 cases of SSPE per year
Mumps	1200 hospital admissions per year. Incidence rate of 130/100 000	Not usually fatal. Most frequent cause of viral meningitis in children (1 in 200–5000) and acquired deafness (1 in 20 000)	8130 cases confirmed in 2004	Not available
Rubella	167 infections in pregnancy in 1987. Incidence of disease of 150/100 000	1 in 6000 develop encephalitis	14 cases confirmed in 2004. 1 infection in pregnancy in 2003	Not available

This table has been compiled using data from http://www.hpa.org.uk and from *Immunisation against infectious disease - the green book*, found at http://www.dh.gov.uk. SSPE, subacute sclerosing panencephalitis.

> Vaccines save our lives. But they come with an imperative. And that is that you have to keep using them. If immunization rates fade, vaccine preventable diseases will be back. And we will be able to experience first-hand what life must have been like in the early twentieth century.
> *Paul Offit, Chief, Division of Infectious Diseases, Children's Hospital of Philadelphia, USA*

Indeed, lack of public confidence in vaccines presents a serious and present threat to child health. The decline in uptake of MMR vaccine in the past decade in the UK,[3] resulting from an unfounded vaccine safety scare, has culminated in outbreaks of measles and the first death in the UK in 2006 since 1992.[4] It is not a big step from here to imagine the return of national epidemics of measles in the UK. For policy makers and public health professionals this issue provides a timely reminder of the importance of communicating public health messages and the need to re-evaluate the approach to dealing with public concerns.[5] MMR does not cause autism, but it has probably prevented more than 1000 measles-related deaths in British children in the past 10–15 years.

> In contrast to the treatment of disease, success in immunisation means that nothing happens, with consequent constant challenges for communicating the great and continuing benefits of vaccines, while emphasising the priority for safety.
> *Peter McIntyre, Director, National Centre for Immunisation Research and Surveillance, Australia*

A particular difficulty in communicating the success of immunisation is that vaccines work so well. In countries with high vaccine coverage, there are too few cases of vaccine-preventable diseases for anyone to notice that the diseases are being prevented. One possible outcome is that the public confidence pendulum swings from high vaccine coverage and low disease rates, to low coverage and rising disease rates, and back. This cannot be allowed to happen and vigorous emphasis on improved communication about vaccines is urgently needed.

> The vaccine risks that scare parents and the diseases risks that will kill their children are very different. For many parents, giving the scientific facts does not convince them that a vaccine is safe and of benefit. Our health care providers need a better background in the psychology of risk perception and better risk communication skills if we are to reach these vaccine doubters. Telling patient stories is an important component in helping to make disease risk real.

Noni Macdonald, Acting Editor-in-Chief, Canadian Medical Association Journal, and Paediatric Infectious Disease Specialist, Halifax, Canada

Picture in your mind a child with devastating meningococcaemia or evolving neurological injury from pneumococcal meningitis or (if you are old enough) presenting with a critical airway from *H influenzae* epiglottitis and it is not difficult to see why we are keen to immunise our own children against these diseases. Paediatricians must not be embarrassed to share their experiences and stories of these awful diseases with parents and non-paediatric colleagues, because anecdote is one traditional way in society to communicate risk, used more effectively than science by those who would undermine vaccination.

We continue to move into an era of fantastic scientific discovery where the most significant infectious diseases (those that cause the greatest morbidity and mortality) in the developed world can or in the future will be controlled with the use of vaccines. What we haven't yet discovered is how to get doctors to offer the vaccines, and patients to accept them.
Gregory A Poland, Director, Vaccine Research Group, Mayo Clinic, USA

Although stories are important in communication, the facts and figures about the vaccines and the diseases they prevent must also be readily accessible. The improved and updated edition of the Department of Health *Green book* should be ''bookmarked'' in all paediatric out-patient clinics to provide current information and advice (go to http://www.dh.gov.uk and search for ''Green book''). Similar information is available from the Centers for Disease Control and Prevention website (http://www.cdc.gov) and equivalent websites in other countries. For some parents it is important to talk more directly about the risks using this information and to contrast it with the risks that they take every day with their children, such as strapping their child into a car seat. In contrast to the pre-vaccine situation described in table 1, there were 141 child deaths in road traffic accidents in 2005 in the UK.[6] With regard to vaccine safety, 130 episodes of anaphylaxis were recorded from 1997 to 2003, but no deaths were reported.[7]

One should keep in mind that most vaccines will be given to healthy individuals, particularly children. The first determinant of a vaccine's future will be its absolute safety. Efficacy will come later.
Paul-Henri Lambert, Professor, Centre of Vaccinology, Centre Medical Universitaire de Genéve, Switzerland

In addition to communicating the benefits of immunisation, we must keep in mind that there are some risks from vaccines, although most adverse events are trivial. Because vaccine regulators have become increasingly concerned that manufacturers demonstrate the safety of vaccines on large cohorts before they are licensed, unanticipated adverse events that occur after vaccine introduction are likely to be rare. For this reason, high quality post-implementation vaccine safety monitoring is essential, so that any event that is temporally associated with immunisation can be investigated quickly and thoroughly. It would be a disaster to deny the benefits of vaccination for children as a result of a chance association with an unrelated clinical event. It would be equally disturbing to miss a significant risk of serious adverse reactions related to vaccine use.

THE NEW UK IMMUNISATION SCHEDULE (FROM SEPTEMBER 2006)

The new UK schedule represents a significant step forward. A new vaccine against *S. pneumoniae* was introduced, using a shortened schedule (only 2 doses in the primary schedule instead of 3). The number of primary doses of meningococcal C vaccine was also reduced to 2, thereby enabling all antigens to be given without additional visits and with only one extra injection. At the same time booster doses of Strep, Hib and Men C will be implemented, ensuring long term protection.
Norman Begg, Vice President, Clinical Development, Paediatric Vaccines, GlaxoSmithKline Biologicals, Belgium

From September 2006, a new immunisation schedule was used in the UK (table 2) and includes some major changes to the way children are immunised. The introduction of a pneumococcal conjugate vaccine (Prevenar, Wyeth vaccines) at 2, 4 and 13 months of age provides the opportunity to prevent most cases of invasive pneumococcal disease in children. This vaccine contains the polysaccharides from seven pneumococcal serotypes conjugated onto a protein carrier (CRM_{197}), with the same design and similar safety profile as the vaccines for Hib and MenC. A recent report from the USA (where the vaccine was introduced in 2000) indicates that there was a 94% reduction in disease caused by the seven pneumococcal serotypes in the vaccine in children under 5 years of age, and an overall 75% reduction in cases of invasive pneumococcal disease.[8] Data from efficacy trials of this and related vaccines, performed in the USA, South Africa and The Gambia, indicates that this vaccine may reduce the number of cases of pneumonia in children by 20% or more.[9–11]

The virtual disappearance of Hib and MenC infections in childhood followed introduction of the vaccines that protect against these disease in 1992 and 1999, respectively. However, careful analysis of effectiveness data by the Health Protection Agency has indicated that the direct protection afforded by the vaccines wanes with time after primary immunisation in early infancy,[12 13] corresponding to the rapid fall in antibody levels in the blood.[14] In order to improve direct protection of children (rather than relying on herd immunity induced by catch up campaigns in older age groups), most countries use a booster dose of Hib vaccine at 1 year of age. In the new schedule for the UK, booster doses of Hib and MenC in a combination vaccine are given at 1 year of age in the expectation that this will provide more sustained immunity. The implementation of booster doses of Hib-MenC vaccine into the UK schedule in response to waning population immunity serves to highlight the importance of adequately funded and careful surveillance for persistence of effectiveness after the implementation of new vaccines.

SPACING AND MAKING SPACE IN IMMUNISATION SCHEDULES

Better use of schedules and combination vaccines are desperately needed, but current schedules are based on history and tradition, not on science.
Heinz-Josef Schmitt, Professor of Paediatric Infectious Diseases, Epidemiology and Vaccine Development, Johannes Gutenberg University, Germany

Combination vaccines have been the key to broadening disease-prevention through immunisation and are essential if new vaccines are to be added to improve child health without

Table 2 The UK immunisation schedule

Vaccine	Birth	1 month	2 months	3 months	4 months	12 months	13 months	3–5 years	13–18 years
Diphtheria, tetanus, pertussis, polio			DTaP-IPV (administered as Pediacel)	DTaP-IPV (administered as Pediacel)	DTaP-IPV (administered as Pediacel)			dTaP-IPV (Repevax) or DTaP-IPV (Infanrix-IPV)	dT-IPV (Revaxis)
Haemophilus influenzae type b			Hib (administered as part of Pediacel)	Hib (administered as part of Pediacel)	Hib (administered as part of Pediacel)	Hib (administered as Menitorix)			
Serogroup C meningococcal				MenC (Menjugate, Meningitec or Neisvac-C)	MenC (Menjugate, Meningitec or Neisvac-C)	MenC (administered as part of Menitorix)			
7-Valent pneumococcal conjugate			PnC7 (Prevenar)		PnC7 (Prevenar)		PnC7 (Prevenar)		
Measles, mumps and rubella							MMR	MMR	
BCG (risk groups only)	BCG								
Hepatitis B (risk groups only)	HBV ± HBIg	HBV	HBV			HBV			

making the vaccine visit traumatic for child, parent and vaccinator. But making combination vaccines is not straightforward because of the possibility of chemical and immunological interaction between components that might compromise immunogenicity. To include even more vaccines into the immunisation schedule requires either broader combinations or revised schedules.

A greater number of different immunisation schedules are used in Europe than there are different countries.[15] Unfortunately, there is a lack of evidence to support any one schedule and little chance of a consensus on a unified European policy on vaccines. It is now difficult to design studies to test the effectiveness of different schedules because many of the diseases that the vaccines prevent have declined so significantly. There are advantages in giving vaccines early because many of the vaccine-preventable diseases are more severe in infants; the current UK accelerated primary schedule of 2, 3, 4 months was driven by the desire to generate early pertussis immunity in this vulnerable age group. However, this schedule is less immunogenic than a more spaced out program (eg, 3, 5, 12 months in Norway, Sweden and Italy), particularly for the conjugate vaccines, so there is a theoretical trade-off between optimal immunogenicity and maximum age-dependent disease prevention. This is an important area for future study. In the case of pertussis, it appears that spread of the organism to the vulnerable infant is most often from parents and siblings[16] and most severe disease is now in infants who are too young to have been immunised. An immunisation schedule that ensured high levels of antibody in parents and siblings may be an improvement to the current infant regime. Indeed, booster doses of pertussis vaccine were included for preschool children in 2004 in the UK because of outbreaks in primary school-aged children.[17] In some countries doses are also given at 1 year of age and there is increasing use of pertussis vaccine as part of the teenage booster to maintain higher levels of population immunity against the disease.[18]

The introduction of MenC and Hib boosters described above, and the inclusion of a pneumococcal conjugate vaccine with the 13 month booster, should improve immunity in early childhood against these three important causes of bacterial meningitis. Currently, we do not know how long this (primary course plus 1 year booster) immunity will be sustained, which is an issue of particular importance for MenC, where there was previously a significant disease burden in the second decade of life. Boosters of MenC in secondary school may yet be required to provide protection for children who have been immunised as infants 15–20 years earlier. Conversely, some countries introduced MenC vaccine as a single dose at 1 year of age (with a catch-up campaign throughout childhood) with improved cost-effectiveness over the UK three doses primary infant immunisation implementation strategy. In September 2006, the primary schedule moved from three doses down to two doses (plus a booster at a 1 year of age). Now that disease is controlled, a further revised schedule that uses fewer doses of MenC vaccine may be feasible in the UK with the removal of one or both of the doses that are now given in the first year of life. The impact of such a change on the duration of immunity will have to be carefully monitored.

> The best way to simplify immunisation schedules is to discover how to better stimulate the neonatal immune system. However, combination vaccines and non-parenteral routes of vaccine administration are crucial at this time.
> *Stanley Plotkin, Emeritus Professor of Paediatrics, University of Pennsylvania, and Medical and Scientific Consultant, Sanofi Pasteur, USA*

Why do young infants require three or more doses of the routine vaccines that we use before generating good immune responses, while older children and adults have a good response with fewer doses? If new strategies of immunisation can be developed that provide better primary responses, and with fewer doses, immunisation could be simplified with fewer vaccine visits. This is an important area for research, not only because such a strategy might allow earlier immunisation and

thus protection in the first few months of life, but also because it might free up space in the schedule to add further antigens and provide broader protection.

With an increasing array of vaccines that can prevent serious diseases in early childhood, the availability of oral, transcutaneous, nasal or mucosal vaccines could provide a more acceptable means of delivery of the vaccine programme for parents. Research on alternative routes of administration is important for the future of immunisation.

The introduction of the new UK programme shows that immunisation schedules are evolving and react to changes in disease epidemiology and the availability of new vaccines. We can be sure that further change will be necessary and desirable as new data become available on better schedules and routes of delivery.

NEW VACCINES TO IMPROVE CHILD HEALTH

> Immunizations are the highest ranking clinical preventive service with regard to high utilization rates and effectiveness in preventing morbidity and mortality associated with many infectious diseases. In the future immunizations will expand from prevention of infectious diseases to prevention of chronic diseases, cancer and autoimmune diseases. We are on the verge of many new and exciting breakthroughs in the field of vaccinology that will continue to improve the quality and duration of life.
> *Larry Pickering, Senior Advisor to the Director, National Center for Immunization and Respiratory Diseases, and Executive Secretary Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, USA*

A number of vaccines available today for use in childhood could provide significant health benefit for children but are not currently used routinely (table 3). Reasons why these vaccines have not yet been recommended for use in the UK include timing, cost, perceptions of benefit, interpretation of local epidemiology and concerns over public acceptance.

Hepatitis B vaccine is universally recommended by the WHO and is widely used in wealthy countries, and there have been recent calls for its use by various individuals and professional bodies in the UK to prevent cirrhosis and malignancy as a consequence of chronic infection.[19] Hepatitis B is included in some infant combination vaccines which could be used in the UK but are not currently available. Hepatitis B vaccine can also be used as a stand-alone antigen and is already used as such in high-risk populations. Health interventions that are targeted at high-risk groups have a poor record of uptake and the WHO is right to demand universal immunisation. However, addition of hepatitis B vaccine in the UK would complicate the primary immunisation schedule if added as another vaccine routinely. To aid global efforts to control hepatitis B infection, an alternative strategy is the use of the vaccine in the early teenage years as part of a programme of immunisation early in the second decade of life, and, at least in Fife (in Scotland), this approach would be acceptable to parents and pupils.[20] Such a programme could be expanded to include new vaccines to protect against diseases of adulthood such as the human papilloma virus (HPV) serotypes associated with cervical cancer. These newly developed HPV vaccines have shown remarkable efficacy[21–23] and have the potential to prevent one of the leading causes of cancer in women. The availability of these vaccines highlights the need for governments to face the significant challenge of implementing robust adolescent immunisation programmes taking account of the difficulties in communication with the target population and societal perception of sexual health issues.

Varicella is a disease which causes misery for most children and results in serious complications or death for some. Varicella vaccine has now been introduced in a number of countries in the second year of life and is more than 84% effective against chickenpox.[24] Breakthrough cases in vaccinated children are usually mild, but a two-dose schedule may be necessary to optimise population immunity. Millions of doses have been given in North America in the past decade and wider use in Europe is planned as a result of the recent availability of combination vaccines containing varicella and MMR,[25] simplifying administration. There is a clear benefit for children in using this vaccine: introduction of the vaccine in the USA led to a 75% reduction in varicella-associated hospitalisations and deaths.[26]

> We need to move toward universal influenza immunization recommendations. Every year we have an epidemic of disease (influenza) that causes more morbidity and mortality than all other vaccine-preventable diseases combined. And every year we fail to use influenza vaccine amongst our highest risk patients.
> *Gregory A Poland, Director, Vaccine Research Group, Mayo Clinic, USA*

Routine use of influenza vaccine in children under 2 years of age is now recommended in North America following increased awareness of the burden of disease in young children.[27] Influenza hospitalisation rates in infancy are similar to those in elderly populations and the annual influenza season generates increased general practice and emergency department visits and antibiotic prescriptions.[28] There is also an excess of morbidity in certain high-risk groups and particularly in those with underlying respiratory diseases.

> As I look to the future of childhood immunisation in industrialized countries, I see increasing attention to address the challenge of how to convince parents of the value of vaccines and of their true track record of safety and effectiveness … the challenges I envision being addressed include enhancing access to immunization services, abbreviating immunization schedules (i.e., fewer doses) and administering vaccines without the use of needles (i.e., mucosal and transcutaneous and needle-free injection devices).
> *Myron Levine, Professor and Director, Center for Vaccine Development, University of Maryland School of Medicine, USA*

I have mentioned above the importance of alternative routes of administration of vaccines that can both simplify the immunisation schedule and improve the acceptability to parents of adding yet more antigens by avoiding the use of needles. Oral immunisation is one strategy. Two new rotavirus vaccines have proven safe and highly efficacious against severe rotavirus gastroenteritis when administered orally.[29 30] Rotavirus is the leading cause of gastroenteritis requiring hospital admission, and is a common nosocomial infection during the annual outbreak. Rotavirus vaccines might prevent as many as 10 000 hospitalisations and 14 deaths per year in the UK and their introduction would transform the practice of hospital acute paediatrics during the winter gastroenteritis season.[31]

> Once vaccines against meningococcus ACYW and B which are in development become available, we will reach an important milestone in medicine because for the first time our

Table 3 Vaccines available (or expected to be available within 5 years) to broaden protection of children against infectious diseases

Vaccine	Availability	Target age group	Use	Additional information
Universal hepatitis B vaccine	Now	As a combination or stand-alone vaccine for infants or pre-adolescents	Prevention of hepatitis B transmission	High efficacy. Used in most developed countries. Recommended by the WHO
Boosters of acellular pertussis vaccine	Now	As a teenage booster vaccine	To reduce disease and transmission of pertussis among young adults and from young parents to their infants	Recommended in the USA
Varicella vaccine	Now	Combined with MMR or as a separate vaccine in toddlers, or as a catch-up for adolescents	Reduction of morbidity and mortality associated with varicella and complications of varicella (especially bacterial superinfection)	Universal immunisation in the USA and Canada
Hepatitis A vaccine	Now	Children over 12 months of age	Control of endemic and epidemic hepatitis A and as a travel vaccine	Used in Israel and recently added to the USA immunisation schedule in response to outbreaks of hepatitis A
Influenza vaccine	Now	Highest disease rates in the those under 2 years of age	Reduction of influenza morbidity and mortality in early childhood	Universal immunisation recommended in the USA
Higher valency pneumococcal conjugate vaccines (PnC10 and PnC13)	Expected within several years	Infant immunisation but has potential benefit for older children and adults	Prevention of bacteraemia, pneumonia and meningitis and reduction of death and disability caused by *Streptococcus pneumoniae*	Coverage of serotypes not included in PnC7 that cause significant burden of disease, such as serotype 1. Efficacy data not available
Rotavirus vaccine	Available since mid-2006	Infants under 6 months of age	Prevention of rotavirus morbidity, hospitalisation and mortality (estimated 14 deaths per year in the UK)	High efficacy against severe disease and hospitalisation. Introduced in Mexico and available on private prescription in Europe
Human papilloma virus vaccines	Available now in some regions	Pre-adolescent girls?	Prevention of cervical cancer and genital warts	High efficacy reported
Meningococcal ACYW vaccines and other various combinations	One vaccine available now and others in the pipeline	As a toddler vaccine for direct protection of children or a teenage vaccine to provide direct protection in this at-risk age group and herd immunity	Broader protection against meningococcal infection	Introduced for teenagers in the USA and Canada

children will be protected against most of the devastating infectious diseases that used to affect mankind in the early years of life.
Rino Rappuoli, Global Head of Vaccines Research, Novartis Vaccines and Diagnostics, Italy

The leading causes of invasive bacterial infection in childhood are the polysaccharide encapsulated bacteria: Hib, *Streptococcus pneumoniae* and *Neisseria meningitidis*. Hib disease has been controlled by vaccines available since the late 1980s. Pneumococcal disease will be reduced by the seven-serotype pneumococcal vaccine that is available today, but broader protection is promised with the arrival of 10- and 13-valent vaccines that are currently in clinical trials. The MenC vaccine has already controlled disease caused by bacteria bearing the serogroup C polysaccharide and several vaccines are now available or in development which are expected to protect against disease caused by meningococci bearing A, Y and W135 capsules. These capsule types are currently uncommon causes of disease in the UK but have been common in the past. Serogroup Y accounts for 28% of disease in the USA.[32] However, most disease in the UK, and in most wealthy nations, is caused by serogroup B meningococci. A vaccine that protects against a substantial proportion of B strains has been elusive, but development of MenB vaccines is now advancing,[33] providing hope for broad control of meningococcal disease.

With the development of these new vaccines there is a real possibility that disease caused by these three encapsulated pathogens could be more completely controlled. If most invasive bacterial disease in childhood were eliminated, paediatric practice would change beyond recognition.

Indeed, if implemented today these ''new'' vaccines can prevent most invasive pneumococcal infections, most hospitalisations from gastroenteritis, most influenza-related hospital admissions and the severe complications of varicella. With continued development of vaccines for serogroup B *N meningitidis* and respiratory syncytial virus, the spectrum of admissions to the paediatric ward could soon be redefined.

GLOBAL CHILD HEALTH AND IMMUNISATION

The next ten years will be the decade for results. Global funding for immunization has never been better. Recent developments have put global immunization funding on the agendas of heads of state and world leaders, and this has amounted to billions of pounds of new funding. Delivering real, measurable changes in child survival in the next ten years as a result of this funding is the key to sustaining it.
Orin Levine, Director, GAVI's Pneumococcal Accelerated Development and Implementation Programme (PneumoADIP), Johns Hopkins University, USA

There have been huge improvements in the delivery of vaccines to the world's children in the last 25 years. In 1980 only 20% of children received three doses of DTP (diphtheria, tetanus,

pertussis) vaccine, but this had risen to 78% by 2004.[34] However, it is quite unacceptable that more than 500 000 children still died in 2002 from diphtheria, tetanus, pertussis or polio.[35] The good news is that there is now an unprecedented amount of funding available through the Global Fund for Immunization and it is now essential that this is used for further investment in the vaccine delivery infrastructure in the world's most resource-poor countries to ensure that these most basic of vaccines are available for all children.

> We still have important (disease) targets without appropriate arrows (vaccines). However, as the situation evolves we may have soon a number of arrows without defined targets. Their potential impact will be mainly guided either by acceptance by people at risk or, in developing countries, by access to these new vaccines. We will ultimately need more and more good archers who will be able to deal with financing and implementing vaccination programmes as well as convincing potential recipients or public authorities.
> *Paul-Henri Lambert, Professor, Centre of Vaccinology, Centre Medical Universitaire de Genéve, Switzerland*

Funding for the addition of more vaccine antigens to the childhood schedule in resource-poor countries can make use of a strengthened vaccine delivery infrastructure to prevent 400 000 Hib deaths, 500 000 measles deaths, 400 000 rotavirus deaths and as many as 700 000 deaths due to infections with *S pneumoniae*.[35]

> Say what you will about Bill Gates, where would we be without him? Great fortunes have frequently supported great advances for all of us, and we should be grateful for that. However, ultimately even the poor countries will have to decide that health is critical to development.
> *Stanley Plotkin, Emeritus Professor of Paediatrics, University of Pennsylvania, and Medical and Scientific Consultant, Sanofi Pasteur, USA*

While the availability of funding for vaccines is unprecedented, there is a real issue over sustainability. Vaccines manufactured in industrialised countries are expensive and cannot be afforded by countries with the greatest need. Introduction of new vaccines into resource-poor countries using donor money must be accompanied by plans for sustainability. Affordable vaccines will likely arise from transfer of technology to manufacturers in developing countries but will still require ongoing investment by donors. Governments in resource-poor countries must be committed to health, as a healthy population is central to economic development.[36] It is quite chilling to consider that even a fraction of the US$1000 billion global spending on warfare could provide vaccines for all of the world's children.

THE FUTURE

> In the face of rising development costs, increasing prices, and demands from parents and providers for exacting studies of vaccine safety, the future use of childhood vaccines depends critically on establishing and communicating effectively their value. An important step this process is to gain wide scientific consensus and to communicate that consensus to less technical audiences. Success will depend on a new framework that requires researchers and practitioners to work closely with communications and marketing experts to assure that evidence-based messages reach key audiences such as the general public and policy-makers.
> *Orin Levine, Director, GAVI's PneumoADIP, Johns Hopkins University, USA*

Vaccines already prevent a vast amount of childhood suffering and death and there is now an avalanche of new opportunities to improve child health still more. For paediatricians vaccines have and will continue to transform our clinical practice, but we must be vigilant in case the importance of immunisation is forgotten.

ACKNOWLEDGEMENTS

I am very grateful to the international experts in vaccinology who generously provided the quotes used in this article.

AJP acts as chief investigator for clinical trials conducted on behalf of Oxford University sponsored by vaccine manufacturers (Sanofi-Pasteur MSD, Novartis Vaccines, GlaxoSmithKline Biologicals, Sanofi-Pasteur and Wyeth Vaccines), and has received assistance from manufacturers to attend scientific meetings. Industry-sourced consultancies and honoraria for lecturing or writing are paid directly to an independent charity or an educational fund held by the Department of Paediatrics, University of Oxford. AJP is also an inventor on a patent application in the area of MenB vaccines, and a Jenner Institute investigator.

REFERENCES

1 **World Health Organization**. *Global immunization vision and strategy 2006–2015*. Geneva: World Health Organisation/UN Children's Fund, 2005.
2 **Plotkin SA**, Mortimer EA. *Vaccines*. Philadelphia: Saunders, 1988.
3 **Friederichs V**, Cameron JC, Robertson C. Impact of adverse publicity on MMR vaccine uptake: a population based analysis of vaccine uptake records for one million children, born 1987–2004. *Arch Dis Child* 2006;**91**(6):465–8.
4 **Health Protection Agency**. Increase in measles cases in 2006, in England and Wales. *CDR Wkly* 2006;**6(12)**.
5 **Burgess DC**, Burgess MA, Leask J. The MMR vaccination and autism controversy in United Kingdom 1998–2005: inevitable community outrage or a failure of risk communication? *Vaccine* 2006;**24**(18):3921–8.
6 **Department for Transport**. *Road casualties in Great Britain. Main results: 2005*. London: Department for Transport, 2006.
7 **Department of Health**. Vaccine safety and the management of adverse events following immunisation. In:*Immunisation against infectious diseases*. London: Department of Health,, 2006.
8 **Centers for Disease Control and Prevention**. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease --- United States, 1998–2003. *MMWR Morb Mortal Wkly Rep* 2005;**54**(36):893–7.
9 **Black S**, Shinefield H, Fireman B, *et al*. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Center Group. *Pediatr Infect Dis J* 2000;**19**(3):187–95.
10 **Cutts FT**, Zaman SM, Enwere G, *et al*. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005;**365**(9465):1139–46.
11 **Klugman KP**, Madhi SA, Huebner RE, *et al*. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003;**349**(14):1341–8.
12 **Ramsay ME**, McVernon J, Andrews NJ, *et al*. Estimating Haemophilus influenzae type b vaccine effectiveness in England and Wales by use of the screening method. *J Infect Dis* 2003;**188**(4):481–5.
13 **Trotter CL**, Andrews NJ, Kaczmarski EB, *et al*. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet* 2004;**364**(9431):365–7.
14 **Snape MD**, Pollard AJ. Meningococcal polysaccharide-protein conjugate vaccines. *Lancet Infect Dis* 2005;**5**(1):21–30.
15 **Schmitt HJ**, Booy R, Weil-Olivier C, *et al*. Child vaccination policies in Europe: a report from the Summits of Independent European Vaccination Experts. *Lancet Infect Dis* 2003;**3**(2):103–8.
16 **Baptista PN**, Magalhaes V, Rodrigues LC, *et al*. Source of infection in household transmission of culture-confirmed pertussis in Brazil. *Pediatr Infect Dis J* 2005;**24**(11):1027–8.
17 **Collins CL**, Salt P, McCarthy N, *et al*. Immunogenicity and safety of a low-dose diphtheria, tetanus and acellular pertussis combination vaccine with either inactivated or oral polio vaccine as a pre-school booster in UK children. *Vaccine* 2004;**22**(31–32):4262–9.
18 **Pichichero ME**, Casey JR. Acellular pertussis vaccines for adolescents. *Pediatr Infect Dis J* 2005;**24**(6 Suppl):S117–26.
19 **English P**. Should universal hepatitis B immunisation be introduced in the UK? *Arch Dis Child* 2006;**91**(4):286–9.

20 **Hinds A**, Cameron JC. Acceptability of universal hepatitis B vaccination among school pupils and parents. *Commun Dis Public Health* 2004;**7**(4):278–82.
21 **Villa LL**, Costa RL, Petta CA, *et al*. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;**6**(5):271–8.
22 **Harper DM**, Franco EL, Wheeler C, *et al*. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;**364**(9447):1757–65.
23 **Harper DM**, Franco EL, Wheeler CM, *et al*. Sustained efficacy up to 4. 5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial, *Lancet* 2006;**367**(9518):1247–55.
24 **Vazquez M**, LaRussa PS, Gershon AA, *et al*. Effectiveness over time of varicella vaccine. *JAMA* 2004;**291**(7):851–5.
25 **Lieberman JM**, Williams WR, Miller JM, *et al*. The safety and immunogenicity of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children: a study of manufacturing consistency and persistence of antibody. *Pediatr Infect Dis J* 2006;**25**(7):615–22.
26 **Grose C**. Varicella vaccination of children in the United States: assessment after the first decade 1995–2005. *J Clin Virol* 2005;**33**:89–95, discussion 96–8, (2).
27 **Poehling KA**, Edwards KM, Weinberg GA, *et al*. The underrecognized burden of influenza in young children. *N Engl J Med* 2006;**355**(1):31–40.
28 **Neuzil KM**, Mellen BG, Wright PF, *et al*. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000;**342**(4):225–31.
29 **Vesikari T**, Matson DO, Dennehy P, *et al*. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;**354**(1):23–33.
30 **Ruiz-Palacios GM**, Perez-Schael I, Velazquez FR, *et al*. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;**354**(1):11–22.
31 **The Pediatric Rotavirus European Committee (PROTECT)**. The paediatric burden of rotavirus disease in Europe. *Epidemiol Infect* 2006;**134**(5):908–16.
32 **Centers for Disease Control and Prevention**. Active Bacterial Core surveillance (ABCs) report, emerging infections program network, Neisseria meningitidis, 2005-provisional. Atlanta: CDC, 2006.
33 **Giuliani MM**, Adu-Bobie J, Comanducci M, *et al*. Inaugural article: a universal vaccine for serogroup B meningococcus. *Proc Natl Acad Sci U S A* 2006;**103**(29):10834–9.
34 **World Health Organization**. *World health statistics 2005*. Geneva: WHO, 2005.
35 **World Health Organization**. *2004 global immunization data*. Geneva: WHO, 2004.
36 **Mexican Commission on Macroeconomics and Health**. *Investing in health for economic development*. Puebla, Mexico: Universidad de las Américas, Puebla, 2004.

IMAGES IN PAEDIATRICS

doi: 10.1136/adc.2006.112474

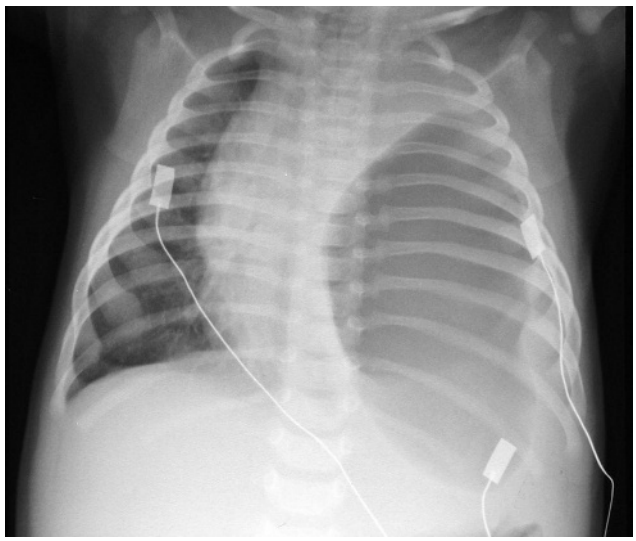
Unusual *x* ray image

This is the *x* ray of a 2½-month-old boy who presented with a 2-week history of cough and recent onset of breathlessness and decreased feeding. He had no previous illnesses and his ante-natal scans were normal. Soon after admission, he developed an oxygen requirement of 0.75 l/min. He was pale and feverish with bilateral wheeze on auscultation. Four hours later, he became mottled and developed reduced skin perfusion. Blood gases showed severe metabolic acidosis (pH 6.9, P_{CO_2} 11, base excess 12.8) and he required multiple fluid boluses to correct this. A chest *x* ray showed a large hyperlucent area in the left hemi-thorax with mediastinal shift to the right—probably congenital cystic adenomatoid malformation/pneumothorax. Six-slice CT showed a large air- and fluid-filled cavity in the left hemithorax with a thin soft-tissue rim. He continued to be acidotic and developed renal compromise. He was ventilated, stabilised and transferred to a tertiary centre. He had full spiral CT with contrast through a nasogastric tube, which showed a diaphragmatic hernial defect with stomach in the left hemithorax. He was operated on the same day and had an uneventful stay later.

Late presentation of congenital diaphragmatic hernia poses considerable diagnostic challenge, often leading to misdiagnosis and risk of inappropriate chest drain insertion.[1] Clinical pathology is due to a mediastinal shift and pulmonary collapse as opposed to pulmonary hypoplasia and hypertension in newborns. Its possibility should be suspected in every child presenting with unusual respiratory symptoms and abnormal chest *x* ray findings.[2 3]

Nagashree Nallapeta, Rachel Delyth Webb, Shipra Mathur
Department of Paediatrics, Warrington General Hospital, Warrington, UK

Correspondence to: Dr N Nallapeta, Department of Paediatrics, Warrington General Hospital, Warrington WA5 1ZB, UK; drnagashree.gmail.com



Chest *x* ray showing a large air-filled cavity in the left hemi-thorax.

Competing interests: None.

References

1 **Sridhar AV**, Nichani S. Late presenting congenital diaphragmatic hernia. *Emerg Med J* 2004;**21**:261–2.
2 **Kitano Y**, Lally KP, Lally PA. Late-presenting congenital diaphragmatic hernia. *J Pediatr Surg* 2005;**40**:1839–43.
3 **Yamamoto H**, Parikh DH. An unusual late presentation of a congenital diaphragmatic hernia. *Pediatr Surg Int* 2005;**21**:1021–2.