VIRAL HEPATITIS

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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **'Combined hepatitis B vaccines,'** Corinthia San Ġorġ Hotel, St Julians, Malta, October 22-23, 2001.

EDITORIAL

The Viral Hepatitis Prevention Board met October 22-23, 2001 in St. Julians, Malta to review combined vaccines in a number of different contexts - legislative, regulatory, and clinical. Of particular interest during this meeting were evaluations of the new hexavalent vaccines that are now licensed in the European Union, providing protection against diphtheria, tetanus, pertussis, poliomyelitis, Hib (*Haemophilus influenzae* type b) disease, and hepatitis B.

While combination vaccines are playing an increasingly important role in national immunisation programmes, the extent to which new combined vaccines are used is linked to a country's vaccine history as well as to the new vaccine's compatibility with existing immunisation programmes. Combination vaccines with a hepatitis B component will have some limitations in countries with universal newborn hepatitis B immunisation: since non-hepatitis B components of a combined vaccine have reduced immunogenicity in infants less than six weeks of age, the monovalent hepatitis B vaccine must continue to be used for the hepatitis B birth dose.

The Viral Hepatitis Prevention Board would welcome additional data based on long-term studies that are needed to evaluate when booster vaccinations are necessary using hexavalent vaccines with a hepatitis B component, especially in immunisation schedules that use only three or four vaccinations in the first year of life, with no booster doses.

Widespread use of the new hexavalent vaccines will provide an extraordinary opportunity to increase compliance and coverage of hepatitis B vaccination and, it is hoped, will also provide the basis for a new move towards harmonising the introduction of new vaccine antigens in Europe.

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on behalf of the Viral Hepatitis Prevention Board

'Combined hepatitis B vaccines' Corinthia San Ġorġ Hotel, St Julians, Malta, October 22-23, 2001 - a VHPB Symposium Report -

Overview of the vaccination programme in Malta

In Malta, as in most developed countries, the availability of effective vaccines, combined with improved living standards, has resulted in a remarkable decrease in the incidence, mortality, and morbidity of certain vaccine-preventable diseases, some of which are on the verge of being eliminated.

Health-for-all-policy for the 21st century (Health21)
The European Region of the WHO has set a series of targets that must be met by each of the member states. Target 7 is concerned with reducing communicable diseases and relates directly to immunisation policies.

According to Health21, poliomyelitis, measles, and neonatal tetanus should be eliminated from the European Region, with poliomyelitis and measles as part of the global eradication effort. Congenital rubella, diphtheria, hepatitis B, mumps, pertussis, and invasive disease caused by *Haemophilus influenzae* should be well controlled through immunisation.

Malta's Advisory Committee on Immunisation Policies

The Advisory Committee on Immunisation Policies (ACIP) in Malta is the official body that advises the Health Division on all immunisation issues by regularly revising and issuing guidelines and warnings relating to the National Immunisation Schedule. The members of the Committee include hospital and community paediatricians, public health physicians, microbiologists, a consultant in infectious diseases, and the managing nursing officer of the National Immunisation Service (NIS).

The work of the Maltese ACIP is strongly influenced by:

- Health21 recommendations;
- United Kingdom (UK) Department of Health recommendations;
- Medical literature (including Internet sources);
- The local epidemiology of vaccine-preventable diseases.

Maltese immunisation legislation

Current Maltese legislation regarding communicable disease immunisation provides for the free administration of immunisation against diphtheria, tetanus, poliomyelitis, and other diseases as determined by the Superintendant of Health. This legislation also requires that parents have their children immunised with the mandatory diphtheria, tetanus, and poliomyelitis vaccines.[1] In addition, there are legal provisions for rubella vaccination of female children aged ten to thirteen years.[2] Hepatitis B as a compulsory vaccination is also being considered. This legislation is currently being updated and re-written under a new Public Health Act.

Vaccine administration and reporting

Vaccines in Malta are administered to children either by the NIS through the various government health centres (free of charge), or by private medical practitioners.

The NIS also offers influenza vaccine free of charge to individuals who are at high risk of complications, and offers advice and vaccination to travellers visiting countries with high risk for certain communicable diseases.

All births in Malta and Gozo are entered into a Department of Primary Health Care database, which also contains information on all scheduled immunisations given to children. While vaccinations that are carried out in government health centres are reported directly to the NIS, a significant number of vaccinations carried out by private practitioners are not reported, resulting in calculation of coverage rates that are below the actual rates.

Maltese legislation requires that there is a statutory obligation for medical practitioners to report any immunisation within one month from the day of immunisation.[3] While the Department of Primary Health Care does not condone non-reporting, it does recognize that the current reporting system may be too cumbersome. A radical reform in the reporting system has, therefore, been undertaken and should result in comprehensive data collection of all immunisations carried out in the private sector.

The NIS periodically compiles lists of defaulters, which are passed on to the Public Health Authorities. Health inspectors then have the painstaking task of tracking down all unimmunised children, and ensuring that the legal obligations regarding disease prevention are fulfilled. In some cases, legal proceedings are carried out against parents who have not complied with the regulations.

Malta's current immunisation schedule

Vaccination against diphtheria, tetanus, and poliomyelitis is mandatory. Diphtheria, tetanus, and pertussis vaccines are administered as a combined vaccine at two, three, and four months of age. The NIS provides the poliomyelitis vaccine in the oral form, but in the private sector in an injectible combined form is used. Booster doses of diphtheria, tetanus, and poliomyelitis vaccines are given at four and sixteen years of age.

Haemophlus influenzae type b (Hib) was first introduced into Malta's immunisation schedule in 1996. It is administered at the same time as the diphtheria, tetanus, pertussis, and poliomyelitis vaccines. The Hib vaccine is administered as a separate vaccine by the NIS, but in the private sector it is combined with diphtheria, tetanus, pertussis, and poliomyelitis vaccination.

The pertussis vaccine is administered as a whole cell vaccine by the NIS. However, most private practitioners are opting for the acellular vaccine. The Maltese ACIP is currently reviewing the pertussis vaccination schedule, and is discussing the introduction of the acellular vaccine on a national level.

The measles-mumps-rubella (MMR) vaccine was introduced into Malta's immunisation schedule in 1990, and is first administered at fifteen months of age. A second MMR vaccine was, until recently, administered between eleven and thirteen years of age but this has been reduced to seven years. A catch-up vaccination programme has simultaneously started for children in between these age groups. Discussions are underway to reduce this even further, possibly together with other pre-school boosters at four years of age. Rubella vaccination is legally required for females between ten and thirteen years of age.

Hepatitis B vaccination started in 1992, and was first given free of charge to selected high-risk groups, such as health care and hospital laboratory workers. Since 1997-1998, hepatitis B vaccine has been given on a national level to children at the age of nine years. It is also given free of charge to babies born to mothers who are chronic carriers of hepatitis B or to mothers who have had acute hepatitis B during pregnancy. Currently, there is a proposal for hepatitis B vaccine to be given at six, seven, and twelve months of age. In the private sector, the recommendations will be to vaccinate against hepatitis B at two, three, and four months as a combined vaccine with diphtheria, tetanus, pertussis, poliomyelitis, and Hib once this becomes available.

The BCG (Bacille Calmette-Guérin) vaccine is recommended in Malta for children between twelve and fourteen years of age, depending on the results of the Heaf or Mantoux tests. It is also offered free of charge to immigrants and refugees from countries with high prevalence of tuberculosis, to their children, and to infants wherever born.

Malta's current immunisation schedule

Age	Vaccine*
2, 3, 4 months	DTP-polio-Hib
15 months	MMR (1)
During the fourth year	DT-polio (booster)
7 years	MMR (2)
9 years	HepB
12-14 years	BCG
16 years	dT-polio (booster)

* DTP = diphtheria, tetanus, pertussis

Immunisation programme performance

The uptake of immunisation schedule vaccines has never been as satisfactory as it has been during the last five years. Vaccination coverage for diphtheria, tetanus, poliomyelitis, and pertussis are above 90%, and coverage rates for MMR vaccination are approximately 90%. However, as global immunisation coverage has increased dramatically over the past two decades, and the incidence of disease has declined, immunisation programme performance today is increasingly measured not by a head count of immunised children but, more importantly, by measuring the reduction in the incidence of disease.

Before the introduction of the diphtheria vaccine in Malta in 1940, the annual crude incidence rate was in the region of 70 per 100,000. The last notified case of diphtheria in Malta occurred in 1969.

Poliomyelitis followed a similar trend with the last case reported in 1964. This success has undoubtedly been the result of the intense efforts put into the immunisation programme over a long period of time.

Measles epidemics had previously occurred every three to four years with thousands of cases being notified. With the massive campaign carried out in 1987, there has been a drastic reduction in the number of reported cases.

Rubella notifications have also declined following the introduction of vaccination. Ever since congenital rubella syndrome was declared a notifiable condition in 1990, there have been no reported cases.

Conclusions

The Maltese ACIP is committed to implementing the necessary strategies to avoid the emergence and re-emergence of vaccine-preventable diseases, and to ensuring the delivery of safe vaccines. In addition, the ACIP, together with other sections of the Maltese Health Division, will continue to collaborate with WHO in its communicable disease eradication programmes.

References

[1] Prevention of Disease Ordinance. Chapter 36, title III - Immunisation against communicable disease, section 57 of the Laws of Malta.

[2] Legal Notice 50 of 1989. Chapter 36 - Vaccination for rubella regulations, Subsidiary legislation 36.31 of the Laws of Malta.

[3] Prevention of Disease Ordinance. Chapter 36, title III - Immunisation against communicable disease, section 63 of the Laws of Malta.

Based on a presentation by Dr Mark Muscat, Department of Public Health, 37-39, Rue D' Argens, Msida MSD 05, Malta.

Countries in Europe where combined vaccines are licensed

Several types of combination vaccines with a hepatitis B component are currently licensed in Europe. Tables 1 and 2 show which combined vaccines are available in various European countries:

Hepatitis B vaccine - monovalent vs. combination formulations

Hepatitis B vaccines are available in monovalent formulations (protecting only against hepatitis B), and in combination formulations (protecting against hepatitis B together with other diseases). Hepatitis B monovalent vaccines can be used for any dose in a hepatitis B vaccination schedule. However, the monovalent hepatitis B vaccine must be used for vaccination at birth, since hepatitis B combination vaccines containing antigens such as DTP and Hib have reduced immunogenicity when given before the age of six weeks. A combination vaccine with a hepatitis B component, therefore, cannot be used for newborns.

Table 3 shows the potential uses of HepB (hepatitis B viral antigen) in European countries, when combined with other antigens, such as DTPa or DTPw.

Tables 1-2. Availability of combined vaccines in Europe, 2001

Combined vaccine*	Country **
DTPa-HepB	Greece Italy Switzerland Ukraine
DTPa-Hib	Austria Germany Slovenia Spain Switzerland United Kingdom***
DTPa-IPV	Austria Belgium*** France*** Germany Ireland Italy Switzerland

Combined vaccine*	Country **
DTPa-IPV-Hib	Austria Belgium Croatia France*** Germany*** Greece Ireland Israel Italy*** Spain*** Sweden*** Switzerland
DTPa-HepB-IPV-Hib	Austria Croatia Germany*** Greece Italy*** Spain*** Switzerland***

* Pa = acellular pertussis vaccine; Pw = whole-cell pertussis vaccine; IPV = inactivated polio vaccine.
** Israel has been included in the list.
*** Two vaccine manufacturers.

Table 3. HepB combined with other antigens in Europe

Country	Universal newborns HepB	Universal infants HepB	DTPa/DTPw	Observations
Austria		3, 4, 5, 13-18 m	Pa 3, 4, 5, 13-18 m	Combination accepted
Belgium		3, 4, 12 m	Pa 2, 3, 4, 13-18 m	Combination possible for 3 doses
Denmark			Pa 3, 5, 12 m	No universal HepB programme
Finland			Pw 3, 4, 5, 20 m	No universal HepB programme
France		2, 3, 9-18 m	Pa/w 2, 3, 4, 15-18 m	Combination considered for 3 doses
Germany		2, 4, 12 m	Pa 2, 3, 4, 11 m	Combination possible for 3 doses
Greece		2, 4, 6-8 m	Pa/w 2, 4, 6, 18 m	Combination considered for 3 doses
Ireland			Pa 2, 4, 6 m	No universal HepB programme
Italy		3, 5, 11 m	Pa 3, 5, 11 m	Combination possible
Luxembourg		1, 3, 11-12 m	Pa 2, 3, 11-12 m	Combination possible for 2 doses
Netherlands			Pw 2, 3, 4, 11 m	No universal HepB programme
Norway			Pa 3, 5, 11 m	No universal HepB programme
Portugal	0, 2, 6 m		Pw 2, 4, 6, 18-24 m	No combination possible
Spain	0, 2, 6 m		Pa/w 2, 4, 6, 18 m	Combination considered for 2 doses
Sweden			Pa/w 2, 3, 4 m	No universal HepB programme
Switzerland			Pa 2, 4, 6, 15-23 m	Adolescent programme
United Kingdom			Pw 3, 5, 12 m	No universal HepB programme

Licensure in Europe, however, does not guarantee that the vaccines are necessarily available in those countries via national vaccination programmes. In some cases they may only be available through private medical care, possibly without reimbursement.

Based on a presentation by Dr Pierre van Damme, Department of Epidemiology and Social Medicine, University of Antwerp, Antwerp, Belgium.

Infant and adolescent vaccination schedules in Europe - 2001

Hepatitis B immunisation schedules vary widely throughout the WHO European Region, where coverage in most countries is less than optimal. It is hoped that the use of a new, combined hexavalent vaccine, which has been available since mid-2000, and already introduced in some infant immunisation schedules, will help increase hepatitis B immunisation coverage. The new vaccines combine DTPa, IPV, Hib, and HepB.

Wide variations in carrier rates

Carrier rates for HBsAg vary widely within the European Region. In Western Europe, HBsAg carrier rates tend to increase from North to South. In the United Kingdom, for example, and the Nordic countries, HBsAg carrier rates are less than 0.5%. However, in Mediterranean areas, such as Italy, Spain, and southern France, carrier rates may range from one to two percent. Within the European Region as a whole, carrier rates increase from West to East. In some East European countries, such as Albania, carrier rates may range as high as 18-19%.[1]

Immunisation schedules

In some countries with HBsAg carrier rates over 0.5%, immunisation programmes have been launched for infants, adolescents, or both. Most countries in the European Region use three doses as a complete series. Adolescent or pre-adolescent programmes are carried out either alone, or as a complement to the infant immunisation programme.

For information regarding immunisation schedules, several sources are available from WHO:

- At regional level, from the Computerized Information System on Infectious Disease: http://cisid.who.dk
- At global level, through the Vaccine-preventable Diseases Monitoring System: http://www-nt.who.int/vaccines/globalsummary/Immunization

Screening for HBsAg

In countries that begin immunisation programmes after birth, systematic screening for HBsAg must be carried out for specific prophylaxis of infants born to infected mothers. Such screening programmes, carried out in twenty-nine European countries, also prevent the transmission of hepatitis B from an infected mother to her newborn.

Changes in immunisation schedules

Recently, most EU countries, and Norway and Switzerland, have made changes to their immunisation schedules:

- Oral polio vaccine (OPV) has been replaced by inactivated polio vaccine (IPV) in most EU countries, except for Greece, Portugal, and Spain;
- Acellular pertussis vaccine has been introduced in Austria, Belgium, Denmark, Germany, Ireland, Italy, Luxembourg, Norway, and Sweden;
- Acellular pertussis vaccine has been introduced as an alternative to whole cell pertussis vaccine in France and Switzerland;
- Most of the countries have adopted a three-dose schedule for hepatitis B vaccination.

Conclusions

Some countries in the European Region have still not implemented routine immunisation programmes against hepatitis B. In some countries that do implement routine hepatitis B vaccination, coverage is very high. However, there may be low or medium levels of coverage in certain countries that are just beginning a hepatitis B immunisation programme, or in countries that are having difficulty in implementing these programmes. In such cases, combined vaccines in infants may be useful in increasing coverage. Such vaccines should be used in accordance with national schedules, and the number of doses of each antigen needed for full protection of the infant/adolescent population.

References

[1] Bonanni P. Report on Working Group 1: Albania, Andorra, Canada, France, Italy, Moldova, Portugal, Poland, Romania and Spain. *Vaccine* 1998; 16 (Suppl.):S58-S60.

Based on a presentation by Dr Nicole Guérin, Comité Technique Vaccinations, Antony, France.

Infant and adolescent hepatitis B vaccination and use of combined vaccines - United States

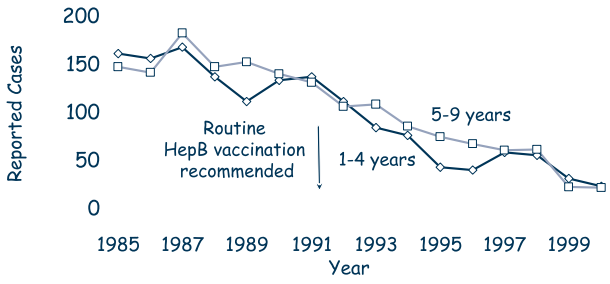
In the United States (USA), current strategies for eliminating hepatitis B virus transmission focus on (1) prevention of perinatal HBV transmission; (2) routine infant vaccination; and (3) catch-up vaccination targeted to eleven to twelve-year old children, children under nineteen years of age, and adults in high-risk groups.

The perinatal hepatitis B prevention programme in the United States was first implemented in 1984, beginning with selective immunisation and progressing to universal immunisation in 1988. Key elements of this programme currently focus on HBsAg testing of all pregnant women, and reporting of HBsAg-seropositive women. In addition, case management and tracking are used to ensure:

- Administration of HBIg and hepatitis B vaccine at birth;
- Completion of vaccine series by 6 months of age;
- Post-vaccination serological testing;
- Identification and vaccination of susceptible sexual contacts.

The United States has seen an impressive decrease in the number of reported cases of acute hepatitis B in children during the period 1985 to 2000 due to the effectiveness of its vaccination and screening programmes. See figure below.

Reported cases of acute hepatitis B in children in the United States, 1985-2000



The rationale for administering hepatitis B vaccine to all infants at birth is based on the view that a safety net is created to eliminate the possibility of missed immunoprophylaxis for infants born to HBsAg-positive mothers - a situation that could occur through medical error. A hepatitis B birth dose assures immunoprophylaxis for infants born to unscreened women or in cases where screening errors occur.

The birth dose strategy is now recommended, for the first time, by the United States' Advisory Committee on Immunization Practices (ACIP), a decision that was taken during the ACIP's meeting on 17 October 2001, and considered a major new step in US hepatitis B policy.

Other factors supporting the US birth dose strategy are:

- Possibility of infant/child exposure to HBV even though mother is HBsAg-negative;
- Possible reduction in the number of hepatitis B vaccine doses that need to be given simultaneously with other vaccines;
- Possible increased likelihood that the hepatitis B series will be given on schedule;
- Possible increased coverage for hepatitis B and other vaccines;
- Conveying the importance of vaccination to parents.

The FDA is currently reviewing two pentavalent combination vaccines, DTPa-HepB-IPV and DTPa-Hib-IPV. In contrast to the situation in Europe, a hexavalent vaccine, DTPa-HepB-IPV-Hib, will only be licensed in the USA within the next years.[1]

References

[1] Decker MD. Principles of pediatric combination vaccines and practical issues related to use in clinical practice. *Pediatr Infect Dis J* 2001; 20 (Suppl):S10-S18.

Based on a presentation by Dr Frederic Shaw, Division of Viral Hepatitis, NCID, CDC, Atlanta, Georgia.

Harmonisation of vaccination calendars in the European countries?

Up to now, all efforts to arrive at harmonisation of vaccination schedules within the fifteen Member States of the European Union have failed. While guidelines for harmonising EU legislation have existed since 1998[1] little progress has been made towards standardising vaccination calendars within the EU.

One of the obstacles in arriving at harmonisation is that each of the fifteen Member States has its own vaccination schedule which, in part, reflects local epidemiological differences. Another obstacle is that different traditions and attitudes towards health care reimbursement influence decisions taken at national level. Each Member State has its own health care system with a unique history and basis for which vaccinations will be paid by their national insurance systems, and which vaccinations offered free of charge.

Another factor contributing to lack of consensus is the complex interaction of policy and decision-making that exists at national level, together with the existence of national associations of physicians, and health insurance companies - each reflecting their own national interests. In addition, EU enlargement extending to twelve applicant countries will compound the challenges in arriving at standardisation of calendars which must take into account different epidemiological situations for each country. Establishing common goals for reducing the threat of major diseases, and establishing specific vaccine coverage targets would be important goals to achieve in arriving at harmonisation of vaccination schedules.

The introduction of new vaccines, such as hexavalent combination vaccines, may also present a new opportunity to accelerate the move towards harmonising vaccination calendars within the European Union.

One of the questions underlying this issue, is whether standardisation of vaccination schedules in the European Union would significantly improve the health protection of its citizens.

References

[1] Decision No 2119/98/EC of the European Parliament and of the Council of 24 September 1998 setting up a network for surveillance and control of communicable diseases in the Community.

Based on a presentation by Dr Michael Pfleiderer, Paul-Ehrlich-Institut, Federal Agency of Sera and Vaccines, Langen, Germany.

European regulatory authorities' view on proving safety and immunogenicity of combined vaccines - General aspects - Recent experiences

Two new hexavalent vaccines were granted licensing authority by the European Union in October 2000. The hexavalent vaccines have been developed by two European vaccine manufacturers - Infanrix®-*hexa* developed by GlaxoSmithKline Biologicals in Belgium, and Hexavac® developed by Aventis Pasteur MSD in France. The vaccines, which have not yet undergone comparison with one another in clinical trials, exist in different pharmaceutical forms:

- Infanrix®-*hexa* in powder and suspension for injection;
- Hexavac® in suspension for injection in pre-filled syringe.

Issues that were examined in granting licensing of these vaccines in the EU concerned quality, efficacy, and safety.

Quality issues
One of the major quality issues in evaluating the dossiers of the hexavalent vaccines was that of cumulative stability of the vaccine intermediates, in terms of:

- Seed lots;
- Live or inactivated harvests from bacterial or viral cultures;
- Purified harvests consisting of toxins, toxoids, polysaccharides, bacterial or viral suspensions;
- Purified antigens;
- Conjugated polysaccharides;
- Final bulk vaccine;
- Vaccine in the final closed container stored at low temperature awaiting label.

The shelf life of intermediates can vary from one or several days up to a period of fifteen years, after which time a vaccine may become uncontrollable. Evaluating the cumulative stability of vaccine intermediates in hexavalent vaccines becomes even more complex as these new vaccines each contain nine or ten different antigens, and up to forty intermediates. As a consequence of these stability issues, EU authorities issued a concept paper (CPMP/BWP/4310/00)* on the 'Development of CPMP points to consider on stability and traceability requirements for vaccine intermediates.' Committee for Proprietary Medicinal Products This paper resulted in guidelines for adequate stability and traceability requirements for vaccine intermediates, and was accepted by the manufacturers in assuring that intermediates that exceeded a certain age would not be used in the manufacture of vaccines.

Efficacy issues - combining antigens is more than mixing
A crucial principle identified during the dossier evaluation of the hexavalent vaccines was that combining antigens to formulate a multivalent vaccine is more than just mixing antigens, based on the following considerations:

- Changes may occur in the immunogenicity due to interference of vaccine antigens;
- Reliable potency testing becomes increasingly complicated;
- Established surrogates/correlates for protection may need re-evaluation.

The acellular pertussis component
With regard to the use of acellular pertussis vaccines, EU authorities concluded that:

- There is no evidence that the number of pertussis antigens determines the clinical efficacy of acellular pertussis vaccines, which has been clearly demonstrated by a number of EU countries.
- There is no evidence that whole-cell pertussis vaccines are clinically more efficient than acellular pertussis vaccines. There has been only one clinical trial that has explored this issue. It would appear that, up to now, there has been no significant difference in efficacy established between the whole-cell and acellular pertussis vaccines.
- There is no evidence that anti-Pa antibodies are surrogates of protection, or that sufficient or insufficient levels of protection can be correlated with Pa antigen levels in the vaccine. Clinical efficacy studies would be needed to examine each of these issues.
- There is no evidence of genetic polymorphism of circulating *Bordetella pertussis* strains driven by acellular pertussis vaccines with only one or two components, nor any evidence of an epidemiological impact.
- There is no evidence that acellular pertussis vaccines are responsible for re-emerging pertussis disease.

The Hib component
Another issue that was raised in the dossier evaluation was that of anamnestic immune response. The conclusion, following evaluation by more than forty experts at European level, was that there is no evidence for increased invasive Hib disease if priming can be achieved with three immunisations with the Hib component. Anamnestic immune response is thus guaranteed even if there are no detectable anti-Hib titres before the booster.

The hepatitis B component
What is known so far about the long-term persistence of hepatitis B immune protection is based mainly on the use of monovalent formulations. More long-term studies are needed to evaluate when booster vaccinations are needed using the hexavalent vaccines with a hepatitis B component, especially crucial in immunisation schedules where there are only three or four vaccinations in the first year of life, with no booster vaccination.

Safety aspects
Fever of > 39°C, inconsolable crying, and severe local reactions were observed during clinical trials. An adverse events may be perceived by parents as a severe impairment to their child's health. This, in turn, could lead to reluctance in returning for booster vaccination and, eventually, to lowered immunisation rates. Further monitoring studies will be needed in order to determine if these adverse events are directly linked with vaccination or not.

Conclusions
The hexavalent vaccines were licensed by the EU on the basis of adequate demonstrations of quality, efficacy, and safety. However, the licensing approvals are linked to a large number of post-marketing conditions including long-term stability testing focused on the age of the intermediates used.

Another follow-up measure is the sampling and testing of the hexavalent vaccines under the auspices of the European Department for the Quality of Medicines which so far has not been necessary for vaccines. A programme would need to be set up to buy back the vaccines from pharmacies for further testing by independent laboratories to determine if the quality of the vaccines can be maintained under market conditions.

Additional post-marketing studies will also be carried out involving:

- Long-term epidemiological surveillance studies to monitor effectiveness of the hexavalent vaccines as well as the distribution and circulation of the natural pathogens;
- Large, controlled safety studies to compare the reactogenicity profile of the hexavalent vaccines compared to the vaccine generations used before (e.g., the pentavalent vaccines).

Pharmacovigilance data from spontaneous reporting will define the rare adverse drug reaction profile of the hexavalent vaccines, and will need to be evaluated carefully in order to eventually amend the Summary of Product Characteristics, and Patient Information Leaflet for each of the vaccines.

* CPMP: Committee for Proprietary Medicinal Products; BWP: Biotechnology Working Party.

Based on a presentation by Dr Michael Pfleiderer, Paul-Ehrlich-Institut, Federal Agency of Sera and Vaccines, Langen, Germany.

Combined vaccines with a hepatitis B component - The role of non-clinical testing in ensuring their safety and immunogenicity

In the European Pharmacopoeia, a monograph has been drawn up on combined vaccines for human use, and is summarised below:

'For a combined vaccine, where there is no monograph to cover a particular combination, the vaccine complies with the monograph for each individual component, with any necessary modifications approved by the competent authority.'

When moving from monovalent to combination vaccines, or when making a significant change in production (e.g., removing thiomersal), reassessment will be needed of various formulation characteristics, such as pH, degree of adsorption, ionic strength and osmolality, and concentration and compatibility of adjuvants, buffer salts, antimicrobials, residual formaldehyde, etc.

For hepatitis B vaccine, for example, testing of the culture and harvest will need to be carried out on the identity, microbial purity, plasmid retention, and consistency of the yield. The purified antigen will also be tested for total protein, antigen content and identity, and the antigen/protein ratio. Further testing will be needed to determine molecular weight, antigenic purity (≥ 95% HBsAg), composition (proteins, lipids, …), host-cell and vector-derived DNA (≤ 10 pg/standard human dose), caesium and/or other chemicals, and sterility.

Testing will continue for antimicrobial preservative and sterility of the final bulk of the vaccine; and for the final lot, testing for identity, aluminium (if it is being used), free formaldehyde, antimicrobial preservative, sterility, and pyrogens.

In vivo or *in vitro* assays are also carried out to determine the potency of the vacine. *In vivo* assays are carried out in mice or guinea pigs by comparing the vaccine's capacity to induce specific antibodies against HBsAg, or *in vitro* by an immuno-chemical determination of the antigen content.

In order to ensure consistency of the vaccine, further testing is carried out to determine possible interactions between antigens. For example, a combined vaccine containing the following antigens will be compared with clinical reference and will be monitored for consistency:

- HepB;
- D and T, without Pw;
- T and Hib;
- Hib and Pa.

Additional research will need to be conducted within the following areas:

- Determining correlates/surrogates of protection, and defining the significance of observed differences;
- Defining how much information has to be available before licensing a vaccine, and which information can be safely left to post-licensing data;
- Close epidemiological monitoring of vaccine coverage, efficacy, adverse reactions, and pathogen circulation upon introduction of new, combined vaccines.

Batch release

In Europe, the main task of the Official Medicines Control Laboratory (OMCL) network is the batch release of vaccine. Other OMCL tasks include the licensing of vaccines, as well as involvement in inspection issues and advising on vaccines at national, EU, and international level with WHO. A batch release involves producer-independent, OMCL-pre-market testing of every final lot before it comes onto the market. Batch release has had a long tradition in Europe (since 1967 in Belgium), and is used for testing vaccine for human and veterinary use, and in applications for plasma derivatives. The purpose of batch release is to verify and monitor the products in conformity with marketing authorities, European pharmacopoeia and, if applicable, with recommendations of WHO.

Mutual recognition

The legal basis for mutual recognition of batch release in the EU Member States has existed since 1995, and is intended to foster good faith and trust in products produced by the various countries of the European Union. The quality system used by national control authorities is EN 4501, which will eventually be replaced by a system of quality assurance, ISO 17025.

In addition, the European Directorate for the Quality of Medicines (EDQM) co-ordinates batch release in Europe, performs joint audits and organises proficiency studies where performance of OCML can be evaluated. OCML-accredited laboratories (using EN 4501) currently exist in Belgium, Denmark, The Netherlands, and the United Kingdom.

WHO also stresses the importance of national control authority in those countries that have a manufacturer producing and supplying vaccines used in WHO-sponsored immunisation programmes.

Hepatitis B (rDNA) vaccine

The routine situation and final steps in the control authority batch release of hepatitis B (rDNA) vaccine involve testing on the bulk purified antigen for identity and purity. Testing for the final vaccine lot involves:

- Assay serving as the identity test;
- If an *in vitro* assay is used to determine the antigen content, it must be done on the final lot;
- If an *in vivo* assay is used, it is required only when a new final bulk has been used.

In some cases, a second phase of testing may be required, based on accidents, incidents, or specific issues that have arisen, and that will need to be investigated before batch release.

Based on a presentation by Dr Roland Dobbelaer, Biological Standardisation Department, Scientific Institiute of Public Health, Brussels, Belgium.

New vaccine supply and financing: a case study of combined vaccines in developing countries

A recent study[1] examines regulatory, supply, and acceptance issues of combination vaccines, and what the public sector can do to maximise the opportunity to introduce new antigens via com bination vaccines into developing countries.

While historically it has taken approximately twenty years for a new vaccine to make its way from developed to developing countries, major efforts are under way in public health to diminish that time frame substantially. The increased use of combination vaccines as a way to introduce new and under-utilised antigens into an immunisation programme provides a case study for the programmatic and supply issues facing national immunisation managers today.

Case study: decision analysis of DTPw-based combinations

DTPw is the vaccine most frequently given in national immunisation programmes in developing countries, and seems one of the most reasonable bases on which to build combination vaccines. Programmatically, adding an antigen to DTPw is a transparent way to introduce an additional antigen with the same delivery schedule, although using a DTPw-based combination would not change the overall coverage.

Benefits and drawbacks

The most obvious benefit is the immunisation of all children receiving DTPw with an additional antigen, but without an additional injection. Other benefits include a reduction in the number of syringes used, resulting in increased injection safety and less vaccine-related waste, as well as reduced thiomersal exposure due to fewer total injections. Some of the drawbacks, however, include less flexibility in the programme (e.g., where a birth dose of hepatitis B vaccine is necessary), and concerns for financial sustainability when prices for combination vaccines are higher than the monovalent or traditional vaccines.

Regulatory issues

As for all vaccines, safety and efficacy must be demonstrated. This implies the need for clinical trials, the establishment of correlates of immunity, and the establishment of standards and reference reagents. However, the issues are more complex for combination vaccines. One reason is that each time a new antigen is added to a combination vaccine, it is a new product, and safety and efficacy need to be established, albeit possibly in a less elaborate study. This would be true even in the case of vaccines that are combined at their point of use.

WHO upholds the concept that products should generally be under the surveillance of the regulatory authority of the country of manufacture. However, there will be some instances where products will be produced solely for a market not located in the country of production, such as the DTPw combination vaccines that are currently produced only in industrialised countries where they are not used.

For vaccines, regulatory surveillance includes adequate review of preclinical and clinical data for licensing, including review of the product file, and assurance that the proposed facility is constructed and run in accordance with the prinicples of GMP. In addition, regulatory surveillance includes activities carried out post-licensing such as lot release, regular GMP inspections, surveillance for field impact including adverse event reports, resolution of complaints, and review and approval of changes in the license. WHO would like to ensure that these activities are carried out effectively for products destined for developing countries, even when the products in question are manufactured in Europe. This is essential in order to retain the current process of assuring product quality for procurement by United Nations agencies such as UNICEF.

Discussions are under way to find solutions to these issues. Currently under consideration is that the European Commission undertake, at the request of WHO, through the European Medicines Evaluation Agency (EMEA) and the Committee for Proprietary Medicinal Products (CPMP), a review of the product file, data and facility for licensing, even through the product would not be licensed by the EMEA, and delegate to the relevant national authority, all remaining regulatory issues.

Another option is the manufacture by contract manufacturer/joint venture partner in a third country, and the performance of all regulatory activities by the National Regulatory Authority (NRA) of that country. Steady improvement of the NRAs in developing countries has occurred, and today sixteen countries classified as ‘developing’ or ‘economies in transition’ have vaccine production and a national regulatory authority accessed by WHO, and judged to be fully functional. In fact, manufacturers in six of these countries are already pre-qualified for sale of certain vaccines to UN agencies.

Antigen allocation: production capacity and supply considerations

When considering the accelerated use of combination vaccines in the developing world, not only the supply of these vaccines must be examined but also their relation to the monovalent or traditional forms of the vaccines. Not all countries will be in a position financially, programmatically, or by choice, to incorporate new vaccines or combinations into their national immunisation programmes. Therefore, the supply situation must be carefuly monitored to maximise the use of antigens through proper allocation.

In recent years, there has been a sharp decline globally in the number of DTPw producers. Many that have chosen to leave manufacturing behind were local producers that could not meet the rigorous quality requirements or chose to close because it was no longer economically feasible to continue production. Without substantial production volume, the less expensive vaccines are not cost effective to produce, as the profit margin for mature, developing country vaccines is not great. Over time, since developed countries have moved from DTPw to the use of DTPa, several manufacturers from developed countries have stopped production of DTPw, leaving only two developed country manufacturers with production for UNICEF purchase. As a result, currently 77% of UNICEF’s DTPw supply comes from two developed country sources, and the amount offered for the tender is only narrowly meeting demand. As DTPw is siphoned for combinations, the supply of DTPw for other programmes could be jeopardised.

While the contributions of developing country vaccine manufacturing have been largely to the global supply of monovalent and traditional vaccines, there is a concerted effort on the part of these manufacturers to work together to combine their components into combinations for pre-qualification. One developing country vaccine manufacturer of pre-qualified vaccines plans to have a DTPw-based combination vaccine ready for pre-qualification in 2002.

Programmatic issues: market characteristics and vaccine prices
Certain important characteristics of a country or region, for instance programmatic issues, can help determine the level of acceptability of a vaccine being considered for addition into its immunisation programme. Acceptance also depends upon the desirability and affordablity of the vaccine. In the case of combination vaccines, their acceptance is based upon the perceived added value of a combination form, and how the premium, when applicable, balances with the perceived value.

Conclusions
Different markets have varying demands for combination vaccines for multiple reasons: programmatic, financial, or political. Combination vaccines serve as a vehicle to help meet the goal of accelerating new vaccine use in developing countries, although the process should be carefully managed to ensure the demands and desires of the countries are met adequately and affordable without jeopardising the global supply of traditional vaccines. Demand and financial sustainability, and how they relate to the price of the vaccine, are the overriding determinants in perceived benefit from and selection of combination vaccines over traditional vaccines.

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Based on a presentation by Dr Susan McKinney, World Health Organization, Geneva, Switzerland.

WHO's Strategic Advisory Group of Experts recommend that:

- WHO review the possible combination vaccines and the implications on supply, regulation, presentation, and price, and take a firm position with regard to the acceptability of *each* combination for national immunisation programmes. Consideration of the role of developing country production and the implications of sole source suppliers are part of this process.
- WHO, in working with partners, provide accurate demand forecasting of the various combination vaccines (meaning vaccines that have been determined by national immunisation programme managers as a benefit to their programmes that are programmatically feasible, financially sustainable, and would be purchased if funding were available for introduction where necessary). This needs to be completed and given to UN agency purchasers and directly to the manufacturers well in advance to avoid a crisis with regard to global supply. WHO and UNICEF speak with one voice to the manufacturing community and make joint recommendations and requests.
- WHO place priority on the continued action to address and monitor progress with regard to the licensing of vaccines in industrialised countries for use in developing countries.

Influence of combined vaccines on infant immunisation coverage - Recent data from Italy, Germany, and Belgium

Factors influencing vaccine uptake in Italy

Vaccination of children in Italy is based on a dual system of (a) compulsory immunisation; and (b) facultative (i.e., recommended, but not obligatory) immunisation. This system has resulted in different rates of coverage for certain infectious diseases.

Coverage is approximately 95% for the four obligatory vaccinations against poliomyelitis, diphtheria, tetanus, and hepatitis B. Until recently, in the mid-1990's, coverage was less than 50% for the recommended vaccines (pertussis, MMR, and Hib) Since the advent of acellular vaccines, and widespread use of combined vaccines containing the pertussis component, coverage in 1998 was 88%. Coverage rates for measles in 1998 ranged from 28% to 88%, with the national average at 56%. For Hib, no official recommendation with target coverage existed in 1998, so that uptake was particularly low, especially in the central and southern regions of Italy.

Rationale for compulsory vaccination in Italy
The rationale behind Italy's system of compulsory vaccination is based on the view that compulsory vaccination:

- Is a social benefit providing protection against target infections;
- Guarantees that a significant amount of public funds are devoted to protecting the population by eliminating or controlling infectious disease;
- Obliges government to maintain an efficient vaccine delivery service available throughout the country.

Abolishing compulsory immunisation
In the long term, it is likely that compulsory immunisations in Italy will be abolished. Traditionally, the common view of Italians was that only mandatory vaccines were important, and optional vaccines hardly important at all. Only when wide and in-depth campaigns on the benefits of vaccination are implemented by central and local health authorities, will abolition of compulsory vaccination be possible.

In order to avoid a dramatic drop in coverage that could threaten Italy's entire vaccination programme, substantial efforts will need to be invested in:

- Actively offering vaccination free of charge;
- Providing information to parents and health care providers on
  - Vaccines;
  - Infectious diseases;
  - Contraindications to vaccination;
- Involving paediatricians and GPs to a greater extent in promoting vaccination.

Attitudes towards immunisation
According to preliminary results of a questionnaire-based study on attitudes of Italian mothers towards vaccination,[1] approximately 80% of mothers responding to the questionnaire believed that vaccination was useful for their child.

Answers to other questions revealed an insufficient knowledge of vaccines and diseases. Paediatricians are seen as the primary source for advice on need for vaccination. See Tables 1-2.

Table 1. What is a vaccine, in your opinion?

• A natural drug	8%
• A stimulator of immune defense	56%
• Do not know	24%
• No answer	12%

Table 2. What was your source of information on vaccines?

Information source	% of respondents
Personal documentation	68.5%
General practitioner	36.6%
Friends and relatives	7.2%
Paediatrician	77.6%
Vaccination service	71.9%
Mass media	24.2%
School	4.1%

Other factors influencing vaccine uptake in Italy
According to a study[2] carried out among Italian mothers on their knowledge, attitudes, and behaviour regarding vaccination, knowledge of mandatory vaccinations is inversely related to the mother's age ($P < 0.05$), and directly related to the mother's educational level ($P < 0.0001$). Other results showed that:

- Possible dangers of vaccines are rarely given as a reason for not vaccinating;
- Over 80% of mothers would like to learn more about various aspects of vaccines and the diseases they prevent;
- As information on vaccine availability grows, and schedules are adapted in order to achieve different immunisations at the same time (e.g., MMR at 12 months), intervening illness becomes the main reason for non-vaccination.

The main conclusions of the survey highlight the need for major efforts to be made in informing both parents and health care professionals about true and false contraindications to vaccination.

Factors influencing vaccine uptake in Germany

Vaccinations in Germany are 'publicly recommended' by the *Ständige Impfkommission* (STIKO) (Advisory Committee for Vaccinations) at the Robert Koch Institute in Berlin and by the sixteen German *Länder* (States).

Publicly recommended vaccines are voluntarily paid for by all health insurance companies. Vaccines that are offered free of charge are:

- DTP, polio vaccine (IPV);
- HepB;
- Hib;
- MMR;
- Adult boosters for tetanus and diphtheria vaccines;
- Influenza and pneumococcal vaccines (for those > 60 years).

Success and limitations of Germany's vaccination programmes
Diseases such as diphtheria, poliomyelitis, and invasive Hib disease have been virtually eliminated through successful vaccination programmes in Germany. However, 10% coverage for primary immunisation series are lacking, and 50% of doses are given too late.[3] Coverage for MMR is low, approximately 70%, outbreaks of measles still occur regularly, and the number of cases of congenital rubella is not known due to under-reporting. Of the fewer than fifty cases of Hib disease that still occur annually in Germany, all related deaths were among unvaccinated or under-vaccinated children.[4] Although enough money is allocated for vaccination in Germany's health care system, barriers still exist that prevent satisfactory levels of health in children and adults to be achieved.

Parents' and doctors' attitudes towards vaccination
Data from a representative survey[5] revealed that the reasons given by parents for incomplete vaccinations were that more than 50% of them felt they were insufficiently informed about vaccination, and over 20% had misconceptions about the benefits and side effects of vaccination. Refusal of vaccination based on ideological principle was very low (between 0.4% and 1.5%).

Germany: Reasons for missed appointments

Parents' explanations	%	Paediatricians' explanations	%
Experiencing disease is important	23	Missed appointments	74.2
Frequent side effects	25	Illness at time of appointment	72.2
Risk for long-term sequelae	8	Social neglect	54.3
Not recommended by physician	8	Parental opposition	37.5
Insufficient information	> 50	Parental information deficit	31.5
Skepticism against vaccination	10-26	Language barriers	20.5
Principle opposition against vaccination	0.4-1.5	Lack of societal support	5.5
		Religious reasons	3.4

Remuneration for paediatricians
If reimbursement for vaccination existed, or if the cost-effectiveness of vaccine use were considered, the above-mentioned reasons for non-vaccination could be remedied. For the hexavalent vaccine (DTPa-IPV-HepB-Hib), a paediatrician in Schleswig-Holstein would currently receive approximately five to ten euro for:

- Explaining the six diseases/complications;
- Explaining treatment/prevention options;
- Describing vaccine effects / adverse events
- Recommending precautions following vaccination;
- Explaining need for booster doses;
- Taking patient's history;
- Physical examination;
- Vaccination;
- Post-vaccination observation of patient for 30 minutes.

Structural constraints to vaccination in Germany
Several constraints to appropriate use of vaccines in Germany have been identified by the Robert Koch Institute, and by a recent health care report.[6] These include:

- Mandatory patient written consent to remind him/her of booster dose necessity, often preventing timely vaccination;
- Existence of 420 health insurances with different systems of reimbursement for 23 local agencies, leading to ambiguities in how a physician is reimbursed and a factor possibly leading to inappropriate vaccine use;
- Low vaccination coverage (30%) in adolescents due to lack of incentives for physician visits, and lack of official information about prevention of disease.

Other constraints include the fact that while vaccine doses are documented in a patient's private vaccination card and in the physician's records, data protection laws in Germany prohibit electronic transfer of patient information to the patient's insurance card. This type of situation may present a barrier to timely vaccination when a patient visits a different physician and neglects to remember his or her private vaccination card. Another structural deficit includes the lack of vaccination courses in the curriculum of most German medical schools, which may explain why many physicians in the country oppose vaccination.

Lack of German epidemiological data for some vaccine-preventable diseases is another barrier to timely vaccinations, and funding for epidemiological research on infectious diseases in Germany is virtually non-existent. In addition, official vaccination coverage data are available only at the time of school entry, information that has extremely limited - if any - value.

Use of combined vaccines in Germany
While STIKO has issued no specific recommendations for combined vaccines, other than DT or dT, there is a general recommendation that combined vaccines should be used '… whenever possible and applicable.' Although no data are currently available on the level of acceptance of hexavalent vaccines in Germany, anecdotal evidence suggests that pentavalent vaccines plus the additional hepatitis B vaccine are the preferred vaccine formulations. It would appear, however, that hexavalent vaccines are gradually beginning to gain acceptance among the general population as well as the medical community. Improving reimbursement to doctors who administer hexavalent vaccines, and promoting the benefits and safety aspects of hexavalent vaccines to parents and doctors, are two factors that would undoubtedly contribute to higher levels of acceptance and use of combined vaccines in Germany.

Factors influencing vaccine uptake in Belgium

In Belgium, poliomyelitis vaccination is the only mandatory infant vaccination. All infant vaccines are offered free of charge (costs borne by the national and regional ministries of health) - for HepB since September 1999 and for Hib since April 2002. If administered in a Mother and Child clinic, no service fee is charged. If the vaccination is given in the private practice of a general practitioner or a paediatrician, a service fee is charged. Belgian recommendations for infant immunisation are:

- Polio vaccine at 2, 3, 4 and 13-14 months (IPV);
- DTP and Hib at 2, 3, 4 and 13-14 months;
- HepB at 3, 4 and 13 months;
- MMR at 15 months.

Vaccination coverage survey - Flanders and Wallonia
In order to estimate infant vaccination coverage among children in Belgium aged 18 to 24 months, a cluster sampling survey[7,8] was carried out in 1999 within the Dutch (Flanders) and French-speaking (Wallonia) communities. The study also offered the opportunity to assess factors that influence vaccination uptake, and to document the reasons for non-vaccination or incomplete vaccination series.

Methodology
In Flanders, 1,110 children were randomly selected from eighty-seven municipalities. Of the 1,110 families contacted, 1,053 (94.8%) agreed to participate. Interviews were carried out for 1,005 children, whose vaccination documents were also made available for verification of the interview data. In Wallonia, 1,088 children were randomly selected from fifty municipalities. Of the 918 families contacted, 866 (94.3%) agreed to participate. Interviews were carried out for children whose families agreed to participate, and vaccination documents for 835 of the children were provided. Socio-demographic factors taken into account in the survey were gender, nationality and origin of the child and the parents, childcare assistance, parents' level of education and type of employment, size of the family, and income.

Survey results - vaccination coverage
Vaccination coverage for Flanders and Wallonia are shown below.

Belgium: Estimated infant and childhood (18-24 months) vaccination coverage (%) in Flanders and Wallonia, 1999*

Vaccine	First dose	Second dose	Third dose	Fourth dose
Polio	99 (99)	99 (99)	96 (96)	
DTP	96 (99)	95 (98)	95 (97)	89 (81)
Hib**			78 (86)	
HepB	74 (59)	73 (56)	68 (50)	
MMR			83 (82)	

* Data for Wallonia shown in brackets. ** Completely vaccinated at 18-24 months of age.

In Flanders, there was no association between coverage and socio-demographic factors. Also in Wallonia, vaccination coverage did not appear to be linked with socio-demographic factors, except for (1) lower coverage for two vaccines (Hib and HepB) that were not yet offered free of charge at the time of the survey, and (2) lower MMR coverage in families with more than one child.

For both Flanders and Wallonia, the choice of a vaccinator appeared to be associated with the educational level and nationality of the parents. Belgian parents and parents with a higher level of education chose to go to a GP and/or paediatrician more often than to a clinic. For 82% of the parents, having their child immunised with more than two shots per visit would not be acceptable.

Reasons for incomplete vaccination or non-vaccination
In Flanders, the main reasons given by parents for non-vaccination were that:

- Physician did not suggest the vaccination;
- Parents were not convinced of the necessity or effectiveness of vaccination;
- Parents were not knowledgable about the vaccine;
- A minority of parents refused vaccination on ideological grounds.

The results for Flanders also suggest that the number of children who are not vaccinated against Hib infection or hepatitis B could be decreased by 40% if parents were informed of the existence of these vaccines. Also, half of the incompleted vaccinations could be completed through better follow-up of the vaccination schedule.

In Wallonia, the main reasons for non-vaccination were due to the attitudes of both parents and physicians towards vaccination. Parents also felt responsible for not having their child complete the course of vaccination. For all of the vaccines, parents mentioned that the attitude of the physician was very influential in their decision to vaccinate the child, but especially with regard to pertussis and hepatitis B immunisations.

Improving infant vaccination coverage
For both Flanders and Wallonia, parents felt that vaccination coverage could be improved by the following:

Ways of improving vaccination coverage	Flanders	Wallonia
Mandatory infant vaccination	**67%**	**81%**
Free vaccination	**84%**	**80%**
Availability of more information on vaccines and vaccine-preventable diseases	**66%**	**77%**

In Flanders, 61% of parents and in Wallonia, 66% of parents had a positive attitude towards the introduction of new vaccines. For parents who did not favour new vaccines, it appeared that vaccine-preventable infections were not important or frequent enough to warrant additional or new vaccines.

Conclusions
The survey results for both Flanders and Wallonia show that providing sufficient information to parents and physicians regarding immunisation is a crucial factor in improving vaccination coverage. This fact underlines the importance of the role that parents, physicians, and nurses play in infant vaccination. Efforts towards increasing the level of knowledge about vaccines and vaccine-preventable diseases should become a priority, and should be targeted to physicians, nurses, as well as students who are following medical courses.

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Based on presentations by Dr Paolo Bonanni, Public Health Department, University of Florence, Florence, Italy, and Dr Wolfgang Jilg, Institute for Medical Microbiology and Hygiene, University of Regensburg, Regensburg, Germany.

Hepatitis B vaccination: an alternative (re)view

While most recipients of three doses of currently available hepatitis B vaccines produce a strong and long-lasting anti-HBs response, 5-10% of healthy adults do not produce protective levels of anti-HBs, and can be considered non-responders.[1] Although non-responsiveness affects only a small fraction of the healthy, adult population, strategies to overcome non or poor responsiveness and to enhance the immunogenicity of hepatitis B vaccines have been devised.

Adding preS-epitopes to HBsAg vaccine - conflicting results
One strategy used to render hepatitis B vaccines more immunogenic is adding preS-epitopes to HBsAg (S-only) vaccine. The rationale for using this approach is based on results shown in a mouse model where the immune response to preS1 and preS2 was regulated independently from the response to the S-region. Prompted by other animal studies, several preS-containing vaccines have been under investigation for several years. In early trials using

preS2-containing vaccines, the vaccines proved to be safe and immunogenic but actually showed no distinct advantage over the existing S-only vaccines.[2-4] The immunogenicity was compared of a yeast-recombinant hepatitis B vaccine containing surface antigen (S) and selected preS1 and preS2 sequences with that of a vaccine containing S alone (Engerix-B®) in thirty-two adults who had previously exhibited poor responsiveness following at least three consecutive monthly doses of hepatitis B vaccines. Although the addition of preS sequences to S did not enhance the *in vivo* humoral and anti-HBs response, the three additional vaccine doses, irrespective of their preS content, did induce seroprotective anti-HBs levels in over 90% of the vaccinees.[5] Other trials, using preS1 and preS2-containing recombinant HBsAg vaccines, seem to indicate that preS sequences do confer increased immunogenicity in proven non-responders.[6-7]

The conflicting results of these studies may be due to the selection of preS1 and preS2 epitopes included in the different vaccines, and to the protease sensitivity and ensuing instability of certain products. It is important that these issues be clarified before definitive statements can be made on the usefulness of preS sequences.

DNA vaccines and HBcAg carriers

DNA immunisation

DNA immunisation is another area currently under investigation, although the concept up until now has been explored mainly in mice. A recent study was carried out on the safety and immunogenicity of DNA vaccine encoding HBsAg delivered by a gene delivery device.[8] The results of the study suggested that using this gene delivery system induced a booster response, but the vaccine at the low doses of DNA used (0.25 µg) did not induce primary immune responses. It still remains to be determined whether DNA-based immunisation will prove to be more effective, less expensive, or safer than recombinant proteins.

HBcAg as carrier

Although HBsAg vaccine is effective in preventing HBV infection, it is a poor immunogen (if not adjuvanted). HBcAg is far more immunogenic, making it extremely attractive for use as a carrier of heterologous B-cell epitopes. As a result of these properties, several investigators have produced recombinant HBcAg chimeric particles containing envelope haptenic sequences inserted at the amino-terminus, or inserted internally into the surface loop structure. These particles show enhanced immunogenicity for the carried hapten.[9] Similar results have also been obtained when non-HBV-related haptens, such as malarial circumsporozoite epitopes, have been inserted in HBcAg.

Enhanced immunogenic adjuvants

Enhanced immunogenicity of vaccines can also be achieved through changing the adjuvant used for delivery rather than the protein composition. For currently licensed vaccines, the only adjuvants approved for use are aluminium salts. The results of recent studies using new adjuvant systems suggest that the problem of poor or non-responsiveness to HBsAg vaccines in genetic non-responders and immune-compromised patients could be eliminated, and candidate vaccines will be tested in these populations. HBV envelope proteins formulated in the adjuvant systems SBAS4 (containing monophosphoryl lipid A) and SBAS2 (consisting of monophosphoryl lipid A, QS21, and an oil in water emulsion) turned out to be more immunogenic than their non-adjuvanted or aluminium-adjuvanted counterparts, and immune responses were significantly higher than those of the control vaccines used in the studies.

Conclusions

It is conceivable that a two-dose hepatitis B vaccine schedule could be achieved using vaccines with enhanced immunogenicity, and eventually lead to reduced vaccine administration costs and improved compliance. However, until such novel vaccines become available, administration of one or more doses of currently available hepatitis B vaccines will remain the only solution to elicit a protective immune response in non-responders.

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Based on a presentation by Dr Geert Leroux-Roels, Center for Vaccinology, Ghent University, Ghent, Belgium.

Importance of combined hepatitis B vaccines - A paediatrician's point of view

Hepatitis B is the only vaccine-preventable disease that can be transmitted vertically from an infected mother to her child through placental leakage *in utero*. The level of risk through perinatal transmission of infection will have an impact on the immunisation strategy used to prevent hepatitis B infection. Depending on the prevalence of hepatitis B in the population, two different strategies are used - either the first dose at birth, or the first dose between two and three months of age.

First vaccine dose at birth
The strategy of giving the first dose of hepatitis B at birth is used in countries with high or moderate incidence of hepatitis B where universal maternal screening does not exist or where selective screening of risk groups of pregnant women may not be reliable. In countries with no maternal screening programmes in place, the focus will be on universal neonatal immunisation.

While combination vaccines are an ideal opportunity for a child to receive several antigens in a single injection, the monovalent hepatitis B vaccine must be used as the birth dose since the non-hepatitis B components of a combination vaccine have reduced immunogenicity in infants under six weeks of age.

The schedules most widely used for hepatitis B vaccination at birth are 0, 1, 6 or 0, 1, 2, 12 months, both of which are effective. In some countries where tuberculosis is still prevalent, BCG is added to the schedule and given to newborns.

First vaccine dose between two and three months of age
The strategy of giving the first dose of hepatitis B vaccine between two and three months of age is used in countries with:

- Low incidence of hepatitis B;
- High incidence of hepatitis B where high coverage of universal maternal screening is achieved and immunisation of newborns is available.

The issue of whether to give a second dose of hepatitis B vaccine after the birth dose will depend on if the mother is a HBsAg carrier or not. If the mother is a known carrier, the second dose must be given before the age of two months. If the second dose is delayed, unless HBIg is given, the protective efficacy has been shown to drop from 95% to 84%. If the mother is not a carrier, the second dose can be given at two to three months as a combined vaccine with DTP. Although in such cases the child will ultimately receive four doses of hepatitis B vaccine, there is no evidence that this is unsafe for the child.

Based on a presentation by Dr Vytautas Usonis, Centre of Paediatrics, Vilnius University, Vilnius, Lithuania.

Immunogenicity profile of combined vaccines in infants

Combined vaccines - minimal immune interference
Recent reports[1-3] on combined DTPa, IPV, HepB and Hib vaccines have shown minimal immune interference, with the exception of reduced responses to the Hib vaccines. Early reports[4-5] showed that combined administration of DTPa (with or without IPV) and Hib vaccines induced a decrease in antibody responses to Hib compared with separate administration of the vaccines, or when combined with the whole-cell pertussis (Pw) vaccine. Although there are reports[6-7] that have confirmed these findings, there are also recent reports of a combination vaccine containing a penta-valent Canadian Pa vaccine showing no immune interference.[6] The significance and clinical implications of the lower anti-Hib antibody concentrations have been questioned in several studies,[6-8] which have been a major obstacle for licensing combined vaccines in the USA. A better understanding of the clinical significance and mechanisms of the decreased anti-Hib antibody concentrations would help in decision-making, and in getting multi-disease combined vaccines into global use. Aside from Hib, no other evidence concerning immune interference with other vaccine combinations has been presented. In fact, recent data[3] from the Republic of Moldova show even higher concentrations of anti-HBs after administration of DTPa-HBV-IPV/Hib than after DTPw-IPV/Hib + HBV.

Undoubtedly antibodies to Hib capsular polysaccharide are protective.[9] Early reports suggested that concentrations that would predict short-term and long-term protection exist; these con-centrations, ≥ 0.15µg/ml and ≥ 1.0µg/ml, respectively, have been used widely as correlates of protection. However, these estimates were based on rather old data from non-immunised individuals or from an efficacy trial with capsular polysaccharide vaccine. At the time that these studies were carried out, such estimates were justified, because it was believed that the protection induced by T-cell independent plain polysaccharide vaccine is offered solely by circulating antibodies, and that the role of immunologic memory is negligible.[10]

The situation is totally different today when using conjugate vaccines that combine polysaccharide with a protein carrier. Protection is also believed to be provided via the development of T-cell dependent immune response and memory, and via the production of high avidity antibodies. Increase in avidity can indicate better functional activity of antibodies,[11] and can be a marker of the development of memory.[12] Good functional activitiy is believed to be important, especially when concentrations of antibodies begin to wane over a period of time.

Several studies show that Hib conjugate vaccines offer protection even if the antibody responses one month after vaccination have been similar or even lower than those induced by the present combination vaccines. The first data supporting this view were from the Finnish efficacy trials[13-14] almost fifteen years ago, and more recently from epidemiological data from the UK and Sweden. More recent data from Germany, where combination vaccines have been in extensive use, show no increase in invasive Hib disease. See table below.

Vaccine efficacy (%) against Hib disease with DTaP/Hib/(IPV) combinations in Germany, in a two-year follow-up after their introduction

Overall	**97.5 (96.3-98.4)**
One dose	**88.6 (76.1-94.3)**
Two doses	**95.1 (92.2-97.0)**
Three doses	**98.8 (98.2-99.3)**

The most recent data suggest that the correlates or surrogates of protection for Hib disease are really not known. In addition to antibody concentration, the induction of immune memory should also be studied. There are no easy ways to directly measure the development of memory responses. However, rather simple study settings and serological methods can be used as a surrogate. For example, high immune response to a dose of plain polysaccharide vaccine, given after the primary series, can be used to show the existence of memory B cells.[7] Furthermore, the concept of affinity maturation during a T-cell dependent immune response can be used, and the measurement of the increase in the avidity of anti-Hib IgG after and during immunisations should be considered.

The present data on immunogenicity and safety of combined vaccines encourage the introduction of these vaccines into immunisation programmes. Phase IV studies after the introduction of the new combined vaccines are of utmost importance.

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Based on a presentation by Dr Helena Käyhty, Department of Vaccines, National Public Health Institute, Helsinki, Finland.

Combined paediatric vaccines for national immunisation programmes

Two new combination vaccines have been developed in parallel by GlaxoSmithKline: (1) Infanrix®-*penta* (combining DTPa, hepatitis B, and polio components); and (2) Infanrix®-*hexa* (combining DTPa, hepatitis B, polio, and Hib components).

In the clinical development of these two vaccines, the general objective was to demonstrate their non-inferiority compared with already licensed vaccines that went into the combined vaccines.

Other clinical objectives were to demonstrate:

- Safety and acceptable reactogenicity;
- Immunogenicity in various schedules;
- Persistence of antibodies up to the time of the booster dose;
- Protective efficacy of each vaccine component;
- Lot-to-lot consistency.

For both Infanrix®-*penta* and Infanrix®-*hexa*, integrated clinical trial programmes were designed in parallel, with the following characteristics:

- Common inclusion and exclusion criteria;
- Common reactogenicity assessment;
- Common serological assays;
- Randomised controlled trials based on pre-defined statistical criteria to demonstrate non-inferiority vs. licensed vaccines.

Infanrix®-penta
Primary immunisation trials for Infanrix®-*penta* were carried out among 7,549 children, aged between one and a half and six months of age, in Belgium, Canada, Estonia, Finland, France, Germany, Lithuania, Moldavia, Turkey, and the USA.

In one clinical trial carried out in the United States, designed on the basis of all the immunisation schedules being used in that country, Infanrix®-*penta* + Hib was compared with the separate administration of antigens. In the same trial, there was little difference in antibody response of D, T, HepB, PT (pertussis toxin), FHA (filamentous haemagglutinin), PRN (pertactin), and polio (types 1, 2, and 3) between Infanrix®-*penta* and vaccines administered as separate antigens.

In terms of reactogenicity, there were slight increases in redness and swelling at the site of injection using Infanrix®-*penta*, but these levels were determined to be clinically acceptable in view of the vaccine's protection against two additional diseases. There was no significant increase in incidence of local pain reactions (based on a three-dose schedule), which indicates that there is no development of hypersensitivity.

Infanrix®-hexa
For Infanrix®-*hexa*, primary immunisation trials were carried out among 4,746 children aged between one and a half and six months of age, in Australia, France, Germany, Philippines, Slovakia, and the USA. Results for the hexavalent vaccine were similar to those for Infanrix®-*penta* regarding immunogenicity for D, T, HepB, PT, FHA, PRN, and polio (types 1, 2, and 3).

Immune response to Hib was somewhat lower with Infanrix®-*hexa*. However, this was not determined to be clinically important as protection was seen to be the same as with monovalent vaccines. In a review[1] of Infanrix®-*hexa* and Hib immunogenicity, the authors concluded:

- In all clinical trials, regardless of vaccination schedule, ≥ 96% of subjects achieved concentrations ≥ 0.15 µg/ml;
- Non-inferiority of Infanrix®-*hexa* compared to licensed DTPa-IPV/Hib vaccine;
- Identical functional capacity of anti-PRP antibodies induced by Infanrix®-*hexa* and by licensed Hib vaccines;
- Effective induction of immune memory;
- Proven field effectiveness of DTPa/Hib and DTPa-IPV/Hib under conditions of routine use.

In all clinical trials (with results based on 23,439 doses of the Infanrix®-*penta* vaccine, and 15,920 doses of Infanrix®-*hexa*) there were no cases reported of hypotonic hyporesponsiveness, encephalopathy, or anaphylaxis.

Conclusions
For both Infanrix®-*penta* and Infanrix®-*hexa*, protective efficacy is not affected by the combination of antigens, and tolerability of primary and booster doses is in line with that of other licensed vaccines.

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Based on a presentation by Dr Francis André, GlaxoSmithKline, Rixensart, Belgium.

A new liquid hexavalent vaccine - Overview of its clinical profile

The obvious advantage of combined vaccines is the reduced number of injections needed in paediatric immunisation, and the potential for new (pneumococcal, meningococcal) combined vaccines to be developed, adding value to the current standard of medical care in protecting against childhood diseases.

Hexavac® is a new hexavalent vaccine (DTPa-IPV-Hib-HepB) developed by Aventis Pasteur MSD for primary and booster vaccination of infants.

The time-frame to develop and market Hexavac® was approximately seven years, beginning in February 1994 when the project first started, until October 2000 when the vaccine received European marketing authorisation, and was first marketed in Germany.

Clinical studies were carried out in France, Germany, Sweden, Turkey, and Chile. In these studies, very high seroprotection rates for all considered antigens were achieved in the majority of infants following a primary series of three doses administered at 1-2 month intervals from two months of age. Hexavac® also induced immunological memory as was evidenced by the strong anamnestic response to booster vaccination at 12-18 months.

Hexavac® has also been shown during clinical trials to be well tolerated. The most frequently reported adverse events after both primary and booster doses were local reactions of redness and swelling and systemic reactions of mild fever, irrespective of the vaccine that had been used for priming.

Hexavac®: summary of safety profile.
Local and systemic reactions (%) within 3 days following primary series in infants and booster in children primed with Hexavac®

Local reactions	First dose n = 3,897	Second dose n = 3,826	Third dose n = 3,784	All doses n = 11,507	Booster n =2,688
Any local reaction	14.1	17.9	19.6	17.2	21.3
Redness ≥ 2 cm	6.8	10.0	12.2	9.4	17.4
Induration and/or swelling ≥ 2 cm	10.2	12.6	13.4	12.0	15.6
Systemic reactions					
Irritability and/or unusual crying	25.7	25.3	22.0	24.4	15.6
Drowsiness	15.2	8.8	6.3	10.1	5.7
Fever 38-38.9°C	9.06	18.0	18.0	15.0	24.9
39-39.9°C	0.44	1.6	2.7	1.6	3.6
≥ 40°C	0.03	0.13	0.16	0.10	0.74

In addition to demonstrating safety and efficacy of the vaccine, another goal of the manufacturer's clinical development plan was to show Hexavac®'s use within various vaccination schedules. Clinical studies comparing the immunogenicity of Hexavac® administered at either 2, 3, and 4 months, or at 2, 4, and 6 months, showed that the vaccine could be used by either vaccination schedule. Another study also supported the use of Hexavac® at 3 and 5 months, with a booster dose at 12 months of age.

Conclusions

This new hexavalent, Hexavac®, vaccine represents an ideal opportunity to offer protection against six important childhood diseases with a single injection for each required medical visit.

Based on a presentation by Dr Benoît Soubeyrand, Aventis Pasteur MSD, Lyon, France.

Economic aspects of combined vaccines

Little academic research has been carried out on the economics of combined vaccines. The research and development costs for these vaccines are high due to technical and regulatory complexity.

The number of components in a combined vaccine and the diversity of vaccination schedules between countries are directly related to the number of required clinical trials to demonstrate vaccine efficacy and safety.

The technicality, the multiple patents and requirements in terms of clinical trials (all demanding great investment) will increase barriers to enter the vaccine market, and are likely to push contemporary competitors out of the market (those who lack the know-how and the necessary investment opportunities) because combined vaccines provide a major competitive advantage (it is a superior product if efficacy and adverse events are identical).[1]

This would lead to more monopolistic behaviour in the vaccine market, with risks to supply, availability, choice, and price.

However, the benefits of using combined vaccines are many[1] and are summarised in the box below.

All these benefits will have to be traded off versus the price of combined vaccines. In view of the high development costs, it seems very likely that combined vaccines will be priced higher than their components separately. The substantial (intangible) benefits to parents and their children are particularly difficult to measure.

In a study in northern California, 1,657 parents who had their 1 to 8-month-old infant vaccinated during the previous 14 days were asked for their 'willingness to pay' (WTP) for reducing the number of childhood injections per visit.[1,2] The median WTP was US$25 for a reduction in the number of injections from 4 to 3, or from 3 to 2, whereas it was US$50 for a reduction from 2 to 1. Parents whose child showed clinical adverse events indicated that the median WTP to avoid these would be US$50.

The very wide range for each of these estimates (minimum

US$0-1,000) may indicate that people have different perceptions of the risks involved, have different attitudes towards risk, and generally have difficulty in quantifying their hypothetical WTP. Nonetheless the median value exceeded the average estimated costs of adverse events (US$7.7 per vaccinated child, including work loss to the parents (53%)) in the total study population.

In summary, it seems very likely that the use of combined vaccines versus their components separately is cost-saving, conditional on price-setting and avoiding bad publicity (due to which the coverage of important antigens in a combination could be damaged).

The cost-effectiveness of a new addition to an existing combination, on the other hand, depends on the disease in question and the starter situation [e.g., MMRV (measles-mumps-rubella-varicella vaccine) vs. MMR; HepA-HepB vs. HepB].

Benefits of using combined vaccines

- Reductions in the number of injections and associated administration costs. These include reduced money, time and pain costs for children and their parents, and a likely reduction in storage, transportation, and equipment costs.

- Free-rider effects: a combined vaccine may include an antigen that suffers from an 'image problem' such as HepB, or an antigen that protects against certain diseases considered less important (such as hepatitis A, chicken pox, or mumps). Combining such antigens together with antigens for other diseases with higher priority (or a 'better' image) in a vaccination programme, such as measles or Hib disease, allows for greater coverage and improved compliance against a greater range of infectious diseases. A potentially negative aspect is that an important vaccine, such as measles, could be brought into question through negative (although unsubstantiated) media coverage of the combined vaccine (MMR), as has occurred in the United Kingdom.

- Reduced transmission of blood-borne infections by contaminated needles (though the role here may be rather limited for combined vaccines). In some countries up to 80% of disposable needles are re-used, but safety of injection seems more related to adapting the needle (auto-disable syringes) than to providing combined vaccines.

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Conclusions of the meeting

Benefits of combined vaccines

- Reduced number of injections per visit, and reduced total number of injections overall, leading to:

  - Reduced number of exposures to possible injection pain;
  - Less or no exposure to thiomersal;
  - Less time spent in doctor visits;
  - Less waste and increased injection safety with fewer syringes;
  - Reduced immunisation programme costs.

- Improved vaccination coverage.
- Simplified implementation of immunisation programmes.
- Facilitated addition of new antigens into existing immunisation programmes.
- Facilitated harmonisation of antigens.
- Decreased disease prevalence and burden.
- Facilitated data collection through easier documentation.
- Reduced costs of storage, transport, cold chain (not valid for developing countries).
- May present a new opportunity to move towards vaccination calendars in the European Union.

Combined vaccines - drawbacks, concerns, and issues

- Possible barriers to the use of certain combination vaccines based on complex issues regarding harmonisation of European vaccination schedules are due to:

  - Different epidemiological patterns per country/region;
  - Different national recommendations for compulsory and facultative immunisations;
  - Different national traditions and attitudes towards health care reimbursement;
  - Complexity of policy and decision-making at national level involving many associations of physicians and health insurance providers.

- Potential decrease in immunisation programme flexibility with increase in number of antigens per dose.
- Shrinking market of vaccine manufacturers (due to mergers) places immunisation programmes at potential risk if a manu facturer of a combined vaccine chooses to stop production and no other supply source exists.
- Increasing complexity and costs of clinical development and trials involving:

  - Need for testing safety and efficacy of each vaccine component;
  - Ethical implications in conducting clinical trials with huge numbers of participants to test against different immunisation schedules;
  - Need to establish new minimum potency and protection levels;
  - Need for new reference materials;
  - Analysis of adverse reactions;
  - Surrogate markers.

- Combined vaccines with a HepB component cannot be used for newborn immunisation since the non-hepatitis B components of combination vaccines have reduced immunogenicity in children less than six weeks of age. The monovalent hepatitis B vaccine must continue to be used as the birth dose.
- More long-term studies will be needed to evaluate when booster vaccinations are needed using hexavalent vaccines with a hepatitis B component, especially in immunisation schedules with only three vaccinations in the first year of life with no booster vaccination.
- Quality issues of hexavalent vaccines focus on the cumulative stability of vaccine intermediates, resulting in CPMP recommendations that have been accepted by manufacturers in assuring that intermediates exceeding a certain age will not be used in the manufacture of vaccines.
- Efficacy issues highlight the need for establishing better or other markers of protection.
- While immunological responses against Hib may be lower in hexavalent vaccines, they still remain at clinically acceptable protective levels.

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